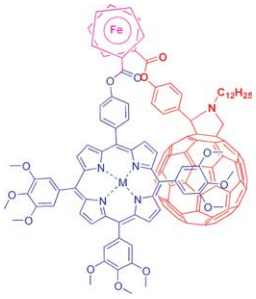
ELSEVIER

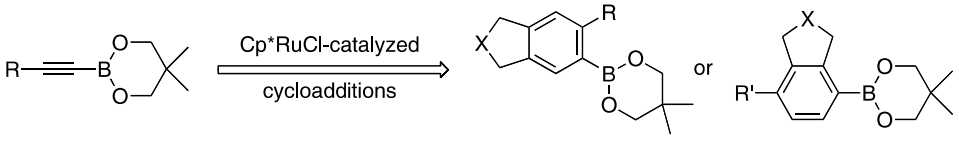
Tetrahedron

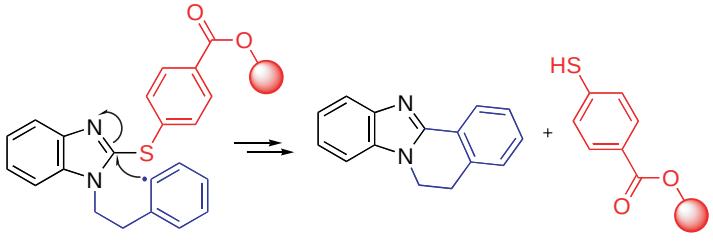
Tetrahedron Vol. 62, No. 18, 2006

Contents

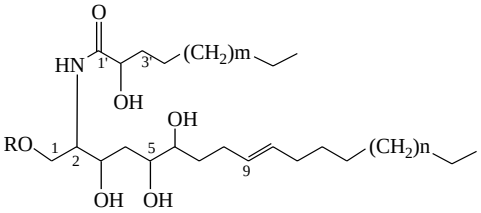
ARTICLES



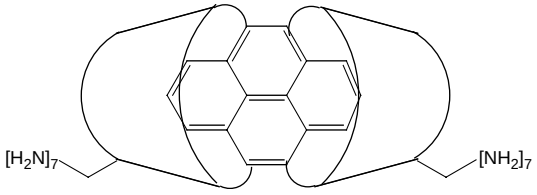


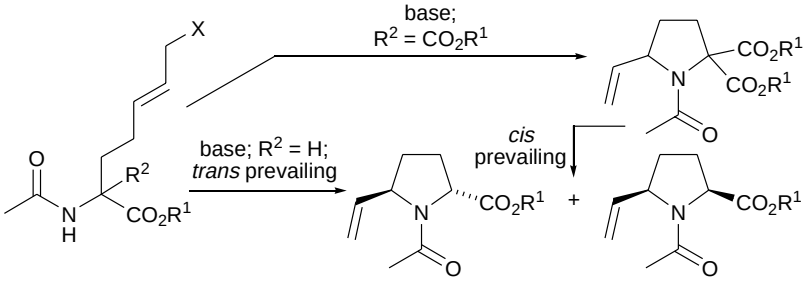


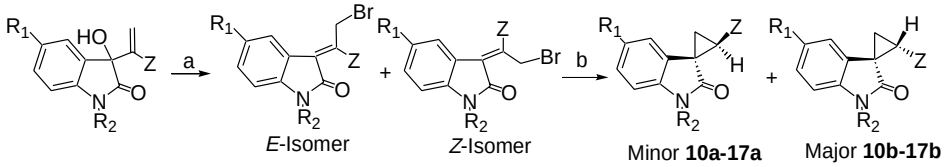
Solid phase synthesis has been used to carry out intramolecular aromatic homolytic substitution with benzoimidazole precursors.



1: R = H, m = 9, n = 11; **2**: R = H, m = 9, n = 9
3: R = H, m = 10, n = 11; **4**: R = -β-D-glu, m = 10, n = 11
5: R = H, m = 12, n = 13; **6**: R = -β-D-glu (1→4)-O-β-D-glu, m = 12, n =13

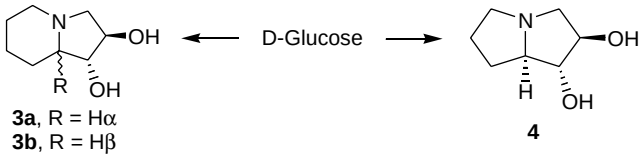






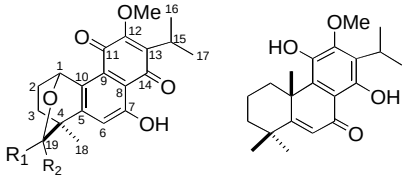
R_1=H, Br; R_2=Me,CH_2Ph, Propargyl; Z =CO_2Et, CN

a: 4 equiv. aquous HBr, silicagel, μw, 750W, 3min; b: 2 equiv. $NaBH_4$, THF, 0.5h



3a, R = Hα
3b, R = Hβ

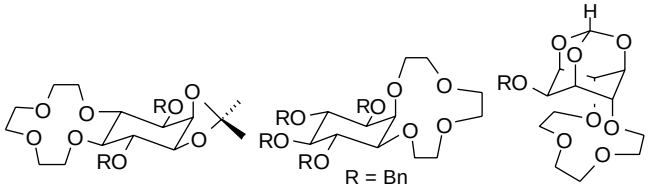
4

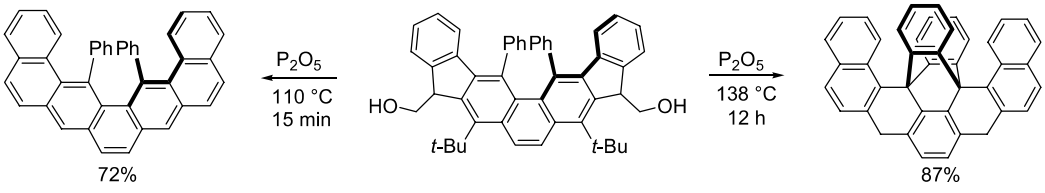


1: R_1=R_2=H
2: R_1,R_2= =O

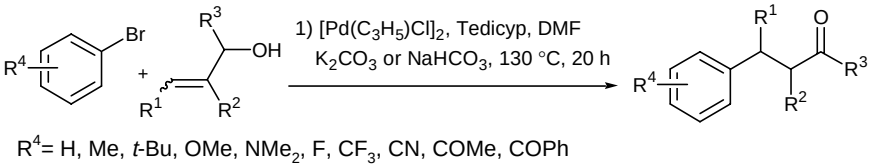
3

Two new diterpenes, dracocequinones A (**1**) and B (**2**), were isolated from *Dracocephalum komarovi* as trypanocidal constituents against epimastigotes of *Trypanosoma cruzi*, together with a new compound, komarovinone A (**3**) and known terpenes.

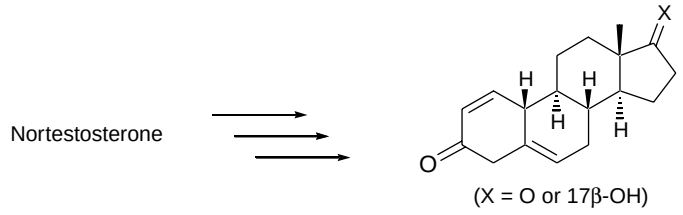




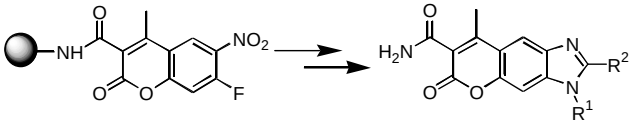
72% 87%

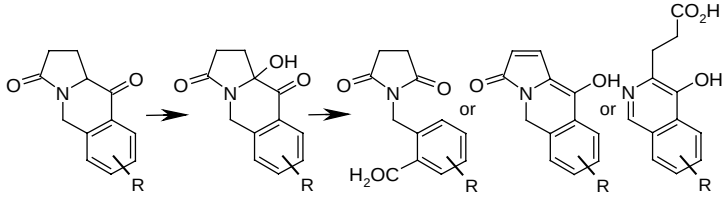


R^4= H, Me, *t*-Bu, OMe, NMe_2, F, CF_3, CN, COMe, COPh

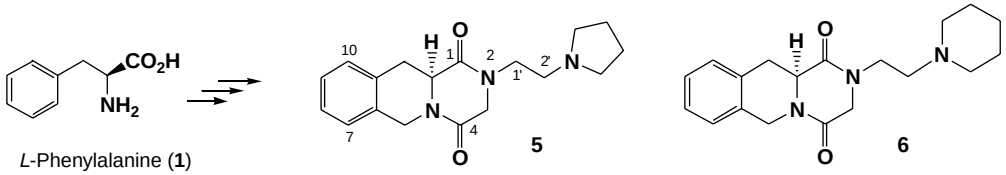


(X = O or 17β-OH)

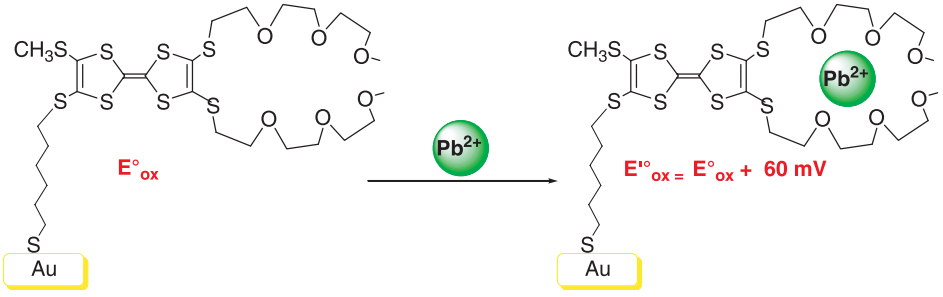


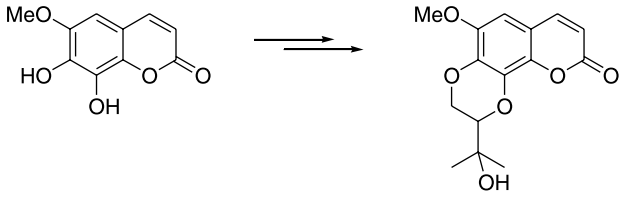


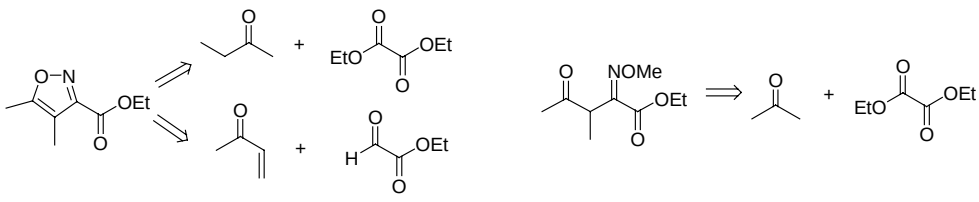
Air oxidation of hexahydrobenz[*f*]indolizine-3,10-diones in MeOH/MeONa yields alcohols which are easily and selectively transformed, in very good yields, to succinimides, isoquinoline propanoic acids or dehydrated to ene lactams.

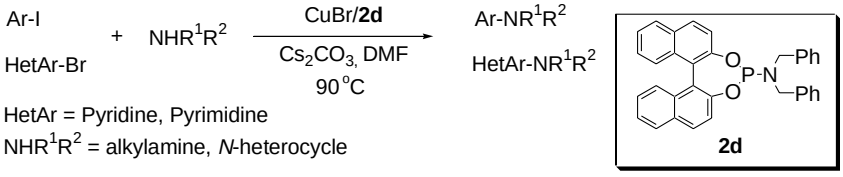


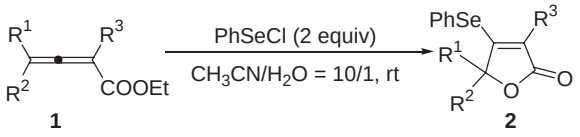
We report herein the synthesis of new dioxopiperazine isoquinolines (**5**, **6**), with a tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione moiety, using the Pictet–Spengler cyclization. The molecular structure of **6** was determined by RHF/3-21G and RB3LYP/6-31G(d) calculations. Both levels of calculations are in agreement with the X-ray data.

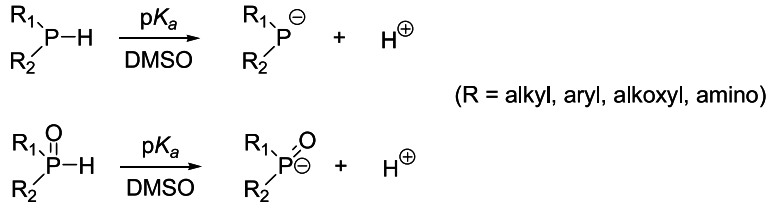


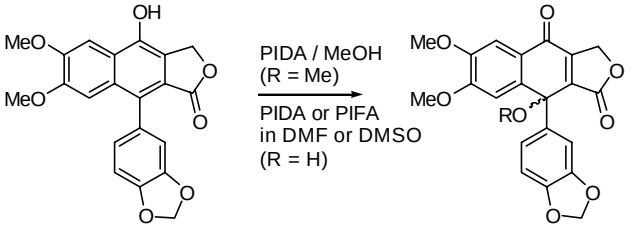


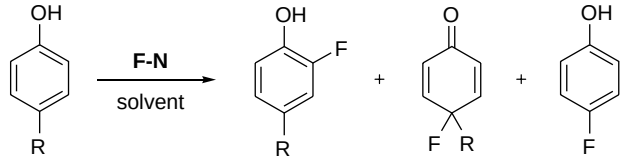




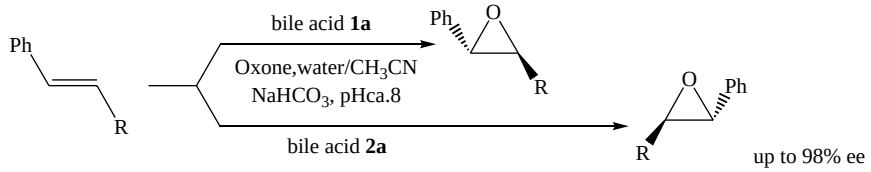


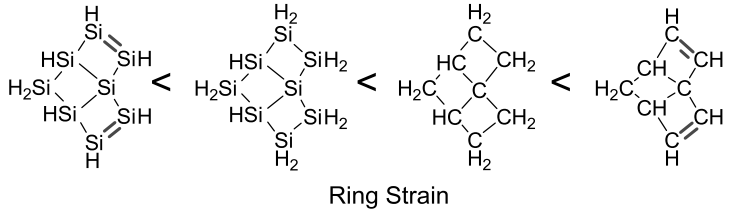


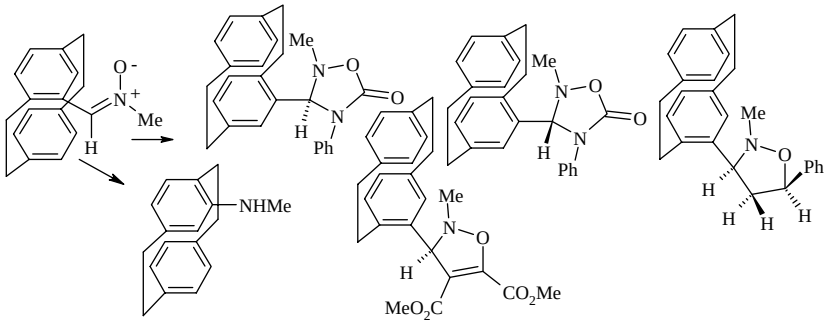


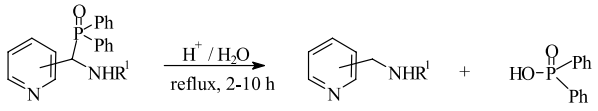


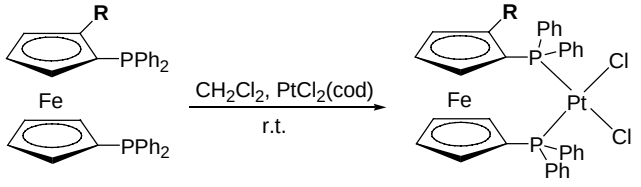
The effect of steric interactions on the regioselectivity of fluorination of *para* alkyl substituted phenols was investigated and a strong effect of the size of the alkyl substituents, the structure of the F–N reagent and the solvent on the site of fluorination was established.

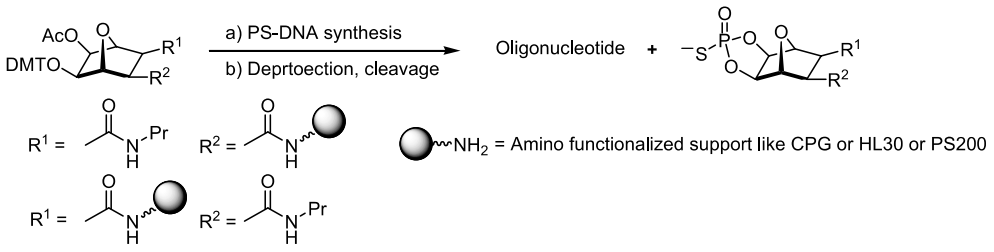


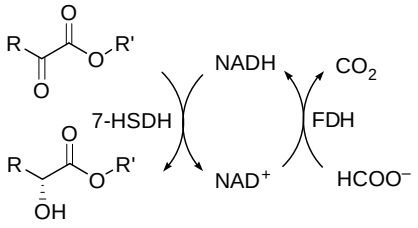


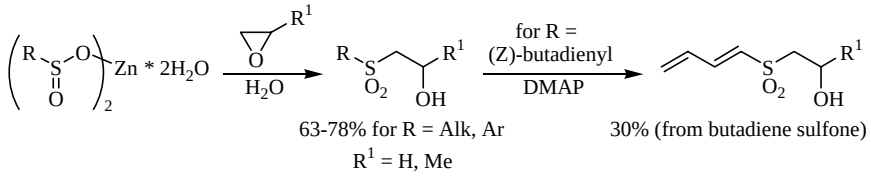




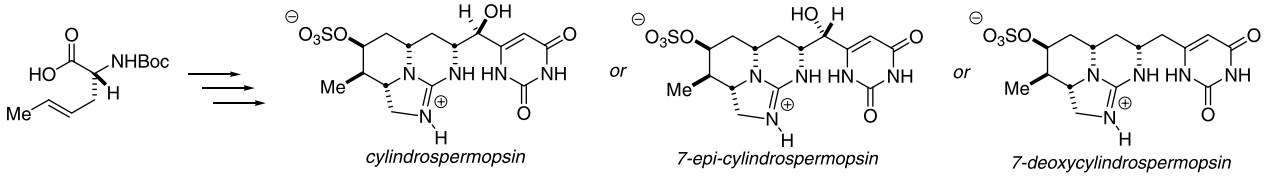


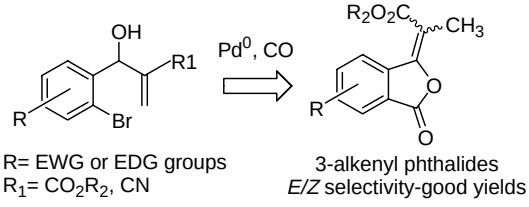


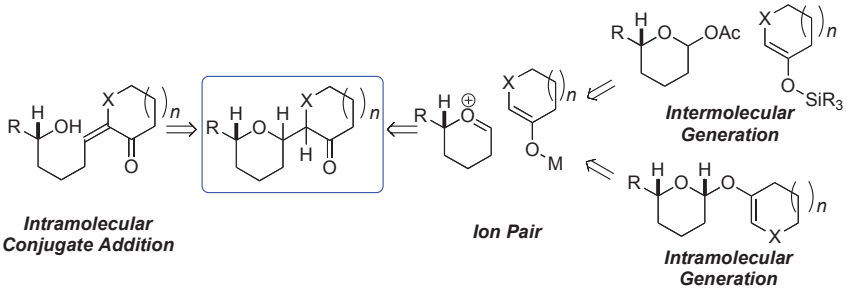


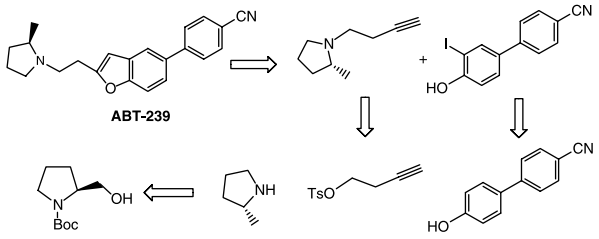


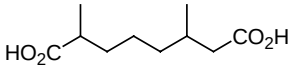
The reaction of zinc sulfinates with hydrophilic epoxides affords β-hydroxy sulfones under essentially neutral aqueous conditions.



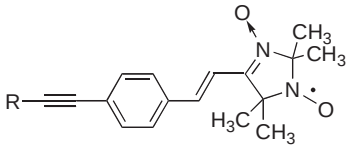


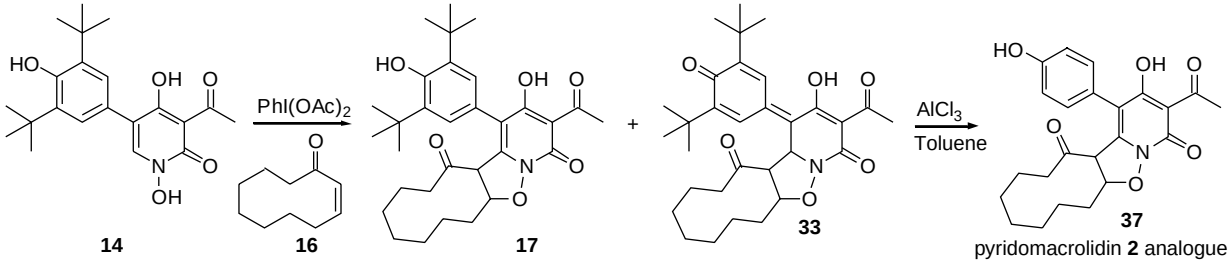


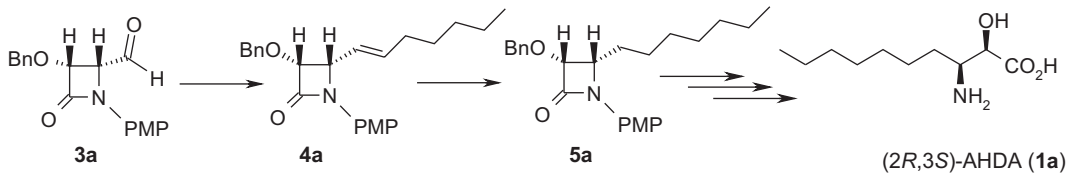




2*R*,6*S*: 2*S*,6*R*: 2*S*,6*S*: 2*R*,6*R* = 43: 38: 18: trace







OTHER CONTENTS

*Corresponding author
Supplementary data available via ScienceDirect

Indexed/Abstracted in: AGRICOLA, Beilstein, BIOSIS Previews, CAB Abstracts, Chemical Abstracts. Current Contents: Life Sciences, Current Contents: Physical, Chemical and Earth Sciences, Current Contents Search, Derwent Drug File, Ei Compendex, EMBASE/Excerpta Medica, Medline, PASCAL, Research Alert, Science Citation Index, SciSearch

ELSEVIER

ISSN 0040-4020

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 4285–4293

Synthesis and characterization of porphyrin–ferrocene–fullerene triads

Yongjun Li,[a] Zhenhai Gan,[b] Ning Wang,[a] Xiaorong He,[a] Yuliang Li,[a,*] Shu Wang,[a] Huibiao Liu,[a] Yasuyuki Araki,[b] Osamu Ito[b,*] and Daoben Zhu[a,*]

[a]*CAS Key Laboratory of Organic Solids, Institute of Chemistry, Chinese Academy of Sciences, Graduate School of Chinese Academy of Sciences, Chinese Academy of Sciences, Beijing 100080, People's Republic of China*
[b]*Institute of Multidisciplinary Research for Advanced Materials, Tohoku University, Katahira, Aoba-ku, Sendai, 980-8577 Japan*

Received 31 December 2005; revised 24 February 2006; accepted 27 February 2006

Abstract—Novel porphyrin–fullerene systems linked by ferrocene and related model compounds were successfully synthesized and characterized. Conformationally flexible 1,1′-disubstituted ferrocene functioned as effective modulator of the conformation between porphyrin and fullerene, as ^{1}H NMR spectra indicated, the porphyrin and C_{60} moieties in the triads showed *gauche* type conformation. The electrochemical and photophysical studies showed that there were considerable interactions between porphyrin and fullerene in the ground state due to intramolecular π-stacking of the these two chromophores, assisted by the ferrocence linker. Fluorescence lifetime measurements indicated there might be two different quenching processes occurring simultaneously (intersystem crossing and electron transfer).

1. Introduction

Studies on systems bearing photoactive and electroactive entities have drawn considerable attention as building blocks to construct artificial light energy harvesting systems and also to develop molecular electronic devices.[1–5] In particular, the combination of porphyrins and fullerene has been employed to attain long-lived charge-separated states in high quantum yields.[6–11] Fullerenes are suitable for efficient electron transfer because of their three-dimensional structure, low reduction potentials, and strong electronic acceptor properties.[12–15] Porphyrins contain an extensively conjugated two-dimensional π system, which is also suitable for efficient electron transfer because the uptake or release of electrons results in minimal structural change upon electron transfer.[16] Rates of electron transfer reactions in donor–acceptor (D–A) systems can be well predicted in light of the Marcus theory of electron transfer,[17,18] once the fundamental electron transfer properties of D and A moieties such as the one-electron redox potentials and the reorganization energies of electron transfer are determined. In other words, the distance between the two groups, their relative spatial orientation, and the nature of the pathway linking the two components can act as conduit for the energy or electron transfer.[2,3,14,19] In order to understand the nature of the dialogue between the C_{60} and the porphyrin chromophores, the topology of the two moieties in dyads has been systematically varied and a wide range of covalent and non-covalent assemblies have been reported.[6,10,14,20,21] Ferrocene derivatives are electron donors with considerably low oxidation potentials, which have been employed for the multi-step charge-separation systems of the triad and tetrad molecules.[22,23] Furthermore, porphyrin–ferrocene conjugates have great potential in many areas such as chemical sensors, porphyrin-assisted electron transfer, solar energy conversion and molecular devices.[24–28] An especially interesting issue is the conformation of the 1,1′-disubstituted ferrocene as for these two arms disposed in the same, *gauche*, or opposite directions. The porphyrin (P) and C_{60} moieties in dyads linked by conformationally flexible 1,1′-disubstituted ferrocene may be in close proximity due to π-stacking interactions. Such conformations can facilitate through-space dialogue between the donor and acceptor, as demonstrated by efficient and rapid quenching of porphyrin fluorescence and generation of C_{60} excited states (by energy transfer) or $P_{Zn}^{\cdot+}$–$C_{60}^{\cdot-}$ CS states (by electron transfer).[29] To get more insight into the influence of molecular topology on photoinduced electron transfer, we designed and synthesized P–Fc–C_{60} triads in which the separation and orientation of the π-systems would be controlled by the 1,1′-disubstituted ferrocene (their chemical structures as shown in Chart 1).

Keywords: Porphyrin; Ferrocene; Fullerene; Conformation.
* Corresponding authors. Tel.: 086 10 6258 8934; fax 086 10 8261 6576 (Y.L.); fax: 081 22 217 5608 (O.I.); e-mail addresses: ylli@iccas.ac.cn; ito@tagen.tohoku.ac.jp

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.076

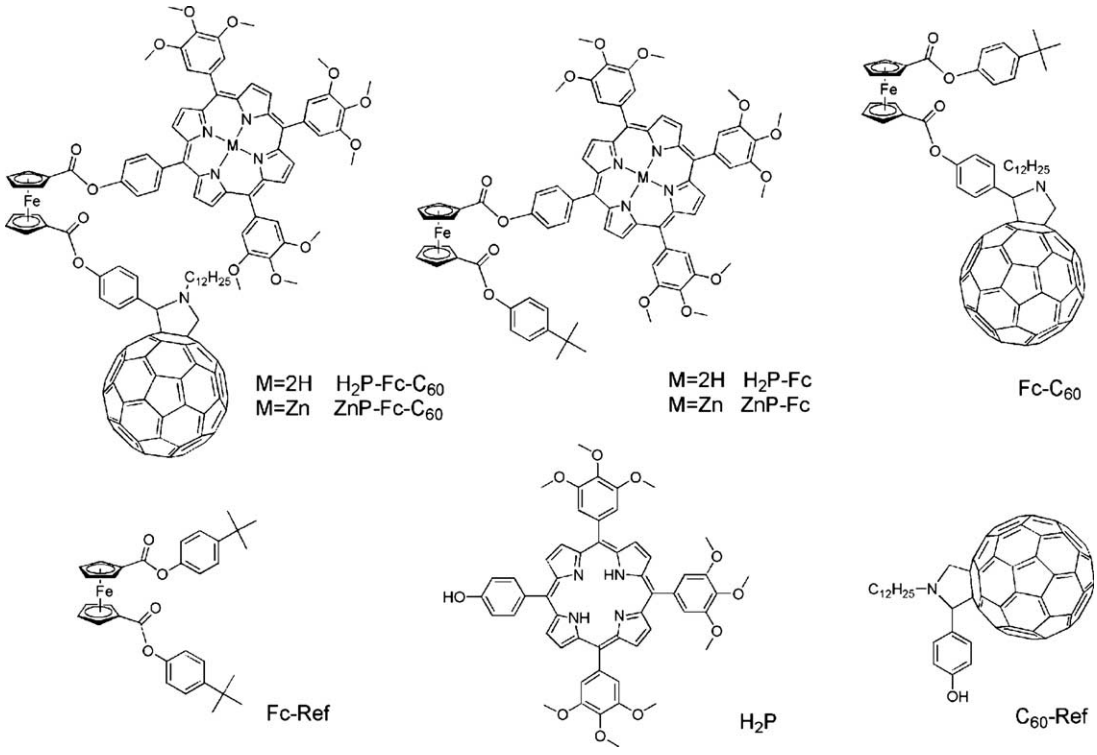
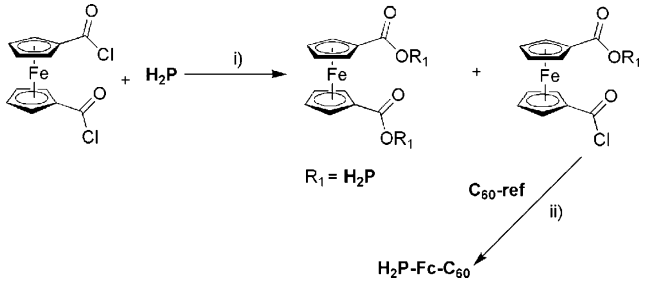


Chart 1.

2. Results and discussion

2.1. Synthesis and characterization

The general strategy employed for the synthesis of **H_2P–Fc–C_{60}** was summarized in Scheme 1. The preparation of **H_2P–Fc–C_{60}** was achieved in a simple 'one-pot' stepwise procedure.[26] **H_2P–Fc**, **Fc–C_{60}** and **Fc-ref** were prepared by following the similar procedures. Their structures were verified by spectroscopic analyses including ^{1}H NMR and MALDI-TOF mass spectra (see Section 4).



Scheme 1. Synthesis route of **H_2P–Fc–C_{60}**: (i) Et_3N/CH_2Cl_2, rt, N_2, 10 min; (ii) Et_3N/CH_2Cl_2, rt, N_2, 3 h.

2.2. Conformations of porphyrin–ferrocene–C_{60} triad

The distance between the electron donor and acceptor in a D–A system is one of the key factors that control the feasibility and kinetics of electron and energy transfer.[21] This distance is regulated by the conformational properties of the system. The conformation of 1,1′-disubstituted ferrocene imposed a notable impact on the mutual orientation of porphyrin and fullerene (Fig. 1).

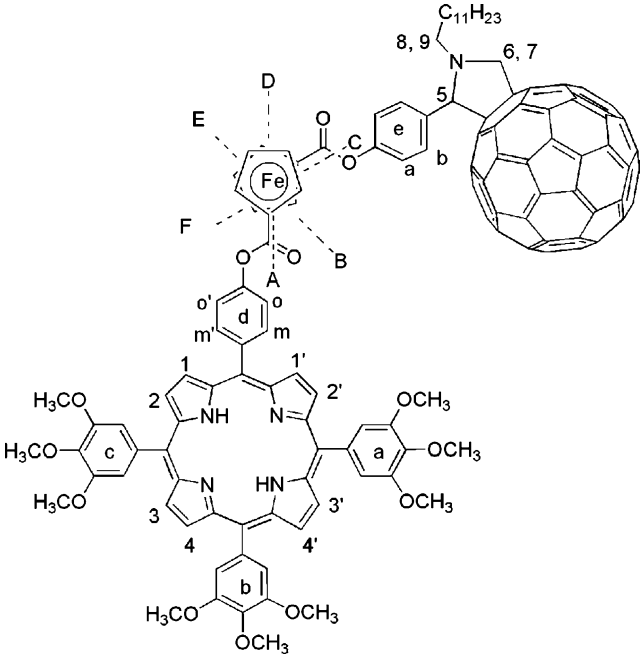


Figure 1. Possible topology of porphyrin–ferrocene–C_{60} hybrids: A-eclipse, B, F-*gauche*, C, D, E-opposite.

There were four conformers of the disubstituted ferrocene as depicted in Figure 1: the 'eclipse' isomer (A), the '*gauche*' isomer (B, F), the 'opposite' isomer (D), and an isomer in which the porphyrin was linked at the ferrocene skeleton at the neighboring position of the 'opposite' isomer (C, E). In particular, the *gauche* type conformation [25] was expected to furnish closer contacts and less overlap with the fullerene than the overlap (eclipse) type conformation due to the steric constraints. In the case of **H_2P–Fc** and **Fc–C_{60}**, there

was no π–π interaction in these molecules, and the steric constraint was little; thus, the ferrocene could freely move. This could be found in the ^{1}H NMR spectra.

In phenyl-substituted pyrrolidinofullerene derivatives, **Fc–C_{60}**, **H_2P–Fc–C_{60}**, **ZnP–Fc–C_{60}**, the NMR signals arising from the protons of the phenyl group attached to the pyrrolidine ring were broadened at room temperature by restricted rotation. [30–33] And we also observed the restricted rotation of ferrocene in the case of **H_2P–Fc–C_{60}**, **ZnP–Fc–C_{60}**. At room temperature, the spectra exhibited the expected features with the characteristic signals arising from ferrocene, two AB quartets for β–H of porphyrin, an AB quartet for phenyl ring **d**, an AB quartet and a singlet for the pyrrolidine protons. As shown in Figure 2, the pyrrole signals (two doublets, 8.90 ppm (J=4.6 Hz) and a singlet, 8.96 ppm) of **H_2P** and **H_2P–Fc** were changed into four doublets in **H_2P–Fc–C_{60}** (9.03, 8.94, 8.81, 8.73 ppm, J=4.6 Hz). The aryl protons of phenyl ring **d** in **H_2P–Fc–C_{60}** were up-shielded from that of **H_2P–Fc** (8.22 ppm) to 7.77 ppm. The aromatic protons of trimethoxyphenyl (**a**, **b** or **b**, **c**) in **H_2P–Fc** (7.48 ppm, s) were split into two single (7.63, 7.35 ppm) in the case of **H_2P–Fc–C_{60}**, which indicated that trimethoxyphenyl **a**, **b**, **c** became non-equivalent. In addition, –OCH_3 protons (4.17 ppm (s, 6H), 3.92 ppm (s, 12H)) in two trimethoxyphenyl were shifted to upfield as compared with that of **H_2P–Fc** (4.19 ppm, 3.98 ppm). The NH signal in porphyrin ring was shifted from −2.79 ppm in **H_2P–Fc** to −3.00 ppm in **H_2P–Fc–C_{60}**.

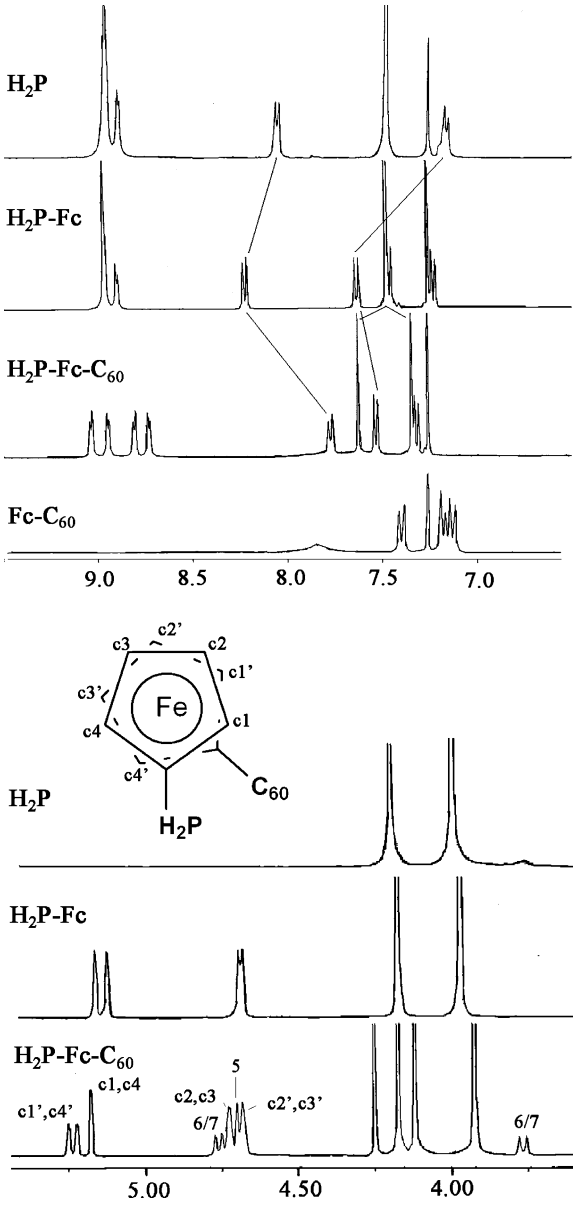


Figure 2. ^{1}H NMR spectra (400 MHz) of **H_2P**, **H_2P–Fc** and **H_2P–Fc–C_{60}** in $CDCl_3$ at room temperature.

The signals corresponding to the protons of the phenyl group directly attached to the pyrrolidine ring were broadened at room temperature. A variable-temperature NMR study showed clear coalescence, and the reversible narrowing of all these peaks revealed a dynamic effect. As typical examples, the ^{1}H NMR spectra of **ZnP–Fc–C_{60}** recorded at different temperatures were shown in Figure 3. At high temperatures, an AB system was seen for the aromatic protons of the phenyl group directly attached to the pyrrolidine ring. And ferrocene rotated faster as attested by the coalescence of some ferrocene protons near 5.25–5.3 ppm. By cooling the solution to −50 °C, the rotation of ferrocene became slow on the NMR timescale, the mutual orientation of porphyrin and fullerene was fixed in a *gauche* type conformation as evidenced by the coalescence of an AB quadruplet for β–H of porphyrin, the broadened signals of *meso*-phenyl group and the methoxy group on it, which was resulted from their position atop the fullerene sphere. At high temperatures, an AA′XX′ system was seen. The exchange between $H_{o/m}$ and $H_{o'/m'}$ was fast on the NMR timescale under these conditions, and both pairs of protons $H_{o/o'}$ and $H_{m/m'}$ appeared equivalent in the ^{1}H NMR spectrum. In contrast, by cooling the solution to −50 °C, the exchange was slow on the NMR timescale, as attested by only one AB quadruplet standing for two protons were observable, and the other two protons facing the fullerene sphere were broadened.

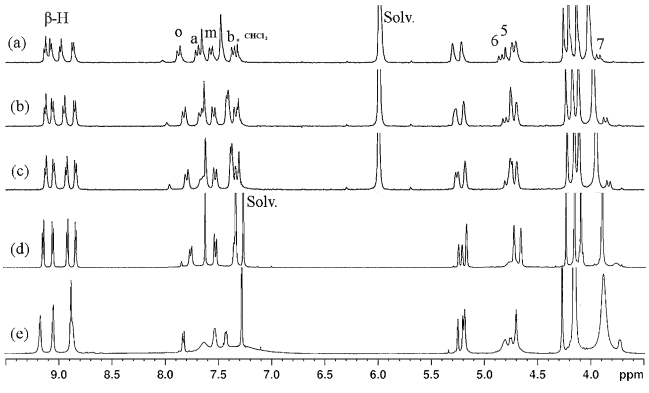


Figure 3. ^{1}H NMR spectra of **ZnP–Fc–C_{60}** recorded in $CDCl_2CDCl_2$ at (a) 107 °C, (b) 67 °C, (c) 47 °C and in $CDCl_3$ at (d) 25 °C, (e) −50 °C.

All these suggested that porphyrin ring was not opposite to C_{60} for steric reasons, but was locked in a *gauche* type conformation.[25] The chemical shifts and the resonance pattern changes of pyrrole protons, the aryl protons of phenyl ring **d**, aromatic protons and –OCH_3 protons of trimethoxyphenyl were all due to the deshielding effect resulted from C_{60} π-electrons, and evidence for these effects

could also be found from UV/vis spectra and electrochemical data for **H_2P–Fc–C_{60}** as shown below.

2.3. Cyclic voltammetric studies

Determination of the redox potentials in the donor–acceptor system is important to prove the existence of charge-transfer interactions between the donor and acceptor in the ground state, and also to evaluate the energetic of electron transfer reactions. The cyclic voltammograms of **H_2P–Fc–C_{60}** and **ZnP–Fc–C_{60}** were shown in Figure 4, and the half-wave potentials ($E_{1/2}$) of them together with those of **H_2P–Fc**, **ZnP–Fc**, **Fc–C_{60}**, **Fc-ref**, and **C_{60}-ref** were summarized in Table 1.

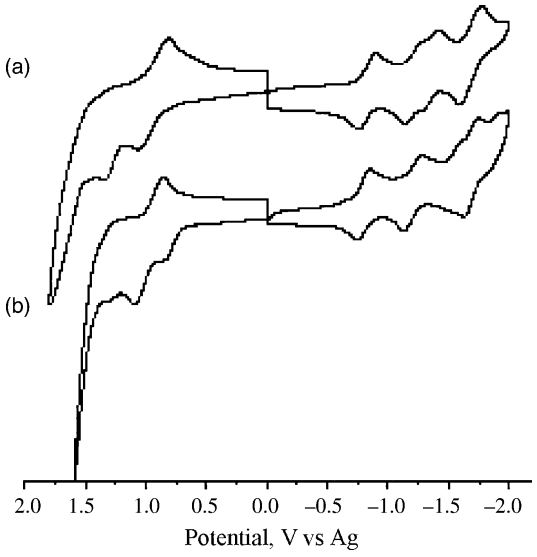


Figure 4. Cyclic voltammograms of (a) **H_2P–Fc–C_{60}** and (b) **ZnP–Fc–C_{60}** in the presence of 0.05 M (n-$C_4H_9)_4PF_6$ in *o*-dichlorobenzene.

The cyclic voltammogram of **H_2P–Fc–C_{60}** showed two reversible reductions with half-wave potentials ($E_{1/2}$) at −0.87 and −1.24 V (vs Ag/Ag^+) based on the fullerene core, one reversible reduction ($E_{1/2}=-1.40$ V) based on porphyrin, and one overlapping reduction ($E_{1/2}=-1.72$ V) corresponding to the fullerene and porphyrin, respectively. The cyclic voltammogram of **ZnP–Fc–C_{60}** showed three reversible reductions at −0.79, −1.20, −1.68 V for the fullerene core, and two reversible reductions at −1.58 and −1.85 V for the porphyrin. The half-wave potentials for the reductions of compounds **H_2P–Fc–C_{60}** and **ZnP–Fc–C_{60}** corresponding to the fullerene moieties were more negative than those of the reference compound **C_{60}-ref** by 80–160 mV, but compared with those of **Fc–C_{60}**, E (**H_2P–Fc–C_{60}** (−0.87 V))$<E$ (**Fc–C_{60}** (−0.83 V))$<E$ (**ZnP–Fc–C_{60}** (−0.79 V)). In **H_2P–Fc–C_{60}**, the one-electron reductions at porphyrin macrocyclic ring occured at more negative potentials as compared to the value of **H_2P–Fc**: E (**H_2P–Fc–C_{60}** (anion radical)) (−1.40 V)$<E$ (**H_2P–Fc**) (−1.34 V). In the case of **ZnP–Fc–C_{60}**, the reductions of porphyrin occured at more positive potentials as compared to the value of **ZnP–Fc**: E (**ZnP–Fc**) (−1.60 V)$<E$ (**ZnP–Fc–C_{60}** (anion radical)) (−1.52 V). That is, the fullerene and porphyrin reduction potentials were anodically shifted in the systems containing the zinc porphyrin, whereas the reverse was observed in the triad with the free-base porphyrin. This could be accounted by another placement of the porphyrin with respect to the fullerene and therefore a different conformation of the molecules, because zinc porphyrin has stronger electron donation ability, it may take a conformation closer to fullerene.

The one-electron oxidation of **H_2P–Fc** and **H_2P–Fc–C_{60}** occurred at the porphyrin macrocyclic ring at 0.94 and 0.95 V, respectively. The one-electron oxidation of ferrocene was overlapped with the oxidation of porphyrin. The first one-electron oxidation potentials of **ZnP–Fc** and **ZnP–Fc–C_{60}** were the same ($E_p=0.84$ V). The second one-electron oxidation potentials ascribed to ferrocene shifted to a more negative value than that of the model compound **Fc-ref** by ∼100 mV for **ZnP–Fc** and ∼40 mV for **ZnP–Fc–C_{60}**. Generally, the zinc porphyrin compounds ($E_p=0.84$ V for **ZnP–Fc–C_{60}** and **ZnP–Fc**, respectively) were considerably easier to oxidize than the corresponding zinc-free porphyrin compounds ($E_{1/2}=0.95$ V for **H_2P–Fc–C_{60}** and $E_{1/2}=0.94$ V for **H_2P–Fc**). Thus, in each case, the first one-electron reduction occurred at the C_{60} moiety, the first one-electron oxidation occurred at the porphyrin macrocyclic ring in the case of **ZnP–Fc–C_{60}**, while in the case of **H_2P–Fc–C_{60}**, it occurred at the porphyrin or ferrocene ring, and there existed interactions between porphyrin and fullerene moiety in the ground state. The **ZnP** and **H_2P** moiety seemed to be electron donating to C_{60}.

2.4. Steady-state absorption spectra

The absorption spectra of **H_2P–Fc–C_{60}**, **H_2P–Fc**, **Fc–C_{60}** and **Fc-ref** in CH_2Cl_2 were shown in Figure 5. The absorption and fluorescence data of **H_2P–Fc–C_{60}**, **H_2P–Fc**, and their zinc complexes were summarized in Table 2. In **H_2P–Fc** and **C_{60}-Fc**, the absorption spectra of the dyads were virtual superposition of the two independent chromophores: the porphyrin component showed a very strong absorption at

Table 1. Half-wave potentials (V vs Ag wire) of triads, dyads and reference compounds in dichlorobenzene containing 0.05 M (n-$C_4H_9)_4PF_6$

	Oxidation			Reduction				
	Porphyrin		Ferrocene	Porphyrin		Fullerene		
	$E_{1/2}(1)$	$E_{1/2}(2)$	$E_{1/2}$	$E_{1/2}(1)$	$E_{1/2}(2)$	$E_{1/2}(1)$	$E_{1/2}(2)$	$E_{1/2}(3)$
Fc-ref			1.01					
C_{60}-ref						−0.71	−1.09	−1.67
Fc–C_{60}			1.00			−0.83	−1.22	−1.81
H_2P–Fc	0.94	1.33[a]	0.94	−1.34	−1.61			
H_2P–Fc–C_{60}	0.95	1.32[a]	0.95	−1.40	−1.72	−0.87	−1.24	−1.72
ZnP–Fc	0.84[a]		0.91	−1.60	−1.77			
ZnP–Fc–C_{60}	0.84[a]	1.30[a]	0.97	−1.52	−1.85	−0.79	−1.20	−1.68

[a] Peak potential.

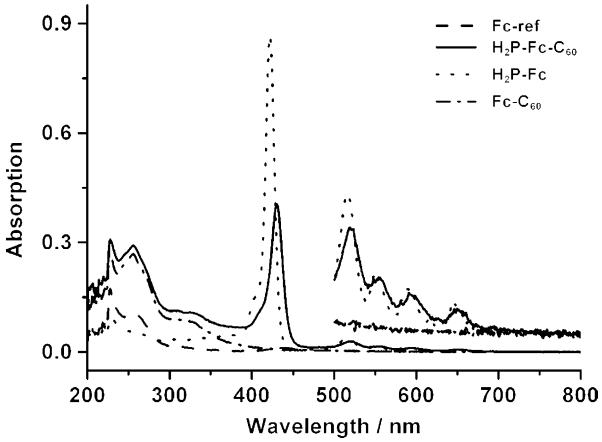


Figure 5. UV/vis spectra of 2 μM of **H_2P–Fc–C_{60}**, **H_2P–Fc**, **Fc–C_{60}**, and **Fc-ref** in CH_2Cl_2 at room temperature, above 500 nm a multiplying factor of 10 is used.

422 nm (Soret band) and four weak absorption at 516, 552, 592 and 646 nm (Q-band), the fullerene showed a strong π–π* band at 330 nm accompanied with weak long-wavelength bands tailing to 700 nm, and the ferrocene had an electronic transition at 444 nm, but its intensity was very weak. Evidently there were no detectable interactions between the chromophores in the ground state. In contrary, a considerable ground-state interaction of the porphyrin and fullerene moieties was seen in the absorption spectrum of **H_2P–Fc–C_{60}** and **ZnP–Fc–C_{60}** in CH_2Cl_2 and less polar solvent as toluene. The close proximity of the porphyrin and fullerene π-systems gave rise to through-space[34–37] and through-bond interaction, which may be detected in the shifts of some absorption bands. As usual, one could observe an absorption band at about 432 nm, a characteristic of the [6, 6] monoadduct of C_{60} in the UV/vis absorption spectra of C_{60} derivatives. In this case, the Soret band at 422 nm of **H_2P** was shifted to 430 nm due to the withdrawing electron effect of C_{60} moiety, the absorption band of the [6, 6] monoadduct of C_{60} was overlapped with that of porphyrin moiety. The absorption maxim of the free-base porphyrin entity in **H_2P–Fc–C_{60}** showed a 8 nm red shift compared to that of the **H_2P–Fc**, 9 nm red-shift was also observed in the case of **ZnP–Fc–C_{60}**, and a strong intensity decrease was seen in **H_2P–Fc–C_{60}**, **ZnP–Fc–C_{60}** when compared to the corresponding absorptions in **H_2P–Fc** and **ZnP–Fc**. Concentration dependence studies (2–20 μM) revealed no changes in the absorption maximal band, suggesting that the interactions were mainly intramolecular in nature.[38] Effectively, red-shifts in the Soret band were observed for covalent C_{60}–porphyrin conjugates due to intramolecular π-stacking of the two chromophores.[39,40]

2.5. Steady-state fluorescence spectra

Fluorescence spectra were taken in both CH_2Cl_2 and toluene with excitation at 420 nm, which excited both porphyrin and C_{60} moieties. The emission spectra of **H_2P–Fc–C_{60}** and **H_2P–Fc** revealed two emission bands located at 652 and 718 nm, respectively. The intensity of these bands of **H_2P–Fc–C_{60}** was significantly quenched as compared to **H_2P–Fc** owing to the presence of the appended C_{60}. A similar phenomenon was observed in the case of **ZnP–Fc–C_{60}** and **ZnP–Fc** (600 and 646 nm). The fluorescence quantum yields (Φ) of these compounds were calculated by the steady-state comparative method using tetraphenylporphyrin (TPP) as a reference (Φ_F=0.11) (Table 2).[41] As can be seen in Figure 6, the fluorescence peak of C_{60} expected to appear at 725 nm may

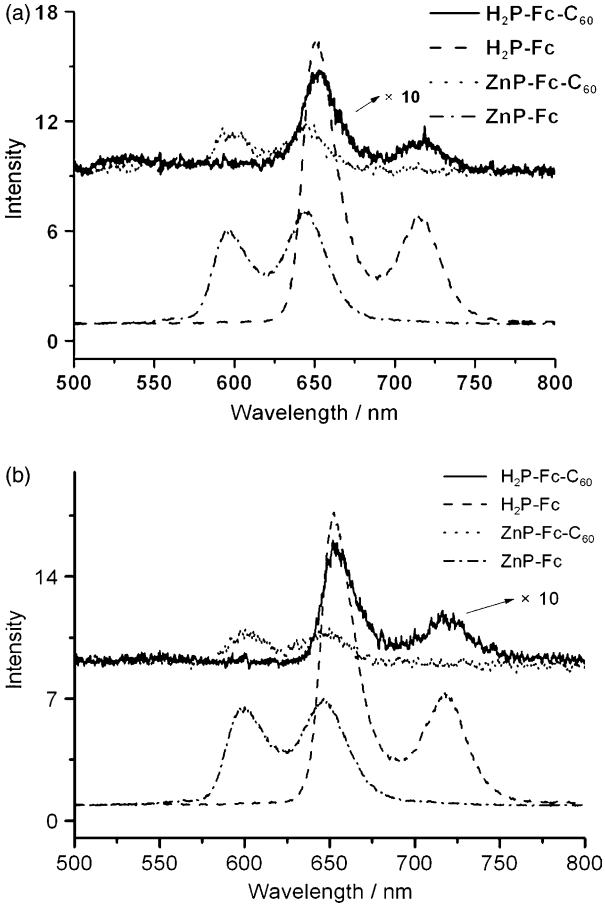


Figure 6. Steady-state fluorescence spectrum of **H_2P–Fc–C_{60}**, **H_2P–Fc**, **ZnP–Fc–C_{60}**, and **ZnP–Fc** (2 μM) in CH_2Cl_2 (a) and toluene (b) at room temperature.

Table 2. Spectroscopic data of the **H_2P–Fc–C_{60}** triads and related compounds

Compound	Solvent	Absorption λ (nm)	Emission for P λ (nm)[a]	Φ ($\times 10^{-3}$) for P[a]
H_2P–Fc–C_{60}	CH_2Cl_2	430, 521, 556, 596, 652	652, 715	7.4
	Toluene	431, 520, 555, 596, 652	653, 718	
ZnP–Fc–C_{60}	CH_2Cl_2	431, 552, 592	596, 644	6.3
	Toluene	433, 553, 593	599, 647	
H_2P–Fc	CH_2Cl_2	422, 516, 552, 592, 646	652, 716	81.9
	Toluene	423, 516, 552, 592, 649	652, 717	
ZnP–Fc	CH_2Cl_2	422, 548, 588	596, 644	44.3
	Toluene	426, 550, 592	599, 646	

[a] λ_{ex}=420 nm.

be hidden in the fluorescence bands of the H_2P moieties, while in the case of **ZnP–Fc–C_{60}**, the fluorescence of the C_{60} moiety was not observed, which suggested that energy transfer from the excited singlet state of the ZnP moiety to the C_{60} moiety may not have taken place, and there was no clear evidence for the existence of the singlet–singlet energy transfer from the porphyrin to the C_{60} in **H_2P–Fc–C_{60}**. These observations indicated that electron transfer predominantly took place from the excited singlet state of the ZnP moiety to the C_{60} moiety through space in CH_2Cl_2 and toluene or intersystem crossing process from singlet porphyrin to triplet porphyrin by ferrocene that had a low-lying triplet state.

2.6. Fluorescence lifetime measurements

To invest the charge separation process, the fluorescence lifetime measurements were carried out from 650 to 800 nm in toluene. Time profiles of the fluorescence intensities of the **H_2P–Fc**, **ZnP–Fc**, **H_2P–Fc–C_{60}** and **ZnP–Fc–C_{60}** in PhCN (λ_{ex}=410 nm.) were shown in Figure 7. In the case of **H_2P–Fc** and **ZnP–Fc**, the decay obeyed single exponential function giving a single fluorescence lifetime as summarized in Table 3. On the other hand decay of **H_2P–Fc–C_{60}** and **ZnP–Fc–C_{60}** consisted of fast decay component and slow component, from which two lifetimes were evaluated as listed in Table 3. Appreciable increase in the decay rates was observed for **H_2P–Fc–C_{60}** when C_{60} was linked to **H_2P–Fc**, while only slight increase was observed for **ZnP–Fc–C_{60}** when C_{60} was linked to **ZnP–Fc**. Similar results were obtained in benzonitrile (Table 3). From the shorter lifetime compared with tetraphenylporphyrin in polar and nonpolar solvents, it was suggested that there may be electron transfer or energy transfer when porphyrin was linked to ferrocene and ferrocene–fullerene. In the **H_2P–Fc** and **ZnP–Fc** case, there was no radical to be found when the samples were excited by 532 nm laser in our preliminary nanosecond transient measurement. So the short lifetime of fluorescence may be due to the addition of ferrocene moiety to accelerate the intersystem crossing process from singlet porphyrin to triplet porphyrin by ferrocene. On the other hand, there were electron transfer or energy transfer be observed from the excited singlet state of porphyrin to fullerene in the case of **H_2P–Fc–C_{60}** and **ZnP–Fc–C_{60}**. These rate constants could be calculated from the fluorescence lifetimes.

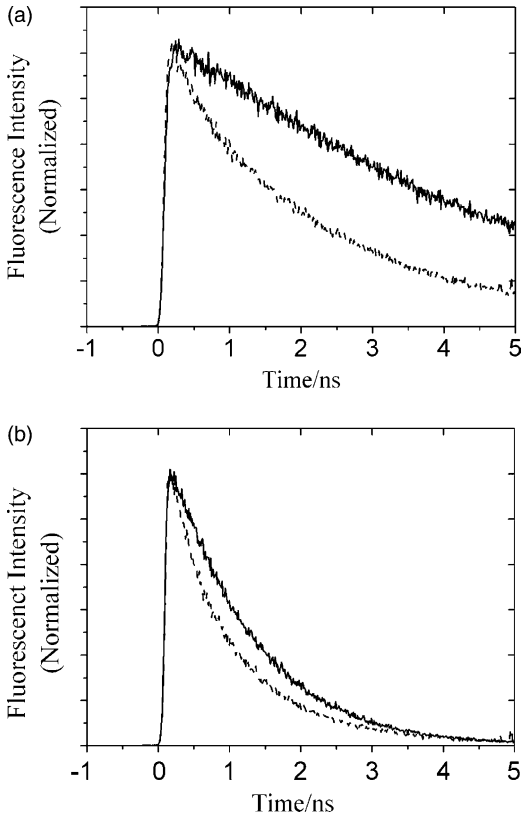


Figure 7. Time profiles of fluorescence lifetime measurement of (a) **H_2P–Fc** (solid line) and **H_2P–Fc–C_{60}** (dotted line, 0.05 mM); (b) **ZnP–Fc** (solid line) and **ZnP–Fc–C_{60}** (dotted line, 0.05 mM) in toluene. λ_{ex}=410 nm.

The rate constants (k_q) and quantum yields (Φ_q) of the fluorescence quenching of ^{1}**H_2P^*** or ^{1}**ZnP***, **H_2P–Fc**, **ZnP–Fc**, **H_2P–Fc–C_{60}** and **ZnP–Fc–C_{60}** in toluene and benzonitrile were evaluated by the following Eqs. 1 and 2, in which the $(\tau_f)_{ref}$ is referred to the fluorescence lifetimes of tetraphenylporphyrins.

$$k_q = (1/\tau_f)_{sample} - (1/\tau_f)_{ref} \quad (1)$$

$$\Phi_q = [(1/\tau_f)_{sample} - (1/\tau_f)_{ref}]/(1/\tau)_{sample} \quad (2)$$

The k_q and Φ_q values were evaluated as listed in Table 3.

The lifetime measurements indicated two components in the fluorescence of the triads, but none of them corresponded to that determined in the porphyrin–ferrocene dyads. There might be two different quenching processes occurring simultaneously (intersystem crossing and electron transfer). From the lifetime data and quenching quantum yields indicated in Table 3, one could observe that intersystem crossing represented an important percentage of the quenching. Besides, the quenching rate of the porphyrin was not sensitive to solvent polarity (Table 3). If electron transfer was the major quenching pathway, the very large

Table 3. Fluorescence lifetime (τ_f), fluorescence quenching rate-constants (k_q), fluorescence quenching quantum-yields (Φ_q) of **H_2P–Fc**, **ZnP–Fc**, **H_2P–Fc–C_{60}** and **ZnP–Fc–C_{60}** in toluene and benzonitrile (PhCN)

Solvent	Sample	τ (ns) (%)	k_q (s^{-1})	Φ_q
Toluene	**H_2P–Fc**	4.66 (100%)	1.4×10^8	0.66
	H_2P–Fc–C_{60}	0.42 (15%), 2.43 (85%)	3.8×10^8	0.84
	ZnP–Fc	1.15 (100%)	5.0×10^8	0.57
	ZnP–Fc–C_{60}	0.57 (52%), 1.35 (48%)	6.9×10^8	0.65
PhCN	**H_2P–Fc**	5.39 (100%)	8.6×10^7	0.47
	H_2P–Fc–C_{60}	0.38 (24%), 4.17 (76%)	2.1×10^8	0.68
	ZnP–Fc	1.21 (100%)	3.5×10^8	0.43
	ZnP–Fc–C_{60}	0.722 (66%), 844 (34%)	4.3×10^8	0.47

difference of the electron transfer driving force when passed from toluene to benzonitrile should alter the kinetics. Furthermore, electron transfer driving force was higher for the **ZnP** system, but surprisingly, it was less quenched than the **H_2P** system.

3. Conclusions

In summary, novel porphyrin–fullerene system linked by ferrocene and related model compounds were synthesized and characterized. The porphyrin (P) and C_{60} moieties in triads linked by conformationally flexible 1,1′-disubstituted ferrocene showed *gauche* type conformation, as indicated by the ^{1}H NMR spectra. The electrochemical and photophysical studies showed that there were considerable interactions between the two chromophores in the ground state and the excited singlet state. Fluorescence lifetime measurements indicated there may be two different quenching processes occurring simultaneously (intersystem crossing and electron transfer). The detailed photophysical study is in progress.

4. Experimental

4.1. General

Reagents were of reagent grade quality, obtained commercially and used without further purification except as noted elsewhere. All solvents were purified using standard procedures. Evaporation and concentration in vacuum were done at water aspirator pressure and compounds were dried at 10^{-2} Torr. FT-IR spectra were recorded as KBr pellets on a Perkin-Elmer system 2000 spectrometer. ^{1}H NMR spectra were measured on Bruker ARX400 or DMX300 spectrometers. Matrix-assisted laser desorption/ionization (MALDI) time-of-flight mass spectra (TOF) were measured on a Bruker Biflex III MALDI-TOF. Steady-state absorption spectra in the UV and the visible regions were measured on a Hitachi U-3010 spectrometer. Steady-state fluorescence spectra were measured on a Hitachi F-4500 spectrometer.

The cyclic voltammetry measurements were performed on a CHI660B electrochemical analyzer in a deaerated *o*-dichlorobenzene solution containing 0.05 M $(C_4H_9)_4PF_6$ as a supporting electrolyte at room temperature (100 mV s^{-1}). The counter electrode was a platinum wire. The measured potentials were recorded with respect to an Ag wire (Ag/Ag^+) reference electrode.

The lifetimes of the fluorescence bands were measured by a single-photon counting method using a second harmonic generation (SHG, 410 nm) of a Ti–sapphire laser (Spectra-Physics, Tsunami 3950-L2S, 1.5 ps fwhm) and a streak-scope (Hamamatsu Photonics, C43334-01) equipped with a polychromator (Action Research, SpectraPro 150) as an excitation source and a detector, respectively. Lifetimes were evaluated with software attached to the equipments.

4.1.1. Synthesis of H_2P–Fc–C_{60}. A solution of 1,1′-bis(chlorocarbonyl) ferrocene[42] (31 mg, 0.1 mmol), 5-(*p*-hydroxyphenyl)-10,15,20-tri (3,4,5-trimethoxyphenyl)-porphyrin[43] (90 mg, 0.1 mmol), and triethylamine (1 ml) in dry CH_2Cl_2 (100 ml) was stirred for 10 min at room temperature under N_2. To the reaction mixture was added **C_{60}-ref**[43] (102 mg, 0.1 mmol), and then the resulting mixture was stirred for another 3 h. The solution was washed with water, dried over anhydrous sodium sulfate. After evaporation, the residue was purified by column chromatography (SiO_2 (160–200 meshes), $CHCl_3/CH_2Cl_2$/EtOAc, 5:5:1) to give **H_2P–Fc–C_{60}** as a dark solid (107 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): 9.03 (d, J=4.6 Hz, 2H), 8.94 (d, J=4.6 Hz, 2H), 8.81 (d, J=4.6 Hz, 2H), 8.73 (d, J=4.6 Hz, 2H), 7.77 (d, J=7.8 Hz, 2H), 7.63 (s, 2H), 7.53 (d, J=7.8 Hz, 2H), 7.35 (s, 4H), 7.32 (d, J=8.6 Hz, 2H), 5.25 (d, J=1.1 Hz, 1H), 5.22 (d, J=1.1 Hz, 1H), 5.17 (d, J=1.6 Hz, 2H), 4.76 (d, J=9.2 Hz, 1H), 4.72 (d, J=1.3 Hz, 2H), 4.70 (s, 1H), 4.65–4.70 (m, 2H), 4.25 (s, 3H), 4.17 (s, 6H), 4.12 (s, 6H), 3.92 (s, 12H), 3.76 (d, J=9.1 Hz, 1H), 3.05–3.20 (m, 1H), 2.34–2.42 (m, 1H), 1.75–1.85 (m, 2H), 1.43–1.24 (m, 18H), 0.87–0.93 (m, 3H), −3.00 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 169.5, 169.2, 155.6, 153.5, 152.6, 152.4, 151.5, 151.3, 150.7, 150.4, 145.7, 145.2, 144.7, 144.1, 143.5, 143.3, 143.1, 142.9, 141.7, 141.5, 141.3, 141.0, 140.1, 139.5, 139.2, 138.8, 138.4, 137.9, 137.8, 137.7, 137.6, 135.8, 134.9, 131.5, 130.4, 120.4, 120.2, 120.1, 119.2, 112.7, 112.6, 96.1, 81.7, 73.0, 72.7, 72.5, 68.3, 66.5, 61.4, 61.3, 56.6, 56.4, 53.1, 31.9, 29.7, 29.3, 28.4, 27.5, 22.7,14.1. UV/vis (CH_2Cl_2) λ_{max} 430, 521, 556, 596, 652 nm; fluorescence (CH_2Cl_2) λ_{max} 652, 715 nm; FT-IR (KBr, cm^{-1}): 3313, 2924, 2851, 1735, 1579, 1502, 1456, 1407, 1357, 1267, 1235, 1197, 1165, 1126, 1104, 1012, 920.5, 801, 730, 526. MALDI-TOF MS *m/z*: 2161 $[M+H]^+$, 1441 $[M+H]^+-720$, calcd=2161.6 ($C_{145}H_{87}N_5O_{13}Fe$). Anal. Calcd for $C_{145}H_{87}N_5O_{13}Fe$: C, 80.51; H, 4.05; N, 3.24. Found: C, 80.44; H, 4.12; N, 3.27.

4.1.2. H_2P–Fc, C_{60}-ref and Fc-ref were prepared according to the same procedure of H_2P–Fc–C_{60}. H_2P–Fc: ^{1}H NMR (400 MHz, $CDCl_3$): 8.96 (s, 6H), 8.90 (d, J=4.6 Hz, 2H), 8.22 (d, J=8.2 Hz, 2H), 7.63 (d, J=8.2 Hz, 2H), 7.48 (s, 6H), 7.46 (d, J=9.2 Hz, 2H), 7.23 (d, J=8.5 Hz, 2H), 5.23 (s, 2H), 5.19 (s, 2H), 4.72–4.75 (m, 4H), 4.19 (s, 9H), 3.98 (s, 18H), 1.30 (s, 9H), −2.79 (s, 2H). UV/vis (CH_2Cl_2) λ_{max} 422, 516, 552, 592, 646 nm; fluorescence (CH_2Cl_2) λ_{max} 652, 716 nm; FT-IR (KBr, cm^{-1}): 3160, 2937, 1733, 1580, 1502, 1457, 1408, 1358, 1271, 1235, 1202, 1169, 1103, 1011, 922, 802, 729, 520. MALDI-TOF MS *m/z*: 1289 $[M+H]^+$, calcd=1288.4 ($C_{75}H_{68}N_4O_{13}Fe$). Anal. Calcd for $C_{75}H_{68}N_4O_{13}Fe$: C, 69.87; H, 5.32; N, 4.35. Found: C, 69.81; H, 5.38; N, 4.28.

Fc–C_{60}: ^{1}H NMR (300 MHz, $CDCl_3$): 7.97–7.75 (s, br, 2H), 7.42 (d, J=8.3 Hz, 2H), 7.19 (d, J=7.5 Hz, 2H), 7.15 (d, J=8.3 Hz, 2H), 5.12 (m, 1H), 5.06 (d, J=5.3 Hz, 4H), 4.63 (s, 4H), 4.15–4.25 (m, 1H), 3.20–3.35 (m, 1H), 2.50–2.71 (m, 1H), 1.85–2.08 (m, 2H), 1.25–1.47 (m, 27H), 0.81–0.95 (m, 3H). FT-IR (KBr, cm^{-1}): 2954, 2923, 2851, 2796, 1735, 1507, 1457, 1270, 1199, 1168, 1102, 1019, 913, 526. MALDI-TOF MS *m/z*: 1412 $[M+H]^+$, 692 $[M+H]^+-720$, calcd=1411.3 ($C_{102}H_{53}NO_4Fe$). Anal. Calcd for $C_{102}H_{53}NO_4Fe$: C, 86.74; H, 3.78; N, 0.99. Found: C, 86.83; H, 3.77; N, 1.02.

Fc-ref:[25] ^{1}H NMR (300 MHz, $CDCl_3$): 7.38 (d, J=8.3 Hz, 4H), 7.11 (d, J=8.3 Hz, 4H), 5.05 (s, 4H), 4.59 (s, H), 1.32

(s, 18H). MALDI-TOF MS *m/z*: 537, 560 $[M+Na]^+$, 576 $[M+K]^+$.

4.1.3. Synthesis of ZnP–Fc–C_{60}. A saturated methanol solution of $Zn(OAc)_2$ (5 ml) was added to a solution of **H_2P–Fc–C_{60}** (20 mg) in $CHCl_3$ (50 ml) and refluxed for 3 h. After cooling, the reaction mixture was washed with water twice and dried over anhydrous Na_2SO_4, and then the solvent was removed. Flash column chromatography on silical gel with $CHCl_3$ as the eluent gave **ZnP–Fc–C_{60}** as a dark solid (98% yield, 21 mg). ^{1}H NMR (400 MHz, $CDCl_3$): 9.12 (d, J=4.6 Hz, 2H), 9.03 (d, J=4.6 Hz, 2H), 8.89 (d, J=4.6 Hz, 2H), 8.81 (d, J=4.6 Hz, 2H), 7.74 (d, J=8.0 Hz, 2H), 7.61 (s, 2H), 7.51 (d, J=8.2 Hz, 2H), 7.35–7.31 (m, 6H), 5.25 (s, 1H), 5.21 (s, 1H), 5.17 (s, 2H), 4.81–4.75 (m, 1H), 4.73 (s, 2H), 4.66 (s, 2H), 4.24 (s, 3H), 4.16 (s, 6H), 4.10 (s, 6H), 3.91 (s, 12H), 3.82–3.73 (m, 1H), 3.18–3.05 (m, 1H), 2.45–2.31 (m, 1H), 1.79–1.67 (m, 2H), 1.39–1.22 (m, 18H), 0.89–0.84 (m, 3H). UV/vis (CH_2Cl_2) λ_{max} 431, 552, 592 nm; fluorescence (CH_2Cl_2) λ_{max} 596, 644 nm; FT-IR (KBr, cm^{-1}): 2923, 2851, 1736, 15797, 1498, 1456, 1406, 1349, 1270, 1238, 1196, 1164, 1126, 1104, 1003, 797, 722, 526. MALDI-TOF MS *m/z*: 2225.3 $[M+H]^+$, 1504.5 $[M+H^+]-720$, calcd=2223 ($C_{145}H_{85}N_5O_{13}FeZn$). Anal. Calcd for $C_{145}H_{85}N_5O_{13}FeZn$: C, 78.22; H, 3.85; N, 3.15. Found: C, 78.29; H, 3.89; N, 3.12.

ZnP–Fc: ^{1}H NMR (400 MHz, $CDCl_3$): 9.02 (s, 6H), 8.95 (d, J=4.6 Hz, 2H), 8.18 (d, J=8.2 Hz, 2H), 7.58 (d, J=8.2 Hz, 2H), 7.43–7.40 (m, 6H), 7.08–7.21 (m, 4H), 5.16 (s, 2H), 5.11 (s, 2H), 4.66 (t, J=1.5 Hz, 4H), 4.13 (s, 9H), 3.94 (s, 18H), 1.29 (s, 9H). UV/vis (CH_2Cl_2) λ_{max} 422, 548 nm, 588 nm; fluorescence (CH_2Cl_2) λ_{max} 596, 644 nm; FT-IR (KBr, cm^{-1}): 2933, 1733, 1579, 1495, 1456, 1406, 1348, 1271, 1236, 1201, 1169, 1125, 1001, 798, 723, 520. MALDI-TOF MS *m/z*: 1351 $[M+H]^+$, calcd=1350.3 ($C_{75}H_{66}N_4O_{13}$-FeZn). Anal. Calcd for $C_{75}H_{66}N_4O_{13}FeZn$: C, 66.60; H, 4.92; N, 4.14. Found: C, 66.63; H, 4.95; N, 4.13.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (10474101, 50372070, 20531060, 20418001 and 20421101) and the National Basic Research 973 Program of China (2006CB300402). This project is partly supported by National Center for Nanoscience and Technology, China.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.076. ^{1}H NMR spectra for **H_2P–Fc–C_{60}**, **H_2P–Fc**, **ZnP–Fc–C_{60}**, **ZnP–Fc**, **Fc–C_{60}** and H–H COSY spectra of **H_2P–Fc–C_{60}** are available.

References and notes

1. Gust, D.; Moore, T. A. *Science* **1989**, *244*, 35–41.
2. Wasielewski, M. R. *Chem. Rev.* **1992**, *92*, 435–461.
3. Paddon-Row, M. N. *Acc. Chem. Res.* **1994**, *27*, 18–25.
4. Bard, A. J.; Fox, M. A. *Acc. Chem. Res.* **1995**, *28*, 141–145.
5. Piotrowiak, P. *Chem. Soc. Rev.* **1999**, *28*, 143–150.
6. Gust, D.; Moore, T. A. In Kadish, K. M., Smith, K. M., Guilard, R., Eds.; The Porphyrin Handbook; Academic: San Diego, CA, 2000; Vol. 8, pp 153–190.
7. Imahori, H.; Yamada, K.; Hasegawa, M.; Taniguchi, S.; Okada, T.; Sakata, Y. *Angew. Chem., Int. Ed.* **1997**, *36*, 2626–2629.
8. Gust, D.; Moore, T. A.; Moore, A. L. *Acc. Chem. Res.* **2001**, *34*, 40–48.
9. Fukuzumi, S.; Imahori, H.; Yamada, H.; El-Khouly, M. E.; Fujitsuka, M.; Ito, O.; Guldi, D. M. *J. Am. Chem. Soc.* **2001**, *123*, 2571–2575.
10. Imahori, H.; Mori, Y.; Matano, Y. *Photochem. Photobiol., C* **2003**, *4*, 51–83.
11. Kanato, H.; Takimiya, K.; Otsubo, T.; Aso, Y.; Nakamura, T.; Araki, Y.; Ito, O. *J. Org. Chem.* **2004**, *69*, 7183–7189.
12. Imahori, H.; Hagiwara, K.; Aoki, M.; Akiyama, T.; Taniguchi, S.; Okada, T.; Shirakawa, M.; Sakata, Y. *J. Am. Chem. Soc.* **1996**, *118*, 11771–11782.
13. Armaroli, N.; Diederich, F.; Dietrich-Bucheeker, C. O.; Flamigni, L.; Marconi, G.; Nierengarten, J. F.; Sauvage, J. P. *Chem. Eur. J.* **1998**, *4*, 406–416.
14. Guldi, D. M. *Chem. Soc. Rev.* **2002**, *31*, 22–36.
15. Delgado, J. L.; de la Cruz, P.; López-Arza, V.; Langa, F.; Kimball, D. B.; Haley, M. M.; Araki, Y.; Ito, O. *J. Org. Chem.* **2004**, *69*, 2661–2668.
16. Fukuzumi, S.; Guldi, D. M. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic: San Diego, CA, 2000; Chapter 8, pp 115–151.
17. Marcus, R. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1111–1121.
18. Marcus, R. A.; Sutin, N. *Biochim. Biophys. Acta* **1985**, *811*, 265–322.
19. Hayashi, T.; Ogoshi, H. *Chem. Soc. Rev.* **1997**, *26*, 355–364.
20. Solladie, N.; Walther, M. E.; Gross, M.; Duarte, T. M. F.; Bourgogne, C.; Nierengarten, J.-F. *Chem. Commun.* **2003**, 2412–2413.
21. Schuster, D. I.; Cheng, P.; Jarowski, P. D.; Guldi, D. M.; Luo, C. P.; Echegoyen, L.; Pyo, S.; Holzwarth, A. R.; Braslavsky, S. E.; Williams, R. M.; Klihm, G. *J. Am. Chem. Soc.* **2004**, *126*, 7257–7270.
22. Fujitsuka, M.; Ito, O.; Imahori, H.; Yamada, K.; Yamada, H.; Sakata, Y. *Chem. Lett.* **1999**, 721–722.
23. Imahori, H.; Tamaki, K.; Guldi, D. M.; Luo, C.; Fujitsuka, M.; Ito, O.; Sakata, Y.; Fukuzumi, S. *J. Am. Chem. Soc.* **2001**, *123*, 2607–2617.
24. Beer, P. D.; Drew, M. G.; Hesek, D.; Jagessar, R. *J. Chem. Soc., Chem. Commun.* **1995**, 1187–1189.
25. Beer, P. D.; Kurek, S. S. *J. Organomet. Chem.* **1987**, *336*, C17–C21.
26. Beer, P. D.; Kurek, S. S. *J. Organomet. Chem.* **1989**, *366*, C6–C8.
27. Wagner, R. W.; Brown, P. A.; Johnson, T. E.; Lindsey, J. S. *J. Chem. Soc., Chem. Commun.* **1991**, 1463–1466.
28. Burrell, A. K.; Campbell, W.; Officer, D. L. *Tetrahedron Lett.* **1997**, *38*, 1249–1252.
29. Schuster, D. I.; Cheng, P.; Wilson, S. R.; Prokhorenko, V.; Katterle, M.; Holzwarth, A. R.; Braslavsky, S. E.; Klihm, G.; Williams, R. M.; Luo, C.-P. *J. Am. Chem. Soc.* **1999**, *121*, 11599–11600.
30. Ajamaa, F.; Duarte, T. M. F.; Bourgogne, C.; Holler, M.; Fowler, P. W.; Nierengarten, J.-F. *Eur. J. Org. Chem.* **2005**, 3766–3774.

31. Eckert, J.-F.; Nicoud, J.-F.; Nierengarten, J.-F.; Liu, S.-G.; Echegoyen, L.; Barigelletti, F.; Armaroli, N.; Ouali, L.; Krasnikov, V.; Hadziioannou, G. *J. Am. Chem. Soc.* **2000**, *122*, 7467–7479.
32. de la Torre, M. D. L.; Marcorin, G. L.; Pirri, G.; Tomé, A. C.; Silva, A. M. S.; Cavaleiro, J. A. S. *Tetrahedron Lett.* **2002**, *43*, 1689–1691.
33. Suárez, M.; Verdecia, Y.; Illescas, B.; Martínez-Alvarez, R.; Alvarez, A.; Ochoa, E.; Seoane, C.; Kayali, N.; Martín, N. *Tetrahedron* **2003**, *59*, 9179–9186.
34. Olmstead, M. M.; Costa, D. A.; Maitra, K.; Noll, B. C.; Phillips, S. L.; van Calcar, P. M.; Balch, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 7090–7097.
35. Boyd, P. D. W.; Hodgson, M. C.; Rickard, C. E. F.; Oliver, A. G.; Chaker, L.; Brothers, P. J.; Bolskar, R. D.; Tham, F. S.; Reed, C. A. *J. Am. Chem. Soc.* **1999**, *121*, 10487–10495.
36. Konarev, D. V.; Neretin, I. S.; Slovokhotov, Y. L.; Yudanova, E. I.; Drichko, N. V.; Shul'ga, Y. M.; Tarasov, B. P.; Gumanov, L. L.; Batsanov, A. S.; Howard, J. A. K.; Lyubovskaya, R. N. *Chem. Eur. J.* **2001**, *7*, 2605–2616.
37. Guldi, D. M.; Hirsch, A.; Scheloske, M.; Dietel, E.; Troisi, A.; Zerbetto, F.; Prato, M. *Chem. Eur. J.* **2003**, *9*, 4968–4979.
38. Souza, F. D.; Deviprasad, G. R.; Zandler, M. E.; El-Khouly, M. E.; Fujitsuka, M.; Ito, O. *J. Phys. Chem. B* **2002**, *106*, 4952–4962.
39. Armaroli, N.; Marconi, G.; Echegoyen, L.; Bourgeois, J.-P.; Diederich, F. *Chem. Eur. J.* **2000**, *6*, 1629–1645.
40. Sun, D.; Tham, F. S.; Reed, C. A.; Chaker, L.; Boyd, P. D. W. *J. Am. Chem. Soc.* **2002**, *124*, 6604–6612.
41. Lee, W. A.; Graetzel, M.; Kalyansundaram, K. *Chem. Phys. Lett.* **1984**, *107*, 308–313.
42. Knobloch, F. W.; Rauscher, W. H. *J. Polym. Sci.* **1961**, *54*, 651–656.
43. Xiao, S.-Q.; Li, Y.-L.; Li, Y.-J.; Yang, C.-H.; Liu, H.-B.; Ning, B.; Liu, Y.; Lu, F.-S.; Fan, L.-Z.; Zhuang, J.-P.; Li, Y.-F.; Zhu, D.-B. *J. Phys. Chem. B* **2004**, *108*, 16677–16685.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 4294–4305
Tetrahedron

Synthesis of arylboronates via Cp*RuCl-catalyzed cycloaddition of alkynylboronates

Yoshihiko Yamamoto,* Kozo Hattori, Jun-ichi Ishii and Hisao Nishiyama

Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Chikusa, Nagoya 464-8603, Japan

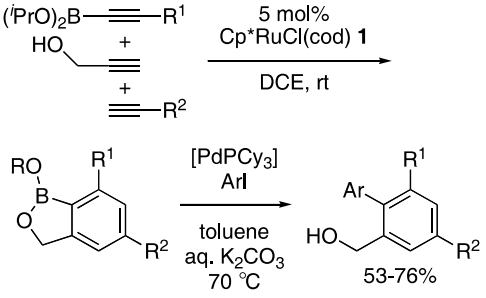
Received 9 February 2006; accepted 23 February 2006

Available online 20 March 2006

Abstract—In the presence of 5–10 mol% Cp*RuCl(cod), 1,6- and 1,7-diynes were allowed to react with an ethynylboronate at ambient temperature to give rise to bicyclic arylboronates in 64–93% isolated yields. 1,6-Diynes bearing a boronate terminal also underwent cycloaddition with monoalkynes to give the corresponding bicyclic arylboronates.

1. Introduction

Arylboronic acids and their congeners have become indispensable reagents in modern organic synthesis. In fact, they are now used for a wide variety of significant organic transformations including Suzuki–Miyaura cross coupling,[1] homo coupling,[2] rhodium-catalyzed asymmetric 1,2- and 1,4-additions to carbonyl compounds,[3,4] Heck-type reaction,[5] Petasis–Mannich condensation,[6,7] and others.[8] Arylboronic acid derivatives have been conventionally prepared by the reactions of arylmagnesium or -lithium reagents with trialkylborates, although reactive functional groups are incompatible with this method.[9] To address this issue, transition-metal-catalyzed couplings of arylhalides, -triflates, or -diazoniums with tetraalkoxydiboranes or dialkoxyboranes have been developed by several research groups.[10] Furthermore, transition-metal-catalyzed direct borylation of aromatic C–H bonds has emerged as an environmentally benign process.[11] In addition to these methods utilizing aromatic precursors, benzannulation or cycloaddition involving unsaturated organoboron reagents realized the assembly of highly substituted arylboronic acid frameworks, which are otherwise difficult to be prepared.[12,13] In this context, we recently developed the ruthenium-catalyzed cyclotrimerization of alkynylboronates, propargyl alcohol, and a terminal alkynes giving rise to arylboronates, which were subjected to one-pot Suzuki–Miyaura coupling to afford highly substituted biaryls as single regioisomers (Scheme 1).[14] As an extension of this study, we also explored the Cp*RuCl-catalyzed cycloaddition of α,ω-diynes with an ethynylboronate, yielding polycyclic arylboronates.[15] Herein, we wish to report the full details of our study on the catalytic partially intramolecular cycloaddition of alkynylboronates and diynylboronates.



Scheme 1.

2. Results and discussion

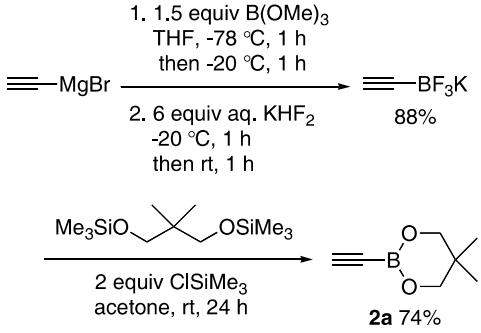
Aubert and co-workers recently reported the cycloaddition of the $Co_2(CO)_6$-complexed alkynylborates with α,ω-diynes bearing various tether lengths.[16] Although their protocol efficiently afforded various bicyclic arylboronates, the direct cycloaddition of diynes with alkynylboronates in the presence of appropriate catalyst is highly desirable in terms of atom economy.[17] Thus, our Cp*RuCl-catalyzed alkyne cyclotrimerization protocol would serve this purpose well.[14,18] In a recent work of Dixneuf and co-workers, Cp*RuCl(cod) also proved to be a competent precatalyst for [2+2] dimerization of an allenylboronate.[19]

Keywords: Ruthenium catalysis; Cyclotrimerization; Alkynylboronate; Arylboronate; Suzuki–Miyaura coupling.
* Corresponding author. Tel.: +81 52 789 3337; fax: +81 52 789 3209; e-mail: yamamoto@apchem.nagoya-u.ac.jp

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.068

2.1. Preparation of ethynylboronate

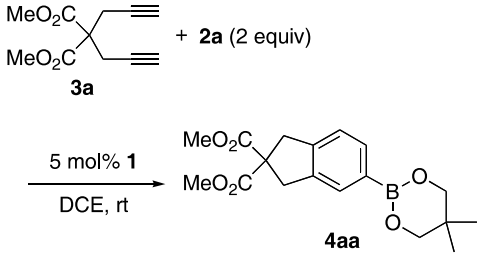
To realize an efficient catalytic protocol, we required an ethynylboronate because internal alkynes proved to be inefficient monoalkyne substrates for the ruthenium catalysis (vide infra).[18] The reaction of ethynylmagnesium bromide and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane with the standard procedures of Brown and co-workers,[20] however, led to the formation of an ethynylboronate in a moderate yield with rather low purity because of its low boiling point. Thus, we turned our attention to an alternative procedure to prepare alkynylboronates reported by Vaultier and co-workers.[21] Although this method gave the desired 2-ethynyl-5,5-dimethyl-1,3,2-dioxaborinane (**2a**), commercially unavailable chlorobis(diisopropylamino)borane is required as a boron source and diaminoborane intermediates are moisture sensitive. To overcome such disadvantages, a modified route was developed by taking advantage of the ligand exchange reaction of alkynyltrifluoroborates.[22] As outlined in Scheme 2, the established procedure was applied to the synthesis of ethynyltrifluoroborate,[23] which was then treated with 2,2-dimethylpropane-1,3-diol bis(trimethylsilyl) ether in the presence of chlorotrimethylsilane in acetone at room temperature to afford ethynylboronate **2a** in a reasonable yield with high purity.



Scheme 2.

2.2. Cp*RuCl-catalyzed cycloaddition of α,ω-diynes with ethynylboronate

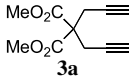
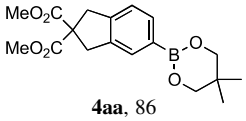
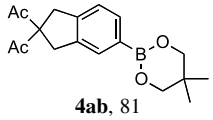
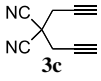
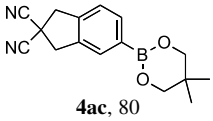
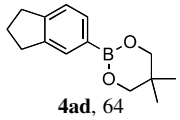
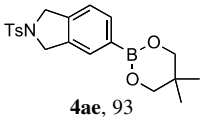
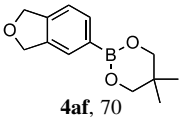
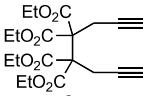
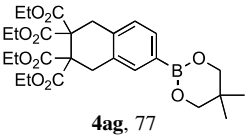
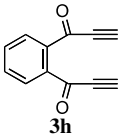
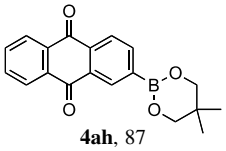
With ethynylboronate **2a** in hand, we next optimized its cycloaddition with dimethyl dipropargylmalonate (**3a**) in the presence of precatalyst Cp*RuCl(cod) (**1**) (Cp*=η^5-C_5Me_5, cod=1,5-cyclooctadiene) as shown in Scheme 3. To suppress diyne dimerization, a solution of **3a** in 1,2-dichloroethane (DCE) was added at room temperature via syringe pump over 1 h to the DCE solution of 5 mol% **1** and 2 equiv of **2a**. As a result, the desired cycloadduct **4aa** was isolated in 77% yield after purification with silica gel column chromatography. A similar yield was obtained with increased amounts of **2a** (4 equiv). On the other hand, the yield was improved to 86%, when the reaction mixture was stirred for 1 h after the syringe-pump addition of **3a**. The obtained product was characterized as bicyclic arylboronate **4aa** by ^{1}H and ^{13}C NMR, IR, mass, and elemental analyses. This structural assignment was also confirmed by X-ray crystallography.[15]



Scheme 3.

The generality of this protocol was well demonstrated by the results obtained with various diyne substrates (Table 1). The present method well tolerated functional groups including an ester, a ketone, and a nitrile, and as a consequence, arylboronates **4aa**–**4ac** were obtained in 80–86% yields (runs 1–3). The quaternary center of the tether is not essential for the cycloaddition. Although an increased

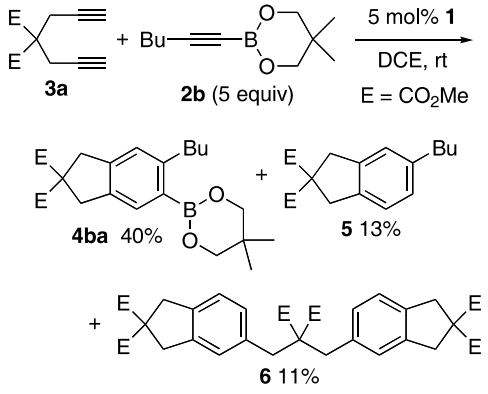
Table 1. Cycloaddition of diynes **3a**–**h** with ethynylboronate **2a**[a]

Run	Diyne	Product, yield (%)
1	 **3a**	 **4aa**, 86
2	 **3b**	 **4ab**, 81
3	 **3c**	 **4ac**, 80
4	 **3d**	 **4ad**, 64
5	 **3e**	 **4ae**, 93
6	 **3f**	 **4af**, 70
7	 **3g**	 **4ag**, 77
8	 **3h**	 **4ah**, 87

[a] A solution of **3** in DCE was added to a DCE solution of 5 mol% (10 mol% for runs 4, 6 and 7) Cp*RuCl(cod) **1** and 2 equiv of ethynyl boronate **2a** by syringe pump over 1 h, and the solution was stirred for 1 h at room temperature.

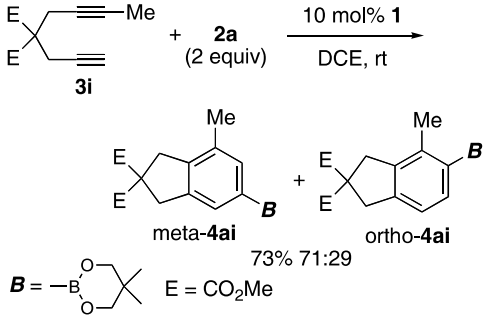
catalyst loading of 10 mol% was required, the parent 1,6-heptadiyne (**3d**) underwent cycloaddition with **2a** to furnish the corresponding product **4ad** in 64% yield (run 4). Similarly, *N*,*N*-dipropargyltosylamide (**3e**) and propargyl ether (**3f**) gave borylated heterocycles **4ae** and **4af** in 93 and 70% yields, respectively (runs 5 and 6). In addition to these 1,6-diynes, 1,7-diynes **3g** and **3h** were able to react with **2a** to give tetrahydronaphthalene derivative **4ag** and anthraquinone derivative **4ah** in 77 and 87% yields, respectively (runs 7 and 8).

As anticipated, internal alkynylboronate **2b** turned out to be less efficient than terminal **2a**. The reaction with diyne **3a** in a similar manner afforded the desired arylboronate **4ba** in a lower yield of 40% (Scheme 4). In this case, two additional by-products, protodeboration product **5** and diyne dimer **6** are formed even with the increased loading of the alkynylboronate (5 equiv).



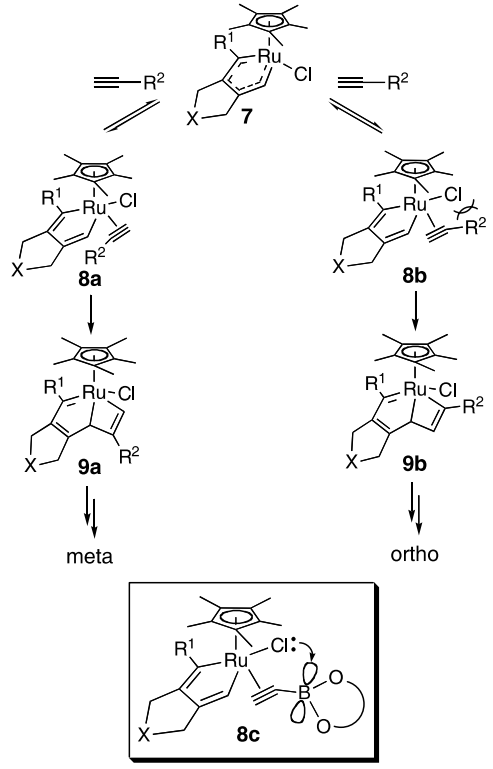
Scheme 4.

We next examined the influence of the terminal substituent on the diyne substrates. In our previous study, it was found that unsymmetrical diynes possessing a terminal substituent on one of the two alkyne moieties reacted with monoalkynes to afford *meta* isomers with excellent regioselectivity as high as *meta*:*ortho*=95:5.[18] On the other hand, the reaction of unsymmetrical diyne **3i** with **2a** was carried out in the presence of 10 mol% **1** to afford a regioisomer mixture of cycloadduct **4ai** in 73% combined yield with a diminished selectivity of *meta*:*ortho*=71:29 (Scheme 5).



Scheme 5.

The plausible regioselection mechanism is outlined in Scheme 6. The catalytic reaction starts with the oxidative cyclization of a diyne on the Cp*RuCl fragment, leading to a ruthenabicycle **7**. On the basis of density functional theory calculations, we and others have proposed the novel alkyne cyclotrimerization mechanism, in which the intermediacy of an unprecedented ruthenatricycle **9** was proposed for the conversion of a ruthenabicycle–alkyne complex **8** to a seven-membered ruthenacycle intermediate.[18,24] The coordinated alkyne is considered to react predominantly with the less substituted Ru–C bond as a consequence of the steric influence of the substituent R^1. In addition, the steric repulsion between the chloro ligand and the substituent R^2 on the coordinated monoalkyne might destabilize ruthenabicycle–alkyne complex **8b**. Therefore, the preferential pathway via alternative complex **8a** leads to the predominant formation of a *meta*-substituted product. In the case for an alkynylboronate, however, the attractive interaction between the non-bonding electron pair on the chlorine ligand and the vacant orbital on the boron center might render intermediate **8c** somewhat favorable, resulting in the decrease of regioselectivity.

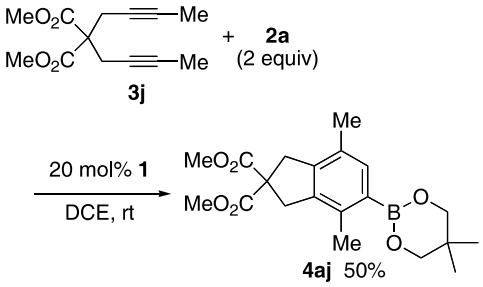


Scheme 6.

The cycloaddition of diyne **3j** bearing methyl substituents on both the alkyne termini suffered from severe steric repulsion between the terminal substituents and the boronate moiety of **2a** (Scheme 7). Consequently, the cycloaddition was carried out overnight with a 20 mol% catalyst loading, but the yield of the desired penta-substituted benzene was not higher than 50%.

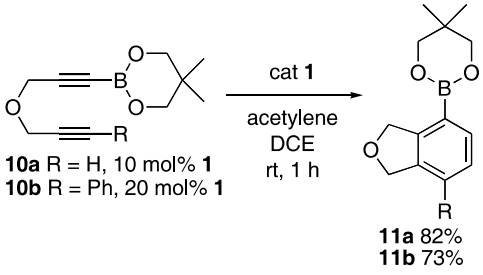
2.3. Cp*RuCl-catalyzed cycloaddition of diynylboronates with monoalkynes

We further explored an alternative partially intramolecular cyclotrimerization assembling bicyclic arylboronates from a diynylboronate and monoalkynes. Diynylboronate **10a**



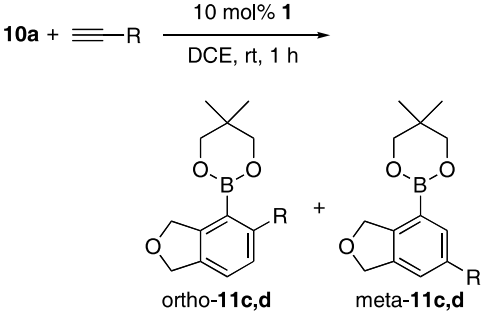
Scheme 7.

derived from dipropargyl ether was treated with 10 mol% **1** in DCE under acetylene atmosphere at room temperature for 1 h to give rise to borylated phthalan **11a** in 82% yield (Scheme 8). It is noteworthy that phthalan boronate isomers **4ah** and **11a** were selectively synthesized by the judicious choice of the precursors in our catalytic cyclotrimerization approach. In a similar manner with a 20 mol% catalyst loading, biphenyl derivative **11b** was obtained in 73% yield from **10b** possessing a phenyl terminal.



Scheme 8.

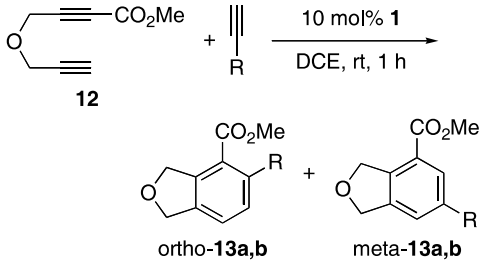
Encouraged by this result, we then examined the regioselectivity of the cycloaddition of **10a** with terminal alkynes (Scheme 9). Thus, **10a** was allowed to react with 4 equiv of 1-hexyne in the same manner. In striking contrast to our expectation of the selective formation of the *meta* isomer, cycloadduct **11c** was obtained as an approximately 1:1 regioisomer mixture in a combined yield of 70%. The total loss of regioselectivity in this system is probably attributed to the electron-withdrawing ability of the boronate terminal of **10a**. To confirm the generality of such an electronic influence, diynylester **12** was subjected to the same reaction conditions as shown in Scheme 10. Consequently, the complete loss of regioselectivity was again observed for



c: R = Bu, 70% yield, ortho:meta = 55:45
d: R = CH_2OMe, 58% yield, ortho:meta = 70:30

Scheme 9.

the formation of benzoate **13**. On the other hand, the moderate *ortho* selectivity was observed for the reaction of **10a** with methyl propargyl ether (5 equiv) resulting in a regioisomer ratio of *ortho*-**11d**:*meta*-**11d** = 70:30 (Scheme 9). The attractive interaction of the ether lone pair with the vacant orbital on the boron center might be a cause of the *ortho* selectivity as depicted in Figure 1 (vide infra). Without such an interaction of the methyl ether terminal, the cycloaddition of ester **12** with 5 equiv methyl propargyl ether under the same conditions lead to the almost complete loss of regioselectivity (Scheme 10).



a: R = Bu, 46% yield, ortho:meta = 51:49
b: R = CH_2OMe, 74% yield, ortho:meta = 55:45

Scheme 10.

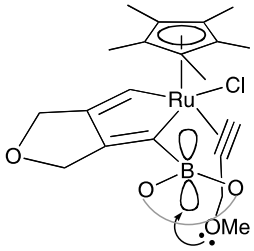
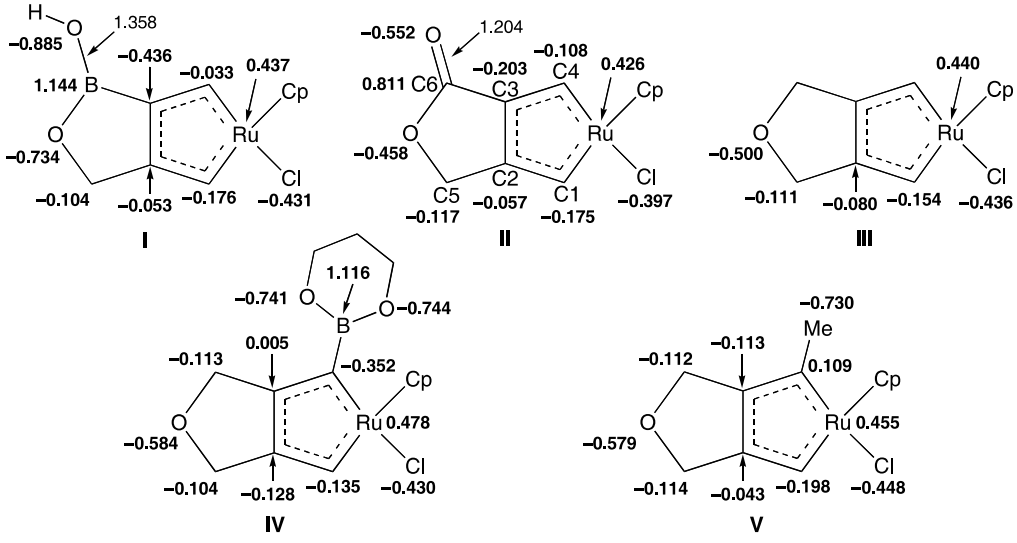


Figure 1. Possible intermediate of cycloaddition of **10** and methyl propargyl ether.

2.4. Density functional calculations of ruthenacycle intermediates

As mentioned above, an electron-withdrawing terminal on a diyne substrate exerted a deteriorative effect on the cycloaddition regioselectivity (Schemes 9 and 10). This is in striking contrast to the fact that internal electron-withdrawing group made favorable contribution to the regioselective cycloadditions.[25,26] To obtain insight into the role of the electron-withdrawing terminal, we carried out density functional theory (DFT) calculations of model ruthenacycle intermediates. Previous DFT calculations revealed that boraruthenacycle **I** and lactone-fused ruthenacycle **II** is electronically unsymmetrical compared to parent **III** as evidenced by the natural charge destributions, although the ruthenacyclopentatriene moieties are almost symmetrical in terms of the bond lengths and angles (Fig. 2).[25,26] Thus, the alkyne insertion was considered to take place at the more negatively charged α carbon anti to the electron-withdrawing boronate and carbonyl groups. With these facts in mind, we further examined ruthenacycles relevant to the present study. At the outset, methyl-substituted ruthenacycle **V** was optimized at the B3LYP/LACVP* level of theory to reveal that its



Typical bond lengths (Å) of model ruthenacycles **I-V.**

	Ru-Cl	Ru-C1	Ru-C4	C1-C2	C2-C3	C3-C4	C2-C5	C5-O	O-C6	C6-C3	O-B	B-C3
I	2.364	1.950	1.954	1.396	1.408	1.397	1.509	1.439	-	-	1.386	1.559
II	2.350	1.963	1.964	1.389	1.398	1.387	1.504	1.444	1.385	1.482	-	-
III	2.366	1.959	-	1.391	1.400	-	1.504	1.437	-	-	-	-
IV	2.364	1.969	1.994	1.381	1.403	1.397	1.505	1.435	1.438	1.505	-	-
V	2.374	1.938	1.989	1.399	1.394	1.397	1.503	1.434	1.437	1.507	-	-

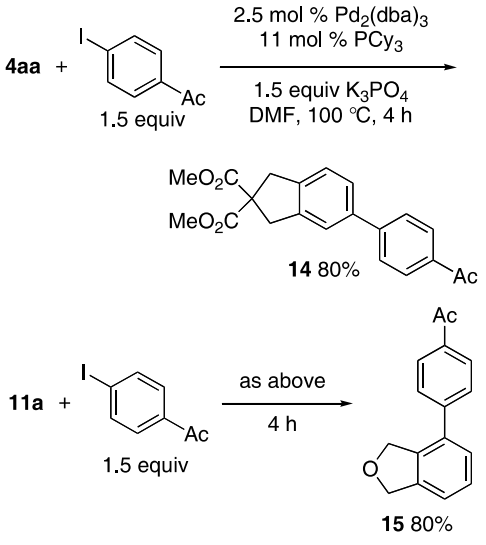
Figure 2. DFT-optimized geometries of model ruthenacycles **I–V** at the B3LYP/LACVP* level (bold numbers indicate natural charges).

ruthenacyclopentatriene moiety is remarkably unsymmetrical. The distance between the ruthenium center and the more substituted α carbon (Ru–C4) is 0.051 Å longer than that of Ru–C1 bond. On the other hand, the C3–C4 bond length is slightly shorter than that for C1–C2 (0.014 Å). Similar trends were observed for boronate-substituted ruthenacycle **IV**, although the difference in the ruthenium–carbon bonds are smaller (0.025 Å).

Further calculations of natural charges were carried out at the same level of theory and the obtained data were shown in Figure 2. The ruthenacyclopentatriene ring of **V** is unsymmetrical in terms of the natural charges compared to parent **III**. The less substituted α carbon C1 is more electronegative so that the alkyne insertion selectively takes place into the Ru–C1 bond as a consequence of the synergistic effect of both the steric and electronic directing effect. On the other hand, the α carbon connected to the boronate group is considerably electronegative (C4: −0.352) compared to the other a carbon (C1: −0.135) in **IV**. On the basis of these results, it is considered that the interference of both electronical and geometrical desymmetrizations of the ruthenacycle ring confuses the cycloaddition regiochemistry.

2.5. Transformations of arylboronates

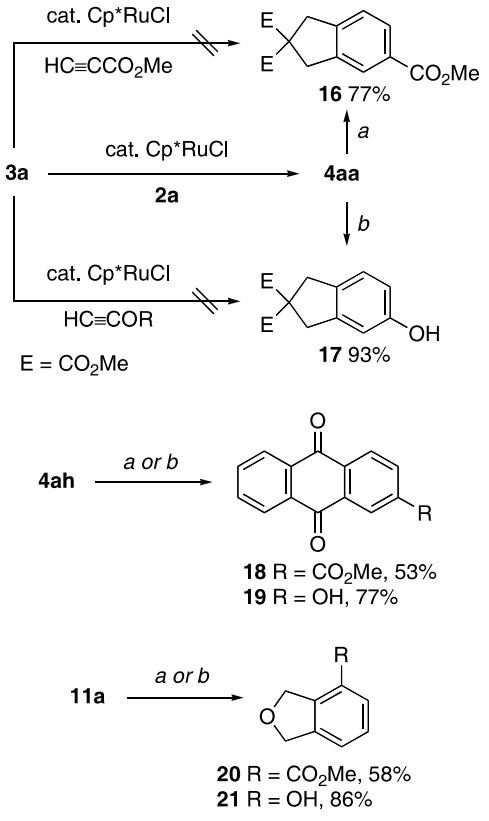
Finally, we demonstrated the synthetic utility of the present method by carrying out the transformations of the obtained arylboronates. The Suzuki–Miyaura couplings of **4aa** and **11a** with *p*-iodoacetophenone were carried out in the presence of 2.5 mol% $Pd_2(dba)_3$ (dba = dibenzylideneacetone), 11 mol% PCy_3, and 1.5 equiv of K_3PO_4 in DMF at 100 °C to give biaryls **14** and **15** in 80% yields (Scheme 11).



Scheme 11.

Electron-deficient monoalkynes such as acetylenedicarboxylates or propiolates are very reactive substrates for the Cp*RuCl-catalyzed cyclotrimerization.[18] Consequently, the cycloaddition of α,ω-diynes with those alkynes has never been accomplished under ruthenium-catalyzed conditions. To obtain the cycloadduct of **3a** and methyl propiolate

indirectly, the catalytic methoxycarbonylation of **4aa** was examined as shown in Scheme 12. The catalytic alkoxycarbonylation of arylboronates, however, has remained almost unexplored,[27] and we recently developed the new protocol to synthesize phthalides by the catalytic carbonylation of boraphthalides.[26] According to our own report, **4aa** was treated with 5 mol% $Pd(OAc)_2$, 11 mol% PPh_3, and 1 equiv of *p*-benzoquinone in MeOH under CO atmosphere at room temperature. The starting material was completely consumed within 2 h to afford the desired benzoate **16** in 77% yield. Electron-rich alkoxyacetylenes are also incompatible monoalkyne substrates for the ruthenium catalysis, although their cycloadducts are valuable pehenol derivatives. In this context, the cycloaddition of **2a** and **3a** followed by oxidation of resultant **4aa** gave bicyclic phenol **17** in a good yield. These methods were further applied to anthraquinone boronate **4ah** to deliver naturally occurring anthraquinone derivatives **18** and **19**.[28,29] Similarly, phthalan derivatives **20** and **21** were obtained from **11a** in 58 and 86% yields, respectively.



Scheme 12. Conditions. (a) 5 mol% $Pd(OAc)_2$, 11 mol% PPh_3, 1 equiv *p*-benzoquinone, 1 atm CO, MeOH, rt, 1.5–2 h; (b) H_2O_2, aq NaOH, THF, rt, 15 min.

3. Conclusion

We successfully developed a novel protocol to prepare bi- or tricyclic arylboronates via Cp*RuCl-catalyzed cycloaddition of 2-ethynyl-5,5-dimethyl-1,3,2-dioxaborinane with various 1,6- and 1,7-diynes. The present protocol tolerates reactive functional groups including an ester, a ketone, a nitrile, and a sulfonamide. Moreover, the Cp*RuCl-catalyzed cycloadditions of diynylboronate with monoalkynes successfully gave rise to similar bicyclic arylboronates albeit with a low regioselectivity. The obtained arylboronate products were further transformed into valuable compounds such as biphenyl, benzoate, and phenol derivatives by means of established procedures.

4. Experimental

4.1. General

Flash chromatography was performed with a silica gel column (Cica silica gel 60 N) eluted with mixed solvents [hexane/AcOEt]. ^1H and ^{13}C NMR spectra were obtained for samples in $CDCl_3$ solution at 25 °C on a Varian Mercury 300 spectrometer. ^1H NMR chemical shifts are reported in δ units, in ppm relative to the singlet at 7.26 ppm for chloroform. Coupling constants are reported in Hz. Infrared spectra were recorded for $CHCl_3$ sample solutions in 0.2 mm path length sodium chloride cavity cells on a JASCO FT/IR-230 spectrometer. Mass spectra were recorded on a JEOL JMS700 mass spectrometer. Elemental analyses were performed by the Instrumental Analysis Facility of Nagoya University. Melting points were obtained on a Büchi B-540 apparatus. 1,2-Dichloroethane and DMF were distilled from CaH_2, and degassed before use. MeOH was distilled from Mg. Cp*RuCl(cod) and $Pd_2(dba)_3 \cdot CHCl_3$ were prepared according to the established procedure.[30,31]

4.1.1. Synthesis of alkynylboronates.

4.1.1.1. 2-Ethynyl-5,5-dimethyl-1,3,2-dioxaborinane 2a. To a solution of ethynylmagnesium bromide in THF (0.5 M THF solution 20 mL, 10.0 mmol + THF 10 mL), trimethylborate (1.59 g, 15.3 mmol) was added at −78 °C. The solution was stirred for 1 h at this temperature, and then stirring was continued for 1 h at −20 °C. To the resultant white suspension, a solution of KHF_2 (4.71 g, 60.3 mmol) in distilled water (15 mL) was added at −20 °C and the solution was stirred at this temperature for 1 h, and at room temperature for 1 h. The obtained reaction mixture was concentrated and dried under reduced pressure over 3 h. The crude product was dissolved in hot acetone and the residue was removed by filtration. The filtrate was concentrated to afford potassium ethynyltrifluoroborate (1.15 g, 87%) as colorless solids (mp 211.2–212.0 °C decomp.).

To a solution of the potassium ethynyltrifluoroborate (1.32 g, 10.0 mmol) and 2,2-dimethyl-1,3-propanediol bis(trimethylsilyl) ether (2.49 g, 10.0 mmol) in dry acetone (10 mL) was added chlorotrimethylsilane (2.17 g, 20.0 mmol) at room temperature, and the solution was stirred overnight. The precipitates were removed by filtration under N_2 atmosphere, and the filtrate was concentrated in vacuo. The crude oil was purified by bulb-to-bulb distillation (80–95 °C/22 mmHg) to give **2a** (1.53 g, 74%) as colorless oil. The spectral data was in good agreement with those reported in the literature.[21] Alkynylboronate **2b**[21] was synthesized in a similar manner.

4.1.1.2. Diynylboronate 10. To a solution of dipropargyl ether (2.83 g, 30.1 mmol) in THF (30 mL), *n*-BuLi (1.6 M solution in hexane, 9.40 mL, 15.0 mmol) was added at −78 °C. The solution was stirred at −78 °C for 30 min, and then at 0 °C for 30 min. To the resultant orange suspension, $B(OMe)_3$ (2.34 g, 22.5 mmol) was added at −78 °C, and the reaction mixture was stirred at −78 °C for 1 h, and then at 0 °C for 1 h. To the reaction mixture, a solution of KHF_2 (7.03 g, 90.0 mmol) in distilled water (16 mL) was added at 0 °C and the reaction mixture was stirred at this temperature for 1 h, and at room temperature for 1 h. The obtained reaction mixture was concentrated and dried under reduced pressure over 4 h. The crude product was dissolved in hot acetone and the residue was removed by filtration. The filtrate was concentrated to afford a potassium diynyltrifluoroborate (1.66 g, 55%) as colorless solids, which was submitted to the following procedure without further purification.

To a solution of the potassium diynyltrifluoroborate (1.60 g, 8.0 mmol) and 2,2-dimethyl-1,3-propanediol bis(trimethylsilyl) ether (1.99 g, 8.0 mmol) in dry acetone (16 mL) was added chlorotrimethylsilane (1.76 g, 16.2 mmol) at room temperature, and the solution was stirred overnight. The precipitates were removed by filtration under N_2 atmosphere, and the filtrate was concentrated in vacuo. The crude oil was purified by bulb-to-bulb distillation (120–130 °C/1.0 mmHg) to give **10a** (1.34 g, 81%) as colorless oil: IR (neat) 3285 (C≡CH), 2213 (C≡C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (s, 6H), 3.64 (s, 4H), 4.26 (d, J=2.1 Hz, 2H), 4.29 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.8, 31.8, 56.4, 56.8, 72.6, 72.9, 78.8; MS (EI): *m/z* (%): 205 (1) [M^+-H], 176 (100) [M^+-H_2CO], 151 (28) [$M^+-OCH_2C{\equiv}CH$]; EA calcd (%) for $C_{11}H_{15}BO_3$ (206.05): C 64.12, H 7.34; found: C 63.93, H 7.47.

Dinynylboronate **10b** was synthesized similarly: mp 43.1–44.3 °C; IR (neat) 2214 (C≡C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (s, 6H), 2.43 (t, J=2.1 Hz, 1H), 3.65 (s, 4H), 4.35 (s, 2H), 4.49 (s, 2H), 7.27–7.33 (m, 3H), 7.41–7.46 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.8, 31.8, 56.9, 57.3, 72.6, 84.1, 86.7, 122.3, 128.1, 128.4, 131.6; MS (EI): *m/z* (%): 282 (33) [M^+], 252 (87) [M^+-H_2CO], 166 (100) [$M^+-H-CH_2C{\equiv}CPh$]; EA calcd (%) for $C_{17}H_{19}BO_3{\cdot}H_2O$ (300.16): C 68.02, H 7.05; found: C 68.07, H 6.95.

4.1.2. Cycloaddition of α,ω-diyne with alkynylboronate: synthesis of arylboronate 4aa from ethynylboronate 2a and dipropargylmalonate 3a. To a solution of Cp*RuCl(cod) (**1**) (17.1 mg, 0.045 mmol) and ethynylboronate **2a** (248.2 mg, 1.80 mmol) in dry degassed 1,2-dichloroethane (4.5 mL) was added a solution of diyne **3a** (187.4 mg, 0.90 mmol) in dry degassed 1,2-dichloroethane (6 mL) over 1 h via syringe pump at room temperature under Ar atmosphere. The solution was stirred at room temperature under Ar atmosphere for 1 h, and then, the solvent was removed under reduced pressure. The residue was purified by silica gel flash column chromatography (hexane/AcOEt 15:1) to give **4aa** (266.5 mg, 86%) as colorless solids (mp 133.6–133.7 °C): IR (neat) 1732 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (s, 6H), 3.59 (s, 2H), 3.60 (s, 2H), 3.73 (s, 6H), 3.75 (s, 4H), 7.19 (d, J=7.5 Hz, 1H), 7.62 (d, J=7.5 Hz, 1H), 7.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9, 31.9, 40.4, 40.7, 52.9, 60.2, 72.2, 123.3, 129.4, 132.5, 138.9, 142.5, 171.8; MS (EI): *m/z* (%): 346 (29) [M^+], 286 (100) [M^+-H-CO_2Me], 227 (13) [$M^+-H-2CO_2Me$]; EA calcd (%) for $C_{18}H_{23}BO_6$ (346.18): C 62.45, H 6.70; found: C 62.41, H 6.69.

4.1.2.1. Compound 4ab. Mp 116.8–116.9 °C; IR ($CHCl_3$) 1699 (COMe) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (s, 6H), 2.16 (s, 6H), 3.49 (s, 2H), 3.51 (s, 2H), 3.76 (s, 4H), 7.19 (d, J=7.5 Hz, 1H), 7.62 (d, J=7.5 Hz, 1H), 7.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9, 26.6, 31.9, 37.5, 37.8, 72.2, 74.5, 123.6, 129.7, 132.7, 138.8, 142.4, 204.7; MS (EI): *m/z* (%): no molecular ion peak 271 (100) [M^+-COMe], 256 (41) [$M^+-Me-COMe$], 228 (18) [$M^+-2COMe$]; EA calcd (%) for $C_{18}H_{23}BO_4$ (314.18): C 68.81, H 7.38; found: C 68.85, H 7.46.

4.1.2.2. Compound 4ac. Mp 169.1–169.3 °C; IR ($CHCl_3$) 2967 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.03 (s, 6H), 3.72 (s, 2H), 3.73 (s, 2H), 3.77 (s, 4H), 7.28 (d, J=7.5 Hz, 1H), 7.73 (s, 1H), 7.75 (d, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9, 31.8, 33.6, 44.6, 44.8, 72.3, 116.3, 123.9, 123.0, 134.04, 135.4, 138.5; MS (EI): *m/z* (%): 280 (100) [M^+], 237 (18) [$M^+-MeCHMe$]; EA calcd (%) for $C_{16}H_{17}BN_2O_2$ (280.13): C 68.60, H 6.12, N 10.00; found: C 68.32, H 6.20, N 9.98.

4.1.2.3. Compound 4ad. Mp 111.4–111.5 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (s, 6H), 2.06 (quint, J=7.5 Hz, 2H), 2.92 (t, J=7.5 Hz, 4H), 3.77 (s, 4H), 7.24 (d, J=7.5 Hz, 1H), 7.60 (d, J=7.5 Hz, 1H), 7.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.0, 25.3, 31.9, 32.6, 33.1, 72.2, 123.6, 129.6, 131.7, 143.3, 147.0; MS (EI): *m/z* (%): 230 (100) [M^+], 187 (35) [$M^+-MeCHMe$]; EA calcd (%) for $C_{14}H_{19}BO_2$ (230.11): C 73.07, H 8.32; found: C 73.00, H 8.47.

4.1.2.4. Compound 4ae. Mp 195.8–196.1 °C; IR ($CHCl_3$) 1320, 1163 (NTs) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.00 (s, 6H), 2.39 (s, 3H), 3.74 (s, 4H), 4.62 (s, 4H), 7.15 (d, J=7.5 Hz, 1H), 7.30 (d, J=8.1 Hz, 1H), 7.60 (s, 1H), 7.66 (d, J=7.5 Hz, 1H), 7.76 (d, J=8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 21.9, 32.0, 53.6, 53.9, 72.3, 121.7, 127.5, 127.9, 129.7, 133.2, 133.6, 135.3, 138.5, 143.5; MS (EI): *m/z* (%): 385 (91) [M^+], 330 (100) [M^+-NTs]; EA calcd (%) for $C_{20}H_{24}BNO_4S$ (385.28): C 62.35, H 6.28, N 3.64; found: C 62.28, H 6.34, N 3.56.

4.1.2.5. Compound 4af. ^1H NMR (300 MHz, $CDCl_3$): δ 1.03 (s, 6H), 3.78 (s, 4H), 5.11 (s, 4H), 7.23 (d, J=7.5 Hz, 1H), 7.68 (s, 1H), 7.71 (d, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.0, 32.0, 72.3, 73.5, 73.6, 120.1, 126.2, 132.9, 138.3, 141.6; MS (EI): *m/z* (%): 232 (100) [M^+], 217 (22) [M^+-Me], 204 (93) [M^+-CO]; EA calcd (%) for $C_{13}H_{17}BO_3$ (232.08): C 67.28, H 7.38; found: C 67.09, H 7.57.

4.1.2.6. Compound 4ag. Mp 116.7–116.8 °C; IR ($CHCl_3$) 1732 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (s, 6H), 1.20 (t, J=7.2 Hz, 12H), 3.52

(s, 2H), 3.54 (s, 2H), 3.75 (s, 4H), 4.12–4.23 (m, 8H), 7.07 (d, J=7.5 Hz, 1H), 7.52 (s, 1H), 7.53 (d, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 22.0, 31.9, 34.6, 34.9, 57.5, 61.7, 72.3, 127.4, 131.4, 131.7, 133.8, 135.3, 169.7, 169.8; MS (EI): *m/z* (%): 532 (42) [M^+], 487 (32) [M^+-OEt], 459 (31) [M^+-CO_2Et], 413 (70) [$M^+-HOEt-CO_2Et$], 385 (50) [$M^+-H-2CO_2Et$], 339 (100) [$M^+-H-HOEt-2CO_2Et$]; EA calcd (%) for $C_{27}H_{37}BO_{10}$ (532.39): C 60.91, H 7.01; found: C 61.11, H 7.25.

4.1.2.7. Compound 4ah. Mp 192.6–193.0 °C; IR ($CHCl_3$) 1673 (quinone) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 6H), 3.83 (s, 4H), 7.78–7.82 (m, 2H), 8.20 (dd, J=7.8, 1.2 Hz, 1H), 8.28 (dd, J=7.8, 0.3 Hz, 1H), 8.30–8.35 (m, 2H), 8.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9, 32.0, 72.4, 125.9, 126.93, 127.0, 132.2, 132.7, 133.4, 133.4, 133.7, 133.9, 134.5, 139.1, 183.0, 183.2; MS (EI): *m/z* (%): 320 (100) [M^+], 280 (85) [$M^+-C_3H_4$], 235 (95) [$M^+-CH_2C(Me)_2CHO$]; EA calcd (%) for $C_{19}H_{17}BO_4$ (320.15): C 71.28, H 5.35; found: C 71.05, H 5.53.

4.1.2.8. Compound 4ba. Mp 38.0–40.8 °C; IR (neat) 1738 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, J=7.2 Hz, 3H), 1.03 (s, 6H), 1.35 (sext, J=7.2 Hz, 2H), 1.46–1.57 (m, 2H), 2.81 (t, J=7.8 Hz, 2H), 3.55 (s, 4H), 3.73 (s, 6H), 3.75 (s, 4H), 6.99 (s, 1H), 7.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 21.9, 22.9, 31.6, 35.5, 35.7, 40.2, 40.7, 52.9, 60.4, 72.2, 125.0, 130.3, 136.1, 141.9, 148.2, 172.0; MS (EI): *m/z* (%): 402 (44) [M^+], 342 (100) [M^+-H-CO_2Me], 299 (24) [M^+-H-CO_2Me-Pr]; EA calcd (%) for $C_{22}H_{31}BO_6\cdot H_2O$ (420.30): C 62.87, H 7.91; found: C 62.79, H 7.98.

4.1.2.9. Compound 4ai. Mp 160.1–160.5 °C; IR ($CHCl_3$) 1732 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *meta*-**4ai** δ 1.01 (s, 6H), 2.26 (s, 3H), 3.54 (s, 2H), 3.60 (s, 2H), 3.74 (s, 6H), 3.75 (s, 4H), 7.43 (s, 1H), 7.47 (s, 1H); *ortho*-**4ai** δ 1.02 (s, 6H), 2.42 (s, 3H), 3.55 (s, 2H), 3.60 (s, 2H), 3.74 (s, 6H), 3.76 (s, 4H), 7.01 (d, J=7.5 Hz, 1H), 7.57 (d, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): *meta*-**4ai** δ 18.9, 21.9, 31.9, 39.6, 40.6, 52.9, 59.8, 72.2, 120.5, 126.8, 133.3, 138.8, 141.5, 172.0; *ortho*-**4ai** δ 18.5, 21.9, 31.6, 39.9, 41.0, 52.9, 59.5, 72.2, 132.7, 134.0, 138.7, 139.5, 141.4, 172.1; MS (EI): *m/z* (%): 360 (31) [M^+], 300 (100) [M^+-H-CO_2Me]; EA calcd (%) for $C_{19}H_{25}BO_6$ (360.21): C 63.35, H 7.00; found: C 63.27, H 7.01.

4.1.2.10. Compound 4aj. Mp 116.1–116.2 °C; IR (neat) 1721 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (s, 6H), 2.21 (s, 3H), 2.39 (s, 3H), 3.54 (s, 2H), 3.56 (s, 2H), 3.75 (s, 6H), 3.76 (s, 4H), 7.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.3, 18.6, 21.9, 31.7, 39.9, 40.2, 53.0, 59.3, 72.2, 129.6, 134.7, 136.6, 138.6, 140.4, 172.2; MS (EI): *m/z* (%): 374 (45) [M^+], 314 (100) [M^+-H-CO_2Me]; EA calcd (%) for $C_{20}H_{27}BO_6$ (374.24): C 64.19, H 7.27; found: C 64.13, H 7.54.

4.1.2.11. Compound 11a. Mp 95.3–95.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.02 (s, 6H), 3.76 (s, 4H), 5.09–5.11 (m, 2H), 5.25 (t, J=2.1 Hz, 2H), 7.23–7.32 (m, 2H), 7.69–7.72 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9, 31.9, 72.2, 73.0, 75.0, 122.9, 126.3, 133.0, 138.0, 145.3; MS (EI): *m/z* (%): 231 (72) [M^+-H], 204 (100) [M^+-CO], 145 (49) [$M^+-OCH_2C(CH_3)_3$]; EA calcd (%) for $C_{13}H_{17}BO_3$ (232.08): C 67.28, H 7.38; found: C 67.26, H 7.40.

4.1.2.12. Compound 11b. Mp 101.6–102.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (s, 6H), 3.79 (s, 4H), 5.21 (t, J=2.1 Hz, 2H), 5.32 (t, J=2.1 Hz, 2H), 7.34 (d, J=7.5 Hz, 1H), 7.36–7.46 (m, 5H), 7.82 (d, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9, 31.9, 72.2, 72.9, 75.1, 126.5, 127.4, 127.7, 128.5, 133.9, 136.0, 137.9, 140.1, 146.3; MS (EI): *m/z* (%): 308 (89) [M^+], 280 (100) [M^+-CO]; EA calcd (%) for $C_{19}H_{21}BO_3$ (308.18): C 74.05, H 6.87; found: C 74.07, H 6.98.

4.1.2.13. Compound 11c. Mp 86.3–86.5 °C; ca. 1:1 mixture of *ortho* and *meta* isomers: ^{1}H NMR (300 MHz, $CDCl_3$): *ortho*-**11b** δ 0.95 (t, J=7.2 Hz, 3H), 1.05 (s, 6H), 1.31–1.45 (m, 2H), 1.51–1.67 (m, 2H), 2.87 (t, J=7.8 Hz, 2H), 3.77 (s, 3H), 5.07–5.09 (m, 2H), 5.20–5.23 (m, 2H), 7.08 (d, J=7.8 Hz, 1H), 7.15 (d, J=7.8 Hz, 1H); *meta*-**11b** δ 0.94 (t, J=7.2 Hz, 3H), 1.02 (s, 6H), 1.31–1.45 (m, 2H), 1.51–1.67 (m, 2H), 2.64 (t, J=7.8 Hz, 2H), 3.76 (s, 3H), 5.07–5.09 (m, 2H), 5.20–5.23 (m, 2H), 7.12 (s, 1H), 7.54 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.04 and 14.07, 21.90 and 21.91, 22.5 and 22.8, 31.6 and 31.8, 34.1 and 35.9, 35.47 and 35.51, 72.0 and 72.1, 72.9 and 73.1, 74.9 and 75.1, 121.8 and 122.9, 128.3 and 133.2, 135.2 and 138.3, 141.0 and 142.7, 145.3 and 148.1; MS (EI): *m/z* (%): 286 (31) [M^+], 243 (25) [$M^+-CH_2CH_2CH_3$]; EA calcd (%) for $C_{17}H_{25}BO_3$ (288.19): C 70.85, H 8.74; found: C 70.85, H 8.73.

4.1.2.14. Compound 11d. Mp 65.8–66.2 °C; ca. 7:3 mixture of *ortho* and *meta* isomers: IR (neat) 1720 (CO_2Me) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *ortho*-**11c** δ 1.04 (s, 6H), 3.38 (s, 3H), 3.75 (s, 4H), 4.65 (s, 2H), 5.06 (s, 2H), 5.19 (t, J=1.8 Hz, 2H), 7.19 (d, J=7.5 Hz, 1H), 7.25 (d, J=7.5 Hz, 1H); *meta*-**11c** δ 1.01 (s, 6H), 3.38 (s, 3H), 3.75 (s, 4H), 4.46 (s, 2H), 5.08 (s, 2H), 5.22 (t, J=1.8 Hz, 2H), 7.29 (s, 1H), 7.65 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): *ortho*-**11c** δ 21.9, 31.7, 58.1, 72.1, 73.0, 74.3, 74.8, 121.7, 126.7, 137.3, 142.5, 145.1; *meta*-**11c** δ 21.9, 31.9, 58.1, 72.2, 72.9, 74.6, 74.9, 122.5, 132.9, 136.4, 138.6, 145.0; MS (EI): *m/z* (%): 279 (100) [M^+], 248 (28) [M^+-HOMe]; EA calcd (%) for $C_{15}H_{21}BO_4$ (276.14): C 65.24, H 7.67; found: C 65.35, H 7.56.

4.1.2.15. Compound 13a. Oil; ca. 1:1 mixture of *ortho* and *meta* isomers: ^{1}H NMR (300 MHz, $CDCl_3$): *ortho*-**13a** δ 0.92 (t, J=7.2 Hz, 3H), 1.36 (sept, J=7.2 Hz, 2H), 1.50–1.65 (m, 2H), 2.92 (t, J=7.8 Hz, 2H), 3.88 (s, 3H), 5.08 (s, 2H), 5.24 (t, J=1.8 Hz, 2H), 7.17 (d, J=7.8 Hz, 1H), 7.24 (d, J=7.8 Hz, 1H); *meta*-**13a** δ 0.92 (t, J=7.2 Hz, 3H), 1.02 (s, 6H), 1.36 (sept, J=7.2 Hz, 2H), 1.50–1.65 (m, 2H), 2.66 (t, J=7.8 Hz, 2H), 3.90 (s, 3H), 5.09 (s, 2H), 5.34 (t, J=1.8 Hz, 2H), 7.23 (s, 1H), 7.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.98 and 14.03, 22.3 and 22.8, 33.7 and 35.3, 34.0 and 34.3, 51.7 and 52.0, 72.9 and 73.1, 74.8 and 74.9, 123.7 and 125.3, 123.9 and 124.0, 128.7 and 130.3, 137.5 and 138.9, 140.6 and 141.2, 142.7 and 143.6, 166.4 and 167.4; MS (EI): *m/z* (%): 234 (100) [M^+], 217 (93) [M^+-H-Me], 206 (42) [M^+-CO], 189 (64)

[$M^+-2H-CH_2CH_2CH_3$]; EA calcd (%) for $C_{14}H_{18}O_3$ (234.29): C 71.77, H 7.74; found: C 71.67, H 7.79.

4.1.2.16. Compound 13b. Analyses other than ^1H NMR were omitted because **13b** was obtained as a mixture with the cyclotrimers of methyl propargyl ether. The yield and regioisomer ratio were determined by ^1H NMR analysis. ^1H NMR (300 MHz, $CDCl_3$): *ortho*-**13b** δ 3.45 (s, 3H), 3.90 (s, 3H), 4.82 (s, 2H), 5.12 (s, 2H), 5.28 (t, $J=1.8$ Hz, 2H), 7.26 (dd, $J=7.8$, 1.8 Hz, 1H), 7.55 (d, $J=7.8$ Hz, 1H); *meta*-**13b** δ 3.41 (s, 3H), 3.91 (s, 3H), 4.50 (s, 2H), 5.12 (s, 2H), 5.38 (t, $J=1.8$ Hz, 2H), 7.42 (s, 1H), 7.89 (s, 1H).

4.1.3. Suzuki–Miyaura coupling of arylboronates. To a solution of arylboronate **4aa** (104.0 mg, 0.30 mmol) and *p*-iodoacetophenone (111.8 mg, 0.45 mmol) in dry DMF (2 mL) was added $Pd_2(dba)_3\cdot CHCl_3$ (8.0 mg, 0.0077 mmol), PCy_3 (8.7 mg, 0.041 mmol), and K_3PO_4 (99.2 mg, 0.47 mmol). The mixture was degassed at −78 °C, and stirred at 100 °C under Ar atmosphere for 4 h. The reaction mixture was diluted with distilled water (10 mL) and extracted with AcOEt (5 mL×3). The organic layer was washed with brine (5 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (hexane/AcOEt 20:1) to give **14** (82.9 mg, 80%) as colorless solids (mp 98.8–99.4 °C): IR ($CHCl_3$) 1733 (CO_2Me), 1680 (COMe) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.63 (s, 3H), 3.65 (s, 2H), 3.67 (s, 2H), 3.77 (s, 6H), 7.29 (d, $J=8.1$ Hz, 1H), 7.44 (d, $J=8.1$ Hz, 1H), 7.45 (s, 1H), 7.65 (d, $J=8.4$ Hz, 2H), 8.01 (d, $J=8.4$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.7, 40.4, 40.6, 53.1, 60.5, 123.0, 124.6, 126.2, 127.1, 127.3, 128.8, 135.6, 138.9, 140.1, 140.7, 145.7, 171.8, 197.5; MS (EI): *m/z* (%): 352 (79) [M^+], 292 (100) [M^+-H-CO_2Me], 277 (22) [M^+-H-CO_2Me-Me]; EA calcd (%) for $C_{21}H_{20}O_5$ (352.38): C 71.58, H 5.72; found: C 71.68, H 5.60.

The Suzuki–Miyaura coupling of **11a** with *p*-iodoacetophenone was carried out in the same manner to give **15**: mp 109.8–110.1 °C; IR ($CHCl_3$) 1681 (COMe) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.64 (s, 3H), 5.18–5.19 (m, 4H), 7.27–7.42 (m, 3H), 7.47–7.52 (m, 2H), 8.01–8.05 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.7, 73.3, 73.6, 120.6, 127.2, 127.9, 128.0, 128.6, 134.7, 135.9, 137.0, 140.1, 144.7, 197.3; MS (EI): *m/z* (%): 238 (100) [M^+], 223 (42) [M^+-Me], 209 (38) [M^+-H-CO], 195 (75) [M^+-COMe]; EA calcd (%) for $C_{16}H_{14}O_2$ (238.28): C 80.65, H 5.92; found: C 80.52, H 5.91.

4.1.4. Methoxycarbonylation of arylboronates. To a solution of arylboronate **4aa** (104.4 mg, 0.30 mmol) in dry MeOH (3 mL) was added $Pd(OAc)_2$ (3.4 mg, 0.015 mmol), PPh_3 (9.3 mg, 0.035 mmol), and *p*-benzoquinone (32.6 mg, 0.30 mmol). The mixture was stirred at room temperature under CO atmosphere for 2 h. The reaction mixture was concentrated in vacuo. The residue was purified by silica gel flash column chromatography (hexane/AcOEt 15:1) to give **16** (68.4 mg, 77%) as colorless solids (mp 90.1–90.3 °C): IR ($CHCl_3$) 1735 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.63 (s, 4H), 3.75 (s, 6H), 3.89 (s, 3H), 7.26 (d, $J=8.1$ Hz, 1H), 7.86–7.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.2, 40.6, 52.0, 53.1, 60.3, 124.0, 125.3, 128.6, 129.0, 140.1, 145.2, 166.8, 171.5; MS (EI): *m/z* (%): 292 (39) [M^+], 261 (23) [M^+-OMe], 232 (100) [M^+-H-CO_2Me], 201 (43) [$M^+-HOMe-CO_2Me$], 173 (51) [$M^+-H-2CO_2Me$]; EA calcd (%) for $C_{15}H_{15}O_6$ (292.28): C 61.64, H 5.52; found: C 61.50, H 5.62.

The methoxycarbonylation of **4ah** and **11a** were carried out in a similar manner. The spectral data for **18** was in good agreement with those reported previously.[28]

Compound **20** mp 61.1–61.3 °C; IR ($CHCl_3$) 1717 (COMe) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.91 (s, 4H), 5.12–5.15 (m, 2H), 5.39 (t, $J=2.1$ Hz, 2H), 7.33–7.44 (m, 2H), 7.91–7.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.0, 72.9, 74.8, 124.3, 125.2, 127.4, 128.6, 140.4, 141.5, 166.2; MS (EI): *m/z* (%): 178 (2) [M^+], 149 (100) [M^+-H-CO]; EA calcd (%) for $C_{10}H_{10}O_3$ (178.18): C 67.41, H 5.66; found: C 67.17, H 5.72.

4.1.5. Oxidation of arylboronates. To a solution of arylboronate **4aa** (104.0 mg, 0.30 mmol) in THF (3.5 mL) was added a basic solution of H_2O_2 (30% aq H_2O_2 0.5 mL + 1 N NaOH 1 mL) at room temperature. The mixture was stirred at room temperature for 15 min. The reaction mixture was diluted with satd NH_4Cl (5 mL) and extracted with AcOEt (5 mL×3). The organic layer was washed with brine (5 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (hexane/AcOEt 10:1) to give **17** (69.5 mg, 93%) as colorless oil: IR (neat) 2449 (OH), 1723 (CO_2Me) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.51 (s, 2H), 3.54 (s, 2H), 3.74 (s, 6H), 4.57 (br s, 1H), 6.63 (dd, $J=8.4$, 2.7 Hz, 1H), 6.67 (m, 1H), 7.03 (d, $J=8.4$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.8, 40.6, 53.1, 60.8, 111.1, 114.1, 124.8, 131.4, 141.3, 155.0, 172.1; MS (EI): *m/z* (%): 250 (35) [M^+], 190 (100) [M^+-H-CO_2Me], 131 (55) [$M^+-H-2CO_2Me$]; EA calcd (%) for $C_{13}H_{14}O_5$ (250.25): C 62.39, H 5.64; found: C 62.37, H 5.67.

The oxidation of **4ah** and **11a** were carried out in a similar manner. The spectral data for **19** and **21** were in good agreement with those reported previously.[29,32]

4.2. Computational methods

The Q-chem 2.0 program[33] in Spartan'02 software package[34] was used for geometry optimizations, and atomic charges for the optimized geometries were obtained with the Gaussian 98 program package.[35] The geometries of ruthenacycles **I–VI** were fully optimized by means of the Becke's three-parameter hybrid density functional method (B3LYP)[36] with the LACVP* basis set, which uses a double-ζ basis set with the relativistic effective core potential of Hay and Wadt (LanL2 ECP)[37] for Ru and the 6-31G(d)[38] basis sets for other elements. Natural charges were computed at the B3LYP/LACVP* level using the natural population analysis method as implemented in Gaussian 98.[39]

Acknowledgements

This research was partially supported by Grant-in-Aid for Young Scientists (A) 17685008 from the Ministry of

Education, Culture, Sports, Science and Technology, Japan. We gratefully acknowledge financial support from Japan Combinatorial Chemistry Focus Group Award in Synthetic Organic Chemistry, Japan.

References and notes

1. (a) For reviews, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695. (d) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419–2440.
2. (a) Song, Z. Z.; Wong, H. N. C. *J. Org. Chem.* **1994**, *59*, 33–41. (b) Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346–2351. (c) Smith, K. A.; Campi, E. M.; Jackson, W. R.; Marcuccio, S.; Naeslund, C. G. M.; Deacon, G. B. *Synlett* **1997**, 131–132. (d) Wong, M. S.; Zhang, X. L. *Tetrahedron Lett.* **2001**, *42*, 4087–4089. (e) Koza, D. J.; Carita, E. *Synthesis* **2002**, 2183–2186. (f) Lei, A.; Zhang, X. *Tetrahedron Lett.* **2002**, *43*, 2525–2528. (g) Kabalka, G. W.; Wang, L. *Tetrahedron Lett.* **2002**, *43*, 3067–3068. (h) Parrish, J. P.; Jung, Y. C.; Floyd, R. J.; Jung, K. W. *Tetrahedron Lett.* **2002**, *43*, 7899–7902. (i) Falck, J. R.; Mohapatra, S.; Bondlela, M.; Venkataraman, S. K. *Tetrahedron Lett.* **2002**, *43*, 8149–8151. (j) Klingensmith, L. M.; Leadbeater, N. E. *Tetrahedron Lett.* **2003**, *44*, 765–768. (k) Yoshida, H.; Yamaryo, Y.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2003**, *44*, 1541–1544. (l) Punna, S.; Díaz, D. D.; Finn, M. G. *Synlett* **2004**, 2351–2354. (m) González-Arellano, C.; Corma, A.; Iglesias, M.; Sánchez, F. *Chem. Commun.* **2005**, 1990–1992.
3. (a) For reviews, see: Hayashi, T. *Synlett* **2001**, 879–887. (b) Hayashi, T.; Yamazaki, K. *Chem. Rev.* **2003**, *103*, 2829–2844.
4. (a) Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 3279–3281. (b) Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128–8129. (c) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584–13585. (d) Otomaru, Y.; Tokunaga, N.; Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7*, 307–310. (e) Otomaru, Y.; Kina, A.; Shintani, R.; Hayashi, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1673–1679.
5. (a) Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martín-Matute, B. *J. Am. Chem. Soc.* **2001**, *123*, 5358. (b) Lautens, M.; Mancuso, J.; Grover, H. *Synthesis* **2004**, 2006–2014. (c) Farrington, E. J.; Brown, J. M.; Barnard, C. F. J.; Rowsell, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 169–171. (d) Farrington, E. J.; Barnard, C. F. J.; Rowsell, E.; Brown, J. M. *Adv. Synth. Catal.* **2005**, *347*, 185–195. (e) Jung, Y. C.; Mishra, R. K.; Yoon, C. H.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2231–2234. (f) Zou, G.; Wang, Z.; Zhu, J.; Tang, J. *Chem. Commun.* **2003**, 2438–2439. (g) Koike, T.; Du, X.; Sanada, T.; Danda, Y.; Mori, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 89–92. (h) Andappan, M. M. S.; Nilsson, P.; Larhed, M. *Chem. Commun.* **2004**, 218–219. (i) Andappan, M. M. S.; Nilsson, P.; von Schenck, H.; Larhed, M. *J. Org. Chem.* **2004**, *69*, 5212–5218.
6. (a) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463–16470. (b) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798–11799. (c) Petasis, N. A.; Patel, Z. D. *Tetrahedron Lett.* **2000**, *41*, 9607–9611. (d) Prakash, G. K. S.; Mandal, M.; Schweizer, S.; Petasis, N. A.; Olah, G. A. *Org. Lett.* **2000**, *2*, 3173–3176. (e) Petasis, N. A.; Boral, S. *Tetrahedron Lett.* **2001**, *42*, 539–542.
7. (a) Wang, Q.; Finn, M. G. *Org. Lett.* **2000**, *2*, 4063–4065. (b) Thompson, K. M.; Hall, D. G. *Chem. Commun.* **2000**, 2379–2380. (c) Klopfenstein, S. R.; Chen, J. J.; Golebiowski, A.; Li, M.; Peng, S. X.; Shao, X. *Tetrahedron Lett.* **2000**, *41*, 4835–4839. (d) Golebiowski, A.; Klopfenstein, S. R.; Chen, J. J.; Shao, X. *Tetrahedron Lett.* **2000**, *41*, 4841–4844. (e) Jiang, B.; Yang, C.-G.; Gu, X.-H. *Tetrahedron Lett.* **2001**, *42*, 2545–2547. (f) Berrée, F.; Debache, A.; Marsac, Y.; Carboni, B. *Tetrahedron Lett.* **2001**, *42*, 3591–3594. (g) Koolmeister, T.; Södergren, M.; Scobie, M. *Tetrahedron Lett.* **2002**, *43*, 5965–5968. (h) Portlock, D. E.; Naskar, D.; West, L.; Li, M. *Tetrahedron Lett.* **2002**, *43*, 6845–6847. (i) Portlock, D. E.; Ostaszewski, R.; Nasker, D.; West, L. *Tetrahedron Lett.* **2003**, *44*, 603–605. (j) Portlock, D. E.; West, L.; Ostaszewski, R.; Chen, J. J. *Tetrahedron Lett.* **2003**, *44*, 5121–5124. (k) Nasker, D.; Roy, A.; Seibel, W. L.; Portlock, D. E. *Tetrahedron Lett.* **2003**, *44*, 5819–5821. (l) Nasker, D.; Roy, A.; Seibel, W. L.; West, L.; Portlock, D. E. *Tetrahedron Lett.* **2003**, *44*, 6297–6300. (m) Nasker, D.; Roy, A.; Seibel, W. L.; Portlock, D. E. *Tetrahedron Lett.* **2003**, *44*, 8865–8868. (n) Nasker, D.; Roy, A.; Seibel, W. L. *Tetrahedron Lett.* **2003**, *44*, 8861–8863. (o) Grigg, R.; Sridharan, V.; Thayaparan, A. *Tetrahedron Lett.* **2003**, *44*, 9017–9019. (p) McLean, N. J.; Tye, H.; Whittaker, M. *Tetrahedron Lett.* **2004**, *45*, 993–995. (q) Nanda, K. K.; Trotter, B. W. *Tetrahedron Lett.* **2004**, *45*, 2025–2028. (r) Sugiyama, S.; Arai, S.; Ishii, K. *Tetrahedron: Asymmetry* **2004**, *15*, 3149–3153. (s) Jourdan, H.; Gouhier, G.; Hijfte, L. V.; Angibaud, P.; Piettre, S. R. *Tetrahedron Lett.* **2005**, *46*, 8027–8031.
8. (a) Selected examples: Oguma, K.; Miura, M.; Satoh, T.; Nomura, M. *J. Am. Chem. Soc.* **2000**, *122*, 10464–10465. (b) Satoh, T.; Ogino, S.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5063–5065. (c) Hayashi, T.; Inoue, K.; Taniguchi, N.; Ogasawara, M. *J. Am. Chem. Soc.* **2001**, *123*, 9918–9919. (d) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54–55. (e) Murakami, M.; Igawa, H. *Chem. Commun.* **2002**, 390–391. (f) Murakami, M.; Igawa, H. *Helv. Chim. Acta* **2002**, *85*, 4182–4188. (g) Matsuda, T.; Makino, M.; Murakami, M. *Org. Lett.* **2004**, *5*, 1257–1259. (h) Miura, T.; Shimada, M.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1094–1095. (i) Miura, T.; Sasaki, T.; Nakazawa, H.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1390–1391. (j) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311–1314. (k) Lautens, M.; Dockendorff, C. *Org. Lett.* **2003**, *5*, 3695–3698. (l) Lautens, M.; Yoshida, M. *J. Org. Chem.* **2003**, *68*, 762–769. (m) Lautens, M.; Marquardt, T. *J. Org. Chem.* **2003**, *68*, 4607–4614. (n) Lautens, M.; Mancuso, J. *J. Org. Chem.* **2004**, *69*, 3478–3487. (o) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698–1699. (p) Kakiuchi, F.; Usui, M.; Ueno, S.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2004**, *126*, 2706–2707. (q) Park, Y. J.; Jo, E.-A.; Jun, C.-H. *Chem. Commun.* **2005**, 1185–1187. (r) Zhou, C.; Larock, R. C. *Org. Lett.* **2005**, *7*, 259–262.
9. (a) Suzuki, A.; Brown, H. C. Organic Synthesis via Boranes. In *Suzuki Coupling*, *Vol. 3*; Aldrich Chemical: Milwaukee, 2003; p 5. (b) Tyrrell, E.; Brookes, P. *Synthesis* **2004**, 469–483.
10. (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510. (b) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447–3450. (c) Ishiyama, T.; Ishida, K.; Miyaura, N. *Tetrahedron* **2001**, *57*, 9813–9816.

(d) Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458–6459. (e) Murata, M.; Oyama, T.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **2000**, *65*, 164–168. (f) Baudoin, O.; Guénard, D.; Guéritte, F. *J. Org. Chem.* **2000**, *65*, 9268–9271. (g) Willis, D. M.; Strongin, R. M. *Tetrahedron Lett.* **2000**, *41*, 8683–8686. (h) Melaimi, M.; Mathey, F.; Le Floch, P. *J. Organomet. Chem.* **2001**, *640*, 197–199. (i) Fürstner, A.; Seidel, G. *Org. Lett.* **2002**, *4*, 541–543. (j) Ma, Y.; Song, C.; Jiang, W.; Xue, G.; Cannon, J. F.; Wang, X.; Andrus, M. B. *Org. Lett.* **2003**, *5*, 4635–4638. (k) Fang, H.; Kaur, G.; Yan, J.; Wang, B. *Tetrahedron Lett.* **2005**, *46*, 1671–1674. (l) Occhiato, E. G.; Galbo, F. L.; Guarna, A. *J. Org. Chem.* **2005**, *70*, 7324–7330.

11. (a) Chen, H.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **1999**, *38*, 3391–3393. (b) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995–1997. (c) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390–391. (d) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056–3058. (e) Takagi, J.; Sato, K.; Hartwig, J. F.; Ishiyama, T.; Miyaura, N. *Tetrahedron Lett.* **2002**, *43*, 5649–5651. (f) Ishiyama, T.; Nobuta, Y.; Hartwig, J. F.; Miyaura, N. *Chem. Commun.* **2003**, 2924–2925. (g) Ishiyama, T.; Takagi, J.; Yonekawa, Y.; Hartwig, J. F.; Miyaura, N. *Adv. Synth. Catal.* **2003**, *345*, 1103–1106. (h) Iverson, C. N.; Smith, M. R., III. *J. Am. Chem. Soc.* **1999**, *121*, 7696–7697. (i) Cho, J.-Y.; Iverson, C. N.; Smith, M. R., III. *J. Am. Chem. Soc.* **2000**, *122*, 12868–12869. (j) Tse, M. K.; Cho, J.-Y.; Smith, M. R., III. *Org. Lett.* **2001**, *3*, 2831–2833. (k) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science* **2002**, *295*, 305–308. (l) Maleczka, R. E., Jr.; Shi, F.; Holmes, D.; Smith, M. R., III. *J. Am. Chem. Soc.* **2003**, *125*, 7792–7793. (m) Chotana, G. A.; Rak, M. A.; Smith, M. R., III. *J. Am. Chem. Soc.* **2005**, *127*, 10539–10544. (n) Shimada, S.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2168–2171.
12. (a) Maderna, A.; Pritzkow, H.; Siebert, W. *Angew. Chem., Int. Ed.* **1996**, *35*, 1501–1503. (b) Ester, C.; Maderna, A.; Pritzkow, H.; Siebert, W. *Eur. J. Inorg. Chem.* **2000**, 1177–1184. (c) Gu, Y.; Pritzkow, H.; Siebert, W. *Eur. J. Inorg. Chem.* **2001**, 373–379. (d) Goswami, A.; Maier, C.-J.; Pritzkow, H.; Siebert, W. *Eur. J. Inorg. Chem.* **2004**, 2635–2645.
13. (a) Davies, M. W.; Johnson, C. N.; Harrity, J. P. A. *Chem. Commun.* **1999**, 2107–2108. (b) Davies, M. W.; Johnson, C. N.; Harrity, J. P. A. *J. Org. Chem.* **2001**, *66*, 3525–3532. (c) Davies, M. W.; Wybrow, R. A. J.; Johnson, C. N.; Harrity, J. P. A. *Chem. Commun.* **2001**, 1558–1559. (d) Moore, J. E.; Goodenough, K. M.; Spinks, D.; Harrity, J. P. A. *Synlett* **2002**, 2071–2073. (e) Moore, J. E.; York, M.; Harrity, J. P. A. *Synlett* **2005**, 860–862. (f) Moore, J. E.; Davies, M. W.; Goodenough, K. M.; Wybrow, R. A. J.; York, M.; Johnson, C. N.; Harrity, J. P. A. *Tetrahedron* **2005**, *61*, 6707–6714.
14. (a) Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2004**, *126*, 3712–3713. (b) Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. *Tetrahedron* **2005**, *61*, 11501–11510.
15. Preliminary results have been reported: Yamamoto, Y.; Hattori, K.; Ishii, J.; Nishiyama, H.; Itoh, K. *Chem. Commun.* **2005**, 4438–4440.
16. Gandon, V.; Leca, D.; Aechtner, T.; Vollhardt, K. P. C.; Malacria, M.; Aubert, C. *Org. Lett.* **2004**, *6*, 3405–3407.
17. (a) Trost, B. M. *Science* **1991**, *254*, 1471–1477. (b) Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 259–281.
18. Yamamoto, Y.; Arakawa, T.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2003**, *125*, 12143–12160.
19. Bustelo, E.; Guérot, C.; Hercouet, A.; Carboni, B.; Toupet, L.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2005**, *127*, 11582–11583.
20. Brown, H. C.; Bhat, N. G.; Srebnik, M. *Tetrahedron Lett.* **1988**, *29*, 2631–2634.
21. Blanchard, C.; Framery, E.; Vaultier, M. *Synthesis* **1996**, 45–47.
22. Kim, B. J.; Matteson, D. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3056–3058.
23. (a) Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* **1999**, 1875–1883. (b) Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8416–8423.
24. Kirchner, K.; Calhorda, M. J.; Schmid, R.; Veiros, L. F. *J. Am. Chem. Soc.* **2003**, *125*, 11721–11729.
25. Yamamoto, Y.; Kinpara, K.; Saigoku, T.; Nishiyama, H.; Itoh, K. *Org. Biomol. Chem.* **2004**, *2*, 1287–1294.
26. Yamamoto, Y.; Ishii, J.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 9625–9631.
27. (a) Miyaura, N.; Suzuki, A. *Chem. Lett.* **1981**, 879–882. (b) Ohe, T.; Ohe, K.; Uemura, S.; Sugita, N. *J. Organomet. Chem.* **1988**, *344*, C5–C7. (c) Cho, C. S.; Ohe, T.; Uemura, S. *J. Organomet. Chem.* **1995**, *496*, 221–226.
28. (a) Sugaya, T.; Kato, N.; Sakaguchi, A.; Tomioka, S. *Synthesis* **1995**, 1257–1262. (b) Liou, M.-J.; Teng, C.-M.; Wu, T.-S. *J. Chin. Chem. Soc.* **2002**, *49*, 1025–1030.
29. (a) Burnett, A. R.; Thomson, R. H. *Phytochemistry* **1968**, *7*, 1421–1422. (b) Mihai, G. G.; Tarassoff, P. G.; Filipescu, N. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1374–1376.
30. Oshima, N.; Suzuki, H.; Moro-oka, Y. *Chem. Lett.* **1984**, 1161–1164.
31. Ukai, T.; Kawazura, T.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253–266.
32. Martín-Matute, B.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2003**, *125*, 5757–5766.
33. Kong, J.; White, C. A.; Krylov, A. I.; Sherrill, D.; Adamson, R. D.; Furlani, T. R.; Lee, M. S.; Lee, A. M.; Gwaltney, S. R.; Adams, T. R.; Ochsenfeld, C.; Gilbert, A. T. B.; Kedziora, G. S.; Rassolov, V. A.; Maurice, D. R.; Nair, N.; Shao, Y.; Besley, N. A.; Maslen, P. E.; Dombroski, J. P.; Daschel, H.; Zhang, W.; Korambath, P. P.; Baker, J.; Byrd, E. F. C.; Voorhis, T. V.; Oumi, M.; Hirata, S.; Hsu, C.-P.; Ishikawa, N.; Florian, J.; Warshel, A.; Johnson, B. G.; Gill, P. M. W.; Head-Gordon, M.; Pople, J. A. *J. Comput. Chem.* **2000**, *21*, 1532–1548.
34. *Spartan'02*, version 1.0.2; Wavefunction, Inc.: Irvine, CA, 2002.
35. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Salvador, P.; Dannenberg, J. J.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.: Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.;

Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.11; Gaussian, Inc.: Pittsburgh PA, 2001.

36. (a) Kohn, W.; Becke, A. D.; Parr, R. G. *J. Phys. Chem.* **1996**, *100*, 12974–12980. (b) Stephen, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. *J. Phys. Chem. Lett.* **1994**, *98*, 11623–11627. (c) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 11623–11627. (d) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.
37. Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299–310.
38. (a) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257–2261. (b) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213–222. (c) Fracl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. *J. Chem. Phys.* **1982**, *77*, 3654–3665.
39. Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *Gaussian NBO*, version 3.1; Gaussian, Inc.: Pittsburgh PA, 2001.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 4306–4316
Tetrahedron

Aromatic homolytic substitution using solid phase synthesis

Steven M. Allin,[a] W. Russell Bowman,[a,*] Rehana Karim[a] and Shahzad S. Rahman[b]

[a]*Department of Chemistry, Loughborough University, Loughborough, Leicestershire LE1 3TU, GB, UK*
[b]*GlaxoSmithKline, New Frontier Science Park North, Harlow, Essex CM19 5AW, GB, UK*

Received 21 December 2005; revised 7 February 2006; accepted 23 February 2006

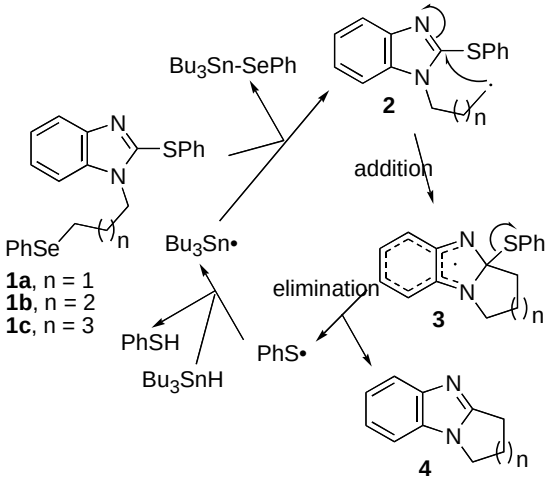
Available online 14 March 2006

Abstract—Solid phase synthesis has been used to carry out intramolecular aromatic homolytic substitution with benzoimidazole precursors. The protocol attaches the radical precursors to the resins via the radical leaving groups (in the aromatic homolytic substitution). When the radical reactions are complete, the leaving group, unaltered starting material and reduced uncylised products remain attached to the resin, which facilitates easy separation of the cyclised products. Novel use of focussed microwave irradiation in solid phase radical reactions drastically shortens the reactions times. Tributylgermanium hydride has been used to replace the toxic and troublesome tributyltin hydride in the radical reactions.

1. Introduction

Solid phase synthesis has become a central tool in organic synthesis. However, there have been surprisingly few applications to radical chemistry. The small amount of literature has been recently reviewed[1] and more recent references continue to show the untapped potential.[2] Solid phase radical reagents have also been developed and show promise. For example, we have recently demonstrated that solid phase triorganogermanium hydride gives good results for a wide range of radical reactions and compares very well with the corresponding solution-phase use of tributyltin or tributylgermanium hydride.[3] Other references to solid phase radical reagents are included in our recent publications.[3,4] We sought to further investigate the potential of radical reactions on solid phase with a view to applications in combinatorial chemistry.

Solid phase synthesis and combinatorial chemistry have centred on the synthesis of heterocycles because of the importance of these compounds to the pharmaceutical industry as likely lead compounds.[5] The use of radical cyclisation for the synthesis of prospective biologically active heterocyclic compounds has also continued to grow in interest.[6] Therefore, in this study we chose radical cyclisation onto benzoimidazoles as a suitable methodology for investigation. We have previously shown that alkyl radical substitution of phenylthiyl radicals at 2-C gave good results and used this in our initial study (Scheme 1).[7]

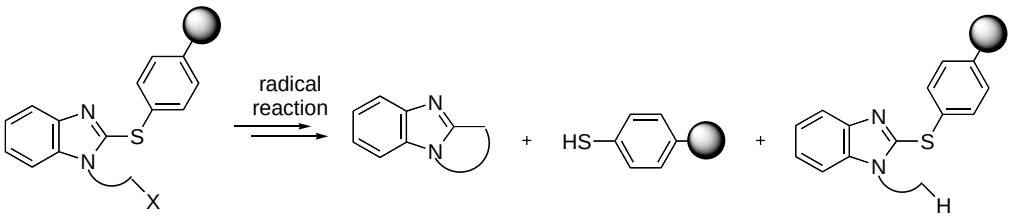


Scheme 1. Homolytic aromatic substitution.

This procedure of intramolecular aromatic homolytic substitution was first developed by Caddick et al. as a novel regioselective methodology for the synthesis of [1,2-*a*]indoles in which SPh, SOPh or SO_2Ar groups on the indole-2-position act as radical leaving groups.[8] Whereas bimolecular homolytic aromatic substitution is relatively unselective and therefore of limited synthetic application, these substitutions are regioselective, controlled by stereo-electronic effects and the good radical leaving groups. Homolytic aromatic substitution has been recently reviewed.[9]

Keywords: Aryl radicals; Radical cyclisation; Solid phase synthesis; Microwave; Benzoimidazoles.
* Corresponding author. Tel.: +44 1509 222569; fax: +44 1509 223925; e-mail: w.r.bowman@lboro.ac.uk

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.071



Scheme 2. Solid phase radical cyclisation protocol.

In our earlier synthetic studies, [1,2-*a*]fused-benzoimidazoles and -imidazoles were synthesised using new methodology.[7] In this procedure, ω-phenylselanyl-alkyl side chains were used in place of ω-bromoalkyl side chains to avoid reaction between the basic benzoimidazole nitrogen atom reacting with alkyl halides. The aromatic homolytic substitution mechanism is shown in Scheme 1. The tributyltin radical ($Bu_3Sn^{\bullet}$) abstracts the phenylselanyl group from the precursor **1** to yield an intermediate radical **2** by an S_H2 mechanism. Cyclisation gives a stabilised σ-complex **3** with the unpaired electron delocalised over the aromatic system. The eliminated phenylsulfanyl radical ($PhS^{\bullet}$) is electrophilic and reacts extremely rapidly with the nucleophilic tributyltin hydride (Bu_3SnH) to complete the chain cycle. This latter process has been termed polarity reversal catalysis (PRC).[10,11]

We sought to use 'building blocks', which could be adapted to combinatorial chemistry. The use of N-alkylation of NH-heteroarenes provides a route for the addition of 'radical' building blocks. The application of *N*-(ω-phenylselanyl)-alkyl 'building blocks' is illustrated in Scheme 1. *N*-(ω-Phenylselanyl)alkyl and *N*-(ω-bromo)alkyl 'building blocks' have also been applied to cyclisation of *N*-(ω-alkyl)-radicals onto pyrroles,[12] imidazoles[12] and pyrazoles[13] with electron withdrawing groups or radical stabilising groups. We have recently shown that 2-(2-bromophenyl)ethyl and 2-(2-bromophenyl)methyl 'building blocks' can be used via aryl radical cyclisation.[11] We sought in the study to use these two groups of building blocks, *N*-(ω-phenylselanyl)alkyl and 2-(2-bromophenyl)alkyl, to explore the use of radicals on solid phase.

The radical reactions were first carried out in solution-phase to determine the best conditions and also to provide an accurate comparison with the equivalent solid phase reactions. The use of the three possible triorgano-metal hydrides, Bu_3SnH, tris-(trimethylsilyl)silane (TTMSS) and tributylgermanium hydride (Bu_3GeH) were investigated. The latter two reagents have the advantage of low toxicity as compared to Bu_3SnH.

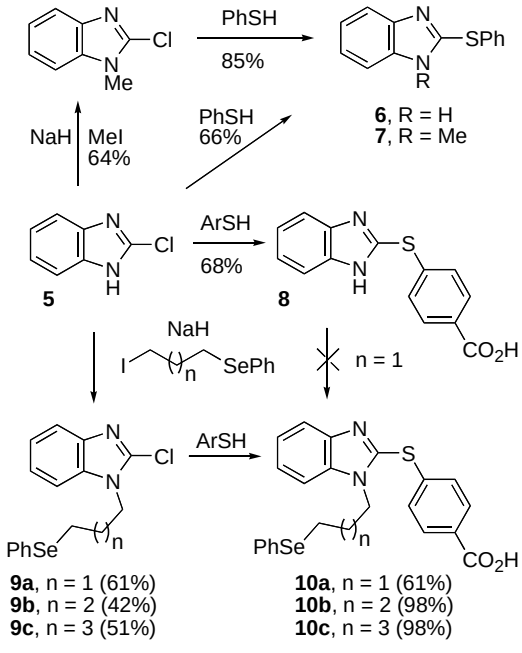
Our studies used the protocol shown in Scheme 2, that is, the radical precursors are attached to the solid phase resin via the arylsulfanyl radical leaving group. The advantage of this protocol is that after the radical reaction, only the cyclised product is released from the resin. Reduced uncyclised products and unaltered starting materials remain attached to the resin and hence do not need to be separated from the desired product. The cyclised benzoimidazoles were separated from the radical reagents by extraction into dilute hydrochloric acid, thereby facilitating a very clean separation.

2. Discussion

2.1. Solution-phase studies with alkyl radicals

Initially, we repeated earlier studies[7] on the cyclisation of the selanides **1a** and **1b** (see Scheme 1) in order to test the conditions for solution-phase homolytic aromatic substitution for comparison with solid phase studies. The five-membered ring cyclisation of **1a** gave low yields (**4a**, 25% as opposed to 49% in earlier studies[7]). Use of hexamethyldiditin did not improve yields of **4a** (26%). The six-membered ring cyclisation of **1b** to **4b** gave much better yields. The best yield (61%) was obtained using acetonitrile as solvent (54% in the earlier study[7]) whereas toluene (**4b**, 25%) and cyclohexane (**4b**, 23%) gave lower yields. Six-membered ring cyclisations onto heteroarene rings are less strained than the five-membered ring cyclisations and hence give higher yields.[7,11–13]

Initially, we synthesised the 2-(phenylsulfanyl)benzoimidazole by lithiation of the 1-trityl protected bezimidazole followed by reaction with diphenyl disulfide. The yields were variable and not suited for the preparation of precursors for solid phase studies. We therefore investigated S_NAr substitution by thiolate of chloride at the 2-C position. 2-Chlorobenzoimidazole **5** is commercially available and cheap. Test reactions showed that chloride was easily replaced from 2-chlorobenzoimidazole or 1-methyl-2-chlorobenzoimidazole (Scheme 3). Potassium hydroxide

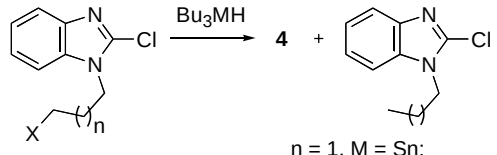


Scheme 3. Synthesis of precursors, ArSH=4-(SH)-$C_6H_4CO_2H$.

(KOH) in ethanol proved best whereas potassium carbonate/acetone, triethylamine/DCM and NaH/DMF gave poor yields. Attempted S_NAr substitution of 1-trityl-2-chlorobenzoimidazole failed, probably due to steric hindrance.

Our original aim was to prepare the benzoimidazole with the linker attached thereby allowing the possibility of alkylation and radical cyclisation on the solid phase resin. S_NAr substitution with the unprotected 2-chlorobenzoimidazole 5 using the solid phase linker, 4-mercaptobenzoic acid, proceeded in a good unoptimised yield (68%) but subsequent alkylations failed (Scheme 3). Alkylation may have been more favourable with the resin acting as protection for the carboxyl group but difficulties were encountered with selectively attaching the 4-mercaptobenzoic acid via the carboxylate to Wang resin. Selective thiol protection followed by attachment also encountered problems. Selective *S*-trityl and *S*-acyl protection of 4-mercaptobenzoic acid gave ca. quantitative yields but trityl removal failed and acyl migration problems were encountered. At this point, we successfully alkylated 2-chlorobenimidazole **5** to afford **9a–c** and carried out the S_NAr substitutions to give **10a–c** in good yields, that is, alkylations were carried out prior to loading on the resins (Scheme 3).

We have also shown that chlorine is a good leaving group and can replace phenylthiyl and phenylsulfonyl groups in intramolecular aromatic homolytic substitutions (Scheme 4). We tested two 2-chlorobenzoimidazoles **9a** and **12** under standard radical cyclisation conditions. The five-membered ring cyclisation again gave a poor yield of cyclisation (10%) with a large amount of uncyclised reduced material **13a** (51%) whereas the six-membered ring cyclisation gave a reasonable yield (54%) with no uncyclised reduced material **13b**. The use of Bu_3GeH allows more time for intermediate radicals to cyclise and syringe pump addition is not required.[3] We suggest that the mechanism is as shown in Scheme 1 (with SPh = Cl).

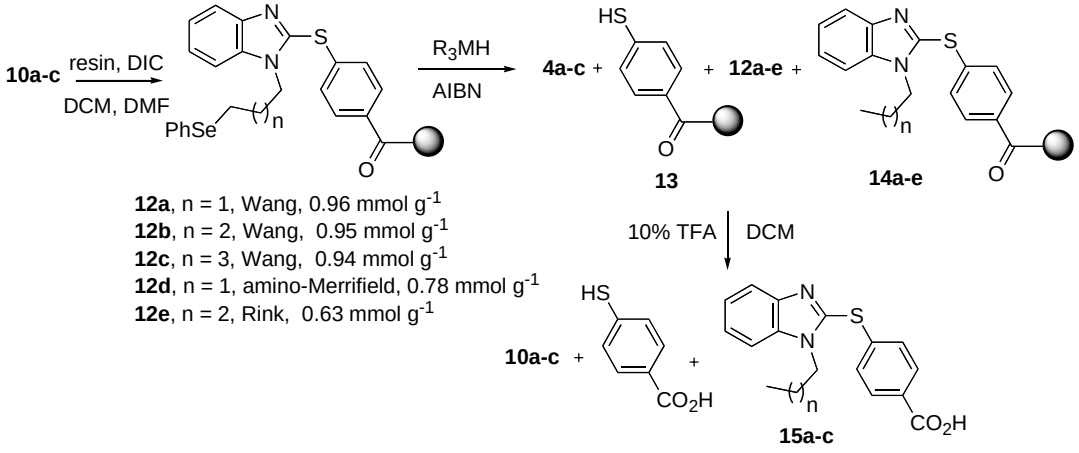


Scheme 4.

2.2. Solid phase studies with alkyl radicals

The alkyl radical precursors (with linker attached) **10a–c** were successfully attached to three resins, Wang, amino-Merrifield and Rink, by standard procedures (Scheme 5). Each loading was assessed by FTIR and MAS (magic angle) ^1H NMR spectroscopy. The FTIR showed formation of an ester linkage for Wang resin attachments. The level of loading was determined by cleavage of the loaded precursor from a portion of each resin. The radical reactions were carried out using a variety of conditions and the results are shown in Table 1. The cyclised products **4a–c** were isolated by filtration of the resin whereas reduced uncyclised products **15a–c** (if formed) and unaltered precursors were cleaved from the resin by TFA hydrolysis and analysed by LCMS and/or isolation. The five-membered ring cyclisation on Wang resin **12a** gave poor yields (maximum 11% yield) as observed for the solution-phase reactions. Slow addition of Bu_3SnH by syringe pump and repeat addition appeared to give better yields. One attempt with the amino-Merrifield precursor **12d** gave very poor yields and was not further investigated.

The six-membered ring cyclisations, as for solution-phase reactions, gave much better yields with the optimised maximum yield of 60%, that is, very similar yields to solution-phase reactions. A more useful comparison would be the solution-phase cyclisation of the carboxylic acids **10a–c** or their respective esters. However, these comparisons were not carried out. Extended addition and reflux times gave much lower yields. The use of TTMSS and Bu_3GeH gave lower yields than Bu_3SnH but further optimisation is needed to determine the relative utility of the three reagents in these reactions. The use of Rink resin in place of Wang resin gave a similar yield of cyclised product **4b** (44%). As for the solution-phase reactions, the seven-membered ring cyclisation also gave very low yields (**4c**, 4%) with largely the reduced uncyclised product (**14c** to **15c**, 72%) being formed.



Scheme 5. Radical reactions on solid phase ($R_3MH = Bu_3SnH$, Bu_3GeH, TTMSS).

Table 1. Radical cyclisation of resin-bound 1-[ω-(phenylselanyl)alkyl]benzoimidazoles **12a–e**

Precursor	Reaction conditions	Yields
12a	Bu_3SnH, syringe pump addition over 26 min, repeat addition after 3 h, AIBN, toluene, reflux, 5 h	**4a** (11%), **10a** and **15a**[a]
12a	Bu_3SnH, syringe pump addition over 2 h, AIBN, benzene, reflux, 5 h	**4a** (5%), **15a**[a]
12a	Bu_3SnH, syringe pump addition over 5 h, repeat addition over 5 h, AIBN, benzene, reflux, 10 h	**4a** (5%), **15a**[a]
12a	Bu_3SnH, syringe pump addition over 7 h, AIBN, benzene, reflux, 10 h	**4a** (3%), **10a** (41%), **15a** (10%)
12a	Bu_3SnH, AIBN, benzene, reflux, 24 or 48 h	**4a** (trace), **15a**[a]
12d	Bu_3SnH, AIBN, benzene, reflux, 18 h	**4a** (trace)
12b	Bu_3SnH, syringe pump addition over 7 h, AIBN, benzene, reflux, 7 h	**4b** (60%), **15b**[a]
12b	Bu_3SnH, syringe pump addition over 2 h, repeat addition after 3 h, AIBN, benzene, reflux, 6.5 h	**4b** (58%, 49%), **15b**[a]
12b	Bu_3SnH, syringe pump addition over 7 h, AIBN, benzene, reflux, 8 h	**4b** (57%), **15b**[a]
12b	Bu_3SnH, syringe pump addition over 7 h, AIBN, benzene, reflux, 7 h	**4b** (49%)
12b	Bu_3SnH, syringe pump addition over 12 h, AIBN, benzene, reflux, 12 h	**4b** (14%), **10b** and**15b**[a]
12b	Bu_3SnH, syringe pump addition over 12 h, AIBN, benzene, reflux, 24 h	**4b** (trace), **10b** and**15b**[a]
12b	Bu_3SnH, AIBN, benzene, reflux, 48 h	**4b** (3%), **10b** and**15b**[a]
12b	Bu_3GeH, AIBN, toluene, reflux, 8 h	**4b** (22%), **10b**[a]
12b	TTMSS, AIBN, benzene, reflux, 10 h	**4b** (20%), **15b**[a]
12b	TTMSS, syringe pump addition over 5 h, AIBN, benzene, reflux, 8 h	**4b** (16%), **15b**[a]
12e	Bu_3SnH, syringe pump addition over 6 h, AIBN, benzene, reflux, 7 h	**4b** (44%), **10b** and **15b**[a]
12c	Bu_3SnH, syringe pump addition over 2.5 h, AIBN, *tert*-butylbenzene, heating at 130 °C, 9 h	**4c** (4%), **15c** (72%)
12c	Bu_3SnH, syringe pump addition over 5 h, AIBN, *tert*-butylbenzene, heating at 130 °C, 10 h	**4c** (2%), **15c**[a]

[a] Qualitative analysis by HPLC.

2.3. Solid phase radical cyclisation using microwave irradiation

We used focussed microwave irradiation to cut down the reactions times of the reactions from hours to minutes (Table 2). Typically, non-radical solid phase reactions using this technique take place in 1–5 min. Although the radical reactions required the longer time of 10–20 min the time is still considerably shorter than the non-irradiated reactions (see Table 1). The technique gave comparable results to the non-irradiated reactions with the highest yield (52%) achieved using a mixture of propan-1-ol and benzene. Propan-1-ol was found to be the most favourable solvent. Polar solvents tend to give the best results with this technique. Propan-1-ol is a reasonably good H-donor, which may account for the formation of the reduced uncyclised (**14b**, and **15b** after cleavage from the resin). However, use of *tert*-butanol, which is not a good H-donor did not improve the yields.

Table 2. Radical cyclisation with Wang resin-bound precursor **12b** using focussed microwave irradiation

Reaction conditions[a]	Yield[b]
10 min, 10 min,[c] 100 °C, PrOH/PhH (1 cm^3 each)	**4b** (52%)[d]
10 min, 10 min,[c] 135 °C, PrOH/PhH (1.25 cm^3 each)	**4b** (44%)[d]
10 min, 135 °C, PrOH/PhH (1.25 cm^3 each)	**4b** (44%)[d]
20 min, 135 °C, PrOH/PhH (1.25 cm^3 each)	**4b** (38%)[d]
10 min, 10 min,[c] 100 °C, *tert*-BuOH/PhH (1.25 cm^3 each)	**4b** (44%)[d]
10 min, 130 °C, PrOH (2.5 cm^3)	**4b** (20%)[d]
10 min, 10 min,[c] 100 °C, MeCN/PhH (1.25 cm^3 each)	**4b** (17%)[d]
10 min, 10 min,[c] 100 °C, DMF/PhH (1.25 cm^3 each)	**4b** (14%)[d]

[a] Bu_3SnH, AMBN [azobismethylisobutyronitrile or by IUPAC nomenclature, 2-(1-cyano-1-methyl-propylazo)-2-methyl-butyronitrile], focussed microwave irradiation.
[b] The % yield of **4b** was measured using ^1H NMR spectroscopy with an internal standard.
[c] Second addition of reagents and further irradiation.
[d] Reduced uncyclised **15b** was observed by LCMS analysis of products cleaved from the resin.

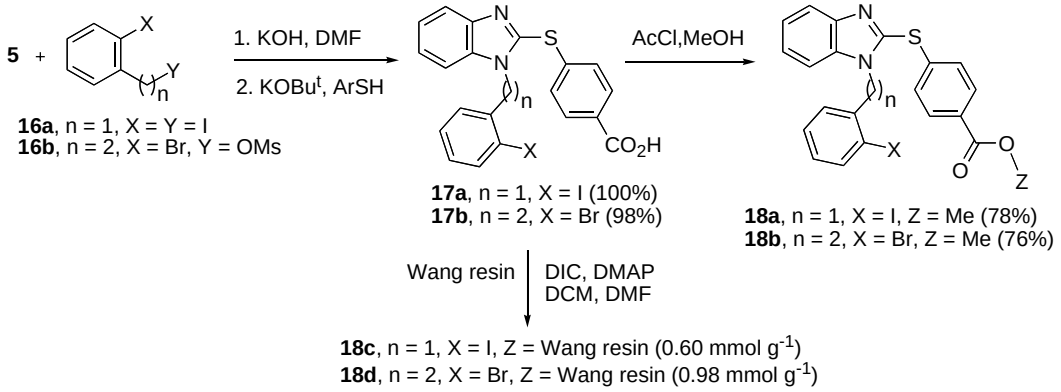
At the time of our study focussed microwave irradiation had not been used for radical reactions on solid phase, but recently an example has been published for the synthesis of oxindoles by 5-*exo* cyclisation of aryl radicals onto α,β-unsaturated amides.[14] We believe that our studies indicate potential for the use of microwave irradiation to shorten reaction times of solid phase radical reactions. Further study should improve yields and determine the most suitable reaction conditions.

The technique was also applied to the five-membered ring cyclisation of the amino-Merrifield bound **12d**. Again, poor results were obtained [**4a** (3%), 20 min, propan-1-ol/benzene, 135 °C] showing no real improvement over the non-irradiated reaction. The cyclisation of the equivalent non-solid phase precursor **10b** under similar condition using microwave irradiation gave inferior yields suggesting that the solid phase reaction may be more efficient [10 min, PrOH/PhH, 1.25 cm^3, Bu_3SnH: (a) AIBN, 135 °C, **4b** (11%), (b) AMBN, 100 °C, **4b** (14%)].

2.4. Solution- and solid phase studies with aryl radicals

With the success of the alkyl radical cyclisation we sought to show that aryl radicals could also be used in solid phase synthesis. 2-(2-Bromophenyl)ethyl and 2-(2-bromophenyl)methyl 'building blocks' have been suceessfully used to generate aryl radicals for cyclisation onto heteroarenes.[11] The same methodology was applied as for the alkyl radicals. The synthesis of aryl radical precursors and attachement to the solid phase is shown in Scheme 6. The methyl esters were prepared for prior testing of the reactions in solution-phase in order to determine the best conditions and to provide an accurate comparison with the equivalent solid phase reactions.

2-Chloro-1*H*-benzoimidazole **5** was alkylated with suitable aryl radical building blocks (**16a** and **16b**) followed by the



Scheme 6. Synthesis of aryl precursors, ArSH=4-(SH)-$C_6H_4CO_2H$.

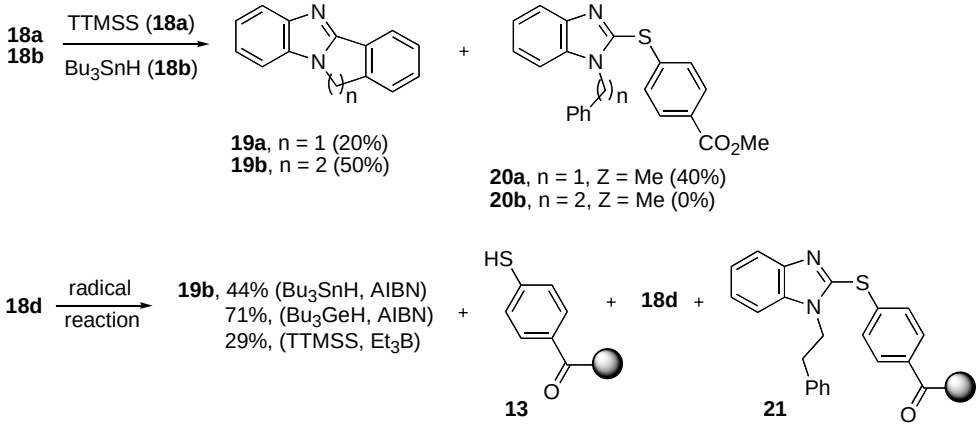
S_NAr protocol using 4-mercaptobenzoic acid to yield **17a** and **17b** in near quantitative yield (Scheme 6). The benzoimidazoles **17a** and **17b** were methylated to provide precursors for the solution studies and attached to Wang resin using carbodiimide-mediated coupling. Good loadings were easily achieved and quantified by cleavage from the resin (TFA/DCM, 9:1) and measurement of the radical precursors. The IR spectrum of the solid supported precursors showed the formation of the ester linkages at 1713 cm^{-1} and MAS ^1H NMR spectra showed complete immobilisation (Scheme 7).

The solution-phase studies were similar to those observed for alkyl radicals. Attempted five-membered cyclisation with the radical precursor **18a** using Bu_3SnH gave only reduced uncyclised material **20a** (60%), even with the use of a syringe pump. However, use of TTMSS, which is a poorer H-donor than Bu_3SnH gave a low yield of the cyclised product **19a** (20%) with **20a** (40%) as the major product. As expected the six-membered cyclisation gave a good yield of cyclised material **19b** (50%) with no traces of the reduced uncyclised product **20b**. The results show that homolytic aromatic substitution by aryl radicals at 2-C of benzoimidazoles is a useful synthetic protocol.

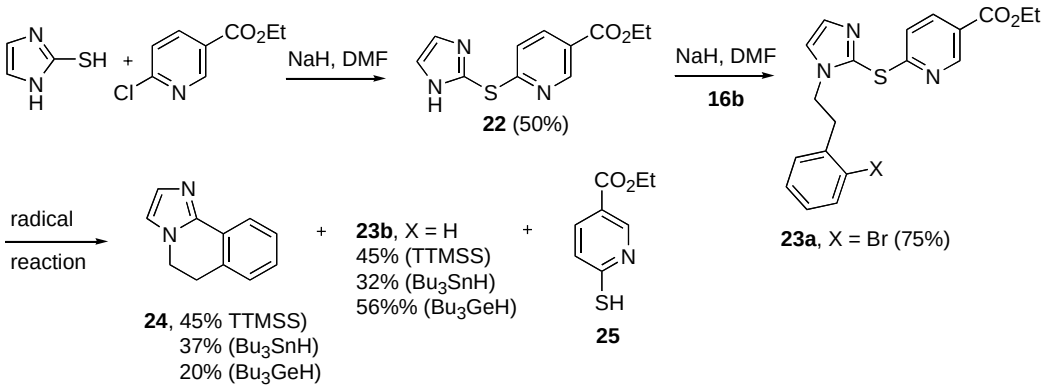
The better yielding six-membered ring cyclisation was chosen for study on solid phase using Wang resin. Syringe pump addition of Bu_3SnH gave the tetracycle **19b** in a reasonable yield (44%). The use of Bu_3GeH proved much more satisafactory with a high yield of **19b** (71%) but TTMSS with Et_3B as initiator at room temperature gave a lower yield (29%). Further optimisation would be likely to give improved yields. The result again illustrates the potential of the non-toxic Bu_3GeH to replace the toxic Bu_3SnH. The by-products were cleaved from the resin and analysed by GC–MS, which showed small amounts of the reduced uncyclised product resulting from **21** and **17b** resulting from unreacted starting material **18d**.

2.5. Homolytic aromatic substitution on imidazole

We had earlier shown that cyclisation via homolytic aromatic substitution onto 2-(phenylsulfanyl)imidazoles gave good yields.[7] We sought to extend the use of the solid phase protocol for the synthesis of bi-and tri-cyclic imidazoles. 2-Chloroimidazole is not readily available so we developed an alternative procedure to widen the scope of our protocol using the cheap and available 2-mercaptoimidazole as shown in Scheme 8. The S_NAr substitution, which is reversed from the previous protocol gave a reasonable yield of **22** (50%), which can be used for a variety of alkylations on the imidazole-NH. The pyridine moiety has a suitable ester handle for attaching to a solid phase resin as required. Alkylation with the 2-(2-bromophenyl)ethyl building block **16b** gave a good yield of a radical precursor for testing the solution-phase cyclisation. Hydrolysis of the ester to the carboxylic acid would facilitate coupling to solid phase resins using carbodiimide coupling.



Scheme 7. Cyclisation of aryl precursors on solid phase.



Scheme 8. Cyclisation of imidazole precursors.

The cyclisation was studied with the precursor **23a** using three radical-mediators of which TTMSS gave the best yield of 5,6-dihydroimidazo[2,1-*a*]isoquinoline **24**. The results show that the pyridine thiol **25** is an equally good radical leaving group in aromatic nucleophilic subsitution to that of the earlier solid phase leaving group **13** or 4-mercaptobenzoic acid methyl ester. TTMSS and Bu_3SnH were added by syringe pump to keep their concentration low to facilitate cyclisation over reduction. The poor result with Bu_3GeH indicates that syringe pump addition is required. Further studies are required to optimise the cyclisation and apply to solid phase synthesis.

3. Conclusions

The solid phase reactions gave very similar yields to equivalent solution-phase reactions indicating the potential use of radical reactions using solid phase synthesis. There does not appear to be any side reactions in the solid phase reactions of the radical intermediates reacting with the resin. We believe that our results give further evidence[1–3] that solid phase synthesis should be fully considered as a useful technique in radical synthesis.

4. Experimental

Commercial dry solvents were used in all reactions except for light petroleum and ethyl acetate, which were distilled from $CaCl_2$ and dichloromethane (DCM) was distilled over phosphorus pentoxide. Light petroleum refers to the bp 40–60 °C fraction. Sodium hydride was obtained as 60% dispersion in oil and was washed with light petroleum. Mps were determined on an Electrothermal 9100 melting point apparatus and are un-corrected. Elemental analyses were determined on a Perkin Elmer 2400 CHN Elemental Analyser in conjunction with a Perkin Elmer AD-4 Autobalance. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer on NaCl plates. ^1H (250 MHz) and ^{13}C (62.5 MHz) NMR spectra were recorded on a Bruker AC-250 spectrometer as solutions of $CDCl_3$ with tetramethylsilane (TMS) as the internal standard for ^1H NMR spectra and deuteriochloroform the standard for ^{13}C NMR spectra unless otherwise specified. Chemical shifts are given in parts per million (ppm) and *J* values in hertz (Hz). MAS Magic angle NMR spectroscopy was carried by GlaxoSmithKline. MAS spectra of the resins were recorded, and again once the radical precursor was loaded. Mass spectra were recorded on a JEOL SX102 mass spectrometer or carried out by the EPSRC Mass Spectrometry Service at University of Wales, Swansea. All mass spectra are electron impact spectra (EI) unless otherwise stated. TLC using silica gel as absorbent was carried out with aluminium backed plates coated with silica gel (Merck Kieselgel 60 F254). Column chromatography was carried out using neutral alumina unless otherwise specified.

1-Iodo-3-(phenylselanyl)propane **11a**,[7] 1-iodo-4-(phenylselanyl)butane **11b**,[7] 1-iodo-5-(phenylselanyl)pentane **11c**,[7] 1*H*-benzo[*d*]imidazol-2-yl phenyl sulfide **6**,[7] 1-[3-(phenylselanyl)propyl]-2-(phenylsulfanyl)-1*H*-benzo[*d*]imidazole **1a**,[7] 1-[4-(phenylselanyl)butyl]-2-(phenylsulfanyl)-1*H*-benzo[*d*]imidazole **1b**,[7] 1-iodo-2-(iodomethyl)benzene **16a**,[11] 2-(2-bromophenyl)ethyl methanesulfonate **16b**[11] and tributylgermanium hydride[4] were prepared by literature procedures.

4.1. General procedure for radical cyclisations. 2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole 4a

4.1.1. Tributyltin hydride. A solution of tributyltin hydride (0.83 cm^3, 3.1 mmol) in toluene (50 cm^3) was added to 1-[3-(phenylselanyl)propyl]-2-(phenylsulfanyl)-1*H*-benzo[*d*]-imidazole **1a** (0.60 g, 1.4 mmol) in toluene (150 cm^3) at reflux over 5 h using a syringe pump. AIBN (0.16 g, 1.4 mmol) was added to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for a further 1 h. Dil, hydrochloric acid was added to the cooled reaction mixture to extract the protonated benzoimidazole compounds into the aqueous layer and washed with light petroleum to remove Bu_3Sn-residues. The acidic aqueous layer was basified with sodium carbonate followed by aqueous sodium hydroxide (few drops) to pH 14. The basic solution was extracted with DCM, and evaporated under reduced pressure to give a pale yellow oil crude product. The residue was purified by column chromatography using silica gel as absorbent with light petroleum and ethyl acetate as eluents to give 2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole **4a** as white crystals (57 mg, 0.36 mmol, 25%), mp 105–107 °C (lit.[7] mp 114–115 °C); δ_H 2.70 (2H, quintet, $J=7.4$ Hz, 2-H), 3.05 (2H, t, $J=7.6$ Hz, 3-C), 4.1 (2H, t, $J=7.2$ Hz, 1-C), 7.25–7.40 (3H, m, ArH) and 7.67–7.73 (1H, m, ArH).

The spectroscopic data were identical to those reported in the literature.[7]

4.1.2. Hexamethylditin. The reaction mixture of 1-[3-(phenylselanyl)propyl]-2-(phenylsulfanyl)-1*H*-benzo[*d*]-imidazole **1a** (89 mg, 0.21 mmol) and hexamethylditin (114 mg, 0.35 mmol) in *tert*-butylbenzene (10.0 cm^3) was irradiated with a sun lamp at 85 °C for 30 h. The work-up was carried out as in the previous experiment to give 2,3-dihydro-1*H*-benzo[*d*]pyrrolo[1,2-*a*]imidazole **4a** (26%).

4.1.3. 1,2,3,4-Tetrahydrobenzo[4,5]imidazo[1,2-*a*]-pyridine 4b. 1-[4-(Phenylselanyl)butyl]-2-(phenylsulfanyl)-1*H*-benzo[*d*]imidazole **1b** was reacted using the general procedure for radical cyclisations except that acetonitrile was used in place of toluene to yield 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridine **4b** as colourless crystals (61%), mp 96–100 °C (lit.[7] mp 99.8–100.1 °C). The spectroscopic data were identical to the reported data.[7]

4.2. General procedure for alkylation

The azole was added slowly to a suspension of NaH (1.15 equiv) in dry THF (240 cm^3). The mixture was stirred and heated at 80 °C for 1 h. A solution of the alkylating agent (1.5 equiv) in THF (10 cm^3) was added dropwise to the reaction mixture, which was heated under reflux for a further 2 h. The salts were removed by filtration on a Celite bed and the solution evaporated under reduced pressure to yield the crude product. The crude product was purified by column chromatography using light petroleum–ethyl acetate (1/4) as the eluent.

4.2.1. 2-Chloro-1-[(3-phenylselanyl)propyl]-1*H*-benzo-[*d*]imidazole 9a. 2-Chlorobenzoimidazole (2.00 g, 13.1 mmol) and 1-iodo-3-(phenylselanyl)propane **11a** gave 2-chloro-1-[(3-phenylselanyl)propyl]-1*H*-benzo[*d*]-imidazole **9a** as a pale yellow oil (2.79 g, 8.0 mmol, 61%) (Found: C, 55.38; H, 4.40; N, 7.94 requires C, 54.95; H, 4.32; N, 8.01%); ν_{max} (neat)/cm^{-1} 2930, 1615, 1578, 1469, 1450, 1375, 1329, 1247, 1154, 1022, 761, 740 and 691; δ_H 2.12–2.33 (2H, m, CH_2), 2.88 (2H, t, J=6.9 Hz, CH_2Se), 4.28 (2H, t, J=7.1 Hz, CH_2N), 7.20–7.23 (6H, m, ArH), 7.43–7.45 (2H, m, ArH) and 7.65–7.68 (1H, m, ArH); δ_C 24.1 (CH_2), 29.3 (CH_2Se), 43.8 (CH_2N), 109.4 and 119.5 (4- and 7-C), 122.7 and 123.2 (5- and 6-C), 127.3 (PhCH), 129.1 (Ph 1-C), 129.2 (PhCH), 133.0 (PhCH), 135.0, 140.3 and 141.7 (2-3a, 7a-C); *m*/*z* EI 350 (M^+, 43%) (Found: M^+, 350.0091. $C_{16}H_{15}ClN_2Se$ requires 350.0089), 315 (55), 165 (62), 91 (100) and 77 (29).

4.3. General procedure for S_NAr substitution at 2-C

4.3.1. 1-Methyl-1*H*-benzo[*d*]imidazol-2-yl phenyl sulfide 7. Benzenethiol (0.31 cm^3, 3.0 mmol) was dissolved in a solution of KOH (0.17 g, 3.0 mmol) in EtOH (30 cm^3) and the mixture was stirred for 5 min. 2-Chloro-1-methyl-1*H*-benzoimidazole (0.50 g, 3.0 mmol) was added to the reaction mixture and the reaction mixture heated under reflux for 18 h. The reaction mixture was filtered and evaporated under reduced pressure to give 1-methyl-1*H*-benzo[*d*]imidazol-2-yl phenyl sulfide **7** as colourless crystals (0.62 g, 2.6 mmol, 85%), mp 66–69 °C (Found: M^+, 240.0726. $C_{14}H_{12}N_2S$ requires 240.0721); ν_{max} (KBr)/cm^{-1} 2373, 1577, 1441, 1409, 1324, 1276, 1078 and 739; δ_H 3.69 (3H, m, CH_3), 7.20–7.29 (6H, m), 7.34 (2H, dd, J=8.2, 1.1 Hz) and 7.75–7.77 (1H, m); δ_C 30.7 (CH_3), 109.4 and 119.8 (4- and 7-C), 122.4 and 123.2 (5- and 6-C), 127.6 (ArCH), 129.4 (ArCH), 130.2 (ArCH), 132.1 and 136.5 (3a- and 7a-C), 143.1 (Ph 1-C) and 147.6 (2-C); *m*/*z* EI 239 (M^+, 100%), 224 (11), 207 (14), 91 (14) and 77 (15).

4.3.2. 4-[(1*H*-Benzo[*d*]imidazol-2-yl)sulfanyl]benzoic acid 8. 4-Mercaptobenzoic acid and 2-chlorobenzoimidazole **5** gave **8** as colourless crystals (68%), mp 270–275 °C (Found: MH^+, 271.0541. $C_{14}H_{10}N_2O_2S$ requires 271.0544); ν_{max} (DCM)/cm^{-1} 3500, 3054, 2987, 1690, 1593, 1567, 1506, 1423 and 1265; δ_H (DMSO-d_6) 7.23–7.26 (2H, m, benzoimidazole 5-H and 6-H), 7.51 (2H, d, J=8.2 Hz, 3- and 5-H), 7.50–7.70 (2H, m, benzoimidazole 4- and 7-H) and 7.94 (2H, d, J=8.3 Hz, 2- and 6-H); δ_C (DMSO-d_6) 122.0 (benzoimidazole 4- and 7-C), 126.5 (benzoimidazole 5- and 6-C), 129.5 (3- and 5-C), 130.1 (1-C), 130.6 (2- and 6-C), 138.6 (4-C), 144.79 (benzoimidazole 2-C) and 167.1 (C=O); *m*/*z* EI 270 (M^+, 72%), 269 (100), 225 (15), 150 (16), 77 (18) and 44 (91).

4.3.3. Radical cyclisation of 1-(4-bromobutyl)-2-chloro-1*H*-benzo-[*d*]imidazole 12b. Tributylgermanium hydride (0.56 cm^3, 2.16 mmol) was added to 1-(4-bromobutyl)-2-chloro-1*H*-benzo[*d*]imidazole **12b** (0.31 g, 1.1 mmol) in toluene (100 cm^3) followed by portion wise addition of AIBN (0.35 g, 2.2 mmol) to the refluxing reaction mixture at equal intervals. The solution was stirred and heated under reflux for 12 h. The reaction mixture was evaporated under reduced pressure to yield a crude product, which was purified by column chromatography with light petroleum and ethyl acetate as eluents to give 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridine **4b** as colourless crystals (0.10 g, 0.58 mmol, 54%); ν_{max} (KBr)/cm^{-1} 1610, 1505, 1425, 1397, 1328, 1278 and 745; δ_H 1.98–2.09 (2H, m, 3-H), 2.10–2.13 (2H, m, 2-H), 3.09 (2H, t, J=7.0 Hz, 4-H), 4.06 (2H, t, J=7.0 Hz, 1-H), 7.21–7.30 (3H, m, ArH) and 7.66–7.69 (1H, m, ArH). The data was identical to data reported in the literature.[7]

4.4. Loading of alkyl radical precursors onto resins

4.4.1. General procedure. Wang resin-bound benzoimidazole 12a. DCM (20 cm^3) was added to a portion of Wang resin (1.0 g, 1.7 mmol) and the resin was left to swell for 1 h under an atmosphere of nitrogen. 4-({1-[3-Phenylselanyl)-propyl]-1*H*-benzo[*d*]imidazol-2-yl}sulfanyl)benzoic acid **10a** (0.55 g, 1.2 mmol), DMAP (0.36 g, 2.9 mmol) and DIC (1.0 cm^3, 5.8 mmol) were added sequentially. The suspension was shaken for 48 h at room temperature. The reaction mixture was filtered and washed with DCM, MeOH, DMF, MeOH and DCM (20 cm^3 each). The resin was dried at 40 °C under vacuum for 24 h. The coupling reaction was repeated. The (MAS) magic angle ^1H NMR spectrum showed complete immobilisation of **10a** onto the Wang resin. FTIR ν_{max} (KBr)/cm^{-1} 3025, 2920, 1713, 1591, 1511, 1447, 1265, 1173, 1097, 1010, 822, 738 and 693.

4.4.2. Wang resin-bound benzoimidazole 12b. The (MAS) magic angle ^{1}H NMR spectrum showed complete immobilisation of the compound onto the Wang resin. FTIR ν_{max} (KBr)/cm^{-1} 3026, 2921, 2363, 1713, 1591, 1512, 1447, 1356, 1265, 1173, 1097, 1011, 822, 739 and 694.

4.4.3. Wang resin-bound benzoimidazole 12c. The (MAS) magic angle ^{1}H NMR spectrum showed complete immobilisation of the compound onto the Wang resin. FTIR ν_{max} (KBr)/cm^{-1} 3024, 2921, 2851, 1943, 1717, 1592, 1511, 1451, 1421, 1374, 1353, 1266, 1238, 1173, 1098, 1013, 824, 758, 738 and 697.

4.4.4. Amino-Merrifield resin-bound benzoimidazole 12d. FTIR ν_{max} (KBr)/cm^{-1} 3424, 3024, 2923, 1655, 1594, 1511, 1478, 1422, 1245, 1014, 838, 736 and 691.

4.4.5. Rink resin-bound benzoimidazole 12e. DCM (15 cm^3) was added to a portion of Rink resin (0.62 g, 0.5 mmol). The resin was left to swell for 1 h under an atmosphere of nitrogen. 4-({1-[4-Phenylselanyl)butyl]-1*H*-benzo[*d*]imidazol-2-yl}sulfanyl)benzoic acid **10b** (0.3 g, 0.6 mmol), HOAT (0.25 g, 1.8 mmol) and DIC (0.5 cm^3, 3.15 mmol) were added sequentially. The suspension was shaken for 48 h at room temperature. The reaction mixture was filtered and washed with DCM, MeOH, DMF, MeOH and DCM (20 cm^3 each). The resin was dried at 40 °C under vacuum for 24 h. The coupling reaction was repeated with equimolar reagents. The (MAS) magic angle ^{1}H NMR spectrum showed immobilisation of the compound onto the Rink resin. FTIR ν_{max} (KBr)/cm^{-1} 3413, 2921, 1659, 1503, 1349, 1207, 1026, 827, 742 and 695.

4.5. Radical cyclisations of resin-bound 1-[ω-(phenylselanyl)]benzoimidazoles

4.5.1. General procedure. Radical cyclisation of Wang resin-bound 12a. A solution of Bu_3SnH (0.10 cm^3, 0.4 mmol) and AIBN (26 mg, 0.16 mmol) in toluene (2.0 cm^3) was added to refluxing suspension of resin-bound benzoimidazole **12a** (170 mg, 0.16 mmol) in toluene (4.0 cm^3) over 26 min using a syringe pump. The reaction was stirred at reflux for 3 h and then a further portion of Bu_3SnH and AIBN in toluene (1 cm^3) was added over 5 min and the reaction mixture was heated under reflux for a further 1.5 h. The reaction mixture was filtered and the resin washed with toluene, DCM and MeOH (20 cm^3 each). The resin was dried at 40 °C under vacuum for 24 h. The LCMS analysis of the filtrate showed cyclised product **4a** (3 mg, 0.018 mmol, 11%). The remaining products were cleaved from the resin using 10% TFA in DCM. The LCMS analysis of the cleaved sample from the resin showed the reduced product **15a**. **4a** was isolated and characterised. All data were identical to aunthentic material.

The reaction was repeated under different conditions. The conditions and yields are reported in Table 1.

4.5.2. Radical cyclisations of resin-bound 12b. The general procedure was used with Wang and Rink resins. The different conditions and yields are reported in Table 1. 1,2,3,4-Tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridine **4b** was isolated by HPLC and characterised in each case. The data were identical to authentic material. In several reactions the reduced uncyclised 4-[(1-butyl-1*H*-benzo[*d*]-imidazol-2-yl)sulfanyl]benzoic acid **15b** was isolated using HPLC and characterised. (Found: MH$^+$, 327.1170. $C_{18}H_{18}N_2O_2S$ requires 327.1167); ν_{max} (KBr)/cm^{-1} 3490, 2934, 2363, 1700, 1594, 1420, 1364, 1258, 1199, 1179, 1122 and 1017; δ_H (DMSO-d_6) 0.78 (3H, t, J=7.4 Hz, CH_3), 1.16–1.25 (2H, m, CH_2), 1.56–1.63 (2H, m, CH_2), 4.27 (2H, t, J=7.3 Hz, NCH_2), 7.23–7.31 (2H, m, ArH), 7.43 (2H, d, J=6.6 Hz, 3-H and 5-H), 7.62–7.65 (2H, m, ArH) and 7.88 (2H, d, J=6.4 Hz, 2-H and 6-H); δ_C (DMSO-d_6) 13.4 (Me), 19.3 (CH_2), 31.3 (CH_2), 44.0 (NCH_2), 110.9 and 119.0 (benzoimidazole 4- and 7-C), 122.4 and 123.3 (benzoimidazole 5- and 6-C), 128.9 (ArCH), 129.7 (1-C), 130.3 (ArCH), 135.6 (benzoimidazole 7a-C), 138.1 (4-C), 142.5 (benzoimidazole 3a-C), 145.1 (benzoimidazole 2-C) and 166.6 (C=O); *m/z* (FAB) 327 (MH$^+$, 100%), 271 (12), 176 (12), 154 (33) and 136 (31).

4.5.3. Radical cyclisations of Wang resin-bound benzoimidazole 12c. The general procedure for radical reactions of resin-bound precursors was used and the conditions and results are reported in Table 1. 7,8,9,10-Tetrahydro-6*H*-benzo[4,5]imidazo[1,2-*a*]-azepine **4c** was analysed by ^{1}H NMR spectroscopy using an internal standard. The data were indentical to those reported in the literature.[7] 4-[(1-Pentyl-1*H*-benzo[*d*]imidazol-2-yl)sulfanyl]benzoic acid **15c** was isolated and characterised. (Found: M$^+$, 340.1242. $C_{19}H_{20}N_2O_2S$ requires 340.1246); ν_{max} (KBr)/cm^{-1} 3056, 2928, 2477, 1910, 1689, 1596, 1463, 1385, 1272, 1115, 1007, 836 and 742; δ_H (DMSO-d_6) 0.76 (3H, t, J=6.9 Hz, CH_3), 1.15–1.24 (4H, m, CH_2CH_2), 1.62–1.68 (2H, m, CH_2), 4.28 (2H, t, J=7.3 Hz, NCH_2), 7.26 (1H, t, J=8.1 Hz, ArH), 7.31 (1H, t, J=7.9 Hz, ArH), 7.44 (2H, d, J=7.7 Hz, 3-H and 5-H), 7.64 (1H, d, J=8.0 Hz, benzoimidazole 7-H), 7.67 (1H, d, J=7.9 Hz, benzoimidazole 4-H) and 7.91 (2H, d, J=6.7 Hz, 2-H and 6-H); δ_C (DMSO-d_6) 13.6 (CH_3), 21.6 (CH_2), 28.1 (CH_2), 28.8 (CH_2), 44.1 (NCH_2), 110.8 and 119.1 (benzoimidazole 4- and 7-C), 122.2 and 123.2 (benzoimidazole 5- and 6-C), 128.7 (ArCH), 130.0 (1-C), 130.2 (ArCH), 135.6 and 138.2 (benzoimidazole 3a- and 7a-C), 142.7 (4-C), 144.9 (benzoimidazole 2-C) and 166.5 (C=O); *m/z* 339 (M$^+$, 100%), 307 (14), 297 (34), 269 (86), 225 (26), 187 (28), 150 (30), 131 (24) and 73 (28).

4.5.4. Radical cyclisation of Wang resin-bound 12b using microwave irradiation. General method. A suspension of the Wang resin-bound **12b** (22 mg, 0.021 mmol) was prepared in propan-1-ol/benzene (1.25 cm^3 of each) was prepared in a microwave pyrex tube. Bu_3SnH (3.57 equiv) and AIBN (3.57 equiv) were added and the pyrex tube sealed and placed in an automated microwave apparatus (Smiths Personnel Chemistry Synthesiser). This synthesiser has an integrated liquid handler, which facilitates automated microwave reactions for up to 96 separate reaction vessels. The sample was irradiated for 10 min at 100 °C. A second addition of reagents the sample was carried out and the reaction irradiated for another 10 min. After 20 min the reaction vessel was removed from the microwave apparatus, cooled to room temperature and unsealed. The reaction mixture was filtered and washed with toluene, DCM and MeOH (20 cm^3 each). LCMS analysis of the filtrate showed

only the presence of the cyclised product 1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridine **4b** (52%) and tributyltin residues. The yield was determined by ^{1}H NMR spectroscopy using the internal standard.

The reaction was repeated under various conditions to optimise the yield and minimise the time. Conditions and yields of reactions are reported in Table 2 and the discussion.

4.6. Alkylations of 2-chloro-1*H*-benzo[*d*]imidazole

4.6.1. 2-Chloro-1-[(2-iodophenyl)methyl]-1*H*-benzo[*d*]-imidazole. (3.00 g, 19.7 mmol) was added to a vigorously stirred suspension of ground potassium hydroxide (3.30 g, 59.0 mmol) in dry DMF (80 cm^3) and stirred for 30 min. 1-Iodo-2-(iodomethyl)benzene **16a** (13.53 g, 39.3 mmol) was added in one portion. The reaction was stirred for 24 h, partitioned between ethyl acetate and water and the organic layer was removed. The organic extract was washed with water followed by brine, dried and evaporated under reduced pressure. The residue was purified by column chromatography using neutral alumina as absorbent and light petroleum–ethyl acetate (4/1) as eluents to afford 2-chloro-1-[(2-iodophenyl)methyl]-1*H*-benzo[*d*]imidazole as cream coloured crystals (6.87 g, 18.7 mmol, 95%), mp 106.2–109.3 °C (Found: M$^+$, 367.9573. $C_{14}H_{10}ClIN_2$ requires 367.9577); ν_{max} (KBr)/cm^{-1} 3059, 2920, 1700, 1615, 1455, 1428, 1329, 1282, 1240, 1198, 1013, 986, 749 and 650; δ_H 5.38 (2H, s, CH_2), 6.48 (1H, d, J=8.0 Hz), 7.00 (1H, dd, J=8.0, 8.0 Hz), 7.08–7.34 (4H, m), 7.75 (1H, d, J=8.0 Hz) and 7.91 (1H, d, J=8.0 Hz); δ_C 52.9 (CH_2), 96.7 (Ar 2-C), 109.9 (CH), 119.7 (CH), 123.1 (CH), 123.6 (CH), 126.6 (CH), 128.9 (CH), 130.1 (CH), 135.0 (3a-C), 136.8 (7a-C), 139.7 (CH), 141.0 (2-C) and 141.8 (Ar 1-C); *m*/*z* (EI) 368 (M$^+$, 62%), 241 (35), 217 (100), 205 (13), 152 (19) and 90 (47).

4.6.2. 1-[2-(2-Bromophenyl)ethyl]-2-chloro-1*H*-benzo-[*d*]imidazole. The general procedure for alkylation was used with 2-chlorobenzoimidazole and 2-(2-bromophenyl)-ethyl methanesulfonate **16b** to afford 1-[2-(2-bromophenyl) ethyl]-2-chloro-1*H*-benzo[*d*]imidazole as cream coloured crystals (98%), mp 73.5–75.4 °C (Found: M$^+$, 333.9871. $C_{15}H_{12}BrClN_2$ requires 333.9872); ν_{max} (KBr)/cm^{-1} 3042, 2932, 1614, 1473, 1452, 1378, 1357, 1329, 1329, 1263, 1170, 1032, 1004, 758, 746, 729 and 655; δ_H 3.20 (2H, t, J=7.3 Hz, CH_2), 4.40 (2H, t, J=7.3 Hz, NCH_2), 6.89 (1H, t, J=6.5 Hz), 7.05–7.10 (2H, m), 7.22–7.23 (3H, m), 7.51–7.54 (1H, t, J=8.0 Hz) and 7.64–7.68 (1H, m); δ_C 35.9 (CH_2), 43.8 (NCH_2), 109.3 (CH), 119.4 (CH), 122.6 (CH), 123.1 (CH), 124.4 (C), 127.8 (CH), 128.9 (CH), 131.1 (CH), 133.0 (CH), 134.9 (C), 136.4 (C), 140.4 (C) and 141.6 (C); *m*/*z* (EI) 334 (M$^+$, 22%), 255 (11), 182 (45), 165 (100), 129 (27), 90 (34) and 70 (32).

4.7. S_NAr substitutions with 4-mercaptobenzoic acid

4.7.1. 4-({1-[(2-Iodophenyl)methyl]-1*H*-benzo[*d*]imidazol-2-yl}sulfanyl)benzene-1-carboxylic acid 17a. 4-Mercaptobenzoic acid (1.54 g, 10.0 mmol) was dissolved in EtOH (60 cm^3) followed by potassium *tert*-butoxide (1.70 g, 15.2 mmol) and the mixture was stirred for 5 min. 2-Chloro-1-[(2-iodophenyl)methyl]-1*H*-benzo[*d*]imidazole (3.74 g, 10.1 mmol) was added to the reaction mixture and heated under reflux overnight. The reaction mixture was filtered and evaporated to dryness to give the crude product, which was purified by column chromatography using silica gel as absorbent and light petroleum–ethyl acetate (1/1) as eluents to afford the benzoimidazole **17a** as pale yellow crystals (4.88 g, 10.0 mmol, 99%), mp 98.2–103.5 °C (Found: M$^+$, 485.9915. $C_{21}H_{15}IN_2O_2S$ requires 485.9905); ν_{max} (KBr)/cm^{-1} 3382, 3056, 2964, 1924, 1695, 1591, 1544, 1434, 1385, 1271, 1185, 838 and 734; δ_H 5.49 (2H, s, CH_2), 6.31 (1H, dd, J=7.6, 1.4 Hz, CH), 7.02 (1H, ddd, J=7.6, 7.6, 1.4 Hz, CH), 7.19 (1H, ddd, J=7.6, 7.6, 1.4 Hz, CH), 7.25–7.28 (2H, m, CH), 7.34 (2H, dd, J=6.6, 1.7 Hz, 3-H and 5-H), 7.40–7.44 (1H, m, CH), 7.69–7.73 (1H, m, CH), 7.81 (2H, dd, J=6.6, 1.7 Hz, 2-H and 6-H), and 7.91 (1H, dd, J=7.6, 1.0 Hz, CH); δ_C 52.8 (CH_2), 98.0 (C–I), 111.1 (CH), 119.5 (CH), 122.8 (CH), 123.8 (CH), 126.8 (CH), 129.0 (CH), 129.9 (CH), 129.9 (CH), 130.4 (CH), 133.0 (C), 136.3 (C), 137.8 (C), 138.3 (C), 139.7 (CH), 143.2 (C), 147.9 (C) and 167.9 (C=O); *m*/*z* (EI) 486 (M$^+$, 4%), 465 (48), 431 (8), 378 (7), 262 (22), 217 (100), 178 (20), 154 (50), 90 (61) and 73 (58).

4.8. Methylation of aryl radical precursors

4.8.1. Methyl 4-({1-[(2-iodophenyl)methyl]-1*H*-benzo-[*d*]imidazol-2-yl}sulfanyl)benzene-1-carboxylate 18a. Acetyl chloride (2.0 cm^3, 28.0 mmol) was added dropwise over 10 min to MeOH (25 cm^3) cooled in an ice bath. The solution was stirred for 5 min and 4-({1-[(2-iodophenyl)-methyl]-1*H*-benzo[*d*]imidazol-2-yl}sulfanyl)benzene-1-carboxylic acid (0.62 g, 1.3 mmol) was added in one portion and the solution heated under reflux for 18 h. The solution was cooled and evaporated under reduced pressure to give the crude methyl ester hydrochloride. Water was added to the crude and the aqueous layer was basified to pH 14 with sodium carbonate and aqueous sodium hydroxide solution. The basic solution was extracted with DCM. The organic extracts were dried and evaporated under reduced pressure. The residue was purified by column chromatography using neutral alumina as absorbent and light petroleum–ethyl acetate (1/1) as eluents to afford methyl ester **18a** as colourless crystals (0.5 g, 1.0 mmol, 78%), mp 179.1–181.2 °C (Found: MH$^+$, 501.0131. $C_{22}H_{17}IN_2O_2S$ requires 501.0134); ν_{max} (KBr)/cm^{-1} 2940, 1713, 1589, 1544, 1428, 1351, 1277, 1107, 1012, 841, 824, 748 and 689; δ_H 3.79 (3H, s, CH_3), 5.33 (2H, s, CH_2), 6.19 (1H, d, J=7.2 Hz), 6.81 (1H, dd, J=7.6, 1.0 Hz), 6.94 (1H, dd, J=7.6, 1.0 Hz), 7.07 (1H, d, J=7.6 Hz), 7.17–7.27 (2H, m), 7.30 (2H, d, J=8.6 Hz, 3-H and 5-H), 7.72–7.74 (2H, m) and 7.76 (2H, d, J=8.6 Hz, 2-H and 6-H); δ_C 51.2 (CH_3), 52.3 (CH_2), 95.8 (C-I), 109.2 (CH), 119.3 (CH), 122.1 (CH), 123.1 (CH), 125.6 (CH), 127.6 (CH), 128.1 (1-C), 128.3 (6-C), 128.4 (CH), 129.3 (CH), 134.8 (CH), 136.2 (3a-C), 137.0 (7a-C), 138.5 (CH), 142.3 (benzoimidazole 2-C), 145.5 (1-C) and 165.2 (C=O); *m*/*z* (FAB) 501 (MH$^+$, 32%), 327 (19), 281 (22), 217 (40), 147 (54) and 136 (100).

4.9. Radical cyclisations of methyl esters 18a and 18b

4.9.1. 5,6-Dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinoline 19b. The general procedure for radical cyclisations was carried out with the methyl ester **18b** with Bu_3SnH added at

reflux over 5 h using a syringe pump. The solution was stirred and heated under reflux for a further 3 h. Colourless crystals (50%), mp 125.0–130.0 °C (Found: M^+, 220.1000. $C_{15}H_{12}N_2$ requires 220.1001); ν_{max} (KBr)/cm^{-1} 2922, 2370, 2344, 1480, 1458, 1406, 1325, 1171 and 736; δ_H 3.30 (2H, t, J=6.9 Hz, 5-H), 4.35 (2H, t, J=6.9 Hz, 6-H), 7.26–7.43 (6H, m, ArH), 7.81–7.85 (1H, m, ArH) and 8.29–8.32 (1H, m, ArH); δ_C 28.3 (5-C), 40.4 (6-C), 109.0 (CH), 119.8 (CH), 122.5 (CH), 122.7 (CH), 125.7 (CH), 126.6 (12b-C), 127.8 (CH), 128.1 (CH), 130.2 (CH), 134.3 (C), 134.6 (C), 143.9 (C) and 149.1 (C); *m/z* (EI) 220 (M^+, 100%), 109 (9), 86 (10) and 77 (9).

4.9.2. 11*H*-Benzo[4,5]imidazo[1,2-*a*]isoindole 19a. The general procedure for radical cyclisations was carried out with the methyl ester **18a** with TTMSS instead of Bu_3SnH to afford the tetracycle **19a** as colourless crystals (20%), mp 144.0–149.0 °C (Found: M^+, 206.0841. $C_{14}H_{10}N_2$ requires 206.0844); ν_{max} (KBr)/cm^{-1} 2927, 2367, 1657, 1433, 1399, 1269 and 740; δ_H 5.27 (2H, s, CH_2), 7.26–7.42 (7H, m, ArH) and 7.70–7.72 (1H, m, ArH); δ_C 46.2 (CH_2), 108.3 (CH), 118.9 (CH), 122.1 (CH), 122.6 (CH), 123.4 (C), 127.1 (CH), 127.5 (CH), 127.8 (CH), 128.8 (CH), 129.1 (C), 134.7 (C), 134.7 (C) and 143.9 (C); *m/z* (EI) 206 (M^+, 46%), 149 (17), 119 (8), 91 (16) and 77 (18). The reduced uncyclised 4-[(1-benzyl-1*H*-benzo[*d*]imidazole-2-yl)sulfanyl]benzene-1-carboxylate **20a** was also isolated as a pale yellow oil (40%) (Found: M^+, 375.1167. $C_{22}H_{18}N_2O_2S$ requires 375.1167); ν_{max} (KBr)/cm^{-1} 2950, 1721, 1594, 1434, 1350, 1276, 1181, 1108, 1016, 824 and 760; δ_H 3.89 (3H, s, CH_3), 5.45 (2H, s, CH_2), 7.06–7.08 (2H, m, ArH), 7.23–7.34 (8H, m, ArH), 7.88 (1H, d, J=7.6 Hz, ArH) and 7.90 (2H, d, J=7.9 Hz, 2-H and 6-H); δ_C 48.3 (CH_3), 52.2 (CH_2), 110.4 (CH), 120.3 (CH), 122.9 (CH), 123.9 (CH), 126.7 (CH), 128.0 (CH), 128.7 (CH), 128.9 (CH), 130.4 (CH), 128.9 (C), 135.5 (C), 136.0 (C), 138.8 (C), 143.5 (C), 146.0 (C) and 166.4 (C=O); *m/z* (FAB) 375 (M^+, 74%), 322 (20), 243 (43), 167 (87), 154 (100) and 136 (74).

4.10. Loading of aryl-radical precursors 17a and 17b onto resins

4.10.1. Wang solid supported benzoimidazole 18d. The general procedure for loading precursors to Wang resin was carried out with the acid **17b**. The loading on the resin (0.98 mmol/g) was determined by cleaving a known amount of resin using TFA–DCM (9/1). FTIR ν_{max} (KBr)/cm^{-1} 3023, 2919, 1713, 1590, 1441, 1263, 1170, 1095, 1090, 1010, 821, 742 and 694. The (MAS) magic angle ^{1}H NMR spectrum showed complete immobilisation of the compound onto the Wang resin.

4.10.2. Wang solid supported benzoimidazole 18c. The loading on the resin (0.60 mmol/g) was determined. FTIR ν_{max} (KBr)/cm^{-1} 3424, 3058, 3024, 2919, 2365, 1944, 1717, 1596, 1510, 1492, 1445, 1371, 1266, 1239, 1173, 1099, 1011, 822, 743 and 696. The (MAS) magic angle ^{1}H NMR spectrum showed complete immobilisation of the compound onto the Wang resin.

4.11. Radical cyclisations of resin-bound benzoimidazole 18d

4.11.1. Bu_3SnH. The general procedure for radical cyclisation of Wang bound precursors with **18d** (100 mg, 0.10 mmol) gave 5,6-dihydrobenzo[4,5]imidazo[2,1-*a*]isoquinoline **19b** as colourless crystals (44%). The data were indentical to authentic material.

4.11.2. Bu_3GeH. The general procedure for radical cyclisation of Wang bound precursors with **18d** (140 mg, 0.14 mmol) using Bu_3GeH added in one portion at the beginning and heated for 8 h gave **19b** (71%).

4.11.3. TTMSS. TTMSS (0.06 cm^3, 0.19 mmol) and Et_3B (1.0 M in cyclohexane, 0.2 mmol) were added dropwise to a suspension of the resin-bound benzoimidazole **18d** (111 mg, 0.11 mmol) in toluene (15 cm^3), The flask was fitted with a rubber septum and air was introduced through a needle during stirring at room temperature for 5 h. Further addition of TTMSS (0.12 mL, 0.38 mmol) and Et_3B (1.0 M in hexane, 0.3 mmol) was carried out and the reaction mixture was stirred for another 10 h. Standard work-up gave **19b** (29%).

4.12. Ethyl 6-({1-[2-(2-bromophenyl)ethyl]-1*H*-imidazol-2-yl}sulfanyl)pyridine-3-carboxylate 23a

4.12.1. Ethyl 6-[(1*H*-imidazol-2-yl)sulfanyl]pyridine-3-carboxylate 22. 2-Mercaptoimidazole (2.00 g, 20.0 mmol) was added slowly to a suspension of NaH (0.58 g, 24.2 mmol) in dry DMF (40 cm^3). The mixture was stirred and heated at 80 °C for 1 h, followed by addition of ethyl 6-chloronicotinate (3.71 g, 20.0 mmol) in DMF (10 cm^3) and the reaction mixture was heated at 80 °C for 12 h. The reaction mixture was evaporated under reduced pressure and the residue purified by column chromatography using silica gel as absorbent and light petroleum–ethyl acetate (1/1) as eluents to afford **22** as colourless crystals (2.49 g, 50%), mp 145.7–146.9 °C (Found: M^+, 249.0573. $C_{11}H_{11}N_3O_2S$ requires 249.0572); ν_{max} (KBr)/cm^{-1} 3079, 2986, 2745, 2502, 1866, 1715, 1574, 1444, 1275, 1113, 1011, 965, 851 and 767; δ_H 1.39 (3H, t, J=7.2 Hz, CH_3), 4.39 (2H, q, J=7.2 Hz, OCH_2), 7.12 (1H, dd, J=8.6, 0.4 Hz, 5-H), 7.23–7.26 (2H, br s, imidazole 4,5-H), 8.10 (1H, dd, J=8.6, 2.4 Hz, 4-H) and 8.98 (1H, dd, J=2.4, 0.4 Hz, 2-H), NH was not observed; δ_C 14.2 (CH_3), 61.5 (OCH_2), 121.3 (5-C), 123.3 (imidazole 4,5-C), 133.2 and 135.1 (3-C and imidazole 2-C), 137.6 (4-C), 150.5 (2-C) and 163.2 and 164.8 (6-C and C=O); *m/z* (EI) 250 (MH^+, 100%), 232 (33), 221 (7), 163 (11), 130 (12), 103 (21), 91 (10) and 77 (11).

4.12.2. Ethyl 6-({1-[2-(2-bromophenyl)ethyl]-1*H*-imidazol-2-yl}sulfanyl)pyridine-3-carboxylate 23a. The standard procedure for alkylation was used with the imidazole **22** and 2-(2-bromophenyl)ethyl methanesulfonate **16b** to afford **23a** as a pale yellow oil (75%) (Found: M^+, 431.0312. $C_{19}H_{18}BrN_3O_2S$ requires 431.0303); ν_{max} (neat)/cm^{-1} 3105, 3056, 2981, 1716, 1584, 1472, 1456, 1429, 1366, 1283, 1269, 1173, 1128, 1025, 854 and 766; δ_H 1.38 (3H, t, J=7.2 Hz, CH_3), 3.13 (2H, t, J=7.2 Hz, CH_2), 4.32 (4H, t, J=7.2 Hz, NCH_2), 4.38 (4H, q, J=7.2 Hz,

OCH_2), 6.88 (1H, dd, J=8.4, 0.4 Hz, 5-H), 6.96 (1H, dd, J=7.5, 1.4 Hz, CH), 7.08 (1H, ddd, J=7.5, 7.5, 1.4 Hz, CH), 7.10 and 7.27 (2H, 2×s, imidazole 4,5-H), 7.16 (1H, ddd, J=7.5, 7.5, 1.4 Hz, CH), 7.49 (1H, dd, J=7.5, 1.4 Hz, CH), 8.04 (1H, dd, J=8.4, 2.0 Hz, 4-H) and 8.96 (1H, dd, 2.0, 0.4, 2-H); δ_C 14.2 (CH_3), 37.9 (CH_2), 46.7 (NCH_2), 61.4 (OCH_2), 120.4 (5-C), 123.1 (Ar 2-C), 123.4 (imidazole 4-C), 124.4 (3-C), 127.7 (imidazole 5-C), 128.9 (CH), 131.0 (CH), 131.2 (CH), 133.0 (CH), 134.4 and 136.3 (Ar 1-C and imidazole 2-C), 137.7 (4-C), 150.9 (2-C), 164.4 and 164.9 (6-C and C=O); m/z (EI) 431 (M^+, 4%), 352 (11), 249 (46), 181 (100), 153 (64), 84 (45) and 49 (39).

4.12.3. 5,6-Dihydroimidazo[2,1-*a*]isoquinoline 24. *Bu_3SnH*. The standard procedure for radical cyclisations was carried out using the imidazole **23a** (150 mg) to afford 5,6-dihydroimidazo[2,1-*a*]isoquinoline **24** as a clear oil (37%) (Found: M^+, 170.0847. $C_{11}H_{10}N_2$ requires 170.0844); ν_{max} (neat)/cm^{-1} 3171, 2923, 1708, 1499, 1466, 1329, 1250, 1195, 1099, 911, 772, 738 and 714; δ_H 3.16 (2H, t, J=6.8 Hz, CH_2), 4.17 (2H, t, J=6.8 Hz, NCH_2), 6.94 (1H, d, J=1.0 Hz, 2/3-H), 7.15 (1H, d, J=1.0 Hz, 2/3-H), 7.26–7.27 (3H, m, ArH) and 8.02 (1H, d, J=8.0 Hz, 10-H); δ_C 28.6 (6-C), 43.3 (5-C), 119.1 (CH), 123.6 (CH), 127.6 (CH), 127.8 (CH), 128.3 (CH), 129.1 (CH), 129.6 (C), 132.3 (C) and 142.9 (C); m/z EI 170 (M^+, 4%), 149 (5), 128 (16), 115 (16), 77 (21) and 57 (23).

TTMSS. **24** (45%). Bu_3GeH. Bu_3GeH was added in one portion at the beginning of the reaction. **24** (20%).

Yields of isolated unreacted starting material **23a** and reduced uncyclised **23b** are reported in Scheme 8.

Acknowledgements

We thank GlaxoSmithKline and Loughborough University for a Postgraduate Studentship (R.K.), GlaxoSmithKline for generous financial support and the EPSRC Mass Spectrometry Unit, Swansea University, Wales for mass spectra.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.071. Supplementary data includes syntheses of compounds in which the general method and a representative example has been included in the paper.

References and notes

1. Review: Ganesan, A. In Renaud, P., Sibi, M. P., Eds.; Radicals in Organic Synthesis; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 81–91.
2. Chevet, C.; Jackson, T.; Santry, B.; Routledge, A. *Synlett* **2005**, 477–480. Qian, H.; Huang, X. *J. Comb. Chem.* **2003**, *5*, 569–576. Harrowven, D. C.; May, P. J.; Bradley, M. *Tetrahedron Lett.* **2003**, *44*, 503–506. Miyabe, H.; Nishimura, A.; Fufishima, Y.; Naito, T. *Tetrahedron* **2003**, *59*, 1901–1907. (e) Curran, D. P.; Yang, F.; Cheong, J.-H. *J. Am. Chem. Soc.* **2002**, *124*, 14993–15000. (f) Dublanchet, A.-C.; Lusinchi, M.; Zard, S. Z. *Tetrahedron* **2002**, *58*, 5715–5721. Caddick, S.; Hamza, D.; Wadman, S. N.; Wilden, J. D. *Org. Lett.* **2002**, *4*, 1775–1779. Kumar, H. M. S.; Charavarthy, P. P.; Rao, M. S.; Reddy, P. S. R.; Yadav, J. S. *Tetrahedron Lett.* **2002**, *43*, 7817–7819.
3. Bowman, W. R.; Krintel, S. L.; Schilling, M. B. *Synlett* **2004**, 1215–1218.
4. Bowman, W. R.; Krintel, S. L.; Schilling, M. B. *Org. Biomol. Chem.* **2004**, 585–592.
5. Krchnák, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61–91.
6. Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1–14. Bowman, W. R.; Cloonan, M. O.; Krintel, S. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2885–2991. Bowman, W. R.; Fletcher, A. J.; Potts, G. B. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2747–2762.
7. Aldabbagh, F.; Bowman, W. R. *Tetrahedron Lett.* **1997**, *38*, 3793–3794. Aldabbagh, F.; Bowman, W. R. *Tetrahedron* **1999**, *55*, 4109–4122.
8. Caddick, S.; Shering, C. L.; Wadman, N. S. *Tetrahedron* **2000**, *56*, 465–473. Caddick, S.; Aboutayab, K.; Jenkins, K.; West, R. I. *J. Chem. Soc., Perkin Trans. 1* **1996**, 675–682. Caddick, S.; Aboutayab, K.; West, R. I. *J. Chem. Soc., Chem. Commun.* **1995**, 1353–1534. Caddick, S.; Aboutayab, K.; West, R. I. *Synlett* **1993**, 231–232.
9. Review: Studer, A.; Bossart, M. In Renaud, P., Sibi, M. P., Eds.; Radicals in Organic Synthesis; Wiley-VCH: Weinheim, 2001; Vol. 2, pp 62–80.
10. Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25–35.
11. Allin, S. M.; Bowman, W. R.; Elsegood, M. R. J.; McKee, V.; Karim, R.; Rahman, S. S. *Tetrahedron* **2005**, *61*, 2689–2696.
12. Aldabbagh, F.; Bowman, W. R.; Mann, E. *Tetrahedron Lett.* **1997**, *38*, 7937–7940. Aldabbagh, F.; Bowman, W. R.; Mann, E.; Slawin, A. M. Z. *Tetrahedron* **1999**, *55*, 8111–8128.
13. Allin, S. M.; Barton, W. R. S.; Bowman, W. R.; McInally, T. *Tetrahedron Lett.* **2002**, *41*, 4191–4193.
14. Akamatsu, H.; Fukase, K.; Kusumoto, S. *Synlett* **2004**, 1049–1053.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 4317–4322
Tetrahedron

Lonijaposides, novel cerebrosides from *Lonicera japonica*☆

Neeraj Kumar, Bikram Singh,* Ajai P. Gupta and Vijay K. Kaul

Institute of Himalayan Bioresource Technology, Palampur, HP 176 061, India

Received 17 December 2005; revised 9 February 2006; accepted 23 February 2006

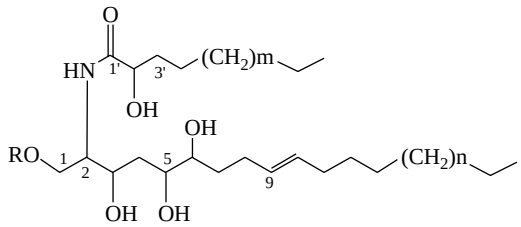
Abstract—Six novel cerebrosides, lonijaposides A_1–A_4, B_1 and B_2 (**1–6**) have been isolated from the flowers of *Lonicera japonica*. Their structures were established on the basis of 1D, 2D (DEPT, HMQC, HMBC and COSY) NMR, ESI-QTOF-MS/MS and chemical evidence.

1. Introduction

The flowers and buds of *Lonicera japonica* Thunb., are used in Chinese herbal medicine for latent-heat-clearing, antipyretic, detoxicant and anti-inflammatory ailments.[1] This plant is known for its properties as an anti-inflammatory agent in Korea since ancient times and is widely used for respiratory infections, diabetes mellitus and rheumatoid arthritis.[2] Iridoid glucosides,[3–5] flavonoids[6–8] and saponins[9,10] have previously been reported from the plant. Cerebrosides are a unique class of secondary metabolites, some of which are reported to have anti-tumour, anti-HIV-1, neuritogenic, hepatoprotective, immunosuppressive, immunostimulatory, anti-ulcerogenic, anti-fungal and antimicrobial activities.[11] It has been proved that the polarity of the cerebrosides is associated with the presence of extra hydroxyls in the sphingoid base and plays a key role in the neuritogenic activities.[12] Moreover, cerebrosides have been observed to be correlated to the tolerance of some plants to chilling stresses.[11] In continuation of our work for a search of novel molecules from the plant bioresource of the western Himalayas,[8,13–15] we now report the isolation and structural elucidation of six new cerebrosides, designated as lonijaposides A_1–A_4, B_1 and B_2, from the flowers of *L. japonica*. To the best of our knowledge this is the first report of novel cerebrosides from the genus *Lonicera* (Fig. 1).

2. Results and discussion

Column chromatography of methanol extract of fresh flowers over silica gel afforded a molecular species LJC-1 as amorphous white solid. The IR spectrum of LJC-1 showed absorption bands at 3350 and 3220, 1620 and 1540, and 1665 cm^{-1} indicated the presence of hydroxyl, amide and olefinic functions, respectively. The ^1H NMR spectrum of LJC-1 (Table 1) showed the presence of two terminal methyls at δ 0.73 (6H, t, $J=7.2$ Hz), methylenes at δ 1.18 (br s), an amide proton signal at δ 8.46 (1H, d, $J=8.7$ Hz), signals of a *trans*-olefinic bond at δ 5.38 (1H, br dt, $J=16.5$, 6.5 Hz) and δ 5.40 (1H, br dt, $J=16.5$, 6.5 Hz) and six characteristic signals of geminal protons to hydroxyl groups were also observed at δ 4.50 (1H, m), 4.40 (1H, dd, $J=10.5$, 4.5 Hz), 4.33 (1H, dd, $J=10.5$, 4.7 Hz), 4.23 (1H, m), 4.10 (2H, m). Another signal at low field was observed at δ 5.01 (1H, m) for a methine proton vicinal to the nitrogen atom of the amide group. The data indicated a phytosphingolipid structure.[16,17] To further confirm, ^{13}C NMR spectra of LJC-1 (Table 1) showed one quaternary carbon at δ 176.5 (CONH), two olefinic methine carbons at δ 132.1 and 131.9 (C=C), five methines at δ 54.5 (CHNH), 78.1 (CHOH), 74.2 (CHOH), 74.1 (CHOH), 73.7 (CHOH) and one methylene at δ 63.2 (CH_2OH). The geometry (*E*) of the double bond in the unsaturated long chain base portion was determined on the basis of the ^{13}C NMR chemical shift



1: R = H, m = 9, n = 11
2: R = H, m = 9, n = 9
3: R = H, m = 10, n = 11

Figure 1. Structures of lonijaposide A_1 (**1**), A_2 (**2**) and A_3 (**3**).

☆ IHBT communication no. 0580.

Keywords: *Lonicera japonica*; Cerebrosides; Lonijaposides A_1–A_4, B_1, B_2.
* Corresponding author. Tel.: +91 1894 230426; fax: +91 1894 230433; e-mail: bikram_npp@rediffmail.com

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.070

Table 1. ^{1}H and ^{13}C NMR (300 and 75.6 MHz) of LJC-1, **1** and **4**

	Compounds					
	LJC-1		**1**		**4**	
No.	δ_C	δ_H m (*J* Hz)	δ_C	δ_H m (*J* Hz)	δ_C	δ_H m (*J* Hz)
1	63.2	4.33dd (10.5, 4.7) 4.40dd (10.5, 4.5)	63.2	4.33dd (10.5, 4.7) 4.41dd (10.5, 4.5)	70.9	4.40dd (10.3, 3.5) 4.71dd (10.3, 6.1)
2	54.2	5.01m	54.2	5.01m	54.9	5.00m
3	78.1	4.23m	78.2	4.23m	78.0	4.21m
4	35.3	2.30m	35.4	2.30m	35.4	2.30m
5	74.1	4.10m	74.1	4.10m	74.3	4.00m
6	74.2	4.10m	74.2	4.10m	74.3	4.10m
7	33.3	2.05	33.4	2.05	33.3	2.01
8	34.5	1.88–2.05m	34.4	1.88–2.05m	34.7	1.89–2.03m
9	131.9	5.38 br dt (16.5, 6.5)	131.9	5.38 br dt (16.5, 6.5)	131.9	5.33 br dt (16.5, 6.5)
10	132.1	5.40 br dt (16.5, 6.5)	132.1	5.40 br dt (16.5, 6.5)	132.2	5.46 br dt (16.5, 6.5)
11	34.2	1.88–2.05m	34.4	1.88–2.05m	34.7	1.89–2.03m
12	33.3	2.05m	33.4	2.05m	33.3	2.05m
$(CH_2)_n$	30.7–31.5	1.18 br s	30.7–31.5	1.18 br s	30.6–31.2	1.23 br s
24	30.8	1.18m	30.8	1.18m	30.6	1.23m
25	24.1	1.18m	24.0	1.18m	24.1	1.23m
26	15.5	0.73t (7.2)	15.5	0.73t (7.2)	15.5	0.67t (7.0)
NH		8.46d (8.7)		8.46d (8.7)		8.60d (8.7)
1′	176.5		176.4		175.4	
2′	73.7	4.50m	73.6	4.50m	73.6	4.62m
3′	36.9	1.88m	36.8	1.88m	37.0	1.90m
4′	27.0	1.64m	27.0	1.64m	27.3	1.66m
$(CH_2)_m$	30.7–31.5	1.18 br s	30.7–31.5	1.18 br s	30.6–31.2	1.23 br s
13′	30.8	1.18	30.8	1.18	30.6	1.23
14′	24.1	1.18m	24.0	1.18m	24.1	1.23m
15′	15.5	0.73t (7.2)	15.5	0.73t (7.2)	15.5	0.67t (7.0)
1′					106.0	4.97d (7.8)
2′					75.9	
3′					78.8	
4′					72.0	3.67–4.50
5′					79.7	
6′					65.4	

value (34.2, 34.5) of the methylene carbon adjacent to the olefinic carbon, which must be observed at $\delta \approx 27$ in (*Z*) isomers and at $\delta \approx 32$ in (*E*) isomers. All these spectral data revealed that the compound LJC-1 possessed two aliphatic chains containing one double bond and five hydroxyl groups and suggesting it to be a phytosphingosine type sphingolipid.[16,17] The positive and negative charged HRESI-QTOF-MS of LJC-1 gave three protonated $[M+H]^+$ and three deprotonated $[M-H]^-$ molecular ion peaks at *m/z* 684.6121, 656.5798, 698.6278 and 682.5965, 654.5655, 696.6133, respectively. This led to the conclusion that LJC-1 is a mixture of three cerebrosides (**1**–**3**), which was further confirmed by methanolysis of LJC-1.

Methanolysis of LJC-1 yielded a mixture of two fatty acid methyl esters (FAM) and two long chain bases (LCB). The fatty acid methyl esters (FAM) were identified by GC–MS as methyl 2-hydroxypentadecanoate and methyl 2-hydroxyhexadecanoate. The positive and negative mode HRESI-QTOF-MS of mixture of long chain bases gave sodiated $[M+Na]^+$ and deprotonated $[M-H]^-$ molecular ion peaks at *m/z* 466.3870 (calcd 466.3872), 438.3556 (calcd 438.3559) and 442.3889 (calcd 442.3897), 414.3579 (calcd 414.3584) corresponding to the molecular formulae $C_{26}H_{53}NO_4$ and $C_{24}H_{49}NO_4$, respectively. The above data suggested that LJC-1 comprised of three cerebroside (**1**–**3**) and among the three, two cerebrosides (**1** and **2**) had identical fatty acids with long chain bases of varying chain lengths (C_{26} and C_{24}, respectively). The third cerebroside (**3**) contained long chain base identical to that of **1** but with a different fatty acid (2-hydroxy hexadecanoic acid). LJC-1 showed a single spot on normal phase TLC, but different retention times in reversed phase HPLC, thus revealing difference in their carbon chains. HPLC of LJC-1 showed the presence of **1** as a major constituent whereas other constituents (**2** and **3**) were in lesser amounts. Therefore, compound **1** was separated by reversed phase prep-HPLC for detailed analysis.

^{1}H and ^{13}C NMR spectra of **1** (Table 1) were identical to those of LJC-1. The molecular formula of **1** was established as $C_{41}H_{81}NO_6$ by positively and negatively charged HRESI-QTOF-MS, which gave protonated $[M+H]^+$ and deprotonated $[M-H]^-$ molecular ion peaks at *m/z* 684.6121 (calcd 684.6142) and 682.5965 (calcd 682.5986).

Methanolysis of **1** yielded methyl 2-hydroxypentadecanoate identified by GC–MS. The existence of the 2-hydroxylpentadecanoyl moiety was also confirmed by the presence of EI-MS at *m/z* 286 $[M]^+$ and 256 $[M-15]^+$ as well as by the release of characteristic fragment ions at *m/z* 227 $[M-59]^+$ and 90 $[CH_2OHCOOCH_3]^+$. Therefore, the long chain base (LCB) was characterized as C_{26}-phytosphingosine having four hydroxyls, one double bond and an amino group.

The positively charged ESI-QTOF-MS/MS of **1** showed fragment ions at *m/z* 428 $[M-CH_3(CH_2)_{12}CHOHCONH]^+$,

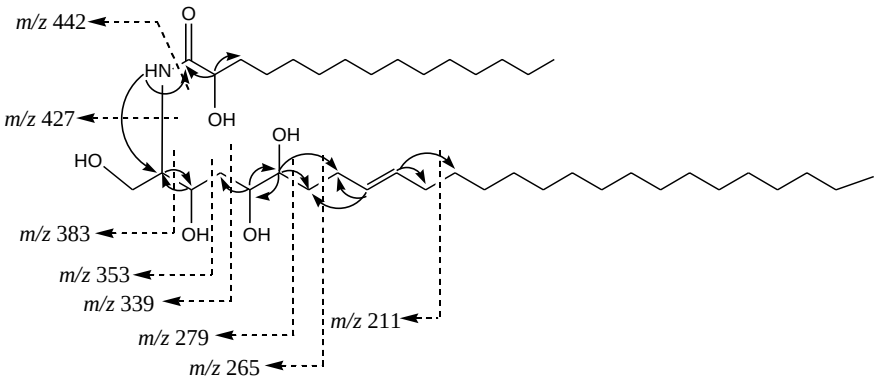
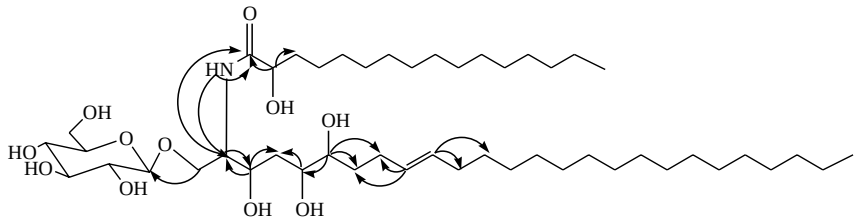


Figure 2. EI mass fragmentation pattern and important HMBC correlations of compound **1**.

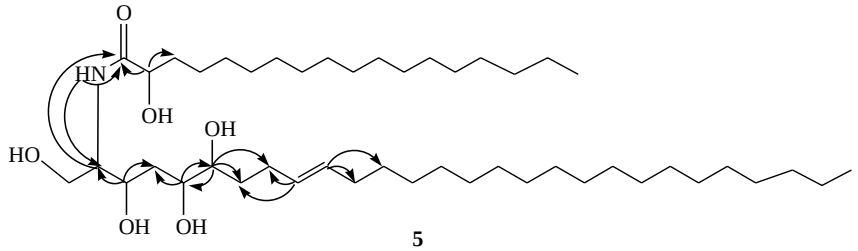
257 $[M-LCB]^+$, 383 $[428-CH_2CH_2OH]^+$, 300 $[257+CH_2CH_2OH]^+$, 282 $[300-H_2O]^+$ and 264 $[300-2\times H_2O]^+$. This further confirmed for 2-hydroxypentadecanoyl and C_{26}-long chain base in **1**. The fragmentation pattern of compound **1** in EI mode was consistent with the pattern obtained in ESI mode (Fig. 2). The presence of 2-amino and 1, 2′, 3, 5, 6 pentahydroxyl groups as well as 9, 10 double bond in the main chain was established by the analysis of ^1H and ^{13}C NMR spectroscopic data of **1**, which was unambiguously assigned by extensive 2D NMR (^1H–^1H COSY, HMQC and HMBC) techniques. The ^1H–^1H COSY spectrum of **1** showed a pair of double doublets of oxygenated methylenes at δ 4.41 (1H, dd, $J=10.5$, 4.5 Hz) and 4.33 (1H, dd, $J=10.5$, 4.7 Hz) coupled to the nitrogen bearing methine signal at δ 5.01 (1H, m), which coupled further to the signal at δ 4.23 (1H, m). Olefinic protons at δ 5.38 (1H, br dt, $J=16.5$, 6.5 Hz) and δ 5.40 (1H, br dt, $J=16.5$, 6.5 Hz) showed coupling with methylene protons resonated at δ 1.88 (1H, m) and 2.05 (1H, m). In the HMBC spectrum of **1**, the signal at δ 4.50 correlated to the quaternary carbon and methylene carbon resonated at δ 176.5 and 36.9, respectively. The proton at δ 5.01 showed correlation with oxygenated methylene (δ 63.2) and oxygenated methines (δ 78.1). Thus, on the basis of the above evidence, compounds **1**, **2** and **3** were assigned structures as 1,3,5,6-tetrahydroxy-2-(2′-hydroxypentadecanoyl amino)-9-(*E*)-hexacosene named as lonijaposide A_1, 1,3,5,6-tetrahydroxy-2-(2′-hydroxypentadecanoyl amino)-9-(*E*)-tetracosene named as lonijaposide A_2 and 1,3,5,6-tetrahydroxy-2-(2′-hydroxyhexadecanoyl amino)-9-(*E*)-hexacosene named as lonijaposide A_3, respectively. The configuration at the chiral centers could not be established due to paucity of the compounds.

Compound **4** was obtained as a white solid showing $[M+Na]^+$ and $[M-H]^-$ peaks in positive and negative mode HRESI-QTOF-MS at *m/z* 882.6621 (calcd 882.6646) and 858.6668 (calcd 858.6671), respectively, corresponding to the molecular formula $C_{48}H_{93}NO_{11}$. The IR spectrum was similar to LJC-1 but in the ^1H NMR spectrum (Table 1) additional peaks due to the glucose moiety were observed. The anomeric proton showed a signal at δ 4.97 (d, $J=$ 7.8 Hz) and J value suggested a β-configuration of the glucose unit. Other protons of glucose, geminal to hydroxyl groups resonated at δ 3.67–4.65. The ^{13}C NMR spectrum (Table 1) also revealed the presence of the sugar moiety, which showed an anomeric carbon at δ 106.0 and hydroxyl containing methine carbons at δ 75.9, 78.8, 72.0 and 79.7 and a signal at δ 65.4 (CH_2OH). The above observations suggested that **4** is a glycoside of **3**. It was also confirmed by ESI-QTOF-MS/MS of *m/z* 882, which showed prominent peak at *m/z* 720 due to the elimination of glucosyl moiety. The further fragmentation pattern observed was similar to compound **3**. The position of the glucose moiety at C-1 was evident by the downfield chemical shift of hydroxymethylene carbon at δ 70.9 in ^{13}C NMR spectrum by 7.8 ppm and further confirmed by HMBC spectrum in which the correlation was observed between the anomeric proton (δ 4.97) with the hydroxymethylene carbon (δ 70.9). In conclusion, glycoside **4** was assigned as 1-*O*-β-D-glucopyranosyl-3,5,6-trihydroxy-2-(2′-hydroxyhexadecanoyl amino)-9-(*E*)-hexacosene designated as lonijaposide B_1 (Fig. 3).

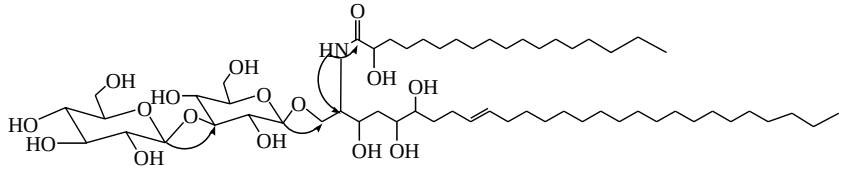
Compound **5** was also obtained as a white powder. The ^1H and ^{13}C NMR of **5** (Table 2) was found to be quite similar to LJC-1. However, its positive and negative HRESI-QTOF-MS gave sodiated $[M+Na]^+$ and deprotonated $[M-H]^-$ molecular ion peaks at *m/z* 776.6721 (calcd 776.6744) and 752.6759 (calcd 752.6768) corresponding to the molecular formula $C_{46}H_{91}NO_6$. The ^1H NMR spectrum of **5** showed the presence of two terminal methyls at δ 0.85 (6H, t, $J=$ 7.1 Hz), methylenes at δ 1.23 (56H, br s), an amide proton signal at δ 8.60 (1H, d, $J=8.7$ Hz), signals of *trans*-olefinic bond at δ 5.33 (1H, br dt, $J=16.5$, 6.5 Hz) and δ 5.46 (1H, br dt, $J=16.5$, 6.5 Hz) and six characteristic signals of geminal protons to hydroxyl groups were also observed at δ 4.62 (1H, m), 4.50 (1H, dd, $J=10.5$, 4.7 Hz), 4.35 (1H, dd, $J=10.5$, 4.5 Hz), 4.21 (1H, m), 4.10 (2H, m). A seventh signal at low field was observed at δ 5.03 (1H, m) identified for a methine proton vicinal to the nitrogen atom of the amide groups. The ^{13}C NMR spectra of **5** showed one quaternary carbon at δ 176.9 (CONH), two olefinic methine carbons at δ 132.1 and 132.3 (C=C), five methines at δ 54.9 (CHNH), δ 78.2 (CHOH), δ 74.1 (CHOH), δ 74.2 (CHOH), δ 73.6 (CHOH) and one methylene at δ 63.8 (CH_2OH). Methanolysis of **5** yielded methyl 2-hydroxyoctadecanoate and one long chain base. The positive HRESI-MS of LCB gave a sodiated $[M+Na]^+$ molecular ion peak at *m/z* 494.4166 (calcd 494.4185) corresponding to the molecular formula $C_{28}H_{57}NO_4Na$. Thus, the molecular mass of LCB together with ^1H and ^{13}C NMR spectroscopic data suggested C_{28}-phytosphingosine-type long chain base containing four hydroxyls, one double bond and an amino group. Therefore, the structure of **5** was assigned to be



4



5



6

Figure 3. Structures and selected HMBC (H→C) of lonijaposide B_1 (**4**), A_4 (**5**) and B_2 (**6**).

Table 2. ^1H and ^{13}C NMR (300 and 75.6 MHz) of **5** and **6**

	Compounds			
	5		**6**	
Position	δ_C	δ_H m (*J* Hz)	δ_C	δ_H m (*J* Hz)
1	63.8	4.35dd (10.5, 4.5), 4.50dd (10.5, 4.7)	70.5	4.30dd (10.5, 4.7), 4.52dd (10.5, 4.5)
2	54.9	5.03m	54.3	5.01m
3	78.2	4.21m	78.2	4.23m
4	35.4	2.30m	35.4	2.28m
5	74.1	4.00m	74.1	4.11m
6	74.2	4.10m	74.2	4.10m
7	33.3	2.01	33.4	2.05
8	34.7	1.89–2.03m	34.4	1.90–2.05m
9	132.1	5.33 br dt (16.5, 6.5)	131.9	5.37 br dt (16.5, 6.5)
10	132.3	5.46 br dt (16.5, 6.5)	132.1	5.40 br dt (16.5, 6.5)
11	34.7	1.89–2.03m	34.4	1.90–2.05m
12	33.3	2.01m	33.4	2.05m
13–23	30.5–31.2	1.23 br s	30.7–31.5	1.21 br s
24	30.6	1.23m	30.8	1.21m
25	24.2	1.23m	24.0	1.21m
26	15.5	0.85t (7.1)	15.5	0.75t (7.2)
NH		8.60d (8.7)		8.46d (8.7)
1′	176.3		176.4	
2′	73.6	4.62m	73.6	4.50m
3′	36.5	1.90m	36.8	1.88m
4′	27.3	1.66m	27.0	1.64m
5′–13′	30.6–31.2	1.23 br s	30.7–31.5	1.18 br s
14′	30.6	1.23	30.8	1.21
15′	24.1	1.23m	24.0	1.21m
16′	15.5	0.85t (7.1)	15.5	0.75t (7.2)
1″			105.9	4.97d (7.9)
2″			75.2	
3″			76.4	
4″			79.8	3.90–4.52
5″			78.4	
6″			63.8	
1‴			105.0	4.68d (7.6)
2‴			75.2	
3‴			78.0	
4‴			72.0	3.90–4.52
5‴			79.3	
6‴			65.4	

1,3,5,6-tetrahydroxy-2-(2′-hydroxyoctadecanoyl amino)-9-(*E*)-octacosene named as lonijaposide A_4 (Fig. 3).

Compound **6** was also obtained as a white solid. The HRESI-QTOF-MS in positive and negative mode gave sodiated $[M+Na]^+$ and deprotonated $[M-H]^-$ molecular ion peak at *m/z* 1100.7798 (calcd 1100.7801) and 1076.7810 (calcd 1076.7825), respectively. On the basis of molecular mass and ^1H and ^{13}C NMR spectral data (Table 2) the molecular formula of **6** was established as $C_{58}H_{111}NO_{16}$. The ^1H and ^{13}C NMR spectra were found to be identical with compound **5** except the presence of additional peaks of two sugar moieties. In ^1H NMR spectrum anomeric peaks of two glucose units were observed at δ 4.97 (1H, d, 7.9) and δ 4.68 (1H, d, 7.6) together with overlapping peaks of other carbons at δ 3.90–4.52. ^{13}C NMR spectrum also revealed the presence of two glucose moieties linked together in C1‴–C4″ pattern. C1‴–C4″ linkage in sugars was evidenced by downfield shift of C4″ carbons by 8 ppm and upfield shift of C3″ and C5″ carbons by 1–1.5 ppm. This linkage was further confirmed by HMBC correlation, which showed the correlation between anomeric proton (δ 4.68) of second glucose with C4″ carbon of first glucose. Thus, the above observations suggested that compound **6** was a diglycoside of **5**. The presence of two glucose units was further confirmed by ESI-QTOF-MS/MS of *m/z* 1100, which showed prominent peaks at *m/z* 938 and 776 due to the sequential elimination of two glucosyl moieties. This is the first report of presence of any diglycoside cerebroside in nature.[11] In conclusion, diglycoside **6** was assigned the structure as 1-*O*-β-D-glucopyranosyl(1→4)-*β*-D-glucopyranosyl-3,5,6-trihydroxy-2-(2′-hydroxyoctadecanoyl amino)-9-(*E*)-octacosene designated as lonijaposide B_2 (Fig. 3).

3. Experimental

3.1. General experimental procedure

Melting points were recoded on Barnstead Electrothermal melting point apparatus and are uncorrected. Optical rotations were determined on Horiba SEPA-300 polarimeter. IR spectra were recorded on a Perkin-Elmer 1760 FT-IR spectrometer with KBr disc. NMR spectra were recorded on a Bruker Avance-300 spectrometer. ESI-QTOF-MS was performed on QTOF-Micro, Waters Micromass and GC–MS was done on Shimadzu QP-2010 operating on EI mode at 70 eV with an ion source temperature of 200 °C; capillary column, BP20 (30 m×0.25 mm, 0.25 μm film thickness); carrier gas, He. HPLC was carried out on Waters prep LC 4000 system. Silica gel (60–120 mesh, Merck) was used for column chromatography. Pre-coated silica gel 60 F_{254} (Merck) plates were used for TLC. All other chemicals used were produced by Merck India Ltd.

3.2. Plant material

The fresh flowers of *L. japonica* were collected from IHBT, Palampur, India during May 2004. A voucher specimen (No. 5909) has been deposited in the Herbarium of IHBT, Palampur, India.

3.3. Extraction and isolation

The fresh flowers (400 g) of *L. japonica* were extracted successively, with *n*-hexane (3×1500 mL) and EtOAc (3×1000 mL) and remaining material was air dried and powdered. The powdered flower material was extracted at room temperature with MeOH (3×800 mL). Evaporation of each solvent in vacuo, yielded *n*-hexane extract (1.36 g), EtOAc (5.00 g) and MeOH extract (33.00 g). The MeOH extract (33.00 g) was subjected to column chromatography over silica gel (60–120 mesh) and eluted with $CHCl_3$, $CHCl_3$–MeOH (95/5), (90/10), (85/15), (80/20), (70/30), (50/50), (30/70), (10/90) and MeOH to give a total of 150 fractions (100 mL each). Fractions 42–45, eluted with $CHCl_3$–MeOH (85/15) were evaporated and the resulting residue (95 mg) was crystallized in MeOH to give white solid LJC-1 (55 mg), which showed a single spot on TLC ($CHCl_3$/MeOH, 90:10). HPLC of LJC-1 (solvent MeOH/H_2O; 40:60; flow rate 7.0 mL/min; column: LichroCART 250×10 mm, Lichrosphere^{100} RP18, particle size 10 μm) showed 3 peaks. Using these conditions, 40 mg of LJC-1 was separated by HPLC to give compound **1** (19.3 mg). Fractions 50–53, eluted with $CHCl_3$–MeOH (85/15) were evaporated and the white residue on crystallization in MeOH yielded compound **5** (22.4 mg). Fractions 56–68 eluted with $CHCl_3$–MeOH (80/20 and 70/30), were mixed and evaporated, and the resultant white residue (92 mg) was rechromatographed over silica gel (60–120 mesh), which on elution with $CHCl_3$–MeOH (85/15), (80/20) and (70/30) provided compound **4** (20 mg) in $CHCl_3$–MeOH (80/20) and compound **6** (23 mg) in $CHCl_3$–MeOH (70/30).

3.3.1. LJC-1. Amorphous powder; IR (KBr) ν_{max} 3350, 3220, 1665, 1620, 1540 cm^{-1}; ^1H and ^{13}C NMR see Table 1; positive-ion HRESI-QTOF-MS *m/z*: 684.6121 $[M+H]^+$, 656.5798 $[M+H]^+$, 698.6278 $[M+H]^+$ and negative-ion HRESI-QTOF-MS *m/z*: 682.5965 $[M-H]^-$, 654.5655 $[M-H]^-$, 696.6133 $[M-H]^-$.

3.3.2. Methanolysis of LJC-1. LJC-1 (10 mg) was refluxed with 1.5 mL of 1 M HCl in 82% aqueous MeOH for 12 h. The reaction mixture was cooled and extracted with *n*-hexane. Hexane layer was concentrated to give a mixture of two fatty acid methyl esters, which could be identified as methyl 2-hydroxypentadecanoate and methyl 2-hydroxyhexadecanoate by GC–MS showing molecular ion peaks at *m/z* 272 and 286, respectively, and characteristic fragments at *m/z* 213 $[M-59]^+$, 90 $[CH_2OHCOOCH_3]^+$ and 227 $[M-59]^+$, 90 $[CH_2OHCOOCH_3]^+$, respectively. The MeOH–H_2O phase was neutralized with Ag_2CO_3, filtrated, and the filtrate was concentrated in vacuo to give a mixture of two long chain bases, which on ESI-QTOF-MS generated molecular ion peaks at *m/z* 466.3870 $[M+Na]^+$, 438.3556 $[M+Na]^+$ and 442.3889 $[M-H]^-$, 414.3579 $[M-H]^-$, respectively.

3.3.3. Lonijaposide A_1 (1). Amorphous powder; mp 136–138 °C; $[\alpha]_D^{24}$ +13.3 (*c* 0.0011, pyridine); ^1H and ^{13}C NMR see Table 1; positive and negative-ion HRESI-QTOF-MS *m/z*: 684.6121 $[M+H]^+$(calcd 684.6142) and 682.5965 $[M-H]^-$ (calcd 682.5986), respectively; positive-ion ESI-MS/MS *m/z* (%): 666 $[M-H_2O]^+$(100), 648

$[M-2\times H_2O]^+$(32), 630 $[M-3\times H_2O]^+$(10), 428 $[M-CH_3\ (CH_2)_{12}CHOHCONH]^+$(10), 383 $[428-CH_2CH_2OH]^+$(17), 301 $[256+CH_2CH_2OH]^+$(28), 283 $[301-H_2O]^+$(57), 265 $[301-2\times H_2O]^+$(48). Lonijaposide A_1 (**1**) was methanolyzed as per the method described for LJC-1 to yield methyl 2-hydroxypentadecanoate as fatty acid methyl ester.

3.3.4. Lonijaposide A_4 (5). Amorphous powder; 128–130 °C; [α] +14.5 (*c* 0.0011, pyridine); ^1H and ^{13}C NMR see Table 1; positive and negative-ion HRESI-QTOF-MS *m/z*: 776.6721 $[M+Na]^+$ (calcd 776.6744) and 752.6759 $[M-H]^-$ (calcd 752.6768), respectively; positive-ion ESI-MS/MS *m/z* (%): 758 $[M+Na-H_2O]^+$(100), 740 $[M+Na-2\times H_2O]^+$(40), 722 $[M+Na-3\times H_2O]^+$(15), 478 $[M+Na-CH_3(CH_2)_{15}CHOHCONH]^+$(12), 433 $[478-CH_2CH_2OH]^+$(15), 321 $[CH_3(CH_2)_{15}CHOHCONH+Na]^+$(6), 366 $[321+CH_2CH_2OH]^+$(9), 348 $[366-H_2O]^+$(25). Lonijaposide A_4 (**5**) was methanolyzed as per the method described for LJC-1 to yield methyl 2-hydroxy-octadecanoate as fatty acid methyl ester.

3.3.5. Lonijaposide B_1 (4). Amorphous powder; mp 120–121 °C; [α] +8.9 (*c* 0.0011, pyridine) ^1H and ^{13}C NMR see Table 1; positive and negative-ion HRESI-QTOF-MS *m/z*: 882.6621 $[M+Na]^+$ (calcd 882.6646) and 858.6668 $[M-H]^-$ (calcd 858.6671), respectively; positive-ion ESI-MS/MS *m/z* (%): 720 $[M+Na\text{-}glu]^+$(20); 702 $[M+Na\text{-}glu-H_2O]^+$(18), 684 $[M+Na\text{-}glu-2\times H_2O]^+$(32), 666 $[M+Na\text{-}glu-3\times H_2O]^+$(10), 450 $[M+Na\text{-}glu-CH_3(CH_2)_{13}CHOHCONH]^+$(10), 405 $[450-CH_2CH_2OH]^+$(17), 315 $[CH_3(CH_2)_{13}CHOHCONHCH_2CH_2OH]^+$(28), 297 $[315-H_2O]^+$(57), 279 $[315-2\times H_2O]^+$(48). Lonijaposide B_1 (**4**) was methanolyzed as per the method described for LJC-1 to yield methyl 2-hydroxyhexadecanoate as fatty acid methyl ester.

3.3.6. Lonijaposide B_2 (6). Amorphous powder; mp 114–115 °C; $[\alpha]_D^{24}$ +9.3 (*c* 0.0011, pyridine) ^1H and ^{13}C NMR see Table 1; positive and negative-ion HRESI-QTOF-MS *m/z*: 1100.7798 $[M+Na]^+$ (calcd 1100.7801) and 1076.7810 $[M-H]^-$ (calcd 1076.7825), respectively; positive-ion ESI-MS/MS *m/z* (%): 938 $[M+Na\text{-}glu]^+$(9), 776 $[M+Na\text{-}2\times glu]^+$(20), 758 $[M+Na\text{-}2\times glu-H_2O]^+$(6), 722 $[M+Na\text{-}2\times glu-3\times H_2O]^+$(4), 478 $[M+Na\text{-}2\times glu-CH_3(CH_2)_{15}CHOHCONH]^+$(10), 306 $[CH_3(CH_2)_{15}CHOHCO+Na]^+$(9), 433 $[478-CH_2CH_2OH]^+$(17), 366 $[CH_3(CH_2)_{15}CHOHCONHCH_2CH_2OH+Na]^+$(28), 348 $[366-H_2O]^+$(27), 330 $[366-2\times H_2O]^+$(48), 347 $[2\times glu+Na]$ (100). Lonijaposide B_2 (**6**) was methanolyzed as per the method described for LJC-1 to yield methyl 2-hydroxyoctadecanoate as fatty acid methyl ester.

Acknowledgements

We are grateful to Dr. P. S. Ahuja, Director, IHBT Palampur, for providing necessary facilities. Technical assistance from Mr. Dhruv Kumar and Mr. Ramesh Kumar are greatly acknowledged.

References and notes

1. Chang, W. C.; Hsu, F. L. *Prostaglandins Leukot. Essent. Fatty Acids* **1992**, *45*, 307–312.
2. Lee, S. J.; Son, K. H.; Chang, H. W.; Kang, S. S.; Kim, H. P. *Phytother Res.* **1998**, *12*, 445–447.
3. Kawai, H.; Kuroyanagi, M.; Umehara, K.; Ueno, A.; Satake, M. *Chem. Pharm. Bull.* **1988**, *36*, 4769–4775.
4. Mehrotra, R.; Singh, C.; Popli, S. P. *J. Nat. Prod.* **1988**, *51*, 319–321.
5. Machida, K.; Sasaki, H.; Ijima, T.; Kikuchi, M. *Chem. Pharm. Bull.* **2002**, *50*, 1041–1044.
6. Son, K. H.; Park, J. O.; Chung, K. C.; Chang, H. W.; Kim, H. P.; Kim, J. S.; Kang, S. S. *Arch. Pharm. Res.* **1992**, *15*, 365–370.
7. Son, K. H.; Kim, J. S.; Kang, S. S.; Kim, H. P.; Chang, H. W. *Kor. J. Pharmacogn.* **1994**, *25*, 24–27.
8. Kumar, N.; Singh, B.; Bhandari, P.; Gupta, A. P.; Uniyal, S. K.; Kaul, V. K. *Phytochemistry* **2005**, *66*, 2740–2744.
9. Son, K. H.; Jung, K. Y.; Chang, H. W.; Kim, H. P.; Kang, S. S. *Phytochemistry* **1994**, *35*, 1005–1008.
10. Kwak, W. J.; Han, C. K.; Chang, H. W.; Kim, H. P.; Kang, S. S.; Son, H. H. *Chem. Pharm. Bull.* **2003**, *51*, 333–335.
11. Tan, R. X.; Jen, J. H. *Nat. Prod. Rep.* **2003**, *20*, 509–534.
12. Koga, J.; Yamauchi, T.; Shimura, M.; Ogawa, N.; Oshima, K.; Umemura, K.; Kikuchi, M.; Ogasawara, N. *J. Biol. Chem.* **1998**, *273*, 31985.
13. Mahmood, U.; Kaul, V. K.; Singh, B. *Phytochemistry* **2002**, *61*, 913–917.
14. Verma, V. H. K.; Mahmood, U.; Singh, B. *Nat. Prod. Lett.* **2002**, *16*, 255–259.
15. Bhandari, P.; Kumar, N.; Singh, B.; Kaul, V. K. *Chem. Pharm. Bull.* **2006**, *54*, 240–241.
16. Natori, T.; Morita, M.; Akimoto, K.; Koezuka, Y. *Tetrahedron* **1994**, *50*, 2771–2784.
17. Gao, J. M.; Yang, X.; Wang, C. Y.; Liu, J. K. *Fitoterapia* **2001**, *72*, 858–864.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 4323–4330

Chiral recognition of protected amino acids by means of fluorescent binary complex pyrene/ heptakis-(6-amino)-(6-deoxy)-β-cyclodextrin

Serena Riela, Francesca D'Anna,* Paolo Lo Meo, Michelangelo Gruttadauria, Rosalia Giacalone and Renato Noto*

Dipartimento di Chimica Organica 'E. Paternò', Università degli Studi di Palermo, Viale delle Scienze-Parco d'Orleans II, 90128 Palermo, Italy

Received 13 December 2005; revised 10 February 2006; accepted 23 February 2006

Abstract—The ability of the binary complex pyrene (**Py**)/heptakis-(6-amino)-(6-deoxy)-β-cyclodextrin (am-β-CD) to act as a chiral selector was tested at two pH values (8.0 and 9.0). Phenylalanine (**Phe**), methionine (**Met**) and histidine (**His**) were used as chiral model molecules. The stability of ternary complexes **Py**/am-β-CD/amino acid was determined by means of spectrofluorimetric measurements. The data collected showed an increase in stability going from the binary to ternary complex and above all the possibility to use the binary complex as a chiral selector. Finally, data collected at two pH values showed that the binary complex is a better chiral selector when charged rather than in its neutral form.

1. Introduction

Chiral recognition is one of the most important topics in modern organic chemistry. Probably this is a consequence of the presence of chiral selectors in nature. For example, biological systems only use L-amino acids for protein synthesis. As amino acids and their derivatives are very important in biological systems, the main target of many studies has been the synthesis of macrocyclic receptors able to discriminate between their enantiomers.[1] On this subject, many different approaches have been tested such as the use of metal complexes,[2] imprinted polymers[3] and synthetic macrocycles like calixarenes[4] and cyclodextrins.[5] All these systems are generally considered as models of biological systems and could be used to identify the hierarchy of factors governing chiral recognition. Recently, Imai et al.[2b] have reported data about the chiral recognition ability of a water soluble zinc porphyrin versus some α-amino acids and peptides, which shows enantioselectivity ratios ranging from 1.2 up to 3.3. Likewise Yatsimirsky et al.[6] have reported data about the chiral recognition ability of *N*,*N*′-dibenzylated *S*,*S*-(+)tetrandrine (DBT) versus some α-amino acids and corresponding *N*-acetyl derivatives. Differently from other macrocyclic hosts, this latter shows higher affinity and higher enantioselectivity with smaller guests such as *N*-acetylalanine ($K_S/K_R \geq 10$.

Among macrocyclic hosts previously considered, cyclodextrins, formed by six (α-CD), seven (β-CD) or eight (γ-CD) α-(D)-glucopyranose units, can act as chiral selectors owing to their intrinsically chiral cavity. Different studies, previously reported, have shown that their chiral discrimination ability with some α-amino acids or small peptides could be due to the presence of substituents on the primary or secondary rim. These can change not only the molecular, but also chiral recognition ability of cyclodextrin.[7] Alternatively, discrimination could be a consequence of the formation of a ternary complex among a functionalised cyclodextrin, a metal ion and a chiral molecule.[8] Charged cyclodextrins have often been used to study chiral recognition processes. On this subject, Lincoln et al. have studied the chiral recognition of 2-phenylpropanoic acid by mono-(6-amino)-(6-deoxy)-β-CD.[9] Likewise the enantiomers of guests having chiral center have been separated by capillary zone electrophoresis using cationic cyclodextrins.[10] To identify new systems able to act as chiral selectors, a few years ago, we reported data about the stability and the chiral recognition ability of the binary complex formed by pyrene (**Py**) in the presence of heptakis-(6-amino)-(6-deoxy)-β-cyclodextrin (am-β-CD) and we

Keywords: Cyclodextrin; Chiral recognition; Fluorescence.
* Corresponding authors. Tel.: +39 091596919; fax: +39 091596825 (F.D.); tel.: +39 091596919; fax: +39 091596825 (R.N.); e-mail addresses: fdanna@unipa.it; rnoto@unipa.it

0040–4020/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tet.2006.02.069

pointed out the good chiral recognition ability of the system versus some α-amino acids and their corresponding methyl esters.[11] In our opinion, this ability was due to the empty volume of the cyclodextrin cavity that, after the inclusion of the **Py** molecule, can be differently taken up by amino acid enantiomers. Recently, we have reported results about the chiral discrimination ability of the binary complexes formed by **Py**, xanthone and anthraquinone in the presence of both β-cyclodextrin and am-β-CD versus enantiomers of phenylalanine, methionine and histidine.[12] Collected data have shown that the chiral discrimination ability is influenced by the structure of the fluorescent guest and the binary complex symmetry. In this light, both in the presence of the β-CD and am-β-CD, the binary complex formed by **Py** was the best chiral selector. Now, to evaluate how different substitution on the carboxy or amino group of the amino acid can influence both the molecular and chiral discrimination ability of the binary complex **Py**/am-β-CD, in this work we report data about the behaviour of some *N*- and *O*-protected α-amino acids; phenylalanine (**Phe**), methionine (**Met**) and histidine (**His**) (Fig. 1).

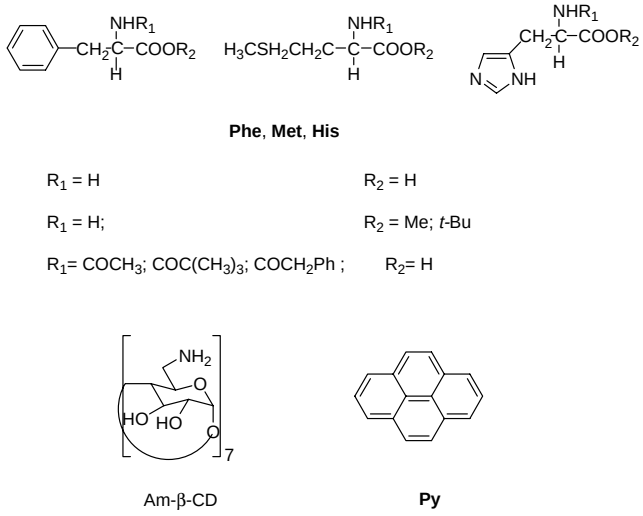


Figure 1. Ternary agents, fluorophore and host structure.

This study was carried out by spectrofluorimetric titration, in borate buffer solution at pH 8.0 and 9.0, to evaluate how the different charge on the host and consequently on the binary complex can influence the interaction with a ternary agent.

2. Results and discussion

In Tables 1 and 2, the stability constant values (β_2) for the ternary complexes formed in the presence of amides and esters are reported. In these Tables, the β_2 values of the binary complex **Py**/am-β-CD and its ternary complexes formed in the presence of amino acids are also reported.[11]

As can be seen from the Tables, in all cases, the complexation of fluorophore to am-β-CD can be described by sequential complexation of cyclodextrin molecules (Eqs. 1 and 2):[13]

$$S + CD \overset{K_1}{\rightleftharpoons} SCD \quad (1)$$

$$SCD + CD \overset{K_2}{\rightleftharpoons} S(CD)_2 \quad (2)$$

In the presence of a ternary agent K_1 and K_2 are conditional equilibrium constants since they include a term related to the ternary agent concentration. The overall association

Table 1. Stability constant values (β_2) of binary complexes **Py**/am-β-CD in the presence of amides of amino acids

Ternary agent	β_2 (M^{-2})/10[6a] pH 8.0	β_2 (M^{-2})/10[6a] pH 9.0
None	1.7[b]	4.8[b]
L-Phe	8.9[b]	5.2[b]
D-Phe	1.2[b]	7.6[b]
N-Ac-L-Phe	4.4	5.8
N-Ac-D-Phe	24.9	2.7
N-Boc-L-Phe	1.4	15.2
N-Boc-D-Phe	3.0	33.2
N-Cbz-L-Phe	3.6	n.d.
N-Cbz-D-Phe	8.3	n.d.
L-Met	13.6[b]	2.2[b]
D-Met	2.5[b]	5.4[b]
N-Ac-L-Met	5.9	10.4
N-Ac-D-Met	12.2	8.7
N-Boc-L-Met	5.9	15.8
N-Boc-D-Met	3.2	32.2
N-Cbz-L-Met	2.6	6.2
N-Cbz-D-Met	3.3	3.3
L-His	7.9[b]	6.2[b]
D-His	6.5[b]	3.5[b]
N-Ac-L-His	2.2	8.0
N-Ac-D-His	3.6	6.9
N-Boc-L-His	1.2	12.1
N-Boc-D-His	5.6	10.7
N-Cbz-L-His	3.7	6.8
N-Cbz-D-His	3.0	7.0

[a] Stability constant values are reproducible within 10%.
[b] See Ref. 11.

Table 2. Stability constant values (β_2) of binary complexes **Py**/am-β-CD in the presence of esters of amino acids

Ternary agent	β_2 (M^{-2})/10[6a] pH 8.0	β_2 (M^{-2})/10[6a] pH 9.0
None	1.7[b]	4.8[b]
L-Phe	8.9[b]	5.2[b]
D-Phe	1.2[b]	7.6[b]
L-PheMe	2.7[b]	3.9[b]
D-PheMe	19.3[b]	21.7[b]
L-Phe-*t*-Bu	7.3	n.d.
D-Phe-*t*-Bu	9.6	n.d.
L-Met	13.6[b]	2.2[b]
D-Met	2.5[b]	5.4[b]
L-MetMe	2.5[b]	1.6[b]
D-MetMe	29.0[b]	5.1[b]
L-Met-*t*-Bu	3.4	5.1
D-Met-*t*-Bu	4.6	3.9
L-His	7.9[b]	6.2[b]
D-His	6.5[b]	3.5[b]
L-HisMe	1.6[b]	3.1[b]
D-HisMe	3.8[b]	2.3[b]
L-His-*t*-Bu	1.0	3.8
D-His-*t*-Bu	1.4	4.4

[a] Stability constant values are reproducible within 10%.
[b] See Ref. 11.

constant β_2 will be given by Eq. 3:

$$\beta_2 = K_1K_2 = [S(CD)_2]/([S][CD]_2) \quad (3)$$

If $[CD] \gg [S]$ the change in the fluorescence intensity as function of CD concentration will be given by Eq. 4:

$$\Delta I = (\Delta\alpha\beta_2 S_t[CD_0]^2)/(1 + \beta_2[CD_0]^2) \quad (4)$$

where $\Delta\alpha$ is the difference of emission quantum yields of free and complexed **Py**, and S_t and CD_0 are the total concentration of the **Py** and am-β-CD, respectively. The Eq. 4 is the non-linearised version of Benesi–Hildebrand treatment.[14] A typical plot of ΔI as a function of $[CD_0]^2$ is shown in Figure 2.

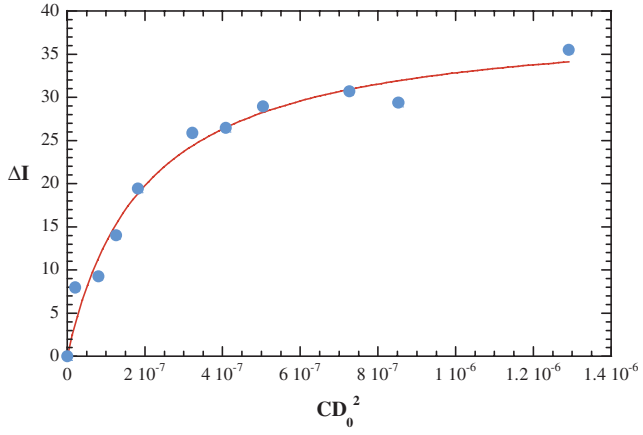


Figure 2. Curve fitting analysis of fluorescence spectral titration of **Py** with am-β-CD in the presence of *N*-Cbz-L-Phe in borate buffer solution at pH 9.0.

The fluorophore used in this work normally shows a good sensitivity to microenvironmental changes. Indeed, upon its inclusion into the am-β-CD cavity, the luminescence is enhanced because the guest molecule is shielded from quenching and non-radiative processes that occur in the bulk solution.[15] Typical fluorescence spectral changes upon addition of am-β-CD to a **Py** and ternary agent solution are shown in Figure 3.

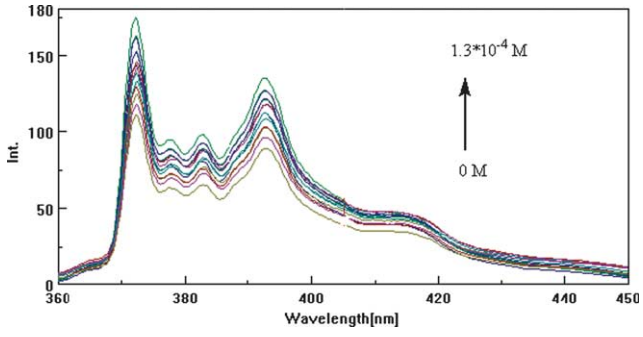


Figure 3. Fluorescence spectra of **Py** and *N*-Cbz-L-Phe in the presence of increasing concentrations of am-β-CD in borate buffer solution at pH 9.0.

Job plot analysis[16] had shown that the binary complex has a (1/2) (**Py**–am-β-CD) stoichiometric ratio.[11] However, in this complex neither of the cavities is completely filled by the **Py** molecule and therefore some water molecules are still present. These are in an energetically disfavoured condition. So the complex stability can be altered by adding a ternary agent.[11,12] As previously reported,[12] a stoichiometric ratio (1/2/2) (fluorophore–cyclodextrin–ternary agent) for ternary complexes studied was determined by means of Job plot analysis.[16] The β_2 value for the ternary complex can be either higher or lower than that for the binary complex. A higher β_2 value means that the ternary complex is more stable than the binary one, while the contrary being due for a lower value. Stabilisation of the ternary complex occurs when residual cavity desolvation prevails on partial displacement of guest molecule. Of course, extensive displacement will cause ternary complex destabilisation. In our case, owing to the sandwich geometry of the binary complex **Py**/am-β-CD (Fig. 4) we visualise the inclusion process for the formation of a (1/2/2) (fluorophore–cyclodextrin–ternary agent) ternary complex as continuous.

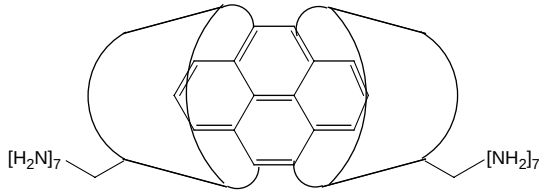


Figure 4. Schematic representation of binary complex **Py**/am-β-CD.

Initially, the ternary agent can displace some water molecules, increasing the stability; successively a deeper inclusion should begin to push out the fluorophore molecule, decreasing the stability. Then the β_2 value should show a somewhat bell shaped trend as function of the inclusion depth of the ternary agent. So the same β_2 value could be referred to two different situations.

The analysed properties of ternary complexes are obviously influenced by the ternary agent; that is, its side chain structure as well as its protecting group structure. In particular, the chosen protecting groups have different steric hindrance (the MR values for Me, *t*-Bu, Ac, Boc and Cbz are 5.65, 19.62, 11.18, 26.77 and 37.20, respectively)[17] and hydrophobicity (the π values for Me, *t*-Bu, Ac, Boc and Cbz are 0.56, 1.58, −0.55, 1.62 and 1.84, respectively).[17] Furthermore, different interactions can be present in the systems studied as a consequence of the different charge present on the primary rim of am-β-CD.[18] Consequently pH variation can be important in determining both the stability and chiral recognition ability of complex.

2.1. Amides

For a quick overall evaluation, data relative to amides are also shown in Figure 5.

Among the *N*-protected amino acids used in this work, the *N*-Cbz-Phe, at pH 9.0, did not allow us to determine the β_2 value. In fact, in this case, solutions of the ternary complex were too turbid to acquire steady-state fluorescence spectra.

As can be seen from data reported in Figure 5, in most cases (30 from 34), both at pH 8.0 and at pH 9.0, addition of

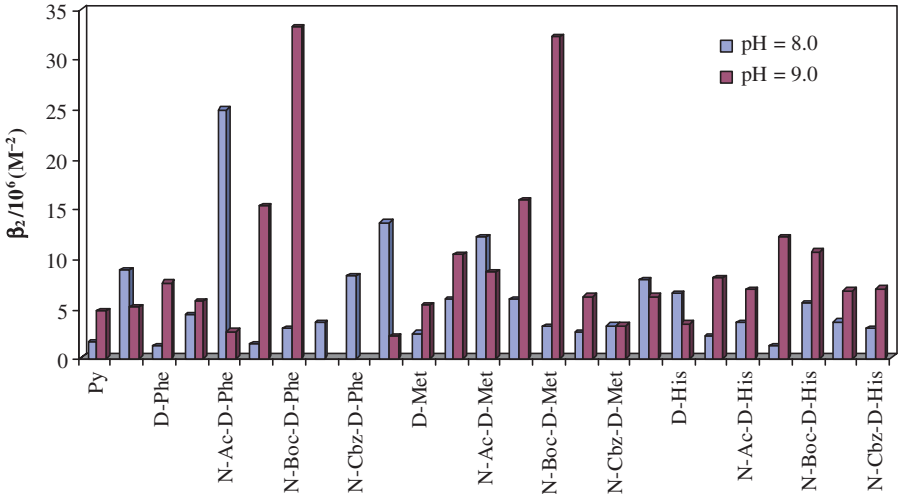


Figure 5. Stability constant values (β_2) of ternary complexes formed by **Py**/am-β-CD in the presence of amides.

amides stabilises the binary complex. Generally these ternary agents, present prevalently as anions,[19] form more stable complexes at pH 9.0 (13 from 16) than at pH 8.0. This seems to indicate that the hydrogen bonds between the carboxylate group of the ternary agents and amino groups of am-β-CD are more efficient than electrostatic interactions, that are operative at pH 8.0, in stabilising the system. These results are completely different from those previously obtained in the presence of the corresponding amino acids.[11] In general, the amount of stabilisation, going from pH 8.0 up to 9.0, seems to increase with hydrophobicity of the protecting group.

To evaluate the effect of N-substitution on amino acids, data collected in this work can be compared with those, previously reported,[11] dealing with the stability of the ternary complexes formed in the presence of the corresponding amino acids. As can be seen from the Table 1, the ternary complexes of L-amides are less stable (at pH 8.0) and more stable (at pH 9.0) than those for the corresponding amino acids. Indeed at pH 8.0, the Coulombic interactions, operating equally in the presence of amino acids or amides, are the main contribution to stability of the ternary complex. On the other hand, at pH 9.0, the presence of a bulky substituent on the amino group, that can increase the contribution of hydrophobic interactions, determines the higher stability of the ternary complexes formed by amides. The different behaviour shown by L- and D- derivatives going from pH 8.0 up to 9.0 could be traced back to the occurrence of a some variation in host shape.

In fact, the am-β-CD in its charged form has a distorted structure owing to electrostatic repulsion among the cationic ammonium groups.[21]

A different trend is shown for D-amides, in fact, the ternary complexes of D-amides are, generally, more stable than those of the corresponding amino acids. **His** constitutes an interesting exception, at pH 8.0 the *N*-substituted complexes of **His**, irrespectively of D,L configuration, are less stable than those of both L- and D-amino acids.

However, data obtained show that the stability of the complexes cannot be rationalised only by considering differences in hydrophobicity or in steric hindrance of the protecting groups. Indeed, the stability of complexes formed by the **Phe** derivatives, at pH 8.0, can be explained by considering the steric hindrance of the substituent present on the amino group, but the same factor does not allow us to rationalise the trend in β_2 values for the ternary complexes formed by derivatives of **Met** and **His**. Probably the stability of these complexes is a result of a balance between these two factors (steric hindrance and hydrophobicity) that can act in opposite directions.

In our opinion, it is important to analyse data in the light of the side chain structure of amino acids. Indeed, as both at pH 8.0 and 9.0 the **His** has a charged side chain, owing to a more difficult desolvation process, it should form less stable complexes. A comparison among data reported in Table 1 shows that, in many cases, this hypothesis is confirmed. Indeed, considering the **Met** derivatives, with the exception of the *N*-Cbz derivatives, ternary complexes formed by this amino acid are more stable than those formed by the **His** derivatives.

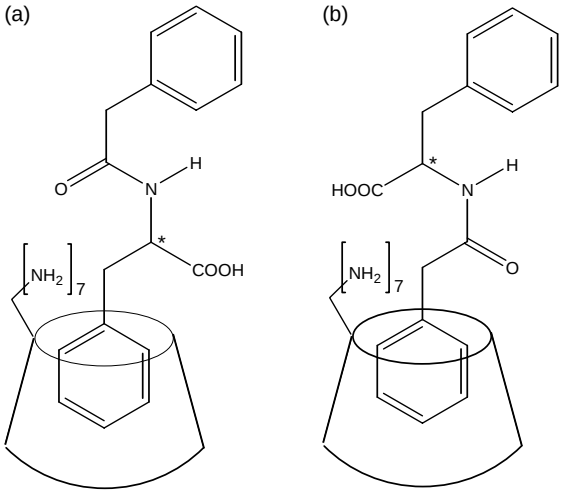


Figure 6. Schematic representation of complex formed by *N*-Cbz-Phe.

The last factor to analyse is the inclusion direction of the ternary agent. On this subject, going from *N*-Ac derivatives to *N*-Cbz derivatives there is an increase in the hydrophobicity, in particular *N*-Cbz-Phe is an example of ditopic ternary agent. So, it could be reasonable to think that there will be a competition between the protecting group and the side chain for the occupancy of the residual cavity of am-β-CD in the binary complex (Fig. 6).

However, in our opinion, in arrangement **b** (Fig. 6) the asymmetric carbon atom of the ternary agent should be too far from the cavity to justify the different β_2 values determined for the enantiomers of the same derivative and consequently their chiral recognition (see later).

2.2. Amino esters

The influence of electrostatic interactions on stabilisation of the ternary complexes has been investigated by esterification of amino acids. Under the experimental conditions these are prevalently present as neutral molecules.[22] In Figure 7, the stability constant values (β_2) for the ternary complexes formed by **Py**/am-β-CD in the presence of amino esters are shown. Among the amino esters studied, only Phe-*t*-Bu, at pH 9.0, did not allow us to determine the β_2 values, because of the high turbidity of solutions.

As can be seen from Figure 7, in most cases (14 from 18), at pH 8.0, the addition of the amino esters increases the stability of the binary complex **Py**/am-β-CD, according to the exclusion of some water molecules from the residual cavity of the am-β-CD. The values collected at pH 9.0 show a diversified behaviour. Indeed, the addition of amino esters in some cases induces an increase in stability and in some others the opposite effect is observed. However, the comparison with the β_2 values obtained in the presence of the corresponding amino acids[11] shows that the amino esters have a very well-defined behaviour. Indeed, in general, L-amino esters, with the exception of the L-Met-*t*-Bu at pH 9.0, form less stable ternary complexes as compared with the corresponding amino acids. On the contrary, the D-amino esters have a less clear behaviour. Indeed, for D-**Phe** the complexes of esters are more stable than those of the acid. The opposite, with the exception of the *t*-Bu ester at pH 9.0, occurs for D-**His**, whereas for D-**Met** the order of stability changes going from pH 8.0 to 9.0. This indicates that generally the increase in hydrophobic interactions going from the amino acid to methyl ester does not counterbalance the decrease in electrostatic interactions by ion-pairing between the amino acid anion and protonated amino groups of the am-β-CD.

In general, the stability of ternary complexes formed by the amino esters increases in the order:

His < Met < Phe

according to the increase of the side chain hydrophobicity.

The two chosen protecting groups (methyl and *t*-butyl) are different in their steric hindrance and hydrophobicity. The increase in steric hindrance should lead to a destabilisation of the complex; on the other hand an increase in hydrophobic interactions, going from methyl esters up to *t*-butyl esters, should lead to a stabilisation of the complex. However, collected data show that the stability of studied ternary complexes cannot be explained considering these factors separately. Indeed, the complex formed by L-PheMe, at pH 8.0, is less stable than that formed by L-Phe-*t*-Bu, according to lower hydrophobicity, but the D-enantiomers show an opposite stability order. Similar behaviour can be observed for the amino esters of **Met** at pH 9.0. Probably, also in this case, as in the presence of amides, stability of the ternary complex is a result of the balance between these two discordant forces and of some variation in the host shape.

2.3. Chiral recognition

In Table 3, the enantioselectivity ratios determined in the presence of amides or esters of amino acids, as a function of pH values are reported. Furthermore, for a useful comparison, enantioselectivity ratios, previously determined for ternary complexes formed in the presence of corresponding amino acids,[11] are also reported.

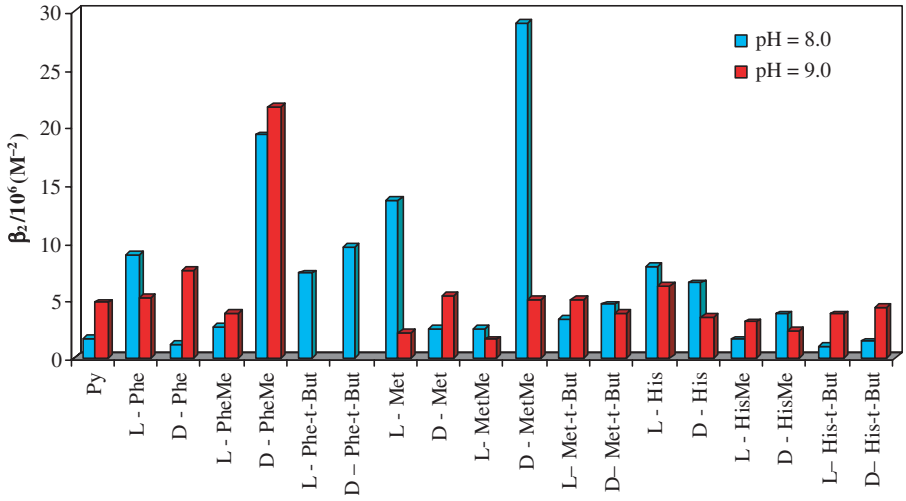


Figure 7. Stability constant values (β_2) of the ternary complexes formed by **Py**/am-β-CD in the presence of amino esters.

Table 3. Enantioselectivity ratios for ternary complexes formed by **Py**/am-β-CD in the presence of amides and esters of amino acids

Ternary agent	E.r. pH 8.0[a]	E.r. pH 9.0[a]
Phe	7.4 (L>D)[b]	6.3 (D>L)[b]
PheMe	7.1 (D>L)[b]	5.6 (D>L)[b]
Phe-*t*-Bu	1.3 (D>L)	n.d.
N-Ac-Phe	5.6 (D>L)	2.2 (L>D)
N-Boc-Phe	2.2 (D>L)	2.2 (D>L)
N-Cbz-Phe	2.4 (D>L)	n.d.
Met	5.4 (L>D)[b]	2.5 (D>L)[b]
MetMe	11.6 (D>L)[b]	3.2 (D>L)[b]
Met-*t*-Bu	1.3 (D>L)	1.3 (L>D)
N-Ac-Met	2.1 (D>L)	1.2 (L>D)
N-Boc-Met	1.8 (L>D)	2.0 (D>L)
N-Cbz-Met	1.3 (D>L)	1.9 (L>D)
His	1.2 (L>D)[b]	1.8 (L>D)[b]
HisMe	2.3 (D>L)[b]	1.4 (L>D)[b]
His-*t*-Bu	1.4 (D>L)	1.2 (D>L)
N-Ac-His	1.6 (D>L)	1.2 (L>D)
N-Boc-His	4.7 (D>L)	1.1 (L>D)
N-Cbz-His	1.2 (L>D)	1.0

[a] E.r. = enantioselectivity ratio.
[b] See Ref. 11.

Also in this case, for a quick overall evaluation, these values are shown in Figure 8.

As can be seen from Figure 8, the binary complex **Py**/am-β-CD is able to recognise amino acids derivatives not only according to their size and shape, but also their chirality. According to the picture previously reported by Kano et al.[23] about the arrangement of α-amino acid derivatives in the cavity of the am-β-CD or of heptakis(6-carboxymethylthio)-(6-deoxy)-β-CD, also in this case it can be supposed that the hydrophobic part of the chiral molecule is anchored by means of interactions between the carboxy or amino group of the ternary agent and the arms of the host.

The chiral discrimination ability of the binary complex **Py**/am-β-CD seems to be affected by pH values.

The analysis of the data reported in Table 3 shows that the enantioselectivity of the studied chiral selector changes with the pH values. In fact at pH 8.0 a higher affinity for D-enantiomers is shown (12 from 15), but increasing the pH induces a higher affinity for L-enantiomers. Moreover, enantioselectivity ratios are higher at pH 8.0 than at 9.0. At pH 8.0 they range from 1.2 for the *N*-Cbz-His up to 11.6 for MetMe; while at pH 9.0 they range from 1.0 for *N*-Cbz-His up to 5.6 for the PheMe. This result seems to indicate that the binary complex is a better chiral selector in charged rather than in its neutral form. Furthermore, above all in the presence of amides, our results seem to indicate that electrostatic interactions play a determining role in recognition of chirality in supramolecular chemistry. This agrees with what was previously reported by Kano et al.[21] about the higher chiral discrimination ability of the mono-(6-amino)-(6-deoxy)-β-CD and am-β-CD, in their charged form, with respect to the native β-CD.

With the exception of the **His** derivatives, a comparison with enantioselectivity ratios, previously determined in the presence of the corresponding amino acids,[11] shows that, in all cases the binary complex is a better chiral selector for unprotected amino acids. In general, the enantioselectivity seems to be affected by the side chain structure of the amino acid; in fact the L-enantioselectivity increases going from **His** derivatives, to **Met** to **Phe** ones, with the increase in hydrophobicity of the side chain. Furthermore, in many cases, for the same derivative, the enantioselectivity ratio decreases going from **Phe** to **His**.

Our data show that the chiral discrimination ability, in many cases, increases with the ternary complex stability. This result agrees with Xie et al.[24] who found higher enantioselectivity with stronger binding, studying the chiral discrimination ability of some homochiral molecular tweezers; but it is in disagreement with Inoue's assertions that stronger binding by cyclodextrin leads to a loss of the chiral recognition.[25] Nevertheless, we believe that the direct substrate-CD interaction is not comparable with substrate-binary complex interaction. Indeed, as we have previously reported,[11] the former leads to the best host–guest fit, whereas the latter should consist of an acceptable arrangement of substrate into the available residual CD cavity of the binary complex.

In general, the enantioselectivity ratios determined by us are comparable or higher than those previously reported. In this light, the enantioselectivity ratio determined by Kano et al.[21] for am-β-CD in the presence of *N*-Ac amino acids ranges from 1.1 for *N*-Ac-Phe up to 1.6 for *N*-Ac-Trp. In our case, this value ranges from 1.2 for *N*-Ac-His up to 5.6 for *N*-Ac-Phe. Likewise Xie et al.[23] reported enantioselectivity ratios for methyl esters of α-amino acids ranging from 1.2

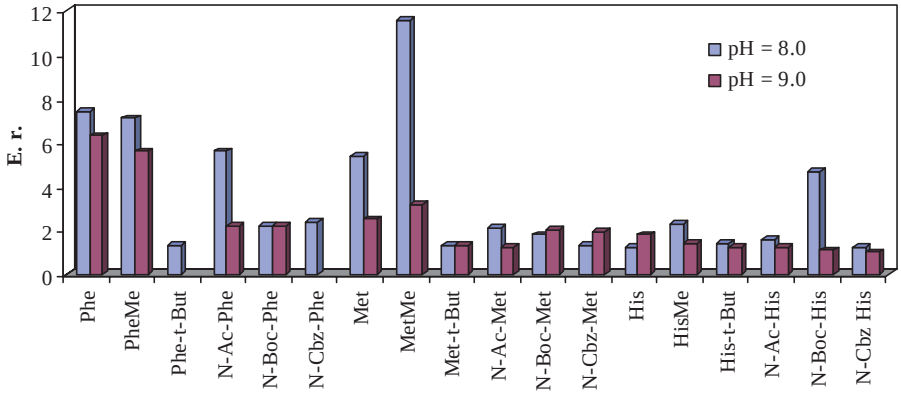


Figure 8. Enantioselectivity ratios (E.r.) as function of pH values.

for AlaMe up to 7.9 for TrpMe. In our case, enantioselectivity ratios in the presence of α-amino esters range from 1.4 for HisMe up to 7.1 for PheMe.

3. Conclusions

The data collected in this work show that generally the complex **Py**/am-β-CD forms stable ternary complexes in the presence of both the *N*- and *O*-protected α-amino acids studied. The actual complex stability is a consequence of the balance of some factors. Among these, steric hindrance and hydrophobicity seem to be the most important. The different stabilities determine a good chiral discrimination ability for the binary complex, making it a useful chiral selector for very dilute solution of enantiomers.

4. Experimental

4.1. Materials

Heptakis-(6-amino)-(6-deoxy)-β-cyclodextrin was synthesised and purified according to the procedure described in literature.[26] The product was dried for 24 h in a dryer under vacuum over phosphorous pentoxide at 60 °C and then was stored in the same apparatus at 40 °C.

D-PheMe, D-MetMe, D-HisMe, D-Phe-*t*-Bu, L- and D-Met-*t*-Bu, L- and D-His-*t*-Bu, *N*-Cbz-D-Phe, *N*-Cbz-D-Met, *N*-Ac-L- and D-His were prepared according to procedures previously reported.[27]

Borate buffer solutions (0.05 M) were prepared according to the standard procedure, using freshly double-distilled decarbonised water. The actual pH of the solutions was recorded using a pH M82 Radiometer equipped with a GK2401C combined electrode.

4.2. Spectrometric measurements

The solution of am-β-CD in borate buffer (1.4×10^{-3} M) was filtered just before use by a Millipore 0.45 μm filter. Pyrene aqueous solution (2×10^{-6} M) was prepared injecting a pyrene methanolic solution (2×10^{-3} M) into a buffer solution, containing the ternary agent (1×10^{-2} M). Measurement solutions were prepared by adding increasing volumes of the am-β-CD to 1 mL of the pyrene and ternary agent into a volumetric flask. In these solutions, the concentrations of the pyrene and the ternary agent were constant and equal to 2×10^{-7} and 1×10^{-3} M, respectively, while the concentration of the am-β-CD increased from 1.4×10^{-4} M up to 1.3×10^{-3} M. All measurement solutions were deareated, before use, by Ar for 12 min.

Steady-state fluorescence spectra were acquired with a JASCO FP-777W spectrofluorimeter. Excitation and emission slits were set at 1.5 nm and excitation wavelength was 337 nm. Spectra were recorded from 360 to 450 nm. Every spectrum was averaged over 50 scans. A suitable wavelength was chosen after recording a 'difference spectrum' by comparison to a sample without cyclodextrin and one with the highest cyclodextrin concentration.

Acknowledgements

Financial support from the University of Palermo (Funds for selected topics) and Italian MIUR within National Project 'Non-aromatic heterocyclic in stereo-controlled processes' is gratefully acknowledged.

References and notes

1. Fitzmaurice, R. J.; Kine, G. M.; Douheret, D.; Kilburn, J. D. *J. Chem. Soc., Perkin Trans. 1* **2002**, 841–864.
2. (a) Bazzicalupi, C.; Bencini, A.; Berni, E.; Bianchi, A.; Fornasari, P.; Giorgi, C.; Valtancoli, B. *Eur. J. Inorg. Chem.* **2003**, 1974–1983. (b) Imai, H.; Munakata, H.; Uemori, Y.; Satura, N. *Inorg. Chem.* **2004**, *43*, 1211–1213. (c) Asif, R.; Chung, D. S.; Hong, J. I. *Tetrahedron Lett.* **2003**, *44*, 4335–4338.
3. Araki, K.; Goto, M.; Furusaki, S. *Anal. Chim. Acta* **2002**, *469*, 173–181.
4. (a) You, J.-S.; Xu, X.-Q.; Zhang, G.-L.; Xiang, Q.-X.; Lan, J.-B.; Xie, R.-G. *Chem. Commun.* **2001**, 1816–1817. (b) Gasparrini, F.; Misiti, D.; Pierini, M.; Villani, C. *Org. Lett.* **2002**, *4*, 3993–3996. (c) Chen, X.; Du, D.-M.; Hua, W.-T. *Tetrahedron: Asymmetry* **2003**, *14*, 999–1007. (d) Zheng, Y.-S.; Zhang, C. *Org. Lett.* **2004**, *6*, 1189–1192.
5. (a) Cooper, A.; MacNicol, D. D. *J. Chem. Soc., Perkin Trans. 2* **1978**, 760–763. (b) Rekharsky, M. V.; Schwarz, F. P.; Tewari, Y. B.; Goldberg, R. N. *J. Phys. Chem.* **1994**, *98*, 10282–10288. (c) Liu, Y.; Li, L.; Li, X. Y.; Zhang, H. Y.; Wada, T.; Inoue, Y. *J. Org. Chem.* **2003**, *68*, 3646–3657. (d) Liu, Y.; Yu, C.-C.; Zhang, H.-Y.; Zhao, Y.-L. *Eur. J. Org. Chem.* **2003**, 1415–1422.
6. Lara, K. O.; Godoy-Alcantar, C.; Eliseev, A. V.; Yatsimirsky, A. K. *Org. Biomol. Chem.* **2004**, *2*, 1712–1718.
7. (a) Hembury, G.; Rekharsky, M.; Nakamura, A.; Inoue, Y. *Org. Lett.* **2000**, *2*, 3257–3260. (b) Mwakibete, H.; Bloor, D. M.; Wyn-Jones, E. *J. Inclusion. Phenom. Mol.* **1991**, *10*, 497–505. (c) Maletic, M.; Wennemers, H.; McDonald, D. Q.; Breslow, R.; Still, W. C. *Angew. Chem.* **1996**, *108*, 1594–1596. (d) Hacket, F.; Simova, S.; Schneider, H.-J. *J. Phys. Org. Chem.* **2001**, *14*, 159–170.
8. (a) Bonomo, R. P.; Cucinotta, V.; Maccarrone, G.; Rizzarelli, E.; Vecchio, G. *J. Chem. Soc., Dalton Trans.* **2001**, 1366–1373. (b) Corradini, R.; Paganizzi, C.; Marchelli, R.; Pagliari, S.; Sforza, S.; Dossena, A.; Galaverna, G.; Duchateau, A. *Chirality* **2003**, *15*, S30–S39. (c) Pagliari, S.; Corradini, R.; Galaverna, G.; Sforza, S.; Dossena, A.; Montalti, M.; Prodi, L.; Zaccheroni, N.; Marchelli, R. *Chem. Eur. J.* **2004**, 2749–2758.
9. Brown, S. E.; Coates, J. H.; Duckworth, P. A.; Lincoln, S. F.; Easton, C. J.; May, B. L. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 1035–1040.
10. (a) Nardi, A.; Eliseev, A.; Bocek, P.; Fanali, S. *J. Chromatogr.* **1993**, *638*, 247–253. (b) Lelievre, F.; Gareil, P.; Jardy, A. *Anal. Chem.* **1997**, *69*, 385–392. (c) Egashira, N.; Mutoh, O.; Kurauchi, Y.; Ohga, K. *Anal. Sci.* **1996**, *12*, 503–510.
11. D'Anna, F.; Riela, S.; Gruttadauria, M.; Lo Meo, P.; Noto, R. *Tetrahedron: Asymmetry* **2002**, *13*, 1755–1760.
12. D'Anna, F.; Riela, S.; Gruttadauria, M.; Lo Meo, P.; Noto, R. *Tetrahedron* **2005**, *61*, 4577–4583.

13. Xu, W.; Demas, J. N.; DeGraff, B. A.; Whaley, M. *J. Phys. Chem.* **1993**, *97*, 6546–6554.
14. Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703–2707.
15. (a) Kobayashi, N.; Saito, R.; Hino, H.; Hino, Y.; Ueno, A.; Osa, T. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1031–1036. (b) Hamai, S. *J. Phys. Chem.* **1989**, *93*, 2074–2078.
16. Job, P. *Ann. Chim.* **1928**, *8*, 113–203.
17. Hansch, C.; Leo, A. J. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley: New York, 1979.
18. Hamelin, B.; Jullien, L.; Guillo, F.; Lehn, J. M.; Jardy, A.; De Robertis, L.; Driguez, H. *J. Phys. Chem.* **1995**, *99*, 17877–17885.
19. The pK_a values of amino acid increase as a consequence of electronic effect of the N-protection. For example, in the case of *N*-acetyl glycine the pK_{a1}, relative to dissociation of carboxylic group, moves from 2.35 to 3.67.[20] The pK_{a2} value, relative to dissociation of ammonium group, should be affected to an even major extent.
20. Dean, J. A. *Handbook of Organic Chemistry*; Mcgraw-Hill Book Company: New York, 1987.
21. Kitae, T.; Nakayama, T.; Kano, K. *J. Chem. Soc., Perkin Trans. 2* **1998**, 207–212.
22. The pK_a value for ammonium dissociation decreases as a consequence of the esterification. For example, in the case of **Phe**, it moves from 9.31 to 7.05.[20]
23. Kano, K.; Nishiyabu, R. *J. Inclusion Phenom. Macro.* **2002**, *44*, 355–359.
24. Du, C.-P.; You, J.-S.; Yu, X.-Q.; Liu, C.-L.; Lan, J.-B.; Xie, R.-G. *Tetrahedron: Asymmetry* **2003**, *14*, 3651–3656.
25. Rekharsky, M. V.; Inoue, Y. *J. Am. Chem. Soc.* **2002**, *124*, 813–826.
26. Ashton, P. R.; Koniger, R.; Stoddart, J. F. *J. Org. Chem.* **1996**, *61*, 903–908.
27. (a) Rachele, J. R. *J. Org. Chem.* **1963**, *28*, 2898. (b) Stephen, C. B.; Cobás, A. A.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 2369–2376. (c) Gibson, F. R.; Bergmeier, S. C.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3216–3218. (d) Kocienski, P. J. *Protecting Groups*; Georg Thieme: Stuttgart, New York, 1994.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 62 (2006) 4331–4341

A new convergent and stereoselective synthesis of 2,5-disubstituted *N*-acylpyrrolidines

Luca Banfi, Andrea Basso, Giuseppe Guanti and Renata Riva*

Dipartimento di Chimica e Chimica Industriale, Via Dodecaneso 31, I-16146 Genova, Italy

Received 7 December 2005; revised 9 February 2006; accepted 23 February 2006

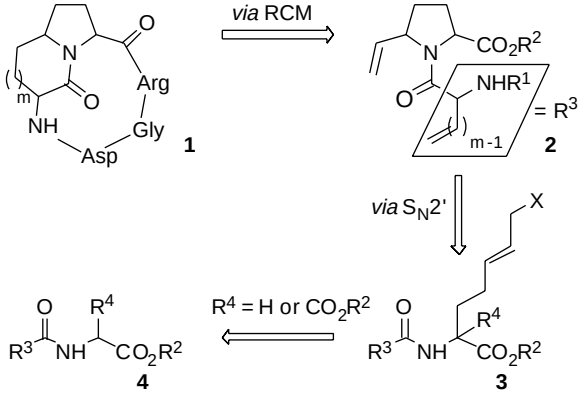
Abstract—A new synthesis of 2,5-disubstituted *N*-acylpyrrolidines through an S_N2' reaction promoted by the nitrogen anion of a secondary amide onto an allylic bromide is reported. A moderate stereoselectivity, in favour of the trans heterocycle, was observed during the cyclization of a chiral precursor, while a good stereoselectivity, this time in favour of the cis one, was obtained when the second stereocentre was introduced after the cyclization step to give the same product.

1. Introduction

Pyrrolidine is a very important heterocycle present in many biologically active compounds, such as proteins or alkaloids and has become one of the priviledged structures in drug discovery.[1] In particular, bicyclic lactams, bearing a pyrrolidine moiety and equipped with suitable appendages, are very popular since they can be used as constrained peptidomimetics.[2] Moreover, they are frequently able to mimic a reverse turn, an important motif responsible for inducing the appropriate conformation in small oligopeptides involved in essential interactions with many biological targets. An example is represented by bicyclic lactams included in a macrocycle together with the RGD sequence: in this case, the bicyclic system acts as an 'external scaffold'[3] and these molecules showed interesting properties as inhibitors of $\alpha_V\beta_3$ or $\alpha_V\beta_5$ integrins.[4] In the last few years, our group has been involved in the synthesis of either mesocyclic lactams[5,6] or bicyclic derivatives[7] as possible inhibitors of integrins.

The previous reported synthesis of [*n*,3,0] (*n*=4, 5, 6, 7) bicyclic systems are based on the construction of the larger ring as the last step, employing usually the highly versatile ring closing metathesis (RCM),[8] but standard lactonization[7] or lactamization reactions[9] or radical cyclizations[10] have been utilized too. Therefore, in the first part of these syntheses, a suitably functionalized pyrrolidine had to be assembled.

In our project, we planned to synthesise a series of [*n*,3,0] bicyclic scaffolds such as **1** (Scheme 1) and, in view of cyclization through RCM as the final step, we would need a convergent synthesis of *N*-acyl-2-carbalkoxy-5-vinylpyrrolidines **2**. An attractive strategy towards this goal involves an S_N2' procedure promoted by a nitrogen nucleophile onto a double bond equipped with a suitable leaving group at the terminal allylic position. The acyclic precursor **3** may be assembled, for example, by alkylation of α-acylaminoesters or malonates **4**. Malonates can be used in place of simple esters; thanks to the possibility of removing the second carbalkoxy group via saponification–decarboxylation. This step can be performed either before or after cyclization. Moreover, for an efficient and convergent approach to **1**, R^3 group should be equipped with both the double bond, to be used in RCM, and NHR^1 group essential, together with



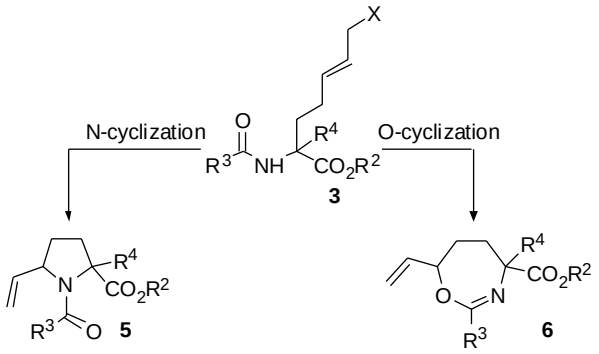
Scheme 1.

Keywords: Pyrrolidine; S_N2'; Peptidomimetics.
* Corresponding author. Tel.: +39 0103536126; fax: +39 0103536118; e-mail: riva@chimica.unige.it

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.073

CO_2R^2, for the creation of the macrocyclic peptidic structure including for example RGD motif.

To the best of our knowledge, intramolecular S_N2' reactions, starting from simple secondary amides, were unprecedented. While in a few cases pyrrolidines or piperidines have been prepared through an S_N2' cyclizations under palladium catalysis,[11] those examples involved the use of carbamates. Thus, the success of the envisaged strategy was not obvious, since it is known that in amides there is often a competition between N and O-alkylation, affording, in our case, **5** or **6**, respectively, as outlined in Scheme 2.[12] In carbamates this competition is less important. The development of a protocol leading in one-pot to *N*-acyl derivatives (and not to carbamates) would considerably shorten the approach to key intermediate **2** (that may be in principle obtained also through a Ugi multicomponent reaction). The feasibility of our hypothesis was studied on a model compound, that is the acetamide corresponding to general formula **3** (R^3 =Me).[13]

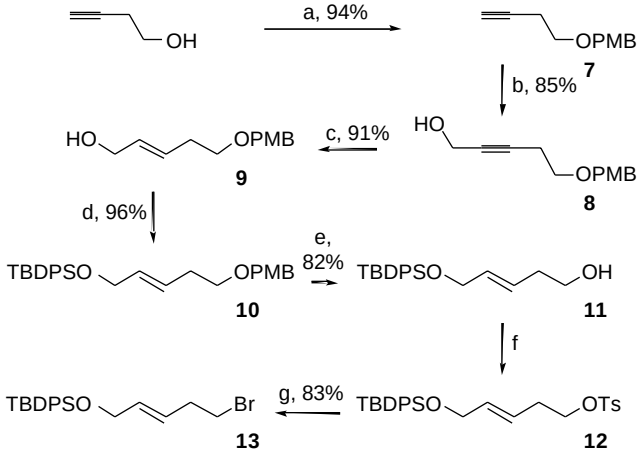


Scheme 2.

2. Results and discussion

N-Acetyl homoallylglycinates are not available commercially either in racemic or in enantiopure form; thus we had to develop a convergent racemic synthesis of them, involving the alkylation of the enolate of unexpensive diethyl acetamido malonate with a suitable homoallylic bromide, equipped with a masked leaving group at the allylic position to be exploited in the cyclization.

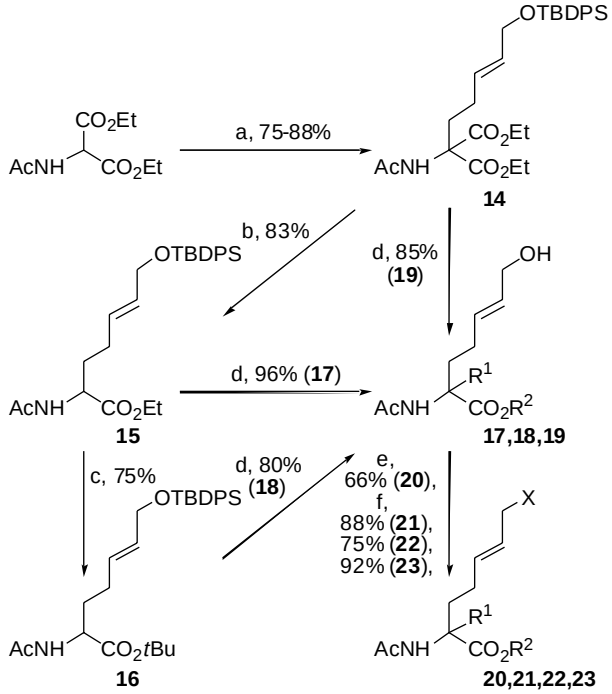
The initial task was therefore the preparation of a 2-pentene substituted at position 5 (a homoallylic carbon) with a good leaving group and at the more reactive position 1 (an allylic carbon), with a poor one. We started from commercially available 3-butyn-1-ol (Scheme 3), that was protected as *p*-methoxybenzyl ether (PMB) and then homologated by treatment of the magnesium acetylide of **7** with paraformaldehyde. Compound **8**, obtained in excellent yield after hydrolysis under basic conditions of the complex mixture of hemiacetalic derivatives of formaldehyde,[14] contained two differentiated primary alcoholic functionalities, that have been elaborated independently during the synthesis.[15] The free propargylic alcohol was reduced to give, with total control of the geometry of the incoming double bond, allylic alcohol **9** in excellent yield.[16] Silylation of **9** allowed to prepare **10**, with two orthogonally protected hydroxy groups. Removal of PMB under oxidative conditions afforded **11**, ready to be converted into bromide



Scheme 3. (a) NaH, *p*-methoxybenzylchloride, DMF, 0 °C; (b) (i) EtMgBr, paraformaldehyde, THF, rt; (ii) K_2CO_3, MeOH, rt; (c) $LiAlH_4$, MeONa, THF, reflux; (d) $Ph_2tBuSiCl$, imidazole, DMF, rt; (e) DDQ, CH_2Cl_2/H_2O 20:1, rt; (f) TsCl, py, rt; (g) KBr, DMF, 100 °C.

13 in excellent overall yield, provided that tosylate **12** is recovered by neutral work-up and submitted immediately to nucleophilic displacement without previous purification. Despite the long preparation, the overall yield of this bromide from 3-butyn-1-ol was a remarkable 48%.

The alkylation of diethyl acetamido malonate was found to be troublesome, most likely because of the propensity of the rather unreactive bromide **13** to undergo competitive reactions, such as elimination, to give the corresponding



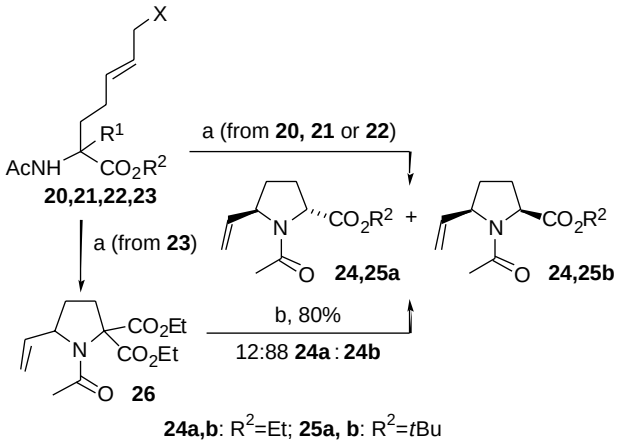
17: R^1 = H, R^2 = Et; **18**: R^1 = H, R^2 = *t*Bu; **19**: R^1 = CO_2Et, R^2 = Et
20: R^1 = H, R^2 = Et, X = Cl; **21**: R^1 = H, R^2 = Et, X = Br;
22: R^1 = H, R^2 = *t*Bu, X = Br; **23**: R^1 = CO_2Et, R^2 = Et, X = Br

Scheme 4. (a) NaH, **13**, DMF, 90 °C; (b) (i) NaOH 6 M in EtOH, EtOH, rt; (ii) H^+; (iii) dioxane, reflux; (c) (i) NaOH 6 N, EtOH, rt; (ii) $CCl_3C(=NH)OtBu$, $BF_3\cdot Et_2O$, CH_2Cl_2, rt; (d) nBu_4NF, THF, rt; (e) CCl_4, PPh_3, reflux; (f) CBr_4, PPh_3, CH_3CN, rt.

conjugated diene. After a careful optimization of the conditions we succeeded in obtaining **14** in good yield (Scheme 4).[17]

Monodecarboxylation, following our protocol developed for structurally similar compounds, afforded finally **15**.[6] As the final step, we studied the transformation of the silyl ether into a halide, via the free alcohol **17**. When we tried to prepare the tosylate,[18] we could not isolate it, but it was readily converted into the corresponding chloride **20**, albeit in unsatisfactory yield. For this reason, we used a direct method, which employed triphenyl phosphine and carbon tetrachloride both as reagent and solvent.[19] Although harsher conditions than the reported ones were required, chloride **20** was finally isolated in acceptable yield. Modified reaction conditions, using carbon tetrabromide and triphenylphosphine in acetonitrile, allowed the preparation of bromide **21** in higher yield and under milder conditions.

During the first cyclization experiment (Scheme 5) we treated chloride **20** with potassium bis(trimethylsilyl)amide (KHMDS) and we were pleased to discover the only products derived from *N*-promoted cyclization. The yield was, however, moderate, whereas a poor diastereoselectivity in favour of the trans stereoisomer **24a** was observed (entry 1, Table 1).[20] Under the same conditions, bromide **21** showed to be, as expected, more reactive, affording **24a**,**b** in higher yield, but with similar diastereoselectivity (entry 2). The following screening was therefore done on the best performing substrate **21**. Other bases, such as NaH gave unsatisfactory results (entry 5), particularly from the stereochemical point of view, while an improved diastereomeric ratio was observed using the lithium anion of bis(trimethylsilyl)amide (LiHMDS).[21] The reaction temperature showed an appreciable influence just on the rate, but not on the stereoselectivity. Also the nature of the solvent was varied, demonstrating that optimal results can be achieved with the aprotic dipolar ones. Interestingly, when apolar toluene was used (entry 7) a reversal of stereoselectivity was observed. However, this reaction was too slow for preparative purposes. Compounds **24a**,**b** showed to be configurationally stable under basic conditions, since no changes in diastereomeric ratio were observed after prolonged storage under the reaction conditions.



Scheme 5. (a) see Table 1; (b) (i) NaOH 6 N, EtOH; (ii) H^+; (iii) dioxane, reflux.

The bulkier *t*-butyl ester **22** was obtained from **15** by a three step procedure (Scheme 4). Its cyclization was slower and required a temperature of at least −50 °C in order to start, while no improvement in the diastereomeric ratio was realized (entry 11).

In order to improve the stereoselectivity and gain access to the minor cis diastereoisomer, we carried out the cyclization also starting from malonate **23** (entry 12). The reaction took place in good yield to give **26**. This reaction is particularly interesting since the monodecarboxylation of **26** affords **24a**,**b** with good stereoselectivity favouring this time the cis diastereoisomer **24b** in a 7.3:1 ratio. Thus, two complementary procedures affording prevailingly either **24a** or **24b** are available and, since the two diastereoisomers can be separated although not easily by chromatography, our protocol constitutes an original new entry for the stereoselective synthesis of vinyl-substituted *N*-heterocycles.

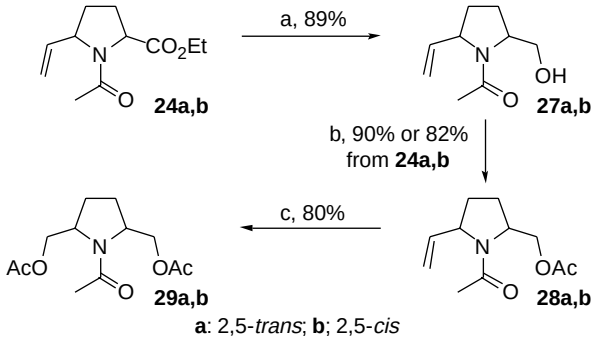
The determination of the relative configuration of **24a** and **24b** was first done tentatively by ^{1}H NMR correlation with

Table 1. Cyclization of halides **20**–**23**, through S_N2' reaction

Entry	Halide	Base[a]	Solvent[b]	Temperature (°C)	Time (h)	Product(s)	Yield (%)[c]	dr[d]
1	**20**	KHMDS[e]	THF/DMF 2:1	−10°→rt	3.5	**24a**,**b**	50	56:44
2	**21**	KHMDS[e]	THF/DMF 2:1	−10°→0°	0.67	**24a**,**b**	80	55:45
3	**21**	LiHMDS[f]	THF/DMF 2:1	−10°	4	**24a**,**b**	81	54:46
4	**21**	LiHMDS[f]	THF/DMF 2:1	−78°→−5°	24	**24a**,**b**	74	67:33
5	**21**	NaH	THF/DMF 2:1	−10°	2	**24a**,**b**	68	51:49
6	**21**	LiHMDS[f]	THF	−10°→rt	46	**24a**,**b**	55	58:42
7	**21**	LiHMDS[f]	Toluene	−10°→rt	50	**24a**,**b**	75	38:62
8	**21**	LiHMDS[f]	THF/DMSO 3:1	−10°→rt	4.25	**24a**,**b**	80	70:30
9	**21**	LiHMDS[f]	DMF	−10°→rt	6	**24a**,**b**	81	63:37
10	**21**	LiHMDS[f]	DMF	−78°	25	**24a**,**b**	90	70:30
11	**22**	LiHMDS[f]	DMF	−78°→−50°	22	**25a**,**b**	75	69:31
12	**23**	LiHMDS[g]	DMF	−15°→8°	2.5	**26**	78	—

[a] 1.5 mol equiv of base.
[b] 0.05–0.07 M with respect to substrate, with the exception of DMF (0.25 M).
[c] In entries 1–11 the yield is referred to the diastereomeric mixture.
[d] By GC–MS.
[e] KHMDS: potassium bis(trimethylsilyl)amide, 0.5 M solution in THF freshly prepared by dissolving solid commercial KHMDS.
[f] LiHMDS: lithium bis(trimethylsilyl)amide, 1.0 M commercial solution in THF.
[g] LiHMDS: 0.5 M solution in THF freshly prepared by dissolving solid commercial LiHMDS.

similar compounds.[22] In particular, while in the trans derivatives the chemical shifts of the terminal vinylic protons are close together, in the cis series a 0.24–0.28 ppm difference was always observed, with the proton trans to the other vinylic one downfield. Moreover, our expectations were confirmed by transforming both stereoisomers into triacetyl derivatives **29a**,**b** (Scheme 6).[23] After chemoselective reduction of the ester with $Ca(BH_4)_2$ and acetylation of the primary alcohol, acetates **28a**,**b** were submitted to ozonolysis and acetylation of the crude product[24] to give, in excellent yield, desired **29a**,**b**. Since **24a** and **24b** are racemic, we reasoned that a different behaviour could, in principle, be observed if **29a** and **29b** are put in a chiral medium, because the first one is racemic and the second one is a *meso* compound. Chiral GLC, using two different functionalized β-cyclodextrin-based columns, always gave one peak for both **29a** and **29b**. On the contrary, HPLC with a Chiralpak AD column, gave an excellent separation, with two peaks eluting with R_t 15.92 and 17.41 min, respectively (see Section 4), for the triacyl compound derived from the major stereoisomer obtained in the S_N2' cyclization. Using the same conditions, the other diastereoisomer eluted as a single peak at R_t 12.65 min. Since, during the transformation of **24a** and **24b** into **29a** and **29b**, the original stereogenic centres were not subjected to manipulations, the behaviour in HPLC allows us to assign the trans stereochemistry to the prevailing stereoisomer obtained in the S_N2' cyclization and the cis stereochemistry to the prevailing stereoisomer obtained in the monodecarboxylation of **26**.



Scheme 6. (a) $Ca(BH_4)_2$, THF/EtOH 2:1, −20 °C; (b) Ac_2O, Et_3N, 4-(dimethylamino)pyridine, CH_2Cl_2, rt; (c) CH_2Cl_2/MeOH 1:1, −78 °C; (ii) $NaBH_4$ −78 °C→rt; (iii) see (b).

3. Conclusions

In this paper, we presented a new high convergent protocol for the synthesis of functionalized *N*-heterocycles that can be further elaborated to more complex structures. Moreover, our methodology could probably be extended for the synthesis of differently sized rings and of different *N*-acylated compounds.

The development of different convergent strategies for the preparation of acyclic precursors **3**, involving, for example, an approach based on multicomponent reactions, may disclose a new way for the synthesis of polycyclic derivatives, through methodologies consistent with diversity oriented synthesis.[25] Studies in this field are still in progress in our laboratory and will be presented in due course.

4. Experimental

4.1. General

NMR spectra were taken in $CDCl_3$ at 200 or 300 MHz (^1H) and 50 or 75 MHz (^{13}C), using TMS as internal standard. Chemical shifts are reported in ppm (δ scale), coupling constants are reported in hertz. Peak assignment in ^1H NMR spectra was also made with the aid of double resonance experiments. Peak assignment in ^{13}C spectra was made with the aid of DEPT experiments. GC–MS were carried out on a HP-5971A instrument, using an HP-1 column (12 m long, 0.2 mm wide), electron impact at 70 eV, and a mass temperature of about 170 °C. Unless otherwise indicated, analyses were performed with a constant He flow of 0.9 ml/min, init. temperature 100 °C, init. time 2 min, rate 20 °C/min, final temperature 260 °C, final time 4 min, inj. temperature 250 °C, det. temperature 280 °C. R_t are in min. HPLC determinations were carried out on a HP-1090 instrument equipped with a DAD detector and using a Chiralpak AD column (25 cm long, 0.4 cm wide). IR spectra were measured with a Perkin–Elmer 881 instrument as $CHCl_3$ solutions. Melting points were determined on a Büchi 535 apparatus and are uncorrected. TLC analyses were carried out on silica gel plates, which were developed by these detection methods: (A) UV; (B) iodine; (C) dipping into a solution of $(NH_4)_4MoO_4\cdot 4H_2O$ (21 g) and $Ce(SO_4)_2\cdot 4H_2O$ (1 g) in H_2SO_4 (31 ml) and H_2O (469 ml) and warming. R_f were measured after an elution of 7–9 cm. Chromatographies were carried out on 220–400 mesh silica gel using the 'flash' methodology. Petroleum ether (40–60 °C) is abbreviated as PE. In extractive work-up, aqueous solutions were always reextracted thrice with the appropriate organic solvent. Organic extracts were washed with brine, dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. All reactions employing dry solvents were carried out under a nitrogen atmosphere, while S_N2' reactions were performed under ultra pure argon.

4.2. 4-(4-Methoxybenzyl)oxybut-1-yne 7

To a solution of 4-methoxybenzyl chloride (7.89 g, 50.4 mmol) in dry DMF (50 ml) previously cooled in an ice bath, 3-butyn-1-ol (3.47 ml, 45.8 mmol) was added via syringe. NaH (2.02 g, 60% in mineral oil, 50.4 mmol) was added portionwise over a period of 15 min and the resulting slurry was stirred at 0 °C for additional 45 min. After adding NH_4Cl satd soln (20 ml), the mixture was partitioned between water and Et_2O and extracted. Chromatography with PE/Et_2O 9:1→8:2 gave **7** (8.19 g, 94%) as a colourless oil. R_f 0.32 (PE/Et_2O 9:1, A, C). Anal. found C, 75.50; H, 7.40. $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42. IR: ν_{max} 3305, 2965, 2397, 1611, 1243, 1172, 1091, 1031. GC–MS: R_t 5.26; *m*/*z* 190 (M^+, 7.8), 189 (13), 159 (11), 135 (25), 122 (9.6), 121 (100), 91 (7.2), 78 (14), 77 (16), 53 (9.2), 52 (5.6), 51 (8.0), 39 (10). ^1H NMR (200 MHz): 1.99 [1H, t, ≡C*H*, J=2.6 Hz]; 2.49 [2H, dt, $CH_2C\equiv$, J=2.6, 7.0 Hz]; 3.57 [2H, t, CH_2CH_2O, J=7.1 Hz]; 3.81 [3H, s, OCH_3]; 4.49

[2H, s, CH_2Ar]; 6.88 [2H, dt, aromatics *ortho* to OMe, $J=$ 2.4, 8.8 Hz]; 7.28 [2H, d, aromatics *meta* to OMe, $J=$ 8.8 Hz]. ^{13}C NMR (50 MHz): 19.80 [$CH_2C{\equiv}$]; 55.17 [CH_3O]; 67.75 [CH_2CH_2O]; 69.25 [${\equiv}CH$]; 72.55 [CH_2Ar]; 81.28 [$C{\equiv}CH$]; 113.72 [2C, aromatics *ortho* to OMe]; 129.26 [2C, aromatics *meta* to OMe]; 130.00 [quat. aromatic]; 159.17 [C–OMe].

4.3. 5-[(4-Methoxybenzyl)oxy]pent-2-yn-1-ol 8

A solution of **7** (7.22 g, 38.0 mmol) in dry THF (100 ml) was cooled to 0 °C and then EtMgBr (3 M soln in Et_2O, 21.5 ml) was dropped via syringe over a period of 2–3 min. After 10 min, the cooling bath was removed and stirring continued at rt for 30 min. Anhydrous paraformaldehyde (8.11 g, 271 mmol) was then added in one-pot and the resulting suspension was stirred at rt for 1 day. Quenching with NH_4Cl satd soln (70 ml) was followed by stirring at rt for 15 min; then the crude was filtered through a Celite pad, washing Celite with Et_2O and AcOEt. After separation of the two layers two additional extractions with Et_2O were performed. Solvent was removed and the crude was dissolved in MeOH (40 ml) and stirred at rt in the presence of anhydrous K_2CO_3 (1.00 g, 7.24 mmol) for 3 h. After filtration of the solid and solvent evaporation, the residue was partitioned between H_2O and AcOEt and extracted with AcOEt. Chromatography with PE/Et_2O 4:6→1:9 gave **8** (7.11 g, 85%) as a colourless oil. R_f 0.44 (PE/Et_2O 3:7, A, C). Anal. found C, 70.75; H, 7.35. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32. IR: ν_{max} 3401, 3003, 2416, 1612, 1506, 1300, 1172, 1087, 924. GC–MS: R_t 7.52; *m/z* 220 (M^+, 0.70), 201 (6.3), 189 (20), 171 (9.2), 135 (10), 122 (9.7), 121 (100), 91 (6.5), 78 (13), 77 (14), 65 (6.5), 51 (6.4), 39 (10). ^1H NMR (200 MHz): 1.72 [1H, t, O*H*, $J=6.0$ Hz]; 2.52 [2H, tt, $CH_2CH_2C{\equiv}$, $J=2.2$, 7.0 Hz]; 3.55 [2H, t, CH_2CH_2O, $J=6.9$ Hz]; 3.81 [3H, s, OCH_3]; 4.24 [2H, broad dt, CH_2OH, $J=2.1$, 5.8 Hz]; 4.48 [2H, s, CH_2Ar]; 6.88 [2H, dt, aromatics *ortho* to OMe, $J=2.4$, 8.4 Hz]; 7.27 [2H, d, aromatics *meta* to OMe, $J=8.8$ Hz]. ^{13}C NMR (50 MHz): 19.99 [$CH_2CH_2C{\equiv}$]; 50.91 [CH_2OH]; 55.15 [CH_3O]; 67.80 [CH_2CH_2O]; 72.44 [CH_2Ar]; 79.56 and 82.69 [2C, $C{\equiv}C$]; 113.71 [2C, aromatics *ortho* to OMe]; 129.28 [2C, aromatics *meta* to OMe]; 129.85 [quat. aromatic]; 159.15 [C–OMe].

4.4. (*E*)-5-[(4-Methoxybenzyl)oxy]pent-2-en-1-ol 9

A suspension of $LiAlH_4$ (3.16 g, 83.2 mmol) in dry THF (120 ml) was cooled to 0 °C and sodium methoxide (8.07 g, 166 mmol) was added. A solution of **8** (6.11 g, 27.7 mmol) in dry THF (30 ml) was dropped through an addition funnel over a period of 15 min and the cooling bath was removed after 5 min. The funnel was substituted with a refrigerator and the mixture was refluxed for 5 h 15 min. After cooling the flask at 0 °C, a solution of NaOH (370 mg in 12.5 ml of water) was added wery slowly and the mixture was stirred overnight at rt. The white solid was readily filtered and washed with Et_2O. The collected organic layers were dryed over Na_2SO_4 and evaporated to give a yellow oil, pure enough (GC–MS) for the following reaction. For analytical purposes the crude was purified by chromatography with PE/Et_2O 1:1→2:8 to give **9** as a pale yellow oil in 91% yield. R_f 0.31 (PE/Et_2O 3:7, A, C). Anal. found C, 70.40; H, 8.25. $C_{13}H_{18}O_3$ requires C, 70.24; H, 8.16. IR: ν_{max} 3462, 2998, 2929, 2864, 1609, 1533, 1419, 1364, 1190, 1088, 972. GC–MS: R_t 7.28; *m/z* 222 (M^+, 1.0), 150 (10), 137 (6.4), 136 (8.3), 135 (7.2), 122 (10), 121 (100), 78 (8.2), 77 (9.6). ^1H NMR (200 MHz): 1.37 [1H, t, O*H*, $J=5.9$ Hz]; 2.36 [2H, centre of m, $CH_2CH_2C=$]; 3.49 [2H, t, CH_2CH_2O, $J=$ 6.6 Hz]; 3.81 [3H, s, OCH_3]; 4.09 [2H, broad s, CH_2OH]; 4.44 [2H, s, CH_2Ar]; 5.62–5.81 [2H, m, C*H*=C*H*]; 6.88 [2H, dt, aromatics *ortho* to OMe, $J=2.4$, 8.8 Hz]; 7.26 [2H, d, aromatics *meta* to OMe, $J=8.8$ Hz]. ^{13}C NMR (50 MHz): 32.53 [$CH_2CH_2CH=$]; 55.17 [CH_3O]; 63.33 [CH_2OH]; 69.23 [CH_2CH_2O]; 72.44 [CH_2Ar]; 113.70 [2C, aromatics *ortho* to OMe]; 128.96 and 130.98 [2C, C*H*=C*H*]; 129.24 [2C, aromatics *meta* to OMe]; 130.29 [quat. aromatic]; 159.09 [*C*–OMe].

4.5. (*E*)-1-[(*t*-Butyldiphenylsilyl)oxy-5-(4-methoxybenzyl)oxy]pent-2-ene 10

A solution of **9** (5.60 g, 25.2 mmol) in dry DMF (40 ml) was cooled to 0 °C and treated with imidazole (3.09 g, 45.3 mmol) and $Ph_2tBuSiCl$ (8.52 ml, 32.8 mmol). After 5 min, the solution was allowed to stir at rt for 3.5 h. The reaction was diluted with PE/Et_2O 1:1 and water and extracted with PE/Et_2O. Chromatography with PE/Et_2O 92:8→85:15 gave **10** as a pale yellow oil (11.14 g, 96%). R_f 0.33 (PE/Et_2O 9:1, A, C). Anal. found C, 75.70; H, 7.85. $C_{29}H_{36}O_3Si$ requires C, 75.61; H, 7.88. IR: ν_{max} 3465, 3001, 2931, 2856, 1610, 1506, 1190, 1109, 1031, 969. GC–MS (usual method but with final temperature 290 °C): R_t 12.89; *m/z* 403 (M^+-57, 0.30), 199 (2.9), 197 (1.5), 183 (1.1), 181 (1.1), 135 (2.2), 123 (1.0), 122 (9.9), 121 (100), 105 (1.1), 91 (1.4), 78 (1.7), 77 (3.2). ^1H NMR (200 MHz): 1.05 [9H, s, *t*Bu]; 2.34 [2H, centre of m, $CH_2CH_2C=$]; 3.46 [2H, t, CH_2CH_2O, $J=6.8$ Hz]; 3.80 [3H, s, OCH_3]; 4.16 [2H, apparent d, $CH_2OTBDPS$, $J=3.2$ Hz]; 4.44 [2H, s, CH_2Ar]; 5.55–5.77 [2H, m, C*H*=C*H*]; 6.86 [2H, dt, aromatics *ortho* to OMe, $J=2.4$, 8.8 Hz]; 7.23–7.46 [8H, m, aromatics]; 7.65–7.73 [4H, m, aromatics]. ^{13}C NMR (50 MHz): 19.21 [$C(CH_3)_3$]; 26.86 [3C, $C(CH_3)_3$]; 32.71 [$CH_2CH_2CH=$]; 55.22 [CH_3O]; 64.48 [$CH_2OTBDPS$]; 69.57 [CH_2CH_2O]; 72.54 [CH_2Ar]; 113.75 [2C, aromatics *ortho* to OMe]; 127.26 and 130.68 [2C, C*H*=C*H*]; 127.59 [4C, aromatics *meta* to Si]; 129.21 [2C, aromatics *meta* to OMe]; 129.55 [2C, aromatics *para* to Si]; 130.59 [quat. aromatic *para* to OMe]; 133.84 [2C, *C ipso* of Ph]; 135.54 [4C, aromatics *ortho* to Si]; 159.13 [*C*–OMe].

4.6. (*E*)-5-[(*t*-Butyldiphenylsilyl)oxy]pent-3-en-1-ol 11

A solution of **10** (8.31 g, 18.0 mmol) in CH_2Cl_2 (50 ml) was cooled to 0 °C and treated with water (2.5 ml) and DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) (6.14 g, 27.1 mmol). After 5 min the solution was allowed to stir at rt for 1 h 10 min. The mixture was partitioned between 5% $NaHCO_3$ and CH_2Cl_2 and filtered over a Celite pad. The filtrate was extracted again with CH_2Cl_2. Chromatography with PE/Et_2O 6:4 gave **11** as a colourless oil (5.04 g, 82%). R_f 0.26 (PE/Et_2O 6:4, A, C). Anal. found C, 74.15; H, 8.25. $C_{21}H_{28}O_2Si$ requires C, 74.07; H, 8.29. IR: ν_{max} 3464, 3006, 2927, 2857, 1680, 1598, 1243, 1108, 1029, 927. GC–MS: R_t 9.52; *m/z* 283 (M^+-57, 15), 253 (14), 205 (27), 201 (5.2), 200 (19), 199 (100), 197 (9.8), 187 (5.1), 181 (10), 175 (18),

174 (5.2), 139 (17), 135 (7.7), 127 (5.2), 121 (6.4), 105 (8.3), 78 (5.4), 77 (22), 67 (6.9), 57 (5.2), 45 (14), 41 (12), 39 (5.7). ^{1}H NMR (200 MHz): 1.06 [9H, s, *t*Bu]; 2.29 [2H, broad q, $CH_2CH_2C=$, $J=6.0$ Hz]; 3.63 [2H, t, CH_2CH_2OH, $J=6.0$ Hz]; 4.19 [2H, apparent d, $CH_2OTBDPS$, $J=3.0$ Hz]; 5.54–5.75 [2H, m, C*H*=C*H*]; 7.33–7.47 [6H, m, aromatics]; 7.66–7.71 [4H, m, aromatics]. ^{13}C NMR (50 MHz): 19.22 [$C(CH_3)_3$]; 26.85 [3C, $C(CH_3)_3$]; 35.62 [$CH_2CH_2CH=$]; 61.85 [CH_2OH]; 64.33 [CH_2-OTBDPS]; 126.58 and 132.22 [2C, *C*H=*C*H]; 127.65 [4C, aromatics *meta* to Si]; 129.65 [2C, aromatics *para* to Si]; 133.75 [2C, *C ipso* of Ph]; 135.56 [4C, aromatics *ortho* to Si].

4.7. (*E*)-5-Bromo-1-[(*t*-butyldiphenylsilyl)oxy]pent-2-ene 13

(1) *Tosylate* **12**. A solution of **11** (2.52 g, 7.42 mmol) in dry pyridine (7 ml) was treated at 0 °C with freshly distilled tosyl chloride (1.98 g, 10.4 mmol) and, after 5 min, allowed to stir at rt for 1 h 45 min (in some cases an addition of 0.4 mol equiv of tosyl chloride was required). The solution was poured into water and extracted with AcOEt. Solvent was removed under vacuo employing also heptane to remove azeotropically residue pyridine and crude tosylate was directly submitted to the nucleophilic displacement. For analytical purposes a sample of the crude was chromatographed with PE/Et_2O 9:1→6:4 to give **12** as a pale yellow oil. R_f 0.63 (PE/Et_2O 6:4, A, C). IR: ν_{max} 3004, 2932, 2855, 1599, 1360, 1191, 1110, 969. GC–MS: not feasible. ^{1}H NMR (200 MHz): 1.04 [9H, s, *t*Bu]; 2.27–2.40 [2H, m, $CH_2CH_2C=$]; 2.42 [3H, s, CH_3 (Ts)]; 4.02 [2H, t, CH_2OTs, $J=6.8$ Hz]; 4.11 [2H, apparent d, $CH_2OTBDPS$, $J=3.0$ Hz]; 5.45–5.68 [2H, m, C*H*=C*H*]; 7.29–7.45 [8H, m, aromatics]; 7.62–7.80 [6H, m, aromatics]. ^{13}C NMR (50 MHz): 19.20 [$C(CH_3)_3$]; 21.61 [CH_3 (Ts)]; 26.81 [3C, $C(CH_3)_3$]; 31.71 [$CH_2CH_2CH=$]; 64.03 [$CH_2OTBDPS$]; 69.61 [CH_2OTs]; 124.03 and 132.59 [2C, *C*H=*C*H]; 127.65 [4C, aromatics *meta* to Si]; 127.88, 129.64 and 129.79 [6C, *C*H of Ts and aromatics *para* to Si]; 133.16 [*C*-Me (Ts)]; 133.60 [2C, *C ipso* of Ph]; 135.49 [4C, aromatics *ortho* to Si]; 144.68 [*C*–SO_2]. (2) *Transformation of* **12** *into* **13**. A solution of crude tosylate from the previous reaction in dry DMF (20 ml) was treated with potassium bromide (1.41 g, 11.9 mmol) and heated at 100 °C for 35 min. The crude was poured into water and extracted with Et_2O. The collected organic layers were washed with water and then with brine. After solvent removal chromatography with PE/Et_2O 100:0→97.5:2.5 afforded pure **13** (2.48 g, 83% two steps) as a colourless oil. R_f 0.35 (PE/Et_2O 99:1, A, C). Anal. found C, 62.65; H, 6.70. $C_{21}H_{27}BrOSi$ requires C, 62.52; H, 6.75. IR: ν_{max} 3303, 2930, 2855, 1422, 1110, 1051, 969, 919. GC–MS: R_t 9.96; *m/z* 348 (11), 347 [$M^+(^{81}Br)-57$, 46], 346 (11), 345 [$M^+(^{79}Br)-57$, 43], 265 (12), 264 (18), 263 (100), 262 (18), 261 (99), 211 (5.1), 204 (5.5), 203 (46), 202 (6.1), 201 (49), 200 (9.7), 199 (48), 197 (23), 187 (10), 183 (12), 182 (6.6), 181 (30), 180 (7.0), 155 (5.7), 152 (8.1), 145 (15), 143 (14), 135 (14), 123 (83), 121 (14), 117 (8.7), 115 (5.6), 105 (28), 91 (24), 79 (5.9), 78 (12), 77 (44), 68 (5.1), 67 (56), 65 (8.1), 57 (28), 53 (13), 51 (11), 45 (31), 42 (5.0), 41 (75), 40 (5.4), 39 (23). ^{1}H NMR (200 MHz): 1.06 [9H, s, *t*Bu]; 2.54–2.64 [2H, m, $CH_2CH_2C=$]; 3.37 [2H, t, CH_2CH_2OH, $J=7.1$ Hz]; 4.17–4.19 [2H, m, $CH_2OTBDPS$]; 5.65–5.70 [2H, m, C*H*=C*H*]; 7.33–7.47 [6H, m, aromatics]; 7.66–7.72 [4H, m, aromatics]. ^{13}C NMR (50 MHz): 19.22 [$C(CH_3)_3$]; 26.83 [3C, $C(CH_3)_3$]; 32.31 [$CH_2CH_2CH=$]; 35.57 [CH_2Br]; 64.10 [$CH_2OTBDPS$]; 126.94 and 131.91 [2C, *C*H=*C*H]; 127.64 [4C, aromatics *meta* to Si]; 129.63 [2C, aromatics *para* to Si]; 133.68 [2C, *C ipso* of Ph]; 135.54 [4C, aromatics *ortho* to Si].

4.8. (*E*)-Diethyl 2-acetamido-2-{5-[(*t*-butyldiphenylsilyl)oxy]pent-3-enyl}malonate 14

A suspension of NaH (60% in mineral oil, 388 mg, 9.70 mmol) in dry DMF (10 ml) was cooled to 0 °C. Then a solution of diethyl acetamidomalonate (2.33 g, 10.7 mmol) in DMF (10 ml) was added through an addition funnel over a period of 10 min. After stirring for additional 5 min at rt, the resulting yellow solution was treated with a solution of bromide **13** (2.94 g, 7.29 mmol) in DMF (10 ml) and immediately heated at 90 °C for 3 h. After this time, the reaction was quenched, even if some unreacted bromide was still present. The resulting solution was cautiously added to saturated aqueous NH_4Cl, diluted with water and extracted with Et_2O. Chromatography with PE/Et_2O 8:2→2:8 afforded pure **14** in 75–88% yield as a pale yellow oil. R_f 0.51 (PE/AcOEt 6:4, A, B). Anal. found C, 66.80; H, 7.60. $C_{30}H_{41}NO_6Si$ requires C, 66.76; H, 7.66. IR: ν_{max} 3411, 2998, 2957, 2856, 1736, 1675, 1187, 1105, 1032, 922. GC–MS (usual method but with final temperature 290 °C): R_t 13.32; *m/z* 483 (15), 482 (M^+-57, 44), 260 (8.9), 238 (6.0), 201 (5.6), 200 (18), 199 (100), 197 (20), 183 (12), 181 (14), 178 (11), 174 (6.5), 173 (7.3), 169 (8.3), 168 (72), 167 (7.6), 140 (10), 139 (16), 137 (6.6), 135 (20), 123 (9.6), 122 (7.5), 121 (8.6), 105 (10), 95 (5.2), 94 (21), 79 (7.2), 77 (83), 67 (12), 43 (43). ^{1}H NMR (200 MHz): 1.05 [9H, s, *t*Bu]; 1.26 [6H, t, CH_2CH_3, $J=7.2$ Hz]; 1.83–1.94 [2H, m, $CH_2CH_2C=$]; 2.04 [3H, s, CH_3CO]; 2.42 [2H, centre of m, $CH_2CH_2C=$]; 4.12 [2H, apparent d, $CH_2OTBDPS$, $J=3.0$ Hz]; 4.24 [4H, q, CH_2CH_3, $J=7.1$ Hz]; 5.47–5.69 [2H, m, C*H*=C*H*]; 6.76 [1H, broad s, N*H*]; 7.32–7.43 [6H, m, aromatics]; 7.64–7.69 [4H, m, aromatics]. ^{13}C NMR (50 MHz): 13.90 [2C, CH_2CH_3]; 19.13 [$C(CH_3)_3$]; 22.97 [CH_3CO]; 26.46 [$CH_2CH_2CH=$]; 26.76 [3C, $C(CH_3)_3$]; 31.53 [$CH_2CH_2CH=$]; 62.42 [2C, CH_2CH_3]; 64.20 [CH_2-OTBDPS]; 66.19 [$C(CO_2Et)_2$]; 127.56 [4C, aromatics *meta* to Si]; 128.78 and 129.76 [2C, *C*H=*C*H]; 129.54 [2C, aromatics *para* to Si]; 133.62 [2C, *C ipso* of Ph]; 135.44 [4C, aromatics *ortho* to Si]; 168.01 [2C, CO_2Et]; 168.94 [CH_3CO].

4.9. (±)-(*E*)-Ethyl 2-acetamido-7-[(*t*-butyldiphenylsilyl)oxy]hept-5-enoate 15

(1) *Monohydrolysis*. A solution of **14** (2.07 g, 3.88 mmol) in 96% EtOH (30 ml) was treated with 6 N aqueous NaOH (832 μl) and stirred at rt for 4 h. In some cases, an additional little amount of NaOH (0.2–0.3 mol equiv) was needed and not always the reaction went to completion. It is, however, preferred not to employ an excess of NaOH in order to avoid the double saponification, while the unreacted malonate can be easily recovered and recycled. A solution of concentrated HCl (400 μl in 1.5 ml of 96% EtOH) was added, followed by 5% aqueous $NH_4H_2PO_4$. The mixture was concentrated

under vacuo, partitioned between brine and AcOEt and extracted with AcOEt, after adjusting the pH to 2. R_f 0.36 (PE/AcOEt 7:3+5% AcOH, A, B). (2) *Decarboxylation*. The crude from the previous reaction was dissolved in dioxane (20 ml) and refluxed under nitrogen for 1 h. After solvent removal chromatography with PE/AcOEt 7:3→4:6 gave **15** as a pale yellow oil (1.50 g, 83%) (in some cases up to 16% unreacted malonate can be recovered). R_f 0.31 (PE/AcOEt 6:4, A, B). Anal. found C, 69.50; H, 7.85. $C_{27}H_{37}NO_4Si$ requires C, 69.34; H, 7.97. IR: ν_{max} 2990, 2955, 2928, 2855, 1730, 1669, 1602, 1110, 1037, 973. GC–MS (usual method but with final temperature 290 °C): R_t 12.30; *m/z* 411 (15), 410 (M^+-57, 48), 200 (15), 199 (79), 197 (12), 183 (9.8), 181 (13), 180 (6.3), 166 (5.8), 139 (15), 138 (26), 137 (5.9), 135 (15), 123 (5.9), 121 (9.2), 105 (11), 102 (6.2), 97 (9.5), 96 (100), 91 (5.2), 81 (7.1), 79 (22), 78 (7.1), 77 (27), 74 (5.6), 68 (9.5), 67 (11), 60 (83), 57 (8.8), 45 (13), 44 (5.5), 43 (92), 42 (6.9), 41 (14). ^{1}H NMR (200 MHz): 1.05 [9H, s, *t*Bu]; 1.29 [3H, t, CH_2CH_3, J=7.0 Hz]; 1.60–2.13 [4H, m, CH_2CH_2C=]; 2.02 [3H, s, CH_3CO]; 4.14 [2H, apparent d, $CH_2OTBDPS$, J=3.2 Hz]; 4.21 [2H, q, CH_2CH_3, J=7.2 Hz]; 4.61 [1H, dt, $CHCO_2Et$, J=5.0, 7.6 Hz]; 5.47–5.72 [2H, m, CH=CH]; 5.98 [1H, broad d, NH, J=8.0 Hz]; 7.32–7.43 [6H, m, aromatics]; 7.64–7.69 [4H, m, aromatics]. ^{13}C NMR (50 MHz): 14.09 [CH_2CH_3]; 19.13 [$C(CH_3)_3$]; 23.08 [CH_3CO]; 26.77 [3C, $C(CH_3)_3$]; 27.91 [CH_2CH_2CH=]; 31.99 [CH_2CH_2CH=]; 51.86 [$CHCO_2Et$]; 61.35 [CH_2CH_3]; 64.24 [$CH_2OTBDPS$]; 127.55 [4C, aromatics *meta* to Si]; 128.92 and 129.96 [2C, CH=CH]; 129.52 [2C, aromatics *para* to Si]; 133.67 [2C, *C ipso* of Ph]; 135.44 [4C, aromatics *ortho* to Si]; 169.72 and 172.51 [2C, CO].

4.10. (±)-(*E*)-*t*-Butyl 2-acetamido-7-[(*t*-butyldiphenylsilyl)oxy]hept-5-enoate 16

(1) *Hydrolysis of the ester*. The same procedure described in the above paragraph was followed starting from 363 mg (777 μmol) of **15**, using this time 1.7 mol equiv of 6 N aqueous NaOH. R_f 0.46 (AcOEt/AcOH 95:5, A, B). (2) *Formation of the t-butyl ester*. A solution of crude acid in dry CH_2Cl_2 (20 ml) was treated with *t*-butyl-2,2,2-trichloroacetimidate (278 μl, 1.55 mmol) and stirred at rt for 1 h 10 min, before $BF_3\cdot Et_2O$ (8 μl, 65 μmol) was added. After stirring for additional 2 h 20 min, solid $NaHCO_3$ (17 mg) was added and the crude was filtered and concentrated under vacuo. Chromatography with PE/AcOEt 7:3→1:1 afforded **16** as a pale yellow oil (289 mg, 75% from **15**). R_f 0.30 (PE/AcOEt 6:4, A, B). Anal. found C, 70.15; H, 8.30. $C_{29}H_{41}NO_4Si$ requires C, 70.26; H, 8.34. IR: ν_{max} 3019, 2926, 2857, 1726, 1667, 1603, 1369, 1192, 1153, 1111, 1056, 928, 876. GC–MS: not feasible. ^{1}H NMR (200 MHz): 1.05 [9H, s, Si*t*Bu]; 1.47 [9H, s, O*t*Bu]; 1.60–2.18 [4H, m, CH_2CH_2C=]; 2.01 [3H, s, CH_3CO]; 4.06–4.22 [2H, m, $CH_2OTBDPS$]; 4.51 [1H, dt, $CHCO_2tBu$, J=5.2, 7.6 Hz]; 5.49–5.72 [2H, m, CH=CH]; 6.08 [1H, broad d, NH, J=7.6 Hz]; 7.32–7.43 [6H, m, aromatics]; 7.64–7.69 [4H, m, aromatics]. ^{13}C NMR (50 MHz): 19.21 [$SiC(CH_3)_3$]; 23.27 [CH_3CO]; 26.83 [3C, $SiC(CH_3)_3$]; 27.92 [CH_2CH_2CH=]; 28.00 [3C, $OC(CH_3)_3$]; 32.28 [CH_2CH_2CH=]; 52.42 [$CHCO_2Et$]; 64.36 [$CH_2OTBDPS$]; 82.22 [$OC(CH_3)_3$]; 127.61 [4C, aromatics *meta* to Si]; 129.26 and 129.83 [2C, CH=CH]; 129.59 [2C, aromatics *para* to Si]; 133.74 [2C, *C ipso* of Ph]; 135.53 [4C, aromatics *ortho* to Si]; 169.73 and 171.83 [2C, CO].

4.11. General procedure for TBDPS removal

A solution of silyl ether (1.58 mmol) in dry THF (5 ml) was cooled to 0 °C and treated with 0.7 M solution of nBu$_4$NF in THF (4.51 ml); after 10 min, the solution was allowed to stir a rt for 2 h. After dilution with brine, an extraction with AcOEt was performed.

4.11.1. (±)-(*E*)-Ethyl 2-acetamido-7-hydroxyhept-5-enoate 17. Chromatography with AcOEt/MeOH 100:0→8:2 gave **17** as a colourless oil in 96% yield. R_f 0.47 (AcOEt/MeOH 95:5, B). Anal. found C, 57.60; H, 8.40. $C_{11}H_{19}NO_4$ requires C, 57.62; H, 8.35. IR: ν_{max} 3428, 3005, 2800, 1730, 1671, 1376, 1245, 1136, 1079, 973, 703. GC–MS: R_t 6.87; *m/z* 229 (M^+, 0.11), 186 (5.5), 156 (15), 152 (29), 138 (18), 124 (12), 123 (9.4), 114 (16), 112 (8.4), 103 (9.0), 102 (58), 97 (11), 96 (95), 95 (6.2), 94 (7.7), 86 (5.4), 84 (5.4), 82 (7.8), 81 (5.2), 80 (5.5), 79 (44), 78 (15), 74 (20), 70 (5.7), 69 (5.6), 68 (6.9), 67 (83), 60 (11), 57 (9.1), 56 (7.9), 55 (7.5), 44 (18), 43 (100), 42 (12), 41 (18), 39 (7.1). ^{1}H NMR (200 MHz): 1.22 [3H, t, CH_2CH_3, J=7.1 Hz]; 1.59–2.11 [4H, m, CH_2CH_2C=]; 1.96 [3H, s, CH_3CO]; 4.02 [2H, broad s, CH_2OH]; 4.14 [2H, q, CH_2CH_3, J=7.2 Hz]; 4.56 [1H, dt, $CHCO_2Et$, J=5.4, 7.8 Hz]; 5.50–5.69 [2H, m, CH=CH]; 6.01 [1H, broad d, NH, J=8.0 Hz]. ^{13}C NMR (50 MHz): 13.98 [CH_2CH_3]; 22.83 [CH_3CO]; 27.88 [CH_2CH_2CH=]; 31.52 [CH_2CH_2CH=]; 51.55 [$CHCO_2Et$]; 61.34 [CH_2CH_3]; 62.83 [CH_2OH]; 130.18 and 130.56 [2C, CH=CH]; 170.34 and 172.59 [2C, CO].

4.11.2. (±)-(*E*)-*t*-Butyl 2-acetamido-7-hydroxyhept-5-enoate 18. Chromatography with AcOEt/MeOH 100:0→9:1 gave **18** as a colourless oil in 80% yield. R_f 0.18 (AcOEt, B). Anal. found C, 60.55; H, 9.10. $C_{13}H_{23}NO_4$ requires C, 60.68; H, 9.01. IR: ν_{max} 3429, 2978, 2871, 1723, 1667, 1370, 1193, 1153, 1075, 973. GC–MS: R_t 7.14; *m/z* 239 (M^+-18, 0.099), 184 (8.4), 183 (14), 158 (8.2), 157 (12), 156 (18), 138 (15), 124 (26), 123 (8.0), 114 (21), 99 (7.1), 97 (10), 96 (100), 86 (5.9), 85 (7.1), 79 (21), 74 (9.4), 60 (9.2), 57 (28), 44 (5.6), 43 (29), 41 (12). ^{1}H NMR (200 MHz): 1.48 [9H, s, *t*Bu]; 1.62–2.18 [4H, m, CH_2CH_2C=]; 2.02 [3H, s, CH_3CO]; 4.09 [2H, broad s, CH_2OH]; 4.53 [1H, dt, $CHCO_2tBu$, J=5.0, 7.6 Hz]; 5.58–5.76 [2H, m, CH=CH]; 6.05 [1H, broad d, NH, J=7.8 Hz]. ^{13}C NMR (50 MHz): 23.32 [CH_3CO]; 27.93 [CH_2CH_2CH=]; 28.01 [3C, $C(CH_3)_3$]; 32.19 [CH_2CH_2CH=]; 52.09 [$CHCO_2Et$]; 63.54 [CH_2OH]; 82.31 [$C(CH_3)_3$]; 130.30 and 131.21 [2C, CH=CH]; 169.69 and 171.80 [2C, CO].

4.11.3. (*E*)-Diethyl 2-acetamido-2-5-(hydroxypent-3-enyl)malonate 19. Chromatography with PE/AcOEt 10:90→0:100 gave **19** as a colourless oil in 85% yield. R_f 0.44 (AcOEt, B). Anal. found C, 55.75; H, 7.80. $C_{14}H_{23}NO_6$ requires C, 55.80; H, 7.69. IR: ν_{max} 3411, 2978, 2868, 1736, 1673, 1474, 1370, 1265, 1089, 1010, 974, 856, 736. GC–MS: R_t 7.85; *m/z* 301 (M^+, 0.092), 228 (11), 217 (5.1), 186 (19), 179 (12), 178 (100), 175 (9.5), 174 (15), 171 (48), 169 (12), 168 (65), 164 (8.8), 151 (6.6), 143 (35), 140 (15), 129 (17), 125 (18), 123 (11), 122 (16), 116 (12), 115 (6.1), 112 (13), 101 (6.4), 95 (8.9), 94 (34), 93 (5.7), 88

(5.1), 84 (83), 80 (5.2), 79 (12), 71 (6.2), 70 (6.4), 68 (5.4), 67 (25), 55 (7.3), 54 (6.8), 53 (5.3), 43 (89), 42 (25), 41 (20), 39 (5.7). ^{1}H NMR (300 MHz): 1.25 [6H, t, CH_2CH_3, J=7.1 Hz]; 1.87–1.94 [2H, m, CH_2CH_2C=]; 2.03 [3H, s, CH_3CO]; 2.44 [2H, centre of m, CH_2CH_2C=]; 4.56 [2H, apparent d, CH_2OH, J=3.6 Hz]; 4.24 [4H, q, CH_2CH_3, J=7.2 Hz]; 5.55–5.69 [2H, m, CH=CH]; 6.79 [1H, broad s, NH]. ^{13}C NMR (75 MHz): 13.84 [2C, CH_2CH_3]; 22.85 [CH_3CO]; 26.38 [CH_2CH_2CH=]; 31.35 [CH_2CH_2CH=]; 62.46 [2C, CH_2CH_3]; 63.11 [CH_2OH]; 66.12 [$C(CO_2Et)_2$]; 130.09 and 130.49 [2C, CH=CH]; 167.94 [2C, CO_2Et]; 169.18 [CH_3CO].

4.12. (±)-(*E*)-Ethyl 2-acetamido-7-chlorohept-5-enoate 20.

A solution of **17** (200 mg, 872 μmol) in dry CCl_4 (1 ml) was treated with PPh_3 (366 mg, 1.40 mmol) and refluxed for 6 h. The reaction was poured into NH_4Cl saturated solution and extracted with AcOEt. Chromatography with Et_2O/AcOEt/8:2 gave **20** as a pale yellow oil in 66% yield. R_f 0.42 (Et_2O/AcOEt 8:2, A, C). Anal. found C, 53.30; H, 7.45. $C_{11}H_{18}ClNO_3$ requires C, 53.33; H, 7.32. IR: ν_{max} 3430, 2978, 1731, 1671, 1494, 1375, 1187, 1125, 1092, 966. GC–MS: R_t 7.31; m/z 249 [M^+(^{37}Cl), 0.039], 247 [M^+(^{35}Cl), 0.12], 212 (40), 176 (5.9), 174 (18), 170 (12), 166 (9.5), 152 (14), 145 (6.5), 138 (18), 134 (25), 133 (5.4), 132 (77), 103 (5.1), 102 (23), 99 (15), 96 (46), 85 (5.5), 81 (5.0), 79 (22), 78 (5.1), 74 (12), 67 (7.3), 60 (17), 53 (14), 44 (8.5), 43 (100), 42 (11), 41 (12), 39 (8.0). ^{1}H NMR (200 MHz): 1.29 [3H, t, CH_2CH_3, J=7.2 Hz]; 1.67–2.18 [4H, m, CH_2CH_2C=]; 2.03 [3H, s, CH_3CO]; 4.02 [2H, apparent d, CH_2Cl, J=6.2 Hz]; 4.21 [2H, q, CH_2CH_3, J=7.2 Hz]; 4.62 [1H, dt, $CHCO_2Et$, J=5.0, 7.8 Hz]; 5.57–5.83 [2H, m, CH=CH]; 6.08 [1H, broad d, NH, J=7.4 Hz]. ^{13}C NMR (50 MHz): 14.16 [CH_2CH_3]; 23.24 [CH_3CO]; 27.82 [CH_2CH_2CH=]; 31.77 [CH_2CH_2CH=]; 45.01 [CH_2Cl]; 51.74 [$CHCO_2Et$]; 61.61 [CH_2CH_3]; 127.15 and 133.94 [2C, CH=CH]; 169.77 and 172.37 [2C, CO].

4.13. General procedure for the direct transformation of alcohols into bromides

To a solution of alcohol (2.85 mmol) in dry CH_3CN (15 ml), previously cooled to 0 °C, PPh_3 (4.27 mmol) and CBr_4 (4.27 mmol) were added and, after 5 min, the resulting solution was allowed to stir at rt for about 35 min. After dilution with saturated aqueous $NaHCO_3$, an extraction with AcOEt was performed.

4.13.1. (±)-(*E*)-Ethyl 2-acetamido-7-bromohept-5-enoate 21. Chromatography with Et_2O/AcOEt 100:0→9:1 gave **21** as a white-gray solid in 88% yield. Crystallization from CH_2Cl_2/iPr_2O afforded white crystals. Mp: 70.1–70.6 °C (CH_2Cl_2/iPr_2O). R_f 0.51 (Et_2O/AcOEt 8:2, A, B, C). Anal. found C, 45.30; H, 6.15. $C_{11}H_{18}BrNO_3$ requires C, 45.22; H, 6.21. IR: ν_{max} 3428, 3004, 1730, 1670, 1376, 1193, 1019, 967. GC–MS: R_t 7.31; m/z 248 [M^+(^{81}Br)−45, 1.1], 246 [M^+(^{79}Br)−45, 0.92], 220 (7.2), 219 (7.1), 213 (5.6), 212 (44), 178 (28), 176 (28), 170 (18), 166 (17), 138 (28), 102 (19), 97 (7.4), 93 (84), 85 (8.2), 81 (6.3), 79 (20), 74 (9.9), 67 (8.1), 60 (27), 53 (11), 44 (6.3), 43 (100), 42 (11), 41 (12), 39 (7.9). ^{1}H NMR (200 MHz): 1.30 [3H, t, CH_2CH_3, J=7.2 Hz]; 1.69–2.22 [4H, m, CH_2CH_2C=]; 2.04 [3H, s, CH_3CO]; 3.87–4.01 [2H, m, CH_2Br]; 4.22 [2H, q, CH_2CH_3, J=7.1 Hz]; 4.62 [1H, dt, $CHCO_2Et$, J=5.0, 7.7 Hz]; 5.69–5.80 [2H, m, CH=CH]; 6.06 [1H, broad d, NH, J=7.6 Hz]. ^{13}C NMR (50 MHz): 14.17 [CH_2CH_3]; 23.25 [CH_3CO]; 27.85 [CH_2CH_2CH=]; 31.74 [CH_2CH_2CH=]; 32.94 [CH_2Br]; 51.62 [$CHCO_2Et$]; 61.62 [CH_2CH_3]; 127.54 and 134.39 [2C, CH=CH]; 169.77 and 172.36 [2C, CO].

4.13.2. (±)-(*E*)-*t*-Butyl 2-acetamido-7-bromohept-5-enoate 22. Chromatography with ETP/AcOEt 2:8 gave **22** as a white foam in 75% yield. R_f 0.50 (ETP/AcOEt 2:8, A, B, C). Anal. found C, 48.75; H, 6.85. $C_{13}H_{22}BrNO_3$ requires C, 48.76; H, 6.92. IR: ν_{max} 3009, 2958, 1723, 1666, 1189, 1149, 1097, 1010, 922. GC–MS: R_t 7.60; m/z 248 [M^+(^{81}Br)−73, 3.1], 246 [M^+(^{79}Br)−73, 3.1], 220 (13), 218 (13), 185 (8.4), 184 (84), 178 (44), 176 (46), 142 (29), 140 (8.0), 138 (20), 97 (5.4), 96 (46), 86 (11), 85 (7.9), 81 (5.5), 79 (14), 74 (11), 60 (19), 57 (67), 56 (6.7), 53 (11), 44 (10), 43 (100), 42 (9.8), 41 (40), 39 (10). ^{1}H NMR (200 MHz): 1.48 [9H, s, *t*Bu]; 1.63–2.18 [4H, m, CH_2CH_2C=]; 2.02 [3H, s, CH_3CO]; 3.86–4.02 [2H, m, CH_2Br]; 4.52 [1H, dt, $CHCO_2tBu$, J=5.4, 7.2 Hz]; 5.63–5.84 [2H, m, CH=CH]; 6.04 [1H, broad d, NH, J=7.6 Hz]. ^{13}C NMR (50 MHz): 23.32 [CH_3CO]; 27.85 [CH_2CH_2-CH=]; 28.02 [3C, $C(CH_3)_3$]; 31.95 [CH_2CH_2CH=]; 33.01 [CH_2Br]; 52.22 [$CHCO_2Et$]; 82.39 [$C(CH_3)_3$]; 127.36 and 134.68 [2C, CH=CH]; 169.65 and 171.54 [2C, CO].

4.13.3. Diethyl 2-acetamido-2-5-(bromopent-3-enyl)-malonate 23. Chromatography with PE/AcOEt/ 2:8→0:100 gave **23** as a pale yellow oil in 92% yield. R_f 0.61 (Et_2O, A, B, C). Anal. found C, 46.25; H, 6.05. $C_{14}H_{22}BrNO_5$ requires C, 46.17; H, 6.09. IR: ν_{max} 3410, 3005, 1734, 1676, 1481, 1369, 1268, 1230, 1094, 1006, 969. GC–MS: R_t 8.28; m/z 320 [M^+(^{81}Br)−45, 0.84], 318 [M^+(^{79}Br)−45, 0.84], 284 (30), 250 (17), 248 (19), 243 (6.1), 242 (42), 238 (5.2), 174 (7.3), 171 (5.0), 169 (11), 168 (98), 151 (5.1), 140 (9.9), 135 (5.3), 133 (6.9), 123 (9.4), 122 (8.6), 116 (5.6), 115 (14), 112 (5.2), 111 (8.3), 96 (6.1), 95 (9.4), 94 (34), 80 (5.0), 79 (15), 77 (6.0), 71 (83), 67 (28), 60 (6.9), 55 (5.3), 54 (8.1), 53 (16), 43 (100), 42 (19), 41 (22), 39 (7.5). ^{1}H NMR (300 MHz): 1.22 [6H, t, CH_2CH_3, J=7.2 Hz]; 1.87–1.94 [2H, m, CH_2CH_2C=]; 2.01 [3H, s, CH_3CO]; 2.40 [2H, centre of m, CH_2CH_2C=]; 3.82–3.95 [2H, m, CH_2Br]; 4.21 [4H, q, CH_2CH_3, J=7.0 Hz]; 5.59–5.73 [2H, m, CH=CH]; 6.77 [1H, broad s, NH]. ^{13}C NMR (75 MHz): 13.85 [2C, CH_2CH_3]; 22.91 [CH_3CO]; 26.34 [CH_2CH_2CH=]; 31.08 [CH_2CH_2CH=]; 32.79 [CH_2Br]; 62.47 [2C, CH_2CH_3]; 66.02 [$C(CO_2Et)_2$]; 127.10 and 134.26 [2C, CH=CH]; 167.77 [2C, CO_2Et]; 169.00 [CH_3CO].

4.14. General procedure for the S_N2' cyclization

Several experiments have been performed, adding the desired base to a solution of halide (compounds **20**–**23**) (for solvent and base, see Table 1) under argon. Reaction times, temperatures, yields and dr are reported in Table 1. Quenching with 5% aqueous $NH_4H_2PO_4$ was followed by extraction with AcOEt.

4.14.1. (2*R,5*R**)- and (2*R**,5*S**)-Ethyl 1-acetyl-5-vinylpyrrolidine-2-carboxylate 24a and 24b.** Chromatography with Et_2O/AcOEt 8:2→6:4 gave diastereomeric products as a pale yellow oil. The same chromatography also allowed to obtain analytically pure diastereoisomers. *trans Derivative (2R*,5R*)*: R_f 0.40 (Et_2O/AcOEt 8:2, B). Anal. found C, 62.60; H, 8.05. $C_{11}H_{17}NO_3$ requires C, 62.54; H, 8.11. IR: ν_{max} 2956, 2919, 2853, 1735, 1631, 1407, 1177, 1094, 1011, 921. GC–MS: R_t 5.42; *m/z* 211 (M^+, 2.3), 138 (30), 97 (7.2), 96 (100), 79 (7.1), 68 (9.1), 43 (25), 41 (9.0), 39 (5.1). ^{1}H NMR (200 MHz): 1.25 [3H, t, CH_2CH_3, J=7.2 Hz]; 1.70–2.42 [4H, m, H_3 and H_4]; 2.04 [3H, s, CH_3CO]; 4.12–4.23 [2H, m, CH_2CH_3]; 4.37–4.60 [2H, m, H_2 and H_5]; 5.07 [1H, dt, CH*H*=CH, J=1.2, 17.2 Hz]; 5.17 [1H, dt, C*H*H=CH, J=1.1, 10.4 Hz]; 5.80 [1H, ddd; CH_2=C*H*, J=5.2, 10.2, 16.8 Hz]. ^{13}C NMR (50 MHz): 14.11 [CH_2CH_3]; 22.06 [CH_3CO]; 26.45 [C_3]; 30.71 [C_4]; 59.15 and 60.71 [2C, C_2 and C_5]; 61.02 [CH_2CH_3]; 115.18 [CH_2=CH]; 137.64 [CH_2=*C*H]; 170.27 and 172.14 [2C, *C*O]. *cis Derivative (2R*,5S*)*: R_f 0.30 (Et_2O/AcOEt 8:2, B). Anal. found C, 62.55; H, 8.15. $C_{11}H_{17}NO_3$ requires C, 62.54; H, 8.11. IR: ν_{max} 3002, 1737, 1637, 1406, 1375, 1356, 1194, 1029, 919. GC–MS: R_t 5.55; *m/z* 211 (M^+, 8.8), 139 (5.2), 138 (59), 97 (6.7), 96 (100), 79 (5.4), 68 (5.2), 43 (8.7). ^{1}H NMR (200 MHz): 1.28 [3H, t, CH_2CH_3, J=7.1 Hz]; 1.81–2.27 [4H, m, H_3 and H_4]; 2.05 [3H, s, CH_3CO]; 4.12–4.52 [4H, m, CH_2CH_3, H_2 and H_5]; 5.22 [1H, dt, CH*H*=CH, J=1.1, 10.4 Hz]; 5.46 [1H, dt, C*H*H=CH, J=1.3, 17.2 Hz]; 5.93 [1H, ddd; CH_2=C*H*, J=6.6, 10.2, 17.2 Hz]. ^{13}C NMR (50 MHz): 14.15 [CH_2CH_3]; 22.13 [CH_3CO]; 27.47 [C_3]; 32.42 [C_4]; 59.98 and 61.07 [2C, C_2 and C_5]; 61.63 [CH_2CH_3]; 116.52 [CH_2=CH]; 137.97 [CH_2=*C*H]; 170.14 and 172.26 [2C, *C*O].

4.14.2. (2*R,5*R**)- and (2*R**,5*S**)-*t*-Butyl 1-acetyl-5-vinylpyrrolidine-2-carboxylate 25a and 25b.** Chromatography with PE/AcOEt 4:6 gave separated diastereomeric products as pale yellow oils. The relative configuration was established to be trans for the major and cis for the minor product on the basis of spectroscopic analogies with the ethyl ester series. *trans Derivative (2R*,5R*)*: R_f 0.37 (PE/AcOEt 4:6, B). Anal. found C, 65.40; H, 8.80. $C_{13}H_{21}NO_3$ requires C, 65.25; H, 8.84. IR: ν_{max} 3001, 1731, 1632, 1407, 1368, 1150. GC–MS: R_t 5.79; *m/z* 239 (M^+, 2.4), 166 (7.0), 139 (8.0), 138 (67), 97 (11), 96 (100), 94 (6.1), 79 (9.3), 68 (9.2), 67 (5.8), 57 (15), 43 (29), 41 (17), 39 (7.0). ^{1}H NMR (200 MHz): 1.45 [9H, s, $C(CH_3)_3$]; 1.62–2.42 [4H, m, H_3 and H_4]; 2.04 [3H, s, CH_3CO]; 4.26–4.52 [2H, m, H_2 and H_5]; 5.07 [1H, dt, CH*H*=CH, J=1.2, 16.8 Hz]; 5.16 [1H, broad d, C*H*H=CH, J=10.6 Hz]; 5.80 [1H, ddd; CH_2=C*H*, J=5.4, 10.6, 17.2 Hz]. ^{13}C NMR (50 MHz): 22.13 [CH_3CO]; 26.52 [C_3]; 27.98 [3C, $C(CH_3)_3$]; 30.72 [C_4]; 59.95 and 60.78 [2C, C_2 and C_5]; 81.17 [$C(CH_3)_3$]; 115.08 [CH_2=CH]; 137.91 [CH_2=*C*H]; 170.10 and 171.40 [2C, *C*O]. *cis Derivative (2R*,5S*)*: R_f 0.23 (PE/AcOEt 4:6, B). Anal. found C, 65.30; H, 8.90. $C_{13}H_{21}NO_3$ requires C, 65.25; H, 8.84. IR: ν_{max} 3005, 1732, 1633, 1407, 1240, 1097, 1009, 924. GC–MS: R_t 5.88; *m/z* 239 (M^+, 1.3), 139 (5.4), 138 (46), 97 (7.3), 96 (100), 79 (5.6), 68 (5.4), 57 (8.7), 43 (16), 41 (9.4). ^{1}H NMR (200 MHz): 1.47 [9H, s, $C(CH_3)_3$]; 1.67–2.35 [4H, m, H_3 and H_4]; 2.04 [3H, s, CH_3CO]; 4.22–4.70 [2H, m, H_2 and H_5]; 5.21 [1H, dt, CH*H*=CH, J=1.0, 10.2 Hz]; 5.43 [1H, dt, C*H*H=CH, J=1.0, 17.2 Hz]; 5.94 [1H, ddd; CH_2=C*H*, J=6.6, 10.6, 17.2 Hz]. ^{13}C NMR (50 MHz): 22.20 [CH_3CO]; 27.50 [C_3]; 28.01 [3C, $C(CH_3)_3$]; 32.42 [C_4]; 60.83 and 61.72 [2C, C_2 and C_5]; 81.16 [$C(CH_3)_3$]; 116.36 [CH_2=CH]; 138.25 [CH_2=*C*H]; 169.82 and 169.89 [2C, *C*O].

4.14.3. (±)-Diethyl 1-acetyl-5-vinylpyrrolidine-2,2-dicarboxylate 26. Chromatography with PE/Et_2O 1:9→0:100 gave diastereomeric products as a colourless oil. R_f 0.43 (Et_2O, B). Anal. found C, 59.50; H, 7.40. $C_{14}H_{21}NO_5$ requires C, 59.35; H, 7.47. IR: ν_{max} 2978, 2869, 1735, 1654, 1394, 1191, 1128, 1092, 1016, 925. GC–MS: R_t 6.79; *m/z* 283 (M^+, 3.6), 240 (2.5), 210 (6.6), 169 (10), 168 (100), 140 (5.3), 94 (4.7), 67 (3.5), 43 (5.0). ^{1}H NMR (300 MHz): 1.28 and 1.27 [6H, 2t, CH_2CH_3, J=7.2 Hz]; 1.73–2.47 [4H, m, H_3 and H_4]; 2.06 [3H, s, CH_3CO]; 4.23 [4H, centre of m, CH_2CH_3]; 4.47 [1H, centre of m, H_5]; 5.22 [1H, broad d, CH*H*=CH, J=10.5 Hz]; 5.40 [1H, dt, C*H*H=CH, J=1.1, 17.1 Hz]; 5.86 [1H, ddd; CH_2=C*H*, J=5.7, 10.2, 16.8 Hz]. ^{13}C NMR (75 MHz): 13.90 and 13.96 [2C, CH_2CH_3]; 22.36 [CH_3CO]; 31.27 and 33.64 [2C, C_3 and C_4]; 61.65 [C_5]; 61.87 and 61.95 [2C, CH_2CH_3]; 73.01 [$C(CO_2Et)_2$]; 116.48 [CH_2=CH]; 137.54 [CH_2=*C*H]; 168.58, 168.75 and 170.16 [3C, *C*O].

4.15. (2*R,5*R**)- and (2*R**,5*S**)-Ethyl 1-acetyl-5-vinylpyrrolidine-2-carboxylate 24a,b from 26**

The same two step procedure described to obtain compound **15** was followed to give **24a**,**b** in 80% overall yield, as a 12:88 trans:cis mixture.

4.16. (2*R,5*R**)- and (2*R**,5*S**)-1-Acetyl-2-hydroxymethyl-5-vinylpyrrolidine 27a and 27b**

Dry $CaCl_2$ (274 mg, 2.47 mmol) was suspended in a solution of dry THF–EtOH (2/1, 4.5 ml) and cooled to −20 °C. Solid $NaBH_4$ (156 mg, 4.12 mmol) was rapidly added and the resulting slurry was stirred for 30 min at −20 °C. A solution of ester **24** (174 mg, 823 μmol) in dry THF (4 ml) was added and the reaction was allowed to stir at the same temperature overnight. Quenching with a 2:1 solution of NH_4Cl (satd soln)/KH_2PO_4 (1 M) was followed by addition of AcOEt and filtration over a Celite pad. After saturation with solid NaCl, the extraction was performed with AcOEt/MeOH 9:1. The crude can then be used as such for the following reaction, or purified by chromatography with AcOEt/MeOH 100:0→95:5 to give pure alcohol as a colourless oil (124 mg, 89%). *trans Derivative (2R*,5R*)*: R_f 0.36 (AcOEt/MeOH 95:5, B). Anal. found C, 63.70; H, 8.90. $C_9H_{15}NO_2$ requires C, 63.88; H, 8.93. IR: ν_{max} 3389, 2985, 2876, 1608, 1411, 1064, 993, 968, 924. GC–MS (parameters changed in the usual method: init. temperature 80 °C, init. time 2 min, rate 10 °C/min, final temperature 260 °C, final time 4 °C, inj. temperature 200 °C): R_t 8.26; *m/z* 169 (M^+, 2.4), 151 (1.4), 139 (5.2), 138 (41), 97 (7.1), 96 (100), 79 (12), 68 (6.3), 43 (23), 41 (7.2), 39 (5.5). ^{1}H NMR (300 MHz): 1.60–2.24 [4H, m, H_3 and H_4]; 2.06 [3H, s, CH_3CO]; 3.61–3.75 [2H, m (became the AB part of an ABX system after exchange with D_2O, ν: 3.59 and 3.70, J_{AB}=11.1 Hz, J_{AX}, J_{BX}=3.6, 7.8 Hz), CH_2OH]; 4.30–4.41 [2H, m, H_2 and H_5]; 4.72 [1H, broad s, O*H*]; 5.05 [1H, d,

CH*H*=CH, J=17.1 Hz]; 5.19 [1H, d, C*H*H=CH, J=10.5 Hz]; 5.78 [1H, ddd; CH_2=C*H*, J=5.4, 10.2, 17.1 Hz]. ^{13}C NMR (75 MHz): 22.96 [CH_3CO]; 25.40 [C_3]; 30.56 [C_4]; 60.65 and 61.74 [2C, C_2 and C_5]; 66.11 [CH_2OH]; 115.04 [CH_2=CH]; 137.42 [CH_2=*C*H]; 172.46 [*C*O]. *cis Derivative (2R*,5S*)*: R_f 0.43 (AcOEt/MeOH 95:5, B). Anal. found C, 63.75; H, 8.85. $C_9H_{15}NO_2$ requires C, 63.88; H, 8.93. IR: ν_{max} 3403, 3344, 2956, 2872, 1612, 1410, 1358, 1252, 1198, 1085, 1009, 926. GC–MS (parameters changed in the usual method: init. temperature 80 °C, init. time 2 min, rate 10 °C/min, final temperature 260 °C, final time 4 °C, inj. temperature 200 °C): R_t 8.30; *m/z* 169 (M^+, 1.7), 151 (1.4), 139 (5.3), 138 (44), 97 (6.8), 96 (100), 79 (12), 68 (5.3), 43 (24), 41 (7.2), 39 (5.4). ^{1}H NMR (200 MHz): 1.47–2.18 [4H, m, H_3 and H_4]; 2.10 [3H, s, CH_3CO]; 3.56–3.65 [2H, m (became the AB part of an ABX system after exchange with D_2O, ν: 3.61 and 3.69, J_{AB}=11.5 Hz, J_{AX}, J_{BX}=2.0, 8.0 Hz), CH_2OH]; 4.40 and 4.18 [2H, centrers of 2 m, H_2 and H_5]; 5.19 [1H, dt, CH*H*=CH, J=1.3, 18.2 Hz]; 5.22 [1H, dt, C*H*H=CH, J=1.3, 9.4 Hz]; 5.52 [1H, broad d, O*H*, J=7.4 Hz]; 5.80 [1H, ddd; CH_2=C*H*, J=5.6, 10.6, 16.8 Hz]. ^{13}C NMR (50 MHz): 22.63 [CH_3CO]; 26.44 [C_3]; 30.71 [C_4]; 62.60 and 62.63 [2C, C_2 and C_5]; 67.48 [CH_2OH]; 115.89 [CH_2=CH]; 137.82 [CH_2=*C*H]; 172.94 [*C*O].

4.17. (2*R**,5*R**)- and (2*R**,5*S**)-2-Acetoxymethyl-1-acetyl-5-vinylpyrrolidine 28a and 28b

A solution of **27** (110 mg, 650 μmol) in dry CH_2Cl_2 (3 ml) was cooled to 0 °C and treated with Et_3N (270 μl, 1.94 mmol), Ac_2O (184 μl, 1.94 mmol) and 4-(dimethylamino)pyridine (7.9 mg, 64.8 μmol). After 5 min the reaction mixture was stirred at rt for 1–2 h and then diluted with water and extracted with CH_2Cl_2. Chromatography with AcOEt/MeOH 100:0→98:2 gave **28** as a colourless oil (123 mg, 90%). When the reaction was performed on crude alcohol the overall yield from **24** was 82%. *trans Derivative (2R*,5R*)*: R_f 0.60 (AcOEt/MeOH 95:5, B). Anal. found C, 62.65; H, 8.00. $C_{11}H_{17}NO_3$ requires C, 62.54; H, 8.11. IR: ν_{max} 2957, 1729, 1640, 1401, 1247, 1186, 1029, 991, 919. GC–MS (parameters changed in the usual method: init. temperature 80 °C, init. time 2 min, rate 7 °C/min, final temperature 200 °C, then: rate 20 °C/min, final temperature 260 °C, final time 4 °C): R_t 11.82; *m/z* 211 (M^+, 1.5), 151 (12), 138 (33), 126 (2.7), 109 (3.5), 97 (6.7), 96 (100), 79 (5.1), 68 (3.5), 43 (24), 41 (4.2). ^{1}H NMR (300 MHz): 1.68–2.32 [4H, m, H_3 and H_4]; 2.01 and 2.03 [6H, 2s, CH_3CO]; 4.12 and 4.25 [2H, AB part of an ABX system, CH_2OAc, J_{AB}=10.7 Hz, J_{AX}, J_{BX}=3.1, 7.3 Hz]; 4.00–4.39 [2H, m, H_2 and H_5]; 5.03 [1H, dt, CH*H*=CH, J=1.0, 17.1 Hz]; 5.16 [1H, dt, C*H*H=CH, J=1.0, 10.5 Hz]; 5.79 [1H, ddd; CH_2=C*H*, J=5.4, 10.5, 17.1 Hz]. ^{13}C NMR (75 MHz): 20.76 and 22.91 [2C, CH_3CO]; 24.59 [C_3]; 30.33 [C_4]; 55.91 and 60.82 [2C, C_2 and C_5]; 63.05 [CH_2OAc]; 114.82 [CH_2=CH]; 137.86 [CH_2=*C*H]; 170.46 and 170.64 [2C, *C*O]. *cis Derivative (2R*,5S*)*: R_f 0.41 (AcOEt/MeOH 95:5, B). Anal. found C, 62.70; H, 8.20. $C_{11}H_{17}NO_3$ requires C, 62.54; H, 8.11. IR: ν_{max} 2925, 2852, 1732, 1630, 1402, 1185, 1081, 989. GC–MS (parameters changed in the usual method: init. temperature 80 °C, init. time 2 min, rate 7 °C/min, final temperature 200 °C, then: rate 20 °C/min, final temperature 260 °C, final time 4 °C): R_t 11.94; *m/z* 211 (M^+, 0.36), 151 (13), 138 (27), 109 (5.2), 97 (7.0), 96 (100), 94 (2.7), 81 (2.5), 79 (6.9), 68 (2.8), 67 (3.1), 54 (2.5), 43 (27), 41 (4.1), 39 (2.7). ^{1}H NMR (300 MHz): 1.60–2.20 [4H, m, H_3 and H_4]; 2.04 and 2.06 [6H, 2s, CH_3CO]; 4.19 and 4.28 [2H, AB part of an ABX system, CH_2OAc, J_{AB}=10.9 Hz, J_{AX}, J_{BX}=3.8, 6.8 Hz]; 4.10–4.41 [2H, m, H_2 and H_5]; 5.18 [1H, d, CH*H*=CH, J=9.9 Hz]; 5.19 [1H, d, C*H*H=CH, J=17.1 Hz]; 5.79 [1H, ddd; CH_2=C*H*, J=6.6, 10.2, 17.1 Hz]. ^{13}C NMR (75 MHz): 20.87 and 22.68 [2C, CH_3CO]; 26.33 [C_3]; 31.63 [C_4]; 56.61 and 61.71 [2C, C_2 and C_5]; 64.37 [CH_2OAc]; 115.54 [CH_2=CH]; 138.85 [CH_2=*C*H]; 170.73 and 170.80 [2C, *C*O].

4.18. (2*R**,5*R**)- and (2*R**,5*S**)-2,5-Bis(acetoxymethyl)-1-acetylpyrrolidine 29a and 29b

(1) *Ozonolysis*. A solution of **28** (100 mg, 475 μmol) in dry CH_2Cl_2/MeOH (1:1, 10 ml) was cooled to −78 °C and ozonolyzed for about 5 min (at maximum power and at a flow of 90 l/h). Ozone production was interrupted and the apparatus was put under a static nitrogen atmosphere. Then the solution was treated with 105 μl of Me_2S, followed by addition of $NaBH_4$ (54 mg, 1.42 mmol). The temperature was allowed to rise to 0 °C in 2 h and the reaction was stirred for additional 5 min at rt. Slowly, addition of NH_4Cl satd soln was followed by dilution with few ml of brine and extraction with $CHCl_3$/MeOH 9:1. After solvent removal the crude yellow oil was submitted directly to acetylation. (2) *Acetylation*. The same procedure described for the preparation of **28** from **27** was followed. However, since the starting alcohols cannot be detected in TLC, an equivalent amount of the reagents was added again after 1 h and the resulting solution was stirred at rt for 2 h. Chromatography with AcOEt/MeOH 100:0→95:5 gave **29** as a colourless oil in 80% overall yield. Since compounds **29** were difficult to be detected in TLC (iodine) the chromatographic purification was followed by GC–MS. *trans Derivative (2R*,5R*)*: R_f 0.44 (AcOEt, B). HPLC (hexane/*i*PrOH 87:13, 0.8 ml/min, λ 220 nm): R_t 15.92 and 17.41 min. Anal. found C, 55.95; H, 7.35. $C_{12}H_{19}NO_5$ requires C, 56.02; H, 7.44. IR: ν_{max} 2999, 1738, 1631, 1385, 1187, 1031. GC–MS (parameters changed in the usual method: init. temperature 80 °C, init. time 2 min, rate 7 °C/min, final temperature 200 °C, then: rate 20 °C/min, final temperature 260 °C, final time 4 °C): R_t 15.80; *m/z* 257 (M^+, 0.0099), 197 (7.1), 184 (14), 155 (5.4), 143 (11), 142 (100), 100 (46), 82 (38), 69 (7.1), 68 (12), 55 (18), 43 (76), 42 (7.9), 41 (7.8). ^{1}H NMR (300 MHz): 1.80–2.18 [4H, m, H_3 and H_4]; 2.03, 2.06 and 2.16 [9H, 3s, CH_3CO]; 3.83 and 4.14 [2H, 2 dd, CH_2OAc, J=8.1, 10.5; 7.8, 10.8 Hz]; 4.04 and 4.29 [2H, 2 broad dt, H_2 and H_5, J=3.9, 7.7; 3.3, 7.1 Hz]; 4.15 and 4.20 [2H, AB part of an ABX system, CH_2OAc, J_{AB}=10.8 Hz, J_{AX}, J_{BX}=2.0, 3.1 Hz]. ^{13}C NMR (75 MHz): 20.76, 20.88 and 22.75 [3C, CH_3CO]; 25.31 and 27.27 [2C, C_3 and C_4]; 56.05 and 57.08 [2C, C_2 and C_5]; 63.10 and 64.40 [2C, CH_2OAc]; 169.82, 170.54 and 170.70 [3C, *C*O]. *cis Derivative (2R*,5S*)*: R_f 0.31 (AcOEt, B). HPLC (hexane/*i*PrOH 87:13, 0.8 ml/min, λ 220 nm): 12.65 min. Anal. found C, 56.15; H, 7.40. $C_{12}H_{19}NO_5$ requires C, 56.02; H, 7.44. IR: ν_{max} 2997, 1736, 1632, 1385, 1365, 1199, 1036. GC–MS (parameters changed in the usual method: init. temperature 80 °C, init. time 2 min, rate 7 °C/min, final temperature 200 °C, then: rate 20 °C/min, final temperature 260 °C, final

time 4 °C): R_t 15.65; *m/z* 214 (M^+-43, 0.11), 197 (5.2), 184 (7.3), 143 (8.7), 142 (100), 100 (41), 82 (37), 69 (5.2), 68 (9.7), 55 (18), 43 (80), 42 (8.0), 41 (7.5). ^{1}H NMR (300 MHz): 1.69–2.16 [4H, m, H_3 and H_4]; 2.06, 2.09 and 2.16 [9H, 3s, CH_3CO]; 3.94–4.33 [5H, m, CH_2OAc, H_2 or H_5]; 4.33 [1H, dd, H_2 or H_5, J=4.8, 12.6 Hz]. ^{13}C NMR (75 MHz): 20.82, 20.93 and 22.58 [3C, *C*H_3CO]; 25.54 and 27.46 [2C, C_3 and C_4]; 56.46 and 57.47 [2C, C_2 and C_5]; 64.06 and 64.94 [2C, *C*H_2OAc]; 170.43, 170.68 and 170.73 [3C, *C*O].

Acknowledgements

The authors gratefully thank Stefano Nuvoloni and Eliana Rondanina for their precious collaboration, Andrea Galatini and Valeria Rocca for performing HPLC analyses and MIUR (PRIN 00 and 02) and Compagnia di S. Paolo, Torino for financial support.

References and notes

1. De Simone, R. W.; Currie, K. S.; Mitchell, S. A.; Darrow, J. W.; Pippin, D. A. *Comb. Chem. High Throughput Screening* **2004**, *7*, 473–493.
2. Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789–12854.
3. Golebiowski, A.; Jozwik, J.; Klopfenstein, S. R.; Colson, A. O.; Grieb, A. L.; Russell, A. F.; Rastogi, V. L.; Diven, C. F.; Portlock, D. E.; Chen, J. J. *J. Comb. Chem.* **2002**, *4*, 584–590.
4. Belvisi, L.; Caporale, A.; Colombo, M.; Manzoni, L.; Potenza, D.; Scolastico, C.; Castorina, M.; Cati, M.; Giannini, G.; Pisano, C. *Helv. Chim. Acta* **2002**, *85*, 4353–4368.
5. Banfi, L.; Basso, A.; Guanti, G.; Riva, R. *Tetrahedron Lett.* **2003**, *44*, 7655–7658.
6. Anthoine Dietrich, S.; Banfi, L.; Basso, A.; Damonte, G.; Guanti, G.; Riva, R. *Org. Biomol. Chem.* **2005**, *3*, 97–106.
7. Banfi, L.; Basso, A.; Guanti, G.; Riva, R. *Tetrahedron Lett.* **2004**, *45*, 6637–6640.
8. Beal, L. M.; Liu, B.; Chu, W.; Moeller, K. D. *Tetrahedron* **2000**, *56*, 10113–10125. Colombo, L.; Di Giacomo, M.; Vinci, M.; Colombo, M.; Manzoni, L.; Scolastico, C. *Tetrahedron* **2003**, *59*, 4501–4513. Duggan, H. M. E.; Hitchcock, P. B.; Young, D. W. *Org. Biomol. Chem.* **2005**, *3*, 2287–2295.
9. Artale, E.; Banfi, G.; Belvisi, L.; Colombo, L.; Colombo, M.; Manzoni, L.; Scolastico, C. *Tetrahedron* **2003**, *59*, 6241–6250.
10. Colombo, L.; Di Giacomo, M.; Belvisi, L.; Manzoni, L.; Scolastico, C.; Salimbeni, A. *Gazz. Chim. It.* **1996**, *126*, 543–554.
11. Hirai, Y.; Terada, T.; Amemiya, Y.; Momose, T. *Tetrahedron Lett.* **1992**, *33*, 7893–7894. Hirai, Y.; Nagatsu, M. *Chem. Lett.* **1994**, 21–22. Takao, K.; Nigawara, Y.; Nishino, E.; Takagi, I.; Maeda, K.; Tadano, K.; Ogawa, S. *Tetrahedron* **1994**, *50*, 5681–5704. Hirai, Y.; Shibuya, K.; Fukuda, Y.; Yokoyama, H.; Yamaguchi, S. *Chem. Lett.* **1997**, 221–222. Hirai, Y.; Watanabe, J.; Nozaki, T.; Yokoyama, H.; Yamaguchi, S. *J. Org. Chem.* **1997**, *62*, 776–777. Yokoyama, H.; Otaya, K.; Yamaguchi, S.; Hirai, Y. *Tetrahedron Lett.* **1998**, *39*, 5971–5974. Yokoyama, H.; Otaya, K.; Kobayashi, H.; Miyazawa, M.; Yamaguchi, S.; Hirai, Y. *Org. Lett.* **2000**, *2*, 2427–2429. Makabe, H.; Kong, L. K.; Hirota, M. *Org. Lett.* **2003**, *5*, 27–29. Lei, A.; Liu, G.; Lu, X. *J. Org. Chem.* **2002**, *67*, 974–980. Takao, K.; Nigawara, Y.; Nishino, E.; Takagi, I.; Maeda, K.; Tadano, K.; Ogawa, S. *Tetrahedron* **1994**, *50*, 5681–5704.
12. Kitagawa, O.; Fujita, M.; Li, H.; Taguchi, T. *Tetrahedron Lett.* **1997**, *38*, 615–618. Fujita, M.; Kitagawa, O.; Suzuki, T.; Taguchi, T. *J. Org. Chem.* **1997**, *62*, 7330–7335.
13. Preliminary data on this work were presented at the 2nd International Conference on Multi Component Reactions, Combinatorial and Related Chemistry (MCR2003), Genova (I), April 14–16, 2003.
14. Guanti, G.; Perrozzi, S.; Riva, R. *Tetrahedron: Asymmetry* **2002**, *13*, 2703–2726.
15. The triple bond is versatile since it can be exploited as precursor of both *Z* and *E* alkenes.
16. Hubschwerlen, C.; Angehrn, P.; Gubernator, K.; Page, M. G. P.; Specklin, J.-L. *J. Med. Chem.* **1998**, *41*, 3972–3975.
17. For minimizing the elimination we usually preferred to stop the reaction before all **13** was consumed, since it was easily recovered and recycled.
18. Treatment with TsCl in pyridine did not promote any reaction and for this reason we added 4-dimethylaminopyridine.
19. Snyder, E. I. *J. Org. Chem.* **1972**, *37*, 1466.
20. Since **24** and **25** are racemic, the absolute configuration of them was arbitrarily reported in Scheme 5.
21. It is noteworthy that, in order to get the highest reproducibility in the synthesis of **24a**,**b** on preparative scale from **21**, the reaction has to be performed employing a solution of LiHMDS in THF, freshly prepared by dissolving solid commercial LiHMDS.
22. Kinsman, R.; Lathbury, D.; Vernon, P.; Gallagher, T. *J. Chem. Soc., Chem. Commun.* **1987**, 243–244. Manfré, F.; Kern, J.-M.; Biellmann, J.-F. *J. Org. Chem.* **1992**, *57*, 2060–2065. Collado, I.; Ezquerra, J.; Pedregal, C. *J. Org. Chem.* **1995**, *60*, 5011–5015.
23. The whole sequence was first tested on the 70:30 diastereomeric mixture of **24a**,**b**, to give **29a**,**b** without appreciable changes in dr and then on the separated diastereoisomers.
24. Intermediate monoalcohol was difficult to be recovered by extractive work up, due to its high affinity for water, and since it was nearly impossible to evidentiate its spot on TLC.
25. Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46–58.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 4342–4348
Tetrahedron

Synthesis of functionalized 3-spirocyclopropane-2-indolones from isomerised Baylis–Hillman adducts of isatin

Ponnusamy Shanmugam,* Vadivel Vaithiyanathan and Baby Viswambharan

Chemical Sciences and Technology Division, Regional Research Laboratory (CSIR), Thiruvananthapuram 695 019, Kerala, India

Received 6 December 2005; revised 6 February 2006; accepted 23 February 2006

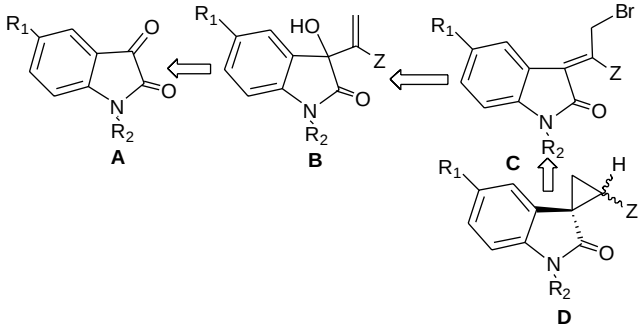
Abstract—A facile, high yield stereoselective synthesis of functionalized diastereomeric 3-spirocyclopropane-2-indolones (**10–17a**,**b**) from the isomerised bromo derivatives of Baylis–Hillman adducts of isatin(**2–9a**,**b**) by reductive cyclization with sodium borohydride is reported.

1. Introduction

Construction of cyclopropane ring systems is of great interest of organic chemists due to its existence as a basic unit in a number of natural products.[1] Cyclopropane ring systems are versatile building blocks in complex molecular construction. In view of their importance as synthons, numerous synthetic methods have been reported for their synthesis.[2] The synthesis of spirocycloindolones are of great interest because they display a variety of biological activities and many of them used as starting materials for alkaloid synthesis.[3] Different synthetic strategies are known for the construction of 3-spirocycloalkylindolones[4] but the synthesis of 3-spirocyclopropane-2-indolones by reductive cyclization of isomerised bromo derivative of Baylis–Hillman adducts of isatin is unexplored to date. Amongst various carbon–carbon bond forming reactions, the Baylis–Hillman reaction is an important reaction giving rise to densely functionalized molecules and is considered atom economic. Highly functionalized Baylis–Hillman adducts have been used as starting materials for various stereoselective preparations of functionalized intermediates and in natural product synthesis.[5] We have been working on novel synthetic applications of the Baylis–Hillman adducts.[6] Thus, in this paper, we wish to outline the synthesis of 3-spirocyclopropane-2-indolones by reductive cyclization of isomerised Baylis–Hillman adducts of isatin for the first time.

2. Results and discussion

The synthetic strategy of present study is depicted in Scheme 1. Reductive cyclization of isomerised bromo derivative of Baylis–Hillman adduct of isatin **C** would provide functionalized 3-spirocyclopropane-2-indolones **D**. The isomerised bromo derivative of Baylis–Hillman adduct of isatin **C** could be synthesized from the Baylis–Hillman adduct of isatin **B** by isomerisation reaction with 46% aqueous HBr under microwave irradiation. In turn, adducts **B** could be prepared from the corresponding substituted isatins **A**.



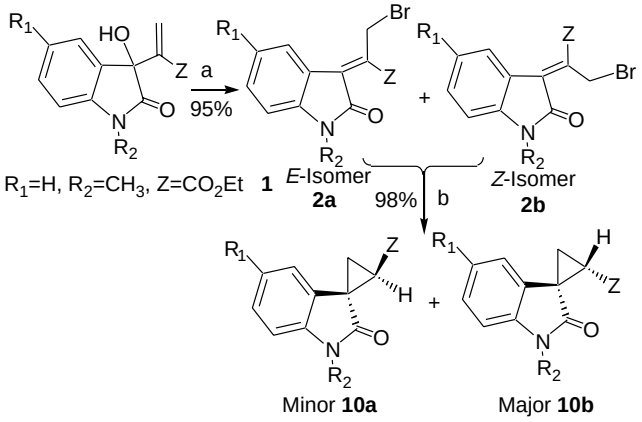
Scheme 1. Retrosynthetic analysis.

The details of the study are shown in Scheme 2. Some of the Baylis–Hillman adducts of isatin used in the present study were prepared according to literature procedure.[7] Thus, as shown, the model substrate **1** was prepared by the treatment of *N*-methyl isatin with ethyl acrylate using 10% mole percent of DABCO in methanol at rt in good yield.

The pure adduct **1** with aqueous HBr (4 equiv) embedded on silica gel (0.2 gm) was irradiated in a microwave oven for

Keywords: Isatin; Spirocyclopropane; Sodium borohydride; 2-Indalones; Baylis–Hillman adduct.
* Corresponding author. Tel.: +91 471 2515275; fax: +91 471 2491712; e-mail: shanmu196@rediffmail.com

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.072



Scheme 2. Cyclopropanation of isomerised BH adducts. Reagents and condition: (a) 4 equiv 46% HBr, silica gel, μw, 750 W, 3 min; (b) 2 equiv, $NaBH_4$, THF, 0.5 h.

3 min to afford a 1:2 mixture of *E*:*Z* isomers of bromo derivative **2a** and **2b** in 95% combined yield after purification by silica gel column chromatography. Stereoselective cyclopropane formation from the mixture **2a** and **2b** in dry THF with 2 equiv of sodium borohydride at rt for 0.5 h afforded functionalized 3-cylopropyl-2-indolones as diastereomeric mixture of **10a** and **10b** in 98% combined yield. The ratio of the products (**10a/10b**) was found as 1:2 as estimated by ^{1}H NMR. The new compounds were characterized by spectral (IR, ^{1}H and ^{13}C NMR) and HRMS data.

In order to study the selectivity in diastereomeric mixture (**10a** and **10b**) formation, we separated the *E* and *Z* isomers of Baylis–Hillman bromo derivatives (**2a** and **2b**) by column chromatography and reduced them under optimized reduction condition separately. To our surprise, the separated geometrical isomers **2a** and **2b** provided the same mixture and same ratio of cyclopropanes **10a** and **10b** on exposure to sodium borohydride. Hence, it is understood that both the isomers are undergoing reductive cyclopropanation through a common stable intermediate. The formation of diastereomeric mixture through a common intermediate could be explained based on the plausible mechanism proposed in Scheme 3. Thus, the hydride ion attack on double bond of the isomerised Baylis–Hillman adducts leads to a common enolate intermediate A, which undergoes cyclopropanation as shown in Scheme 3.

Characterization of the minor and major products (**10a** and **10b**) was achieved based on the analysis of ^{1}H NMR spectra and coupling constant studies. In order to confirm the projection of ester group (α or β) in isomers **13a** and **13b**, the chemical shift variation of aromatic protons H_d and $H_{d'}$ was used as a tool. These are visualised in Figures 1 and 2. For example, the H_d proton appeared at δ 7.51 due to anisotropic influence of ester carbonyl in **13a** while the $H_{d'}$ proton appeared at δ 6.94 due to no influence of ester group

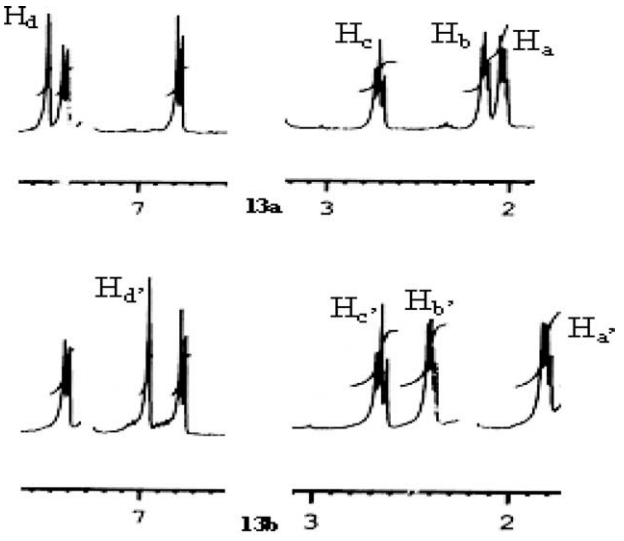


Figure 1.

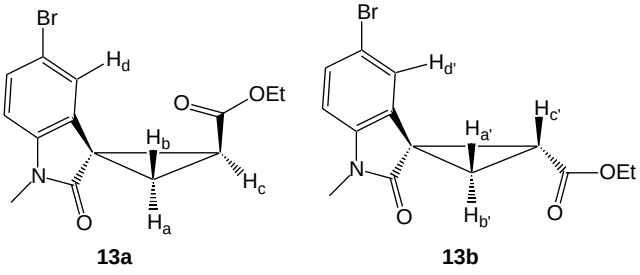
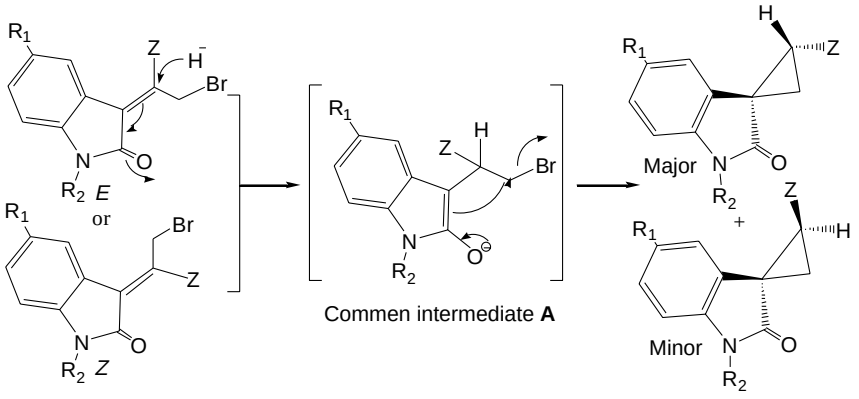
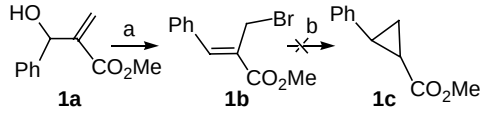


Figure 2.

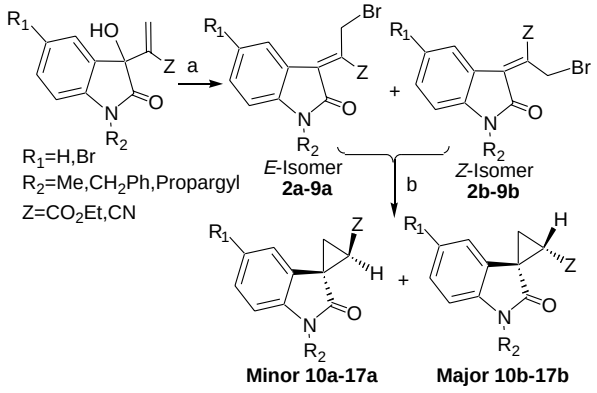


Scheme 3. Plausible mechanism for cyclopropanation.

in **13b**. To fix the nature of protons of the cyclopropane rings, the coupling constant and chemical shift correlation studies were used as a tool. Thus, in compound **13a**, the H_a proton appeared at δ 2.03 (dd, $J_{gem}=4.5$ Hz, $J_{cis}=8.7$ Hz), H_b proton appeared at δ 2.13 (dd, $J_{gem}=4.5$ Hz, $J_{trans}=7.2$ Hz) and H_c proton appeared at δ 2.71 (dd, $J_{cis}=8.7$ Hz, $J_{trans}=7.2$ Hz). In contrary, in compound **13b**, the $H_{a'}$ proton appeared at δ 1.80 (dd, $J_{gem}=5.1$ Hz, $J_{cis}=8.7$ Hz), $H_{b'}$ proton appeared at δ 2.38 (dd, $J_{gem}=5.1$ Hz, $J_{trans}=8.1$ Hz) and $H_{c'}$ proton appeared at δ 2.64 (dd, $J_{cis}=8.7$ Hz, $J_{trans}=8.1$ Hz). Hence, the structure with relative stereochemistry of minor and major compounds **13a** and **13b** was assigned as shown in Figure 2.



Scheme 4. Cyclopropanation of simple isomerised BH adduct. (a) 4 equiv 46% HBr, CH_2Cl_2, rt, 0.5 h; (b) 2 equiv $NaBH_4$, THF, 0.5 h.



Scheme 5. Generality of the cyclopropanation. (a) 4 equiv 46% HBr, silica gel, μw, 750 W, 3 min; (b) 2 equiv $NaBH_4$, THF, 0.5 h.

To investigate the limitation and applicability of cyclopropanation reaction to the simple Baylis–Hillman adducts, the adduct **1a** derived from benzaldehyde with methyl acrylate on isomerisation with aqueous HBr at rt to afford corresponding isomerised product **1b** as a single isomer. The isomerised bromo derivative **1b** in dry THF upon reduction with 2 equiv of $NaBH_4$ (optimised conditions) did not yield the expected cyclopropane derivative **1c**. Careful repeatation and altering the reaction conditions provided only the unreacted starting material. Thus, it is clear that only isomerised bromo derivative of isatins are suitable substrates for the cyclopropanation under reductive cyclization condition. The reaction is shown in Scheme 4.

Encouraged by the preliminary results and to show the generality of the reaction, the reaction of isomerised bromo adducts of isatin **2ab–9ab** under optimized conditions afforded the corresponding functionalized 3-cylopropyl-2-indolones **10a/10b–17a/17b** in excellent yield. The reaction is showed in Scheme 5 and the results are summarized in Table 1. All the new compounds were thoroughly characterized by spectral (IR, ^{1}H and ^{13}C NMR, DEPT-135) and HRMS data.

Table 1. Synthesis of 3-spirocyclopropane-2-indolones

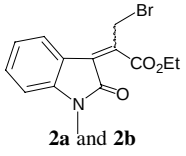
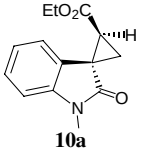
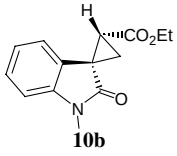
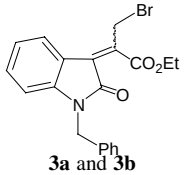
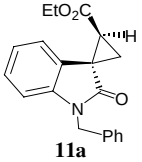
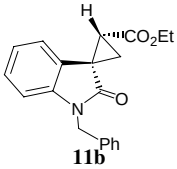
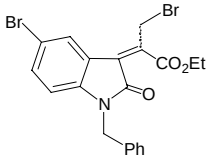
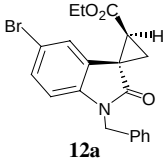
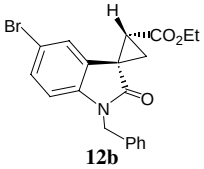
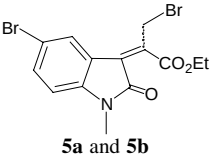
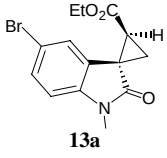
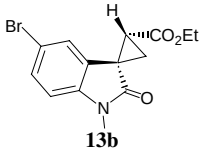
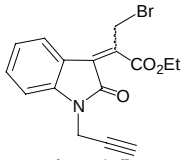
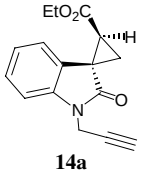
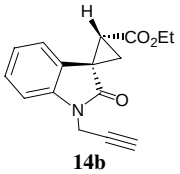
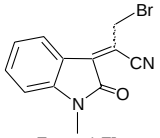
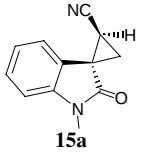
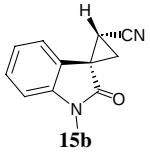
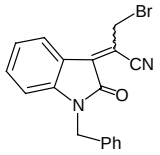
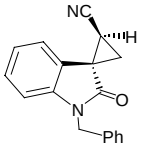
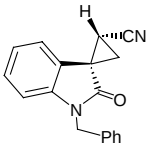
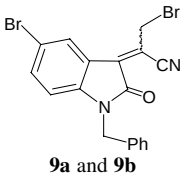
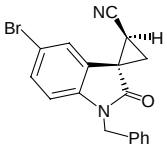
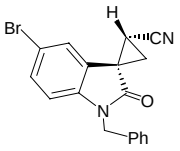
Entry	Reactant (*E* and *Z*)[a]	Condition[b]	Products[c]		Ratio	Combined yield (%)[d]
			Minor	Major		
1	 **2a** and **2b**	2 equiv $NaBH_4$, THF, 0.5 h, rt	 **10a**	 **10b**	1:2	98
2	 **3a** and **3b**	2 equiv $NaBH_4$, THF, 0.5 h, rt	 **11a**	 **11b**	1:2	93
3	 **4a** and **4b**	2 equiv $NaBH_4$, THF, 0.5 h, rt	 **12a**	 **12b**	1:2	95
4	 **5a** and **5b**	2 equiv $NaBH_4$, THF, 0.5 h, rt	 **13a**	 **13b**	1:1.5	96

Table 1 (*continued*)

Entry	Reactant (*E* and *Z*)[a]	Condition[b]	Products[c]		Ratio	Combined yield (%)[d]
			Minor	Major		
5	 **6a** and **6b**	2 equiv $NaBH_4$, THF, 0.5 h, rt	 **14a**	 **14b**	1:2	88
6	 **7a** and **7b**	2 equiv $NaBH_4$, THF, 0.5 h, rt	 **15a**	 **15b**	1:2	94
7	 **8a** and **8b**	2 equiv $NaBH_4$, THF, 0.5 h, rt	 **16a**	 **16b**	1:2.5	98
8	 **9a** and **9b**	2 equiv $NaBH_4$, THF, 0.5 h, rt	 **17a**	 **17b**	1:1.5	86

[a] *E*/*Z* mixture was used as starting material.
[b] See typical procedure.
[c] The isomers were separated by column chromatography.
[d] Estimated after column purification of the products.

3. Conclusion

In conclusion, we have demonstrated a short, novel and facile method for the synthesis of functionalized diastereomeric 3-spirocyclopropane-2-indolones from isomerised bromo derivatives of Baylis–Hillman adducts of isatin by reductive cyclopropanation methodology as a key step for the first time. Further studies to apply this strategy for the synthesis of natural products are underway in our laboratory.

4. Experimental

4.1. General consideration

All the experiments were carried out in oven-dried glassware. Analytical thin-layer chromatography was performed on silica gel TLC plates. Purification by gravity column chromatography was carried out using silica gel (100–200 mesh). Mixture of ethyl acetate and hexane and pure ethyl acetate were used as eluent as required. IR spectra were run on a Nicolet (impact 400D FT-IR) spectrophotometer. NMR spectra were obtained using chloroform-*d* as solvent on Bruker DPX 300 MHz NMR spectrometer. Chemical shifts are given in δ scale with TMS as internal reference. HRMS were measured at the JMS 600 JEOL Mass Spectrometer. Yields refer to quantities obtained after chromatography. Solvents used are reagents grade and were purified before use according to the literature procedure.[8]

4.2. Typical experimental procedure for isomerisation of Baylis–Hillman adducts

A mixture of Baylis–Hillman adduct **1** derived from isatin (100 mg, 0.382 mmol) was added 4 equiv of 46% HBr and silica gel (0.2 g) to make a slurry. The slurry was subjected to microwave irradiation (750 W, 5 s pulse) over a period of 3 min. The crude mixture was cooled to rt and then extracted with CH_2Cl_2 and the organic phase was washed with water. The organic layer was separated and dried (Na_2SO_4) and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography using a gradient elution with hexane and hexane and EtOAc as eluent to afford pure isomerised bromo derivatives **2a** and **2b** in 95% combined yield (118 mg).

4.3. Typical experimental procedure for the synthesis of 3-spirocyclopropane-2-indolones

A mixture of isomerised bromo derivatives of Baylis–Hillman adducts **2a** and **2b** (40 mg, 0.123 mmol) in dry tetrahydrofuran (3 mL) was added 2 equiv of sodium borohydride (9.3 mg, 0.245 mmol). The mixture was stirred

at rt until complete disappearance of starting material (TLC, ca. 0.5 h). Then, the THF was removed under reduced pressure. The crude material was extracted with ethyl acetate (2×30 mL) and the combined organic layer was washed with water followed by brine. The organic layer was separated and dried (Na_2SO_4) and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography using a gradient elution with hexane and hexane and EtOAc as eluent to afford pure cyclopropane derivatives **10a** and **10b** in 98% combined yield (29 mg).

4.4. Spectral data of new compounds

4.4.1. Spiro[cyclopropane-1,3′-[3*H*]indole]-2-carboxylic acid, 1′,2′-dihydro-1′-methyl-2′-oxo-, ethyl ester, 10a. IR (CH_2Cl_2) 2968, 2925, 2863, 1746, 1722, 1617, 1468 cm^{-1}; ^1H NMR (300.1 MHz/$CDCl_3$): δ 1.20 (t, J=6.9 Hz, 3H), 2.01 (dd, J=4.5, 8.7 Hz, 1H), 2.13 (dd, J=4.5, 7.5 Hz, 1H), 2.70 (dd, J=7.5, 8.7 Hz, 1H), 3.28 (s, 3H), 4.13 (q, J=6.9 Hz, 2H), 6.90 (d, J=7.8 Hz, 1H, Ar), 7.02 (t, J=7.8 Hz, 1H, Ar), 7.29 (t, J=7.8 Hz, 1H, Ar), 7.36 (d, J=7.8 Hz, 1H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.33, 20.89, 26.87, 29.54, 32.94, 61.43, 108.21, 122.40, 122.80, 126.06, 127.86, 144.45, 169.03, 175.29; HRMS: Calcd for $C_{14}H_{15}NO_3$: 245.1052; Found: 245.1045.

4.4.2. Spiro[cyclopropane-1,3′-[3*H*]indole]-2-carboxylic acid, 1′,2′-dihydro-1′-methyl-2′-oxo-, ethyl ester, 10b. IR (CH_2Cl_2): 3057, 2963, 2937, 2852, 1739, 1709, 1611, 1466 cm^{-1}; ^1H NMR (300.1 MHz/$CDCl_3$): δ 1.21 (t, J=6.9 Hz, 3H), 1.72 (dd, J=4.8, 8.4 Hz, 1H), 2.31 (dd, J=4.8, 8.1 Hz, 1H), 2.57 (dd, J=8.1, 8.4 Hz, 1H), 3.19 (s, 3H), 4.14 (q, J=6.9 Hz, 2H), 6.77 (d, J=7.2 Hz, 1H, Ar), 6.82 (d, J=7.8 Hz, 1H, Ar), 6.98 (t, J=7.5 Hz, 1H, Ar), 7.22 (t, J=7.8 Hz, 1H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.36, 20.73, 27.07, 29.42, 32.87, 61.84, 108.82, 122.67, 122.48, 126.53, 127.76, 143.56, 168.68, 174.29; HRMS: Calcd for $C_{14}H_{15}NO_3$: 245.1052; Found: 245.1043.

4.4.3. Spiro[cyclopropane-1,3′-[3*H*]indole]-2-carboxylic acid, 1′,2′-dihydro-1′-benzyl -2′-oxo-, ethyl ester, 11a. IR (CH_2Cl_2): 2927, 2849 (cyclopropane), 1721 (ester, amide), 1608 (Ar), 1464 (cyclopropane) cm^{-1}; ^1H NMR (300.1 MHz/$CDCl_3$): δ 1.25 (t, J=6.9 Hz, 3H), 2.08 (dd, J=4.2, 8.4 Hz, 1H), 2.18 (dd, J=4.2, 7.5 Hz, 1H), 2.77 (dd, J=7.5, 8.4 Hz, 1H), 4.15 (q, J=6.9 Hz, 2H), 5.10 (s, 2H), 6.84–7.45 (m, 9H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.35, 21.27, 32.12, 33.15, 44.52, 61.51, 109.24, 118.80, 122.73, 122.95, 124.93, 127.55, 127.79, 127.85, 128.40, 128.99, 136.03, 143.60, 168.99, 175.11; HRMS: Calcd for $C_{20}H_{19}NO_3$: 321.1363; Found: 321.1359.

4.4.4. Spiro[cyclopropane-1,3′-[3*H*]indole]-2-carboxylic acid, 1′,2′-dihydro-1′ -benzyl -2′-oxo-, ethyl ester, 11b. IR (CH_2Cl_2): 2983, 2927, 1735, 1705, 1613, 1466 cm^{-1}; ^1H NMR (300.1 MHz/$CDCl_3$): δ 1.25 (t, J=7.1 Hz, 3H), 1.85 (dd, J=4.8, 8.4 Hz, 1H), 2.43 (dd, J=4.8, 7.8 Hz, 1H), 2.68 (dd, J=7.8, 8.4 Hz, 1H), 4.17 (q, J=7.1 Hz, 2H), 4.89 (d, J=15.6 Hz, 1H), 5.04 (d, J=15.6 Hz, 1H), 6.76–7.26 (m, 9H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.38, 21.16, 32.44, 33.79, 44.25, 61.63, 109.33, 118.39, 122.46, 127.38, 127.51, 127.77, 127.82, 128.93 (2C), 129.14, 136.14, 142.95, 167.23, 173.67; HRMS: Calcd for $C_{20}H_{19}NO_3$: 321.1365; Found: 321.1363.

4.4.5. Spiro[cyclopropane-1,3′-[3*H*]indole]-2-carboxylic acid, 1′,2′-dihydro-1′-benzyl-5′-bromo-2′-oxo-, ethyl ester, 12a. IR (CH_2Cl_2): 2931, 2854, 1727, 1713, 1603, 1473 cm^{-1}; ^1H NMR (300.1 MHz/$CDCl_3$): δ 1.23 (t, J=6.9 Hz, 3H), 2.10 (dd, J=4.5, 8.7 Hz, 1H), 2.17 (dd, J=4.5, 7.5 Hz, 1H), 2.78 (dd, J=7.5, 8.7 Hz, 1H), 4.18 (q, J=6.9 Hz, 2H), 4.99 (2d, J=15.6 Hz, 2H), 6.65 (d, J=8.4 Hz, 1H, Ar), 7.26–7.32 (m, 6H, Ar, Ph), 7.52 (d, J=2.1 Hz, 1H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.15, 21.48, 31.91, 33.24, 44.35, 61.57, 110.36, 115.14, 116.63, 125.98, 127.24 (2C), 127.82, 128.87 (2C), 130.41, 135.29, 142.36, 167.98, 175.01; HRMS: Calcd for $C_{20}H_{18}BrNO_3$: 399.0470; Found: 399.0466.

4.4.6. Spiro[cyclopropane-1,3′-[3*H*]indole]-2-carboxylic acid, 1′,2′-dihydro-1′-benzyl-5′-bromo-2′-oxo-, ethyl ester, 12b. IR (CH_2Cl_2): 3060, 2988, 2925, 1741, 1713, 1617, 1483 cm^{-1}; ^1H NMR (300.1 MHz/$CDCl_3$): δ 1.26 (t, J=7.2 Hz, 3H), 1.86 (dd, J=5.1, 8.7 Hz, 1H), 2.25 (dd, J=5.1, 8.1 Hz, 1H), 2.69 (dd, J=8.1, 8.7 Hz, 1H), 4.26 (q, J=7.2 Hz, 2H), 4.87 (d, J=15.6 Hz, 1H), 5.02 (d, J=15.6 Hz, 1H), 6.62 (d, J=8.1 Hz, 1H, Ar), 6.95 (d, J=2.1 Hz, 1H), 7.24–7.33 (m, 6H, Ar, Ph); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.13, 19.81, 32.01, 33.85, 44.09, 61.56, 110.51, 114.96, 121.93, 127.19 (2C), 127.73, 128.80 (3C), 130.36, 131.01, 135.39, 166.58, 172.87; HRMS: Calcd for $C_{20}H_{18}BrNO_3$: 399.0470; Found: 399.0464.

4.4.7. Spiro[cyclopropane-1,3′-[3*H*]indole]-2-carboxylic acid, 1′,2′-dihydro-1′ -methyl-5′-bromo-2′-oxo-, ethyl ester, 13a. IR (CH_2Cl_2): 2984, 2921 (cyclopropane), 1717 (ester, amide), 1606 (Ar), 1464 cm^{-1}; ^1H NMR (300.1 MHz/$CDCl_3$): δ 1.23 (t, J=6.9 Hz, 3H), 2.03 (dd, J=4.5, 8.7 Hz, 1H), 2.13 (dd, J=4.5, 7.2 Hz, 1H), 2.71 (dd, J=7.2, 8.7 Hz, 1H), 3.26 (s, 3H), 4.17 (q, J=6.9 Hz, 2H), 6.76 (d, J=8.1 Hz, 1H, Ar), 7.42 (d, J=8.1 Hz, 1H, Ar), 7.51 (d, J=1.8 Hz, 1H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.15, 21.11, 26.76, 29.67, 33.06, 61.50, 108.04, 115.03, 125.86, 127.94, 130.49, 143.30, 168.46, 174.17; HRMS: Calcd for $C_{14}H_{14}BrNO_3$: 323.0157; Found: 323.0149.

4.4.8. Spiro[cyclopropane-1,3′-[3*H*]indole]-2-carboxylic acid, 1′,2′-dihydro-1′ -methyl-5′-bromo-2′-oxo-, ethyl ester, 13b. IR (CH_2Cl_2): 2982, 1741, 1712, 1610, 1465 cm^{-1}; ^1H NMR (300.1 MHz/$CDCl_3$): δ 1.27 (t, J=7.2 Hz, 3H), 1.80 (dd, J=5.1, 8.7 Hz, 1H), 2.38 (dd, J=5.1, 8.1 Hz, 1H), 2.64 (dd, J=8.1, 8.7 Hz, 1H), 3.24 (s, 3H), 4.20 (q, J=7.2 Hz, 2H), 6.75 (d, J=8.1 Hz, 1H, Ar), 6.94 (d, J=1.8 Hz, 1H, Ar), 7.40 (dd, J=8.1, 1.8 Hz, 1H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.13, 21.32, 26.67, 32.15, 33.39, 61.53, 109.52, 114.85, 121.85, 130.02, 131.02, 142.68, 166.67, 172.75; HRMS: Calcd for $C_{14}H_{14}BrNO_3$: 323.0157; Found: 323.0142.

4.4.9. Spiro[cyclopropane-1,3′-[3*H*]indole]-2-carboxylic acid, 1′,2′-dihydro-1′-propargyl-2′-oxo-, ethyl ester, 14a. IR (CH_2Cl_2): 3063, 2959, 2927, 2846, 1728, 1706, 1611, 1462 cm^{-1}; ^1H NMR (300.1 MHz/$CDCl_3$): δ 1.21 (t, J=7.1 Hz, 3H), 2.05 (m, 1H), 2.17 (m, 1H), 2.26 (t, J=2.4 Hz, 1H), 2.74 (m, 1H), 4.11 (q, J=7.1 Hz, 2H), 4.57–4.62

(d, J=2.4 Hz, 2H), 6.75–7.48 (m, 4H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.83, 21.72, 29.79, 32.76, 33.29, 47.92, 61.65, 72.54, 109.83, 119.20, 122.85, 127.94, 128.44, 142.21, 167.50, 173.13; HRMS: Calcd for $C_{16}H_{15}NO_3$: 269.1052; Found: 269.1050.

4.4.10. Spiro[cyclopropane-1,3′-[3*H*]indole]-2-carboxylic acid, 1′,2′-dihydro-1′-propargyl-2′-oxo-, ethyl ester, 14b. IR (CH_2Cl_2): 3054, 2986, 2930, 1740, 1719, 1612, 1467 cm^{-1}; ^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.26 (t, J= 7.2 Hz, 3H), 1.82 (dd, J=5.1, 8.7 Hz, 1H), 2.24 (t, J=2.4 Hz, 1H), 2.39 (dd, J=5.1, 8.1 Hz, 1H), 2.66 (dd, J=8.1, 8.7 Hz, 1H), 4.19 (q, J=7.2 Hz, 2H), 4.48–4.68 (d, J=2.4 Hz, 2H), 6.86 (d, J=7.2 Hz, 1H, Ar), 7.05–7.34 (m, 3H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.32, 21.52, 29.70, 32.42, 33.68, 47.97, 61.62, 72.48, 109.37, 118.79, 122.83, 127.91, 128.95, 141.91, 167.04, 172.55; HRMS: Calcd for $C_{16}H_{15}NO_3$: 269.1052; Found: 269.1047.

4.4.11. Spiro[cyclopropane-1,3′-[3*H*]indole]-1′,2′-dihydro-1′-methyl -2′-oxo-2-nitrile, 15a. IR (CH_2Cl_2): 3086, 3027, 2236, 1701, 1614, 1469 cm^{-1}; ^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.89 (dd, J=4.8, 6.9 Hz, 1H), 2.13 (dd, J=4.8, 9.3 Hz, 1H), 2.44 (dd, J=6.9, 9.3 Hz, 1H), 3.30 (s, 3H), 6.97 (d, J=7.8 Hz, 1H, Ar), 7.12–7.42 (m, 3H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.78, 21.31, 26.85, 31.70, 108.66, 116.85, 120.91, 122.89, 124.07, 128.83, 144.10, 172.97; HRMS: Calcd for $C_{12}H_{10}N_2O$: 198.0793; Found: 198.0790.

4.4.12. Spiro[cyclopropane-1,3′-[3*H*]indole]-1′,2′-dihydro-1′-methyl -2′-oxo-2-nitrile, 15b. IR (CH_2Cl_2): 3031, 2963, 2916, 2848, 2247, 1705, 1611, 1466 cm^{-1}; ^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.99 (dd, J=5.1, 9.3 Hz, 1H), 2.19 (dd, J=5.1, 7.2 Hz, 1H), 2.35 (dd, J=7.2, 9.3 Hz, 1H), 3.34 (s, 3H), 6.79 (d, J=7.1 Hz, 1H, Ar), 6.96 (d, J= 7.1 Hz, 1H, Ar), 7.07 (t, J=7.8 Hz, 1H), 7.35 (t, J=7.8 Hz, 1H, Ar); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 15.09, 21.14, 26.90, 31.83, 108.41, 115.89, 118.84, 122.56, 126.02, 128.87, 144.17, 171.49; HRMS: Calcd for $C_{12}H_{10}N_2O$: 198.0793; Found: 198.0795.

4.4.13. Spiro[cyclopropane-1,3′-[3*H*]indole]-1′,2′-dihydro-1′ -benzyl -2′-oxo-2-nitrile, 16a. IR (CH_2Cl_2): 3030, 2925, 2855 (cyclopropane), 2240 (CN), 1717 (amide), 1612 (Ar), 1465 cm^{-1}; ^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.94 (dd, J=5.1, 6.9 Hz, 1H), 2.20 (dd, J=5.1, 9.3 Hz, 1H), 2.52 (dd, J=6.9, 9.3 Hz, 1H), 4.95 (s, 2H), 6.87 (d, J= 7.8 Hz, 1H, Ar), 6.96 (d, J=7.1 Hz, 1H, Ar), 7.07 (t, J= 7.8 Hz, 1H), 7.05–7.34 (m, 8H, Ar, Ph); ^{13}C NMR (75.3 MHz/$CDCl_3$): 15.00, 21.58, 30.91, 44.50, 109.67, 116.84, 121.00, 122.92, 124.08, 127.34 (2C), 127.88, 128.76, 128.89 (2C), 135.32, 143.27, 173.16; HRMS: Calcd for $C_{18}H_{14}N_2O$: 274.1106; Found: 274.1103.

4.4.14. Spiro[cyclopropane-1,3′-[3*H*]indole]-1′,2′-dihydro-1′ -benzyl -2′-oxo-2-nitrile, 16b. IR (CH_2Cl_2): 3032, 2928, 2252, 1719, 1618, 1467 cm^{-1}; ^{1}H NMR (300.1 MHz/$CDCl_3$): δ 2.03 (dd, J=4.8, 9.0 Hz, 1H), 2.25 (dd, J=4.8, 7.5 Hz, 1H), 2.35 (dd, J=7.5, 9.0 Hz, 1H), 4.95–5.08 (2d, J=15.6 Hz, 2H), 6.81–7.33 (m, 9H, Ar, Ph); ^{13}C NMR (75.3 MHz/$CDCl_3$): 15.35, 21.35, 31.84, 44.48, 109.74, 115.82, 118.93, 122.58, 126.02, 127.55, 127.83 (2C), 128.73, 128.86 (2C), 135.58, 143.18, 171.62; HRMS: Calcd for $C_{18}H_{14}N_2O$: 274.1106; Found: 274.1098.

4.4.15. Spiro[cyclopropane-1,3′-[3*H*]indole]-1′,2′-dihydro-1′ -benzyl-5′-bromo -2′-oxo-2-nitrile, 17a. IR (CH_2Cl_2): 2975, 2852 (cyclopropane), 2249 (CN), 1721 (CO), 1613 (Ar), 1479 (cyclopropane) cm^{-1}; ^{1}H NMR (300.1 MHz/$CDCl_3$): δ 1.94 (dd, J=5.1, 7.2 Hz, 1H), 2.21 (dd, J=5.1, 9.3 Hz, 1H), 2.55 (dd, J=7.2, 9.3 Hz, 1H), 4.98 (s, 2H), 6.72 (d, J=8.1 Hz, 1H, Ar), 7.27–7.40 (m, 7H, Ar, Ph); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 14.18, 21.01, 44.59, 31.56, 109.67, 122.92, 124.23, 127.26, 127.48, 127.87, 128.75, 128.89, 128.99, 131.68, 134.85, 135.44, 142.3, 172.60; HRMS: Calcd for $C_{18}H_{13}BrN_2O$: 352.0211; Found: 352.0203.

4.4.16. Spiro[cyclopropane-1,3′-[3*H*]indole]-1′,2′-dihydro-1′-benzyl-5′-bromo-2′-oxo-2-nitrile, 17b. IR (CH_2Cl_2): 2926, 2853, 2246, 1714, 1614, 1480 cm^{-1}; ^{1}H NMR (300.1 MHz/$CDCl_3$): δ 2.03 (dd, J=5.1, 9.3 Hz, 1H), 2.29 (dd, J=5.1, 7.5 Hz, 1H), 2.37 (dd, J=7.5, 9.3 Hz, 1H), 4.93–5.07 (2d, J=15.6 Hz, 2H), 6.70 (d, J=8.4 Hz, 1H, Ar), 6.94 (s, 1H, Ar), 7.26–7.34 (m, 6H, Ar, Ph); ^{13}C NMR (75.3 MHz/$CDCl_3$): δ 15.34, 21.54, 31.63, 44.58, 111.05, 11.23, 121.63, 125.22, 127.26, 127.47, 128.01, 128.11, 128.95, 131.52, 131.67, 135.83, 142.16, 172.03; HRMS: Calcd for $C_{18}H_{13}BrN_2O$: 352.0211; Found: 352.0193.

5. Supplementary data

Scanned copies of the ^{1}H and ^{13}C NMR spectra of all the diastereomeric mixtures available as supporting data.

Acknowledgements

The authors thank Prof. T.K. Chandrashekar, Director, RRL-T for providing infrastructure facilities. V.V and B.V thank CSIR (New Delhi) for the award of a Junior Research Fellowship (JRF). Thanks are due to Mrs. Viji for providing HRMS data. The authors thank the referee of this manuscript for critical suggestions on mechanism of cyclopropanation.

References and notes

1. Faust, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2251–2253.
2. (a) Ye, T.; Mckervey, M. A. *Chem. Rev.* **1994**, *94*, 1091–1160. (b) Yoshimatsu, M.; Ohara, M. *Tetrahedron Lett.* **1997**, *38*, 5651–5654. (c) Agami, C.; Dechoux, L.; Doris, E.; Mioskowski, C. *Tetrahedron Lett.* **1997**, *38*, 4071–4074. (d) Noels, A. F.; Demonceau, A., 2nd ed. In *Applied Homogeneous Catalysis with Organometallic Compounds*, *Vol. 2*; Wiley-VCH: Weinheim, 1996; pp 733–747.
3. (a) Hansch, C., Sammes, P. G., Taylor, J. B., Drayton, C. J., Eds.; Comprehensive Medicinal Chemistry; Pergamon: Oxford, UK, 1990; Vol. 6. (b) Kokkinos, A. M. P.; Hassila, H. *Acta Chem. Scand.* **1996**, *50*, 323–327. (c) Flann, C. J.; Overman, L. E.; Sarkar, A. K. *Tetrahedron Lett.* **1991**, *32*, 6993 and references cited therein. (d) Benson, D. A.; Karsch-Mizrachi, I.;

Lipman, D. J.; Ostell, J.; Rapp, B. A.; Wheeler, D. L. *Nucleic Acids Res.* **2000**, *28*, 15–18.

4. (a) Grigg, R.; Putnicovic, B.; Urch, C. J. *Tetrahedron Lett.* **1996**, *37*, 695–698 and references cited therein. (b) Okada, K.; Kondo, M.; Tanino, H.; Kakoi, H.; Inoue, S. *Heterocycles* **1992**, 589–597 and references cited therein. (c) Wenkert, E.; Liu, S. *Synthesis* **1992**, 323–327. (d) Hart, D. J.; Wu, S. C. *Tetrahedron Lett.* **1991**, *32*, 4099–4102 and references cited therein. (e) Flann, C. J.; Overman, L. E.; Sarkar, A. K. *Tetrahedron Lett.* **1991**, *32*, 6993–6996. (f) Grigg, R.; Stevenson, P.; Worakun, T. *Tetrahedron* **1988**, *44*, 2049–2054. (g) Fleming, I.; Loreto, M. A.; Wallace, I. H. M.; Michael, J. P. *J. Chem. Soc., Perkin Trans. 1* **1986**, 349–359. (h) Jones, K.; Thompson, M.; Wright, C. *J. Chem. Soc., Chem. Commun.* **1986**, 115–116. (i) Joshi, K.; Jain, R.; Chand, P. *Heterocyles* **1985**, *23*, 957–996 and references cited therein. (j) Richael, C. G.; Thurston, D. E. *Tetrahedron* **1983**, *39*, 1817–1821. (k) Okada, K.; Sakuma, H.; Kondo, M.; Inoue, S. *Chem. Lett.* **1979**, 213–216. (l) Kieslich, K. *Justus Liebigs Ann. Chem.* **1978**, *5*, 717–725.
5. (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891. (b) Derewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653–5670.
6. (a) Shanmugam, P.; Rajasingh, P. *Synlett* **2001**, 1314–1316. (b) Shanmugam, P.; Rajasingh, P. *Chem. Lett.* **2002**, 1212–1213. (c) Shanmugam, P.; Rajasingh, P. *Tetrahedron* **2004**, *60*, 9283–9295. (d) Shanmugam, P.; Rajasingh, P. *Synlett* **2005**, 939. (e) Shanmugam, P.; Rajasingh, P. *Tetrahedron Lett.* **2005**, *46*, 3369–3372. (f) Shanmugam, P.; Rajasingh, P. *Chem. Lett.* **2005**, 1494. (g) Shanmugam, P.; Vaithiyanathan, V.; Baby, V. *Synlett*, submitted for publication, 2006.
7. Garden, S. J.; Skakle, J. M. S. *Tetrahedron Lett.* **2002**, *43*, 1969–1972.
8. Perrin, D. D.; Armearego, W. F. L. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: New York, 1988.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 4349–4354
Tetrahedron

Synthesis of (−)-lentiginosine, its 8a-epimer and dihydroxylated pyrrolizidine alkaloid from D-glucose

Vinod D. Chaudhari, K. S. Ajish Kumar and Dilip D. Dhavale*

Department of Chemistry, Garware Research Centre, University of Pune, Pune 411 007, Maharashtra, India

Received 29 November 2005; revised 7 February 2006; accepted 23 February 2006

Available online 20 March 2006

Abstract—The D-glucose derived α,β-unsaturated ester **5** on 1,2-acetonide deprotection, oxidative diol cleavage followed by treatment with *N*-benzylamine in the presence of $NaBH_3CN$ undergoes reductive amination and a concomitant intramolecular conjugate addition reaction leading to the formation of dihydroxypyrrolidine-ester **6a** and monohydroxypyrrolidine-γ-lactone **6b**. Intermediates **6a** and **6b** were efficiently converted to (−)-lentiginosine **3a**, its 8a-epimer **3b**, and pyrrolizidine azasugar **4** in good overall yield.

1. Introduction

Polyhydroxylated indolizidine alkaloids such as castanospermine **1**, swainsonine **2** and lentiginosine **3a** (Fig. 1) are known to be the potential glycosidase inhibitors.[1] Among these, the least hydroxylated lentiginosine **3a**, was found to be the selective inhibitor (IC_{50} 5 μg/mL) of amyloglucosidase enzyme and also exhibit anti-HIV activity.[2,3] (−)-Lentiginosine **3a** was isolated from the leaves of *Astragalus lentiginous* in 1990,[3a] however, its sign of rotation and the stereochemical assignments raised controversy[4] and therefore aroused synthetic interest in the past decade. The known synthetic strategies mainly involve asymmetric pathways starting from either chiral or achiral starting materials,[3,5] however, the use of carbohydrate substrates has received limited attention.[6] While working in the area of azasugars,[7] we have recently exploited D-glucose derived α,β-unsaturated ester **5** in the synthesis of trihydroxylated pyrrolidine alkaloids **A** and **B** (Scheme 1). Thus, opening of 1,2-acetonide group in **5** followed by oxidative cleavage afforded ethyl D-*threo*-hex-4-enoate, which on one pot reductive amination and intramolecular conjugate addition afforded hydroxy ester **6a** and γ-lactone **6b** in the ratio 42:58 (81%) that were converted to **A** and **B**, respectively.[7c] Now, we describe herein the utility of **6a/6b** in the synthesis of lentiginosine **3a**, its 8a-epimer **3b** and dihydroxylated pyrrolizidine alkaloid **4**.

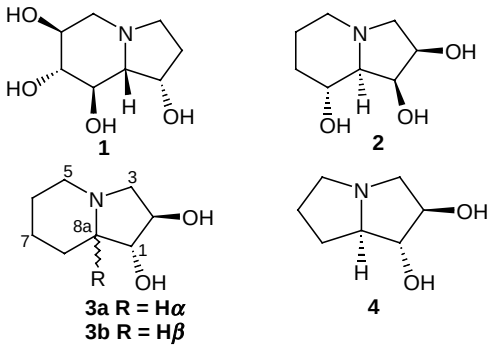
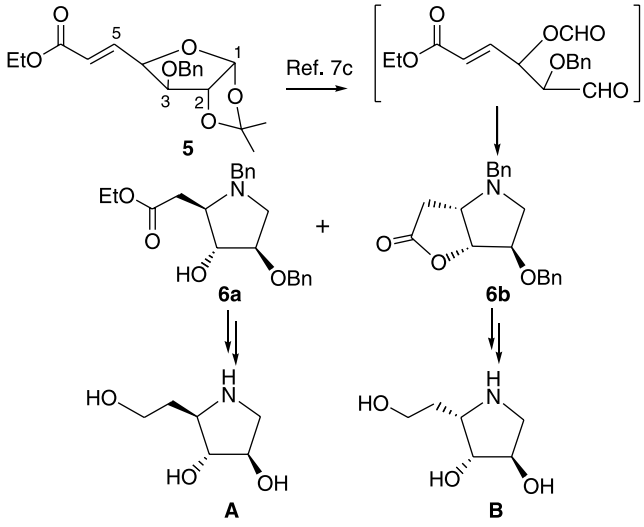


Figure 1. Indolizidine and pyrrolizidine alkaloids.



Scheme 1. Synthesis of pyrrolidine alkaloids.

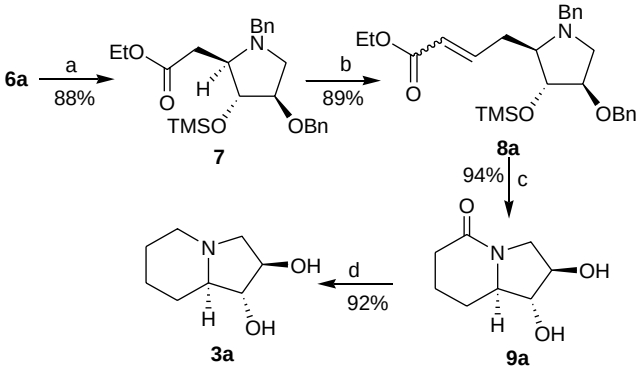
Keywords: Alkaloids; Wittig olefination; Azasugars.
* Corresponding author. Tel.: +91 20 25601225; fax: +91 20 25691728; e-mail: ddd@chem.unipune.ernet.in

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.074

2. Results and discussion

2.1. Synthesis of (−)-lentiginosine 3a

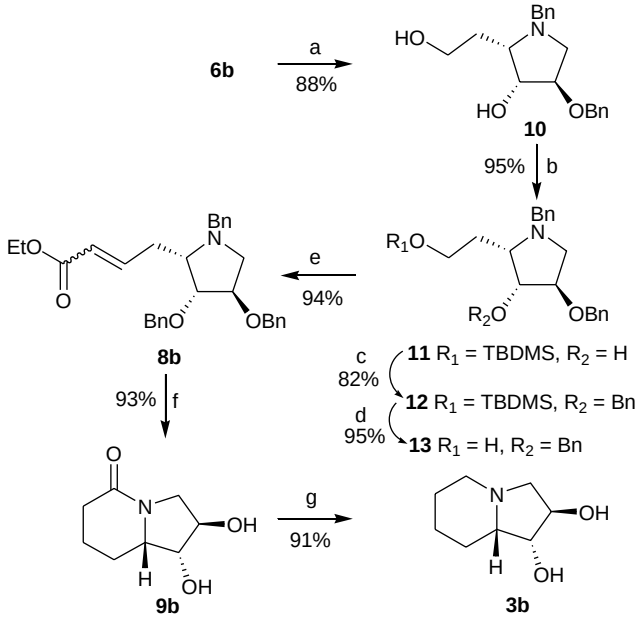
As shown in Scheme 2, treatment of hydroxy ester **6a** with hexamethyldisilazane in the presence of catalytic amount of both TMSCl and ammonium thiocyanate afforded 3-*O*-TMS protected ester **7**.[8] Reduction of the ester functionality in **7** with DIBAL-H followed by Wittig olefination (Ph_3P=CHCOOEt) gave α,β-unsaturated ester **8a** (*E*/*Z*=4:1 based on ^{1}H NMR). Hydrogenation of **8a** using ammonium formate, 10% Pd/C afforded bicyclic lactam **9a**. This one pot four-step process involves reduction of the double bond, hydrogenolysis of –*O*Bn and –*N*Bn groups, desilylation and concomitant cyclization to give δ-lactam **9a**. The products **7**, **8a** and **9a** were characterized by spectral and analytical techniques, and the data was found to be in agreement with the structures. In the next step, LAH reduction of **9a** in THF under reflux followed by column chromatography purification gave (−)-lentiginosine **3a** as white solid. This compound [observed $[\alpha]_D$ −3.5 (*c* 1.0, MeOH); lit.[3b,5c,g,o,6d] −1.6, −2.6, −3.05, −2.0, −4.5] had spectral and analytical data in agreement with that in the literature.[3,5,6]



Scheme 2. Reagents and conditions: (a) HMDS, cat. TMSCl, cat. NH_4SCN, CH_2Cl_2, 25 °C, 30 min; (b) (i) DIBAL-H, CH_2Cl_2, −50 °C, 2.5 h; (ii) $Ph_3PCHCOOEt$, CH_2Cl_2, 25 °C, 30 min; (c) $HCOONH_4$, 10% Pd/C, cat. AcOH, MeOH, reflux, 1 h; (d) LAH, THF, reflux, 8 h.

2.2. Synthesis of 1,2-epilentiginosine 3b

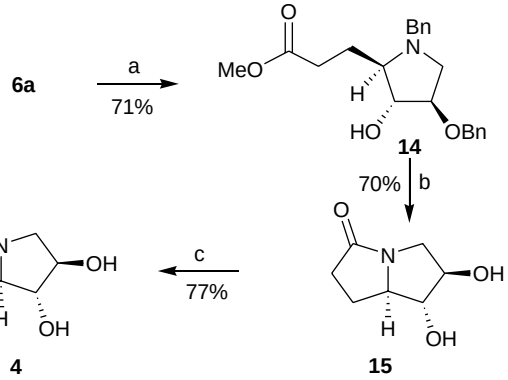
Similar methodology was attempted for the γ-lactone **6b**, however, DIBAL-H reduction afforded lactol, which on the Wittig olefination led to the formation of a diastereomeric mixture of an unexpected product.[9] As an alternative, reduction of γ-lactone **6b** with LAH in THF afforded diol **10** (Scheme 3). The primary hydroxy group in **10** was selectively protected using TBDMSCl to get **11** that on benzylation afforded **12**. Treatment of **12** with TBAF in THF furnished alcohol **13**, which on Swern oxidation and Wittig olefination gave α,β-unsaturated ester **8b** (*E*/*Z*=4:1 based on ^{1}H NMR). Hydrogenation of ester **8b** using ammonium formate and 10% Pd/C gave bicyclic lactam **9b**. Finally, reduction of **9b** with LAH afforded **3b**, an 8a-epimer of **3a**. This compound [observed $[\alpha]_D$+4.3 (*c* 0.5, MeOH); lit.[5k] +3.4 (*c* 0.41, MeOH)] had spectral and analytical data in agreement with that in the literature.[5k,10]



Scheme 3. Reagents and conditions: (a) LAH, THF, 0 °C, 30 min; (b) TBSCl, imidazole, CH_2Cl_2, 25 °C, 3 h; (c) NaH, BnBr, THF, 0 °C, 6 h; (d) TBAF, THF, 25 °C, 4 h; (e) (i) $(COCl)_2$, DMSO, NEt_3, −78 °C, 2 h; (ii) $PPh_3CHCOOEt$, CH_2Cl_2, 25 °C 1 h; (f) $HCOONH_4$, 10% Pd/C, MeOH, reflux, 1 h; (g) LAH, THF, reflux, 10 h.

2.3. Synthesis of dihydroxylated pyrrolizidine alkaloid 4

The hydroxyl ester **6a** was utilized in the synthesis of dihydroxylated pyrrolizidine alkaloid **4** (Scheme 4). Thus, hydrolysis of **6a** with lithium hydroxide and activation of carboxylate group using ethylchloroformate and triethyl amine afforded mixed anhydride, which on treatment with diazomethane in diethyl ether followed by Wolff rearrangement using silver benzoate in methanol furnished one carbon homologated methyl ester **14**.[7b] Treatment of methyl ester **14** with ammonium formate and 10% Pd/C afforded bicyclic lactam **15** that was reduced with LAH to give dihydroxylated pyrrolizidine alkaloid **4**. The spectral data and analytical data of **4** was found to be identical with that reported[5o] [observed $[\alpha]_D$ +6.5 (*c* 0.25, MeOH), lit.[5o] $[\alpha]_D$ +7.6 (*c* 1.3, MeOH)].



Scheme 4. Reagents and conditions: (a) (i) LiOH, methanol–water, 0–25 °C, 4 h; (ii) ClCOOEt, NEt_3, THF, 0–25 °C, 30 min; (iii) CH_2N_2, diethyl ether, 25 °C, 1.5 h; (iv) PhCOOAg, NEt_3, methanol, 25 °C, 3 h; (b) $HCOONH_4$, 10% Pd/C, methanol, reflux, 1 h; (c) LAH, THF, reflux, 10 h.

3. Conclusion

In conclusion, a new synthetic protocol for (−)-lentiginosine **3a**, and its 8a-*epi*-analogue **3b** and dihydroxylated pyrrolizidine alkaloid **4** has been developed starting from D-glucose derived α,β-unsaturated ester **5**. With our methodology the hydroxylated C-3/C-4 carbons of D-glucose, both with the *R* configuration, are retained in the target molecule **3a**. It is therefore obvious that (−)-lentiginosine **3a** has (1*R*,2*R*,8a*R*) absolute configuration as reported earlier.[5c,o,6d]

4. Experimental

4.1. General

Melting points were recorded with Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded with Shimadzu FTIR-8400 as a thin film or in Nujol mull or using KBr pellets and are expressed in reciprocal centimetre (cm^{-1}). ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded with Varian Mercury 300 using $CDCl_3$ or D_2O as a solvent. Chemical shifts were reported in δ unit (ppm) with reference to TMS as an internal standard and *J* values are given in Hertz. Elemental analyses were carried out with Elemental Analyser Flash 1112. Optical rotations were measured using a Bellingham Stanley-ADP digital polarimeter with sodium light (589.3 nm) at 25 °C. Thin-layer chromatography was performed on Merck pre-coated plates (0.25 mm, silica gel 60 F_{254}). Column chromatography was carried out with silica gel (100–200 mesh). The reactions were carried out in oven-dried glassware under dry N_2. Methanol, DMF, THF were purified and dried before use. Petroleum ether (PE) that was used is a distillation fraction between 40–60 °C. LAH, DIBAL-H, 10% Pd–C were purchased from Aldrich and/or Fluka. After decomposition of the reaction with water, the work-up involves—washing of combined organic layer with water, brine, drying over anhydrous sodium sulfate and evaporation of solvent at reduced pressure.

4.1.1. Ethyl 2-((2*R*,3*R*,4*R*)-1-benzyl-4-benzyloxy-3-trimethylsilyloxy-pyrrolidin-2-yl)acetate (7). To a solution of hydroxyester[7c] **6a** (1.00 g, 2.71 mmol) in dichloromethane (10 mL) was added HMDS (0.34 mL, 1.60 mmol) followed by catalytic amount of both TMSCl (0.04 mL, 0.30 mmol) and ammonium thiocyanate (0.01 g, 0.13 mmol) at 25 °C. The reaction mixture was stirred for 30 min and extracted with dichloromethane (2×30 mL). The combined organic layer was concentrated, adsorbed on neutral alumina and purification by column chromatography on neutral alumina (7% ethyl acetate/*n*-hexane) afforded **7** (1.10 g, 88%) as thick oil; [found: C, 67.82; H, 7.90. $C_{25}H_{35}NO_4Si$ requires C, 67.99; H, 7.99]; R_f (10% ethyl acetate/*n*-hexane) 0.47; $[\alpha]_D$ −4.0 (*c* 0.50, $CHCl_3$); ν_{max} (neat) 1728, 1217 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 0.22 (s, 9H), 1.25 (t, *J*=7.1 Hz, 3H), 2.38 (dd, *J*=10.9, 6.3 Hz, 1H), 2.47 (d, *J*=5.7 Hz, 2H), 2.73 (dd, *J*=11.8, 5.7 Hz, 1H), 2.80 (dd, *J*=10.9, 1.9 Hz, 1H), 3.14 (d, *J*=13.1 Hz, 1H), 3.61–3.65 (m, 1H), 3.89 (d, *J*=13.1 Hz, 1H), 3.98 (dd, *J*=7.1, 4.6 Hz, 1H), 3.99 (q, *J*=7.1 Hz, 2H), 4.27 (ABq, *J*=11.8 Hz, 2H), 7.05–7.23 (m, 10H); δ_C (75 MHz, $CDCl_3$) δ 0.13 (s), 14.1, 36.6, 56.3, 58.3, 60.3, 66.9, 71.4, 80.9, 83.5, 126.8, 127.5, 127.6 (s), 128.1 (s), 128.2 (s), 128.6 (s), 138.0, 138.8, 171.9.

4.1.2. Ethyl(*E*)-4-((2*R*,3*R*,4*R*)-1-benzyl-4-benzyloxy-3-trimethylsilyloxy-pyrrolidin-2-yl)but-2-enoate (8a). To a solution of **7** (2.00 g, 4.50 mmol) in dichloromethane (20 mL) was added DIBAL-H (6.43 mL, 5.42 mmol) at −50 °C and stirred for 2.5 h. The reaction mixture was quenched with saturated solution of NH_4Cl (5 mL), filtered through Celite to afford aldehyde. To a solution of aldehyde (1.78 g, 4.29 mmol) in dichloromethane (10 mL) was added $PPh_3CHCOOEt$ (1.17 g, 5.15 mmol) at 25 °C and stirred for 30 min. Reaction mixture was adsorbed on neutral alumina and purified by column chromatography on neutral alumina (10% ethyl acetate/*n*-hexane) afforded **8a** (1.89 g, 89%) as a thick oil; [found: C, 69.42; H, 7.88. $C_{27}H_{37}NO_4Si$ requires C, 69.37; H, 7.97]; R_f (10% ethyl acetate/*n*-hexane) 0.43; $[\alpha]_D$ −36.4 (*c* 0.27, $CHCl_3$); ν_{max} (neat) 1718, 1259 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 0.18 (s, 9H), 1.25 (t, *J*=7.1 Hz, 3H), 2.51–2.60 (m, 4H), 3.02 (br d, *J*=12.0 Hz, 1H), 3.29 (br d, *J*=13.1 Hz, 1H), 3.78 (dt, *J*=5.7, 2.4 Hz, 1H), 4.01 (dd, *J*=5.7, 3.2 Hz, 1H), 4.06 (d, *J*=13.1 Hz, 1H), 4.23 (q, *J*=7.1 Hz, 2H), 4.44 (ABq, *J*=11.2 Hz, 2H), 5.39 (d, *J*=15.6 Hz, 1H), 7.01–7.40 (m, 11H); δ_C (75 MHz, $CDCl_3$) δ 0.1 (s), 14.2, 33.4, 56.3, 58.0, 60.1, 68.8, 71.5, 81.0, 83.6, 123.1, 127.0, 127.5 (s), 127.7 (s), 128.2 (s), 128.3, 137.9, 138.4, 145.6, 166.2. Our attempt to isolate the *Z*-isomer in pure form was unsuccessful and the 89% yield reflects the total yield of *E* and *Z* mixtures.

4.1.3. (1*R*,2*R*,8a*R*)-Hexahydro-1,2-dihydroxyindolizidin-5(1*H*)-one (9a). A solution of **8a** (0.50 g, 1.10 mmol), ammonium formate (0.22 g, 7.49 mmol), 10% Pd/C (0.20 g) and acetic acid (0.02 mL, 0.34 mmol) in methanol (10 mL) was refluxed for 1 h. The solution was filtered, concentrated and purified by column chromatography (10% methanol/chloroform) to afford **9a** (0.17 g, 94%) as a white solid, mp 122–124 °C; [found: C, 56.21; H, 7.54. $C_8H_{13}NO_3$ requires C, 56.13; H, 7.65]; R_f (10% methanol/chloroform) 0.34; $[\alpha]_D$ +12.0 (*c* 0.25, MeOH); ν_{max} (KBr) 3357, 1720, 1656.7, 1452, 1028 cm^{-1}; δ_H (300 MHz, D_2O) δ 1.30–1.47 (m, 1H), 1.60–1.76 (m, 1H), 1.90–2.00 (m, 1H), 2.13–2.20 (m, 1H); 2.21–2.43 (m, 2H), 3.31 (dd, *J*=12.6, 6.8 Hz, 1H), 3.39 (ddd, *J*=15.3, 11.5, 3.5 Hz, 1H), 3.65–3.72 (m, 2H), 4.19 (dd, *J*=15.3, 7.1 Hz, 1H); δ_C (75 MHz, D_2O) δ 19.3, 25.5, 29.8, 48.6, 61.5, 72.7, 79.7, 172.4.

4.1.4. (1*R*,2*R*,8a*R*)-(−)-1,2-Dihydroxyindolizidine (3a). To an ice-cooled suspension of LAH (0.06 g, 1.50 mmol) in THF (3 mL) was added lactam **9a** (0.07 g, 0.41 mmol) in THF (7 mL). The reaction mixture was warmed to room temperature, refluxed for 8 h and quenched with ethyl acetate (2 mL) and aq NH_4Cl (0.3 mL). Filtration through Celite, the filtrate was adsorbed on silica gel and column chromatography (20% methanol/chloroform) gave **3a** (0.06 g, 92%) as a white solid, mp 106–108 °C; lit.[3b,5g] 106–107 °C; [found: C, 61.08; H, 9.59. $C_8H_{15}NO_2$ requires C, 61.12; H, 9.62]; R_f (20% methanol/chloroform) 0.30; [observed $[\alpha]_D$ −3.5 (*c* 1.0, MeOH); lit.[3b,5c,g,o,6d] −1.6, −2.6, −3.05, −2.0, −4.5]; ν_{max} (neat) 3578, 2929, 1134 cm^{-1}; δ_H (300 MHz, D_2O) δ 1.14–1.25 (m, 2H), 1.34–1.41 (m, 1H), 1.52–1.60 (m, 1H), 1.73–1.74 (m, 1H);

1.85–1.91 (m, 2H), 1.98 (ddd, J=14.0, 11.5, 2.7 Hz, 1H), 2.56 (dd, J=11.2, 7.6 Hz, 1H), 2.76 (dd, J=11.2, 1.6 Hz, 1H), 2.87 (d, J=10.9 Hz, 1H), 3.56 (dd, J=8.7, 3.8 Hz, 1H), 4.00 (ddd, J=7.6, 3.8, 1.6 Hz, 1H); δ_C (75 MHz, D_2O) δ 25.3, 26.3, 29.9, 54.9, 62.5, 70.8, 77.9, 85.2.

4.1.5. (2*S*,3*R*,4*R*)-1-Benzyl-4-benzyloxy-2-(2-hydroxyethyl)pyrrolidin-3-ol (10). To an ice-cooled suspension of LAH (0.19 g, 4.76 mmol) in THF (4 mL) was added a solution of γ-lactone **6b** (0.50 g, 2.46 mmol) in THF (10 mL) and stirred for 30 min at 25 °C. Work up as described for **3a** and purification by column chromatography (30% ethyl acetate/*n*-hexane) afforded **10** (0.44 g, 88%) as thick oil; [found: C, 73.41; H, 7.71. $C_{20}H_{25}NO_3$ requires C, 73.37; H, 7.70]; R_f (50% ethyl acetate/*n*-hexane) 0.43; $[\alpha]_D$ +84.8 (*c* 0.33, $CHCl_3$); ν_{max} (neat) 3300–3600 (broad) cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 1.90–1.97 (m, 2H), 2.18 (dd, J=10.8, 6.4 Hz, 1H), 2.73–2.79 (m, 1H), 3.22 (d, J=12.8 Hz, 1H), 3.24 (dd, J=10.8, 6.3 Hz, 1H), 3.56 (br s, exchangeable with D_2O, 2H), 3.67–3.75 (m, 1H), 3.81–3.86 (m, 1H), 3.89 (dt, J=6.4, 2.6 Hz, 1H), 4.00 (d, J=12.8 Hz, 1H), 4.19 (dd, J=5.8, 2.6 Hz, 1H), 4.52 (ABq, J=11.7 Hz, 2H), 7.22–7.36 (m, 10H); δ_C (75 MHz, $CDCl_3$) δ 28.9, 57.2, 58.3, 59.8, 66.4, 71.6, 76.7, 83.5, 127.2, 127.6, 127.7 (s), 128.3 (s), 129.0 (s), 137.7, 137.9.

4.1.6. (2*S*,3*R*,4*R*)-1-Benzyl-4-benzyloxy-2-(2-*tert*-butyldimethysilyloxyethyl)pyrrolidin-3-ol (11). To a solution of diol **10** (0.40 g, 1.22 mmol), in dichloromethane (15 mL) was added TBDMSCl (0.22 g, 1.46 mmol) followed by imidazole (1.00 g, 1.46 mmol) and stirred for 3 h at 25 °C. Water was added to the reaction mixture and extracted with (3×10 mL) dichloromethane. The combined organic layer was concentrated, adsorbed on silica gel and purified by column chromatography (20% ethyl acetate/*n*-hexane) afforded **11** (0.81 g, 95%) as thick oil; [found: C, 70.65; H, 8.93. $C_{26}H_{39}NO_3Si$ requires C, 70.70; H, 8.90]; R_f (20% ethyl acetate/*n*-hexane) 0.23; $[\alpha]_D$ +65.5 (*c* 0.58, $CHCl_3$); ν_{max} (neat) 3429, 2930, 1460, 1254 cm^{-1}; δ_H (300 MHz, $CDCl_3+D_2O$) δ 0.20 (s, 6H), 0.82 (s, 9H), 1.90–2.15 (m, 2H), 2.25 (dd, J=10.1, 6.5 Hz, 1H), 2.73–2.79 (m, 1H), 3.29 (d, J=13.1 Hz, 1H), 3.32 (dd, J=10.1, 6.8 Hz, 1H), 3.73 (ddd, J=12.0, 9.3, 3.0 Hz, 1H), 3.91–3.99 (m, 2H), 4.03 (d, J=13.1 Hz, 1H), 4.23 (dd, J=5.7, 2.4 Hz, 1H), 4.6 (ABq, J=11.8 Hz, 2H), 7.13–7.21 (m, 10H); δ_C (75 MHz, $CDCl_3$) δ 18.1, 25.8 (s), 29.5, 57.5, 58.1, 61.2, 67.3, 71.6, 76.8, 83.3, 127.0, 127.5, 127.7 (s), 128.2 (s), 128.3 (s), 128.9 (s), 137.9, 138.1.

4.1.7. (2*S*,3*R*,4*R*)-1-Benzyl-3,4-bis(benzyloxy)-2-(2-*tert*-butyldimethysilyloxyethyl)pyrrolidine (12). To a hexane washed sodium hydride (0.03 g, 1.25 mmol) was added a solution of alcohol **11** (0.43 g, 0.97 mmol) in THF (8 mL) dropwise at 0 °C and stirred for 30 min. A solution of benzyl bromide (0.13 mL, 1.07 mmol) in THF (2 mL) was added dropwise, followed by addition of TBAI (0.02 g, 0.05 mmol) and stirred for 5 h at 25 °C. The reaction mixture was neutralized with water concentrated under vaccum, extracted using (3×10 mL) dichloromethane. The combined organic layer was concentrated, adsorbed on silica gel and purified using column chromatography (10% ethyl acetate/*n*-hexane) afforded **12** (0.41 g, 82%) as a thick liquid; [found: C, 74.52; H, 8.43. $C_{33}H_{45}NO_3Si$ requires C, 74.53; H, 8.53]; R_f (20% ethyl acetate/*n*-hexane) 0.75; $[\alpha]_D$ +48.6 (*c* 0.7, $CHCl_3$); ν_{max} (neat) 2926, 1456, 1252, 1092 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.88 (s, 9H), 1.69–1.91 (m, 2H), 2.02–2.09 (m, 1H), 2.18–2.56 (m, 1H), 2.91 (m, 1H), 3.43–3.48 (m, 1H), 3.54–5.56 (m, 1H), 3.67–3.74 (m, 1H), 3.90 (dd, J=6.0, 2.1 Hz, 1H), 3.99 (ddd, J=7.6, 6.0, 2.1 Hz, 1H), 4.06 (d, J=13.1 Hz, 1H), 4.44 (s, 2H), 4.45 (d, J=12.0 Hz, 1H), 4.63 (d, J=12.0 Hz, 1H), 7.25–7.38 (m, 15H); δ_C (75 MHz, $CDCl_3$) δ 18.2, 25.9 (s), 30.2, 57.3, 58.4, 60.7, 63.3, 71.4, 81.5, 82.9, 127.1, 127.6 (s), 127.7 (s), 128.0 (s), 128.2 (s), 128.3 (s), 128.4 (s), 129.3, 138.0.

4.1.8. 2-((2*S*,3*R*,4*R*)-1-Benzyl-3,4-bis(benzyloxy)pyrrolidin-2-yl)ethanol (13). To a solution of **12** (0.15 g, 0.29 mmol), in THF (10 mL) was added TBAF (0.18 g, 0.58 mmol) and stirred for 4 h at 25 °C. The reaction mixture was concentrated under vaccum and extracted with (3×15 mL) dichloromethane. The combined organic layers were concentrated, adsorbed on silica gel and purified by column chromatography (10% ethyl acetate/*n*-hexane) afforded **13** (0.12 g, 95%) as thick oil; [found: C, 77.63; H, 7.50. $C_{27}H_{31}NO_3$ requires C, 77.67; H, 7.48]; R_f (20% ethyl acetate/*n*-hexane) 0.19; $[\alpha]_D$ +21.4 (*c* 0.28, $CHCl_3$); ν_{max} (neat) 3494, 2922, 1377, 1217 cm^{-1}; δ_H (300 MHz, $CDCl_3+D_2O$) δ 1.81–1.86 (m, 1H), 1.92–2.03 (m, 1H), 2.30–2.35 (m, 1H), 3.13–3.14 (m, 1H), 3.24 (dd, J=10.4, 5.5 Hz, 1H), 3.39 (br d, J=12.6 Hz, 1H), 3.68–3.75 (m, 1H), 3.81–3.88 (m, 1H), 4.02–4.11 (m, 3H), 4.46 (s, 2H), 4.35 (d, J=11.8 Hz, 1H), 4.64 (d, J=11.8 Hz, 1H), 7.22–7.34 (m, 15H); δ_C (75 MHz, $CDCl_3$) δ 29.3, 55.4, 59.5, 61.4, 64.8, 71.8, 72.0, 82.3, 83.9, 127.2, 127.5 (s), 127.6 (s), 128.3 (s), 129.0 (s), 137.7, 137.8.

4.1.9. Ethyl (*E*)-4-((2*S*,3*R*,4*R*)-1-benzyl-3,4-bis(benzyloxy)pyrrolidin-2-yl)but-2-enoate (8b). To a solution of oxalyl chloride (0.03 mL, 0.31 mmol) in dichloromethane (1 mL) at −78 °C was added slowly a solution of DMSO (0.04 mL, 0.58 mmol) in dichloromethane (1 mL). After 10 min, a solution of alcohol **13** (0.11 g, 0.26 mmol) in dichloromethane (2 mL) was added and the reaction was stirred at −78 °C for 2 h. Triethylamine (0.18 mL, 1.31 mmol) was added and the mixture was stirred at −78 °C for 30 min. Usual work up afforded aldehyde as a thick liquid. To the solution of aldehyde (0.11 g, 0.30 mmol) in dichloromethane (10 mL) was added PPh_3-CHCOOEt (0.12 g, 0.36 mmol) and stirred for 1 h at 25 °C. The reaction mixture was adsorbed on silica gel and purification by column chromatography (10% ethyl acetate/*n*-hexane) afforded **8b** (0.12 g, 94%) as thick oil; [found: C, 76.61; H, 7.18. $C_{31}H_{35}NO_4$ requires C, 76.67; H, 7.26]; R_f (10% ethyl acetate/*n*-hexane) 0.73; $[\alpha]_D$ +44.0 (*c* 0.25, $CHCl_3$); ν_{max} (neat) 1724, 1244 cm^{-1}; δ_H (300 MHz, $CDCl_3$) δ 1.20 (t, J=7.1 Hz, 3H), 2.19 (dd, J=9.9, 5.7 Hz, 1H), 2.36–2.41 (m, 1H), 2.56–2.58 (m, 1H), 2.80–2.81 (m, 1H), 3.19–3.27 (m, 2H), 3.82 (dd, J=6.0, 2.4 Hz, 1H), 3.89 (d, J=12.9 Hz, 1H), 3.87–3.89 (m, 1H), 4.08 (q, J=7.1 Hz, 2H), 4.33 (s, 2H), 4.36 (d, J=11.8 Hz, 1H), 4.51 (d, J=11.8 Hz, 1H), 5.75 (d, J=15.6 Hz, 1H), 6.90 (dt, J=15.6, 7.1 Hz, 1H), 7.19–7.25 (m, 15H); δ_C (75 MHz, $CDCl_3$) δ 14.4, 30.9, 57.3, 58.6, 60.1, 65.2, 71.4, 71.7, 81.4, 83.3, 122.5, 126.9, 127.4 (s), 127.5 (s), 127.6 (s), 127.9 (s), 128.1 (s), 137.7, 146.7, 166.3. Our attempt to isolate the *Z*-isomer

in pure form was unsuccessful, 94% yield reflects the total yield of *E* and *Z* isomer.

4.1.10. (1*R*,2*R*,8a*S*)-Hexahydro-1,2-dihydroxyindolizin-5(1*H*)-one (9b). The reaction of **8b**, (0.12 g, 0.25 mmol) with 10% Pd/C (0.08 g) and ammonium formate (0.11 g, 1.73 mmol) as described for the synthesis of **9a** afforded **9b** (0.04 g, 93%) as a white solid, mp 174–176 °C; [found: C, 56.10; H, 7.59. $C_8H_{13}NO_3$ requires C, 56.13; H, 7.65]; R_f (10% methanol/chloroform) 0.34; $[\alpha]_D$ −19.0 (*c* 0.42, MeOH); ν_{max} (KBr) 3441, 2926, 1711, 1653, 1212 cm^{-1}; δ_H (300 MHz, D_2O) δ 1.46 (m, 1H), 1.74–1.82 (m, 1H), 1.94–2.04 (m, 2H), 2.19–1.45 (m, 2H), 3.32 (d, J=13.7 Hz, 1H), 3.74–3.84 (m, 2H), 4.08–4.09 (m, 1H), 4.23 (dd, J= 4.9, 0.8 Hz, 1H); δ_C (75 MHz, D_2O) δ 20.0, 21.6, 30.1, 51.6, 60.8, 72.1, 76.1, 173.18.

4.1.11. (1*R*,2*R*,8a*S*)-(+)-1,2-Dihydroxyindolizidine (3b). The reaction of lactam **15** (0.07 g, 0.04 mmol) with LAH (0.06 g, 1.50 mmol) as described for the synthesis of **3a** afforded **3b** (0.06 g, 91%) as a sticky solid; [found: C, 56.21; H, 7.68. $C_8H_{15}NO_2$ requires C, 56.13; H, 7.65]; R_f (20% methanol/chloroform) 0.30; [observed $[\alpha]_D$ +4.3 (*c* 0.5, MeOH); lit.[5k] +3.4 (*c* 0.41, MeOH)]; ν_{max} (neat) 3355, 2934, 1121 cm^{-1}; δ_H (300 MHz, D_2O) δ 1.57–1.79 (m, 3H), 1.95–2.08 (m, 3H), 2.90 (dd, J=13.2, 3.0 Hz, 1H), 3.02–3.10 (m, 1H), 3.36 (d, J=11.8 Hz, 1H), 3.66 (d, J=12.1 Hz, 1H), 4.03 (dd, J=12.1, 6.3 Hz, 1H), 4.18 (d, J=3.0 Hz, 1H), 4.31 (dd, J=6.3, 3.0 Hz, 1H); δ_C (75 MHz, D_2O) δ 22.9, 24.7, 25.2, 53.1, 62.2, 66.9, 77.8, 81.1.

4.1.12. Methyl 3-((2*R*,3*R*,4*R*)-1-benzyl-4-benzyloxy-3-hydroxypyrrolodin-2-yl)propanoate (14). To an ice-cooled solution of **6a** (0.63 g, 1.30 mmol) in methanol–water (5 mL, 4/1) was added lithium hydroxide monohydrate (0.30 g, 5.22 mmol) and stirred for 4 h at 25 °C. The solution was neutralized and worked up to afford the acid. To a solution of an acid in THF (5 mL) was added triethylamine (0.28 mL, 2.02 mmol) and ethylchloroformate (0.19 mL, 2.02 mmol). After 15 min, the suspension was allowed to warm to 25 °C and filtered. The filtrate was cooled to 0 °C and a freshly prepared solution of diazomethane in diethyl ether (0.24 g, 5.80 mmol) was added dropwise and stirred for 3 h at 25 °C. The solvent was evaporated to afford thick oil. To a solution of diazoketone in methanol (8 mL) was added dropwise a solution of silver benzoate (0.11 g, 0.49 mmol) in triethylamine (0.50 mL) and stirred for 3 h at 25 °C. The solvent was evaporated and the residue was purified by column chromatography (20% ethyl acetate/*n*-hexane) to give **14** (0.45 g, 71%) as a thick liquid; [found: C, 71.46; H, 7.46. $C_{22}H_{27}NO_4$ requires C, 71.52; H, 7.37]; R_f (25% ethyl acetate/*n*-hexane) 0.68; $[\alpha]_D$ −24.0 (*c* 0.5, $CHCl_3$); ν_{max} (neat) 3345, 1728, 1457, 1134 cm^{-1}; δ_H (300 MHz, $CDCl_3+D_2O$): δ 1.25–1.28 (m, 2H), 2.56–2.76 (m, 3H), 2.90–3.33 (m, 2H), 2.98 (br d, J= 13.1 Hz, 1H), 3.72 (s, 3H), 3.87 (d, J=6.8 Hz, 1H), 3.96 (br d, J=13.1 Hz, 1H), 4.11 (d, J=3.8 Hz, 1H), 4.33 (ABq, J= 12.0 Hz, 2H), 7.26–7.34 (m, 10H); δ_C (75 MHz, $CDCl_3$) δ 29.5, 36.7, 52.0, 57.0, 57.8, 67.1, 71.0, 82.5, 82.8, 127.2, 127.5, 127.7 (s), 128.3 (s), 128.6 (s), 128.8 (s), 137.7, 138.0, 173.9.

4.1.13. (6*R*,7*R*,7a*R*)-Hexahydro-6,7-dihydroxypyrrolizin-3-one (15). The reaction of **14** (0.20 g, 0.54 mmol) with 10% Pd/C (0.10 g) and ammonium formate (0.23 g, 3.70 mmol) as described for the synthesis of **9a** afforded **15** (0.06 g, 70%) as a sticky gum; [found: C, 53.51; H, 7.03. $C_7H_{11}NO_3$ requires C, 53.49; H, 7.05]; R_f (10% methanol/chloroform) 0.35; $[\alpha]_D$ −15.3 (*c* 0.5, MeOH); ν_{max} (neat) 3335, 1723, 1659, 1433, 1214 cm^{-1}; δ_H (300 MHz, D_2O) δ 1.54–1.79 (m, 2H), 2.58 (dd, J=10.7, 0.8 Hz, 1H), 3.16–3.24 (m, 2H), 3.42–3.58 (m, 2H); 3.82 (dd, J=5.7, 1.8 Hz, 1H), 4.12–4.16 (m, 1H); δ_C (75 MHz, D_2O) δ 32.4, 49.7, 58.3, 63.2, 74.1, 78.6, 180.5.

4.1.14. (1*R*,2*R*,7a*R*)-(+)-1,2-Dihydroxypyrrolizidine (4). The reaction of lactam **15** (0.10 g, 0.63 mmol) with LAH (0.10 g, 2.54 mmol) as described for **3b** afforded **4** (0.07 g, 77%) as thick oil; [found: C, 58.68; H, 9.19. $C_7H_{13}NO_2$ requires C, 58.72; H, 9.15]; R_f (20% methanol/chloroform) 0.32; [observed $[\alpha]_D$ +6.5 (*c* 0.25, MeOH), lit.[5o] $[\alpha]_D$ +7.6 (*c* 1.3, MeOH)]; ν_{max} (neat) 3300–3600 (broad) cm^{-1}; δ_H (300 MHz, D_2O) δ 1.76–1.91 (m, 1H); 1.95–2.16 (m, 1H), 2.18–2.27 (m, 2H), 2.86–2.98 (m, 2H), 3.11 (dd, J=11.2, 4.9 Hz, 1H), 3.23 (dd, J=11.2, 3.8 Hz, 1H), 3.35–3.41 (m, 1H), 3.92–4.04 (m, 1H), 4.17–4.25 (m, 1H); δ_C (75 MHz, D_2O) δ 28.7, 32.4, 59.8, 62.2, 72.1, 80.2, 82.3.

Acknowledgements

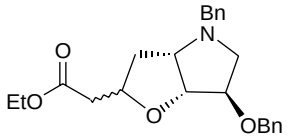
We are thankful to the DST (SP/S1/G23-2000), New Delhi for financial support and the UGC, New Delhi for the grant to procure high field (300 MHz) NMR facility.

References and notes

1. Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645.
2. Review: Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045.
3. (a) Isolation: Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 1886. (b) Activity: Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806.
4. The natural lentiginosine with all *S* configurations is reported to have $[\alpha]_D$ −3.3, while Yoda et al. and Brandi et al. have reported the synthesis of lentiginosine starting from L-tartaric acid and gave a value $[\alpha]_D$ +0.19 and +3.2, respectively. The synthesis of both enantiomers of lentiginosine was reported by Gurjar et al., starting from (*R*) and (*S*)-pipecolinic acid and showed that the (−)-lentiginosine has the all *R* stereochemistry. However, the subsequent report of Brandi et al. claim that natural lentiginosine is not levorotatory but dextrorotatory and this has the (1*S*,2*S*,8a*S*) configuration.
5. (a) Yoda, H.; Kitayama, H.; Katagiri, T.; Tkabe, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1455. (b) Cordero, F. M.; Cicchi, S.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **1994**, *35*, 949. (c) Gurjar, M. K.; Ghosh, L.; Syamala, M.; Jayasree, V. *Tetrahedron Lett.* **1994**, *35*, 8871. (d) Giovannini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1995**, *60*, 5706. (e) Goti, A.; Cardona, F.; Brandi, A. *Synlett* **1996**, 761. (f) Goti, A.; Cardona, F.; Brandi, A. *Tetrahedron: Asymmetry*

1996, *7*, 1659. (g) McCaig, A. E.; Meldrum, K. P.; Wightman, R. H. *Tetrahedron* **1998**, *54*, 9429. (h) Ha, D.-C.; Yun, C.-S.; Lee, Y. *J. Org. Chem.* **2000**, *65*, 621. (i) Klitzke, C. F.; Pilli, R. C. *Tetrahedron Lett.* **2001**, *42*, 5605. (j) Yoda, H.; Katoh, H.; Ujihara, Y.; Takabe, K. *Tetrahedron Lett.* **2001**, *42*, 2509. (k) Nakui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *69*, 398. (l) Rasmussen, M. O.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2001**, *66*, 5438. (m) Lim, S. H.; Ma, S.; Beak, P. *J. Org. Chem.* **2001**, *66*, 9056. (n) Feng, Z.-X.; Zhou, W.-S. *Tetrahedron Lett.* **2003**, *44*, 497. (o) Ayad, T.; Genisson, Y.; Baltas, M.; Gorrichon, L. *Chem. Commun.* **2003**, 582. (p) Sha, C.-K.; Chau, C.-M. *Tetrahedron Lett.* **2003**, *44*, 499–501. (q) Raghavan, S.; Sreekanth, T. *Tetrahedron: Asymmetry* **2004**, *15*, 565.

6. (a) Yoda, H.; Kawauchi, M.; Takabe, K. *Synlett* **1998**, 137. (b) Paolucci, P.; Mattioli, L. *J. Org. Chem.* **2001**, *66*, 4787. (c) Rabiczako, Z.; Urbanczyk-Lipkowska, Z.; Chmielewski, M. *Tetrahedron* **2002**, *58*, 1433. (d) Chandra, K. L.; Chandrasekar, M.; Singh, V. K. *J. Org. Chem.* **2002**, *67*, 4630.
7. (a) D-Glucose derived α,β-unsaturated ester was utilized by us in the synthesis of azasugars see: (a) Desai, V. N.; Saha, N. N.; Dhavale, D. D. *J. Chem. Soc., Chem. Commun.* **1999**, 1719. (b) Patil, N. T.; Tilekar, J. N.; Dhavale, D. D. *J. Org. Chem.* **2001**, *66*, 1065. (c) Chaudhari, V. D.; Ajish Kumar, K. S.; Dhavale, D. D. *Tetrahedron Lett.* **2004**, *45*, 8363. (d) Dhavale, D. D.; Matin, M. M.; Sharma, T.; Sabharwal, S. G. *Bioorg. Med. Chem.* **2003**, *11*, 3295. (e) Dhavale, D. D.; Markad, S. D.; Karanjule, N. S.; Prakashareddy, J. *J. Org. Chem.* **2004**, *69*, 4760. . For other references on azasugars see: Karanjule, N. S.; Markad, S. D.; Sharma, T.; Sabharwal, S. G.; Puranik, V. G.; Dhavale, D. D. *J. Org. Chem.* **2005**, *70*, 1356 and references cited therein.
8. This is an unpublished work from our laboratory. For details see: Chiron approaches to polyhydroxylated pyrrolidine, indolizidine, pyrrolizidine alkaloids and sphingolipids, Chaudhari, V. D. Ph. D. dissertation, University of Pune, October 2005.
9. Reaction of γ-lactone **6b** with DIBAL-H afforded corresponding lactol, which on the Wittig olefination led to the formation of inseparable diastereomeric mixture of unexpected conjugate addition adduct **X**.



X

10. For enantiomer of **3b** see: Paolucci, C.; Musiani, L.; Venturelli, F.; Fava, V. *Synthesis* **1997**, 1415.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 4355–4359

Trypanocidal constituents of *Dracocephalum komarovi*

Nahoko Uchiyama,[a,e] Fumiyuki Kiuchi,[b] Michiho Ito,[a] Gisho Honda,[a,*] Yoshio Takeda,[c] Olimjon K. Khodzhimatov[d] and Ozodbek A. Ashurmetov[d]

[a]*Graduate School of Pharmaceutical Sciences, Kyoto University, Kyoto 606-8501, Japan*
[b]*Research Center for Medicinal Plant Resources, National Institute of Biomedical Innovation, 1-2 Hachimandai, Tsukuba 305-0843, Japan*
[c]*Faculty of Integrated Arts and Sciences, The University of Tokushima, Tokushima 770-8502, Japan*
[d]*Scientific Production Center 'Botanika' of Uzbek Academy of Sciences, Tashkent 700143, Uzbekistan*
[e]*Faculty of Pharmaceutical Sciences, Doshisha Women's College of Liberal Arts, Kodo, Kyotanabe-city, Kyoto 610-0395, Japan*

Received 28 November 2005; revised 16 February 2006; accepted 23 February 2006

Abstract—Trypanocidal constituents of *Dracocephalum komarovi* were investigated. Under guidance of the in vitro trypanocidal activity against epimastigotes of *Trypanosoma cruzi*, the causative agent of Chagas' disease, two new diterpenes, dracocequinones A (**1**) and B (**2**), and two known triterpene acids, ursonic acid and ursolic acid, were isolated as trypanocidal constituents, in addition to previously reported diterpenes, cyclocoulterone (**4**), komaroviquinone (**5**), dracocephalone A (**6**) and komarovispirone (**7**). Furthermore a new diterpene, komarovinone A (**3**), was isolated, together with four known terpenes. Among these compounds, komaroviquinone (**5**) showed the most potent activity with minimum lethal concentration of 0.4 μM. Structure elucidation of the new diterpenes **1–3** was described.

1. Introduction

Chagas' disease is a major public health problem endemic in Central and South American countries, with 18–20 million infected people, 25% of the human population at risk of infection, ca. 200,000 new cases, and 21,000 deaths per year.[1] Its causative agent is *Trypanosoma cruzi*, a parasitic protozoan transmitted to mammalian host by blood-sucking triatomine bugs. *T. cruzi* undergoes three main developmental stages during its life cycle, that is, the replicative epimastigote form in insect vectors and the trypomastigote and amastigote forms in mammalian hosts. Non-dividing and infective trypomastigotes circulate in the blood with their free flagellum before invading host cells, preferably muscle cells, where they lose their flagellum to differentiate into replicative amastigotes.[2] Infections by *T. cruzi* result in a life-threatening, acute and/or chronic disease with severe cardiac complications. This situation is worsened by the lack of effective vaccines, undesirable side effects of anti-chagasic drugs in use such as nifurtimox and benznidazole, and the emergence of parasite resistance to these drugs. Therefore, development of new chemotherapeutic agents is urgently needed.

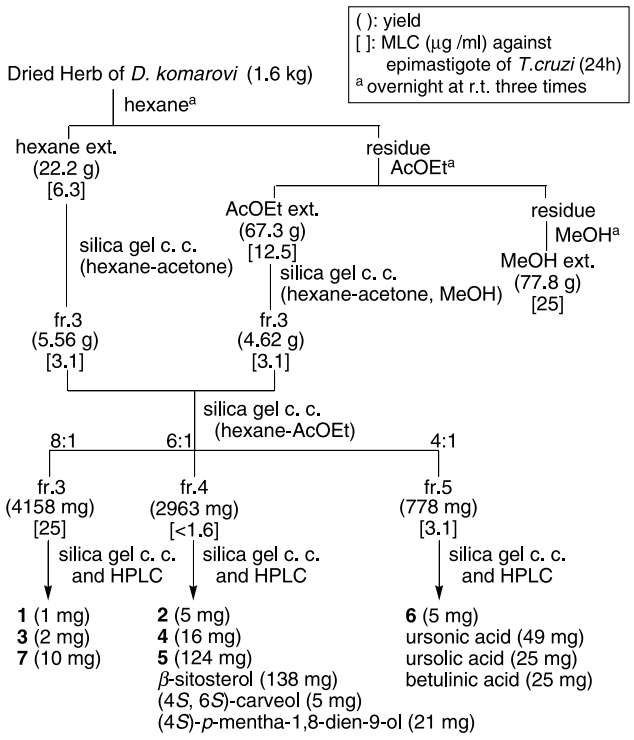
The genus *Dracocephalum* is an annual or perennial herb of the Labiatae family, occurring widely in Southern Europe and temperate Asia. Some of its species are used as an astringent and a carminative,[3] and are reported to show antihyperlipidemic effect,[4] immunomodulatory effect[5] and antinociceptive effect.[6] *Dracocephalum komarovi* Lipsky is a perennial semishrub that grows at around 2300–3600 m above sea level in the West Tien Shan mountain system.[7] It is called 'buzbosh' in Uzbekistan and the local people use the aerial parts in a tea to cure various disorders such as inflammatory diseases and hypertony. During our screening of medicinal plants of Uzbekistan for trypanocidal activity, this plant showed trypanocidal activity, and we previously reported the isolation of four new diterpenes, cyclocoulterone (**4**), komaroviquinone (**5**), dracocephalone A (**6**)[8] and komarovispirone (**7**)[9] from the hexane and EtOAc extracts. In this paper, we report a full account of the elucidation of trypanocidal constituents of *D. komarovi*, including the isolation and structure elucidation of three new diterpenes.

2. Results and discussion

Dried whole plants of *D. komarovi* were extracted as described previously[8] (Scheme 1). The hexane and EtOAc

Keywords: *Dracocephalum komarovi*; Diterpene; *Trypanosoma cruzi*; Trypanocidal activity.
* Corresponding author. Tel.: +81 75 753 4534; fax: +81 75 753 4591; e-mail: ghonda@pharm.kyoto-u.ac.jp

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.067



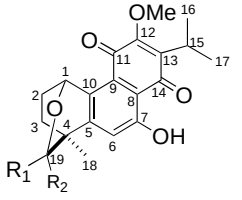
Scheme 1.

extracts were fractionated by silica gel column chromatography using hexane–acetone and MeOH as eluents. The fractions that were eluted with hexane–acetone (6/1) from the hexane extract, and hexane–acetone (8/1) from the EtOAc extract, showed strong in vitro trypanocidal activity against epimastigotes of *T. cruzi*. These fractions were further separated by silica gel column chromatography and HPLC to give seven new compounds **1** (1 mg), **2** (5 mg), **3** (2 mg), **4** (16 mg), **5** (124 mg), **6** (5 mg) and **7** (10 mg), together with ursonic acid,[10] ursolic acid,[11] betulinic acid,[12] β-sitosterol,[13] (4*S*,6*S*)-carverol[14] and (4*S*)-*p*-mentha-1,8-diene-9-ol.[15] The structures of compounds **4** (cyclocoulterone), **5** (komaroviquinone), **6** (dracocephalone A), **7** (komarovispirone) were reported previously.[8,9] The known compounds were identified by comparisons of the physical and spectroscopic data with those reported.

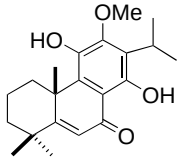
Compound **1** was obtained as an orange oil. The molecular formula $C_{20}H_{22}O_5$ was revealed by high-resolution electron-impact mass spectrum (HREIMS). The presence of a tetra-substituted *p*-benzoquinone moiety (δ_C 112.4, 124.5, 183.4, 159.2, 138.5, 191.3) with methoxy (δ_C 60.9) and isopropyl (δ_C 20.2, 20.4, 24.3) groups, which is similar to that found in komaroviquinone (**5**),[8] was concluded from its ^{13}C NMR and HMBC spectra (Table 1, Fig. 1). However, the chemical shifts of the ring juncture carbons (C-8, δ_C 112.4; C-9, δ_C 124.5) suggested the presence of further conjugation. In fact, HMBC correlations from the chelated hydroxy (δ_H 12.97) and olefin (δ_H 7.12) protons connected this enol system to the *p*-benzoquinone part to form a hydroxy naphthoquinone moiety (Fig. 1). Homo-gated decoupling (HOM) experiments revealed an ^1H–^1H coupling network between an oxymethine proton (δ_H 6.09; δ_C 64.7) and protons of two methylenes (δ_H 1.36, 1.64, 1.80, 2.41). This part structure was connected to the hydroxy naphthoquinone moiety through a quarterly carbon (δ_C 35.4), which also had a methyl (δ_C 18.6) and an oxymethylene (δ_C 71.6) groups. Finally, the two oxygen-bearing carbons (δ_C 64.7 and 71.6) were connected through an ether linkage, because there was only one oxygen atom left in the molecule. Irradiation of the H-6 proton (δ_H 7.12) resulted in a nuclear Overhauser effect (NOE) on H-18 (δ_H 1.34, α-methyl) (Figure 2). Thus, compound **1** was concluded to have the structure indicated, and was named dracocequinone A.

Compound **2** was obtained as an orange oil. This compound showed very similar NMR spectra to those of **1**. However, compound **2** showed no oxymethylene protons corresponding to H-19 in **1**, and instead of the oxygen-bearing carbon at δ_C 71.6 in **1**, compound **2** had an ester carbonyl at δ_C 174.2. This was compatible with its molecular formula $C_{20}H_{20}O_6$ revealed by HRMS. Thus, compound **2** was concluded to be a 19-keto derivative of **1**, and was named dracocequinone B.

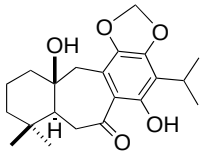
Compound **3** was obtained as a yellow amorphous solid. The ^{13}C NMR spectrum showed very similar chemical shifts for C-1 to C-7 carbons to those of salvinolone (**8**)[16] (Table 1). However, the molecular formula $C_{21}H_{28}O_4$ (HREIMS) together with the ^1H and ^{13}C NMR spectra indicated the presence of an additional methoxy group



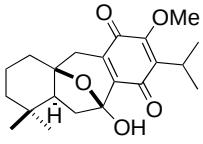
dracocequinone A (**1**): R_1=R_2=H
dracocequinone B (**2**): R_1,R_2= =O



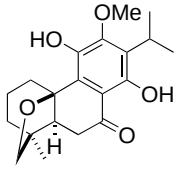
komarovinone A (**3**)



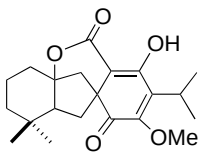
cyclocoulterone (**4**)



komaroviquinone (**5**)



dracocephalone A (**6**)



komarovispirone (**7**)

Table 1. NMR Data of **1**–**3**[a]

No.	**1**			**2**			**8**[b]	**3**		
	^{13}C	^{1}H	HMBC[c]	^{13}C	^{1}H	HMBC[c]	^{13}C	^{13}C	^{1}H	HMBC[c]
1	64.7	6.09, m		73.1	6.87, d, J=2.8 Hz		33.9	34.3	3.33, overlap	20
									1.45, td, J=12.5, 4.0 Hz	
2	25.9	2.41, m		25.9	2.49, dddd, J=14.0, 10.4, 5.5, 2.8 Hz	3	18.2	18.7	1.95, m	
		1.64, m			1.88, br t, J=14.0 Hz				1.61, dt, J=14.3, 4.6 Hz	
3	30.1	1.80, ddd, J=14.0, 10.7, 3.7 Hz	18, 19	29.2	2.04, ddd, J=13.1, 10.4, 3.1 Hz	18	39.0	40.4	1.73, dt, J=13.2, 4.6 Hz	18, 19
		1.36, m			1.60, br td, J=12.8, 5.5 Hz				1.43, overlap	
4	35.4		6, 18	45.1		3, 6, 18	37.6	38.2		6, 18, 19
5	153.6		18, 19	149.2		1, 3, 18	173.9	176.5		18, 19, 20
6	117.3	7.12, s	OH	118.2	7.16, s	OH	122.6	123.2	6.36, s	18
7	161.4		6, OH	162.0		6, OH	183.8	190.9		
8	112.4		6	113.0		6, OH	122.6	111.1		6
9	124.5			125.7			137.6	135.4		20, 11-OH
10	134.6		6	130.3		6	41.6	43.0		6, 20
11	183.4			182.9			142.5	138.1		11-OH
12	159.2		OMe	159.0		15, OMe	147.5	150.8		15, OMe, 11-OH
13	138.5		16, 17	139.2		15, 16, 17	134.2	125.8		15, 16, 14-OH
14	191.3		15	190.9		15	114.1	156.7		15, 14-OH
15	24.3	3.42, sept, J=7.0 Hz	16, 17	24.4	3.42, sept, J=7.4 Hz	16, 17	24.6	26.1	3.33, overlap	16
16	20.4[d]	1.29, d, J=7.0 Hz	15, 17	20.4[d]	1.29, d, J=7.4 Hz	17	22.8[d]	20.4[d]	1.43, d, J=7.3 Hz	15, 17
17	20.2[d]	1.27, d, J=7.0 Hz	16	20.2[d]	1.28, d, J=7.4 Hz	15, 16	22.6[d]	20.3[d]	1.41, d, J=7.3 Hz	15, 16
18	18.6	1.34, s		16.2	1.68, s		29.1	33.0	1.26, s	19
19	71.6	3.80, d, J=7.9 Hz	18	174.2		1, 3, 18	26.1	29.4	1.35, s	1, 18
		3.20, dd, J=7.9, 3.4 Hz								
20							32.9	24.8	1.65, s	
OMe	60.9	4.05, s		61.1	4.09, s			62.1	3.80, s	
OH		12.97, s			12.93, s				5.81, s (C-11); 13.52, s (C14)	

[a] Recorded in $CDCl_3$ at 500 MHz (^{1}H) and 125 MHz (^{13}C), respectively; data in δ ppm (J in Hz).
[b] Recorded in DMSO-d_6; *Phytochemistry*, **1989**, *28*, 177.
[c] Protons correlated with the carbon.
[d] The assignments may be interchanged within each column.

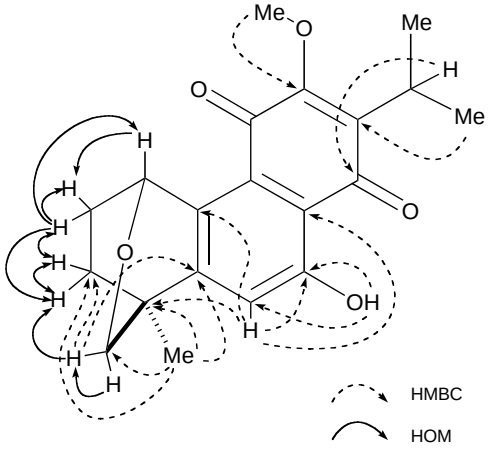


Figure 1. Key HMBC correlations and ^{1}H–^{1}H coupling network revealed by HOM experiments in **1**.

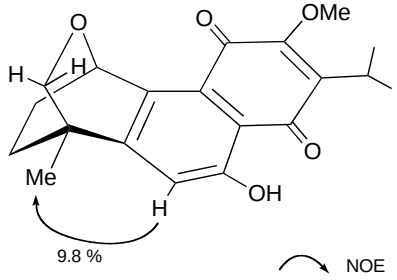


Figure 2. Observed NOEs in **1**.

(δ_H 3.80; δ_C 62.1). From the HMBC spectrum, the hydroxy groups were located at C-11 and C-14 and the methoxy group was concluded to be at C-12. In NOE difference experiments (Fig. 3), irradiation of the H-18 proton (δ_H 1.26, α-methyl) resulted in NOEs on H-6 (δ_H 6.36) and H-19 protons (δ_H 1.35, β-methyl), whereas irradiation of the H-20 proton (δ_H 1.65) enhanced the signal intensity

of H-19. These results indicated the stereochemistry at C-10 to be 10β. Thus, **3** was determined to have the indicated structure, and was named komarovinone A.

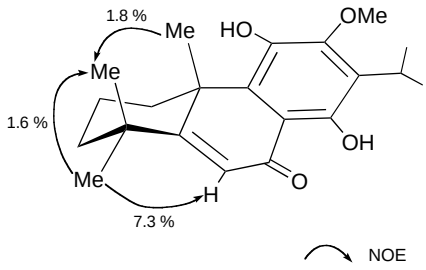


Figure 3. Observed NOEs in **3**.

Trypanocidal activities of the isolated compounds are summarized in Table 2. Dracocequinone A (**1**) and B (**2**) showed trypanocidal activity against epimastigotes of *T. cruzi* with a minimum lethal concentration (MLC) of 12.5 and 25 μM, respectively. The MLC of **1** and **2** are similar to that of **4** (20 μM) and **7** (23 μM), but higher than that of **5** (0.4 μM) under the same conditions. On the contrary, komarovinone A (**3**), which lacks the quinone moiety the same as **6** (200 μM), did not show trypanocidal activity even at 200 μM. Two triterpenes showed moderate trypanocidal activity: ursonic acid, MLC=50 μM; ursolic acid, MLC=100 μM. Betulinic acid, β-sitosterol and monoterpene alcohols; (4*S*,6*S*)-carveol and (4*S*)-*p*-mentha-1,8-dien-9-ol did not show trypanocidal activity even at 200 μM. These results indicated that **5** was the major trypanocidal component of *D. komarovi*. The MLC of gentian violet, which is used to disinfect trypanosomes from transfusion blood in Latin America, was 6.3 μM under the same assay conditions. Several types of natural quinones have been reported to show trypanocidal activity, and their activities have been partly ascribed to the production of a reactive oxygen species in the parasite.[17] In fact, we found that **5** underwent one electron reduction by *T. cruzi* old yellow enzyme to produce its semiquinone radical, which subsequently generates superoxide anion radicals.[18] Thus, the trypanocidal activity of **1**, **2** and **5** may be due to the generation of a reactive oxygen species. Previously, trypanocidal activity of several types of diterpenes and triterpenes has been reported. Da Costa et al. reported that kaurane diterpenes; (−)-*ent* kaur-16-en-19-oic acid, (−)-trachyloban-19-oic acid, (−)-kaur-16-en-19-ol and (−)-kauran-16-α-ol were effective against trypomastigotes of *T. cruzi* with IC_{50} of 1.66, 1.66, 0.69 and 1.72 mM, respectively.[19,20] Cassane diterpenes were also reported to show trypanocidal activity against trypomastigotes and amastigotes of *T. cruzi* with IC_{50} in the range of 11.5 to 104 μM and 16.6 to 95.5 μM, respectively.[21,22] Thus, trypanocidal activity of **1**, **2**, **4** and **7** were in the same range as those of cassane diterpenes. However, **5** showed more potent activity than the other diterpenes.

Table 2. Trypanocidal activity of isolated compounds from *D. komarovi*

Compound	MLC (μM)[a]
Dracocequinone A (**1**)	12.5
Dracocequinone B (**2**)	25
Komarovinone A (**3**)	>200
Cyclocoulterone (**4**)[8]	20
Komaroviquinone (**5**)[8]	0.4
Dracocephalone A (**6**)[8]	200
Komarovispirone (**7**)[9]	23
Ursonic acid	50
Ursolic acid	100
Betulinic acid	>200
β-Sitosterol	>200
(4*S*,6*S*)-Carveol	>200
(4*S*)-*p*-Mentha-1,8-dien-9-ol	>200
Gentian violet	6.3

[a] Minimum lethal concentration against epimastigotes of *T. cruzi*.

We will test the activity of the newly isolated diterpenes against trypomastigotes and the intracellular amastigotes of *T. cruzi*.

In this work, we isolated trypanocidal constituents from *D. komarovi* obtained in Uzbekistan, and trypanocidal constituents were also isolated from *D. kotschyi*[23] and *D. subcapitatum*[24] collected in Iran. Thus, we examined trypanocidal activity of some other *Dracocephalum* species (Table 3). The ethyl acetate extract of *D. integrifolium* collected in Uzbekistan showed moderate activity, whereas *D. nutans* collected in Kazakhstan and *D. argunense* grown in Japan showed weak trypanocidal activity. Elucidation of the trypanocidal constituents of these species will be a future interest.

Table 3. Minimum lethal concentration (MLC) of *Dracocephalum* extracts against epimastigotes of *T. cruzi*

Origin	MLC (μg/ml)		
	AcOEt	Acetone	MeOH
D. komarovi	—	<25	<25
D. integrifolium Bunge[a]	25	—	>100
D. nutans L.[b]	100	—	>100
D. ruyschiana L.[b]	>100	—	>100
D. argunense Fisch[c]	100	—	>100
D. argunense Fisch[d]	>100	—	>100

[a] Collected in Uzbekistan.
[b] Collected in Kazakhstan.
[c] Grown in Nagano prefecture, Japan.
[d] Grown in Hokkaido prefecture, Japan.

3. Experimental

3.1. General experimental procedures

Optical rotations were determined on a JASCO DIP-370 polarimeter. ^1H and ^{13}C NMR spectra were measured on a JEOL JNM-LA500 spectrometer with tetramethylsilane as an internal standard, and chemical shifts are given as δ values. Mass spectra were measured on a JEOL JMS-HX/HX110A spectrometer. UV and IR spectra were recorded on Hitachi U-3210 and Shimadzu FTIR-8700 spectrometers, respectively.

3.2. Extraction and isolation

Dried whole plants of *D. komarovi* were purchased at a local market in Kumyshkan, Uzbekistan, and identified by one of the authors (O.K.K.). A voucher specimen (ESM-4235) was deposited at the Experimental Station of Medicinal Plants, Faculty of Pharmaceutical Sciences, Kyoto University.

Dried whole plants of *D. komarovi* (1.6 kg) were cut into small pieces and successively extracted with hexane and EtOAc at room temperature overnight to give hexane (22.2 g) and EtOAc (67.3 g) extracts. Each extract was subjected to silica gel column chromatography using hexane–acetone (10/1, 8/1, 6/1, 4/1, 0/1) and MeOH as eluents. The fractions from the hexane extract (eluted with 6:1, 5.6 g), and the EtOAc extract (eluted with 8:1, 4.6 g) were combined and fractionated by silica gel column chromatography (CC) with hexane–EtOAc to give six fractions: fr.1 (8:1, 0.23 g); fr.2 (8:1, 0.16 g); fr.3 (8:1, 4.16 g); fr.4 (6:1, 3.0 g); fr.5 (4:1, 0.78 g); fr.6 (0:1, 0.50 g). Repeated fractionation of fr. 3 by silica gel CC with benzene–EtOAc (10/0, 10/1), hexane–EtOAc (20/1), hexane–acetone (15/1), hexane–benzene (1/10) gave compounds **1** (1 mg), **3** (2 mg), **7** (komarovispirone, 10 mg). Repeated separation of fr. 4 by silica gel CC with $CHCl_3$–acetone (200/1, 100/1), benzene–EtOAc (30/1, 20/1), hexane–EtOAc (8/1), hexane–$CHCl_3$ (1/1) and HPLC (YMC Pack SIL-06, hexane–EtOAc=6:1, 5:1) afforded compounds **2** (5 mg), **4** (cyclocoulterone, 16 mg), **5** (komaroviquinone, 124 mg), (4*S*,6*S*)-carveol (5 mg),[14] (4*S*)-*p*-mentha-1,8-dien-9-ol (21 mg),[15] and β-sitosterol (138 mg).[13] Fractionation of fr. 5 by silica gel CC with $CHCl_3$–acetone (100/1), $CHCl_3$–EtOAc (100/1), HPLC (benzene–EtOAc=30:1, hexane–acetone=8:1) and silica gel CC with hexane–EtOAc (8/1) gave compound **6** (dracocephalone A, 5 mg), ursonic acid (49 mg),[10] ursolic acid (25 mg),[11] and betulinic acid (25 mg).[12]

3.2.1. Dracocequinone A (1). An orange oil; $[\alpha]_D^{25}$ +85.8 (*c* 0.1, MeOH); UV (MeOH) λ_{max} (log ε) 251 (4.07), 291 (3.94), 428 (3.60) nm; IR (KBr) ν_{max} 2932, 2858, 1666, 1632, 1601 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz): see Table 1; EIMS *m*/*z* 342 [M^+] (100), 328 (66), 314 (66), 298 (95), 285 (48); HREIMS *m*/*z* 342.1477 (calcd for $C_{20}H_{22}O_5$, 342.1461).

3.2.2. Dracocequinone B (2). An orange oil; $[\alpha]_D^{25}$ −42.9 (*c* 0.48, MeOH); UV (MeOH) λ_{max} (log ε) 255 (3.94), 292 (3.74), 421 (3.41) nm; IR (KBr) ν_{max} 2943, 1755, 1666, 1632, 1601 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz): see Table 1; EIMS *m*/*z* 356 [M^+] (25), 342 (6), 312 (100), 298 (36), 297 (49), 283 (21); HREIMS *m*/*z* 356.1254 (calcd for $C_{20}H_{20}O_6$, 356.1260).

3.2.3. Komarovinone A (3). Yellow amorphous solid, mp 193–195°C; $[\alpha]_D^{25}$ +29 (*c* 0.12, MeOH); UV (MeOH) λ_{max} (log ε) 238 (4.13), 258 (4.26), 298 (3.84), 393 (3.78) nm; IR (KBr) ν_{max} 3333, 2959, 2936, 1639, 1582, 1458, 1420, 1400 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz): see Table 1; EIMS *m*/*z* 344 [M^+] (95), 329 (100), 297 (15), 274 (43), 262 (45); HREIMS *m*/*z* 344.1993 (calcd for $C_{21}H_{28}O_4$, 344.1988).

3.3. Trypanocidal assay

Trypanocidal activity against epimastigotes of *T. cruzi* (Tulahuen strain) was determined as described previously.[25] Each assay was performed in duplicate.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research (No. 12576027) from the Japan Society for the Promotion of Science.

References and notes

1. Urbina, J. A.; Docampo, R. *Trends Parasitol.* **2003**, *19*, 495–501.
2. Nakajima-Shimada, J.; Hirota, Y.; Aoki, T. *Antimicrob. Agents Chemother.* **1996**, *40*, 2455–2458.
3. Amin, G. *Popular Medicinal Plants of Iran*; Ministry of Health Publications: Tehran, 1991; p 41.
4. Ebrahim Sajjadi, S.; Movahedian Atar, A.; Yektaian, A. *Pharma. Acta Helv.* **1998**, *73*, 167–170.
5. Amirghofran, Z.; Azadbakht, M.; Karimi, M. H. *J. Ethnopharmacol.* **2000**, *72*, 167–172.
6. Golshani, S.; Karamkhani, F.; Monsef-Estehani, H. R.; Abdollahi, M. *J. Pharm. Pharmaceut. Sci.* **2004**, *7*, 76–79.
7. Vvedenski, A. I. In *Flora Uzbekistana*, *Vol. 5*; Editio Academiae Scientiarum UzSSR: Tashkent, 1961; p 313.
8. Uchiyama, N.; Kiuchi, F.; Ito, M.; Honda, G.; Takeda, Y.; Khodzhimatov, O. K.; Ashurmetov, O. A. *J. Nat. Prod.* **2003**, *66*, 128–131.
9. Uchiyama, N.; Ito, M.; Kiuchi, F.; Honda, G.; Takeda, Y.; Khodzhimatov, O. K.; Ashurmetov, O. A. *Tetrahedron Lett.* **2004**, *45*, 531–533.
10. Shashi, B. M.; Asish, P. K. *Phytochemistry* **1994**, *37*, 1517–1575.
11. Alves, J. S.; de Castro, J. C. M.; Freire, M. O.; da-Cunha, E. V. L.; Barbosa-Filho, J. M.; de Silva, M. S. *Magn. Reson. Chem.* **2000**, *38*, 201–206.
12. Ikuta, A.; Itokawa, H. *Phytochemistry* **1988**, *27*, 2813–2815.
13. Nes, W. D.; Norton, R. A.; Benson, M. *Phytochemistry* **1992**, *31*, 805–811.
14. Grandi, R.; Pagnoni, U. M.; Trave, R. *Tetrahedron* **1974**, *30*, 4037–4040.
15. Buckingham, J., Bradley, H. M., Eds.; Dictionary of Natural Products; Chapman and Hall: London, 1993; Vol. 4, p 3823.
16. Lin, L. Z.; BlaskÓ, G.; Cordell, G. A. *Phytochemistry* **1989**, *28*, 177–181.
17. Sepúlveda-Boza, S.; Cassels, B. K. *Planta Med.* **1996**, *62*, 98–105.
18. Uchiyama, N.; Kabututu, Z.; Kubata, B. K.; Kiuchi, F.; Ito, M.; Nakajima-Shimada, J.; Aoki, T.; Ohkubo, K.; Fukuzumi, S.; Martin, S. K.; Honda, G.; Urade, Y. *Antimicrob. Agents Chemother.* **2005**, *49*, 5123–5126.
19. Da Costa, F. B.; Albuquerque, S.; Vichnewski, W. *Planta Med.* **1996**, *62*, 557–559.
20. Alves, T. M.; Chaves, P. P.; Santos, L. M.; Nagem, T. J.; Murta, S. M.; Ceravolo, I. P.; Romanha, A. J.; Zani, C. L. *Planta Med.* **1995**, *61*, 85–87.
21. Torres-Mendoza, D.; Urena-Gonzalez, L. D.; Ortega-Barria, E.; Coley, P. D.; Kursar, T. A.; Capson, T. L.; McPhail, K.; Cubilla-Rios, L. *J. Nat. Prod.* **2004**, *67*, 1711–1715.
22. Torres-Mendoza, D.; Urena-Gonzalez, L. D.; Ortega-Barria, E.; Capson, T. L.; Cubilla-Rios, L. *J. Nat. Prod.* **2003**, *66*, 928–932.
23. Saeidnia, S.; Gohari, A. R.; Uchiyama, N.; Ito, M.; Honda, G.; Kiuchi, F. *Chem. Pharm. Bull.* **2004**, *52*, 1249–1250.
24. Saeidnia, S.; Gohari, A. R.; Ito, M.; Kiuchi, F.; Honda, G. *Z. Naturforsh.* **2005**, 22–24.
25. Kiuchi, F.; Itano, Y.; Uchiyama, N.; Honda, G.; Tsubouchi, A.; Nakajima-Shimada, J.; Aoki, T. *J. Nat. Prod.* **2002**, *64*, 509–512.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 4360–4363
Tetrahedron

Cyclitol based metal complexing agents. Preference for the extraction of lithium by *myo*-inositol based crown-4-ethers depends on the relative orientation of crown ether oxygen atoms

Shailesh S. Dixit, Mysore S. Shashidhar* and Subramanian Devaraj

Division of Organic Synthesis, National Chemical Laboratory, Pashan Road, Pune 411 008, Maharashtra, India

Received 19 October 2005; revised 3 February 2006; accepted 23 February 2006

Available online 20 March 2006

Abstract—*myo*-Inositol derived crown-4-ethers in which two of the oxygen atoms in the crown ether moiety have different relative orientations were prepared. Metal picrate binding studies revealed that the crown ether having 1,3-diaxial orientation shows the highest selectivity for binding to lithium although the crown ether having 1,2-diequatorial orientation exhibited the highest binding constant for lithium picrate. These results suggest that relative binding affinity of metal ions to crown ethers can be tuned by varying the relative orientation of crown ether oxygen atoms. The relevance of these results to the previously observed regioselectivity during the O-substitution of *myo*-inositol orthoesters is discussed.

1. Introduction

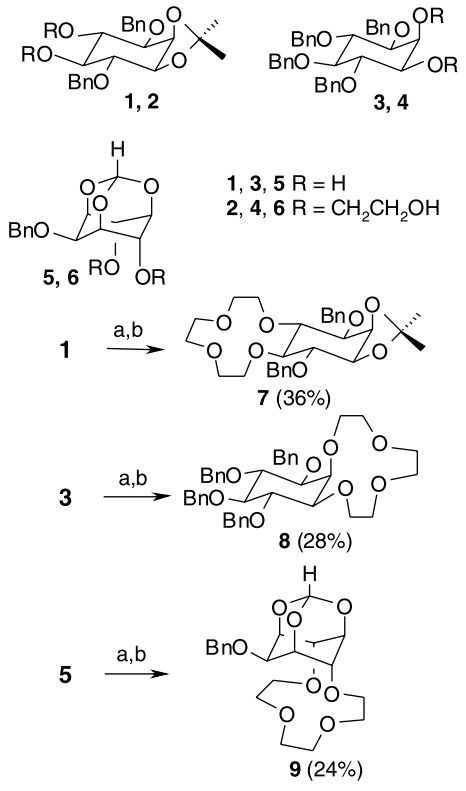
The realization of the existence of phosphoinositol based cellular signal transduction mechanisms in eukaryotic cells[1] and the role played by *myo*-inositol in the anchoring of certain proteins to the cell membranes[2] has driven chemists to devise novel methods for the efficient synthesis of cyclitol derivatives.[3–5] These synthetic investigations revealed several unusual reactions of *myo*-inositol derivatives.[5] In particular, the regioselectivities encountered during O-alkylation,[6,7] O-acylation,[8] O-sulfonylation,[9] and transesterification[10] reactions of *myo*-inositol 1,3,5-orthoformate and its derivatives, was attributed to their chelation with metal ions. To investigate the extent of the binding of metal ions with inositol derivatives, we carried out lithium and sodium picrate extraction studies of several *myo*-inositol derivatives.[11] Most of the *myo*-inositol derivatives bound lithium picrate better than other alkali metal picrates. Studies on the binding of lithium to inositol derivatives are of potential interest due to the ability of lithium to inhibit the activity of *myo*-inositol-1-phosphate phosphatase.[12–14] This has been implicated for the therapeutic effect of lithium, which is used as a drug for manic depression.[15] Lithium selective ligands[16–18] are also of interest in supramolecular chemistry. The reports[19,20] on the chemistry and biology cited above prompted us to prepare inositol-based crown-4-ethers to investigate their ability to bind lithium selectively. Although several carbohydrate derived crown ethers have been reported in the literature as tools for asymmetric Michael addition,[21–23] asymmetric hydrogenation,[24] O-alkylation of carbohydrates and nucleosides,[25] other enantioselective reactions[26–28] and molecular recognition,[29,30] there are only a few reports on inositol derived crown ethers.[31,32] Earlier work in our laboratory had shown that some *myo*-inositol based podands[33] and crown ethers[32] bind silver ions preferentially. The present work deals with the preparation and metal ion binding study of *myo*-inositol derived crown-4-ethers.

2. Results and discussion

The *myo*-inositol-derived crown ethers (Scheme 1) were prepared by the reaction of the diols **1**, **3** and **5** with triethyleneglycol ditosylate, in the presence of sodium hydride. The crown ethers **7**, **8** and **9** could not be easily separated from the ditosylate by column chromatography. Hence the crude product obtained was refluxed with sodium methoxide in methanol to convert the unreacted triethyleneglycol ditosylate to the corresponding dimethyl ether, from which the required crown ethers were separable. In the crown-4-ethers **7**, **8** and **9**, two of the oxygen atoms in the ionophoric ring have varying relative orientations (1,2-diequatorial in **7**, 1,2-axial-equatorial in **8**, 1,3-diaxial in **9**), as they are part of the *myo*-inositol ring. The association

Keywords: Crown ether; Cyclitol; Inositol; Lithium; Ligand; Metal complex.
* Corresponding author. Tel.: +91 20 2590 2055; fax: +91 20 2590 2132; e-mail: ms.shashidhar@ncl.res.in

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.075



Scheme 1. (a) $TsO(CH_2CH_2O)_3Ts$, NaH, THF, reflux, 24 h; (b) NaOMe, MeOH, reflux, 8 h.

constants (Table 1) of these inositol based crown ethers with alkali metal picrates as well as ammonium and silver picrates, were evaluated by Cram's picrate method.[34] For the calculation of the association constants shown in Table 1 we have assumed the formation of 1:1 complexes with all metal ions.

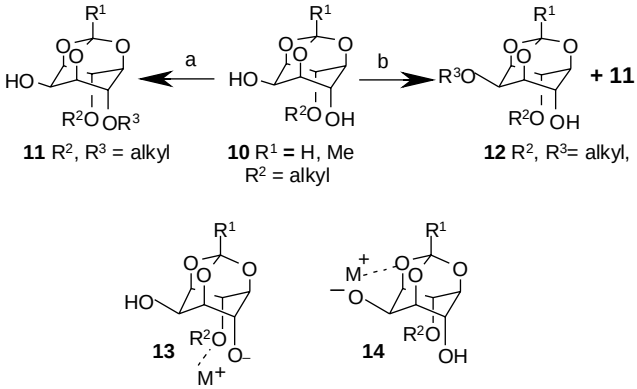
Table 1. Association constants ($Ka\times10^{-4}$ dm^3 mol^{-1}) in $CDCl_3$, for the binding of crown-4-ethers **7**–**9** (27 °C) with metal picrates

Crown	Li^+	Na^+	K^+	Cs^+	NH_4^+	Ag^+
7	100	25.4	6.27	20.2	2.96	14.4
8	19.9	3.95	0.97	2.12	3.97	15.9
9	27.2	2.96	0.69	0.62	0.21	0.9
			$Ka_{(Li^+)}/Ka_{(M^+)}$			
7		4	16	5	34	7
8		5	20	9	5	1
9		9	40	44	130	30

From Table 1, it is seen that all three crown-4-ethers exhibit the highest binding constant for lithium picrate (among the picrates tested) as expected. Lithium picrate binds better to inositol based crown-4-ethers when compared to 12-crown-4-ether ($Ka=1.6\times10^4$).[35] Among the three crown ethers, the crown ether **7** derived from the diequatorial diol **1** binds lithium picrate best. Comparison of the association constants for the extraction of lithium picrate for the crown-4-ethers with inositol derived crown-5 and crown-6-ethers[32] shows that as expected, crown-4-ethers bind lithium picrate more effectively than the larger crown ethers. We had earlier reported[33] the metal picrate binding characteristics of a few *myo*-inositol-derived podands, which are open chain analogs of crown-4-ethers. An increase in the value of the association constants on going from podands to crown ethers (ratio of Ka's=4 to 43; Ka for podands:[33] 2.3×10^4, 5.3×10^4 and 2.3×10^4, respectively, for the diols **2**, **4** and **6**) indicates the contribution of the ionophoric ring towards the binding of metal picrates.

The magnitude of the preference of individual crown ethers for binding to a metal ion (Ml) among a group of '*n*' metal ions can be estimated by the ratio of association constants (K_{Ml}/K_{Mn}), for binding to the same crown ether. The ratio of the binding constant for lithium picrate to that of other metal picrates shows that the crown ether **9**, having 1,3-diaxial orientation exhibits the highest selectivity for lithium as compared to other metal picrates. It is pertinent to note that although all the crown ethers have four oxygen atoms in the ionophoric ring, in the diequatorial (**7**) and axial-equatorial (**8**) crown ethers all the oxygen atoms are separated by two carbon atoms, whereas, in the diaxial crown ether (**9**), oxygen atoms attached to the inositol ring (at C-4 and C-6) are separated by three carbon atoms, but are closer to each other due to their diaxial disposition. Interestingly, these differences lead to better selectivity for binding to lithium picrate. A comparison of the ratio of association constants between crown-4-ethers having different relative orientations of the two of the oxygen atoms (attached to the inositol ring) reveals that this difference matters most for the binding of cesium ions ($K_{a(7)}/K_{a(9)}=33$).

The observed trend in the extraction of the metal picrates by inositol-derived crown-4-ethers, especially for lithium, is interesting with regard to the experimentally observed regioselectivity for the alkylation of *myo*-inositol orthoesters assisted by sodium hydride and butyllithium (Scheme 2). Reaction of triols (**10** $R^2=H$) with alkyl halides[6] in the presence of 1 equiv of sodium hydride resulted in exclusive reaction at the C4(6)–O-position to yield the monoether **10** ($R^2=$alkyl); further reaction of these diols with alkyl halides in the presence of sodium hydride resulted in the formation of a mixture of diethers **11** and **12** (Scheme 2).



Scheme 2. (a) LiH or BuLi, R^3X; (b) NaH, R^3X.

The use of butyllithium or lithium hydride[11] instead of sodium hydride for the same reaction resulted in better regioselectivity, with the exclusive formation of the 4,6-di-*O*-substituted derivatives **11**. Reaction of the monoether (such as **10**, $R^2=$alkyl) with alkyl halides in the absence of metal ions provided the unsymmetrical diether **12** as

the major product.[36] The fact that the reaction assisted by butyllithium gave the diaxial diether **11** as the major product was attributed to the better chelation of lithium ions (as compared to sodium ions) by the 4,6-diaxial oxygen atoms resulting in relatively higher stability of the chelate **13** (as compared to **14**). The observed metal ion selectivity in picrate extraction studies (Table 1), that is, better selectivity for the binding of lithium exhibited by the 1,3-diaxial crown-4 **9** as compared to crown-4-ethers with other orientations, now strongly supports this possibility.

3. Conclusions

A comparison of the metal picrate binding characteristics of inositol derived crown-4-ethers shows that although the strength of binding of metal picrates to these crown ethers could depend on various factors, the selectivity of binding of metal ions can be modulated by reducing the flexibility of the crown ether oxygen atoms.[37–40] These results also complement the observed regioselectivity for the O-substitution reactions of *myo*-inositol 1,3,5-ortho-esters in the presence of metal ions and support the involvement of chelates during these reactions. We are presently investigating the possibility of modulation of metal ion binding to inositol derived crown ethers by tuning the protecting groups on the hydroxyl groups (not involved in crown ether formation) in inositol derived crown ethers.

4. Experimental

4.1. General methods

For details on general methods see Ref. 32. Flash column chromatographic separations were carried out using ethyl acetate–light petroleum mixtures. The racemic isopropylidine derivative **1**,[41] the tetrabenzyl ether **3**,[42] and the orthoformate **5**[9] were prepared according to the literature procedures. Metal picrate–crown ether binding constants were estimated by the method of Cram.[34]

4.2. Synthesis of crown ethers. General procedure

A solution of triethyleneglycol ditosylate (1.2–1.3 mmol) in dry THF (50 mL) was added dropwise over 2 h to a refluxing solution of the required *myo*-inositol derived diol (1 mmol) and sodium hydride (4 mmol) in dry THF (100 mL), in an atmosphere of nitrogen. Refluxing was continued for another 24 h, after which the reaction mixture was cooled to ambient temperature and the solvent was evaporated under reduced pressure. The residue was extracted with chloroform and washed successively with water and brine. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure to give a gum. The crude product was dissolved in dry methanol (7–10 mL) and heated under reflux with sodium methoxide (5–10 mmol) for 8–12 h (to convert unreacted triethyleneglycol ditosylate to triethyleneglycol dimethyl ether, which is easily separable from crown ethers). Methanol was evaporated under reduced pressure to get a gum, which was purified by column chromatography on silica gel using ethyl acetate and light petroleum (gradient elution) as eluent to obtain the crown ether as a gum.

4.2.1. Racemic 1,2-*O*-isopropylidine-3,6-di-*O*-benzyl-4,5-(12-crown-4)-*myo*-inositol (7). The diol **1** (0.4 g, 1 mmol), sodium hydride (0.096 g, 4 mmol) and triethyleneglycol ditosylate (0.596 g, 1.3 mmol) were used to obtain the crown ether **7** as a gum (0.188 g, 36%). IR (neat): ν 1497, 1604, 2872, 2924, 3350–3570 cm^{-1}. δ_H (200 MHz; $CDCl_3$): 7.15–7.60 (10H, m), 4.50–5.0 (4H, m), 4.18 (1H, t, $J=4.4$ Hz), 3.55–4.10 (16H, m), 3.16 (1H, t, $J=9$ Hz), 1.48 (3H, s), 1.33 (3H, s). δ_C (50.3 MHz; $CDCl_3$): 138.7, 138.4, 128.4, 128.2, 127.9, 127.7, 127.4, 109.7, 82.7, 82.5, 81.2, 79.1, 74.6, 74.0, 73.3, 72.5, 72.3, 71.0, 70.7, 27.8, 25.9. Anal. Found: C, 63.69; H, 7.41. $C_{29}H_{38}O_8\cdot 2H_2O$ requires C, 63.25; H, 7.68%.

4.2.2. Racemic 1,2-(12-crown-4)-3,4,5,6-tetra-*O*-benzyl-*myo*-inositol (8). The diol **3** (0.541 g, 1 mmol), sodium hydride (0.096 g, 4 mmol) and triethyleneglycol ditosylate (0.550 g, 1.2 mmol) were used to obtain the crown ether **8** as a gum (0.185 g, 28%). IR (neat): ν 1499, 1602, 2867, 2921, 3200–3600 cm^{-1}. δ_H (200 MHz; $CDCl_3$): 7.15–7.50 (20H, m), 4.55–5.0 (8H, m), 3.90–4.20 (5H, m), 3.55–3.85 (10H, m), 3.30–3.45 (2H, m), 3.16 (1H, d, $J=10$ Hz). δ_C (50.3 MHz; $CDCl_3$): 138.9, 138.4, 129.7, 128.1, 127.8, 127.6, 127.5, 127.2, 83.5, 81.6, 81.2, 80.7, 80.6, 75.6, 72.8, 72.6, 72.5, 72.3, 71.9, 70.7, 70.5. Anal. Found: C, 69.33; H, 6.92. $C_{40}H_{46}O_8\cdot 2H_2O$ requires C, 69.54; H, 7.29%.

4.2.3. 2-*O*-Benzyl-4,6-(13-crown-4)-*myo*-inositol 1,3,5-orthoformate (9). The diol **5** (0.280 g, 1 mmol), sodium hydride (0.096 g, 4 mmol) and triethyleneglycol ditosylate (0.596 g, 1.3 mmol) were used to prepare the crown ether **9** as a gum (0.094 g, 24%). IR (neat): ν 1496, 1604, 2864, 2904, 3006, 3200–3600 cm^{-1}. δ_H (200 MHz; $CDCl_3$): 7.25–7.50 (5H, m), 5.55 (1H, s), 4.75 (2H, s), 4.51 (1H, m), 4.25–4.35 (2H, m), 4.15–4.25 (2H, m), 3.99 (1H, s), 3.35–3.90 (12H, m). δ_C (50.3 MHz; $CDCl_3$): 137.9, 128.4, 128.1, 127.8, 103.2, 74.4, 72.9, 71.2, 70.4, 70.3, 69.7, 67.6, 66.9. Anal. Found: C, 58.60; H, 7.14. $C_{20}H_{26}O_8\cdot H_2O$ requires C, 58.24; H, 6.84%.

Note: As revealed by spectroscopy and analytical data, crown ethers **7**, **8** and **9** always contain water and furthermore are not stable either as gums or in solution for long periods of time (few weeks). We suspect that some of the benzylic methylene groups undergo oxidation on storage. This was indicated by the infrared and ^1H NMR spectra of samples stored over long periods of time.

Acknowledgements

S.S.D. and S.D. thank the Council of Scientific and Industrial Research, New Delhi, for Senior Research Fellowships. Financial support for this work was provided by the Department of Science and Technology, New Delhi.

References and notes

1. *Phosphoinositides: Chemistry, Biochemistry and Biomedical Applications*; Bruzik, K. S., Ed.; ACS Symposium Series 718; American Chemical Society: Washington DC, USA, 1999.
2. Ferguson, M. A. J.; Williams, A. F. *Annu. Rev. Biochem.* **1988**, *57*, 285–320.
3. Billington, D. C. *The Inositol Phosphates. Chemical Synthesis and Biological Significance*; VCH: New York, 1993.
4. Potter, B. V. L.; Lampe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1933–1972.
5. Sureshan, K. M.; Shashidhar, M. S.; Praveen, T.; Das, T. *Chem. Rev.* **2003**, *103*, 4477–4504.
6. Billington, D. C.; Baker, R.; Kulagowski, J. J.; Mawer, I. M.; Vacca, J. P.; deSolms, S. J.; Huff, J. R. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1423–1429.
7. Das, T.; Shashidhar, M. S. *Carbohydr. Res.* **1997**, *297*, 243–249.
8. Sureshan, K. M.; Shashidhar, M. S. *Tetrahedron Lett.* **2000**, *41*, 4185–4188.
9. Sureshan, K. M.; Shashidhar, M. S. *Tetrahedron Lett.* **2001**, *42*, 3037–3039.
10. Praveen, T.; Das, T.; Sureshan, K. M.; Shashidhar, M. S.; Samanta, U.; Pal, D.; Chakrabarti, P. *J. Chem. Soc., Perkin Trans. 2* **2002**, 358–365.
11. Devaraj, S.; Shashidhar, M. S.; Dixit, S. S. *Tetrahedron* **2005**, *61*, 529–536.
12. Ebstein, R. P.; Lerer, B.; Bennett, E. R.; Shapira, B.; Kindler, S.; Shemesh, Z.; Gerstenhaber, N. *Psychiatry Res.* **1988**, *24*, 45–52.
13. Miller, D. J.; Surfraz, M. B.-U.; Akhtar, M.; Gani, D.; Allemann, R. K. *Org. Biomol. Chem.* **2004**, *2*, 671–688.
14. Surfraz, M. B.-U.; Miller, D. J.; Gani, D.; Allemann, R. K. *Tetrahedron Lett.* **2003**, *44*, 7677–7679.
15. Emilien, G.; Maloteaux, J. M.; Seghers, A.; Charles, G. *Arch. Int. Pharmacodyn. Ther.* **1995**, *330*, 251–278.
16. Paquette, L. A.; Tae, J. *J. Am. Chem. Soc.* **2001**, *123*, 4974–4984.
17. Grote, Z.; Lehaire, M.-L.; Scopelliti, R.; Severin, K. *J. Am. Chem. Soc.* **2003**, *125*, 13638–13639.
18. Hilmey, D. G.; Paquette, L. A. *J. Org. Chem.* **2004**, *69*, 3262–3270.
19. Larner, J.; Price, J. D.; Heimark, D.; Smith, L.; Rule, G.; Piccariello, T.; Fonteles, M. C.; Pontes, C.; Vale, D.; Huang, L. *J. Med. Chem.* **2003**, *46*, 3283–3291.
20. Kesel, A. J. *Bioorg. Med. Chem.* **2003**, *11*, 4599–4613.
21. Bakó, T.; Bakó, P.; Keglevich, G.; Báthori, N.; Czugler, M.; Tatai, J.; Novak, T.; Parlagh, G.; Tőke, L. *Tetrahedron: Asymmetry* **2003**, *14*, 1917–1923.
22. Bakó, P.; Bajor, Z.; Tőke, L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3651–3655.
23. Vicent, C.; Martín-Lomas, M.; Penadés, S. *Tetrahedron* **1989**, *45*, 3605–3612.
24. Faltin, F.; Fehring, V.; Kadyrov, R.; Arrieta, A.; Schareina, T.; Selke, R.; Miethchen, R. *Synthesis* **2001**, 638–646.
25. Bessodes, M.; Shamsazar, J.; Antonakis, K. *Synthesis* **1988**, 560–562.
26. Novak, T.; Bakó, P.; Keglevich, G.; Dobó, A.; Vékey, K.; Tőke, L. *J. Incl. Phenom. Macrocycl. Chem.* **2001**, *40*, 207–212.
27. Faltin, F.; Fehring, V.; Miethchen, R. *Synthesis* **2002**, 1851–1856.
28. Azev, V. N.; d'Alarcao, M. *J. Org. Chem.* **2004**, *69*, 4839–4842.
29. Turgut, Y.; Işgin, E. S.; Hoşgören, H. *J. Chem. Res.* **2004**, 605–607.
30. Wenzel, T. J.; Thurston, J. E.; Sek, D. C.; Joly, J.-P. *Tetrahedron: Asymmetry* **2001**, *12*, 1125–1130.
31. Akiyama, T.; Hara, M.; Fuchibe, K.; Sakamoto, S.; Yamaguchi, K. *Chem. Commun.* **2003**, 1734–1735.
32. Sureshan, K. M.; Shashidhar, M. S.; Varma, A. J. *J. Org. Chem.* **2002**, *67*, 6884–6888.
33. Sureshan, K. M.; Shashidhar, M. S.; Varma, A. J. *J. Chem. Soc., Perkin Trans. 2* **2001**, 2298–2302.
34. Moore, S. S.; Tarnowski, T. L.; Newcomb, M.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6398–6405.
35. Iimori, T.; Erickson, S. D.; Rheingold, A. L.; Still, W. C. *Tetrahedron Lett.* **1989**, *30*, 6947–6950.
36. Baudm, G.; Glänzer, B. I.; Swaminathan, K. S.; Vasella, A. *Helv. Chim. Acta* **1988**, *71*, 1367–1378.
37. Costero, A. M.; Villarroya, J. P.; Gil, S.; Aurell, M. J.; Ramirez de Arellano, M. C. *Tetrahedron* **2002**, *58*, 6729–6734.
38. Yamato, K.; Bartsch, R. A.; Broker, G. A.; Rogers, R. D.; Dietz, M. L. *Tetrahedron Lett.* **2002**, *43*, 5805–5808.
39. Samoshin, V. V.; Chertkov, V. A.; Gremyachinskiy, D. E.; Dobretsova, E. K.; Shestakova, A. K.; Vatlina, L. P. *Tetrahedron Lett.* **2004**, *45*, 7823–7826.
40. Mlinarić-Majerski, K.; Kragol, G. *Tetrahedron* **2001**, *57*, 449–457.
41. Gigg, J.; Gigg, R.; Payne, S.; Conant, R. *J. Chem. Soc., Perkin Trans. 1* **1987**, 423–429.
42. Gigg, R.; Warren, C. D. *J. Chem. Soc. C* **1969**, 2367–2371.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 4364–4371
Tetrahedron

Ring expansion of 11*H*-benzo[*b*]fluorene-11-methanols and related compounds leading to 17,18-diphenyldibenzo[*a*,*o*]pentaphene and related polycyclic aromatic hydrocarbons with extended conjugation and novel architectures

Yonghong Yang, Weixiang Dai, Yanzhong Zhang, Jeffrey L. Petersen† and Kung K. Wang*

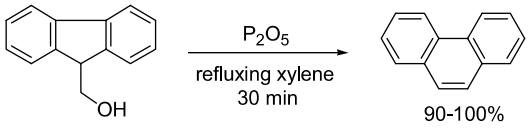
C. Eugene Bennett Department of Chemistry, West Virginia University, Morgantown, WV 26506-6045 USA

Received 26 December 2005; revised 22 February 2006; accepted 22 February 2006

Abstract—Condensation between 7-(1,1-dimethylethyl)-13-phenyl-8*H*-indeno[2,1-*b*]phenanthrene and paraformaldehyde produced the corresponding 9-fluorenylmethanol derivative, which on treatment with P_2O_5 to promote a Wagner–Meerwein rearrangement for ring expansion furnished 14-phenyldibenzo[*a*,*j*]anthracene in 88% yield. Similarly, 17,18-diphenyldibenzo[*a*,*o*]pentaphene possessing a helical twist and bearing two phenyl substituents at the most sterically congested C17 and C18 positions and other related compounds were likewise synthesized. Subsequent intramolecular arylation reactions involving the phenyl substituents produced polycyclic aromatic hydrocarbons with novel architectures.

1. Introduction

The Wagner–Meerwein rearrangement of 9-fluorenylmethanols and related fluorene derivatives provides an efficient pathway for ring expansion to form phenanthrenes.[1] Specifically, the phosphorous pentoxide-induced rearrangement of the parent 9-fluorenylmethanol occurs in refluxing xylene to produce phenanthrene in excellent yield (Eq. 1).[2] We recently reported the synthesis of a variety of 11*H*-benzo[*b*]fluorenes and related derivatives via the benzannulated enediynyl propargylic alcohols.[3–10] We now report the use of these benzofluorenyl derivatives to prepare 11*H*-benzo[*b*]fluorene-11-methanols for the subsequent Wagner–Meerwein rearrangement leading to phenanthrenes having extended conjugation and bearing one or two aryl substituents at the sterically most hindered positions. The presence of these aryl substituents also allows intramolecular electrophilic aromatic substitution reactions to occur, producing polycyclic aromatic hydrocarbons with novel architectures.



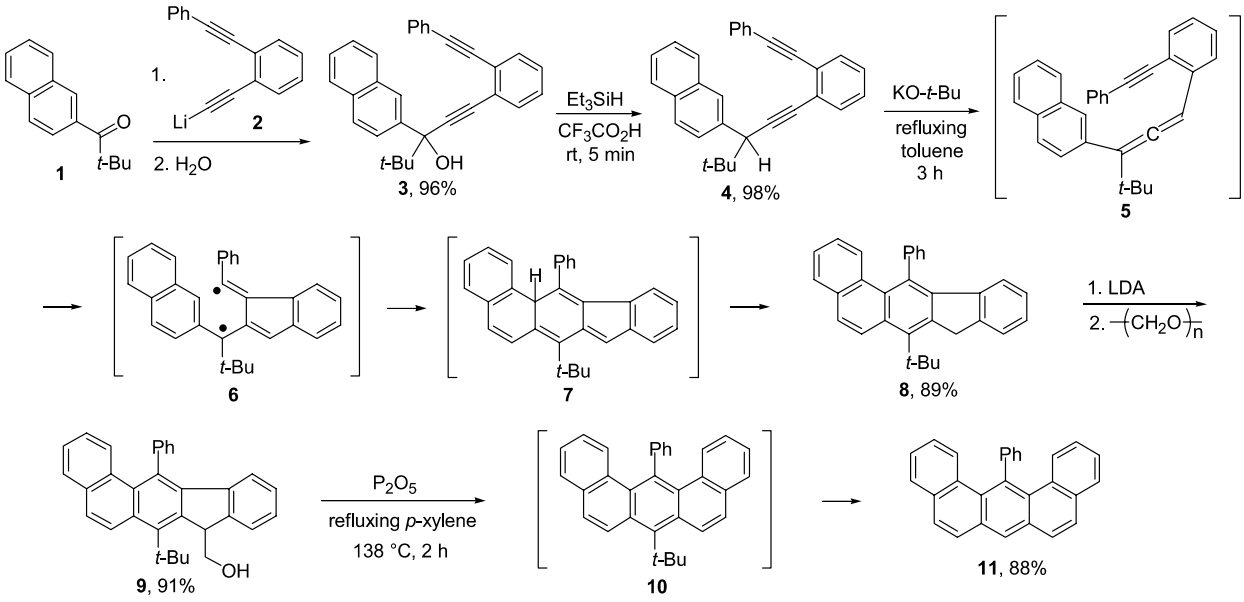
(1)

2. Results and discussion

Indenophenanthrene **8** was prepared by a synthetic sequence reported previously[3] involving condensation between *tert*-butyl 2-naphthyl ketone (**1**) and the benzannulated enediynyl lithium acetylide **2** to form the benzannulated enediynyl propargylic alcohol **3** followed by reduction with triethylsilane in the presence of trifluoroacetic acid to give **4** (Scheme 1). Treatment of **4** with potassium *tert*-butoxide in refluxing toluene for 3 h then provided 7-(1,1-dimethylethyl)-13-phenyl-8*H*-indeno[2,1-*b*]phenanthrene (**8**) in 89% yield. Presumably, a cascade sequence of reactions occurred as reported previously[3] involving an initial 1,3-prototropic rearrangement to form the benzannulated enyne-allene **5** followed by a Schmittel cyclization reaction[11–15] to generate biradical **6** for the subsequent intramolecular radical–radical coupling to furnish **7** and, after a second prototropic rearrangement, indenophenanthrene **8**. It is

Keywords: 9-Fluorenylmethanols; Wagner–Meerwein rearrangement; Ring expansion; 17,18-Diphenyldibenzo[*a*,*o*]pentaphene; Polycyclic aromatic hydrocarbons.
* Corresponding author. Tel.: +1 304 293 3068x6441; fax: +1 304 293 4904; e-mail: kung.wang@mail.wvu.edu
† To whom correspondence concerning the X-ray structures should be addressed. Tel.: +1 304 293 3435x6423; fax: +1 304 293 4904; e-mail: jeffrey.petersen@mail.wvu.edu

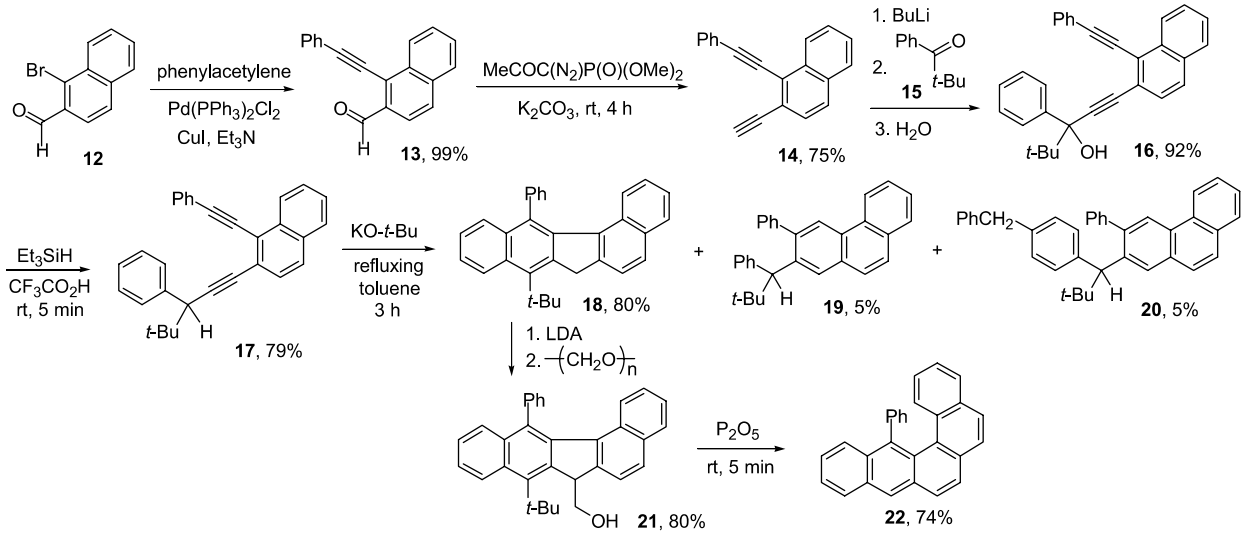
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.066



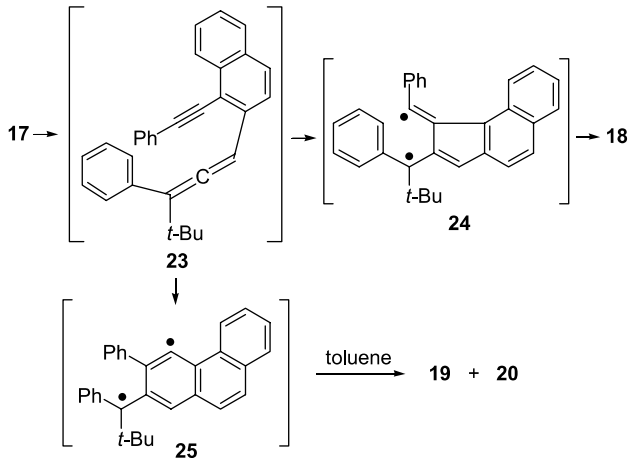
Scheme 1.

worth noting that the intramolecular radical–radical coupling reaction of biradical **6** involved only the α-position of the naphthyl ring to produce **7** preferentially. Attaching the β-position to form an indeno-fused anthracene derivative did not appear to occur. The higher reactivity of the α-position than the β-position of naphthalene in homolytic addition may be responsible for the regioselectivity.[16–17] Conversion of **8** to the 9-fluorenylmethanol derivative **9** was readily accomplished by treatment of **8** with lithium diisopropylamide (LDA) followed by paraformaldehyde.[18] Unlike the parent 9*H*-fluorene, the presence of a sterically demanding *tert*-butyl group in **9** appeared to prevent it from condensation with a second molecule of formaldehyde even in the presence of excess LDA and paraformaldehyde. On exposure to P_2O_5, **9** was transformed smoothly via the Wagner–Meerwein rearrangement to form **10** in situ followed by the loss of the *tert*-butyl group to give 14-phenyldibenzo[*a*,*j*]anthracene (**11**) in 88% yield. The *tert*-butyl group is removed from **10** by protonation of the C7 carbon followed by dealkylation as observed previously in other aromatic systems.[19–22] It is also possible that the *tert*-butyl group was first removed from **9** followed by a Wagner–Meerwein rearrangement to furnish **11**.

Similarly, the benzannulated enediynyl propargylic alcohol **16** was synthesized by condensation between 2,2-dimethylpropiophenone (**15**) and the benzannulated enediyne **14**, which was readily prepared by the Sonogashira reaction between phenylacetylene and **12** to form **13** followed by treatment of **13** with dimethyl (1-diazo-2-oxopropyl)-phosphonate[23] (Scheme 2). Reduction of **16** followed by treatment of the resulting **17** with potassium *tert*-butoxide in refluxing toluene then afforded 8-(1,1-dimethylethyl)-13-phenyl-7*H*-dibenzo[*b*,*g*]fluorene (**18**) in 80% yield along with two minor adducts **19** and **20**. Presumably, a 1,3-prototropic rearrangement of **17** gave the benzannulated enyne-allene **23**, which could undergo either a Schmittel cyclization reaction to give biradical **24** leading to **18** or a



Scheme 2.

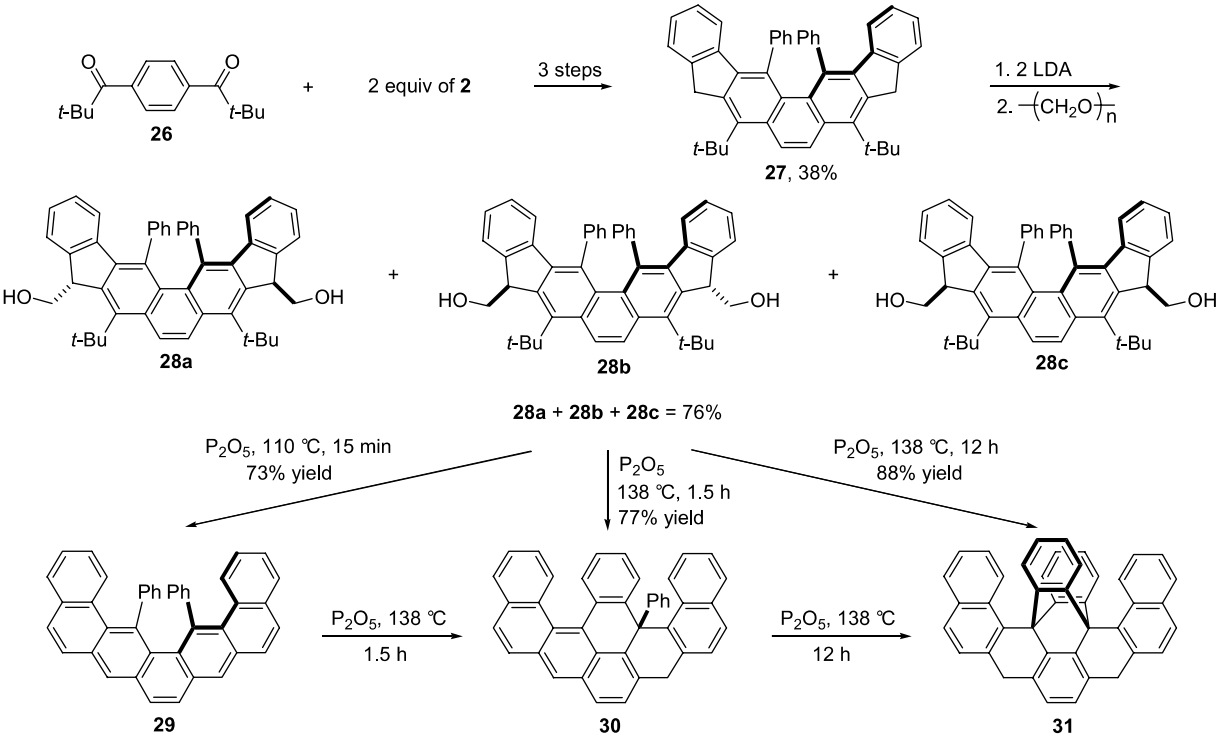


Scheme 3.

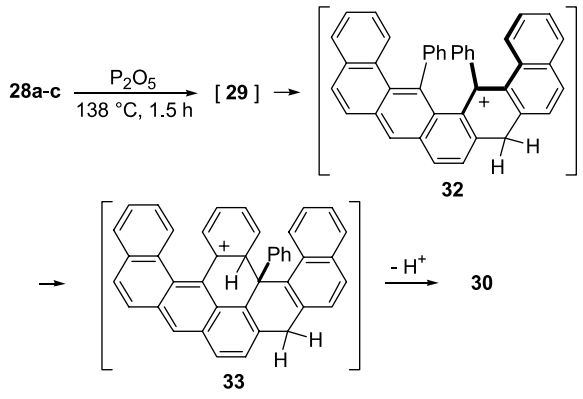
Myers–Saito cyclization reaction[24–27] to form biradical **25** leading to **19** and **20** (Scheme 3). Treatment of **18** with LDA followed by paraformaldehyde then produced **21** for the subsequent Wagner–Meerwein rearrangement to furnish 14-phenylnaphth[1,2-*a*]anthracene (**22**) with the phenyl substituent at one of the most sterically hindered positions in 74% yield. Because of steric hindrance, the rotation of the carbon–carbon bond attaching the phenyl substituent to the naphth[1,2-*a*]anthracene system is restricted. As a result, the ^{1}H NMR signals (600 MHz) of the *ortho* and *meta* hydrogens of the phenyl substituent appeared as broad humps at δ 8.2, 7.5, 6.7, and 6.1 at 25 °C. However, at −20 °C two doublets at δ 8.24/6.14 for the *ortho* hydrogens and two triplets at δ 7.49/6.67 for the *meta* hydrogens could be clearly discerned. The coalescence temperatures were determined to be at 50 °C for the *ortho* hydrogens and at 40 °C for the *meta* hydrogens on a 270 MHz spectrometer, corresponding to rotational barriers of 14.4 and 14.5 kcal/mol at these two temperatures, which are slightly higher than those of 1-phenylbenzo[*a*]phenanthrenes ($\Delta G^{\ddagger}_{rot}$ = ca. 13 kcal/mol) reported earlier.[28]

The diindeno-fused phenanthrene **27** was synthesized previously from diketone **26** and 2 equiv of **2** in three steps in 38% overall yield (Scheme 4).[6] The X-ray structure of **27** showed that the presence of the two phenyl substituents at the congested C4 and C5 positions of the phenanthrene moiety caused a severe helical twist of the diindeno-fused phenanthrene system. Treatment of **27** with 2 equiv of LDA followed by paraformaldehyde produced **28a–c** as a mixture of three diastereomers in a 63 (**28a** or **28b**): 34 (**28c**): 3 (**28a** or **28b**) ratio in 76% combined yield. The major isomer (**28a** or **28b**) having a C_2 symmetry and **28c** without a C_2 symmetry were separated by silica gel chromatography to allow structural elucidation. The use of a mixture of **28a–c** containing all three diastereomers for two consecutive Wagner–Meerwein rearrangements, promoted by P_2O_5 in *p*-xylene at 110 °C for 15 min, was also successful, giving rise to 17,18-diphenyldibenzo[*a*,*o*]pentaphene (**29**) with the two phenyl substituents at the most sterically congested C17 and C18 positions.

Interestingly, when a mixture of **28a–c** was exposed to P_2O_5 at a higher temperature (138 °C) in refluxing *p*-xylene for 1.5 h, compound **30** was produced in 77% yield. Treatment of **29** with P_2O_5 under the same condition (refluxing *p*-xylene, 1.5 h) also produced **30**. Apparently under this reaction condition, the transformation from **28a–c** to **30** proceeds via an initial formation of **29** in situ followed by protonation of the C7 carbon of **29** to furnish **32** (Scheme 5). A subsequent intramolecular electrophilic aromatic substitution reaction involving the phenyl substituent at the C17 position to form



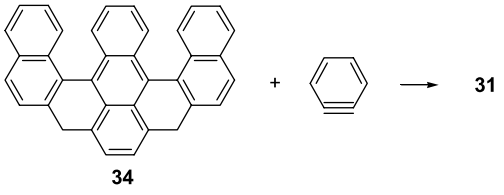
Scheme 4.



Scheme 5.

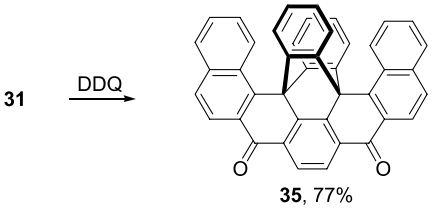
33 followed by deprotonation then gave **30**. The reaction sequence of protonation followed by an intramolecular electrophilic aromatic substitution reaction is reminiscent of what was reported previously in the transformation of 1-phenylbenzo[*a*]anthracene to dibenzo[*a*,*l*]pyrene.[29]

It was also possible to promote a second intramolecular electrophilic aromatic substitution reaction involving the phenyl substituent of **30** by protonation of the C10 carbon. Treatment of either **28a–c** or **30** with P_2O_5 in refluxing *p*-xylene over a longer period of time (12 h) furnished **31** having a C_2 symmetry and two vertical planes of symmetry and thus belonging to the group C_{2v}. It is interesting to note that **31** can be regarded as the Diels–Alder adduct of the cycloaddition reaction between the central benzene ring of the central anthracene unit of **34** and benzyne to produce the triptycene moiety in **31** (Eq. 2).[30–32]



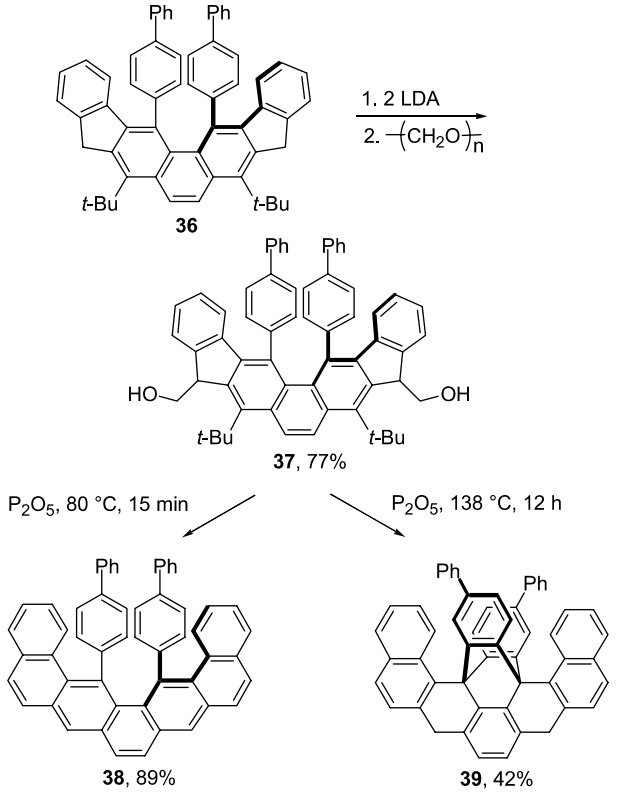
(2)

Compare to **30** in which an AB quartet of ^{1}H NMR signals at δ 4.83 (J=22.8 Hz) and δ 4.77 (J=23.0 Hz) were observed for the two methylene hydrogens because of the lack of symmetry, a singlet ^{1}H NMR signal at δ 4.42 was observed for the four methylene hydrogens of **31**. Oxidation of **31** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) produced **35** (Eq. 3), which has its structure established by X-ray structure analysis.



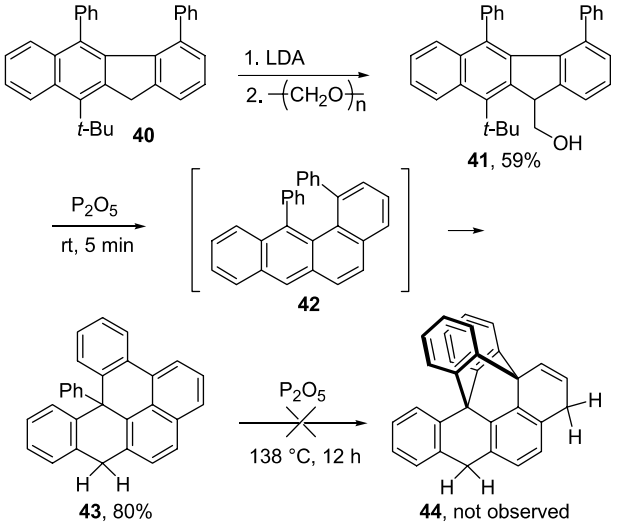
(3)

Similarly, treatment of **36**[6] with 2 equiv of LDA and paraformaldehyde gave **37** as a mixture of two diastereomers (isomer ratio=55:45), which on exposure to P_2O_5 in refluxing benzene at 80 °C for 15 min underwent two Wagner–Meerwein rearrangements to give **38** (Scheme 6). Under a harsher reaction condition (P_2O_5, *p*-xylene at 138 °C, 12 h), **39** was likewise produced. Compared to **31**, which belongs to the group C_{2v}, the structure of **39** retains the C_2 symmetry but no longer has the two planes of symmetry and thus belongs to the group C_2. The chirality of the helical structure is lost in the transformation from **27** to **31**, whereas the chirality of **36** is retained in **39**. As a result, the ^{1}H NMR signals of the diastereotopic methylene hydrogens of **39**, recorded on a 600 MHz NMR spectrometer, were observed as an AB quartet at δ 4.46 (J=21.6 Hz) and δ 4.43 (J=21.0 Hz).



Scheme 6.

The benzo[*b*]fluorene derivative **40**[9] was also successfully employed to produce **41** (Scheme 7). However, attempts to promote the Wagner–Meerwein rearrangement to give **42**



Scheme 7.

resulted in the formation of **43** even under mild reaction conditions (P_2O_5, 25 °C, 5 min). The structure of **43** was established by X-ray structure analysis. Apparently, protonation of the initially formed **42** and the subsequent intramolecular electrophilic aromatic substitution reaction are very facile under the reaction condition, preventing **42** from being isolated. However, the resulting **43** is resistant to further transformation to **44** on heating in refluxing *p*-xylene at 138 °C for 12 h. Apparently, it is difficult to protonate the naphthalene moiety of **43** for the subsequent intramolecular electrophilic aromatic substitution reaction.

3. Conclusion

The Wagner–Meerwein rearrangement was successfully applied to a variety of 11*H*-benzo[*b*]fluorene-11-methanols and related fluorene derivatives leading to highly conjugated aromatic systems bearing one or two aryl substituents at the most sterically hindered positions. These sterically congested aromatic systems are prone to protonation for subsequent intramolecular electrophilic aromatic substitution reactions, leading to polycyclic aromatic hydrocarbons with novel architectures not easily attainable by other synthetic methods. The synthetic sequence is simple and straightforward, making it easily adoptable for the synthesis of other polycyclic aromatic compounds.

4. Experimental

4.1. General

All reactions were conducted in oven-dried (120 °C) glassware under a nitrogen atmosphere. Diethyl ether and tetrahydrofuran (THF) were distilled from benzophenone ketyl prior to use. *n*-Butyllithium (2.5 M) in hexanes, *tert*-butyllithium (1.7 M) in pentane, lithium diisopropylamide (LDA, 2.0 M) in heptane/THF/ethylbenzene, triethylsilane, trifluoroacetic acid, potassium *tert*-butoxide (1.0 M) in THF, 2-naphthoyl chloride, 1-bromo-2-naphthalenecarboxaldehyde (**12**), phenylacetylene, $Pd(PPh_3)_2Cl_2$, copper(I) iodide, $CuBr \cdot SMe_2$, triethylamine, 2,2-dimethylpropiophenone (**15**), paraformaldehyde, and phosphorus pentoxide were purchased from chemical suppliers and were used as received. 1,2-Bis[(2-ethynylphenyl)ethynyl]benzene was prepared as reported previously.[6] Melting points were uncorrected. ^1H (270 MHz) and ^{13}C (67.9 MHz) NMR spectra were recorded in $CDCl_3$ using $CHCl_3$ (^1H δ 7.26) and $CDCl_3$ (^{13}C δ 77.0) as internal standards unless otherwise indicated for those recorded on a 600-MHz NMR spectrometer.

4.1.1. 7-(1,1-Dimethylethyl)-13-phenyl-8*H*-indeno[2,1-*b*]phenanthrene-8-methanol (9). To a solution of 0.317 g (0.796 mmol) of **8** in 8 mL of THF under a nitrogen atmosphere at 0 °C was added 0.53 mL of a 2.0 M solution of LDA (1.06 mmol) in heptane/tetrahydrofuran/ethylbenzene. After 10 min at 0 °C, 0.030 g (1.00 mmol) of paraformaldehyde was introduced via a 120° angle glass tubing fitted with ground joints at both ends. The reaction mixture was then allowed to warm to room temperature. After an additional 15 min, 5 mL of a saturated sodium bicarbonate solution was introduced, and the reaction mixture was extracted with diethyl ether. The combined organic extracts were washed with brine and water, dried over magnesium sulfate, and concentrated. The residue was purified by flash column chromatography (silica gel/20% diethyl ether in hexanes) to afford 0.311 g of **9** (0.727 mmol, 91%) as a white solid: mp 207–209 °C; IR 3401 (br), 832, 750, 697 cm^{-1}; ^1H δ 8.50 (1H, d, J=9.6 Hz), 7.79 (1H, dd, J=7.9, 1.5 Hz), 7.69–7.52 (7H, m), 7.41–7.31 (2H, m), 7.21 (1H, td, J=7.4, 1.0 Hz), 7.04–6.93 (2H, m), 5.94 (1H, d, J=7.9 Hz), 5.02 (1H, dd, J=7.5, 3.8 Hz), 4.43 (1H, m), 3.53 (1H, m), 1.91 (9H, s), 1.50 (1H, OH); ^{13}C δ 146.3, 143.3, 142.9, 140.8, 139.9, 139.4, 134.2, 132.8, 132.5, 131.4, 130.2, 130.0, 129.9, 128.7, 127.9, 127.6, 126.9, 126.8, 126.2, 125.6, 124.5, 124.28, 124.25, 123.6, 67.8, 51.4, 38.5, 34.6; MS *m*/*z* 429 (MH^+), 415, 355.

4.1.2. 14-Phenyldibenzo[*a*,*j*]anthracene (11). To a flask containing 0.069 g (0.161 mmol) of **9** were added 0.256 g (1.80 mmol) of phosphorus pentoxide and 10 mL of *p*-xylene. The reaction mixture was heated under reflux for 2 h. After the reaction mixture was allowed to cool to room temperature, 10 mL of a saturated sodium bicarbonate solution was introduced, and the organic layer was separated. The aqueous layer was back extracted with diethyl ether. The combined organic extracts were washed with water, dried over magnesium sulfate, and concentrated. The residue was purified by flash column chromatography (silica gel/10% methylene chloride in hexanes) to provide 0.050 g of **11** (0.141 mmol, 88%) as a white solid: mp 259–261 °C; IR 1443, 878, 790, 743, 696 cm^{-1}; ^1H δ 8.35 (1H, s), 7.82 (2H, d, J=8.9 Hz), 7.79 (2H, dd, J=8.2, 1.5 Hz), 7.69 (2H, d, J=8.7 Hz), 7.66–7.58 (3H, m), 7.52–7.48 (2H, m), 7.39 (2H, ddd, J=7.9, 6.9, 1.0 Hz), 7.21 (2H, d, J=8.7 Hz), 6.99 (2H, ddd, J=8.7, 6.9, 1.7 Hz); ^{13}C δ 145.4, 138.8, 134.2, 131.5, 131.3, 131.2, 130.6, 129.0, 128.4, 128.2, 128.13, 128.10, 127.8, 126.9, 125.9, 124.5; MS *m*/*z* 354 (M^+), 337, 313; HRMS calcd for $C_{28}H_{18}$ 354.1409, found 354.1402.

4.1.3. Diols 28a–c. To a solution of 0.344 g (0.557 mmol) of **27** in 60 mL of benzene and 50 mL of THF under a nitrogen atmosphere at 0 °C was added 1.80 mL of a 2.0 M solution of LDA (3.60 mmol) in heptane/tetrahydrofuran/ethylbenzene. After 20 min at 0 °C, 0.220 g (7.33 mmol) of paraformaldehyde was transferred into the reaction mixture via a 120° angle glass tubing fitted with ground joints at both ends. The reaction mixture was then allowed to warm to room temperature. After an additional 30 min, 10 mL of a saturated sodium bicarbonate solution was introduced, and the reaction mixture was extracted with diethyl ether. The combined organic extracts were washed with brine and water, dried over magnesium sulfate, and concentrated. The residue was purified by flash column chromatography (silica gel/50% diethyl ether in hexanes) to afford 0.287 g of **28a–c** (0.423 mmol, 76%, a mixture of three isomers, isomer ratio=63:34:3) as a pale yellow solid. The ^1H NMR spectrum suggested that all three diastereomers, **28a** and **28b** having a C_2 symmetry (63 and 3% not necessarily respectively) and **28c** without a C_2 symmetry (34%), were produced. The major isomer (**28a** or **28b**) and **28c** were further separated by column chromatography on a silica gel

column. **28a–c**: mp 221–225 °C; IR 3412 (br), 1052, 704 cm^{-1}; ^1H (**28a** or **28b**) δ 7.81 (2H, s), 7.49 (2H, d, J=7.5 Hz), 7.13 (2H, tm, J=7.5, 1 Hz), 7.10 (2H, tm, J=7.5, 1 Hz), 6.99 (4H, t, J=7.5 Hz), 6.78 (2H, t, J=7.2 Hz), 6.46 (4H, d, J=6.9 Hz), 6.22 (2H, d, J=7.9 Hz), 4.70 (2H, dd, J=5.9, 3.0 Hz), 4.47 (2H, m), 3.82 (2H, m), 1.82 (18H, s), 1.13 (2H, OH); ^{13}C (**28a** or **28b**) δ 146.6, 140.7, 140.6, 138.7, 137.4, 135.1, 134.9, 132.1, 131.2, 128.2, 126.56, 126.51, 126.0, 123.8, 122.9, 121.9, 67.0, 50.7, 37.7, 34.3; ^1H (**28c**) δ 7.97 (1H, d, J=9.7 Hz), 7.88 (1H, d, J=9.3 Hz), 7.50 (1H, d, J=7.5 Hz), 7.45 (1H, d, J=7.1 Hz), 7.19–6.91 (8H, m), 6.83–6.74 (2H, m), 6.47 (4H, t, J=8.1 Hz), 6.32 (2H, t, J=6.9 Hz), 4.85 (1H, dd, J=7.7, 3.8 Hz), 4.73 (1H, dd, J=6.1, 3.2 Hz), 4.47 (1H, m), 4.36 (1H, m), 3.74 (1H, m), 3.47 (1H, t, J=8 Hz), 1.86 (9H, s), 1.85 (9H, s), 1.64 (1H, OH), 1.17 (1H, OH); ^{13}C (**28c**) δ 146.7, 146.6, 140.8, 140.5, 140.4, 139.0, 138.9, 138.5, 138.4, 137.3, 135.9, 134.9, 134.6, 133.3, 133.0, 132.5, 132.2, 127.7, 126.9, 126.6, 126.1, 123.8, 123.5, 123.3, 123.0, 122.8, 122.1, 69.6, 67.2, 52.2, 50.7, 38.3, 37.8, 34.5, 34.2; The ^1H NMR signals attributable to the minor isomer having a C_2 symmetry (**28a** or **28b**) were observed at δ 8.05 (2H, s) and 1.90 (18H, s); MS m/z 678 (M^+), 664, 647, 605; HRMS calcd for $C_{50}H_{46}O_2$ 678.3492, found 678.3496.

4.1.4. 17,18-Diphenyldibenzo[*a*,*o*]pentaphene (29). To a flask containing 0.0134 g (0.0198 mmol) of a mixture of **28a–c** were added 0.100 g (0.704 mmol) of phosphorus pentoxide and 10 mL of *p*-xylene. The reaction mixture was heated at 110 °C for 15 min. After the reaction mixture was allowed to cool to room temperature, 10 mL of a saturated sodium bicarbonate solution was introduced. The organic layer was separated, and the aqueous layer was back extracted with diethyl ether. The combined organic extracts were washed with water, dried over magnesium sulfate, and concentrated. The residue was purified by flash column chromatography (silica gel/10% methylene chloride in hexanes) to provide 0.0076 g of **29** (0.014 mmol, 73%) as a light yellow solid: mp 272–275 °C; IR 1437, 879, 797, 744, 697 cm^{-1}; ^1H δ 8.03 (2H, s), 7.71 (2H, d, J=8.9 Hz), 7.65 (2H, d, J=7.7 Hz), 7.61 (2H, d, J=8.9 Hz), 7.44 (2H, s), 7.19 (2H, td, J=7.9, 1.0 Hz), 7.00 (2H, tt, J=7.4, 1.0 Hz), 6.81 (4H, t, J=7.7 Hz), 6.62 (2H, td, J=7.8, 1.5 Hz), 6.51 (2H, d, J=8.7 Hz), 6.40 (4H, d, J=8.0 Hz); ^{13}C δ 141.2, 139.3, 133.9, 132.52, 132.45, 132.3, 130.9, 128.90, 128.84, 128.2, 127.7, 127.2, 127.0, 126.37, 126.35, 126.0, 125.5, 123.6, 122.8; MS m/z 530 (M^+), 453, 437, 424; HRMS calcd for $C_{42}H_{26}$ 530.2035, found 530.2035.

4.1.5. Hydrocarbon 30. To a flask containing 0.083 g (0.12 mmol) of a mixture of **28a–c** were added 0.310 g (2.2 mmol) of phosphorus pentoxide and 15 mL of *p*-xylene. The reaction mixture was heated under reflux for 1.5 h. After the reaction mixture was allowed to cool to room temperature, 10 mL of a saturated sodium bicarbonate solution was introduced. The organic layer was separated, and the aqueous layer was back extracted with diethyl ether. The combined organic extracts were washed with water, dried over magnesium sulfate, and concentrated. The residue was allowed to precipitate out from hexanes to provide 0.050 g of **30** (0.094 mmol, 77%) as a bright yellow solid: mp 260–262 °C; IR 1443, 873, 738, 703 cm^{-1}; ^1H δ 9.50 (1H, dd, J=6.4, 3.5 Hz), 8.31 (2H, d, J=8.2 Hz), 8.12 (1H, s), 7.90–7.70 (6H, m), 7.64–7.58 (3H, m), 7.45 (1H, d, J=8.4 Hz), 7.36 (1H, td, J=7.1, 1.0 Hz), 7.31–7.22 (3H, m), 7.06–6.92 (3H, m), 6.61 (3H, br s), 4.83 (1H, d, J=22.8 Hz), 4.77 (1H, d, J=23.0 Hz); ^{13}C δ 149.1, 139.5, 136.1, 133.7, 133.3, 133.0, 132.4, 131.9, 131.8, 130.5, 130.4, 130.1, 129.3, 129.2, 128.72, 128.65, 128.4, 128.2, 127.9, 127.63, 127.58, 127.0, 126.9, 126.3, 126.2, 125.7, 125.6, 125.2, 125.1, 124.6, 53.4, 35.8; MS m/z 530 (M^+), 453, 435, 424; HRMS calcd for $C_{42}H_{26}$ 530.2035, found 530.2030.

4.1.6. Hydrocarbon 31. To a flask containing 0.048 g (0.071 mmol) of a mixture of **28a–c** were added 0.496 g (3.49 mmol) of phosphorus pentoxide and 20 mL of *p*-xylene. The reaction mixture was heated under reflux for 12 h before it was allowed to cool to room temperature. A saturated sodium bicarbonate solution (10 mL) was introduced, and the organic layer was separated. The aqueous layer was back extracted with diethyl ether. The combined organic extracts were washed with water, dried over magnesium sulfate, and concentrated. The residue was allowed to precipitate out from hexanes to provide 0.033 g of **31** (0.062 mmol, 88%) as a light brown solid: mp > 380 °C; IR 1455, 797, 779, 744 cm^{-1}; ^1H δ 8.02 (2H, d, J=8.2 Hz), 7.99 (2H, d, J=8.7 Hz), 7.75 (2H, d, J=8.4 Hz), 7.60 (2H, d, J=8.4 Hz), 7.49 (2H, td, J=7.7, 0.9 Hz), 7.27 (2H, td, J=8, 1 Hz), 6.85 (2H, s), 6.79–6.71 (8H, m), 4.42 (4H, s); ^{13}C δ 146.0, 134.8, 133.4, 132.5, 130.5, 128.8, 128.6, 128.2, 126.7, 125.6, 124.9, 124.7, 124.1, 123.7, 54.1, 33.8; MS m/z 530, 453; HRMS calcd for $C_{42}H_{26}$ 530.2035, found 530.2025.

4.1.7. Diketone 35. To a flask containing 0.021 g (0.040 mmol) of **31** were added 0.101 g (0.445 mmol) of DDQ and 25 mL of benzene. The reaction mixture was heated under reflux for 72 h before it was allowed to cool to room temperature. The reaction mixture and then diethyl ether solvent were allowed to flow through an aluminum oxide column. The effluent was concentrated, and the residue was purified by flash column chromatography (silica gel/10% diethyl ether in hexanes) to provide 0.017 g of **35** (0.030 mmol, 77%) as a light yellow solid: mp >370 °C; IR 1654, 758 cm^{-1}; ^1H δ 8.82 (2H, d, J=8.7 Hz), 8.31 (2H, d, J=8.9 Hz), 8.17 (2H, d, J=8.2 Hz), 8.12 (2H, s), 7.88 (2H, d, J=8.7 Hz), 7.74 (2H, ddd, J=8.0, 6.8, 1.2 Hz), 7.45 (2H, ddd, J=8.4, 6.9, 1.2 Hz), 6.84 (4H, dd, J=5.7, 3.2 Hz), 6.72 (4H, dd, J=5.7, 3.2 Hz); ^{13}C δ 182.6, 150.8, 143.6, 136.7, 136.5, 132.5, 131.7, 131.4, 130.3, 129.9, 129.2, 128.5, 125.79, 125.75, 125.70, 124.5, 122.9, 53.3; MS m/z 558 (M^+), 529, 498, 479, 464; HRMS calcd for $C_{42}H_{22}O_2$ 558.1620, found 558.1603. Recrystallization of **35** from CH_2Cl_2/2-propanol produced a single crystal suitable for X-ray structure analysis.

4.1.8. Diol 37. The same procedure was repeated as described for **28** except that 0.094 g (0.122 mmol) of **36** in a mixture of 30 mL of benzene and 20 mL of THF was treated with 0.50 mL of a 2.0 M solution of LDA (1.0 mmol) in heptane/tetrahydrofuran/ethylbenzene followed by 0.050 g (1.67 mmol) of paraformaldehyde to afford 0.078 g of **37** (0.094 mmol, 77%, a mixture of two isomers, isomer ratio=55:45) as a bright yellow solid. The major isomer does not possess a C_2 symmetry, whereas

the minor isomer has a C_2 symmetry. Compound **37**: mp 235–238 °C; IR 3416 (br), 768, 728, 696 cm^{-1}; ^1H δ 8.00 (major isomer, 0.55H, d, $J=9.4$ Hz), 7.90 (major isomer, 0.55H, d, $J=9.4$ Hz), 7.85 (minor isomer, 0.9H, s), 7.68–7.62 (4H, m), 7.51–7.25 (12H, m), 7.13–7.05 (2H, m), 6.80–6.73 (2H, m), 6.62–6.58 (4H, m), 6.47–6.34 (2H, m), 4.88–4.71 (2H, m), 4.54–4.38 (2H, m), 3.92–3.73 and 3.54–3.46 (2H, m), 1.88 (major isomer, s, *t*-Bu), 1.87 (major isomer, s, *t*-Bu), 1.84 (minor isomer, s, *t*-Bu), 1.10 (br, OH); ^{13}C δ (two isomers) 146.8, 146.6, 141.1, 141.00, 140.8, 140.73, 140.67, 140.6, 140.5, 140.4, 139.3, 139.15, 139.08, 138.91, 138.87, 137.9, 137.7, 137.56, 137.53, 137.4, 136.1, 134.9, 134.6, 134.5, 134.3, 133.0, 132.6, 132.2, 132.0, 131.2, 131.0, 128.85, 128.76, 127.2, 126.8, 126.7, 126.6, 126.4, 126.2, 126.1, 126.0, 123.9, 123.6, 123.3, 123.0, 122.9, 122.8, 122.3, 122.0, 69.6, 67.1, 66.9, 52.3, 50.7, 38.3, 37.8, 37.7, 34.5, 34.3, 34.2; MS *m/z* 830 (M^+), 799, 681, 656; HRMS calcd for $C_{62}H_{54}O_2$ 830.4118, found 830.4073.

4.1.9. Hydrocarbon 38. The same procedure was repeated as described for **29** except that 0.0085 g (0.0102 mmol) of **37**, 0.100 g (0.704 mmol) of phosphorus pentoxide, and 10 mL of benzene were used. The reaction mixture was heated under refluxing benzene at 80 °C for 15 min to afford 0.0062 g of **38** (0.0091 mmol, 89%) as a yellow solid: mp 264–267 °C; IR 1449, 732, 697 cm^{-1}; ^1H δ 8.06 (2H, s), 7.73 (2H, d, $J=8.7$ Hz), 7.65–7.54 (8H, m), 7.47 (2H, s), 7.40 (4H, t, $J=7.3$ Hz), 7.33–7.26 (2H, m), 7.17 (2H, tt, $J=7.9$, 1.3 Hz), 7.12 (4H, d, $J=8.4$ Hz), 6.68–6.59 (4H, m), 6.54 (4H, d, $J=8.2$ Hz); ^{13}C δ 140.7, 140.5, 138.8, 138.6, 134.0, 132.7, 132.5, 132.4, 130.9, 129.0, 128.7, 128.1, 127.9, 127.5, 127.3, 127.2, 126.7, 126.5, 125.9, 125.6, 123.9, 122.9; MS *m/z* 682 (M^+), 528, 448, 425; HRMS calcd for $C_{54}H_{34}$ 682.2661, found 682.2687.

4.1.10. Hydrocarbon 39. The same procedure was repeated as described for **31** except that 0.038 g (0.046 mmol) of **37**, 0.300 g (2.11 mmol) of phosphorus pentoxide, and 40 mL of *p*-xylene were used. The reaction mixture was heated under reflux for 12 h to afford 0.013 g of **39** (0.019 mmol, 42%) as a yellow solid: mp 186–189 °C; ^1H δ (600 MHz) 8.034 (2H, d, $J=7.8$ Hz), 8.021 (2H, d, $J=7.2$ Hz), 7.90 (2H, d, $J=9.0$ Hz), 7.61 (2H, d, $J=8.4$ Hz), 7.54 (2H, ddd, $J=8.1$, 6.6, 1.2 Hz), 7.35 (2H, ddd, $J=7.8$, 6.6, 1.2 Hz), 7.17–7.08 (6H, m), 7.03–7.01 (4H, m), 6.983 (2H, s), 6.976 (2H, dd, $J=7.2$, 2.4 Hz), 6.89 (2H, s), 6.86 (2H, d, $J=8.4$ Hz), 4.46 (2H, d, $J=21.6$ Hz), 4.43 (2H, d, $J=21.0$ Hz); ^{13}C δ (150 MHz) 146.6, 145.3, 142.2, 141.0, 137.2, 134.9, 133.5, 132.6, 130.4, 129.0, 128.8, 128.4, 128.2, 127.0, 126.9, 126.7, 126.5, 125.9, 125.1, 124.8, 124.1, 123.1, 54.1, 33.9; MS *m/z* 682 (M^+), 529, 425; HRMS calcd for $C_{54}H_{34}$ 682.2661, found 682.2663.

Acknowledgements

We thank Professor Denis W. H. MacDowell for suggesting the Wagner–Meerwein rearrangement to us. The financial support of the Petroleum Research Fund (38169-AC1), administered by the American Chemical Society, and the National Science Foundation (CHE-0414063) is gratefully acknowledged. K.K.W. thanks the National Science Council of Taiwan, the Republic of China, for a grant to support sabbatical leave in the Department of Chemistry at the National Taiwan University. J.L.P. acknowledges the support (CHE-9120098) provided by the National Science Foundation for the acquisition of a Siemens P4 X-ray diffractometer. The financial support of the NSF-EPSCoR (1002165R) for the purchase of a 600 MHz NMR spectrometer is also gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.066. Experimental procedures and spectroscopic data for **1**, **3**, **4**, **8**, **13**, **14**, **16**–**22**, **41**, and **43**; ^1H and ^{13}C NMR spectra of compounds **1**, **3**, **4**, **8**, **9**, **11**, **13**, **14**, **16**–**22**, **28a** or **28b**, **28c**, **29**–**31**, **35**, **37**–**39**, **41**, and **43**; ORTEP drawings of the crystal structures of **18**, **35**, **41**, and **43**. Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre. The CCDC nos. 292502, 292503, 292504, and 292505 have been assigned for the compounds **18**, **41**, **43**, and **35**, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

References and notes

1. Floyd, A. J.; Dyke, S. F.; Ward, S. E. *Chem. Rev.* **1976**, *76*, 509–562.
2. Brown, W. G.; Bluestein, B. *J. Am. Chem. Soc.* **1940**, *62*, 3256–3257.
3. Li, H.; Zhang, H.-R.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2001**, *66*, 6662–6668.
4. Wang, K. K.; Zhang, H.-R.; Petersen, J. L. *J. Org. Chem.* **1999**, *64*, 1650–1656.
5. Zhang, H.-R.; Wang, K. K. *J. Org. Chem.* **1999**, *64*, 7996–7999.
6. Li, H.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2001**, *66*, 7804–7810.
7. Yang, Y.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2003**, *68*, 5832–5837.
8. Yang, Y.; Petersen, J. L.; Wang, K. K. *J. Org. Chem.* **2003**, *68*, 8545–8549.
9. Dai, W.; Petersen, J. L.; Wang, K. K. *Org. Lett.* **2004**, *6*, 4355–4357.
10. Han, X.; Zhang, Y.; Wang, K. K. *J. Org. Chem.* **2005**, *70*, 2406–2408.
11. Schmittel, M.; Strittmatter, M.; Vollmann, K.; Kiau, S. *Tetrahedron Lett.* **1996**, *37*, 999–1002.
12. Schmittel, M.; Strittmatter, M.; Kiau, S. *Angew. Chem., Int. Ed.* **1996**, *35*, 1843–1845.
13. Schmittel, M.; Keller, M.; Kiau, S.; Strittmatter, M. *Chem. Eur. J.* **1997**, *3*, 807–816.
14. Schmittel, M.; Vavilala, C. *J. Org. Chem.* **2005**, *70*, 4865–4868.
15. Wang, K. K. In Krause, N., Hashmi, A. S. K., Eds.; Modern Allene Chemistry; Wiley-VCH: Weinheim, Germany, 2004; Vol. 2, pp 1091–1126.
16. Tinnemans, A. H. A.; Laarhoven, W. H. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1115–1120.

17. Tinnemans, A. H. A.; Laarhoven, W. H. *J. Am. Chem. Soc.* **1974**, *96*, 4617–4622.
18. Chong, J. M.; Lajoie, G.; Tjepkema, M. W. *Synthesis* **1992**, 819–820.
19. Smith, M. B.; March, J. *March's Advanced Organic Chemistry* 5th ed.; Wiley-Interscience: New York, 2001; pp 730–731.
20. Tashiro, M. *Synthesis* **1979**, 921–936.
21. Tashiro, M.; Fukata, G. *Org. Prep. Proced. Int.* **1976**, *8*, 51–74.
22. Hofman, P. S.; Reiding, D. J.; Nauta, W. T. H. *Recl. Trav. Chim. Pays-Bas* **1960**, *79*, 790–793.
23. Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521–522.
24. Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057–8059.
25. Myers, A. G.; Dragovich, P. S. *J. Am. Chem. Soc.* **1989**, *111*, 9130–9132.
26. Nagata, R.; Yamanaka, H.; Okazaki, E.; Saito, I. *Tetrahedron Lett.* **1989**, *30*, 4995–4998.
27. Nagata, R.; Yamanaka, H.; Murahashi, E.; Saito, I. *Tetrahedron Lett.* **1990**, *31*, 2907–2910.
28. Laarhoven, W. H.; Peters, W. H. M.; Tinnemans, A. H. A. *Tetrahedron* **1978**, *34*, 769–777.
29. Vingiello, F. A.; Yanez, J.; Campbell, J. A. *J. Org. Chem.* **1971**, *36*, 2053–2056.
30. Stiles, M.; Miller, R. G. *J. Am. Chem. Soc.* **1960**, *82*, 3802.
31. Friedman, L.; Logullo, F. M. *J. Am. Chem. Soc.* **1963**, *85*, 1549.
32. Kitamura, T.; Yamane, M.; Inoue, K.; Todaka, M.; Fukatsu, N.; Meng, Z.; Fujiwara, Y. *J. Am. Chem. Soc.* **1999**, *121*, 11674–11679.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 4372–4383
Tetrahedron

Synthesis of β-aryl ketones by tetraphosphine/palladium catalysed Heck reactions of 2- or 3-substituted allylic alcohols with aryl bromides

Florian Berthiol, Henri Doucet* and Maurice Santelli*

Laboratoire de Synthèse Organique, Faculté des Sciences de Saint Jérôme, UMR 6180 CNRS and Université d'Aix-Marseille III: 'Chirotechnologies:catalyse et biocatalyse', Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France

Received 30 January 2006; revised 21 February 2006; accepted 21 February 2006

Available online 13 March 2006

Abstract—Through the use of $[PdCl(C_3H_5)]_2$/*cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane as a catalyst, a range of aryl bromides undergoes Heck reaction using 2- or 3-subtituted allylic alcohols. With these sterically congested alkenes, the selective formation of β-aryl ketones was observed when appropriate reaction conditions were used. The influence of the functional group on the aryl bromide and of the base on the selectivity is remarkable. With several substrates, much higher selectivities were obtained using $NaHCO_3$ instead of K_2CO_3 as base. Furthermore, this catalyst can be used at low loading with several substrates.

1. Introduction

Aryl ketones are important building blocks in organic synthesis. The palladium-catalysed Heck reaction using alkenol derivatives and aryl halides is a powerful method for the preparation of such compounds.[1,2] The reaction of alkenols with terminal double bonds such as alk-1-en-3-ol derivatives generally gave regioselectively the corresponding 1-arylalkan-3-one derivatives by migration of the double bond. The reaction using allyl alcohols with disubstituted double bonds has attracted less attention. The reaction with such substrates is slower than with alk-1-enols for steric reasons, and most of the results were described using aryl iodides.[3–8] Only a few results were obtained with aryl bromides.[9–11] Caló et al. described the efficiency of a Pd–benzothiazole–carbene complex for the Heck reaction of 2-methylprop-1-en-3-ol, but-2-en-1-ol[11a] or Baylis–Hillman adducts[11b] with aryl bromides. They performed the reactions using tetrabutylammonium bromide as solvent with 1–2% catalyst. The best result had been obtained by Littke and Fu.[12] They described the reaction of 4-chlorobenzonitrile with 2-methylprop-1-en-3-ol using 1.5% $Pd_2(dba)_3$ and 3% of P(*t*-Bu)$_3$ as catalyst. The Heck reaction of arenediazonium salts with substituted allylic alcohols using $Pd(dba)_2$ as catalyst has also been described recently.[13] If monophosphine or carbene ligands have been successfully used for the Heck reaction of allyl alcohols with disubstituted double bonds, to the best of our knowledge, the efficiency of polydentate phosphine ligands has not been demonstrated. Moreover, an effective and selective method using high substrate/catalyst ratios for the reaction of these allyl alcohols with aryl bromides is still subject to significant improvement.

In order to find more efficient palladium catalysts, we have prepared the tetrapodal phosphine ligand, tedicyp[14] (Fig. 1). We have reported several results obtained in allylic substitution,[14] Suzuki cross-coupling,[15] Sonogashira[16] and Heck reaction[17–20] using tedicyp as ligand. Here, in order to further establish the requirements for a successful Heck reaction, we wish to report on the coupling of aryl bromides with 2- or 3-substituted allyl alcohols such as 2-methylpent-1-en-3-ol or pent-3-en-2-ol using tedicyp as the ligand.

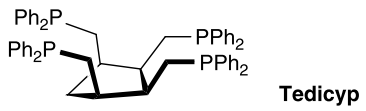


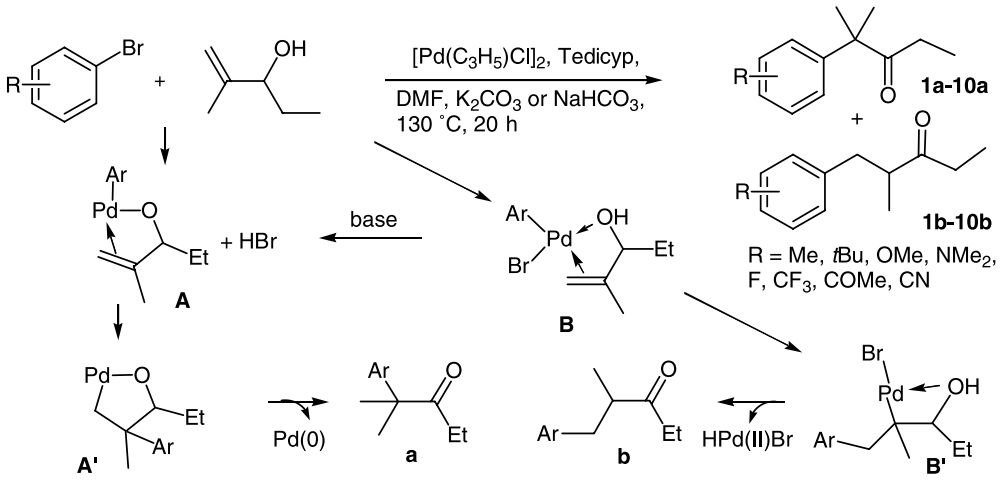
Figure 1.

2. Results and discussion

The regioselectivity of the insertion of Heck reaction is mainly controlled by steric factors, and with 1,1-disubstituted alkenes we should observed selectively the addition on the unsubstituted carbon of the alkene.[17g] On the other hand, with 1,2-disubstituted alkenes, the selectivity of the insertion

Keywords: Heck reaction; Baylis–Hillman adduct; Tedicyp; β-aryl.
* Corresponding authors. Tel.: +33 4 91 28 84 16; fax: +33 4 91 98 38 65 (H.D.); tel.: +33 4 91 28 88 25 (M.S.); e-mail addresses: henri.doucet@univ.u-3mrs.fr; m.santelli@univ.u-3mrs.fr

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.061



Scheme 1.

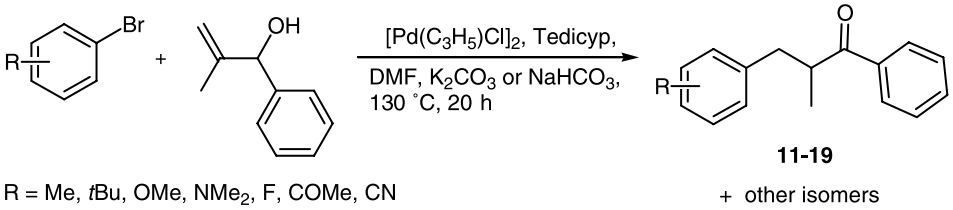
depends on the electronic and steric effects and also of the functions of the alkene substituents. The regioselectivity of the insertion can be partially controlled by the presence of functions capable of coordinating the palladium catalyst. Alcohol function of alkenols is capable of such coordination and imposes conformational changes in the structures of the (aryl)Pd(alkenol) intermediates. Therefore, the electronic or steric control of the regioselectivity of the addition appears to be modified by an adjacent alcohol function on the alkene. The reaction with alkenols is part of the Heck substrate-directed reactions. For these reasons, the regioselectivity of the reactions with the disubstituted alkenes: 2-methylpent-1-en-3-ol or pent-3-en-2-ol is quite unpredictable and should depend on the reaction conditions.

First, we studied the reactivity of 2-methylpent-1-en-3-ol (Scheme 1, Table 1). With this alkenol, for steric reasons, the formation of isomer **b** should be favoured. For this study, based on previous results,[17–20] DMF was chosen as the solvent for polarity reasons and potassium carbonate as the base. The reactions were generally performed at 130 °C under argon in the presence of a ratio 1:2 of $[Pd(C_3H_5)Cl]_2$/tedicyp as

Table 1. Palladium–tedicyp catalysed Heck reactions with 2-methylpent-1-en-3-ol (Scheme 1)

Entry	Aryl bromide	Ratio substrate/catalyst	Base	Product number	Ratio **a/b**	Yield (%)[a]
1	4-*t*-Butylbromobenzene	1000	K_2CO_3	**1a**,**b**	18/82	71 (100)
2	4-*t*-Butylbromobenzene	10,000	K_2CO_3	**1a**,**b**	12/88	(81)
3	4-*t*-Butylbromobenzene	100	$NaHCO_3$	**1a**,**b**	4/96	(61)
4	4-Bromoanisole	10,000	K_2CO_3	**2a**,**b**	5/95	92 (100)
5	4-Bromoanisole	25,000	K_2CO_3	**2a**,**b**	8/92	(63)
6	4-*N*,*N*-Dimethylaminobromobenzene	1000	K_2CO_3	**3a**,**b**	10/90	85 (100)
7	4-*N*,*N*-Dimethylaminobromobenzene	10,000	K_2CO_3	**3a**,**b**	8/92	(54)
8	4-Fluorobromobenzene	1000	K_2CO_3	**4a**,**b**	8/92	87 (100)
9	4-Fluorobromobenzene	10,000	K_2CO_3	**4a**,**b**	14/86	(69)
10	4-Trifluoromethylbromobenzene	1000	K_2CO_3	**5a**,**b**	24/76	65 (100)
11	4-Trifluoromethylbromobenzene	2500	K_2CO_3	**5a**,**b**	23/77	(76)
12	4-Trifluoromethylbromobenzene	100	$NaHCO_3$	**5a**,**b**	5/95	89 (100)
13	4-Trifluoromethylbromobenzene	1000	$NaHCO_3$	**5a**,**b**	2/98	(67)
14	4-Bromoacetophenone	1000	K_2CO_3	**6a**,**b**	19/81	76 (100)
15	4-Bromoacetophenone	10,000	K_2CO_3	**6a**,**b**	27/73	(51)
16	4-Bromoacetophenone	100	$NaHCO_3$	**6a**,**b**	8/92	88 (100)
17	4-Bromoacetophenone	1000	$NaHCO_3$	**6a**,**b**	5/95	(86)
18	4-Bromobenzonitrile	250	K_2CO_3	**7a**,**b**	47/53	(60)
19	4-Bromobenzonitrile	100	$NaHCO_3$	**7a**,**b**	9/91	90 (100)
20	4-Bromobenzonitrile	1000	$NaHCO_3$	**7b**	0/100	(39)
21	2-Bromotoluene	10,000	K_2CO_3	**8a**,**b**	16/84	78 (100)
22	2-Bromotoluene	25,000	K_2CO_3	**8b**	0/100	(10)
23	2-Bromotoluene	100	$NaHCO_3$	**8a**,**b**	4/96	93 (100)
24	2-Bromotoluene	1000	$NaHCO_3$	**8b**	0/100	(48)
25	3-Bromopyridine	250	K_2CO_3	**9a**,**b**	40/60	51 (100)
26	3-Bromopyridine	1000	K_2CO_3	**9a**,**b**	31/69	(19)
27	3-Bromopyridine	100	$NaHCO_3$	**9a**,**b**	9/91	80 (100)
28	3-Bromopyridine	1000	$NaHCO_3$	**9b**	0/100	(63)
29	3-Bromoquinoline	250	K_2CO_3	**10a**,**b**	31/69	66 (100)
30	3-Bromoquinoline	1000	K_2CO_3	**10a**,**b**	30/70	(50)
31	3-Bromoquinoline	100	$NaHCO_3$	**10a**,**b**	2/98	97 (100)
32	3-Bromoquinoline	1000	$NaHCO_3$	**10a**,**b**	1/99	(71)

[a] Conditions: catalyst: $[ClPd(C_3H_5)]_2$/tedicyp=1:2, aryl bromide (1 equiv), 2-methylpent-1-en-3-ol (1.2 equiv), K_2CO_3 or $NaHCO_3$ (2 equiv), DMF, 130 °C, 20 h, isolated yields of products **1b–10b**. Yields in parenthesis are GC and NMR conversions.



Scheme 2.

catalyst. The results presented in the Table 1, using these conditions, disclose a medium to high selectivity of the insertion of the allylic alcohol. With electron-rich aryl bromides such as 4-*t*-butylbromobenzene, 4-bromoanisole or 4-*N*,*N*-dimethylaminobromobenzene, selectivities of 88–95% in favour of the formation of isomer **1b–3b** were obtained (Table 1, entries 2–7). Moreover, these reactions were performed using as little as 0.1–0.004% catalyst. On the other hand, using electron-poor aryl bromides, lower selectivities were obtained. For example, with 4-trifluoromethylbromobenzene or 4-bromobenzonitrile, 24 and 47% of isomers **5a** and **7a** were obtained, respectively (Table 1, entries 10 and 18). The formation of this isomer **a** probably comes from the palladium intermediates **A** and **A′** in Scheme 1, which arise from the formation of the alcoholate of 2-methylpent-1-en-3-ol.[12]

The selectivity of this reaction seems to depend on the structures of the palladium intermediates. In order to improve the selectivity of the reaction with electron-poor aryl bromides, we performed the coupling using the weaker base: $NaHCO_3$. With this base, the formation of the alcoholate of 2-methylpent-1-en-3-ol is probably not favoured therefore **B** is obtained as the major intermediate. Then, the formation of intermediate **B′** is favoured for steric reasons, and isomers **1b–10b** were obtained in 91–100% selectivities. For example, the electron-poor aryl bromides 4-trifluoromethylbromobenzene or 4-bromoacetophenone gave isomers **5b** and **6b** in high selectivities (98 and 95%) and in high TONs (Table 1, entries 13 and 17). However, with $NaHCO_3$ as base, much slower reactions were observed with electron-rich aryl bromides and 1% catalyst had to be used (Table 1, entries 3 and 23). The influence of the base on the reaction rates might come from a slower coordination of the alkenols to palladium to form intermediate **B**, or to a slower reductive elimination of HBr on HPdBr intermediate at the end of the catalytic cycle.

Pyridines or quinolines are π-electron deficient. As expected, with 3-bromopyridine or 3-bromoquinoline using K_2CO_3 as base, low selectivities of 60–70% in favour of isomers **9b** and **10b** were obtained (Table 1, entries 25, 26, 29 and 30). Again, more selective reactions were obtained using $NaHCO_3$. Selectivities of 99 and 100% were obtained with this base (Table 1, entries 28 and 32).

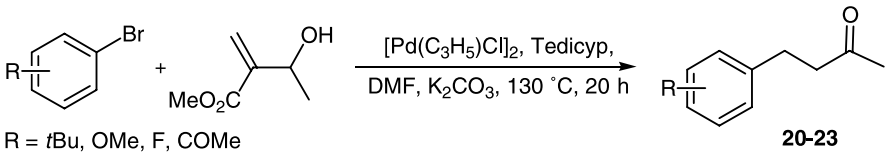
In summary, with 2-methylpent-1-en-3-ol, the best results in terms of selectivities and ratio substrate/catalyst were obtained using K_2CO_3 as base for electron-rich aryl bromide; $NaHCO_3$ should be preferred with electron-poor aryl bromides.

Heck reaction using 2-methyl-3-phenylprop-1-en-3-ol gave quite different results than the reaction with 2-methylpent-1-en-3-ol (Scheme 2, Table 2). With this allyl alcohol, low

Table 2. Palladium–tedicyp catalysed Heck reactions with 2-methyl-3-phenylprop-1-en-3-ol (Scheme 2)

Entry	Aryl bromide	Ratio substrate/catalyst	Base	Product number	Ratio ketone **11–19**/other isomers	Yield (%)[a]
1	4-*t*-Butylbromobenzene	1000	K_2CO_3	**11**	43/57	38 (100)
2	4-*t*-Butylbromobenzene	2500	K_2CO_3	**11**	43/57	(60)
3	4-*t*-Butylbromobenzene	100	$NaHCO_3$	**11**	90/10	(24)
4	4-Bromoanisole	1000	K_2CO_3	**12**	45/55	40 (100)
5	4-Bromoanisole	100	$NaHCO_3$	**12**	71/29	(26)
6	4-*N*,*N*-Dimethylaminobromobenzene	1000	K_2CO_3	**13**	37/63	23 (100)
7	4-*N*,*N*-Dimethylaminobromobenzene	2500	K_2CO_3	**13**	39/61	(25)
8	4-*N*,*N*-Dimethylaminobromobenzene	100	$NaHCO_3$	**13**	93/7	(15)
9	4-Fluorobromobenzene	1000	K_2CO_3	**14**	47/53	(100)
10	4-Fluorobromobenzene	2500	K_2CO_3	**14**	50/50	(93)
11	4-Fluorobromobenzene	1000	$NaHCO_3$	**14**	90/10	88 (100)
12	4-Bromoacetophenone	1000	K_2CO_3	**15**	40/60	(100)
13	4-Bromoacetophenone	2500	K_2CO_3	**15**	41/59	(48)
14	4-Bromoacetophenone	100	$NaHCO_3$	**15**	94/6	86 (96)
15	4-Bromoacetophenone	1000	$NaHCO_3$	**15**	94/6	(14)
16	4-Bromobenzonitrile	250	K_2CO_3	**16**	39/61	(100)
17	4-Bromobenzonitrile	100	$NaHCO_3$	**16**	94/6	87 (100)
18	4-Bromobenzonitrile	1000	$NaHCO_3$	**16**	94/6	(69)
19	2-Fluorobromobenzene	2500	K_2CO_3	**17**	45/55	(100)
20	2-Fluorobromobenzene	10,000	K_2CO_3	**17**	49/51	(13)
21	2-Fluorobromobenzene	100	$NaHCO_3$	**17**	93/7	66 (79)
22	3-Bromopyridine	1000	K_2CO_3	**18**	30/70	(100)
23	3-Bromopyridine	100	$NaHCO_3$	**18**	95/5	36 (42)
24	2-Bromothiophene	1000	K_2CO_3	**19**	30/70	19 (100)
25	2-Bromothiophene	100	$NaHCO_3$	**19**	30/70	(90)

[a] Conditions: catalyst: $[ClPd(C_3H_5)]_2$/tedicyp=1:2, aryl bromide (1 equiv), 2-methyl-3-phenylprop-1-en-3-ol (1.2 equiv), K_2CO_3 or $NaHCO_3$ (2 equiv), DMF, 130 °C, 20 h, isolated yields of products **11–19**. Yields in parenthesis are GC and NMR conversions.



Scheme 3.

selectivities of 30–50% in favour of isomers **11**–**19** were obtained when K_2CO_3 was used. With this alkenol, the formation of unidentified products was also observed. Here again, much better selectivities of 71–95% in compounds **11**–**19**, but slow reactions were observed using $NaHCO_3$. The best result in terms of selectivity and ratio substrate/catalyst was obtained with 4-bromobenzonitrile (Table 2, entries 17 and 18) with a selectivity of 94% in isomer **16** and a TON of 690.

Methyl-3-hydroxy-2-methylenebutenoate as coupling partner gave disappointing results (Scheme 3, Table 3). With this substrate, a decarbomethoxylation of the Baylis–Hillman adduct was observed to give selectively the β-arylated ketones **20**–**23**. The formation of the expected arylketoesters was not observed. Such decarbomethoxylation of the Baylis–Hillman adducts had already been described by Caló et al. with a Pd–benzothiazole–carbene complex[11b] and by Bhat et al. using $Pd(OAc)_2/PPh_3$ as catalyst.[9] Caló et al. explained the exclusive formation of the β-arylated ketones by a fast decarbomethoxylation of the expected arylketoester in tetrabutylammonium bromide as solvent. Our attempts to avoid this decarbomethoxylation using lower reaction temperatures or weaker bases were unsuccessful. The synthesis of 1-arylbutan-3-ones **20**–**23** using a Baylis–Hillman adduct is not attractive, since they can be prepared more easily by Heck reaction of simple alk-1-en-3-ols.[19]

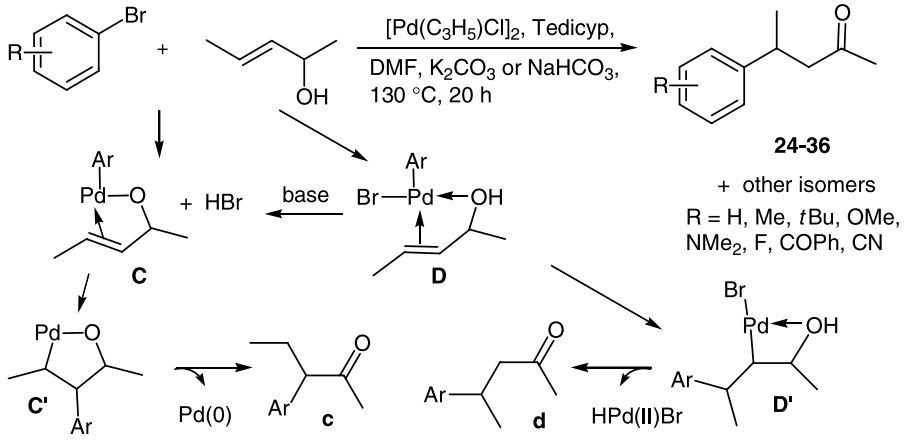
Table 3. Palladium–tedicyp catalysed Heck reactions with methyl-3-hydroxy-2-methylenebutenoate (Scheme 3)

Entry	Aryl bromide	Ratio substrate/catalyst	Product number	Yield (%)[a]
1	4-*t*-Butylbromobenzene	100	**20**	75 (100)
2	4-*t*-Butylbromobenzene	250	**20**	(88)
3	4-Bromoanisole	100	**21**	87 (100)
4	4-Bromoanisole	250	**21**	(62)
5	4-Fluorobromobenzene	100	**22**	85 (100)
6	4-Fluorobromobenzene	250	**22**	(73)
7	4-Bromoacetophenone	2500	**23**	91 (100)
8	4-Bromoacetophenone	10,000	**23**	(50)

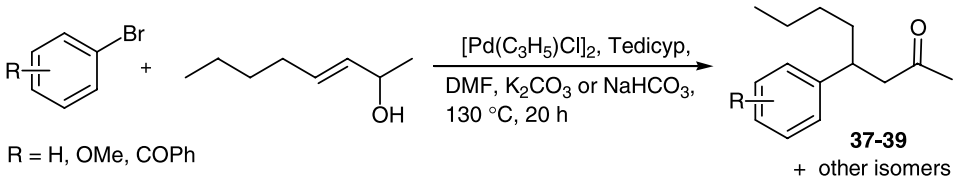
[a] Conditions: catalyst: $[ClPd(C_3H_5)]_2$/tedicyp = 1:2, aryl bromide (1 equiv), methyl-3-hydroxy-2-methylenebutenoate (1.2 equiv), K_2CO_3 or $NaHCO_3$ (2 equiv), DMF, 130 °C, 20 h, isolated yields of products **20**–**23**. Yields in parenthesis are GC and NMR conversions.

Then, we studied the selectivity of the reaction using three 3-substituted allylic alcohols: pent-3-en-2-ol, oct-3-en-2-ol and hept-2-en-4-ol (Schemes 4–6, Tables 4–6). The coupling of pent-3-en-2-ol with electron-rich aryl bromides such as 4-*t*-butylbromobenzene or 4-*N*,*N*-dimethylaminobromobenzene using K_2CO_3 as base gave β-aryl ketones **25**–**28** in 45–68% selectivities (Table 4, entries 4, 5, 7, 9, 10, 12 and 13). Reactions of pent-3-en-2-ol with the electron-poor aryl bromides 4-bromobenzophenone or 4-bromobenzonitrile were less selective, and the β-aryl ketones **31** and **32** were obtained in 28 and 39% selectivities (Table 4, entries 21, 22, 25 and 26). Presumably, with K_2CO_3, the formation of the alcoholate of pent-3-en-2-ol led to the intermediates **C** and **C′** of Scheme 4, then, intermediate **C′** gave the α-aryl ketone **c** with a mixture of isomers due to the partial migration of the double bond.

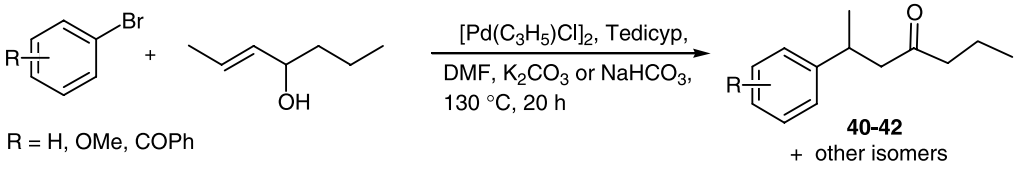
Again, using $NaHCO_3$ as base, higher selectivities and slower reactions were observed in all cases. With this base, the formation of the alcoholate of pent-3-en-2-ol is probably not favoured, therefore **D** and **D′** in Scheme 4 are formed as the major intermediates and β-aryl ketones **d** were obtained in 80–100% selectivities. An interaction of the alcohol function with the palladium centre probably imposes a conformation in the structures of the (aryl)-Pd(alkenol) intermediate leading to an higher regiocontrol of the insertion. This interaction might also control the migration of the double bond. With electron-rich aryl bromides, selectivities of 80–93% in β-aryl ketones **25**–**27**



Scheme 4.



Scheme 5.



Scheme 6.

were obtained (Table 4, entries 6, 8 and 11). Electron-poor aryl bromides gave products **30**–**32** in 81–85% selectivities (Table 4, entries 20, 23, 24, 27 and 28). As expected, the reactions with the heteroaromatic substrates 3-bromopyridine and 3-bromoquinoline also led to higher selectivities with $NaHCO_3$ as base (Table 4, entries 36–42).

Oct-3-en-2-ol gave quite similar selectivities than pent-3-en-2-ol (Scheme 5, Table 5). Very low selectivities were

Table 4. Palladium–tedicyp catalysed Heck reactions with pent-3-en-2-ol (Scheme 4)

Entry	Aryl bromide	Ratio substrate/catalyst	Base	Product number	Ratio ketone **24**–**36**/other isomers	Yield (%)[a]
1	Bromobenzene	2500	K_2CO_3	**24**	54/46	(97)
2	Bromobenzene	250	$NaHCO_3$	**24**	81/19	77 (100)
3	Bromobenzene	1000	$NaHCO_3$	**24**	82/18	(79)
4	4-Bromotoluene	1000	K_2CO_3	**25**	68/32	60 (100)
5	4-Bromotoluene	2500	K_2CO_3	**25**	45/55	(97)
6	4-Bromotoluene	100	$NaHCO_3$	**25**	93/7	(25)
7	4-*t*-Butylbromobenzene	2500	K_2CO_3	**26**	54/46	39 (97)
8	4-*t*-Butylbromobenzene	1000	$NaHCO_3$	**26**	80/20	(38)
9	4-Bromoanisole	1000	K_2CO_3	**27**	47/53	(100)
10	4-Bromoanisole	2500	K_2CO_3	**27**	49/51	41 (97)
11	4-Bromoanisole	250	$NaHCO_3$	**27**	80/20	31 (43)
12	4-*N*,*N*-Dimethylaminobromobenzene	2500	K_2CO_3	**28**	56/44	46 (100)
13	4-*N*,*N*-Dimethylaminobromobenzene	10,000	K_2CO_3	**28**	46/54	(49)
14	6-Methoxy-2-bromonaphthalene	1000	K_2CO_3	**29**	57/43	45 (94)
15	6-Methoxy-2-bromonaphthalene	2500	K_2CO_3	**29**	50/50	(31)
16	6-Methoxy-2-bromonaphthalene	250	$NaHCO_3$	**29**	81/19	77 (100)
17	6-Methoxy-2-bromonaphthalene	1000	$NaHCO_3$	**29**	83/17	(18)
18	4-Fluorobromobenzene	1000	K_2CO_3	**30**	64/36	58 (100)
19	4-Fluorobromobenzene	2500	K_2CO_3	**30**	50/50	(40)
20	4-Fluorobromobenzene	100	$NaHCO_3$	**30**	82/18	66 (89)
21	4-Bromobenzophenone	1000	K_2CO_3	**31**	39/61	(100)
22	4-Bromobenzophenone	2500	K_2CO_3	**31**	28/72	(47)
23	4-Bromobenzophenone	100	$NaHCO_3$	**31**	82/18	76 (100)
24	4-Bromobenzophenone	1000	$NaHCO_3$	**31**	81/19	(31)
25	4-Bromobenzonitrile	250	K_2CO_3	**32**	28/72	(100)
26	4-Bromobenzonitrile	1000	K_2CO_3	**32**	39/61	(40)
27	4-Bromobenzonitrile	100	$NaHCO_3$	**32**	85/15	82 (100)
28	4-Bromobenzonitrile	1000	$NaHCO_3$	**32**	84/16	(26)
29	2-Bromotoluene	1000	K_2CO_3	**33**	58/42	51 (100)
30	2-Bromotoluene	2500	K_2CO_3	**33**	70/30	(18)
31	2-Bromotoluene	50	$NaHCO_3$	**33**	—	(0)
32	1-Bromonaphthalene	1000	K_2CO_3	**34**	63/37	55 (100)
33	1-Bromonaphthalene	2500	K_2CO_3	**34**	57/43	(52)
34	1-Bromonaphthalene	100	$NaHCO_3$	**34**	100/0	97 (100)
35	1-Bromonaphthalene	1000	$NaHCO_3$	**34**	100/0	(68)
36	3-Bromopyridine	250	K_2CO_3	**35**	62/38	53 (100)
37	3-Bromopyridine	100	$NaHCO_3$	**35**	84/16	72 (100)
38	3-Bromopyridine	1000	$NaHCO_3$	**35**	83/17	(34)
39	3-Bromoquinoline	250	K_2CO_3	**36**	69/31	61 (100)
40	3-Bromoquinoline	1000	K_2CO_3	**36**	63/37	(72)
41	3-Bromoquinoline	100	$NaHCO_3$	**36**	81/19	78 (100)
42	3-Bromoquinoline	1000	$NaHCO_3$	**36**	83/17	(46)

[a] Conditions: catalyst: $[ClPd(C_3H_5)]_2$/tedicyp = 1:2, aryl bromide (1 equiv), pent-3-en-2-ol (1.2 equiv), K_2CO_3 or $NaHCO_3$ (2 equiv), DMF, 130 °C, 20 h, isolated yields of products **24**–**36**. Yields in parenthesis are GC and NMR conversions.

Table 5. Palladium–tedicyp catalysed Heck reactions with oct-3-en-2-ol (Scheme 5)

Entry	Aryl bromide	Ratio substrate/catalyst	Base	Product number	Ratio ketone **37–39**/other isomers	Yield (%)[a]
1	Bromobenzene	250	K_2CO_3	**37**	65/35	55 (100)
2	Bromobenzene	1000	K_2CO_3	**37**	68/32	(95)
3	Bromobenzene	100	$NaHCO_3$	**37**	83/17	53 (71)
4	4-Bromoanisole	100	K_2CO_3	**38**	68/32	47 (100)
5	4-Bromoanisole	250	K_2CO_3	**38**	80/20	(80)
6	4-Bromoanisole	50	$NaHCO_3$	**38**	—	(0)
7	4-Bromobenzophenone	1000	K_2CO_3	**39**	26/74	(100)
8	4-Bromobenzophenone	2500	K_2CO_3	**39**	14/86	(51)
9	4-Bromobenzophenone	100	$NaHCO_3$	**39**	81/19	75 (100)
10	4-Bromobenzophenone	1000	$NaHCO_3$	**39**	85/15	(11)

[a] Conditions: catalyst: $[ClPd(C_3H_5)]_2$/tedicyp=1:2, aryl bromide (1 equiv), oct-3-en-2-ol (1.2 equiv), K_2CO_3 or $NaHCO_3$ (2 equiv), DMF, 130 °C, 20 h, isolated yields of products **37–39**. Yields in parenthesis are GC and NMR conversions.

Table 6. Palladium–tedicyp catalysed Heck reactions with hept-2-en-4-ol (Scheme 6)

Entry	Aryl bromide	Ratio substrate/catalyst	Base	Product number	Ratio ketone **40–42**/other isomers	Yield (%)[a]
1	Bromobenzene	1000	K_2CO_3	**40**	24/76	(100)
2	Bromobenzene	2500	K_2CO_3	**40**	42/58	(88)
3	Bromobenzene	1000	$NaHCO_3$	**40**	73/27	69 (100)
4	4-Bromoanisole	1000	K_2CO_3	**41**	34/66	22 (100)
5	4-Bromoanisole	2500	K_2CO_3	**41**	51/49	(57)
6	4-Bromoanisole	100	$NaHCO_3$	**41**	78/22	71 (100)
7	4-Bromoanisole	1000	$NaHCO_3$	**41**	71/29	(18)
8	4-Bromobenzophenone	1000	K_2CO_3	**42**	34/66	(100)
9	4-Bromobenzophenone	1000	$NaHCO_3$	**42**	71/29	64 (100)

[a] Conditions: catalyst: $[ClPd(C_3H_5)]_2$/tedicyp=1:2, aryl bromide (1 equiv), hept-2-en-4-ol (1.2 equiv), K_2CO_3 or $NaHCO_3$ (2 equiv), DMF, 130 °C, 20 h, isolated yields of products **40–42**. Yields in parenthesis are GC and NMR conversions.

observed for the coupling with 4-bromobenzophenone using K_2CO_3 as base: 14 and 26%, but with $NaHCO_3$, β-aryl ketone **39** was obtained in 81–85% selectivities (Table 5, entries 7–10). Bromobenzene or 4-bromoanisole using K_2CO_3 gave **37** and **38** in 65–80% selectivities (Table 5, entries 1, 2, 4 and 5). On the other hand, hept-2-en-4-ol gave ketones **40–42** with low selectivities (24–51%) in all cases using K_2CO_3 as base (Scheme 6, Table 6). Again, higher selectivities in β-aryl ketones **40–42** were obtained with $NaHCO_3$: 71–78% (Table 6, entries 3, 6, 7 and 9).

In summary, we have established that the tedicyp–palladium system provides an efficient catalyst for the selective synthesis of β-aryl ketones from allylic alcohols with disubstituted double bonds and aryl bromides. The electronic properties and steric hindrance of the aryl bromide has an important effect on the selectivities of the reactions. In general, medium to high selectivities in β-aryl ketones were obtained using electron-rich aryl bromides and K_2CO_3 as base. More selective reactions were generally obtained using $NaHCO_3$ as base, especially with electron-poor aryl bromides, however, with this base slower reactions were observed in most cases. With sterically hindered aryl bromides higher selectivities in favour of the formation of the β-aryl ketones were obtained. A wide range of functions such as methoxy, fluoro, acetyl, formyl, benzoyl, dimethylamino or nitrile on the aryl bromide are tolerated. A few heteroaromatic substrates have also been used successfully. Electron-poor and electron-rich aryl bromides can be reacted at similar substrate/catalyst ratios when K_2CO_3 was used as base indicating that the oxidative addition of the aryl bromide is not the rate-limiting step for the reaction with this catalyst. It should de noted that the formation of non-arylated ketones deriving from allylic rearrangement was not observed. With this Pd–tetraphosphine catalyst, these reactions can be performed with as little as 0.01% catalyst with some substrates without further optimisation of the reaction conditions. Due to the high price of palladium, the practical advantage of such low catalyst loadings can become increasingly important for industrial processes. Moreover, these allylic alcohols are commercially available and this is a practical advantage of this reaction.

3. Experimental

3.1. General remarks

All reactions were run under argon in Schlenk tubes using vacuum lines. DMF analytical grade was not distilled before use. Potassium carbonate (99+) or sodium hydrogen carbonate (99+) were used. Commercial aryl bromides and allylic alcohols were used without purification. The reactions were followed by GC and NMR for high boiling point substrates and by GC for low boiling point substrates. ^1H and ^{13}C spectrum were recorded with a Bruker 300 MHz spectrometer in $CDCl_3$ solutions. Chemical shift are reported in parts per million relative to $CDCl_3$ (7.25 for ^1H NMR and 77.0 for ^{13}C NMR). Flash chromatography were performed on silica gel (230–400 mesh). GC and NMR yields in the tables are conversions of the aryl halides into the product calculated with GC and ^1H NMR spectrum of the crude mixtures.

3.1.1. Preparation of the Pd–tedicyp catalyst. An oven-dried 40-mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was charged with $[Pd(C_3H_5)Cl]_2$ (30 mg, 81 μmol) and tedicyp (140 mg, 162 μmol). Anhydrous DMF (10 mL) were added, then the solution was stirred at room temperature for 10 min. The appropriate catalyst concentration was obtained by successive dilutions. ^{31}P NMR (162 MHz, $CDCl_3$) δ 25 ($w=80$ Hz), 19.4 ($w=110$ Hz).

3.2. General procedure

In a typical experiment, the aryl halide (1 mmol), allylic alcohols (1.2 mmol) and K_2CO_3 (0.276 g, 2 mmol) or $NaHCO_3$ (0.168 g, 2 mmol) were dissolved in DMF (3 mL) under an argon atmosphere. The prepared Pd–tedicyp catalyst complex (see Tables) was then transferred to the reaction flask via cannula. The reaction mixture was stirred at 130 °C for 20 h. The solution was diluted with H_2O (5 mL), then the product was extracted three times with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography.

3.2.1. 1-(4-*tert*-Butylphenyl)-2-methylpentan-3-one (1b) (Table 1, entry 1). From 4-*tert*-butylbromobenzene (0.213 g, 1 mmol), 2-methylpent-1-en-3-ol (0.120 g, 1.2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (1 μmol), product **1b** was obtained in 71% (0.165 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, $J=8.3$ Hz, 2H), 7.06 (d, $J=8.3$ Hz, 2H), 2.92 (dd, $J=13.2$, 6.8 Hz, 1H), 2.82 (sext., $J=7.0$ Hz, 1H), 2.52 (dd, $J=13.2$, 7.3 Hz, 1H), 2.44 (dq, $J=17.8$, 7.3 Hz, 1H), 2.29 (dq, $J=17.8$, 7.3 Hz, 1H), 1.29 (s, 9H), 1.07 (d, $J=6.8$ Hz, 3H), 0.97 (t, $J=7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.9, 149.0, 136.7, 128.6, 125.2, 47.9, 38.7, 35.0, 34.3, 31.4, 16.6, 7.6; MS (70 eV); *m/z* (%) 232 ($M^{+\cdot}$, 40); $C_{16}H_{24}O$: calcd C 82.70, H 10.41; Found C 82.76, H 10.24. Before purification **1a** was also observed ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (t, $J=7.4$ Hz, 3H).

3.2.2. 1-(4-Methoxyphenyl)-2-methylpentan-3-one (2b) (Table 1, entry 4). From 4-bromoanisole (0.187 g, 1 mmol), 2-methylpent-1-en-3-ol (0.120 g, 1.2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.1 μmol), product **2b** was obtained in 92% (0.190 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, $J=8.7$ Hz, 2H), 6.80 (d, $J=8.7$ Hz, 2H), 3.77 (s, 3H), 2.89 (dd, $J=13.1$, 7.3 Hz, 1H), 2.79 (sext., $J=6.9$ Hz, 1H), 2.50 (dd, $J=13.1$, 6.8 Hz, 1H), 2.42 (dq, $J=17.8$, 7.3 Hz, 1H), 2.24 (dq, $J=17.8$, 7.3 Hz, 1H), 1.06 (d, $J=6.8$ Hz, 3H), 0.96 (t, $J=7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.0, 158.0, 131.9, 129.8, 113.8, 55.2, 48.1, 38.5, 35.2, 16.5, 7.6; MS (70 eV); *m/z* (%) 206 ($M^{+\cdot}$, 37); $C_{13}H_{18}O_2$: calcd C 75.69, H 8.80; Found C 75.43, H 8.73. Before purification **2a** was also observed ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, $J=7.3$ Hz, 3H).

3.2.3. 1-(4-(Dimethylamino)phenyl)-2-methylpentan-3-one (3b) (Table 1, entry 6). From 4-bromo-*N*,*N*-dimethylaniline (0.200 g, 1 mmol), 2-methylpent-1-en-3-ol (0.120 g, 1.2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (1 μmol), product **3b** was obtained in 85% (0.186 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.00 (d, $J=8.7$ Hz, 2H), 6.67 (d, $J=8.7$ Hz, 2H), 2.90 (s, 6H), 2.86 (dd, $J=12.9$, 6.8 Hz, 1H), 2.78 (sext., $J=6.9$ Hz, 1H), 2.49 (dd, $J=12.9$, 6.9 Hz, 1H), 2.41 (dq, $J=17.9$, 7.2 Hz, 1H), 2.27 (dq, $J=17.9$, 7.2 Hz, 1H), 1.05 (d, $J=6.8$ Hz, 3H), 0.97 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.3, 149.1, 129.5, 127.9, 112.9, 48.2, 40.8, 38.4, 35.1, 16.4, 7.6; MS (70 eV); *m/z* (%) 219 ($M^{+\cdot}$, 67); $C_{14}H_{21}NO$: calcd C 76.67, H 9.65; Found C 76.77, H 9.57. Before purification **3a** was also observed ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (t, $J=7.5$ Hz, 3H).

3.2.4. 1-(4-Fluorophenyl)-2-methylpentan-3-one (4b) (Table 1, entry 8). From 4-fluorobromobenzene (0.175 g, 1 mmol), 2-methylpent-1-en-3-ol (0.120 g, 1.2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (1 μmol), product **4b** was obtained in 87% (0.169 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.08 (dd, $J=8.7$, 5.5 Hz, 2H), 6.94 (t, $J=8.7$ Hz, 2H), 2.93 (dd, $J=13.3$, 7.5 Hz, 1H), 2.79 (sext., $J=7.1$ Hz, 1H), 2.51 (dd, $J=13.3$, 6.9 Hz, 1H), 2.43 (dq, $J=17.8$, 7.3 Hz, 1H), 2.23 (dq, $J=17.8$, 7.3 Hz, 1H), 1.07 (d, $J=6.9$ Hz, 3H), 0.95 (t, $J=7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.6, 161.9 (d, $J_{C-F}=243.8$ Hz), 135.5 (d, $^4J_{C-F}=3.4$ Hz), 130.2 (d, $^3J_{C-F}=8.0$ Hz), 115.1 (d, $^2J_{C-F}=21.3$ Hz), 47.9, 38.3, 35.2, 16.6, 7.6; MS (70 eV); *m/z* (%) 194 ($M^{+\cdot}$, 25); $C_{12}H_{15}FO$: calcd C 74.20, H 7.78; Found C 74.36, H 7.81. Before purification **4a** was also observed ^1H NMR (300 MHz, $CDCl_3$) δ 1.16 (t, $J=7.3$ Hz, 3H).

3.2.5. 1-(4-(Trifluoromethyl)phenyl)-2-methylpentan-3-one (5b) (Table 1, entry 12). From 4-trifluoromethylbromobenzene (0.225 g, 1 mmol), 2-methylpent-1-en-3-ol (0.120 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (10 μmol), product **5b** was obtained in 89% (0.217 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, $J=8.1$ Hz, 2H), 7.24 (d, $J=8.1$ Hz, 2H), 3.04 (dd, $J=13.4$, 7.4 Hz, 1H), 2.84 (sext., $J=7.0$ Hz, 1H), 2.61 (dd, $J=13.4$, 7.2 Hz, 1H), 2.47 (dq, $J=17.8$, 7.3 Hz, 1H), 2.25 (dq, $J=17.8$, 7.3 Hz, 1H), 1.09 (d, $J=7.1$ Hz, 3H), 0.97 (t, $J=7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.0, 144.1, 129.3, 128.6 (q, $^2J_{C-F}=32.4$ Hz), 125.3 (q, $^3J_{C-F}=4.0$ Hz), 124.2 (q, $J_{C-F}=271.9$ Hz), 47.6, 38.7, 35.1, 16.8, 7.6; MS (70 eV); *m/z* (%) 244 ($M^{+\cdot}$, 62); $C_{13}H_{15}F_3O$: calcd C 63.93, H 6.19; Found C 64.04, H 6.16. Before purification **5a** was also observed ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, $J=7.3$ Hz, 3H).

3.2.6. 1-(4-Acetylphenyl)-2-methylpentan-3-one (6b) (Table 1, entry 16). From 4-bromoacetophenone (0.199 g, 1 mmol), 2-methylpent-1-en-3-ol (0.120 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (10 μmol), product **6b** was obtained in 88% (0.192 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, $J=8.4$ Hz, 2H), 7.22 (d, $J=8.4$ Hz, 2H), 3.03 (dd, $J=13.0$, 7.3 Hz, 1H), 2.85 (sext., $J=6.9$ Hz, 1H), 2.62 (dd, $J=13.0$, 6.8 Hz, 1H), 2.56 (s, 3H), 2.45 (dq, $J=17.9$, 7.2 Hz, 1H), 2.21 (dq, $J=17.9$, 7.2 Hz, 1H), 1.09 (d, $J=6.8$ Hz, 3H), 0.96 (t, $J=7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.0, 197.7, 145.7, 135.4, 129.2, 128.5, 47.5, 39.0, 35.1, 26.5, 16.8, 7.8; MS (70 eV); *m/z* (%) 218 ($M^{+\cdot}$, 80); $C_{14}H_{18}O_2$: calcd C 77.03, H 8.31; Found C 77.12, H 8.38. Before purification **6a** was also observed ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, $J=7.3$ Hz, 3H).

3.2.7. 1-(4-Cyanophenyl)-2-methylpentan-3-one (7b) (Table 1, entry 19). From 4-bromobenzonitrile (0.182 g, 1 mmol), 2-methylpent-1-en-3-ol (0.120 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (10 μmol), product **7b** was obtained in 90% (0.181 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J=8.1 Hz, 2H), 7.24 (d, J=8.1 Hz, 2H), 3.04 (dd, J=13.4, 7.5 Hz, 1H), 2.81 (sext., J=7.1 Hz, 1H), 2.61 (dd, J=13.4, 6.8 Hz, 1H), 2.47 (dq, J=17.8, 7.3 Hz, 1H), 2.23 (dq, J=17.8, 7.3 Hz, 1H), 1.09 (d, J=6.9 Hz, 3H), 0.96 (t, J=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.5, 145.5, 132.0, 129.6, 118.7, 109.9, 47.2, 38.7, 34.8, 16.7, 7.4; $C_{13}H_{15}NO$: calcd C 77.58, H 7.51; Found C 77.32, H 7.72. Before purification **7a** was also observed ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (t, J=7.3 Hz, 3H).

3.2.8. 2-Methyl-1-(*o*-tolyl)pentan-3-one (8b) (Table 1, entry 23). From 2-methylbromobenzene (0.171 g, 10 mmol), 2-methylpent-1-en-3-ol (0.120 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (10 μmol), product **8b** was obtained in 93% (0.177 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.13–7.05 (m, 4H), 2.96 (dd, J=13.4, 7.0 Hz, 1H), 2.83 (sext., J=7.0 Hz, 1H), 2.56 (dd, J=13.5, 7.3 Hz, 1H), 2.42 (dq, J=17.9, 7.3 Hz, 1H), 2.31 (s, 3H), 2.23 (dq, J=17.9, 7.3 Hz, 1H), 1.09 (d, J=6.7 Hz, 3H), 0.96 (t, J=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.9, 138.0, 136.0, 130.4, 129.7, 126.3, 125.9, 46.4, 36.5, 35.3, 19.4, 16.6, 7.6; MS (70 eV); m/z (%) 190 ($M^{+\cdot}$, 15); $C_{13}H_{18}O$: calcd C 82.06, H 9.53; Found C 82.01, H 9.72. Before purification **8a** was also observed ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, J=7.3 Hz, 3H).

3.2.9. 2-Methyl-1-(3-pyridinyl)pentan-3-one (9b) (Table 1, entry 27). From 3-bromopyridine (0.158 g, 1 mmol), 2-methylpent-1-en-3-ol (0.120 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (10 μmol), product **9b** was obtained in 80% (0.142 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 8.39 (dd, J=4.8, 1.6 Hz, 1H), 8.37 (d, J=2.0 Hz, 1H), 7.41 (dt, J=7.8, 2.0 Hz, 1H), 7.14 (ddd, J=7.8, 4.8, 0.7 Hz, 1H), 2.96 (dd, J=13.5, 7.3 Hz, 1H), 2.78 (sext., J=7.0 Hz, 1H), 2.56 (dd, J=13.5, 7.0 Hz, 1H), 2.43 (dq, J=17.9, 7.3 Hz, 1H), 2.22 (dq, J=17.9, 7.3 Hz, 1H), 1.06 (d, J=6.9 Hz, 3H), 0.93 (t, J=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.8, 150.2, 147.6, 136.4, 135.2, 123.2, 47.4, 35.9, 35.0, 16.7, 7.5; $C_{11}H_{15}NO$: calcd C 74.54, H 8.53; Found C 74.72, H 8.38. Before purification **9a** was also observed ^1H NMR (300 MHz, $CDCl_3$) δ 1.14 (t, J=7.3 Hz, 3H).

3.2.10. 2-Methyl-1-(3-quinolyl)pentan-3-one (10b) (Table 1, entry 31). From 3-bromoquinoline (0.136 mL, 1 mmol), 2-methylpent-1-en-3-ol (0.120 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (10 μmol), product **10b** was obtained in 97% (0.220 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 8.74 (d, J=1.8 Hz, 1H), 8.07 (d, J=8.6 Hz, 1H), 7.90 (d, J=1.8 Hz, 1H), 7.75 (dd, J=8.2, 1.0 Hz, 1H), 7.65 (td, J=8.2, 1.4 Hz, 1H), 7.51 (td, J=8.1, 1.1 Hz, 1H), 3.18 (dd, J=13.7, 7.4 Hz, 1H), 2.93 (sext., J=7.1 Hz, 1H), 2.74 (dd, J=13.7, 6.9 Hz, 1H), 2.50 (dq, J=17.8, 7.3 Hz, 1H), 2.26 (dq, J=17.8, 7.3 Hz, 1H), 1.15 (d, J=6.9 Hz, 3H), 0.96 (t, J=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.8, 151.8, 146.7, 135.4, 132.6, 129.0, 128.9, 128.0, 127.4, 126.8, 47.5, 36.1, 35.1, 16.9, 7.6; MS (70 eV); m/z (%) 227 ($M^{+\cdot}$, 100); $C_{15}H_{17}NO$: calcd C 79.26, H 7.54; Found C 79.35, H 7.46. Before purification **10a** was also observed ^1H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, J=7.3 Hz, 3H).

3.2.11. 3-(4-*tert*-Butylphenyl)-2-methyl-1-phenylpropan-1-one (11) (Table 2, entry 1). From 4-*tert*-butylbromobenzene (0.213 g, 1 mmol), 2-methyl-3-phenylprop-1-en-3-ol (0.178 g, 1.2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (1 μmol), product **11** was obtained in 38% (0.107 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J=7.4 Hz, 2H), 7.52 (t, J=7.4 Hz, 1H), 7.42 (t, J=7.4 Hz, 2H), 7.29 (d, J=8.4 Hz, 2H), 7.11 (d, J=8.4 Hz, 2H), 3.73 (sext., J=7.0 Hz, 1H), 3.13 (dd, J=13.8, 6.1 Hz, 1H), 2.65 (dd, J=13.8, 7.9 Hz, 1H), 1.28 (s, 9H), 1.20 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9, 149.0, 136.8, 136.5, 132.8, 128.7, 128.6, 128.3, 125.2, 42.7, 38.8, 34.3, 31.4, 17.4; MS (70 eV); m/z (%) 280 ($M^{+\cdot}$, 58); $C_{20}H_{24}O$: calcd C 85.67, H 8.63; Found C 85.59, H 8.66.

3.2.12. 3-(4-Methoxyphenyl)-2-methyl-1-phenylpropan-1-one (12) (Table 2, entry 4). From 4-bromoanisole (0.187 g, 1 mmol), 2-methyl-3-phenylprop-1-en-3-ol (0.178 g, 1.2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (1 μmol), product **12** was obtained in 40% (0.102 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J=7.4 Hz, 2H), 7.54 (t, J=7.4 Hz, 1H), 7.44 (t, J=7.4 Hz, 2H), 7.10 (d, J=8.6 Hz, 2H), 6.80 (d, J=8.6 Hz, 2H), 3.76 (s, 3H), 3.70 (sext., J=7.1 Hz, 1H), 3.13 (dd, J=13.8, 6.6 Hz, 1H), 2.63 (dd, J=13.8, 7.7 Hz, 1H), 1.19 (d, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9, 158.0, 136.5, 132.9, 132.0, 130.0, 128.6, 128.3, 113.8, 55.2, 43.0, 38.5, 17.3; MS (70 eV); m/z (%) 254 ($M^{+\cdot}$, 40).

3.2.13. 3-[4-(Dimethylamino)phenyl]-2-methyl-1-phenylpropan-1-one (13) (Table 2, entry 6). From 4-bromo-*N*,*N*-dimethylaniline (0.200 g, 1 mmol), 2-methyl-3-phenylprop-1-en-3-ol (0.178 g, 1.2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (1 μmol), product **13** was obtained in 23% (0.062 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, J=7.4 Hz, 2H), 7.54 (t, J=7.4 Hz, 1H), 7.44 (t, J=7.4 Hz, 2H), 7.08 (d, J=8.7 Hz, 2H), 6.68 (d, J=8.7 Hz, 2H), 3.70 (sext., J=7.0 Hz, 1H), 3.07 (dd, J=13.9, 5.9 Hz, 1H), 2.90 (s, 6H), 2.59 (dd, J=13.8, 8.0 Hz, 1H), 1.19 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.1, 158.0, 136.6, 129.7, 128.6, 128.3, 127.6, 126.4, 112.9, 43.0, 40.8, 38.4, 17.1; MS (70 eV); m/z (%) 267 ($M^{+\cdot}$, 40); $C_{18}H_{21}NO$: calcd C 80.86, H 7.92; Found C 80.78, H 8.05.

3.2.14. 3-(4-Fluorophenyl)-2-methyl-1-phenylpropan-1-one (14) (Table 2, entry 11). From 4-fluorobromobenzene (0.175 g, 1 mmol), 2-methyl-3-phenylprop-1-en-3-ol (0.178 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (1 μmol), product **14** was obtained in 88% (0.213 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J=7.4 Hz, 2H), 7.54 (t, J=7.4 Hz, 1H), 7.43 (t, J=7.4 Hz, 2H), 7.14 (dd, J=8.7, 5.3 Hz, 2H), 6.93 (d, J=8.8 Hz, 2H), 3.71 (sext., J=6.9 Hz, 1H), 3.13 (dd, J=13.8, 6.8 Hz, 1H), 2.67 (dd, J=13.8, 7.9 Hz, 1H), 1.19 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5, 161.4 (d, J_{C-F}=243.8 Hz), 136.4, 135.5 (d, $^4J_{C-F}$=2.9 Hz), 133.0, 130.5 (d, $^3J_{C-F}$=8.0 Hz), 128.6, 128.2, 115.1 (d, $^2J_{C-F}$=21.3 Hz), 42.8, 38.5,

17.5; MS (70 eV); *m/z* (%) 242 ($M^{+\cdot}$, 41); $C_{16}H_{15}FO$: calcd C 79.32, H 6.24; Found C 79.50, H 6.36.

3.2.15. 3-(4-Acetylphenyl)-2-methyl-1-phenylpropan-1-one (15) (Table 2, entry 14). From 4-bromoacetophenone (0.199 g, 1 mmol), 2-methyl-3-phenylprop-1-en-3-ol (0.178 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (10 μmol), product **15** was obtained in 86% (0.229 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, $J=7.3$ Hz, 2H), 7.84 (d, $J=8.3$ Hz, 2H), 7.54 (t, $J=7.3$ Hz, 1H), 7.44 (t, $J=7.4$ Hz, 2H), 7.28 (d, $J=8.3$ Hz, 2H), 3.77 (sext., $J=7.0$ Hz, 1H), 3.22 (dd, $J=13.7$, 6.9 Hz, 1H), 2.76 (dd, $J=13.7$, 7.3 Hz, 1H), 2.55 (s, 3H), 1.21 (d, $J=7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.1, 197.8, 145.8, 136.2, 135.4, 133.1, 129.3, 128.7, 128.5, 128.2, 42.4, 39.2, 26.5, 17.7; MS (70 eV); *m/z* (%) 266 ($M^{+\cdot}$, 51); $C_{18}H_{18}O_2$: calcd C 81.17, H 6.81; Found C 81.12, H 6.96.

3.2.16. 3-(4-Cyanophenyl)-2-methyl-1-phenylpropan-1-one (16) (Table 2, entry 17). From 4-bromobenzonitrile (0.182 g, 1 mmol), 2-methyl-3-phenylprop-1-en-3-ol (0.178 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (10 μmol), product **16** was obtained in 87% (0.217 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, $J=7.3$ Hz, 2H), 7.53 (d, $J=8.2$ Hz, 2H), 7.52 (t, $J=7.3$ Hz, 1H), 7.45 (t, $J=7.4$ Hz, 2H), 7.29 (d, $J=8.2$ Hz, 2H), 3.75 (sext., $J=7.0$ Hz, 1H), 3.22 (dd, $J=13.7$, 7.3 Hz, 1H), 2.77 (dd, $J=13.7$, 6.9 Hz, 1H), 1.22 (d, $J=6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 145.7, 136.0, 133.2, 132.2, 129.9, 129.5, 128.7, 128.2, 110.1, 42.3, 39.2, 18.0; MS (70 eV); *m/z* (%) 249 ($M^{+\cdot}$, 31); $C_{17}H_{15}NO$: calcd C 81.90, H 6.06; Found C 81.82, H 6.06.

3.2.17. 3-(2-Fluorophenyl)-2-methyl-1-phenylpropan-1-one (17) (Table 2, entry 21). From 2-fluorobromobenzene (0.175 g, 1 mmol), 2-methyl-3-phenylprop-1-en-3-ol (0.178 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (10 μmol), product **17** was obtained in 66% (0.160 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, $J=7.4$ Hz, 2H), 7.54 (t, $J=7.4$ Hz, 1H), 7.46 (t, $J=7.4$ Hz, 2H), 7.21–7.10 (m, 2H), 6.94–7.02 (m, 2H), 3.82 (sext., $J=7.0$ Hz, 1H), 3.16 (dd, $J=13.6$, 6.3 Hz, 1H), 2.72 (dd, $J=13.6$, 7.2 Hz, 1H), 1.19 (d, $J=7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.5, 161.3 (d, $J_{C-F}=245.0$ Hz), 136.3, 133.0, 131.8 (d, $^3J_{C-F}=5.2$ Hz), 129.4, 128.6, 128.3, 128.1 (d, $^2J_{C-F}=9.2$ Hz), 123.9 (d, $^3J_{C-F}=3.5$ Hz), 115.2 (d, $^2J_{C-F}=21.8$ Hz), 41.0, 33.1, 17.2; MS (70 eV); *m/z* (%) 242 ($M^{+\cdot}$, 52); $C_{16}H_{15}FO$: calcd C 79.32, H 6.24; Found C 79.41, H 6.36.

3.2.18. 2-Methyl-1-phenyl-3-(3-pyridinyl)propan-1-one (18) (Table 2, entry 23). From 3-bromopyridine (0.158 g, 1 mmol), 2-methyl-3-phenylprop-1-en-3-ol (0.178 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (10 μmol), product **18** was obtained in 36% (0.081 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.42 (d, $J=4.8$ Hz, 1H), 7.89 (d, $J=7.5$ Hz, 2H), 7.54 (m, 2H), 7.46 (d, $J=7.5$ Hz, 2H), 7.19 (dd, $J=7.8$, 4.9 Hz, 1H), 3.74 (sext., $J=7.0$ Hz, 1H), 3.17 (dd, $J=13.9$, 7.1 Hz, 1H), 2.72 (dd, $J=13.9$, 7.0 Hz, 1H), 1.22 (d, $J=7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.9, 150.0, 147.3, 137.0, 136.1, 135.6, 133.2, 128.7, 128.3, 123.4, 42.5, 36.3, 17.8; MS (70 eV); *m/z* (%) 225 ($M^{+\cdot}$, 45); $C_{15}H_{15}NO$: calcd C 79.97, H 6.71; Found C 79.71, H 6.85.

3.2.19. 1-Phenyl-2-[(2-thienyl)methyl]propan-1-one (19) (Table 2, entry 24). From 2-bromothiophene (0.163 g, 1 mmol), 2-methyl-3-phenylprop-1-en-3-ol (0.178 g, 1.2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (1 μmol), product **19** was obtained in 19% (0.044 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, $J=7.3$ Hz, 2H), 7.54 (t, $J=7.3$ Hz, 1H), 7.46 (d, $J=7.3$ Hz, 2H), 7.09 (dd, $J=5.1$, 1.3 Hz, 1H), 6.88 (dd, $J=5.1$, 3.4 Hz, 1H), 6.80 (dd, $J=3.4$, 1.0 Hz, 1H), 3.77 (sext., $J=7.0$ Hz, 1H), 3.38 (ddd, $J=14.8$, 6.7, 0.8 Hz, 1H), 2.94 (dd, $J=13.8$, 7.3 Hz, 1H), 1.24 (d, $J=7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 142.4, 136.3, 133.0, 128.7, 128.3, 126.8, 125.6, 123.6, 43.2, 33.2, 17.8; MS (70 eV); *m/z* (%) 230 ($M^{+\cdot}$, 70); $C_{14}H_{14}OS$: calcd C 73.01, H 6.13; Found C 72.88, H 6.01.

3.2.20. 4-(4-*tert*-Butylphenyl)butan-2-one (20) (Table 3, entry 1). From 4-*tert*-butylbromobenzene (0.213 g, 1 mmol), methyl-3-hydroxy-2-methylenebutyrate (0.175 g, 1.2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (10 μmol), product **20** was obtained in 75% (0.153 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, $J=8.4$ Hz, 2H), 7.11 (d, $J=8.4$ Hz, 2H), 2.86 (t, $J=7.7$ Hz, 2H), 2.75 (t, $J=7.7$ Hz, 2H), 2.14 (s, 3H), 1.30 (s, 9H).

3.2.21. 4-(4-Methoxyphenyl)butan-2-one (21) (Table 3, entry 3). From 4-bromoanisole (0.187 g, 1 mmol), methyl-3-hydroxy-2-methylenebutyrate (0.175 g, 1.2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (10 μmol), product **21** was obtained in 87% (0.155 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, $J=8.7$ Hz, 2H), 6.82 (d, $J=8.7$ Hz, 2H), 3.77 (s, 3H), 2.83 (t, $J=7.3$ Hz, 2H), 2.71 (t, $J=7.3$ Hz, 2H), 2.12 (s, 3H).

3.2.22. 4-(4-Fluorophenyl)butan-2-one (22) (Table 3, entry 5). From 4-fluorobromobenzene (0.175 g, 1 mmol), methyl-3-hydroxy-2-methylenebutyrate (0.175 g, 1.2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (10 μmol), product **22** was obtained in 85% (0.141 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.13 (dd, $J=8.5$, 5.5 Hz, 2H), 6.95 (t, $J=8.7$ Hz, 2H), 2.86 (t, $J=7.0$ Hz, 2H), 2.72 (t, $J=7.0$ Hz, 2H), 2.12 (s, 3H).

3.2.23. 4-(4-Acetylphenyl)butan-2-one (23) (Table 3, entry 7). From 4-bromoacetophenone (0.199 g, 1 mmol), methyl-3-hydroxy-2-methylenebutyrate (0.175 g, 1.2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.4 μmol), product **23** was obtained in 91% (0.173 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, $J=8.2$ Hz, 2H), 7.26 (d, $J=8.2$ Hz, 2H), 2.93 (t, $J=7.4$ Hz, 2H), 2.76 (t, $J=7.4$ Hz, 2H), 2.55 (s, 3H), 2.13 (s, 3H).

3.2.24. 4-Phenylpentan-2-one (24) (Table 4, entry 2). From bromobenzene (0.157 g, 1 mmol), pent-3-en-2-ol (0.103 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (4 μmol), product **24** was obtained in 77% (0.125 g) yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.14 (m, 5H), 3.30 (sext., $J=7.0$ Hz, 1H), 2.75 (dd, $J=16.1$, 6.5 Hz, 1H), 2.64 (dd, $J=16.3$, 7.8 Hz, 1H), 2.05 (s, 3H), 1.26 (d, $J=6.9$ Hz, 3H).

3.2.25. 4-(*p*-Tolyl)pentan-2-one (25) (Table 4, entry 4). From 4-bromotoluene (0.171 g, 1 mmol), pent-3-en-2-ol (0.103 g, 1.2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (1 μmol), product **25** was obtained in 60% (0.106 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (m, 4H), 3.26 (sext., J=6.9 Hz, 1H), 2.73 (dd, J=16.1, 6.1 Hz, 1H), 2.63 (dd, J=16.2, 7.9 Hz, 1H), 2.30 (s, 3H), 2.05 (s, 3H), 1.24 (d, J=7.0 Hz, 3H).

3.2.26. 4-(4-*tert*-Butylphenyl)pentan-2-one (26) (Table 4, entry 7). From 4-*tert*-butylbromobenzene (0.213 g, 10 mmol), pent-3-en-2-ol (0.103 g, 1.2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.4 μmol), product **26** was obtained in 39% (0.085 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, J=8.3 Hz, 2H), 7.12 (d, J=8.3 Hz, 2H), 3.26 (sext., J=6.9 Hz, 1H), 2.74 (dd, J=16.2, 6.2 Hz, 1H), 2.63 (dd, J=16.3, 8.1 Hz, 1H), 2.06 (s, 3H), 1.29 (s, 9H), 1.26 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.1, 149.0, 143.0, 126.3, 125.4, 52.1, 34.8, 34.3, 31.4, 30.5, 21.9; MS (70 eV); *m/z* (%) 218 ($M^{+\cdot}$, 11); $C_{15}H_{22}O$: calcd C 82.52, H 10.16; Found C 82.45, H 10.12.

3.2.27. 4-(4-Methoxyphenyl)pentan-2-one (27) (Table 4, entry 10). From 4-bromoanisole (0.187 g, 1 mmol), pent-3-en-2-ol (0.103 g, 1.2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.4 μmol), product **27** was obtained in 41% (0.079 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J=8.7 Hz, 2H), 6.83 (d, J=8.7 Hz, 2H), 3.77 (s, 3H), 3.25 (sext., J=6.9 Hz, 1H), 2.71 (dd, J=16.1, 6.1 Hz, 1H), 2.61 (dd, J=16.2, 7.7 Hz, 1H), 2.04 (s, 3H), 1.24 (d, J=6.9 Hz, 3H).

3.2.28. 4-[4-(Dimethylamino)phenyl]pentan-2-one (28) (Table 4, entry 12). From 4-bromo-*N*,*N*-dimethylaniline (0.200 g, 1 mmol), pent-3-en-2-ol (0.103 g, 1.2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.4 μmol), product **28** was obtained in 46% (0.095 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, J=8.7 Hz, 2H), 6.70 (d, J=8.7 Hz, 2H), 3.21 (sext., J=7.0 Hz, 1H), 2.91 (s, 6H), 2.71 (dd, J=15.9, 6.7 Hz, 1H), 2.60 (dd, J=15.9, 8.0 Hz, 1H), 2.04 (s, 3H), 1.23 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5, 149.2, 134.3, 127.3, 113.0, 52.4, 40.8, 34.7, 30.5, 22.2; MS (70 eV); *m/z* (%) 205 ($M^{+\cdot}$, 83); $C_{13}H_{19}NO$: calcd C 76.06, H 9.33; Found C 76.13, H 9.25.

3.2.29. 4-(6-Methoxynaphthalen-2-yl)-pentan-2-one (29) (Table 4, entry 16). From 6-methoxy-2-bromonaphthalene (0.237 g, 10 mmol), pent-3-en-2-ol (0.103 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (4 μmol), product **29** was obtained in 77% (0.187 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J=8.5 Hz, 2H), 7.54 (s, 1H), 7.31 (d, J=8.5 Hz, 1H), 7.15–7.07 (m, 2H), 3.90 (s, 3H), 3.43 (sext., J=7.0 Hz, 1H), 2.83 (dd, J=16.2, 6.6 Hz, 1H), 2.71 (dd, J=16.3, 7.8 Hz, 1H), 2.05 (s, 3H), 1.32 (d, J=6.9 Hz, 3H).

3.2.30. 4-(4-Fluorophenyl)pentan-2-one (30) (Table 4, entry 20). From 4-fluorobromobenzene (0.175 g, 1 mmol), pent-3-en-2-ol (0.103 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (10 μmol), product **30** was obtained in 66% (0.119 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (dd, J=8.4, 5.4 Hz, 2H), 6.96 (t, J=8.7 Hz, 2H), 3.29 (sext., J=7.0 Hz, 1H), 2.72 (dd, J=16.4, 6.7 Hz, 1H), 2.63 (dd, J=16.3, 7.5 Hz, 1H), 2.05 (s, 3H), 1.24 (d, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 161.3 (d, J_{C-F}=243.8 Hz), 141.7, 128.1 (d, $^3J_{C-F}$=8.0 Hz), 115.2 (d, $^2J_{C-F}$=20.6 Hz), 52.0, 34.7, 30.6, 22.1; MS (70 eV); *m/z* (%) 180 ($M^{+\cdot}$, 100); $C_{11}H_{13}FO$: calcd C 73.31, H 7.27; Found C 73.29, H 7.40.

3.2.31. 4-(4-Benzoylphenyl)pentan-2-one (31) (Table 4, entry 23). From 4-bromobenzophenone (0.261 g, 1 mmol), pent-3-en-2-ol (0.103 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (10 μmol), product **31** was obtained in 76% (0.202 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J=7.3 Hz, 2H), 7.75 (d, J=8.2 Hz, 2H), 7.57 (t, J=7.3 Hz, 1H), 7.47 (t, J=7.3 Hz, 2H), 7.32 (d, J=8.2 Hz, 2H), 3.40 (sext., J=7.0 Hz, 1H), 2.80 (dd, J=16.7, 6.7 Hz, 1H), 2.71 (dd, J=16.3, 7.5 Hz, 1H), 2.09 (s, 3H), 1.29 (d, J=7.0 Hz, 3H).

3.2.32. 4-(4-Cyanophenyl)pentan-2-one (32) (Table 4, entry 27). From 4-bromobenzonitrile (0.182 g, 1 mmol), pent-3-en-2-ol (0.103 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (10 μmol), product **32** was obtained in 82% (0.154 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, J=8.4 Hz, 2H), 7.31 (d, J=8.4 Hz, 2H), 3.42 (sext., J=7.0 Hz, 1H), 2.76 (dd, J=17.0, 6.8 Hz, 1H), 2.71 (dd, J=17.1, 7.3 Hz, 1H), 2.10 (s, 3H), 1.26 (d, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.6, 151.8, 132.4, 127.7, 118.9, 110.2, 51.2, 35.2, 30.5, 21.6.

3.2.33. 4-(*o*-Tolyl)pentan-2-one (33) (Table 4, entry 29). From 2-bromotoluene (0.171 g, 1 mmol), pent-3-en-2-ol (0.103 g, 1.2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (1 μmol), product **33** was obtained in 51% (0.090 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.03 (m, 4H), 3.55 (sext., J=6.9 Hz, 1H), 2.75 (dd, J=16.5, 6.0 Hz, 1H), 2.64 (dd, J=16.5, 8.3 Hz, 1H), 2.36 (s, 3H), 2.07 (s, 3H), 1.21 (d, J=6.8 Hz, 3H).

3.2.34. 4-Naphthalen-1-yl-pentan-2-one (34) (Table 4, entry 34). From 1-bromonaphthalene (0.207 g, 1 mmol), pent-3-en-2-ol (0.103 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (10 μmol), product **34** was obtained in 97% (0.206 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, J=8.2 Hz, 1H), 7.86 (d, J=8.4 Hz, 1H), 7.72 (d, J=8.0 Hz, 1H), 7.57–7.33 (m, 4H), 4.21 (sext., J=6.8 Hz, 1H), 2.91 (dd, J=16.9, 4.8 Hz, 1H), 2.77 (dd, J=16.9, 9.0 Hz, 1H), 2.13 (s, 3H), 1.40 (d, J=6.8 Hz, 3H).

3.2.35. 4-(3-Pyridinyl)pentan-2-one (35) (Table 4, entry 37). From 3-bromopyridine (0.158 g, 1 mmol), pent-3-en-2-ol (0.103 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (10 μmol), product **35** was obtained in 72% (0.118 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, J=1.5 Hz, 1H), 8.44 (dd, J=4.7, 1.5 Hz, 1H), 7.55 (dt, J=7.9, 2.0 Hz, 1H), 7.24 (dd, J=7.9, 4.7 Hz, 1H), 3.35 (sext., J=7.1 Hz, 1H), 2.77 (dd, J=15.6, 4.4 Hz, 1H), 2.72 (dd, J=15.7, 7.1 Hz, 1H), 2.08 (s, 3H), 1.28 (d, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 148.4, 147.4, 141.6, 134.8, 123.6, 51.3, 32.8, 30.5, 21.7; MS (70 eV); *m/z* (%) 163 ($M^{+\cdot}$, 28); $C_{10}H_{13}NO$: calcd C 73.59, H 8.03; Found C 73.38, H 8.00.

3.2.36. 4-(3-Quinolyl)pentan-2-one (36) (Table 4, entry 41). From 3-bromoquinoline (0.208 g, 1 mmol), pent-3-en-2-ol (0.103 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (10 μmol), product **36** was obtained in 78% (0.167 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (d, J=2.3 Hz, 1H), 8.08 (d, J=8.4 Hz, 1H), 7.95 (d, J=2.3 Hz, 1H), 7.77 (d, J=7.8 Hz, 1H), 7.66 (t, J=7.0 Hz, 1H), 7.52 (t, J=7.0 Hz, 1H), 3.55 (sext., J=7.0 Hz, 1H), 2.89 (dd, J=17.0, 6.8 Hz, 1H), 2.80 (dd, J=17.0, 7.5 Hz, 1H), 2.10 (s, 3H), 1.38 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 150.6, 146.8, 138.7, 133.1, 129.0, 128.9, 128.1, 127.5, 126.8, 51.4, 32.8, 30.6, 21.7; MS (70 eV); *m/z* (%) 213 ($M^{+\cdot}$, 92); $C_{14}H_{15}NO$: calcd C 78.84, H 7.09; Found C 78.97, H 6.98.

3.2.37. 4-Phenyloctan-2-one (37) (Table 5, entry 1). From bromobenzene (0.157 g, 1 mmol), oct-3-en-2-ol (0.154 g, 1.2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (4 μmol), product **37** was obtained in 55% (0.112 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (m, 2H), 7.22–7.13 (m, 3H), 3.15–3.03 (m, 1H), 2.70 (d, J=7.2 Hz, 2H), 2.00 (s, 3H), 1.65–1.40 (m, 2H), 1.30–1.00 (m, 4H), 0.81 (t, J=7.0 Hz, 3H).

3.2.38. 4-(4-Methoxyphenyl)octan-2-one (38) (Table 5, entry 4). From 4-bromoanisole (0.187 g, 1 mmol), oct-3-en-2-ol (0.154 g, 1.2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (10 μmol), product **38** was obtained in 47% (0.110 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J=8.7 Hz, 2H), 6.82 (d, J=8.7 Hz, 2H), 3.77 (s, 3H), 3.10–2.98 (m, 1H), 2.66 (d, J=7.3 Hz, 2H), 1.99 (s, 3H), 1.65–1.40 (m, 2H), 1.30–1.00 (m, 4H), 0.81 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 158.0, 128.3, 127.0, 113.8, 55.2, 51.2, 40.6, 36.3, 30.7, 29.7, 22.6, 14.0; MS (70 eV); *m/z* (%) 234 ($M^{+\cdot}$, 60); $C_{15}H_{22}O_2$: calcd C 76.88, H 9.46; Found C 76.71, H 9.38.

3.2.39. 4-(4-Benzoylphenyl)octan-2-one (39) (Table 5, entry 9). From 4-bromobenzophenone (0.261 g, 1 mmol), oct-3-en-2-ol (0.154 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (10 μmol), product **39** was obtained in 75% (0.231 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79–7.70 (m, 4H), 7.55 (t, J=7.5 Hz, 1H), 7.46 (t, J=7.5 Hz, 2H), 7.28 (d, J=8.2 Hz, 2H), 3.26–3.15 (m, 1H), 2.75 (d, J=7.1 Hz, 2H), 2.04 (s, 3H), 1.70–1.45 (m, 2H), 1.40–1.05 (m, 4H), 0.81 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 196.4, 149.9, 137.7, 135.6, 132.2, 130.4, 129.9, 128.2, 127.4, 50.4, 41.0, 35.9, 30.6, 29.5, 22.5, 13.8; MS (70 eV); *m/z* (%) 308 ($M^{+\cdot}$, 92); $C_{21}H_{24}O_2$: calcd C 81.78, H 7.84; Found C 81.65, H 8.03.

3.2.40. 2-Phenylheptan-4-one (40) (Table 6, entry 3). From bromobenzene (0.157 g, 1 mmol), hept-2-en-4-ol (0.137 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (1 μmol), product **40** was obtained in 69% (0.132 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J=7.4 Hz, 2H), 7.40–7.10 (m, 3H), 3.31 (sext., J=7.0 Hz, 1H), 2.72 (dd, J=16.1, 6.5 Hz, 1H), 2.61 (dd, J=16.2, 7.9 Hz, 1H), 2.35–2.20 (m, 2H), 1.53 (sext., J=7.4 Hz, 2H), 1.25 (d, J=7.0 Hz, 3H), 0.84 (t, J=7.5 Hz, 3H).

3.2.41. 2-(4-Methoxyphenyl)heptan-4-one (41) (Table 6, entry 6). From 4-bromoanisole (0.187 g, 1 mmol), hept-2-en-4-ol (0.137 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (10 μmol), product **41** was obtained in 71% (0.156 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J=8.6 Hz, 2H), 6.82 (d, J=8.6 Hz, 2H), 3.76 (s, 3H), 3.42 (sext., J=7.0 Hz, 1H), 2.67 (dd, J=16.0, 6.7 Hz, 1H), 2.57 (dd, J=16.0, 7.7 Hz, 1H), 2.32–2.18 (m, 2H), 1.52 (sext., J=7.4 Hz, 2H), 1.22 (d, J=6.9 Hz, 3H), 0.83 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1, 157.9, 138.3, 127.6, 113.8, 55.1, 51.3, 45.3, 34.6, 22.1, 17.0, 13.6; $C_{14}H_{20}O_2$: calcd C 76.33, H 9.15; Found C 76.04, H 8.94.

3.2.42. 2-(4-Benzoylphenyl)heptan-4-one (42) (Table 6, entry 9). From 4-bromobenzophenone (0.261 g, 1 mmol), hept-2-en-4-ol (0.137 g, 1.2 mmol), $NaHCO_3$ (0.168 g, 2 mmol) and Pd complex (1 μmol), product **42** was obtained in 64% (0.189 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80–7.71 (m, 4H), 7.56 (t, J=7.4 Hz, 1H), 7.46 (d, J=7.4 Hz, 2H), 7.31 (d, J=8.2 Hz, 2H), 3.42 (sext., J=7.0 Hz, 1H), 2.76 (dd, J=16.5, 6.7 Hz, 1H), 2.66 (dd, J=16.5, 7.5 Hz, 1H), 2.38–2.23 (m, 2H), 1.55 (sext., J=7.4 Hz, 2H), 1.28 (d, J=7.0 Hz, 3H), 0.85 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.4, 196.4, 151.4, 137.8, 135.6, 132.2, 130.5, 129.9, 128.2, 126.8, 50.6, 45.4, 35.2, 21.8, 17.1, 13.6; MS (70 eV); *m/z* (%) 294 ($M^{+\cdot}$, 100); $C_{20}H_{22}O_2$: calcd C 81.60, H 7.53; Found C 81.73, H 7.38.

Registry no. Beilstein: **12**, 9393189; CAS: **20**, 65170-86-7; **21**, 104-20-1; **22**, 63416-61-5; **23**, 57918-94-2; **24**, 17013-10-9; **25**, 451-25-2; **27**, 18344-26-8; **29**, 56600-70-5; **31**, 65170-91-4; **32**, 189119-45-7; **33**, 652994-34-8; **34**, 182482-36-6; **37**, 35583-33-6; 40, 59540-81-7.

Acknowledgements

We thank CNRS for financial support.

References and notes

1. For reviews on the palladium-catalysed Heck reaction see: (a) Heck, R. F. In Trost, B. M., Fleming, I., Eds.; Vinyl Substitution with Organopalladium Intermediates in Comprehensive Organic Synthesis; Pergamon: Oxford, 1991; Vol. 4. (b) Reetz, R. Z. In *Transition Metal Catalysed Reactions*; Davies, S. G., Murahashi, S.-I., Eds.; Blackwell Science: Oxford, 1999. (c) Beletskaya, I.; Cheprakov, A. *Chem. Rev.* **2000**, *100*, 3009. (d) Withcombe, N.; Hii (Mimi), K. K.; Gibson, S. *Tetrahedron* **2001**, *57*, 7449. (e) Littke, A.; Fu, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (f) Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553.
2. Muzart, J. *Tetrahedron* **2005**, *61*, 4179.
3. Melpolder, J. B.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 265.
4. For examples of synthesis of aryl ketones by Heck reactions with 1,1-disubstituted alkenes and aryl iodides see: (a) Reymond, J.-L.; Chen, Y. *J. Org. Chem.* **1995**, *60*, 6970. (b) Evans, J.; O'Neill, L.; Kambhampati, V. L.; Rayner, G.; Turin, S.; Genge, A.; Dent, A. J.; Neisius, T. *J. Chem. Soc., Dalton Trans.* **2002**, 2207. (c) Hosokawa, T.; Kamiike, T.; Murahashi, S.-I.; Shimada, M.; Sugafuji, T. *Tetrahedron Lett.* **2002**, *43*, 9323.
5. For examples of synthesis of aryl ketones by Heck reactions with 2- or 3-substituted allylic alcohols and aryl iodides see: (a) Sho, T.-L. *Synth. Commun.* **1981**, *11*, 579.

(b) Solabannavar, S. B.; Wadgaonkar, P. P.; Desai, U. V.; Mane, R. B. *Org. Prep. Proced. Int.* **2003**, *35*, 418.
6. For examples of Heck reactions with Baylis–Hillman adducts and aryl iodides see: Kumareswaran, R.; Vankar, Y. D. *Synth. Commun.* **1998**, *28*, 2291.
7. Bouquillon, S.; Ganchegui, B.; Estrine, B.; Hénin, F.; Muzart, J. *J. Organomet. Chem.* **2001**, *634*, 153.
8. Larock, R. C.; Kuo, M.-Y. *Tetrahedron Lett.* **1991**, *32*, 569.
9. Sundar, N.; Bhat, S. V. *Synth. Commun.* **1998**, *28*, 2311.
10. Basavaiah, D.; Muthukumaran, K. *Tetrahedron* **1998**, *54*, 4943.
11. (a) Caló, V.; Nacci, A.; Monopoli, A.; Spinelli, M. *Eur. J. Org. Chem.* **2003**, 1382. (b) Caló, V.; Nacci, A.; Lopez, L.; Napola, A. *Tetrahedron Lett.* **2001**, *42*, 4701.
12. Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.
13. Masllorens, J.; Bouquillon, S.; Roglans, A.; Hénin, F.; Muzart, J. *J. Organomet. Chem.* **2005**, *690*, 3822.
14. Laurenti, D.; Feuerstein, M.; Pèpe, G.; Doucet, H.; Santelli, M. *J. Org. Chem.* **2001**, *66*, 1633.
15. Feuerstein, M.; Laurenti, D.; Bougeant, C.; Doucet, H.; Santelli, M. *Chem. Commun.* **2001**, 325.
16. Feuerstein, M.; Berthiol, F.; Doucet, H.; Santelli, M. *Org. Biomol. Chem.* **2003**, 2235.
17. (a) Feuerstein, M.; Doucet, H.; Santelli, M. *J. Org. Chem.* **2001**, *66*, 5923. (b) Feuerstein, M.; Doucet, H.; Santelli, M. *Synlett* **2001**, 1980. (c) Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2002**, *43*, 2191. (d) Berthiol, F.; Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2002**, *43*, 5625. (e) Berthiol, F.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2003**, *44*, 1221. (f) Berthiol, F.; Doucet, H.; Santelli, M. *Synlett* **2003**, 841. (g) Kondolff, I.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2003**, *44*, 8487. (h) Kondolff, I.; Doucet, H.; Santelli, M. *Synlett* **2004**, 1561. (i) Lemhadri, M.; Doucet, H.; Santelli, M. *Tetrahedron* **2004**, *50*, 11533. (j) Battace, A.; Zair, T.; Doucet, H.; Santelli, M. *J. Organomet. Chem.* **2005**, *690*, 3790. (k) Battace, A.; Zair, T.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2006**, *47*, 459.
18. Berthiol, F.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2005**, 1367.
19. Berthiol, F.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2004**, *45*, 5633.
20. Berthiol, F.; Doucet, H.; Santelli, M. *Synthesis* **2005**, 3589.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 4384–4392

First synthesis of a steroid containing an unstable 19-nor-androsta-1,5-dien-3-one system

Christine Cadot,[a] Donald Poirier[a,*] and Anie Philip[b,*]

[a]*Medicinal Chemistry Division, Oncology and Molecular Endocrinology Research Center, CHUQ-Pavillon CHUL and Université Laval, Québec Qc, Canada G1V 4G2*
[b]*Plastic Surgery Research, Department of Surgery, and Department of Obstetrics and Gynecology, McGill University, Montréal Qc, Canada H3G 1A4*

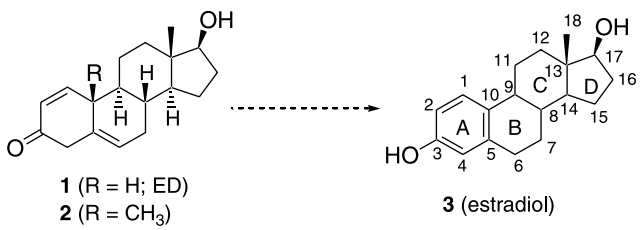
Received 6 January 2006; revised 17 February 2006; accepted 21 February 2006

Available online 22 March 2006

Abstract—Mechanisms involved in the maintenance of human pregnancy and initiation of labour are poorly defined. A novel steroid hormone named estradienolone (ED), and having an unusual 19-nor-androsta-1,5-dien-3-one system, was previously reported. However, ED is scarcely available from urine, placenta and blood of pregnant women. For this reason, we have synthesized ED in order to verify its proposed structure. Although a 1,5-dien-3-one system had already been described for a C19-steroid (androstane) nucleus (no possible aromatization), the synthesis of the 19-nor-analogue is a major challenge because this system is very sensitive to aromatization. We now describe the successful construction and characterization of this unstable system. Starting from nortestosterone, the synthesis of 17β-hydroxy-19-nor-androsta-1,5-dien-3-one (**1**) is based on a protection of the 5,6-double bond, the introduction of the second 1,2-double bond, the careful recovery of the *exo* double bond and a final regioselective oxidation or reduction.

1. Introduction

Mechanisms involved in the maintenance of human pregnancy and initiation of labour are poorly defined. Philip's group isolated a novel steroid hormone, namely estradienolone (ED), which may have the potential to maintain pregnancy.[1] Since the levels of ED in plasma, placenta and urine are high during pregnancy, but markedly decrease both in the placenta and blood at the moment of term or premature labour, this decrease may provide the signal to initiate parturition in humans. This new steroid was identified along with three other low-polarity ligands of sex hormone-binding globulin (SHBG) in pregnant women.[2,3] These included two weakly-bound and well-known steroids, 5α-pregnane-3,20-dione and progesterone, and two strongly-bound substances, 2-methoxyestrone and the new steroid named ED. The identification of the first three ligands was based on chromatographic elution patterns, binding characteristics and gas chromatography–mass spectrometry. The identification of the fourth peak, the new steroid, was based on similar kinds of evidence and, in addition, on ultraviolet absorption spectra and solubility characteristics. Furthermore, ED can transform into estradiol in alkali conditions, suggesting a dearomatized form of the potent estrogenic hormone estradiol. Thus, the proposed structure of ED is 17β-hydroxy-19-nor-androsta-1,5-dien-3-one (**1**), a C18-steroid (estrane) nucleus comprising an unusual and unstable 1,5-dien-3-one system (Scheme 1). Since it is scarcely available from urine, placenta and blood from pregnant women, the low quantity of natural ED thus isolated has not allowed confirming its chemical structure yet. Its chemical synthesis thus seemed an attractive approach for confirming, or invalidating, the proposed structure, as well as for providing a substantial quantity of the hormone for biological studies.



Scheme 1.

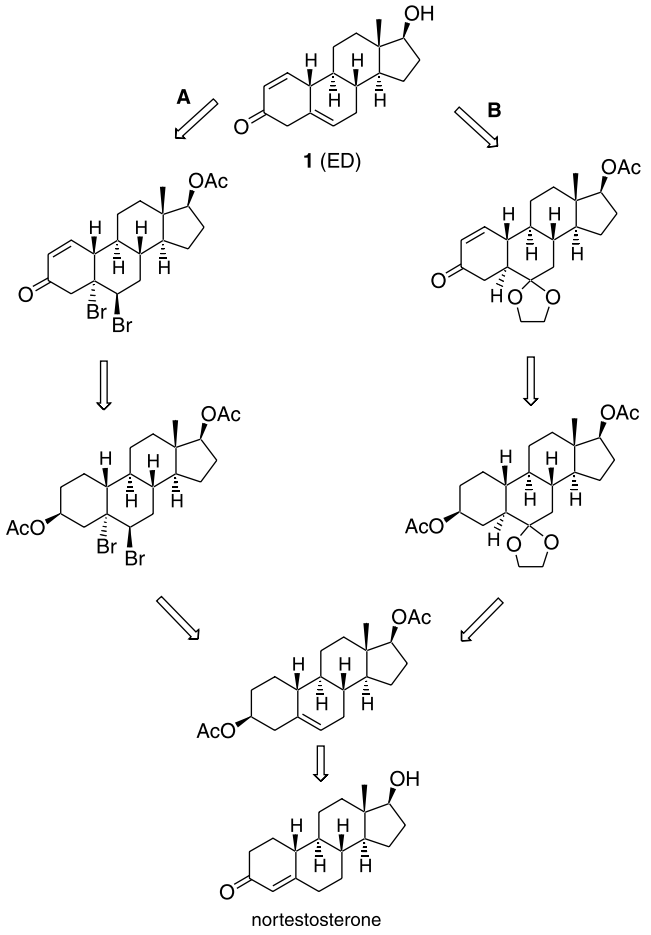
Keywords: Steroid; Total synthesis; Nortestosterone; 1,5-Dien-3-one system; Protecting group; NMR.
* Corresponding authors. Tel.: +1 418 654 2296; fax: +1 418 654 2761 (D.P.); tel.: +1 514 934 1934x44533; fax: +1 514 934 8289 (A.P.); e-mail addresses: donald.poirier@crchul.ulaval.ca; anie.philip@mcgill.ca

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.063

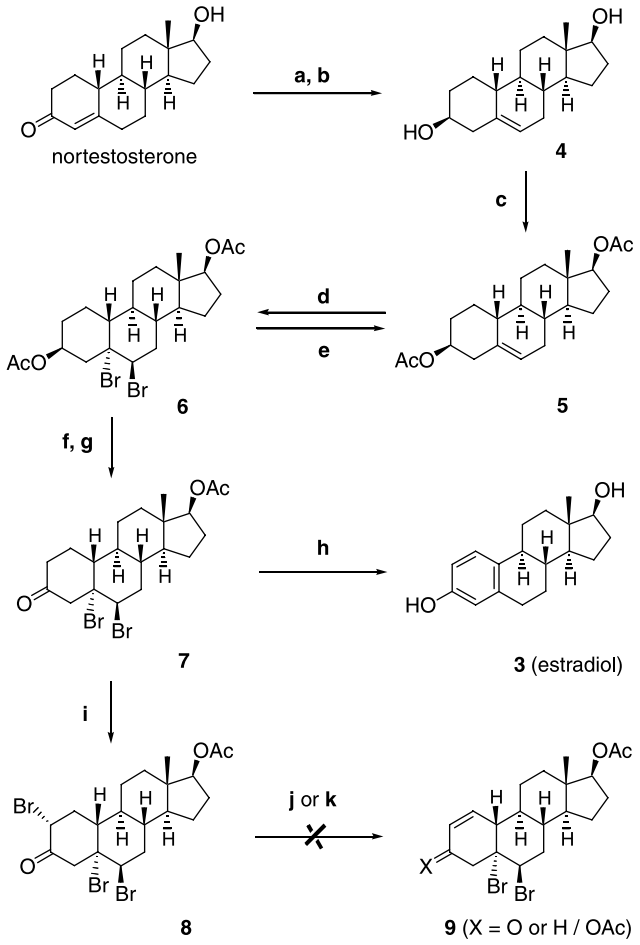
Although the elaboration of 1,5-dien-3-one systems is well documented for C19- and C21-steroids,[4–8] as exemplified by compound **2** in Scheme 1, this is not the case for the C18-steroid derivative **1** (ED), which is expected to be very sensitive to aromatization under an acid or base treatment, giving estradiol (**3**). Contrary to **1**, a steroid like **2** is stable because the aromatization of ring A is not possible with the presence of an angular methyl group at position 10. Considering the serious constraints associated with the instability of the 1,5-dien-3-one system in a C18-steroid (19-nor-androstane), the synthesis of **1** represents an interesting challenge. In this paper, we report the successful chemical synthesis of compound **1** from nortestosterone.

2. Results and discussion

Two retrosynthetic approaches (A and B) were tested for the synthesis of **1** (Scheme 2). These strategies have in common the double bond deconjugation of nortestosterone, but differ by the nature of the protecting group for the double bond, a 5,6-dibromo or a 6-ketal derivative. In the first approach (A), depicted more comprehensively in Scheme 3, the 4,5-double bond of nortestosterone was first deconjugated with KO-*t*-Bu to form the 5,6-double bond,[9] and the 3-ketone was reduced with $LiAlH_4$ to avoid reconjugation of the double bond.[10] The resulting diol **4**, obtained in 77% yield, was then acetylated in standard conditions to afford the diacetylated compound **5**. The 5,6-double bond of **5** was protected by bromination using Br_2 in acetic acid[11] to give the dibromo compound **6** in 57% yield; this product was found to be quite stable when left for a long time at rt in an inert and dark atmosphere. The double bond deprotection was tested and found satisfactory. In an attempt to recover the 5,6-double bond, it was not possible to use the standard NaI procedure described for the C19-steroids;[11] the C18-steroid **6** was successfully treated instead with $Na_2S{\cdot}H_2O$.[12–14] Thereafter, the 3-acetate group of **6** was hydrolyzed selectively with K_2CO_3 in MeOH and the resulting alcohol submitted to oxidative conditions (PCC/NaOAc, PDC or TPAP/NMO) to obtain ketone **7**. The latter was not very stable, however, being easily converted into estradiol (**3**). Only PCC gave **7** in 95% yield, but this compound cannot be purified by chromatography and is only stable in inert atmosphere and at low temperature in darkness. Using LDA in the presence of PhSeBr or PhSeCl[15] followed by a treatment with H_2O_2 did not allow introducing the 1,2-double bond because **7** was instead transformed into **3**. Alternatively, an additional



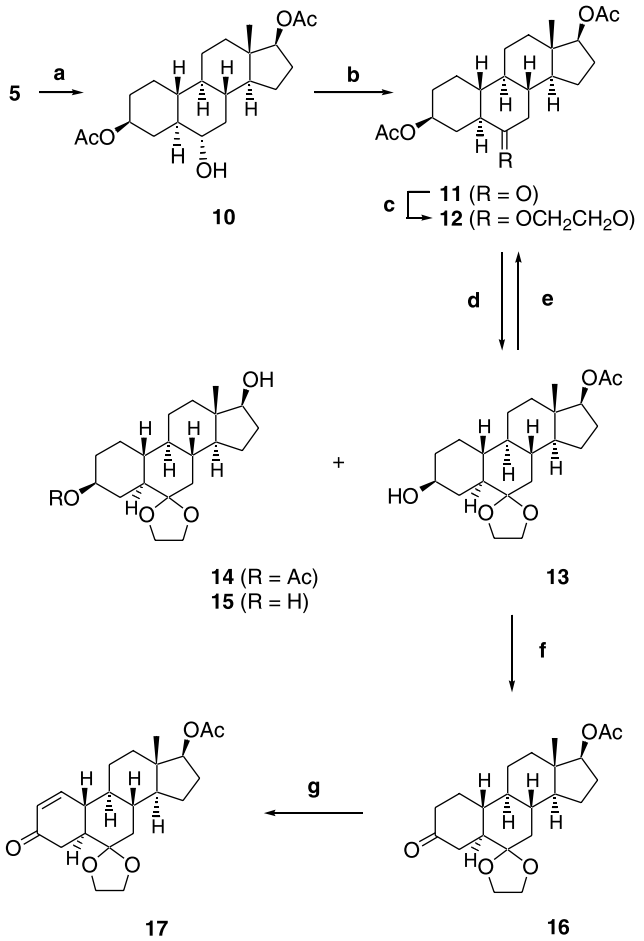
Scheme 2. Two retrosynthetic approaches for the synthesis of ED.



Scheme 3. Reagents and conditions. (a) KO-*t*-Bu, *t*-BuOH, THF, rt, 18 h; (b) $LiAlH_4$, THF, 0 °C, 2.5 h (77%, two steps); (c) Ac_2O, pyridine, DMAP, rt, 3 h (91%); (d) AcOH, Br_2, KOAc, Et_2O, 0 °C, 2 h and rt, 12 h (57%); (e) $Na_2S{\cdot}9H_2O$, DMF, rt, 3 h (99%); (f) K_2CO_3, MeOH, CH_2Cl_2, H_2O, 80 °C, 5 h (59%); (g) PCC, CH_2Cl_2, rt, 3 h (95%); (h) THF, LDA, 0 °C, 10 min; $CDCl_3$, rt, 12 h; or neat, rt, 12 h; (i) AcOH, Br_2, Et_2O, 0 °C, 2 h and rt, 12 h (91%); (j) $CaCO_3$, DMA, 170 °C, 10 min or $CaCO_3$, DMA, C_6H_6, 80 °C, 10 min; (k) (i) $NaBH_4$, MeOH, THF, 0 °C, 1.5 h; (ii) Ac_2O, pyridine, DMAP, rt, 12 h (77%, two steps); (iii) DBU, C_6H_6, rt, 12 h or 80 °C, 8 h.

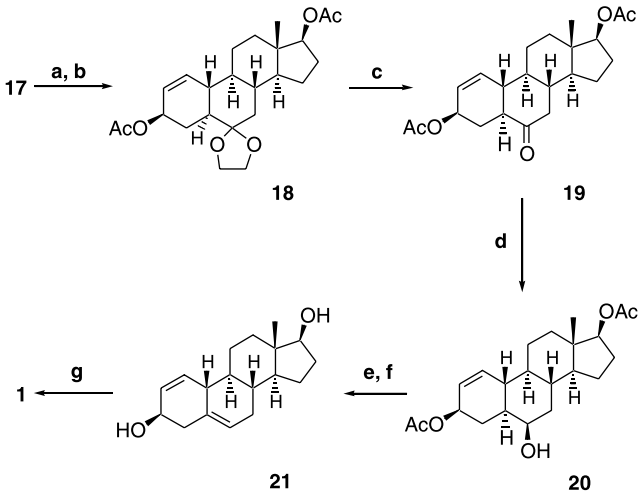
bromide was introduced at position 2 using Br_2 in acetic acid to give the tribromide derivative **8**. Unfortunately, the methods we tried for the dehydrobromination[16–18] failed to provide the enone system of compound **9**.

In the second approach (B), briefly outlined in Scheme 2 and reported in details in Schemes 4 and 5, the 5,6-double bond of **5** was hydroxylated at position 6 using $BH_3 \cdot THF$ and H_2O_2/NaOH at rt.[19] The alcohol **10** was obtained in 62% yield, but two more compounds, deacetylated in C-17 or in C-3, were also observed in 28% yield. Before introducing the 1,2-double bond, **10** was first oxidized into **11** with PCC and then protected as ketal **12** in 96% yield. The regio-deprotection by removal of the 3-acetate group with K_2CO_3 was less selective than previously observed for approach A. Thus, when **12** was treated with K_2CO_3 in MeOH/H_2O, only 15% yield of **13** was obtained after 3 h. A better yield of 51% was, however, obtained with aq $NaHCO_3$. Furthermore, the by-products of this reaction, alcohol **14** and diol **15**, can be recycled by an acetylation step allowing the recovery of **12**.



Scheme 4. Reagents and conditions. (a) (i) $BH_3 \cdot THF$, THF, rt, 2 h; (ii) H_2O_2, NaOH, 0 °C, 0.5 h and rt, 1 h (62%); (b) PCC, CH_2Cl_2, rt, 3 h (97%); (c) ethylene glycol, $HC(OEt)_3$, *p*-TsOH, CH_2Cl_2, rt, 3.5 h (99%); (d) $NaHCO_3$, MeOH, H_2O, 67 °C, 72 h (51%); (e) Ac_2O, pyridine, DMAP, rt, 3 h (99%); (f) PCC, CH_2Cl_2, rt, 3 h (96%); (g) (i) PhSeCl, AcOEt, rt, 3 h; (ii) pyridine, H_2O_2, rt, 15 min then 80 °C, 15 min (70%).

The construction of the 1-en-3-one system was finally achieved by oxidation of the 3-hydroxy group of **13** to its



Scheme 5. Reagents and conditions. (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, EtOH, MeOH, −78 °C, 1.5 h; (b) Ac_2O, pyridine, DMAP, rt, 3 h (99%, two steps); (c) 1% HCl in acetone, rt, 0.5 h (64%); (d) K-Selectride, THF, −78 °C, 5.5 h (72%); (e) $POCl_3$, pyridine, rt, 1 h; (f) K_2CO_3, MeOH, H_2O, 100 °C, 1 h (63%, two steps); (g) $BaMnO_4/Al_2O_3$ (neutral), $CuSO_4 \cdot 5H_2O$, CH_2Cl_2, rt, 4 h (13%).

corresponding ketone **16**, followed by the double bond introduction giving **17**. Previously, we successfully applied classical methods for the introduction of a double bond, such as LiBr/Li_2CO_3,[20] *N*-bromosuccinimide/DBU,[16] TMSCl/$Pd(OAc)_2$,[21,22] PhSeBr,[15] or $PySO_2CH_3$,[23] to a model compound (19-nor-dihydrotestosterone-17β-*O*-TBDMS), allowing the formation of 1,2-conjugated 3-ketone in 41–61% yields. Unfortunately, these methods were not compatible with the functional group of **16**. The double bond was, however, introduced using Reich's methodology,[15] modified so as not to require LDA.[24] Thus, a sequential treatment of PhSeCl in anhydrous EtOAc and H_2O_2/pyridine at rt and then at reflux yielded the conjugated ketone **17** in 70% yield from **16**.

After successfully elaborating the 1-en-3-one system, the next step was to regenerate the 5,6-double bond carefully in order to avoid the aromatization of ring A. In order to do this, the C-3 carbonyl of **17** was first reduced with $NaBH_4/CeCl_3 \cdot 7H_2O$ and the resulting allylic alcohol protected as diacetate **18** in excellent yield (Scheme 5). The ketal group was next hydrolyzed at rt in acetone and *p*-TsOH (1.4 equiv),[25] but ketone **19** was found to be quite unstable under these conditions, with only 19% isolated. However, carrying out the same reaction using 1% HCl in acetone instead resulted in a mixture of 5α-H and 5β-H isomers in a ratio of 67:33 and a much better yield of 64% for **19** after chromatography. The conditions for the transformation of **19** into **20** were first studied with **11** as a model compound. Indeed, it is known that a 5α-H and a 6β-OH in trans diaxial configuration can be eliminated with $POCl_3$ in pyridine in order to regenerate the 5,6-double bond.[26] When **11** was reduced with $NaBH_4$ in MeOH at 0 °C, the 6α-OH derivative **10** and 6β-OH analogue were obtained in a ratio of 45:55, according to ^1H NMR analysis (3.30 ppm for 6β-CH of 6α-OH derivative **10** and 3.80 ppm for 6α-CH of 6β-OH analogue). When this reduction was performed using $NaBH_4/CeCl_3 \cdot 7H_2O$ in MeOH at −78 °C only the 6α-alcohol **10** was obtained.[27] However, we could

not proceed to the inversion of 6α-OH into 6β-OH because the well known modified Mitsunobu methodology (PPh_3, DEAD and PNBA followed by an ester hydrolysis)[28,29] is not compatible with acetate groups, and accordingly we changed the reductive reagent. Thus, the 6β-OH epimer of **10** was the single isomer isolated using K-Selectride in THF at −78 °C. Finally, the preparation of **21** was completed by (1) a stereoselective reduction of **19** into **20** using the K-Selectride methodology discussed above; (2) a dehydration of the 6β-OH group with $POCl_3$ in pyridine; and (3) a deprotection by removal of diacetate groups with K_2CO_3.

Before the last step in the synthesis of **1**—a compound expected to be very sensitive to usual acid and base conditions—the precursor compound **21** was fully analyzed by NMR spectroscopy. We were especially interested in confirming the 10β-H stereochemistry, because this stereocenter will not be modified in the last step of compound **1** synthesis. Using a combination of NMR experiments (COSY, HSQC, HMBC, and NOESY),[30] all proton and carbon signals were fully identified (see Section 4 and Supporting information). Using the signal at 2.46 ppm (10-CH), the NOESY spectra allowed identifying four interactions of different intensity with 11β-CH (strong), 4β-CH (medium), 8β-CH (weak) and 1-CH (weak) (Fig. 1). Furthermore, no NOE was observed between the hydrogen atoms at positions 10 and 9α. Taken together, these data clearly established the 10β-H stereochemistry in compound **21**.

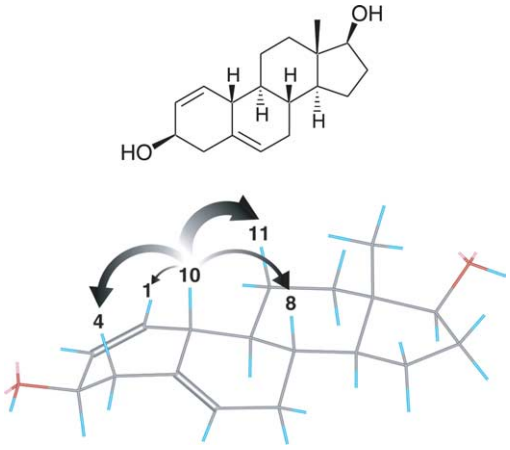
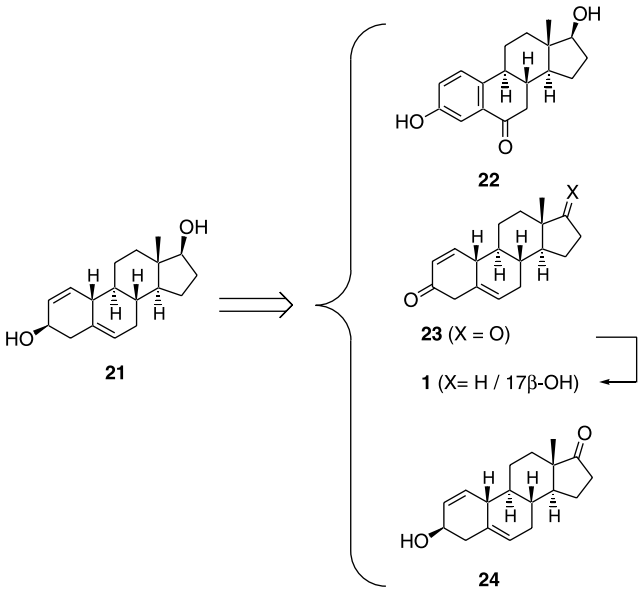


Figure 1. 2D and 3D representations of **21**. The important NOE results are represented by four arrows. The 3D structure was generated with CSChem 3D std 5.0 (Cambridge Soft Corporation, Cambridge, MA). The stereocenters at C-8, 9, 13, 14, and 17 were already fixed in the starting natural steroid and were not affected by the following sequence of reactions.

The last crucial step in the synthesis of **1** was the regioselective oxidation of the allylic 3-OH versus the 17-OH of diol **21** in neutral and mild conditions avoiding the aromatization of the 1,5-dien-3-one system. Four methods, MnO_2,[16,31–33] Dess–Martin,[34] IBX–polystyrene,[35] and $BaMnO_4$ on alumina,[36,37] were selected to be tested for this transformation (Scheme 6 and Table 1). With MnO_2 in acetone, the transformation of **21** switched toward the aromatized compound **22** (entry 1 of Table 1). The weak basicity (pH 8) and oxidative property of MnO_2 explain the



Scheme 6. The reagents and conditions are reported in Table 1 except for the reduction of **23** into **1** ($NaBH_4$, MeOH, CH_2Cl_2, −35 °C, 13 min).

A-ring aromatization and B-ring oxidation. No reaction was observed when benzene and CH_2Cl_2 were used as aprotic solvents. Diol **21** was next treated with Dess–Martin periodinane (2 equiv), which resulted in the isolation of diketone **23** in 72% yield after 30 min (entry 2). In an attempt to capitalise on the less reactive character of the hindered 17β-OH versus the more reactive allylic 3β-OH, diol **21** was reacted with only 1 equiv of Dess–Martin reagent. A mixture of compounds **21**, **23**, **24**, and **1** was, however, obtained (entry 3), clearly showing the non regioselectivity of this methodology. Furthermore, it was not possible to separate the compounds by chromatography. IBX–polystyrene, a polymer-supported version of iodoxybenzoic acid reported to be selective for allylic alcohol, was also tested for the oxidation of **21**. Considering the low stability expected for compound **1**, we found worthy using this polymer-supported reagent for its mild reactivity, its more hindered nature, and the simple workup (only filtration is needed). Although this reagent is less reactive than hypervalent iodine analogue reagent (Dess–Martin periodinane), a selective oxidation was nonetheless not possible (entries 4–8).

The last reagent tested was a solid mixture of $BaMnO_4$ on basic or neutral alumina and $CuSO_4 \cdot 5H_2O$. We previously obtained promising results with a model diol containing two secondary alcohols. In fact, a mixture of starting material, 3β,17β-dihydroxy-4-androstene, and of the desired compound, 17β-hydroxy-4-androsten-3-one, was obtained in a ratio of 1:2 following the conditions described in the literature (basic alumina, benzene). The same ratio was obtained with CH_2Cl_2, as well as when replacing basic alumina by neutral alumina, a kind of alumina much more compatible with the low stability of **1**. These results prompted us to employ this selective oxidizing agent with diol **21**. In the last two assays (entries 9 and 10), ratios of 60:40 and 63:37 were determined for **21** and **1** by ^1H NMR.

Table 1. Yields (%) under different conditions tested for the regioselective oxidation of **21** into **1**

Entry	Reagents and conditions	**21**	**22**	**23**	**24**	**1**
1	MnO_2 (15 equiv), acetone, rt, 12 h	32[a]	37	0	0	0
2	Dess–Martin (2 equiv), CH_2Cl_2, rt, 30 min	0	0	72	0	0
3	Dess–Martin (1 equiv), CH_2Cl_2, rt, 1 h	*22*[b]	*0*	*23*	*23*	*32*
4	IBX–polystyrene (4 equiv), CH_2Cl_2, rt, 15 min	*65*	*0*	*8*	*13*	*14*
5	IBX–polystyrene (4 equiv), CH_2Cl_2 rt, 30 min	*43*	*0*	*18*	*20*	*19*
6	IBX–polystyrene (2 equiv), CH_2Cl_2, rt, 10 min	*65*	*0*	*13*	*6*	*16*
7	IBX–polystyrene (2 equiv), CH_2Cl_2, rt, 20 min	*62*	*0*	*19*	*3*	*16*
0	IBX–polystyrene (2 equiv), CH_2Cl_2, rt, 45 min	*19*	*0*	*38*	*20*	*23*
9	$BaMnO_4/Al_2O_3$ (neutral), $CuSO_4 \cdot 5H_2O$, CH_2Cl_2, rt, 6 h	*60*	*0*	*0*	*0*	*40*
10	$BaMnO_4/Al_2O_3$ (neutral), $CuSO_4 \cdot 5H_2O$, CH_2Cl_2, rt, 4 h	63 *(63)*	0	0	0	13 *(37)*

[a] Isolated yield (%) after purification by silica gel chromatography (normal characters).
[b] Percentage of compounds as determined by ^1H NMR analysis (italic characters).

In the last assay, ketone **1** was isolated in 13% yield after careful reverse-phase chromatographic steps, which also permitted recovery of the starting diol **21** in 63% yield. This regioselective oxidation remains to be optimized, especially regarding the workup and purification procedures.

As an alternative strategy to obtain **1** more easily, we attempted the regioselective reduction of **23** into **1** (Scheme 6). Indeed, a ketone can be reduced in the presence of a conjugated enone using the conditions reported by Ward et al. ($NaBH_4$ in $MeOH/CH_2Cl_2$ (50/50) at −78 °C).[38] In our case, the ketone at C17 was reduced before the conjugated ketone at C3. No reaction was observed at −78 °C, but the reduction proceeds with a good regioselectivity between −40 and −35 °C. Although the reaction temperature and time appear to be critical for selectivity, an interesting ratio of 41:54:5, for **1**:**23**:**21** was obtained at −35 °C. Compound **1** was thus isolated in a better yield (40%) and much more easily by the regioselective reduction than by the regioselective oxidation.

Compounds **23** and **1** were analysed by ^1H and ^{13}C NMR to confirm the formation of the 1,5-estradien-3-one system. We had previously assessed the stability of **23** at rt during a period of 1 month when dissolved in various deuterated solvents (Fig. 2).

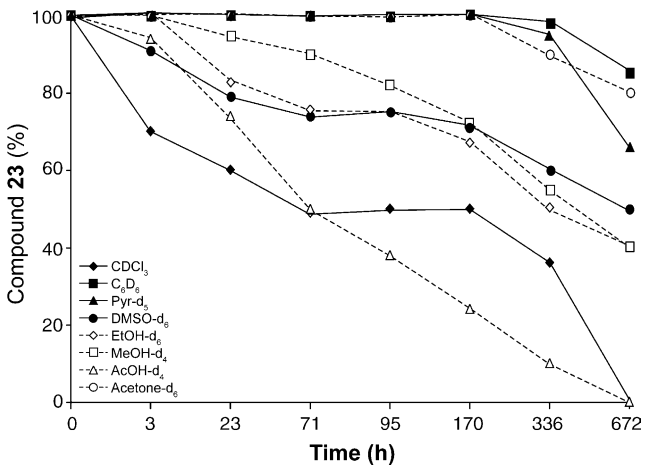
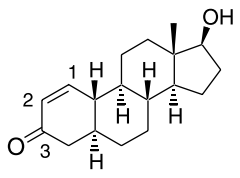


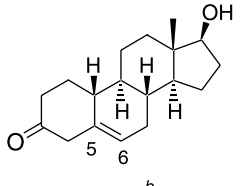
Figure 2. Stability of **23** (1 mg) at rt when dissolved in deuterated solvents as determined by NMR analysis.

In chloroform, **23** underwent only aromatization of the steroidal A-ring giving estrone (100%) after 4 weeks, while it was fully degraded in acetic acid. The formation of aromatized and degraded compounds gradually occurred in methanol, ethanol, or dimethylsulfoxide, but ~70 and 40% of **23** still remained after 1 and 4 weeks. However, the 1,5-dien-3-one system was fully stable in benzene, pyridine, or acetone until 14 days and few degradation (15–34%) was observed at the end of the experiment. We then selected C_6D_6 for our NMR analysis, and data for ketone **1**, diketone **23**, and model compounds **25** and **26** are reported in Table 2. Clearly the CH-1 and CH-2 signals of **1** and **23** are close to the corresponding signals observed for model compound **25**. The same conclusion was also obtained for the C-5 and CH-6 signals of **1** and **23** when compared to the *exo* 5,6-double bond of **26**. Taken together these data clearly confirmed the 1,5-dien-3-one system of **23** and **1**.

Table 2. Characteristic NMR signals (ppm) in C_6D_6 observed for compounds **25**, **26**, **23**, and **1**



25[a]



26[b]

Carbon number	**25**[a] H, C	**26**[b] H, C	**23** H, C	**1** H, C
1	6.48, 150.6	—	6.24, 149.4	6.33, 149.8
2	6.02, 129.7	—	5.99, 128.9	6.00, 128.7
3	—, 198.0	—, 206.8	—, 196.4	—, 196.7
5	—	—, 135.7	—, 132.4	—, 132.2
6	—	5.20, 122.2	5.16, 122.8	5.18, 123.2

[a] Compound **25** was obtained by treatment of 19-nor-dihydrotestosterone-17β-*O*-TBDMS with $Pd(OAc)_2$ followed by a TBDMS hydrolysis.
[b] Compound **26** was obtained as an intermediate during the synthesis of **4**.

3. Conclusion

The successful synthesis of **23** and **1**, two dearomatized forms of potent estrogenic hormones estrone and estradiol, respectively, was described starting from nortestosterone. To the best of our knowledge, the synthesis of a steroidal 1,5-dien-3-one system without a methyl 19 group at position 10 had never been reported before. This unusual chemical

arrangement explains the low stability of **23** and **1** that complicated the chemical synthesis. In fact a careful planning of the sequence of reactions was necessary to overcome the synthetic difficulty associated with the high reactivity of a 19-nor-androsta-1,5-dien-3-one system toward acids and bases. As reported for natural ED,[3] **1** was treated with 3 N NaOH in acetone at rt giving as expected the aromatized compound **3** (estradiol) in 70% yield. However, **1** may not be identical to natural ED since a biological assay has shown its potency to be lower (20% of that of natural ED). LC/MS analysis and Sephadex chromatography also confirmed the non-identity of **1** and natural ED. They nonetheless have in common certain unstable properties and it is possible that both compounds contain the same unusual 1,5-dien-3-one system. Preliminary studies also determined the range of stability of this 19-nor-androsta-1,5-dien-3-one system under different solvents.

4. Experimental

4.1. General remarks

Anhydrous reactions were performed in oven-dried glassware under positive argon pressure using commercially available anhydrous solvents, except THF, which was distilled from sodium/benzophenone ketyl under argon. Flash chromatography was performed on Silicycle 60 230–400-mesh silica gel. Thin-layer chromatography (TLC) was performed on 0.25-mm silica gel 60 F_{254} plates and compounds were visualized by exposure to UV light (254 nm), a solution of ammonium molybdate/sulphuric acid/water and/or a solution of *para*-anisaldehyde/sulphuric acid/acetic acid/ethanol (plus heating). Infrared (IR) spectra were obtained from a thin film of the solubilized compound on NaCl pellets (usually in CH_2Cl_2) or in a KBr pellets containing the solid compound. Only significant bands are reported (in cm^{-1}). ^1H and ^{13}C spectra were recorded, respectively, at 300 and 75.5 MHz or at 400 (^1H) and 100 (^{13}C) MHz. The chemical shifts (δ) are expressed in ppm and referenced to chloroform (7.26 and 77.0 ppm), methanol (3.31 and 49.0 ppm) or benzene (7.16 and 128.0 ppm) for ^1H and ^{13}C, respectively. All new compounds were determined to be >95% pure by ^1H NMR spectroscopy. Melting points were recorded on an Electrothermal IA9300 SERIES Digital Melting Point Apparatus and are uncorrected. High-resolution mass spectra (HRMS) were obtained with a dual spray ESI source on positive mode.

4.2. Synthesis of compounds 1 and 23

4.2.1. Synthesis of 3β,17β-dihydroxy-19-nor-androst-5-ene (4).[39] A mixture of nortestosterone (15.00 g, 54.74 mmol) and KO-*t*-Bu (13.82 g, 136.85 mmol) in *t*-BuOH (260 mL) and THF (150 mL) was stirred under nitrogen for 18 h at rt and then quenched by the rapid addition of 10% aq AcOH (930 mL) to the resulting slurry. Saturated aq $NaHCO_3$ was added and the product was isolated by an extraction with diethyl ether. The combined organic layer was washed with excess aq $NaHCO_3$, dried over $MgSO_4$, and evaporated. The crude unconjugated ketone was added to a stirred solution of $LiAlH_4$ (2.29 g, 60.21 mmol) in dry THF (675 mL) at 0 °C. After being stirred at 0 °C for 2.5 h, the reaction mixture was quenched with saturated aq NH_4Cl (100 mL) and extracted with EtOAc. The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The crude residue was purified by chromatography (hexanes/EtOAc, 80:20) to afford diol **4** (11.68 g, 77% yield) as a white solid. IR (film) ν 3362 (OH); ^1H NMR (300 MHz, MeOH-d_4) δ 0.76 (s, 18-CH_3), 0.80–2.05 (m, 19H, CH and CH_2 of steroid skeleton), 2.40 (m, 1H), 3.40 (m, 3α-CH), 3.58 (t, J=8.5 Hz, 17α-CH), 5.44 (dd, J_2=5.7 Hz, J_1=1.5 Hz, 6-CH); ^{13}C NMR (75 MHz, MeOH-d_4) δ 11.5 (C18), 24.1, 28.0, 30.6, 31.4, 31.6, 36.1, 37.8, 38.0, 44.1, 44.2, 45.7, 47.2, 51.7, 71.8 (C3), 82.5 (C17), 122.1 (C6), 138.8 (C5); HRMS calcd for $C_{18}H_{29}O_2$ $[M+H]^+$ 277.21621, found 277.21689.

4.2.2. Synthesis of 3β,17β-diacetoxy-19-nor-androst-5-ene (5).[39] To a stirred solution of **4** (11.68 g, 42.32 mmol) in CH_2Cl_2 (640 mL) were added pyridine (7.50 mL), Ac_2O (6.83 mL) and a catalytic amount of DMAP. The reaction mixture was stirred under nitrogen for 3 h at rt, poured into ice cold aq 1 M HCl (230 mL), and extracted with EtOAc. The combined organic layer was washed with saturated aq $NaHCO_3$, dried over $MgSO_4$, and evaporated. The crude product was purified by chromatography (hexanes/EtOAc, 90:10) to afford **5** (13.86 g, 91% yield) as a white solid. IR (film) ν 1732 (C=O, esters); ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 18-CH_3), 0.80–2.10 (m, 19H, CH and CH_2 of steroid skeleton), 2.02 (s, 2×$OCOCH_3$), 2.50 (m, 1H), 4.59 (m, 3α-CH and 17α-CH), 5.46 (dd, J_2=5.7 Hz, J_1=1.5 Hz, 6-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9 (C18), 21.1 (OCO*CH*$_3$), 21.4 (OCO*CH*$_3$), 23.3, 26.5, 27.4, 30.0, 30.2, 31.5, 36.1, 36.5, 40.7, 42.6, 42.7, 45.2, 49.9, 73.2 (C3), 82.7 (C17), 122.2 (C6), 136.1 (C5), 170.5 (O*CO*CH$_3$), 171.2 (O*CO*CH$_3$); HRMS calcd for $C_{22}H_{33}O_4$ $[M+H]^+$ 361.23734, found 361.23767.

4.2.3. Synthesis of 3β,17β-diacetoxy-6α-hydroxy-19-nor-5α-androstane (10). To a solution of **5** (16.32 g, 45.33 mmol) in dry THF (620 mL) was added 1 M BH_3 in THF (91 mL) dropwise at 0 °C, and the mixture was stirred for 2 h at rt. Then 3 N NaOH (40 mL) and H_2O_2 (33% w/v, 15 mL) were added at 0 °C, and the mixture was stirred 0.5 h at 0 °C and 1 h at rt. The mixture was poured into H_2O (500 mL). The aq phase was extracted with CH_2Cl_2, and the organic phase was washed with brine, dried over $MgSO_4$, and evaporated. Purification by flash chromatography (hexanes/EtOAc, 70:30) afforded **10** (10.62 g, 62%) as a white solid. Mp 199–200 °C (Et_2O/MeOH); IR (film) ν 3528 (OH), 1736 and 1709 (C=O, esters); ^1H NMR (400 MHz, $CDCl_3$) δ 0.61 (m, 1H), 0.75 (s, 18-CH_3), 0.78–2.20 (m, 19H, CH and CH_2 of steroid skeleton), 1.98 (s, $OCOCH_3$), 2.00 (s, $OCOCH_3$), 2.40 (m, 1H), 3.24 (m, 6β-CH), 4.55 (t, J=8.4 Hz, 17α-CH), 4.66 (m, 3α-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0 (C18), 21.2 (OCO*CH*$_3$), 21.4 (OCO*CH*$_3$), 23.3, 25.2, 27.4, 28.0, 31.5, 34.5, 36.6, 38.6, 39.7, 42.7, 43.9, 47.2, 48.2, 49.5, 72.7 (C3 or C6), 73.7 (C6 or C3), 82.7 (C17), 170.6 (O*CO*CH$_3$), 171.2 (O*CO*CH$_3$); HRMS calcd for $C_{22}H_{34}O_5Na$ $[M+Na]^+$ 401.22985, found 401.22938.

4.2.4. Synthesis of 3β,17β-diacetoxy-6-oxo-19-nor-5α-androstane (11). A solution of **10** (18.40 g, 48.67 mmol) and PCC (26.16 g, 121.69 mmol) in dry CH_2Cl_2 (270 mL)

was stirred for 3 h at rt. Celite was then poured into the mixture and the resulting suspension was filtered through a cake of Celite and silica gel. The filter cake was washed with hexanes/EtOAc, 50:50 (1.5 L), and the filtrate was concentrated under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 70:30) to afford **11** (17.70 g, 97% yield) as a white solid. Mp 187–188 °C (Et_2O/MeOH); IR (film) ν 1736 and 1708 (C=O, esters and ketone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (s, 18-CH_3), 1.10–2.38 (m, 21H, CH and CH_2 of steroid skeleton), 2.03 (s, $OCOCH_3$), 2.05 (s, $OCOCH_3$), 4.65 (t, J=8.4 Hz, 17α-CH), 4.70 (m, 3α-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9 (C18), 21.1 ($OCOCH_3$), 21.3 ($OCOCH_3$), 23.1, 25.2, 27.3, 29.0, 30.8, 31.0, 36.3, 42.2, 43.0, 45.8, 47.2, 47.4, 50.3, 52.3, 72.3 (C3), 82.3 (C17), 170.6 ($OCOCH_3$), 171.2 ($OCOCH_3$), 209.7 (C6); HRMS calcd for $C_{22}H_{33}O_5$ $[M+H]^+$377.23225, found 377.23253.

4.2.5. Synthesis of 3β,17β-diacetoxy-6,6-ethylenedioxy-19-nor-5α-androstane (12). A mixture of **11** (17.70 g, 47.07 mmol), triethyl orthoformate (28.5 mL), ethylene glycol (26 mL), and a catalytic amount of *p*-TSA in CH_2Cl_2 (1 L) was stirred for 3.5 h at rt. The reaction was quenched by addition of H_2O, then the organic phase was washed with H_2O, dried over $MgSO_4$, and evaporated to afford **12** (19.60 g, 99%) as a white solid. Mp 135–136 °C (Et_2O/pentane); IR (film) ν 1732 (C=O, esters); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.64 (m, 1H), 0.79 (s, 18-CH_3), 0.90–2.20 (m, 20H, CH and CH_2 of steroid skeleton), 2.01 (s, $OCOCH_3$), 2.02 (s, $OCOCH_3$), 3.93 (m, OCH_2CH_2O), 4.58 (t, J=8.4 Hz, 17α-CH), 4.68 (m, 3α-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0 (C18), 21.1 ($OCOCH_3$), 21.4 ($OCOCH_3$), 23.2, 25.1, 27.4, 28.5, 29.8, 31.3, 36.7, 37.5, 39.6, 42.6, 42.8, 47.4, 47.7, 49.5, 64.9 (OCH_2), 65.3 (OCH_2), 73.1 (C3), 82.7 (C17), 109.2 (C6), 170.5 ($OCOCH_3$), 171.2 ($OCOCH_3$); HRMS calcd for $C_{24}H_{37}O_6$ $[M+H]^+$421.25847, found 421.25801.

4.2.6. Synthesis of 17β-acetoxy-6,6-ethylenedioxy-3β-hydroxy-19-nor-5α-androstane (13). Compound **12** (9.80 g, 23.44 mmol) was dissolved in MeOH (290 mL) and a solution of $NaHCO_3$ (1.97 g, 23.44 mmol) in H_2O (96 mL) was added. The resulting mixture was warmed at 67 °C for 72 h. Then, the mixture was extracted with CH_2Cl_2 and the combined organic layer was dried over $MgSO_4$ and evaporated. The crude residue was purified by chromatography (hexanes/EtOAc, 70:30 to 50:50) to afford **13** (4.49 g, 51% yield) as a white amorphous solid. In addition to **13**, purification yielded **12** (1.86 g, 19% yield), **14** (0.74 g, 8% yield) and **15** (1.94 g, 25% yield), all as white solids. Data are reported only for **13**. IR (film) ν 3434 (OH), 1736 (C=O, ester); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.65 (m, 1H), 0.81 (s, 18-CH_3), 0.80–2.20 (m, 20H, CH and CH_2 of steroid skeleton), 2.04 (s, $OCOCH_3$), 3.60 (m, 3α-CH), 3.95 (m, OCH_2CH_2O), 4.60 (t, J=8.4 Hz, 17α-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1 (C18), 21.2 ($OCOCH_3$), 23.2, 25.2, 27.4, 28.8, 33.7, 35.2, 36.7, 37.5, 39.8, 42.6, 42.8, 47.6, 47.9, 49.6, 65.0 (OCH_2), 65.4 (OCH_2), 70.6 (C3), 82.7 (C17), 109.5 (C6), 171.2 ($OCOCH_3$); HRMS calcd for $C_{22}H_{35}O_5$ $[M+H]^+$379.24790, found 379.24827.

4.2.7. Synthesis of 17β-acetoxy-6,6-ethylenedioxy-3-oxo-19-nor-5α-androstane (16). A solution of **13** (8.16 g, 21.70 mmol) and PCC (11.66 g, 54.25 mmol) in dry CH_2Cl_2 (140 mL) was stirred for 3 h at rt. Then Celite was poured into the mixture and the resulting suspension was filtered through a cake of Celite and silica gel. The filter cake was washed with hexanes/EtOAc, 50:50 (0.5 L), and the filtrate was concentrated under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 70:30) to afford **16** (7.80 g, 96% yield) as a white solid. Mp 136–138 °C (Et_2O); IR (film) ν 1736 (C=O, ester), 1720 (C=O, ketone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (m, 1H), 0.83 (s, 18-CH_3), 1.05–1.90 (m, 14H, CH and CH_2 of steroid skeleton), 2.04 (s, $OCOCH_3$), 2.10–2.50 (m, 6H, CH and CH_2 of steroid skeleton), 3.85 (m, 1H of OCH_2CH_2O), 3.95 (m, 3H of OCH_2CH_2O), 4.60 (t, J=8.4 Hz, 17α-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1 (C18), 21.1 ($OCOCH_3$), 23.2, 25.3, 27.4, 30.3, 36.6, 37.4, 39.3, 39.6, 40.8, 42.3, 42.8, 47.2, 49.4, 49.6, 64.9 (OCH_2), 65.4 (OCH_2), 82.6 (C17), 108.9 (C6), 171.1 ($OCOCH_3$), 212.2 (C3); HRMS calcd for $C_{22}H_{33}O_5$ $[M+H]^+$377.23225, found 377.23210.

4.2.8. Synthesis of 17β-acetoxy-6,6-ethylenedioxy-3-oxo-19-nor-5α-androst-1-ene (17). Phenylselenyl chloride (2.49 g, 13.10 mmol) was added to **16** (7.80 g, 10.42 mmol) in dry EtOAc (110 mL) and the resulting reaction mixture was stirred for 3 h at rt. Pyridine (3.14 mL) was then added to the reaction mixture cooled at 0 °C, followed by the addition of H_2O_2 (33% w/v, 2.66 mL) over a period of 6 min. The reaction mixture was stirred at rt for 15 min, then refluxed for 15 min, cooled, and diluted with EtOAc (110 mL). The organic layer was washed with brine (25 mL) and saturated aq $NaHCO_3$ (25 mL), dried over $MgSO_4$, and evaporated. The crude residue was purified by chromatography (hexanes/EtOAc, 75:25) to afford **17** (5.40 g, 70% yield) as a white solid. Mp 137–139 °C (Et_2O); IR (film) ν 1709 (C=O, ester), 1664 (C=O, conjugated ketone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (s, 18-CH_3), 0.80–2.35 (m, 16H, CH and CH_2 of steroid skeleton), 2.04 (s, $OCOCH_3$), 2.60 (dd, J_2=16.4 Hz, J_1=2.6 Hz, 4-CH), 3.95 (m, OCH_2CH_2O), 4.63 (t, J=8.0 Hz, 17α-CH), 5.99 (dd, J_2=10.2 Hz, J_1=2.2 Hz, 2-CH), 7.07 (dd, J_2=10.2 Hz, J_1=1.6 Hz, 1-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2 (C18), 21.1 ($OCOCH_3$), 23.1, 24.9, 27.4, 36.5, 36.8, 38.0, 39.1, 42.9, 43.2, 45.1, 47.8, 49.4, 65.2 (OCH_2), 65.4 (OCH_2), 82.4 (C17), 108.2 (C6), 129.3 (C2), 151.2 (C1), 171.2 ($OCOCH_3$), 199.9 (C3); HRMS calcd for $C_{22}H_{31}O_5$ $[M+H]^+$375.21660, found 375.21681.

4.2.9. Synthesis of 3β,17β-diacetoxy-6,6-ethylenedioxy-19-nor-5α-androst-1-ene (18). $NaBH_4$ (21 mg, 0.555 mmol) in EtOH (2.5 mL) was added to a cooled (−78 °C) solution of **17** (176 mg, 0.473 mmol) and $CeCl_3 \cdot 7H_2O$ (194 mg, 0.520 mmol) in MeOH (6 mL) over a period of 0.25 h. After the mixture was stirred for 1.5 h, the reaction was quenched by addition of a saturated aq NH_4Cl solution and the extraction was performed with CH_2Cl_2. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated to dryness. To obtain the protected C-3 alcohol, the crude product (176 mg) was dissolved in dry CH_2Cl_2 (2 mL), and pyridine (50 μL), Ac_2O (50 μL) and a catalytic amount of DMAP were added. The reaction mixture was stirred under nitrogen for 3 h at rt, poured into an ice-cold aq 1 M HCl (2 mL), and extracted with CH_2Cl_2. The combined organic layer was washed with

saturated aq $NaHCO_3$, dried over Na_2SO_4, and evaporated. Purification of the crude compound by flash chromatography (hexanes/EtOAc, 75:25) afforded **18** (195 mg, 99% yield) as a white amorphous solid. IR (film) ν 1736 (C=O, esters); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.75 (m, 1H), 0.82 (s, 18-CH_3), 1.05–2.35 (m, 16H, CH and CH_2 of steroid skeleton), 2.04 (s, $OCOCH_3$), 2.05 (s, $OCOCH_3$), 3.95 (m, OCH_2CH_2O), 4.61 (t, J=8.4 Hz, 17α-CH), 5.42 (m, 3α-CH), 5.60 (d app, J=10.3 Hz, 2-CH), 5.97 (d app, J=10.3 Hz, 1-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2 (C18), 21.1 ($OCO\mathit{CH_3}$), 21.3 ($OCO\mathit{CH_3}$), 23.2, 24.9, 27.2, 27.4, 36.6, 38.3, 39.5, 42.8, 43.0, 46.3 (2×), 49.5, 65.2 (OCH_2), 65.3 (OCH_2), 71.2 (C3), 82.6 (C17), 108.9 (C6), 127.2 (C2), 132.3 (C1), 170.7 ($O\mathit{CO}CH_3$), 171.1 ($O\mathit{CO}CH_3$); HRMS calcd for $C_{24}H_{34}O_6Na$ $[M+Na]^+$ 441.22476, found 441.22587.

4.2.10. Synthesis of 3β,17β-diacetoxy-6-oxo-19-nor-5α-androst-1-ene (19). A solution of **18** (12 mg, 0.032 mmol) in acetone (1 mL) was treated with concentrated HCl (0.01 mL). The resulting mixture was stirred at rt for 0.5 h. The reaction was neutralized with saturated aq $NaHCO_3$ and the crude product was extracted with CH_2Cl_2. The organic phase was washed with brine and dried over Na_2SO_4. The crude ketone was a 67:33 mixture of 5α-CH and 5β-CH diastereomers. Purification of this mixture by flash chromatography (hexanes/EtOAc, 90:10) afforded the 5α-CH diastereomer **19** (7.0 mg, 64% yield) and the 5β-CH analogue (3.0 mg, 27% yield) as white solids. Data are reported only for **19**. Mp 201–203 °C (Et_2O); IR (film) ν 1736 and 1708 (C=O, esters and ketone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (s, 18-CH_3), 1.10–2.50 (m, 17H, CH and CH_2 of steroid skeleton), 2.05 (s, $OCOCH_3$), 2.06 (s, $OCOCH_3$), 4.65 (t, J=8.4 Hz, 17α-CH), 5.42 (m, 3α-CH), 5.64 (d app, J=10.3 Hz, 2-CH), 6.00 (d app, 1H, J=10.3 Hz, 1-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0 (C18), 21.2 ($OCO\mathit{CH_3}$), 21.3 ($OCO\mathit{CH_3}$), 23.1, 25.0, 27.3, 27.7, 36.2, 42.7, 43.1, 45.5, 46.3, 46.8, 50.2, 50.6, 70.3 (C3), 82.2 (C17), 128.2 (C2), 130.9 (C1), 170.8 ($O\mathit{CO}CH_3$), 171.2 ($O\mathit{CO}CH_3$), 209.0 (C6); HRMS calcd for $C_{22}H_{30}O_5Na$ $[M+Na]^+$ 397.19855, found 397.19885.

4.2.11. Synthesis of 3β,17β-diacetoxy-6β-hydroxy-19-nor-5α-androst-1-ene (20). To a solution of **19** (1.23 g, 3.28 mmol) in dry THF (30 mL) under argon atm at −78 °C was added 1 M K-Selectride in THF (4.93 mL, 4.93 mmol). The mixture was stirred for 5.5 h at −78 °C, and then quenched by addition of a saturated aq NH_4Cl solution. The aq phase was extracted with CH_2Cl_2, and the organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The crude residue was purified by chromatography (hexanes/EtOAc, 90:10 to 80:20) to afford **19** (0.15 g, 12% yield) and **20** (0.89 g, 72%) as a white solid. Mp 123–125 °C (Et_2O); IR (film) ν 3474 (OH), 1732 (C=O, esters); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (s, 18-CH_3), 0.80–2.30 (m, 17H, CH and CH_2 of steroid skeleton), 2.04 (s, $OCOCH_3$), 2.06 (s, $OCOCH_3$), 3.90 (br s, 6α-CH), 4.60 (t, J=8.4 Hz, 17α-CH), 5.46 (m, 3α-CH), 5.56 (d app, J=10.3 Hz, 2-CH), 6.00 (d app, J=10.3 Hz, 1-CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2 (C18), 21.2 ($OCO\mathit{CH_3}$), 21.4 ($OCO\mathit{CH_3}$), 23.2, 24.8, 27.4, 32.6, 35.0, 36.6, 37.7, 38.8, 42.9, 43.3, 46.9, 49.5, 70.1 (C3), 71.5 (C6), 82.7 (C17), 126.7 (C2), 132.8 (C1), 171.0 ($O\mathit{CO}CH_3$), 171.3 ($O\mathit{CO}CH_3$); HRMS calcd for $C_{22}H_{32}O_5Na$ $[M+Na]^+$ 399.21420, found 399.21367.

4.2.12. Synthesis of 3β,17β-dihydroxy-19-nor-androsta-1,5-diene (21). $POCl_3$ (1.45 mL) was added to a solution of **20** (545 mg, 1.45 mmol) in pyridine (14 mL) under argon atm at rt. After the mixture was stirred for 1 h, the reaction was diluted with CH_2Cl_2 (50 mL), quenched by addition of aq 1 M HCl, and extracted with CH_2Cl_2. The combined organic layer was washed with saturated aq $NaHCO_3$, dried over $MgSO_4$, and evaporated to dryness. The crude alkene (534 mg) was dissolved in MeOH (20 mL) and a solution of K_2CO_3 (1.00 g, 7.24 mmol) in H_2O (6.5 mL) was added. The resulting mixture was refluxed for 1 h. Then, the mixture was extracted with CH_2Cl_2 and the combined organic layer was dried over $MgSO_4$ and evaporated. The crude residue was purified by chromatography (hexanes/EtOAc, 70:30) to afford **21** (250 mg, 63% yield) as a white solid. Mp 150–151 °C (Et_2O); IR (film) ν 3364 (OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.79 (s, 18-CH_3), 0.85 (ddd, J_3=22.0 Hz, J_2=10.6 Hz, J_1=4.5 Hz, 9α-CH), 1.01 (m, 14α-CH), 1.14 (td, J_2=12.9 Hz, J_1=3.9 Hz, 12α-CH_2), 1.26 (m, 11β-CH_2 and 15β-CH_2), 1.40–1.70 (m, 7β-CH_2, 8β-CH, 15α-CH_2 and 16β-CH_2), 1.84 (dt, J_2=12.3 Hz, J_1=3.2 Hz, 12β-CH_2), 1.95–2.20 (m, 4β-CH_2, 7α-CH_2, 11α-CH_2 and 16α-CH_2), 2.46 (d app, J=9.8 Hz, 10β-CH), 2.64 (ddd, J_3=11.8 Hz, J_2=5.9 Hz, J_1=1.2 Hz, 4α-CH_2), 3.66 (t, J=8.5 Hz, 17α-CH), 4.25 (m, 3α-CH), 5.50 (s app, 6-CH), 5.68 (d app, J=10.1 Hz, 2-CH), 5.84 (d app, J=10.1 Hz, 1-CH); ^{13}C NMR (75 and 100 MHz, $CDCl_3$) δ 11.0 (C18), 23.1 (C15), 26.1 (C11), 30.2 (C7), 30.4 (C16), 36.3 (C12), 36.7 (C8), 42.5 (C4 and C10), 42.9 (C13), 44.0 (C9), 50.4 (C14), 69.2 (C3), 81.8 (C17), 122.0 (C6), 130.6 (C1), 131.2 (C2), 134.3 (C5); HRMS calcd for $C_{18}H_{26}O_2Na$ $[M+Na]^+$ 297.18250, found 297.18303.

4.2.13. Synthesis of 19-nor-androsta-1,5-dien-3,17-dione (23). Dess–Martin periodinane (37 mg, 0.088 mmol) was added to a solution of **21** (12 mg, 0.044 mmol) in dry CH_2Cl_2 (4.5 mL) under argon atm at rt. After the mixture was stirred for 30 min, the reaction was diluted with CH_2Cl_2 (50 mL), quenched by addition of H_2O, and extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, and evaporated to dryness. The crude diketone was purified with a preparative silica gel TLC (hexanes/EtOAc, 50:50) to afford **23** (8.5 mg, 72% yield) as a white solid. Mp 161–163 °C (Et_2O/MeOH); IR (film) ν 1734, 1676 (C=O, ketones); ^{1}H NMR (400 MHz, C_6D_6) δ 0.58 (s, 18-CH_3), 0.49–2.09 (m, 14H, CH and CH_2 of steroid skeleton), 2.84 (dd, J_2=16.5 Hz, J_1=1.5 Hz, 4-CH), 3.05 (d app, J=16.5 Hz, 4-CH), 5.16 (dd, J_2=5.2 Hz, J_1=2.3 Hz, 6-CH), 5.99 (dd, J_2=10.1 Hz, J_1=2.8 Hz, 2-CH), 6.24 (dd, J_2=10.1 Hz, J_1=1.9 Hz, 1-CH); ^{13}C NMR (75 MHz, C_6D_6) δ 13.5 (C18), 21.4, 25.7, 29.1, 31.6, 35.4, 36.0, 42.8, 43.3, 47.4, 47.9, 50.3, 122.8 (C6), 128.9 (C2), 132.4 (C5), 149.4 (C1), 196.4 (C3), 217.5 (C17); HRMS calcd for $C_{18}H_{23}O_2$ $[M+H]^+$ 271.16926, found 271.16866.

4.2.14. Synthesis of 17β-hydroxy-19-nor-androsta-1,5-dien-3-one (1). *Method A* (*from* **21**). To a mixture of $BaMnO_4$ (192 mg, 3.36 mmol) and neutral Al_2O_3 (94 mg, 0.94 mmol) in dry CH_2Cl_2 (1.6 mL) under argon atm was added $CuSO_4\cdot 5H_2O$ (15 mg, 0.06 mmol) and **21** (35 mg, 0.128 mmol). After 4 h at rt, the adsorbed reagent was removed by filtration on Celite and washed with CH_2Cl_2. The filtrate was evaporated and the crude product was purified with three reverse-phase (C18 silica gel) column chromatographies

[(CH_3CN/H_2O, 4:3)/MeOH, 91:9]. The organic layer of chromatographic tubes was extracted with CH_2Cl_2, dried over Na_2SO_4, and evaporated to afford **1** (4.6 mg, 13% yield).

Method B (*from* **23**). $NaBH_4$ (10.2 mg, 0.268 mmol) was added to a solution of **23** (18.0 mg, 0.067 mmol) in dry CH_2Cl_2/MeOH (1/1) (0.5 mL) under argon at −78 °C. The resulting mixture was then stirred for 13 min at −35 °C, quenched by addition of H_2O at −35 °C, and the crude products isolated by an extraction with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4 and evaporated to dryness. The mixture was purified with a preparative silica gel TLC (hexanes/EtOAc, 50:50) to afford the starting material **23** (9.8 mg, 54% yield) and **1** (7.3 mg, 40% yield).

White solid. Mp 137–139 °C (Et_2O); IR (film) ν 1665 (C=O, ketone); ^{1}H NMR (400 MHz, C_6D_6) δ 0.67 (s, 18-CH_3), 0.54–2.09 (m, 14H, CH and CH_2 of steroid skeleton), 2.94 (dd, J_2=16.5 Hz, J_1=1.4 Hz, 4-CH), 3.06 (d app, J=16.5 Hz, 4-CH), 3.36 (t, J=8.5 Hz, 17α-CH), 5.18 (dd, J_2=5.3 Hz, J_1=2.3 Hz, 6-CH), 6.00 (dd, J_2=10.1 Hz, J_1=3.0 Hz, 2-CH), 6.33 (dd, J_2=10.1 Hz, J_1=2.0 Hz, 1-CH); ^{13}C NMR (75 MHz, C_6D_6) δ 11.1 (C18), 23.2, 26.2, 29.9, 30.7, 36.5, 36.7, 42.9, 43.1, 43.5, 47.9, 50.2, 81.4 (C17), 123.2 (C6), 128.7 (C2), 132.2 (C5), 149.8 (C1), 196.7 (C3); HRMS calcd for $C_{18}H_{25}O_2$ $[M+H]^+$ 273.18491, found 273.18418.

Acknowledgements

We thank the Canadian Institutes of Health Research (CIHR) for an operating grant (#FRN 43926 to A.P.). We are grateful to Richard Labrecque for providing the optimized conditions of diketone reduction, to Dr. Jean-Yves Sancéau for helpful discussions and to Patrick Bélanger for LC/MS analysis. Careful reading of the manuscript by Sylvie Méthot is also greatly appreciated.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.063. NMR experimental data (COSY, HSQC, HMBC, and NOESY) for **21**, as well as ^{1}H and ^{13}C NMR spectra of **21**, **23**, and **1**.

References and notes

1. Philip, A.; Murphy, B. E. P. Canadian Patent #1292467, 1991.
2. Philip, A.; Murphy, B. E. P. *J. Steroid Biochem.* **1989**, *32*, 865–872.
3. Philip, A.; Murphy, B. E. P. *J. Steroid Biochem.* **1989**, *32*, 873–885.
4. Nussbaum, A. L.; Topliss, G. B.; Popper, T. L.; Oliveto, E. P. *J. Am. Chem. Soc.* **1959**, *81*, 4574–4577.
5. Nann, B.; Gravel, D.; Schorta, R.; Wehrli, H.; Schaffner, K.; Jeger, O. *Helv. Chim. Acta* **1963**, *66*, 2473–2482.
6. Nann, B.; Wehrli, H.; Schaffner, K.; Jeger, O. *Helv. Chim. Acta* **1965**, *48*, 1680–1712.
7. Shapiro, E. L.; Legatt, T.; Weber, L.; Oliveto, E. P.; Tanabe, M.; Crowe, D. F. *Steroids* **1964**, *3*, 183–188.
8. Tanabe, M.; Crowe, D. F. *Tetrahedron* **1967**, *23*, 2115–2121.
9. Ringold, H. J.; Malhotra, S. K. *Tetrahedron Lett.* **1962**, *3*, 669–672.
10. Birch, A. J. *J. Chem. Soc.* **1950**, 2325–2326.
11. Solo, A. J.; Singh, B. *J. Org. Chem.* **1965**, *30*, 1658–1659.
12. Fukunaga, K.; Yamaguchi, H. *Synthesis* **1981**, 879–880.
13. Nakayama, J.; Machida, H.; Hoshino, M. *Tetrahedron Lett.* **1983**, *24*, 3001–3004.
14. Landini, D.; Milesi, L.; Quadri, M. L.; Rolla, F. *J. Org. Chem.* **1984**, *49*, 152–153.
15. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434–5447.
16. Ziegler, F. E.; Hwang, K.-J.; Kadow, J. F.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Org. Chem.* **1986**, *51*, 4573–4579.
17. Sakurai, H.; Sasaki, K.; Hosomi, A. *Tetrahedron Lett.* **1980**, *21*, 2329–2332.
18. Gray, R. T.; Djerassi, C. *J. Org. Chem.* **1970**, *35*, 753–758.
19. Sam, K. M.; Auger, S.; Luu-The, V.; Poirier, D. *J. Med. Chem.* **1995**, *38*, 4518–4528.
20. Bell, R. P. L.; Sobolev, A.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1998**, *63*, 122–128.
21. Liu, Z.; Meinwald, J. *J. Org. Chem.* **1996**, *61*, 6693–6699.
22. Bull, J. R.; Loedolff, M. C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1269–1276.
23. Trost, B. M.; Parquette, J. R. *J. Org. Chem.* **1993**, *58*, 1579–1581.
24. Zoretic, P. A.; Chambers, R. J.; Marbury, G. D.; Riebiro, A. A. *J. Org. Chem.* **1985**, *50*, 2981–2987.
25. Rosenkranz, G.; Velasco, M.; Sondheimer, F. *Steroids* **1954**, *76*, 5024–5026.
26. Beard, C. C. In *Introduction of Double Bond into the Steroid System*; Fried, J., Edwards, J. A., Eds.; Organic Reactions in Steroid Chemistry; Van Nostrand Reinhold Company: New York, 1972, Vol. 1, pp. 334–335.
27. Cui, J. G.; Lin, C. W.; Zeng, L. M.; Su, J. Y. *Steroids* **2002**, *67*, 1015–1019.
28. Dionne, P.; Tchédam-Ngatcha, B.; Poirier, D. *Steroids* **1997**, *62*, 674–681.
29. Dodge, J. A.; Lugar, C. W., III. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1–2.
30. Claridge, T. D. W. In *High-resolution NMR Techniques in Organic Chemistry*; Baldwin, J. E., Williams, R. M., Eds.; Tetrahedron Organic Chemistry Series; Pergamon: New York, 1999; Vol. 19, p 382.
31. Sondheimer, F.; Amendolla, C.; Rosenkranz, G. *J. Am. Chem. Soc.* **1953**, *75*, 5930–5932.
32. Pratt, E. F.; van de Castle, J. F. V. *J. Org. Chem.* **1961**, *26*, 2973–2975.
33. Katsumura, S.; Kimura, A.; Isoe, S. *Tetrahedron* **1989**, *45*, 1337–1346.
34. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
35. Sorg, G.; Mendel, A.; Jung, G.; Rademann, J. *J. Angew. Chem., Int. Ed.* **2001**, *40*, 4395–4397.
36. Kim, K. S.; Chung, S.; Cho, I. H.; Hahn, C. S. *Tetrahedron Lett.* **1989**, *30*, 2559–2562.
37. de la Puente, M. L.; Ley, S. V.; Simmonds, M. S. J.; Blanez, W. M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1523–1529.
38. Ward, D. E.; Rhee, C. K.; Zoghaib, W. M. *Tetrahedron Lett.* **1988**, *29*, 517–520.
39. Lorenc, L.; Bondarenko, L.; Rajkovic, M.; Milovanovic, A.; Mihailovic, M. L. *Tetrahedron* **1983**, *39*, 3609–3617.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 4393–4399

Facile solid-phase synthesis of 2,3-disubstituted 6*H*-pyrano[2,3-*f*]benzimidazole-6-ones

Aimin Song, Lucy Wu, Laura Ho and Kit S. Lam*

Division of Hematology and Oncology, Department of Internal Medicine, UC Davis Cancer Center, University of California, Davis, 4501 X Street, Sacramento, CA 95817, USA

Received 21 November 2005; revised 20 February 2006; accepted 21 February 2006

Available online 15 March 2006

Abstract—We report herein the facile solid-phase synthesis of 2,3-disubstituted 6*H*-pyrano[2,3-*f*]benzimidazole-6-ones using 7-fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic acid as the scaffold. The fluorine of the resin-bound scaffold was first replaced by a primary amine. Reduction of the nitro group with tin(II) chloride afforded an *o*-dianilino intermediate that was treated with an aldehyde followed by the addition of 2,3-dichloro-5,6-dicyanoquinone (DDQ). 2,3-Disubstituted 6*H*-pyrano[2,3-*f*]benzimidazole-6-ones were obtained in high purity and good yield after cleavage.

1. Introduction

Natural products and their derivatives have played a major role in drug discovery and development.[1] In the past few years, significant attention has been focused on the design, synthesis and screening of natural product-based combinatorial libraries as this approach combines the 'drug-like' quality of natural products with the efficiency of combinatorial chemistry.[2] Solid-phase synthetic routes to natural products and natural product-like small molecules are of great interest for their ability to generate large combinatorial libraries in a time- and cost-effective manner.[3]

Coumarin (2*H*-1-benzopyran-2-one) derivatives constitute an important class of natural products, which are widely distributed in the plant kingdom.[4] Coumarins and related compounds have a broad range of biological activities, including antibiotic, anticoagulant, anticancer, antiinflammatory, antioxidant, and antimitotic effects.[5] A number of natural or synthetic coumarins have been widely used as therapeutic agents,[6] fluorescent probes,[7] and photosensitizers.[8] As a part of our continuing effort to construct natural product-based small molecule libraries, we recently reported the synthesis and applications of 7-fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic acid as a novel scaffold for combinatorial synthesis of coumarin derivatives.[9] Combinatorial libraries of 2-alkylthioimidazocoumarins[10] and 2-arylaminoimidazocoumarins[11] were prepared in solid-phase using this scaffold.

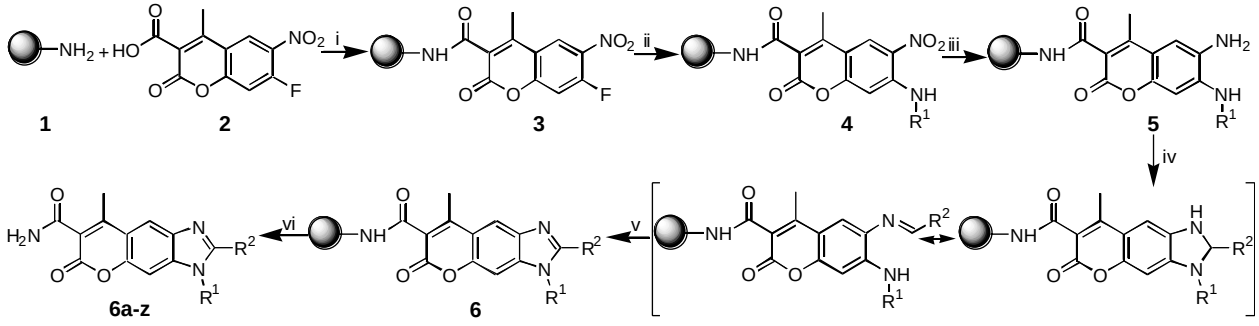
In this report, we describe a facile solid-phase method for parallel synthesis of 2,3-disubstituted 6*H*-pyrano[2,3-*f*]benzimidazole-6-ones (2,3-disubstituted imidazocoumarins). Unlike the imidazocoumarin derivatives that we have previously reported, the substituent at C-2 position in this class of compounds is connected directly to the imidazole ring via a C–C bond. This combinatorial synthesis method is highly efficient. The imidazole ring closure reaction is mild and it enables one to incorporate large number of commercially available aldehydes into the final imidazocoumarin structure. We anticipate that the synthesis of the 2,3-disubstituted imidazocoumarin library will provide a rich source of highly diverse and innovative natural product-based small molecules for our anticancer drug development program.

2. Results and discussion

Our strategy for the solid-phase synthesis of 2,3-disubstituted 6*H*-pyrano[2,3-*f*]benzimidazole-6-ones is illustrated in Scheme 1. 7-Fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic acid **2** was first tethered to Rink amide resin **1** using 1,3-diisopropylcarbodiimide (DIC)/1-hydroxybenzotriazole (HOBt) as the activating system. The fluorine in the resin-bound

Keywords: Solid-phase synthesis; Imidazocoumarins; Combinatorial chemistry.
* Corresponding author. Tel.: +1 916 734 8012; fax: +1 916 734 7946; e-mail: kit.lam@ucdmc.ucdavis.edu

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.064



Scheme 1. Solid-phase synthesis of 2,3-disubstituted 6*H*-pyrano[2,3-*f*]benzimidazole-6-ones. Reagents and conditions: **1**, Rink amide resin; (i) 2 equiv of 7-fluoro-4-methyl-6-nitro-coumarin-3-carboxylic acid, 2 equiv of DIC and 2 equiv of HOBt in DMF, rt, 16 h; (ii) 2 equiv of R^1NH_2 in 5% DIPEA/DMF, rt, overnight; (iii) 1 M of $SnCl_2 \cdot H_2O$ in DMF, rt, 24 h; (iv) 4 equiv of R^2CHO in DMF, rt, 2 h; (v) 1 equiv of DDQ in DMF, rt, 5 h; (vi) 95% TFA/H_2O, rt, 2 h.

scaffold **3** was subsequently replaced by a primary amine. The optimal reaction conditions were determined to be 2 equiv of the amine in 5% *N*,*N*-diisopropylethylamine (DIPEA)/*N*,*N*-dimethylformamide (DMF), while higher concentration of the amine caused undesired side reaction on the pyranone ring. A number of structurally diverse primary amines were successfully tested for the aromatic nucleophilic substitution (see Table 1 for representative structures).

Reduction of the nitro group by treatment with tin(II) chloride (1 M solution in DMF) afforded the *o*-dianilino intermediate **5** smoothly. However, the formation of imidazole ring was problematic. The solid-phase synthesis of benzimidazoles via an *o*-dianilino intermediate have been reported by several groups.[12–14] The *o*-dianilino intermediate was usually acylated with a carboxylic acid followed by treatment with a strong mineral acid,[12] or condensed with an aldehyde under oxidative conditions or elevated temperature.[13,14] When we applied these methods to our synthesis, the results were unsatisfactory. For example, when we followed the convenient 'one-pot' solid-phase synthesis method of benzimidazoles, reported by Wu et al.,[14] by heating the polymer-bound 2-nitroaniline with an aldehyde in DMF in the presence of tin(II) chloride at 60 °C, we were able to prepare the desired products **6** from only a few simple aromatic aldehydes such as benzaldehyde and *p*-tolualdehyde. However, reactions with most of substituted aromatic aldehydes, heterocyclic aldehydes and aliphatic aldehydes all yielded complex mixtures, which were not further elucidated. We believe this is due to the electron-rich nature of 6,7-diaminocoumarin intermediate **5**, making it unstable to the harsh reaction conditions.

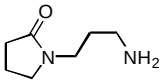
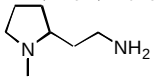
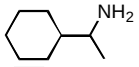
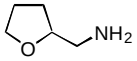
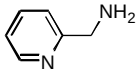
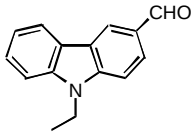
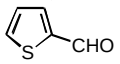
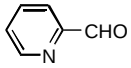
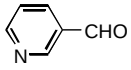
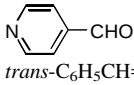
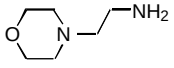
After evaluating various reagents and reaction conditions, we were finally able to establish an efficient and convenient procedure for imidazole ring formation. The resin-bound intermediate **5** was first incubated with 4 equiv of an aldehyde at room temperature for 2 h to allow the condensation, followed by the addition of 1 equiv of 2,3-dichloro-5,6-dicyanoquinone (DDQ). It is important to follow this protocol because we have found that when DDQ was added together with the aldehyde, the resin became very dark and a complex mixture was obtained after cleavage by trifluoroacetic acid (TFA). Excess DDQ should be avoided as it will form a complex with the final product causing problem in subsequent purification. Among the aldehydes we tested (see Table 1 for representative structures), aromatic aldehydes (**6a–n**), heterocyclic aldehydes (**6o–t**), and α-branched aliphatic aldehydes (**6y** and **6z**) reacted smoothly to afford the desired products in high purity. Steric hindrance and substituents on the aromatic aldehydes did not adversely affect the cyclization. Electron-rich aldehydes such as 2,4-dimethoxybenzaldehyde and 4-dimethylaminobenzaldehyde, which were known to be unstable to strong oxidants,[15] were well tolerated. Functionalities such as phenolic hydroxyl (**6h**) and carboxyl (**6i**) groups did not require protection. Cinnamaldehydes (**6u** and **6v**) and linear aliphatic aldehydes (**6w** and **6x**) also underwent the cyclization to yield the desired products but in slightly lower purity.

Using the established method, we synthesized 26 2,3-disubstituted 6*H*-pyrano[2,3-*f*]benzimidazole-6-ones with diverse structures (Table 1). The final products were released from the solid support via TFA treatment, analyzed and purified by HPLC, and characterized by ^1H, ^{13}C NMR and ESI-FTMS. Most of the compounds were obtained in high purity with good isolated yield.

3. Conclusion

To summarize, we have developed a facile solid-phase approach for parallel synthesis of 2,3-disubstituted 6*H*-pyrano[2,3-*f*]benzimidazole-6-ones. The desired products were obtained in high purity. The compounds prepared by this method have two sites of chemical diversity. The building blocks used for the synthesis are easily available. The methodology is ideally suited for automated high-throughput synthesis as all of the reactions were performed under ambient conditions.

Table 1. Preparation of compounds **6a–z** via Scheme 1

Entry	R^1NH_2	R^2CHO	Yield (%)[a]	Purity (%)[b]
6a	$CH_3(CH_2)_2NH_2$	C_6H_5CHO	81	92
6b	$C_6H_5OCH_2CH_2NH_2$	2-$CH_3C_6H_4CHO$	83	95
6c	4-$ClC_6H_4CH_2CH_2NH_2$	4-$CH_3OC_6H_4CHO$	78	91
6d	$(CH_3)_2CHCH_2NH_2$	3,4,5-$(CH_3O)_3C_6H_2CHO$	72	88
6e		2,4-$(CH_3O)_2C_6H_3CHO$	74	90
6f	$(C_2H_5)_2CHNH_2$	4-$(CH_3)_2NC_6H_4CHO$	83	97
6g	4-$CH_3OC_6H_4CH_2CH_2NH_2$	4-$CH_3CONHC_6H_4CHO$	79	91
6h	2-$FC_6H_4CH_2CH_2NH_2$	4-HOC_6H_4CHO	80	95
6i	2,4-$(CH_3O)_2C_6H_3CH_2NH_2$	4-$HOOCC_6H_4CHO$	81	94
6j		2,6-$Cl_2C_6H_3CHO$	70	86
6k		4-NCC_6H_4CHO	77	92
6l		3-$O_2NC_6H_4CHO$	72	88
6m	$(CH_3)_2CHCH_2NH_2$	4-$O_2NC_6H_4CHO$	78	94
6n		1-$C_{10}H_7CHO$	71	87
6o	$(CH_3)_2CHCH_2NH_2$		73	84
6p	3,4-$(CH_2O_2)C_6H_3CH_2NH_2$		81	96
6q	$C_2H_5(CH_3)CHNH_2$		75	91
6r	*c*-$C_5H_9NH_2$		76	92
6s	*c*-$C_6H_{11}NH_2$		81	97
6t	*c*-$C_6H_{11}CH_2NH_2$		69	88
6u	$CH_3(CH_2)_2NH_2$	*trans*-$C_6H_5CH{=}CHCHO$	66	79
6v	$CH_3(CH_2)_3NH_2$	*trans*-4-$(CH_3)_2NC_6H_4CH{=}CHCHO$	70	84
6w	$C_6H_5CH_2NH_2$	CH_3CH_2CHO	55	72
6x	$C_2H_5O(CH_2)_3NH_2$	$C_6H_5CH_2CH_2CHO$	56	66
6y	$CH_3(CH_2)_2NH_2$	$(CH_3)_2CHCHO$	73	90
6z		*c*-$C_6H_{11}CHO$	68	89

[a] Yields were calculated based on the purified products.
[b] Purity was determined by HPLC analysis (UV detection at 254 nm) of crude products.

4. Experimental

4.1. General

7-Fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic acid was prepared using our published procedure.[9] DIC and TFA were purchased from Advanced ChemTech (Louisville, KY). Rink amide MBHA resin (0.45 mmol/g) was purchased from Nankai Hecheng (Tianjin, China). HOBt was purchased from GL Biochem (Shanghai, China). All solvents and other chemical reagents were purchased from Aldrich (Milwaukee, WI) and were analytical grade. Analytical HPLC analyses (Vydac column, 4.6 mm×250 mm, 5 μm, 300 Å, C_{18}, 1.0 mL/min, 25 min gradient from 100% aqueous media (0.1% TFA) to 100% CH_3CN (0.1% TFA), 214, 220, 254 and 280 nm) and preparative HPLC purification (Vydac column, 20 mm×250 mm, 5 μm, 300 Å, C_{18}, 7.0 mL/min, 45 min gradient from 100% aqueous media (0.1% TFA) to 100% CH_3CN (0.1% TFA), 254 nm) were performed on a Beckman System Gold HPLC system (Fullerton, CA). ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX 500 MHz spectrometer

(Billerica, MA) at 25 °C. All of the experiments were carried out at room temperature unless otherwise noted.

4.2. General procedure for solid-phase synthesis of 2,3-disubstituted 6*H*-pyrano[2,3-*f*]benzimidazole-6-ones

Rink amide MBHA resin (100 mg, 0.045 mmol) was swollen in DMF overnight. The supernatant was removed, and a 20% piperidine solution in DMF (1 mL) was added to the resin. The mixture was agitated for 15 min, and the supernatant was removed. This process was repeated. The resin was washed with DMF, methanol (MeOH), and DMF. To the resin was added a solution of 7-fluoro-4-methyl-6-nitro-2-oxo-2*H*-1-benzopyran-3-carboxylic acid (24.1 mg, 0.090 mmol), HOBt (12.2 mg, 0.090 mmol) and DIC (14.1 μL, 0.090 mmol) in DMF (1 mL). The resulting mixture was agitated for 16 h. The complete coupling was confirmed by a negative ninhydrin test. The supernatant was removed, and the resin was washed with DMF, dichloromethane (DCM), MeOH, and DMF. To the resin was added a solution of a primary amine (0.090 mmol) in 5% DIPEA/DMF (2 mL). The resulting mixture was agitated overnight. The supernatant was removed, and the resin was washed with DMF, DCM, MeOH, and DMF. To the resin was added 1 M $SnCl_2 \cdot H_2O$ solution in DMF (2 mL), and the resulting mixture was agitated for 24 h. The supernatant was removed, and the resin was washed with DMF, DCM, MeOH, and DMF. To the resin was added a solution of an aldehyde (0.180 mmol) in DMF (1 mL). The resulting mixture was agitated for 2 h, and a solution of DDQ (10.2 mg, 0.045 mmol) in DMF (1 mL) was added. After additional 5 h of agitation, the supernatant was removed. The resin was washed thoroughly with DMF, 5% DIPEA/DMF, DCM, MeOH, and DCM, and then dried in vacuo. To the dried resin was added 2 mL of 95% TFA solution in water at ice-bath temperature. The mixture was slowly warmed to room temperature and allowed to mix for 2 h. The supernatant was then collected and the resin was washed with neat TFA (3×1 mL). The combined supernatants were concentrated to dryness under a stream of nitrogen, and further dried in vacuo. The crude product was analyzed and purified by HPLC.

4.2.1. 8-Methyl-6-oxo-2-phenyl-3-propyl-6*H*-pyrano-[2,3-*f*]benzimidazole-7-carboxamide 6a. Yield 81%; ^{1}H NMR (DMSO-d_6) δ 8.20 (s, 1H), 7.91 (s, 1H), 7.89 (s, 1H), 7.83 (t, 2H, J=3.3 Hz), 7.66 (s, 1H), 7.63 (m, 3H), 4.35 (t, 2H, J=7.1 Hz), 2.53 (s, 3H), 1.68 (m, 2H), 0.73 (t, 3H, J=7.3 Hz); ^{13}C NMR (DMSO-d_6) δ 166.7, 158.9, 156.2, 149.7, 149.1, 138.9, 138.7, 131.3, 130.0, 129.8, 129.7, 129.1, 123.3, 116.1, 115.6, 99.1, 46.8, 23.0, 16.9, 11.5; ESI-FTMS m/z calcd for $C_{21}H_{19}N_3O_3+H^+$: 362.14992; found: 362.14982.

4.2.2. 8-Methyl-2-(2-methylphenyl)-6-oxo-3-(2-phenoxyethyl)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6b. Yield 83%; ^{1}H NMR (DMSO-d_6) δ 8.21 (s, 1H), 8.00 (s, 1H), 7.93 (s, 1H), 7.69 (s, 1H), 7.62 (d, 1H, J=7.4 Hz), 7.54 (t, 1H, J=7.4 Hz), 7.48 (d, 1H, J=7.4 Hz), 7.43 (t, 1H, J=7.4 Hz), 7.19 (m, 2H), 6.87 (t, 1H, J=7.3 Hz), 6.69 (d, 2H, J=7.9 Hz), 4.57 (t, 2H, J=4.6 Hz), 4.21 (t, 2H, J=4.6 Hz), 2.53 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.7, 158.9, 158.4, 156.1, 149.7, 149.1, 138.5, 138.0, 137.3, 131.3, 131.1, 130.2, 128.7, 126.7, 123.5, 121.7, 116.4, 115.9, 115.8, 114.8, 99.7, 65.8, 44.8, 20.1, 16.9; ESI-FTMS m/z calcd for $C_{27}H_{23}N_3O_4+H^+$: 454.17614; found: 454.17608.

4.2.3. 3-[2-(4-Chlorophenyl)ethyl]-2-(4-methoxyphenyl)-8-methyl-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6c. Yield 78%; ^{1}H NMR (DMSO-d_6) δ 8.13 (s, 1H), 7.93 (s, 1H), 7.92 (s, 1H), 7.70 (s, 1H), 7.57 (d, 2H, J=8.7 Hz), 7.15 (d, 2H, J=8.3 Hz), 7.11 (d, 2H, J=8.7 Hz), 6.91 (d, 2H, J=8.3 Hz), 4.64 (t, 2H, J=6.7 Hz), 3.87 (s, 3H), 2.99 (t, 2H, J=6.7 Hz), 2.52 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.7, 161.8, 158.8, 155.9, 149.8, 148.9, 137.8, 137.7, 137.0, 132.1, 131.5, 131.2, 128.9, 123.6, 120.4, 116.5, 115.1, 115.0, 99.6, 56.2, 46.8, 34.4, 16.9; ESI-FTMS m/z calcd for $C_{27}H_{22}ClN_3O_4+H^+$: 488.13716; found: 488.13714.

4.2.4. 8-Methyl-3-(2-methylpropyl)-6-oxo-2-(3,4,5-trimethoxyphenyl)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6d. Yield 72%; ^{1}H NMR (DMSO-d_6) δ 8.18 (s, 1H), 7.95 (s, 1H), 7.88 (s, 1H), 7.68 (s, 1H), 7.16 (s, 2H), 4.32 (d, 2H, J=7.4 Hz), 3.87 (s, 6H), 3.78 (s, 3H), 2.52 (s, 3H), 1.95 (m, 1H), 0.72 (d, 6H, J=6.6 Hz); ^{13}C NMR (DMSO-d_6) δ 166.8, 158.8, 155.9, 153.8, 149.8, 149.0, 140.1, 138.7, 137.4, 124.5, 123.5, 116.4, 115.5, 107.6, 99.6, 61.0, 57.0, 52.5, 29.1, 20.2, 16.8; ESI-FTMS m/z calcd for $C_{25}H_{27}N_3O_6+H^+$: 466.19727; found: 466.19723.

4.2.5. 2-(2,4-Dimethoxyphenyl)-8-methyl-6-oxo-3-[3-(2-oxo-1-pyrrolidinyl)propyl]-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6e. Yield 74%; ^{1}H NMR (DMSO-d_6) δ 8.18 (s, 1H), 8.03 (s, 1H), 7.94 (s, 1H), 7.71 (s, 1H), 7.54 (d, 1H, J=8.5 Hz), 6.86 (d, 1H, J=2.0 Hz), 6.81 (dd, 1H, J=8.5, 2.0 Hz), 4.14 (t, 2H, J=7.5 Hz), 3.12 (t, 2H, J=6.4 Hz), 3.05 (t, 2H, J=6.9 Hz), 2.52 (s, 3H), 2.09 (t, 2H, J=8.3 Hz), 1.83 (m, 2H), 1.74 (m, 4H); ^{13}C NMR (DMSO-d_6) δ 174.7, 166.5, 164.4, 159.4, 158.6, 153.4, 150.0, 148.7, 136.5, 135.0, 133.5, 124.0, 117.1, 114.4, 107.9, 106.9, 99.8, 99.5, 56.7, 56.5, 46.6, 43.4, 39.6, 31.0, 27.1, 18.0, 16.9; ESI-FTMS m/z calcd for $C_{27}H_{28}N_4O_6+H^+$: 505.20817; found: 505.20826.

4.2.6. 2-(4-Dimethylaminophenyl)-3-(1-ethylpropyl)-8-methyl-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6f. Yield 83%; ^{1}H NMR (DMSO-d_6) δ 8.18 (s, 1H), 8.12 (s, 1H), 7.91 (s, 1H), 7.73 (s, 1H), 7.57 (d, 2H, J=8.8 Hz), 6.95 (d, 2H, J=8.8 Hz), 4.42 (m, 1H), 3.05 (s, 6H), 2.52 (s, 3H), 2.21 (m, 2H), 2.04 (m, 2H), 0.68 (t, 6H, J=7.3 Hz); ^{13}C NMR (DMSO-d_6) δ 166.4, 158.5, 157.0, 152.9, 149.8, 148.3, 134.3, 133.5, 131.8, 124.5, 117.5, 113.3, 112.5, 111.6, 101.6, 62.8, 40.4, 25.7, 16.8, 11.3; ESI-FTMS m/z calcd for $C_{25}H_{28}N_4O_3+H^+$: 433.22342; found: 433.22348.

4.2.7. 2-(4-Acetylaminophenyl)-3-[2-(4-methoxyphenyl)-ethyl]-8-methyl-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6g. Yield 79%; ^{1}H NMR (DMSO-d_6) δ 10.29 (s, 1H), 7.92 (s, 1H), 7.89 (s, 1H), 7.76 (d, 2H, J=8.5 Hz), 7.69 (s, 1H), 7.55 (d, 2H, J=8.5 Hz), 6.80 (d, 2H, J=8.4 Hz), 6.67 (d, 2H, J=8.4 Hz), 4.59 (t, 2H, J=5.9 Hz), 3.67 (s, 1H), 2.93 (t, 2H, J=5.9 Hz), 2.52 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 169.6, 166.7, 158.8,

155.9, 149.8, 148.9, 142.2, 137.9, 137.2, 130.6, 130.4, 129.8, 123.6, 122.8, 119.8, 119.3, 116.4, 115.2, 114.5, 99.6, 55.7, 47.2, 34.2, 24.9, 16.9; ESI-FTMS *m/z* calcd for $C_{29}H_{26}N_4O_5+H^+$: 511.19760; found: 511.19763.

4.2.8. 3-[2-(2-Fluorophenyl)ethyl]-2-(4-hydroxyphenyl)-8-methyl-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6h. Yield 80%; ^{1}H NMR (DMSO-d_6) δ 10.2 (s, br, 1H), 8.21 (s, 1H), 7.92 (s, 1H), 7.88 (s, 1H), 7.70 (s, 1H), 7.47 (d, 2H, J=8.6 Hz), 7.19 (m, 1H), 7.02 (m, 1H), 6.99–6.91 (m, 4H), 4.66 (t, 2H, J=6.8 Hz), 3.05 (t, 2H, J=6.8 Hz), 2.52 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.6, 161.4 (d, $^1J_{CF}$=242.5 Hz), 160.8, 158.7, 156.1, 149.8, 148.8, 137.5 (d, $^3J_{CF}$=7.3 Hz), 135.9, 132.0, 131.7, 129.8 (d, $^3J_{CF}$=7.9 Hz), 125.1, 124.5 (d, $^2J_{CF}$=15.6 Hz), 123.8, 117.8, 116.7, 116.5, 115.7 (d, $^2J_{CF}$=21.5 Hz), 114.5, 99.6, 45.7, 28.6, 16.9; ESI-FTMS *m/z* calcd for $C_{26}H_{20}FN_3O_4+H^+$: 458.15107; found: 458.15113.

4.2.9. 4-[7-Carbamoyl-3-[(2,4-dimethoxyphenyl)-methyl]-8-methyl-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazol-2-yl]benzoic acid 6i. Yield 81%; ^{1}H NMR (DMSO-d_6) δ 13.3 (s, br, 1H), 8.21 (s, 1H), 8.11 (d, 2H, J=8.2 Hz), 7.92 (d, 2H, J=8.2 Hz), 7.85 (s, 1H), 7.65 (s, 1H), 7.58 (s, 1H), 6.86 (d, 1H, J=8.4 Hz), 6.47 (s, 1H), 6.40 (dd, 1H, J=9.1, 1.4 Hz), 5.50 (s, 2H), 3.68 (s, 3H), 3.54 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 167.5, 166.7, 161.2, 158.9, 158.5, 156.1, 149.5, 149.2, 140.2, 139.2, 134.6, 132.7, 130.3, 130.1, 129.8, 123.2, 116.8, 116.3, 115.9, 105.3, 99.3, 56.0, 55.9, 44.9, 16.8; ESI-FTMS *m/z* calcd for $C_{28}H_{23}N_3O_7+H^+$: 514.16088; found: 514.16077.

4.2.10. 2-(2,6-Dichlorophenyl)-8-methyl-3-[2-(1-methyl-2-pyrrolidinyl)ethyl]-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6j. Yield 70%; ^{1}H NMR (DMSO-d_6) δ 8.23 (s, 1H), 7.97 (s, 1H), 7.92 (s, 1H), 7.79–7.66 (m, 4H), 4.22 (m, 1H), 4.03 (m, 1H), 3.53 (m, 1H), 3.22 (m, 1H), 3.01 (m, 1H), 2.76 (d, J=4.1 Hz, 3H), 2.54 (s, 3H), 2.38 (m, 1H), 2.03 (m, 1H), 1.91 (m, 1H), 1.82 (m, 2H), 1.39 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 166.7, 158.9, 150.7, 149.9, 149.3, 140.3, 137.3, 135.9, 135.8, 134.3, 129.6, 128.7, 123.3, 117.7, 116.1, 98.9, 66.1, 55.8, 42.1, 39.4, 30.4, 29.3, 21.7, 16.9; ESI-FTMS *m/z* calcd for $C_{25}H_{24}Cl_2N_4O_3+H^+$: 499.12983; found: 499.12978.

4.2.11. 2-(4-Cyanophenyl)-3-(1-cyclohexylethyl)-8-methyl-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6k. Yield 77%; ^{1}H NMR (DMSO-d_6) δ 8.22 (s, 1H), 8.09 (s, 1H), 8.08 (m, 2H), 7.98 (s, 1H), 7.88 (m, 3H), 7.68 (s, 1H), 4.08 (m, 1H), 2.52 (s, 3H), 2.15 (m, 1H), 1.88 (m, 1H), 1.76 (d, J=6.7 Hz, 3H), 1.64 (m, 1H), 1.47 (m, 1H), 1.34 (m, 1H), 1.21 (m, 1H), 0.99–0.75 (m, 3H), 0.59 (m, 1H), 0.36 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 166.7, 158.8, 155.7, 149.3, 149.0, 140.1, 136.3, 134.8, 133.6, 131.3, 123.5, 119.0, 117.0, 116.2, 113.6, 100.7, 59.6, 40.4, 30.4, 29.8, 26.0, 25.8, 25.7, 17.6, 16.8; ESI-FTMS *m/z* calcd for $C_{27}H_{26}N_4O_3+H^+$: 455.20777; found: 455.20782.

4.2.12. 8-Methyl-2-(3-nitrophenyl)-6-oxo-3-[(tetrahydro-2-furanyl)methyl]-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6l. Yield 72%; ^{1}H NMR (DMSO-d_6) δ 8.80 (t, 1H, J=1.5 Hz), 8.42 (dd, 1H, J=8.3, 1.5 Hz), 8.32 (d, 1H, J=7.9 Hz), 8.22 (s, 1H), 7.92–7.85 (m, 3H), 7.67 (s, 1H), 4.51 (dd, 1H, J=15.0, 2.4 Hz), 4.34 (dd, 1H, J=15.0, 9.2 Hz), 4.27 (m, 1H), 3.60 (dd, 1H, J=14.5, 6.9 Hz), 3.55 (dd, 1H, J=14.5, 7.3 Hz), 2.52 (s, 3H), 2.04 (m, 1H), 1.78 (m, 2H), 1.55 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 166.7, 158.9, 154.7, 149.7, 149.1, 148.6, 139.8, 139.1, 136.7, 132.0, 131.2, 125.4, 125.1, 123.3, 116.8, 116.1, 99.5, 77.2, 68.1, 49.7, 29.4, 25.9, 16.9; ESI-FTMS *m/z* calcd for $C_{23}H_{20}N_4O_6+H^+$: 449.14557; found: 449.14561.

4.2.13. 8-Methyl-3-(2-methylpropyl)-2-(4-nitrophenyl)-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6m. Yield 78%; ^{1}H NMR (DMSO-d_6) δ 8.42 (d, 2H, J=8.8 Hz), 8.24 (s, 1H), 8.16 (d, 2H, J=8.8 Hz), 7.92 (s, 1H), 7.88 (s, 1H), 7.67 (s, 1H), 4.32 (d, 2H, J=7.5 Hz), 2.52 (s, 3H), 1.87 (m, 1H), 0.65 (d, 6H, J=6.6 Hz); ^{13}C NMR (DMSO-d_6) δ 166.7, 158.9, 154.5, 149.8, 149.1, 148.9, 140.1, 139.6, 137.0, 131.3, 124.7, 123.3, 117.2, 116.1, 99.4, 52.2, 29.3, 20.1, 16.9; ESI-FTMS *m/z* calcd for $C_{22}H_{20}N_4O_5+H^+$: 421.15065; found: 421.15060.

4.2.14. 8-Methyl-2-(1-naphthalenyl)-6-oxo-3-(2-pyridinylmethyl)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6n. Yield 71%; ^{1}H NMR (DMSO-d_6) δ 8.34–8.28 (m, 2H), 8.14 (d, 1H, J=8.2 Hz), 8.04 (d, 1H, J=8.2 Hz), 7.90 (s, 1H), 7.81–7.76 (m, 2H), 7.73 (s, 1H), 7.68 (s, 1H), 7.66–7.61 (m, 2H), 7.58 (t, 1H, J=7.6 Hz), 7.50 (t, 1H, J=7.6 Hz), 7.18 (dd, 1H, J=7.0, 5.4 Hz), 7.05 (d, 1H, J=7.8 Hz), 5.54 (s, 2H), 2.56 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.7, 158.8, 155.6, 155.2, 149.8, 149.7, 149.2, 139.0, 138.6, 138.0, 133.8, 132.0, 131.5, 129.6, 129.1, 127.9, 127.3, 126.6, 125.9, 125.8, 123.7, 123.4, 122.5, 116.4, 116.3, 99.3, 49.8, 16.9; ESI-FTMS *m/z* calcd for $C_{28}H_{20}N_4O_3+H^+$: 461.16082; found: 461.16083.

4.2.15. 2-(9-Ethyl-9*H*-carbazol-3-yl)-8-methyl-3-(2-methylpropyl)-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6o. Yield 73%; ^{1}H NMR (DMSO-d_6) δ 8.73 (s, 1H), 8.31 (d, 1H, J=7.7 Hz), 8.19 (s, 1H), 8.06 (s, 1H), 7.97 (d, 1H, J=8.6 Hz), 7.88 (t, 2H, J=7.9 Hz), 7.71 (t, 2H, J=7.6 Hz), 7.56 (t, 1H, J=7.4 Hz), 7.30 (t, 1H, J=7.4 Hz), 4.55 (m, 2H), 4.45 (d, 2H, J=7.3 Hz), 2.55 (s, 3H), 1.96 (m, 1H), 1.38 (t, 3H, J=7.0 Hz), 0.67 (d, 6H, J=6.6 Hz); ^{13}C NMR (DMSO-d_6) δ 166.6, 158.8, 157.0, 149.9, 148.9, 141.3, 140.9, 138.5, 136.5, 127.5, 127.4, 123.7, 123.1, 122.8, 122.7, 121.7, 120.4, 118.6, 116.6, 114.7, 110.4, 99.9, 52.5, 38.0, 28.9, 20.2, 16.9, 14.5; ESI-FTMS *m/z* calcd for $C_{30}H_{28}N_4O_3+H^+$: 493.22342; found: 493.22333.

4.2.16. 3-(1,3-Benzodioxol-5-ylmethyl)-8-methyl-6-oxo-2-(2-thienyl)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6p. Yield 81%; ^{1}H NMR (DMSO-d_6) δ 8.20 (s, 1H), 7.85 (m, 2H), 7.73 (s, 1H), 7.65 (d, 2H, J=3.6 Hz), 7.24 (t, 1H, J=8.9 Hz), 6.82 (d, 1H, J=8.0 Hz), 6.70 (s, 1H), 6.46 (d, 1H, J=8.0 Hz), 5.97 (s, 2H), 5.74 (s, 2H), 2.51 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 166.7, 158.8, 150.4, 149.8, 149.1, 148.5, 147.4, 139.8, 139.6, 131.9, 131.3, 130.6, 129.5, 129.4, 123.2, 120.0, 116.4, 116.3, 109.3, 107.5, 101.9, 98.6, 48.2, 16.8; ESI-FTMS *m/z* calcd for $C_{24}H_{17}N_3O_5S+H^+$: 460.09617; found: 460.09612.

4.2.17. 8-Methyl-3-(1-methylpropyl)-6-oxo-2-(3-thienyl)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6q. Yield 75%; ^{1}H NMR (DMSO-d_6) δ 8.17 (s, 1H), 8.14 (dd,

1H, J=2.8, 1.2 Hz), 7.97 (s, 1H), 7.90 (s, 1H), 7.85 (dd, 1H, J=5.0, 2.8 Hz), 7.68 (s, 1H), 7.51 (dd, 1H, J=5.0, 1.2 Hz), 4.62 (m, 1H), 2.51 (s, 3H), 2.16 (m, 1H), 1.93 (m, 1H), 1.68 (d, 3H, J=6.9 Hz), 0.57 (t, 3H, J=7.3 Hz); ^{13}C NMR (DMSO-d_6) δ 166.7, 158.8, 152.4, 149.3, 148.9, 138.5, 135.6, 130.1, 129.5, 129.1, 128.7, 123.6, 116.3, 115.7, 100.6, 56.0, 27.4, 19.6, 16.8, 11.3; ESI-FTMS m/z calcd for $C_{20}H_{19}N_3O_3S+H^+$: 382.12199; found: 382.12203.

4.2.18. 3-Cyclopentyl-8-methyl-6-oxo-2-(2-pyridinyl)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6r. Yield 76%; ^{1}H NMR (DMSO-d_6) δ 8.78 (s, 1H), 8.25 (s, 1H), 8.19 (d, 1H, J=7.8 Hz), 8.06 (t, 1H, J=7.8 Hz), 7.90 (s, 1H), 7.68 (s, 2H), 7.59 (m, 1H), 5.93 (m, 1H), 2.52 (s, 3H), 2.22 (m, 2H), 2.12 (m, 2H), 2.02 (m, 2H), 1.70 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 166.7, 158.9, 154.0, 150.1, 149.8, 149.2, 149.0, 140.2, 138.4, 136.7, 126.2, 125.6, 123.4, 117.3, 116.0, 100.1, 58.2, 30.1, 25.2, 16.8; ESI-FTMS m/z calcd for $C_{22}H_{20}N_4O_3+H^+$: 389.16082; found: 389.16086.

4.2.19. 3-Cyclohexyl-8-methyl-6-oxo-2-(3-pyridinyl)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6s. Yield 81%; ^{1}H NMR (DMSO-d_6) δ 8.95 (d, 1H, J=1.2 Hz), 8.19 (dd, 1H, J=4.8, 1.2 Hz), 8.24–8.19 (m, 2H), 8.05 (s, 1H), 7.92 (s, 1H), 7.72 (dd, 1H, J=7.7, 5.0 Hz), 7.68 (s, 1H), 4.24 (m, 1H), 2.52 (s, 3H), 2.31 (m, 2H), 1.96 (m, 2H), 1.83 (m, 2H), 1.60 (m, 1H), 1.47 (m, 1H), 1.30 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 166.7, 158.9, 153.5, 151.0, 149.6, 149.2, 149.0, 140.3, 138.8, 136.5, 127.1, 124.9, 123.5, 116.8, 115.9, 100.9, 58.1, 30.8, 26.1, 24.7, 16.8; ESI-FTMS m/z calcd for $C_{23}H_{22}N_4O_3+H^+$: 403.17647; found: 403.17644.

4.2.20. 3-(Cyclohexylmethyl)-8-methyl-6-oxo-2-(4-pyridinyl)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6t. Yield 69%; ^{1}H NMR (DMSO-d_6) δ 8.90 (dd, 2H, J=4.9, 1.1 Hz), 8.25 (s, 1H), 8.05 (dd, 2H, J=4.9, 1.1 Hz), 7.93 (s, 1H), 7.88 (s, 1H), 7.68 (s, 1H), 4.37 (d, 2H, J=7.2 Hz), 2.52 (s, 3H), 1.60 (m, 1H), 1.49 (m, 3H), 1.28 (m, 2H), 1.98 (m, 3H), 0.79 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 166.7, 158.8, 153.4, 149.9, 149.3, 149.2, 149.1, 140.3, 139.9, 139.6, 124.9, 123.4, 117.4, 116.4, 99.5, 51.1, 38.4, 30.4, 26.3, 25.6, 16.9; ESI-FTMS m/z calcd for $C_{24}H_{24}N_4O_3+H^+$: 417.19212; found: 417.19208.

4.2.21. 8-Methyl-6-oxo-2-[(*E*)-2-phenylethenyl]-3-propyl-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6u. Yield 66%; ^{1}H NMR (DMSO-d_6) δ 8.09 (s, 1H), 7.95 (d, 1H, J=15.9 Hz), 7.89 (s, 1H), 7.87–7.82 (m, 3H), 7.67 (s, 1H), 7.55 (d, 1H, J=15.9 Hz), 7.48 (m, 2H), 7.44 (m, 1H), 4.51 (t, 2H, J=7.3 Hz), 2.51 (s, 3H), 1.79 (m, 2H), 0.90 (t, J=7.3 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 166.7, 158.8, 153.7, 149.7, 148.9, 139.9, 138.1, 137.9, 136.0, 130.6, 129.7, 128.8, 123.4, 116.5, 114.6, 113.3, 98.8, 45.4, 23.8, 16.9, 11.6; ESI-FTMS m/z calcd for $C_{23}H_{21}N_3O_3+H^+$: 388.16557; found: 388.16554.

4.2.22. 3-Butyl-2-[(*E*)-2-(4-dimethylaminophenyl)-ethenyl]-8-methyl-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6v. Yield 70%; ^{1}H NMR (DMSO-d_6) δ 7.99 (s, 1H), 7.94–7.87 (m, 3H), 7.72 (s, 1H), 7.66 (d, 2H, J=8.8 Hz), 7.17 (d, 1H, J=15.8 Hz), 6.76 (d, 2H, J=8.8 Hz), 4.52 (t, 2H, J=7.3 Hz), 3.02 (s, 6H), 2.50 (s, 3H), 1.75 (m, 2H), 1.34 (m, 2H), 0.89 (t, J=7.3 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 166.5, 158.5, 153.5, 152.8, 150.1, 148.5, 144.4, 136.4, 132.7, 131.3, 124.1, 122.6, 117.5, 112.6, 111.7, 103.3, 99.6, 44.4, 40.4, 32.0, 19.9, 16.8, 14.3; ESI-FTMS m/z calcd for $C_{26}H_{28}N_4O_3+H^+$: 445.22342; found: 445.22344.

4.2.23. 3-Benzyl-2-ethyl-8-methyl-6-oxo-6*H*-pyrano-[2,3-*f*]benzimidazole-7-carboxamide 6w. Yield 55%; ^{1}H NMR (DMSO-d_6) δ 8.13 (s, 1H), 7.86 (s, 1H), 7.78 (s, 1H), 7.67 (s, 1H), 7.36 (t, 2H, J=7.3 Hz), 7.31 (t, 1H, J=7.1 Hz), 7.20 (d, 2H, J=7.2 Hz), 5.64 (s, 2H), 3.01 (m, 2H), 2.50 (s, 3H), 1.31 (t, 3H, J=7.4 Hz); ^{13}C NMR (DMSO-d_6) δ 166.5, 160.0, 158.7, 149.8, 148.9, 148.8, 137.4, 136.4, 129.6, 128.7, 127.6, 123.7, 116.4, 114.5, 99.1, 47.6, 20.8, 16.9, 11.6; ESI-FTMS m/z calcd for $C_{21}H_{19}N_3O_3+H^+$: 362.14992; found: 362.14998.

4.2.24. 3-(3-Ethoxypropyl)-8-methyl-6-oxo-2-(2-phenylethyl)-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6x. Yield 56%; ^{1}H NMR (DMSO-d_6) δ 8.13 (s, 1H), 7.90 (s, 1H), 7.79 (s, 1H), 7.69 (s, 1H), 7.33–7.27 (m, 4H), 7.22 (m, 1H), 4.34 (t, 2H, J=6.3 Hz), 3.37–3.26 (m, 6H), 3.19 (t, 2H, J=7.5 Hz), 2.51 (s, 3H), 1.94 (m, 2H), 1.03 (t, 3H, J=7.0 Hz); ^{13}C NMR (DMSO-d_6) δ 166.6, 158.7, 158.0, 149.7, 148.8, 140.9, 137.0, 135.4, 129.2, 129.1, 127.1, 123.7, 116.4, 114.2, 99.1, 66.8, 66.1, 41.8, 33.0, 29.4, 28.5, 16.9, 15.7; ESI-FTMS m/z calcd for $C_{25}H_{27}N_3O_4+H^+$: 434.20744; found: 434.20745.

4.2.25. 8-Methyl-2-(1-methylethyl)-6-oxo-3-propyl-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6y. Yield 73%; ^{1}H NMR (DMSO-d_6) δ 8.11 (s, 1H), 7.95 (s, 1H), 7.91 (s, 1H), 7.69 (s, 1H), 4.34 (t, 2H, J=7.2 Hz), 3.51 (m, 1H), 2.49 (s, 3H), 1.79 (m, 2H), 1.41 (d, 6H, J=6.7 Hz), 0.94 (t, 3H, J=7.3 Hz); ^{13}C NMR (DMSO-d_6) δ 166.5, 162.9, 158.6, 149.8, 148.7, 136.6, 134.4, 123.9, 116.7, 113.8, 99.6, 46.1, 26.3, 23.3, 21.8, 16.8, 11.5; ESI-FTMS m/z calcd for $C_{18}H_{21}N_3O_3+H^+$: 328.16557; found: 328.16553.

4.2.26. 2-Cyclohexyl-8-methyl-3-[2-(4-morpholinyl)-ethyl]-6-oxo-6*H*-pyrano[2,3-*f*]benzimidazole-7-carboxamide 6z. Yield 68%; ^{1}H NMR (DMSO-d_6) δ 8.11 (s, 1H), 7.91 (s, 1H), 7.81 (s, 1H), 7.66 (s, 1H), 4.68 (t, 2H, J=7.9 Hz), 3.90 (m, 4H), 3.52 (t, 2H, J=7.9 Hz), 3.42 (m, 4H), 3.05 (m, 1H), 2.49 (s, 3H), 1.97 (m, 2H), 1.84 (m, 2H), 1.75 (m, 1H), 1.65 (m, 2H), 1.47 (m, 2H), 1.30 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 166.7, 162.2, 158.8, 149.5, 149.2, 138.5, 137.2, 123.2, 115.8, 115.5, 98.5, 64.2, 53.6, 52.2, 38.4, 35.5, 32.1, 26.1, 26.0, 16.9; ESI-FTMS m/z calcd for $C_{24}H_{30}N_4O_4+H^+$: 439.23399; found: 439.23406.

Acknowledgements

This work was supported by NIH R33CA-86364, R33CA-99136, R01CA-098116, R21CA-102732, and NSF CHE-0302122. The 500 MHz NMR spectrometer was purchased in part with the grant NSF 9724412. We thank Dr. Alan Lehman for editorial assistance.

References and notes

1. (a) Cragg, G. M.; Newman, D. J.; Snader, K. M. *J. Nat. Prod.* **1997**, *60*, 52–60. (b) Newman, D. J.; Cragg, G. M.; Snader, K. M. *Nat. Prod. Rep.* **2000**, *17*, 215–234. (c) Clardy, J.; Walsh, C. *Nature* **2004**, *432*, 829–837.
2. (a) Wessjohann, L. A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 303–309. (b) Hall, D. G.; Manku, S.; Wang, F. *J. Comb. Chem.* **2001**, *3*, 125–150. (c) Lee, M.-L.; Schneider, G. *J. Comb. Chem.* **2001**, *3*, 284–289. (d) Nielsen, J. *Curr. Opin. Chem. Biol.* **2002**, *6*, 297–305. (e) Ortholand, J.-Y.; Ganesan, A. *Curr. Opin. Chem. Biol.* **2004**, *8*, 271–280.
3. (a) Franzén, R. G. *J. Comb. Chem.* **2000**, *2*, 195–214. (b) Ganesan, A. *Drug Discovery Today* **2002**, *7*, 47–55.
4. Sethna, S. M.; Shah, N. M. *Chem. Rev.* **1945**, *36*, 1–62.
5. (a) Murray, R. D. H.; Mendez, J.; Brown, S. A. *The Natural Coumarins: Occurrence, Chemistry and Biochemistry*; Wiley: New York, 1982. (b) Hoult, J. R.; Paya, M. *Gen. Pharmacol.* **1996**, *27*, 713–722. (c) *Coumarins: Biology, Applications and Mode of Action*; O'Kennedy, R., Thornes, R. D., Eds.; Wiley: Chichester, UK, 1997.
6. Borges, F.; Roleira, F.; Milhazes, N.; Santana, L.; Uriarte, E. *Curr. Med. Chem.* **2005**, *12*, 887–916.
7. (a) Hemmila, I. A. *Appl. Fluorescence Technol.* **1989**, *1*, 1–8. (b) Katerinopoulos, H. E. *Curr. Pharm. Des.* **2004**, *10*, 3835–3852.
8. (a) Zarebska, Z.; Waszkowska, E.; Caffieri, S.; Dall'Acqua, F. *Farmaco* **2000**, *55*, 515–520. (b) Bethea, D.; Fullmer, B.; Syed, S.; Seltzer, G.; Tiano, J.; Rischko, C.; Gillespie, L.; Brown, D.; Gasparro, F. P. *J. Dermatol. Sci.* **1999**, *19*, 78–88.
9. Song, A.; Zhang, J.; Lam, K. S. *J. Comb. Chem.* **2004**, *6*, 112–120.
10. Song, A.; Zhang, J.; Lebrilla, C. B.; Lam, K. S. *J. Comb. Chem.* **2004**, *6*, 604–610.
11. Song, A.; Lam, K. S. *Tetrahedron* **2004**, *60*, 8605–8612.
12. (a) Smith, J. M.; Krchňák, V. *Tetrahedron Lett.* **1999**, *40*, 7633–7636. (b) Mazurov, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 67–70.
13. (a) Mayer, J. P.; Lewis, G. S.; McGee, C.; Bankaitis-Davis, D. *Tetrahedron Lett.* **1998**, *39*, 6655–6658. (b) Tumelty, D.; Schwarz, M. K.; Cao, K.; Needels, M. C. *Tetrahedron Lett.* **1999**, *40*, 6185–6188. (c) Vourloumis, D.; Takahashi, M.; Simonsen, K. B.; Ayida, B. K.; Barluenga, S.; Winters, G. C.; Hermann, T. *Tetrahedron Lett.* **2003**, *44*, 2807–2811.
14. Wu, Z.; Rea, P.; Wickham, G. *Tetrahedron Lett.* **2000**, *41*, 9871–9874.
15. Beaulieu, P. L.; Haché, B.; von Moos, E. *Synthesis* **2003**, 1683–1692.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 4400–4407
Tetrahedron

Studies on pyrrolidinones. Oxidations and rearrangements in the hexahydrobenz[*f*]indolizine-3,10-dione series

Anne Bourry,[a,†] Daniel Couturier,[b] Gérard Sanz,[c] Luc Van Hijfte,[c] Jean-Pierre Hénichart[d,†] and Benoît Rigo[a,*,†]

[a]*Ecole des Hautes Etudes Industrielles, 13 rue de Toul, 59046 Lille, France*
[b]*Laboratoire d'Ingénierie Moléculaire, Université des Sciences et Technologies, 59655 Villeneuve d'Ascq, France*
[c]*Johnson and Johnson Pharmaceutical Research and Development, Campus de Maigremont, 27106 Val de Reuil, France*
[d]*Institut de Chimie Pharmaceutique Albert Lespagnol, Université de Lille 2, 59006 Lille, France*

Received 21 November 2005; revised 20 February 2006; accepted 21 February 2006

Available online 20 March 2006

Abstract—Air oxidation of hexahydrobenz[*f*]indolizine-3,10-diones in MeOH/MeONa yields alcohols, which are easily and selectively transformed, in very good yields, to succinimides, isoquinoline propanoic acids or dehydrated to ene lactams.

1. Introduction

We have already described the synthesis of many *N*-arylmethylpyroglutamic acids **1**[1] and their ring closure into ketones **2** and **3**.[2] Studies on reactions of heterocycles **2** in acidic conditions led to the specific synthesis of dienes **4** and **5**,[3] isoquinolines **6** and **7**, and dimers **8**.[3a,4] During the ring closure of acids **1** to ketones **2**,[2a,b] some by-products such as **7** or **9** were frequently isolated by crystallization or distillation (Fig. 1).[2f,4] We recently performed a purification of crude **2a** (R=H) by using preparative chromatography on SiO_2. We thus isolated new compounds in minute

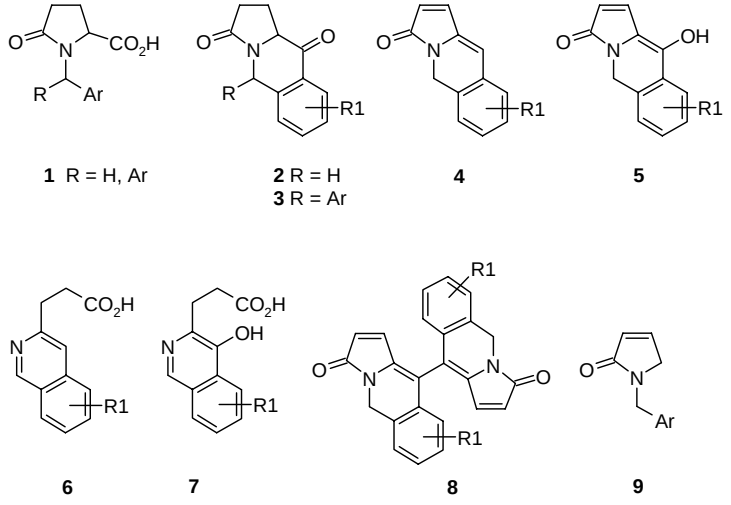
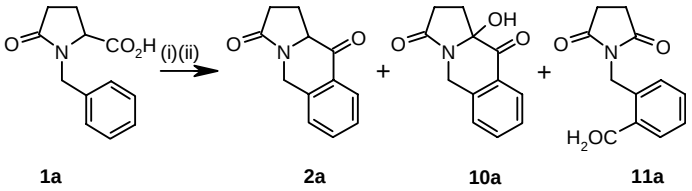


Figure 1. Acids **1**, ketones **2** and **3**, and some compounds issued from their transformations.

Keywords: Pyroglutamic derivatives; Pyrrolidinone oxidation; *N*-acyliminium salts.
* Corresponding author. Tel.: +33 28 38 48 58; fax: +33 28 38 48 04; e-mail: rigo@hei.fr
† Groupe de Recherche sur l'Inhibition de la Prolifération Cellulaire, EA 2692 Lille, France.

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.060



Scheme 1. (i) $SOCl_2$, $ClCH_2CH_2Cl$; (ii) $AlCl_3$ (**10a**, **11a** < 1%).

amounts, alcohol **10a** and succinimide **11a** (Scheme 1). We now have been studying the formation of alcohols **10** and their reactivity.

2. Results and discussion

2.1. Oxidation of ketones 2

Alcohol **10a** was obviously formed from peroxidation of ketone **2a** with oxygen from air. Indeed we have already observed that heterocycle **2a** was rapidly degraded in the presence of oxygen,[2a] and oxidation of the CO–N–CH–CO group has often been described,[5] leading to compounds such as hydroperoxides **12a**–**c**[6] or alcohols such as **12d**[7] (Fig. 2). It is known that a hydroxy group can be introduced in the α-position of lactams by electrochemical oxidation.[8] Thus, we attempted to obtain **10a** by electrolysis of lactam **2a** in a MeOH/MeONa solution. Interestingly, transformation to alcohol **10a** was entirely obtained before connecting the carbon electrodes to the power line (Scheme 2).

Thus compound **2a** was spontaneously oxidized in the reaction media. It is known that electron-rich compounds like enolates can react with oxygen triplet, by intermediate formation of carbon centered radicals, to yields alcohols.[9] Therefore, oxidation of heterocycles **2a**–**c**[2a,b] was realized by stirring these ketones in an open to air MeONa/MeOH solution. In these conditions, alcohols **10a–c** were obtained in 70–75% yields (Scheme 2). Noteworthy, further reaction of products **10** with O_2 and MeONa were not observed (see Section 2.2); it showed also to be important to perform purification of these alcohols by using EtOAc and not CH_2Cl_2 as the solvent during the extraction step (see Section 2.3). In the same way, it was necessary to use citric acid and not HCl to realize the neutralization of MeONa (see Section 2.4).

Interestingly only one aromatic group is included in the structure of alcohols **10**. It was thought previously that complex α-ketocarbinolamides needed to be stabilized by the presence of two neighboring aromatic rings.[10]

2.2. Transformations of the CON–C(OR)–CO group described in literature

The alcohol function of compounds **10** is vicinal to a lactam and a ketone group. Literature indicates that the CON–C(OOH)–CO and CON–C(OH)–CO scaffold are rather reactive when they are exposed to sodium methoxide or sodium hydroxide; for instance, in the chemistry of berberines, the opening in theses conditions of the ketone ring of hydroperoxides **13** and **14**[10] or of alcohol **15**[11a] and **16**[11b] was described (Scheme 3).

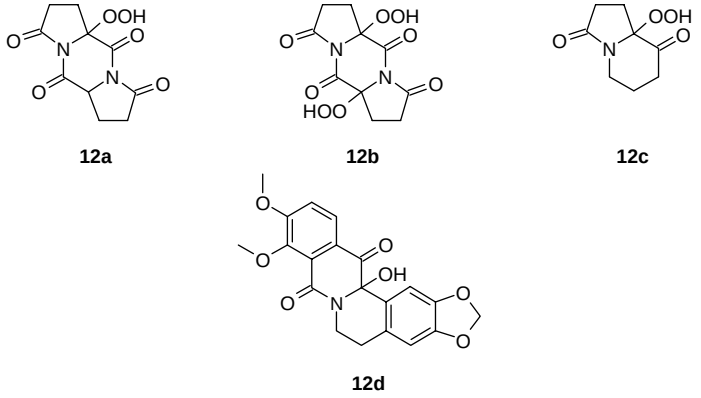
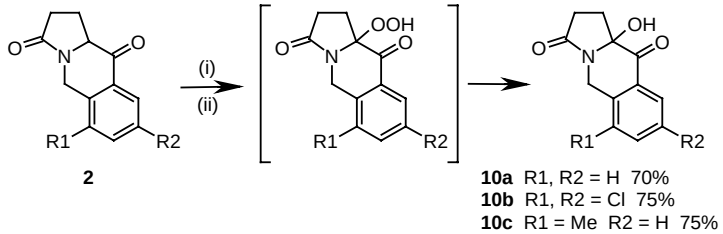
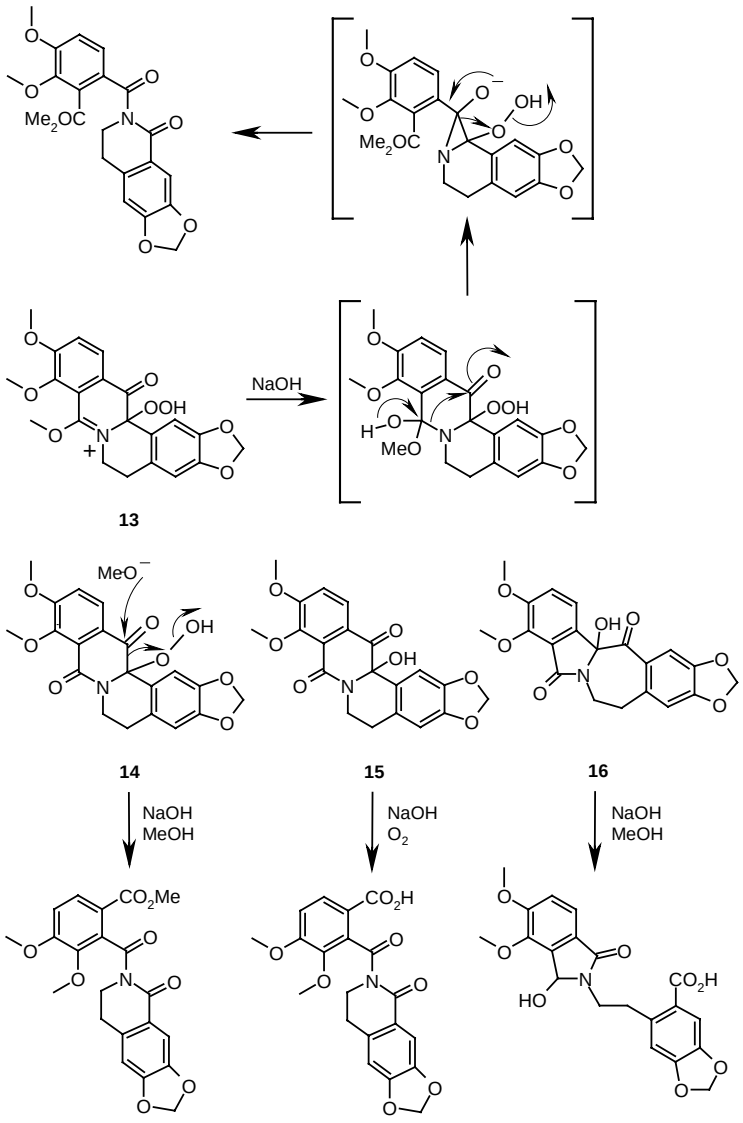


Figure 2. Products obtained from oxidation of a CO–N–CHCO group.



Scheme 2. Reaction conditions: (i) MeOH, MeONa, dissolved O_2, 30 min, 20 °C; (ii) citric acid (70–75%).



Scheme 3. Transformation of hydroperoxides or alcohols described in literature.

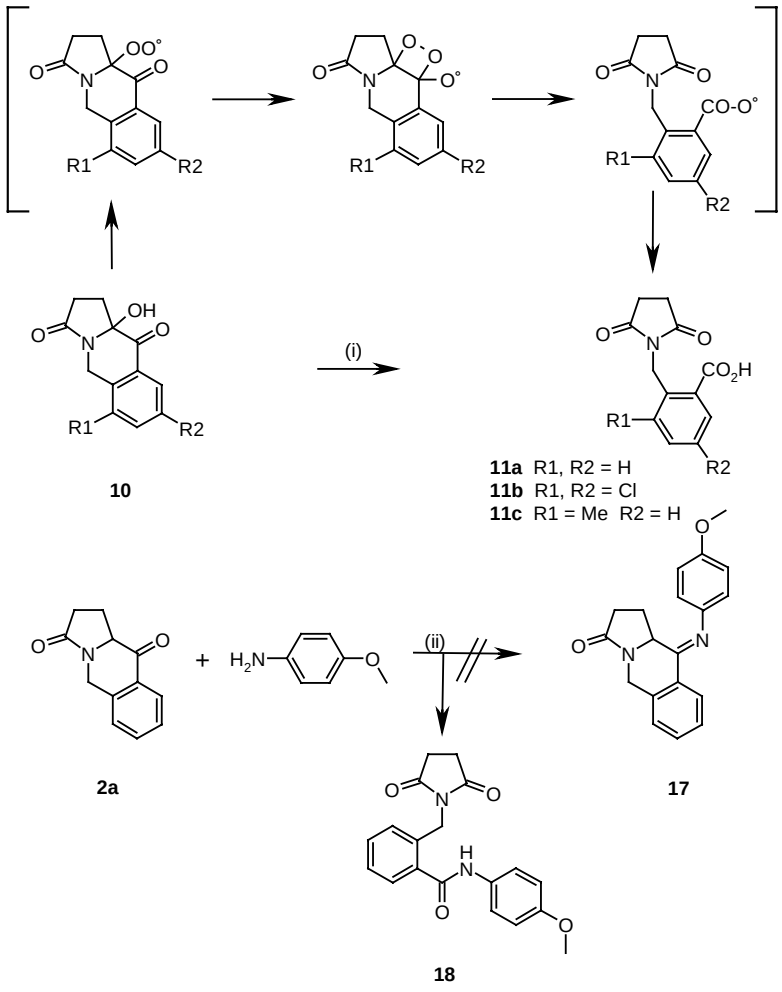
2.3. Oxidation of alcohol 10 to succinimides 11

Unlike hydroxylactams **15** or **16**, alcohols **10** remained unaltered in the presence of sodium methoxide and, after their formation, they can be isolated by extraction with ethyl acetate; when the extraction step was performed with dichloromethane, these compounds were slowly converted to succinimides **11**. The same transformation was observed when pure alcohols **10** were solubilized in CH_2Cl_2, and was accelerated by heating, even under a nitrogen atmosphere. Succinimides **11** were also rapidly obtained by stirring compounds **10** in a solution of trifluoroacetic acid in dichloromethane or by refluxing **10a** 1 h with *p*-toluenesulfonic acid in toluene. These reactions explained the result obtained in an attempt to synthesize imine **17**: a mixture of ketone **2a**, PTSA and anisidine was refluxed in toluene to give amide **18** as the only isolated product; that also focus on the low reactivity of the ketone function of heterocycles **2** towards amines (Scheme 4).

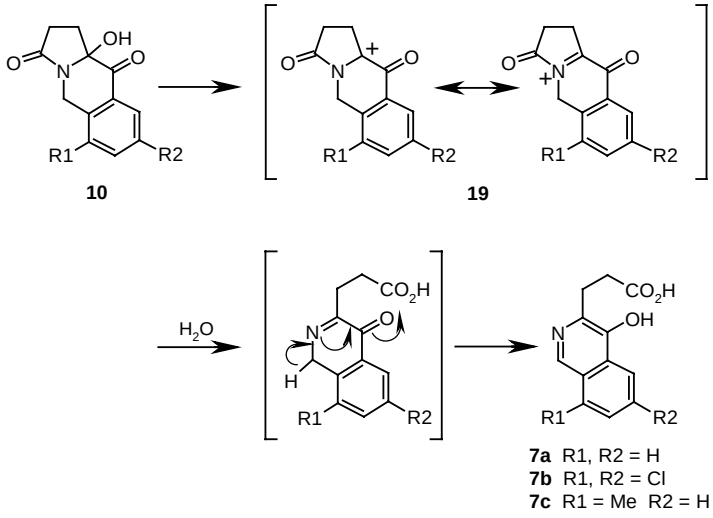
These results can be explained by the fact that trace amount of oxygen still remained in the solvent used.[12a] The dichloromethane utilized was dehydrated by distillation on P_2O_5, and reaction rates decreased in the presence of hydroquinone, or if the solvent was deoxygenated with nitrogen. Thus it is clear that oxygen dissolved in the solvent leads to incorporation of an oxygen atom in the structure of the heterocycle; although exact mechanism of this oxidation was not studied, it is not apparented to the Bayer–Villiger reaction,[12b] and it is possible to suggest a pathway (Scheme 4) based on the results of Compostella.[12c]

2.4. Rearrangement of alcohols 10 to hydroxyisoquinolines 7

We have indicated in Section 2.3 that alcohols **10** were not rapidly oxidized in ethyl acetate. In that solvent, trifluoroacetic acid gave not succinimide **11** but water and an acyliminium salt **19**.[13] Water acting as a nucleophile open the lactam ring, and then aromatization led to a very good



Scheme 4. Reaction conditions: (i) CH_2Cl_2, CF_3CO_2H, 30 min, 20 °C, 100%; (ii) PTSA, toluene, reflux, 72 h, 41%.

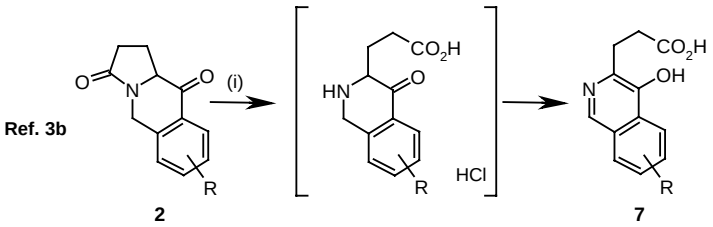


Scheme 5. Reaction conditions: (i) EtOAc, hydroquinone, N_2, CF_3CO_2H, 2 h, 20 °C, 100%.

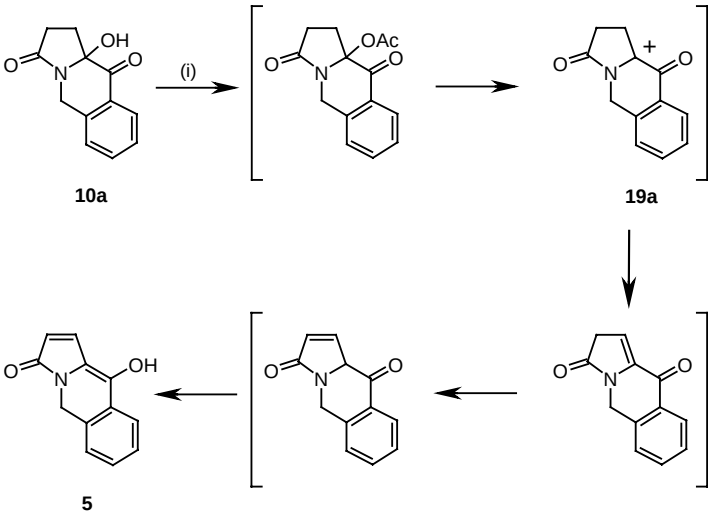
yield of hydroxyisoquinolines **7** (Scheme 5). Noteworthy, formation of heterocycles **7** was very easy when using that route (oxidation of **2** in basic medium, then acidic rearrangement) and gave no by-products, whereas another method already described (reflux of ketones **3** in HCl, Scheme 6), gave lower yields and needed a considerable purification of acids **7** (Scheme 6).[3b]

2.5. Dehydration of alcohol 10a to pyrroloisoquinoline 5

Reaction of alcohols **10** with an organic base in dichloromethane was not studied, but in that solvent with trifluoroacetic acid yielded iminium salts **19**, which led to acids **7** (Scheme 5). In other conditions, reaction of **10a** with acetyl chloride in deoxygenated ethyl acetate gave good

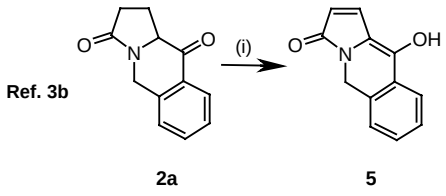


Scheme 6. Rearrangement of ketones **2** to isoquinolines (lit. 3b). Reaction conditions: (i) Concd HCl/H_2O 60/40, air, 55–70 °C, 5–20 h, 60–90%.



Scheme 7. Reaction conditions: (i) EtOAc, N_2, CH_3COCl, 3 h, 20 °C, 70%.

yield of pyrrolinone **5**. As shown in Scheme 7, acyliminium salt **19a** was again an intermediate: in the absence of a good nucleophile such as water, lactam ring opening did not occur, and elimination of the proton α to the carbocation, followed by migration of the double bond gave a 3-pyrrolinone.[2f,3,14] Enolization of the ketone group then yielded compound **5**. We have already described that heterocycle **5** can be obtained less efficiently by bubbling oxygen in a solution of ketone **10a** in hydrochloric acid at room temperature (Scheme 8).[3b]



Scheme 8. Rearrangement of ketones **2a** to ene lactam **5** (lit. 3b). Reaction conditions: (i) Concd HCl, O_2, 18 h, 20 °C, 40%.

2.6. Attempted generalization of the oxidations

As indicated previously, the oxidation of ketones **2** in basic media is a property common to many compounds with the CO–N–CH–CO scaffold. We attempted to generalize the same reaction to ester **20**[1h] and ketone **21**.[2a] These oxidations did not succeed; however, when a solution of ketone **3a**[2d] and sodium methylate in methanol was stirred in the presence of air, anthraquinone **22** and lactone **23**[15] were rapidly formed (Scheme 9).

It is known that the photo-oxygenation[16] of some protoberberine derivatives yields products such as **24**, which decomposes to **25** via **26** then **27** (Scheme 10). Taking these results in account, we think that formation of an epidioxide **28** (Scheme 9) led to intermediate **29**. The N–C$(Ar)_2$ bound in the latter was broken due to the presence of two aromatic groups, and ring closure of the resulting acyl radical yielded **22** and **23**.

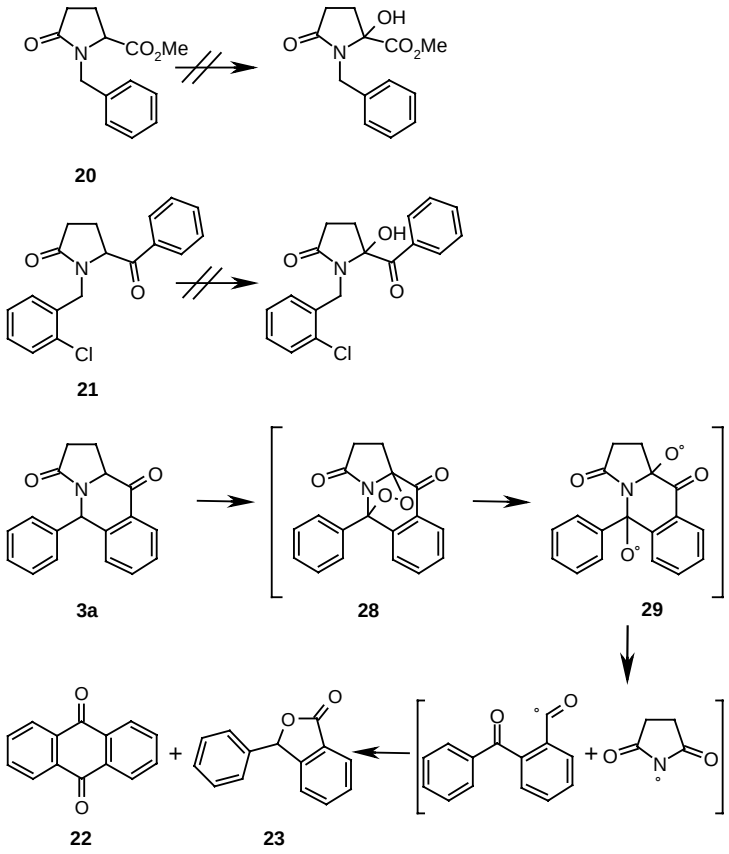
3. Conclusion

Oxidation of the anion of ketones **2** is a general reaction, which occurs readily in methanol. The a-hydroxylactams thus obtained are oxidized in high yields to give new succinimides or, via acyliminium salts, are transposed in isoquinolines derivatives. It is now by far easier to synthesize and purify lactam **5** and hydroxy isoquinolines **7**.

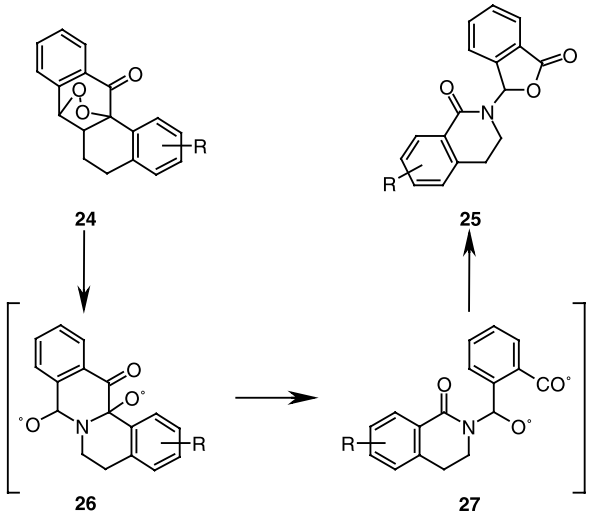
4. Experimental

4.1. Materials

Melting points were determined using an Electrothermal apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained on a Varian Gemini 2000 at 200 and 50 MHz, respectively. IR spectra were carried out in ATR mode on a FTIR Bruker Tensor 27. Thin-layer chromatography was performed on precoated Kieselgel 60F_{254} plates. Micro-analyses were performed by the 'Service Central de



Scheme 9. Reaction conditions: (i) MeOH, MeONa, dissolved O_2, 30 min, 20 °C, 40%.



Scheme 10. Evolution of an epidioxide described in literature.

Microanalyses' of CNRS in Vernaison, France, or at the University of Dijon, France.

4.1.1. 10a-Hydroxy-1,10a-dihydropyrrolo[1,2-*b*]isoquinoline-3,10(2*H*,5*H*)-dione (10a). Ketone **2a**,[2a,b] (2 g, 9.9 mmol) was added to a solution of sodium methoxide (10.2 mmol) in methanol (250 ml). The yellow solution was stirred at room temperature for 30 min, and then acidified to pH 5 with an aqueous solution of citric acid (the yellow color disappeared). The solvent was evaporated and the residue was dissolved in ethyl acetate. After washings (water then $NaHCO_3$ solution) the organic phase was dried (Na_2SO_4) then evaporated. The solid obtained was recrystallized from ethyl acetate to give 70% of alcohol **10a**; mp 133–134 °C; R_f 0.60 (EtOAc); IR: ν (cm^{-1}) 2980, 1698, 1628, 1607, 1456, 1200; ^1H NMR ($CDCl_3$): δ (ppm) 2.16–2.51 (m, 2H), 2.60–2.85 (m, 2H), 2.99 (br s, 1H, deuterium oxide exchangeable), 4.48 (d, $J=17.8$ Hz, 1H), 5.09 (d, $J=17.8$ Hz, 1H), 7.34 (d, $J=7.6$ Hz, 1H), 7.44 (t, $J=7.6$ Hz, 1H), 7.62 (t, $J=7.6$ Hz, 1H), 8.11 (d, $J=7.6$ Hz, 1H). Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45; O, 22.10. Found: C, 66.22; H, 5.05; N, 6.44; O, 22.27.

4.1.2. 6,8-Dichloro-10a-hydroxy-1,10a-dihydropyrrolo-[1,2-*b*]isoquinoline-3,10(2*H*,5*H*)-dione (10b). This product was obtained from **2b**,[2a] in the same way as for **10a**, yield 75%; mp 135–136 °C (EtOAc); R_f 0.75 (EtOAc); IR: ν (cm^{-1}) 3210, 3080, 1715, 1668, 1591, 1462, 1172; ^1H NMR (NaOD/D_2O): δ (ppm) 1.85–2.10 (m, 1H), 2.40–2.90 (m, 3H), 4.14 (d, $J=19$ Hz, 1H), 4.67 (d, $J=19$ Hz, 1H), 7.61 (s, 1H), 7.75 (s, 1H). Anal. Calcd for $C_{12}H_9Cl_2NO_3$: C, 50.38; H, 3.17; N, 4.90. Found: C, 50.19; H, 3.04; N, 5.11.

4.1.3. 10a-Hydroxy-6-methyl-1,10a-dihydropyrrolo[1,2-*b*]isoquinoline-3,10(2*H*,5*H*)-dione (10c). This compound was obtained from **2c**,[2a] in the same way as for **10a**, yield 75%; mp 103–104 °C (EtOAc); R_f 0.65 (EtOAc); IR: ν (cm^{-1}) 3100, 1710, 1650, 1597, 1451, 1178; ^1H NMR (NaOD/D_2O): δ (ppm) 1.88–2.05 (m, 1H), 2.26 (s, 3H), 2.30–2.82 (m, 3H), 4.18 (d, $J=18.4$ Hz, 1H), 4.63 (d, $J=18.4$ Hz, 1H), 7.31 (t, $J=7.3$ Hz, 1H), 7.44 (d, $J=7.3$ Hz,

1H), 7.77 (d, J=7.3 Hz, 1H); ^{1}H NMR (DMSO-d_6): δ (ppm) 18.0 (CH_3), 27.5 (CH_2), 28.5 (CH_2), 37.1 (CH_2), 86.1 (C), 125.1 (CH), 127.2 (CH), 128.9 (C), 135.1 (CH, C), 137.3 (C), 173.4 (C), 190.3 (C). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06; O, 20.76. Found: C, 67.64; H, 5.53; N, 5.99; O, 20.98.

4.1.4. 2-[(2,5-Dioxo-1-pyrrolidinyl)methyl]benzoic acid (11a). Alcohol **10a** (1 g, 4.6 mmol) was added to a solution of trifluoroacetic acid (0.5 ml, 0.74 g, 6.5 mmol) in dichloromethane (50 ml). The solution was stirred for 30 min at room temperature and then the solvents were evaporated to give a quantitative yield of succinimide **11a**; mp 214–215 °C (EtOAc); R_f 0.65 (MeOH); IR: ν (cm^{-1}) 3010, 1781, 1691, 1578, 1493, 1060; ^{1}H NMR ($CDCl_3$/CF_3CO_2H): δ (ppm) 2.95 (s, 4H), 5.23 (s, 2H), 7.16 (d, J= 8.0 Hz, 1H), 7.44 (t, J=8.0 Hz, 1H), 7.58 (tt, J=8.0, 1.3 Hz, 1H), 8.10 (dt, J=8.0, 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$/CF_3CO_2H): 28.2 ($2CH_2$), 40.9 (CH_2), 127.4 (CH), 127.9 (C), 128.3 (CH), 132.3 (CH), 134.2 (CH), 136.5 (C), 173.4 (C), 179.7 (2C). Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01; O, 27.44. Found: C, 61.84; H, 4.73; N, 6.11; O, 27.72.

4.1.5. 3,5-Dichloro-2-[(2,5-dioxo-1-pyrrolidinyl)methyl]-benzoic acid (11b). This compound was obtained in the same way as for **11a**, yield 100%; mp 270–272 °C (EtOAc); R_f 0.70 (MeOH); IR; ν (cm^{-1}) 3290, 1706, 1613, 1572, 1427, 1008; ^{1}H NMR (D_2O/NaOD): δ (ppm) 1.91 (s, 4H), 4.01 (s, 2H), 6.83 (s, 1H), 7.02 (s, 1H). Anal. Calcd for $C_{12}H_9Cl_2NO_4$: C, 47.71; H, 3.00; N, 4.64. Found: C, 47.58; H, 2.89; N, 4.77.

4.1.6. 2-[(2,5-Dioxo-1-pyrrolidinyl)methyl]-3-methyl-benzoic acid (11c). This compound was obtained in the same way as for **11a**, yield 100%; mp 144–145 °C (EtOAc); R_f 0.60 (MeOH); IR: ν (cm^{-1}) 3025, 1772, 1700, 1595, 1453, 1060 ^{1}H NMR (D_2O/NaOD): δ (ppm) 2.31 (s, 3H), 2.44 (s, 4H), 4.43 (s, 2H), 7.17–7.30 (m, 3H). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66; O, 25.88. Found: C, 63.22; H, 5.42; N, 5.45; O, 26.03.

4.1.7. 2-[(2,5-Dioxo-1-pyrrolidinyl)methyl]-*N*-(4-methoxyphenyl)benzamide (18). A stirred mixture of ketone **2a**,[2a,b] (3 g, 14.9 mmol), *p*-anisidine (1.8 g, 14.9 mmol) and *p*-toluenesulfonic acid hydrate (0.14 g, 0.7 mmol) was refluxed in toluene (75 ml) for 72 h while removing the azeotrope. The solid obtained upon cooling was washed with ether then recrystallized from methanol to give 41% of amide **17**; mp 218–220 °C; R_f 0.40 (EtOAc); IR: ν (cm^{-1}) 3266, 1770, 1701, 1636, 1597, 1529, 1512, 1466, 1444, 1027; ^{1}H NMR ($CDCl_3$): δ (ppm) 2.81 (s, 4H), 3.81 (s, 3H), 4.89 (s, 2H), 6.90 (d, J=9.0 Hz, 2H), 7.21 (m, 1H), 7.36 (t, J=5.2 Hz, 1H), 7.40 (t, J=5.2 Hz, 1H), 7.61 (m, 1H), 7.69 (d, J=9.0 Hz, 2H), 9.5 (br s, 1H, deuterium oxide exchangeable); ^{13}C NMR ($CDCl_3$): δ (ppm) 28.2 ($2CH_2$), 39.5 (CH_2), 55.4 (CH_3), 113.9 (2CH), 121.0 (2CH), 128.1 (CH), 128.2 (CH), 128.6 (CH), 130.3 (CH), 131.3 (C), 131.7 (C), 137.1 (C), 156.0 (C), 166.4 (C), 177.4 (2C). Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.45; H, 5.36; N, 8.28; O, 18.91. Found: C, 67.43; H, 5.35; N, 8.34; O, 19.21.

4.1.8. 3-(4-Hydroxy-3-isoquinolinyl)propanoic acid (7a). Nitrogen gas was bulled for 30 min into stirred ethyl acetate (300 ml), and then hydroquinone (1 g) was added. Nitrogen gas was bulled again for 15 min then alcohol **10a** (2 g, 9.2 mmol) and trifluoroacetic acid (1.5 ml, 2.2 g, 19.5 mmol) were added. After stirring at room temperature for 2 h (nitrogen) the solution was evaporated. The residue was stirred with ether, collected by filtration then washed with dichloromethane to give 100% yield of acid **7a** with the same properties as already described.[3b]

4.1.9. 3-(6,8-Dichloro-4-hydroxy-3-isoquinolinyl)propanoic acid (7b). This compound was obtained in the same way as for **7a**, yield 100%; mp 144–146 °C (acetone); R_f 0.20 (EtOAc/MeOH, 80/20); IR: ν (cm^{-1}) 1698, 1660, 1620, 1590, 1555; ^{1}H NMR (D_2O/NaOD): δ (ppm) 2.32–2.50 (m, 2H), 2.85–3.11 (m, 2H), 7.38 (s, 1H), 8.02 (s, 1H), 8.36 (s, 1H). Anal. Calcd for $C_{12}H_9Cl_2NO_3$: C, 50.38; H, 3.17; N, 4.90. Found: C, 50.02; H, 3.36; N, 4.63.

4.1.10. 3-(4-Hydroxy-8-methyl-3-isoquinolinyl)propanoic acid (7c). This product was obtained in the same way as for **7a**; yield 100% of compound with the same properties as already described.[3b]

4.1.11. 10-Hydroxypyrrolo[1,2-*b*]isoquinolin-3(5*H*)-one (5). Nitrogen gas was bulled for 30 min into stirred ethyl acetate (20 ml) then alcohol **10a** (2 g, 9.2 mmol) was added. Upon solubilization, acetyl chloride (2 ml, 2.2 g, 28 mmol) was added and the solution was stirred for 3 h. The solid obtained upon evaporation of solvents was dissolved in dilute sodium hydroxide. Upon acidification with dilute hydrochloric acid, compound **5** was obtained in 70% yield with the same properties as already described.[3b]

Acknowledgements

We thank the Norbert Segard Foundation for A.B.'s scholarship.

References and notes

1. (a) Kolocouris, N.; Rigo, B. *Chim. Chron. New Ser.* **1982**, *11*, 309–317. (b) Rigo, B.; Fossaert, E.; de Quillacq, J.; Kolocouris, N. *J. Heterocycl. Chem.* **1984**, *21*, 1381–1383. (c) Rigo, B.; Couturier, D. *J. Heterocycl. Chem.* **1985**, *22*, 207–208. (d) Rigo, B.; Dolaine, R.; El Ghammarti, S.; Couturier, D. *J. Heterocycl. Chem.* **1996**, *33*, 1063–1066. (e) Rigo, B.; Gautret, P.; Legrand, A.; Hénichart, J.-P.; Couturier, D. *Synlett* **1997**, 998–1000. (f) Rigo, B.; Gautret, P.; Legrand, A.; Hénichart, J.-P.; Couturier, D. *J. Heterocycl. Chem.* **1998**, *35*, 567–573. (g) Bourry, A.; Rigo, B.; Sanz, G.; Couturier, D. *J. Heterocycl. Chem.* **2002**, *39*, 119–124. (h) Bourry, A.; Akué-Gédu, R.; Rigo, B.; Hénichart, J.-P.; Sanz, G.; Couturier, D. *J. Heterocycl. Chem.* **2003**, *40*, 989–993.
2. (a) Rigo, B.; Kolocouris, N. *J. Heterocycl. Chem.* **1983**, *20*, 893–898. (b) Rigo, B.; Gautret, P.; Legrand, A.; El Ghammarti, S.; Couturier, D. *Synth. Commun.* **1994**, *24*, 2609–2615. (c) Al Akoum Ebrik, S.; Legrand, A.; Rigo, B.;

Couturier, D. *J. Heterocycl. Chem.* **1999**, *36*, 997–1000. (d) Legrand, A.; Rigo, B.; Gautret, P.; Hénichart, J.-P.; Couturier, D. *J. Heterocycl. Chem.* **1999**, *36*, 1263–1270. (e) Legrand, A.; Rigo, B.; Hénichart, J.-P.; Norberg, B.; Camus, F.; Durant, F.; Couturier, D. *J. Heterocycl. Chem.* **2000**, *37*, 215–227. (f) Akué-Gédu, R.; Al Akoum Ebrik, S.; Witczak-Legrand, A.; Fasseur, D.; El Ghammarti, S.; Couturier, D.; Decroix, B.; Othman, M.; Debacker, M.; Rigo, B. *Tetrahedron* **2002**, *58*, 9239–9247. (g) Bourry, A.; Akué-Gédu, R.; Hénichart, J.-P.; Sanz, G.; Rigo, B. *Tetrahedron Lett.* **2004**, *45*, 2097–2101.

3. (a) Rigo, B.; Tulier, E.; Barbry, D.; Couturier, D.; Warin, V.; Lamiot, J.; Baert, F. *J. Heterocycl. Chem.* **1990**, *27*, 1383–1386. (b) Akué-Gédu, R.; Bourry, A.; Camus, F.; Norberg, B.; Durant, F.; Couturier, D.; Debacker, M.; Rigo, B. *Heterocycles* **2004**, *63*, 1855–1873.
4. Rigo, B.; Barbry, D.; Couturier, D. *Synth. Commun.* **1991**, *21*, 741–747.
5. Sánchez, J. D.; Ramos, M. T.; Avendaño, C. *J. Org. Chem.* **2001**, *66*, 5731–5735. This oxidation can be catalyzed by metals such as ruthenium: Murahashi, S.-I.; Saito, T.; Naota, T.; Kumobayashi, H.; Akutagawa, S. *Tetrahedron Lett.* **1991**, *32*, 5991–5994.
6. Haeusler, J.; Jahn, R.; Schmidt, U. *Chem. Ber.* **1978**, *111*, 361–366. Yates, P.; McLachland, F. M. *J. Indian. Chem. Soc.* **1978**, *55*, 1116–1121.
7. Kessar, V. S.; Singh, T.; Vohra, R. *Indian J. Chem., Sect. B* **1991**, *30*, 299–301.
8. Mori, M.; Kimura, M.; Uozumi, Y.; Ban, Y. *Tetrahedron Lett.* **1985**, *26*, 5947–5950 and references cited therein.
9. Dörwald, F. Z. *Side Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2005; pp 50–51. Barton, D. H. R.; Jones, D. L. *J. Chem. Soc., Chem. Commun.* **1965**, 3563–3570.
10. (a) Moniot, J. L.; Shamma, M. *J. Org. Chem.* **1979**, *44*, 4337–4342. For other leading references on the chemistry of α-keto carbinolamides in the Berberin series, see: Moniot, J. L.; Shamma, M. *J. Am. Chem. Soc.* **1976**, *98*, 6714–6715. Dorn, C. R.; Koszyk, F. J.; Lenz, G. R. *J. Org. Chem.* **1984**, *49*, 2642–2644. Fang, F. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1981**, *30*, 2747–2750. (e) Fajardo, V.; Cárcamo, C.; Moreno, B. *Heterocycles* **1996**, *43*, 949–951. Yoda, H.; Inoue, K.; Ujihara, Y.; Mase, N.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 9057–9060. Imai, J.; Kondo, Y. *Heterocycles* **1977**, *6*, 959–963. Elango, V.; Shamma, M. *J. Org. Chem.* **1983**, *48*, 4879–4881. Koseki, Y.; Kusano, S.; Sakata, H.; Nagasaka, T. *Tetrahedron Lett.* **1999**, *40*, 2169–2172.
11. (a) Moniot, J. L.; Hindenlang, D. M.; Shamma, M. *J. Org. Chem.* **1979**, *44*, 4343–4346. (b) Alonso, R.; Castedo, L.; Dominguez, D. *Tetrahedron Lett.* **1985**, *26*, 2925–2928. However, see also: Moniot, J. L.; Hindenlang, D. M.; Shamma, M. *J. Org. Chem.* **1979**, *44*, 4347–4351 for a previously attributed structure.
12. (a) Bhattacharya, G.; Su, T.-L.; Chia, C.-M.; Chen, K.-T. *J. Org. Chem.* **2001**, *66*, 426–432. (b) Renz, M.; Meunier, B. *Eur. J. Org. Chem.* **1997**, 737–750. (c) Compostella, F.; Colombo, D.; Modica, E.; Scala, A.; Toma, L.; Bovio, B.; Ronchetti, F. *Steroids* **2002**, *67*, 111–117.
13. (a) Winn, M.; Zaugg, H. E. *J. Org. Chem.* **1968**, *33*, 3779–3783. Boer-Terpstra, T. J.; Dijhink, J.; Shoemaker, H. E.; Speckamp, W. N. *Tetrahedron Lett.* **1977**, *11*, 939–942. Maryanoff, B. E.; McComsey, D. F.; Duhl-Emswiler, B. A. *J. Org. Chem.* **1983**, *48*, 5062–5074. Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367–4416. Hiemstra, H.; Speckamp, W. N. In *The Alkaloids*, *Vol. 32*; Academic: New York, 1988; p 271. Maryanoff, B. E.; Rebarchak, M. C. *Synthesis* **1992**, 1245–1248. Lee, J. Y.; Baek, N. J.; Lee, S. J.; Park, H.; Lee, Y. S. *Heterocycles* **2001**, *55*, 1519–1526. (b) No attempts were performed to isolate iminium salt **19** as a tetrafluoroborate or a perchlorate salt.
14. Rigo, B.; El Ghammarti, S.; Couturier, D. *Tetrahedron Lett.* **1996**, *37*, 485–486.
15. Jones, P. B.; Porter, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 2753–2761. Jones, P. B.; Pollastri, M. P.; Porter, N. A. *J. Org. Chem.* **1996**, *61*, 9455–9461.
16. Kondo, Y.; Imai, J.; Inoue, H. *J. Chem. Soc., Perkin Trans. 1* **1980**, 911–918. Kondo, Y.; Imai, J.; Nozoe, S. *J. Chem. Soc., Perkin Trans. 1* **1980**, 919–926.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 4408–4418

Efficient synthesis and structural analysis of new dioxopiperazine isoquinolines

Nuria Cabedo,[a] Noureddine El Aouad,[a] Inmaculada Berenguer,[a] Miguel Zamora,[b] M. Carmen Ramírez de Arellano,[c] Fernando Suvire,[b] Almudena Bermejo,[a,†] Daniel Enriz[b] and Diego Cortes[a,*]

[a]*Laboratorio de Farmacognosia, Departamento de Farmacología, Facultad de Farmacia, Universidad de Valencia, 46100 Burjassot, Valencia, Spain*
[b]*Departamento de Química, Universidad Nacional de San Luis, Chacabuco 917, 5700 San Luis, Argentina*
[c]*Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Valencia, 46100 Burjassot, Valencia, Spain*

Received 22 September 2005; revised 21 February 2006; accepted 21 February 2006

Available online 20 March 2006

Abstract—We report herein the synthesis of new dioxopiperazine isoquinolines using the Pictet–Spengler cyclisation. Our synthetic strategy for the preparation of two new compounds (**5**, **6**), with a tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione moiety was developed in only four steps. To understand better the crucial step of the synthesis reported here, theoretical calculations using semiempirical (PM3), ab initio and DFT computations were carried out on a reduced system model. The structure of chlorohydrate water solvate of tetrahydro (2-piperidinylethyl)-6*H*-pyrazino [1,2-*b*]isoquinoline-1,4-dione (**6**·HCl·2H_2O) was determined by X-ray diffraction. Theoretical calculations (RHF/3-21G and RB3LYP/6-31G(d)) were also performed for compound **6** neutralised with a chloride ion.

1. Introduction

Substituted 1,2,3,4 isoquinolines represent a class of natural and synthetic compounds that has received considerable attention because of their significant and powerful biological activities, including antitumor, antibiotic and anticonvulsant properties.[1–4] In many studies aimed at developing simple and efficient syntheses of polyfunctional heteroaromatic fused isoquinolines,[5] it has been reported that the exact structure of the reaction compounds could not be established unequivocally, because several closely similar isomeric products could be formed.[6,7]

In the present paper, as a part of our search for new polyfunctional heterocycles,[8,9] we report the synthesis of two new tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-diones. The rigid framework of these triclyclic compounds incorporates both L-phenylalanine and piperazine-2,5-dione bones using Pictet–Spengler cyclisation. We have introduced a flexible linker into the molecule bearing basic nitrogen as a means of improving aqueous solubility. We describe a short and convenient method in the asymmetric total synthesis of this type of compounds that may be of potential use for the construction of several functionalised piperazine isoquinoline derivatives and will serve as building blocks for natural products.[3] To know better the alkylation–cyclisation step of the synthesis reported here, theoretical calculations using semiempirical (PM3), ab initio and density functional theory (DFT) computations were carried out on a reduced system model. Structure elucidation of the new products was established by spectroscopy and X-ray crystallography. In addition, geometrical optimisations using both RHF/3-21G and RB3LYP/6-31G(d) calculations were performed for tetrahydro (2-piperidinylethyl)-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione (compound **6**) neutralised with a chloride ion with the aim to compare these computations with the experimental results.

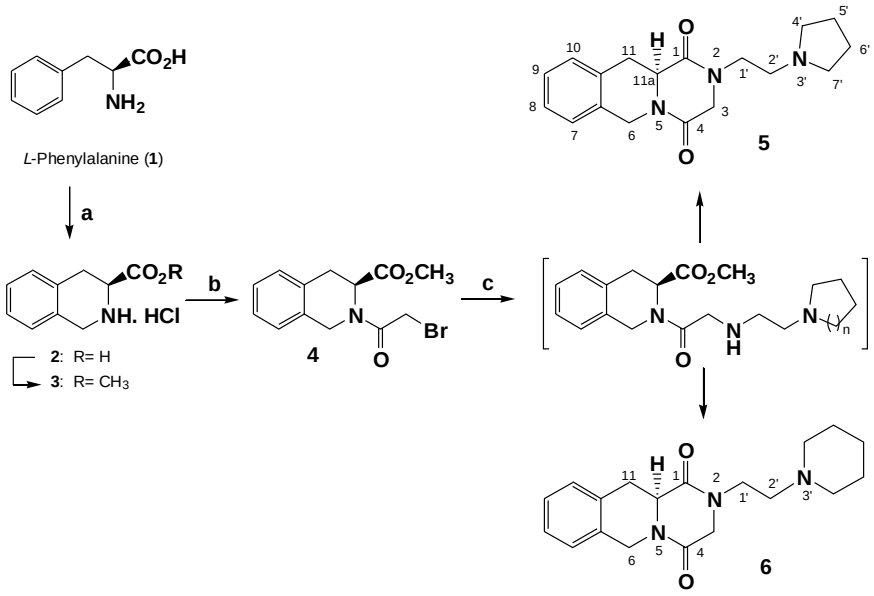
2. Results and discussion

2.1. Synthesis

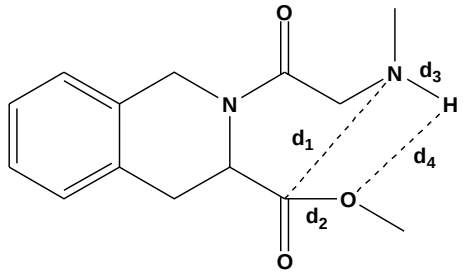
Our approach is based on the use of Pictet–Spengler cyclisation, reaction that was readily adaptable to preparing

Keywords: Dioxopiperazine isoquinolines; Synthesis; Pictet–Spengler; X-ray; Semiempirical (PM3); Ab initio and DFT calculations.
* Corresponding author. Tel.: +34 963 54 49 75; fax: +34 963 54 49 43; e-mail: dcortes@uv.es
† Current address: Departamento de Citricultura, IVIA, Carretera Moncada-Náquera Km 4.5, 46113 Moncada, Valencia, Spain.

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.065



Scheme 1. Reagents and conditions: (a) (i) HCHO/37% HCl, 95 °C, 3 h 30 min; (ii) MeOH, concd H_2SO_4, rt, 2 h; (30%); (b) $BrCOCH_2Br$, Et_3N, CH_2Cl_2, 0 °C to rt, 3 h (65%); (c) 1-(2-aminoethyl) pyrrolidine or 1-(2-aminoethyl)piperidine, K_2CO_3, CH_2Cl_2, reflux, 4 h (49% for **5** and 57% for **6**).



Scheme 2. Reduced model employed to simulate the alkylation–cyclisation process, showing the critical distances d_1, d_2, d_3 and d_4.

substituted 1,2,3,4 isoquinolines.[10] Our synthetic strategy for the obtention of two new compounds with a tetrahydro-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione motif (**5** and **6**), was developed in only four steps (Scheme 1).

As shown, the starting material L-phenylalanine, unsubstituted on the phenyl ring, was chosen as chiral synthon in the construction of these tetrahydroisoquinoline derivatives. Thus, the amino acid (**1**) was condensed with formaldehyde in the presence of 37% HCl through a Pictet–Spengler cyclisation to form the corresponding tetrahydroisoquinoline 3-carboxylic acid, **2**.[11] Fischer esterification of **2**

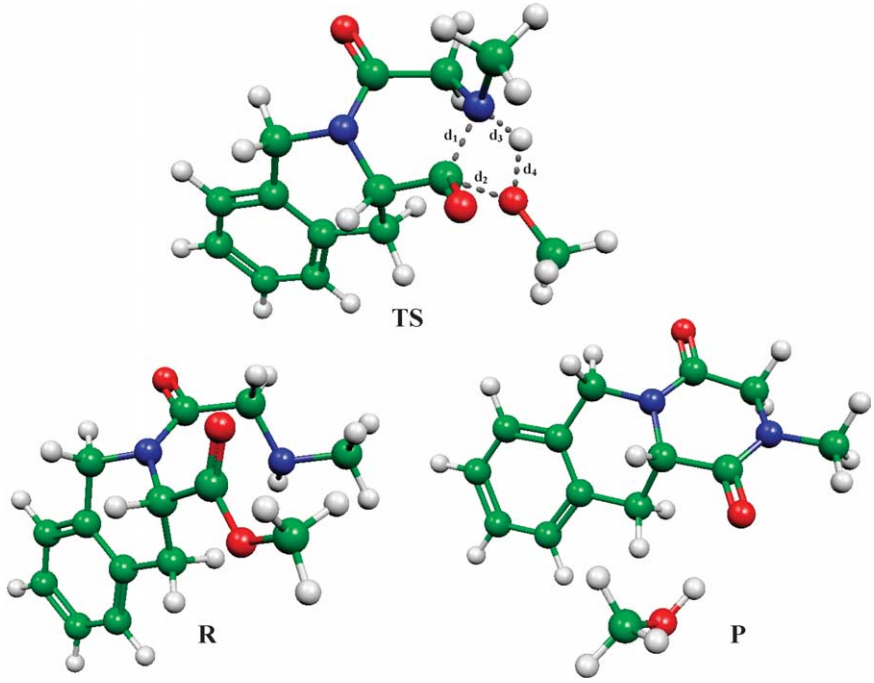


Figure 1. RB3LYP/6-31++G(d,p) optimised geometries of the **R**, **TS** and **P** species. The critical interatomic distances (d_1, d_2, d_3 and d_4) are denoted in the **TS** structure.

Table 1. Absolute energy (Hartrees), ZPE and selected interatomic distances (in Å) for **R**, **TS** and **P** obtained at four different levels of theory

	R						**TS**						**P**			
	d_1(C–N)	d_2(C–O)	d_3(N–H)	d_4(O–H)	ZPE[a]	Energy[b]	d_1(C–N)	d_2(C–O)	d_3(N–H)	d_4(O–H)	ZPE[a]	Energy[b]	d_1(C–N)	d_4(O–H)	ZPE[a]	Energy[b]
RPM3	3.2411	1.3714	0.9983	3.1359	0.301166	0.154138	1.5580	2.2263	1.1137	1.5743	0.297266	0.230009	1.4219	0.9503	0.299940	0.127293
RHF/6-31G(d)	2.7734	1.3206	1.0022	3.8871	0.334195	−873.798579	1.5083	2.1368	1.0573	1.5641	0.331551	−873.711906	1.340	0.951	0.332148	−873.820268
RB3LYP/6-31G(d)	2.7480	1.3496	1.0189	3.8883	0.310578	−879.195706	1.5673	1.9988	1.1588	1.3830	0.306233	−879.142514	1.3548	0.9779	0.309381	−879.217963
RB3LYP/6-31++G(d,p)	2.7575	1.3491	1.0178	3.8801	0.308766	−879.256720	1.5619	1.9934	1.1465	1.3935	0.304681	−879.206621	1.3529	0.9761	0.307591	−879.284985

Note that d_2 and d_3 distances are broken bonds in **P**.
[a] ZPE: zero-point correction (Hartree/particle).
[b] Sum of electronic and zero-point energies (Hartree).

Table 2. Selected interatomic distances, RMS gradient and relative energies obtained for the different steps of RHF/6-31G(d) IRC calculations

	R	Step 1	Step 2	Step 3	Step 4	**TS**	Step 5	Step 6	Step 7	Step 8	**P**
d_1 (Å)	2.84564	1.63727	1.58800	1.55364	1.52802	1.50828	1.49039	1.47075	1.44784	1.42215	1.33921
d_2 (Å)	1.32393	1.55005	1.69054	1.85012	2.00375	2.13677	2.23566	2.28991	2.31531	2.35812	3.24820
d_3 (Å)	1.00003	1.00141	1.00593	1.01716	1.03155	1.05732	1.11020	1.22108	1.37514	1.54342	3.15195
d_4 (Å)	3.01654	1.83646	1.77164	1.71428	1.64998	1.56406	1.44288	1.28427	1.12102	1.00359	0.95019
RMS gradient (Hartree/bohr)	5.81×10^{-5}	3.07×10^{-3}	3.18×10^{-3}	2.05×10^{-3}	8.23×10^{-4}	2.93×10^{-5}	9.11×10^{-4}	3.88×10^{-3}	7.49×10^{-3}	6.04×10^{-3}	3.06×10^{-6}
ΔE (kcal/mol)	0.00	35.92	42.32	47.61	50.40	51.16	50.39	46.20	34.42	20.48	−16.56

The optimised values of these parameters obtained for **R** and **P** are also included for comparison. The total energy of **R** (−874.124984907 Hartree) was taken as reference value.

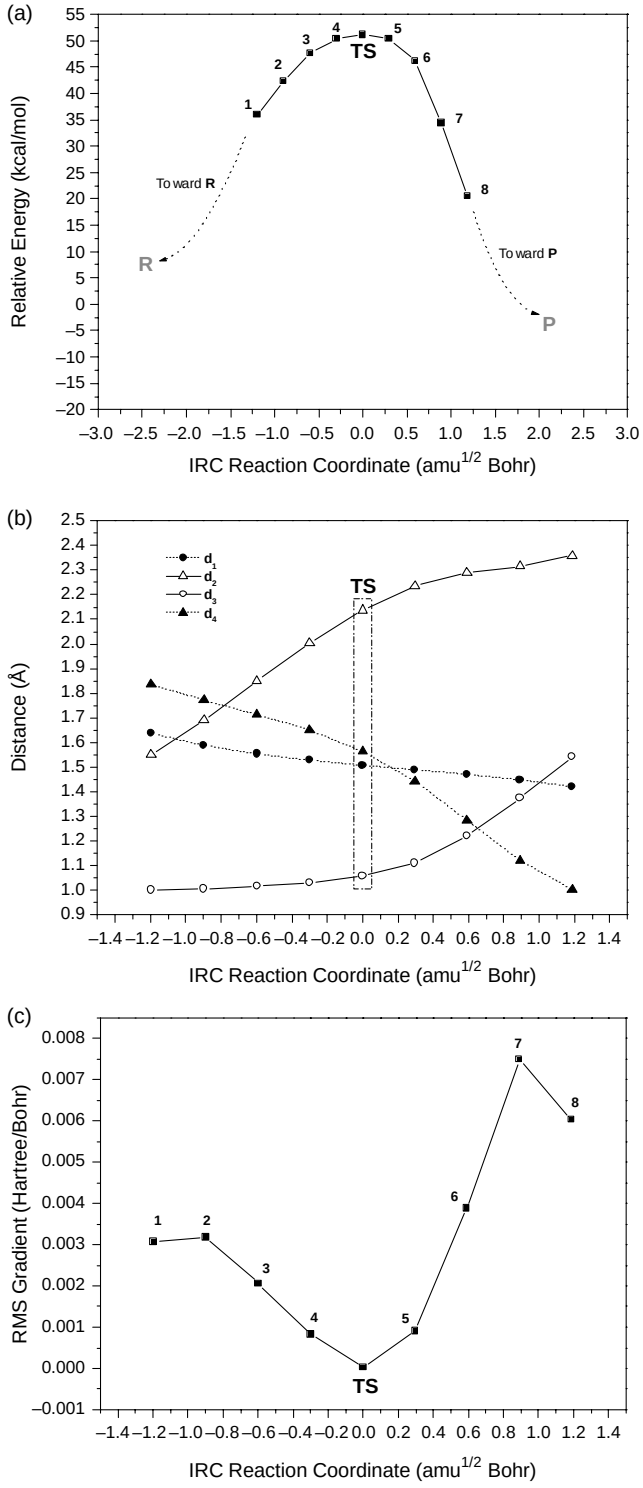


Figure 2. RHF/6-31G(d) IRC calculations showing, respectively. Relative energies (a), interatomic distances (b) and RMS gradient (c) versus the IRC coordinates.

provided a stable tetrahydroisoquinoline methyl carboxylate **3**. N-acylation of the ester, which was carried out by treatment with bromoacetyl bromide at room temperature with 1.5 equiv of triethylamine in dichloromethane afforded the amide **4**.[12] In a crucial last step, **4** was reacted with primary amines such as 2-pyrrolidinylethylamine and 2-piperidinylethylamine under standard conditions.[13] A spontaneous alkylation–cyclisation reaction proceeded

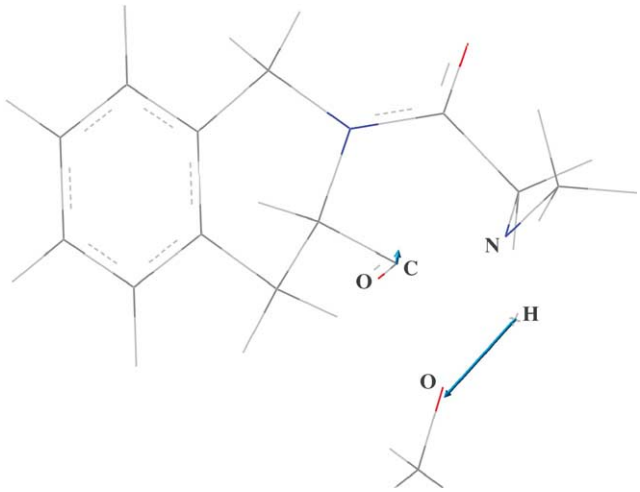


Figure 3. Molecular geometry and the result of the vibrational analysis of the transition state obtained from RB3LYP/6-31++G(d,p) calculations. The length of each arrow is proportional to the degree of vibration of the atom.

affording the tetrahydro (2-pyrrolidinylethyl)-6*H*-pyrazino[1,2-*b*]isoquinoline-1,4-dione derivative **5** and its homologue 2-piperidinylethyl **6**, respectively. Compound **6**·HCl was subjected to single crystal X-ray analysis and the experimental results were compared with ab initio RHF/3-21G and B3LYP/6-31G(d) calculations (see Section 2.3). The X-ray structure determination revealed that the carbon C-12 has the same configuration as in the starting material.

2.2. Alkylation–cyclisation reaction

Formation of tricyclic compounds (**5** and **6**) suggested that the mechanism operating in this transformation involved the spontaneous cyclisation, rationalised by considering that the conformation of **4** adopts a boat-like conformer in which the ester and the amide are proximal in pseudo-equatorial orientations allowed for easy approach of the amino group on the ester carbonyl. To understand better this one-pot reaction, we conducted a computer-assisted study simulating the alkylation–cyclization process. The purpose was to obtain more precise information about this mechanism of reaction.

A reduced model (NCH_3 instead of *N*-piperidinylethyl moiety) (see Scheme 2) was used to perform the theoretical calculations. The use of a reduced model to calculate the PES and to simulate the reaction mechanism is convenient since compounds **5** and **6** are too large for accurate quantum mechanic calculations. When choosing the model compound, the ability to reproduce electronic properties of the entire molecules **5** and **6** were considered.

The critical points (**R**, **TS** and **P**) were obtained using different levels of theory: semiempirical (PM3), ab initio (restricted Hartree–Fock calculations with the basis set 6-31G(d)) and DFT (RB3LYP/6-31G(d)) computations. In addition, to improve our results, we optimise these critical points using an extended basis set including diffuse and polarisation functions (RB3LYP/6-31++G(d,p)). The differences between the geometries obtained at the RB3LYP/6-31G(d) and RB3LYP/6-31++G(d,p) levels

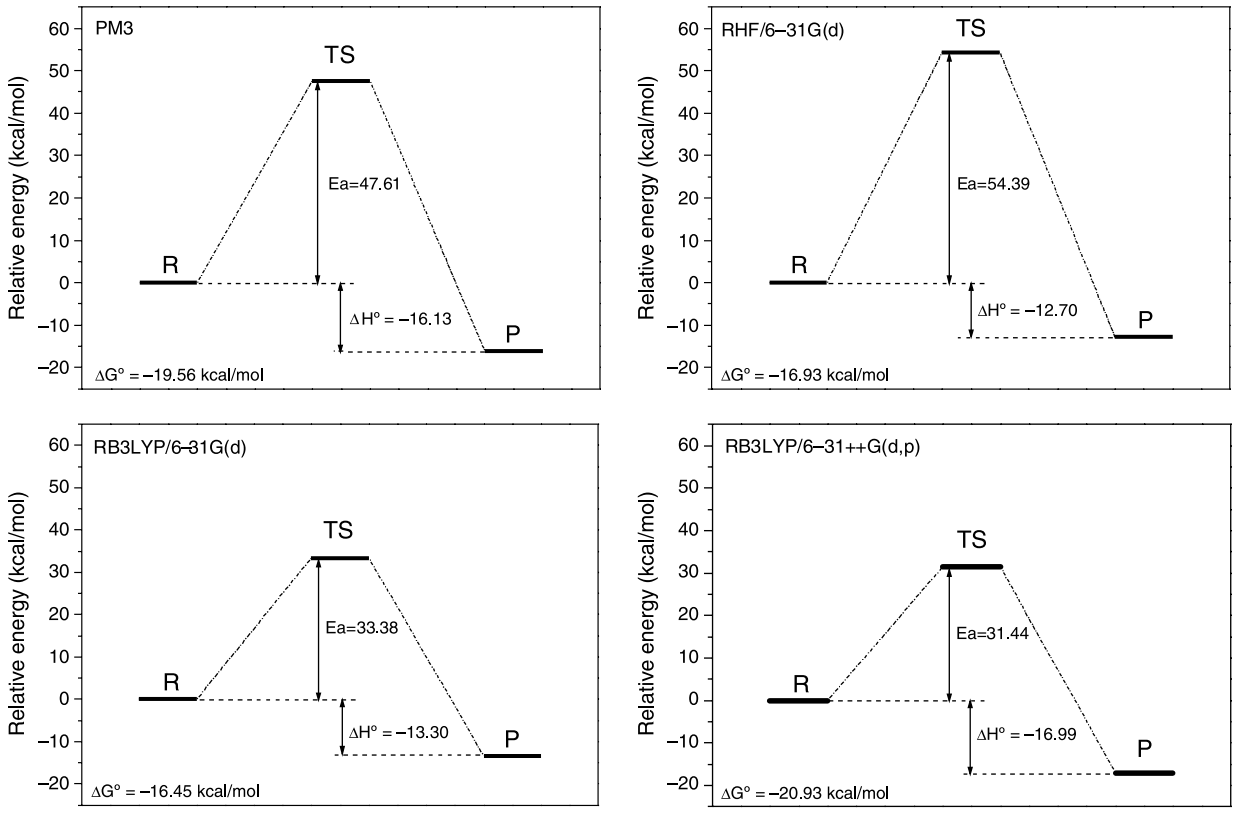


Figure 4. Schematic diagram of the potential energy surface showing the possible mechanism for the alkylation–cyclisation calculated at four different levels of theory. $T=298.15$ K and $P=1$ atm.

are almost negligible. The differences between bond lengths are smaller than 0.01 Å and bond angles show agreement within 0.5°. However, some differences were observed for the activation energy, $\Delta_r H^\circ$ and $\Delta_r G^\circ$ values.

The optimised geometries of **R**, **TS** and **P** calculated at RB3LYP/6-31++G(d,p) level have been collected in Table S1 (Supplementary material) and a spatial view of these structures is shown in Figure 1. Selected interatomic distances for **R**, **TS** and **P** are listed in Table 1.

To determine if the transition state connects to the desired reactant and products, we traced the reaction path from the **TS** to the **R** and **P**, respectively. Thus we calculate the RHF/6-31G(d) intrinsic reaction coordinates (IRC), which formed the path that should be followed by a particle moving along the steepest descent paths with an infinitesimal step from the **TS** down to both the reactant and the product sides on the PES. In order to verify the true minimum, we optimised the last IRC point to the next local minimum. In the forward RHF/6-31G(d) IRC calculations, the last IRC point was obtained at a C–N distance (d_1) of 1.42 Å and an O–H distance (d_4) of 1.00 Å. RHF/6-31G(d) IRC calculations in backward direction showed that the last IRC point was obtained at a C–N distance of 1.63 Å and an O–H distance of 1.83 Å (see Table 2). Figure 2a–c summarises the results obtained from the RHF/6-31G(d) IRC calculations showing, respectively, the relative energies, distances and RMS gradient versus the IRC coordinates.

The characterisation of the **TS** showed that the structure has only one negative eigenvalue. The calculated vibrational frequency (i876.47 cm^{-1} at RB3LYP/6-31++G(d,p) level) showed that the eigenvector that corresponds to the imaginary frequency is primarily a translation of the hydrogen (*N*–H) towards the oxygen atom (d_4 spatial orientation in Scheme 2). This result might be well appreciated in Figure 3. In addition, in this figure we can also observe a lower degree of vibration between the *O* and C atom (in the carbonyl group of ester moiety). It should be noted that in the transition state structure, the nitrogen atom (*N*–H group) is rotated toward the carbon atom (carbonyl group) in order to form the new C–*N* bond in **P**. The course of the cyclisation is characterised by the approach of *N* to C (d_1 in Scheme 2). Further approach of the *N* to *C* along the pathway, raises the energy of the complex until it reaches a transition state (**TS**) at a *C*–*N* distance of 1.5619 Å (at RB3LYP/631++G(d,p) level). Along this path of approach, this state has the characteristics of a real transition state, with a single negative eigenvalue, in the Hessian matrix of force constants. From this transition state the complex moves down the potential energy surface to produce **P**, which is the product of the alkylation–cyclisation.

All the frequencies obtained for the **TS** structure using DFT (RB3LYP/6-31G(d) and RB3LYP/6-31++G(d,p)) calculations are given in Table S2 in the Supplementary material.

The potential energy diagram along the reaction coordinate calculated at four different levels of theory is schematically drawn in Figure 4. As outlined in Section 4.3 barrier heights have been corrected by ZPE (zero-point energies) using the ZPE values summarised in Table 1. Reaction enthalpies are

Table 3. Geometrical parameters obtained for compound **6** from X-ray, ab initio (RHF/3-21G) and DFT (B3LYP/6-31G(d)) calculations

Bond	Bond length (Å)			Internal angle	Angle (°)			Torsional angle	Angle (°)		
	X-ray	RHF	DFT		X-ray	RHF	DFT		X-ray	RHF	DFT
O(4)–C(4)	1.233	1.219	1.253	C(1)–N(2)–C(3)	123.6	119.7	120.2	C(1)–N(2)–C(1′)–C(2′)	−105.3	−105.8	−106.1
O(1)–C(1)	1.238	1.227	1.259	C(1)–N(2)–C(1′)	121.2	120.0	120.0	C(3)–N(2)–C(1′)–C(2′)	70.5	72.2	70.1
N(2)–C(1)	1.330	1.352	1.368	C(3)–N(2)–C(1′)	115.1	120.0	119.7	C(8′)–N(3′)–C(2′)–C(1′)	−179.3	−178.4	−178.5
N(2)–C(3)	1.452	1.470	1.478	C(2′)–N(3′)–C(8′)	108.8	109.4	109.7	C(4′)–N(3′)–C(2′)–C(1′)	57.8	56.5	55.7
N(2)–C(1′)	1.467	1.453	1.462	C(2′)–N(3′)–C(4′)	113.6	114.0	114.2	N(2)–C(1′)–C(2′)–N(3′)	66.7	59.5	60.2
N(3′)–C(2′)	1.497	1.508	1.512	C(8′)–N(3′)–C(4′)	110.0	111.1	111.4	C(2′)–N(3′)–C(4′)–C(5′)	179.7	−178.7	−178.8
N(3′)–C(8′)	1.497	1.520	1.527	C(4)–N(5)–C(12)	125.5	120.2	120.5	C(8′)–N(3′)–C(4′)–C(5′)	57.5	57.1	56.2
N(3′)–C(4′)	1.498	1.518	1.523	C(4)–N(5)–C(6)	118.4	119.1	118.6	N(3′)–C(4′)–C(5′)–C(6′)	−57.5	−57.9	−56.6
N(5)–C(4)	1.335	1.350	1.364	C(12)–N(5)–C(6)	114.5	120.2	120.6	C(4′)–C(5′)–C(6′)–C(7′)	56.0	57.7	55.5
N(5)−C(12)	1.458	1.473	1.487	N(2)–C(1′)–C(2′)	113.5	113.6	114.6	C(5′)–C(6′)–C(7′)–C(8′)	−55.2	−56.7	−54.7
N(5)–C(6)	1.473	1.475	1.483	N(3′)–C(2′)–C(1′)	115.8	115.1	115.5	C(2′)–N(3′)–C(8′)–C(7′)	177.6	176.0	176.5
C(1′)–C(2′)	1.521	1.538	1.538	N(3′)–C(4′)–C(5′)	110.9	109.9	110.4	C(4′)–N(3′)–C(8′)–C(7′)	−57.4	−57.2	−56.1
C(4′)–C(5′)	1.520	1.533	1.533	C(6′)–C(5′)–C(4′)	110.5	111.4	112.0	C(6′)–C(7′)–C(8′)–N(3′)	56.2	57.0	55.5
C(5′)–C(6′)	1.510	1.536	1.539	C(5′)–C(6′)–C(7′)	110.8	109.2	109.9	C(1)–N(2)–C(3)–C(4)	−2.7	−46.3	−41.5
C(6′)–C(7′)	1.516	1.537	1.539	C(8′)–C(7′)–C(6′)	110.5	110.8	111.6	C(1′)–N(2)–C(3)–C(4)	−178.5	−135.8	−142.3
C(7′)–C(8′)	1.505	1.532	1.532	N(3′)–C(8′)–C(7′)	112.1	110.9	111.3	C(12)–N(5)–C(4)–O(4)	−172.3	−173.1	−175.0
C(3)–C(4)	1.487	1.520	1.522	N(2)–C(3)–C(4)	117.5	109.9	111.7	C(6)–N(5)–C(4)–O(4)	−7.7	−0.2	−0.9
C(1)–C(12)	1.507	1.516	1.526	O(4)–C(4)–N(5)	123.2	124.4	124.0	C(12)–N(5)–C(4)–C(3)	8.8	7.1	4.4
C(12)–C(11)	1.530	1.532	1.538	O(4)–C(4)–C(3)	118.8	122.3	121.2	C(6)–N(5)–C(4)–C(3)	173.4	−179.9	178.5
C(11)–C(14)	1.503	1.511	1.511	N(5)–C(4)–C(3)	118.1	113.3	114.8	N(2)–C(3)–C(4)–O(4)	176.8	−139.9	−143.1
C(6)–C(13)	1.500	1.512	1.510	O(1)–C(1)–N(2)	122.2	123.2	122.7	N(2)–C(3)–C(4)–N(5)	−4.2	39.8	37.4
C(14)–C(13)	1.391	1.389	1.408	O(1)–C(1)–C(12)	117.7	123.0	122.1	C(3)–N(2)–C(1)–O(1)	−177.2	−176.3	−175.8
C(14)–C(10)	1.399	1.382	1.400	N(2)–C(1)–C(12)	120.0	113.8	115.2	C(1′)–N(2)–C(1)–O(1)	−1.6	1.7	0.4
C(10)–C(9)	1.362	1.385	1.399	N(5)–C(12)–C(1)	114.8	108.4	110.4	C(3)–N(2)–C(1)–C(12)	5.3	3.5	2.3
C(9)–C(8)	1.389	1.383	1.400	N(5)–C(12)–C(11)	109.2	110.0	110.5	C(1′)–N(2)–C(1)–C(12)	−179.2	−178.5	178.5
C(8)–C(7)	1.394	1.385	1.399	C(1)–C(12)–C(11)	110.8	111.1	111.7	C(4)–N(5)–C(12)–C(1)	−6.2	−49.4	−43.1
C(7)–C(13)	1.393	1.382	1.400	C(14)–C(11)–C(12)	111.9	108.9	110.2	C(6)–N(5)–C(12)–C(1)	−171.3	137.7	143.0
				N(5)–C(6)–C(13)	112.3	111.0	112.3	C(4)–N(5)–C(12)–C(11)	−131.2	−171.1	−167.1
				C(13)–C(14)–C(10)	118.5	119.7	119.6	C(6)–N(5)–C(1)–C(11)	63.6	16.0	19.0
				C(13)–C(14)–C(11)	121.2	116.9	117.4	O(1)–C(1)–C(12)–N(5)	−178.9	−137.5	−143.0
				C(10)–C(14)–C(11)	120.3	123.3	123.0	N(2)–C(1)–C(12)–N(5)	−1.2	42.7	38.8
				C(9)–C(10)–C(14)	120.8	120.3	120.4	O(1)–C(1)–C(12)–C(11)	−54.6	−16.5	−19.6
				C(10)–C(9)–C(8)	121.1	120.0	120.0	N(2)–C(1)–C(12)–C(11)	123.1	163.7	162.2
				C(9)–C(8)–C(7)	118.9	119.9	119.9	N(5)–C(12)–C(11)–C(14)	−48.3	−55.0	−53.5
				C(13)–C(7)–C(8)	120.0	120.1	120.3	C(1)–C(12)–C(11)–C(14)	−175.6	−175.1	−178.0
				C(14)–C(13)–C(7)	120.6	120.1	119.9	C(4)–N(5)–C(6)–C(13)	150.4	−141.4	−148.1
				C(14)–C(13)–C(6)	121.9	117.4	118.4	C(12)–N(5)–C(6)–C(13)	−43.3	31.5	25.9
				C(7)–C(13)–C(6)	117.5	122.4	121.7	C(12)–C(11)–C(14)–C(13)	17.5	47.5	44.1
								C(12)–C(11)–C(14)–C(10)	−161.6	−131.5	−135.0
								C(13)–C(14)–C(10)–C(9)	−2.8	0.6	0.8
								C(11)–C(14)–C(10)–C(9)	176.3	179.6	179.8
								C(14)–C(10)–C(9)–C(8)	2.2	−0.5	−0.7
								C(10)–C(9)–C(8)–C(7)	−0.5	−0.1	0.0
								C(9)–C(8)–C(7)–C(13)	−0.6	0.6	0.6
								C(10)–C(14)–C(13)–C(7)	1.7	−0.2	−0.1
								C(11)–C(14)–C(13)–C(7)	−177.4	−179.1	−179.2
								C(10)–C(14)–C(13)–C(6)	−178.8	−179.2	−178.3
								C(11)–C(14)–C(13)–C(6)	2.1	1.8	2.6
								C(8)–C(7)–C(13)–C(14)	0.0	−0.4	−0.6
								C(8)–C(7)–C(13)–C(6)	−179.6	178.6	177.5
								N(5)–C(6)–C(13)–C(14)	9.5	−41.7	−38.1
								N(5)–C(6)–C(13)–C(7)	−170.9	139.3	143.8

moreover corrected for thermal energy calculated at 298.15 K. Inspection of the collected data in Figure 4 indicates that the barrier heights are sensitive to the employed theory level. Thus, PM3 and RHF/6-31G(d) calculations predict an activation energy of 47.61 and 54.39 kcal/mol, whereas RB3LYP/6-31G(d) and RB3LYP/6-31++G(d,p) calculations suggest 33.38 and 31.44 kcal/mol, respectively. Analysis of the DFT data indicates that enlarging the basis set (from 6-31G(d) to 6-31++G(d,p)) increases the stability of the transition state structure by 1.94 kcal/mol. It is interesting to note that the free energy of activation of the reaction at the highest level of theory is 31.44 kcal/mol, an indicative value of which the reaction can be carried out at room temperature at a reasonable rate.

The reaction enthalpies ($\Delta_r H^\circ$) for the alkylation–cyclisation calculated within the different approaches employed in this study are summarised in Figure 3. In contrast with the features found in the barrier height analysis, the calculated values are quite similar at the different levels of theory. Our theoretical results strongly suggest that the alkylation–cyclisation is an exothermic process ($\Delta_r H^\circ = -17.13$ kcal/mol at RB3LYP/6-31++G(d,p) level), which is in agreement with our experimental data. It occurs if the reagent can assume the proper orientation. The proposed reaction mechanism with four-centre **TS** that has been characterised, as described previously, is a true reaction path that shows to be reasonable according to the estimated activation energy.

The E_a, $\Delta_r H^\circ$ and $\Delta_r G^\circ$ values obtained from DFT calculations for the alkylation–cyclisation could explain the spontaneous nature of this process. However, it should be noted that our theoretical calculations had been performed for a reduced model system in vacuum; therefore caution is needed in these interpretations, because the complete molecular systems as well as solvent effects could change somewhat these results.[14]

2.3. Crystal structure analysis

The solid state structure of **6**·HCl·2H$_2$O was determined by single crystal X-ray diffraction (Table 3, Fig. 5). Crystal structure confirms the absolute configuration (*S*) on *C*(12) which is in accordance with the starting material, L-phenylalanine. The three fused rings are not coplanar and present a half-folded conformation. The plane formed by the aromatic ring C7–C8–C9–C10–C13–C14 and C6 and C11 (mean deviation 0.019 Å) makes a dihedral angle of 33.7(2)° with the C1–N2–C3–C4–N5–C12 ring plane (mean deviation 0.029 Å). The piperidine ring adopts the chair conformation with the flexible connecting chain in the equatorial position. The bond lengths of *N*(3′)–C(2′) (1.497(5) Å), *C*(2′)–*C*(1′) (1.519(6) Å) and *C*(1′)–*N*(2) (1.469(5) Å) show the C–*N* and C–C single bond character. The ammonium hydrogen atom is acting as hydrogen bond donor to the chloride atom (N3′···Cl1 3.159(4) Å, H3′···Cl1 2.26 Å, N3′-H3′···Cl1 168.3°). Other hydrogen bonds have been found involving the two water solvated molecules hydrogen atoms and the carbonyl or the water oxygen atoms or the chloride ion (O5–H5A···O1 163(5)°, O5···O1 2.793(5) Å, H5A···O1 1.92(2); O5–H5B···O4^{i} 166(5)°, (i) $-x+1$, $y-1/2$, $-z+1/2$, O5···O4^{i} 2.812(5) Å, H5B···O4^{i} 1.94(2) Å; O6–H6D···Cl1 131(5)°, O6···Cl1 3.249(6) Å, H6D···Cl1 2.60(5) Å; O6–H6C···O5^{ii} 161(6), (ii) $-x+1$, $y+1/2$, $-z+1/2$, O6···O5^{ii} 2.874(7) Å, H6C···O5^{ii} 2.02(4) Å).

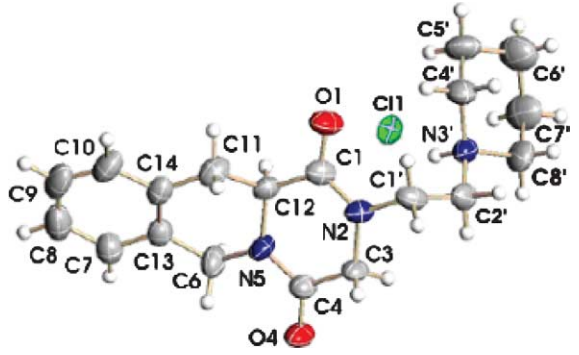


Figure 5. X-ray ellipsoid plot of the cation of **6**·HCl (H$_2$O molecules have been removed for a better view of the crystal structure).

We were also interested to learn whether the experimentally obtained structure of **6**·HCl·2H$_2$O could also be reproduced with reasonable agreement by standard computational methods. Thus we calculate compound **6** neutralised with a chloride (Cl^-) ion. To perform these optimisations we chose as starting geometry the conformation obtained from X-ray where the chloride was located at an arbitrary C–*N*H distance of 3.07 Å. The *z*-matrix of the optimised geometry at the B3LYP/6-31G(d) level is given in Table S3 the supplementary material. In order to obtain information about the electronic aspects, we calculate the molecular electrostatic potential (MEP) using RB3LYP/6-31G(d) calculations. A spatial view of the MEP obtained for compound **6** neutralised with a chloride Cl^- is shown in Figure 6.

The geometry optimisations have been carried out at the restricted Hartree–Fock (RHF) level with 3-21G basis set and RB3LYP/6-31G(d) level of theory. Table 3 gives the main geometrical parameters for the RHF/3-21G and DFT optimised geometries. Both levels of calculations well reproduce the bond distances and angles observed at X-ray even when periodical conditions were not considered in our calculations. Agreements between the calculated structures and the experimentally determined X-ray crystal structure were excellent; a strikingly significant correlation $R=0.99904$ (RHF/3-21G) and $R=0.99911$ (B3LYP/6-31G(d)) was found between the bond lengths optimised at both levels of theory and those obtained from X-ray. The experimentally determined bond lengths are slightly shorter than those observed in the DFT calculated geometry. These differences in bond lengths may be due to the short intermolecular contacts in the crystal. Inspection of Figure 7 reveals the similarity between the X-ray, RHF/3-21G and RB3LYP/6-31G(d) geometries. Specifically, only minute deviation was found between torsion angle values found at X-ray when compared to those found at RHF/3-21G or at RB3LYP/6-31G(d) levels; being the main difference the spatial position of the piperidine ring (see Table 2). The different environments, that is, crystal versus isolated molecule may yield differences between both experimental and theoretical structures due to the role played by

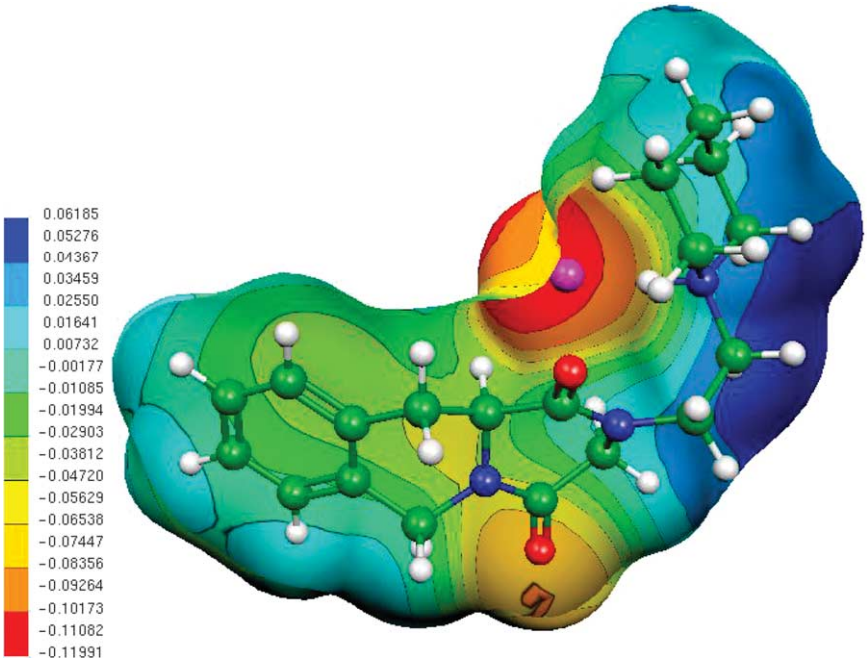


Figure 6. Electrostatic potential-encoded electron density surfaces of the core structures of compound **6** interacting with a chloride ion. The surfaces were generated using RB3LYP/6-31G(d) calculations. The coloring represents electrostatic potential with red indicating the strongest attraction to a positive point charge and blue indicating the strongest repulsion. The electrostatic potential is the energy of interaction of the positive point charge with the nuclei and electrons of a molecule. It provides a representative measure of overall molecular charge distribution.

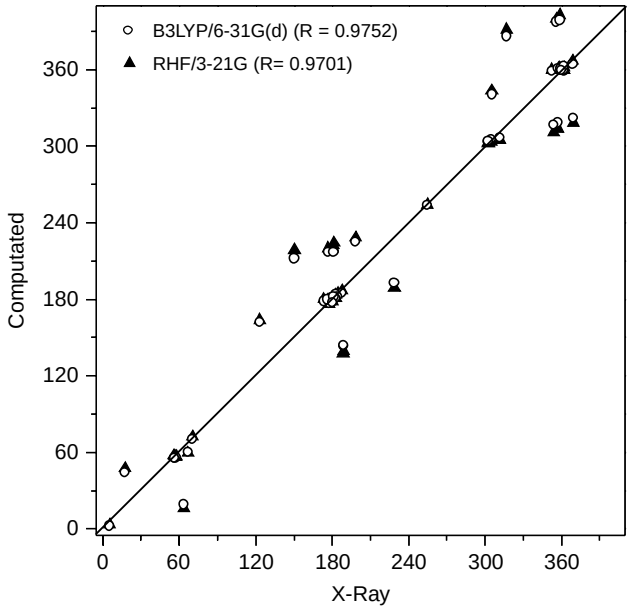


Figure 7. A graph showing the correlation between the torsional angles of compound **6** optimised at RHF/3-21G and B3LYP/6-31G(d) versus torsional angles obtained from X-ray analysis.

the intermolecular forces. However, it is clear that there is a complete agreement between theoretical calculations and experimental data. Comparisons between Figures 5 and 6 illustrate well this situation.

3. Conclusions

A selective and easy route to tetrahydro-6*H*-pyrazino-[1,2-*b*]isoquinoline-1,4-dione from L-phenylalanine via the Pictet–Splenger reaction, N-acylation followed by alkylation–cyclisation, was developed. Our results indicate that semiempirical and ab initio calculations combined with RB3LYP/6-31++G(d,p) computations can well interpret the crucial step of the title reaction. The molecular structure of **6** neutralised with a chloride ion was optimised using RHF/3-21G and B3LYP/6-31G(d) calculations and compared with experimental data to assess the accuracy of the theoretical methods. Both levels of calculations are in agreement with the X-ray data.

4. Experimental

4.1. General

Optical rotations were determined with a Perkin-Elmer 241 polarimeter. IR spectra (film) were run on a Perkin-Elmer 1750 FTIR Spectrometer. EIMS, LSIMS and HREIMS were determined on a VG Auto Spec Fisons instrument, and electrospray ionisation (LC-MSD, API-Electrospray positive) was determined on a Hewlett-Packard (HP-1100). NMR spectra were recorded on Bruker AC-250, Varian Unity-300 or Varian Unity-400 spectrometer at 250, 300 or 400 MHz for ^{1}H, and 75 or 100 MHz for ^{13}C. Multiplicities of ^{13}C NMR signals were assigned by DEPT experiments. COSY 45, HSQC and HMBC correlations were recorded at 400 MHz. All reactions were monitored by analytical TLC with silica gel 60 F_{254} (Merck 5554). The residues were purified through 60 H silica gel column (5–40 μm, Merck 7736), and by flash chromatography (230–400 μm, Merck 9385).

4.1.1. (*S*)-Methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride (3). A suspension of L-phenylalanine (**1**, 500 mg, 3.0 mmol) and formaldehyde (1 mL of

a 37% aqueous solution) in concd HCl (5 mL) was heated for 30 min at 95 °C. Then concd HCl (1 mL) and formaldehyde (0.5 mL) were added and the mixture was heated at 95 °C for another 3 h. The mixture reaction was allowed to cool to room temperature overnight and the solid was filtered and washed with H_2O. Then, the residue of THIQ **2** hydrochloride was dissolved in hot MeOH (10 mL), treated with concd H_2SO_4 (0.2 mL) and shaken at room temperature for 2 h. The solvent was concentrated under reduced pressure to give 204 mg of the methyl ester hydrochloride **3** (0.9 mmol, 30%) as a white solid, which was used directly in the next step.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.86 (br s, 1H, NH), 2.91 (dd, J=16.2, 10.2 Hz, 1H, CH_2-4a), 3.05 (dd, J=16.2, 4.8 Hz, 1H, CH_2-4b), 3.71 (dd, J=10.2, 4.8 Hz, 1H, CH-3), 3.73 (s, 3H, OCH_3), 4.05 (s, 2H, CH_2-1), 6.95–7.14 (m, 4H, ArH); ^{13}C NMR (300 MHz, $CDCl_3$) δ: 31.0 (CH_2-4), 46.6 (CH_2-1), 52.0 (OCH_3), 55.3 (CH-3), 125.9 (CH), 126.1 (CH), 126.2 (CH), 128.8 (CH), 132.4 (2C), 172.9 (*C*OOCH$_3$); APIES positive *m*/*z* (%): 214 (100) [M^++ Na^+], 192 (52) [MH^+].

4.1.2. (*S*)-Methyl-2-(2-bromoacetyl)-1,2,3,4-tetrahydro-isoquinoline-3-carboxylate (4a,4b). Under N_2, bromoacetyl bromide (0.045 mL, 0.52 mmol, 1 equiv) was added to a stirred solution of THIQ methyl ester hydrochloride, **3** (118 mg, 0.52 mmol, 1 equiv) and Et_3N (0.11 mL, 0.78 mmol, 1.5 equiv) in anhydrous CH_2Cl_2 (4 mL) at 0 °C and then, stirred at room temperature for 3 h. The reaction mixture was washed with saturated $NaHCO_3$ solution, H_2O and brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/EtOAc, 9.6:0.4) to afford 105 mg of bromoacetamide-THIQ derivative **4** (65%) as a mixture of rotamers in a 2:1 ratio of **4a**:**4b** rotamers.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.15 (dd, J=16.0, 6.0 Hz, 1H, CH_2a-4, rotamer-4a), 3.26 (dd, J=16.0, 4.0 Hz, 1H, CH_2b-4, rotamer-4a), 3.29–3.42 (m, 2H, CH_2-4, rotamer-4b), 3.62 (s, 3H, OCH_3, rotamer-4b), 3.63 (s, 3H, OCH_3, rotamer-4a), 3.93 (m, 2H, CH_2Br, rotamer-4b), 4.0 (d, J=10.8 Hz, 1H, CH_2a–Br, rotamer-4a), 4.06 (d, J=10.8 Hz, 1H, CH_2b–Br, rotamer-4a), 4.53 (d, J=17.6 Hz, 1H, CH_2a-1, rotamer-4b), 4.78 (s, 2H, CH_2-1, rotamer-4a), 4.95 (d, J=17.6 Hz, 2H, CHb-1 and CH-3, rotamer-4b), 5.37 (dd, J=6.0, 4.0 Hz, 1H, CH-3, rotamer-4a), 7.10–7.30 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.1 (CH_2Br), 30.5 (CH_2-4), 46.2 (CH_2-1), 52.0 (OCH_3), 52.4 (CH-3), 126.0 (CH), 126.8 (CH), 127.0 (CH), 128.3 (CH), 131.4 (C), 131.8 (C), 166.6 (CO), 170.8 (*C*OOCH$_3$); EIMS *m*/*z* (%): 312 (5) [M^+], 232 (100) [M^+−Br], 190 (75) [M^+−$COCH_2$Br], 146 (88) [M^+−$COCH_2$Br–CH_3], 130 (79).

4.1.3. (*S*)-2,3,11,11a-Tetrahydro-2-(2′-(pyrrolidin-3′-yl)ethyl)-6*H*-pyrazino-[1,2-*b*]isoquinoline-1,4-dione (5) and its 2-(2′-piperidin-3′-yl)ethyl homologue (6). Under N_2, a stirred suspension of (*S*)-methyl-2-(2-bromoacetyl)-1,2,3,4-tetrahydro-isoquinoline-3-carboxylate, **4** (100 mg, 0.32 mmol, 1 equiv), 1-(2-aminoethyl)piperidine (0.046 mL, 0.32 mmol, 1 equiv) and anhydrous K_2CO_3 (70 mg) in dry CH_2Cl_2 (6 mL) was refluxed for 4 h. Then, the reaction mixture was cool to room temperature, and washed with H_2O, brine, dried over $NaSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH/NH_4OH, 9.6:0.4:1 drop) to obtain 60 mg of compound **6** (57%). The same procedure using 1-(2-aminoethyl)pyrrolidine was accomplished for compound **5** (49 mg, 49%).

Compound **5**. $[\alpha]_D$=−142° (*c* 0.9, EtOH); IR (dry film) ν_{max}: 3470, 2944, 1673, 1456, 1325 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.70–1.84 (m, 4H, CH_2-5′ and CH_2-6′), 2.50–2.60 (m, 4H, CH_2-4′ and CH_2-7′), 2.71 (t, J=6.5 Hz, 2H, CH_2-2′), 3.01 (dd, J=15.9, 3.4 Hz, 1H, CH_2a-11), 3.43 (dd, J=15.9, 12.4 Hz, 1H, CH_2b-11), 3.50–3.66 (m, 2H, CH_2-1′), 4.19 (s, 2H, CH_2-3), 4.16–4.25 (m, 1H, CH-11a), 4.33 (d, J=17.1 Hz, 1H, CH_2a-6), 5.29 (d, J=17.1 Hz, 1H, CH_2b-6), 7.10–7.30 (m, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.4 (CH_2-5′ and CH_2-6′), 33.5 (CH_2-11), 43.89 (CH_2-6), 44.9 (CH_2-1′), 50.3 (CH_2-3), 53.0 (CH_2-4′and CH_2-7′), 54.1 (CH_2-2′), 55.5 (CH-11a), 126.2 (CH), 126.9 (CH), 128.6 (2CH), 131.2 (C-10a), 132.4 (C-6a), 162.6 (C-1), 164.8 (C-4); LSIMS *m*/*z* 314 [MH^+].

Compound **6**. $[\alpha]_D^{25}$ −156° (*c* 0.8, EtOH); IR (dry film) ν_{max}: 3486, 2934, 1661, 1470, 1325 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.34–1.45 (m, 1H, H-6′), 1.50–1.60 (m, 4H, CH_2-5′and CH_2-7′), 2.35–2.48 (m, 4H, CH_2-4′ and CH_2-8′), 2.54 (t, J=6.3 Hz, 2H, CH_2-2′), 3.01 (dd, J=16.0, 12.4 Hz, 1H, CH_2a-11), 3.40 (dd, J=16.0, 3.7 Hz, 1H, CH_2b-11), 3.44–3.54 (m, 1H, CH_2a-1′), 3.58–3.68 (m, 1H, CH_2b-1′), 4.15 (s, 2H, CH_2-3), 4.18–4.24 (m, 1H, CH-11a), 4.30 (d, J=17 Hz, 1H, CH_2a-6), 5.25 (d, J=17 Hz, 1H, CH_2b-6), 7.12–7.30 (m, 4H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.1 (CH_2-6′), 25.8 (CH_2-5′ and CH_2-7′), 33.4 (CH_2-11), 43.1 (CH_2-1′), 43.7 (CH_2-6), 50.3 (CH_2-3), 54.5 (CH_2-4′ and CH_2-8′), 55.5 (CH-11a), 55.7 (CH_2-2′), 126.1 (CH), 126.8 (CH), 128.6 (2CH), 131.3 (C-10a), 132.4 (C-6a), 162.6 (C-4), 164.73 (C-1); HRMS (EI) *m*/*z* calcd for $C_{19}H_{25}N_3O_2$ [M^+] 327.1947, found 327.1943.

4.2. Crystal structure determination of 6·HCl·2H$_2$O

A colourless lath of 0.79×0.23×0.07 mm size was mounted on a glass fibre and transferred to the diffractometer (orthorhombic, $P2_12_12_1$, a=7.9742(16), b=12.875(3), c=19.791(4) Å, V=2032.0(7) Å^3, Z=4, ρ_{calcd}=1.307 g cm^{-3}, θ_{max}=24.98, Mo Kα, λ=0.71073 Å, ω-scan, diffractometer Nonius CAD4, T=293(2) K, 5953 reflections collected of which 3557 were independent, R_{int}=0.052). The structure was solved by direct methods and refined anisotropically on F^2 (SHELXS-97 and SHELXL-97, Sheldrick, University of Göttingen, 1997). The water hydrogen atoms were located in a difference Fourier synthesis and refined with restrained O–H bond length. Other hydrogen atoms were included using a riding model. The absolute structure was determined (Flack parameter 0.03(13); Flack, H. D. *Acta Crystallogr., Sect. A*, **1983**, *39*, 876).

4.3. Theoretical calculations

All the calculations have been performed with the GAUSSIAN 03 suit of programs.[15] The geometries of all

the relevant points along the reaction path for the alkylation–cyclisation (**R**, **TS** and **P**), have been optimised at PM3, RHF/6-31G(d), RB3LYP/6-31G(d) and RB3LYP/6-31++G(d,p) levels of theory. Vibrational frequencies for the optimised structures were computed to evaluate the zero-point energies (ZPE) as well as to confirm the nature of the singular points along the potential energy surface. The stationary points have been identifies as a minimum with no imaginary frequencies, or as a maximum characterised by the existence of only one imaginary frequency in the normal mode coordinate analysis. Transition state structures were located until the Hessian matrix had only one imaginary eigenvalue, and the transition states were also confirmed by animating the negative eigenvectors coordinate with a visualisation program and internal reaction coordinate (IRC) calculations.[16,17] RHF/6-31G(d) IRC calculations were performed on the transition state (**TS**) structure to check that the **TS** structure leads to reactants and to the reaction product (forward and reverse directions of the reaction path). IRC calculations steps 4 points in cartesians coordiantes in the forward direction and 4 points in the reverse direction, in steps of 0.3 amu$^{1/2}$ bohr along the path were carried out. Correlation effects were included using density functional theory (DFT) with the Becke3-Lee-Yang-Parr (B3LYP)[18] functional. The B3LYP method gave reasonable relative energies with diffuse basis sets, and, for example, 6-31+G(d,p) was suggested by Csonka,[19] and Hoffman and Rychlewsky[20] as sufficient but still computationally economical choice. However, regarding the basis set superimposition errors (BSSEs), the basis set should be extended to 6-31++G(d,p).[20]

Molecular geometry optimisations for the conformation obtained from X-ray neutralised with a chloride were performed at two levels of theory, RHF/3-21G and RB3LYP/6-31G(d). The electronic study of this conformation was carried out using molecular electrostatic potentials (MEPs).[21,22] MEPs were calculated using RB3LYP/6-31G(d) wave function from Gaussian 03 program. The Molekel program[23] was used as the graphic interface to visualise the MEPs.

Acknowledgements

The authors want to thank the Fundación Ana y José Royo for postdoctoral fellowship to N.C. This work was partially supported by grants from Universidad Nacional de San Luis-Argentina. R.D.E. is member of the Scientific staff of CONICET (Argentina). Lic M.F. Massman originally carried out some calculations reported here and we gratefully acknowledge his contribution to this research.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.065. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 284187. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +1 44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk]. Deposited information necessary to guarantee reproducibility.

Table S2 gives the analytical frequencies of **TS** obtained from RB3LYP/6-31G(d) and RB3LYP/6-31++g(d,p) calculations.

Table S3 gives the RB3LYP/6-31G(d) optimised geometry of compound **6** neutralised with a chloride.

References and notes

1. Bentley, K. W. *Nat. Prod. Rep.* **2005**, *22*, 249.
2. Hamburger, M. *Phytochem. Rev.* **2002**, *1*, 333.
3. Hätzelt, A.; Laschat, S.; Jones, P. G.; Grunenberg, J. *Eur. J. Org. Chem.* **2002**, 3936.
4. Gitto, R.; Caruso, R.; Orlando, V.; Quartarone, S.; Barreca, M. L.; Ferreri, G.; Russo, E.; De Sarro, G.; Chimirri, A. *Il Farmaco* **2004**, *59*, 7.
5. Awad, E. M.; Elwan, N. M.; Hassaneen, H. M.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2001**, *84*, 1172.
6. Elwan, N. M.; Abdelhadi, H. A.; Abdellah, T. A.; Hassaneen, H. M. *Tetrahedron* **1996**, *52*, 3451.
7. Herberich, B.; Kinugawa, M.; Vazquez, A.; Williams, R. M. *Tetrahedron Lett.* **2001**, *42*, 543.
8. Cabedo, N.; Protais, P.; Cassels, B. K.; Cortes, D. *J. Nat. Prod.* **1998**, *61*, 709.
9. Cabedo, N.; Andreu, I.; Ramírez de Arellano, M. C.; Chagraoui, A.; Serrano, A.; Bermejo, A.; Protais, P.; Cortes, D. *J. Med. Chem.* **2001**, *44*, 1794.
10. (a) Pictet, A.; Spengler, T. *Ber.* **1911**, *44*, 2030. (b) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.
11. (a) Julian, P.-L.; Karpel, W.-J.; Magnani, A.; Meyer, E.-W. *J. Am. Chem. Soc.* **1948**, *70*, 180. (b) Monsees, A.; Laschat, S.; Kotila, S.; Fox, T.; Würthwein, E.-U. *Liebigs Ann./Recueil.* **1997**, 533.
12. Gois, P. M. P.; Afonso, C. A. M. *Eur. J. Org. Chem.* **2003**, 3798.
13. Chiou, C.-M.; Kang, J.-J.; Lee, S.-S. *J. Nat. Prod.* **1998**, *61*, 46.
14. Suvire, F. D.; Rodriguez, A. M.; Mak, M. L.; Papp, J.; Enriz, R. D. *J. Mol. Struct. (Theochem)* **2001**, *540*, 257.
15. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.;

Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision B.05, Gaussian, Inc.: Pittsburgh PA, 2003.
16. Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154.
17. Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1990**, *94*, 5523.
18. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
19. Csonka, G. I. *J. Mol. Struct. (Theochem)* **2002**, *584*, 1.
20. Hoffman, M.; Rychlewski, J. *Comput. Meth. Sci. Technol.* **2000**, *6*, 61.
21. Polilzer, P.; Truhlar, D. G. *Chemical Applications of Atomic and Molecular Eletrostatic Potentials*; Plenum: New York, 1991.
22. Greeling, P.; Langenaeker, W.; De Proft, F.; Baeten, A. *Molecular Electrostatic Potentials: Concepts and Aplications*; Theoretical and Computational Chemistry; Elsevier Science B.V.: Amsterdam, 1996; Vol. 3; pp 587–617.
23. Flükiger, P.; Lüthi, H. P.; Portmann, S.; Weber, J. *MOLEKEL 4.0*; Swiss Center for Scientific Computing: Manno, Switzerland, 2000.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 4419–4425

Tetrathiafulvalene-based podands bearing one or two thiol functions: immobilization as self-assembled monolayers or polymer films, and recognition properties

Joël Lyskawa,[a,b] Maïtena Oçafrain,[a] Gaëlle Trippé,[a] Franck Le Derf,[a] Marc Sallé,[a,*] Pascal Viel[b] and Serge Palacin[b]

[a]*Laboratoire CIMMA, UMR CNRS 6200, Université d'Angers, 2 Bd Lavoisier, F-49045 Angers Cedex, France*
[b]*CEA Saclay, DSM/DRECAM/SPCSI, CSI, Gif-sur-Yvette F-91191, France*

Received 24 January 2006; revised 14 February 2006; accepted 20 February 2006

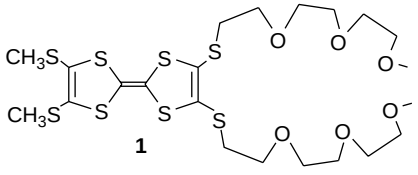
Abstract—The synthesis of various thiol and dithiol derivatives of a tetrathiafulvalene-based receptor is presented, as well as their immobilization on gold as self-assembled monolayers (SAMs). The formation of films incorporating TTF units is also shown by electrooxidation of TTF–dithiol derivatives. The ability of the monolayers to electrochemically recognize Pb^{2+} is demonstrated.

1. Introduction

Self-assembled monolayers (SAMs) incorporating electroactive probes are subject to intensive works, in particular for sensing applications.[1]

On this basis, several groups have described in the last decade, the preparation of SAMs involving the tetrathiafulvalene framework.[2] This electroactive unit is known for its well-established redox properties, involving three stable redox states (neutral, cation-radical, dication) reached upon two successive reversible one-electron redox processes.[3] The continuous synthetic efforts led around this species,[4] have allowed to introduce a great variety of functionalities on its periphery, including thiol or disulfide functions for the preparation of SAMs.[2] In addition to anchoring –SH or –S–S– groups, binding units for metal cation recognition have also been introduced onto TTF, in order to generate SAMs able to electrochemically respond upon complexation of a guest cation.[2b–e,5]

We have recently communicated the redox-switchable binding properties of a TTF–podand assembly **1** for Pb(II).[6] In particular, this system, once immobilized into a conducting film, binds or expulses Pb^{2+} just by tuning the TTF redox state (Scheme 1).



Scheme 1.

Whereas modification of electrodes by formation of SAMs with adsorbates bearing one sulfur-based grafting site (thiol or disulfide group) is well-known,[1] much less attention has been given to systems bearing two or more thiol groups. In that case, it was demonstrated that a tetrathiol–TTF derivative can be deposited either as SAMs or as polymer films.[2f]

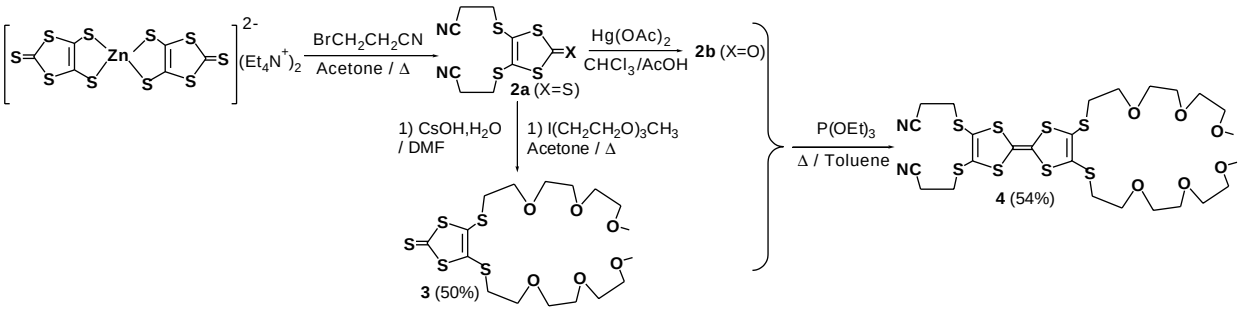
In this paper, we present our results concerning the synthesis of various thiol and dithiol derivatives of ligand **1** as well as their immobilization on gold as SAMs. The formation of polymer films incorporating TTF units is also shown by electrooxidation of TTF–dithiol derivatives. Finally, the ability of the SAMs to electrochemically recognize Pb^{2+} is demonstrated.

2. Results and discussion

The synthetic strategy involves the thiolate protection/deprotection methodology previously developed in the TTF series by Becher et al.[7] The starting five-member heterocycles **2a** and **2b** were synthesized according to the

Keywords: SAMs; Tetrathiafulvalene; Cyclic voltammetry; Polydisulfides.
* Corresponding author. Tel.: +33 2 41 73 54 39; fax: +33 2 41 73 54 05; e-mail: marc.salle@univ-angers.fr

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.054



Scheme 2.

literature,[7] from the bis(2-thioxo-1,3-dithiole-4,5-dithio)-zincate salt (Scheme 2).[8] The counter part **3** to reach a TTF skeleton, was obtained from **2a** and ω-iodo triethyleneglycol monomethyl ether[9] as the electrophile. Cross coupling of **2b** and **3** in presence of triethylphosphite afforded the key dissymetrical TTF intermediate **4** in 54% yield.

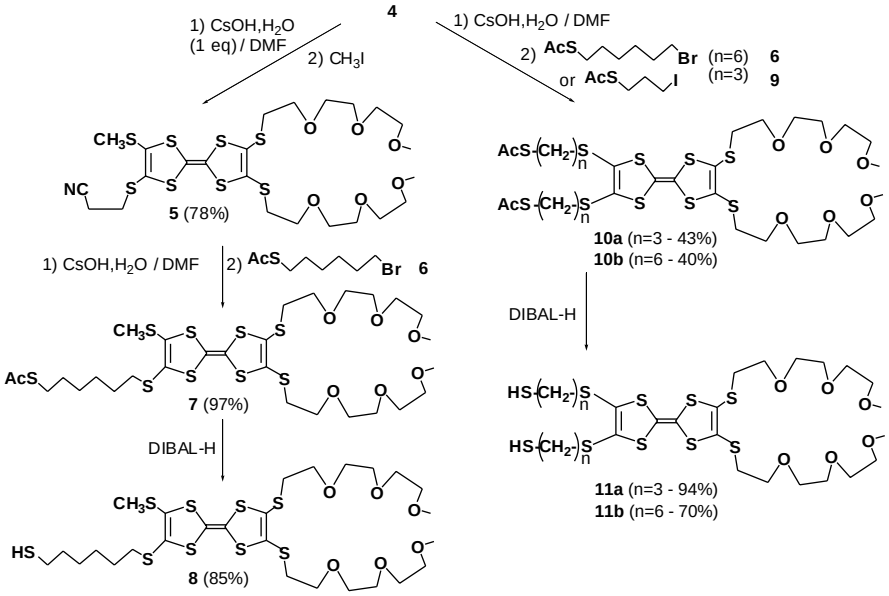
Compound **4** bearing two protected thiolate functionalities, allows introduction of one or two grafting sites on the periphery of the TTF skeleton (Scheme 3).

One equivalent of cesium hydroxide was added to **4**, and the TTF–thiolate intermediate was treated by iodomethane to produce the monomethylated derivative **5** in 78% yields. Subsequent deprotection of the residual thiolate of **5** under basic conditions followed by a nucleophilic substitution onto thioester **6**, allowed introduction of the lateral hexamethylene chain of **7** in quantitative yields. The brominated derivative **6**[5] was prepared by a Mitsunobu reaction with 6-bromohexanol in presence of thioacetic acid.

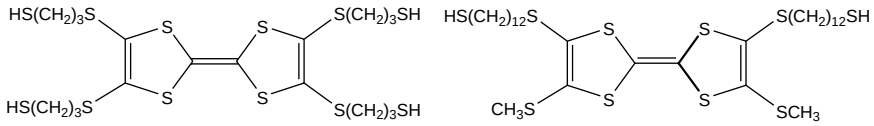
Similarly, two lateral chains incorporating either six or three methylene fragments were introduced by reaction of the dithiolate derivatives generated from **4** with CsOH, H_2O, and thioesters **6** or **9**, respectively. The iodinated precursor **9** was prepared by halogen exchange (NaI, acetone), from the corresponding commercially available chlorinated analogue.

Finally, the target mono- and dithiol derivatives could be obtained in good yields by reduction with DIBAL-H. These compounds have been fully characterized and their ^{1}H NMR spectra exhibit in particular, a triplet located at 1.34–1.38 ppm corresponding to the SH signal. It should be noted that this signal tends to disappear within a few hours, which is assigned to the self-oxidation of these thiols to the corresponding disulfides. Similar observations have already been made recently with other TTF-substituted thiols, and are attributed to an electron-transfer process involving catalytic amounts of $TTF^{\cdot +}$.[2g,5]

The electrochemical behaviour of TTF–thiols derivatives **8**, **11a** and **11b** was studied by cyclic voltammetry under homogeneous conditions with a Pt working electrode. The three compounds behave similarly, and show the expected two successive one electron redox systems of the TTF framework at $E^1_{ox}=0.55$–0.57 V and $E^2_{ox}=0.86$–0.90 V versus Ag, AgCl. In the cases of the dithiol derivatives **11a**,**b**, we could observe a third wave, irreversible, located at a higher oxidation potential ($E^3_{ox}=1.25$ V) and attributed to the oxidation of the thiol functionalities into a disulfide.



Scheme 3.

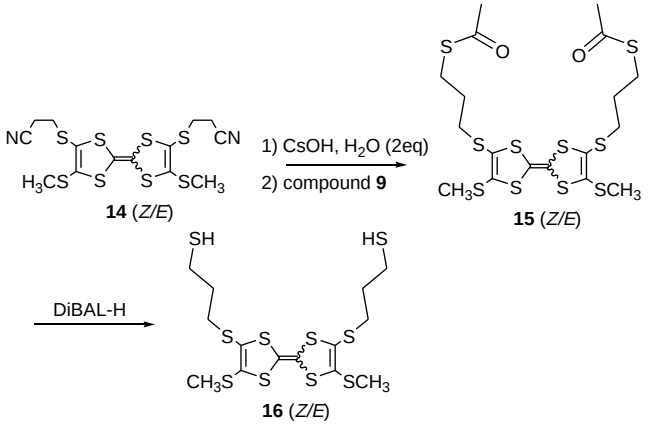


12 **13** (*Z*/*E*)

Scheme 4.

Considering this observation, as well as the presence of two thiol functions per TTF unit in **11a**,**b**, we checked the possibility to electrodepose these compounds as poly(disulfides) via an intermolecular reaction. A polymerization, carried out on glassy carbon electrodes, was already described by Fujihara et al. from TTF–tetrathiol derivatives **12** (Scheme 4) under potentiodynamic conditions.[2f] Nevertheless, no film growing could be observed with our TTF–dithiol derivatives **11a**,**b** by scanning the potentials between 0.10 and 1.60 V Ag, AgCl on a Pt, Au or a glassy carbon electrode.

In order to check the effect of the localization of the thiol linkers on the film formation ability of TTF–polythiols, we therefore synthesize TTF–dithiol **16** for which both functions are located on the 2,7-positions of the TTF framework. According to a similar synthetic methodology as for compounds **8** or **11**, and starting from the dicyano TTF derivative **14**,[10] we could isolate the model compound **16** in two steps (Scheme 5), as a mixture of *Z*/*E* isomers. TTF–dithiol derivatives with longer thiol linkage (C_{12}) (compound **13**), were also recently prepared by Hellberg et al. according to a different synthetic strategy.[2h]



14 (*Z*/*E*) **15** (*Z*/*E*) **16** (*Z*/*E*)

Scheme 5.

CV experiments led on **16** with a gold electrode are particularly significant. Recurrent scanning of the potentials between 0 and 1.20 V, allowed a very regular film deposition on the surface (Fig. 1a), denoted by a progressive increase of both peaks intensity. In particular, the shape of the two redox waves becomes thinner upon increasing, as expected from a change from diffusion-controlled to surface-confined redox processes. The modified electrode was then thoroughly rinsed with methylene chloride and dipped in a monomer-free electrolytic solution (Fig. 1b). Two well-defined reversible oxidation peaks are observed, whose shape is characteristic of surface confined redox couples.[11] In addition, the anodic–cathodic peaks separation for both redox steps is very closed to 0 V confirming that the redox processes of the TTF system are not limited by charge and/or mass transport within the film.

As expected, and in contrast with conducting polypyrroles or polythiophenes bearing pendant TTF units that we described recently,[6,12] for which the conducting polymer backbone can be characterized on the CV besides the two redox waves belonging to TTF, no additional electrochemical signature is observed besides the TTF signals in the case of poly(**16**). Finally, no alteration of the CV was observed upon recurrent potentials cycling, illustrating the stability of the films obtained.

It appears therefore that compound **16** presents a similar ability as the TTF–tetrathiol **12**[2f] to polymerize. Conversely, using the same conditions as for **16** (recurrent scanning of the potentials between 0 and 1.20 V), we could not observe any film formation from TTF–dithiol **11**. On this basis, we can extrapolate that two thiol linkages are enough to promote electropolymerization (compare **16** vs **12**), but providing that both of them are located on the 2,7-positions of TTF (**16** vs **11**) and that the chains are not too long (**16** vs **13**).[13] Such observations can be rationalized by the analysis of the parameters favouring intra- versus inter-molecular disulfide bonds formation. With short linkages located on the 2,7 positions (**12** and **16**), the intramolecular disulfide bond is unlikely to arise because of the important strain, which would be generated in the resulting macrocycle fused to the rigid TTF skeleton. On the contrary, intra-molecular disulfides are likely to occur when thiol functions can be spatially closed, as it is the case with **11** for which the pendant thiol functions occupy vicinal positions on the TTF, or for **13** for which the chains can mutually arrange spatially more easily because of their length, which is also confirmed by the isolation of the intra-molecular disulfide product.[2h]

The ability of the receptor molecules **8** and **11** to form self-assembled monolayers (SAMs), was then explored. SAMs of **8** and **11** were prepared in a glovebox under Ar atmosphere. Gold (111) bead electrodes[14,15] were immersed in a dichloromethane solution of **8**, **11a** or **11b** (1×10^{-3} M) for 24–48 h, and the resulting modified electrodes were thoroughly rinsed with dichloromethane, and introduced in a freshly prepared electrolytic acetonitrile solution (Bu_4NPF_6, 0.1 M). The efficiency in SAMs formation was evaluated by cyclic voltammetry.

The CV response of the SAMs obtained from **8** or **11** shows the expected two one-electron oxidation processes corresponding to the successive reversible oxidation of neutral TTF (TTF°) to the radical-cation ($TTF^{\cdot+}$) and to dication (TTF^{2+}) (Fig. 2). Upon sequential scanning from 0.3 to 1.1 V (200 cycles in acetonitrile, (Bu_4NPF_6, 0.1 M)), the SAMs derived from **8** and **11** demonstrate a good stability,

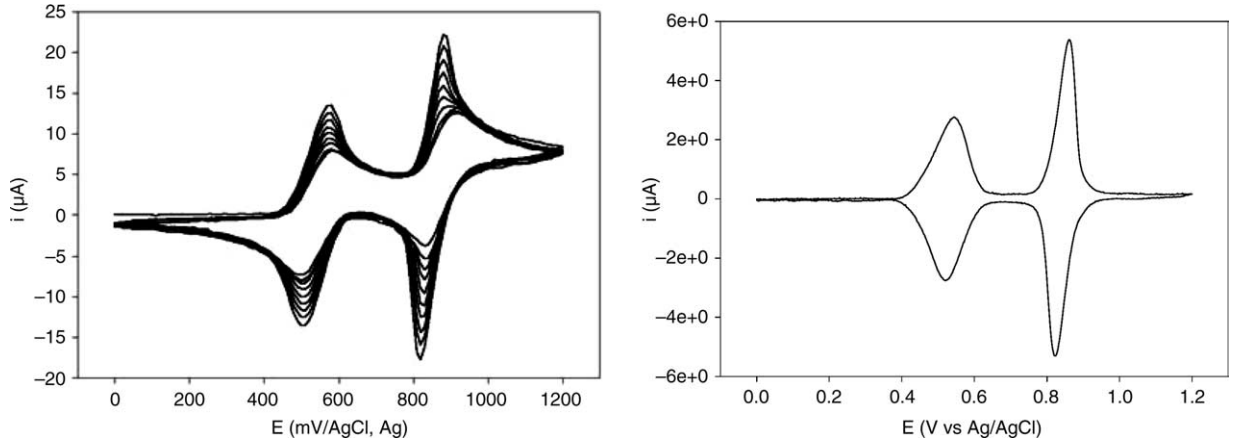


Figure 1. (a) Growing of the film from **16** (1 mM), in 0.10 M Bu_4NPF_6/CH_2Cl_2, 10 cycles at 100 mV s^{-1}, Au; (b) CV response of the film ($\Gamma=1.1\times10^{-9}$ mol TTF cm^{-2}), in 0.10 M Bu_4NPF_6/CH_2Cl_2, Au.

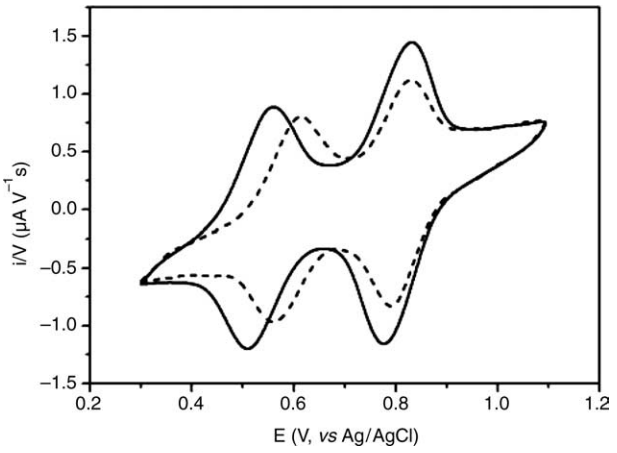


Figure 2. Cyclic voltammogram for self-assembled monolayers of compound **8** without (solid line) and in the presence (dashed) of 1.2×10^{-2} mM $Pb(ClO_4)_2$, Au electrode; $\Gamma=1\times10^{-10}$ mol cm^{-2}, CH_3CN, Bu_4NPF_6 (0.1 mol L^{-1}) versus Ag/AgCl.

as shown by the constant peaks intensity. It is surprising that we could not observe any significant difference in the stability of these monolayers depending on the number of anchoring sites or on the length of the linker. The electrochemical response of these SAMs is consistent with a redox system confined at the electrode surface, as shown by the linearity of both oxidative peak currents with the scan rate ν ($\nu=1$–30 V s^{-1}), by the constant values of the anodic (E^i_{ox}) and cathodic (E^i_{red}) peaks and of ΔE ($=E^i_{ox}-E^i_{red}$) on varying ν. The surface coverage (Γ)[15] reaches a value of $\Gamma=1\times10^{-10}$ mol cm^{-2} for **8**, in the expected range for a monolayer. The coverage is significantly larger for the TTF–dithiol analogues **11**, since we observed $\Gamma=1.4\times10^{-10}$ mol TTF cm^{-2} for **11b** and 8×10^{-10} mol TTF cm^{-2} for **11a**. Possible formation of small quantities of TTF oligomers by formation of intermolecular TTF–disulfide bonds, in addition to the SAM formation, may explain these values.

Addition of Pb^{2+} ($C=1.2\times10^{-2}$ mM) to the electrolytic solution containing the SAMs modified electrodes, led to a positive shift of E^1_{ox} (+60 mV), whereas E^2_{ox} remains constant (Fig. 2). Such high level of electrochemical recognition is consistent—though of lower degree—with observations made with the parent TTF–ligand (without any thiol linkage) in homogeneous solution ($\Delta E^1_{ox}=+120$ mV), or once immobilized on a surface via a conducting polymer ($\Delta E^1_{ox}=+100$ mV),[6] and results from the electrostatic interactions occurring between the metal cation and the positively charged oxidized species of TTF. A possible explanation to justify the lower degree of the E^1_{ox} positive shifting in the case of SAMs of **8** compared to the corresponding polythiophene film,[6] can be found in the difference of density in TTF–podands between the two cases. The nature of the grafting sites (–SH vs ethylene (dioxy)thiophene) leads to a more compact arrangement for the SAMs, where the ligands are therefore spatially closer, which may alter their ability to bind a given cation. Finally, no significant differences in the recognition properties were observed between the SAMs obtained from **8** and **11b**[16] (see Supplementary data).

3. Conclusion

To conclude, we have synthesized a series of TTF–mono and –dithiol derivatives **8**, **11a** and **11b** incorporating polyether chains for the recognition of Pb(II). Dithiol derivatives **11** could not be electropolymerized, presumably because of the vicinal positions of the thiol-linkages on the periphery of the TTF core, which favour intra- rather than inter-molecular disulfide bonds formation. This was rationalized by the synthesis of a corresponding TTF–dithiol substituted on the 2,7-positions **16**, which exhibits a very good ability to electropolymerize. SAMs formation could be achieved with the three podand TTF–dithiol **8**, **11a** and **11b**. The monolayers obtained, present in the three cases a good stability and demonstrate a very good ability to electrochemically recognize Pb(II).

4. Experimental

4.1. Instrumentation

NMR spectra were recorded on a Bruker Advance DRX500 spectrometer operating at 500 and 125.7 MHz for ^1H and ^{13}C, respectively, δ values are given in ppm (relative to TMS). Electrochemical experiments were carried out with

a PAR273 Potentiostat-Galvanostat. Characteristics of the gold electrodes are given in Refs. 14 and 15. Solvents used were of electrochemical grade, and electrochemical studies were carried out in glovebox under Ar atmosphere.

4.2. Synthesis

4.2.1. 4,5-Bis[2-[2-(2-methoxyethoxy)ethoxy]ethylsulfanyl]-1,3-dithiole-2-thione (3). Cesium hydroxide monohydrate (6.9 g, 2.5 equiv, 4.11×10^{-2} mol) in dry methanol (10 mL) was added to thione **2a** (5 g, 1.64×10^{-2} mol) dissolved in dry and degassed DMF (200 mL). The reaction mixture was stirred during 10 min. Then, 1-(2-iodoethoxy)-2-(2-methoxyethoxy)ethane (3.77×10^{-2} mol, 2.3 equiv) in dry and degassed DMF (20 mL) was added in one portion. The reaction mixture was stirred for one night. The solvent was removed in vacuo, the residue was dissolved in dichloromethane (150 mL), washed with three times with water and dried over magnesium sulfate. The mixture was concentrated in vacuo and the orange residue was purified by chromatography on a silica gel column (eluent: petroleum ether/ethyl acetate: 1:1). Yield 50%; red oil; $C_{17}H_{30}O_6S_5$; ^{1}H NMR ($CDCl_3$): 3.72 (t, 4H, CH_2OMe), 3.65 (m, 12H, CH_2O), 3.55 (m, 4H, SCH_2CH_2O), 3.38 (s, 6H, CH_3O), 3.05 (t, 4H, CH_2S); ^{13}C NMR ($CDCl_3$): 211.0 (C=S), 136.6 (C=C), 72.0, 70.7, 70.6, 70.65, 69.9 (CH_2O), 59.0 (OCH_3), 36.2 (SCH_2CH_2O); HRMS (EI), $(M)^+$ Theo.: 490.0646, found: 490.0643.

4.2.2. 6,7-Bis(2-cyanoethylsulfanyl)-2,3-bis[2-[2-(2-methoxyethoxy)ethoxy]ethylsulfanyl]tetrathiafulvalene (4). 1,3-Dithiole-2-one **2b** (0.6 g, 2.08×10^{-3} mol) and thione **3** (1.0 g, 2.04×10^{-3}) were introduced in toluene (25 mL) and 10 mL of triethylphosphite was then added. The mixture was refluxed for 3 h, and then cooled down to rt. Solvents are evaporated in vacuo. The resulting residue was dissolved in 150 mL de CH_2Cl_2, washed three times with water and then dried over $MgSO_4$. After evaporation of the solvent, the product was obtained as red oil (0.82 g, 54% yield) after a silicagel column chromatography (dichloromethane 7/ethyl acetate 3). Yield 54%; red oil; $C_{26}H_{38}O_6N_2S_8$; ^{1}H NMR (acetone-d_6): 3.69 (t, 4H, CH_2OMe), 3.57 (m, 12H, CH_2O), 3.46 (t, 4H, SCH_2CH_2O), 3.29 (s, 6H, CH_3O), 3.24 (t, 4H, SCH_2CH_2CN), 3.07 (t, 4H, CH_2S), 2.94 (t, 4H, CH_2CN); ^{13}C NMR ($CDCl_3$): 128.1, 128.0 (lateral C=C), 117.4 (CN), 114.1, 107.7 (central C=C), 71.9, 70.6, 70.5, 70.4, 70.0 (CH_2O), 59.0, 58.9 (OCH_3); 35.5 (SCH_2CH_2O); 31.3 (SCH_2CH_2CN); 18.9 (CH_2CN); HRMS (ESI+): $(M+Na)^+$ Theo.: 753.0496, found: 753.0440.

4.2.3. 2,3-Bis[2-[2-(2-methoxyethoxy)ethoxy]ethylsulfanyl]-6-(2-cyanoethylsulfanyl)-7-(methylsulfanyl)tetrathiafulvalene (5). Cesium hydroxide monohydrate (0.154 g, 9.2×10^{-4} mol) in dry methanol (10 mL) was added to tetrathiafulvalene dicyano derivative **4** (0.61 g, $8.36.10^{-4}$ mol) dissolved in dry and degassed DMF (50 mL). The reaction mixture was stirred during 10 min, the colour becoming dark red. Then, an excess of iodomethane (2 mL) was added in one portion. The colour of the reaction mixture turned back to orange, and the reaction mixture was stirred at rt for 1 h. The solvent was removed in vacuo, the residue was dissolved in dichloromethane (100 mL), washed three times with water and dried over magnesium sulfate. The mixture was concentrated in vacuo and the residue was purified by chromatography on a silica gel column (eluent: ethyl acetate). Compound **5** was obtained in 78% yield (0.45 g) as a red oil. Yield 78%; red oil; $C_{24}H_{37}O_6NS_8$; ^{1}H NMR (CD_3CN): 3.62 (t, 4H, CH_2OMe), 3.53 (m, 12H, CH_2O), 3.45 (t, 4H, SCH_2CH_2O), 3.28 (s, 6H, CH_3O), 3.01 (m, 6H, $4\times CH_2S+2\times SCH_2CH_2CN$), 2.71 (t, 2H, CH_2CN), 2.45 (s, 3H, SCH_3); ^{13}C NMR ($CDCl_3$): 135.1, 128.2, 127.8, 120.3 (lateral C=C), 117.5 (CN), 112.2, 109.4 (central C=C), 72.0, 70.6, 70.6, 70.1, 70.1 (CH_2O), 59.0 (OCH_3), 35.5 (SCH_2CH_2O), 31.3 (SCH_2CH_2CN), 19.1 (SCH_3), 18.8 (CH_2CN); HRMS (ESI+): (M^+) Theo.: 691.0387, found: 691.0400; microanalysis: % Calcd: C, 41.65; H, 5.39; N, 2.02; O, 13.87, %. Found: C, 42.41; H, 5.35; N, 1.91; O, 13.95.

4.2.4. 2,3-Bis[2-[2-(2-methoxyethoxy)ethoxy]ethylsulfanyl]-6-(6-acetylsulfanylhexyl-1-sulfanyl)-7-(methylsulfanyl)tetrathiafulvalene (7). Cesium hydroxide monohydrate (0.092 g, 5.46×10^{-4} mol) in dry methanol (5 mL) was added to tetrathiafulvalene derivative **5** (0.27 g, 3.9×10^{-4} mol) dissolved in dry and degassed DMF (30 mL). The reaction mixture was stirred during 10 min, the colour becoming dark red. Then, thioacetyl derivative **6** (0.186 g, 7.8×10^{-4} mol), was added in one portion. The colour of the reaction mixture turned back to orange, and the reaction mixture was stirred at rt for 2 h. The solvent was removed in vacuo, the residue was dissolved in dichloromethane (100 mL), washed three times with water and dried over magnesium sulfate. The mixture was concentrated in vacuo and the residue was purified by chromatography on a silica gel column (eluent: ethyl acetate). Compound **7** was obtained in 97% yield (0.30 g) as an orange oil. Yield: 97%; orange oil; $C_{29}H_{48}O_7S_9$; ^{1}H NMR ($CDCl_3$): 3.60–3.73 (m, 16H, CH_2O), 3.55 (m, 4H, SCH_2CH_2O), 3.39 (s, 6H, OCH_3), 3.02 (t, 4H, SCH_2CH_2O), 2.92 (2t, 4H, CH_2), 2.43 (s, 3H, SCH_3), 2.32 (s, 3H, $COCH_3$), 1.52–1.75 (m, 4H, CH_2), 1.30–1.50 (m, 4H, CH_2); ^{13}C NMR ($CDCl_3$): 195.9 (C=O); 129.5, 127.8, 127.7, 125.6 (lateral C=C), 110.94, 109.95 (central C=C), 71.9, 70.6, 70.5, 70.5, 70.0 (CH_2O), 59.0 (OCH_3), 36.1, 35.4, 30.6, 29.4, 29.3, 28.9, 28.2, 27.8 (SCH_2, $SCOCH_3$, CH_2), 19.2 (SCH_3); HRMS (ESI+): $(M+Na)^+$ Theo.: 819.0784, found: 819.0780.

4.2.5. 2,3-Bis[2-[2-(2-methoxyethoxy)ethoxy]ethylsulfanyl]-6-(6-mercaptohexyl-1-sulfanyl)-7-(methylsulfanyl)-tetrathiafulvalene (8). Thioacetyl derivative **7** (0.150 g, 1.88×10^{-4} mol) was dissolved in 50 mL of dry dichloromethane. A solution of DIBAL-H (1 M in toluene, 9.42×10^{-4} mol) was added dropwise to **7** cooled at −78 °C, in 15 min under nitrogen. After 45 min stirring at −78 °C, the reaction mixture was treated with a chlorhydric acid solution (3 M) in methanol. At rt, 80 mL of dichloromethane were added. The organic phase was washed with water and dried over $MgSO_4$. Evaporation of the solvent, and silicagel chromatography (ethyl acetate), afforded **8** (120 mg) as an orange oil. Yield: 85%; orange oil; $C_{27}H_{46}O_6S_9$; ^{1}H NMR ($CDCl_3$): 3.64–3.68 (m, 16H, CH_2O), 3.55 (m, 4H, SCH_2CH_2O), 3.38 (s, 6H, OCH_3), 3.01 (t, 4H, SCH_2CH_2O), 2.82 (t, 2H, SCH_2), 2.53 (dd, 2H, CH_2SH), 2.43 (s, 3H, SCH_3), 1.60–1.65 (m, 4H, CH_2), 1.41–1.44 (m, 4H, CH_2), 1.34 (t, 1H, SH); ^{13}C NMR ($CDCl_3$):

129.6, 127.8, 127.8, 125.6 (lateral C=C), 110.9, 110.0 (central C=C), 71.9, 70.6, 70.6, 70.5, 70.0 (CH_2O), 59.0 (OCH_3), 36.1, 35.4, 33.8, 29.5, 27.8, 27.7 (CH_2, SCH_2), 24.5 (CH_2SH), 19.2 (SCH_3); HRMS (ESI+): $(M+Na)^+$ Theo.: 777.0679, found: 777.0662.

4.2.6. 1-Iodo-3-thioacetyl propane (9). A solution of the commercially available 3-chloropropyl thioacetate (12 g, 0.049 mol) and sodium iodide (36 g) in 300 mL of acetone, was refluxed for 12 h. The solvent was evaporated and the resulting mixture was dissolved in dichloromethane (200 mL), washed with water, and dried over magnesium sulfate. The iodinated product was isolated from a silicagel chromatography (dichloromethane/petroleum ether 1:1), as a yellow oil (2.9 g, 90%). Yield 90%; yellow oil; C_5H_9OSI; ^1H NMR ($CDCl_3$): 3.20 (t, 2H, CH_2I), 2.95 (t, 2H, SCH_2), 2.33 (s, 3H, $SCOCH_3$), 2.07 (q, 2H, $CH_2CH_2CH_2$).

4.3. Bis(thioacetyl)–TTF derivatives (10a) and (10b)

Compounds **10a** and **10b** were prepared according a similar procedure as for monothioacetyl–TTF derivative **7**, starting from the dicyano–TTF derivative **4** and using 2.5 equiv of cesium hydroxide monohydrate. Compounds **10a** and **10b** were purified by silicagel column chromatography (ethyl acetate).

4.3.1. 2,3-Bis[2-[2-(2-methoxyethoxy)ethoxy]ethylsulfanyl]-6,7-bis(3-acetylsulfanylpropyl-1-sulfanyl)tetrathiafulvalene (10a). Yield 43%; orange oil; $C_{30}H_{48}O_8S_{10}$; ^1H NMR ($CDCl_3$): 363–3.70 (m, 16H, CH_2O), 3.56 (m, 4H, SCH_2CH_2O), 3.38 (s, 6H, OCH_3), 3.01 (m, 8H, CH_2), 2.87 (t, 4H, CH_2), 2.34 (s, 6H, $SCOCH_3$), 1.91 (c, 4H, CH_2); ^{13}C NMR ($CDCl_3$): 195.3 (COMe), 128.0, 127.90 (lateral C=C), 110.4, 110.3 (central C=C), 72.0, 70.6, 70.5, 70.1 (CH_2O), 59.0 (OCH_3), 35.5, 34.9, 30.6, 29.5, 27.7 (SCH_2, CH_2, $SCOCH_3$); HRMS (ESI+): $(M+Na)^+$ Theo.: 879.0454, found: 879.0417.

4.3.2. 2,3-Bis[2-[2-(2-methoxyethoxy)ethoxy]ethylsulfanyl]-6,7-bis(6-acetylsulfanylhexyl-1-sulfanyl)tetrathiafulvalene (10b). Yield 40%; orange oil; $C_{36}H_{60}O_8S_{10}$; ^1H NMR ($CDCl_3$): 3.59–3.75 (m, 16H, CH_2O), 3.55 (m, 4H, SCH_2CH_2O), 3.37 (s, 6H, OCH_3), 3.01 (t, 4H, SCH_2CH_2O), 2.76–2.87 (2t, 8H, CH_2), 2.31 (s, 6H, $COCH_3$), 1.52–1.79 (m, 8H, CH_2), 1.34–1.50 (m, 8H, CH_2); ^{13}C NMR ($CDCl_3$): 195.8 (COMe), 127.9, 127.79 (lateral C=C), 110.9, 109.5 (central C=C), 72.0, 70.6, 70.6, 70.1 (CH_2O), 59.0 (OCH_3), 36.2, 35.5, 30.6, 29.4, 29.3, 29.0, 28.3, 28.1 (SCH_2, CH_2, $SCOCH_3$); HRMS (ESI+): $(M+Na)^+$ Theo.: 963.1393, found: 963.1412.

4.4. TTF–dithiol derivatives (11a) and (11b)

Compounds **11a** and **11b** were prepared according a similar procedure as for monothiol–TTF derivative **8**, starting from the bis(thioacetyl)–TTF derivative **10a** and **10b**, respectively. They were purified by silicagel column chromatography (ethyl acetate).

4.4.1. 2,3-Bis[2-[2-(2-methoxyethoxy)ethoxy]ethylsulfanyl]-6,7-bis(3-mercaptopropyl-1-sulfanyl)tetrathiafulvalene (11a). $C_{26}H_{44}O_6S_{10}$; orange oil; Yield: 94%; ^1H NMR ($CDCl_3$): 3.64–3.69 (m, 16H, CH_2O), 3.55 (m, 4H, SCH_2CH_2O); 3.38 (s, 6H, OCH_3), 3.00 (t, 4H, SCH_2CH_2O), 2.95 (t, 4H, SCH_2), 2.68 (dd, 4H, CH_2SH), 1.93 (c, 4H, CH_2), 1.38 (t, 2H, SH); ^{13}C NMR ($CDCl_3$): 128.0 (lateral C=C), 110.7 (central C=C), 72.0, 70.7, 70.6, 70.1 (CH_2O), 59.0 (OCH_3), 35.5, 34.5, 33.4, (SCH_2, CH_2), 23.0 (CH_2SH); HRMS (ESI+): $(M+Na)^+$) Theo.: 793.0264, found: 793.0063.

4.4.2. 2,3-Bis[2-[2-(2-methoxyethoxy)ethoxy]ethylsulfanyl]-6,7-bis(6-mercaptohexyl-1-sulfanyl)tetrathiafulvalene (11b). Yield 70%; orange oil; $C_{32}H_{56}O_6S_{10}$; ^1H NMR ($CDCl_3$): 3.64–3.69 (m, 16H, CH_2O), 3.56 (m, 4H, SCH_2CH_2O), 3.38 (s, 6H, OCH_3), 3.00 (t, 4H, SCH_2CH_2O), 2.82 (t, 4H, SCH_2), 2.52 (dd, 4H, CH_2SH), 1.60–1.66 (m, 8H, CH_2), 1.41–1.43 (m, 8H, CH_2), 1.35 (t, 2H, SH); HRMS (ESI+): $(M+Na^+)$ Theo.: 877.1030, found: 877.1025.

4.4.3. 2,6(7)-Bis(methylsulfanyl)-3,7(6)-bis(3-acetylsulfanylpropyl-1-sulfanyl)tetrathiafulvalene (15). Compounds **15** was prepared according a similar procedure as for monothioacetyl–TTF derivative **7**, starting from the dicyano–TTF derivative **14**[10] and using 2.6 equiv of cesium hydroxide monohydrate. Compound **15** was purified by silicagel column chromatography (petroleum ether/dichloromethane: 9:1) and was obtained as a mixture of *Z*/*E* isomers. Yield 97%; Orange solid; $C_{18}H_{24}O_2S_{10}$; ^1H NMR ($CDCl_3$): 3.01 (t, $J=7.1$ Hz, 4H, CH_2SCOCH_3), 2.86 (t, $J=7.1$ Hz, 4H, CH_2S), 2.43, 2.44 (two s, 6H, CH_3S), 2.34 (s, 6H, CH_3CO), 1.91 (quint., $J=7.1$ Hz, 4H, CH_2CH_2S); ^{13}C NMR ($CDCl_3$): 195.3 (CO, 31.0 and 131.1 (lateral C=C), 124.6, 124.4, 110.6 (central C=C), 34.9 (SCH_2), 30.6 ($SCOCH_3$), 29.4, 29.7 (CH_2CH_2S), 27.6 (CH_2SCO), 19.2 (SCH_3); MS (FAB): 591.8 (M^+); HRMS (FAB): (M^+) Theo.: 591.8983, found: 591.8994.

4.4.4. 2,6(7)-Bis(methylsulfanyl)-3,7(6)-bis(3-mercaptopropyl-1-sulfanyl)tetrathiafulvalene (16). Compounds **16** was prepared according a similar procedure as for monothiol–TTF derivative **8**, starting from the bis(thioacetyl)–TTF derivative **15**. The final product **16**, obtained as a *Z*/*E* mixture, was purified by silicagel column chromatography (petroleum ether/dichloromethane: 9:1). Yield 92%; Orange oil; $C_{14}H_{20}S_{10}$; ^1H NMR ($CDCl_3$): 2.94 (t, $J=6.8$ Hz, 4H, CH_2S), 2.69 (dd, $J=7.0$, 7.7 Hz, 4H, CH_2SH), 2.44 (s, 6H, CH_3S), 1.93 (m, 4H, CH_2CH_2S), 1.38 (t, $J=8.1$ Hz, 2H, SH); ^{13}C NMR ($CDCl_3$): 130.9, 131.1 (lateral C=C); 124.6, 124.5, 110.6 and 110.7 (central C=C), 33.3, 34.4 (CH_2S and CH_2CH_2SH), 23.0 (CH_2SH), 19.2 (SCH_3); MS (FAB): 507.9 (M^+); HRMS (FAB): (M^+) Theo.: 507.8772, found: 507.8754.

Acknowledgements

This work was supported by a Ph.D. grant (J.L.) from CEA and ADEME, which are acknowledged, and by a LRC CEA (DSM 01-25) in collaboration between CIMMA and CSI. M.S. thanks the Institut Universitaire de France (IUF) for financial support. M. S. thanks Professor Alain Gorgues for fruitful discussions and suggestions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.054. Electrochemical (CV) titration study for self-assembled monolayers of compound **11b** with $Pb(ClO_4)_2$.

References and notes

1. (a) Finklea, H. O. *Electroanal. Chem.* **1996**, *19*, 109–335. (b) Ferretti, S.; Paynter, S.; Russell, D. A.; Sapsford, K. E.; Richardson, D. J. *Trends Anal. Chem.* **2000**, *19*, 530–540. (c) Liu, Y.; Mu, L.; Liu, B.; Kong, J. *Chem. Eur. J.* **2005**, *11*, 2622–2631. (d) Love, J. C.; Estroff, L. A.; Kriebel, J. K.; Nuzzo, R. G.; Whitesides, G. M. *Chem. Rev.* **2005**, *105*, 1103–1169. (e) Cooke, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4860–4870.
2. (a) Yip, M.; Ward, M. D. *Langmuir* **1994**, *10*, 549–556. (b) Moore, A. J.; Goldenberg, L. M.; Bryce, M. R.; Petty, M. C.; Monkman, A. P.; Mareno, C.; Yarwood, J.; Joyce, M. J.; Port, S. N. *Adv. Mater.* **1998**, *10*, 395–398. (c) Moore, A. J.; Goldenberg, L. M.; Bryce, M. R.; Petty, M. C.; Moloney, J.; Howard, J. A. K.; Joyce, M. J.; Port, S. N. *J. Org. Chem.* **2000**, *65*, 8269–8276. (d) Liu, H.; Liu, S.; Echegoyen, L. *Chem. Commun.* **1999**, 1493–1494. (e) Liu, S.-G.; Liu, H.; Bandyopadhyay, K.; Echegoyen, L. *J. Org. Chem.* **2000**, *65*, 3292–3298. (f) Fujihara, H.; Nakai, H.; Yoshihara, M.; Maeshima, T. *Chem. Commun.* **1999**, 737–738. (g) Herranz, M. A.; Yu, L.; Martin, N.; Echegoyen, L. *J. Org. Chem.* **2003**, *68*, 8379–8385. (h) Dahlstedt, A.; Hellberg, J.; Petoral, R. M., Jr.; Uvdal, K. *J. Mater. Chem.* **2004**, *14*, 81–85. (i) Gomar-Nadal, E.; Ramachandran, G. K.; Chen, F.; Burgin, I.; Rovira, C.; Amabilino, D. B.; Lindsay, S. M. *J. Phys. Chem. B*. **2004**, *108*, 7213–7218.
3. For recent reviews, see: Batail, P., Ed. *Chem. Rev.*, Molecular Conductors (Thematic issue), *104*, **2004**.
4. For recent reviews on synthetic aspects of TTF, see: (a) Brondstedt Nielsen, M.; Lomholt, C.; Becher, J. *Chem. Soc. Rev.* **2000**, *29*, 143–164. (b) Segura, J. L.; Martin, N. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1372–1409. (c) Yamada, J. I.; Akutsu, H.; Nishikawa, H.; Kikuchi, K. *Chem. Rev.* **2004**, *104*, 5057–5083. (d) lyoda, M.; Hasegawa, M.; Miyake, Y. *Chem. Rev.* **2004**, *104*, 5085–5113. (e) Jeppesen, J. O.; Brøndsted Nielsen, M.; Becher, J. *Chem. Rev.* **2004**, *104*, 5115–5131. (f) Fabre, J. M. *Chem. Rev.* **2004**, *104*, 5133–5150. (g) Gorgues, A.; Hudhomme, P.; Salle, M. *Chem. Rev.* **2004**, *104*, 5151–5184. (h) Lorcy, D.; Bellec, N. *Chem. Rev.* **2004**, *104*, 5185–5202. (i) Frère, P.; Skabara, P. *Chem. Soc. Rev.* **2005**, *34*, 69–98. (j) Otsubo, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 43–58. (k) Bendikov, M.; Wudl, F.; Perepichka, D. F. *Chem. Rev* **2004**, *104*, 4891–4945.
5. Trippé, G.; Oçafrain, M.; Besbes, M.; Monroche, V.; Lyskawa, J.; Le Derf, F.; Sallé, M.; Becher, J.; Colonna, B.; Echegoyen, L. *New J. Chem.* **2002**, *26*, 1320–1323.
6. Lyskawa, J.; Le Derf, F.; Levillain, E.; Mazari, M.; Sallé, M.; Dubois, L.; Viel, P.; Bureau, C.; Palacin, S. *J. Am. Chem. Soc.* **2004**, *126*, 12194–12195.
7. (a) Svenstrup, N.; Rasmussen, K. M.; Hansen, T. K.; Becher, J. *Synthesis* **1994**, 809–812. (b) Simonsen, K. B.; Svenstrup, N.; Lau, L.; Simonsen, O.; Mørk, P.; Kristensen, G. J.; Becher, J. *Synthesis* **1996**, 407–418.
8. (a) Steimecke, G.; Sieler, H. J.; Kirmse, R.; Hoyer, E. *Phosphorus Sulfur* **1979**, *7*, 49. (b) Wang, C.; Batsanov, A. S.; Bryce, M. R.; Howard, J. A. K. *Synthesis* **1998**, 1615–1618.
9. 1-(2-Iodoethoxy)-2-(2-methoxyethoxy) ethane was prepared from triethylene glycol monomethyl ether by successive tosylation and iodination.
10. Becher, J.; Lau, J.; Leriche, P.; Mørk, P.; Svenstrup, N. *J. Chem. Soc., Chem. Commun.* **1994**, 2715.
11. Murray, R. W. In *'Chemically Modified Electrodes'*; Bard, A. J., Ed.; Electroanalytical Chemistry; Marcel Dekker: New York, 1984; Vol. 13, p 191.
12. Trippé, G.; Le Derf, F.; Lyskawa, J.; Mazari, M.; Roncali, J.; Gorgues, A.; Levillain, E.; Sallé, M. *Chem. Eur. J.* **2004**, *10*, 6497–6509.
13. No mention of any ability to polymerize has been given in the literature for compound **13** (Ref. 2h).
14. The gold bead electrodes were prepared and cleaned according to: Liu, S.; Liu, H.; Bandyopadhyay, K.; Gao, Z.; Echegoyen, L. *J. Org. Chem.* **2000**, *65*, 3292.
15. The geometric areas of the gold electrodes were deduced from comparison between the slopes of the linear plots of the cathodic peak current versus the square root of the scan rate, obtained for the diffusion-controlled reduction of $Fe(CN)_6^{3-}$ (10^{-2} M in 0.5 M NaCl, 25 °C) for: (i) the working gold bead electrodes, and (ii) gold disk electrodes of known surface (2 mm diameter from Radiometer Analytical SA). Typical electrode surfaces range from 0.02 to 0.04 cm^2. Surface coverages of the SAMs of TTF derivatives were calculated by integration of the current during the first scan.
16. As pointed by one referee that we acknowledge, the previous hypothesis—a higher TTF density leads to a lower electrochemical recognition—may be supported by the fact that a slight decrease of ΔE^1_{ox} ($=+50$ mV) is observed with SAMs from **11b** ($\Gamma = 1.4\times10^{-10}$ mol TTF cm^{-2}) compared to SAMs from **8** (same alkyl chain length) ($\Gamma = 1.0\times10^{-10}$ mol TTF cm^{-2} for **8**).

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 4426–4429
Tetrahedron

Synthesis of purpurasol, a highly oxygenated coumarin from *Pterocaulon purpurascens*

Dominick Maes,[a] Kris Van Syngel,[a] Silvia Debenedetti[b] and Norbert De Kimpe[a,*]

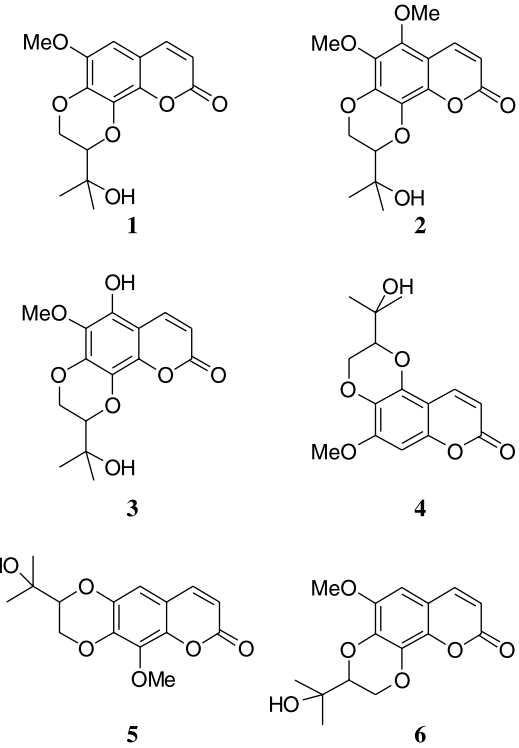
[a]*Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium*
[b]*Department of Biological Sciences, Faculty of Sciences, National University of La Plata, Calle 115 and 47, 1900 La Plata, Argentina*

Received 23 January 2006; revised 13 February 2006; accepted 20 February 2006

Abstract—Purpurasol **1**, a 6,7,8-trioxygenated coumarin, isolated from *Pterocaulon purpurascens* (Asteraceae) and *Haplophyllum obtusifolium* (Rutaceae), was synthesized for the first time by a three-step synthesis starting from the natural coumarin fraxetin. This synthesis confirmed unambiguously the structure of purpurasol **1** and obtusifol.

1. Introduction

The genus *Pterocaulon* is widely distributed in north eastern Argentina, southern Brazil and Paraguay. Plants of this genus are traditionally used in folk medicine for various purposes. The aerial parts of *Pterocaulon purpurascens* are used against snakebites and as an insecticide.[1,2] A number of strongly related tri- and tetraoxygenated coumarins were isolated from *P. purpurascens*, more precisely purpurenol **2**,[1] purpurasol **1**[2] and purpurasolol **3**.[3] Isopurpurasol **4**, a regioisomer of purpurasol, was isolated from another *Pterocaulon* species, namely *Pterocaulon virgatum*.[4] All these coumarins show a characteristic benzodioxine moiety, which is very rare in natural coumarins.[5] The present report deals with the synthesis of purpurasol **1** in order to secure unambiguously its structure and those of analogous coumarins **2** and **3**. The structure of purpurasol **1** was revealed based on spectroscopic data and by comparison with the earlier described purpurenol, of which the structure was unequivocally established based on X-ray spectroscopic analysis.[1] Later it was discovered that the spectroscopic, as well as the physical data obtained for purpurasol **1**, matched completely with those from an earlier described coumarin from *Haplophyllum obtusifolium*.[6,7] The structure of this coumarin, which was given the trivial name obtusifol, was first proposed as **5**,[6] but was later revised to **6**.[7,8] Based on spectroscopic evidence it was shown that the coumarin from *H. obtusifolium* was identical to purpurasol **1**.[9] In order to confirm this hypothesis, a synthesis of purpurasol was developed.



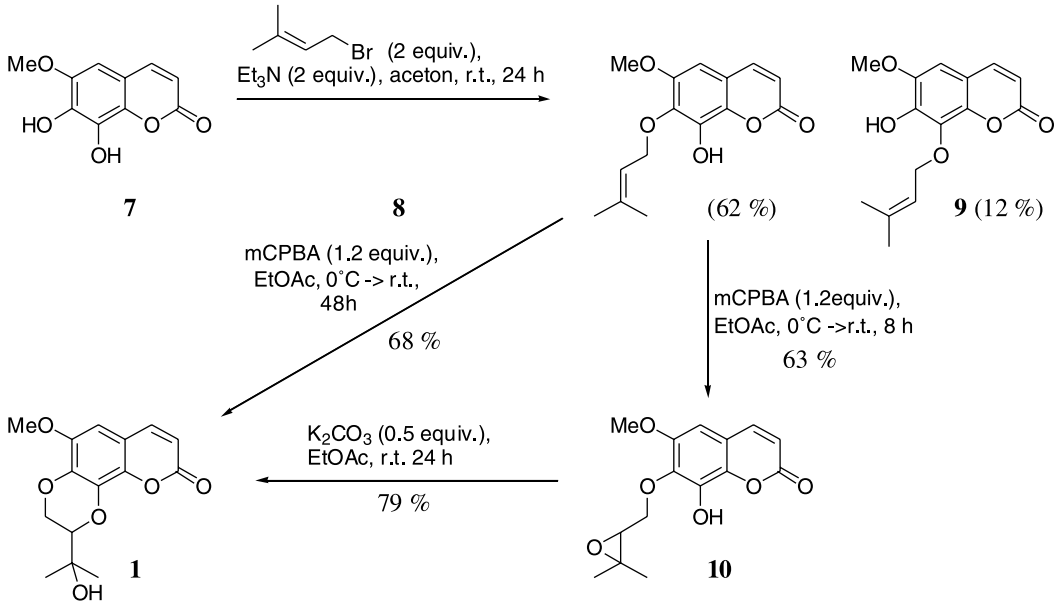
2. Results and discussion

Purpurasol **1** was synthesized starting from 7,8-dihydroxy-6-methoxy-2*H*-1-benzopyran-2-one, known as fraxetin **7**. Fraxetin **7** is a natural coumarin that occurs in many plant

Keywords: Coumarin; Purpurasol; Pterocaulon purpurascens.
* Corresponding author. Tel.: +32 9 264 59 51; fax: +32 9 264 62 43; e-mail: norbert.dekimpe@ugent.be

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.055

species, including *Aesculus turbinate* (Hippocastanacea)[10] and several *Fraxinus* spp. (Oleaceae).[11,12] Fraxetin **7** was also isolated from *P. purpurascens*,[3] which indicates that fraxetin **7** might be a natural precursor in the biosynthesis of purpurasol. The first synthetic step involved regioselective prenylation of fraxetin. Because of delocalization towards the electron withdrawing carbonyl group, the 7-OH group is



more acidic than the OH group at the 8-position. Although selective prenylation of fraxetin **7** was described before in 70% yield using sodium bicarbonate and 4-bromo-2-methyl-2-butene,[13] in our hands only, and after numerous experiments under these and other reaction conditions, very low yields of the desired capensin **8** [8-hydroxy-6-methoxy-7-(3′-methyl-2′-butenyloxy)coumarin] were obtained. This problem of reproducibility is probably due to hydrolysis during aqueous workup. However, when the workup only consisted of the filtration of the reaction mixture, followed by rinsing the filter with dry acetone, the obtained yields were also very low. These low yields demanded for further evaluation of the reaction conditions. Much better results were obtained when the reaction was performed with triethylamine as a base. When fraxetin **7** was reacted with 2 equiv of prenylbromide and 2 equiv of triethylamine at room temperature for 24 h, the desired product, capensin **8** [8-hydroxy-6-methoxy-7-(3′-methyl-2′-butenyloxy)coumarin] was isolated in 62% yield. The regioisomeric 7-hydroxy-6-methoxy-8-(3′-methyl-2′-butenyloxy)coumarin **9** was isolated in 12% yield. In this reaction, purification was achieved by evaporating acetone from the reaction mixture and purifying the residual crude mixture by column chromatography. Capensin **8** is a naturally occurring coumarin and was isolated from several plant species, including *Phyllosma capensis*[14] and *Bupleurum fruticosum*.[15] To our knowledge 7-hydroxy-6-methoxy-8-(3′-methyl-2′-butenyloxy)coumarin **9** has never been reported from natural sources. The next step in the synthesis involved the epoxidation of the double bond of the prenyl group of capensin **8**. When capensin **8** was treated with 3-chloroperbenzoic acid in ethyl acetate, after 8 h 63% of 7-(2,3-epoxy-3-methylbutoxy)-8-hydroxy-6-methoxycoumarin **10** was obtained. Cyclisation of epoxide **10** to purpurasol **1** was accomplished by treating it with potassium carbonate in ethyl acetate, affording purpurasol **1** in 79% yield. Purpurasol **1** could also be obtained in one step from capensin **8** by reaction with 3-chloroperbenzoic acid in ethyl acetate for 48 h, affording purpurasol **1** in 68% yield.

3. Experimental

3.1. General

^{1}H NMR spectra (300 MHz) and ^{13}C NMR spectra (75 MHz) were recorded with a Joel Eclipse FT 300 NMR spectrometer. IR spectra were recorded on a Perkin Elmer Spectrum One spectrophotometer. Mass spectra were recorded on an Agilent 1100 Series VL mass spectrometer (ES 70 eV) or on a Varian MAT 112 mass spectrometer (EI 70 eV). Melting points were measured with a Büchi B-450 apparatus. Elemental analyses were measured with a Perkin-Elmer 2400 Elemental Analyzer. Flash chromatography was performed with ACROS silica gel (particle size 0.035–0.070 mm, pore diameter ca. 6 nm) using a glass column. 7,8-Dihydroxy-6-methoxycoumarin was obtained from Aldrich Chemical Company. All other reagents were obtained from Acros Organics and were used as such, except for 3-chloroperbenzoic acid. 3-Chloroperbenzoic acid ($\leq$77%, remainder 3-chlorobenzoic acid and water) was obtained from Acros Organics and was kept under reduced pressure (5 mmHg) at room temperature for 3 h in order to remove most of the water.

3.2. Synthetic procedures

3.2.1. 8-Hydroxy-6-methoxy-7-(3′-methyl-2′-butenyloxy)-coumarin (capensin) 8 and 7-hydroxy-6-methoxy-8-(3′-methyl-2′-butenyloxy)coumarin 9. 7,8-Dihydroxy-6-methoxycoumarin **7** (208 mg, 1 mmol) was dissolved in 10 ml acetone, and 202 mg (2 mmol) of triethylamine and 298 mg (2 mmol) of 4-bromo-2-methyl-2-butene were added.

After stirring at room temperature for 24 h, the acetone was evaporated in vacuo and the residue was chromatographed over silica gel using 40% hexane, 50% diethyl ether and 10% tetrahydrofuran as mobile phase. This procedure yielded 62% (172 mg) of 8-hydroxy-6-methoxy-7-(3′-methyl-2′-butenyloxy)coumarin (capensin) **8** (R_f=0.23) and 12% (21 mg) 7-hydroxy-6-methoxy-8-(3′-methyl-2′-butenyloxy)coumarin **9** (R_f=0.14), both appearing as a yellow powder.

8-Hydroxy-6-methoxy-7-(3′-methyl-2′-butenyloxy)-coumarin (capensin) **8**

Mp (°C): 135 (lit. 135–136[1]). IR (KBr, cm^{-1}): 3392 (broad, OH); 1692 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.68 (3H, s, 4′-CH_3); 1.75 (3H, s, 5′-CH_3); 3.90 (3H, s, OCH_3); 4.69 (1*H*, d, J=7.4 Hz, 1′-CH_2); 5.52 (1*H*, t, J=7.4 Hz, 2′-C*H*); 6.16 (1H, br s, O*H*); 6.34 (1H, d, J=9.6 Hz, 3-C*H*); 6.50 (1H, s, 5-C*H*); 7.62 (1H, d, J=9.6 Hz, 4-C*H*). ^{13}C NMR (68 MHz, $CDCl_3$): δ 18.0 en 25.9 (2×*C*H_3); 56.2 (O*C*H_3); 70.0 (1′-*C*H_2); 100.0 (5-*C*H); 114.4 (C_q); 115.2 (3-*C*H); 119.5 (2′-*C*H); 137.8 (C_q); 138.0 (2×C_q); 140.5 (3′-C_q); 143.7 (4-*C*H); 149.8 (6-C_q); 160.4 (*C*=O). MS (70 eV, ES, *m/z* (%)): 275 (M−1). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21%; H, 5.84%. Found: C, 65.01%; H, 5.68%.

7-Hydroxy-6-methoxy-8-(3′-methyl-2′-butenyloxy)-coumarin **9**

Mp (°C): 126.5. IR (KBr, cm^{-1}): 3401 (broad, OH); 1702 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.70 (3H, s, 4′-CH_3); 1.75 (3H, s, 5′-CH_3); 3.93 (3H, s, OCH_3); 4.80 (1*H*, d, J=7.4 Hz, 1′-CH_2); 5.55 (1*H*, t, J=7.4 Hz, 2′-C*H*); 6.27 (1H, d, J=9.6 Hz, 3-C*H*); 6.66 (1H, s, 5-C*H*); 7.61 (1H, d, J=9.6 Hz, 4-C*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1 en 25.9 (2×*C*H_3); 56.4 (O*C*H_3); 70.3 (1′-*C*H_2); 103.5 (5-*C*H); 111.1 (C_q); 113.3 (3-*C*H); 119.4 (2′-*C*H); 133.1 (C_q); 140.6 (C_q); 143.0 (C_q); 143.2 (C_q); 143.9 (4-*C*H); 144.6 (6-C_q); 160.7 (*C*=O). MS (70 eV, ES, *m/z* (%)): 275 (M−1). Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.21%; H, 5.84%. Found: C, 65.39%; H, 5.98%.

3.2.2. 7-(2,3-Epoxy-3-methylbutoxy)-8-hydroxy-6-methoxycoumarin 10. 8-Hydroxy-6-methoxy-7-(3′-methyl-2′-butenyloxy)coumarin (capensin) **8** (69 mg, 0.25 mmol) was dissolved in 2.5 ml of ethyl acetate. The reaction mixture was cooled to 0 °C and 52 mg (0.3 mmol) of 3-chloroperoxybenzoic acid was added, after which the reaction was stirred at room temperature for 8 h. The solvent was evaporated in vacuo and the resulting mixture was dissolved in dichloromethane (25 ml) and washed with 25 ml of saturated aqueous sodium bicarbonate and 20 ml of water, respectively. The organic phase was dried ($MgSO_4$) and after filtration and evaporation of the solvent, 46 mg (63%) of crude 7-(2,3-epoxy-3-methylbutoxy)-8-hydroxy-6-methoxycoumarin **10** (purity: 95%) was obtained as a sticky residue, which was used without further purification.

IR (KBr, cm^{-1}): 3419 (broad, OH); 1715 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 en 1.38 (each 3H, each s, $(CH_3)_2$C=), 3.23 (1H, dd, J=6.60, 4.68 Hz, OC*H*CH_2O), 3.90 (3H, s, OCH_3), 4.16 (1H, dd, J=6.60, 11.56 Hz, OCHC$H_a$$H_b$O), 4.44 (1H, dd, J=4.68, 11.56 Hz, OCHCH_a-H_bO), 6.35 (1H, d, J=9.63 Hz, 3-C*H*), 6.50 (1H, s, 5-C*H*), 7.62 (1H, d, 4-C*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7 en 24.6 (2×*C*H_3); 56.1 (O*C*H_3); 59.3 (3′-C_q); 61.5 (2′-*C*H); 72.1 (1′-*C*H_2); 99.7 (5-*C*H); 114.6 (C_q); 115.2 (3-*C*H); 138.0 (2×C_q); 138.3 (C_q); 143.8 (4-*C*H); 149.8 (6-C_q); 160.6 (*C*=O). MS (70 eV, EI, *m/z* (%)): 292 (M^+, 16); 208 (100); 193 (15); 139 (20); 85 (75); 83 (17); 71 (52); 69 (64); 55 (32); 49 (16); 43 (73).

3.2.3. Purpurasol 1.

Procedure 1

7-(2,3-Epoxy-3-methylbutoxy)-8-hydroxy-6-methoxycoumarin **10** (29 mg, 0.1 mmol) was dissolved in 1 ml of EtOAc. 0.05 mmol (7 mg) of potassium carbonate was added and the reaction was stirred at room temperature for 24 h. Water (10 ml) and ethyl acetate (5 ml) were added, and the aqueous phase was further extracted with 2×10 ml of ethyl acetate. The combined organic layers were dried ($MgSO_4$) and, after filtration and evaporation of the solvent, 23 mg (79%) of purpurasol was obtained as a white crystalline solid, which was recrystallized from ethanol.

Procedure 2

8-Hydroxy-6-methoxy-7-(3′-methyl-2′-butenyloxy)-coumarin (capensin) **8** (28 mg, 0.1 mmol) was dissolved in 1 ml of ethyl acetate. The reaction mixture was cooled to 0 °C and 20 mg (0.12 mmol) of 3-chloroperoxybenzoic acid was added. The reaction was stirred at room temperature for 48 h. The solvent was evaporated and the resulting mixture was dissolved in dichloromethane (10 ml) and washed with 10 ml of saturated aqueous sodium bicarbonate and 10 ml of water, respectively. The organic phase was dried ($MgSO_4$) and, after filtration and evaporation of the solvent, 20 mg (69%) of purpurasol was obtained as a white solid.

Mp (°C): 148 (lit. 148–149[2]). IR (KBr, cm^{-1}): 3400 (broad, OH); 1702 (C=O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 en 1.46 (2×3H, s, CH_3); 2.75 (1H, br s, O*H*); 3.92 (3H, s, OCH_3); 3.99 (1H, dd, J_{ax}=9.1 Hz, J_{bx}=1.9 Hz, 2′-C*H*); 4.13 (1H, dd, J_{ab}=11.3 Hz, J_{ax}=9.1 Hz, 1′-C$H_a$$H_b$); 4.65 (1H, dd, J_{ab}=11.3 Hz, J_{bx}=1.9 Hz, 1′-CH$_a$$H_b$); 6.31 (1H, d, J=9.6 Hz, 3-C*H*); 6.51 (1H, s, 5-C*H*); 7.61 (1H, d, J=9.6 Hz, 4-C*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.1 en 26.0 (2×*C*H_3); 56.4 (O*C*H_3); 65.5 (1′-*C*H_2); 70.6 (3′-C_q); 79.0 (2′-C_q); 100.1 (5-*C*H); 111.6 (4a-C_q), 114.1 (3-*C*H); 132.4 (8-C_q); 136.7 (8a-C_q); 139.0 (7-C_q); 143.8 (4-*C*H); 145.7 (6-C_q); 160.9 (*C*=O). MS (70 eV, EI, *m/z* (%)): 293 (M+1, 35); 292 (M^+, 99); 235 (26); 234 (100); 219 (57); 208 (46); 207 (23); 206 (23); 205 (78); 191 (23); 176 (25); 79 (35); 71 (21); 59 (92); 57 (52); 51 (26); 47 (23); 43 (75). Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64%; H, 5.52%. Found: C, 61.49%; H, 5.40%.

References and notes

1. Debenedetti, S. L.; Nadinic, E. L.; Coussio, J. D.; De Kimpe, N.; Feneau-Dupont, J.; Declercq, J.-P. *Phytochemistry* **1991**, 2757–2758.
2. Debenedetti, S. L.; Nadinic, E. L.; Gomez, M. A.; Coussio, J. D.; De Kimpe, N.; Boeykens, M. *Phytochemistry* **1992**, 3284–3285.

3. Debenedetti, S. L.; Nadinic, E. L.; Gomez, M. A.; Coussio, J. D.; De Kimpe, N.; Boeykens, M. *Phytochemistry* **1996**, 563–564.
4. Debenedetti, S. L.; Abbaspour Tehrani, K.; Van Puyvelde, L.; De Kimpe, N. *Phytochemistry* **1999**, 701–703.
5. Murray, R.D.H. *Fortschritte der Chemie organisher Naturstoffe—Progress in the Chemistry of Organic Natural Compounds*; Springer-Verlag: Vienna, 2002; Vol. 83.
6. Gashimov, N. F.; Kuznetsova, G. A. *Khim. Prir. Soedin.* **1974**, 303.
7. Abyshev, A. Z.; Gashimov, N. F. *Khim. Prir. Soedin.* **1979**, 401.
8. Abyshev, A. Z.; Zmeykov, V. P.; Sidorova, I. P. *Khim. Prir. Soedin.* **1982**, 301.
9. Boeykens, M.; De Kimpe, N.; Debenedetti, S. L.; Nadinic, E. L.; Gomez, M. A.; Coussio, J. D.; Abyshev, A. Z.; Gindin, V. A. *Phytochemistry* **1994**, 1559–1560.
10. Shimada, H. *Yakugaku Zasshi (J. Pharm. Soc. Jpn.)* **1937**, 148.
11. Shimada, H. *Yakugaku Zasshi (J. Pharm. Soc. Jpn.)* **1938**, 185.
12. Shimada, H. *Yakugaku Zasshi (J. Pharm. Soc. Jpn.)* **1952**, 63.
13. Ahluwalia, V. K.; Khanna, M.; Singh, R. P. *Gazz. Chim. Ital.* **1981**, *111*, 503.
14. Campbell, W. E.; Gragg, G. M. L. *Phytochemistry* **1979**, 688–689.
15. Pistelli, L.; Bertoli, A.; Bilia, A. R.; Morelli, I. *Phytochemistry* **1996**, 1579–1582.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 4430–4434
Tetrahedron

Short and efficient preparations of isoxazole-3-carboxylic acid and imino-oxopentanoic acid potent precursors of 4-hydroxyisoleucine

Jean-Michel Becht, Sandra De Lamo Marin, Martine Maruani, Alain Wagner* and Charles Mioskowski*

Laboratoire de Synthèse Bioorganique, UMR 7514 associée au CNRS, Faculté de Pharmacie, Université Louis Pasteur de Strasbourg, 74 Route du Rhin, 67400 Illkirch, France

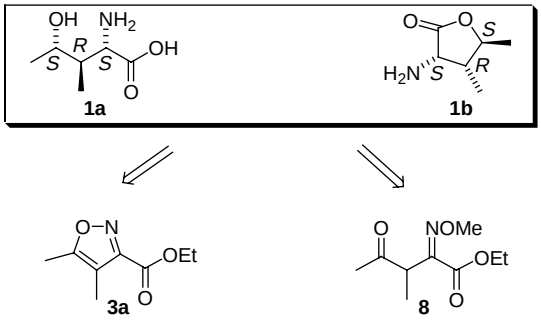
Received 18 January 2006; revised 14 February 2006; accepted 20 February 2006

Available online 10 March 2006

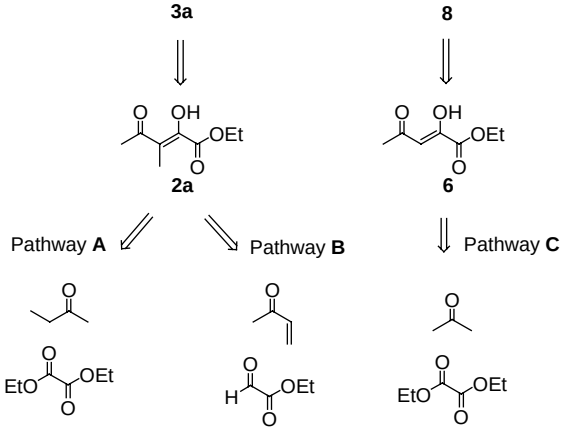
Abstract—Herein, we describe short and efficient syntheses of isoxazole-3-carboxylic acid **3a** and imino-oxopentanoic acid **8** achiral precursors of 4-hydroxyisoleucine. The developed procedures involve readily available and cheap starting materials and can easily be transposed to the large scale.

1. Introduction

It has been estimated that more than 200 million people in the world will have diabetes mellitus in the next decade. Therefore, the development of improved antidiabetic drugs has concentrated huge interest in medicinal chemistry.[1] (2*S*,3*R*,4*S*)-4-Hydroxyisoleucine **1a**, a natural product extracted from fenugreek seeds has emerged as a promising candidate.[2] However, production of this compound through an extraction process is not practicable for pharmaceutical supply. To date, only two stereoselective syntheses of (2*S*,3*R*,4*S*)-**1a** have been reported.[3,4] These syntheses suffer from many drawbacks that prohibit their use for the large scale production. For instance, they involve more than six steps and proceed with low overall yields. They also require the use of expensive starting materials, chiral auxiliaries as well as enzymatic resolutions. For these reasons, we have focused our attention to the development of a short and efficient synthesis of the natural occurring (2*S*,3*R*,4*S*)-**1a** and its corresponding lactone (3*S*,4*R*,5*S*)-3-amino-4,5-dimethyl-2-oxotetrahydrofuran **1b** from achiral 4,5-dimethyl-isoxazole-3-carboxylic acid ethyl ester **3a** and 2-methoxyimino-3-methyl-4-oxo-pentanoic acid ethyl ester **8** (Scheme 1). The compounds **1a** and **1b** can be obtained using as a key step stereoselective reductions and kinetic resolutions of **3a** and **8**.[5,6] Herein, we describe straightforward and inexpensive methodologies for large scale syntheses of substrates **3a** and **8** from readily available starting materials (Scheme 2).[7] The results concerning stereoselective reductions of **3a** and **8** will be reported in due course.



Scheme 1. Retrosynthetic analysis for the synthesis of **1a** and **1b**.



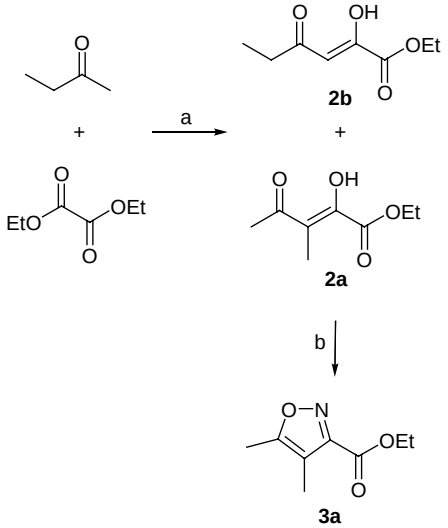
Scheme 2. Retrosynthetic analysis for the synthesis of **3a** and **8**.

Keywords: Achiral precursors; Organic phase; Stereoselective.
* Corresponding authors. Tel.: +33 (0)3 90 24 42 97; fax: +33 (0)3 90 24 43 06; e-mail: mioskowski@bioorga.u-strasbg.fr

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.056

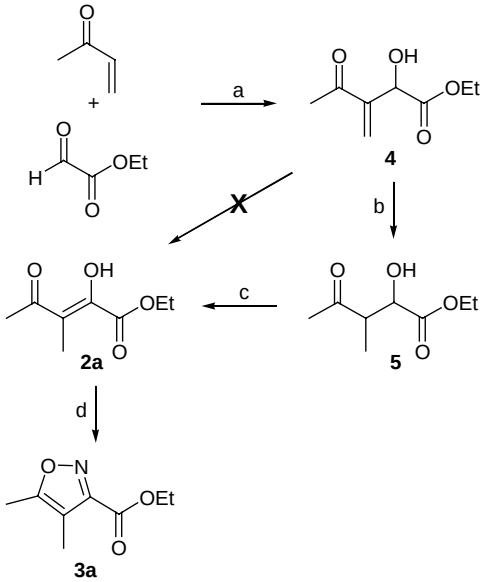
2. Results and discussion

The most common strategy for the synthesis of isoxazoles involves cycloaddition reactions of a nitrone or a nitrile oxide and an alkene or an alkyne.[8] The major drawbacks of these procedures are the low reactivity of the dipolarophiles and the dimerisation side reactions of the nitrile oxides to generate furoxanes.[8] Moreover, these reactions require expensive starting materials and are not easily amenable to the large scale. Therefore, we have turned our attention to the reaction of 2-hydroxy-3-methyl-4-oxo-pent-2-enoic acid ethyl ester **2a** with hydroxylamine to generate **3a** (Scheme 3). The first approach for the synthesis of **2a** involves the aldol condensation of the cheap and commercially available butanone and diethyloxalate in the presence of EtONa in EtOH at rt for 10 min (Scheme 2, pathway A).[9] As expected, a mixture of 2-hydroxy-3-methyl-4-oxo-pent-2-enoic acid ethyl ester **2a** and 2-hydroxy-4-oxo-hex-2-enoic acid ethyl ester **2b** were obtained in quantitative yield (Scheme 3). The separation of **2a** and **2b** by crystallization, distillation or flash-chromatography on silica-gel or alumina failed. Interestingly, we found a simple and efficient method to isolate the desired compound **2a**. EtOH was firstly distillated under reduced pressure and the crude reaction mixture dissolved in AcOEt. The organic phase was washed with a saturated solution of brine and the aqueous phase was extracted three times with AcOEt. ^{1}H NMR showed that compound **2b** was selectively extracted from the crude reaction mixture. The aqueous phase was then carefully acidified to pH 6 with HCl 10% and extracted three times with AcOEt. Noteworthy, by lowering the pH of the aqueous phase below 6, lactonisation of **2a** took place to afford 3-ethoxy-3-hydroxy-4,5-dimethyl-3*H*-furan-2-one.[10] We observed that washing the organic phase with water or by using diethylether for the extraction, the separation of **2a** and **2b** was much less efficient. After drying the combined organic phases with $MgSO_4$ and removal of the solvent under vacuum, **2a** was isolated in 35% yield (70% of the presence in the crude reaction mixture).[11a] We then turned our attention to the functionalization of **2a** with hydroxylamine. The reaction of the carbonyl group at the α position of an ester function with an amine is generally performed in the presence of an acid catalyst and an excess of amine.[12] By reacting non-symmetrical 1,3-diketones with amines, mixtures of regioisomers are generally obtained.[13] In some cases, the regioselectivity of this reaction can be controlled by adjusting the pH of the reaction medium.[13c,d] We have shown that a regioselective reaction occurs at the α position of the ester group by using hydroxylamine hydrochloride and at the γ position by using the free amine.[11b] Hydroxylamine hydrochloride was then added slowly at rt to a solution of **2a** in a 1:1 mixture of EtOH/THF, giving **3a** as the only product in 71% isolated yield.



Scheme 3. Reagent and conditions: (a) Na, EtOH, rt, 10 min, 35%. (b) $HONH_2$.HCl, EtOH/THF 1:1, rt, 24 h, 71%.

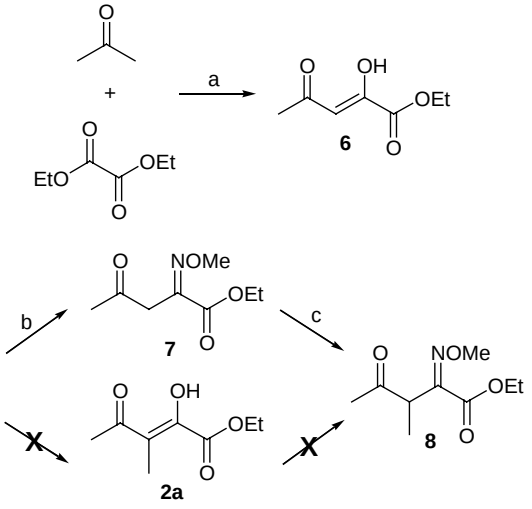
In order to improve the yield obtained for the synthesis of **2a** (Scheme 3), we have investigated another pathway based on a Baylis–Hillmann condensation of methylvinylketone (MVK) and ethylglyoxalate (Scheme 2, pathway B).[14] In the presence of catalytic amounts of DABCO in dioxane, the Baylis–Hillmann adduct **4** was isolated in 77% yield after rapid filtration on silica-gel (Scheme 4). Noteworthy, another Baylis–Hillmann strategy for the synthesis of **2a** implies as a key-step the condensation of 2-oxo-but-3-enoic acid ethyl ester and acetaldehyde. Several reaction conditions were tested for this purpose but we observed only dimerisation of 2-oxo-but-3-enoic acid ethyl ester. Interestingly, the C–C double bond isomerisation of **4** into **2a** failed under acidic (i.e., formic acid, HCl, TFA) or basic (i.e., K_2CO_3, *t*-BuOK, DBU) conditions. Similar results were obtained in the presence of transition metal catalysts (i.e., Ir, Ni, Pd, Ru, Rh). In each case, **4** was quantitatively recovered. Compound **4** was then reduced with H_2/Pd/$CaCO_3$ in EtOH at rt for 3 h to give **5** in 85% yield, followed by Swern oxidation to afford **2a** in 81% isolated yield.[15] The extraction of **2a** was firstly performed with a phosphate buffer (pH 6.8) or a borax buffer (pH 9.6). The desired compound was, respectively, isolated in 42 and 75% yield. Improved yield was obtained by performing the extraction



Scheme 4. Reagent and conditions: (a) DABCO, dioxane, rt, 30 h, 77%. (b) Pd/$CaCo_3$, H_2, EtOH, rt, 3 h, 85%. (c) TFAA, DMSO, DCM, −78 °C, 2 h then TEA, −78 °C to rt, 2 h, 81% (d) $HONH_2$.HCl, EtOH/THF 1:1, rt, 24 h, 71%.

at pH 6 by using a KCl/NaOH buffer (pH 12). Under these work-up conditions, pure **2a** was obtained in 81% yield and did not require further purification. Finally, by reacting **2a** with hydroxylamine hydrochloride in a 1:1 mixture of EtOH/THF, **3a** was isolated in 71% yield.

We then focused our attention to the synthesis of **8**. Compound **2a**, synthesized as described above, was firstly reacted with methoxylamine hydrochloride or with free methoxylamine and catalytic amounts of acids in various solvents (i.e., EtOH, EtOH/H_2O, THF, THF/H_2O). Unfortunately, **8** was never obtained in reasonable yield (Scheme 5). Complex reaction mixtures were generally observed. We tried a completely different pathway based on the reaction of 2-hydroxy-4-oxo-pent-2-enoic acid ethyl ester **6** with methoxylamine hydrochloride, followed by methylation reaction to generate **8** (Scheme 2, pathway C). The aldol condensation of acetone and diethyloxalate in the presence of EtONa in EtOH at rt for 2 h gave pure **6** in 89% yield (Scheme 5).[9] This reaction has been transposed efficiently on a 100 g scale without any noticeable loss in efficacy. Several attempts to perform the methylation of **6** before the amination reaction failed by using various bases (i.e., EtONa, *t*-BuOK, K_2CO_3), solvents (i.e., EtOH, DMF, THF, acetone) or methylating reagents (i.e., MeI or dimethylsulfate). Complex reaction mixtures or dimethylated product were generally obtained. Compound **6** was then firstly reacted with benzyloxyamine, benzylamine and methoxylamine hydrochlorides at rt for 12 h in a 1:1 mixture EtOH/H_2O to afford the expected products in 43, 74 and 88% yields, respectively.[16] The methylation reaction conditions were then optimized with **7** as model substrate. The use of MeI, various bases (i.e., K_2CO_3, NaH, $NaNH_2$) and solvents (i.e., EtOH, DMF, acetone) did not afford the expected product. Similar results were obtained with dimethylsulfate as a methylating reagent. Degradation by-products were also observed in this case. Better results were obtained by reacting **7** in the presence of *t*-BuOK and MeI in THF. Under these reaction conditions, we isolated **8** in 90% yield after rapid filtration on silica-gel.



Scheme 5. Reagent and conditions: (a) Na, EtOH, rt, 2 h, 89%. (b) $MeONH_2.HCl$, EtOH/H_2O 1:1, rt, 12 h, 88%. (c) *t*-BuOK, THF, 0 °C, 30 min then MeI, 0 °C to rt, 12 h, 90%

3. Conclusions

We have described short and efficient syntheses of achiral 4-hydroxyisoleucine precursors **3a** and **8**. The described procedures require only cheap and readily available substrates and can efficiently be transposed on the large scale. The results concerning stereoselective reductions of **3a** and **8** to generate optically pure 4-hydroxyisoleucine will be reported in due course.

4. Experimental

4.1. General methods

^1H and ^{13}C NMR spectra were recorded using whether a 200 or 300 MHz instrument in $CDCl_3$. Chemical shifts are reported in parts per million (δ) downfield from TMS. Spin multiplicities are indicated by the following symbol: s (singlet), d (doublet), t (triplet) and m (multiplet). IR absorbances are reported in reciprocal centimeters (cm^{-1}). The mass spectra were recorded by the ionization technique using ammonia gas. THF was distilled from sodium/benzophenone. Acetone, EtOH and DMSO were dried on molecular sieves 4 Å.

4.1.1. Preparations of 2-hydroxy-3-methyl-4-oxo-pent-2-enoic acid ethyl ester (2a). *Procedure 1*. A solution of EtONa is generated by reacting sodium (528 mmol, 12.1 g, 1.2 equiv) in anhydrous EtOH (800 mL) at rt for 2 h. Butanone (440 mmol, 39.4 mL, 1.0 equiv) is then added dropwise at rt and the reaction mixture is stirred at rt for 1 h. Diethyloxalate (880 mmol, 119.5 mL, 2.0 equiv) is quickly added at rt. After 10 min vigorous stirring, the solvent is removed under reduced pressure and the crude reaction mixture is dissolved in AcOEt (900 mL). The organic phase is washed with a saturated solution of brine (900 mL). The aqueous phase is again extracted with AcOEt (3×900 mL). The aqueous phase is carefully acidified to pH 6 by adding dropwise a solution of HCl 10% under vigorous stirring. The aqueous phase is then extracted with AcOEt (3×900 mL). The combined organic phases are dried with $MgSO_4$ and concentrated under reduced pressure to give **2a** and a dimeric structure in 35% yield (26.6 g).

Procedure 2. Trifluoroacetic anhydride (82.5 mmol, 11.5 mL, 2.9 equiv) is added at −78 °C to a solution of DMSO (6.5 mL) in DCM (100 mL). After 10 min stirring, a solution of **5** (28.4 mmol, 5.0 g, 1.0 equiv) in DCM (30 mL) is added dropwise at −78 °C. The resulting solution is stirred at −78 °C for 2 h. Triethylamine (187 mmol, 26.1 mL, 6.6 equiv) is then added dropwise. The reaction mixture is stirred for another 2 h at −78 °C, warmed to rt and poured into a pH 12 buffer (12 mL) obtained from KCl 0.2 M (25 mL) and NaOH 0.2 M (6 mL). The aqueous phase is extracted with DCM (2×50 mL). The combined organic phases are dried with $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture is purified by flash-chromatography on silica-gel (eluant: hexane/AcOEt 7:3) to give **2a** and a dimeric structure as an orange oil in 81% yield (3.98 g). Orange oil. ^1H NMR (200 MHz, $CDCl_3$): δ 1.36 (m, 6H), 1.97 (s, 3H), 2.24 (s, 3H), 2.30 (s, 2H), 4.32 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 11.2, 13.6, 28.8, 62.5,

101.1, 160.2, 190.5, 205.0. IR ($CHCl_3$): 3452, 3054, 2987, 1731, 1264, 742, 703. M.S: $[M+H]^+=173$.

4.1.2. Preparation of 4,5-dimethyl-isoxazole-3-carboxylic acid ethyl ester (3a). Hydroxylamine hydrochloride (13.2 mmol, 917 mg, 1.2 equiv) is slowly added in 12 portions over 3 h to a solution of **2a** (11.0 mmol, 1.90 g, 1.0 equiv) in a 1:1 mixture of EtOH/THF (30 mL). The reaction mixture is stirred at rt for 24 h. The solvent is removed under reduced pressure. The crude reaction mixture is poured into a saturated solution of NaCl (40 mL). The aqueous phase is extracted with AcOEt (3× 50 mL). The combined organic phases are dried with $MgSO_4$ and concentrated under reduced pressure. The crude product is purified by flash-chromatography on silica-gel (eluant: hexane/AcOEt 95:5) to give **3a** in 71% yield (1.32 g). Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.39 (t, 3H, $J=7.2$ Hz), 2.10 (s, 3H), 2.36 (s, 3H), 4.40 (q, 2H, $J=7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.5, 10.9, 14.2, 61.8, 111.4, 154.9, 161.0, 167.6. IR (CH_2Cl_2): 2985, 2943, 1783, 1631, 1389, 1295, 1083, 934, 787, 650. M.S: $[M+H]^+=170$.

4.1.3. Preparation of 5-hydroxy-3,4-dimethyl-4,5-dihydro-isoxazole-5-carboxylic acid ethyl ester (3b). Hydroxylamine hydrochloride (13.2 mmol, 917 mg, 1.2 equiv) and sodium acetate (13.2 mmol, 1.08 g, 1.2 equiv) are added in one portion to a solution of **2a** (11.0 mmol, 1.90 g, 1.0 equiv) in EtOH (60 mL). The reaction mixture is stirred at rt for 4 h. The solvent is removed under reduced pressure. The crude reaction mixture is poured into a saturated solution of $NaHCO_3$ (10 mL). The aqueous phase is extracted with dichloromethane (3×40 mL). The combined organic phases are washed with distilled water (2×20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture is purified by crystallization in diethyl ether to give **3b** in 92% yield (1.81 g). White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (d, 3H, $J=7.5$ Hz), 1.35 (t, 3H, $J=7.2$ Hz), 1.99 (s, 3H), 3.70 (q, 1H, $J=7.5$ Hz), 4.32 (q, 2H, $J=7.2$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): δ 8.3, 10.9, 13.6, 49.7, 62.8, 102.5, 159.3, 168.6. M.S: $[M+H]^+=188$.

4.1.4. Preparation of 3-acetyl-2-hydroxy-but-3-enoic acid ethyl ester (4). DABCO (5.3 mmol, 594 mg, 0.09 equiv) is added in one portion at 0 °C to a solution of methylvinylketone (60 mmol, 4.9 mL, 1.0 equiv) and ethylglyoxalate 50% w in toluene (72.0 mmol, 14.2 mL, 1.2 equiv) in dioxane (30 mL). The reaction mixture is warmed to rt for 30 h. The crude reaction mixture is then poured in HCl 10% (10 mL) and the aqueous phase is extracted with AcOEt (2×50 mL). The combined organic phases are dried with $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture is rapidly filtered on silica-gel (eluant: hexane/AcOEt 1:2) to give **4** in 77% yield (7.98 g). Orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (t, 3H, $J=7.2$ Hz), 2.37 (s, 3H), 3.44 (d, 1H, $J=6.1$ Hz), 4.23 (q, 2H, $J=7.2$ Hz), 4.82 (d, 1H, $J=6.1$ Hz), 6.14 (s, 1H), 6.22 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 26.0, 62.1, 70.9, 128.7, 146.1, 172.6, 198.5. IR (CH_2Cl_2): 3481, 2985, 2938, 1741, 1681, 1636, 1371, 1216, 1027, 912, 741, 585. M.S: $[M+H]^+=173$.

4.1.5. Preparation of 2-hydroxy-3-methyl-4-oxo-pentanoic acid ethyl ester (5). Pd/$CaCO_3$ (26.1 mmol, 1.8 g, 0.5 equiv) is added to a solution of **4** (52.2 mmol, 9.03 g, 1.0 equiv) in EtOH (200 mL). The mixture is purged several times with H_2. After 3 h vigorous stirring at rt, the crude mixture is filtered with Celite®, washed with EtOH (2× 50 mL) and concentrated under reduce pressure. The crude product is purified by flash-chromatography on silica-gel (eluant: hexane/AcOEt 7:3) to give a 62:38 mixture of diastereoisomers **5** in 85% yield (7.76 g). Orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (d, 1.8H, $J=7.2$ Hz), 1.17 (d, 1.2H, $J=7.2$ Hz), 1.18 (t, 1.2H, $J=7.2$ Hz), 1.22 (t, 1.8H, $J=7.2$ Hz), 2.11 (s, 1.2H), 2.16 (s, 1.8H), 2.89 (m, 1H), 3.24 (d, 0.6H, $J=3.7$ Hz), 3.37 (d, 0.4H, $J=6.9$ Hz), 4.19 (m, 2.4H), 4.51 (m, 0.6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.4, 12.8, 14.2, 28.4, 28.9, 50.0, 50.1, 61.8, 62.1, 71.0, 72.5, 173.3, 173.4, 209.2, 210.2. IR (CH_2Cl_2): 3429, 2984, 1714, 1739, 1615, 1365, 1218, 1027, 973, 741, 585. M.S: $[M+H]^+=175$.

4.1.6. Preparation of 2-hydroxy-4-oxo-pent-2-enoic acid ethyl ester (6). A solution of EtONa is generated by reacting sodium (336 mmol, 7.72 g, 1.2 equiv) in anhydrous EtOH (800 mL) at rt for 2 h. A solution of diethyloxalate (280 mmol, 38.0 mL, 1.0 equiv) in acetone (280 mmol, 20.6 mL, 1.0 equiv) is then added dropwise at rt. The reaction mixture is vigorously stirred at rt for 2 h. The solvent is then removed under reduced pressure and water (400 mL) is poured to the crude reaction mixture. Ice (100 g) is added, followed by concentrated sulfuric acid (30 mL). The aqueous phase is extracted with AcOEt (3× 500 mL). The combined organic phases are dried with $MgSO_4$ and concentrated under reduced pressure to give **6** in 89% yield (39.4 g). Orange oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (t, 3H, $J=7.1$ Hz), 2.24 (s, 3H), 4.32 (q, 2H, $J=7.1$ Hz), 6.36 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 27.7, 62.6, 102.2, 162.1, 167.0, 200.1. IR ($CHCl_3$): 3561, 2987, 1739, 1643, 1602, 1465, 1419, 1370, 1269, 1212, 1119, 1018, 910, 776, 732. M.S: $[M+NH_4]^+=176$.

4.1.7. Preparation of 2-methoxyimino-4-oxo-pentanoic acid ethyl ester (7). A solution of *N*-methoxylamine hydrochloride (190 mmol, 15.9 g, 1.0 equiv) in water (150 mL) is added dropwise at rt to a solution of **6** (190 mmol, 33.4 g, 1.0 equiv) in a mixture of EtOH (300 mL) and water (150 mL). The reaction mixture is stirred at rt for 12 h. The solvent is then removed under vacuum and water (200 mL) is poured to the crude reaction mixture. The aqueous phase is extracted with AcOEt (3× 400 mL). The combined organic phases are dried with $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture is rapidly filtered on silica-gel to give **7** in 88% yield (34.4 g). Orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (t, 3H, $J=7.2$ Hz), 2.21 (s, 3H), 3.72 (s, 2H), 4.07 (s, 3H), 4.34 (q, 2H, $J=7.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 29.5, 40.0, 61.9, 63.3, 146.3, 162.8, 203.8. IR ($CHCl_3$): 2982, 2941, 1716, 1375, 1308, 1215, 1230, 1049, 1026, 732. M.S: $[M+NH_4]^+=205$.

4.1.8. Preparation of 2-methoxyimino-3-methyl-4-oxo-pentanoic acid ethyl ester (8). A 1 M solution of *t*-BuOK in THF (174 mmol, 174.0 mL, 1.5 equiv) is added dropwise at 0 °C to a solution of **7** (116 mmol, 23.9 g, 1.0 equiv) in

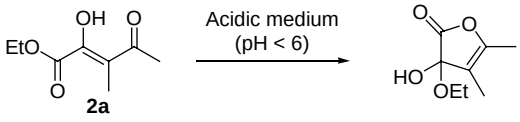
anhydrous THF (1200 mL). The reaction mixture is stirred at 0 °C for 30 min. Methyl iodide (174 mmol, 10.8 mL, 1.5 equiv) is then added at 0 °C. The reaction mixture is warmed to rt for 12 h. The solvent is removed under vacuum and HCl 10% (300 mL) is poured to the crude reaction mixture. The aqueous phase is extracted with AcOEt (3× 500 mL). The combined organic phases are dried with $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture is rapidly filtered on silica-gel to give **8** in 90% yield (21.4 g). White solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (d, 3H, J=7.1 Hz), 1.37 (t, 3H, J=7.1 Hz), 2.10 (s, 3H), 3.92 (q, 1H, J=7.1 Hz), 4.07 (s, 3H), 4.35 (q, 2H, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.5, 13.7, 27.2, 45.0, 61.8, 63.1, 151.1, 162.4, 203.5. IR ($CHCl_3$): 2987, 2941, 1721, 1375, 1254, 1176, 1044, 913, 734, 652. M.S: $[M+NH_4]^+$=219.

Acknowledgements

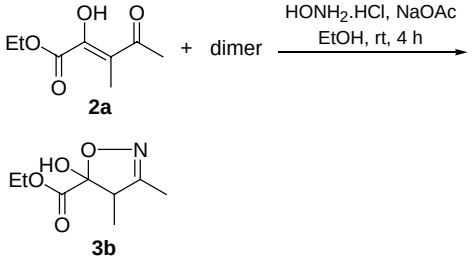
We thank the Ministère de la Recherche et de l'Enseignement Supérieur for financial support of this work through a MENRT grant to J.-M. Becht and Innodia through grants to S. De Lamo Marin and M. Maruani.

References and notes

1. Amos, A. F.; McCarthy, D. J.; Zimmet, P. *Diabet. Med.* **1997**, *14*, 1.
2. (a) Ribes, G.; Sauvaire, Y.; Baccou, J. C.; Valette, G.; Chenon, D.; Trimble, E. R. *Ann. Nutr. Metab.* **1984**, *28*, 37. (b) Ribes, G.; Sauvaire, Y.; Costa, C. D.; Baccou, J. C.; Loubatieres-Mariani, M. M. *Proc. Soc. Exp. Biol. Med.* **1986**, *182*, 159. (c) Fowden, L.; Pratt, H. M.; Smith, A. *Phytochemistry* **1973**, *12*, 1707. (d) Sauvaire, Y.; Petit, P.; Broca, C.; Manteghetti, M.; Baissac, Y.; Fernandez-Alvarez, J.; Gross, R.; Roye, M.; Leconte, A.; Gomis, R.; Ribes, G. *Diabetes* **1998**, *47*, 206. (e) Broca, C.; Gross, R.; Petit, P.; Sauvaire, Y.; Manteghetti, M.; Tournier, M.; Masiello, P.; Gomis, R.; Ribes, G. *American Journal of Physiology* **1999**, *277*, E617.
3. (a) Wang, Q.; Ouazzani, J.; Sasaki, N. A.; Potier, P. *Eur. J. Org. Chem.* **2002**, 834. (b) Rolland-Fulcrand, V.; Rolland, M.; Roumestant, M.-L.; Martinez, J. *Eur. J. Org. Chem.* **2004**, *4*, 873.
4. Other isomers of 4-hydroxyisoleucine are known as part of natural products. Syntheses of the corresponding molecules have been reported: (a) Jamieson, A. G.; Sutherland, A.; Willis, C. L. *Org. Biomol. Chem.* **2004**, *2*, 808. (b) Kassem, T.; Wehbe, J.; Rolland-Fulcrand, V.; Roumestant, M.-L.; Martinez, J. *Tetrahedron: Asymmetry* **2001**, *12*, 2657. (c) Gull, R.; Schöllkopf, U. *Synthesis* **1985**, 1052. (d) Inghardt, T.; Fredj, T.; Svensson, G. *Tetrahedron* **1991**, *47*, 6469. (e) Englisch-Peters, S. *Tetrahedron* **1989**, *45*, 6127.
5. (a) Lee, S. Y.; Lee, B. S.; Lee, C.-W.; Oh, D. Y. *J. Org. Chem.* **2000**, *65*, 256. (b) Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795. (c) Baraldi, G.; Barco, A.; Benetti, S.; Pollini, G. P.; Simoni, D. *Synthesis* **1987**, 857. (d) Veronese, A. C.; Callegari, R.; Morelli, C. F.; Vincentini, C. B. *Tetrahedron Lett.* **1997**, *53*, 14497. (e) Zhou, P.; Natale, N. R. *Tetrahedron Lett.* **1998**, *39*, 8249. (f) Burkhart, D. J.; Twamley, D.; Natale, N. R. *Tetrahedron Lett.* **2001**, *42*, 8415. (g) Burkhart, D. J.; Zhou, P.; Blumenfeld, A.; Twamley, B.; Natale, N. R. *Tetrahedron* **2001**, *57*, 8039. (h) Chuang, C.-P.; Wu, Y.-L.; Jiang, M.-C. *Tetrahedron* **1999**, *55*, 11229. (i) Piaz, V. D.; Giovannoni, M. P.; Castellana, C. *J. Med. Chem.* **1997**, *40*, 1417.
6. (a) Bartoli, G.; Cupone, G.; Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Procopio, A.; Tagarelli, A. *Tetrahedron Lett.* **2002**, *43*, 7441. (b) Kozikowski, A. P.; Adamczyk, M. *Tetrahedron Lett.* **1982**, *23*, 3123.
7. Becht, J.-M.; Catala, C.; De Lamo Marin, S.; Wagner, A.; Mioskowski, C., patent PCT/FR03/03542, 2002.
8. (a) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Pergamon: New York, 1992; pp 1069–1109. (b) Wade, P. A. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Pergamon: New York, 1992; pp 1111–1168. (c) Torsell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, 1988. (d) Adams, J. P.; Patterson, J. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3695. (e) Ghorai, S.; Mukhopadhyay, R.; Kundu, A. P.; Bhattacharjya, A. *Tetrahedron* **2005**, *61*, 2999. (f) Lautens, M.; Roy, A. *Org. Lett.* **2000**, *2*, 555.
9. Manfredini, S.; Simoni, D.; Zanirato, V.; Casolari, A. *Tetrahedron Lett.* **1988**, *29*, 3997.
10. Reaction of **2a** in acidic medium (pH<6) leads to 3-ethoxy-3-hydroxy-4,5-dimethyl-3*H*-furan-2-one:



11. (a) Compound **2a** was isolated in the presence of a by-product, which is, as shown by mass spectrometry, a dimeric structure of **2a**. (b) The addition of hydroxylamine hydrochloride and sodium acetate to a mixture of **2a** and its dimer afforded compound **3b** with a 92% isolated yield. This result confirms that **2a** and its dimer exhibit the same reactivity.



12. (a) Boeykens, M.; Kimpe, N. D.; Tehrani, K. A. *J. Org. Chem.* **1994**, *59*, 6973. (b) Feistauer, H.; Neidlein, R. *Helv. Chim. Acta* **1995**, *78*, 1806.
13. (a) Brunnelle, H.; Singam, P. R.; Narayanan, B. A.; Bradshaw, C. W.; Liou, J. S. *Synthesis* **1997**, 439. (b) Seki, K.; Isegawa, J.; Fukuda, M.; Ohki, M. *Chem. Pharm. Bull.* **1984**, *32*, 1568. (c) Yokoyama, M.; Tsuji, K.; Kushida, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 67. (d) Baraldi, P. G.; Moroder, F.; Pollini, G. P.; Simoni, D.; Barco, A.; Benetti, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, *12*, 2983.
14. (a) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1988**, *44*, 4653. (b) Shi, M.; Jiang, J.-K. *Tetrahedron* **2000**, *56*, 4793.
15. Amon, C. M.; Banwell, M. G.; Lance Gravatt, G. *J. Org. Chem.* **1987**, *52*, 4851.
16. (a) Smith, L. I. *Chem. Rev.* **1938**, *23*, 193. (b) Beak, P.; Selling, G. W. *J. Org. Chem.* **1989**, *54*, 5574.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 62 (2006) 4435–4443

Highly efficient and practical phosphoramidite–copper catalysts for amination of aryl iodides and heteroaryl bromides with alkylamines and N(H)-heterocycles

Zhanjin Zhang, Jincheng Mao, Di Zhu, Fan Wu, Huilin Chen and Boshun Wan*

Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 457 Zhongshan Road, Dalian 116023, China

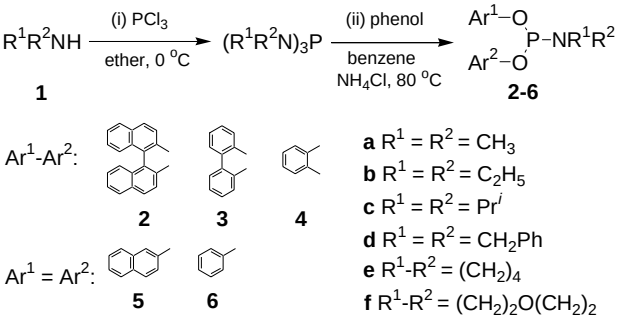
Received 14 December 2005; revised 20 February 2006; accepted 20 February 2006

Available online 13 March 2006

Abstract—A highly efficient copper-catalyzed system using phosphoramidite as ligands was applied to N-arylation of alkylamines and N(H)-heterocycles with aryl iodides and heteroaryl bromides. The reactions were carried out in relative mild conditions and good to excellent yields were obtained.

1. Introduction

N-Arylamines, *N*-arylpyrazoles, *N*-arylimidazoles, *N*-arylpyridine and *N*-arylpyrimidine have attracted a great deal of interest recently due to their importance in fields such as natural products, photograph and materials.[1–3] Palladium-catalyzed C–N bond formation reactions have been extensively explored in the past several years.[4–7] However, the copper-promoted *N*-arylation in mild conditions has become a focus of research for large and industrial-scale production from the practical point of view.[8–11] Recently, many ligands, such as 1,10-phenanthroline,[12–16] *trans*-1,2-cyclohexanediamine,[17–21] ethylene glycol,[22,23] amino acid,[1b,24,25] and other nitrogen, oxygen-containing ligands[26–29] have been developed and applied in copper-catalyzed aminations under mild conditions. However, only several papers have been contributed to *N*-arylation of alkylamines and just a few ligands were found to be effective in this transformation.[30–32] Furthermore, two major factors that hamper the application are the cost and the availability of the catalysts, in particular of the ligands that are often prepared in a tedious multi-step synthesis. Therefore, to find more cost-effective and highly efficient ligands is still desirable. Our group has embarked on a program aimed at the ligands that are low-cost and easily prepared in short pathway from readily available starting materials.[33,34] Very recently, the application of phosphoramidite to amination of aryl iodide has been reported in our communication (Scheme 1).[35] In this paper, we further explored the scope of substrates and applied this catalytic system to copper-catalyzed *N*-arylation of alkylamines and N(H)-heterocycles with aryl iodides and heteroaryl bromides and found the ligand was highly effective for the coupling reactions for a broader range of substrates.



Scheme 1. Phosphoramidite ligands.

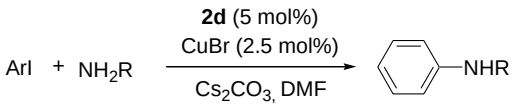
2. Results and discussion

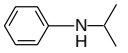
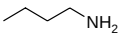
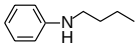
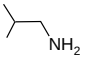
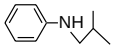
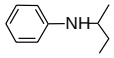
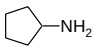
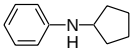
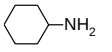
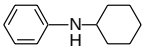
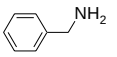
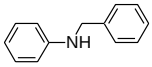
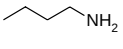
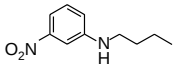
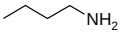
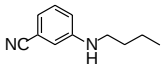
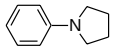
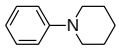
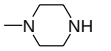
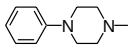
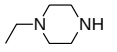
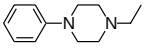
Initially, the CuBr/**2d**/DMF/Cs_2CO_3 was screened as the best catalytic system for the coupling of aliphatic primary and secondary amines with aryl iodides. The results were summarized in Table 1. It was found that phosphramidite **2d** was a powerful promoter for coupling reaction in DMF at 90 °C. When primary alkylamines were employed as substrates, excellent yields were obtained (Table 1, entries

Keywords: Amination; Phosphoramidite; Heteroaryl bromide; Copper; Catalysis.
* Corresponding author. Tel./fax: +86 411 84379260;
e-mail: bswan@dicp.ac.cn

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.062

Table 1. Coupling of aryl iodides with primary and secondary amines[a]



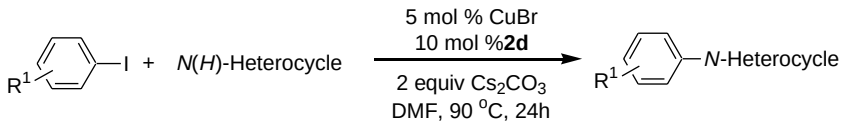
Entry	ArI	NH_2R	Product	Yield (%)[b]
1				96
2				96
3				96
4				98
5				97
6				98
7				98
8				99
9				98
10				90
11				87
12				86
13				92
14				83
15				90
16				87
17				99
18				78
19				80

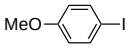
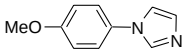
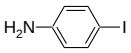
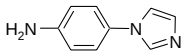
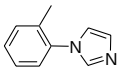
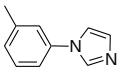
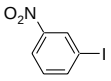
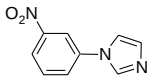
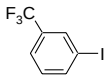
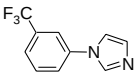
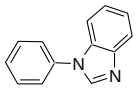
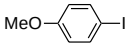
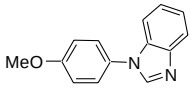
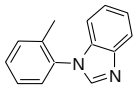
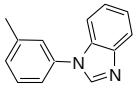
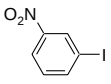
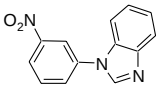
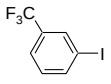
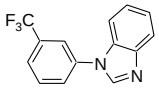
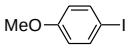
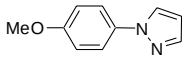
[a] Reaction conditions: CuBr (0.025 mmol), **2d** (0.5 mmol), ArI (1.0 mmol), amine (1.5 mmol), and Cs_2CO_3 (3 mmol) in DMF (1 mL), 90 °C, 24 h.
[b] Isolated yields (average of two runs).

1–9). We then extended the scope of the substrates to secondary amines. Good yields were observed in coupling reaction (entries 10–19), but they were lower than that of primary alkylamines. A wide variety of functional groups such as cyano, nitro, methoxy could be tolerated on the aryl iodide component under the reaction conditions. Significant electronic effects were observed for substituted aryl iodides. Excellent yields for the aryl iodides containing electron-withdrawing groups were achieved (entries 14–18).

As can be seen from Table 2, several *N*-heterocycles could be converted to the desired products effectively when the amounts of CuBr and the ligand were doubled. The *N*-arylation of imidazole could be smoothly carried out using various aryl iodides (Table 2, entries 1–6). Benzimidazole could be successfully coupled with good yields (entries 7–12). The arylation of pyrazole could also be carried out smoothly under mild reaction conditions (entry 13). Noticeably, electronic and steric factors played important roles in the coupling reactions, high yields were obtained for substrates possessing electron-withdrawing groups (entries 5, 6, 11 and 12). A sterically hindered aryl iodide gave lower yields (entries 3 and 9). Aryl iodides containing a nitro, methoxy group, free NH_2 were efficiently transformed to products.

Table 2. Coupling of aryl iodides with various *N*-heterocycles[a]



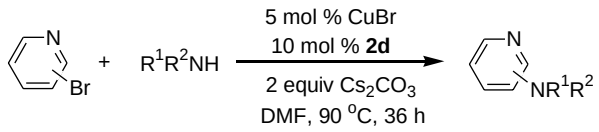
Entry	ArI	N(H)-heterocycle	Product	Yield (%)[b]
1				78
2				69
3				65
4				75
5				87
6				85
7				82
8				80
9				67
10				76
11				90
12				86
13				76

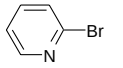
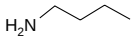
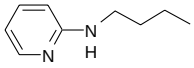
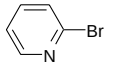
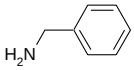
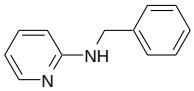
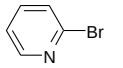
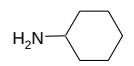
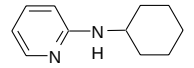
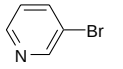
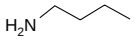
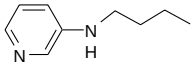
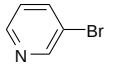
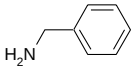
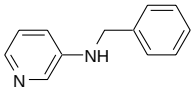
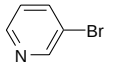
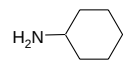
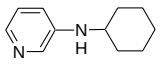
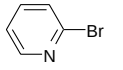
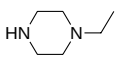
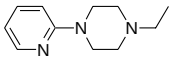
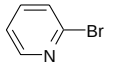
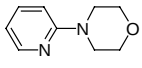
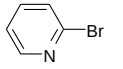
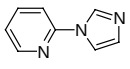
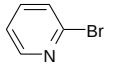
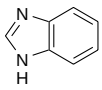
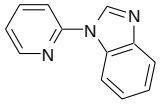
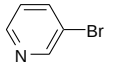
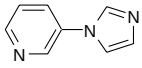
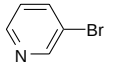
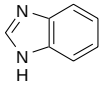
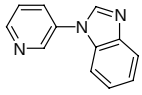
[a] Reaction conditions: 1.0 mmol ArI, 1.5 mmol amine, 0.05 mmol CuBr, 0.1 mmol **2d**, 2 mmol Cs_2CO_3, in DMF (1 mL), at 90 °C for 24 h.
[b] Isolated yields (average of two runs).

Although chloro- and bromopyridine have been used as effective coupling partners in Pd-catalyzed amination reaction,[7f,36] to the best of our knowledge, except one paper,[1b] it was rarely reported that bromopyridines were employed as coupling substrates in Cu-catalyzed amination. When reaction time was prolonged to 36 h under above reaction conditions, 2-bromopyridine and 3-bromopyridine could be efficiently coupled with aliphatic primary, secondary cyclic amines and N(H)-heterocycles (Table 3). As seen in Table 3, in general, aliphatic primary amines were excellent substrates for the coupling with bromopyridine (Table 3, entries 1–6). Good results were observed for coupling of aliphatic secondary cyclic amines and N(H)-heterocycles (entries 7–12).

Although 5-bromopyrimidine has been utilized as effective coupling substrates in Pd-catalyzed amination reactions, it was less used in Cu-catalyzed amination.[7d,28] Fortunately, when phosphoramidite was used as the ligand in Cu-catalyzed *N*-arylpyrimidine, a number of amines could be coupled with 5-bromopyrimidine in good to excellent yields in 36 h at 90 °C (Table 4). 5-bromopyrimidine could be successfully reacted with aliphatic primary, secondary cyclic amines and N(H)-heterocycles. Aliphatic primary amines were excellent substrates for the coupling with 5-bromopyrimidine (Table 4, entries 1–8). Furthermore, good results were also obtained for coupling of aliphatic secondary cyclic amines and N(H)-heterocycles (entries 9–14).

Table 3. Coupling of bromopyridines with various amines[a]



Entry	Bromopyridine	R^1R^2NH	Product	Yield (%)[b]
1				95
2				97
3				92
4				94
5				96
6				90
7				85
8				82
9				76
10				78
11				74
12				77

[a] Reaction conditions: 1.0 mmol bromopyridine, 1.5 mmol amine, 0.05 mmol CuBr, 0.1 mmol **2d**, 2 mmol Cs_2CO_3, in DMF (1 mL) at 90 °C for 36 h.
[b] Isolated yield.

3. Conclusion

In conclusion, we developed a mild and practical copper-catalyzed *N*-arylation of alkylamines and N(H)-heterocycles with aryl iodides and heteroaryl bromides using phosphoramidite ligand. It demonstrated that all reactions could be smoothly carried out at relatively low temperature in good to excellent yields. The ligands were stable, cost-effective, and easily synthesized from inexpensive, commercially available starting materials using a simple, efficient method.

4. Experimental

4.1. Materials and methods

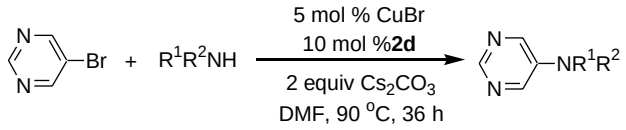
Melting points were measured on a YAZAWA micro melting point apparatus (uncorrected). ^1H, ^{31}P and ^{13}C NMR spectra were measured on a Bruker DRX-400 NMR spectrometer (400 MHz) with TMS as an internal reference. $CDCl_3$ was used as the solvent for all NMR spectra. High resolution mass spectra (HRMS) were recorded on a Mariner 5303 (Applied Biosystems, USA). All products were characterized by ^1H NMR and HRMS and compared with the previously reported data.[19,20,24,28,30,37,38]

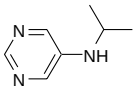
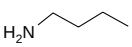
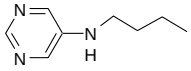
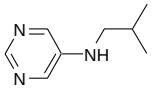
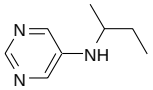
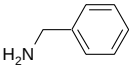
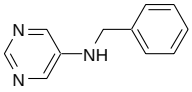
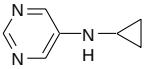
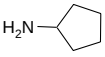
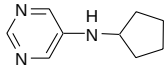
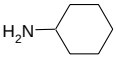
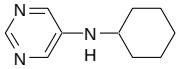
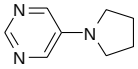
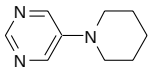
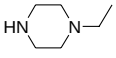
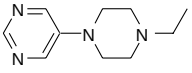
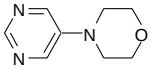
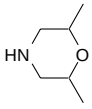
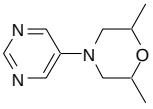
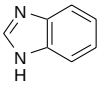
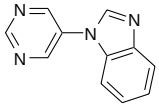
All reactions were carried out under an argon atmosphere. Column chromatography purifications were performed using silica gel. All solvents were dried and degassed by standard methods and all starting materials were commercially available. Petroleum ether refers to the boiling range of 60–90 °C. When solvent gradient was used, the increase of polarity was made gradually from petroleum ether to mixtures of petroleum ether/ethyl acetate until the isolation of the products.

4.2. Typical experimental procedure of *N*-arylation

CuBr (3.6 mg, 0.025 mmol), Cs_2CO_3 (977.5 mg, 3 mmol) and ligand **2d** (25.6 mg, 0.05 mmol) were added to

Table 4. Coupling of 5-bromopyrimidine with various amines[a]



Entry	R^1R^2NH	Product	Yield (%)[b]
1			90
2			97
3			94
4			89
5			96
6			92
7			94
8			95
9			83
10			85
11			80
12			86
13			78
14			73

[a] Reaction conditions: 1.0 mmol bromopyrimidine, 1.5 mmol amine, 0.05 mmol CuBr, 0.1 mmol **2d**, 2 mmol Cs_2CO_3, in DMF (1 mL) at 90 °C for 36 h.
[b] Isolated yield.

a Schlenk tube. The Schlenk tube was then evacuated and backfilled with argon (5 cycles). DMF (1 mL), amine (1.5 mmol) (if liquid), and aryl iodide (1 mmol) were added by syringe at room temperature. The Schlenk tube was then charged with argon and sealed. The reaction mixture was heated at 90 °C under stirring for 24 h. After cooling to ambient temperature, the resulting mixture was added with 4 mL of ethyl acetate and 10 mL of water. The organic layer was separated and the aqueous layer was further extracted with ethyl acetate (4×10 mL). The combined organic phase was washed with brine and dried over Na_2SO_4. Solvent was removed in vacuo and the residue was further purified by flash column chromatography on silica gel to afford the desired product.

4.3. Cross-coupling data of aryl iodides with primary and secondary amines

4.3.1. *N*-(*iso*-Propyl)aniline (Table 1, entry 1). Colorless liquid (0.1298 g, 96%). ^{1}H NMR: δ 1.17 (d, J=8.0 Hz, 6H), 3.35 (br, 1H), 3.56–3.62 (m, 1H), 6.54–6.56 (m, 2H),

6.63–6.67 (m, 1H), 7.12–7.16 (m, 2H). HRMS (APCI) calcd for $C_9H_{14}N$ ($M+H^+$): 136.1121, found: 136.1120.

4.3.2. *N*-(Butyl)aniline (Table 1, entry 2). Colorless liquid (0.1433 g, 96%). ^1H NMR: δ 0.94 (t, $J=8.0$ Hz, 3H), 1.36–1.45 (m, 2H), 1.53–1.61 (m, 2H), 3.07 (t, $J=8.0$ Hz, 2H), 3.54 (br, 1H), 6.56–6.58 (m, 1H), 6.65–6.69 (m, 2H), 7.13–7.33 (m, 2H). HRMS (APCI) calcd for $C_{10}H_{16}N$ ($M+H^+$): 150.1277, found: 150.1268.

4.3.3. *N*-(*iso*-Butyl)aniline (Table 1, entry 3). Colorless liquid (0.1433 g, 96%). ^1H NMR: δ 0.95 (d, $J=4.0$ Hz, 6H), 1.82–1.88 (m, 1H), 2.89 (d, $J=8.0$ Hz, 2H), 3.61 (br, 1H), 6.56 (d, $J=8.0$ Hz, 2H), 6.64–6.68 (m, 1H), 7.13–7.16 (m, 2H). HRMS (APCI) calcd for $C_{10}H_{16}N$ ($M+H^+$): 150.1277, found: 150.1288.

4.3.4. *N*-(*sec*-Butyl)aniline (Table 1, entry 4). Colorless liquid (0.1462 g, 98%). ^1H NMR: δ 0.91–0.97 (m, 3H), 1.14 (d, $J=4.0$ Hz, 3H), 1.41–1.48 (m, 1H), 1.54–1.61 (m, 1H), 3.35–3.40 (m, 2H), 6.56 (d, $J=8.0$ Hz, 2H), 6.63–6.66 (m, 1H), 7.12–7.16 (m, 2H). HRMS (APCI) calcd for $C_{10}H_{16}N$ ($M+H^+$): 150.1277, found: 150.1265.

4.3.5. *N*-Cyclopentylaniline (Table 1, entry 5). Colorless liquid (0.1564 g, 97%). ^1H NMR: δ 1.18–1.26 (m, 8H), 3.41 (br, 1H), 3.58–3.62 (m, 1H), 6.57 (d, $J=8.0$ Hz, 2H), 6.64–6.68 (m, 1H), 7.13–7.17 (m, 2H). HRMS (APCI) calcd for $C_{11}H_{16}N$ ($M+H^+$): 162.1277, found: 162.1265.

4.3.6. *N*-Cyclohexylaniline (Table 1, entry 6). Colorless liquid (0.1717 g, 98%). ^1H NMR: δ 1.09–1.21 (m, 3H), 1.32 (t, $J=16.0$ Hz, 2H), 1.62 (t, $J=8.0$ Hz, 1H), 1.71–1.76 (m, 2H), 2.02 (d, $J=12.0$ Hz, 2H), 3.18–3.24 (m, 1H), 3.44 (br, 1H), 6.55 (d, $J=8.0$ Hz, 2H), 6.63 (t, $J=4.0$ Hz, 1H), 7.13 (t, $J=8.0$ Hz, 2H). HRMS (APCI) calcd for $C_{12}H_{18}N$ ($M+H^+$): 176.1434, found: 176.1430.

4.3.7. *N*-(Phenyl)benzylamine (Table 1, entry 7). White solid (0.1796 g, 98%); mp 33–34 °C. ^1H NMR: δ 3.99 (br, 1H), 4.29 (s, 2H), 6.61 (d, $J=8.0$ Hz, 2H), 6.68–6.72 (m, 1H), 7.14–7.18 (m, 2H), 7.24–7.27 (m, 1H), 7.30–7.36 (m, 4H). HRMS (APCI) calcd for $C_{13}H_{14}N$ ($M+H^+$): 184.1121, found: 184.1129.

4.3.8. *N*-(Butyl)-3-nitroaniline (Table 1, entry 8). Yellow liquid (0.1923 g, 99%). ^1H NMR: δ 0.96 (t, $J=8.0$ Hz, 3H), 1.39–1.48 (m, 2H), 1.58–1.66 (m, 2H), 3.14 (t, $J=8.0$ Hz, 2H), 4.05 (br, 1H), 6.84–6.86 (m, 1H), 7.24 (t, $J=8.0$ Hz, 1H), 7.36 (s, 1H), 7.47 (d, $J=8.0$ Hz, 1H). HRMS (APCI) calcd for $C_{10}H_{15}N_2O_2$ ($M+H^+$): 195.1128, found: 195.1113.

4.3.9. *N*-(Butyl)-3-nitrylaniline (Table 1, entry 9). Greenish liquid (0.1708 g, 98%). ^1H NMR: δ 0.96 (t, $J=8.0$ Hz, 3H), 1.38–1.48 (m, 2H), 1.57–1.64 (m, 2H), 3.09 (t, $J=8.0$ Hz, 2H), 3.93 (br, 1H), 6.76 (t, $J=8.0$ Hz, 2H), 6.92 (d, $J=8.0$ Hz, 1H), 7.18–7.27 (m, 1H), 7.47 (d, $J=8.0$ Hz, 1H). HRMS (APCI) calcd for $C_{11}H_{15}N_2$ ($M+H^+$): 175.1230, found: 175.1218.

4.3.10. *N*-(Phenyl)pyrrolidine (Table 1, entry 10). Colorless liquid (0.1325 g, 90%). ^1H NMR: δ 1.93–1.97 (m, 4H), 3.23 (t, $J=8.0$ Hz, 4H), 6.53 (d, $J=8.0$ Hz, 2H), 6.62–6.65 (m, 1H), 7.18–7.22 (m, 2H). HRMS (APCI) calcd for $C_{10}H_{14}N$ ($M+H^+$): 148.1121, found: 148.1131.

4.3.11. *N*-(Phenyl)piperidine (Table 1, entry 11). Colorless liquid (0.1403 g, 87%). ^1H NMR: δ 1.52–1.58 (m, 2H), 1.66–1.72 (m, 4H), 3.13 (t, $J=8.0$ Hz, 4H), 6.79–6.82 (m, 1H), 6.93 (d, $J=8.0$ Hz, 2H), 7.18–7.25 (m, 2H). HRMS (APCI) calcd for $C_{11}H_{16}N$ ($M+H^+$): 162.1277, found: 162.1271.

4.3.12. *N*-Phenyl-*N*-(methyl)piperazine (Table 1, entry 12). Colorless liquid (0.1516 g, 86%). ^1H NMR: δ 2.33 (s, 3H), 2.55 (t, $J=4.0$ Hz, 4H), 3.19 (t, $J=4.0$ Hz, 4H), 6.83–6.91 (m, 3H), 7.24–7.27 (m, 2H). HRMS (APCI) calcd for $C_{11}H_{17}N_2$ ($M+H^+$): 177.1386, found: 177.1376.

4.3.13. *N*-Phenyl-*N*-(ethyl)piperazine (Table 1, entry 13). White solid (0.1750 g, 92%); mp 38–39 °C. ^1H NMR: δ 1.11–1.15 (m, 3H), 2.45–2.50 (m, 2H), 2.61 (t, $J=8.0$ Hz, 4H), 3.22 (t, $J=8.0$ Hz, 4H), 6.83–6.87 (m, 1H), 6.93 (d, $J=12.0$ Hz, 2H), 7.24–7.34 (m, 2H). HRMS (APCI) calcd for $C_{12}H_{19}N_2$ ($M+H^+$): 191.1543, found: 191.1528.

4.3.14. *N*-(Phenyl)piperazincarboxylethylether (Table 1, entry 14). White solid (0.1812 g, 83%); mp 57–58 °C. ^1H NMR: δ 1.28 (t, $J=8.0$ Hz, 3H), 3.13 (t, $J=4.0$ Hz, 4H), 3.62 (t, $J=8.0$ Hz, 4H), 4.14–4.19 (m, 2H), 6.87–6.94 (m, 3H), 7.25–7.35 (m, 2H). HRMS (APCI) calcd for $C_{13}H_{19}N_2O$ ($M+H^+$): 235.1441, found: 235.1436.

4.3.15. *N*-(Phenyl)morpholine (Table 1, entry 15). White solid (0.1469 g, 90%); mp 53–54 °C. ^1H NMR: δ 3.14 (t, $J=8.0$ Hz, 4H), 3.85 (t, $J=8.0$ Hz, 4H), 6.86–6.92 (m, 3H), 7.23–7.30 (m, 2H). HRMS (APCI) calcd for $C_{10}H_{14}NO$ ($M+H^+$): 164.1070, found: 164.1058.

4.3.16. *N*-Phenyl-3,5-dimethylmorpholine (Table 1, entry 16). Colorless liquid (0.1664 g, 87%). ^1H NMR: δ 1.23–1.30 (m, 6H), 2.35–2.41 (m, 2H), 3.42 (d, $J=12.0$ Hz, 2H), 3.76–4.12 (m, 2H), 6.83–6.90 (m, 3H), 7.23–7.27 (m, 2H). HRMS (APCI) calcd for $C_{12}H_{18}NO$ ($M+H^+$): 192.1383, found: 192.1387.

4.3.17. *N*-(3-Nitrophenyl)pyrrolidine (Table 1, entry 17). Yellow solid (0.1903 g, 99%); mp 33–34 °C. ^1H NMR: δ 2.04–2.09 (m, 4H), 3.33 (t, $J=8.0$ Hz, 4H), 6.79 (t, $J=4.0$ Hz, 1H), 7.26–7.32 (m, 2H), 7.44–7.46 (m, 1H). HRMS (APCI) calcd for $C_{10}H_{13}N_2O_2$ ($M+H^+$): 193.0972, found: 193.0967.

4.3.18. *N*-(4-Methoxyphenyl)piperazine (Table 1, entry 18). White solid (0.1492 g, 78%); mp 64–65 °C. ^1H NMR: δ 1.51–1.57 (m, 2H), 1.69–1.75 (m, 4H), 3.02 (t, $J=4.0$ Hz, 4H), 3.75 (d, $J=8.0$ Hz, 3H), 6.83 (t, $J=8.0$ Hz, 2H), 6.92 (d, $J=8.0$ Hz, 2H). HRMS (APCI) calcd for $C_{12}H_{18}NO$ ($M+H^+$): 192.1383, found: 192.1371.

4.3.19. *N*-(4-Methoxyphenyl)morpholine (Table 1, entry 19). White solid (0.1546 g, 80%); mp 66–67 °C. ^1H NMR: δ 3.06 (d, $J=4.0$ Hz, 4H), 3.77 (s, 3H), 3.86 (s, 4H), 6.84–6.91 (m, 4H). HRMS (APCI) calcd for $C_{11}H_{16}NO_2$ ($M+H^+$): 194.1176, found: 194.1184.

4.4. Cross-coupling data of aryl iodides with various *N*-heterocycles

4.4.1. *N*-(4-Methoxyphenyl)imidazole (Table 2, entry 1). White solid (0.1359 g, 78%); mp 121–122 °C. ^{1}H NMR: δ 3.82 (s, 3H), 6.94–6.98 (m, 2H), 7.17–7.29 (m, 4H), 7.72–7.81 (s, 1H). HRMS (APCI) calcd for $C_{10}H_{11}N_2O$ ($M+H^+$): 175.0866, found: 175.0853.

4.4.2. *N*-(4-Aminophenyl)imidazole (Table 2, entry 2). White solid (0.1098 g, 69%); mp 138–139 °C. ^{1}H NMR: δ 3.53 (br, 2H), 6.74 (d, J=8.0 Hz, 2H), 7.15 (d, J=4.0 Hz, 4H), 7.81 (s, 1H). HRMS (APCI) calcd for $C_9H_{10}N_3$ ($M+H^+$): 160.0869, found: 160.0854.

4.4.3. *N*-(2-Methylphenyl)imidazole (Table 2, entry 3). Colorless liquid (0.1028 g, 65%). ^{1}H NMR: δ 2.18 (s, 3H), 7.14–7.27 (m, 4H), 7.28–7.37 (m, 2H), 8.46 (s, 1H). HRMS (APCI) calcd for $C_{10}H_{11}N_2$ ($M+H^+$): 159.0917, found: 159.0912.

4.4.4. *N*-(3-Methylphenyl)imidazole (Table 2, entry 4). Colorless liquid (0.1187 g, 75%). ^{1}H NMR: δ 2.41 (s, 3H), 7.16–7.49 (m, 6H), 7.86 (s, 1H). HRMS (APCI) calcd for $C_{10}H_{11}N_2$ ($M+H^+$): 159.0917, found: 159.0902.

4.4.5. *N*-(3-Nitrophenyl)imidazole (Table 2, entry 5). Yellowish solid (0.1646 g, 87%); mp 93–94 °C. ^{1}H NMR: δ 7.27–7.38 (m, 2H), 7.69–7.78 (m, 2H), 7.95 (s, 1H), 8.23–8.28 (m, 2H). HRMS (APCI) calcd for $C_9H_8N_3O_2$ ($M+H^+$): 190.0611, found: 190.0600.

4.4.6. *N*-(3-Trifluoromethylphenyl)imidazole (Table 2, entry 6). Colorless liquid (0.1803 g, 85%). ^{1}H NMR: δ 7.25–7.73 (m, 6H), 8.01 (s, 1H). HRMS (APCI) calcd for $C_{10}H_8F_3N_2$ ($M+H^+$): 213.0634, found: 213.0623.

4.4.7. *N*-(Phenyl)benzimidazole (Table 2, entry 8). Colorless liquid (0.1554 g, 80%). ^{1}H NMR: δ 7.24–7.30 (m, 2H), 7.34–7.38 (m, 3H), 7.44–7.48 (m, 3H), 7.86 (d, J=8.0 Hz, 1H), 8.04 (s, 1H). HRMS (APCI) calcd for $C_{13}H_{11}N_2$ ($M+H^+$): 195.0917, found: 195.0903.

4.4.8. *N*-(4-Methoxyphenyl)benzimidazole (Table 2, entry 9). White solid (0.1741 g, 80%); mp 94–95 °C. ^{1}H NMR: δ 3.87 (s, 3H), 7.05–7.07 (m, 2H), 7.30–7.33 (m, 2H), 7.39–7.45 (m, 3H), 7.86–7.88 (m, 1H), 8.06 (s, 1H). HRMS (APCI) calcd for $C_{14}H_{13}N_2O$ ($M+H^+$): 225.1022, found: 225.1036.

4.4.9. *N*-(2-Methylphenyl)benzimidazole (Table 2, entry 10). Colorless liquid (0.1395 g, 67%). ^{1}H NMR: δ 2.09 (s, 3H), 7.16–7.45 (m, 6H), 7.90 (d, J=4.0 Hz, 2H), 8.00 (s, 1H). HRMS (APCI) calcd for $C_{14}H_{13}N_2$ ($M+H^+$): 209.1073, found: 209.1087.

4.4.10. *N*-(3-Methylphenyl)benzimidazole (Table 2, entry 11). Colorless liquid (0.1583 g, 76%). ^{1}H NMR: δ 2.42 (s, 3H), 7.21–7.51 (m, 6H), 7.85–7.87 (m, 2H), 8.07 (s, 1H). HRMS (APCI) calcd for $C_{14}H_{13}N_2$ ($M+H^+$): 209.1073, found: 209.1054.

4.4.11. *N*-(3-Nitrophenyl)benzimidazole (Table 2, entry 12). Yellowish solid (0.2153 g, 90%); mp 145–146 °C. ^{1}H NMR: δ 7.38–7.40 (m, 2H), 7.51–7.58 (m, 1H), 7.78–7.83 (m, 1H), 7.90 (d, J=8.0 Hz, 2H), 8.19 (s, 1H), 8.32 (d, J=12.0 Hz, 1H), 8.43 (s, 1H). HRMS (APCI) calcd for $C_{13}H_{10}N_3O_2$ ($M+H^+$): 240.0767, found: 240.0754.

4.4.12. *N*-(3-Trifluoromethylphenyl)benzimidazole (Table 2, entry 13). Colorless liquid (0.2255 g, 86%). ^{1}H NMR: δ 7.32–7.36 (m, 2H), 7.48–7.51 (m, 1H), 7.69–7.72 (m, 3H), 7.79 (1H), 7.86–7.89 (m, 1H), 8.13 (s, 1H). HRMS (APCI) calcd for $C_{14}H_{10}F_3N_2$ ($M+H^+$): 263.0791, found: 263.0805.

4.4.13. *N*-(4-Methoxyphenyl)pyrazole (Table 2, entry 7). White solid (0.1428 g, 82%); mp 32–33 °C. ^{1}H NMR: δ 3.84 (s, 3H), 6.43–6.44 (m, 1H), 6.95–6.98 (m, 2H), 7.58–7.61 (m, 2H), 7.69 (s, 1H), 7.81 (d, J=4.0 Hz, 1H). HRMS (APCI) calcd for $C_{10}H_{11}N_2O$ ($M+H^+$): 175.0866, found: 175.0872.

4.5. Cross-coupling data of bromopyridine with various amines

4.5.1. 2-(Butylamimo)pyridine (Table 3, entry 1). White solid (0.1427 g, 95%); mp 32–33 °C. ^{1}H NMR: δ 0.93 (t, J=8.0 Hz, 3H), 1.36–1.45 (m, 2H), 1.54–1.61 (m, 2H), 3.19–3.24 (m, 2H), 4.75 (br, 2H), 6.34 (d, J=8.0 Hz, 2H), 6.50–6.53 (m, 1H), 7.35–7.40 (m, 1H), 8.03 (d, J=4.0 Hz, 1H). HRMS (APCI) calcd for $C_9H_{15}N_2$ ($M+H^+$): 151.1230, found: 151.1221.

4.5.2. 2-(Benzylamimo)pyridine (Table 3, entry 2). White solid (0.1787 g, 97%); mp 79–80 °C. ^{1}H NMR: δ 4.47 (d, J=4.0 Hz, 2H), 5.06 (br, 1H), 6.34 (d, J=4.0 Hz, 1H), 6.52–6.57 (m, 1H), 7.26–7.39 (m, 1H), 8.06 (d, J=4.0 Hz, 1H). HRMS (APCI) calcd for $C_{12}H_{13}N_2$ ($M+H^+$): 192.1495, found: 192.1508.

4.5.3. 2-(Cyclohexylamimo)pyridine (Table 3, entry 3). White solid (0.1622 g, 92%); mp 103–104 °C. ^{1}H NMR: δ 1.18–1.24 (m, 3H), 1.35–1.42 (m, 2H), 1.60–1.78 (m, 3H), 2.01–2.05 (m, 2H), 3.48–3.56 (m, 1H), 4.48 (br, 1H), 6.35 (d, J=8.0 Hz, 1H), 6.49–6.54 (m, 1H), 7.91 (d, J=8.0 Hz, 1H), 8.04 (d, J=4.0 Hz, 1H). HRMS (APCI) calcd for $C_{11}H_{17}N_2$ ($M+H^+$): 177.1386, found: 177.1381.

4.5.4. 3-(Butylamimo)pyridine (Table 3, entry 4). White solid (0.1412 g, 94%); mp 35–36 °C. ^{1}H NMR: δ 0.94 (t, J=4.0 Hz, 3H), 1.39–1.44 (m, 2H), 1.57–1.62 (m, 2H), 3.02–3.16 (m, 2H), 4.07 (br, 1H), 6.84–6.86 (m, 1H), 7.04–7.07 (m, 1H), 7.90 (d, J=4.0 Hz, 1H), 8.00 (d, J=4.0 Hz, 1H). HRMS (APCI) calcd for $C_9H_{15}N_2$ ($M+H^+$): 151.1230, found: 151.1237.

4.5.5. 3-(Benzylamimo)pyridine (Table 3, entry 5). White solid (0.1768 g, 96%); mp 77–78 °C. ^{1}H NMR: δ 4.28–4.36 (m, 2H), 5.23 (br, 1H), 6.84–6.87 (m, 1H), 7.03–7.06 (m, 1H), 7.93 (d, J=4.0 Hz, 1H), 8.04 (s, 1H). HRMS (APCI) calcd for $C_{12}H_{13}N_2$ ($M+H^+$): 185.1073, found: 185.1056.

4.5.6. 3-(Cyclohexylamimo)pyridine (Table 3, entry 6). White solid (0.1587 g, 90%); mp 91–92 °C. ^{1}H NMR:

δ 1.15–1.24 (m, 3H), 1.35 (t, J=16.0 Hz, 1H), 1.62–1.74 (m, 1H), 1.74–1.79 (m, 2H), 2.02–2.06 (m, 2H), 3.17–3.27 (m, 1H), 3.64 (br, 1H), 6.83–6.86 (m, 1H), 7.03–7.06 (m, 1H), 7.89 (d, J=4.0 Hz, 1H), 7.96 (d, J=20.0 Hz, 1H). HRMS (APCI) calcd for $C_{11}H_{17}N_2$ ($M+H^+$): 177.1386, found: 177.1378.

4.5.7. *N*-(2-Pyridinyl)-*N*-(ethyl)piperazine (Table 3, entry 7). Colorless liquid (0.1626 g, 85%). ^{1}H NMR: δ 1.13 (t, J=8.0 Hz, 3H), 2.44–2.49 (m, 2H), 2.55 (t, J=4.0 Hz, 4H), 3.53–3.58 (m, 4H), 6.59–6.65 (m, 2H), 7.44–7.53 (m, 1H), 8.18–8.19 (m, 1H). HRMS (APCI) calcd for $C_{11}H_{18}N_3$ ($M+H^+$): 192.1495, found: 192.1508.

4.5.8. *N*-(2-Pyridinyl)morpholine (Table 3, entry 8). Colorless liquid (0.1346 g, 82%). ^{1}H NMR: δ 3.47 (t, J=4.0 Hz, 4H), 3.79 (t, J=6.0 Hz, 4H), 6.60–6.65 (m, 2H), 7.45–7.49 (m, 1H), 8.18–8.20 (m, 1H). HRMS (APCI) calcd for $C_9H_{13}N_2O$ ($M+H^+$): 165.1022, found: 165.1015.

4.5.9. *N*-(2-Pyridinyl)imidazole (Table 3, entry 9). Colorless liquid (0.1104 g, 76%). ^{1}H NMR: δ 7.21–7.25 (m, 2H), 7.35 (t, J=4.0 Hz, 1H), 7.68 (d, J=16.0 Hz, 1H), 7.80–7.84 (m, 1H), 8.38 (s, 1H), 8.46–8.48 (m, 1H). HRMS (APCI) calcd for $C_8H_8N_3$ ($M+H^+$): 146.0713, found: 146.0707.

4.5.10. *N*-(2-Pyridinyl)benzoimidazole (Table 3, entry 10). Colorless liquid (0.1242 g, 78%). ^{1}H NMR: δ 7.23 (s, 1H), 7.33–7.36 (m, 2H), 7.48 (d, J=8.0 Hz, 1H), 7.80 (d, J=4.0 Hz, 1H), 7.85 (t, J=6.0 Hz, 1H), 8.03 (t, J=4.0 Hz, 1H), 8.56 (s, 2H). HRMS (APCI) calcd for $C_{12}H_{10}N_3$ ($M+H^+$): 196.0869, found: 196.0851.

4.5.11. *N*-(3-Pyridinyl)imidazole (Table 3, entry 11). Colorless liquid (0.1074 g, 74%). ^{1}H NMR: δ 7.30–7.36 (m, 2H), 7.44–7.47 (m, 1H), 7.74–7.76 (m, 1H), 7.94 (s, 1H), 8.62 (t, J=4.0 Hz, 1H), 8.74 (s, 1H). HRMS (APCI) calcd for $C_8H_8N_3$ ($M+H^+$): 146.0713, found: 146.0700.

4.5.12. *N*-(3-Pyridinyl)benzoimidazole (Table 3, entry 12). White solid (0.1503 g, 77%); mp 89–91 °C. ^{1}H NMR: δ 7.36–7.38 (m, 2H), 7.50–7.56 (m, 2H), 7.86–7.90 (m, 2H), 8.16 (s, 1H), 8.73 (d, J=4.0 Hz, 1H), 8.86 (s, 1H). HRMS (APCI) calcd for $C_{12}H_{10}N_3$ ($M+H^+$): 196.0869, found: 196.0860.

4.6. Cross-coupling data of 5-bromopyrimidine with various amines

4.6.1. 5-(*iso*-Propylamino)pyrimidine (Table 4, entry 1). White solid (0.1235 g, 90%); mp 49–50 °C. ^{1}H NMR: δ 1.25 (d, J=8.0 Hz, 6H), 3.64–3.65 (m, 1H), 3.85 (br, 1H), 8.10 (s, 2H), 8.55 (s, 1H). HRMS (APCI) calcd for $C_7H_{12}N_3$ ($M+H^+$): 138.1026, found: 138.1012.

4.6.2. 5-(Butylamimo)pyrimidine (Table 4, entry 2). White solid (0.1467 g, 97%); mp 73–74 °C. ^{1}H NMR: δ 0.91–0.99 (m, 3H), 1.42–1.47 (m, 2H), 1.60–1.66 (m, 2H), 3.15 (t, J=8.0 Hz, 2H), 4.05 (br, 1H), 8.06 (s, 2H), 8.55 (s, 1H). HRMS (APCI) calcd for $C_8H_{14}N_3$ ($M+H^+$): 152.1182, found: 152.1169.

4.6.3. 5-(*iso*-Butylamimo)pyrimidine (Table 4, entry 3). Colorless liquid (0.1421 g, 94%). ^{1}H NMR: δ 0.99–1.01 (d, J=8.0 Hz, 6H), 1.77–1.84 (m, 1H), 3.03 (d, J=8.0 Hz, 2H), 4.69 (br, 1H), 8.01 (s, 2H), 8.19 (s, 1H). HRMS (APCI) calcd for $C_8H_{14}N_3$ ($M+H^+$): 152.1182, found: 152.1174.

4.6.4. 5-(*sec*-Butylamimo)pyrimidine (Table 4, entry 4). Colorless liquid (0.1354 g, 89%). ^{1}H NMR: δ 0.95–0.99 (m, 3H), 1.21 (d, J=8.0 Hz, 3H), 1.51–1.63 (m, 2H), 3.38–3.45 (m, 1H), 3.97 (br, 1H), 8.09 (s, 2H), 8.53 (s, 1H). HRMS (APCI) calcd for $C_8H_{14}N_3$ ($M+H^+$): 152.1182, found: 152.1168.

4.6.5. 5-(Benzylamimo)pyrimidine (Table 4, entry 5). White solid (0.1778 g, 96%); mp 99–100 °C. ^{1}H NMR: δ 4.30–4.39 (m, 2H), 5.21 (br, 1H), 8.16 (s, 2H), 8.57 (s, 1H). HRMS (APCI) calcd for $C_{11}H_{12}N_3$ ($M+H^+$): 186.1026, found: 186.1031.

4.6.6. 5-(Cylcopropylamino)pyrimidine (Table 4, entry 6). White solid (0.1244 g, 92%); mp 86–87 °C. ^{1}H NMR: δ 0.54–0.58 (m, 2H), 0.76–0.84 (m, 2H), 2.44–2.49 (m, 1H), 4.60 (br, 1H), 8.27 (s, 2H), 8.60 (s, 1H). HRMS (APCI) calcd for $C_7H_{10}N_3$ ($M+H^+$): 136.0869, found: 136.0861.

4.6.7. 5-(Cylcopentylamino)pyrimidine (Table 4, entry 7). Colorless liquid (0.1534 g, 94%). ^{1}H NMR: δ 1.48–1.52 (m, 2H), 1.63–1.76 (m, 4H), 2.02–2.08 (m, 2H), 3.75–3.81 (m, 1H), 4.31 (br, 1H), 8.12 (s, 2H), 8.54 (s, 1H). HRMS (APCI) calcd for $C_9H_{14}N_3$ ($M+H^+$): 164.1182, found: 164.1171.

4.6.8. 5-(Cyclohexylamimo)pyrimidine (Table 4, entry 8). White solid (0.1683 g, 95%); mp 109–110 °C. ^{1}H NMR: δ 1.18–1.26 (m, 3H), 1.37 (t, J=8.0 Hz, 2H), 1.62–1.73 (m, 1H), 1.76–1.81 (m, 2H), 2.03–2.07 (m, 2H), 3.25–3.30 (m, 1H), 3.71 (s, 1H), 8.09 (s, 2H), 8.54 (s, 1H). HRMS (APCI) calcd for $C_{10}H_{16}N_3$ ($M+H^+$): 178.1139, found: 178.1328.

4.6.9. 5-(Pyrimidinyl)pyrrolidine (Table 4, entry 9). Colorless liquid (0.1238 g, 83%). ^{1}H NMR: δ 1.94–2.02 (m, 4H), 3.20–3.24 (m, 4H), 8.00 (s, 2H), 8.53 (s, 1H). HRMS (APCI) calcd for $C_8H_{12}N_3$ ($M+H^+$): 150.1026, found: 150.1029.

4.6.10. 5-(Pyrimidinyl)piperidine (Table 4, entry 10). Colorless liquid (0.1387 g, 85%). ^{1}H NMR: δ 1.55–1.62 (m, 2H), 1.63–1.72 (m, 4H), 3.20–3.27 (m, 4H), 8.35 (s, 1H), 8.61 (s, 1H). HRMS (APCI) calcd for $C_9H_{14}N_3$ ($M+H^+$): 164.1182, found: 164.1172.

4.6.11. *N*-(5-Pyrimidinyl)-*N*-(ethyl)piperazine (Table 4, entry 11). Colorless liquid (0.1538 g, 80%). ^{1}H NMR: δ 1.13 (t, J=8.0 Hz, 3H), 2.46–2.51 (m, 2H), 2.62 (t, J=4.0 Hz, 4H), 3.29 (t, J=4.0 Hz, 4H), 8.37 (s, 2H), 8.68 (s, 1H). HRMS (APCI) calcd for $C_{10}H_{17}N_4$ ($M+H^+$): 193.1448, found: 193.1434.

4.6.12. *N*-(5-Pyrimidinyl)morpholine (Table 4, entry 12). Colorless liquid (0.1421 g, 86%). ^{1}H NMR: δ 3.22 (t, J=4.0 Hz, 4H), 3.87 (t, J=4.0 Hz, 4H), 8.36 (s, 2H), 8.64 (s, 1H). HRMS (APCI) calcd for $C_8H_{12}N_3O$ ($M+H^+$): 166.0975, found: 166.0960.

4.6.13. *N*-(5-Pyrimidinyl)-2,6-dimethylmorpholine (Table 4, entry 13). Colorless liquid (0.1508 g, 78%). ^{1}H NMR: δ 1.29 (t, J=8.0 Hz, 6H), 2.50 (t, J=6.0 Hz, 4H), 3.79–3.83 (m, 2H), 8.36 (s, 2H), 8.69 (s, 1H). HRMS (APCI) calcd for $C_{10}H_{16}N_3O$ ($M+H^+$): 194.1288, found: 194.1279.

4.6.14. *N*-(5-Pyrimidinyl)benzoimidazole (Table 4, entry 14). White solid (0.1432 g, 73%); mp 143–144 °C. ^{1}H NMR: δ 7.40–7.44 (m, 2H), 7.52 (d, J=4.0 Hz, 4H), 7.93 (t, J=8.0 Hz, 1H), 9.03 (s, 1H), 9.34 (s, 1H). HRMS (APCI) calcd for $C_{11}H_9N_4$ ($M+H^+$): 197.0822, found: 197.0812.

Acknowledgements

Financial support from the National Key Project for Basic Research (2003CB114402) is gratefully acknowledged.

References and notes

1. (a) Buckingham, J. B. In *Dictionary of Natural Products*, *Vol. 1*; CRC Press 1994. (b) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164–5173.
2. Loutfy, R. O.; Hsiao, C. K.; Kazmaier, P. M. *Photogr. Sci. Eng.* **1983**, *27*, 5–9.
3. D'Aprano, G.; Leclerc, M.; Zotti, G.; Schiavon, G. *Chem. Mater.* **1995**, *7*, 33–36.
4. Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125–146.
5. Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805–818.
6. Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046–2067.
7. (a) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599–1626. (b) Tewari, A.; Hein, M.; Zapf, A.; Beller, M. *Tetrahedron* **2005**, *61*, 9705–9709. (c) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965–3968. (d) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442–4489. (e) Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2005**, *44*, 1371–1375.
8. Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670–674.
9. Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. J. *J. Am. Chem. Soc.* **2000**, *122*, 5043–5051.
10. Hassan, J.; Sevifnon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469.
11. Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449.
12. Arterburn, J. B.; Pannala, M.; Gonzalez, A. M. *Tetrahedron Lett.* **2001**, *42*, 1475–1477.
13. Collman, J. P.; Zhong, M.; Zhang, C.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 7892–7897.
14. Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803–3805.
15. Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315–4317.
16. Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133–136.
17. Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729.
18. Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428.
19. Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684–11688.
20. Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578–5587.
21. Mallesham, B.; Rajesh, B. M.; Reddy, P. R.; Srinivas, D. S. *Org. Lett.* **2003**, *5*, 963–965.
22. Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581–584.
23. Enguehard, C.; Allouchi, H.; Gueiffier, A.; Buchwald, S. L. *J. Org. Chem.* **2003**, *68*, 4367–4370.
24. Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453–2455.
25. Deng, W.; Wang, Y.-F.; Zou, Y.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2004**, *45*, 2311–2315.
26. Antilla, J. C.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 2077–2079.
27. Collman, J. P.; Zhong, M.; Zeng, L.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 1528–1531.
28. Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793–796.
29. (a) Chiang, G. C. H.; Olsson, T. *Org. Lett.* **2004**, *6*, 3079–3082. (b) Kuil, M.; Bekekam, E. K.; Visser, G. M.; van den Hoogenband, A.; Terpstra, J. W.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; van Strijdonek, G. P. F. *Tetrahedron Lett.* **2005**, *46*, 2405–2409. (c) Lu, Z.; Twieg, R. J. *Tetrahedron* **2005**, *61*, 903–918. (d) Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2005**, *70*, 8107–8109. (e) Jerphagnon, T.; van Klink, G. P. M.; de Vries, J. G.; van Koten, G. *Org. Lett.* **2005**, *7*, 5241–5244.
30. Lu, Z.; Twieg, R. J.; Huang, S. D. *Tetrahedron Lett.* **2003**, *44*, 6289–6292.
31. Okano, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 4987–4990.
32. Yamada, K.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Synlett* **2002**, 231–234.
33. Mao, J.; Wan, B.; Wang, R.; Wu, F.; Lu, S. *J. Org. Chem.* **2004**, *69*, 9123–9127.
34. (a) Xu, L.; Zhu, D.; Wu, F.; Wang, R.; Wan, B. *Tetrahedron* **2005**, *61*, 6553–6560. (b) Zhang, Z.; Mao, J.; Wang, R.; Wu, F.; Chen, H.; Wan, B. *J. Mol. Catal. A: Chem.* **2006**, *243*, 239–243.
35. Zhang, Z.; Mao, J.; Zhu, D.; Wu, F.; Chen, H.; Wan, B. *Catal. Commun.* **2005**, *6*, 784–787.
36. Cristau, H. J.; Cellier, P. P.; Spindler, J. F.; Taillefer, M. *Eur. J. Org. Chem.* **2004**, *69*, 695–700.
37. Son, S. K.; Park, I. K.; Park, J.; Hyeon, T. *Chem. Commun.* **2004**, 778–779.
38. Ji, J.; Li, T.; Bunnelle, W. H. *Org. Lett.* **2003**, *5*, 4611–4614.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 4444–4452

Studies on electrophilic addition reaction of 2,3-allenoates with PhSeCl

Guofei Chen,[a] Chunling Fu[a,*] and Shengming Ma[a,b,*]

[a]*Laboratory of Molecular Recognition and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou, Zhejiang 310027, People's Republic of China*
[b]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, People's Republic of China*

Received 12 December 2005; revised 16 February 2006; accepted 17 February 2006

Available online 13 March 2006

Abstract—β-Organoselenium substituted butenolides were prepared from 2,3-allenoates and PhSeCl in the presence of water. The yields of the products depend largely on the structures of 2,3-allenoates. The addition of water is crucial for some of this electrophilic cyclization. The reaction of simple unsubstituted methyl 2,3-butadienoate afforded methyl 4-chloro-3-phenylselanylbut-2(*Z*)-enoate in good yield and stereoselectivity.

1. Introduction

Since the 19th century, selenium has been recognized as an essential trace element in the diet.[1] In modern synthetic organic chemistry, organoseleniums have also been considered as important synthetic intermediates.[1,2] On the other hand, butenolides are a class of compounds present in many natural and unnatural products with biological importance.[3] Butenolides are, of course, also important intermediates in organic synthesis due to the presence of the conjugated C=C bond as well as the five-membered lactone ring.[4] Thus, the preparation of organoseleno-substituted butenolides is of current interest.[5]

This group has developed some methods for the efficient synthesis of differently substituted butenolides.[6] In addition, we have also reported the electrophilic cyclization of 2,3-allenoic acids[7] with PhSeCl or PhSCl leading to the synthesis of β-organoselenium or β-organosulfur substituted butenolides in moderate yields.[8] However, 2,3-allenoic acids were usually prepared from the hydrolysis of 2,3-allenoates, in which alkynoic acids may also be formed as the byproducts.[9] In this paper, we wish to report our recent studies on the reaction of 2,3-allenoates with PhSeCl in aqueous MeCN.

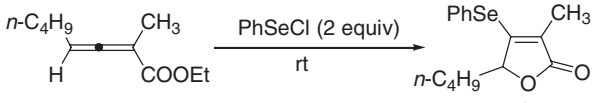
Keywords: Cyclization; Selenium; 2,3-Allenoates; Yield; Butenolide; Water effect.
* Corresponding authors. Fax: +86 21 64167510; e-mail: masm@mail.sioc.ac.cn

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.053

2. Results and discussion

We initiated this study with the electrophilic cyclization of ethyl 2-methyl-2,3-octadienoate **1a** with PhSeCl. However, when the reaction was carried out at room temperature in CH_3CN with 2 equiv of PhSeCl, the reaction conditions applied for the electrophilic cyclization of 2,3-allenoic acids with PhYCl (Y=S, Se),[8] the yield of **2a** was only 13% (entry 1, Table 1). Further investigation showed that water is very important in this reaction.[10] When the reaction was conducted according to the procedure described in Ref. 10, the yield of **2a** was still low and an unidentified product was formed. When a little amount of water was added to the

Table 1. Cyclization of PhSeCl with ethyl 2-methyl-2,3-octadienoate[a]



1a **2a**

Entry	CH_3CN/H_2O	Time (h)	Yield (%)[b]
1	100/0	6.5	13
2	800/1[c]	1.5	26
3	100/1[c]	1	45
4	**10/1**[c]	**1**	**100**

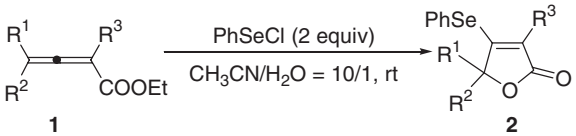
[a] The reaction was carried out using 0.2 mmol of ethyl 2-methyl-2,3-octadienoate and 2 equiv PhSeCl in 2 mL of CH_3CN.
[b] Isolated yield.
[c] H_2O was added to a solution of PhSeCl in CH_3CN, then a solution of **1a** was added immediately.

solution of PhSeCl in MeCN first, the yield of **2a** was improved (entry 2, Table 1). When $CH_3CN/H_2O=10:1$ was used, to our surprise, the yield of **2a** was quantitative (entry 4, Table 1).

With the optimized reaction conditions in hand, the scope of this reaction was explored. Some typical results are summarized in Table 2. It is obvious that differently substituted 2,4-disubstituted 2,3-allenoates can be applied to afford β-phenylselanyl butenolides in fairly good yields (77–100%) (entries 1–11, Table 2). Several types of substituents R^1 such as H, alkyl or aryl, R^2 such as H or alkyl, and R^3 such as alkyl or benzyl could be introduced into the products. The reaction of 4,4-disubstituted 2,3-allenoate **1m** afforded the product **2m** in 55% yield (entry 12, Table 2). The products were also afforded in moderate yields when 4-mono-substituted 2,3-allenoates **1n** or **1o** were treated with PhSeCl (entries 13 and 14, Table 2). In the reaction of 2-mono-substituted 2,3-allenoates **1p** or **1q**, the ratio of $MeCN/H_2O$ should be 1:1 for a higher yield of **2p** or **2q** (compare entry 15 with entry 16, Table 2). However, 2,4,4-trisubstituted 2,3-allenoates **1r** and **1s** can be applied to afford the products **2r** and **2s** in good yields even in the absence of water although the related yields are relatively lower probably due to the highly electrophilic nature of the allene moiety (entries 18–21, Table 2). Compared with results obtained with the corresponding 2,3-allenoic acids, the yields of this method are higher, in most cases, when 2,4-disubstituted 2,3-allenoate was applied. However, the reaction of 4-mono-substituted 2,3-allenoates afforded the products in relatively lower yield.

To our surprise, when we applied the current standard conditions to methyl 2,3-butadienoate **1t**, instead of

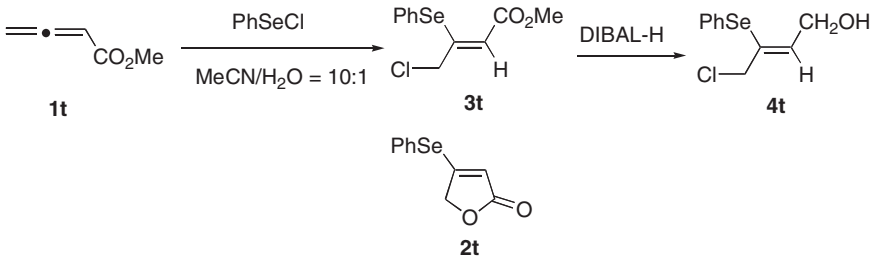
Table 2. Cyclization of PhSeCl with different ethyl 2,3-allenoate[a]



1 **2**

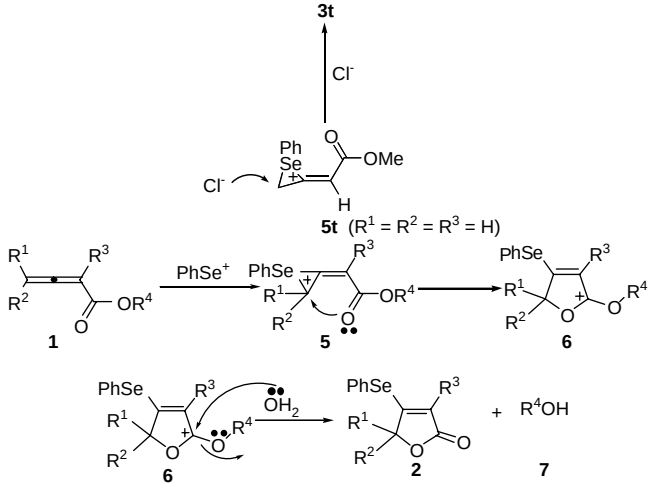
Entry	R^1	R^2	R^3	Time (h)	Yield (%)[b]
1	n-C_4H_9	H	CH_3 (**1a**)	1	100 (**2a**)
2	n-C_4H_9	H	n-C_3H_7 (**1b**)	1	92 (**2b**)
3	n-C_4H_9	H	Bn (**1c**)	1	96 (**2c**)
4	n-C_7H_{15}	H	CH_3 (**1d**)	2	94 (**2d**)
5	n-C_7H_{15}	H	n-C_3H_7 (**1e**)	1	95 (**2e**)
6	n-C_6H_{13}	H	Bn (**1f**)	3	82 (**2f**)
7	Ph	H	CH_3 (**1g**)	1	95 (**2g**)
8	Ph	H	n-C_3H_7 (**1h**)	1	99 (**2h**)
9	Ph	H	Bn (**1i**)	1	80 (**2i**)
10	α-Naphthyl	H	CH_3 (**1j**)	1	79 (**2j**)
11	α-Naphthyl	H	n-C_3H_7 (**1k**)	1	77 (**2k**)
12	CH_3	CH_3	H (**1m**)	1	55 (**2m**)
13	n-C_4H_9	H	H (**1n**)	3.5	55 (**2n**)
14	n-C_7H_{15}	H	H (**1o**)	1.5	52 (**2o**)
15	H	H	n-C_3H_7 (**1p**)	1	22 (**2p**)[c]
16[d]	H	H	n-C_3H_7 (**1p**)	1	49 (**2p**)[c]
17[d]	H	H	Bn (**1q**)	1	48 (**2q**)[c]
18	Ph	CH_3	CH_3 (**1r**)	1	100 (**2r**)
19	Ph	CH_3	CH_3 (**1r**)	1	92 (**2r**)[e]
20	$-(CH_2)_5-$		CH_3 (**1s**)	1	96 (**2s**)
21	$-(CH_2)_5-$		CH_3 (**1s**)	1	84 (**2s**)[e]

[a] The reaction was carried out using 0.2–0.3 mmol of ethyl 2,3-allenoate and 2 equiv of PhSeCl in 4–6 mL of CH_3CN.
[b] Isolated yield.
[c] Another unidentified product was also formed in this case.
[d] $CH_3CN/H_2O=1:1$.
[e] No water was added.

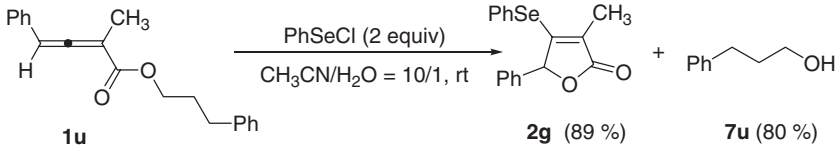


1t **3t** **4t** **2t**

Scheme 1.



Scheme 2.



Scheme 3.

butenolide **2t**, only compound *Z*-**3t** was isolated in 81% yield. The stereoselectivity was determined by NOE study of **3t** and **4t** (Scheme 1).

A plausible mechanism for this reaction is depicted in Scheme 2. The electrophile PhSeCl reacted with the relatively electron-rich C=C bond in 2,3-allenoates **1** forming intermediate **5**, which may be followed by the intramolecular attack of the carbonyl oxygen to form the cyclic intermediate **6**. Subsequent attack of water would be followed by intramolecular proton transfer and the elimination of R^4OH to produce butenolide **2** and the alcohol **7**. In case of $R^1=R^2=R^3=H$, that is, **1t**, the related intermediate **5t** may be easily attacked by Cl^- to form **3t** due to the unsubstituted nature of the allene moiety. The stereochemical outcome is still under investigation. However, the effect of the interaction of PhSeCl with water on the reaction is still unclear.

In order to probe the mechanistic nature of this reaction, we synthesized the 3′-phenylpropyl 2-methyl-3-phenyl-2,3-butadienoate **1u**. After the reaction, we isolated the corresponding butenolide **2g** and 3-phenylpropanol **7u**[11] in 89 and 80% yields, respectively. This further supports the proposed mechanism and explains why water is important for this reaction (Scheme 3).

3. Conclusion

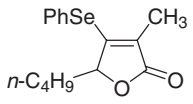
In conclusion, we have developed a facile and effective synthesis of β-organoselenium substituted butenolides from 2,3-allenoates. As a result of the easy availability of starting materials, the convenient operation and the usefulness of the products, the reaction may have potential utility in organic synthesis. The reaction of simple unsubstituted methyl 2,3-butadienoate afforded methyl 4-chloro-3-phenylselanylbut-2(*Z*)-enoate in good yield and stereoselectivity. Further studies in this area are being pursued in our laboratory.

4. Experimental

4.1. Typical procedure for the preparation of 2a

To a solution of PhSeCl (77.2 mg, 0.40 mmol) in 2 mL of MeCN was added 0.4 mL of H_2O. Then a solution of **1a** (37.1 mg, 0.20 mmol) in MeCN (2 mL) was subsequently added and the resulting mixture was stirred at room temperature for 1 h. The mixture was then evaporated directly and purified by column chromatography on silica gel (petroleum ether/ethyl acetate=10:1) to afford **2a** (64.9 mg, 100%) as a liquid.

4.1.1. 5-(*n*-Butyl)-3-methyl-4-phenylselanyl-5*H*-furan-2-one (2a).

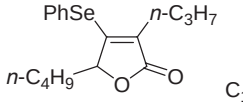


$C_{15}H_{18}O_2Se$

Compound **2a**: liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, $J=8.4$ Hz, 2H), 7.40–7.31 (m, 3H), 4.71–4.67 (m, 1H), 1.81 (d, $J=1.6$ Hz, 3H), 1.80–1.73 (m, 1H), 1.36–1.12 (m, 5H), 0.78 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 156.0, 135.1, 129.7, 129.2, 127.5, 124.9, 82.9, 32.7, 26.1, 21.9, 13.7, 10.5; MS (70 eV, EI) *m/z* (%): 310 ($M^+(^{80}Se)$, 100), 308 ($M^+(^{78}Se)$ or $M^+(^{77}Se)+1$, 50.18) 312 ($M^+(^{82}Se)$, 19.20), 306 ($M^+(^{76}Se)$, 19.15), 307

(M^+(^{77}Se) or M^+(^{76}Se)+1, 19.31), 304 (M^+(^{74}Se), 1.87), 311 (M^+(^{80}Se)+1, 17.02); IR ν (cm^{-1}): 2957, 1755, 1627, 1401, 1280, 1087; HRMS calcd for $C_{15}H_{19}O_2^{80}Se^+$ (M^++H): 311.0545. Found: 311.0543.

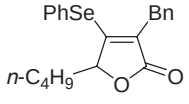
4.1.2. 5-(*n*-Butyl)-4-phenylselanyl-3-(*n*-propyl)-5*H*-furan-2-one (2b).



$C_{17}H_{22}O_2Se$

The reaction of 41.8 mg (0.20 mmol) of **1b** and 77.4 mg (0.40 mmol) of PhSeCl in 0.4 mL of H_2O and 4 mL of MeCN afforded 62.2 mg (92%) of **2b**: liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J=7.6 Hz, 2H), 7.42–7.31 (m, 3H), 4.67–4.64 (m, 1H), 2.40–2.30 (m, 1H), 2.29–2.19 (m, 1H), 1.80–1.71 (m, 1H), 1.60–1.49 (m, 2H), 1.38–1.06 (m, 5H), 0.91 (t, J=7.4 Hz, 3H), 0.77 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 156.5, 135.3, 131.6, 129.8, 129.3, 125.0, 82.5, 32.8, 27.3, 25.9, 22.0, 21.0, 13.8, 13.7; MS (70 eV, EI) *m*/*z* (%): 338 (M^+(^{80}Se), 39.97), 336 (M^+(^{78}Se) or M^+(^{77}Se)+1, 33.74), 340 (M^+(^{82}Se), 24.20), 334 (M^+(^{76}Se), 7.45), 335 (M^+(^{77}Se) or M^+(^{76}Se)+1, 25.43), 333 (M^+(^{74}Se)+1, 2.65), 337 (M^+(^{78}Se)+1, 54.80), 341 (M^+(^{82}Se)+1, 20.66), 339 (M^+(^{80}Se)+1, 100); IR ν (cm^{-1}): 2959, 2931, 1754, 1621; HRMS calcd for $C_{17}H_{22}O_2^{80}Se$: 338.0791. Found: 338.0797.

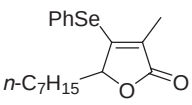
4.1.3. 3-Benzyl-5-(*n*-butyl)-4-phenylselanyl-5*H*-furan-2-one (2c).



$C_{21}H_{22}O_2Se$

The reaction of 52.6 mg (0.20 mmol) of **1c** and 79.0 mg (0.41 mmol) of PhSeCl in 0.4 mL of H_2O and 4 mL of MeCN afforded 75.8 mg (96%) of **2c**: liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J=8.0 Hz, 2H), 7.40–7.18 (m, 8H), 4.66 (dd, J_1=7.6 Hz, J_2=3.2 Hz, 1H), 3.76 (d, J=14.4 Hz, 1H), 3.57 (d, J=14.4 Hz, 1H), 1.76–1.64 (m, 1H), 1.28–1.00 (m, 5H), 0.73 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 157.9, 137.5, 135.4, 130.2, 129.8, 129.5, 128.7, 128.5, 126.6, 124.8, 82.7, 32.8, 31.4, 26.0, 21.9, 13.6; MS (70 eV, EI) *m*/*z* (%): 386 (M^+(^{80}Se), 39.73), 384 (M^+(^{78}Se) or M^+(^{77}Se)+1, 34.01), 388 (M^+(^{82}Se), 26.58), 382 (M^+(^{76}Se), 8.28), 383 (M^+(^{77}Se) or M^+(^{76}Se)+1, 26.08), 387 (M^+(^{80}Se)+1, 98.17), 385 (M^+(^{78}Se)+1, 57.04), 389 (M^+(^{82}Se)+1, 19.54), 381 (M^+(^{74}Se)+1, 3.55), 115 (100); IR ν (cm^{-1}): 2956, 2928, 1751, 1618, 1063; HRMS calcd for $C_{21}H_{22}O_2^{80}Se$: 386.0793. Found: 386.0808.

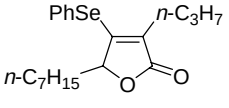
4.1.4. 5-(*n*-Heptyl)-3-methyl-4-phenylselanyl-5*H*-furan-2-one (2d).



$C_{18}H_{24}O_2Se$

The reaction of 43.7 mg (0.20 mmol) of **1d** and 75.2 mg (0.40 mmol) of PhSeCl in 0.4 mL of H_2O and 4 mL of MeCN afforded 64.7 mg (94%) of **2d**: liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J=8.0 Hz, 2H), 7.42–7.31 (m, 3H), 4.72–4.70 (m, 1H), 1.82 (d, J=2.0 Hz, 3H), 1.79–1.69 (m, 1H), 1.36–1.00 (m, 11H), 0.85 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 156.1, 135.1, 129.7, 129.2, 127.5, 124.9, 82.9, 33.1, 31.6, 28.8, 24.0, 22.5, 14.0, 10.5; MS (70 eV, EI) *m*/*z* (%): 352 (M^+(^{80}Se), 45.68), 350 (M^+(^{78}Se) or M^+(^{77}Se)+1, 36.25), 354 (M^+(^{82}Se), 25.58), 348 (M^+(^{76}Se), 8.67), 349 (M^+(^{77}Se) or M^+(^{76}Se)+1, 26.78), 353 (M^+(^{80}Se)+1, 98.04), 351 (M^+(^{78}Se)+1, 53.98), 355 (M^+(^{82}Se)+1, 18.24), 347 (M^+(^{74}Se)+1, 3.10), 41 (100); IR ν (cm^{-1}): 2926, 2856, 1755, 1628, 1281, 1091; HRMS calcd for $C_{18}H_{24}O_2^{80}Se$: 352.0948. Found: 352.0957.

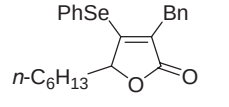
4.1.5. 5-(*n*-Heptyl)-4-phenylselanyl-3-(*n*-propyl)-5*H*-furan-2-one (2e).



$C_{20}H_{28}O_2Se$

The reaction of 51.7 mg (0.21 mmol) of **1e** and 76.1 mg (0.40 mmol) of PhSeCl in 0.4 mL of H_2O and 4 mL of MeCN afforded 73.7 mg (95%) of **2e**: liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J=8.0 Hz, 2H), 7.40–7.31 (m, 3H), 4.66–4.64 (m, 1H), 2.37–2.32 (m, 1H), 2.26–2.21 (m, 1H), 1.74–1.71 (m, 1H), 1.60–1.48 (m, 2H), 1.40–1.00 (m, 11H), 0.90 (t, J=7.2 Hz, 3H), 0.85 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 156.5, 135.3, 131.6, 129.7, 129.3, 125.0, 82.5, 33.1, 31.6, 28.80, 28.77, 27.3, 23.8, 22.5, 21.0, 14.0, 13.7; MS (70 eV, EI) *m*/*z* (%): 380 (M^+(^{80}Se), 24.79), 378 (M^+(^{78}Se) or M^+(^{77}Se)+1, 20.09), 382 (M^+(^{82}Se), 14.94), 376 (M^+(^{76}Se), 4.93), 377 (M^+(^{77}Se) or M^+(^{76}Se)+1, 16.41), 381 (M^+(^{80}Se)+1, 57.51), 379 (M^+(^{78}Se)+1, 32.78), 383 (M^+(^{82}Se)+1, 11.69), 375 (M^+(^{74}Se)+1, 2.09), 41 (100); IR ν (cm^{-1}): 2958, 2928, 1755, 1622, 1459, 1065; HRMS calcd for $C_{20}H_{28}O_2^{80}Se$: 380.1262. Found: 380.1284.

4.1.6. 3-Benzyl-5-(*n*-hexyl)-4-phenylselanyl-5*H*-furan-2-one (2f).

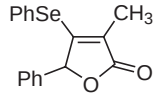


$C_{23}H_{26}O_2Se$

The reaction of 56.8 mg (0.20 mmol) of **1f** and 76.2 mg (0.40 mmol) of PhSeCl in 0.4 mL of H_2O and 4 mL of MeCN afforded 67.5 mg (82%) of **2f**: liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J=8.0 Hz, 2H), 7.46–7.22 (m, 8H), 4.72 (dd, J_1=7.6 Hz, J_2=2.8 Hz, 1H), 3.81 (d, J=14.8 Hz, 1H), 3.62 (d, J=14.8 Hz, 1H), 1.74–1.71 (m, 1H), 1.39–1.02 (m, 9H), 0.86 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 157.9, 137.5, 135.4, 130.2, 129.8, 129.5, 128.7, 128.5, 126.5, 124.8, 82.7, 33.1, 31.4, 31.3, 28.4, 23.7, 22.3, 13.9; MS (70 eV, EI) *m*/*z* (%): 414 (M^+(^{80}Se), 35.39), 412 (M^+(^{78}Se) or M^+(^{77}Se)+1, 31.77), 416 (M^+(^{82}Se), 27.40), 410 (M^+(^{76}Se), 6.10), 411

($M^+(^{77}Se)$ or $M^+(^{76}Se)+1$, 24.19), 415 ($M^+(^{80}Se)+1$, 98.21), 413 ($M^+(^{78}Se)+1$, 56.87), 417 ($M^+(^{82}Se)+1$, 19.99), 409 ($M^+(^{74}Se)+1$, 3.50), 43 (100); IR ν (cm^{-1}): 2927, 2857, 1751, 1618, 1578, 1454, 1439, 1082; HRMS calcd for $C_{23}H_{26}O_2^{80}Se$: 414.1107. Found: 414.1120.

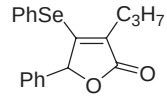
4.1.7. 3-Methyl-5-phenyl-4-phenylselanyl-5*H*-furan-2-one (2g).



$C_{17}H_{14}O_2Se$

The reaction of 39.9 mg (0.20 mmol) of **1g** and 75.9 mg (0.40 mmol) of PhSeCl in 0.4 mL of H_2O and 4 mL of MeCN afforded 61.8 mg (95%) of **2g**: liquid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.15 (m, 8H), 6.86 (d, $J=8.4$ Hz, 2H), 5.56 (q, $J=1.6$ Hz, 1H), 1.92 (d, $J=1.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 156.4, 135.9, 134.2, 129.4, 129.3, 129.2, 128.5, 127.5, 126.6, 123.8, 84.7, 10.5; MS (70 eV, EI) *m/z* (%): 330 ($M^+(^{80}Se)$, 51.07), 328 ($M^+(^{78}Se)$ or $M^+(^{77}Se)+1$, 25.82), 332 ($M^+(^{82}Se)$, 10.77), 326 ($M^+(^{76}Se)$, 9.96), 327 ($M^+(^{77}Se)$ or $M^+(^{76}Se)+1$, 11.40), 331 ($M^+(^{80}Se)+1$, 8.42), 329 ($M^+(^{78}Se)+1$, 23.14), 333 ($M^+(^{82}Se)+1$, 8.07), 105 (100); IR ν (cm^{-1}): 3031, 2918, 1759, 1630, 1440, 1302, 1284, 1107, 1087. Anal. Calcd for $C_{17}H_{14}O_2Se$: C 62.03, H 4.29. Found: C 62.01, H 4.27.

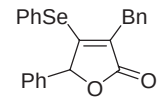
4.1.8. 5-Phenyl-4-phenylselanyl-3-(*n*-propyl)-5*H*-furan-2-one (2h).



$C_{19}H_{18}O_2Se$

The reaction of 45.6 mg (0.20 mmol) of **1h** and 79.2 mg (0.41 mmol) of PhSeCl in 0.4 mL of H_2O and 4 mL of MeCN afforded 70.0 mg (99%) of **2h**: liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.08 (m, 8H), 6.74 (d, $J=6.8$ Hz, 2H), 5.44 (s, 1H), 2.42–2.34 (m, 1H), 2.29–2.20 (m, 1H), 1.65–1.54 (m, 2H), 0.93 (t, $J=7.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 156.6, 135.9, 134.2, 130.5, 129.2, 129.1, 129.0, 128.3, 127.3, 123.6, 84.2, 27.2, 20.7, 13.8; MS (70 eV, EI) *m/z* (%): 358 ($M^+(^{80}Se)$, 69.96), 356 ($M^+(^{78}Se)$ or $M^+(^{77}Se)+1$, 38.30), 360 ($M^+(^{82}Se)$, 21.28), 354 ($M^+(^{76}Se)$, 14.63), 355 ($M^+(^{77}Se)$ or $M^+(^{76}Se)+1$, 17.96), 352 ($M^+(^{74}Se)$, 1.54), 359 ($M^+(^{80}Se)+1$, 63.26), 357 ($M^+(^{78}Se)+1$, 33.41), 361 ($M^+(^{82}Se)+1$, 13.45), 353 ($M^+(^{74}Se)+1$, 1.80), 105 (100); IR ν (cm^{-1}): 2960, 2930, 2871, 1755, 1618, 1456, 1295, 1116. Anal. Calcd for $C_{19}H_{18}O_2Se$: C 63.88, H 5.08. Found: C 63.81, H 5.10.

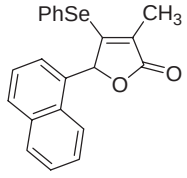
4.1.9. 3-Benzyl-5-phenyl-4-phenylselanyl-5*H*-furan-2-one (2i).



$C_{23}H_{18}O_2Se$

The reaction of 52.1 mg (0.19 mmol) of **1i** and 79.3 mg (0.41 mmol) of PhSeCl in 0.4 mL of H_2O and 4 mL of MeCN afforded 60.5 mg (80%) of **2i**: liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.38 (m, 5H), 7.37–7.32 (m, 2H), 7.29–7.21 (m, 6H), 6.81 (d, $J=7.2$ Hz, 2H), 5.60 (s, 1H), 3.94 (d, $J=14.8$ Hz, 1H), 3.77 (d, $J=14.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 158.0, 137.3, 136.2, 134.2, 129.5, 129.4, 129.2, 128.8, 128.7, 128.5, 127.6, 126.7, 123.6, 84.5, 31.5; MS (70 eV, EI) *m/z* (%): 406 ($M^+(^{80}Se)$, 40.50), 404 ($M^+(^{78}Se)$ or $M^+(^{77}Se)+1$, 24.72), 408 ($M^+(^{82}Se)$, 15.13), 402 ($M^+(^{76}Se)$, 8.71), 403 ($M^+(^{77}Se)$ or $M^+(^{76}Se)+1$, 11.53), 400 ($M^+(^{74}Se)$, 1.18), 407 ($M^+(^{80}Se)+1$, 37.57), 405 ($M^+(^{78}Se)+1$, 21.48), 409 ($M^+(^{82}Se)+1$, 8.34), 401 ($M^+(^{74}Se)+1$, 0.23), 203 (100); IR ν (cm^{-1}): 3030, 2907, 1740, 1607, 1455, 1175, 1082, 1064. Anal. Calcd for $C_{23}H_{18}O_2Se$: C 68.16, H 4.48. Found: C 68.39, H 4.66.

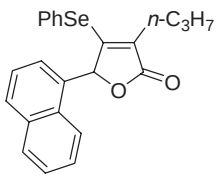
4.1.10. 3-Methyl-5-(1′-naphthyl)-4-phenylselanyl-5*H*-furan-2-one (2j).



$C_{21}H_{16}O_2Se$

The reaction of 53 mg (0.21 mmol) of **1j** and 77 mg (0.40 mmol) of PhSeCl in 0.4 mL of H_2O and 4 mL of MeCN afforded 63 mg (79%) of **2j**: solid. Mp 149–150 °C (petroleum ether/ethyl acetate). ^1H NMR (300 MHz, $CDCl_3$) δ 7.83 (t, $J=7.2$ Hz, 2H), 7.67 (d, $J=8.4$ Hz, 1H), 7.48–7.37 (m, 3H), 7.28 (d, $J=7.5$ Hz, 1H), 7.12 (d, $J=6.6$ Hz, 2H), 7.04 (t, $J=7.4$ Hz, 1H), 6.91 (t, $J=7.2$ Hz, 2H), 6.38 (q, $J=1.8$ Hz, 1H), 2.00 (d, $J=1.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 156.8, 135.7, 133.5, 131.6, 130.04, 130.02, 129.0, 128.9, 128.5, 127.2, 126.4, 125.9, 125.7, 125.0, 123.3, 122.1, 80.5, 10.6; MS (70 eV, EI) *m/z* (%): 380 ($M^+(^{80}Se)$, 81.24), 378 ($M^+(^{78}Se)$ or $M^+(^{77}Se)+1$, 44.30), 382 ($M^+(^{82}Se)$, 17.34), 376 ($M^+(^{76}Se)$, 15.68), 377 ($M^+(^{77}Se)$ or $M^+(^{76}Se)+1$, 17.69), 374 ($M^+(^{74}Se)$, 1.56), 381 ($M^+(^{80}Se)+1$, 19.74), 379 ($M^+(^{78}Se)+1$, 11.13), 383 ($M^+(^{82}Se)+1$, 3.48), 45 (100); IR ν (cm^{-1}): 1737, 1623, 1280, 1091. Anal. Calcd for $C_{21}H_{16}O_2Se$: C 66.50, H 4.25. Found: C 66.63, H 4.30.

4.1.11. 5-(1′-Naphthyl)-4-phenylselanyl-3-(*n*-propyl)-5*H*-furan-2-one (2k).

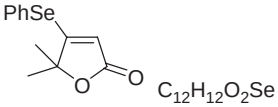


$C_{23}H_{20}O_2Se$

The reaction of 55.1 mg (0.20 mmol) of **1k** and 77.8 mg (0.41 mmol) of PhSeCl in 0.4 mL of H_2O and 4 mL of MeCN afforded 61.4 mg (77%) of **2k**: solid. Mp 105–107 °C (hexane/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (t, $J=8.8$ Hz, 2H), 7.53 (d, $J=8.8$ Hz, 1H), 7.34

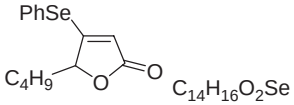
(q, J=7.6 Hz, 2H), 7.26 (t, J=7.8 Hz, 1H), 7.19 (d, J=6.8 Hz, 1H), 7.01 (d, J=7.2 Hz, 2H), 6.93 (t, J=7.4 Hz, 1H), 6.79 (t, J=7.4 Hz, 2H), 6.26 (s, 1H), 2.50–2.41 (m, 1H), 2.40–2.30 (m, 1H), 1.70–1.63 (m, 2H), 1.00 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 157.1, 136.0, 133.5, 131.7, 131.4, 130.2, 130.0, 129.05, 129.00, 128.5, 126.4, 125.9, 125.7, 125.1, 123.3, 122.1, 80.3, 27.6, 21.0, 14.1; MS (70 eV, EI) *m/z* (%): 408 (M^+(^{80}Se), 79.87), 406 (M^+(^{78}Se) or M^+(^{77}Se)+1, 41.82), 410 (M^+(^{82}Se), 16.71), 404 (M^+(^{76}Se), 15.31), 405 (M^+(^{77}Se) or M^+(^{76}Se)+1, 15.91), 402 (M^+(^{74}Se), 1.98), 409 (M^+(^{80}Se)+1, 20.27), 407 (M^+(^{78}Se)+1, 10.53), 411 (M^+(^{82}Se)+1, 3.93), 127 (100); IR ν (cm^{-1}): 2960, 2930, 2871, 1733, 1621, 1438, 1319, 1067. Anal. Calcd for $C_{23}H_{20}O_2Se$: C 67.82, H 4.95. Found: C 67.71, H 4.86.

4.1.12. 5,5-Dimethyl-4-phenylselanyl-5*H*-furan-2-one (2m).[12]



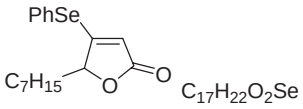
The reaction of 42.4 mg (0.30 mmol) of **1m** and 116.8 mg (0.61 mmol) of PhSeCl in 0.6 mL of H_2O and 6 mL of MeCN afforded 44.6 mg (55%) of **2m**: liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J=6.4 Hz, 2H), 7.49–7.38 (m, 3H), 5.29 (s, 1H), 1.56 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 169.9, 136.0, 130.2, 130.1, 124.6, 114.5, 87.5, 26.9; MS (EI) *m/z* (%): 268 (M^+(^{80}Se), 100), 266 (M^+(^{78}Se) or M^+(^{77}Se)+1, 52.38), 270 (M^+(^{82}Se), 23.81), 264 (M^+(^{76}Se), 23.80), 265 (M^+(^{77}Se) or M^+(^{76}Se)+1, 22.62), 262 (M^+(^{74}Se), 3.57), 269 (M^+(^{80}Se)+1, 19.05), 267 (M^+(^{78}Se)+1, 9.52), 271 (M^+(^{82}Se)+1, 4.76); IR ν (cm^{-1}): 2980, 1747, 1573, 1239, 1117.

4.1.13. 5-(*n*-Butyl)-4-phenylselanyl-5*H*-furan-2-one (2n).



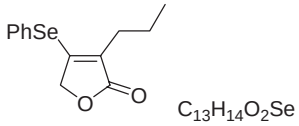
The reaction of 36.9 mg (0.22 mmol) of **1n** and 77.9 mg (0.41 mmol) of PhSeCl in 0.4 mL of H_2O and 4 mL of MeCN afforded 35.8 mg (55%) of **2n**: liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J=6.8 Hz, 2H), 7.50–7.39 (m, 3H), 5.47 (d, J=0.8 Hz,1H), 5.06–5.01 (m, 1H), 1.96–1.88 (m, 1H), 1.68–1.57 (m, 1H), 1.53–1.28 (m, 4H), 0.92 (t, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 169.7, 135.9, 130.2, 130.1, 124.5, 115.9, 84.2, 33.7, 26.0, 22.3, 13.8; MS (70 eV, EI) *m/z* (%): 296 (M^+(^{80}Se), 73.33), 294 (M^+(^{78}Se) or M^+(^{77}Se)+1, 38.51), 298 (M^+(^{82}Se), 1.60), 293 (M^+(^{77}Se) or M^+(^{76}Se)+1, 15.54), 297 (M^+(^{80}Se)+1, 10.86), 295 (M^+(^{78}Se)+1, 5.56), 299 (M^+(^{82}Se)+1, 4.36), 239 (100); IR ν (cm^{-1}): 2957, 2931, 1748, 1571, 1439, 1246, 1159. Anal. Calcd for $C_{14}H_{16}O_2Se$: C 56.97, H 5.46. Found: C 57.21, H 5.70.

4.1.14. 5-(*n*-Heptyl)-4-phenylselanyl-5*H*-furan-2-one (2o).



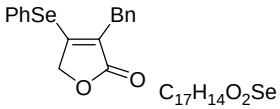
The reaction of 43.6 mg (0.21 mmol) of **1o** and 77.2 mg (0.40 mmol) of PhSeCl in 0.4 mL of H_2O and 4 mL of MeCN afforded 36.7 mg (52%) of **2o**: liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J=8.4 Hz, 2H), 7.49–7.39 (m, 3H), 5.47 (d, J=1.6 Hz, 1H), 5.06–5.01 (m, 1H), 1.96–1.86 (m, 1H), 1.68–1.56 (m, 1H), 1.53–1.28 (m, 10H), 0.89 (t, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 169.8, 135.9, 130.2, 130.0, 124.4, 115.9, 84.2, 33.9, 31.6, 29.1, 28.9, 23.9, 22.5, 14.0; MS (70 eV, EI) *m/z* (%): 338 (M^+(^{80}Se), 56.96), 336 (M^+(^{78}Se) or M^+(^{77}Se)+1, 32.34), 340 (M^+(^{82}Se), 27.85), 335 (M^+(^{77}Se) or M^+(^{76}Se)+1, 16.41), 334 (M^+(^{76}Se), 11.04), 339 (M^+(^{80}Se)+1, 53.15), 337 (M^+(^{78}Se)+1, 30.09), 341 (M^+(^{82}Se)+1, 4.74), 41 (100); IR ν (cm^{-1}): 2927, 2856, 1751, 1572, 1440, 1245, 1158. Anal. Calcd for $C_{17}H_{22}O_2Se$: C 60.54, H 6.57. Found: C 60.47, H 6.80.

4.1.15. 4-Phenylselanyl-3-(*n*-propyl)-5*H*-furan-2-one (2p).



The reaction of 47.6 mg (0.31 mmol) of **1p** and 117.1 mg (0.61 mmol) of PhSeCl in 0.6 mL of H_2O and 6 mL of MeCN afforded 19.2 mg (22%) of **2p**: liquid. The reaction of 47.3 mg (0.31 mmol) of **1p** and 111.5 mg (0.58 mmol) of PhSeCl in 2 mL of H_2O and 2 mL of MeCN afforded 42.3 mg (49%) of **2p**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J=7.2 Hz, 2H), 7.46 (t, J=7.2 Hz, 1H), 7.38 (t, J=7.4 Hz, 2H), 4.38 (s, 2H), 2.31 (t, J=7.4 Hz, 2H), 1.66–1.55 (m, 2H), 0.96 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 153.7, 136.3, 129.93, 129.91, 128.8, 123.0, 72.1, 27.3, 20.7, 13.9; MS (EI) *m/z* (%): 282 (M^+(^{80}Se), 100), 280 (M^+(^{78}Se) or M^+(^{77}Se)+1, 53.33), 284 (M^+(^{82}Se), 23.11), 278 (M^+(^{76}Se), 21.33), 279 (M^+(^{77}Se) or M^+(^{76}Se)+1, 20.44), 276 (M^+(^{74}Se), 1.11), 283 (M^+(^{80}Se)+1, 17.78), 281 (M^+(^{78}Se)+1, 9.33), 285 (M^+(^{82}Se)+1, 6.22), 277 (M^+(^{74}Se)+1, 0.44); IR ν (cm^{-1}): 2960, 1755, 1619, 1436, 1058, 1019; HRMS calcd for $C_{13}H_{14}O_2^{80}SeNa^+$ (M^++Na): 305.0061. Found: 305.0047.

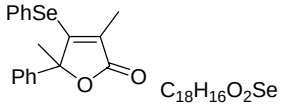
4.1.16. 3-Benzyl-4-phenylselanyl-5*H*-furan-2-one (2q).



The reaction of 59.8 mg (0.30 mmol) of **1q** and 115.3 mg (0.60 mmol) of PhSeCl in 2 mL of H_2O and 2 mL of MeCN afforded 46.8 mg (48%) of **2q**: liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J=8.0 Hz, 2H), 7.37 (t, J=7.6 Hz, 1H), 7.32–7.21 (m, 6H), 7.20–7.15 (m, 1H), 4.28 (s, 2H), 3.60

(s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 155.1, 137.2, 136.3, 130.0, 129.9, 129.0, 128.6, 127.4, 126.8, 122.9, 72.2, 31.4; MS (EI) *m/z* (%): 330 (M^+(^{80}Se), 23.75), 328 (M^+(^{78}Se) or M^+(^{77}Se)+1, 11.85), 332 (M^+(^{82}Se), 4.65), 326 (M^+(^{76}Se), 4.53), 327 (M^+(^{77}Se) or M^+(^{76}Se)+1, 4.58), 324 (M^+(^{74}Se), 0.41), 331 (M^+(^{80}Se)+1, 4.53), 329 (M^+(^{78}Se)+1, 2.53), 333 (M^+(^{82}Se)+1, 0.89), 129 (100); IR ν (cm^{-1}): 3059, 1747, 1618, 1454, 1439, 1341, 1172, 1055, 1023; HRMS calcd for $C_{17}H_{14}O_2^{80}SeNa^+$ (M^++Na): 353.0063. Found: 353.0077.

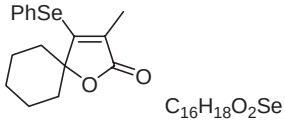
4.1.17. 3,5-Dimethyl-5-phenyl-4-phenylselanyl-5*H*-furan-2-one (2r).



$C_{18}H_{16}O_2Se$

The reaction of 40.8 mg (0.19 mmol) of **1r** and 76.9 mg (0.40 mmol) of PhSeCl in 0.4 mL of H_2O and 4 mL of MeCN afforded 64.5 mg (100%) of **2r**. The reaction of 42.9 mg (0.20 mmol) of **1r** and 78.3 mg (0.41 mmol) of PhSeCl in 4 mL of MeCN afforded 62.6 mg (92%) of **2r**: liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.17 (m, 8H), 7.11 (t, J=7.6 Hz, 2H), 1.85 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 160.9, 138.1, 134.2, 129.4, 128.6, 128.5, 128.3, 125.7, 125.4, 89.1, 24.6, 10.5; MS (EI) *m/z* (%): 344 (M^+(^{80}Se), 62.65), 342 (M^+(^{78}Se) or M^+(^{77}Se)+1, 32.53), 346 (M^+(^{82}Se), 14.45), 340 (M^+(^{76}Se), 13.25), 341 (M^+(^{77}Se) or M^+(^{76}Se)+1, 13.20), 338 (M^+(^{74}Se), 1.20), 345 (M^+(^{80}Se)+1, 14.50), 343 (M^+(^{78}Se)+1, 7.23), 347 (M^+(^{82}Se)+1, 2.41), 187 (100); IR ν (cm^{-1}): 3063, 1751, 1615, 1481, 1440, 1053, 1028; HRMS calcd for $C_{18}H_{16}O_2Se^{80}Na^+$ (M^++Na): 367.0220. Found: 367.0231.

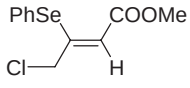
4.1.18. 3-Methyl-4-phenylselanyl-1-oxaspiro[4.5]dec-3-en-2-one (2s).



$C_{16}H_{18}O_2Se$

The reaction of 38.0 mg (0.20 mmol) of **1s** and 76.5 mg (0.40 mmol) of PhSeCl in 0.4 mL of H_2O and 4 mL of MeCN afforded 60.2 mg (96%) of **2s**. The reaction of 39.4 mg (0.20 mmol) of **1s** and 76.1 mg (0.40 mmol) of PhSeCl in 4 mL of MeCN afforded 54.6 mg (84%) of **2s**: solid. Mp 63–65 °C (hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J=8.0 Hz, 2H), 7.30–7.20 (m, 3H), 1.79–1.59 (m, 7H), 1.47 (s, 3H), 1.46 (d, J=9.6 Hz, 2H), 1.15–1.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 160.3, 133.8, 129.5, 128.5, 126.5, 89.1, 34.8, 24.3, 22.0, 10.5; MS (70 eV, EI) *m/z* (%): 322 (M^+(^{80}Se), 72.04), 320 (M^+(^{78}Se) or M^+(^{77}Se)+1, 37.71), 324 (M^+(^{82}Se), 14.70), 319 (M^+(^{77}Se) or M^+(^{76}Se)+1, 16.60), 318 (M^+(^{76}Se), 17.66), 316 (M^+(^{74}Se), 2.67), 323 (M^+(^{80}Se)+1, 14.61), 325 (M^+(^{82}Se)+1, 3.45), 165 (100); IR ν (cm^{-1}): 2935, 2858, 1751, 1635, 1575, 1475, 1449, 1439, 1291, 1283, 1199, 1097. Anal. Calcd for $C_{16}H_{18}O_2Se$: C 59.83, H 5.65. Found: C 60.06, H 5.73.

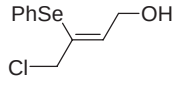
4.1.19. Methyl 4-chloro-3-phenylselanylbut-2(*Z*)-enoate (3t).



$C_{11}H_{11}ClO_2Se$

The reaction of 101.1 mg (1.03 mmol) of **3t** and 384.1 mg (2.01 mmol) of PhSeCl in 2 mL of H_2O and 20 mL of MeCN afforded 242.0 mg (81%) of **3t**: liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J=8.0 Hz, 2H), 7.45 (t, J=7.6 Hz, 1H), 7.36 (t, J=7.2 Hz, 2H), 6.60 (t, J=1.1 Hz, 1H), 3.95 (d, J=1.1 Hz, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 154.1, 137.6, 129.7, 129.3, 125.3, 116.0, 51.6, 46.7; MS (EI) *m/z* (%): 290 (M^+(^{80}Se, ^{35}Cl) or M^+(^{78}Se, ^{37}Cl) or M^+(^{77}Se, ^{37}Cl)+1, 97.00), 288 (M^+(^{78}Se, ^{35}Cl) or M^+(^{76}Se, ^{37}Cl) or M^+(^{77}Se, ^{35}Cl)+1, 48.00), 292 (M^+(^{80}Se, ^{37}Cl) or M^+(^{82}Se, ^{35}Cl), 44.00), 286 (M^+(^{76}Se, ^{35}Cl) or M^+(^{74}Se, ^{37}Cl), 15.00), 287 (M^+(^{77}Se, ^{35}Cl) or M^+(^{76}Se, ^{35}Cl)+1 or M^+(^{74}Se, ^{37}Cl)+1, 17.00), 284 (M^+(^{74}Se, ^{35}Cl), 1.00), 291 (M^+(^{80}Se, ^{35}Cl)+1 or M^+(^{78}Se, ^{37}Cl)+1, 12.00), 289 (M^+(^{77}Se, ^{37}Cl) or M^+(^{78}Se, ^{35}Cl)+1 or M^+(^{76}Se, ^{37}Cl)+1, 11.00), 293 (M^+(^{80}Se, ^{37}Cl)+1 or M^+(^{78}Se, ^{37}Cl)+1, 6.00), 294 (M^+(^{82}Se, ^{37}Cl), 6.00), 158 (100); IR ν (cm^{-1}): 2955, 1701, 1598, 1437, 1329, 1271, 1201, 1021; HRMS calcd for $C_{11}H_{11}O_2^{80}Se^{35}ClNa^+$ (M^++Na): 312.9508. Found: 312.9523.

4.1.20. 4-Chloro-3-phenylselanylbut-2(*Z*)-en-1-ol (4t).

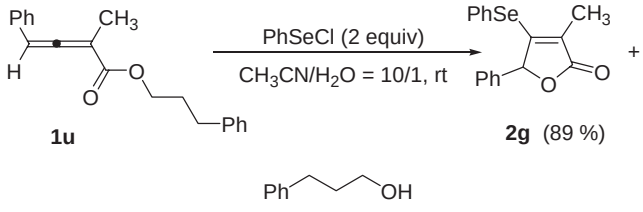


$C_{10}H_{11}ClOSe$

A solution of **3t** (103.6 mg, 0.36 mmol) in 2 mL of toluene was added 2 mL of DIBAl-H (1.0 M in toluene) at −78 °C followed by stirring at this temperature for 3 h. The mixture was quenched with 2 mL of MeOH and 5 mL of water. The mixture was then extracted with diethyl ether (25 mL×3) and dried over anhydrous Na_2SO_4. Evaporation and column chromatography on silica gel (petroleum ether/ethyl acetate=5:1) afforded **4t** (78.9 mg, 84%) as a liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.37 (m, 2H), 7.22–7.18 (m, 3H), 6.42 (t, J=6.2 Hz, 1H), 4.33 (d, J=6.4 Hz, 2H), 4.05 (d, J=1.2 Hz, 2H), 2.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 132.9, 129.9, 129.4, 128.1, 127.8, 62.1, 48.8; MS (EI) *m/z* (%): 262 (M^+(^{80}Se, ^{35}Cl) or M^+(^{78}Se, ^{37}Cl) or M^+(^{77}Se, ^{37}Cl)+1, 47.09), 260 (M^+(^{78}Se, ^{35}Cl) or M^+(^{76}Se, ^{37}Cl) or M^+(^{77}Se, ^{35}Cl)+1, 22.49), 264 (M^+(^{80}Se, ^{37}Cl) or M^+(^{82}Se, ^{35}Cl), 44.00), 258 (M^+(^{76}Se, ^{35}Cl) or M^+(^{74}Se, ^{37}Cl), 7.79), 259 (M^+(^{77}Se, ^{35}Cl) or M^+(^{76}Se, ^{35}Cl)+1 or M^+(^{74}Se, ^{37}Cl)+1, 7.19), 256 (M^+(^{74}Se, ^{35}Cl), 0.71), 263 (M^+(^{80}Se, ^{35}Cl)+1 or M^+(^{78}Se, ^{37}Cl)+1, 5.01), 261 (M^+(^{77}Se, ^{37}Cl) or M^+(^{78}Se, ^{35}Cl)+1 or M^+(^{76}Se, ^{37}Cl)+1, 4.57), 265 (M^+(^{80}Se, ^{37}Cl)+1 or M^+(^{78}Se, ^{37}Cl)+1, 2.26), 266 (M^+(^{82}Se, ^{37}Cl), 2.48), 158 (100); IR ν (cm^{-1}): 3356, 1578,

1476, 1438, 1261, 1071, 1021; HRMS calcd for $C_{10}H_{11}O^{80}Se^{35}ClNa^{+}$ ($M^{+}+Na$): 284.9561. Found: 284.9572.

4.2. Mechanistic study



The reaction of 59 mg (0.20 mmol) of **1u** and 77 mg (0.40 mmol) of PhSeCl in 0.4 mL of H_2O and 4 mL of MeCN afforded 59 mg (89%) of **2g** and 22 mg (80%) of 3-phenylpropanol **7u**. The analytic data for compound **2g** are the same as reported in Section 4.1.7. **7u** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.19 (m, 2H), 7.16–7.11 (m, 3H), 3.62 (t, $J=6.3$ Hz, 2H), 2.65 (t, $J=7.8$ Hz, 2H), 1.89–1.81 (m, 2H), 1.50 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.8, 128.39, 128.37, 125.8, 62.2, 34.2, 32.0; MS (EI) *m/z* (%): 136 (M^{+}, 13.72), 91 (100); IR ν (cm^{-1}): 3339, 2939, 1496, 1454, 1059, 1031.

Acknowledgements

Financial supports from the National Natural Science Foundation of China (No. 20572093), Zhejiang Provincial Natural Science Foundation of China (No. Y0404262) and the Major State Basic Research Development Program (Grant No. G2000077500), Cheung Kong Scholar Programme. S.M. is jointly appointed by Zhejiang University and Shanghai Institute of Organic Chemistry. This work was conducted at Zhejiang University.

References and notes

1. (a) Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Products Synthesis*; CIS: Philadelphia, 1984. (b) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Oxford, 1986. (c) Liotta, D. *Organoselenium Chemistry*; Wiley: New York, 1987. (d) Back, T. G. *Organoselenium Chemistry: A Practical Approach*; Oxford University Press: Oxford, 1999. (e) Wirth, T. *Organoselenium Chemistry: Modern Developments in Organic Synthesis*; Springer: Berlin, 2000. (f) Hatfield, D. L. *Selenium: Its Molecular Biology and Role in Human Health*; Kluwer: Hingham, 2001. (g) Sanotskii, I. V. *Selenium Compounds and Health*; Rossiiskaya Akademiya Meditsinskikh Nauk: Moscow, 2004.
2. For some of the most recent examples, see: (a) Fujiwara, S.; Shikano, Y.; Shin-ike, T.; Kambe, N.; Sonoda, N. *J. Org. Chem.* **2002**, *67*, 6275. (b) Silveira, C. C.; Braga, A. L.; Guerra, R. B. *Tetrahedron Lett.* **2002**, *43*, 3395. (c) Iwasaki, K.; Nakatani, M.; Inoue, M.; Katoh, T. *Tetrahedron Lett.* **2002**, *43*, 7937. (d) Mlochowski, J.; Brzaszcz, M.; Giurg, M.; Palus, J.; Wojtowicz, H. *Eur. J. Org. Chem.* **2003**, *22*, 4329. (e) Kim, J. H.; Lim, H. J.; Cheon, S. H. *Tetrahedron* **2003**, *59*, 7501. (f) Miranda, N.; Daublain, P.; Horner, J. H.; Newcomb, M. *J. Am. Chem. Soc.* **2003**, *125*, 5260. (g) Tiecco, M.; Testaferri, L.; Santi, C.; Tomassini, C.; Marini, F.; Bagnoli, L.; Temperini, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3131. (h) Aprile, C.; Gruttadauria, M.; Amato, M. E.; D'Anna, F.; Meo, P. L.; Riela, S.; Noto, R. *Tetrahedron* **2003**, *59*, 2241. (i) Besev, M.; Engman, L. *Org. Lett.* **2003**, *4*, 3023. (j) Tang, E.; Lin, X.; Huang, X. *Chin. J. Chem.* **2004**, *22*, 1192. (k) Huang, X.; Tang, E. *J. Chem. Res.* **2004**, *1*, 32. (l) Krief, A.; Derock, M. *Synlett* **2005**, *6*, 1012. (m) Tiecco, M.; Testaferri, L.; Temperini, A.; Terlizzi, R.; Bagnoli, L.; Marini, F.; Santi, C. *Synthesis* **2005**, *4*, 579.
3. (a) Larock, R. C.; Riefling, B.; Fellows, C. A. *J. Org. Chem.* **1978**, *43*, 131 and the references cited therein. (b) Tanabe, A. Jpn. Kokai Tokyo Koho, JP 63211276, 88211276, 1988; *Chem. Abstr.* **1989**, *110*, 94978q. (c) Lee, G. C. M. Eur. Pat. Appl. EP 372940, 1990; *Chem. Abstr.* **1990**, *113*, 191137j. (d) Brima, T. S. U.S. Patent US 4968817, 1990; *Chem. Abstr.* **1991**, *114*, 185246y. (e) Lee Gary, C. M.; Garst, M. E. PCT Int. Appl. WO 9116055, 1991; *Chem. Abstr.* **1992**, *116*, 59197m. (f) Ducharme, Y.; Gauthier, J. Y.; Prasit, P.; Leblanc, Y.; Wang, Z.; Leger, S.; Therien, M. PCT Int. Appl. WO 9500501, 1995; *Chem. Abstr.* **1996**, *124*, 55954y. (g) Beck, B.; Magnin-Lachaux, M.; Herdtweck, E.; Doemling, A. *Org. Lett.* **2001**, *3*, 2875. (h) Marshall, J. A.; Piettre, A.; Paige, M. A.; Valeriote, F. *J. Org. Chem.* **2003**, *68*, 1780. (i) Ghisalberti, E. L.; Hargreaves, J. R.; McConville, E. *Nat. Prod. Res.* **2004**, *18*, 105. (j) Kapferer, T.; Brueckner, R.; Herzig, A.; Koenig, W. A. *Chemistry* **2005**, *11*, 2154. (k) Zhao, Y.; Jiang, S.; Guo, Y.; Yao, Z. *Chin. J. Org. Chem.* **2005**, *23*, 173. (l) Zhang, H.; Van Hung, N.; Cuong, N. M.; Soejarto, D. D.; Pezzuto, J. M.; Fong, H. H. S.; Tan, G. T. *Planta Med.* **2005**, *71*, 452.
4. For some of the most recent examples, see: (a) Knight, D. W. *Synthesis* **1994**, *1*, 287. (b) Damtoft, S.; Jensen, S. R. *Phytochemistry* **1995**, *40*, 157. (c) Seki, T.; Satake, M.; Mackenzie, L.; Kaspar, H. F.; Yasumoto, Y. *Tetrahedron Lett.* **1995**, *36*, 7093. (d) Guo, S.; Wang, L.; Chen, D. *Indian J. Chem., Sect. B* **1997**, *36*, 339. (e) Negishi, E.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707. (f) Cortez, D. A. G.; Fernandes, J. B.; Vieria, P. C.; Silva, M. F. G. F.; Ferreira, A. G.; Cass, Q. B.; Pirani, J. R. *Phytochemistry* **1998**, *49*, 2493. (g) Otsuka, H.; Kotani, K.; Bando, M.; Kido, M.; Takeda, Y. *Chem. Pharm. Bull.* **1998**, *46*, 1180. (h) Chia, Y.; Chang, F.; Wu, Y. *Tetrahedron Lett.* **1999**, *40*, 7513. (i) Takahashi, S.; Maeda, K.; Hirota, S.; Nakata, T. *Org. Lett.* **1999**, *1*, 2025. (j) Siddiqui, B. S.; Afshan, F.; Ghiasuddin Faizi, S.; Naqvi, S. N. H.; Tariq, R. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, *1*, 2367. (k) Jacobi, P. A.; Lee, K. *J. Am. Chem. Soc.* **2000**, *122*, 4295. (l) Rousset, S.; Thibonnet, J.; Abarbri, M.; Duchene, A.; Parrain, J. *Synlett* **2000**, *2*, 26. (m) Maheut, G.; Liao, L.; Catel, J.; Jaffres, P.; Villemin, D. *J. Chem. Edu.* **2001**, *78*, 654. (n) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701. (o) Romeo, G.; Iannazzo, D.; Piperno, A.; Romeo, R.; Corsaro, A.; Rescifina, A.; Chiacchio, U. *Mini-Rev. Org. Chem.* **2005**, *2*, 59.
5. (a) Gill, G. B.; Idris, Muhammad, S. H. *Tetrahedron Lett.* **1985**, *26*, 4811. (b) Back, T. G.; Krishna, M. V. J. *J. Org. Chem.* **1988**, *53*, 2533. (c) Hollingworth, G. J.; Perkins, G.; Sweeney, J. *B. J. Chem. Soc., Perkin Trans. 1* **1996**, 1913. (d) Staroske, T.; Hennig, L.; Welzel, P.; Hofmann, H.; Müller, D.; Häusler, T.; Sheldrick, W. S.; Zillikens, S.; Gretzer, B.; Pusch, H.; Glitsch, H. G. *Tetrahedron* **1996**, *52*, 12723. (e) Ogawa, A.; Kuniyasu, H.; Sonoda, N.; Hirao, T. *J. Org. Chem.* **1997**,

62, 8361. (f) Bella, M.; Piancatelli, G.; Pigro, M. C. *Tetrahedron* **1999**, *55*, 12387. (g) Bella, M.; Piancatelli, G.; Squarcia, A.; Trolli, C. *Tetrahedron Lett.* **2000**, *41*, 3669. (h) Paintner, F. F.; Bauschke, G.; Kestel, M. *Tetrahedron Lett.* **2000**, *41*, 9977. (i) Bella, M.; Piancatelli, G.; Squarcia, A. *Tetrahedron* **2001**, *57*, 4429. (j) Kurbangalieva, A. R.; Bogdanov, A. V.; Movchan, A. I.; Chmutova, G. A. *Russ. J. Org. Chem.* **2004**, *40*, 1216.

6. (a) Ma, S.; Shi, Z. *J. Org. Chem.* **1998**, *63*, 6387. (b) Ma, S.; Wu, S. *J. Org. Chem.* **1999**, *64*, 9314. (c) Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron Lett.* **1999**, *40*, 2393. (d) Ma, S.; Shi, Z.; Yu, Z. *Tetrahedron* **1999**, *55*, 12137. (e) Ma, S.; Duan, D.; Shi, Z. *Org. Lett.* **2000**, *2*, 1419. (f) Ma, S.; Shi, Z.; Wu, S. *Tetrahedron: Asymmetry* **2001**, *12*, 193. (g) Ma, S.; Yu, Z.; Wu, S. *Tetrahedron* **2001**, *57*, 1585. (h) Ma, S.; Wu, S. *Chem. Commun.* **2001**, 441. (i) Ma, S.; Shi, Z. *Chin. J. Chem.* **2001**, *19*, 1280. (j) Ma, S.; Yu, Z. *Angew. Chem., Int. Ed.* **2002**, *41*, 1775. (k) Ma, S.; Duan, D.; Wang, Y. *J. Comb. Chem.* **2002**, *4*, 239. (l) Ma, S.; Shi, Z. *Chem. Commun.* **2002**, 540.
7. (a) . 2,3-Allenoic acids were prepared according to the known procedure: (a) Bestmann, H. J.; Hartung, H. *Chem. Ber.* **1966**, *99*, 1198. (b) Clinet, J. C.; Linstrumelle, G. *Synthesis* **1981**, 875. (c) Ma, S.; Wu, S. *J. Org. Chem.* **1999**, *64*, 9314.
8. Ma, S.; Pan, F.; Hao, X.; Huang, X. *Synlett* **2004**, 85.
9. (a) Bestmann, H. J.; Hartung, H. *Chem. Ber.* **1966**, *99*, 1198. (b) Mohammed, A.; Olivier, C.; Jerome, G.; Bernard, C. *Tetrahedron Lett.* **1997**, *38*, 5277. (c) Ma, S.; Wu, S. *J. Org. Chem.* **1999**, *64*, 9314. (d) Ma, S.; Xie, H.; Wang, G.; Zhang, J.; Shi, Z. *Synthesis* **2001**, 713. (e) Ma, S.; Wu, S. *Tetrahedron Lett.* **2001**, *42*, 4075. (f) Ma, S.; Jiao, N.; Zhao, S.; Hou, H. *J. Org. Chem.* **2002**, *67*, 2837. (g) Ma, S.; Wu, B.; Shi, Z. *J. Org. Chem.* **2004**, *69*, 1429.
10. Fu, C.; Ma, S. *Eur. J. Org. Chem.* **2005**, 3942.
11. Kajiro, H.; Mitamura, S.; Miro, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1999**, 1553.
12. Ogawa, A.; Kuniyasu, H.; Sonoda, N.; Hirao, T. *J. Org. Chem.* **1997**, *62*, 8361.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 4453–4462

What are the pK_a values of organophosphorus compounds?

Jia-Ning Li, Lei Liu,* Yao Fu and Qing-Xiang Guo*

Department of Chemistry, University of Science and Technology of China, Hefei 230026, China

Received 30 November 2005; revised 10 February 2006; accepted 17 February 2006

Abstract—A first-principle theoretical protocol was developed, which could successfully predict the pK_a values of a number of amines and thiols in DMSO with a precision of about 1.1 pK_a unit. Using this protocol we calculated the pK_a values of diverse types of organophosphorus compounds in DMSO. The accuracy of these predicted values was estimated to be about 1.1 pK_a because phosphorus is in the same group as nitrogen and in the same period as sulfur. The theoretical predictions were also consistent with all the available experimental data. Thus, a scale of reliable pK_a values was constructed for the first time for organophosphorus. These pK_a values would be helpful to synthetic chemists who need to design the experimental conditions for handling deprotonated organophosphorus. On the basis of these pK_a values we also studied, for the first time, some interesting topics such as the substituent effects on the pK_a values of various types of organophosphorus, and the differences between the pK_a values of organophosphorus and organic amines.

1. Introduction

Organophosphorus are organic compounds that contain phosphorus as an integral part of the molecule.[1] Common examples for organophosphorus include phosphines, phosphinites, phosphonites, phosphites, phosphinous amides, phosphinous diamides, phosphinous triamides, phosphonium salts, phosphine oxides, phosphinates, phosphonates, and phosphates (Fig. 1).

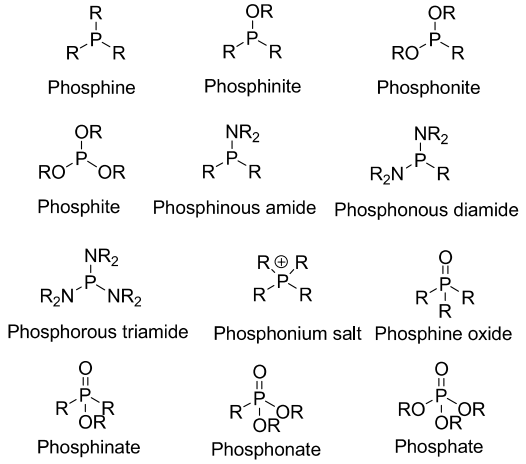


Figure 1. Common organophosphorus compounds.

Organophosphorus compounds have widespread use throughout the world, mainly in agriculture as insecticides, herbicides, and plant growth regulators.[2] They have also been used as nerve agents in chemical warfare (e.g., Sarin gas), and as therapeutic agents, such as ecothiopate used in the treatment of glaucoma.[3] In academic researches organophosphorus compounds find important applications in organic synthesis (Wittig, Mitsunobu, Staudinger, organocatalysis etc.).[4] The use of organophosphorus compounds as achiral or chiral ligands for transition metal-catalyzed transformations is also rapidly growing in both laboratory synthesis and industrial production.[5] Furthermore, organophosphorus compounds can be used as flame retardants for fabrics and plastics, plasticising and stabilising agents in the plastics industry, selective extractants for metal salts from ores, additives for petroleum products, and corrosion inhibitors.[1]

Several general methods have been developed for the synthesis of organophosphorus.[1,6] The two most popular of these are: reaction of an organometallic reagent with a phosphorus halide, and reaction of a metal phosphide with an organic electrophile. In the second method, a metal phosphide is often prepared by deprotonation of the corresponding P–H containing compound with a base[7] (e.g., *t*-BuOK, EtONa, NaH, etc. see Fig. 2 for some recent examples). This is successful only if the base is obtained from a compound that is a weaker proton acid than the phosphine. Thus, there is a strong need for organic chemists to know the solution-phase pK_a values of the P–H bonds in different organophosphorus, both for scientific curiosity and for practical reasons. Unfortunately, because phosphorus-centered anions are

Keywords: Organophosphorus; pK_a; DMSO; Ab initio.
* Corresponding authors. Tel.: +86 551 360 7466; fax: +86 551 360 6689 (L.L.); (Q.-X.G.);
e-mail addresses: leiliu@ustc.edu; qxguo@ustc.edu.cn

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.049

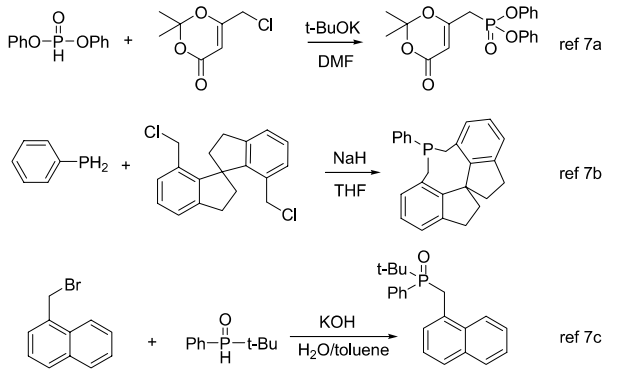


Figure 2. Some recent syntheses in which a metal phosphide reacted with an organic electrophile.

usually highly unstable species, it has been a formidable challenge to design experimental approaches to determine the pK_a's of organophosphorus. Up to now the solution-phase acidities of organophosphorus remain almost entirely unknown except for PH_3 (pK_a=29 in water); and there has not been a single pK_a value for any P–H bond in the famous Bordwell scale of acidities. Only Issleib and Kummel once reported the experimental solution-phase acidities of six phosphines in tetrahydrofuran.[8]

We recently launched a program to systematically investigate how to utilize the modern quantum-chemical methods to acquire useful, quantitative data for realistic, solution-phase organic chemistry. In the first step of the program, we developed a generally applicable, ab initio protocol to calculate the pK_a values of diverse organic acids in dimethyl sulfoxide (DMSO).[9] The first version of the protocol could reach a precision of about 2 pK_a units in the calculation of pK_a values of over 100 structurally-unrelated organic molecules. This protocol was utilized to predict the pK_a's of a variety of organosilanes in DMSO that have not been experimentally measured. In the present study, we attempted to improve our previous protocol so that it could more accurately predict the pK_a values of amines (for N–H bonds) and thiols (for S–H bonds) in DMSO that have been experimentally measured. Once this was accomplished, it would be legitimate to consider that the improved ab initio protocol was able to reliably predict the pK_a values of various organophosphorus compounds in DMSO that still remain largely unknown. The reason for this is that phosphorus is in the same group as nitrogen and in the same period as sulfur. If a method based on the first principles can successfully handle both nitrogen and sulfur, it should be able to handle phosphorus as well.

Armed with the carefully benchmarked theoretical protocol, we systematically calculated for the first time the pK_a values of various types of organophosphorus compounds in DMSO. The accuracy of these calculated values was estimated to be about 1.1 pK_a units, which is sufficient for most practical applications. With these pK_a values in hand, synthetic chemists can more rationally design the experimental conditions for the reactions that require the use of deprotonated organophosphorus. The availability of these pK_a values also enabled us to study, for the first time, some interesting topics such as the substituent effects on the pK_a values of various types of organophosphorus, and the differences between the pK_a values of organophosphorus and organic amines. Thus, it is truly valuable to have an extensive and reliable tabulation of the pK_a values for various types of organophosphorus. By supplying trustworthy and useful data that are difficult to obtain via the experiments, we also hope to better demonstrate that computational chemistry is becoming an enabling tool to make realistic predictions for synthetic organic chemistry.

2. Gas-phase acidities

Before we try to calculate the solution-phase pK_a value of an organophosphorus compound A–H, it is important to ascertain that we can reliably calculate its gas-phase acidity defined as the free energy change of the following reaction in the gas phase at 298 K, 1 atm.

$$A-H(g) \rightarrow A^-(g) + H^+(g) \quad (1)$$

However, up to now there have been only five experimental gas-phase acidity values reported for neutral organophosphorus (see Table 1), and it would not be sensible to use these five values to evaluate the performance of a particular theoretical approach. Thus, we included the gas-phase acidity data of 25 amines and 14 thiols in Table 1,[10] and we utilized the B3LYP/6-311++G(2df,p)//B3LYP/6-31+G(d) method to calculate the N–H, S–H, and P–H gas-phase acidities of these 44 compounds. In the calculation, the geometry of each species was optimized using the B3LYP/6-31+G(d) method. The electronic energy of the species was then calculated using the B3LYP/6-311++G(2df,p) method. The free energy of each species was calculated using the above electronic energy and zero-point vibrational energy, thermal corrections (0→298 K), and the entropy term obtained at the B3LYP/6-31+G(d) level (unscaled).

Comparing the experimental and theoretical gas-phase acidities, we obtained the following regression Eq. 2 (also see Fig. 3):

$$\Delta G_{exp} = \Delta G_{theor} + 0.6 \quad (r = 0.996,\ sd = 1.9,\ N = 44) \quad (2)$$

The slope of the regression equaled unity and the mean error (i.e., the intercept of the regression) was as low as 0.6 kcal/mol. The correlation coefficient (r) was 0.996 and the standard deviation (sd) was 1.9 kcal/mol for 44 compounds. Because the experimental errors of the gas-phase acidities are mostly about 2.0 kcal/mol (see Table 1), it was obvious that the theoretical predictions at the B3LYP/6-311++G(2df,p)//B3LYP/6-31+G(d) level were sufficiently accurate for N–H, S–H, and P–H gas-phase acidities.

3. Computing pK_a's of amines and thiols in DMSO

As mentioned previously, there has not been a single experimental pK_a value for organophosphorus in DMSO. Thus, it is impossible to evaluate the reliability of the theoretical predictions by comparing some of the predicted values with the corresponding experimental data. In order to

Table 1. The experimental (ΔG_{exp}) and theoretical (ΔG_{theor}) gas-phase acidities (kcal/mol)

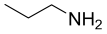
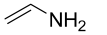
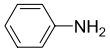
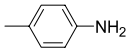
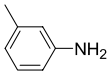
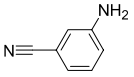
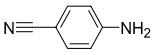
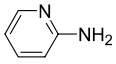
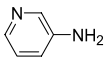
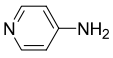
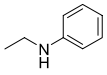
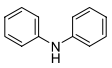
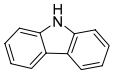
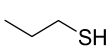
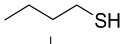
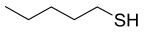
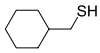
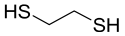
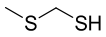
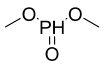
Compound	ΔG_{exp}	ΔG_{theor}
NH_3	396.9±0.4	395.5
$H_3C–NH_2$	395.7±0.7	394.5
	391.7±0.7	389.0
	391.0±3.0	389.4
	389.9±3.0	387.0
	369.6±2.0	367.3
	359.1±2.0	360.0
	360.1±2.0	361.5
	359.6±2.0	360.3
	345.7±2.0	346.4
	341.5±2.0	341.3
	355.6±2.0	355.5
	353.3±2.0	354.2
	349.8±2.0	350.9
	389.2±0.6	385.6
	387.4±2.0	384.0
	382.8±0.4	380.7
	357.5±2.0	358.1
	356.8±2.0	358.3
	343.8±2.0	344.5
	382.3±0.4	382.2
	350.9±2.0	352.6
	346.4±2.0	348.2
	341.9±2.0	343.5
	337.4±2.0	338.8
H_2S	344.4±3.0	343.8
$H_3C–SH$	350.6±2.0	349.8
	348.9±2.0	348.0
	347.9±2.0	347.3
	347.1±2.0	346.6
	347.4±2.0	347.8
	346.8±2.0	346.2

Table 1 (*continued*)

Compound	ΔG_{exp}	ΔG_{theor}
	346.2±2.0	346.5
	345.4±2.0	345.8
	346.2±2.5	348.5
	346.3±2.0	346.2
	333.8±2.0	332.3
	339.2±2.1	337.8
	343.0±4.0	340.3
PH_3	361.0±2.0	359.8
	353.0±2.3	350.7
	365.9±2.8	363.7
	331.0±3.0	330.7
	349.3±3.5	342.5

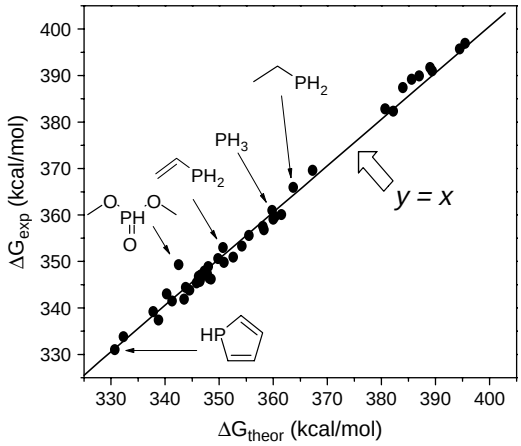


Figure 3. The correlation between the experimental and theoretical gas-phase acidities.

solve this problem we hypothesized that an ab initio method must be able to reliably handle phosphorus if the same method was known to be successful for handling both nitrogen and sulfur. The scientific basis for this hypothesis is that phosphorus is in the same group as nitrogen and in the same period as sulfur.

In Table 2 we collected a number of experimental pK_a values for amines and thiols in DMSO. Our mission was to develop an ab initio method that could accurately predict all the pK_a values in Table 2. In order to accomplish this mission, we firstly needed to derive the equations for the pK_a calculation. Thus, we considered the following proton-exchange reaction between an acid AH and aniline anion[9,11]

$$AH + C_6H_5NH^- \rightarrow A^- + C_6H_5NH_2 \quad (3)$$

Table 2. The experimental and theoretical pK_a values for 27 amines and 13 thiols in DMSO

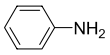
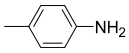
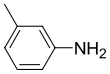
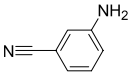
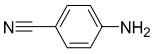
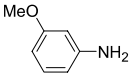
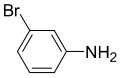
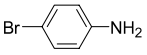
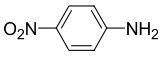
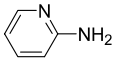
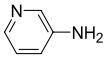
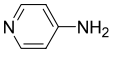
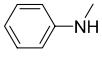
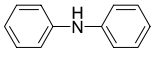
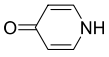
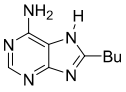
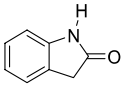
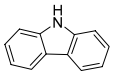
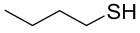
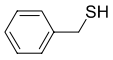
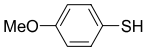
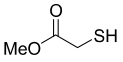
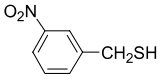
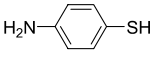
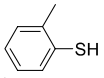
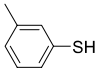
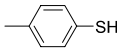
Compound	pK_a (exp)	f=1.00	f=1.05	f=1.10	f=1.15	f=1.20	f=1.25	f=1.30
	30.6	30.6	30.6	30.6	30.6	30.6	30.6	30.6
NH_3	41.0	38.6	39.0	39.3	39.7	40.1	40.5	40.8
	31.0	30.5	30.6	30.6	30.7	30.7	30.7	30.7
	31.0	30.8	31.0	31.0	31.0	31.0	31.1	31.0
	27.5	28.2	28.0	27.7	27.5	27.2	27.0	26.7
	25.3	25.7	25.5	25.2	24.9	24.6	24.3	24.0
	30.5	30.4	30.5	30.5	30.5	30.5	30.5	30.5
	28.4	29.0	28.9	28.8	28.6	28.4	28.3	28.1
	29.1	29.7	29.4	29.3	29.1	29.0	28.9	28.8
	20.9	21.9	21.6	21.4	21.0	20.8	20.4	20.0
	27.7	27.5	27.4	27.4	27.3	27.3	27.2	27.2
	28.5	28.7	28.5	28.4	28.3	28.2	28.1	27.9
	26.5	26.7	26.7	26.6	26.4	26.3	26.1	26.0
	29.5	31.2	31.3	31.2	31.3	31.2	31.2	31.1
	25.0	26.4	26.4	26.2	26.1	25.9	25.7	25.4
	44.0	41.4	41.7	41.9	42.2	42.4	42.6	42.8
	14.8	17.0	16.4	15.8	15.4	14.9	14.5	14.2
	23.0	23.6	23.6	23.5	23.6	23.5	23.5	23.5
	19.8	19.5	19.3	19.2	19.1	19.0	19.0	19.0
	13.9	13.3	12.9	12.5	12.2	11.9	11.7	11.5
	14.8	14.8	14.2	13.9	13.6	13.3	13.1	12.9
	21.0	22.2	22.0	21.9	21.8	21.6	21.5	21.3
	16.4	17.6	17.2	16.8	16.5	16.3	16.0	15.8
	14.2	14.0	13.3	12.7	12.2	11.7	11.2	10.8
	15.3	15.2	14.8	14.3	14.2	13.7	13.3	12.9

Table 2 (*continued*)

Compound	pK_a (exp)	f=1.00	f=1.05	f=1.10	f=1.15	f=1.20	f=1.25	f=1.30
	18.5	18.5	18.3	18.2	18.1	18.0	17.9	17.9
	19.9	21.5	21.3	21.1	21.0	20.8	20.6	20.4
	17.1	15.1	15.0	15.1	15.2	15.3	15.5	15.8
	17.1	14.5	14.4	14.4	14.6	14.8	15.0	15.2
	17.9	15.8	15.9	15.8	16.2	16.2	16.7	16.6
	10.3	10.7	10.4	10.1	10.0	10.0	10.0	9.9
	15.4	15.5	15.3	15.2	15.2	15.3	15.4	15.5
	11.2	12.3	12.0	11.7	11.7	11.6	11.6	11.7
	13.0	12.1	11.9	11.7	11.8	11.8	11.9	12.0
	14.2	13.8	13.5	13.3	13.2	13.1	13.0	13.0
	12.5	11.9	11.6	11.4	11.5	11.5	11.6	11.7
	11.4	14.4	14.3	14.2	14.2	14.2	14.2	14.2
	10.7	11.4	11.2	11.0	10.9	10.9	10.8	10.8
	10.6	10.9	10.6	10.4	10.3	10.3	10.3	10.3
	10.8	11.1	10.8	10.5	10.5	10.4	10.5	10.5
r	—	0.9898	0.9907	0.9915	0.9924	0.9927	0.9929	0.9926
sd	—	1.213	1.147	1.122	1.087	1.106	1.128	1.183

If the free energy change of the above reaction in the DMSO solution was defined as $\Delta G_{exchange}$, the pK_a of the acid AH could be calculated by Eq. 4.

$$pK_a(AH) = pK_a(C_6H_5NH_2) + \frac{\Delta G_{exchange}}{2.303 \times RT} \quad (4)$$

It was noteworthy that here we chose aniline for the proton exchange reaction because we wished to develop a method that was the most effective for amines, thiols, and phosphines. Since the chemical properties of nitrogen, phosphorus, and sulfur are relatively close to each other in the periodic table, we envisaged that it was probably more sensible to calculate $\Delta G_{exchange}$ as a quantity relative to a well-defined nitrogen- or sulfur-containing compound such as aniline.

The experimental pK_a value for aniline is 30.6.[12] It is also known from the previous studies that the gas-phase free energy change of Eq. 3 can be fairly accurately calculated.[8,10] Thus, whether the theory can reproduce the experimental pK_a's mainly relies on the quality of the solvation energy calculations. In order to attain maximum accuracy, herein we utilized the most recent version of the polarized continuum model, that is, IEF-PCM (integral equation formalism PCM),[13] to calculate the solvation free energies. The central idea of this solvation model is the construction of a solvent-inaccessible cavity in which the solute molecule resides.[14] In practice, this solvent-inaccessible cavity is built as a union of overlapping spheres entered on the nuclei of atoms or chemical groups. The sphere radii are usually proportional to the atomic radii with a scale factor (f). For each combination of solvation model, scale of atomic radii, and solvent, the f value has to be specifically optimized.

In the present study, we chose Bondi's atomic radii[15] and the solvent here was DMSO. Our present mission was to find the optimal f value so that the standard deviation between the experimental pK_a's listed in Table 2 and the corresponding theoretical predictions reached the minimum. Using the IEF-PCM/Bondi model, we examined different f

values (f=1.00, 1.05, 1.10, 1.15, 1.20, 1.25, 1.30) in the calculation of pK_a's in DMSO. Comparing the experimental data and the theoretical predictions (see Table 2), we found that the predicted results in the present study were not very sensitive to the f values. Nonetheless, it was determined that a scale factor of 1.15 was the most desirable. The standard deviation and correlation coefficient between the theoretical and experimental pK_a values using this scale factor were 1.1 pK_a unit and 0.992 for 27 amines and 13 thiols, respectively (see Fig. 4).

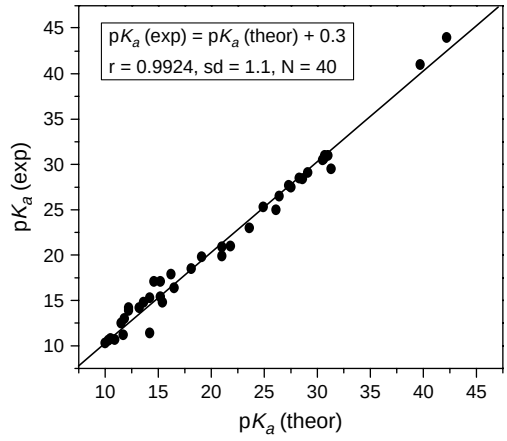


Figure 4. The correlation between the experimental and theoretical pK_a values for 27 amines and 13 thiols (f=1.15).

4. Predicting pK_a's of organophosphorus in DMSO

Armed with the carefully benchmarked theoretical method that can predict the pK_a values of diverse amines and thiols with a precision of 1.1 pK_a unit, we systematically calculated the pK_a values of various types of organophosphorus compounds in DMSO (see Table 3). Because phosphorus is in the same group as nitrogen and in the same period as sulfur, we assumed that the error bar for the predicted pK_a values listed in Table 3 was also about 1.1 pK_a unit.

It was noteworthy that the predicted pK_a values in DMSO could now be compared with the experimental pK values in THF,[8] as a result of the recent finding by Streitwieser et al. that there was a good correlation between the pK's in THF with the absolute pK_a's in DMSO:[16]

$$pK(\text{THF}) = -0.963 + 1.046\ pK_a(\text{DMSO}) \quad (5)$$

Using the above empirical equation and the experimental pK values in THF (see Table 3), we calculated that the corresponding 'experimental' pK_a values in DMSO should be 35.6, 35.0, 33.1, 31.8, 24.3, and 21.7 for di-*tert*-butylphosphine, dicyclohexylphosphine, diethylphosphine, cyclohexylphosphine, phenylphosphine, and diphenylphosphine, respectively. It was gratifying to see that these values were in good agreement with our current predictions, which are 36.1, 34.6, 34.9, 29.6, 22.4, and 22.9, respectively. This confirmed that the predicted pK_a values in Table 3 were fairly accurate.

Thus, all the above analyses made us confident that we had constructed the first scale of reliable pK_a values for diverse organophosphorus compounds in DMSO (see Fig. 5). On the basis of this scale of data, it was found that the pK_a values of organophosphorus ranged widely from about +9 to +37. Since the pK_a value of NH_3 is 41.0, it is obvious that essentially all the organophosphorus can be deprotonated by the strong bases such as $NaNH_2$, $NaN(SiMe)_2$, $LiN(i\text{-}Pr)_2$, and *n*-BuLi. Except for monoalkylphosphine (p$K_a \approx 30$), dialkylphophines (p$K_a \approx 35$), phosphonous diamides (p$K_a \approx 37$), and phosphonites (p$K_a \approx 33$), most of organophosphorus can be deprotonated by the modestly strong bases such as *t*-BuOK (pK_a of *t*-BuOH is 32.2) and EtONa (pK_a of EtOH is 29.8). Finally, almost no organophosphorus can be deprotonated by the weak bases such as Et_3N (pK_a of Et_3NH^+ is 9.0) and pyridine (pK_a of pyridinium is 4.1).

5. Structural–properties relationships

5.1. Trivalent organophosphorus

Trivalent organophosphorus that possess a P–H bond include primary phosphines, secondary phosphines, phosphinites, phosphonites, phosphinous amides, and phosphonous diamides. The pK_a values of these compounds vary from 22.4 to 36.5. These values are lower than the pK_a's of their nitrogen counterparts (see Fig. 6).

The pK_a of PH_3 is 24.1 in DMSO. This value is about 16 pK_a units lower than that of NH_3 (39.7). When an α-substituent is introduced, the pK_a values of $MePH_2$ (29.6), $MeOPH_2$ (27.3), and Me_2NPH_2 (28.2) are about 6, 3, and 4 pK_a units higher than that of PH_3. In comparison, the pK_a value of $MeNH_2$ (42.9) is only 3.2 pK_a unit higher than that of NH_3, while the pK_a values of $MeONH_2$ (36.5), and Me_2NNH_2 (35.9) are about 5 pK_a units lower than that of NH_3.

Change of the methyl groups to the phenyl groups in the α-substituents decrease the pK_a values of both phosphines and amines. From $MePH_2$ to $PhPH_2$ the pK_a value decreased by 7.2 pK_a units, while from $MeNH_2$ to $PhNH_2$ the pK_a value decreased by 12.3 pK_a units. From $MeOPH_2$ to $PhOPH_2$ the pK_a value decreases by 1.2 pK_a units, while from $MeONH_2$ to $PhONH_2$ the pK_a value decreased by 3.2 pK_a units. From Me_2NNH_2 to Ph_2NNH_2 the pK_a value increased by 0.6 pK_a units, while from Me_2NPH_2 to Ph_2NPH_2 the pK_a value remains the same.

5.2. Pentavalent organophosphorus

Pentavalent organophosphorus that possess a P–H bond include phosphine oxides, phosphinates, and phosphonates. These compounds in solution exist as an equilibrium mixture of two tautomeric forms (Scheme 1), a tetracoordinated P(V) form and a tricoordinated P(III) form. Previous studies have indicated that these equilibria are usually heavily shifted to the left.[17] The pK_a values of pentavalent organophosphorus vary from 9.0 to 26.9. It is not difficult to understand that the pK_a values of pentavalent organophosphorus are usually much lower than the pK_a values of trivalent organophosphorus. Furthermore, the pK_a's of different pentavalent organophosphorus decrease

Table 3. Theoretical gas-phase acidities (kcal/mol) and pK_a values in DMSO for diverse types of organophosphorus[a]

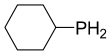
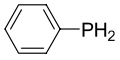
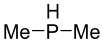
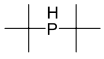
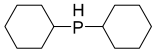
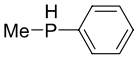
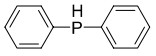
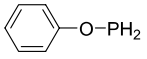
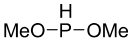
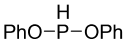
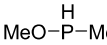
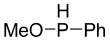
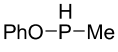
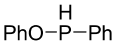
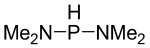
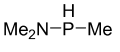
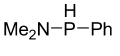
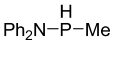
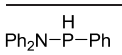
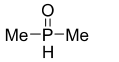
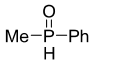
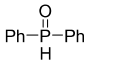
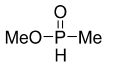
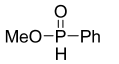
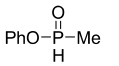
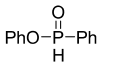
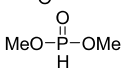
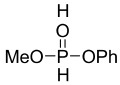
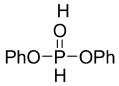
Compound	Gas-phase acidity	pK_a
PH_3	359.8	24.1
$Me–PH_2$	366.2	29.6
	363.7	29.3
	362.6	29.3
	361.7	29.8
	361.8	29.6 (32.3)
	346.9	22.4 (24.5)
	370.9	34.8
	367.3	34.9 (33.7)
	365.1	35.0
	363.8	36.1 (36.3)
	364.0	34.6 (35.7)
	352.6	26.7
	343.7	22.9 (21.7)
	368.8	35.2
$MeO–PH_2$	360.8	27.3
	352.0	26.1
	367.1	33.6
	350.4	28.2
	362.5	30.6
	368.0	33.7
	349.9	26.1
	357.6	31.2
	342.0	24.0
$Me_2N–PH_2$	359.7	28.2
$Ph_2N–PH_2$	347.6	28.2
	366.7	36.1
	361.3	31.7
	368.9	36.5
	352.1	29.1
	352.5	32.1

Table 3 (*continued*)

Compound	Gas-phase acidity	pK_a
	340.0	23.7
	353.4	26.9
	345.7	23.9
	337.8	20.6
	352.6	26.9
	345.4	22.0
	342.2	20.3
	339.5	20.7
	334.6	17.9
	347.4	23.3
	342.5	18.4
	330.7	13.9
	324.0	9.0
	340.9	17.3
	330.7	9.9
	329.8	12.9
	330.0	15.2
	339.3	21.7
	339.8	22.3
	343.2	23.8
	337.7	20.7

[a] The values in the parentheses are the experimental pK values in THF reported in Ref. 7.

roughly in the order: phosphine oxides > phosphinates > phosphonates.

The pK_a values for dimethylphosphine oxide is 26.9 (see Fig. 7). Changing one of the methyl groups to phenyl lowers the pK_a to 23.9. Changing both of the methyl groups to phenyl further lowers the pK_a to 20.6. Similar substituent

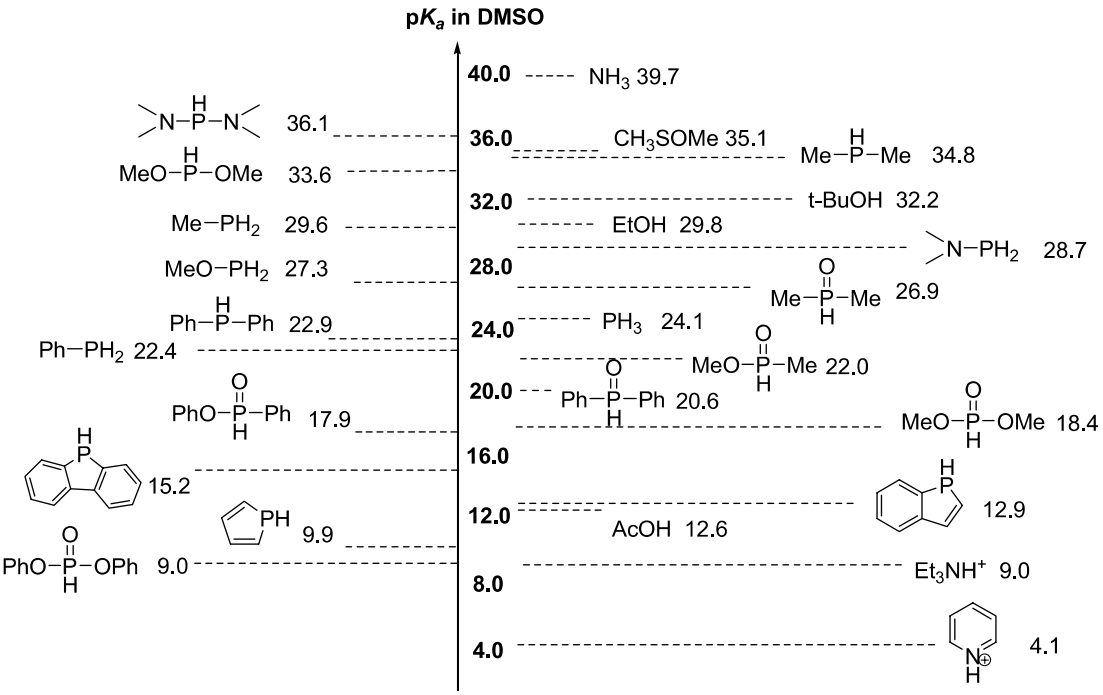


Figure 5. A scale of pK_a values for organophosphorus in DMSO.

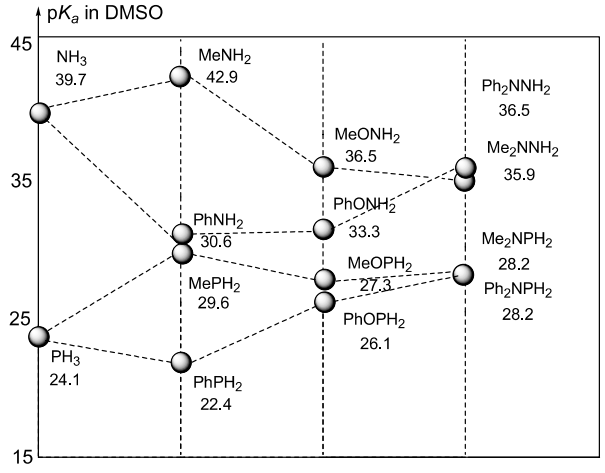


Figure 6. Comparing the pK_a values of trivalent organophosphorus and amines in DMSO.

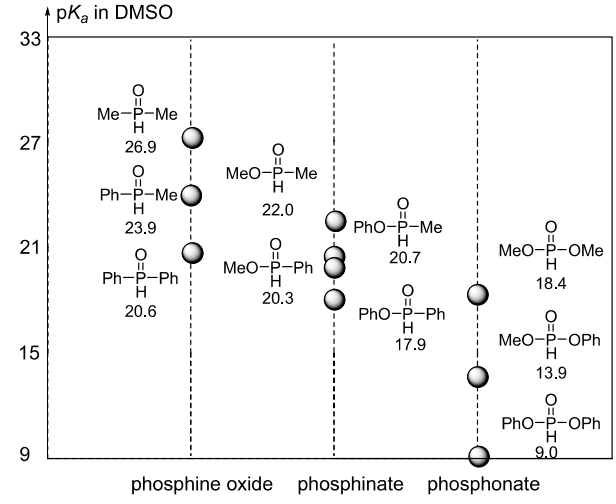
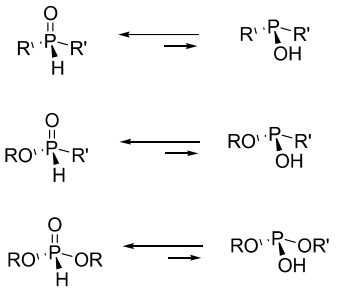


Figure 7. The pK_a values of pentavalent organophosphorus in DMSO.



Scheme 1.

effects are seen for phosphonates. Thus, changing one of the methyl groups in dimethyl phosphonate to phenyl lowers the pK_a from 18.4 to 13.9, while changing both of the methyl groups to phenyl further lowers the pK_a to 9.0.

In contrast to phosphine oxides and phosphonates, the pK_a values of phosphinates are much less sensitive to the substituents. The highest pK_a value (22.0) is predicted for methyl methylphosphinate, while the lowest pK_a value (17.9) is predicted for phenyl phenylphosphinate. The pK_a value of methyl phenylphosphinate is predicted to be slightly lower than that of methyl methylphosphinate by 1.3 pK_a unit. The pK_a value of phenyl phenylphosphinate is also predicted to be slightly lower than that of methyl phenylphosphinate by 2.8 pK_a unit. The pK_a values of methyl phenylphosphinate (20.7) and phenyl methylphosphinate (20.3) are very close. Nonetheless, it is important to remember that the error bar of the predicted pK_a values is about 1.1 pK_a unit.

5.3. Phosphorus heterocycles

Phosphorus heterocycles are peculiar compounds that have interested physical organic chemists for decades.[18] Very recently, phosphorus heterocycles have also become interesting to synthetic chemists as some of them, such as phosphabenzenes and phosphaferrocenes, have been found to be versatile ligands in highly efficient catalysts.[19] In the present study, we have predicted, for the first time, the pK_a values of a few interesting phosphorus heterocycles (see Table 3). The pK_a values of some phosphorus heterocycles, such as 9,10-dihydroacridophosphine and its derivatives (pK_a=20.2–23.3), are very close to their acyclic counterparts (e.g., diphenylphosphine, pK_a=22.9). However, the pK_a values of two phosphorus heterocycles (i.e., 1*H*-phosphole, pK_a=9.9; and 1*H*-phosphindole, pK_a=12.9) are remarkably lower than almost all the other organophosphorus.

The fact that the pK_a's of 1*H*-phosphole (9.9) and 1*H*-phosphindole (12.9) are about 10–13 pK_a units lower than that of diphenylphosphine (22.9) is actually surprising, because for the nitrogen cases the pK_a's of 1*H*-pyrrole (23.0) and 1*H*-indole (21.9) are only 2–3 pK_a units lower than that of diphenylamine (25.0). A careful examination of the optimized structure of 1*H*-phosphole reveals that the molecule is not a planar species (see Fig. 8). However, after deprotonation the phosphol-1-ide anion becomes planar. As recently discussed by Nguyen et al.,[20] 1*H*-pyrrole is probably not aromatic but the phosphol-1-ide anion is. Thus, the exceptionally low pK_a of 1*H*-phosphole is due to the aromatization effect during deprotonation. The same explanation can be applied to 1*H*-phosphindole, because before deprotonation this molecule is not planar, either (see Fig. 8). It is worth noting that Nief et al. once produced the phosphindolyl anion from 1-phenylphosphindole.[21] From the ^{31}P NMR analysis they found that the phosphindolyl anion had a higher basicity than the phospholyl anion. This experimental finding is consistent with our theoretical predictions, because pK_a of 1*H*-phosphindole (12.9) is calculated to be higher than that of 1*H*-phosphole (9.9).

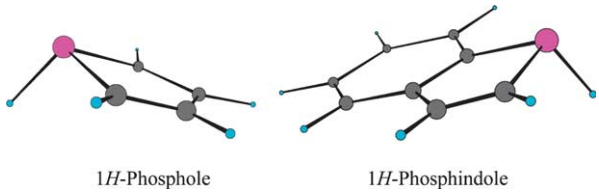


Figure 8. The optimized structures of 1*H*-phosphole and 1*H*-phosphindole.

6. Summary

A first-principle theoretical protocol was developed, which could successfully predict the pK_a values of a number of amines and thiols in DMSO with a precision of about 1.1 pK_a unit. Using this protocol we calculated the pK_a values of diverse types of organophosphorus compounds in DMSO. The accuracy of these predicted values was estimated to be about 1.1 pK_a because phosphorus is in the same group as nitrogen and in the same period as sulfur. The theoretical predictions were also consistent with all the available experimental data. Thus, a scale of reliable pK_a values was constructed for the first time for organophosphorus. These pK_a values will be helpful to synthetic chemists who need to design the experimental conditions for handling deprotonated organophosphorus. On the basis of these pK_a values we have also studied, for the first time, some interesting topics such as the substituent effects on the pK_a values of various types of organophosphorus, and the differences between the pK_a values of organophosphorus and organic amines.

7. Computational methodology

All of the theoretical calculations were conducted using the Omega programs[22] and the Gaussian 03 programs.[23] The conformation search for each compound was carried out by using Omega, which used rule-based torsion driving to generate multiple conformations under the Merck molecular force field. These conformations were then used as initial structures for the B3LYP/6-31G(d) calculations. The conformation with the lowest energy was used for all the following calculations.The gas-phase energy calculations were conducted using the standard B3LYP/6-311++G(2df,2p)//B3LYP/6-31G(d) method. The PCM solvation model was used in its integral equation formalism (IEF-PCM)[13] to calculate the solvation free energies in DMSO. Although it was demonstrated that the change of geometry by the solvation effect was usually not significant,[14] we performed geometry optimizations in the DMSO solution to calculate the solvation free energies. All the IEF-PCM calculations were performed at B3LYP/6-311++G(2df,2p) level (version=MATRIX INVERSION, cavity=PENTAKISDODECAHEDRA, Icomp=4, TSNUM=60, TSARE=0.4, radii=Bondi, alpha=1.00–1.30).

Acknowledgements

This study was supported by the National Natural Science Foundation of China (No. 20332020 and No. 20472079). We also thank the USTC Supercomputer Center.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.049. The cartesian coordinates of the optimized molecules, the calculated electronic energies, thermal corrections to Gibbs free energies, and solvation free energies.

References and notes

1. (a) Corbridge, D. E. C. *Phosphorus: An Outline of its Chemistry, Biochemistry and Technology*, 3rd ed.; Elsevier: New York, 1985. (b) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley: New York, 2000. (c) Vereshchagina, Ya. A.; Ishmaeva, E. A.; Zverev, V. V. *Russ. Chem. Rev.* **2005**, *74*, 297–315.
2. (a) Yuan, C.-Y. *Chin. J. Org. Chem.* **2001**, *21*, 862–868. (b) Morales-Rojas, H.; Moss, R. A. *Chem. Rev.* **2002**, *102*, 2497–2521. (c) Wu, J.; Hudson, H. R. *Chin. J. Chem.* **2002**, *20*, 1598–1601.

3. (a) Burd, P. F.; Ferry, C. B.; Smith, J. W. *British J. Pharm.* **1989**, *98*, 243–251. (b) Kovacic, P. *Curr. Med. Chem.* **2003**, *10*, 2705–2709. (c) Casida, J. E.; Quistad, G. B. *Chem. Res. Toxicol.* **2004**, *17*, 983–998. (d) Zhao, J.-S.; Wang, B.; Dai, Z.-X.; Wang, X.-D.; Kong, L.-R.; Wang, L.-S. *Chin. Sci. Bull.* **2004**, *49*, 240–245. (e) Wang, Z.-Y.; Han, X.-Y.; Wang, L.-S.; Zhai, Z.-C. *Chin. Sci. Bull.* **2004**, *49*, 1437–1441.
4. (a) Lu, X.-Y.; Zhang, C.-M.; Xu, Z.-R. *Acc. Chem. Res.* **2001**, *34*, 535–544. (b) Du, Y.-S.; Feng, J.-Q.; Yu, Y.-H. *J. Org. Chem.* **2002**, *67*, 8901–8905. (c) Lu, C.; Lu, X.-Y. *Org. Lett.* **2002**, *4*, 4677–4679. (d) Du, Y.-S.; Lu, X.-Y.; Zhang, C.-M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1035–1037. (e) Du, Y.-S.; Lu, X.-Y. *J. Org. Chem.* **2003**, *68*, 6463–6465. (f) Lu, C.; Lu, X.-Y. *Tetrahedron* **2004**, *60*, 6575–6577. (g) Du, Y.-S.; Feng, J.-Q.; Lu, X.-Y. *Org. Lett.* **2005**, *7*, 1987–1989. (h) Koehn, M.; Breinbauer, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 3106–3109. (i) Vedejs, E. *J. Org. Chem.* **2004**, *69*, 5159–5167. (j) Che, C.; Zhang, Z. N.; Huang, G. L.; Wang, X. X.; Qin, Z. H. *Chin. Chem. Lett.* **2004**, *15*, 675–678.
5. (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3070. (b) Xu, L.-W.; Xia, C.-G.; Sun, W.; Li, F.-W.; Wang, H.-W. *Chin. J. Org. Chem.* **2003**, *23*, 919–932. (c) Grushin, V. V. *Chem. Rev.* **2004**, *104*, 1629–1662. (d) Zhang, T.-Z.; Xu, L.-J.; Sun, W.-H. *Prog. Chem.* **2004**, *16*, 90–98.
6. *Organophosphorus Reagents*; Murphy, P. J., Ed.; Oxford University Press: London, 2004.
7. (a) Ji, N.; Rosen, B. M.; Myers, A. G. *Org. Lett.* **2004**, *6*, 4551–4553. (b) Zhu, S.-F.; Yang, Y.; Wang, L.-X.; Liu, B.; Zhou, Q.-L. *Org. Lett.* **2005**, *7*, 2333–2335. (c) Lebel, H.; Morin, S.; Paquet, V. *Org. Lett.* **2003**, *5*, 2347–2349.
8. (a) Issleib, K.; Kümmel, R. *J. Organomet. Chem.* **1965**, *3*, 84–91. (b) It is important to note that the solution-phase acidities reported by Issleib and Kummel are not pK_a's, but pK only pK_a should correspond to free ion acidity in the solution. However, in Issleib and Kummel's experiments the phosphide anions actually existed in a contact ion pair with lithium cation.
9. Fu, Y.; Liu, L.; Li, R.-Q.; Liu, R.; Guo, Q.-X. *J. Am. Chem. Soc.* **2004**, *126*, 814–822.
10. Gas-phase acidities are taken from NIST Standard Reference Database 69, March 1998 Release: *NIST Chemistry WebBook* (data compiled by J. E. Bartmess).
11. For other pK_a calculation methods, see: (a) da Silva, C. O.; da Silva, E. C.; Nascimento, M. A. C. *J. Phys. Chem. A* **1999**, *103*, 11194–11199. (b) da Silva, C. O.; da Silva, E. C.; Nascimento, M. A. C. *J. Phys. Chem. A* **2000**, *104*, 2402–2409. (c) Liptak, M. D.; Shields, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 7314–7319. (d) Toth, A. M.; Liptak, M. D.; Phillips, D. L.; Shields, G. C. *J. Chem. Phys.* **2001**, *114*, 4595–4606. (e) Liptak, M.; Shields, G. C. *Int. J. Quantum Chem.* **2001**, *85*, 727–741. (f) Liptak, M. D.; Gross, K. C.; Seybold, P. G.; Feldgus, S.; Shields, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6421–6427. (g) Namazian, M.; Heidary, H. *THEOCHEM* **2003**, *620*, 257–263. (h) Saracino, G. A. A.; Improta, R.; Barone, V. *Chem. Phys. Lett.* **2003**, *373*, 411–415. (i) Pliego, J. R. *Chem. Phys. Lett.* **2003**, *367*, 145–149. (j) Klamt, A.; Eckert, F.; Diedenhofen, M.; Beck, M. E. *J. Phys. Chem. A* **2003**, *107*, 9380–9386. (k) Namazian, M.; Halvani, S.; Noorbala, M. R. *THEOCHEM* **2004**, *711*, 13–18. (l) Magill, A. M.; Yates, B. F. *Aust. J. Chem.* **2004**, *57*, 1205–1210. (m) am Busch, M. S.; Kanpp, E.-W. *ChemPhysChem* **2004**, *5*, 1513–1522. (n) Soriano, E.; Cerdan, S.; Ballesteros, P. *THEOCHEM* **2004**, *684*, 121–128. (o) Barone, V.; Improta, R.; Rega, N. *Theor. Chem. Acc.* **2004**, *111*, 237–245. (p) Qi, Y.-H.; Zhang, Q.-Y.; Luo, C.-C.; Wang, J.; Xu, L. *Chem. J. Chin. Univ.* **2004**, *25*, 1100–1103. (q) De Abreu, H. A.; De Almeida, W. B.; Duarte, H. A. *Chem. Phys. Lett.* **2004**, *383*, 47–52. (r) Almerindo, G. I.; Tondo, D. W.; Pliego, J. R., Jr. *J. Phys. Chem. A* **2004**, *108*, 166–171. (s) Nakamura, S.; Hirao, H.; Ohwada, T. *J. Org. Chem.* **2004**, *69*, 4309–4316. (t) Murlowska, K.; Sadlej-Sosnowska, N. *J. Phys. Chem. A* **2005**, *109*, 5590–5595. (u) Han, J.; Deming, R. L.; Tao, F.-M. *J. Phys. Chem. A* **2005**, *109*, 1159–1167. (v) Gao, D.; Svoronos, P.; Wong, P. K.; Maddalena, D.; Hwang, J.; Walker, H. *J. Phys. Chem. A* **2005**, *109*, 10776–10785. (w) Wang, X.; Li, S.-H.; Jiang, Y.-S. *J. Phys. Chem. A* **2005**, *109*, 10770–10775. (x) Philips, D. L.; Zhao, C.; Wang, D. *J. Phys. Chem. A* **2005**, *109*, 9653–9673. (y) Eckert, F.; Klamt, A. *J. Comput. Chem.* **2006**, *27*, 11–19.
12. Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463 and references therein.
13. Cossi, M.; Scalmani, G.; Rega, N.; Barone, V. *J. Chem. Phys.* **2002**, *117*, 43–54.
14. Cramer, C. J.; Truhlar, D. G. *Chem. Rev.* **1999**, *99*, 2161–2200.
15. Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441–451.
16. Streitwieser, A.; Wang, D. Z.; Stratakis, M.; Facchetti, A.; Gareyev, R.; Abbotto, A.; Krom, J. A.; Kilway, K. V. *Can. J. Chem.* **1998**, *76*, 765–769 and references therein.
17. Stawinski, J.; Kraszewski, A. *Acc. Chem. Res.* **2002**, *35*, 952–960.
18. Nyulaszi, L. *Chem. Rev.* **2001**, *101*, 1229–1246.
19. Weber, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 563–572.
20. Delaere, D.; Pham-Tran, N.-N.; Nguyen, M. T. *J. Phys. Chem. A* **2003**, *107*, 7514–7523.
21. Nief, F.; Charrier, C.; Mathey, F.; Simalty, M. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1982**, *13*, 259–267.
22. Boström, J. *J. Comput. Aided Mol. Des.* **2002**, *15*, 1137–1152.
23. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, Revision C. 02; Gaussian, Inc.: Pittsburgh, PA, 2003.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 62 (2006) 4463–4473

Transformations of lignans. Part 11: Oxidation of diphyllin with hypervalent iodine reagents and reductive reactions of a resulting 1-methoxy-1-aryl-4-oxonaphthalene lactone

R. Venkateswarlu,[a,*] C. Kamakshi,[a] P. V. Subhash,[a,†] S. G. A. Moinuddin,[a,‡] D. Rama Sekhara Reddy,[a] R. S. Ward,[b,*] A. Pelter,[b] T. Gelbrich,[c] M. B. Hursthouse,[c] S. J. Coles[c] and M. E. Light[c]

[a]*Department of Organic Chemistry, Andhra University, Visakhapatnam 530 003, India*
[b]*Department of Chemistry, University of Wales Swansea, Singleton Park, Swansea SA2 8PP, UK*
[c]*EPSRC National Crystallography Service, School of Chemistry, University of Southampton, Southampton SO17 1BJ, UK*

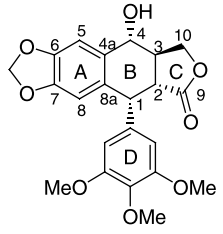
Received 23 November 2005; revised 31 January 2006; accepted 16 February 2006

Available online 10 March 2006

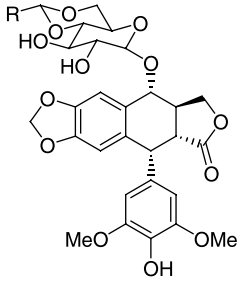
Abstract—Treatment of diphyllin **4** with phenyliodonium diacetate (PIDA) in methanol affords a 1-methoxy-1-aryl-4-oxonaphthalene lactone **6**. Reduction of **6** with lithium aluminium hydride yields, inter alia, 3,4-dihydrodiphyllin **13**, while reaction with sodium in ethanol yields **8** as a major product. These reactions illustrate that selective oxidation followed by reduction provides a facile route for the conversion of a 1-arylnaphthalene lactone to novel functionalised naphthalene and dihydronaphthalene derivatives. Of particular interest is that the oxidation indirectly activates the methylene position (C-10) of the γ-lactone, which may then potentially be substituted to give a new series of lignans. Reaction of **6** with hydroxylamine and benzyloxyamine also proceeds by way of initial attack at C-10.

1. Introduction

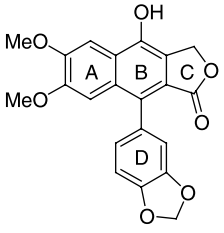
The anti-cancer properties of lignans such as podophyllotoxin **1** and its derivatives etoposide **2** and teniposide **3**, have prompted studies of their synthetic transformations[1,2] and biological activities.[3] Structure–activity relationship studies have revealed that di- and tetrahydronaphthalenes having a *trans*-lactone and a β-hydroxyl at C-4 have high therapeutic indices in tests for anti-neoplastic and anti-viral effects.[4] Although the conversion of di- and tetrahydronaphthalene lignans to naphthalene derivatives is facile,[5] the reduction of naphthalene lignans to the corresponding di- and tetrahydro derivatives is more difficult to accomplish.



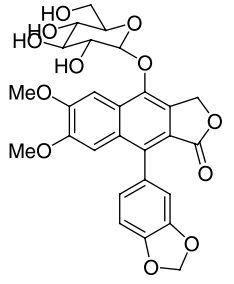
1



2 R = CH_3
3 R = 2-thienyl



4



5

Keywords: Lignans; Oxidative nucleophilic substitutions; Diphyllin; Synthesis; 3,4-Dihydrodiphyllin; Oxazinone; Benzyloxyoxime.
* Corresponding authors. Tel.: +91 891 2575179; fax: +91 891 2525611 (R.V.); tel.: +44 1792 295274; fax: +44 1792 295747 (R.S.W); e-mail addresses: rvorgchem_au@yahoo.com; r.s.ward@swan.ac.uk
† Present address: Universite Louis Pasteur Strasbourg, F-67401 Illkrich-Graffenstaden, France.
‡ Present address: Institute of Biological Chemistry, Washington State University, Pullman, WA 99164-6340, USA.

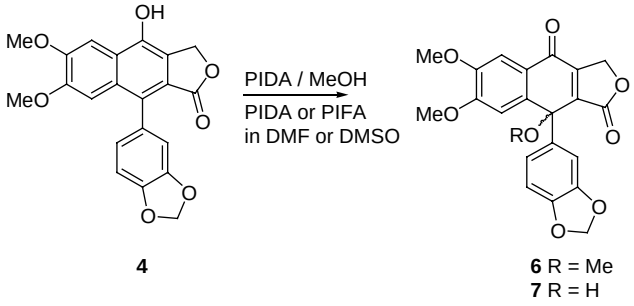
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.050

We have been studying the reactions of lignans in a bid to uncover novel chemistry that has been overlaid by the relative ease of structure establishment by modern physical methods.[6–14] A further general interest is the oxidation of phenols with hypervalent iodine compounds[15–17] and the possible mechanism of such reactions.[18] Drawing these interests together, we have previously reported the reactions of lignans of the dibenzylbutyrolactone series with phenyliodonium diacetate (PIDA) and phenyliodonium bis-trifluoroacetate (PIFA).[19,20] We have now used PIDA and PIFA to oxidise diphyllin **4**, a lignan isolated along with its glycoside cleistanthin **5** from *Cleistanthus collinus*,[21] and the result of that reaction and the transformations of the product are presented below.

2. Results and discussion

2.1. Oxidation of diphyllin 4 with PIDA or PIFA

Treatment of diphyllin **4** with 1 equiv of PIDA in dry methanol at room temperature for 1 h produced in 80% yield a yellow crystalline solid **6**, mp 230 °C, $C_{22}H_{18}O_8$ (Scheme 1). Its UV spectrum showed absorption maxima at 290 and 246 nm and its IR had peaks at 1740 (γ-lactone), 1702 (C=O) and 1600 cm^{-1}. In its ^1H NMR spectrum five aromatic proton signals were observed at δ 7.63s, 6.83s, 6.91d (J=1.9 Hz), 6.68d (J=8.3 Hz) and 6.81dd (J=1.9, 8.3 Hz), three of which exhibited the typical couplings of a 3,4-disubstituted pendant aryl group. Its ^1H NMR spectrum further showed an aliphatic methoxyl at δ 3.16 in addition to two aromatic methoxyls at δ 3.88 and 4.01. The ^{13}C NMR spectrum revealed the presence of a ketone carbonyl at δ 179.6 in addition to the lactone carbonyl at δ 168.8 and an aliphatic signal at δ 76.9, which could be assigned to a quaternary carbon (C-1) bearing a methoxyl substituent.



4 **6** R = Me **7** R = H

Scheme 1.

The presence of an aliphatic methoxyl and conjugated carbonyl in **6** can be explained by oxidation of the phenolic hydroxyl of diphyllin **4** followed by nucleophilic attack by methanol at C-1 (*para* to the phenolic group) to form the 1-methoxy-1-aryl-4-oxonaphthalene lactone **6** and this structure was confirmed by X-ray analysis (Fig. 1). This product was exactly as expected based upon our previous work and our calculations on the mechanism of the reaction.[18]

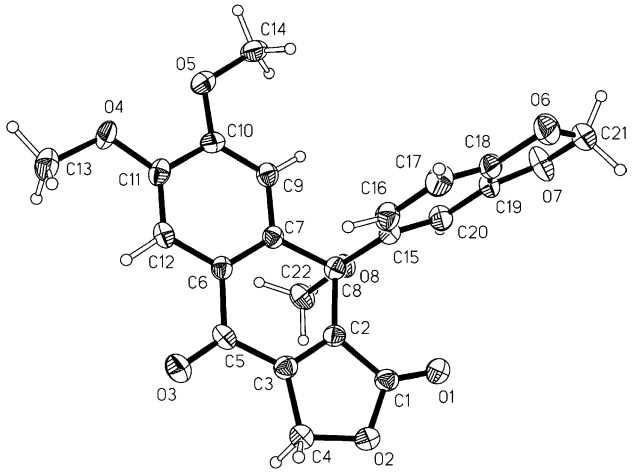
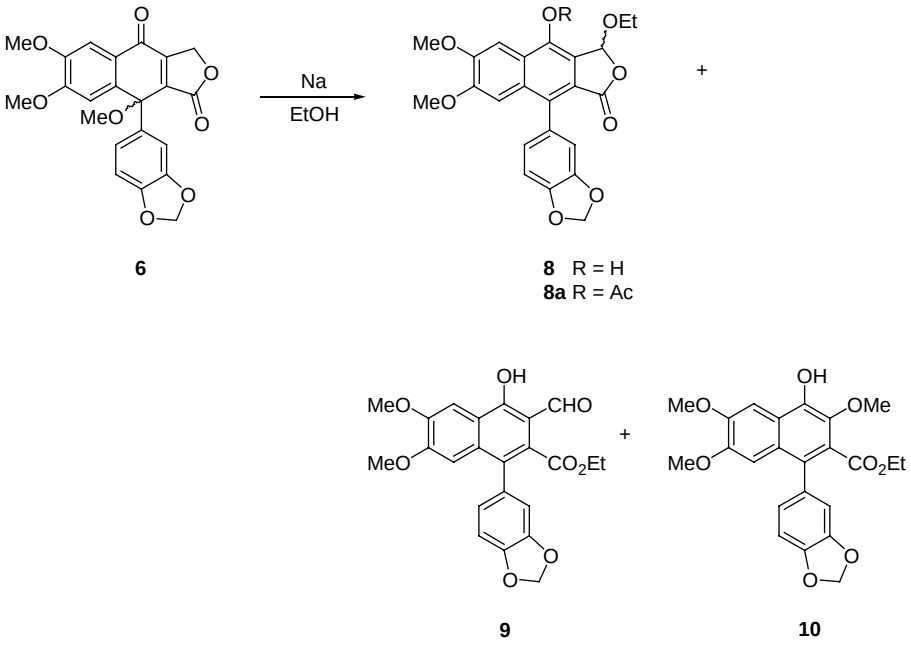


Figure 1. Structure of **6**.

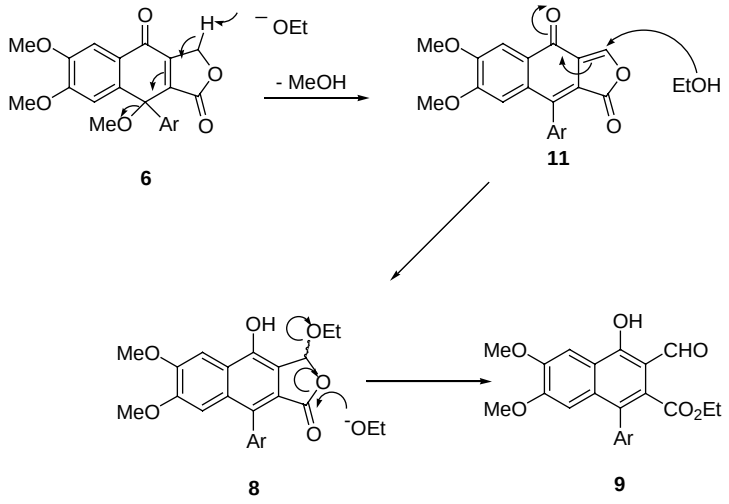
Treatment of diphyllin **4** with 1 equiv of PIDA or PIFA in DMF or DMSO at room temperature for 1 h, gave a pale yellow amorphous powder **7**, mp 210 °C, that had the molecular formula $C_{21}H_{16}O_8$. Compound **7** had almost identical spectral properties to **6** except for replacement of the methoxyl group at C-1 by a hydroxyl group.

2.2. Reaction of 6 with sodium in ethanol

Treatment of **6** with 1 equiv of sodium in ethanol gave a mixture of three compounds **8**, **9**, and **10** (Scheme 2). Compound **8** was obtained in 62% yield as a crystalline solid, mp 177 °C, $C_{23}H_{20}O_8$. Its ^1H NMR spectrum revealed two singlets at δ 6.48 and 6.45 besides the five aromatic protons. The singlet at δ 6.45 disappeared on D_2O exchange indicating the presence of a phenolic OH. The ^1H NMR spectrum also contained two one-proton multiplets at δ 4.03 and 3.90 and a double triplet for three protons at δ 1.37 (J=1.2, 7.0 Hz) indicating the presence of an OEt group. The one proton singlet at δ 6.48, which replaced the signals due to the lactone methylene in **6** suggested that an ethoxy group has been introduced at C-10, the lactone methylene position. The ^{13}C NMR spectrum of **8** lacked the carbonyl signal that in **6** showed at δ 179.6 as well as the quaternary carbon signal at δ 76.9, instead showing a pattern of carbon signals similar to that of diphyllin. Furthermore, the presence of a carbon signal at δ 99.1 in **8**, in place of the carbon signal of the lactone methylene at δ 67.9 in **6**, indicated that under nucleophilic conditions aromatisation and substitution into the γ-lactone at C-10 had both occurred to produce 10-ethoxydiphyllin **8** (Scheme 3). Compound **8** gave a monoacetate **8a**, mp 220 °C, having the molecular formula $C_{25}H_{24}O_9$. The fact that none of the other signals was affected by the introduction of the acetyl group confirms that the OH group is phenolic as in diphyllin **4**. The production of **8** can be explained (Scheme 3) by the production of key intermediate **11** by facile elimination followed by attack by ethanol on the β position (C-10) of the enone with concomitant aromatization. It is fascinating to note that by oxidation of ring B, the methylene position of the γ-lactone has been



Scheme 2.



Scheme 3.

activated to nucleophilic substitution. This route opens the way to the production, in good yields, of a wide variety of related compounds substituted at C-10 in the γ-lactone ring. It is noteworthy that there is no overall reduction in the process leading from **6** to **8**.

Compound **9** was obtained in 10% yield as orange crystals, mp 122 °C, and had molecular formula $C_{23}H_{20}O_8$. Its ^{1}H NMR spectrum showed characteristic signals for a strongly chelated phenolic hydroxyl group at δ 13.38s and an aldehyde at 9.95s, as well as a multiplet at δ 4.03 and triplet at 1.35 for the ethoxyl group. Its ^{13}C NMR spectrum showed a signal at δ 194.7 (CHO) and aliphatic carbons at δ 62.0 and 14.0 (OEt). Based upon the ^{1}H and ^{13}C NMR spectra, **9** was identified as ethyl 1-(3,4-methylenedioxyphenyl)-3-formyl-4-hydroxynaphthalene-2-carboxylate **9**. Its formation could be readily explained as arising from **8** by attack by ethanol (Scheme 3).

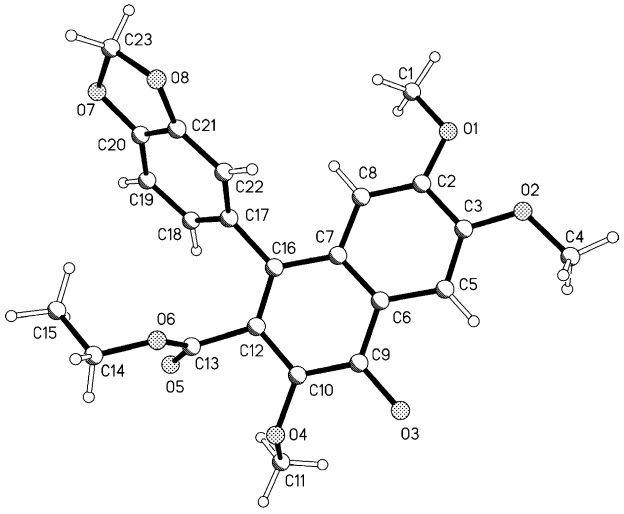
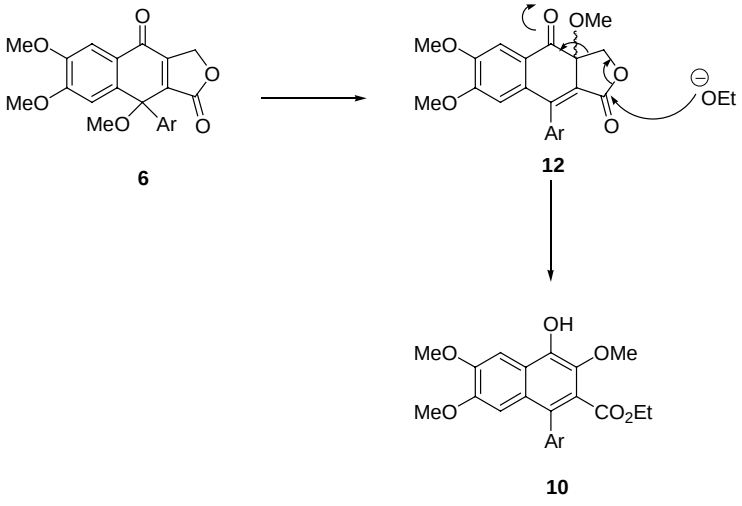


Figure 2. Structure of **10**.

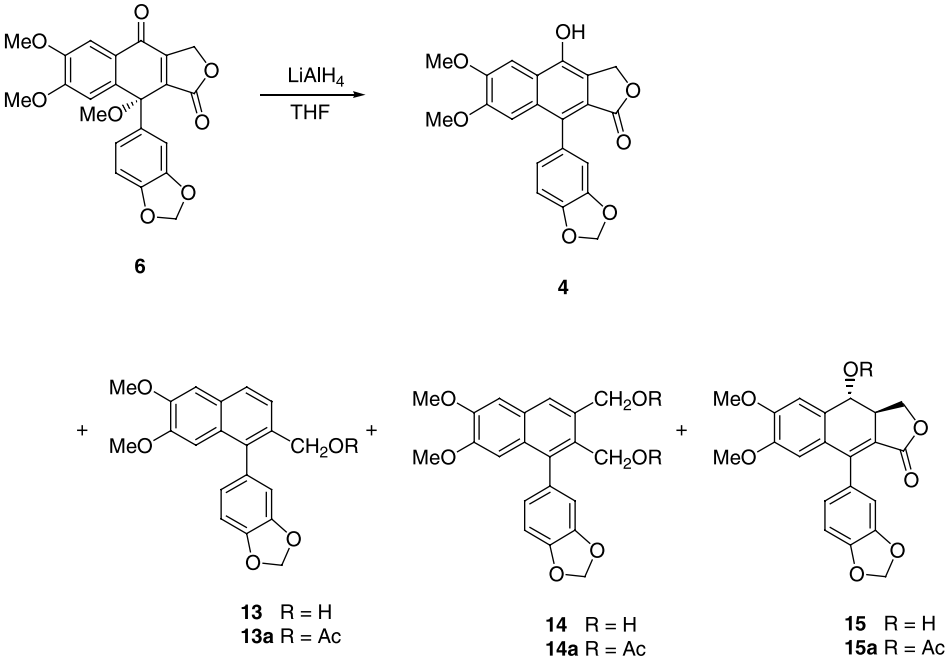
Compound **10** was obtained in 17% yield as a yellow amorphous powder, mp 150 °C, and had molecular formula $C_{23}H_{22}O_8$. Its ^{1}H NMR spectrum lacked signals for the lactone methylene in **6**, showing instead the presence of an extra aromatic methoxyl group, in addition to a triplet at δ 1.07 and a quartet at δ 4.12 due to an ethyl ester. Its ^{13}C NMR spectrum also showed the absence of the lactone methylene present in **6**, but showed signals for the extra methoxyl group at δ 62.8 and for the ethyl ester at δ 13.9 and 61.2. Thus based upon its spectral characteristics, the structure of this compound was assigned as ethyl 1-(3,4-methylenedioxyphenyl)-3-methoxy-4-hydroxy-naphthalene-2-carboxylate **10** and its structure was confirmed by X-ray analysis (Fig. 2). A possible mechanism for its formation involving allylic migration of methoxyl to C-3 to give intermediate **12**, followed by cleavage of the lactone by ethoxide and deformylation, is shown in Scheme 4.

2.3. Reduction of 4-oxo-lactone 6 with lithium aluminium hydride

When compound **6** was treated with 2 equiv of lithium aluminium hydride in THF, it yielded a mixture of four products, one of which was readily identified as diphyllin **4** (15%) by comparison with an authentic sample. Compounds **13** (14%) and **14** (15%) were identified as 1-(3,4-methylenedioxyphenyl)-2-hydroxymethylnaphthalene and 1-(3,4-methylenedioxyphenyl)-2,3-bis(hydroxy-



Scheme 4.



Scheme 5.

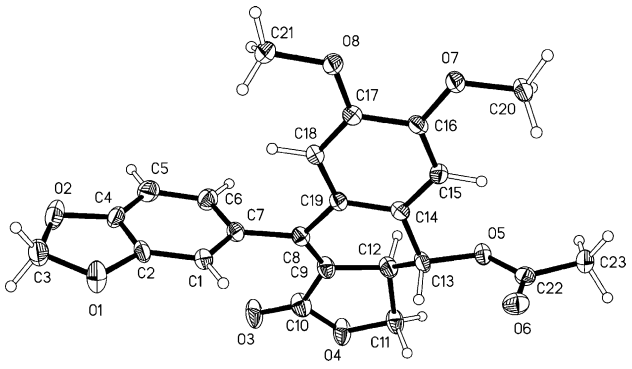


Figure 3. Structure of **15a**.

methyl)naphthalene, respectively. Compound **15** was identified as 3,4-dihydrodiphyllin (Scheme 5). The formation of **13** and **14** could be explained by reduction of **6** followed by aromatisation, dehydration and deformylation, steps that are well known in the chemistry of 1-aryltetralin lignans.[5]

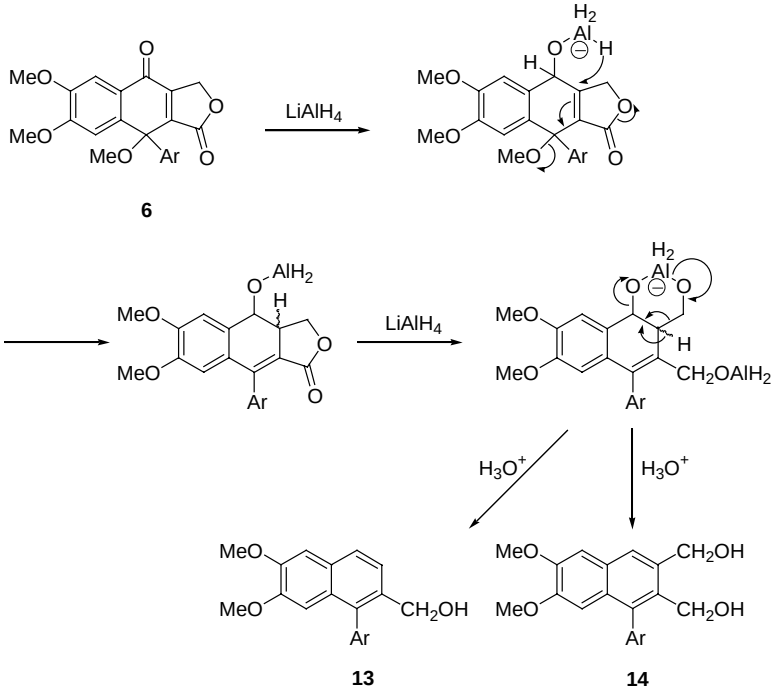
Compound **15** (32%) was obtained as a colourless solid, mp 238 °C, $C_{21}H_{18}O_7$. Its UV spectrum showed absorption maxima at 350, 265 and 235 nm and its IR spectrum contained bands at 3340 (OH), 1746 (γ-lactone), and 1602 (conj. C=C) cm^{-1}. Its ^1H NMR spectrum showed five aromatic protons at δ 7.47d (J= 0.7 Hz), 7.01d (J=8.0 Hz), 6.90m, 6.80s, 6.65s, three of which showed coupling consistent with the presence of a pendant 3,4-disubstituted aryl ring. Among the aliphatic protons the two protons of the lactone methylene appeared as two triplets at δ 4.80 (J=8.9 Hz) and 4.35 (J=8.9 Hz), and a multiplet at δ 3.46–3.54 is assigned to H-3. Compound **15** gave a monoacetate **15a** as a colourless solid, mp 152 °C. The ^1H NMR spectrum of **15** showed an aliphatic proton at δ 5.04dd (J=6.8, 13.8 Hz), which moved downfield to δ 6.16d (J=13.0 Hz) in the ^1H NMR spectrum of its acetate, **15a**, and is assigned to H-4. The trans relationship between H_3–H_4 is based on the observed large coupling constant ($J_{3,4}$=6.8 Hz).[22] The ^{13}C NMR spectrum of **15** showed two olefinic carbon signals at δ 119.8 and 128.5, assigned to C-1 and C-2, a lactone carbonyl at δ 167.0 and the lactone methylene at δ 70.6. The carbon signal at δ 73.3 is assigned to C-4, where hydroxyl is present. Thus based upon the ^1H and ^{13}C NMR spectra of **15** and its acetate **15a**, the structure was assigned as 3,4-dihydrodiphyllin **15** and this was confirmed by X-ray analysis of **15a** (Fig. 3). Possible mechanisms for the formation of compounds **13**, **14** and **15** from **6** are shown in Schemes 6 and 7.

It is interesting to note that the 3,4-dihydrodiphyllin **15** has neither been previously reported as a natural compound nor produced by synthesis.

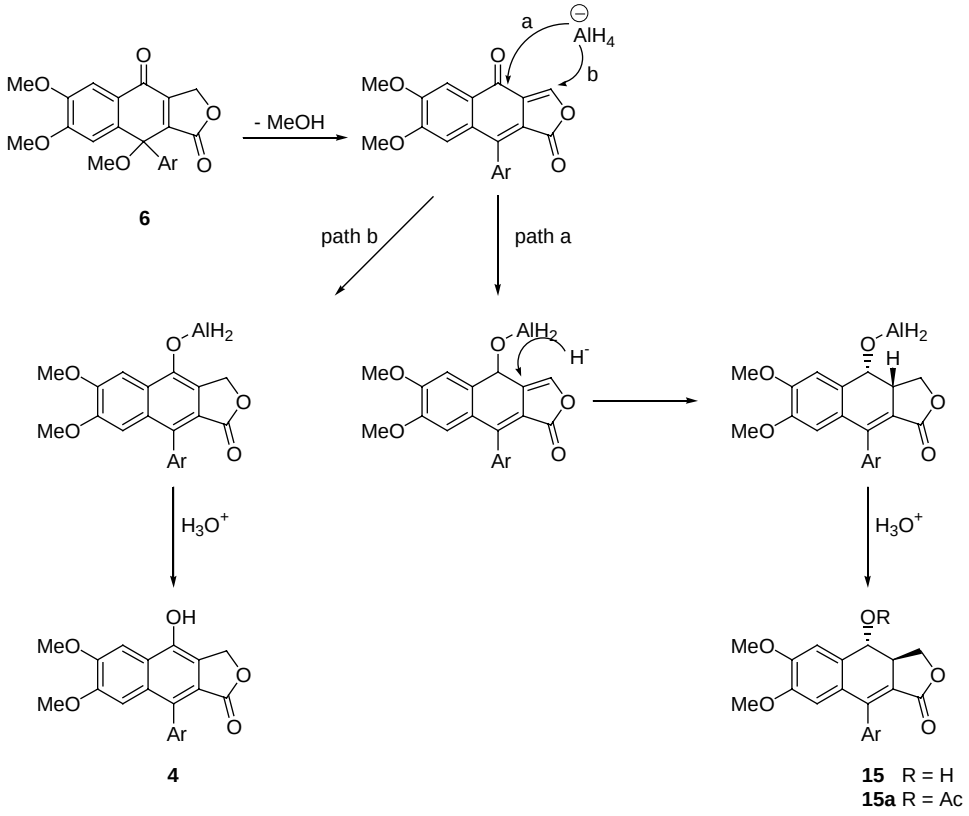
2.4. Reactions of 6 with hydroxylamine and with benzyloxyamine

Having noted that isoxazolone derivatives of lignans had been produced,[23] we attempted to introduce nitrogen at C-4 of the 4-oxolactone **6**. However, when **6** was reacted with either hydroxylamine or benzyloxyamine, nitrogen is introduced at C-10 and not at either the ketone or lactone carbonyl of **6**.

When **6** was treated with 2 equiv of hydroxylamine hydrochloride in the presence of Na_2CO_3 or triethylamine

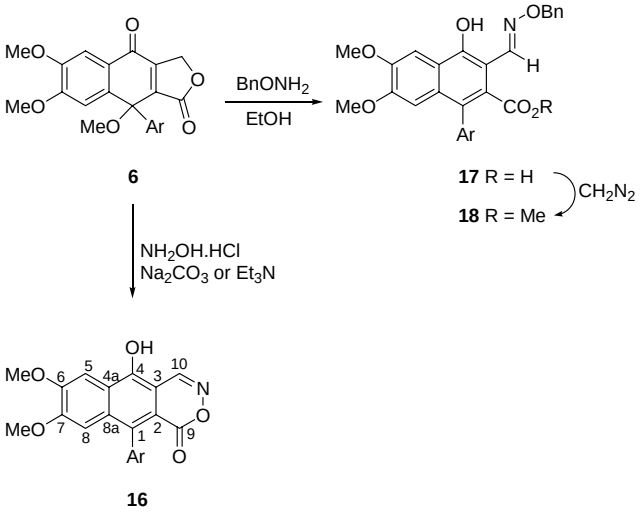


Scheme 6.



Scheme 7.

in ethanol, an amorphous solid, mp 195 °C **16** (40%) was obtained. This had molecular formula $C_{21}H_{15}O_7N$ and its IR spectrum showed bands at 3467 (OH), 1708 (C═O), 1645 (C═N), and 1617 (arom. C═C) cm^{-1}. Its ^1H NMR spectrum showed five aromatic protons at δ 7.65s, 6.88s, 6.86d ($J=1.2$ Hz), 6.83dd ($J=7.9$, 1.4 Hz) and 6.94d ($J=7.9$ Hz) of which three showed couplings consistent with the presence of a 3,4-disubstituted pendant aryl ring. Further, a highly deshielded proton was observed as a singlet at δ 8.40, which may be due to the imine proton at C-10. Its ^{13}C NMR spectrum showed a lactone carbonyl at δ 169.6 and a signal at δ 153.70, which is assigned to an imino carbon (C═N–O) and on this basis the oxazinone structure **16** was assigned (Scheme 8). In order to prove that nucleophilic attack on **6** by hydroxylamine took place at C-10, compound **6** was treated with 1 equiv of benzyloxyamine hydrochloride and gave the expected benzyloximinocarboxylic acid **17** as a crystalline solid, mp 264 °C, $C_{28}H_{23}O_8N$.



Scheme 8.

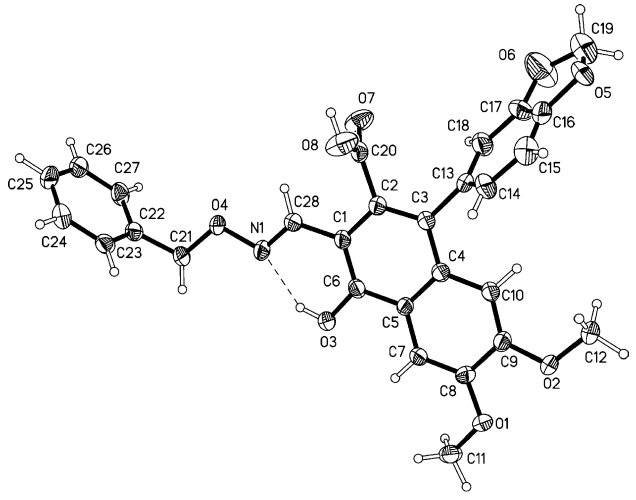
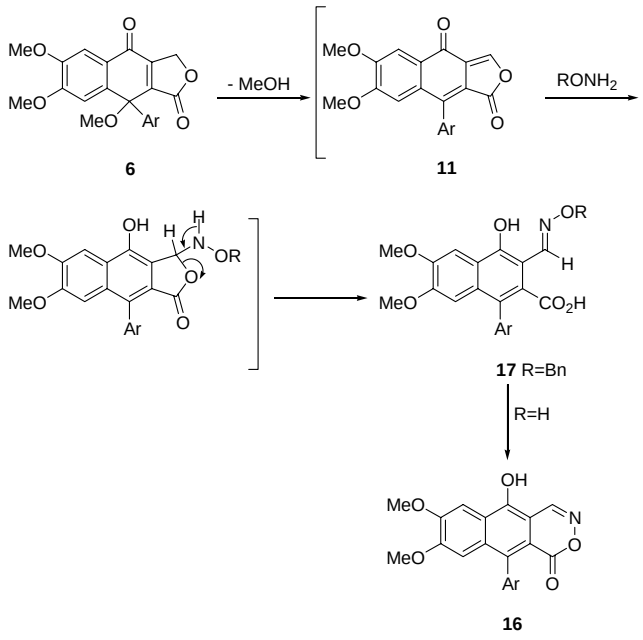


Figure 4. Structure of **17**.



Scheme 9.

Its ^{1}H NMR spectrum showed an acidic proton as a broad singlet at δ 11.4 for the –COOH and another highly deshielded proton as a singlet at δ 8.54 for the imino proton (H–C═N–O). The benzyloxy methylene was observed as a singlet at δ 5.2. Its ^{13}C NMR spectrum showed signals at δ 170.5 for the carboxylic acid, an imino carbon at δ 150.6, and a signal due to a benzyloxymethylene group at δ 77.26. Based upon its NMR spectra structure **17** was assigned. The presence of a carboxyl group in **17** was confirmed by the production of its methyl ester **18**. The X-ray structure of **17** is shown in Figure 4. Possible pathways for the formation of **16** and **17** are shown in Scheme 9. Once more attack on **6** occurs at C-10 through the intermediacy of the elimination product **11**.

3. Conclusion

Oxidation of diphyllin **4** by PIDA and PIFA proceeds, as expected, on the aromatic ring bearing a free phenolic group, which is dearomatised selectively to yield 1-methoxy- or 1-hydroxy-1-aryl-4-oxonaphthalene lactones **6** and **7**. The 4-oxolactone **6** can be converted to a number of unusual products caused by elimination and attack at C-10, in the lactone ring. On reduction of **6** the production of, previously unknown, dihydrophyllin **15** was observed.

4. Experimental

4.1. General procedure

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 400 instrument at 400 and 100 MHz, respectively. All spectra used tetramethylsilane as internal standard and were run in $CDCl_3$. Mass spectra were recorded either on a VG 12-250 quadrupole instrument or on a VG Micromass Quattro II instrument. Accurate mass measurements were made using either a ZAB-E high-resolution double focussing instrument or a Finnigan Mat 900 instrument. Infra-red spectra were recorded either as a Nujol mull or as films on NaCl plates using a Perkin-Elmer Fourier transform 1725X spectrophotometer. Dichloromethane was purified by passing it down on alumina column followed by distillation over calcium hydride. Silica gel-G was used for column chromatography and for TLC. Melting points were recorded on an Electrothermal 9100 melting point apparatus and are uncorrected.

Crystal structure data for (**6**), (**10**), (**15a**) and (**17**) are given in Table 1. Cell dimensions and intensity data were recorded at 150 K, using either a Bruker Nonius KappaCCD or an Enraf Nonius FAST equipped with a rotating anode; standard procedures were followed. Crystallographic data (excluding structure factors) for the structures in this paper

Table 1. Crystal data for **6**, **10**, **15a** and **17**

Compound	**6**	**10**	**15a**	**17**
Formula	$C_{22}H_{18}O_8$	$C_{23}H_{22}O_8$	$C_{23}H_{20}O_8$	$C_{28}H_{23}NO_8$
Crystal	Yellow prism	Yellow needle	Colourless block	Colourless plate
M	410.36	426.40	424.39	501.47
Crystal system	Monoclinic	Monoclinic	Monoclinic	Triclinic
Space group	$P2_1/c$	$P2_1/n$	$P2_1/c$	$P\bar{1}$
a (Å)	11.9852(5)	11.349(2)	11.2554(8)	9.0768(18)
b (Å)	14.3476(10)	18.540(4)	24.3001(14)	10.020(2)
c (Å)	11.1874(6)	20.056(4)	7.6694(4)	16.638(3)
α (°)	90	90	90	94.50(3)
β (°)	110.07(3)	104.39(3)	109.076(3)	90.86(3)
γ (°)	90	90	90	114.68(3)
U (Å^3)	1806.95(18)	4087.8(14)	1982.4(2)	1368.8(5)
Z	4	8	4	2
Density (g cm^{-3})	1.508	1.382	1.422	1.217
μ (Mo Kα) (mm)	0.116	0.105	0.108	0.090
Reflections coll.	12,467	41,975	13,049	10,124
Indep. refs./R_{int}	3526/0.0984	9342/0.1623	3448/0.1402	4173/0.0674
Parameters/restraints	344/0	568/18	281/0	354/0
$R1$ ($F>4\sigma$)	0.0455	0.1893	0.0737	0.0769
$wR2$ (all data)	0.0950	0.4769	0.2228	0.1648

have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 276028 (**6**) 217955 (**10**), 217992 (**15a**), 223292 (**17**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.1.1. Reaction of diphyllin 4 with PIDA in methanol: isolation of 1-methoxy-1-(3,4-methylenedioxyphenyl)-4-oxo-6,7-dimethoxynaphthalene-2,3-lactone 6. To a solution of diphyllin (**4**) (0.20 g, 0.52 mmol) in dry methanol (10 ml) was added PIDA (0.16 g, 0.50 mmol) and the mixture stirred at room temperature for 1 h. The reaction was quenched with aq $NaHCO_3$ and the mixture was poured into ice-water and extracted with EtOAc (3×20 ml). The combined EtOAc extracts were washed with brine (3× 20 ml), then dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure gave a yellow residue (0.2 g). Column chromatography on silica gel-G (eluent: hexane/EtOAc, 8:2) yielded (**6**) as a yellow powder (0.16 g, 78%) which crystallised from methanol to give yellow crystals, mp 230 °C; *m/z* (EI) 410 (M^+, 5%), 395 (70), 380 (44), 351 (33), 321 (40), 293 (100), 265 (20), 163 (46); λ_{max} ($CHCl_3$) 290 (1.12), 246 (1.80) nm; ν_{max} (Nujol) 1740 (γ-lactone), 1702 (C═O), 1600 (arom.) and 940 (OCH_2-O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.63 (1H, s, H-5), 6.91 (1H, d, J=1.9 Hz, H-2′), 6.83 (1H, s, H-8), 6.81 (1H, dd, J=1.9, 8.3 Hz, H-6′), 6.68 (1H, d, J=8.3 Hz, H-5′), 5.93 (1H, d, J=1.3 Hz, OC*H*$_2$O), 5.92 (1H, d, J=1.3 Hz, OC*H*$_2$O), 5.15 (1H, d, J=18.1 Hz, H-10), 5.10 (1H, d, J=18.1 Hz, H-10), 4.01 (3H, s, ArOMe), 3.88 (3H, s, ArOMe), 3.16 (3H, s, ROMe); δ_C (100 MHz, $CDCl_3$) 179.6 (C-4), 168.8 (C-9), 155.3 (C-2), 153.5 (C-3), 149.8 (C-8a), 147.7 (C-6), 147.5 (C-7), 141.9 (C-3′), 141.2 (C-4′), 133.5 (C-1′), 126.1 (C-4a), 120.2 (C-6′), 109.6 (C-5), 108.1 (C-8), 107.3 (C-2′), 107.1 (C-5′), 101.3 (O*C*H$_2$O), 76.9 (C-1), 67.9 (C-10), 56.5 and 56.3 (ArOMe), 52.7 (ROMe); Found: M^+410.1004, $C_{22}H_{18}O_8$ requires 410.1002.

4.1.2. Reaction of 4 with PIDA or PIFA in DMSO: isolation of 1-hydroxy-1-(3,4-methylenedioxyphenyl)-4-oxo-6,7-dimethoxynaphthalene-2,3-lactone 7. To a solution of diphyllin **4** (0.2 g, 0.52 mmol) in DMSO (10 ml) was added PIDA (0.116 g, 0.50 mmol) [or diphyllin (0.3 g, 0.78 mmol) and PIFA (0.4 g, 0.93 mmol)] and the reaction was stirred at room temperature for 1 h. The mixture was quenched with aq $NaHCO_3$ and worked up as described in experiment (Section 4.1.1). Column chromatography of the residue on silica gel-G (eluent: hexane/EtOAc, 8:2) yielded **7** as a yellow powder (0.14 g, 71%), mp 210 °C; *m/z* (EI) 396 (M^+, 10%), 378 (15), 351 (60), 322 (30), 247 (80), 219 (60); λ_{max} ($CHCl_3$) 240 (1.82), 280 (1.18) nm; ν_{max} (Nujol) 3468 (OH), 1740 (γ-lactone), 1692 (C═O) and 927 (OCH_2O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.53 (1H, s, H-5), 6.92 (1H, s, H-8), 6.87 (1H, dd, J=1.9, 8.2 Hz, H-6′), 6.78 (1H, d, J=1.9 Hz, H-2′), 6.74 (1H, d, J=8.2 Hz, H-5′), 5.94 (1H, d, J=1.3 Hz, OC*H*$_2$O), 5.93 (1H, d, J=1.3 Hz, OC*H*$_2$O), 5.20 (1H, d, J=18.0 Hz, H-10), 5.12 (1H, d, J=18.0 Hz, H-10), 3.97 (3H, s, ArOMe), 3.95 (1H, s, ROH), 3.89 (3H, s, ArOMe); δ_C (100 MHz, $CDCl_3$) 179.5 (C-4), 170.5 (C-9), 154.9 (C-2), 149.9 (C-3), 149.4 (C-8a), 148.2 (C-6), 147.6 (C-7), 142.5 (C-3′), 142.2 (C-4′), 134.2 (C-1′), 123.4 (C-4a), 118.6 (C-6′), 109.3 (C-5), 108.5 (C-8), 107.2 (C-2′), 105.8 (C-5′), 101.4 (O*C*H$_2$O), 70.9 (C-1), 68.5 (C-10), 56.3 and 56.2 (ArOMe); Found: $[M+NH_4]^+$414.1187, $C_{21}H_{20}NO_8$ requires 414.1189; Found: $[M+H]^+$397.0917, $C_{21}H_{17}O_8$ requires 397.0923.

4.1.3. Reaction of 6 with sodium and ethanol: isolation of 10-ethoxydiphyllin 8, ethyl 1-aryl-3-formyl-4-hydroxynaphthalene-2-carboxylate 9, and ethyl 1-(3,4-methylenedioxyphenyl)-3-methoxy-4-hydroxynaphthalene-2-carboxylate 10. To a solution of **6** (0.6 g, 1.5 mmol) in ethanol (20 ml) was added sodium (0.033 g, 1.5 mmol) and the mixture stirred for 2 h, and then quenched with aq NH_4Cl solution. After removal of the ethanol under reduced pressure the reaction mixture was poured into crushed ice and extracted with EtOAc (3×20 ml). The combined EtOAc extracts were washed with brine (3×20 ml), then dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure gave a brown residue (0.6 g). Column chromatography on silica gel (eluent: hexane/EtOAc, 9:1) yielded 10-ethoxydiphyllin **8** (0.37 g, 58%) as a pale yellow gum, which was crystallised from methanol, mp 177 °C; λ_{max} ($CHCl_3$) 285 (3.2), 246 (1.7), 202 (0.8) nm; *m/z* (EI) 424 (M^+, 20%), 379 (30%), 378 (100), 350 (10), 322 (80), 307 (35), 264 (20), 163 (60), 150 (90); ν_{max} (KBr) 3368 (broad OH), 1721 (C═O), 1617 (arom.) and 947 (OCH_2-O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.61 (1H, s, H-5), 7.06 (1H, d, J=0.8 Hz, H-8), 6.93 (1H, d, J=8.1 Hz, H-5′), 6.85 (1H, d, J=1.5 Hz, H-2′), 6.80 (1H, dd, J=1.5, 8.1 Hz, H-6′), 6.48 (1H, s, H-10), 6.45 (1H, s, O*H*), 6.07 (1H, s, OCH_2O), 6.00 (1H, s, OCH_2O), 4.07 (3H, s, ArOMe), 4.03 (1H, m, OC*H*$_2$CH$_3$), 3.90 (1H, m, OC*H*$_2$CH$_3$), 3.82 (3H, s, ArOMe), 1.37 (3H, dt, J=1.2, 7.0 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 167.9 (C-9), 151.2 (C-6), 150.7 (C-7), 147.5 (C-4′), 147.4 (C-3′), 145.7 (C-4), 132.2 (C-4a), 131.5 (C-8a), 128.4 (C-1′), 128.3 (C-2), 128.0 (C-3), 123.8 (C-6′), 119.4 (C-1), 111.0 (C-5), 108.2 (C-8), 108.2 (C-2′), 106.2 (C-5′), 101.2 (O*C*H$_2$O), 99.1 (C-10), 65.3 (O*C*H$_2$CH$_3$), 56.1 and 55.8 (OMe), 15.2 (OCH_2CH_3); Found: M^+424.1152, $C_{23}H_{20}O_8$ requires 424.1158. Compound **9** (0.06 g, 9%) crystallised from methanol as orange coloured crystals, mp 122 °C; λ_{max} ($CHCl_3$) 280 (3.1), 266 (2.9) nm; *m/z* (EI) 424 (M^+, 100%), 422 (30), 394 (100), 378 (20), 322 (40); ν_{max} (KBr) 1729 (CO), 1602 (arom.), 931 (OCH_2O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.96 (1H, s, H-9), 7.74 (1H, s, H-5), 6.92 (1H, dd, J=1.6, 7.9 Hz, H-6′), 6.84 (1H, d, J=1.6 Hz, H-2′), 6.82 (1H, s, O*H*), 6.78 (1H, s, H-8), 6.78 (1H, d, J=7.9 Hz, H-5′), 6.04 (1H, d, J=1.2 Hz, OCH_2O), 6.03 (1H, d, J=1.2 Hz, OCH_2O), 4.13 (2H, q, J=7.1 Hz, OC*H*$_2$CH$_3$), 4.06 (3H, s, ArOMe), 4.05 (3H, s, ArOMe), 1.37 (3H, t, J=7.1 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 194.7 (C-10), 167.6 (C-9), 152.4 (C-6), 150.0 (C-7), 149.7 (C-4), 147.5 (C-4′), 147.2 (C-3′), 133.0 (C-3), 132.9 (C-2), 130.7 (C-8a), 129.7 (C-1′), 129.0 (C-4a), 124.4 (C-6′), 119.8 (C-1), 110.9 (C-5), 108.3 (C-8), 106.1 (C-2′), 103.0 (C-5′), 101.2 (OCH_2O), 61.6 (O*C*H$_2$CH$_3$), 56.2 and 55.9 (OMe), 13.9 (OCH_2CH_3); Found: M^+424.1153, $C_{23}H_{20}O_8$ requires 424.1158. Compound **10** (0.11 g, 17%) was obtained from methanol as yellow amorphous powder mp 150 °C; λ_{max} 290 (4.1), 279 (3.5), 226 (1.2) nm; *m/z* (EI) 426 (M^+, 100%), 380 (50), 365 (80), 350 (20), 337 (70); ν_{max} (KBr) 3436 (chelated OH), 1727, 1653 (C═O), 1617 (arom.) and 924 (OCH_2O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.47 (1H, s, H-5), 6.81 (1H, dd, J=1.6, 7.9 Hz, H-6′), 6.86 (1H, d, J=1.6 Hz,

H-2′), 6.12 (1H, s, O*H*), 6.88 (1H, s, H-8), 6.88 (1H, d, J=7.9 Hz, H-5′), 6.05 (1H, d, J=1.3 Hz, OCH_2O), 6.01 (1H, d, J=1.3 Hz, OCH_2O), 4.12 (2H, q, J=7.1 Hz, OCH_2CH_3), 4.04 (3H, s, ArOMe), 3.93 (3H, s, ArOMe), 3.77 (3H, s, ArOMe), 1.07 (3H, t, J=7.1 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 167.5 (C-9), 149.9 (C-6), 149.5 (C-7), 142.1 (C-4), 147.0 (C-4′), 147.3 (C-3′), 137.1 (C-3), 125.7 (C-2), 131.5 (C-8a), 125.8 (C-1′), 128.5 (C-4a), 123.9 (C-6′), 120.3 (C-1), 111.0 (C-5), 108.1 (C-8), 105.4 (C-2′), 100.4 (C-5′), 101.1 (OCH_2O), 62.8 (OMe), 61.2 (OCH_2CH_3), 56.0 and 55.7 (OMe), 13.9 (OCH_2CH_3); Found: M^+426.1312, $C_{23}H_{22}O_8$ requires 426.1315.

4.1.4. Preparation of 4-*O*-acetyl-10-ethoxydiphyllin 8a. To a solution of **8** (0.1 g, 0.21 mmol) in dry pyridine (2 ml) was added acetic anhydride (2 ml) and the mixture was heated under reflux for 1 h on an oil bath. The reaction mixture was then poured onto crushed ice and extracted with EtOAc (3×20 ml). The combined EtOAc extracts were washed successively with dil HCl (2×20 ml) and brine (3×20 ml), then dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure gave a light brown residue (0.1 g). Column chromatography on silica gel-G (eluent: hexane/EtOAc, 4:1) yielded **8a**, (0.08 g, 80%) as a gum, which crystallised from methanol to give colourless plates, mp 220 °C; *m/z* (EI) 466 (M^+, 25%), 424 (10), 378 (90), 350 (10), 322 (45), 307 (15); λ_{max} 279 (3.0), 270 (2.9), 245 (1.2) nm; ν_{max} 1721, 1653 (C=O), 1617 (arom.) and 924 (OCH_2O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.25 (1H, s, H-5), 7.09 (1H, d, J=0.9 Hz, H-8), 6.96 (1H, d, J=7.9 Hz, H-5′), 6.85 (1H, d, J=1.5 Hz, H-2′), 6.82 (1H, dd, J=1.5, 7.9 Hz, H-6′), 6.38 (1H, s, H-10), 6.09 (1H, d, J=1.1 Hz, OCH_2O), 6.05 (1H, d, J=1.1 Hz, OCH_2O), 4.05 (3H, s, ArOMe), 3.94 (1H, m, OCH_2CH_3), 3.81 (1H, m, OCH_2CH_3), 3.81 (3H, s, ArOMe), 2.53 (3H, s, OAc), 1.31 (3H, t, J=7.0 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 167.9 (C-9), 166.7 ($OCOCH_3$), 152.2 (C-6), 150.8 (C-7), 147.7 (C-3′), 147.6 (C-4′), 139.7 (C-4), 131.7 (C-4a), 131.7 (C-8a), 127.9 (C-3), 127.1 (C-1′), 126.2 (C-2), 123.6 (C-6′), 120.0 (C-1), 110.7 (C-5), 110.4 (C-8), 108.3 (C-2′), 106.4 (C-5′), 101.3 (OCH_2O), 99.8 (C-10), 65.1 (OCH_2CH_3), 56.0 and 55.9 (OMe), 20.8 ($OCOCH_3$), 15.1 (OCH_2CH_3); Found: M^+466.1259, $C_{25}H_{22}O_9$ requires 466.1264.

4.1.5. Reaction of 6 with lithium aluminium hydride: isolation of 2-(hydroxymethyl)-1-(3,4-methylenedioxyphenyl)naphthalene 13, 2,3-bis-(hydroxymethyl)-1-(3,4-methylenedioxy phenyl)naphthalene 14, diphyllin 4, and 3,4-dihydrodiphyllin 15. To solution of **6** (0.6 g, 0.14 mmol) in dry THF (10 ml) at −80 °C, was added $LiAlH_4$ (0.11 g, 0.28 mmol) and the mixture stirred for 0.5 h and then brought to room temperature. The excess $LiAlH_4$ was decomposed with EtOAc (10 ml), then poured into crushed ice and extracted with EtOAc (3×20 ml). The combined EtOAc extracts were washed with brine (3×20 ml), then dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure gave a light brown residue (0.6 g). Column chromatography on silica gel (eluent: hexane/EtOAc, 3:2) yielded **13** (0.09, 14%) as a gum, λ_{max} 286, 270, 262 nm; ν_{max} ($CHCl_3$) 3443 (OH), 1623 (arom.) and 933 (OCH_2O) cm^{-1}; *m/z* (EI) 338 (M^+, 100%), 322 (25), 309 (15), 289 (40), 263.1 (20), 205 (25), 176 (45); δ_H (400 MHz, $CDCl_3$) 7.70 (1H, dd, J=1.6, 7.9 Hz, H-6′), 7.66 (1H, d, J=8.4 Hz, H-4), 7.47 (1H, d, J=8.4 Hz, H-3), 7.08 (1H, s, H-5), 6.76 (1H, d, J=7.9 Hz, H-5′), 6.74 (1H, d, J=1.6 Hz, H-2′), 6.73 (1H, s, H-8), 6.08 (1H, d, J=1.2 Hz, OCH_2O), 6.04 (1H, d, J=1.2 Hz, OCH_2O), 4.50 (1H, s, H-9), 3.99 (3H, s, ArOMe), 3.75 (3H, s, ArOMe), 3.13 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) 150.0 (C-3′), 149.6 (C-6), 149.5 (C-7), 147.9 (C-4′), 136.4 (C-4a), 134.5 (C-8a), 132.3 (C-1′), 128.6 (C-2), 126.2 (C-4), 124.4 (C-3), 123.5 (C-1), 123.3 (C-6′), 110.5 (C-5), 108.5 (C-8), 106.2 (C-2′), 105.2 (C-5′), 101.0 (OCH_2O), 63.5 (C-9), 55.6 and 55.4 (OMe); Found: M^+338.1143, $C_{20}H_{18}O_5$ requires 338.1149. Compound **14** (0.09, 15%) crystallised from methanol as a white crystalline solid, mp 218 °C; λ_{max} 289, 270, 265 nm; ν_{max} ($CHCl_3$) 333 (OH), 1622 (arom.) and 932 (OCH_2O) cm^{-1}; *m/z* (EI) 368 (M^+, 100%), 350 (85), 321 (35), 291 (31), 277 (20), 189 (40), 176 (35); δ_H (400 MHz, $CDCl_3$) 7.70 (1H, s, H-4), 7.13 (1H, s, H-5), 6.95 (1H, d, J=7.8 Hz, H-5′), 6.83 (1H, d, J=1.7 Hz, H-2′), 6.82 (1H, s, H-8), 6.77 (1H, dd, J=1.7, 7.8 Hz, H-6′), 6.10 (1H, d, J=1.4 Hz, OCH_2O), 6.05 (1H, d, J=1.4 Hz, OCH_2O), 4.91 (1H, s, H-9), 4.63 (1H, s, H-10), 4.01 (3H, s, ArOMe), 3.76 (3H, s, ArOMe), 3.13 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) 149.7 (C-6), 149.6 (C-7), 147.6 (C-3′), 146.9 (C-4′), 138.8 (C-2), 135.6 (C-4a), 133.2 (C-8a), 132.4 (C-3), 128.8 (C-4), 128.6 (C-1′), 127.4 (C-1), 124.0 (C-6′), 108.3 (C-5), 106.2 (C-8), 104.5 (C-2′), 103.8 (C-5′), 99.4 (OCH_2O), 61.0 (C-10), 57.2 (C-9), 53.0 and 52.7 (OMe); Found: $[M+Na]^+$391.1157, $C_{21}H_{20}O_6$ requires 391.1152. Diphyllin **4** (0.09, 15%) was obtained from methanol as a pale yellow solid, mp 290 °C; λ_{max} ($CHCl_3$) 350, 265, 235 nm; ν_{max} (Nujol) 3200 (OH), 1730 (γ-lactone), 1610 (arom.) and 930 (OCH_2O) cm^{-1}; *m/z* (EI) 380 (M^+, 100%); δ_H (400 MHz, $CDCl_3$) 7.46 (1H, s, H-5), 7.12 (1H, s, H-8), 6.97 (1H, d, J=7.1 Hz, H-5′), 6.86 (1H, s, H-2′), 6.72 (1H, d, J=7.1 Hz, H-6′), 6.08 (1H, s, OCH_2O), 4.09 (3H, s, ArOMe), 3.83 (3H, s, ArOMe); δ_C (100 MHz, $CDCl_3$) 169.6 (C-9), 150.6 (C-4′), 149.8 (C-3′), 146.7 (C-6), 146.7 (C-7), 145.0 (C-4), 129.7 (C-4a), 129.7 (C-8a), 129.0 (C-1′), 123.7 (C-6′), 123.5 (C-3), 121.7 (C-2), 118.8 (C-1), 110.0 (C-8), 107.7 (C-5′), 105.8 (C-2′), 101.0 (OCH_2O), 100.8 (C-5), 66.6 (C-10), 55.6 and 55.2 (OMe). Compound **15** (0.18, 32%) was obtained from methanol as colourless solid, mp 238 °C; λ_{max} 350, 265, and 235 nm; ν_{max} ($CHCl_3$) 3340 (OH), 1746 (γ-lactone), 1602 (arom.) and 930 (OCH_2O) cm^{-1}; *m/z* (EI) 382 (M^+, 10%), 354 (100), 335 (10), 319 (10), 305 (20), 277 (30), 176 (30), 162.9 (60); δ_H (400 MHz, $CDCl_3$) 7.47 (1H, d, J=0.7 Hz, H-5), 7.01 (1H, d, J=8.0 Hz, H-6′), 6.90 (1H, m, H-5′), 6.80 (1H, s, H-2′), 6.65 (1H, s, H-8), 6.18 (1H, d, J=1.5 Hz, OCH_2O), 6.16 (1H, d, J=1.5 Hz, OCH_2O), 5.10 (1H, d, J=6.8 Hz, OH), 5.04 (1H, dd, J=6.8, 13.8 Hz, H-4), 4.80 (1H, t, J=8.9 Hz, H-10), 4.35 (1H, t, J=8.9 Hz, H-10), 4.00 (3H, s, ArOMe), 3.71 (3H, s, ArOMe), 3.46–3.54 (1H, m, H-3); δ_C (100 MHz, $CDCl_3$) 167.0 (C-9), 152.1 (C-6), 148.8 (C-7), 148.6 (C-3′), 147.9 (C-4′), 146.9 (C-4a), 135.9 (C-8a), 128.9 (C-1′), 128.5 (C-2), 119.8 (C-1), 113.8 (C-6′), 108.5 (C-5), 108.2 (C-8), 108.2 (C-5′), 108.2 (C-2′), 102.1 (OCH_2O), 73.3 (C-4), 70.6 (C-10), 56.2 and 56.1 (OMe), 44.1 (C-3); Found: $[M+H]^+$383.1134, $C_{21}H_{19}O_7$ requires 383.1131.

4.1.6. Acetylation of 13. To a solution of **13** (0.01 g, 0.029 mmol) in dry pyridine (2 ml) was added acetic anhydride (2 ml) and the mixture was stirred at room temperature for 3 h. The reaction mixture was then poured

into crushed ice and extracted with EtOAc (3×20 ml). The combined EtOAc extracts were washed successively with dil HCl (2×20 ml) and brine (3×20 ml), then dried ($MgSO_4$) and filtered. Removal of solvent under reduced pressure gave light brown residue (0.1 g). Column chromatography on silica gel-G (eluent: hexane/EtOAc, 4:1) yielded **13a** (0.08 g, 80%) as a colourless gum, λ_{max} ($CHCl_3$) 289, 260, 252 nm; *m/z* (EI) 380 (M^+, 100%), 338 (5), 320 (20), 289 (35), 263 (15), 176 (30); δ_H (400 MHz, $CDCl_3$) 7.66 (1H, d, J=8.4 Hz, H-4), 7.33 (1H, d, J=8.4 Hz, H-3), 7.07 (1H, s, H-5), 6.86 (1H, d, J=7.9 Hz, H-5′), 6.72 (1H, d, J=1.7 Hz, H-2′), 6.72 (1H, s, H-8), 6.67 (1H, dd, J=1.7, 7.9 Hz, H-6′), 6.08 (1H, d, J=1.2 Hz, OCH_2O), 6.04 (1H, d, J=1.2 Hz, OCH_2O), 4.94 (1H, s, H-9), 4.00 (3H, s, ArOMe), 3.75 (3H, s, ArOMe), 2.05 (3H, s, OAc); δ_C (100 MHz, $CDCl_3$) 169.0 ($OCOCH_3$), 149.6 (C-3′), 149.6 (C-6), 149.5 (C-7), 149.5 (C-4′), 137.9 (C-4a), 137.9 (C-8a), 129.2 (C-1′), 128.6 (C-2), 126.2 (C-4), 124.9 (C-3), 123.4 (C-1), 123.4 (C-6′), 110.6 (C-5), 108.3 (C-8), 106.2 (C-2′), 105.4 (C-5′), 101.1 (OCH_2O), 65.0 (C-9), 55.9 and 55.7 (OMe), 21.4 ($OCOCH_3$); Found: $[M+NH_4]^+$398.1599, $C_{22}H_{20}O_6$ requires 398.1598.

4.1.7. Acetylation of 14. To a solution of **14** (0.1 g, 0.27 mmol) in dry pyridine (2 ml) was added acetic acid anhydride (2 ml) and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was then poured into crushed ice and extracted with EtOAc (3×20 ml). The combined EtOAc extracts were washed successively with dil HCl (2×20 ml) and brine (3×20 ml) then dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure gave a light brown residue (0.1 g). Column chromatography on silica gel-G (eluent: hexane/EtOAc, 3:2) yielded **14a** (0.08, 80%) as a gum, λ_{max} $CHCl_3$ 290, 286, 270 nm; *m/z* (EI) 452 (40%), 392 (40), 350 (67), 332 (100), 319 (35), 289 (40), 189 (65); δ_H (400 MHz, $CDCl_3$) 7.79 (1H, s, H-4), 7.16 (1H, s, H-5), 6.93 (1H, d, J=7.9 Hz, H-5′), 6.77 (1H, dd, J=1.7, 7.9 Hz, H-6′), 6.74 (1H, s, H-8), 6.73 (1H, d, J=1.7 Hz, H-2′), 6.10 (1H, d, J=1.4 Hz, OCH_2O), 6.06 (1H, d, J=1.4 Hz, OCH_2O), 5.33 (1H, d, J=3.4 Hz, H-9), 5.05 (1H, dd, J=3.4, 12.1 Hz, H-10), 4.02 (3H, s, ArOMe), 3.76 (3H, s, ArOMe), 2.13 (3H, s, OAc), 2.04 (3H, s, OAc); δ_C (100 MHz, $CDCl_3$) 170.3 and 170.0 ($OCOCH_3$), 150.2 (C-6), 150.0 (C-7), 147.7 (C-4′), 147.1 (C-3′), 140.4 (C-2), 131.9 (C-4a), 130.9 (C-8a), 129.2 (C-1′), 128.8 (C-3), 128.0 (C-1), 127.9 (C-4), 123.3 (C-6′), 110.9 (C-5), 108.1 (C-8), 106.2 (C-2′), 105.7 (C-5′), 101.2 (OCH_2O), 64.8 (C-10), 62.0 (C-9), 55.8 and 55.6 (OMe), 21.5 and 20.9 ($OCOCH_3$); Found: $[M+NH_4]^+$470.1810, $C_{23}H_{28}NO_8$ requires 470.1815.

4.1.8. Acetylation of 15: isolation of 3,4-dihydrodiphyllin acetate 15a. To a solution of **15** (0.1 g, 0.26 mmol) in dry pyridine (2 ml) was added acetic anhydride (2 ml) was added acetic anhydride (2 ml) and the reaction mixture was poured into crushed ice and extracted with EtOAc (3×20 ml). The combined EtOAc extracts were washed successively with dil HCl (3×20 ml) and brine (3×20 ml), then dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure gave a light yellow residue (0.1 g). Column chromatography on silica gel (eluent: CH_2Cl_2/EtOAc, 8:2) yielded **15a** (0.08 g, 80%) as colourless gum, which crystallised from benzene as a colourless crystalline solid, mp 152 °C; λ_{max} 1746 (γ-lactone), 1602 (arom.), 930 (OCH_2O) cm^{-1}; *m/z* (EI) 425 ($M+H^+$, 25%), 386 (10), 365 (100), 335 (10), 323 (15); δ_H (400 MHz, $CDCl_3$) 6.85 (1H, d, J=7.8 Hz, H-2′), 6.74–6.84 (1H, m, H-6′), 6.74–6.84 (1H, m, H-5′), 6.72 (1H, s, H-5), 6.53 (1H, s, H-8), 6.16 (1H, d, J=13.0 Hz, H-4), 6.04 (1H, s, OCH_2O), 6.02 (1H, s, OCH_2O), 4.56 (1H, t, J=9.0 Hz, H-10), 4.27 (1H, t, J=9.0 Hz, H-10), 3.91 (3H, s, ArOMe), 3.67 (3H, s, ArOMe), 3.45–3.56 (1H, m, H-3), 2.29 (3H, s, OAc); δ_C (100 MHz, $CDCl_3$) 170.3 ($OCOCH_3$), 167.0 (C-9), 150.9 (C-6), 148.6 (C-7), 148.2 (C-4′), 147.3 (C-3′), 147.1 (C-4a), 128.5 (C-8a), 128.1 (C-1′), 126.9 (C-2), 124.0 (C-6′), 117.4 (C-1), 112.0 (C-5), 107.9 (C-5′), 107.8 (C-8), 107.3 (C-2′), 101.2 (OCH_2O), 74.6 (C-4), 67.1 (C-10), 55.8 and 53.4 (OMe), 41.6 (C-3), 20.8 ($OCOCH_3$); Found: $[M+H]^+$425.1235, $C_{23}H_{21}O_8$ requires 425.1236.

4.1.9. Reaction of 6 with benzyloxyamine hydrochloride: isolation of 17. To a solution of **6** (0.2 g, 0.48 mmol) in ethanol (20 ml) was added benzyloxyamine hydrochloride (0.077 g, 0.48 mmol) and Na_2CO_3 (50 mg) and the mixture was heated under reflux for 4 h. The reaction mixture was poured into cold water and extracted with EtOAc (3×20 ml). The combined extracts were washed with brine (3×20 ml), then dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure gave a light brown residue (0.2 g). Column chromatography on silica gel yielded a gum, which crystallised from DMF and water to give **17** as a coloured crystalline solid, (0.16 g, 80%), mp 264 °C; λ_{max} 280, 275, 266 nm; ν_{max} ($CHCl_3$) 3446 (OH), 1742 (C=N–O and –CO–OH), 1610 (arom.) and 935 (OCH_2O) cm^{-1}; *m/z* (EI), 501 (M^+, 10%), 484 (15), 425 (90), 409 (80); δ_H (400 MHz, $CDCl_3$) 11.40 (1H, 3, CO_2H), 8.54 (1H, s, H-10), 7.68 (1H, s, H-5), 7.36–7.48 (5H, m, OCH_2Ph), 6.87 (1H, dd, J=1.5, 7.9 Hz, H-6′), 6.84 (1H, s, H-8), 6.82 (1H, d, J=7.9 Hz, H-5′), 6.81 (1H, d, J=1.5 Hz, H-2′), 6.06 (1H, d, J=1.4 Hz, OCH_2O), 6.03 (1H, d, J=1.4 Hz, OCH_2O), 5.20 (2H, s, OCH_2Ph), 4.06 (3H, s, ArOMe), 3.79 (3H, s, ArOMe), 3.74 (1H, s, OH); δ_C (100 MHz, $CDCl_3$) 170.5 (C-9), 153.7 (C-6), 151.3 (C-7), 150.6 (C-10), 149.9 (C-3′), 147.4 (C-4′), 147.1 (C-4), 136.5 (C-8a), 131.4 (C-1′), 136.8, 129.8, 128.8, and 128.6 (OCH_2Ph), 129.7 (C-4a), 127.9 (C-3), 123.9 (C-2), 123.9 (C-6′), 120.3 (C-1), 110.9 (C-5), 108.2 (C-8), 105.7 (C-5′), 102.0 (C-2′), 101.1 (OCH_2O), 77.3 (OCH_2Ph), 56.0 and 55.7 (OMe); Found: $[M+H]^+$502.1496, $C_{28}H_{23}NO_8$ requires 502.1496.

4.1.10. Reaction of 17 with diazomethane: isolation of benzyloxime ester 18. To a solution of benzyloxime **17** (0.1 g, 0.20 mmol) in ether was added an ethereal solution of diazomethane at −10 °C. The reaction mixture was left overnight. After evaporation of the solvent a light yellow residue (0.1 g) was obtained. Column chromatography on silica gel G (eluent: hexane/EtOAc, 4:1) yielded **18** as a gum (0.05 g, 50%) which was crystallised from methanol as colourless plates, mp 165 °C; λ_{max} 280, 275, 245 nm; ν_{max} ($CHCl_3$) 3428 (chelated OH), 1720, 1670 (C=O), 1615 (arom.) and 925 (OCH_2O) cm^{-1}; *m/z* (CI) 516 ($M+H^+$, 100%), 439 (25), 410 (25), 269 (10), 210 (15), 152 (20); δ_H (400 MHz, $CDCl_3$) 11.18 (1H, s, CO_2H), 8.30 (1H, s, H-10), 7.61 (1H, s, H-5), 7.25–7.40 (5H, m, OCH_2Ph), 6.83 (1H, dd, J=1.2, 6.9 Hz, H-6′), 6.78 (1H, s, H-8), 6.74 (1H, d, J=6.9 Hz, H-5′), 6.71 (1H, d, J=1.2 Hz, H-2′), 6.04 (1H, s, OCH_2O), 6.02 (1H, s, OCH_2O), 5.14 (2H, s, OCH_2Ph), 4.03 (3H, s, ArOMe), 3.77 (3H, s, ArOMe), 3.55 (3H, s, CO_2Me);

δ_C (100 MHz, $CDCl_3$) 168.8 (C-9), 153.8 (C-6), 151.4 (C-7), 150.4 (C-10), 149.9 (C-4′), 149.2 (C-3′), 147.0 (C-4), 141.4 (C-2), 136.5 (C-8a), 129.6 (C-1′), 129.5 (C-4a), 128.5, 128.5, and 128.3 (OCH_2Ph), 127.9 (C-3), 123.8 (C-6′), 120.5 (C-1), 110.9 (C-5), 108.0 (C-8), 105.4 (C-5′), 102.1 (C-2′), 101.0 (OCH_2O), 76.7 (OCH_2Ph), 55.7 and 55.5 (OMe), 51.8 (CO_2Me); Found: $[M+H]^+$516.1661, $C_{29}H_{25}NO_8$ requires 516.1658.

4.1.11. Reaction of 6 with hydroxylamine hydrochloride: isolation of oxazinone 16. To a solution of **6** (0.1 g, 0.24 mmol) in ethanol (20 ml) was added hydroxylamine hydrochloride (0.034 g, 0.48 mmol) and Na_2CO_3 (50 mg) and the mixture was refluxed for 4 h. The reaction mixture was filtered and the solvent was removed under reduced pressure to leave a brown residue (60 mg). Column chromatography on silica gel-G yielded oxazinone **16** as a gum, which was crystallised from methanol to give a light yellow powder, (40 mg, 40%), mp 195 °C; λ_{max} ($CHCl_3$) 3467 (OH), 1708 (C=O), 1617 (arom.), 1645 (C=N) and 940 (OCH_2O) cm^{-1}; *m/z* (EI) 393 (M^+, 10%), 385 (5), 348 (10), 320 (15), 307 (20), 247 (70), 249 (35), 150 (37); δ_H (400 MHz, $CDCl_3$) 8.40 (1H, s, H-10), 7.65 (1H, s, H-5), 6.94 (1H, d, $J=7.9$ Hz, H-5′), 6.88 (1H, s, H-8), 6.86 (1H, d, $J=1.4$ Hz, H-2′), 6.83 (1H, dd, $J=1.4$, 7.9 Hz, H-6′), 6.08 (1H, d, $J=1.0$ Hz, OCH_2O), 6.05 (1H, d, $J=1.0$ Hz, OCH_2O), 3.94 (3H, s, ArOMe), 3.84 (3H, s, ArOMe); δ_C (100 MHz, $CDCl_3$) 169.6 (C-9), 153.7 (C-6), 152.4 (C-7), 151.0 (C-3′), 150.8 (C-10), 148.3 (C-4′), 148.0 (C-4), 132.3 (C-4a), 131.2 (C-8a), 130.2 (C-1′), 127.7 (C-3), 124.9 (C-2), 124.9 (C-6′), 120.6 (C-1), 111.8 (C-5), 108.7 (C-8), 106.4 (C-5′), 102.4 (C-2′), 102.1 (OCH_2O), 55.9 and 55.6 (OMe); Found: $[M+H]^+$394.0922, $C_{21}H_{15}NO_7$ requires 394.0921.

Acknowledgements

The authors express their thanks to SERC (DST), New Delhi for their financial assistance to R. Venkateswarlu and C. Kamakshi.

References and notes

1. Ward, R. S. *Phytochem Rev.* **2003**, *2*, 391.
2. Ward, R. S. *Synthesis* **1992**, 719.
3. Ayres, D. C.; Loike, J. D. *Lignans: Chemical, Biological and Clinical Properties*; Cambridge University Press: Cambridge, 1990.
4. Charlton, J. L. *J. Nat. Prod.* **1998**, *61*, 1447.
5. Rodrigo, R. *Tetrahedron* **1998**, 2093.
6. Ramachandra Row, L.; Venkateswarlu, R.; Pelter, A.; Ward, R. S. *Tetrahedron Lett.* **1980**, *21*, 2919.
7. Pelter, A.; Ward, R. S.; Venkateswarlu, R.; Kamakshi, C. *Tetrahedron* **1989**, *45*, 3451.
8. Pelter, A.; Ward, R. S.; Venkateswarlu, R.; Kamakshi, C. *Tetrahedron* **1991**, *47*, 1275.
9. Pelter, A.; Ward, R. S.; Venkateswarlu, R.; Kamakshi, C. *Tetrahedron* **1992**, *48*, 7209.
10. Anjaneyulu, A. S. R.; Santhikumar, D.; Venkateswarlu, R.; Kamakshi, C. *Indian J. Chem., Sect. B* **1995**, *34*, 897.
11. Ward, R. S.; Pelter, A.; Venkateswarlu, R.; Kamakshi, C.; Lakshmi, A. *Tetrahedron* **1996**, *52*, 14349.
12. Ward, R. S.; Pelter, A.; Venkateswarlu, R.; Kamakshi, C.; Subhash, P. V.; Moinuddin, S. G. A.; Hursthouse, M. B.; Coles, S. J.; Hibbs, D. E. *Tetrahedron* **1999**, *55*, 13071.
13. Venkateswarlu, R.; Kamakshi, C.; Moinuddin, S. G. A.; Subhash, P. V.; Ward, R. S.; Pelter, A.; Hursthouse, M. B.; Light, M. E. *Tetrahedron* **1999**, *55*, 13087.
14. Venkateswarlu, R.; Kamakshi, C.; Moinuddin, S. G. A.; Subhash, P. V.; Ward, R. S.; Pelter, A.; Hursthouse, M. B.; Light, M. E.; Coles, S. J. *Tetrahedron* **2001**, *57*, 5625.
15. Pelter, A.; Ward, R. S.; El-Ghani, A. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1353.
16. Pelter, A.; Hussain, A.; Smith, G.; Ward, R. S. *Tetrahedron* **1997**, *53*, 5879.
17. Pelter, A.; Ward, R. S. *Tetrahedron* **2001**, *57*, 273.
18. Kürti, L.; Herczegh, P.; Visy, J.; Simonyi, M.; Antus, S.; Pelter, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 379.
19. Pelter, A.; Satchwell, P.; Ward, R. S.; Blake, K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2201.
20. Ward, R. S.; Pelter, A.; Abd- El-Ghani, A. *Tetrahedron* **1996**, *52*, 1303.
21. Anjaneyulu, A. S. R.; Ramaiah, P. A.; Row, L. R.; Venkateswarlu, R.; Pelter, A.; Ward, R. S. *Tetrahedron* **1981**, *37*, 3641.
22. Kunroda, T.; Takahashi, M.; Kondo, K.; Iwasaki, T. *J. Org. Chem.* **1996**, *61*, 9560.
23. Jose, M.; del Corral, M.; Gordaliza, M.; Castro, M. A.; Vazquez, M. L. L.; Gracia-Gravalos, M. D.; Broughton, H. B.; San Feliciano, A. *Tetrahedron* **1997**, *53*, 6555.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 4474–4481

The role of F–N reagent and reaction conditions on fluoro functionalisation of substituted phenols

Igor Pravst,[a] Maja Papež Iskra,[a] Marjan Jereb,[a] Marko Zupan[a,b] and Stojan Stavber[b,*]

[a]*Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, 1000 Ljubljana, Slovenia*
[b]*Laboratory for Organic and Bioorganic Chemistry, 'Jozef Stefan' Institute, Jamova 39, 1000 Ljubljana, Slovenia*

Received 18 November 2005; revised 26 January 2006; accepted 16 February 2006

Abstract—The effect of steric interactions on the regioselectivity of fluorination of *para* alkyl substituted phenols was investigated and the strong effect of size of the alkyl substituent, the structure of the F–N reagent and the solvent on the site of fluorination was established. The course of reaction obeyed a second order rate equation, while the fluorination process required higher $\Delta H^{\neq}$ activation than oxidation or oxidative demethylation. Solvent polarity variations had a small effect on the rate of functionalisation, while an excellent Hammett correlation with $\rho^{+} = -2.3$ was determined.

1. Introduction

Hydroxy substituted aromatic molecules are important compounds in the chemistry of life and consequently in health chemistry, today being very popular as antioxidising, anticarcinogenic molecules, etc.[1] These molecules bear at least one hydroxy group, but the second and third substituents play important roles in their chemical reactivity. Usually at least one alkoxy group is present while the third substituent modulates the electron density of the aromatic ring. They can be classified into one of three major classes: *class A*, the most electron-rich molecules with at least one additional hydroxy or alkoxy group, preferably *para* to the hydroxyl group, have a very low oxidising potential and are very strong radical inhibitors. In *class B*, the molecule bears an sp^3 hybridized carbon atom in the *para* position, while in *class C* an sp^2 carbon atom is present at the *para* position. On the other hand, the important role of the alkoxy group (usually methoxy in the position *ortho* to the hydroxyl group) has been shown in modulation of the biological activity of various types of phenols, connected with the possibility of hydrogen bond formation between the methoxy and hydroxy groups and consequently in the geometry of the molecule and its hydrogen atom donation properties.

The fluorine atom has several times been used as a convenient substituent or modulator in the field of bioactive molecules[2] and is also very effective in the bioisosterism strategy.[3] The mild and selective introduction of a fluorine atom into organic molecules has been a specialised field of investigation in the last three decades, and various types of reagents were developed. Hydroxy substituted benzene derivatives have been used as model substrates in fluorination studies on several occasions,[4] but the effectiveness of preparation of fluoro substituted molecules also varies with the other substituents present. The course of fluorination is greatly dependent on the strong oxidation capacity of this family of reagents. In the field of mild fluorination, studies have been mainly connected with the effect of the structure of the F–L reagent[4] on the type of transformation of the organic molecule, its regioselectivity, the effect of solvent, inhibitors, etc.

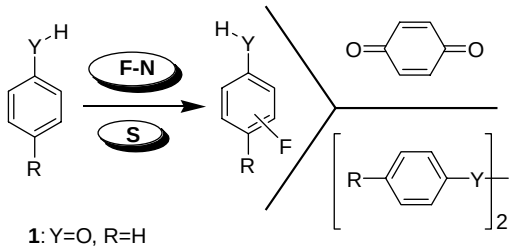
Valuable information about the mechanism involved that could be provided from kinetic data (rate of reaction, activation parameters, Hammett correlations, etc.) are rare, due to the high reactivity and high sensitivity of F–L reagents (CF_3OF, CF_3COOF, $CsSO_4F$, XeF_2) to the reaction conditions (small amounts of HF, presence of water, solvent polarity, reaction of the solvent with the reagent, etc.). This type of investigation is possible with the class of F–N reagents,[5] as they are quite reactive, stable, non-explosive and selective in their fluorination of organic molecules. We have already demonstrated that the reactions of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor™ F-TEDA-BF_4), a representative of the F–N class of reagent, could be easily monitored by iodometric titration.[6] F–N reagents have been

Keywords: Fluorination; F–N reagents; Selectfluor F-TEDA-BF_4; Substituted phenols; Kinetics; Solvent effects; Substituent effects.
* Corresponding author. Tel.: +386 1 477 3660; fax: +386 1 251 9385; e-mail: stojan.stavber@ijs.si

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.051

used for fluorination of aromatic molecules; however, the type of functionalisation strongly depends on the structure of the F–N reagent, the functional groups attached to the aromatic molecule and the reaction conditions (solvent e.g., acetonitrile, methanol, water, trifluoroacetic acid; catalyst and reaction temperature). The types of ring transformations observed include ring substitution, *ipso* substitution, the addition process and oxidation.[4–11]

In order to obtain further information about the course of functionalisation of aromatic molecules with the F–N type of reagents, we decided to study the effect of substituents and solvent polarity on mild functionalisation of substituted phenols with Selectfluor™ F-TEDA-BF_4, Accufluor™ NFTh (1-hydroxy-4-fluoro-1,4-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate)) and FP-B800 (*N*-fluoro-2,6-dichloropyridinium tetrafluoroborate). Because of the importance of the substituent on the phenol in the *para* position on the course of the functionalisation with F–N reagents, we studied the effect of the alkyl group in the context of steric interactions on the one hand and leaving group properties on the other (Scheme 1).

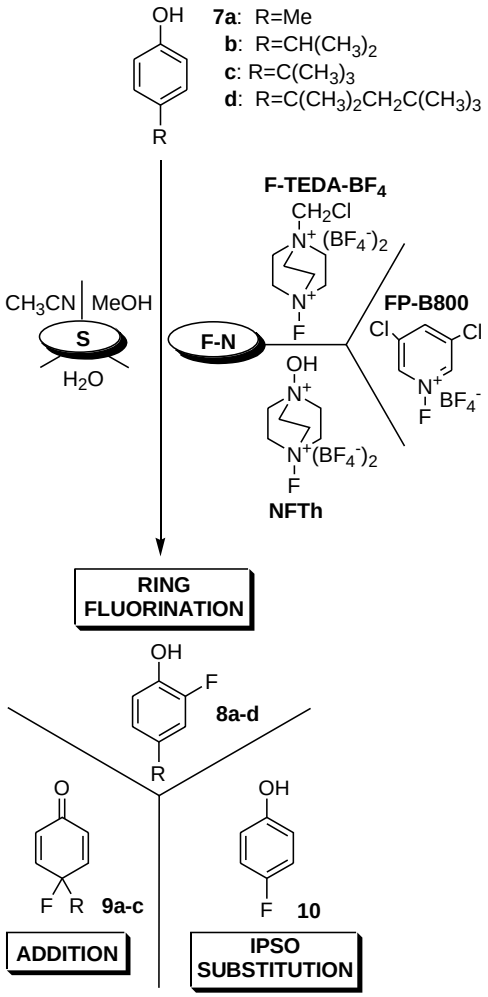


1: Y=O, R=H
2: Y=O, R=OH
3: Y=O, R=OCH_3
4: Y=O, R=$COOCH_3$
5: Y=O, R=CN
6: Y=S, R=H

Scheme 1.

2. Results and discussion

We started by investigating the effect of the bulk substituent, the structure of the reagent and the solvent on the course of functionalisation of *para* substituted phenols (Scheme 2); the effect of these three parameters is presented in Table 1. Fluorination with F-TEDA-BF_4 in acetonitrile at reflux temperature resulted in three types of product: 2-fluoro-4-alkyl-phenoles (**8**) as a result of *ortho* fluorination, 4-alkyl-4-fluoro-cyclohexa-2,5-di-enone addition products (**9**) and *ipso* substituted 4-fluoro-phenol (**10**). The alkyl substituent has an important effect on the reaction path, bulky alkyl substituents increasing *ortho* fluorination (Me: 34%, *i*Pr: 40%, *t*Bu: 60%, *t*Oct(1,1,3,3-tetramethyl-butyl): 88%) and reducing *para* attack. The structure of the alkyl group (tertiary, secondary, primary carbon atom) also has an important role in the competition between two types of functionalisation at the *para* position and is graphically presented in Figure 1.



Scheme 2.

Table 1. Effect of the structure of 4-substituted phenols, fluorination agents and solvents on reaction channels in fluoro functionalisation[a]

R subst.	Reagent	Product distribution **8**:**9**:**10** (yield (%)) in[b]	
		MeCN	MeOH
Me (**7a**)	F-TEDA-BF_4	34:66:0 (55)	100:0:0 (52)
	NFTh	41:59:0 (53)	100:0:0 (60)
	FP-B800	(<5)	
*i*Pr (**7b**)	F-TEDA-BF_4	40:60:0 (78)	62:38:0 (84)
	NFTh	47:52:0 (87)	67:33:0 (88)
	FP-B800	100:0:0 (22)	
*t*Bu (**7c**)	F-TEDA-BF_4	60:0:40 (84)	81:0:19 (83)
	NFTh	61:0:39 (92)	90:0:10 (91)
	FP-B800	63:0:36 (43)	
*t*Oct (**7d**)	F-TEDA-BF_4	88:0:12 (55)	88:0:12 (60)

[a] Reaction conditions: substrate (1 mmol), fluorinating reagent (1 mmol), solvent (10 mL), reflux temperature, 2 h.
[b] Relative distribution in percentage determined from ^{19}F NMR spectra of isolated reaction mixtures; total yield of fluorinated products was determined from ^{19}F NMR spectra of isolated reaction mixtures using octafluoronaphthalene as internal standard.

In fluoro functionalisation the regioselectivity and type of transformation were found to be dependent on both the solvent and the substituent. Methanol in comparison to acetonitrile completely changed the regioselectivity in the case of 4-methyl phenol (**7a**) where exclusive *ortho*

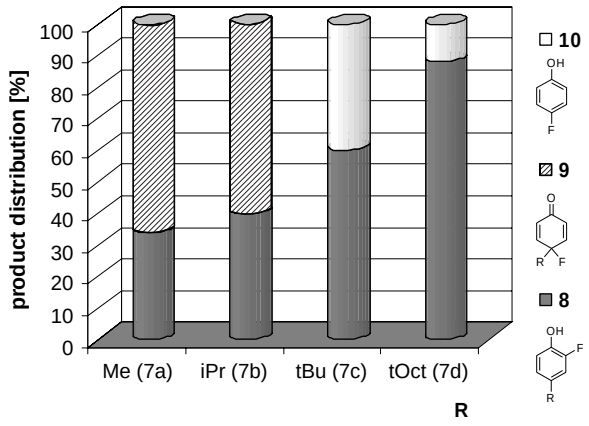


Figure 1. Effect of the alkyl substituent on reaction channels in fluorination of 4-alkyl phenols (**7a–d**) with F-TEDA-BF_4 in acetonitrile. Relative distribution in % determined from ^{19}F NMR spectra of isolated reaction mixtures. Reaction conditions: substrate (1 mmol), F-TEDA-BF_4 (1 mmol), acetonitrile (10 mL), 2 h.

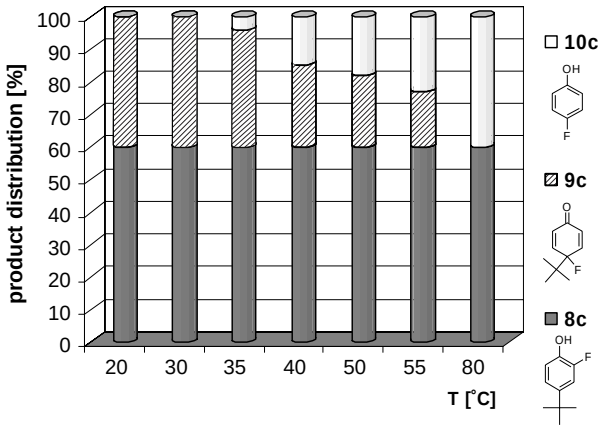
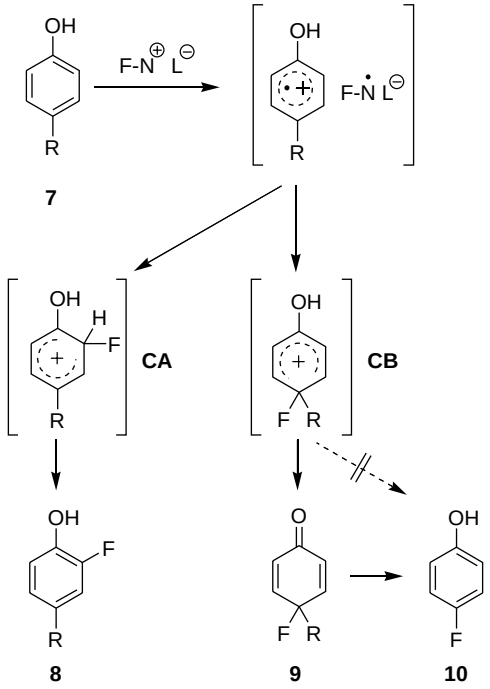


Figure 2. Effect of temperature on competition between the electrophilic substitution process, *ipso* substitution and addition functionalisation of 4-*tert*-butyl phenol (**7c**) with NFTh in acetonitrile. Relative distribution in percentage determined from ^{19}F NMR spectra of isolated reaction mixtures. Reaction conditions: substrate (1 mmol), fluorinating reagent (1 mmol), solvent (10 mL), 2–24 h (2 h for at 80 °C, 8 h at 50 and 55 °C, 24 h at 20, 30 and 35 °C).

fluorination was observed, but the effect was less pronounced with other phenols (Table 1).

Further, we investigated the effect of reagent structure on the course of functionalisation of phenols and found that the structurally similar NFTh is a comparable reagent but with higher *ortho* regioselectivity, as evident from Table 1. The pyridinium fluorinating reagent proved to be much less reactive; conversions achieved after 2 h reflux were also dependent on the substituent (5, 22, 43% for **7a**, **7b**, **7c**, respectively) with similar selectivity to F-TEDA-BF_4 and NFTh in the case of *tert*-butyl derivative **7c**, but exclusive *ortho* fluorination with *iso*-propyl derivative **7b**. As evident from Table 1 the alkyl group not only has an effect on the regioselectivity, but also on the further transformation of the intermediate formed after *para* attack. In the case of the methyl group, the hydroxyl group lost a proton and the dienone derivative **9a** was formed exclusively, but in the case of the *tert*-butyl derivative the alkyl group left the molecule giving 4-fluoro phenol (**10**). This reaction channel could be explained by the stability of the *tert*-butyl cation as a leaving group from the intermediate formed after *para* attack, or by the instability of 4-*tert*-butyl-4-fluoro-cyclohexa-2,5-dienone. To clarify the reaction pathways yielding addition or *ipso* substitution products at the *para* position, we studied the effect of temperature on fluorination of 4-*tert*-butyl phenol (**7c**) with NFTh in acetonitrile and found that the product distribution was significantly dependent on the temperature used. As evident from Figure 2, at room temperature 60% of *ortho* attack was accompanied by 40% of the addition process, yielding cyclohexadienone product **9c**.

At higher temperature (80 °C) the regioselectivity was unchanged, the amount of *ortho* attack remaining unchanged, while the cyclohexadienone product is no longer found and 40% of 4-fluoro phenol (**10**) was formed with comparably high conversions in all experiments (85–95%). Further, we studied the stability of 4-*tert*-butyl-4-fluoro-cyclohexa-2,5-dienone (**9c**) in acetonitrile or methanol under reflux and after 2 h no conversion to **10** was observed. On the other hand, when the reaction mixture obtained after fluorination of **7c** at room temperature (60% **8c**, 40% **9c**) was heated for another hour at 80 °C, the dienone product **9c** was completely converted to 4-fluorophenol (**10**). This conversion was also independently confirmed recently.[12] These experiments indicate that 4-fluorophenol (**10**) was probably formed from cyclohexadienone derivative **9** under the given reaction conditions and not by the *ipso* substitution process from the precursor carbonium ion (**CB**, Scheme 3).



Scheme 3.

In continuation, we investigated the kinetics of the reaction of phenol (**1**) with F-TEDA-BF_4 in water and acetonitrile, monitoring the process of transformation by iodometric titration and found that the rates of fluorination obey the

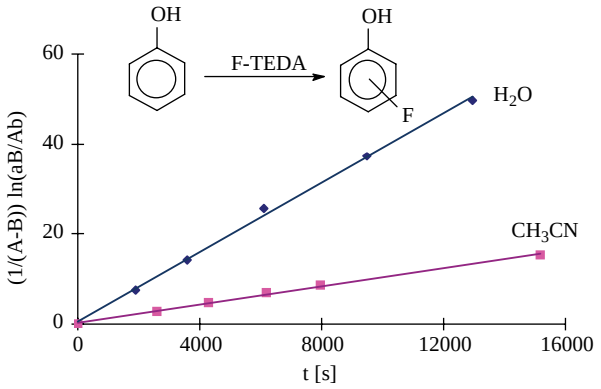


Figure 3. Effect of solvent on the reaction of phenol (**1**) with F-TEDA-BF_4 at 40 °C.

simple rate equation (Fig. 3):

$$v = \mathrm{d[F\text{–}N]}/\mathrm{d}t = k_2[\mathrm{F\text{–}N}][Y\text{-}C_3H_4\text{–}OH]$$

Table 2. Effect of solvent and reaction temperature on the second order rate constants for the functionalisation of phenol (**1**), *p*-hydroquinone (**2**), *p*-methoxyphenol (**3**), 4-methylphenol (**7a**), 4-*iso*-propylphenol (**7b**), 3-methyl-4-*iso*-propylphenol (**11a**) and 3,4,5-trimethylphenol (**11b**) with F-TEDA-BF_4

Subst.	Solvent	T (°C)	k_2 (10^{-3} M^{-1} s^{-1})[a]	$\Delta H^{\neq}$ (kJ/mol)	$\Delta S^{\neq}$ (J/mol K)
1		35	2.3		
	H_2O	40	3.9	83±1	−27±1
		45	6.5		
		35	0.63		
	MeCN	40	1.0	80±3	−49±3
		45	1.7		
2		7	21		
	H_2O	12	36	59±3	−68±8
		17	51		
		7	11		
	MeCN	12	19	68±4	−39±4
		17	30		
3		17	38		
	H_2O	22	54	58±3	−74±5
		26	81		
		19	22		
	MeCN	22	36	60±7	−70±12
		25	41		
	MeOH/	19	75		
	H_2O	22	102	73±4	−18±1
	9:1	26	137		
7a		35	4.8		
	MeCN	40	8.7	86±2	−10±0.4
		46	14		
7b		35	5.1		
	MeCN	40	8.6	85±2	−14±0.5
		46	15		
11a		15	7.9		
	MeCN	20	15	76±2	−21±0.4
		25	24		
11b		0	22		
	MeCN	2	28	70±2	−17±0.5
		5	50		

[a] An average from at least three measurements with no more than 3% relative error.

As evident from Table 2, reaction was faster in water than in acetonitrile. Oxidation of *p*-hydroquinone (**2**) with F-TEDA-BF_4 to *p*-quinone[8] also obeyed a second order rate equation, but the process was much faster than fluorination of the aromatic ring in **1** and the effect of solvent polarity less pronounced than in the fluorination process ($k_2^{\text{water}}/k_2^{\text{acetonitrile}}=1.9$ for oxidation and 3.6 for fluorination). The reactivity of the *p*-methoxy derivative (**3**), which is also converted to *p*-quinone,[8] lay in between that of hydroquinone and phenol and the effect of solvent polarity on the oxidation–demethylation process was less pronounced than in the case of the above mentioned processes (Table 2) ($k_2^{\text{water}}/k_2^{\text{acetonitrile}}=1.5$). However, transformation in methanol–water mixture (9/1) was almost twice as fast than in water alone. Introduction of a methyl group at the *para* position enhanced functionalisation in acetonitrile by a factor of 7.6 while no substantial increase was observed when the methyl group is replaced by *iso*-propyl (Table 2). A further increase in reactivity was achieved when one or two additional alkyl groups were introduced into the aromatic ring, that is, 3-methyl-4-*iso*-propylphenol (**11a**) or 3,4,5-trimethylphenol (**11b**).

Important information about the course of functionalisation of aromatic molecules with the F–N type of reagents could be obtained from the activation parameters, but up to now no such data were available for this kind of reagent. We therefore investigated the activation parameters for all three types of transformations on the phenyl ring and also studied the effect of solvent. It is evident that the highest activation enthalpy is required for fluorination, while for oxidation and oxidative demethylation almost the same $\Delta H^{\neq}$ was established, the activation enthalpy increasing in methanol–water solution for the transformation of **3**. As also evident from Table 2, differences in activation entropies that were observed in both the type of functionalisation and in the effect of solvent on the geometry of the process are important. In the fluorination process, a decrease of solvent polarity was reflected in a lowering of activation entropy, while the opposite effect was observed in oxidation (−68± 8 J/mol K for water and −39±4 J/mol K for acetonitrile). The most interesting case is the oxidation–demethylation process where differences between water and acetonitrile were not so pronounced, but the transition state in the presence of methanol must be much less ordered than in the case of water. Introduction of a methyl group in phenyl ring increased the activation enthalpy of fluoro functionalisation in acetonitrile and caused significant changes in activation entropies (−49 J/mol K for **1**, −10 for **7a**; Table 2). Further introduction of alkyl groups (**11a**, **11b**) decreased activation enthalpies and changed activation entropies.

Important information about the nature of the intermediate in the functionalisation of the aromatic molecule could be obtained by using solvents with various dielectric constants or by using mixtures of solvents for which the Grunwald–Winstein *Y* values have already been determined;[13] very large variations were observed for acetonitrile–water solutions.[14] Unfortunately, reactions with F–N type of reagents are solvent dependent, where small changes could completely halt the process or alter its course. Functionalisation of substituted phenols with F-TEDA-BF_4 proceeded very well in acetonitrile or water, and fortunately

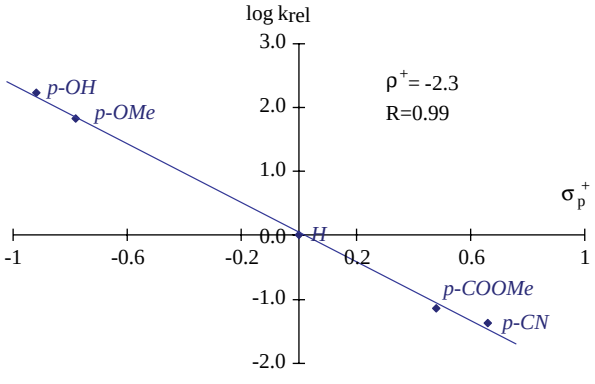
Table 3. Effect of solvent polarity (Y_{benzyl}) on the second order rate constants for the reactions of phenol (**1**), *p*-hydroquinone (**2**), *p*-methoxyphenol (**3**) and 3-methyl-4-*iso*-propyphenol (**11a**) with F-TEDA-BF_4 in acetonitrile–water solutions[a]

Solvent[b]	Y_{benzyl}[c]	k_2 (10^{-3} M^{-1} s^{-1})			
		1	**2**	**3**	**11a**
90An	−1.45	1.8	63	40	29
80An	−0.35	1.5	51	29	20
60An	0.81	1.3	42	19	15
40An	1.74	1.7	38	23	
20An	2.72	2.8	43	35	

[a] Reactions at 40 °C for **1**, at 17 °C for **2**, at 22 °C for **3** and at 25 °C for **11a**.
[b] % v/v of acetonitrile in water solution.
[c] Values from Ref. 14.

acetonitrile–water mixtures have a very large range of *Y* values.[14] However, as evident from Table 3, variation of *Y* in the range of 4.17 units had only a small effect on second order rate processes for functionalisation of phenol (**1**), *p*-hydroquinone (2), *p*-methoxyphenol (**3**) and 3-methyl-4-*iso*-propylphenol (**11a**). The small effect of solvent polarity on the second order rate constants indicated a small change in the polarity of the rate determining transition state in comparison to the reactants.

Hammett correlations have several times been used in investigating the effect of substituents on the transformation of aromatic molecules.[15] A very good kinetic correlation with σ_p^+ has been demonstrated in the reactions of *para* substituted phenols with peroxynitrite ($ONOO^-$), in spite of the fact that functionalisation (nitration or hydroxylation) occurred at the position meta to the substituent.[16] We undertook a similar investigation, although reactions with phenols bearing electron withdrawing groups give complex reaction mixtures, fluoro substituted products not being the major ones, while in the case of a hydroxyl substituent, a high yield oxidation process took place and oxidation followed by demethoxylation giving *p*-quinone was observed with *p*-methoxyphenol (**3**).



Y	σ_p^+	k_2 [$M^{-1}s^{-1}$]	log $k_{rel.}$
p-OH (**2**)	-0.92	2.8	2.24
p-OMe (**3**)	-0.78	1.1	1.83
H (**1**)	0	1.6×10^{-2}	0.00
p-COOMe (**4**)	0.48	1.2×10^{-3}	-1.14
p-CN (**5**)	0.66	7.1×10^{-4}	-1.36

Figure 4. Hammett correlation plot (log k_{rel}/σ_p^+) for the functionalisation of *para* substituted phenols (**1–5**) with F-TEDA-BF_4 at 70 °C in acetonitrile.

As evident from Figure 4 an excellent correlation with σ_p^+ with a value of $\rho^+ = -2.3$ was established. It is interesting that the correlation was excellent in spite of the fact that different types of phenyl ring functionalisation were involved. The similar behaviour of *para* substituted phenols on functionalisation as in the case of nitration and hydroxylation could be explained by the formation of cation radicals after one electron transfer from the aromatic nucleus to the F–N reagent, while further reactions resulted in various types of product. Formation of cation radicals has also been confirmed by UV and ESR spectroscopy in halogenations with N–X reagents (NBS, NCS, …) of electron-rich aromatic molecules.[17,18] Effective transformation of cation radicals to fluoro substituted products in our case was best achieved when alkyl groups (**7**, **11**) are present at position four.

Two reaction channels resulting after fluorine attack at position 2 or 4 giving fluoro carbonium ions are presented in Scheme 3 (**CA** and **CB**). As evident from an independent experiment, 4-fluorophenol (**10**) was formed from cyclohexadienone derivative **9** at higher temperature as was observed with substrates bearing a substituted tertiary carbon atom (i.e., in the case of the *tert*-butyl derivative **7c**).

3. Conclusion

In summarizing our observations, we can state that steric interactions and reaction conditions strongly influenced the regioselectivity of fluorination of *para* alkyl substituted phenols with F–N reagents. The site of fluorination depended on the size of the substituent, the structure of the F–N reagent and the solvent. In MeCN, the methyl group favoured attack at the *para* position (66%), while bulky alkyl substituents like *t*Bu or the 1,1,3,3-tetramethyl-butyl (*t*Oct) group caused a change of the regioselectivity and *ortho* fluorination (60 and 88%) was found to be dominant. On the other hand, analogous reactions in MeOH resulted in exclusive fluorination of the position two in the case of 4-methylphenol, and predominant fluorofunctionalisation at the same position in the case of other 4-alkyl-substituted phenols. The structure of the alkyl substituents also influenced the type of fluorofunctionalisation, since attack at the *para* position resulted in the addition process thus forming 4-fluoro-4-alkyl-cyclohexa-2,5-dienone derivatives **9**, while the substitution process resulting in formation of 2-fluoro-4-alkylphenol derivatives **8** followed *ortho* attack. Reactions of F-TEDA-BF_4 with phenol derivatives bearing electron withdrawing substituents (**4**, **5**) resulted in complex reaction mixtures, while *p*-hydroquinone (**2**) and *p*-methoxyphenol were transformed to *p*-quinone. Kinetic studies on the transformation of *para* substituted phenols with F-TEDA-BF_4 carried out in water, acetonitrile or water–acetonitrile mixtures at various temperatures established that the course of the reaction obeyed the simple rate equation $v = d[F\text{–}N]/dt = k_2[F\text{–}N][Y\text{-}C_6H_4\text{–}OH]$ for all types of transformations. Higher $\Delta H^{\neq}$ activation was required for the fluorination process ($\Delta H^{\neq}$: 80–83 kJ/mol) than for oxidation ($\Delta H^{\neq}$: 59–68 kJ/mol) or oxidative demethylation ($\Delta H^{\neq}$: 58–73 kJ/mol). A very pronounced effect of solvent polarity on activation entropies was observed in all three types of functionalisation (fluorination,

oxidation, oxidative demethylation), but the effect depended on the type of transformation. In order to obtain more insight into the nature of the rate determining step in transformations of *para* substituted phenols with F-TEDA-BF_4, Grunwald–Winstein correlation analysis carried out and since only a small effect of solvent polarity variation on reaction rates was established we can presume that the polarity of the rate determining state is not so different from the reactants. On the basis of the excellent Hammett correlation plot obtained for reactions of *para* substituted phenols with with F-TEDA-BF_4 ($\rho^+ = -2.3$; $R = 0.99$) we can also anticipate similar nature of the key intermediate of these reactions, although the type of products strongly depended on the substituents.

4. Experimental

Melting points were determined on a Büchi 535 apparatus. ^{1}H NMR spectra were recorded on a Varian EM 360L at 60 MHz or on a Varian INOVA 300 spectrometer at 300 MHz, and ^{13}C NMR spectra on the same instrument at 76 MHz. Chemical shifts are reported in parts per million from TMS as the internal standard. ^{19}F NMR spectra were recorded on a Varian EM 360L at 56.4 MHz and chemical shifts are reported in parts per million from CCl_3F as internal standard. IR spectra were recorded on a Perkin-Elmer 1310 spectrometer. Standard KBr pellet procedures were used to obtain IR spectra of solids, while a film of neat material was used to obtain IR spectra of liquid products. Mass spectra were obtained on an Autospec Q instrument under electron impact (EI) conditions at 70 eV. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN analyzer or obtained from Mikranalytisches Labor Pascher, Germany. 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)[19] (Selectfluor™ F-TEDA-BF_4; Air Products) was crystallised from an acetonitrile–methanol mixture and dried in a vacuum at 20 °C. 1-Fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate) (Accufluor™ NFTh, 50% w/w on Al_2O_3) was received as a gift from Allied Signal and used as obtained. *N*-Fluoro-2,6-dichloropyridinium tetrafluoroborate (FP-B800) was received from Chichibu Onoda Cement Corp., Japan, and also used as obtained. Other starting materials were obtained from commercial sources. Acetonitrile and methanol were purified by distillation and stored over molecular sieves.

4.1. Fluorination of phenols (7) with 'F–N' reagents; general procedure

To a solution of substrate **7** (1 mmol) in 10 mL of solvent (MeCN, MeOH or CH_2Cl_2) 1 mmol of fluorinating agent (F-TEDA-BF_4, NFTh or FP-B800 was added, the reaction mixture stirred at reflux temperature until the fluorinating agent was consumed (KI starch paper). The reaction solvent was removed under reduced pressure, the crude reaction mixture dissolved in 50 mL of dichloromethane, washed with water (20 mL), dried over Na_2SO_4, the solvent evaporated, the reaction mixture analyzed by ^{1}H and ^{19}F NMR spectroscopy and the relative distribution of products was determined. The amount of fluorinated products present in the reaction mixture was determined from ^{19}F NMR spectra using octafluoronaphthalene (OFN) as internal standard. Pure compounds were isolated by column chromatography and identified on the basis of spectroscopic data and elemental combustion analysis or high resolution MS spectroscopy, while in the case of known compounds comparison with literature data was made. Sufficient purity of all compounds was determined by ^{1}H NMR spectroscopy.

4.1.1. 2-Fluoro-4-methyl-phenol (8a).[20] Reaction conditions: F-TEDA-BF_4/MeOH/reflux/2 h: 120 mg crude reaction mixture (contained 65 mg of **8a**, determined by OFN), column chromatography (SiO_2/CH_2Cl_2) gave 43 mg (34%) of oily product.

4.1.2. 2-Fluoro-4-isopropyl-phenol (8b). Reaction conditions: F-TEDA-BF_4/MeOH/reflux/2 h: 135 mg crude reaction mixture (contained 80 mg of **8b**, determined by OFN), column chromatography (SiO_2/$CHCl_3$) gave 65 mg (42%) of brown oily product. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, $J=6.9$ Hz, 6H, Me), 2.83 (heptet, $J=6.9$ Hz, 1H, CH), 3.79 (d, $J=2.3$ Hz, 1H, OH), 6.87–6.89 (m, 1H, ArH), 6.90–6.92 (m, 1H, ArH), 6.94–6.95 (m, 1H, ArH); ^{13}C NMR (76 MHz, $CDCl_3$) δ 24.0 (CH_3), 33.3 (CH), 113.3 (d, $J=$ 17.4 Hz, ArCH), 116.9 (d, $J=1.3$ Hz, ArCH), 122.4 (d, $J=$ 2.3 Hz, ArCH), 141.2 (d, $J=14.2$ Hz, ArCOH), 142.0 (d, $J=4.9$ Hz, ArC), 150.9 (d, $J=237.2$ Hz, ArCF); ^{19}F NMR (56.4 MHz, $CDCl_3$) δ −141.0 (m); MS (EI, 70 eV) *m/z* 154 (30, M^+), 139 (100), 109, 91; high resolution MS: *m/z* 154.079503 (calcd for $C_9H_{11}FO$ *m/z* 154.079393).

4.1.3. 2-Fluoro-4-*tert*-butyl-phenol (8c)[8] Reaction conditions: F-TEDA-BF_4/MeOH/reflux/4 h: 141 mg crude reaction mixture (contained 113 mg of **8c**, determined by OFN), column chromatography (SiO_2/$CHCl_3$) gave 75 mg (45%) of oily product.

4.1.4. 2-Fluoro-4-(1,1,3,3-tetramethyl-butyl)-phenol (8d). Reaction conditions: F-TEDA-BF_4/MeOH/reflux/4 h: 177 mg crude reaction mixture (contained 118 mg of **8d**, determined by OFN), column chromatography (SiO_2/CH_2Cl_2) gave 75 mg (33%) of light brown crystalline product, mp 59–60 °C, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.72 (s, 9H, *t*Bu), 1.32 (s, 6H, $2CH_3$), 1.68 (s, 2H, CH_2), 5.12 (s, 1H, OH), 6.90 (m, 1H, ArH), 7.01 (m, 1H, ArH), 7.06 (m, 1H, ArH); ^{13}C NMR (76 MHz, $CDCl_3$) δ 31.6 (CH_3), 31.7 (CH_3), 32.3 (C), 38.1 (C), 56.9 (CH_2), 113.4 (d, $J=18.4$ Hz, ArCH), 116.3 (d, $J=$ 2.1 Hz, ArCH), 122.2 (d, $J=3.0$ Hz, ArCH), 140.7 (d, $J=$ 14.7 Hz, ArCOH), 143.5 (d, $J=4.7$ Hz, ArC), 150.6 (d, $J=$ 235.6 Hz, ArCF); ^{19}F NMR (56.4 MHz, $CDCl_3$) δ −141.6 (m); MS (EI, 70 eV) *m/z* 224 (5, M^+), 153 (100), 57 (35); high resolution MS: *m/z* 224.158320 (calcd for $C_{14}H_{21}FO$ *m/z* 224.157644). Anal. Calcd for $C_{14}H_{21}FO \cdot 1/4H_2O$ C, 73.49; H, 9.47. Found: C, 73.34; H, 9.26.

4.1.5. 4-Fluoro-4-methyl-cyclohexa-2,5-dienone (9a).[21] Reaction conditions: F-TEDA-BF_4/MeCN/reflux/2 h: 102 mg crude reaction mixture (contained 46 mg of **9a**, determined by OFN), column chromatography (SiO_2/CH_2Cl_2) gave 33 mg (26%) of dense oily product.

4.1.6. 4-Fluoro-4-isopropyl-cyclohexa-2,5-dienone (9b).[10] Reaction conditions: F-TEDA-BF_4/MeCN/reflux/2 h: 125 mg crude reaction mixture (contained 72 mg of **9b**,

determined by OFN), column chromatography (SiO_2/CH_2Cl_2) gave 48 mg (31%) of dense oily product.

4.1.7. 4-*tert*-Butyl-4-fluoro-cyclohexa-2,5-dienone (9c).[12] Reaction conditions: NFTh/MeCN/20 °C/24 h: 160 mg crude reaction mixture (contained 59 mg of **9c**, determined by OFN), column chromatography (SiO_2/CH_2Cl_2) gave 49 mg (29%) of yellow crystals, mp 63.1–63.4 °C; ^{1}H NMR (60 MHz, CCl_4) δ 1.1 (d, $J=19$ Hz, 9H), 6.3 (d, $J=13$ Hz, 2H), 7.0 (dd, $J=17$, 13 Hz, 2H); ^{19}F NMR (56.4 MHz, CCl_4) δ −165.3 (m); MS (EI, 70 eV) *m/z* 168 (M^+, 21%), 153 (75), 135 (65), 125 (35), 107 (25), 91 (12), 83 (15), 57 (100); high resolution MS: *m/z* 168.0957 (calcd for $C_{10}H_{13}FO$: 168.0950).

4.1.8. 4-Fluorophenol (10).[22] Reaction conditions: 4-*tert*-butyl-phenol/NFTh/MeCN/reflux/2 h: 170 mg crude reaction mixture (contained 38 mg of **10**, determined by OFN), column chromatography (SiO_2/CH_2Cl_2) gave 25 mg (18%) of crystalline product, mp 46 °C (lit.[22] 43–45 °C).

4.2. Determination of second rate order constants and acti vation parameters for functionalisation of phenol (1), *p*-hydroquinone (2), *p*-methoxyphenol (3), 4-methylphenol (7a), 4-*iso*-propylphenol (7b)3-methyl-4-*iso*-propylphenol (11a) and 3,4,5-trimethylphenol (11b) with F-TEDA-BF_4

To 40 mL of a thermostatted acetonitrile solution of substrate (0.3, 0.6, 0.9, 1.2, 1.8 mmol), 20 mL of a thermostatted solution of F-TEDA-BF_4 (0.66 mmol) was added and stirred at various temperatures. The progress of F-TEDA-BF_4 consumption was monitored by iodometric titration. Second order rate constants were calculated from

$$1/(A-B)\ln(Ba/Ab) = k_2 t \quad (1)$$

and a linear relationship was found. The effect of solvent on second order rate constants for the functionalisation of **1**, **2**, **3**, **7a**, **7b**, **11a** and **11b** with F-TEDA-BF_4 is presented in Table 2 and Figure 3. Rate constants are averages from at least three measurements with no more than 3% relative error. Further we investigated the effect of temperature on k_2; a linear correlation was found and activation parameters were calculated by linear regression from

$$\ln(k_2/T) = \ln(k_B/h) + \Delta S^{\neq}/R - \Delta H^{\neq}/RT \quad (2)$$

Second order rate constants for Hammett correlation studies for the reaction of substrates **4** and **5** with F-TEDA-BF_4 were determined in acetonitrile at 70 °C, while k_2 for substrates **1**, **2** and **3** under the same reaction conditions were calculated from Eq. 2 and the results are presented in Figure 4.

4.3. The effect of solvent polarity on second order rate con stants for functionalisation of phenol (1), *p*-hydroquinone (2), *p*-methoxyphenol (3) and 3-methyl-4-*iso*-propylphenol (11a)

1.2 mmol of substrate was dissolved in 40 mL of various acetonitrile–water mixtures (acetonitrile–water = 34+6; 28+12; 16+24; 10+30; 4+36; 0+40), thermostatted at 40 °C for **1**, 17 °C for **2**, at 22 °C for **3** and at 25 °C for **11a**, 20 mL of a thermostatted acetonitrile solution containing 0.6 mmol F-TEDA-BF_4 was added and stirred. The progress of F-TEDA-BF_4 consumption was monitored by iodometric titration. The results are presented in Table 3.

Acknowledgements

The authors are grateful to K. Žmitek, A. Gačeša and Dr. J. Plavec for NMR spectra and to the Ministry of Higher Education, Science and Technology of the Republic of Slovenia for financial support.

References and notes

1. (a) Rappoport, Z. *The Chemistry of Phenols. Part 1*; Wiley: Chichester, 2003. (b) Patai, S.; Rappoport, Z. *The Chemistry of Phenols. Part 2*; Wiley: Chichester, 2003.
2. (a) Filler, R.; Kobayashi, Y.; Yagupolskii, L. M. *Organo-fluorine Compounds in Medicinal Chemistry and Biological Applications*; Elsevier: Amsterdam, 1993. (b) Filler, R.; Kobayashi, Y. *Biomedical Aspects of Fluorine Chemistry*; Elsevier: Amsterdam, 1982. (c) Welch, J. T.; Eswarakrishanan, S. *Fluorine in Bioorganic Chemistry*; Wiley: Canada, 1991.
3. Patani, G. A.; Lavoie, E. J. *Chem. Rev.* **1996**, *96*, 3147–3176.
4. (a) Tius, M. A. *Tetrahedron* **1995**, *24*, 6605–6634. (b) Wilkinson, J. A. *Chem. Rev.* **1992**, *92*, 505–519. (c) Rozen, S. In *The Formation of the C–F Bond: The Last Twelve Years*; Patai, S., Rappoport, Z., Eds.; The Chemistry of Functional Groups, Supplement D2: The Chemistry of Halides, Psevdo--Halides and Azides, Part 1 and 2; Wiley: Chichester, 1995; pp 629–708. (d) Rozen, S. *Chem. Rev.* **1996**, *96*, 1717–1736. (e) Zupan, M. In *Functionalization of Organic Molecules by Xenon Fluorides*; Patai, S., Rappoport, Z., Eds.; The Chemistry of Functional Groups, Supplement D2: The Chemistry of Halides, Psevdo-Halides and Azides. Part 1 and 2; Wiley: Chichester, 1995; pp 821–860. (f) *New Fluorinating Agents in Organic Synthesis*; German, L., Zemskov, S., Eds.; Springer: Berlin, 1989. (g) *Methods in Organic Chemistry (Hauben-Weyl)*; Baasner, B., Hagenann, H., Tatlow, J. C., Eds.; Organo-fluorine Compounds; Thieme: Stuttgart, 1999; Vol. E 10a. (h) Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, 2004.
5. (a) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737–1755. (b) Banks, R. B. *J. Fluorine Chem.* **1998**, *87*, 1–17. (c) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431–12477. (d) Furin, G. G.; Fainzilberg, A. A. *Russ. Chem. Rev.* **1999**, *68*, 653–684. (e) Singh, R. P.; Shreeve, J. M. *Acc. Chem. Res.* **2004**, *37*, 31–44. (f) Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192–212. (g) Stavber, S.; Zupan, M. *Acta Chim. Slov.* **2005**, *52*, 13–26. (h) Stavber, S.; Zupan, M. In *N*-Fluoro-diazonia-bicyclo[2.2.2]octane dication Salts; Efficient Fluorination Agents and Functionalization Mediators for Organic Compounds; Rahman, A., Laali, K. K., Eds.; Advances in Organic Synthesis; Bentham Science: San Francisco, 2006; Vol. 2, pp 213–267.
6. Zupan, M.; Papez, M.; Stavber, S. *J. Fluorine Chem.* **1996**, *78*, 137–140.
7. Zupan, M.; Iskra, J.; Stavber, S. *J. Fluorine Chem.* **1995**, *70*, 7–8.

8. Zupan, M.; Iskra, J.; Stavber, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1655–1660.
9. Zupan, M.; Iskra, J.; Stavber, S. *Tetrahedron* **1996**, *52*, 11341–11348.
10. Stavber, S.; Jereb, M.; Zupan, M. *Synlett* **1999**, 1375–1378.
11. Stavber, S.; Jereb, M.; Zupan, M. *J. Phys. Org. Chem.* **2002**, *15*, 56–61.
12. Bienvenu, A.; Barthelemy, A.; Boichut, S.; Marquet, B.; Billard, T.; Langlois, B. R. *Collect. Czech. Chem. Commun.* **2002**, *67*, 1467–1478.
13. Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* **1948**, *70*, 846–854.
14. Bentley, T. W.; Dauschmidt, J. P.; Llewellyn, G.; Mayr, H. *J. Org. Chem.* **1992**, *57*, 2387–2392.
15. Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195.
16. Nonoyama, N.; Chiba, K.; Hisatome, K.; Suzuki, H.; Shintani, F. *Tetrahedron Lett.* **1999**, *40*, 6933–6937.
17. Eberson, L.; Hartshorn, M. P.; Radner, F.; Persson, O. *J. Chem. Soc., Perkin Trans. 2* **1998**, 59–70.
18. Eberson, L.; Hartshorn, M. P.; Radner, F.; Persson, O. *J. Chem. Soc., Chem. Commun.* **1996**, 215–216.
19. Banks, R. E.; Mohialdinkhaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G. *J. Chem. Soc., Chem. Commun.* **1992**, 595–596.
20. Singh, S.; Desmarteau, D. D.; Zuberi, S. S.; Witz, M.; Huang, H. N. *J. Am. Chem. Soc.* **1987**, *109*, 7194–7196.
21. Misaki, S. *J. Fluorine Chem.* **1981**, *17*, 159–171.
22. Stavber, S.; Zupan, M. *J. Org. Chem.* **1985**, *50*, 3609–3612.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 4482–4490
Tetrahedron

Two-way enantioselective control in the epoxidation of alkenes with the keto bile acid–Oxone® system

Olga Bortolini,[a,*] Giancarlo Fantin,[b] Marco Fogagnolo[b,*] and Lara Mari[b]

[a]*Dipartimento di Chimica, Università della Calabria, Via Bucci 12 C, 87036 Rende CS, Italy*
[b]*Dipartimento di Chimica, Università di Ferrara, Via Borsari 46, 44100 Ferrara, Italy*

Received 9 November 2005; revised 30 January 2006; accepted 16 February 2006

Available online 22 March 2006

Abstract—A number of 3-keto bile acid derivatives has been prepared and evaluated in the asymmetric epoxidation of unfunctionalized olefins with Oxone. The control of the enantioselectivity with the production of both enantiomers is strictly regulated by the bile acid inductor, as a function of substitution at carbons C(7) or C(12). Up to 98% ee has been achieved. The stereochemical outcome of the reaction may be rationalized in terms of spiro transition state model.

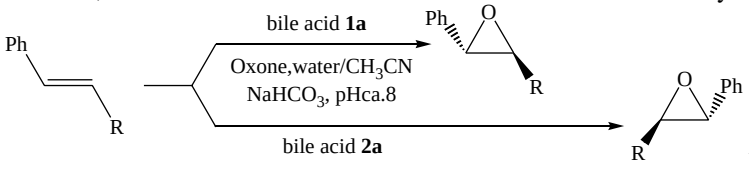
1. Introduction

Optically active epoxides are useful chiral synthons in organic synthesis and various chemical and biological methods have been developed for the preparation of these derivatives.[1] The asymmetric epoxidation of alkenes represents the most direct approach to these compounds[2] and impressive results have been achieved by many research groups in the epoxidation of allylic alcohols,[3] non-activated olefins[4,5] and in the nucleophilic epoxidation of electron-poor alkenes.[6,7] Chiral dioxiranes embody a new generation of enantioselective oxidants for olefin epoxidation[8] and *vic*-diol oxidation.[8c] These non-metal peroxidic oxygen transferring agents are readily prepared from suitable optically active ketones and potassium monoperoxysulfate (Oxone®) under buffered and mild conditions.

The epoxidation is stereospecific and occurs using the in situ generated dioxiranes both in stoichiometric and catalytic conditions.[8] Since the first report by Curci et al.[9] utilizing an optically active butanone derivative, various chiral ketones have been investigated by many laboratories and considerably high enantiomeric excess values have been reported for terminal, trans- and cis-disubstituted and trisubstituted alkenes, as well as for functionalized carbon–carbon double bonds.[8] In particular, the high enantioselective epoxidation of styrenes represented an important challenge for many research groups, with results ranging from good to excellent.[10]

With this background and based on our recent work, we have reported that bile acid-derived ketones **1** of Chart 1, in association with Oxone, served as efficient oxidant in the asymmetric epoxidation of electron-poor[11] and simple olefins.[12]

In this epoxidation procedure, the control of the sense of the enantioselection was strictly regulated by the bile acid inductor, as a function of substitution at carbons C(7) or C(12) of the steroidal framework. As an example, in the epoxidation of cinnamic acid derivatives, specific and stereochemically appropriate C(7) substitution led to the formation of (−) epoxides of (2*R*,3*S*) absolute configuration,[13] whereas C(12) substituted bile acids promote the formation of the opposite (+)-(2*S*,3*R*) epoxides **2** of Chart 1.[11,13] This important stereochemical control has also been found in the oxidation of mono-, trans-, *gem*-disubstituted and trisubstituted unfunctionalized alkenes,[12] with a systematic inversion of the epoxide configuration by



(1)

Keywords: Enantioselective epoxidation; Oxone; Bile acids; Chiral dioxiranes.
* Corresponding authors. Tel.: +39 0984 492850; fax: +39 0984 493307 (O.B.); fax: +39 0532 240709 (M.F.); e-mail addresses: o.bortolini@unical.it; fgr@unife.it

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.052

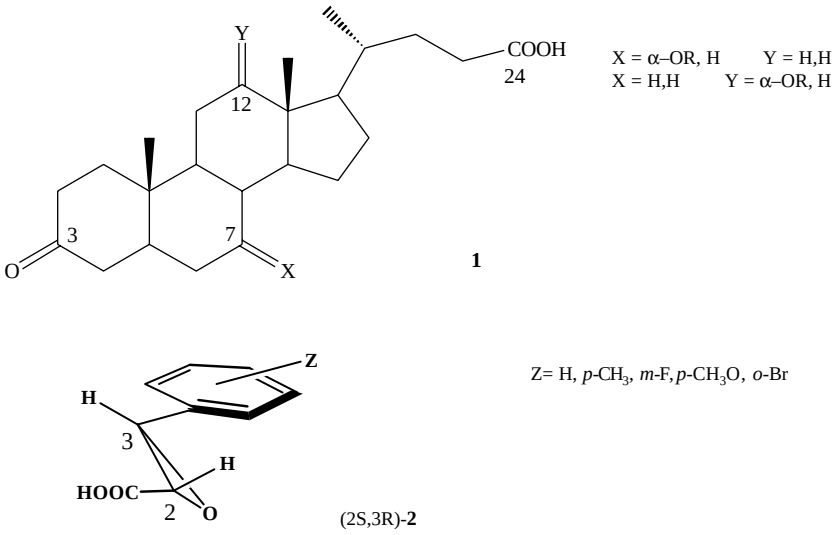
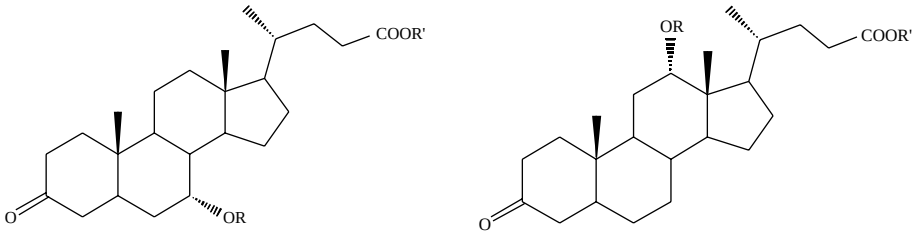


Chart 1. Bile acid-derived ketones **1** and (2*S*,3*R*)-cinnamic acid epoxides **2**.

changing the position of the C(7)/C(12) substituent on **1**, (Eq. 1).

As part of our efforts to understand the structural requirements and factors involved in this asymmetric epoxidation, we have synthesized some new **1**-type bile acid derivatives all having a C(3) carbonyl function and substituents at C(7) or C(12) of different polarity and bulkiness. In addition, the stereochemical outcome of the



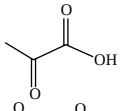
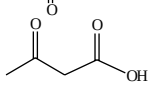
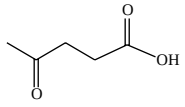
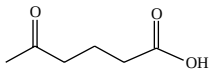
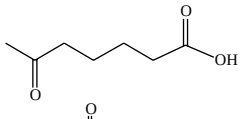
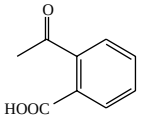
7-substituted bile acid	R	R'	12-substituted bile acid
3a	H	H	**4a**
3b		CH_3	**4b**
3c		CH_3	**4c**
3d		H	--
--		CH_3	**4d**
3e		CH_3	**4e**
3f		CH_3	**4f**
3g		CH_3	**4g**
3h		H	**4h**

Chart 2. 3-Keto-5-β-cholan-24-oic acids investigated in this study.

reaction has been rationalized with the help of the spiro transition state model.[8a]

2. Results and discussion

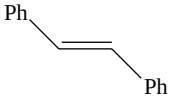
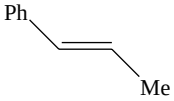
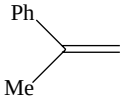
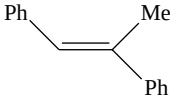
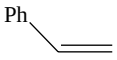
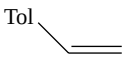
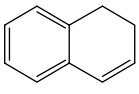
2.1. Epoxidation studies

The systematic study of the role played by the C(7)/C(12) substituent characteristics and steric size was carried out by preparing the ketones **3a–h** and **4a–h**, and by investigating their performances with respect to enantioselectivity. Ketones **3a–h** and **4a–h**, shown in Chart 2, are readily obtained from common, low cost and commercially available bile acids by adapting literature procedures.

The structure of the bile acids is characterized by a remarkable robustness and rigidity that prevents any distortion, thus maintaining the chiral elements of the carbonyl function also after its conversion into dioxirane. The epoxidation reaction was carried out in water–CH_3CN (1/1) EDTA, pH ca. 8 using equimolar concentrations of substrate and bile acid in the presence of an excess of Oxone. The results of the epoxidation of various alkenes are shown in Table 1.

With all substrates the epoxidation is complete in 12 h at 0 °C, with enantiomeric excesses varying from excellent

Table 1. Asymmetric epoxidation of selected unfunctionalized alkenes with Oxone in the presence of 3-keto-7-substituted and 3-keto-12-substituted bile acids[a]

Substrate	7-Substituted bile acids				12-Substituted bile acids			
		Yield (%)	ee (%)	Absolute configuration		Yield (%)	ee (%)	Absolute configuration
	**1a**	90	54	(−)-(*S*,*S*)[18]	**2a**	55	43	(+)-(*R*,*R*)[18]
	1b	90	80		**2b**	90	90	
	1c	60	80		**2c**	45	80	
	1d	92	40		**2d**	45	60	
	1e	70	80		**2e**	45	85	
	1f	60	70		**2f**	40	70	
	1g	80	60		**2h**[b]	50	98	
	**1a**	99	37	(−)-(*S*,*S*)[19]	**2a**	80	15	(+)-(*R*,*R*)[19]
	1b[c]	25	70		**2b**[c]	50	70	
	1c	99	70		**2c**	70	50	
	1d	60	47		**2d**[d]	10	78	
	1e[e]	40	60		**2e**	99	65	
	1f	95	60		**2f**[f]	30	55	
	1g	40	70		**2h**	20	66	
	**1a**	99	33	(+)-*S*[20]	**2a**	75	41	(−)-*R*[20]
	1b	99	50		**2b**	99	76	
	1c	60	55		**2c**	70	65	
	1d	98	50		**2d**	70	45	
	1e	99	57		**2e**	99	65	
	1f	60	50		**2f**	70	40	
	1g	40	30		**2h**	40	65	
	**1a**	50	49	(−)-(*S*,*S*)[21]	**2a**	75	44	(+)-(*R*,*R*)[21]
	1b	93	57		**2b**	83	20	
	1c	70	70		**2c**	70	84	
	1d	90	30		**2d**	50	85	
	1e	90	60		**2e**	40	75	
	1f	70	70		**2f**	90	50	
	1g	79	49		**2h**	80	85	
	**1a**	40	30	(+)-(*S*)[20]	**2a**	45	34	(−)-(*R*)[20]
	1b	55	50		**2b**	65	60	
	1c	25	50		**2c**	60	50	
	1d	80	40		**2d**	50	40	
	1e	80	35		**2e**	70	50	
	1f	50	30		**2f**	50	30	
	1g	40	40		**2h**	30	70	
	**1a**	95	30	(+)-(*S*)[22]	**2a**	65	48	(−)-(*R*)[22]
	1b	70	58		**2b**	50	60	
	1c	40	55		**2c**	50	60	
	1d	70	40		**2d**	50	60	
	1e	90	45		**2e**	99	35	
	1f	30	30		**2f**	75	50	
	1g	40	40		**2h**	45	70	
	**1b**	99	33	(+)-(1*R*,2*S*)[23]	**2b**	45	50	(−)-(1*S*,2*R*)[23]
	1c	60	30		**2c**	99	35	
	1e	80	25		**2e**	97	30	
	1g	99	20		**2h**	99	30	

[a] Reaction time usually 12 h.
[b] Reaction time (3 h), after 12 h yield 85%, ee 80%.
[c] Reaction time (3 h), after 12 h yield 90%, ee 50%.
[d] Reaction time (1 h), after 12 h yield 85%, ee 52%.
[e] Reaction time (3 h), after 12 h yield 98%, ee 35%.
[f] Reaction time (3 h), after 12 h yield 88%, ee 30%.

(98%) to moderate (30–40%) and with the systematic inversion of the configuration as a function of C(7)/C(12) bile acid substitution. The length of the alkyl chain between the carboxylic functions of the C(7)/C(12) substituent was shown to play a minor role, since the best results were obtained with oxalic (**3b**, **4b**) and phthalic (**3g**, **4h**) derivatives. Short substituents such as formyl gave results comparable to those obtained with the hydroxyl derivatives **3a** and **4a**. The protection of the bile acid as a C(24) methyl ester does not affect the course of the epoxidation reaction. Stilbene is epoxidized by Oxone in the presence of the protected derivative **3g** in 80% yield (ee 60%, see Table 1) and with the same yield but slightly higher ee (70%) when in the presence of the unprotected derivative **4h**. On the other hand, the epoxidation of β-methyl styrene gave 40% yield (ee 70%, Table 1) and 50% yield (ee 60%) if mediated by the protected **3g** or unprotected bile acid **4h**, respectively.

The α-β, that is, axial–equatorial, stereochemistry of the C(7) and C(12) substituents of the bile acid has been extensively reported in a previous paper[11a] and the results also confirmed in this case. In particular, an axial stereochemistry in both these positions is crucial for efficient enantioselective control on the formation of either one or the opposite enantiomer (see Fig. 1 for details). Equatorial substituents at C(7), in fact, gave the same epoxy enantiomers as axial substituents at C(12).[11a] Worthy of note, 3-keto-12-substituted bile acids afforded higher enantiomeric excesses compared with 3-keto-7-substituted homologues.

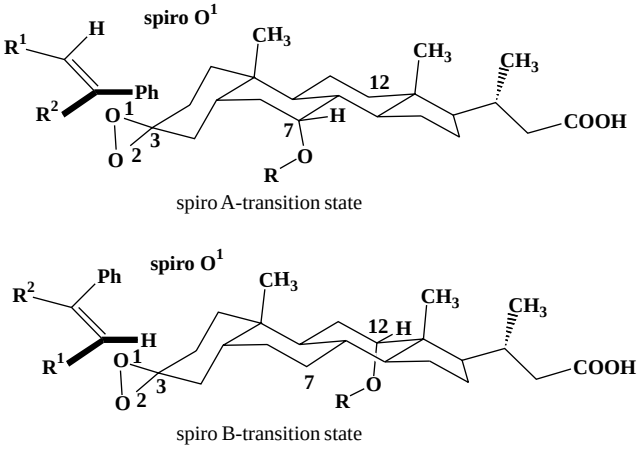


Figure 1. Spiro A-transition state for C(7)-substituted bile acids, spiro B-transition state for C(12)-substituted bile acids.

Ketones **3a–h** and **4a–h** demonstrated a remarkable structural durability with minor decomposition (ca. 10% in 24 h, likely by Baeyer–Villiger oxidation[11a]), under the oxidative reaction conditions. However, in some cases, we observed a decrease of the ee values as a function of the progress of the reaction. As an example, when β-methyl styrene is epoxidized with Oxone in the presence of the chiral ketone **3b** an ee value of 70% was measured after 3 h, that decreases to 50% after the period required to complete the oxidation (12 h). Attempts to minimize this parallel unselective oxidation are, at the moment, only moderately successful. The oxidation system may also be applied to the oxyfunctionalization of *cis*-alkenes.[14] Dihydronaphthalene, used as model substrate, is quantitatively oxidized to the corresponding epoxide, either to the (1*R*,2*S*) or to the (1*S*,2*R*) form, with enantiomeric excesses of 33 and 50%, respectively, depending on bile acid (Table 1, last entry).

Many studies reported that halogen substituents strongly increase the reactivity of the carbonyl group in the dioxirane mediated epoxidation. The use of fluorine substitution was first introduced into dioxirane chemistry by Curci et al.[15] in 1988 and then applied to chiral ketones for asymmetric catalysis by many research groups.[10c,16] In this frame, we have investigated 3-keto bile acid derivatives having halogen substituents near to the carbonyl function, in particular the 4-bromo derivatives **5** and **6** shown in Chart 3.[17]

Both chiral inductors are particularly active in the epoxidation reaction (yield 99% in 6 h at 0 °C), thus confirming the effect of halogen substituents on increasing of the carbonyl electrophilic reactivity.[10c] The enantiomeric excesses, however, are modest with values of 23 and 50%, respectively, using β-methyl styrene. We are currently encountering serious difficulties in the synthesis of the corresponding fluorinated bile acids.

Terminal olefins were confirmed difficult in epoxidation reactions and good enantioselectivities, ca. 70%, are obtained only after the partial conversion (50%) of the substrate. In 1999, Furstoss et al.[20] reported a detailed study on the determination of the absolute configuration of α-methyl styrene oxide and several styrene epoxide derivatives, that is, *p*-Cl, *m*-Cl, *o*-Cl, *p*-Br, *p*-NO_2. Conflicting optical rotation signs and, consequently, opposite absolute configurations were, in fact, described by many authors for these enantiomeric molecules. In our oxidation conditions by using 7-substituted bile acids **3a–h**, the optical rotation signs of the isolated α-methyl styrene epoxide and styrene epoxide were positive (solvent $CHCl_3$, $c=1$) and therefore assigned to a (*S*)-configuration (Table 1). The opposite (−)-*R* enantiomers were obtained for oxidations carried out in the presence of 12-substituted bile acids **4a–h**. Note that the optical rotation signs reported in our preliminary communication were not measured in chloroform.[12] Table 1 also includes the results observed with *para*-methyl styrene. A positive rotation sign was determined on the related isolated epoxide for oxidation with Oxone mediated by **3a–h** (solvent $CHCl_3$, $c=1$), however; no association with an absolute configuration might be found in the literature. The *para*-methyl styrene oxide and the styrene oxide have an identical chromatographic elution order in GC, on the chiral column used for these analysis, being the second peak the most abundant. On the other hand, based on the oxidation mechanism discussed below and depicted in Figure 1, the two alkenes should approach the dioxirane in a similar way. Following these considerations but keeping well in mind the cautions in the use of similar arguments[20] we tentatively attribute to *para*-methyl styrene oxide a (+)-*S* absolute configuration.

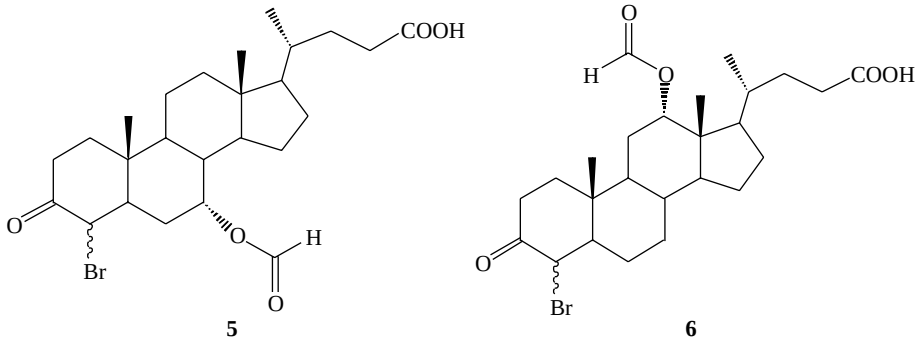
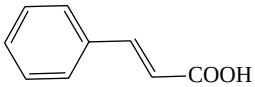
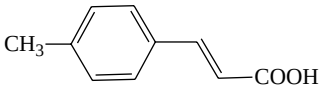
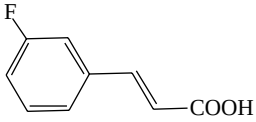
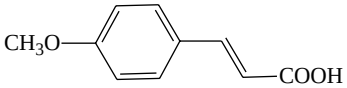
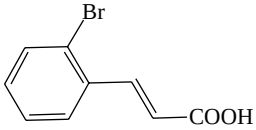


Chart 3. 3-Keto-4-bromo-5-β-cholan-24-oic acids, β predominant isomer, substituted at C(7) or C(12).

Table 2. Epoxide absolute configuration for the oxidation of cinnamic acid derivatives with Oxone, mediated by 7-substituted and 12-substituted bile acids[11a]

Substrate	7-Substituted bile acids	12-Substituted bile acids
	Epoxide absolute configuration	Epoxide absolute configuration
	(−)-(2*R*,3*S*)[13a]	(+)-(2*S*,3*R*)
	(−)-(2*R*,3*S*)[13b,d]	(+)-(2*S*,3*R*)
	(−)-(2*R*,3*S*)[13b,d,e]	(+)-(2*S*,3*R*)
	(−)-(2*R*,3*S*)[13e,16a]	(+)-(2*S*,3*R*)
	(−)-(2*R*,3*S*)[13b,d,e]	(+)-(2*S*,3*R*)

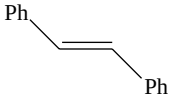
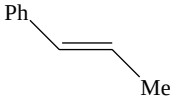
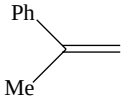
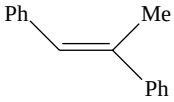
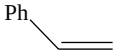
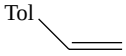
2.2. Mechanistic studies

In a previous paper on the epoxidation of cinnamic acid derivatives with the bile acid–Oxone system we have evaluated the minimized dioxirane–alkene adducts with the help of MM2 methods.[11a] Despite the low level of the calculations, the theoretical approach is effectively limited by such large system, evidence was provided for a preferential approach of the olefin to the lipophilic face of the bile acid, approach spiro O^1, with the phenyl substituent of the olefin directed toward this face. Computational studies have shown that spiro transition states are favored for the epoxidation of ethylene with dimethyldioxirane[24] and in the epoxidation of *trans*-di- and trisubstituted olefins with Oxone in the presence of fructose-derived ketones.[8a,25] On the other hand, the occurrence of an attractive interaction between π-conjugating substituents and the lipophilic face of the bile acid may parallel similar interactions proposed by Shi et al. in fructose mediated oxidations.[8a] The importance of asynchronicity in the dioxirane enantioselective epoxidation has been recently demonstrated.[26] According to the general view tending to rationalize the stereochemical course of this epoxidation in terms of a spiro model, the stereochemical outcome of the reaction for cinnamic acids, that is, R^1=COOH and R^2=H, should give rise, on the basis of the absolute configuration of the resulting epoxides collected in Table 2, to a spiro A-transition state when the bile acid is C(7) substituted, or a spiro B-transition state, when C(12) substituted (Fig. 1).

The absolute configuration of the resulting cinnamic acid epoxides is based on literature data[13] and recent VCD calculations.[13b,d] We have now applied the mechanistic approach shown in Figure 1 to the epoxidation of the unfunctionalized alkenes of this study, all containing at least a phenyl ring. The spiro A-transition state, related to a C(7) substitution of the bile acids, fully accounts for the stereochemical outcome of the reaction, as shown in Table 3.

The switch to a spiro B-transition state, proposed for C(12) substituted bile acids, gives rise to the opposite enantiomeric epoxides. From these considerations we may assert that at least for cinnamic acid-like and unfunctionalized alkenes, all containing a phenyl ring in the molecular framework, the proposed spiro model well predicts the experimental findings. We would like to point out, however, that, at this stage and taking into account the low level of

Table 3. Expected absolute configuration, based on the proposed spiro transition state model of Figure 1, and experimentally found absolute configuration for the epoxidation of the unfunctionalized alkenes of this study with 3-keto-7-substituted bile acids

Substrate	Expected absolute configuration	Found absolute configuration
	(*S*,*S*)	(−)-(*S*,*S*)[18]
	(*S*,*S*)	(−)-(*S*,*S*)[19]
	(*S*)	(+)-(*S*)[20]
	(*S*,*S*)	(−)-(*S*,*S*)[21]
	(*S*)	(+)-(*S*)[20]
	(*S*)	(+)-(*S*)[22]

calculations, the alternative spiro O^2 approach cannot be completely excluded. Work is in progress on this important problem.

3. Conclusions

In summary, we have demonstrated that the use of bile acid inducers having a carbonyl function at carbon C(3) and suitable axial C(7) or C(12) substituents has a fundamental effect on the reactivity and selectivity in asymmetric epoxidations with Oxone. The two-way enantioselective control of the stereochemistry of the resulting epoxide is strictly regulated by the bile acid inductor as a function of substitutions at carbons C(7) or C(12). Also in this case, the spiro transition state model may be successfully applied to predict the stereochemical outcome of the reaction.

4. Experimental

4.1. General methods

Oxidation reactions were monitored by quantitative GC analysis using a Megadex DETTBSβ capillary column. Optical rotations were measured in $CHCl_3$. Oxone and the alkenes of this study are all commercially available products used as received.

4.2. General procedure for epoxidation reactions

In a 10 mL volumetric flask the alkene (0.085 mmol) and the chiral ketone **3a**–**h** or **4a**–**h** (0.085 mmol) were dissolved in 2 mL of CH_3CN and mixed with 2 mL of an aqueous solution of 5% $NaHCO_3$, pH ca. 8. After cooling to 0 °C, 0.255 mmol of Oxone and 0.85 mmol of $NaHCO_3$ dissolved in 1 mL of water containing 4×10^{-4} M EDTA were added under stirring. After 1 h reaction time a second portion of the solution containing the oxidant was added to the reaction mixture. Samples of the mixture were taken out at fixed times of 1, 3, 12 h, respectively, extracted with ethyl acetate and submitted to GC analysis on the chiral column to estimate both the alkene conversion and the enantiomeric excess. For the epoxidations carried out on preparative scale, the reaction mixtures were treated as described above and the epoxides were separated from the crude mix by column chromatography over silica gel, characterized by ^1H and ^{13}C NMR analysis and submitted to optical rotation measurement. The absolute configuration were obtained by comparison with literature values, see text for details.

4.2.1. 3-Keto-7α-hydroxy- and 3-keto-12α-hydroxy-5β-cholan-24-oic acid (3a, 4a). Three grams (7.6 mmol) of commercially available chenodeoxycholic or deoxycholic acid are dissolved in MeOH (30 mL) and reacted with 1 mL of concentrated H_2SO_4. The solution is refluxed for 1 h, concentrated and treated with aqueous saturated $NaHCO_3$ (30 mL). The reaction mixture is extracted with ethyl acetate and dried over anhydrous Na_2SO_4. The solvent was removed in vacuum to give the crude methyl ester in almost quantitative yield. The further oxidation of the C(3) hydroxy function was carried out via oxidation with the Oppenauer's reagent[27] according to the following simple and straightforward procedures. The appropriate ester and aluminium *tert*-butoxide (3.6 g, 14.6 mmol) in a mixture of dry benzene (90 mL) and dry acetone (40 mL) were boiled under reflux for 18 h. The turbid reaction product was cooled and poured with stirring into 2 N sulphuric acid (60 mL). The benzene layer was separated and washed (twice) with water, aqueous sodium hydrogen carbonate and water. After drying (Na_2SO_4), the solvent was removed under reduced pressure to give the expected carbonyl derivative. The foregoing precursor was hydrolyzed by boiling it for 4 h under reflux with 20 mL of 10% NaOH in methyl alcohol (40 mL). The solution was then diluted with water (70 mL) and concentrated under reduced pressure to remove methyl alcohol. After cooling the solution was acidified with HCl 5%. Crystalline product was filtered off in nearly 50% yield. Compound **3a**: White crystals; mp 111–114 °C (lit.[28] 113–115 °C); $[\alpha]_D^{20}$ +13.5 (*c* 1.7, $CHCl_3$); selected ^1H NMR[28,29] resonances (300 MHz, CD_3OD): δ 0.69 (s, 3H, C*H*$_3$-18), 1.01 (d, $J=6.2$ Hz, 3H, C*H*$_3$-21), 1.07 (s, 3H, C*H*$_3$-19), 3.52 (dd, $J=J'=14.6$ Hz, 1H, *H*-4axial), 3.90 (br s, 1H, *H*-7β). Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.35; H, 9.80. Compound **4a**: white crystals; mp 154–156 °C (lit.[28] 155–157 °C); $[\alpha]_D^{20}$ +44.1 (*c* 1.6, $CHCl_3$); selected ^1H NMR[28,29] resonances (300 MHz, CD_3OD): δ 0.69 (s, 3H, C*H*$_3$-18), 1.05 (d, $J=$ 5.7 Hz, 3H, C*H*$_3$-21), 1.08 (s, 3H, C*H*$_3$-19), 2.87 (dd, $J=J'=14.0$ Hz, 1H, *H*-11axial), 4.05 (br s, 1H, *H*-12β). Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.47; H, 9.50.

4.2.2. 3-Keto-7α-succinyloxy-5β-cholan-24-oic acid (3d).[11a] Five grams of chenodeoxycholic acid were suspended in ethyl acetate (30 mL) in the presence of succinic anhydride (6 g, 60 mmol), triethylamine (1.27 mL, 12.7 mmol) and DMAP (0.15 g, 1.27 mmol). The reaction mixture, monitored by TLC, was refluxed for 40 h. Ethyl acetate (20 mL) and 15 mL of water were then added to the

mixture. The organic layer was washed with acid water pH ca.1, dried over anhydrous Na_2SO_4 and evaporated to obtain the bis-hemisuccinate. The identity of the intermediate could be validated by ^{1}H NMR (300 MHz, $CDCl_3$/CD_3OD 1:1 v/v): δ 0.69 (s, 3H, CH_3-18), 0.87 (s, 3H, CH_3-19), 0.87 (d, J=6.5 Hz, 3H, CH_3-21), 4.55 (m, 1H, H-3β), 4.82 (br s, 1H, H-7β). The C(3) hydrolysis of the product was obtained by dissolving the it in MeOH–NaOH 5% (1/1 v/v) After 1 h the solution is acidified with dilute H_2SO_4. Addition of 50 mL of H_2O caused the precipitation of the 3α-hydroxy-7α-hemisuccinate derivative that was recovered by filtration. The further oxidation of the C(3) hydroxy function was carried out via oxidation with the Jones' reagent.[30] This reagent is obtained by adding 2.2 g of chromium trioxide to 2.8 mL of concentrated sulfuric acid and the solution diluted to 10 mL with water. Thus, the hydoxy bile acid precursor was dissolved in 100 mL of acetone and treated with Jones' reagent until a slight permanent orange color was obtained. After standing for 5 min, several drops of isopropyl alcohol were added to destroy the oxidant in excess. The reaction mixture was filtrated over Celite, concentrated under reduced pressure, diluted with 20 mL of water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed in vacuum to give 3.5 g (70% overall yield) of the expected carbonyl derivative. Compound **3d**: mp 120–125 °C (dec) (hexane–EtOAc); $[\alpha]_D^{20}$ +17.3 (*c* 1.5, $CHCl_3$); selected ^{1}H NMR resonances (300 MHz, $CDCl_3$): δ 0.70 (s, 3H, CH_3-18), 0.95 (d, J=6.5 Hz, 3H, CH_3-21), 1.04 (s, 3H, CH_3-19), 2.98 (dd, $J=J'$=14.6 Hz, 1H, H-4axial), 5.05 (br s, 1H, H-7β). Calcd for $C_{28}H_{42}O_7$: C, 68.54; H, 8.63. Found: C, 68.16; H, 9.01.

4.2.3. 3-Keto-7α-oxalyloxy- (3b), 3-keto-12α-oxalyloxy- (4b), 3-keto-12α-succinyloxy- (4d), 3-keto-7α-glutaryloxy- (3e), 3-keto-12α-glutaryloxy- (4e), 3-keto-7α-adipoyloxy- (3f), 3-keto-12α-adipoyloxy-5β-cholan-24-oic methyl ester (4f). One gram (2.5 mmol) of **3a**- or **4a**-methyl esters were dissolved in 10 mL of CH_2Cl_2 containing TEA (2.5 mmol) and slowly added, under stirring, to a solution of the appropriate dichloride derivative, that is, oxalyl, succinyl, glutaryl or adipoyl dichloride, 7.5 mmol dissolved in 5 mL of CH_2Cl_2. After 12 h at room temperature the reaction mixture was treated with 10 mL of acid water (HCl 5%) and left under stirring for 4 h. The organic layer was separated, dried on anhydrous Na_2SO_4, concentrated and the expected derivatives purified by column chromatography (petroleum ether/ethyl acetate/acetic acid 60:40:1). Compound **3b**: syrup, 85% yield; $[\alpha]_D^{20}$ −16.2 (*c* 5.0, $CHCl_3$); selected ^{1}H NMR resonances (300 MHz, $CDCl_3$): δ 0.70 (s, 3H, CH_3-18), 0.93 (d, J=6.8 Hz, 3H, CH_3-21), 1.07 (s, 3H CH_3-19), 3.20 (dd, $J=J'$=14.6 Hz, 1H, H-4axial), 3.62 (s, 3H, OCH_3), 5.17 (br s, 1H, H-7β). Calcd for $C_{28}H_{40}O_7$: C, 68.83; H, 8.25. Found: C, 68.36; H, 8.30. Compound **4b**: syrup, 83% yield; $[\alpha]_D^{20}$ +74.4 (3.4, $CHCl_3$); selected ^{1}H NMR resonances (300 MHz, $CDCl_3$): δ 0.80 (s, 3H, CH_3-18), 0.82 (d, J=6.2 Hz, 3H, CH_3-21), 1.12 (s, 3H, CH_3-19), 2.72 (dd, $J=J'$=14.0 Hz, 1H, H-11axial), 3.63 (s, 3H, OCH_3), 5.32 (br s, 1H, H-12β). Calcd for $C_{28}H_{40}O_7$: C, 68.83; H, 8.25. Found: C, 68.45; H, 8.09. Compound **4d**: 76% yield, mp 138–141 °C (hexane–EtOAc); $[\alpha]_D^{20}$ +66.4 (*c* 2.5, $CHCl_3$); selected ^{1}H NMR resonances (300 MHz, $CDCl_3$): δ 0.78 (s, 3H, CH_3-18), 0.81 (d, J=6.1 Hz, 3H, CH_3-21), 1.00 (s, 3H, CH_3-19), 2.62 (m, 5H, H-11axial, $(COCH_2)_2$), 3.67 (s, 3H, OCH_3), 5.15 (br s, 1H, H-12β). Calcd for $C_{29}H_{44}O_7$: C, 69.02; H, 8.79. Found: C, 68.76; H, 9.11. Compound **1e**: syrup, 72% yield; $[\alpha]_D^{20}$ +4.2 (*c* 3.5, $CHCl_3$); selected ^{1}H NMR resonances (300 MHz, $CDCl_3$): δ 0.70 (s, 3H, CH_3-18), 0.94 (d, J=6.0 Hz, 3H, CH_3-21), 1.02 (s, 3H, CH_3-19), 2.98 (dd, $J=J'$=14.6 Hz, 1H, H-4axial), 3.64 (s, 3H, OCH_3), 5.01 (br s, 1H, 1H, H-7β). Calcd for $C_{31}H_{46}O_7$: C, 70.16; H, 8.74. Found: C, 71.00; H, 8.88. Compound **4e**: syrup, 74% yield; $[\alpha]_D^{20}$ +57.5 (*c* 1.2, $CHCl_3$); selected ^{1}H NMR resonances (300 MHz, $CDCl_3$): δ 0.75 (s, 3H, CH_3-18), 0.80 (d, J=5.8 Hz, 3H, CH_3-21), 0.99 (s, 3H, CH_3-19), 2.68 (dd, $J=J'$=14.0 Hz, 1H, H-11axial), 3.62 (s, 3H, OCH_3), 5.12 (br s, 1H, H-12β). Calcd for $C_{31}H_{46}O_7$: C, 70.16; H, 8.74. Found: C, 71.02; H, 8.18. Compound **3f**: syrup, 37% yield; $[\alpha]_D^{20}$ +5.6 (*c* 1.3, $CHCl_3$); selected ^{1}H NMR resonances (300 MHz, $CDCl_3$): δ 0.71 (s, 3H, CH_3-18), 0.96 (d, J=6.2 Hz, 3H, CH_3-21), 1.05 (s, 3H, CH_3-19), 3.00 (dd, $J=J'$=14.6 Hz, 1H, H-4axial), 3.64 (s, 3H, OCH_3), 5.01 (br s, 1H, H-7β). Calcd for $C_{32}H_{48}O_7$: C, 70.56; H, 8.88. Found: C, 70.12; H, 8.47. Compound **4f**: syrup, 40% yield; $[\alpha]_D^{20}$ +61.2 (*c* 2.5, $CHCl_3$); selected ^{1}H NMR resonances (300 MHz, $CDCl_3$): δ 0.78 (s, 3H, CH_3-18), 0.80 (d, J=6.1 Hz, 3H, CH_3-21), 1.01 (s, 3H, CH_3-19), 2.70 (dd, $J=J'$=14.0 Hz, 1H, H-11axial), 3.66 (s, 3H, OCH_3), 5.15 (br s, 1H, H-12β). Calcd for $C_{32}H_{48}O_7$: C, 70.56; H, 8.88. Found: C, 70.21; H, 8.74.

4.2.4. 3-Keto-7α-malonyloxy- (3c), 3-keto-12α-malonyloxy-5β-cholan-24-oic methyl ester (4c). One gram (2.5 mmol) of **3a**- or **4a**-methyl esters dissolved in anhydrous toluene (30 mL) were added to a solution containing 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid, 2.75 mmol). The reaction mixture was kept under reflux for 4 h, cooled and concentrated under reduced pressure affording the malonyl derivatives in almost quantitative yield. Compound **3c**: sticky oil; $[\alpha]_D^{20}$ −1.8 (*c* 2.0, $CHCl_3$); selected ^{1}H NMR resonances (300 MHz, $CDCl_3$): δ 0.68 (s, 3H, CH_3-18), 0.95 (d, J=6.2 Hz, 3H, CH_3-21), 1.02 (s, 3H, CH_3-19), 2.91 (dd, $J=J'$=14.6 Hz, 1H, H-4axial), 3.42 (m, 2H, $COCH_2CO$), 3.64 (s, 3H, OCH_3), 5.03 (br s, 1H, H-7β). Calcd for $C_{29}H_{42}O_7$: C, 69.29; H, 8.42. Found: C, 68.86; H, 8.55. Compound **4c**: mp 143–145 °C, (hexane–EtOAc); $[\alpha]_D^{20}$ +73.1 (*c* 1.3, $CHCl_3$); selected ^{1}H NMR resonances (300 MHz, $CDCl_3$): δ 0.78 (s, 3H, CH_3-18), 0.83 (d, J=6.4 Hz, 3H, CH_3-21), 1.02 (s, 3H, CH_3-19), 2.70 (dd, $J=J'$=14.0 Hz, 1H, H-11axial), 3.42 (m, 2H, $COCH_2CO$), 3.68 (s, 3H, OCH_3), 5.21 (br s, 1H, H-12β). Calcd for $C_{29}H_{42}O_7$: C, 69.29; H, 8.42. Found: C, 68.16; H, 8.57.

4.2.5. 3-Keto-7α-phtaloyloxy- (3g), 3-keto-12α-phtaloyloxy-5β-cholan-24-oic methyl ester (4g). To a toluene solution (40 mL) containing **3a**- or **4a**-methyl esters (1 g, 2.5 mmol), phtalic anidride (3.75 mmol) and imidazole (2.5 mmol) were added under stirring. The mixture was refluxed for 40 h, monitoring the progress of the reaction by TLC (petroleum ether/ethyl acetate 4:1). After completion the mixture was washed with acid water (15 mL, HCl 5%) and extracted with ethyl acetate. The organic layer was separated, dried on anhydrous Na_2SO_4, concentrated and the expected derivatives purified by column chromatography

(petroleum ether/ethyl acetate/acetic acid 80:20:1). Yields 83 and 87%, respectively. Compound **3g**: mp 105–110 °C (dec), (hexane–EtOAc); $[\alpha]_D^{20}$ −15.1 (*c* 1.1, $CHCl_3$); selected ^{1}H NMR resonances (300 MHz, $CDCl_3$): δ 0.72 (s, 3H, CH_3-18), 0.95 (d, J=6.0 Hz, 3H, CH_3-21), 1.08 (s, 3H, CH_3-19), 2.92 (dd, $J=J'$=14.6 Hz, 1H, *H*-4axial), 3.68 (s, 3H, OCH_3), 5.35 (br s, 1H, *H*-7β), 7.44 (d, J=7.2 Hz, 1H, Ar-*H*), 7.60 (m, 2H, Ar-*H*), 7.98 (d, J=7.0 Hz, 1H, Ar-*H*). Calcd for $C_{33}H_{44}O_7$: C, 71.71; H, 8.02. Found: C, 71.24; H, 7.89. Compound **4g**: the ^{1}H NMR spectrum is almost identical to that of **4h** except for the methyl ester resonance δ 3.65 (s, 3H, OCH_3).

4.2.6. 3-Keto-12α-phtaloyloxy-5β-cholan-24-oic acid (4h). The free bile acid **4h** was obtained from **4g** upon reaction with KOH 5% (20 mL) under reflux for 1 h. The reaction mixture was treated with concentrated HCl and extracted with ethyl acetate. The organic layer, separated, dried and concentrated afforded the expected product in almost quantitative yield. Compound **4h**: mp 92–98 °C (dec), (hexane–EtOAc); $[\alpha]_D^{20}$ +46.7 (*c* 1.4, $CHCl_3$); selected ^{1}H NMR resonances (300 MHz, $CDCl_3$): δ 0.86 (s, 3H, CH_3-18), 0.98 (d, J=6.2 Hz, 3H, CH_3-21), 1.05 (s, 3H, CH_3-19), 2.72 (dd, $J=J'$=14.0 Hz, 1H, *H*-11axial), 5.44 (br s, 1H, *H*-12β), 7.60 (m, 3H, Ar-*H*), 7.90 (d, J=7.1 Hz, 1H, Ar-*H*). Calcd for $C_{32}H_{42}O_7$: C, 71.35; H, 7.86. Found: C, 72.02; H, 8.20.

4.2.7. 3-Keto-4β-bromo-7α-formyloxy-5β-cholan-24-oic acid (5). This derivative was prepared from the corresponding 3-keto-7α-formyloxy-5β-cholan-24-oic acid by treatment with bromine in DMF, according with literature procedures;[17,31] diasteromeric α/β ratio 1:9, mp 164–166 °C (hexane–EtOAc); selected ^{1}H NMR resonances (300 MHz, $CDCl_3$): δ 0.70 (s, 3H, CH_3-18), 0.94 (d, J=5.4 Hz, 3H, CH_3-21), 1.10 (s, 3H, CH_3-19), 5.15 (m, 1H, *H*-7), 5.33 (d, J=11.7 Hz, 1H, *H*-4), 8.08 (s, 1H, 7-CHO).

4.2.8. 3-Keto-4β-bromo-12α-formyloxy-5β-cholan-24-oic acid (6). This derivative was prepared from the corresponding 3-keto-12α-formyloxy-5β-cholan-24-oic acid by treatment with bromine in DMF, according with literature procedures[17,31]; diasteromeric α/β ratio ca. 1:9, mp 183–184 °C (hexane–Et_2O); selected ^{1}H NMR resonances (300 MHz, $CDCl_3$): δ 0.80 (s, 3H, CH_3-18), 0.84 (d, J=6.3 Hz, 3H, CH_3-21), 1.07 (s, 3H, CH_3-19), 4.95 (d, J=11.7 Hz, 1H, *H*-4), 5.29 (m, 1H, *H*-12), 8.11 (s, 1H, 12-CHO).

Acknowledgements

This work was supported by MURST (Italy) PRIN 2003 and Universities of Calabria and Ferrara.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.052.

References and notes

1. (a) Marco-Contelles, J.; Molina, M. T.; Anjum, S. *Chem. Rev.* **2004**, *104*, 2857–2899. (b) Behrens, C. H.; Sharpless, K. B. *Aldrichim. Acta* **1983**, *16*, 67–80.
2. Xia, Q.-H.; Ge, H.-Q.; Ye, C.-P.; Liu, Z.-M.; Su, K.-X. *Chem. Rev.* **2005**, *105*, 1603–1662 and references.
3. Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2024–2032 and references.
4. Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp 159–202.
5. Katsuki, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 2000; pp 287–325.
6. Porter, M. J.; Skidmore, J. *Chem. Commun.* **2000**, 1215–1225.
7. Lauret, C.; Roberts, S. M. *Aldrichim. Acta* **2002**, *35*, 47–51.
8. (a) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488–496. (b) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497–505. (c) Adam, W.; Saha-Moller, C. R.; Ganeshpure, P. A. *Chem. Rev.* **2001**, *101*, 3499–3548 and references.
9. Curci, R.; Fiorentino, M.; Serio, M. R. *J. Chem. Soc., Chem. Commun.* **1984**, 155–156.
10. (a) Hickey, M.; Goeddel, D.; Crane, Z.; Shi, Y. *PNAS* **2004**, *101*, 5794–5798. (b) Chan, W.-K.; Yu, W.-Y.; Che, C.-M.; Wong, M.-K. *J. Org. Chem.* **2003**, *68*, 6576–6658. (c) Denmark, S. E.; Matsuhashi, H. *J. Org. Chem.* **2002**, *67*, 3479–3486. (d) Tian, H.; She, X.; Xu, J.; Shi, Y. *Org. Lett.* **2001**, *3*, 1929–1931. (e) Wang, Z.-X.; Miller, S. M.; Anderson, O. P.; Shi, Y. *J. Org. Chem.* **2001**, *66*, 521–530. (f) Armstrong, A.; Hayter, B. R. *Chem. Commun.* **1998**, 621–622. (g) Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Zheng, J.-H.; Cheung, K.-K. *J. Am. Chem. Soc.* **1996**, *118*, 491–492.
11. (a) Bortolini, O.; Fantin, G.; Fogagnolo, M.; Forlani, R.; Maietti, S.; Pedrini, P. *J. Org. Chem.* **2002**, *67*, 5802–5806. (b) Bortolini, O.; Fogagnolo, M.; Fantin, G.; Maietti, S.; Medici, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1113–1115.
12. Bortolini, O.; Fantin, G.; Fogagnolo, M.; Mari, L. *Tetrahedron: Asymmetry* **2004**, *15*, 3831–3833.
13. (a) Plucinska, K.; Kasprzykowski, F.; Kozian, E. *Tetrahedron Lett.* **1997**, *38*, 861–864. (b) Stephens, P. J.; Devlin, F. J.; Cheeseman, J. R.; Frisch, M. J.; Bortolini, O.; Besse, P. *Chirality* **2003**, *15*, S57. (c) Yamamoto, M.; Hayashi, M.; Masaki, M.; Nohira, H. *Tetrahedron: Asymmetry* **1991**, *2*, 403–406. (d) Stephens, P. J.; Devlin, F. J.; Bortolini, O. *Tetrahedron: Asymmetry* **2005**, *16*, 2653–2663. (e) For *p*-OCH_3 and *o*-Br cinnamic acid epoxides: Bortolini, O.; Fantin, G.; Fogagnolo, M. Unpublished results.
14. (a) Shu, L.; Wang, P.; Gan, Y.; Shi, Y. *Org. Lett.* **2003**, *5*, 293–296. (b) Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* **2002**, *67*, 2435–2446. (c) Tian, H.; She, X.; Shu, L.; Yu, H.; Shi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 11551–11552.
15. Mello, R.; Fiorentino, M.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1988**, *53*, 3890–3891.
16. (a) Solladié-Cavallo, A.; Bouérat, L. *Org. Lett.* **2000**, *2*, 3531–3534. (b) Armstrong, A.; Hayter, B. R. *Chem. Commun.* **1998**, 621–622. (c) Denmark, S. E.; Wu, Z.; Crudden, C. M.; Matsuhashi, H. *J. Org. Chem.* **1997**, *62*, 8288–8289.
17. Ida, T.; Tamaru, T.; Chang, F. C.; Goto, J.; Nambara, T. *J. Lipid Res.* **1991**, *32*, 649–658.
18. Chang, H.-T.; Sharpless, K. B. *J. Org. Chem.* **1996**, *61*, 6456–6457.

19. Witkop, B.; Foltz, C. M. *J. Am. Chem. Soc.* **1957**, *79*, 197–201.
20. Optical rotation sign in $CHCl_3$: Archelas, A.; Furstoss, R. *J. Org. Chem.* **1999**, *64*, 6112–6114.
21. Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378–4380.
22. The stereochemistry was tentatively assigned based on similarity of the GC elution order on a chiral column in comparison with styrene oxide. See also the text for discussion.
23. Sasaki, H.; Irie, R.; Hamada, T.; Suzuki, K.; Katsuki, T. *Tetrahedron* **1994**, *50*, 11827–11838.
24. (a) Jenson, C.; Liu, J.; Houk, K. N.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1997**, *119*, 12982–12983. (b) Houk, K. N.; Liu, J.; DeMello, N. C.; Condroski, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10147–10152.
25. Tu, Y.; Wang, Z.-X.; Frohn, M.; He, M.; Yu, H.; Tang, Y.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 8475–8485.
26. Singleton, D. A.; Wang, Z. *J. Am. Chem. Soc.* **2005**, *127*, 6679–6685.
27. Jones, A. S.; Webb, M.; Smith, F. *J. Chem. Soc., Chem. Commun.* **1949**, 2164–2168.
28. Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P.; Cova, U. *Steroids* **1993**, *58*, 524–526.
29. Bettarello, L.; Bortolini, O.; Fantin, G.; Guerrini, A. *Il Farmaco* **2000**, *55*, 51–55.
30. Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc., Chem. Commun.* **1946**, 39–45.
31. Iida, T.; Komatsubara, I.; Chang, F. C.; Goto, J.; Nambara, T. *Steroids* **1991**, *56*, 114–122.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 4491–4497

π-Relaxation of the ring strain: design of polycyclic unsaturated silicon molecules

Yuji Naruse,[a] Jing Ma,[b] Kunihiro Takeuchi,[a] Takahiro Nohara[a] and Satoshi Inagaki[a,*]

[a]*Department of Chemistry, Gifu University, 1-1 Yanagido Gifu 501-1193, Japan*
[b]*Department of Chemistry, Nanjing University, Nanjing 210093, People's Republic of China*

Received 24 October 2005; revised 16 February 2006; accepted 16 February 2006

Available online 14 March 2006

Abstract—Introduction of a double bond into cyclic silanes lowers the ring strain by the cyclic delocalization of π-electrons through the hyperconjugation with the σ bonds, which is favored by the high π-orbital energy of the Si=Si bond and the low σ*-orbital energy of the Si–H bonds. The π-relaxation of strains significantly occurs in the small rings. Unsaturated small silicon ring molecules are less strained than the saturated ones and the unsaturated carbon congeners. We calculated a series of polycyclic silicon molecules to confirm the π-relaxation and suggested that some unknown molecules could be prepared due to the low strain.

1. Introduction

Introduction of a double bond into cycloalkanes increases the ring strain. For example, cyclopropane **1** is less strained by 16.7 kcal mol^{-1} than cyclopropene **2** (SE= 53.8 kcal mol^{-1}).[1] The ring strain of cyclopropane (**1**) is usually attributed to the acute bond angle of 60°, which deviates greatly from the normal tetrahedral angle of 109.5°.[2] The deviation of the bond angles in cyclopropene (**2**) is even greater from the sp^2-hybrid bond angle of 120°. There are two mechanisms of strain relaxation of small ring systems[3]—σ-relaxation[3,4] and π-relaxation.[3,5] The π-relaxation originates from cyclic delocalization of π-electrons in the double bond through the hyperconjugation with σ bonds of the saturated ring atoms[5–8] under control of the orbital phase property.[9] In this paper, we report the π-relaxation of ring strain of unsaturated silicon molecules.[5]

1.1. Theoretical background

We have investigated the effects of introduction of a double bond into cyclic saturated molecules on ring strains.[5] The π-electrons delocalize through the cyclic interaction of the π-bonding orbital with the anitibonding σ* orbital(s) of the bond(s) on the saturated ring atom(s). The cyclic interaction satisfies the orbital phase continuity conditions (Fig. 1):[9] (i) electron-donating orbitals are out of phase; (ii) the electron-donating orbital and the electron-accepting orbital are in phase; (iii) electron-accepting orbitals are in phase. The π bonding orbital is electron-donating. The σ* orbitals are electron-accepting. The cyclic (π, σ*,…,σ*) interaction is favored by the phase continuity.

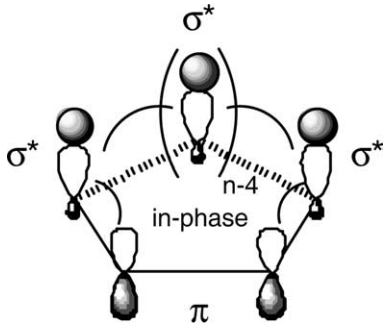


Figure 1. Cyclic orbital interaction for the π-relaxation of ring strains favored by the phase continuity.

The qualitative theory for the ring strains is examined by the bond model analysis previously developed[10] and successfully applied to various chemical phenomena.[10–14] The single Slater determinant Ψ for the electronic structure is expanded into electron configurations:

$$\Psi = C_G \Phi_G + \sum C_T \Phi_T + \cdots$$

where Φ_G and Φ_T are the ground and electron-transferred configurations, respectively. In the ground configuration Φ_G, a pair of electrons occupies a bonding orbital of a chemical bond (a nonbonding orbital of a lone pair). In Φ_T,

Keywords: Ring strain; π-relaxation; Unsaturated silicon molecules; Polycyclic molecules.
* Corresponding author.; e-mail: inagaki@apchem.gifu-u.ac.jp

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.039

an electron shifts from a bonding orbital of one bond to an antibonding orbital of another.

The bond orbitals or the hybrid atomic orbitals are optimized to give the maximum value for the coefficient of the ground configuration (C_G). The bonding and antibonding orbitals of the ith bond ϕ_i and ϕ_i*, are obtained by diagonalization of the 2×2 Fock matrix on the basis of the hybrid atomic orbitals χ_{ia} and χ_{ib} on the bonded atoms a and b.[10b]

$$\phi_i = c_{ia}\chi_{ia} + c_{ib}\chi_{ib}$$

$$\phi_i^* = c_{ia}^*\chi_{ia} + c_{ib}^*\chi_{ib}$$

where the coefficients of the hybrid orbitals are denoted by c_{ia}, c_{ib}, c_{ia}^* and c_{ib}^*.

To estimate the interactions between the bond orbitals i and j, we used the interbond energy IBE,[11] which was defined as:

$$\mathrm{IBE}_{ij} = P_{ij}(H_{ij} + F_{ij})$$

where P_{ij}, H_{ij}, and F_{ij} are the elements of the density, Fock and core Hamiltonian matrices, respectively.

We used the GAUSSIAN98 program[15] to calculate the electronic structures, which were used for the bond model analysis.

2. Results and discussion

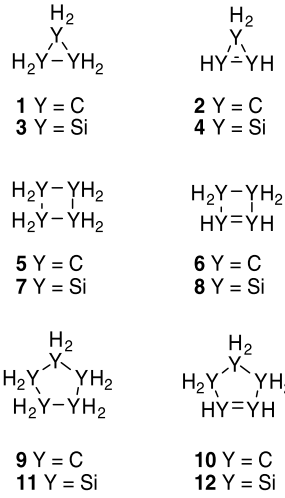
2.1. Monocyclic oligosilenes[5]

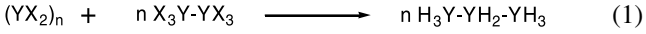
The cyclic delocalization of π-electrons significantly occurs in the molecules with π and σ* high and low in energy, respectively. The π relaxation is expected to be remarkable in cyclooligosilenes (e.g., **4**, **8**, **12**, etc.), while it is not so effective in cycloalkenes. The electron-donating π orbital of a Si=Si bond is higher in energy than that of a C=C bond, while an electron-accepting σ^*_{SiH} orbital is lower than that of a σ^*_{CH} orbital. In fact, it was confirmed by the heat of the homodesmotic reactions (Eqs. 1 and 2)[16] calculated at the B3LYP/6-311++G(3*df*,2*p*)//B3LYP/6-31G(d) level[15] that cyclooligosilenes **4**,[8] **8** and **12** (SE=34.5, 9.1, and 0.9 kcal mol^{-1})[1d,5] are less strained than the saturated analogs **3**, **7** and **11** (SE=35.5, 12.9, and 3.0 kcal mol^{-1})[1d,5], respectively (Table 1). These results show the appreciable relaxation of the strain of the monocyclic oligosilenes.

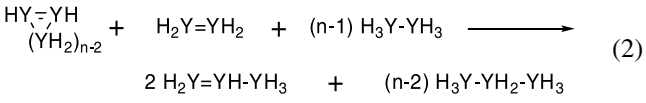
Table 1. Strain energies (SE in kcal mol^{-1}) calculated at the B3LYP/6-311++G(3*df*,2*p*)//B3LYP/6-31G(d) level

	SE			ΔSE
	Saturated		Unsaturated	
1	25.5[a]	**2**	55.5[a]	30.0
3	35.5[a]	**4**	34.5[a]	−1.0
5	22.6	**6**	28.7	6.1
7	12.9	**8**	9.1	−3.8
9	4.7	**10**	4.5	−0.6
11	3.0	**12**	0.9	−2.1

[a] From Ref. 8.







The π–σ* interactions are found in Table 2 to stabilize **4** ($\mathrm{IBE}_{\pi SiSi-\sigma^*SiH}$ = −0.354 a.u.) more than **2** (−0.200 a.u.). This results from the high π-orbital energy (−0.278 a.u.) and low σ*-orbital energy (0.442 a.u.) in **4** relative to the corresponding energies in **2** (−0.371 and 0.767 a.u.). Similar results were obtained for the four-membered ring **8**. The delocalization between two σ^*_{SiH} orbitals in **8** is more bonding ($\mathrm{IBE}_{\sigma^*SiH-\sigma^*SiH}$ = −0.015 a.u.) than that between the σ^*_{CH} orbitals in **6** ($\mathrm{IBE}_{\sigma^*CH-\sigma^*CH}$ = −0.007 a.u.). The cyclic orbital interaction occurs more effectively in **8**. The π–σ* interaction in **12** is greater ($\mathrm{IBE}_{\pi SiSi-\sigma^*SiH}$ = −0.357 a.u.) than that in **10** ($\mathrm{IBE}_{\pi CC-\sigma^*CH}$ = −0.238 a.u.). The σ*–σ* interactions of the distant σ_{Si-H} bonds are bonding in **12** ($\mathrm{IBE}_{\sigma^*SiH-\sigma^*SiH}$ = −0.004 a.u.), while they are antibonding in **10** ($\mathrm{IBE}_{\sigma^*CH-\sigma^*CH}$ = 0.002 a.u.).

Table 2. Interbond energies (IBE in a.u.) and bond orbital energies (F_{ii} in a.u.)

	IBE (πYY–σ^*YH)	IBE (σ^*YH–πYH)	$F_{ii(\pi YY)}$	$F_{ii(\sigma^*YY)}$
2 Y=C	−0.200		−0.371	0.767
4 Y=Si	−0.354		−0.278	0.442
6 Y=C	−0.246	−0.007	−0.349	0.728
8 Y=Si	−0.367	−0.015	−0.274	0.413
10 Y=C	−0.238	0.002	−0.342	0.738
12 Y=Si	−0.357	−0.004	−0.275	0.411

2.2. Polycyclic oligosilenes

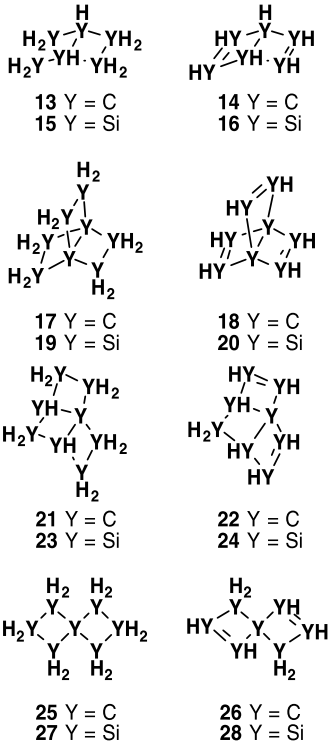
The preceding results prompt us to generalize the π-relaxation of the ring strain in polycyclic unsaturated silicon molecules with the reduced strain, which remain to be explored in near future. We calculated the strain energies

Table 3. Homodesmotic reactions

Molecule + m $H_3Y–YH_3$ + n $X_2Y{=}YX_2$ → p $H_3Y–YH_2–YH_3$ + q $H_3Y–YH{=}YH_2$ + r $(H_3Y)_3YH$ + s $(H_3Y)_4Y$

Molecule	m	n	p	q	r	s
13, **15**	7	0	4	0	2	0
14, **16**	5	2	0	4	2	0
17, **19**	10	0	6	0	0	2
18, **20**	7	3	0	6	0	2
21, **23**	10	0	5	0	2	1
22, **24**	8	2	1	4	2	1
25, **27**	8	0	6	0	0	1
26, **28**	6	2	2	4	0	1

of the saturated and unsaturated molecules composed of the two- (**13**–**16**) and three fused four-membered rings (**17**–**24**) and the spiro molecules (**25**–**28**) composed of two four-membered rings, according to the homodesmotic reactions (Table 3). The strain energies are summarized in Table 4. The optimized structures are shown in Figure 2.



The calculated strain energies of the bicyclo[2.2.0]systems including bicyclo[2.2.0]hexane **13**[17], bicyclo[2.2.0]hexa-2,5-diene (Dewer benzene) **14**[18] and their silicon congeners **15**[19] and **16**[20] support the π-relaxation of the ring strain. The unstaturated silicon molecule **16** is 3.0 kcal mol^{-1} less strained than the saturated one **15**. For the hydrocarbons, the unsaturated molecule **14** is 14.9 kcal mol^{-1} more strained than the saturated one **13**. The bond lengths support the significant delocalization of π-electrons in the unsaturated silicon compound **16**. The Si–Si fusion bond is shortened on the unsaturation from 2.398 Å in **15** to 2.373 Å in **16**. In contrast, there is no appreciable difference between the saturated and unsaturated carbon compounds **13** and **14** in the fusion bond lengths (1.573 Å in **13** and 1.574 Å in **14**). The bond shortening was expected from the π-delocalization.

Table 4. Calculated strain energies (SE in kcal mol^{-1}) of the polycyclic molecules at the B3LYP/6-31++G(3*df*,2*p*)//B3LYP/6-31G(d) level

SE				ΔSE
Saturated		Unsaturated		
13	44.9	**14**	59.8	14.9
15	25.0	**16**	22.0	−3.0
17	79.2	**18**	100.7	21.5
19	43.0	**20**	38.2	−4.8
21	65.4	**22**	78.7	13.3
23	35.6	**24**	30.1	−5.5
25	41.5	**26**	54.4	12.9
27	23.8	**28**	16.5	−7.3

The π-relaxation of the ring strain was further confirmed by the calculation of the tricyclic molecules composed of three fused rings. The unsaturated hydrocarbon **18** (tricyclo[2.2.2.0^{1,4}]octa-2,5,7-triene)[21] is more strained than the saturated one **17**[22] (tricyclo[2.2.2.0^{1,4}]octane or [2.2.2]propellane) by 21.5 kcal mol^{-1}. However, the dehydrogenated silicon congener **20** is less strained by 4.8 kcal mol^{-1} than the saturated one **19**.[23] The single Si–Si bond (2.368 Å) of **20** is shorter than the corresponding bonds (2.409 Å) of **19**, whereas a single C–C bond (1.574 Å) of the unsaturated carbon congener **18** is longer than the corresponding bond (1.538 Å) of **17**. The bond shortening on the dehydrogenation of the silicon molecule supports the delocalization of the π electrons. The propellane **17** was calculated as a highly-strained molecule[22] and the dehydrogenated molecule **18** was expected to be much less stable.[21]

Tricyclo[4.2.0.0^{1,4}]octasila-2,7-diene **24** is less strained by 5.5 kcal mol^{-1} than the saturated silane, tricyclo-[4.2.0.0^{1,4}]octasilane **23**, in agreement with the π-relaxation whereas the unsaturated carbon congener **22** is more strained by 13.3 kcal mol^{-1} than the saturated hydrocarbon, tricyclo[4.2.0.0^{1,4}]octane **21**. The single Si–Si bonds of the unsaturated four-membered rings in **24** are all shorter than the corresponding bonds in the saturated silane **23** while the fused single C–C bond in the unsaturated carbon congener **22** is longer than the corresponding bond in the saturated one **21**. The contrast of the silicon molecules to the carbon congeners in the bond length supports the significant π-delocalization. Tricyclo[4.2.0.0^{1,4}]octane **21**[24] was synthesized before[25], while the unsaturated **22** is yet unknown.

We calculated the strain energies of the spiro molecules **25**–**28** composed of the four-membered rings. Spiro[3.3]-heptasila-1,5-diene **28** is less strained by 7.3 kcal mol^{-1} than the saturated spirosilane **27**, whereas spiro[3.3]-hepta-1,5-diene **26**[26,27] is more strained than the hydrogenated spirohydrocarbon, **25**[27] by 12.9 kcal mol^{-1}. The significant π-delocalization shortens the single bond vicinal to the double bond. The single bond (Si3–Si4 2.339 Å) of **28** is shorter than the corresponding bonds (2.375, 2.378 Å) of **27**, whereas the single bond (C3–C4 1.578 Å) of the unsaturated carbon congener **26** is longer than the corresponding bonds (1.549, 1.556 Å) of **25**.

Highly strained polycyclic molecules are synthetic targets because of unique chemical bonding and function. Few experimental reports have appeared for the polycyclic silicon congeners studied here, except for **15**[28] and **16**[29], whereas most of the carbon congeners have been synthesized. Kira reported the synthesis of a derivative of spiro[2.2]pentasiladiene **29**, whose ring strain was calculated to 67.5 kcal mol^{-1}.[8] A derivative of tricyclo-[2.1.0.$0^{1,3}$]pentasilane **30** was very recently synthesized.[30] All the molecules studied here, except **18**, are less strained than **30** (the calculated strain energy: 86.4 kcal mol^{-1}).[31] The strain energies suggest that the polycyclic silicon molecules, especially the unsaturated ones, should be thermodynamically stable.

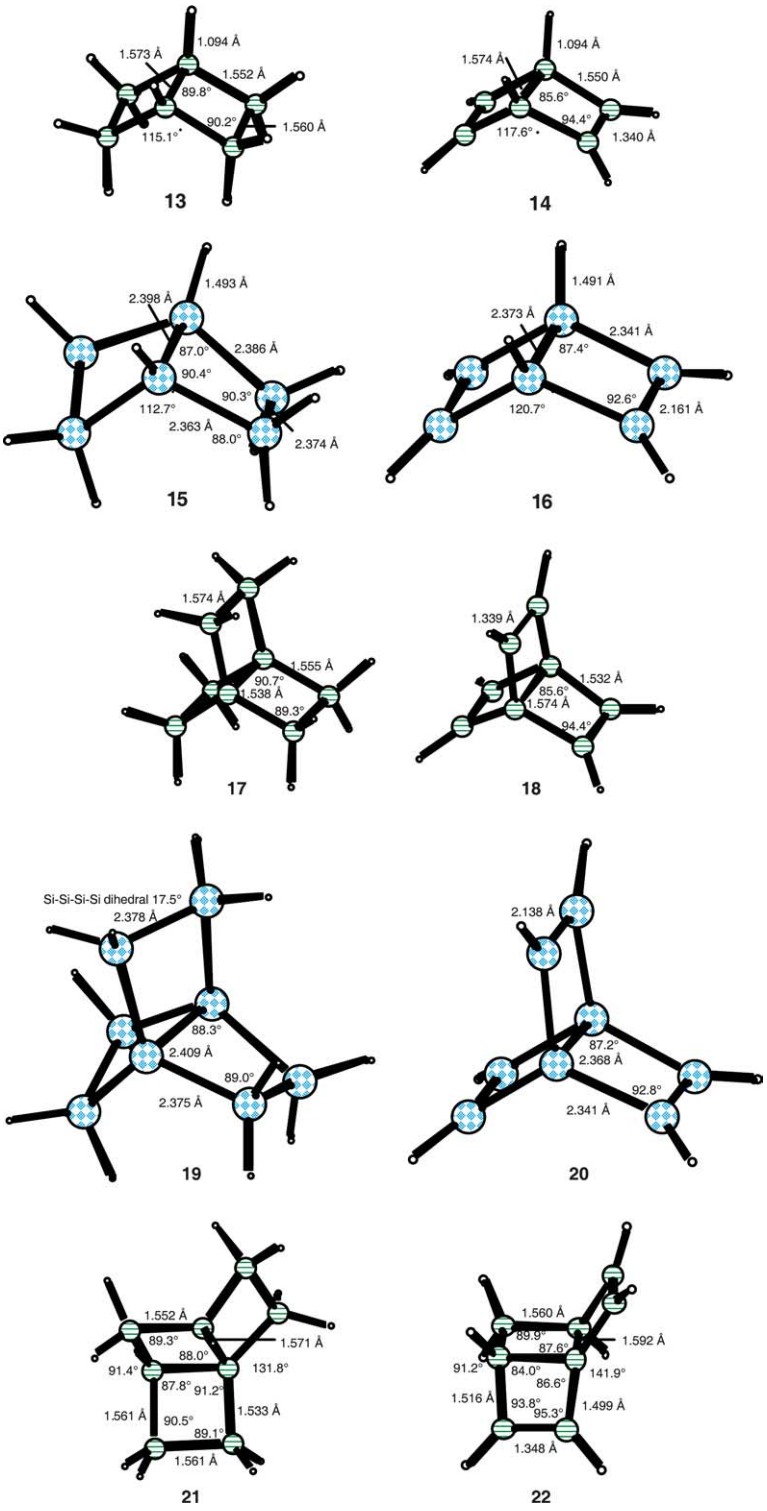


Figure 2. Calculated structures of the polycyclic compounds.

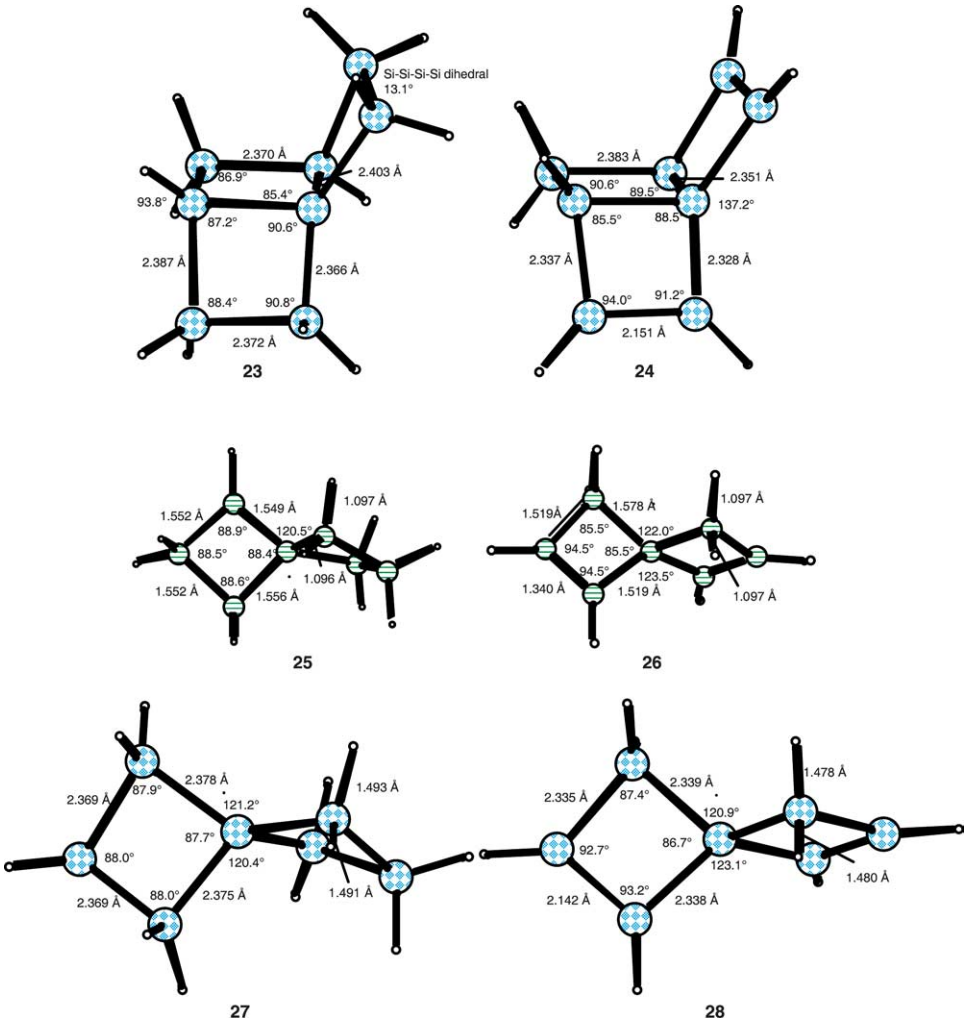
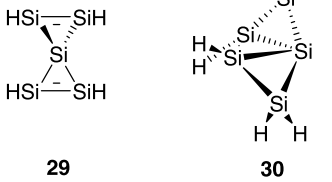


Figure 2 (*continued*)



29

30

3. Conclusion

The strain of small ring silicon molecules has been shown to be relaxed by the cyclic delocalization of the π electrons or the cyclic interaction of π and σ* orbital(s). The π-relaxation occurs not only in three-membered ring molecules[8,9], but also in four-, and five-membered rings. The π-relaxation is enhanced by an electron donating π bond (e.g., Si═Si) and electron accepting σ bond(s) (e.g., Si–H) on the saturated ring atoms. The cyclooligosilenes **4**, **8** and **12** are less strained than the saturated cyclooligosilanes, **3**, **7** and **11**, respectively. The cyclooligosilenes are also less strained than the cycloalkenes, **2**, **6** and **10**, respectively. This is also the case with the polycyclic silicon molecules, **16**, **20**, **24** and **28**. The strain of the small ring silicon molecules decreases on the unsaturation while that of the carbon congeners increases. Syntheses of the polycyclic silicon molecules are expected to be promising. Especially, the unsaturated silicon compounds, **24** and **28**, are good synthetic targets because of the low ring strain.

Acknowledgements

This work was supported by the research promotion grant, Gifu University. J.M. thanks the financial support by National Science Foundations of China (No. 20103004).

References and notes

1. (a) Cox, J. D.; Plicher, G. *Thermochemistry of Organic and Organometallic Compounds*; Academic: London, 1970. For reviews of small ring strain, see: (b) Wiberg, K. B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312. (c) Hengge, E.; Janoschek, R. *Chem. Rev.* **1995**, *95*, 1495. (d) Gimarc, B. M.; Zhao, M. *Coord. Chem. Rev.* **1997**, *158*, 385. See also for this problem: (e) Horner, D. A.; Grev, R. S.; Schaefer, H. F., III *J. Am. Chem. Soc.* **1992**, *114*, 2093.

2. March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; pp 150–161.
3. Naruse, Y.; Ma, J.; Inagaki, S. *J. Phys. Chem. A* **2003**, *107*, 2860.
4. (a) Inagaki, S.; Goto, N.; Yoshikawa, K. *J. Am. Chem. Soc.* **1991**, *113*, 7144. (b) Inagaki, S.; Yoshikawa, K.; Hayano, Y. *J. Am. Chem. Soc.* **1993**, *115*, 3706. (c) Inagaki, S.; Ishitani, Y.; Kakefu, T. *J. Am. Chem. Soc.* **1994**, *116*, 5954.
5. For a preliminary communication, see: Naruse, Y.; Ma, J.; Inagaki, S. *Tetrahedron Lett.* **2001**, *42*, 6553.
6. (a) Goller, A.; Heydt, H.; Clark, T. *J. Org. Chem.* **1996**, *61*, 5840. (b) Tsutsui, S.; Sakamoto, K.; Kabuto, C.; Kira, M. *Organometallics* **1998**, *17*, 3819. (c) Göller, A.; Clark, T. *J. Mol. Model.* **2000**, *6*, 133.
7. (a) Kira, M.; Iwamoto, T.; Kabuto, C. *J. Am. Chem. Soc.* **1996**, *118*, 10303. (b) Wiberg, N.; Auer, H.; Noth, H.; Knizek, J.; Polborn, K. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2869. (c) Ichinohe, M.; Matsuno, T.; Sekiguchi, A. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2194. (d) Fukawa, T.; Lee, V. Y.; Nakamoto, M.; Sekiguchi, A. *J. Am. Chem. Soc.* **2004**, *126*, 11758. (e) Lee, V. Y.; Takahashi, K.; Nakamoto, M.; Sekiguchi, A. *Russ. Chem. Bull.* **2004**, *53*, 1102. For review, see: (f) Sekiguchi, A.; Lee, V. Y. *Chem. Rev.* **2003**, *103*, 1429.
8. Iwamoto, T.; Tamura, M.; Kabuto, C.; Kira, M. *Science* **2000**, *290*, 504.
9. (a) Fukui, K.; Inagaki, S. *J. Am. Chem. Soc.* **1975**, *97*, 4445. (b) Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4693. For recent applications, see: (c) Ma, J.; Inagaki, S. *J. Phys. Chem.* **2000**, *104*, 8989. (d) Ma, J.; Ikeda, H.; Inagaki, S. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 273. (e) Ma, J.; Inagaki, S. *J. Am. Chem. Soc.* **2001**, *123*, 1193. (f) Ma, J.; Ding, Y.; Hattori, K.; Inagaki, S. *J. Org. Chem.* **2004**, *69*, 4245.
10. (a) Iwase, K.; Inagaki, S. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2781. (b) Inagaki, S.; Ikeda, H. *J. Org. Chem.* **1998**, *63*, 7820. See also: (c) Inagaki, S.; Goto, N. *J. Am. Chem. Soc.* **1987**, *109*, 3234. For another method of the bond model analysis, see: (d) Ikeda, H.; Inagaki, S. *J. Phys. Chem. A* **2001**, *47*, 10711.
11. (a) Inagaki, S.; Yamamoto, T.; Ohashi, S. *Chem. Lett.* **1997**, 977. See also: (b) Ikeda, H.; Naruse, Y.; Inagaki, S. *Chem. Lett.* **1999**, 363. (c) Inagaki, S.; Ohashi, S.; Kawashima, T. *Org. Lett.* **1999**, *1*, 1145. (d) Inagaki, S.; Ikeda, H.; Kawashima, T. *Tetrahedron Lett.* **1999**, *40*, 8893. (e) Ikeda, H.; Ushioda, N.; Inagaki, S. *Chem. Lett.* **2001**, 166. (f) Ikeda, H.; Kato, T.; Inagaki, S. *Chem. Lett.* **2001**, 270. (g) Naruse, Y.; Hayashi, A.; Sou, S.; Ikeda, H.; Inagaki, S. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 245. (h) Ohashi, S.; Naruse, Y.; Inagaki, S. *J. Organomet. Chem.* **2003**, *682*, 119. (i) Naruse, Y.; Hayashi, Y.; Inagaki, S. *Tetrahedron Lett.* **2003**, *44*, 8509. (j) Naruse, Y.; Sugiura, M.; Inagaki, S. *Phosphorus, Sulfur, Silicon* **2003**, *178*, 2447.
12. (a) Ma, J.; Inagaki, S. *J. Phys. Chem. A* **2000**, *104*, 8989. (b) Ma, J.; Hozaki, A.; Inagaki, S. *Inorg. Chem.* **2002**, *41*, 1876. (c) Ma, J.; Hozaki, A.; Inagaki, S. *Phosphorus, Sulfur, Silicon* **2002**, *177*, 1705.
13. (a) Iwase, K.; Sakai, S.; Inagaki, S. *Chem. Lett.* **1994**, 1601. (b) Inagaki, S.; Ohashi, S. *Theo. Chem. Acc.* **1999**, *102*, 65. (c) Ma, J.; Ikeda, H.; Inagaki, S. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 273. (d) Ma, J.; Inagaki, S. *J. Am. Chem. Soc.* **2001**, *123*, 1193.
14. (a) Ohwada, T.; Miura, M.; Tanaka, H.; Sakamoto, S.; Yamaguchi, K.; Ikeda, H.; Inagaki, S. *J. Am. Chem. Soc.* **2001**, *123*, 10164. (b) Otani, Y.; Nagae, O.; Naruse, Y.; Inagaki, S.; Ohno, M.; Yamaguchi, K.; Yamamoto, G.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* **2003**, *125*, 15191.
15. Frisch, J. R.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, M. J.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *GAUSSIAN98*; Revision A.7, Gaussian, Inc.: Pittsburgh PA, 1998.
16. George, P.; Trachtman, M.; Bock, C. W.; Brett, A. M. *Tetrahedron* **1976**, *32*, 317. All calculated strain energies are ZPE corrected.
17. Dinadayalane, T. C.; Priyakumar, U. D.; Sastry, G. N. *J. Phys. Chem. A* **2004**, *108*, 11433 and references cited therein.
18. (a) Khoury, P. R.; Goddard, J. D.; Tam, W. *Tetrahedron* **2004**, *60*, 8103. (b) Nagase, S.; Kudo, T. *J. Chem. Soc., Chem. Commun.* **1990**, 630. (c) Hrovat, D. A.; Borden, W. T. *J. Am. Chem. Soc.* **1988**, *110*, 4710. (d) Wiberg, K. B. *J. Am. Chem. Soc.* **1983**, *105*, 1227.
19. Nagase, S.; Kudo, T. *J. Chem. Soc., Chem. Commun.* **1988**, 54. See also Ref. 18b.
20. (a) Nagase, S.; Kudo, T.; Aoki, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1121. (b) Sax, A. F.; Kalcher, J.; Janoschek, R. *J. Comput. Chem.* **1988**, *9*, 564. (c) Slanina, Z. *Thermochim. Acta* **1991**, *175*, 141. (d) Janoschek, R. *J. Inorg. Organomet. Polym.* **1995**, *5*, 155.
21. Tricyclo[2.2.2.$0^{1,4}$]octa-2,5,7-triene (2.2.2-propellatriene) **18** was calculated as a stable molecule at the CASSCF[2,2]/6-31G* level.[21a] However, UB3LYP/6-31G** calculation suggests that **18** should be unstable and that the structure of *p*-phenylenebismethylene might be more likely, which was assisted by the experimental evidence.[21b] (a) Davidson, E. R. *J. Am. Chem. Soc.* **1997**, *119*, 1449. (b) Subban, W.; Rempals, P.; Sheridan, R. S. *J. Am. Chem. Soc.* **1998**, *120*, 11528 and references cited therein.
22. (a) Stohrer, W. D.; Hoffmann, R. *J. Am. Chem. Soc.* **1972**, *94*, 779. (b) Newton, M. D.; Schulman, J. M. *J. Am. Chem. Soc.* **1972**, *94*, 4391. (c) Wiberg, K. B.; Epling, G. A.; Jason, M. *J. Am. Chem. Soc.* **1974**, *96*, 912. (d) Wiberg, K. B.; Pratt, W. E.; Bailey, W. F. *J. Am. Chem. Soc.* **1977**, *99*, 2297. (e) Gasteiger, J.; Dammer, O. *Tetrahedron* **1978**, *34*, 2939. (f) Gund, P.; Gund, T. *J. Am. Chem. Soc.* **1981**, *103*, 4458. (g) Wiberg, K. B.; Matturro, M. G. *Tetrahedron Lett.* **1981**, *22*, 3481. (h) Wiberg, K. B. *J. Am. Chem. Soc.* **1983**, *105*, 1227. (i) Doldziuk, H. *J. Comput. Chem.* **1984**, *5*, 571. (j) Wiberg, K. B.; Bader, R. F. W.; Lau, C. D. H. *J. Am. Chem. Soc.* **1987**, *109*, 985. (k) Wiberg, K. B.; Bader, R. F. W.; Lau, C. D. H. *J. Am. Chem. Soc.* **1987**, *109*, 1001. (l) Faller, D.; Davidson, E. R. *J. Am. Chem. Soc.* **1987**, *119*, 1449. (m) Zhao, C.; Wei, T.; Qiu, W. *Huaxue Xuebao* **1991**, *49*, 546. (n) Zhao, C.-Y.; Zhang, Y.; You, X.-Z. *J. Phys. Chem. A* **1997**, *101*, 5174. (o) Chirkina, E. A.; Sergeeva, O. R.; Krivdin, L. B. *Russ. J. Org. Chem.* **1999**, 18. See also Refs. 1b and 18.
23. Nagase, S.; Kudo, T. *Organometallics* **1987**, *6*, 2456.

24. (a) Takeuchi, K.; Horiguchi, A.; Inagaki, S. *Tetrahedron* **2005**, *61*, 2601. (b) Chen, K.-H.; Allinger, N. L. *THEOCHEM* **2002**, *581*, 215. (c) Agosta, W. C.; Wolff, S. *Pure Appl. Chem.* **1982**, *54*, 1579. (d) Wiberg, K. B.; Olli, L. K.; Golembeski, N.; Adams, R. D. *J. Am. Chem. Soc.* **1980**, *102*, 7467. See also Ref. 22f.
25. (a) Houbiers, J. P.; Hulshof, L. A.; Wiberg, H. *J. Chem. Soc., Chem. Commun.* **1969**, 91. (b) Hulshof, L. A.; Wiberg, H. *J. Am. Chem. Soc.* **1974**, *96*, 1291.
26. Kao, J.; Radom, L. *Tetrahedron* **1977**, *34*, 2515.
27. (a) Rice, L. M.; Grogan, C. H. *J. Org. Chem.* **1961**, *26*, 54. (b) Weinstein, K. B.; Ellison, G. B. *Tetrahedron* **1974**, *30*, 1573.
28. A recent report: Unno, M.; Tanaka, R.; Tanaka, S.; Takeuchi, T.; Kyushin, S.; Matsumoto, H. *Organometallics* **2005**, *24*, 765 and references cited therein.
29. Sekiguchi, A.; Yatabe, T.; Doi, S.; Sakurai, H. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1994**, *93–94*, 193.
30. Scheshcekewitz, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 2954.
31. Takeuchi, K.; Uemura, D.; Inagaki, S. *J. Phys. Chem. A* **2005**, *109*, 8632.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 4498–4505
Tetrahedron

Cycloadditions of α-(4-[2.2]paracyclophanyl)-*N*-methyl nitrone

Ashraf A. Aly,[a,*] Henning Hopf,[b,†] Peter G. Jones[c,‡] and Ina Dix[c]

[a]*Chemistry Department, Faculty of Science, El-Minia University, 61519-El-Minia, Egypt*
[b]*Institut für Organische Chemie, Technische Universität Braunschweig, Hagenring 30, D-38106 Braunschweig, Germany*
[c]*Institut für Anorganische und Analytische Chemie, Technische Universität Braunschweig, Postfach 3329, Hagenring 30, D-38023 Braunschweig, Germany*

Received 12 October 2005; revised 3 February 2006; accepted 16 February 2006

Available online 13 March 2006

Abstract—Cycloadditions of the newly synthesized α-(4-[2.2]paracyclophanyl)-*N*-methyl nitrone (**9**) with selected dipolarophiles such as phenyl isocyanate (**10**), styrene (**13**), dimethyl acetylenedicarboxylate (**15**) and methylene sulfene (**17**) are reported. Two isolated diastereomeric oxadiazolones **11** and **12** are obtained by the reaction of **9** with **10**, whereas the reaction of **9** with either **13** and/or **15** gives only one diastereomer isoxazole **14** and/or **16**. 4-([2.2]Paracylophanyl)-*N*-methylamine (**20**) was obtained by the reaction of **9** with **17**. The structure of compounds **9**, **11** and **14** are assigned by X-ray structural analysis.

1. Introduction

For a long time, [2.2]paracyclophane ([PC]) and its derivatives were mostly studied because of their unusual geometry, their steric, transannular, and ring strain effects as well as the electronic interaction between their aromatic rings.[1,2] Recently, the stereochemical properties of these systems especially their planar chirality have been the focus of studies in this field. In particular [2.2]-paracyclophanes carrying a nitrogen atom in the 4-position are of growing interest as auxiliaries.[3,4] PC derivatives having substituted amino functions have also been shown to be useful as effective photoconductive components.[5] Since isoxazoles are nitrogen heterocycles, which have often been encountered in molecules of medicinal interest,[6] a simple and efficient procedure for their synthesis would be a welcome advance. Additionally, examination of the electronic properties of isoxazoles has recently become an interesting field of research.[7]

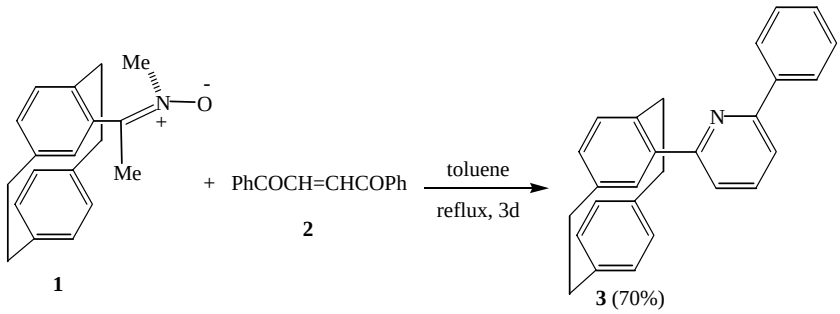
Cycloaddition reactions still play an important part in the synthesis of various classes of polycyclic and/or heterocyclic compounds derived and/or fused to the [2.2]paracyclophane moiety.[8] Our initial studies on the chemistry of nitrones have dealt with the synthesis of 2-(4′-[2.2]paracyclophanyl)-6-phenylpyridine (**3**) formed by the reaction of (*E*)-*N*,α-dimethyl-α-(4-[2.2]paracyclophanyl)nitrone (**1**) with dibenzoylethylene (**2**) (Scheme 1).[9a] Furthermore, **1** yields various classes of five-member heterocyclic rings (imidazole, isoxazole and pyrrole derivatives of PC), when it is allowed to react with other dipolarophiles.[9b] Encouraged by these results, we decided to investigate the chemical behavior of another class of nitrones viz. α-(4-[2.2]paracyclophanyl)-*N*-methyl nitrone (**9**) towards different types of dipolarophiles.

2. Results and discussion

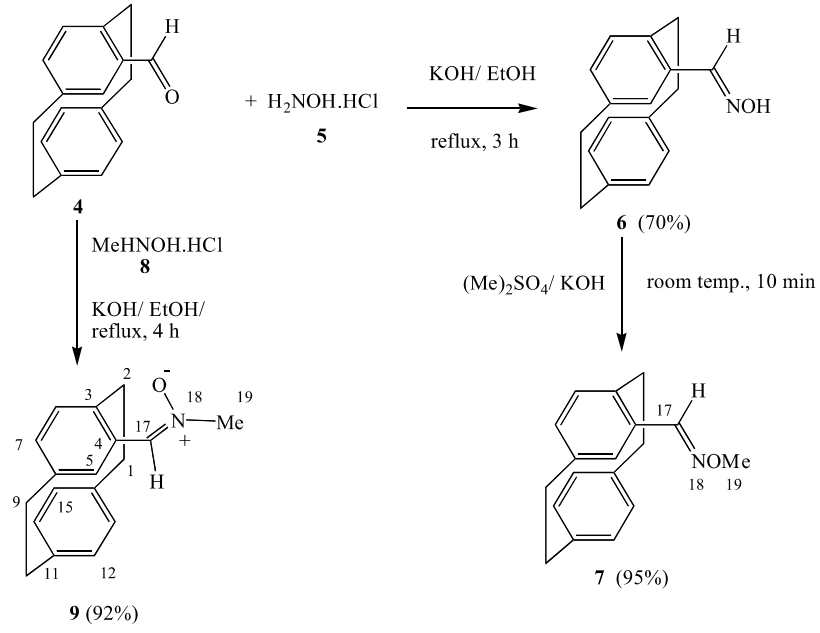
Isomerization[10] of aromatic aldoximes is a well-established method of synthesizing nitrones. We therefore prepared the aldoxime **6**[11] (derived from 4-formyl-[2.2]paracyclophane (**4**)[12]) and reacted it with dimethyl sulfate in ethanolic potassium hydroxide solution. The reaction was completed within 10 min but provided the *O*-ether derivative **7** (95%) rather than the nitrone **9** (Scheme 2). A successful alternative strategy involved treatment of **4** with *N*-methylhydroxylamine hydrochloride (**8**) in alcoholic potassium hydroxide leading to product **9** in 92% yield (Scheme 2). The structure of **9** was established by conventional spectroscopic methods (see Section 3) as well as elemental analysis. Moreover, that **9** is the *Z*-diastereomer was established by X-ray structural analysis (Fig. 1, Table 1). The ^{1}H NMR spectrum revealed slight differences in the δ values between compounds **7** and **9**; for example the methyl protons in compound **9** appear at $\delta=3.94$, whereas in **7**, they appeared at $\delta=4.02$. In the ^{13}C NMR spectra the methyl group signal (19-C) in **9** resonates at $\delta=54.9$, whereas in **7** it

Keywords: Cyclophanes; Dipolarophiles; Diastereomers; Cycloadditions; X-ray structure analyses.
* Corresponding author. Tel./fax: +2 86 2346876; e-mail: ashraf160@yahoo.com
† Fax: +49 531 391 5388.
‡ Fax: +49 531 391 5387.

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.047



Scheme 1. Reaction of (*E*)-*N*,α-dimethyl-α-(4-[2.2]paracyclophane)nitrone (**1**) with dibenzoylethylene (**2**); synthesis of 2-(4′-[2.2]paracyclophanyl)-6-phenylpyridine (**3**).



Scheme 2. Synthesis of α-(4-[2.2]paracyclophane)-*N*-methyl nitrone (**9**).

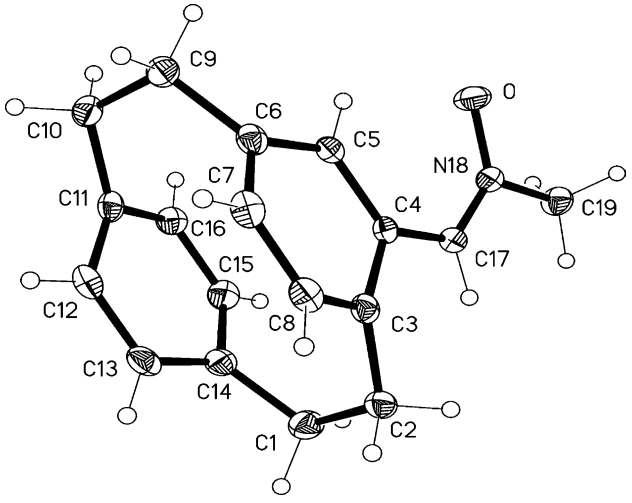


Figure 1. The structure of compound **9** in the crystal. Ellipsoids represent 30% probability levels. Selected bond lengths (Å) and angles (°): N18–O 1.294(3), C17–N18 1.302(3), N18–C19 1.467(3); O–N18–C17 125.9(2), O–N18–C19 114.4(2), C17–N18–C19 119.7(2).

appears at $\delta=61.9$. The UV spectrum showed an absorption for **9** at $\lambda_{max}=322$ nm, whereas it exhibits absorption at $\lambda_{max}=278$ nm for **7**.

2.1. Reaction of 9 with phenyl isocyanate (10)

The reaction of phenyl isocyanate (**10**) with **9** gives, after 3 d of refluxing in benzene, the two diastereomers 3′*R**,4*R**-3′(*H*)-2′-methyl-4′-phenyl-(4-[2.2]-paracyclophanyl)-1′,2′,4′-oxadiazole-5′-one (**11**) and 3′*R**,4*S**-3′(*H*)-2′-methyl-4′-phenyl-(4-[2.2]-paracyclophanyl)-1′,2′,4′-oxadiazole-5′-one (**12**) in 1:1 ratio (Scheme 3). The formation of products **11** and **12** is mostly caused by the presence of the nitrone **9**, during the course of reaction, in equilibration between its *Z* and *E* forms. Consequently, each form reacts with **10** to form the diastereomers **11** and **12**, respectively. The structures of **11** and **12** were established on the basis of the ^{1}H, ^{13}C NMR-, IR-, and MS-spectra as well as elemental analyses. Mass spectra and elemental analyses established the molecular formula of the both diastereomers as $C_{25}H_{24}N_2O_2$. The IR spectra showed the carbonyl group for both compounds at $\nu_{max}=1750\ cm^{-1}$. These carbonyl groups appeared, at $\delta=$ 155.2 for **11** and at $\delta=155.0$ for **12**, in the ^{13}C NMR spectra.

Table 1. Details of X-ray structural analyses of **9**, **11** and **14**

Compound	**9**	**11**	**14**
Formula	$C_{18}H_{19}NO$	$C_{25}H_{24}N_2O_2$	$C_{26}H_{27}NO$
M_r	265.34	384.46	369.49
Habit	Colorless tablet	Colorless tablet	Colorless prism
Crystal size (mm)	0.8×0.44×0.04	0.8×0.4×0.16	0.8×0.38×0.32
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/n$
Cell constants:			
a (Å)	13.538(4)	8.310(2)	7.538(2)
b (Å)	9.314(3)	10.996(3)	13.372(3)
c (Å)	11.440(4)	21.434(4)	19.779(4)
α (°)	90	90	90
β (°)	109.98(3)	90.06(2)	91.59(2)
γ (°)	90	90	90
V (Å^3)	1355.8	1958.6	1992.9
Z	4	4	4
D_x (mg m^{-3})	1.300	1.304	1.231
μ (mm^{-1})	0.08	0.08	0.07
$F(000)$	568	816	792
T (°C)	−130	−130	−120
$2\theta_{max}$	50	50	56
No. of reflections:			
Measured	2810	3749	13105
Independent	2397	3463	4830
R_{int}	0.033	0.027	0.021
Parameters	182	263	254
$wR(F^2$, all refl.)	0.150	0.135	0.169
$R(F, >4\sigma(F))$	0.056	0.052	0.063
S	1.02	1.05	1.05
Max. $\Delta\rho/e$ (Å^{-3})	0.19	0.23	0.58

Compounds **11** and **12** had ^{1}H NMR spectra with surprisingly different chemical shifts for a number of corresponding protons. The most characteristic difference was noted in the chemical shifts of 15-H and 5-H. Proton 15-H in **11** resonates at $\delta=6.83$, whereas for **12** it appears at $\delta=6.43$. Moreover, proton 5-H in **11** is deshielded by 0.9 ppm relative to its position in **12** ($\delta=5.65$). Therefore, they were initially believed to be constitutionally different. However, all signal multiplicities and 2D correlations, importantly also those based on $^nJ_{CH}$ ($n=2$, 3), are analogous for both isomers, which proves them to be diastereoisomers that differ in the relative configurations of the planar-chiral cyclophane system and the chiral center connected to 4-C. The relative configuration of **11** was secured by X-ray diffraction (Fig. 2, Table 1), hence the other of **12** follows from the indication of NMR spectra is of identical constitution.

2.2. Reaction of 9 with styrene (13)

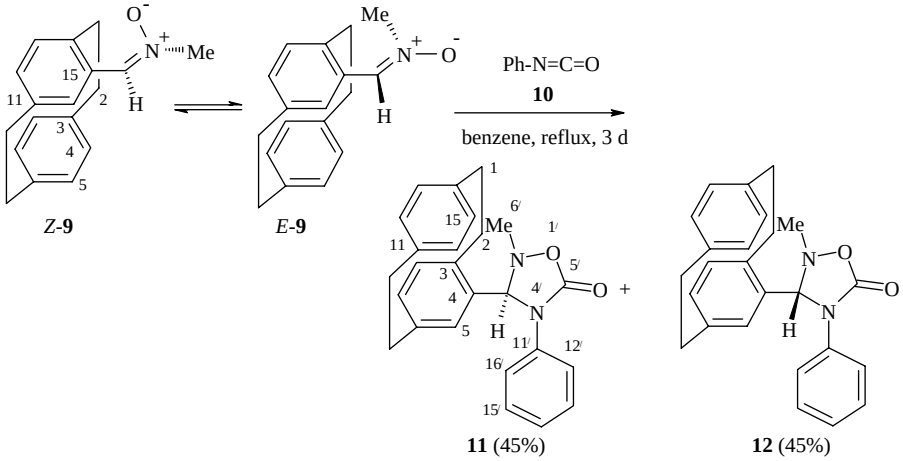
Reaction of **9** with styrene (**13**) gives **14** as the only diastereomer in 68% yield (Scheme 4). The ^{1}H NMR spectrum of compound **14** showed two unresolved double-doublets (apparent pseudo triplets), one at $\delta=5.25$ ($J=8.0$ Hz) arising from 5-H and the other at $\delta=4.06$ ($J=7.8$ Hz) coupled with 3-H. One of the CH_2 protons of 4-C appears as a multiplet at $\delta=2.05$–1.95, whereas the other is superimposed with the ethano protons of the paracyclophane moiety (see Section 3). In the ^{13}C NMR spectrum the 5-, 4- and 3-C signals absorb at $\delta=78.2$, 69.7, and 46.4, respectively. The X-ray structural analysis (Fig. 3, Table 1) confirms the structure of **14** as illustrated in Scheme 4.

2.3. Reaction of 9 with dimethyl acetylenedicarboxylate (15)

The reaction of **9** with dimethyl acetylenedicarboxylate (**15**) yields the cycloadduct **16** in 61% yield (Scheme 4). The NMR spectra confirmed the structural features of the obtained diastereomer **16**, which was identified as dimethyl 2-methyl-5-(4′-[2.2]paracyclophanyl)-3*H*-isoxazole-4,5-dicarboxylate. For example, the ^{13}C NMR spectrum displays five distinctive signals at $\delta=162.5$, 159.5, 149.6, 110.5 and 77.0 corresponding to 6-, 7-, 5-, 4- and 3-C (the ^{1}H NMR spectrum revealed 3-H at $\delta=5.20$), respectively. In addition, the 4-C′ and the N*Me* signals resonate at $\delta=149.6$ and 47.8, respectively (see Section 3).

2.4. Reaction of 9 with methylene sulfene (17)

It has been reported that aromatic nitrones react in situ with the reactive methylene sulfene **17** species to provide azasulfone derivatives.[13] Surprisingly, the reaction of **9** with methylene sulfene (**17**), generated from methanesulfonyl chloride and triethylamine, gives mainly 4-[2.2]paracyclophanyl-*N*-methylamine (**20**)[14] in 80% yield (Scheme 5). The preparation of compound **20** by such



Scheme 3. Stereoselective formation of oxadiazolones **11** and **12** during the reaction of nitrone **9** with phenyl isocyanate (**10**).

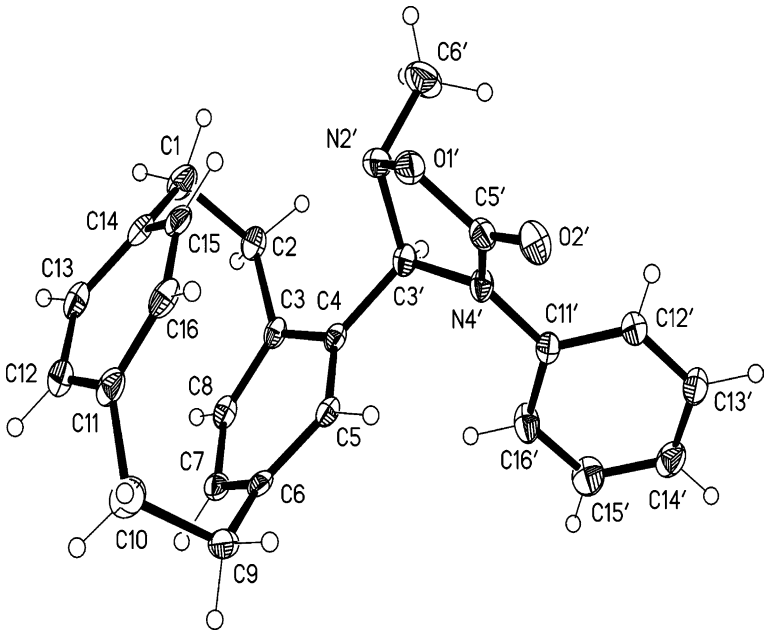
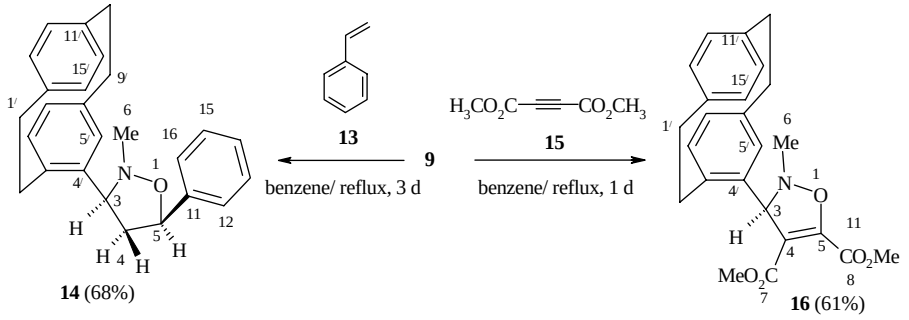


Figure 2. The structure of compound **11** in the crystal. Ellipsoids represent 30% probability levels. Selected bond lengths (Å) and angles (°): O1′–N2′ 1.464(3), N4′–C5′ 1.359(3), N4′–C3′ 1.460(3), O1′–C5′ 1.372(3), N2′–C3′ 147.6(3); C5′-O1′–N2′ 108.7(2), O1′–N2′–C3′ 102.2(2), O2′–C5′–N4′ 130.2(2), N4′–C5′–O1′ 108.1(2), C5′–N4′–C3′ 109.9(2), N4′–C3′–N2′ 102.3(2), O2′–C5′–O1′ 121.7(2).



Scheme 4. Stereospecific formation of isoxazoles **14** and **16** during the reaction of nitrone **9** with styrene (**13**) and dimethyl acetylenedicarboxylate (**15**).

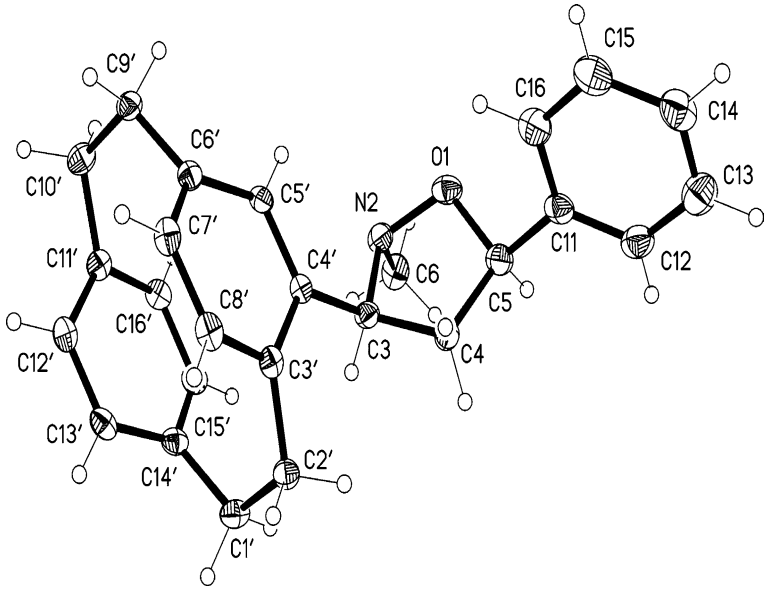
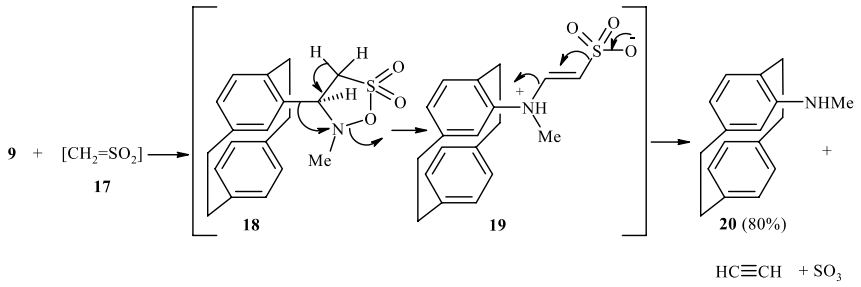


Figure 3. The structure of compound **14** in the crystal. Ellipsoids represent 30% probability levels. Selected bond lengths (Å) and angles (°): C5–O1 1.438(3), C4–C5 1.539(3), N2–O1 1.440(2), N2–C3 1.487(2), C3–C4 1.547(3); C5–O1–N2 107.8(2), O1–N2–C3 104.2(2), N2–C3–C4 106.5(2), C3–C4–C5 103.3(2), C4–C5–O1 104.4(2).



Scheme 5. Synthesis of 4-([2.2]paracyclophanyl)-*N*-methyl amine (**20**).

a simple method is a viable alternative for its known synthesis that suffers from a long procedure taking place in overall poor yield.[14] The mechanism rationalizing the formation of compound **20**, as shown in Scheme 5, is based upon formation of cycloadduct **18**. Subsequently, the intermediate **18** undergoes ring opening followed by intramolecular rearrangement involving the migration of the paracyclophane anion concerted with the proton loss to form the iminium–enamine nitrogen as in intermediate **19** (this is more favorable under acidic conditions). Elimination of acetylene and sulfur trioxide from **19** produces the stable corresponding amine **20** (Scheme 5). The formal proposed mechanism is supported by the reported literature, which indicated that isoxazole can be prepared by the addition of triethylamine and acetylene to (*Z*)-2-chloro-2-aryl-ethenol.[15]

3. Experimental

3.1. General remarks

Melting points were determined on Kofler hot stage and they are uncorrected. NMR: were recorded on Bruker AM-400, solvent: $CDCl_3$, internal standards: TMS ($\delta=0.00$) for ^1H, $CDCl_3$ ($\delta=77.05$) for ^{13}C. The results of NOE difference experiments are given in the form: irradiated signal→enhanced signal. When a complex ^1H multiplet comprising several protons was not analyzed, the individual proton chemical shifts obtained from the C,H-HETCOR spectra are given in the parentheses following the δ-range of the multiplet. Chromatography columns were packed with silica gel 7714 (Merck). For preparative layer chromatography (PLC), glass plates (20 cm×48 cm) were covered with slurry of silica gel Merck PF_{254} and air-dried using the solvents listed for development. Zones were detected by the quenching of indicator fluorescence upon exposure to 254-nm UV light. Elemental analyses were performed in the Institut für Anorganische Chemie, Technische Universität Braunschweig. Mass spectra were carried out on Finnigan MAT 8430 spectrometer at 70 eV. IR spectra were recorded on Nicolet 320 FT-IR using KBr pellets.

3.1.1. 4-([2.2]Paracyclophanyl)-*N*-methoxy-ylidene-amine (7). To a solution of *N*-hydroxylimino-4-[2.2]paracyclophane (**6**)[11] (251 mg, 1 mmol) in absolute ethanol (20 mL), a solution of sodium hydroxide (5 mL, 0.2 M) was added followed by dimethyl sulfate (252 mg, 2 mmol). The mixture was stirred at room temperature for 10 min. The organic layer was extracted with dichloromethane, washed several times with water and dried over $MgSO_4$. The solvent was concentrated under vacuum and the residue was purified by column chromatography (silica gel) with dichloromethane. Compound **7** was obtained (253 mg, 95%) as colorless plates (benzene), mp 93 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H, 17-H), 6.77 (d, 1H, 5-H, $J=1.7$ Hz), 6.62–6.45 (m, 6H), 4.02 (s, 3H, 19-H), 3.64–3.58 (m, 1H, ethano bridge), 3.08–2.80 (m, 7H, ethano bridge); ^{13}C NMR (400 MHz, $CDCl_3$) δ 147.9 (17-C), 141.1, 139.4, 139.2, 139.1, 139.0 (C), 135.3, 133.8, 132.1, 132.6, 132.1, 131.9, 130.0 (CH), 61.9 (19-C), 35.3, 34.9, 34.8, 33.9 (all t, ethano bridge carbons); IR ν_{max} (KBr): 3060–2900 cm^{-1} (Ar-CH, s), 2860–2850 (aliph.-CH, m), 1600 (C=N, s), 1010 (OCH_3, s), 1210 (w), 980 (m); UV (CH_3CN): λ_{max} (log ε)=278 nm (2.98); *m/z* (%): 265 [M^+] (54), 234 (12), 160 (50), 149 (60), 130 (100), 104 (30), 103 (20), 77 (16), 57 (18). Anal. Calcd for $C_{18}H_{19}NO$ (265.36): C, 81.48; H, 7.22; N, 5.28. Found: C, 81.35; H, 7.20; N, 5.32.

3.1.2. α-(4-[2.2]Paracyclophanyl)-*N*-methyl nitrone (9). To a refluxing stirred solution of 4-formyl-[2.2]paracyclophane (**4**,[12] 2.36 g, 10 mmol) in ethanol (200 mL), a solution of *N*-methylhydroxylamine hydrochloride (**8**, 2.50 g, 30 mmol) in water (10 mL) was added, followed by a solution of potassium hydroxide (2.50 g, 35 mmol) in water (5 mL) and ethanol (10 mL). The mixture was refluxed for 4 h, and then extracted with diethyl ether (500 mL). The organic layer was washed several times with water and dried over $MgSO_4$. The solvent was removed in vacuo and the residue was subjected to column chromatography (silica gel) with diethyl ether–EtOH (1/1) to give compound **9** (2.45 g, 92%) as colorless needles (toluene), mp 150 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H, 17-H), 7.34 (s, 1H, 5-H), 6.60 (dd, 1H, 12-H, $J=7.8$, 2.0 Hz), 6.52 (dd, 1H, 13-H, $J=7.8$, 2.0 Hz), 6.49 (dd, 1H, 7-H, $J=7.8$, 1.8 Hz), 6.46 (d, 1H, 8-H, $J=1.8$ Hz), 6.44 (dd, 1H, 15-H, $J=8.0$, 1.8 Hz), 6.38 (dd, 1H, 16-H, $J=8.0$, 1.8 Hz), 3.94 (s, 3H, N*Me*), 3.55–2.85 [m, 8H, $2CH_2CH_2$; shifts from C,H-HETCOR: 3.55, 3.34, 3.28, 3.20, 3.12, 3.00, 2.90, 2.85]; NOEs: 17-H→5-H; ^{13}C NMR (400 MHz, $CDCl_3$) δ 148.2 (s, 17-C), 139.8 (s, 6-C), 138.5 (s, 11-C), 138.3 (s, 14-C), 134.6 (s, 3-C), 134.3 (d, 8-C), 133.2 (d, 7-C), 132.5 (s, 4-C), 132.3 (d, 13-C), 131.6 (d, 12-C), 130.5 (d, 16-C), 130.2 (d, 15-C), 130.0 (d, 5-C), 54.9 (q, 19-C), 35.3, 35.1, 34.2, 34.00 (all t, ethano bridge carbons); IR ν_{max} (KBr): 3080–2960 cm^{-1} (Ar-CH, s), 2990–2851 (aliph.-CH, m), 1588 (C=N, s), 1167 (N–O, s); UV (CH_3CN): λ_{max} (log ε)= 322 nm (3.10); *m/z* (%): 265 [M^+] (48), 234 (18), 160 (32), 148 (22), 130 (100), 104 (24), 103 (18), 77 (42), 57 (16).

Anal. Calcd for $C_{18}H_{19}NO$ (265.36): C, 81.48; H, 7.22; N, 5.28. Found: C, 81.25, H, 7.20; N, 5.35.

3.1.3. Reaction of nitrone 9 with phenyl isocyanate (10). A mixture of **9** (530 mg, 2 mmol) and phenyl isocyanate (**10**, 238 mg, 2 mmol) was heated under reflux in absolute benzene (100 mL) for 3 d. The solvent was evaporated under vacuum and the residue was separated by preparative thin-layer chromatography (silica gel) with toluene. Two zones were isolated, the fastest-moving one contained compound **11**, while the slowest contained compound **12**.

3.1.4. 3′*R,4*R**-3′(*H*)-2′-Methyl-4′-phenyl-(4-[2.2]paracyclophanyl)-1′,2′,4′-oxadiazole-5′-one (11).** (344 mg, 45%) as colorless needles (ethanol), R_f=0.5, toluene, mp 192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.12 (m, 4H, 12′-,16′-,13′-,15′-H), 7.07–7.02 (m, 1H, 14′-H), 6.83 (dd, 1H, 15-H, J=8.0, 2.0 Hz), 6.55 (s, 1H, 5-H), 6.48 (d, 1H, 8-H, J=7.8 Hz), 6.45 (dd, 1H, 12-H, J=7.7, 2.1 Hz), 6.44–6.39 (m, 3H, 7-,13-,16-H), 5.66 (s, 1H, 3′-H), 3.22 (s, 3H, N*Me*), 3.15–2.84 (m, 7H, ethano bridge), 3.37–3.32 (m, 1H, ethano bridge); ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.2 (s, 5′-C), 141.0 (s, 4-C), 139.5 (s, 3-C), 138.7 (s, 14-C), 137.7 (s, 11-C), 137.3 (s, 6-C), 136.2 (s, 11′-C), 135.7 (d, 8-C), 134.2 (d, 7-C), 133.1 (d, 13-C), 132.7 (d, 5-C), 132.3 (d, 16-C), 131.8 (d, 15-C), 129.1 (d, 2C, 13′-,15′-C), 128.8 (d, 12-C), 125.0 (d, 14′-C), 120.2 (d, 2C, 12′,16′-C), 81.3 (s, 3′-C), 46.7 (q, 6′-C), 35.4, 35.2, 35.1, 32.8 (all t, ethano bridge carbons); IR ν_{max} (KBr): 3032–2994 cm^{-1} (Ar-CH, s), 2955–2851 (aliph.-CH, m), 1750 (C=O, vs), 1600, 1127 (N–O, s); UV (CH_3CN): λ_{max} (log ε)=254 nm (2.76); *m/z* (%): 385 [M+1] (28), 384 [M$^+$] (100), 367 (34), 341 (28), 340 (64), 339 (76), 325 (38), 311 (22), 265 (38), 236 (24), 218 (12), 206 (18), 161 (48), 144 (90), 119 (28), 104 (26), 91 (18), 77 (8). Anal. Calcd for $C_{25}H_{24}N_2O_2$ (384.48): C, 78.10; H, 6.29; N, 7.29. Found: C, 77.90; H, 6.19; N, 7.15.

3.1.5. 3′*R,4*S**-3′(*H*)-2′-Methyl-4′-phenyl-(4-[2.2]paracyclophanyl)-1′,2′,4′-oxadiazole-5′-one (12).** (344 mg, 45%) as colorless needles (ethanol), R_f=0.4, toluene, mp 168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.40 (m, 4H, 12′-,16′-,13′-,15′-H), 7.26–7.22 (m, 1H, 14′-H), 6.55–6.49 (m, 3H, 7-,12-,13-H), 6.43 (dd, 1H, 15-H, J=7.8, 1.8 Hz), 6.41 (dd, 1H, 16-H, J=7.8, 2.0 Hz), 6.37 (d, 1H, 8-H, 7.8 Hz), 5.72 (s, 1H, 3′-H), 5.65 (d, 1H, 5-H, J=1.8 Hz), 3.39–3.32 (m, 1H, ethano bridge), 3.17 (s, 3H, N*Me*), 3.13–2.78 (m, 7H, ethano bridge); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.0 (s, 5′-C), 140.0 (s, 4-C), 139.4 (3-C), 139.0 (s, 14-C), 138.3 (s, 11-C), 136.7 (s, 6-C), 134.5 (s, 11′-C), 134.3 (d, 8-C), 132.9 (d, 7-C), 132.7 (d, 13-C), 131.9 (d, 16-C), 130.8 (d, 15-C), 129.7 (d, 12-C), 129.3 (d, 2C, 13′-,15′-C), 126.0 (d, 14′-C), 125.8 (d, 5-C), 122.0 (d, 2C, 12′-,16′-C), 84.3 (s, 3′-C), 46.9 (q, 6′-C), 35.2, 35.0, 34.9, 32.6 (all t, ethano bridge carbons); IR ν_{max} (KBr): 3007–2990 cm^{-1} (Ar-CH, s), 2960–2854 (aliph.-CH, m), 1750 (C=O, vs), 1595, 1127 (N–O, s); UV (CH_3CN): λ_{max} (log ε)=248 nm (2.70); *m/z* (%): 385 [M+1] (28), 384 [M$^+$] (100), 367 (30), 341 (20), 340 (42), 339 (56), 325 (28), 311 (14), 265 (24), 236 (24), 206 (32), 161 (24), 144 (88), 119 (16), 104 (20), 91 (12), 77 (8). Anal. Calcd for $C_{25}H_{24}N_2O_2$ (384.48): C, 78.10; H, 6.29; N, 7.29. Found: C, 77.94; H, 6.22; N, 7.20.

3.1.6. 3(4′-[2.2]Paracyclophanyl)-3,4,4,5-tetrahydro-2-methyl-5-phenyl-isoxazole (14). A mixture of **9** (530 mg, 2 mmol) and styrene (**13**, 342 mg, 3 mmol) was refluxed in absolute benzene (200 mL) for 3 days. The solvent was evaporated in vacuo and the residue was purified by column chromatography on silica gel with toluene. (480 mg, 68%) of **14** was obtained as colorless crystals (ethanol), mp 138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, 1H, J=8.0, 2.0 Hz), 7.20–7.00 (m, 4H), 6.80 (br s, 1H, 5′-H), 6.64 (dd, 1H, 13′-H, J=7.8, 1.8 Hz), 6.56 (dd, 1H, 12′-H, J=8.0, 1.8 Hz), 6.54 (dd, 1H, 7′-H, J=8.0, 1.8 Hz), 6.48 (d, 1H, 8′-H, J=7.8, 2.0 Hz), 6.42 (dd, 1H, 16′-H, J=8.0, 1.8 Hz), 6.22 (dd, 1H, 15′-H, J=7.8, 1.8 Hz), 5.25 (t, 1H, J=8.0 Hz, 5-H), 4.06 (t, 1H, J=7.8 Hz, 3-H), 3.32–2.60 (m, 12H, ethano bridge, 4-H, N*Me*), 2.05–1.95 (m, 1H, 4-H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 140.5 (s, 4′-C), 139.9 (s, 14′-C), 138.9 (s, 6′-C), 138.4 (s, 11′-C), 135.0 (d, 8′-C), 135.3, 134.8, 133.4, 133.3, 132.9 (C), 132.4 (d, 13′-C), 131.5 (d, 12′-C), 129.6 (s, 11-C), 129.0 (d, 2C, 13-,15-C), 128.3 (d, 2C, 12-,16-C), 127.7 (d, 14-C), 78.2 (5-C), 69.7 (3-C), 46.4 (4-C), 45.6 (q, 6-C), 35.4, 35.2, 34.4, 33.2 (all t, ethano bridge carbons); IR ν_{max} (KBr): 3024–2975 cm^{-1} (Ar-CH, s), 2946–2852 (aliph.-CH, s), 1592 (s), 1490 (m), 1455 (s), 916 (m); UV (CH_3CN): λ_{max} (log ε)=320 nm (3.34); *m/z* (%): 370 [M+1] (30), 369 [M$^+$] (100), 338 (10), 323 (20), 265 (52), 250 (12), 222 (10), 219 (18), 159 (48), 144 (70), 129 (24), 91 (24), 77 (20). Anal. Calcd for $C_{26}H_{27}NO$ (369.51): C, 84.45; H, 7.36; N, 3.79. Found: C, 84.35; H, 7.30; N, 3.68.

3.1.7. Dimethyl 2-methyl-5-(4′-[2.2]paracyclophanyl)-3*H*-isoxazole-4,5-dicarboxylate (16). A mixture of **9** (530 mg, 2 mmol) and dimethyl acetylenedicarboxylate (**15**, 284 mg, 2 mmol) was heated under reflux in absolute benzene (100 mL) for 1 d. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel with toluene. **16** was obtained (500 mg, 61%) as pale yellow crystals (ethanol), mp 105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, 1H, 5′-H, J=1.8 Hz), 6.72 (dd, 1H, 12′-H, J=8.0, 2.0 Hz), 6.62 (d, 1H, 8′-H, J=8.0 Hz), 6.58 (dd, 1H, 13′-H, J=8.0, 1.8 Hz), 6.50 (dd, 1H, 7′-H, J=8.0, 1.8 Hz), 6.50–6.30 (m, 2H, 15′-,16′-H), 5.20 (s, 1H, 3-H), 3.85 (s, 3H, *Me*, 8-H), 3.52 (s, 3H, *Me*, 9-H), 3.20 (s, 3H, N*Me*), [m, 2H, shifts: 3.22–3.00 (2′-,1′-H)], 2.90–2.78 [m, 2H, shifts: 3.13 (2×9′-H)], 2.70–2.45 [(m, 4H, (2×10′)-,1′-,2′-H)]; ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.5 (s, 7-C), 159.5 (s, 6-C), 149.6, (s, 5-C), 143.2 (s, 4′-C), 140.6 (s, 14′-C), 140.4 (s, 11′-C), 139.6 (s, 6′-C), 139.5 (s, 3′-C), 138.8 (d, 8′-C), 138.0 (d, 15′-C), 137.1 (d, 7′-C), 136.3 (d, 16′-C), 134.9 (d, 13′-C), 133.0 (s, 12′-C), 132.0 (d, 5′-C), 110.5 (d, 4-C), 77.0 (s, 3-C), 52.3 (q, 9-*Me*), 51.7 (q, 8-*Me*), 47.8 (q, N*Me*), 35.3 (t, 10′-C), 35.0 (t, 9′-C), 34.9 (t, 1′-C), 33.54 (t, 2′-C); IR ν_{max} (KBr): 3030–2988 cm^{-1} (Ar-CH, s), 2880–2850 (aliph.-CH, m), 1597 (C=N, m), 1730 (CO, s), 1560 (C=C, s), 1280 (m), 980 (m), 760 (s); UV (CH_3CN): λ_{max} (log ε)=360 nm (380); *m/z* (%): 407 [M$^+$] (14), 349 (24), 348 (84), 347 (26), 321 (18), 320 (76), 303 (10), 276 (38), 265 (78), 264 (100), 236 (42), 104 (80), 78 (14). Anal. Calcd for $C_{24}H_{25}NO_5$ (407.47): C, 70.75; H, 6.18; N, 3.44. Found: C, 70.55; H, 6.10; N, 3.40.

3.1.8. 4-([2.2]Paracyclophanyl)-*N*-methylamine (20). A solution of **9** (530 mg, 2 mmol) in dry benzene (100 mL) was prepared under nitrogen in a three-necked flask

equipped with two dropping funnels. Equivalent amounts of methylenesulfonyl chloride (229 mg, 2 mmol) and fresh anhydrous triethylamine (182 mg, 2 mmol), each in dry benzene (30 mL), were added simultaneously over a period of 15 min. The reaction was further warmed to 60 °C for 1 h. Triethylammonium chloride precipitated during this period, and the color became more intensely yellow. The precipitate was filtered off and the residue was subjected to column chromatography (silica gel) with toluene. Compound **20** was obtained (250 mg, 80%) as pale red crystals (ethanol), mp 105 °C (lit.[14] 105 °C); NMR spectroscopic data is in a good agreement with that reported in Ref. 14.

3.2. X-ray structure determinations

The structures of compounds **9**, **11** and **14** were confirmed by X-ray analysis (Figs. 1–3). Bond lengths and angles are normal (see Figure captions for important values). The five-membered rings of compounds **11** and **14** display envelope conformations, in which N2′ (**11**) lies 0.44 and O1 (**14**) 0.51 Å out of the plane of the other four atoms (mean deviations 0.02, 0.01 Å, respectively).

Some intermolecular contacts are significant. In **9**, there is a short contact C19–H19A···O via the 2_1 axis, with H···O 2.40 Å and C–H···O 150°. In **11**, the molecules are linked in inversion–symmetric pairs by the contacts C12′–H12′···O1′ [H···O 2.55 Å, C–H···O 155°] and C6′–H6′3···O2′ [H···O 2.50 Å, C–H···O 143°]. In **14**, the molecules are again linked in inversion–symmetric pairs by the contact C5′–H5′···O1 [H···O 2.40 Å, C–H···O 147°]; within the pair and between pairs there are also C–H···π contacts involving ring centroids ('Cent') [C10–H10B···Cent (C11-16) with H···Cent 2.79 Å, C–H···Cent 156° and C4–H4B···Cent (C12′,13′,15′,16′) with H···Cent 2.61 Å, C–H···Cent 152°, respectively] (Figs. 3 and 4).

3.3. Data collection and reduction

Crystals were mounted in inert oil on glass fibres and transferred to the cold gas stream of the diffractometer (**9**, **11**: Stoe STADI4; **14**: Siemens SMART area detector). Measurements were performed with monochromatic Mo Kα radiation. *Structure refinement*: the structures were refined anisotropically against F^2 (Sheldrick G. M. *SHELXL-97: program*, University of Göttingen). H atoms were included with a riding model or with rigid methyl groups. Complete Crystallographic data (excluding structure factors) has been deposited in Cambridge Crystallographic Data under the numbers 23138 (**9**), 238139 (**11**),

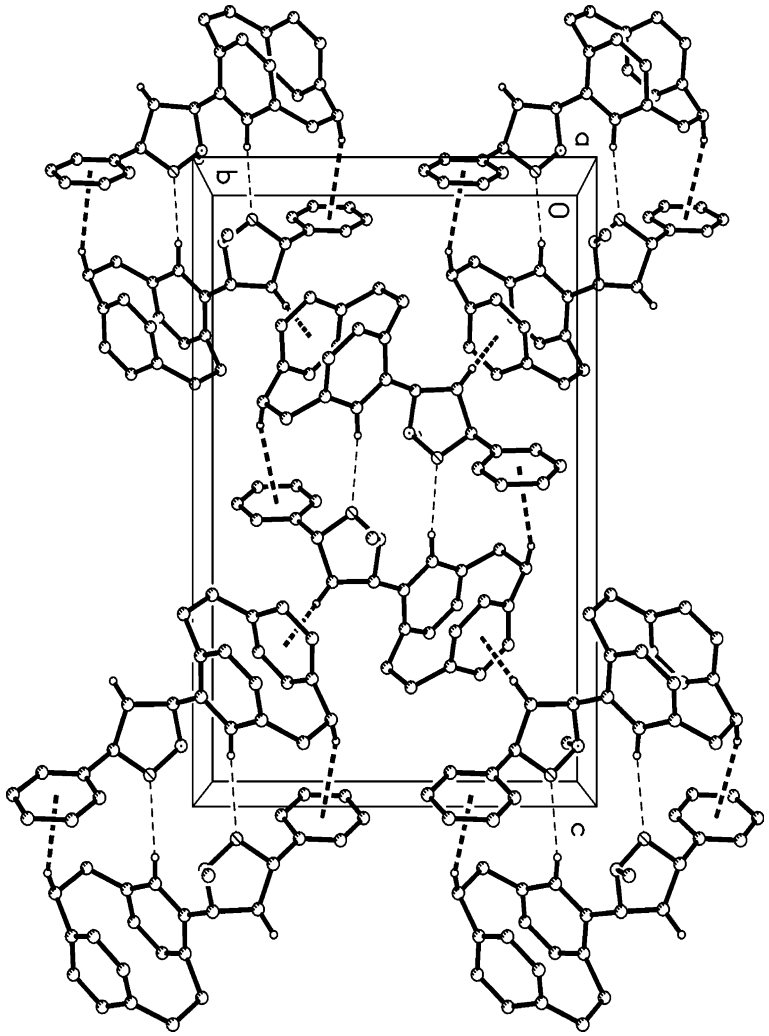


Figure 4. Packing diagram of compound **14**. C–H···O interactions are indicated by thin and C–Hπ interactions by thick dashed lines.

238140 (**14**). Copies may be requested free of charge from the director, CCDC, 12 Union Road, Cambridge CB2 1EZ, England (e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

Prof. Dr. Ashraf A. Aly thanks the DAAD for financial support.

References and notes

1. For leading references, see: (a) Hopf, H. In *Modern Cyclophane Chemistry*; Gleiter, R., Hopf, H., Eds.; Wiley-VCH: Weinheim, 2004; Chapter 17, pp 435–462. (b) Rozenberg, V.; Kharitonov, V.; Antonov, D.; Sergeeva, E.; Aleshkin, A.; Ikonnikov, N.; Orlova, S.; Belokon, Y. *Angew. Chem.* **1994**, *106*, 106–108. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 91–93. (c) Hopf, H.; Barrett, D. G. *Liebigs Ann.* **1995**, 449–451. (d) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207–6208. (e) Rossen, K.; Pye, P. J.; Maliakal, A.; Volante, R. P. *J. Org. Chem.* **1997**, *62*, 6462–6468. (f) Pelter, A.; Kidwell, H.; Crump, R. A. N. C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3137–3139. (g) Cipiciani, A.; Fringuelli, F.; Mancini, V.; Piermatti, O.; Pizzo, F.; Ruzziconi, R. *J. Org. Chem.* **1997**, *62*, 3744–3747. (h) Lyssenko, K. A.; Korlyukov, A. A.; Antipin, M. Yu. *Mendeleev Commun.* **2005**, *3*, 90–92. (i) Furo, T.; Mori, T.; Wada, T.; Inoue, Y. *J. Am. Chem. Soc.* **2005**, *127*, 8242–8243. (j) Stanger, A.; Ben-Mergui, Na.; Perl, S. *Eur. J. Org. Chem.* **2003**, *14*, 2709–2712. (k) Aly, A. A.; Hassan, A. A.; Mourad, A. E. *Can. J. Chem.* **1993**, *71*, 1845–1849. (l) Aly, A. A. *Spectrochim. Acta, Part A* **1999**, *55*, 79–88. (m) Haenel, M. W.; Schweitzer, D. *Adv. Chem Ser.* **1988**, *217*, 333–355. (n) Otsubo, T.; Horita, H.; Koizumi, Y.; Misumi, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1677–1682. (o) Boekelheide, V. *Pure Appl. Chem.* **1975**, *44*, 751–765.
2. (a) Birsa, M. L.; Jones, P. G.; Hopf, H. *Eur. J. Org. Chem.* **2005**, *15*, 3263–3270. (b) Minuti, L.; Taticchi, A.; Marrocchi, A.; Landi, S.; Gacs-Baitz, E. *Tetrahedron Lett.* **2005**, *46*, 5735–5737. (c) Ueda, T.; Kanomata, N.; Machida, H. *Org. Lett.* **2005**, *7*, 2365–2368.
3. (a) Altava, B.; Burguete, M. I.; Luis, V. S.; Miravet, J. F.; Garcia-Espana, E.; Marcelino, V.; Soriano, C. *Tetrahedron* **1997**, *53*, 4751–4762. (b) Haticchi, A.; Minuti, L.; Lanari, D.; Marrocchi, A.; Tesei, I.; Gacs-Baitz, E. *Tetrahedron* **2004**, *60*, 11759–11764. (c) Aly, A. A.; Mourad, A. E. *Tetrahedron* **1993**, *49*, 7325–7336. (d) Aly, A. A. *Tetrahedron* **2003**, *9*, 1739–1747. (e) Aly, A. A. *Org. Biomol. Chem.* **2003**, *1*, 756–761. (f) Aly, A. A. *Tetrahedron Lett.* **2005**, *46*, 443–446.
4. (a) Dix, I.; Hopf, H.; Jones, P. G. *Acta Crystallogr., Sect. C* **1999**, *55*, 756–759. (b) Kryvenko, L. I.; Soldatenkov, A. T.; Zvolinskii, O. V.; Kuleshova, L. N.; Khrustalev, V. N.; Gryshev, V. N.; Soldatova, S. A. *Chem. Heterocycl. Compds* **1997**, *33*, 691–697. (c) Shimada, T.; Sasaki, M.; Ariga, T. *Jpn. Kokai Tokkyo Koho* **1990**, *6*, 240–245.
5. (a) Ota, M. *Jpn. Kokai Tokkyo Koho* **1987**, *5*, 224–228. (b) Prakash, S.; Singh, N. L. *Indian J. Pure Appl. Phys.* **1965**, *3*, 374–376. (c) Held, I.; Villinger, A.; Zipse, H. *Synthesis* **2005**, *9*, 1425–1430.
6. Trond, V.; Hansen, P. W.; Valery, V. F. *J. Org. Chem.* **2005**, *70*, 7761–7764.
7. Angeles, P.-G.; Jesús, R.-O.; Enrique, M. C.-L. *Eur. J. Org. Chem.* **2005**, 3228–3232.
8. (a) Aly, A. A.; Hopf, H.; Ernst, L. *Eur. J. Org. Chem.* **2000**, 3021–3029. (b) Aly, A. A.; Ehrhardt, S.; Hopf, H.; Dix, I.; Jones, P. G. *Eur. J. Org. Chem.* **2006**, 335–350.
9. (a) Hopf, H.; Aly, A. A.; Swaminathan, V. N.; Ernst, L.; Dix, I.; Jones, P. G. *Eur. J. Org. Chem.* **2005**, 68–71. (b) Aly, A. A.; Hopf, H.; Ernst, L.; Jones, P. G.; Dix, I. *Eur. J. Org. Chem.* **2006**, in press.
10. (a) Rossiter, S.; Dobbs, A. P. *Imines and their N*-Substituted Derivatives: Oximes and their *O-R* Substituted Analogies; Comprehensive Organic Functional Group Transformations II; 2005, 451–467. (b) Houk, K. N.; Sims, J.; Ducke, R. E.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287–7301.
11. Eltamany, S. H. *Indian J. Chem., Sect. B* **1992**, *31*, 238–242.
12. (a) Hopf, H.; Eltamany, S. H. *Chem. Ber.* **1983**, *116*, 1682–1685. (b) Hopf, H.; Eltamany, S.; Raulfs, F. W. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 633–638.
13. (a) Huisgen, R. *Angew. Chem.* **1963**, *75*, 604–634. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565–595. (b) Huisgen, R. *Angew. Chem.* **1963**, *75*, 742–746. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633–637. (c) Huisgen, R.; Knorr, R. *Naturwiss. (Science in Deutsch)* **1961**, *48*, 716–720. (d) Seidl, V.; Huisgen, R.; Grashey, R. *Chem. Ber.* **1969**, *102*, 926–930. (e) Huisgen, R.; Hauck, H.; Grashey, R.; Seidl, V. *Chem. Ber.* **1969**, *102*, 736–745.
14. (a) Cram, D. J.; Allinger, N. L. *J. Am. Chem. Soc.* **1955**, *77*, 6289–6294. (b) Falk, H.; Reich-Rohrwig, P.; Schlögl, K. *Tetrahedron* **1970**, *26*, 511–515. (c) Nakazaki, N.; Yamamoto, K.; Maeda, M. *Chem. Lett.* **1980**, 1553–1555.
15. Nakamura, T.; Sato, M.; Kakinuma, H.; Miyata, N.; Taniguchi, K.; Bando, K.; Koda, A.; Kameo, K. *J. Med. Chem.* **2003**, *46*, 5416–5427.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 4506–4518
Tetrahedron

Aminophosphine oxides in a pyridine series. Studies on the cleavage of pyridine-2- and pyridine-4-yl-(*N*-benzylamino)-methyldiphenylphosphine oxides in acidic solutions

Waldemar Goldeman,[a] Tomasz K. Olszewski,[a] Bogdan Boduszek[a,*] and Wanda Sawka-Dobrowolska[b]

[a]*Department of Organic Chemistry, Faculty of Chemistry, Wroclaw University of Technology, Wybrzeze Wyspianskiego 27, 50-370 Wrocław, Poland*
[b]*Department of Chemistry, University of Wroclaw, F. Joliot-Curie 14, 50-383 Wrocław, Poland*

Received 27 September 2005; revised 27 January 2006; accepted 16 February 2006

Available online 7 March 2006

Abstract—The synthesis and reactions of 1-(*N*-benzylamino)-1-(2-pyridyl)- and 1-(*N*-benzylamino)-1-(4-pyridyl)-methyldiphenylphosphine oxides are described. It was found that these compounds were exceptionally easy to cleave in aqueous sulfuric acid solutions to form diphenylphosphinic acid and the corresponding *N*-(pyridylmethyl)-benzylamines. The structure of a single diastereoisomer, that is, the (*R*)-(+)-1-[*N*-(α-methylbenzylamino)]-1-(4-pyridyl)-(*S*)-methyldiphenylphosphine oxide was determined by X-ray crystallography. The acidic alcoholysis of the selected model chiral pyridine aminophosphine oxides was investigated by means of ^{31}P NMR spectroscopy. The cleavage kinetics were also studied. On the basis of the obtained results, a mechanism of the cleavage was formulated.

1. Introduction

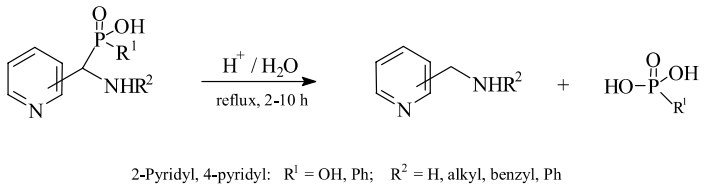
Organophosphorus compounds, aminophosphonic acids in particular, are believed to be stable, durable compounds, resistant to decomposition in both basic and acidic solutions. However, there were a few reports describing the C–P bond cleavage in some functionalized phosphonate compounds in acidic conditions.[1–8] For example, the acid-catalyzed fragmentation of aromatic α-oxyiminophosphonates was reported in the late 1980s.[1–3] Recently, an example of the oxidative cleavage of a C–P bond in 1-amino-1-(3,4-dihydroxyphenyl)-methylphosphonic acid in low pH was described.[4] First of all, we reported[5–7] that certain heterocyclic aminophosphonates were amenable to definite cleavage in acidic solutions at elevated temperatures. It mainly concerned the pyridine derivatives of aminomethylphosphonic acid, namely the pyridine-2-yl or pyridine-4-yl-(*N*-alkylamino)-methylphosphonic acids[5,6] and their esters,[5] which are easily cleaved when heated for a few hours in aqueous sulfuric, or hydrochloric acid at 95 °C. As a result, the formation of secondary *N*-(pyridylmethyl)-alkylamines and phosphoric acid (H_3PO_4) was observed. Similarly, some oxygen heterocyclic phosphonic acids, that is, the pyrone-2, chromone-2 and coumarin-4 derivatives of the aminomethylphosphonic acid were reportedly cleaved in the same manner.[7] Interestingly, we also observed[8] that the pyridine aminophosphinic acids were likewise cleaved by aqueous sulfuric acid to form the corresponding secondary pyridylamines and arylphosphonic acids. The latter cleavage proceeded quickly, even at room temperature.[8] All of these cleavages, which occurred on pyridine aminophosphonic acids and related phosphorus compounds, are illustrated in Scheme 1.

The chemical nature of these cleavage reactions still remains unclear, despite some attempts to explain it.[5–7] Therefore, these reactions became the subject of a more detailed study in our laboratory.

Particular importance was placed on pyridine aminophosphine oxides, which are suitable compounds for studying the cleavage in acidic conditions due to the exceptional ease of the C–P bond cleavage. Likewise, the actual possibility of the synthesis of certain optically active pyridine aminophosphine oxides with a definite configuration at α-carbon and (or) at phosphorus atom is of great importance in clarifying the basic questions connected with the plausible mechanism of these cleavage reactions.

Keywords: Aminophosphine oxides; Pyridine; Acidic solutions.
* Corresponding author. Tel.: +48 713202917; fax: +48 713284064; e-mail: bogdan.boduszek@pwr.wroc.pl

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.048



Scheme 1. Cleavage of the pyridine aminophosphonic acids in acidic solutions.

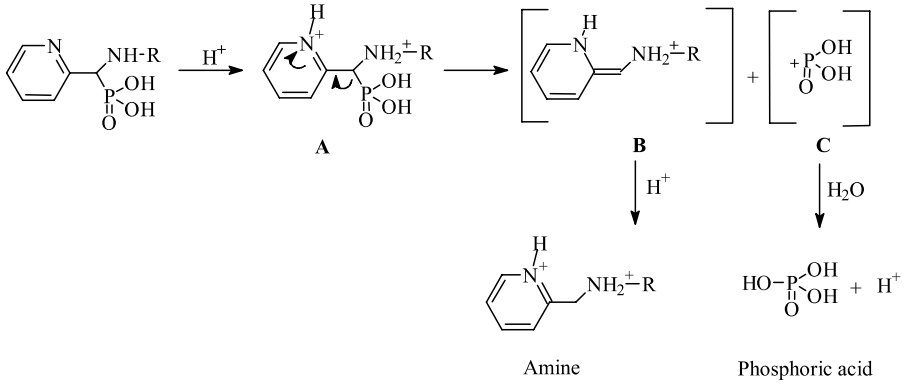
There are two main alternative mechanisms for a C–P bond breaking in the functionalized phosphonates in acidic conditions presented in the chemical literature.[2]

The first mechanism is a dissociative-type mechanism [$S_N1(P)$], which assumes the formation of a monomeric metaphosphate moiety after the rupture of a C–P bond. The metaphosphate, as a reactive intermediate, is then trapped by the solvent to form products in a nucleophilic process. The second mechanism is an associative-type mechanism [$S_N2(P)$], which involves a direct nucleophilic attack of a solvent molecule at phosphorus in the phosphonate prior to the breaking of a C–P bond. The aforementioned alternative mechanisms would be taken in consideration for the cleavage of the pyridine aminophosphonic acids on the condition that in the considered dissociative mechanism, the formed species is really 'protonated' metaphosphate moiety **C** due to the strong acidic conditions. These mechanisms are shown in Schemes 2 and 3, respectively.

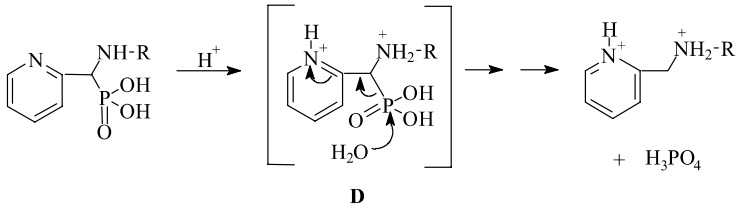
The proposed dissociative mechanism,[5,6] shown in Scheme 2, relies upon the breaking of a C–P bond in aminophosphonate **A** and the formation of two fragmentary products (**B**, **C**). One of the intermediates is an enamine-like moiety **B** and the second one is a metaphosphate-like moiety **C**. The **C** is actually the 'protonated' metaphosphate (a phosphinylium,[12,13] or phosphacylium cation[14,15]) and therefore, as a reactive intermediate, can react with solvent (water) to form a final product. The **B** fragment transforms into the amine (Scheme 2), by incorporating the proton. A driving force to trigger the cleavage is the presence of a positive charge of protonated nitrogen in the aminophosphonate **A**.

An alternative associative mechanism[6] assumes that after the preceding protonation of an oxygen atom in a phosphoryl group coincides with an attack of a solvent molecule at a positively charged phosphorus atom in the aminophosphonate **D** (Scheme 3). Further reorganization of the **D** gives the final fragmentary products as a result of the breaking of the C–P bond.

In this paper, we describe in detail the results of our studies regarding the cleavage of racemic and optically active pyridine aminophosphine oxides **4a–i** in aqueous acidic solutions. Additionally, the cleavage of aminophosphine oxides in the presence of some alcohols was explored. Also, the use of certain optically active aminophosphine oxides with defined configurations at phosphorus and α-carbon



Scheme 2. Dissociative mechanism of the cleavage of pyridine aminophosphonic acids.



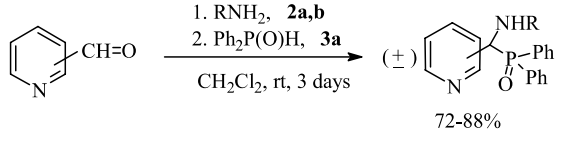
Scheme 3. Associative mechanism of the cleavage of pyridine aminophosphonic acids.

atoms was studied in order to find the final conclusions about the proposed mechanism.

2. Results and discussion

2.1. Synthesis of pyridine aminophosphine oxides

The new pyridine aminophosphine oxides were prepared from pyridinecarboxaldehydes, primary amines and phosphine oxides, according to a method described earlier.[8] Thus, treatment of the pyridinecarboxaldehydes **1a**,**b** with benzylamine **2a**, or butylamine **2b**, followed by the addition of diphenylphosphine oxide **3a**, led to the formation of racemic 1-(*N*-alkylamino)-1-(2-pyridyl)- and 1-(*N*-alkylamino)-1-(4-pyridyl)-methyldiphenylphosphine oxides **4a–d** in high yields (Scheme 4).



1a: 2-pyridyl
1b: 4-pyridyl

2a: R = $PhCH_2$
2b: R = *n*-Bu

4a: 2-pyridyl, R = $PhCH_2$
4b: 4-pyridyl, R = $PhCH_2$
4c: 2-pyridyl, R = *n*-Bu
4d: 4-pyridyl, R = *n*-Bu

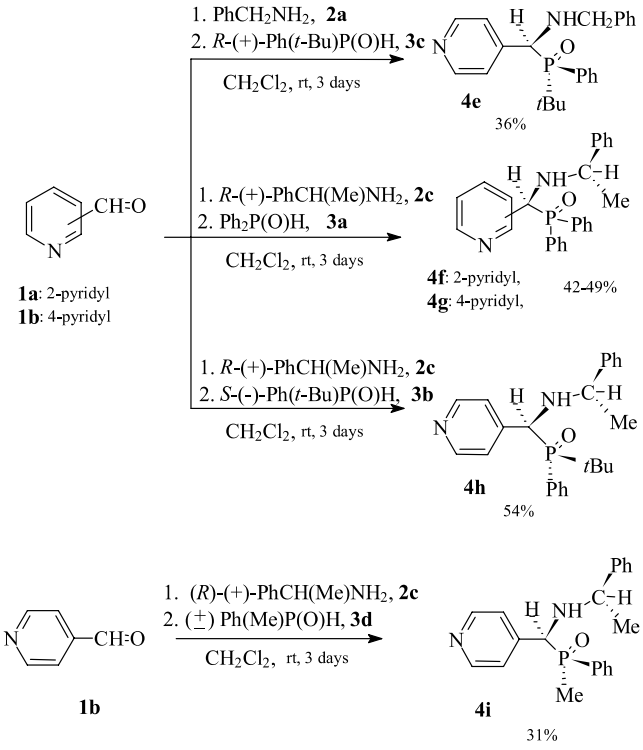
Scheme 4. Synthesis of the racemic pyridine aminophosphine oxides.

The most obvious route for the synthesis of optically active aminophosphine oxides is the addition of enantiomerically pure *P*-chiral phosphine oxides to chiral imines, or imines bearing a chiral auxiliary.[9] Thus, diastereomerically pure pyridine aminophosphine oxides **4e–h** were obtained in a sequence of reactions starting from the corresponding pyridinecarboxaldehyde **1** and enantiomerically pure (*R*)-(+)-α-methylbenzylamine (**2c**) and (*S*)-(−)-*tert*-butylphenylphosphine oxide (**3b**),[11b] or (*R*)-(+)-*tert*-butylphenylphosphine (**3c**),[11b] respectively (Scheme 5).

These reactions proceeded with significant stereoselectivity and gave a non-equal mixture of two diastereoisomers. The ratios of the stereoisomers were determined by ^{31}P NMR spectroscopy and were equal to 60:40 for **4e**, 75:25 for **4f**, 84:16 for **4g**, and 82:18 for **4h**. The separation of the major diastereoisomers was achieved by a simple crystallization from acetone to give, in each case, the prevailing diastereoisomer (Scheme 5).

Major diastereoisomers (**4e–h**) possessed with a *S* configuration on the tertiary α-carbon atom (in the methine group), according to the ^{1}H and ^{31}P NMR spectra of the aminophosphine oxides and by comparison with X-ray analysis for the diastereoisomer **4g** (Fig. 1). The predominance in the formation of the diastereoisomers with a *S* configuration at the α-carbon is in agreement with the literature data.[9]

Optically active phosphine oxides **3b** and **3c** (*S* and *R* enantiomers), used for the synthesis of aminophosphine oxides **4h** and **4e**, were obtained from racemic *tert*-butylphenylphosphine oxide[10] by resolution of the racemate with the use of (*S*)-(+)-mandelic acid, according to a method described by Drabowicz, et al.[11a]



Scheme 5. Synthesis of the optically active pyridine aminophosphine oxides.

For further cleavage studies, one more example of an optically active aminophosphine oxide, that is, the (+)-1-[*N*-(α-methylbenzylamino)]-1-(4-pyridyl)-methyl-phenylmethylphosphine oxide (**4i**), was synthesized (Scheme 5). The aminophosphine oxide was obtained from pyridine-4-carboxaldehyde (**1b**), (*R*)-(+)-α-methylbenzylamine (**2c**) and racemic phenylmethylphosphine oxide **3d**.[37,39]

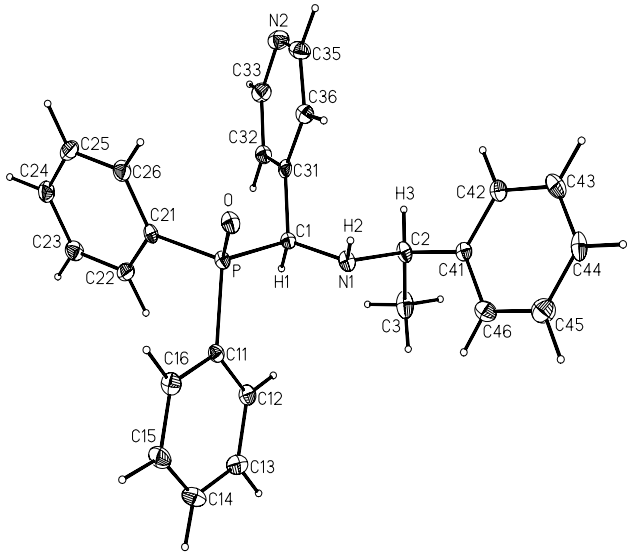


Figure 1. Structure of pyridine-4-yl-(*N*-α-methylbenzylamino)-methyldiphenylphosphine oxide **4g**.

The single diastereoisomer **4i** was isolated from the product by recrystallization from acetone.

By analogy to the preceding results, the **4i** was assigned as the stereoisomer with a *S* configuration at the α-carbon. The configuration at phosphorus was the same as in the case of **4e** (see the Sections 2.7 and 4.8.6).

In summary, all of the syntheses were carried out in dichloromethane solutions at room temperature, in a simple way, to give the diastereomerically pure pyridine aminophosphine oxides **4a–h** as crystalline solids in moderate yields.

2.2. Cleavage of pyridine aminophosphine oxides 4a–h

The cleavage of pyridine aminophosphine oxides **4a–h** occurred when the solution of these aminophosphine oxides in aqueous 10% sulfuric acid was heated at 95 °C for 2–10 h. As a result, there was the formation of the *N*-(pyridylmethyl)-alkylamines **5a–c**, **6a–c** and diphenylphosphinic acid **7**, or *tert*-butylphenylphosphinic acid **8**, respectively. Because of a low solubility of the formed phosphinic acids in the aqueous medium, the acids **7** and **8** separated from the reaction solution. In turn, amines **5a–c**, **6a–c** were isolated by extraction from alkaline reaction mixture. The overall cleavage of the **4a–h** is shown in Scheme 6.

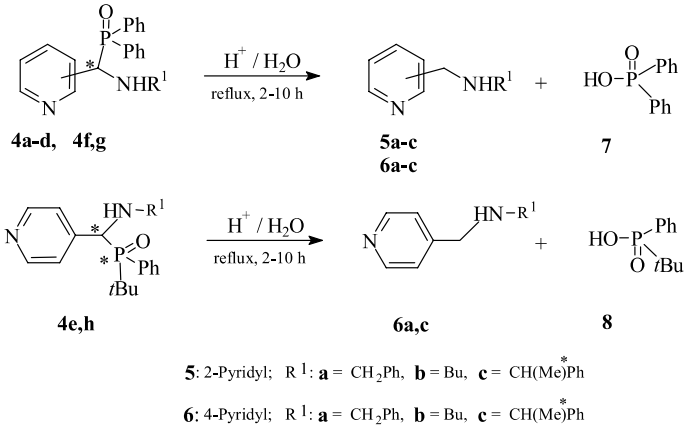
The cleavage of **4a–h** also proceeded at room temperature; however, much slower, requiring a considerable longer period of time to complete the reaction. It was found, according to the ^{31}P NMR data, that the pyridine-2 aminophosphine oxides were cleaved 3–4 times faster than corresponding pyridine-4 compounds.

2.3. Kinetic measurements

For kinetic purposes, the cleavage of the selected aminophosphine oxides (**4a**,**b**,**f**,**g**,**h**) were run in 50% (v/v) aqueous methanol solutions, containing a definite quantity of sulfuric acid. The use of aqueous methanol was to evade the precipitation of the formed phosphinic acid **7** (or **8**), during kinetic measurements. The reactions were run and measured in NMR tubes by ^{31}P NMR spectroscopy and the relative quantities of the phosphorus-containing products and starting materials were estimated from the corresponding integrated ^{31}P NMR signals. In this case, the appearance of a signal due to phosphinic acid **7** (or **8**), together with the subsequent decay of a signal corresponding to the **4** was observed. On the basis of ^{31}P NMR data, the rate constants were calculated. The measured cleavages followed pseudo-first-order kinetics. It was found that the rate constants were strongly dependent on the concentration of the sulfuric acid (entry; 1 and 2, Table 1).

The measured cleavages followed pseudo-first-order kinetics. It was found that the rate constants were strongly dependent on the concentration of the sulfuric acid (entry; 1 and 2, Table 1). It was also illustrative that the 2-pyridyl derivative **4a** underwent cleavage 3–4 times faster than the corresponding 4-pyridyl one (**4b**). The runs, which were performed in deuterated solvents and with the use of deuterated reagents, proved that the cleavages were considerably faster in solutions of common, non-deuterated acids. It was also possible to calculate the kinetic isotope effects in some cases (entry; 4, 6, 8, data for **4f**, **4g** and **4h**, Table 1). All kinetic results demonstrate that the protonation of pyridine aminophosphine oxides has a profound effect on the cleavage of C–P bonds. The kinetic isotope effects pointed out that the protons were involved on the rate-determining step of the cleavage. Such values of the kinetic isotope effects ($k_H/k_D > 2$, Table 1) rather exclude an alleged nucleophilic attack of the solvent molecule on the phosphorus atom in the aminophosphine oxide, because in such a case $k_H/k_D < 1$ should be expected (due to a higher concentration of deuterated phosphorus species in D_2O, in comparison with the concentration of the corresponding protonated ones in H_2O). The obtained rate constants are summarized in Table 1.

It is noteworthy that the rate constants were calculated from estimated ^{31}P NMR integrated signals, and therefore, these results should not be considered as exact data for mere kinetic studies. More persuasive arguments for the proposed mechanism were found during further studies on the cleavage of optically active pyridine aminophosphine oxides in methanolic solutions.



Scheme 6. Cleavage of the pyridine aminophosphine oxides in acidic solutions.

Table 1. Rate constants for cleavage of the aminophosphine oxides (**4a**,**b** and **4f**,**g**,**h**) at 20 °C

Entry	Compound	Solvent	Concn of compound mol L^{-1}	Concn of acid mol L^{-1}	Kinetic parameters	
					10^2 k_{obsd} h^{-1}	$t_{1/2}$, k_H/k_D
1	**4a**	50% Aqueous methanol	0.10	0.5 (H_2SO_4)	0.83	$t_{1/2}$[a] = 11.2 h
			0.10	1.0 (H_2SO_4)	6.17	
			0.10	2.0 (H_2SO_4)	15.08	
2	**4b**	50% Aqueous methanol	0.10	0.5 (H_2SO_4)	1.17	$t_{1/2}$[a] = 38.9 h
			0.10	1.0 (H_2SO_4)	1.78	
			0.10	2.0 (H_2SO_4)	2.78	
3	**4f**	50% Aqueous methanol	0.10	1.0 (H_2SO_4)	1.08	$t_{1/2}$ = 64.2 h
4	**4f**	50% CH_3OD in D_2O	0.10	1.0 (D_2SO_4)	0.43	$t_{1/2}$ = 161 h, k_H/k_D = 2.53
5	**4g**	50% Aqueous methanol	0.10	1.0 (H_2SO_4)	0.95	$t_{1/2}$ = 73.0 h
6	**4g**	50% CH_3OD in D_2O	0.10	1.0 (D_2SO_4)	0.30	$t_{1/2}$ = 231 h, k_H/k_D = 3.17
7	**4h**	50% Aqueous methanol	0.20	1.0 (H_2SO_4)	0.81	$t_{1/2}$ = 85.3 h
8	**4h**	50% CH_3OD in D_2O	0.20	1.0 (D_2SO_4)	0.34	$t_{1/2}$ = 202 h, k_H/k_D = 2.36

[a] $t^{1/2}$ was measured for 1 M H_2SO_4 solution.

2.4. Cleavage of (*R*)-(+)-1-[*N*-(α-methylbenzylamino)]-1-(2-pyridyl)-(*S*)-methyldiphenylphosphine oxide (4f) and (*R*)-(+)-1-[*N*-(α-methylbenzylamino)]-1-(4-pyridyl)-(*S*)-methyldiphenylphosphine oxide (4g) in D_2O

The basic question connected with a mechanism of the considered cleavage is the formation of a highly reactive intermediate, that is, the metaphosphate, or its equivalent. The dissociative mechanism assumes the formation of such species by a rupture of a C–P bond and the elimination of a 'protonated' metaphosphate (a phosphinylium cation[12,13]) in the first stage of a reaction. In order to find out that the phosphinylium cation is formed, a trapping agent for it should be used. Usually, in aqueous solutions, the corresponding phosphinic acids were formed. If alcohol is used as a solvent, the corresponding phosphoester should be obtained. In turn, the final amine may be formed by the incorporation of a proton to an enamine-like heterocyclic fragment, or by a bimolecular process, in which, the attachment of the proton coincides with the departure of the phosphinylium cation. In this case, the amine would be formed directly, as a result of the electrophilic substitution of the phosphorus moiety.

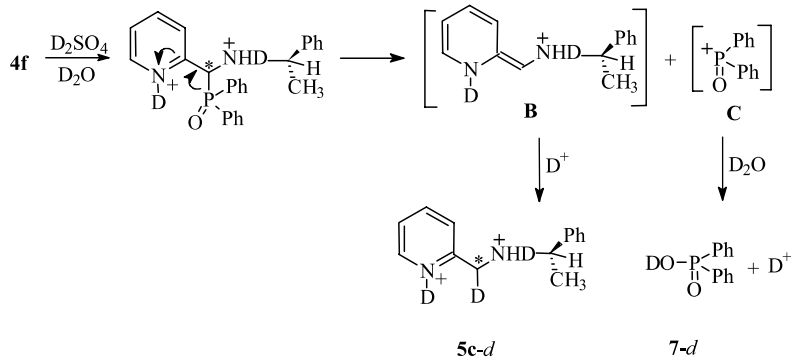
On the other hand, the cleavage might be caused by a direct nucleophilic attack of the solvent on a phosphorus atom with a positive charge in the aminophosphine oxide molecule. Such displacement might be considered a nucleophilic substitution occurring at phosphorus in the aminophosphine oxide.

It was described[14–16] that the heterolytic cleavage of a bond between phosphorus and a leaving group, occurring on a chiral center, should lead to the formation of racemic products, in the case of a dissociative mechanism. Likewise, the inversion of the configuration at phosphorus should be observed in the case of a bimolecular, associative mechanism, that is, the nucleophilic substitution of a phosphorus atom.[15,16]

The questions that arise with the mechanism of the present cleavage could be answered by the use of appropriate optically active aminophosphine oxides. Therefore, we took the aminophosphine oxides (**4f**, **4g**) into account for further studies. The cleavage of **4f** and **4g** was invoked by D_2SO_4 in D_2O solutions. The use of D_2SO_4 should generate an additional stereogenic center at the α-carbon of the formed amine due to formation of the CHD group. One might expect that the cleavage of aminophosphine oxide by the elimination of phosphorus moiety should lead to racemization at the α-carbon in the amine due to the formation of a planar, imine-like intermediate. Such a course of reaction is illustrated in Scheme 7 for the cleavage of **4f** and the formation of the deuterated amine **5c–d**, via the intermediate **B**.

The experiments have demonstrated that the cleavages of **4f** and **4g** led to the racemization at the α-carbon (as shown by ^1H NMR spectra of the formed amines).

Signals attributed to the CHD groups in the amines **5c–d**, **6c–d**, with deuterium incorporated can be easily



Scheme 7. Mechanism of the cleavage of aminophosphine oxide **4f** in D_2SO_4 solution.

rationalized by analyzing the corresponding ^{1}H NMR spectra. The ratios of the formed diastereoisomers were determined from ^{1}H NMR signals of the CHD groups. A similar question was exploited by Japanese researchers[17] and others[18] for some titanium, and chromium complexes of deuterated benzylamine derivatives, where the proper ratio of the diastereoisomers with the incorporated deuterium were calculated from integrated ^{1}H NMR signals.

These results support a dissociative mechanism, at least in the case of **4f** and **4g**, which is connected with the formation of a phosphinylium species (**C**, Scheme 7).

The four-coordinate phosphinylium cation **C** that is assumed to be formed in the first stage of the fragmentation of the **4f** and **4g** is closely associated with the monomeric metaphosphate ($HOPO_2$), which is well-known. The metaphosphate and its chemistry is also the subject of two reviews.[19,20] First of all, the metaphosphate, as transient species, is postulated as the putative intermediate in biological phosphoryl-transfer reactions[20] and in many fragmentations of organophosphorus compounds.[19,20]

2.5. Cleavage of 1-(*N*-benzylamino)-1-(2-pyridyl)-methyldiphenylphosphine oxide (4a) in aqueous solutions of different alcohols

One of the commonly accepted diagnostic tests for an involvement of metaphosphate, is phosphorylation of alcohols, especially hindered alcohols,[19–21] or amines.[22] The metaphosphate ($ROPO_2$) is considered a strong electrophile,[19] and therefore, it takes place in an aromatic substitution, coinciding with an activated aromatic ring.[23] This criterion was examined in the present work by the cleavage of the representative aminophosphine oxide **4a**, in aqueous solutions of different alcohols. The formation of phosphoesters (i.e., the corresponding alkyl esters of diphenylphosphinic acid, in this case) was expected if the 'protonated' metaphosphate (a phosphinylium cation) was involved in the cleavage.

The cleavages of **4a** were carried out in 50% aqueous solutions of various alcohols. The solutions containing methanol, ethanol, isopropanol, or *tert*-butanol and a definite amount of sulfuric acid were used. The progress of the reaction was monitored by ^{31}P NMR spectroscopy. The solutions were kept for 2 weeks at room temperature to complete the reaction and then worked-up to isolate the products. The products were phosphinic alkyl esters **9a–d**, *N*-(2-pyridylmethyl)-benzylamine (**5a**) and diphenyl-phosphinic acid (**7**). The structures of the phosphoesters **9a–d** were established on the basis of their literature data.[27–32] A course of the reaction is shown in Scheme 8.

Due to the steric effects linked with a particular alcohol, the yield of the phosphoesters should fall in this order: MeOH > EtOH > *i*-PrOH > *t*-BuOH. This is seen in the present case.

The formation of the phosphoesters confirms the assumed dissociative mechanism of the cleavage of the aminophosphine oxide **4a**. The formation of the **9a–d** and diphenylphosphinic acid **7**, with the amounts corresponding to the molar ratio of alcohol and water, additionally verifies this assumption. These results exclude an alternative associative mechanism, at least in the case of the aminophosphine oxide **4a**.

More convincing proof for the proposed mechanism of the cleavage should come from the cleavage of the *P*-chiral aminophosphine oxide **4e**.

2.6. Methanolysis of (+)-1-(*N*-benzylamino)-1-(4-pyridyl)-(*S*)-methyl-*t*-butylphenyl-(S_P)-phosphine oxide (4e)

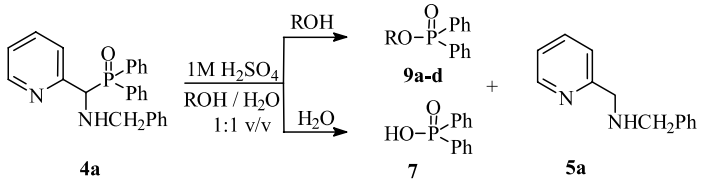
The phosphinylium species, which is allegedly formed in the case of the cleavage of a *P*-chiral aminophosphine oxide, should lead to the formation of racemic products, that is, the formation of the racemic methyl phosphoester when the cleavage is carried out in methanol. On the contrary, if the product is formed by a bimolecular process (a nucleophilic substitution at phosphorus), the formed phosphoester should exhibit optical activity (an inversion of configuration is expected in this case).

In order to verify such a hypothesis, the *P*-chiral, aminophosphine oxide **4e** was cleaved by 1 M sulfuric acid in methanol.

The projected cleavages were carried out at room temperature. The reactants were kept for a month to accomplish the reaction. Surprisingly, the major products found and isolated from the reaction mixtures were starting reagents; that is, the phosphine oxide **3c** and the imine **11** (see the Scheme 9). The expected phosphoester **10** was formed in a minimal amount.

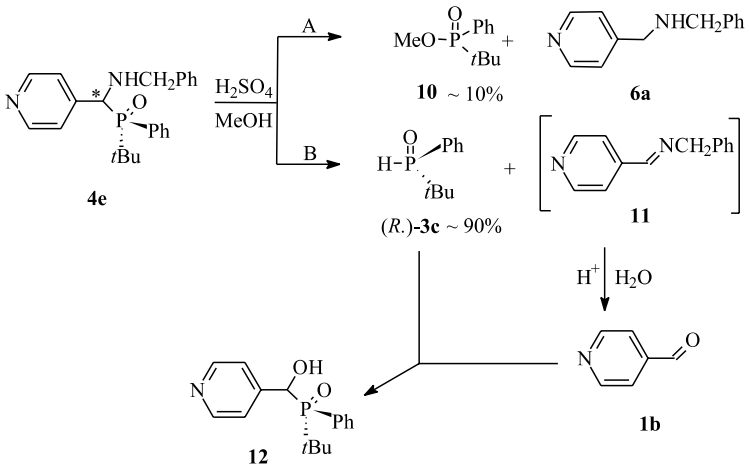
The cleavage was in fact a reverse reaction of the formation of pyridine aminophosphine oxide **4e**. Such a reaction was observed only in pure methanol, in the presence of sulfuric acid.

During work-up, the formed products underwent further transformations. The imine **11** decomposed to aldehyde **1b**,



9a: R = Me, **9b**: R = Et, **9c**: R = *i*Pr, **9d**: *t*Bu

Scheme 8. Cleavage of the pyridine aminophosphine oxide **4a** in 50% aqueous alcohols.



Scheme 9. Cleavage of the pyridine aminophosphine oxide **4e** in pure methanol.

which partially reacted with phosphine oxide **3c** to give the pyridine hydroxyphosphine oxide **12**, as a final, stable product (see the Scheme 9).

In this case, there are two competitive reactions, shown in the Scheme 9, relying upon the site of an attack of an electrophile in the aminophosphine oxide **4e**. If a proton attacks the α-carbon, it should lead to methyl ester **10** (pathway A, Scheme 9) via the elimination of metaphosphate-like moiety. In the second case, while the proton attacks the phosphorus atom (pathway B, Scheme 9), such a process should give the phosphine oxide **3c** by the elimination of the imine **11** (see the Scheme 10).

It was assumed[15,16] that the heterolytic bond cleavage between phosphorus and carbon would lead to the formation of the products with a retained configuration. It happened in the considered case, where the substitution at phosphorus caused the formation of *t*-butylphenylphosphine oxide **3c**, with the retained configuration. Such a pathway seems to be preferable for the pyridine aminophosphine oxides with a bulky group at phosphorus, demonstrating a large steric effect, as for example, the *tert*-butyl group.

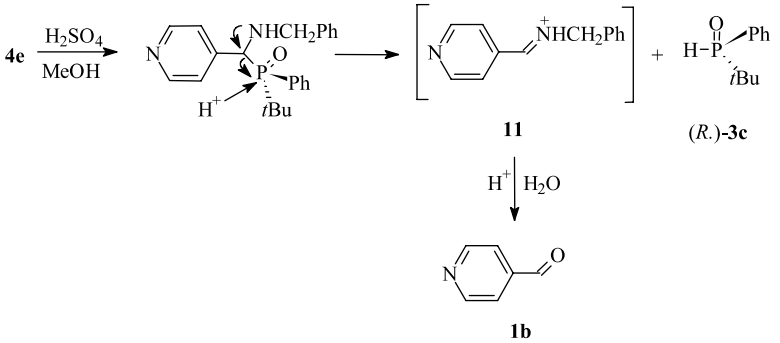
The expected methyl *t*-butylphenylphosphinate (**10**)[11a,33–36] was also formed, but the quantity was very low. Due to the small amount of ester, isolation and the measurement of the optical activity of **10** was hard to realize. In order to avoid such difficulties, we turned to another optically active aminophosphine oxide **4i**, which ended up being more suitable for the isolation of the corresponding phosphoester. The aminophosphine oxide **4i** comprised the methyl and phenyl groups at phosphorus, which should not offer such steric obstacles responsible for the pathway B.

2.7. Methanolysis of the (+)-1-[*N*-(α-methylbenzylamino)]-1-(4-pyridyl)-methyl-phenylmethylphosphine oxide (4i)

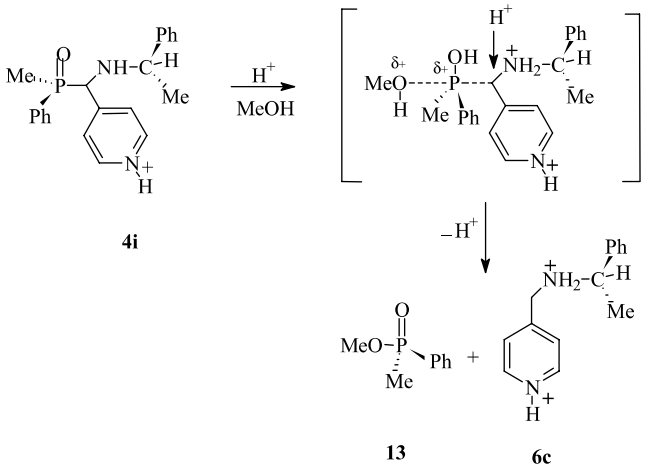
The optically active aminophosphine oxide **4i**, $\{[\alpha]^{20}_D$ +33.0 (*c* 1.0, $CHCl_3$)} was cleaved in the methanolic solution of sulfuric acid. Likewise, as in the previous case, the phosphine oxide **3d**[37,39] and methyl phosphoester **13**,[40,41] together with the corresponding amine **6c** and aldehyde **1b**, were isolated from the reaction mixture (see the Scheme 11).

The ester **13** and phosphine oxide **3d** were formed roughly in a molar ratio equal to 1:1.

After the separation of the ester **13** and phosphine oxide **3d**, the corresponding optical rotations of the **3d** and **13** were measured. Phosphine oxide **3d** showed the optical activity $\{[\alpha]^{20}_D$ +26.0 (*c* 0.4, $CHCl_3$)}, likewise as did the ester **13**, which has the optical activity $\{[\alpha]^{20}_D$ +20.0 (*c* 0.4, $CHCl_3$)}. The formation of the optically active ester **13** indicates that the cleavage of **4i** is a complex process, having among other things a bimolecular character (Scheme 11).



Scheme 10. Substitution at phosphorus in **4e** (pathway B).



Scheme 11. Cleavage of the pyridine aminophosphine oxide **4i** in pure methanol.

In the transition state (Scheme 11), methanol is displacing the enamine-like moiety in the **4i**, which is attached to a phosphorus atom, in the bimolecular process. However, the decrease of the optical activity of the ester indicates that a partial racemization of the product also occurred during the cleavage. The enantiomerically pure (+)-(R_P)-methyl phenylmethylphosphinate[40,41] (**13**) has the specific rotation: $[\alpha]^{20}_D$ +45.2 (*c* 3.7, MeOH).[41]

Aminophosphine oxides possessing aliphatic, or more basic groups at phosphorus (**4e**, **4i**) are more preferential for the bimolecular process, involving an attack of the proton on the α-carbon and the simultaneous formation of the phosphoester by an interaction of methanol with a positively charged phosphine oxide moiety. In turn, the corresponding phosphine oxide (**3c** or **3d**) is formed in a parallel process, involving an attack of the proton at phosphorus.

Examining the cleavage of amino-diphenylphosphine oxides **4a**, **4f** and **4g**, possessing electron-withdrawing groups at phosphorus, it looks that the monomolecular, dissociative mechanism is preferable there.

3. Conclusions

A series of racemic and optically active pyridine aminophosphine oxides were prepared by the addition of the phosphine oxides to chiral and achiral pyridine aldimines. The obtained pyridine aminophosphine oxides were easily cleaved in acidic solutions to form the corresponding *N*-(pyridylmethyl)-benzylamines and aryl(alkyl)phosphinic acids. The cleavage of pyridine aminophosphine oxides was studied in different solutions, containing water, deuterium oxide and various alcohols, respectively. The obtained results demonstrated that the cleavage was a dissociative process and proceeded via a phosphinylium cation stage, in the case of the pyridine aminodiphenylphosphine oxides **4a** and **4b**. In the case of aminophosphine oxides **4e** and **4i**, possessing bulky groups at phosphorus, the cleavage in methanol underwent by two parallel, different ways. It was found that the main products were initial *t*-butyl- and methylphenylphosphine oxides, with the retention of the configuration at phosphorus. In the case of **4i**, the corresponding phosphoester **13** was also formed, with the inversion of the configuration.

The *t*-butylphosphine oxide (**3c**) was formed in an action of the proton on the phosphorus atom in the hindered aminophosphine oxide **4e**, accompanied by the elimination of the corresponding aldimine.

The formation of methyl phosphoester **13** with the inversion of the configuration at phosphorus indicates that, in the case of **4i**, the cleavage had a bimolecular character, and a prospective formation of the metaphosphate-like moiety was doubtful. However, a partial loss of the optical activity of the formed ester suggested that the dissociative mechanism was possible to some extent.

The results showed that the presented cleavages of the pyridine aminophosphine oxides have had diversified mechanisms depending on the chemical nature of the groups attached to phosphorus.

4. Experimental

4.1. General

^{1}H and ^{31}P NMR spectra were measured on a Bruker Avance 300 MHz spectrometer using TMS as an internal standard. IR spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. GC/MS analyses were determined on a Hewlett Packard 5890 II gas chromatograph (HP-5, 25 m capillary column) with a Hewlett Packard mass spectrometer 5971 A (EI, 70 eV) and on a Finnigan TSQ 700 instrument (electrospray ionization on mode: ESI+ Q1MS). Optical rotations were measured at 589 nm using an Optical Activity Ltd. Model AA-5 automatic polarimeter. Melting points were determined using an Electrothermal 9200 apparatus and a Boetius hot-stage apparatus and were uncorrected. Elemental analyses were done in the Laboratory of Instrumental Analysis in the Institute. Thin-layer chromatography analyses were performed on silica gel 60 precoated plates (Merck). Reagents used were obtained from the Sigma–Aldrich Company (Poznań, Poland). Solvents were of commercial quality and purchased from a local supplier (POCh Gliwice, Poland).

Racemic methylphenylphosphine oxide **3d**[37] was prepared from ethyl methylphosphinate[38] according to the procedure described in.[39]

Resolution of the racemic *t*-butylphosphine oxide was done by the method described by Drabowicz et al.[11a]

4.2. Procedure for preparation of racemic pyridine aminophosphine oxides 4a–d

To a solution of pyridine aldehyde (**1a** or **1b**; 1.07 g, 10 mmol) in dichloromethane (25 mL) benzylamine (**2a**; 1.07 g, 10 mmol), or butylamine (**2b**; 0.73 g, 10 mmol) was added, respectively, and a mixture was left for 24 h at room temperature. After this, anhydrous sodium sulfate (5 g) was added, followed by addition of diphenylphosphine oxide

(**3a**; 2.02 g, 10 mmol). The whole mixture was left for 24 h and filtered. Filtrate was evaporated to dryness and an oily residue was kept at 60 °C for 2 h to finish up the reaction. Solidified products were crystallized from acetone (25 mL); (4-pyridyl derivatives), or from a mixture of toluene and hexane (1:1 v/v, 25 mL); (2-pyridyl derivatives). After cooling separated crystals were filtered off, washed with hexane and dried to give the racemic pyridine aminophosphine oxides **4a**–**d**.

4.2.1. Compound 4a. White solid, 3.50 g, yield 88%, mp 120–122 °C, lit.[8] 102–104 °C. Spectroscopic data consistent with that reported.[8]

4.2.2. Compound 4b. White solid, 2.87 g, yield 72%, mp 158–160 °C, lit.[8] 148–149 °C. Spectroscopic data consistent with that reported.[8]

4.2.3. Compound 4c. White solid, 2.95 g, yield 81%, mp 100–102 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 8.37 (1H, d, J=4.8 Hz, 6-Py*H*); 7.84–7.08 (13H, m, Py*H*, Ar*H*); 4.72 (1H, d, J=13.3 Hz, C*H*–P); 2.59–2.43 (2H, m, NCH_2); 1.41 (2H, m, CH_2); 1.23 (2H, m, CH_2); 0.81 (3H, t, J=7.3 Hz, CH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 29.62 (s). IR, ν_{max} (KBr): 3387 (NH); 3039; 2916; 2806; 1578; 1471; 1428; 1146 (P=O); 1108; 1037; 990; 831; 744; 733 (P–C); 690; 634; 611; 549; 511 cm^{-1}. Anal. Calcd for $C_{22}H_{25}N_2OP$, requires C, 72.51; H, 6.92; N, 7.69; P, 8.45. Found: C, 72.21; H, 6.98; N, 7.54; P, 8.43%.

4.2.4. Compound 4d. White solid, 3.13 g, yield 86%, mp 145–147 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 8.43 (2H, d, J=5.9 Hz, 2,6-Py*H*); 7.85 (2H, m, 3,5-Py*H*); 7.62–7.21 (10H, m, Ar*H*); 4.56 (1H, d, J=12.7 Hz, C*H*–P); 2.53–2.41 (2H, m, NCH_2); 1.40 (2H, m, CH_2); 1.23 (2H, m, CH_2); 0.83 (3H, t, J=7.3 Hz, CH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 30.52 (s). IR, ν_{max} (KBr): 3297 (NH); 3046; 3006; 2973; 2808; 1582; 1493; 1455; 1326; 1154 (P=O); 1112; 987; 835; 772; 732 (P–C); 681; 641; 558; 512; 491 cm^{-1}. Anal. Calcd for $C_{22}H_{25}N_2OP$, requires C, 72.51; H, 6.92; N, 7.69; P, 8.45. Found: C, 72.31; H, 7.08; N, 7.55; P, 8.52%.

4.3. Procedure for preparation of optically active pyridine aminophosphine oxides 4e–h

To a solution of pyridine aldehyde (**1a** or **1b**; 1.07 g, 10 mmol) in dichloromethane (25 mL) benzylamine (**2a**; 1.07 g, 10 mmol), or (*R*)-(+)-α-methylbenzylamine (**2c**; 1.21 g, 10 mmol) was added, respectively, and a mixture was left for 48 h at room temperature. Then, the solution was dried (anh. Na_2SO_4), filtered, and diphenylphosphine oxide (**3a**; 2.02 g, 10 mmol), or (*S*)-(−)-*tert*-butylphenylphosphine oxide[11] **3b**, 1.82 g, 10 mmol, $[\alpha]^{20}_D$ −24.8 (*c* 1.0, $CHCl_3$), or (*R*)-(+)-*tert*-butylphenylphosphine[11] **3c**, 1.82 g, 10 mmol, $[\alpha]^{20}_D$ +24.6 (*c* 1.0, $CHCl_3$) was added, respectively. The formed solution was left for 24 h and evaporated to dryness to give an oily residue, which was kept for 2 h at 60 °C. After this, the oil turned to a whitish solid. The solid was dissolved in warm acetone (25 mL) and the solution was kept at room temperature for several hours. The product crystallized out from the solution. The product was collected by filtration and dried. If necessary, the crystallization from acetone was repeated. In the case of 4-pyridyl derivative, the product **4g** was crystallized from a mixture of methylene chloride and hexane (1:1, v/v), while in the case of 2-pyridyl derivative **4f**, the crude product was treated first with warm acetone (5 mL) in order to remove an unsoluble by-product (the 1-hydroxy-1-(2-pyridyl)-methyl-diphenyl-phosphine oxide). The filtrate was evaporated to dryness and the residue was recrystallized from methylene chloride and hexane (1:1, v/v).

The remaining mother solution was evaporated to give a product, composed with two stereoisomers, in which the *R*,*R* stereoisomer was predominant over of the *S*,*R* one.

4.3.1. Compound 4e. White solid, 1.36 g, yield 36%, mp 162–165 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 8.55 (2H, d, J=5.9 Hz, 2,6-Py*H*); 7.60 (2H, m, 3,5-Py*H*); 7.50–6.86 (10H, m, Ar*H*); 4.05 (1H, d, J=7.6 Hz, C*H*–P); 3.62 (1H, d, J=13.4 Hz, NCH_2); 3.22 (1H, d, J=13.4 Hz, NCH_2); 2.22 (1H, br s, N*H*), 0.79 (9H, d, J=14.6 Hz, *t*-Bu). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 50.15 (s). IR, ν_{max} (KBr): 3350; 3259 (NH); 3028; 2961; 2868; 1593; 1495; 1437; 1165 (P=O); 1105; 818; 743 (P–C); 699; 640; 554; 490 cm^{-1}. $[\alpha]^{20}_D$ +2.1 (*c* 0.7, $CHCl_3$). Anal. Calcd for $C_{23}H_{27}N_2OP$, requires C, 72.99; H, 7.19; N, 7.40; P, 8.18. Found: C, 72.81; H, 7.28; N, 7.25; P, 8.22%.

4.3.2. Compound 4f. White solid, 1.73 g, yield 42%, mp 135–137 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 8.34 (1H, d, J=4.8 Hz, 6-Py*H*); 7.95–7.87 (4H, m, Py*H*, Ar*H*); 7.55–7.40 (9H, m, Ar*H*); 7.20–7.15 (2H, m, Ar*H*); 7.13–7.05 (3H, m, Ar*H*); 4.76 (1H, d, J=13.5 Hz, C*H*–P); 3.51 (1H, q, J=6.5 Hz, C*H*); 3.23 (1H, br s, N*H*); 1.30 (3H, d, J=6.5 Hz, CH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 31.37 (s). IR, ν_{max} (KBr): 3439 (NH); 3053; 3005; 2926; 2875; 2808; 1601; 1584; 1566; 1470; 1447; 1437; 1431; 1375; 1309; 1262; 1186 (P=O); 1119; 1101; 1067; 1048; 1038; 1030; 993; 912; 831; 747; 738 (P–C); 722 (P–C); 693; 639; 606; 555; 515; 487 cm^{-1}. $[\alpha]^{20}_D$ +29 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{25}H_{23}N_2OP$, requires N, 6.79; P, 7.51. Found: N, 6.49; P, 7.28%.

4.3.3. Compound 4g. White solid, 2.02 g, yield 49%, mp 174–176 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 8.39 (2H, d, J=4.7 Hz, 2,6-Py*H*); 7.96 (2H, dd, J=4.7, 3.1 Hz, 3,5-Py*H*); 7.64–7.02 (15H, m, Ar*H*); 4.61 (1H, d, J=11.2 Hz, C*H*–P); 3.62 (1H, q, J=6.4 Hz, C*H*); 2.59 (1H, br s, N*H*); 1.29 (3H, d, J=6.4 Hz, CH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 32.22 (s). IR, ν_{max} (KBr): 3337 (NH); 3057; 3026; 2973; 2848; 2808; 1590; 1560; 1494; 1469; 1451; 1436; 1378; 1326; 1176 (P=O); 1121; 1102; 1070; 1025; 991; 833; 795; 773; 742 (P–C); 723 (P–C); 691; 639; 603; 559; 531; 514; 495 cm^{-1}. $[\alpha]^{20}_D$ +79 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{25}H_{23}N_2OP$, requires N, 6.79; P, 7.51. Found: N, 6.60; P, 7.77%.

4.3.4. Compound 4h. White solid, 2.12 g, yield 54%, mp 210–212 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 8.21 (2H, d, J=5.9 Hz, 2,6-Py*H*); 7.44 (2H, d, J=5.9 Hz, 1.7 Hz, 3,5-Py*H*); 7.20–7.05 (10H, m, Ar*H*); 4.51 (1H, d, J=8.3 Hz, C*H*–P); 3.43 (1H, q, J=6.4 Hz, C*H*); 2.65 (1H, br s, N*H*); 1.31 (9H, d, J=15.0 Hz, *t*-Bu); 1.24 (3H, d, J=6.4 Hz, CH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 48.97 (s). IR, ν_{max} (KBr): 3351 (NH); 3064; 2967; 2868; 1592; 1557; 1459;

1437; 1162 (P=O); 1105; 822; 752 (P–C); 698; 642; 557; 492 cm^{-1}. $[\alpha]^{20}_D$ +121.8 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{24}H_{29}N_2OP$, requires N, 7.14; P, 7.89. Found: N, 7.01; P, 7.87%.

4.4. Procedure for preparation of optically active pyridine aminophosphine oxide 4i

To a solution of pyridine-4-carboxaldehyde (**1b**; 250 mg, 2.34 mmol) in dichloromethane (25 mL) (*R*)-(+)-α-methylbenzylamine **2c** (280 mg, 2.34 mmol) was added and a mixture was left for 48 h at room temperature. Then, the mixture was dried (anh. Na_2SO_4), filtered, and the racemic methylphenylphosphine oxide **3d** (330 mg, 2.35 mmol) was added. The solution was refluxed for 4 h and left for 24 h. After evaporation of the solvent, an oily product was obtained (840 mg). The product was dissolved in warm acetone (10 mL) and refrigerated. After several hours, white crystals separated out, which were then collected by filtration and dried on air. The obtained product was a pure stereoisomer **4i**, according to the NMR data.

4.4.1. Compound 4i. White solid, 252 mg, yield 31%, mp 138–140 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 8.41 (2H, d, *J*=4.3 Hz, 2,6-Py*H*); 7.53–7.53–7.40 (5H, m, Py*H*, Ar*H*); 7.19–6.95 (8H, m, Ar*H*); 4.06 (1H, d, *J*=13.5 Hz, C*H*–P); 3.48 (1H, q, *J*=6.45 Hz, C*H*); 1.86 (1H, br s, N*H*); 1.59 (3H, d, *J*=15.3 Hz, P–CH_3); 1.17 (3H, d, *J*=6.45 Hz, CH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 39.11 (s). IR, ν_{max} (KBr): 3265 (NH); 3051; 2955; 2810; 1588; 1437; 1160 (P=O); 1105; 820; 751 (P–C); 695; 641; 552 cm^{-1}. $[\alpha]^{20}_D$ +33.0 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{21}H_{23}N_2OP$, requires C, 71.98; H, 6.62; N, 8.00; P, 8.84. Found: C, 71.81; H, 6.75; N, 7.88; P, 8.72%.

4.5. Cleavage of pyridine aminophosphine oxides 4a–h and isolation of the products

A sample of pyridine aminophosphine oxide **4a**–**h** (1.0 mmol) was dissolved in 10% aqueous H_2SO_4 solution (10 mL) and heated at 95–100 °C for 2 h for 2-pyridyl derivatives, or 10 h for 4-pyridyl derivatives. The reaction mixture was allowed to stand at room temperature for 24 h in order to separate the phosphinic acids (**7** or **8**). Crystals of the phosphinic acids were collected by filtration and dried on air. Yield of the **7**: 67–90% diphenylphosphinic acid **7** is a known, commercial compound and its data are given elsewhere.

4.5.1. *t*-Butylphenylphosphinic acid 8. Crystalline solid, yield 131–143 mg, 66–72% (depending from the experiment), mp 157–158 °C, lit.[24] 154–156 °C, lit.[26] 155–157 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 7.75–7.69 (2H, m, Ar*H*); 7.49–7.43 (1H, m, Ar*H*); 7.39–7.33 (2H, m, Ar*H*); 5.67 (br s, 1H, PO*H*); 1.03 (9H, d, *J*=15.7 Hz, *t*-Bu). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 54.178 (s). ^{31}P NMR; δ_P (DMSO; 121.5 MHz): 49.883 (s).

Spectroscopical and physico-chemical data of the *t*-butylphenylphosphinic acid **8** were in agreement with the literature data.[24–26]

4.5.2. Amines 5a–c, 6a–c. The remained filtrate was alkalized with an excess of aqueous sodium bicarbonate solution and extracted with methylene chloride (25 mL). Evaporation of the extract gave the crude amines **5a–c** and **6a–c**, which were characterized as oxalate salts. The oxalates were obtained by a following way; the crude amine dissolved in acetone (5 mL) and oxalic acid [$(COOH)_2 \cdot 2H_2O$ (0.25 g, 2 mmol)] in acetone (5 mL) was added and the mixture refrigerated. The separated precipitate was filtered, washed with acetone and dried on air.

The spectroscopic data for *N*-(pyridylmethyl)-benzyl(butyl)amines **5a**,**b** and **6a**,**b** are consistent with those reported.[5,8] The amines **5c** and **6c** are new compounds and their spectroscopic data are given below.

4.5.2.1. *N*-(2-Pyridyl-methyl)-(*R*)-(+)-α-methylbenzyl amine 5c. Compound **5c** oxalate; white solid, 229 mg, yield 76%, mp 135–137 °C. ^{1}H NMR; δ_H (D_2O; 300 MHz): 8.46 (1H, d, *J*=4.5 Hz, 6-Py*H*); 7.79 (1H, dt, *J*=1.65, 7.8 Hz, 4-Py*H*); 7.44–7.28 (7H, m, Py*H*, Ar*H*); 4.43 (1H, q, *J*=6.9 Hz, C*H*CH_3); 4.20 (1H, d, *J*=14.3 Hz, NCH_2); 4.05 (1H, d, *J*=14.3 Hz, NCH_2); 1.64 (3H, d, *J*=6.9 Hz, CH_3). $[\alpha]^{20}_D$ +9.0 (*c* 1.0, H_2O).

For GC/MS analysis, a sample of oxalate (50 mg) was treated with 10% aqueous solution of Na_2CO_3 (3 mL), extracted with 5 mL CH_2Cl_2, the extract dried (anh. Na_2SO_4) and evaporated to give the free amine **5c**, as an oil (31 mg). GC/MS (HP-5 column, 25 m, temperature program; 100/6/290): t_R (retention time)=10.41 min; *m*/*z* (EI, 70 eV): 212 (0.1, M^+), 211 (1, M−1), 197 (18), 180 (3), 135 (5), 120 (76), 105 (19), 93 (100), 92 (28), 79 (8), 77 (10), 65 (10), 51 (5%).

4.5.2.2. *N*-(4-Pyridyl-methyl)-(*R*)-(+)-α-methylbenzyl amine 6c. Compound **6c** oxalate; white solid, 208 mg, yield 69%, mp 178–181 °C. ^{1}H NMR; δ_H (D_2O; 300 MHz): 7.80 (2H, d, *J*=6.7 Hz, 2,6-Py*H*); 7.62 (2H, d, *J*=6.7 Hz, 3,5-Py*H*); 7.36 (5H, br s, Ar*H*); 4.44 (1H, q, *J*=6.9 Hz, C*H*CH_3); 4.37 (1H, d, *J*=14.8 Hz, NCH_2); 4.15 (1H, d, *J*=14.8 Hz, NCH_2); 1.62 (3H, d, *J*=6.9 Hz, CH_3). $[\alpha]^{20}_D$ +4.0 (*c* 1.0, H_2O).

For GC/MS analysis, a sample of oxalate (50 mg) was treated with 10% aqueous solution of Na_2CO_3 (3 mL), extracted with 5 mL CH_2Cl_2, the extract dried (anh. Na_2SO_4) and evaporated to give the free amine **6c**, as an oil (28 mg). GC/MS (HP-5 column, 25 m, temperature program; 100/25/290): t_R (retention time)=7.49 min; *m*/*z* (EI, 70 eV): 212 (1, M^+), 211 (1, M−1), 197 (100), 135 (13), 105 (33), 92 (64), 79 (14), 77 (18), 65 (23), 51 (9%).

4.6. Kinetic measurements

Solutions of samples of the corresponding pyridine aminophosphine oxides (*c* 0.1 mL^{-1}) in aqueous 50% methanol, containing an appropriate quantity of H_2SO_4 (the 0.5, 1.0 and 2.0 m L^{-1} H_2SO_4 solutions) in NMR tubes were prepared and thermostated at 20 °C for a desired period of time (1, 2, 4, 8, 16 h, respectively). The ^{31}P NMR spectra were consecutively recorded. The kinetic runs in D_2O/MeOD with use of D_2SO_4 were done similarly. The use of

different concentrations of H_2SO_4, (or D_2SO_4) was allowed to calculate the pseudo-first-order rate constants (k_{obsd}). The rate constants were determined by plotting the dependence of $\log(a-x)$ on time (where the 'a' is a relative quantity of the starting aminophosphine oxide and the '$a-x$' represents a relative quantity of unreacted aminophosphine oxide).

4.7. Cleavage of optically active pyridine aminophosphine oxides 4f and 4g in D_2O/D_2SO_4 solution

A sample of optically active pyridine aminophosphine oxide (**4f** or **4g**, 0.412 g, 1.0 mmol) was dissolved in 10% D_2SO_4/D_2O solution (10 mL) and heated at 95–100 °C for 3 h. The reaction mixture was allowed to stand at room temperature for 24 h in order to separate the phosphinic acid **7**. Crystals of the phosphinic acid **7** were collected by filtration and dried on air. Yield of the **7** was 93% in the case of **4f**, and 82% in the case of **4g**.

The remaining filtrate was alkalized with an excess of aqueous sodium bicarbonate solution and extracted with methylene chloride (25 mL). Evaporation of the extract gave the deuterated amines **5c–d** (181 mg) and **6c–d** (170 mg), as thick oils, which were transformed to the corresponding oxalate salts, likewise as described in the preceding case. The oxalates were equimolar mixtures of *S*,*R* and *R*,*R* stereoisomers of the corresponding amines (according to the NMR data).

4.7.1. Mixture of *S*,*R* and *R*,*R* stereoisomers of deuterated *N*-(2-pyridylmethyl)-(*R*)-(+)-α-methylbenzylamine 5c–d. Oxalate; white solid, yield 233 mg, (77%). ^{1}H NMR; δ_H (D_2O; 300 MHz): 8.46 (1H, d, J= 4.8 Hz, 6-Py*H*); 7.79 (1H, dt, J=1.5, 7.8 Hz, 4-Py*H*); 7.40–7.28 (7H, m, Py*H*, Ar*H*); 4.43 (1H, q, J=6.9 Hz, C*H*CH_3); 4.17 (0.5H, br t, J=not determined, NC*H*D); 4.05 (0.5H, br t, J=not determined, NC*H*D); 1.64 (3H, d, J=6.9 Hz, CH_3).

Free amine; GC/MS (HP-5 column, 25 m, temperature program; 100/6/290): t_R=10.38 min; m/z (EI, 70 eV): 213 (0.1, M^+), 212 (0.4, M−1), 198 (16), 136 (5), 120 (81), 105 (18), 94 (100), 93 (37), 79 (8), 77 (10), 66 (10), 51 (5%).

4.7.2. Mixture of *S*,*R* and *R*,*R* stereoisomers of deuterated *N*-(4-pyridylmethyl)-(*R*)-(+)-α-methylbenzylamine 6c–d. Oxalate: white solid, yield 215 mg, (71%). ^{1}H NMR; δ_H (D_2O; 300 MHz): 7.84 (2H, d, J= 6.0 Hz, 2,6-Py*H*); 7.64 (2H, d, J=6.0 Hz, 3,5-Py*H*); 7.36 (5H, br s, Ar*H*); 4.45 (1H, q, J=6.8 Hz, C*H*CH_3); 4.38 (0.5H, br t, J=not determined, NC*H*D); 4.17 (0.5H, br t, J=not determined, NC*H*D); 1.63 (3H, d, J=6.8 Hz, CH_3).

Free amine; GC/MS (HP-5 column, 25 m, temperature program; 100/25/290): t_R=7.49 min; m/z (EI, 70 eV): 213 (1, M^+), 212 (1, M−1), 199 (29), 198 (100), 197 (20), 136 (9), 105 (19), 93 (32), 79 (7), 77 (10), 66 (9), 51 (4%).

4.8. Cleavage of 4a in the presence of 50% aqueous alcohols

Samples of the pyridine-2-methyl-(*N*-benzylamino)-diphenylphosphine oxide (**4a**) (0.40 g, 1.0 mmol), were dissolved in 10 mL aqueous-alcoholic solutions (1:1, v/v), containing 0.98 g (10 mmol) H_2SO_4. The particular solutions contained methanol, ethanol, *iso*-propanol and *tert*-butanol, respectively. The solutions were kept for 2 weeks at room temperature. Progress of the reaction was monitored by ^{31}P NMR spectroscopy. The formed diphenylphosphinic acid (**7**) crystallized partially in the reaction mixtures. The mixtures were filtered to remove the acid **7** and treated with an excess of aqueous 5% $NaHCO_3$ solution. An oily product separated, which was extracted with dichloromethane (25 mL). The extract was dried (anhydrous Na_2SO_4), filtered and evaporated to give an oil (0.22–0.28 g), which was a mixture of *N*-(2-pyridylmethyl)-benzylamine **5a** and corresponding alkyl phosphoester **9a–d**. Separation of the esters and amines was done as follows; the whole mixture was treated with 1 M aqueous HCl (10 mL) and extracted with dichloromethane (25 mL). After drying (anh. Na_2SO_4), the extract was evaporated to give the ester (**9a–d**), as an oily product, solidified after several hours.

The formed amine **5a** was isolated from the remaining acidic solutions by subsequent alkalization with aqueous $NaHCO_3$ and extraction with methylene chloride as described in Section 4.5.2. Yield of the **5a** exceeded 90%.

4.8.1. Methyl ester 9a. A whitish solid, yield 75 mg (27%), mp 52–55 °C, lit.[30] 55–57 °C, lit.[31] 50 °C, lit.[32] 56–58 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 7.77–7.70 (4H, m, Ar*H*); 7.43–7.37 (6H, m, Ar*H*); 3.71–3.67 (3H, d, J=10.1 Hz, OCH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 34.908 (s).

4.8.2. Ethyl ester 9b. A colorless oil, yield: 35 mg (14%), lit.[29] oil. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 7.77–7.70 (4H, m, Ar*H*); 7.41–7.35 (6H, m, Ar*H*); 4.08–3.98 (2H, m, OCH_2), 1.29 (3H, t, J=7.1 Hz, CH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 33.058 (s).

4.8.3. *iso*-Propyl ester 9c. White solid, yield: 18 mg (7%), mp 99–101 °C, lit.[27] 97–99 °C, lit.[29] 100.6–101.5 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 7.77–7.70 (4H, m, Ar*H*); 7.40–7.35 (6H, m, Ar*H*); 4.66–4.55 (1H, m, OC*H*), 1.27 (6H, d, J=6.2 Hz, CH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 31.397 (s).

4.8.4. *tert*-Butyl ester 9d. White solid, yield: 14 mg (5%), mp 108–110 °C, lit.[28] 111.5–112 °C. lit.[29] 108.6–109.6 °C. ^{1}H NMR; δ_H ($CDCl_3$; 300 MHz): 7.75–7.68 (4H, m, Ar*H*); 7.39–7.30 (6H, m, Ar*H*); 1.26 (9H, d, J=2.0 Hz, CH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 32.582 (s).

4.8.5. Cleavage of 4e in the presence of methanol. A sample of optically active the pyridine-4-methyl-(*N*-benzylamino)-*tert*-butylphenyl-phosphine oxide (**4e**) (0.38 g, 1.0 mmol), was dissolved in methanol (10 mL), containing 0.98 g (10 mmol) H_2SO_4. The solution was refluxed for 5 h, cooled and left for 2 weeks. After this, the solvent (methanol) was evaporated, the resulting oil was dissolved in water (10 mL) and heated at 60 °C for 5 h, cooled and extracted with methylene chloride (50 mL). The extract was dried (anh. Na_2SO_4), filtered and evaporated to give an oil, which solidified after several hours. The obtained product was mainly the (*R*)-(+)-*tert*-butylphenyl-phosphine oxide **3c**, mixed with a small quantity of the

methyl ester of *tert*-butylphenylphosphinic acid (**10**). Additional purification of the obtained product by crystallization from hexane–diethyl ether gave the pure (*R*)-(+)-*tert*-butylphenylphosphine oxide (**3c**)[11a,b]. White solid, yield 54 mg (29%), mp 69–72 °C, lit.[11b] 72–74 °C. $[\alpha]^{20}_D$ +23.5 (*c* 1.0, $CHCl_3$), lit.[11a] $[\alpha]^{20}_D$ +14.6 (*c* 1.68, MeOH). ^1H NMR; δ_H ($CDCl_3$; 300 MHz): 7.62–6.11 (1H, d, J=453.2 Hz, P–*H*); 7.55–7.32 (5H, m, Ar*H*); 1.01–0.95 (9H, d, J=16.6 Hz, *t*-Bu). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 51.764 (s). Evaporation of mother liquid gave an oily product, partially solidified (18 mg), which was composed with the phosphine oxide **3c** and methyl ester **10**, in a ratio 2:1, approximately. The NMR spectrum ($CDCl_3$) of the crude product showed the dublet of the OMe group at 3.69–3.65 ppm (J=10.45 Hz), which was consistent with the literature data[11a,33–36].

The remaining aqueous layer was made alkaline by adding of an excess of aqueous sodium bicarbonate solution and extraction with chloroform (50 mL). The extract was dried (anh. Na_2SO_4), filtered and evaporated to give an oil, solidified after short time (0.21 g). Recrystallization of the product from acetone gave a white crystalline solid, which was the pyridine hydroxyphosphine oxide **12**, as a diastereomeric mixture. **12**; white solid, yield 120 mg (42%), mp=172–175 °C. ^1H NMR; δ_H (DMSO; 300 MHz): 8.25 (2H, d, J=4.9 Hz, 2,6-Py*H*); 7.71 (2H, m, 3,5-Py*H*); 7.39–7.19 (5H, m, Ar*H*); 6.70–6.45 (1H, m, CHO*H*); 5.52–5.41 (1H, m, C*H*–P); 1.14–0.92 (9H, m, *t*-Bu). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 44.848 (s), 44.565 (s) in a ratio 1:1.25. IR, ν_{max} (KBr): 3409; 3207; 3081; 2973; 2868; 1597; 1475; 1436; 1415;1149 (P=O); 1107; 833; 747; 715; 697; 610; 572; 551; 517 cm^{-1}. MS; (ESI+Q1MS): 291.0 (43, M^++1), 313.1 (100, M^++1+Na). Anal. Calcd for $C_{16}H_{20}NO_2P$, requires N, 4.84; P, 10.71. Found: N, 4.67; P, 10.59.

4.8.6. Cleavage of 4i in the presence of methanol. A sample of optically active (+)-1-[*N*-(α-methylbenzylamino)]-1-(4-pyridyl)-methyl-phenyl-methylphosphine oxide (**4i**) (108 mg, 0.31 mmol), was dissolved in methanol (5 mL), containing 0.49 g (5 mmol) H_2SO_4. The solution was refluxed for 3 h, cooled, left for 24 h and the solvent (methanol) was evaporated. The resulting oil was dissolved in water (5 mL) and extracted twice with methylene chloride (2×25 mL). The combined extracts were dried (anh. Na_2SO_4), filtered and evaporated to give an oil (47 mg). According to NMR data, the product was a mixture composed with methylphenylphosphine oxide (**3d**) and methyl phenylmethylphosphinate (**13**), in a ratio ~1:1. Separation of the mixture for individual products was done by column chromatography (silica gel, eluent; pure acetone) to afford the products: (+)-(R)$_P$ methyl phenylmethylphosphinate (**13**), as a colorless oil.[40] R_f 0.88, yield 22 mg (0.13 mmol), $[\alpha]^{20}_D$ +20.0 (*c* 0.4, $CHCl_3$), lit.[41] $[\alpha]^{20}_D$ +45.2 (*c* 3.7, MeOH). ^1H NMR; δ_H ($CDCl_3$; 300 MHz): 7.79–7.72 (2H, m, Ar*H*); 7.53–7.45 (3H, m, Ar*H*); 3.60–3.56 (3H, d, J=11.3 Hz, POCH_3); 1.66–1.61 (3H, d, J=14.6 Hz, PCH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 45.734 (s); methylphenylphosphine oxide (**3d**), as a colorless oil[37–39] R_f 0.32, yield 20 mg (0.14 mmol), $[\alpha]^{20}_D$ +26.0 (*c* 0.4, $CHCl_3$). ^1H NMR; δ_H ($CDCl_3$; 300 MHz): 8.28–6.71 (1H, dq, J=471.5, 3.8 Hz, P–*H*); 7.61–7.53 (2H, m, Ar*H*); 7.42–7.36 (3H, m, Ar*H*); 1.67–1.61 (3H, dd, J=13.9, 3.8 Hz, PCH_3). ^{31}P NMR; δ_P ($CDCl_3$; 121.5 MHz): 21.747 (s).

The remaining aqueous layer was made alkaline by adding an excess of aqueous sodium bicarbonate solution and extracted twice with chloroform (2×25 mL). The extract was dried (anh. Na_2SO_4), filtered and evaporated to give an oil (45 mg), which was a mixture of amine **6c** and aldehyde **1b** and traces of other not identified products, according to NMR data.

Supplementary data are deposited with the Cambridge Crystallographic Data Centre as a supplementary publication numbers CCDC 283498 (CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK; e-mail; deposit@ccdc.cam.ac.uk).

The X-ray diffraction measurements were performed in Department of Chemistry, University of Wroclaw, on a Kuma KM4 CCD four circle diffractometer, equipped with an Oxford Cryosystem Cooler, using graphite monochromated Mo K_α radiation.

The structure of **4g** was solved by direct methods using SHELXS-97[42] and refined on S^2 by full-matrix least-squares methods using SHELXL-97.[43] Non-hydrogen atoms were refined with anisotropic thermal parameters. During the refinement, an extinction and absorption correction was applied. The correction for the absorption was done using the empirical method included in the SHELXA program from the SHELXL-97[43] package. The XP package[44] was used to generate the molecular drawings.

The absolute configuration of the molecule **4g** was assigned as (*S*,*R*) with reference to the known *R* configuration of the (+)-α-methylbenzylamino moiety.

Acknowledgements

This research was supported by an internal grant from the Faculty of Chemistry, Wroclaw University of Technology. We thank Mr. Rafał Kowalczyk for measuring the optical rotations, Mr. Rafał Kozicki for measuring the NMR spectra, Mrs. Elżbieta Mróź for recording the IR spectra, Dr. Andrzej Nosal for determining the GC/MS analyses and Mrs. Czesława Andrzejewska for performing the elemental analyses in the Institute.

References and notes

1. Breuer, E.; Karaman, R.; Leader, H.; Goldblum, A. *J. Chem. Commun.* **1987**, 671–672.
2. Katzhendler, J.; Karaman, R.; Gibson, D.; Breuer, E. *J. Chem. Soc., Perkin Trans. 2* **1989**, 589–594.
3. Quin, L. D.; Xiao-Ping, W.; Breuer, E.; Mahajna, M. *Tetrahedron Lett.* **1990**, 6281–6282.
4. Drag, M.; Jezierski, A.; Kafarski, P. *Chem. Commun.* **2004**, 1132–1133.
5. Boduszek, B. *Tetrahedron* **1996**, *52*, 12483–12494.
6. Boduszek, B.; Latajka, R.; Leśniak, W. *Phosphorus, Sulfur, Silicon* **2000**, *165*, 53–75.

7. Boduszek, B.; Latajka, R.; Walkowiak, U. *Polish J. Chem.* **2001**, *75*, 63–69.
8. Boduszek, B. *Synth. Commun.* **2003**, *33*, 4087–4094.
9. Szabo, A.; Jaszay, Z. M.; Hegedüs, L.; Töke, L.; Petnehazy, I. *Tetrahedron Lett.* **2003**, *44*, 4603–4606.
10. Hoffmann, H.; Schellenbeck, P. *Chem. Ber.* **1966**, *99*, 1134–1142.
11. (a) Drabowicz, J.; Łyżwa, P.; Omelańczuk, J.; Pietrusiewicz, K. M.; Mikołajczyk, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2757–2763. (b) Haynes, R. K.; Au-Yeung, T.; Chan, W.; Lam, Z.; Yeung, L.; Chan, A. S. C.; Li, P.; Koen, M.; Mitchell, C. R.; Vonwiller, S. C. *Eur. J. Org. Chem.* **2000**, 3205–3216.
12. Haake, P.; Ossip, D. A. *Tetrahedron Lett.* **1970**, 3513–3516.
13. Haake, P.; Ossip, D. A. *Tetrahedron Lett.* **1970**, 4841–4844.
14. Skrzypczyński, Z. *J. Phys. Org. Chem.* **1990**, *3*, 23–34.
15. Skrzypczyński, Z. *J. Phys. Org. Chem.* **1990**, *3*, 35–37.
16. Stec, W. J. *Bull. Acad. Polon. Sci., Ser. Sci. Chem.* **1973**, *10*, 709–720.
17. Fukuhara, K.; Okamoto, S.; Saro, F. *Org. Lett.* **2003**, *5*, 2145–2148.
18. David, D. M.; Kane-Maguire, A. P.; Pyne, S. G. *J. Chem. Soc., Dalton Trans.* **1994**, *3*, 289–295.
19. Westheimer, F. H. *Chem. Rev.* **1981**, *81*, 313–326.
20. Quin, L. D. *Coord. Chem. Rev.* **1994**, *137*, 525–559.
21. Ramirez, F.; Marecek, J. F. *Tetrahedron* **1980**, *36*, 3151–3160.
22. Friedman, J. M.; Knowles, J. R. *J. Am. Chem. Soc.* **1985**, *107*, 6126–6127.
23. Satterthwait, A. C.; Westheimer, F. H. *J. Am. Chem. Soc.* **1978**, *100*, 3197–3203.
24. Brooks, R.; Bunton, C. A. *J. Org. Chem.* **1970**, *35*, 2642–2647.
25. Brooks, R. J.; Bunton, C. A. *J. Org. Chem.* **1975**, *40*, 2059–2064.
26. Wasiak, J.; Helinski, J.; Dębkowski, W.; Skrzypczyński, Z.; Michalski, J. *Polish J. Chem.* **1995**, *69*, 1027–1032.
27. Berlin, K. D.; Austin, T. H.; Nagabhushanam, M. *J. Org. Chem.* **1965**, *30*, 1267–1268.
28. Sosnovsky, G.; Zaret, E. H.; Schmitt, K. D. *J. Org. Chem.* **1970**, *35*, 336–340.
29. Haake, P.; Diebert, C. E. *J. Am. Chem. Soc.* **1971**, *93*, 6931–6937.
30. Harger, M. J. P.; Westlake, S. *Tetrahedron* **1982**, *38*, 1511–1516.
31. Schuman, M.; Lopez, X.; Karplus, M.; Gouverneur, V. *Tetrahedron* **2001**, *57*, 10299–10308.
32. Albanese, D.; Landini, D.; Maia, A. *J. Org. Chem.* **2001**, *66*, 3249–3252.
33. Omelańczuk, J.; Mikołajczyk, M. *J. Am. Chem. Soc.* **1979**, *101*, 7292–7295.
34. Krawiecka, B.; Michalski, J.; Wojna-Tadeusiak, E. *J. Org. Chem.* **1986**, *51*, 4201–4208.
35. Au-Yeung, Tin-Lok. ; Chan, Ka-Yee.; Chan, Wai-Kuen.; Haynes, R. K.; Williams, I. D.; Yeung, L. L. *Tetrahedron Lett.* **2001**, *42*, 453–456.
36. Makowiec, S.; Rachoń, J. *Phosphorus, Sulfur, Silicon* **2002**, *177*, 941–955.
37. Pietrusiewicz, K. M.; Wiśniewski, W.; Zabłocka, M. *Tetrahedron* **1989**, *45*, 337–348.
38. Kehler, J.; Ebert, B.; Dahl, O.; Krogsgaard-Larsen, P. *Tetrahedron* **1999**, *55*, 771–780.
39. Olszewski, T.; Boduszek, B. *Polish J. Chem.* **2005**, *79*, 553–559.
40. Harger, M. J. P. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1294–1297.
41. Koizumi, T.; Yanada, R.; Tagaki, H.; Hirai, H.; Yoshii, E. *Tetrahedron Lett.* **1981**, 571–572.
42. Sheldrick, G. M. *SHELXS-97: Program for the Solution of Crystal Structures;* University of Göttingen: Göttingen, Germany, 1997.
43. Sheldrick, G. M. *SHELXL-97: Program for the Refinement of Crystal Structures;* University of Göttingen: Göttingen, Germany, 1997.
44. *SHELXTL*, version 5.10; Bruker AXS Inc.: Madison, Wisconsin, USA, 1997.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 4519–4527

Synthesis and structural characterisation of novel platinum-based drug candidates with extended functionality by incorporation of bis(diphenylphosphino)ferrocene units as metal chelators

Haris Bjelosevic,[a] Christer Spégel,[b] Åse Sykfont Snygg,[c] Lo Gorton,[b] Sofi K. C. Elmroth[c] and Tina Persson[a,*]

[a]*Department of Organic Chemistry, Chemical Center, Lund University, PO Box 124, SE-221 00 Lund, Sweden*
[b]*Department of Analytical Chemistry, Chemical Center, Lund University, PO Box 124, SE-221 00 Lund, Sweden*
[c]*Department of Biochemistry, Chemical Center, Lund University, PO Box 124, SE-221 00 Lund, Sweden*

Received 1 September 2005; revised 26 January 2006; accepted 16 February 2006

Available online 13 March 2006

Abstract—Among the metal-based anticancer drugs, cisplatin (*cis*-diaminedichloroplatinum(II)) is the most widely used species in therapy. Despite its clinical success, cisplatin still suffers in generating resistance, as well as being highly toxic due to poor selectivity between healthy and sick cells. By molecular design it ought to be possible to generate new *cis*-platinum compounds with increased selectivity and improved cellular behaviour. In this paper, we report a synthetic pathway for construction of derivatives of 1,1′-bis(diphenylphosphino)-ferrocene, together with their corresponding *cis*-platinum compounds with the aim testing them for their interaction capacity with respect to various DNA models. We also report a synthetic route for a nucleoside-based *cis*-platinum compound containing a bidentate ferrocenylphosphine derivative connected through a succinamic-based linker to the 5-position of the heterocyclic moiety of uridine. Our preliminary kinetic investigation of 5-{*N*-[1-[1′,2-bis(diphenylphosphino)ferrocenyl]ethyl]-*N*′-[prop-2-yn-3-yl]succinamide} uridinedichloroplatinum(II) showed that this compound reacted faster with the phosphorothioate containing oligonucleotides d(T_6p(S)T_6), with an observed first-order rate constant $k_{obs}=(1.4\pm0.1)\times10^{-4}\ s^{-1}$, compared with the G-N7 target in d(T_7GGT_7), for which the observed first-order rate constant is $k_{obs}=(7.2\pm0.5)\times10^{-4}\ s^{-1}$.

1. Introduction

In the 1960s, Rosenburg discovered that cell division could be inhibited by the platinum complex *cis*-[$PtCl_2(NH_3)_2$], also known as 'cisplatin'.[1,2] Cisplatin was introduced to the clinic around 1980 and the drug has been successfully used against many forms of cancer, particularly for the treatment of testicular and ovarian cancers.[3,4] The mechanism of action of cisplatin has not been fully elucidated, and is still a matter of intense research.[5–7] So far, it has been suggested that cisplatin acts on nuclear DNA preferentially by formation of GG and AG adducts along the DNA sequence.[4] It has been shown that formation of such adducts results in disruption of the DNA double helical structure[8,9] with consequences for the cellular machinery involved in both DNA repair and the induction of apoptosis[5–7] Nevertheless, there is growing evidence that nuclear DNA is not the only intracellular target and cellular components such as *t*RNA and structural elements along the *m*RNA sequence also could function as targets sites for cisplatin.[10]

Despite its clinical success, cisplatin has several side effects comprising toxicity and resistance[11] as a result of its non-selective interaction with healthy as well as cancer cells. As a result, there is an urgent need for novel compounds with an improved reactivity spectrum, preferentially with properties able to reduce the general toxicity but with retained target localisation. So far, only a few alternatives to cisplatin are available, namely oxaliplatin, carboplatin and nedaplatin.[5,7,12,13]

The long-term goal of this project is to develop a straightforward synthetic pathway for the production of ferrocenyl-based platinum compounds to be used as tentative replacement drugs for cisplatin in the clinic. Earlier studies have shown that this class of compound exhibits promising both antineoplastic and antimicrobial activity.[14,15] In this article, the synthetic pathway for some new chiral derivatives of 1,1′-bis-(diphenylphosphino)ferrocene and

Keywords: Cisplatin; Pt(dppf); Anticancer; Kinetics; Nucleoside analogue; Linker.
* Corresponding author. Tel.: +46 46 222 81 20; fax: +46 46 222 41 19; e-mail: tina.persson@organic.lu.se

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.057

their corresponding *cis*-platinum complexes is described. We also describe a synthetic route for the production of a uridine analogue containing a bidentate ferrocenylphosphine derivative connected through a linker arm to the 5-position of the heterocyclic moiety of the uridine molecule. The preliminary kinetic data reveals a reactivity of these compounds towards short DNA oligonucleotides of a magnitude similar to that of cisplatin.

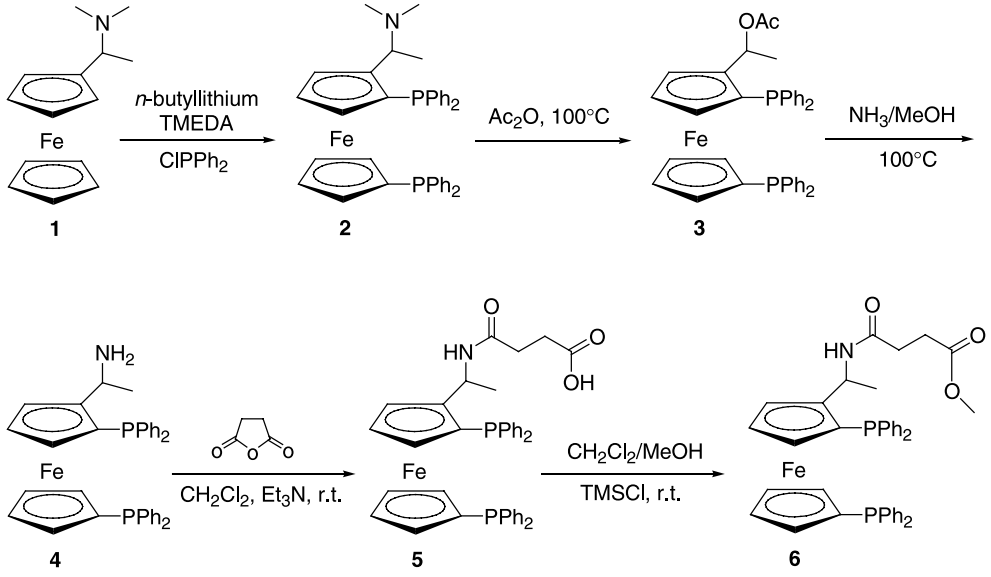
2. Results and discussion

2.1. Synthesis of ferrocenylphosphine derivatives

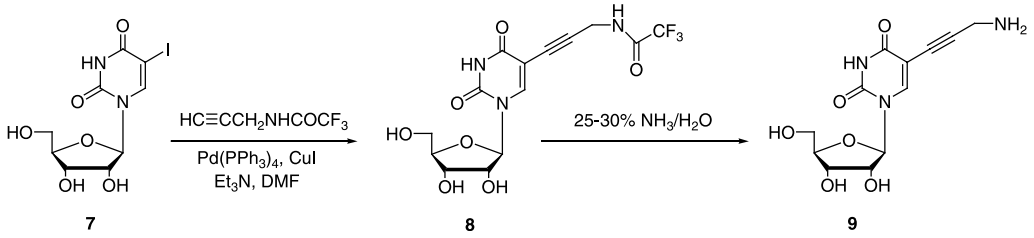
The ferrocenylphosphine derivatives were prepared from the commercially-available racemic mixture of (+/−)-*N*,*N*-dimethyl-1-ferrocenylethylamine **1**. Compound **4** was prepared according to the literature,[16] but its synthesis is briefly described as the purification steps were modified to simplify procedures for large scale production.

In the first step, the cyclopentadienyl rings of compound **1** were lithiated using *n*-butyllithium and *N*,*N*,*N*′*N*′-tetramethylethylenediamine (TMEDA). The organolithium reagent alone is not reactive enough, but the enhanced reactivity of using a mixture consisting of *n*-butyllithium and TMEDA allows for lithiation on both cyclopentadienyl rings of ferrocene.[17] The dilithiation of ferrocene is performed by stepwise addition of butyllithium in hexane to the reaction mixture, followed by the addition of *n*-butyllithium-TMEDA. The following diphenylphosphination to produce compound **2** was performed by an in situ reaction with chlorodiphenylphosphine with a yield of 56% (Scheme 1). Besides the central element of chirality, also a planar element of chirality exists due to the 1,2-unsymmetrically substituted ferrocene of compound **2**. Previous studies have demonstrated that because of the highly diastereoselective *ortho*-lithiation in this particular reaction sequence and substrate all compounds synthesised from **1** are assumed to be racemic mixtures consisting of (*R*)(*S*) and (*S*)(*R*) enantiomers in equal amounts.[16,18] and their corresponding diastereomers (*R*)(*R*) and (*S*)(*S*) are produced in a minor amount of 4%. All compounds produced will be tested in in vitro assay systems as mixture of isomers and only separated if they exhibit any interesting biological activity.

Purification, producing pure **2**, was achieved by silica gel column chromatography using toluene–diethyl ether–Et_3N (89/10/1) as the eluent. Transformation of the dimethylamino substituent on the ferrocene molecule to an amino group (Scheme 1) was accomplished via the formation of an acetoxy group by treatment of pure acetic anhydride at 100 °C.[16] Orange crystals precipitated directly in the reaction vessel, which were isolated in 90% yield. The desired amino-containing ferrocenyl compound **4** was created by reacting **3** with a saturated solution of ammonia in methanol in a sealed tube at 100 °C.[16] The two-step transformation of **2** to **4** both involve nucleophilic substitution reactions, which are both known to proceed with retention of configuration on the stereogenic carbon center.[16] Molecule **5** was produced by treatment of **4** with succinic anhydride in the presence of triethylamine (Scheme 1). Purification of **5** by silica gel column chromatography using CH_2Cl_2/MeOH as eluent produced dark red crystals in 81% yield. The carboxylic acid group in compound **5** was methylated by using chlorotrimethylsilane (TMSCl) as reagent in a solvent mixture consisting of MeOH–CH_2Cl_2 (2/1). The resulting compound **6** was purified by silica gel column chromatography using a gradient of heptane–EtOAc–EtOH (69/30/1) to EtOAc–EtOH (99/1) as eluents producing dark red crystals after removal of the solvents in vacuo in 74% yield. Uridine derivative **9** was synthesised to enable connection of the ferrocenyl complex **5** to the C-5 position of the heterocyclic moiety of uridine (Scheme 3). The synthesis of **9** was performed according to the literature in a two-step strategy (Scheme 2).[19] In the first step a Sonogashira reaction[20] between 5-iodouridine **7** and *N*-trifluoroacetyl propargyl amine[19] in the presence of $Pd(PPh_3)_4$, CuI and Et_3N in dry *N*,*N*-dimethylformamide (DMF) was utilised. The resulting



Scheme 1. Synthesis of target molecules **5** and **6**.



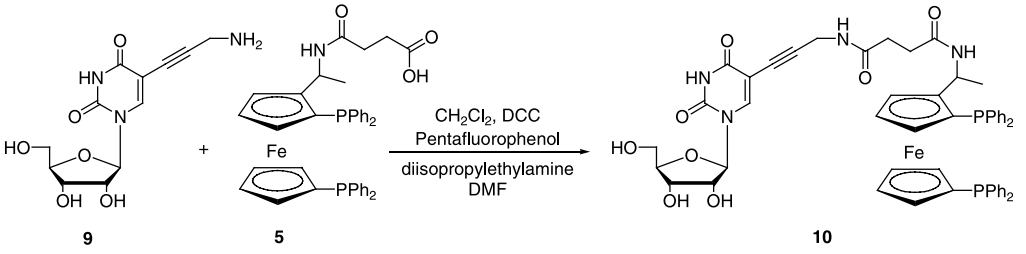
Scheme 2. Synthesis of the nucleoside derivative **9**.

nucleoside derivative **8** was purified by silica gel column chromatography using CH_2Cl_2–MeOH (9/1) as eluent resulting in orange crystals in 80% yield. In the second step, the trifluoroacetyl group was removed by treatment of **8** with 25–30% NH_3/H_2O at 4 °C producing **9** in a yield of 77%.

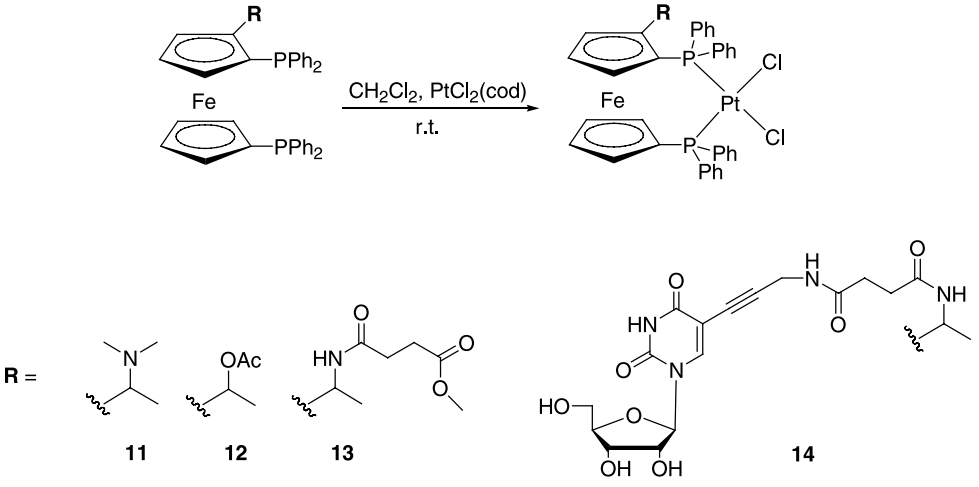
As discussed above, reacting succinic anhydride with the free amino group of the ferrocenyl complex **4**, a carbon chain linker with an internal amide bond and a free carboxylic acid group was created (Scheme 1). The ferrocenyl complex **5** was attached to the C-5 position of the heterocyclic moiety of uridine by reacting with uridine derivative **9** (Scheme 3). The coupling reaction between **9** and **5** was accomplished by using pentafluorophenol, *N*,*N*-dicyclohexylcarbodiimide (DCC) and diisopropylethylamine using CH_2Cl_2 and DMF as solvent producing **10** in 78% yield. The nucleoside-based ferrocenyl complex **10** was purified by silica gel chromatography using CH_2Cl_2–MeOH (93/7) as the eluent. Recently, it has been shown that the introduction of chemical modifications at the C-5 position are tolerated by both the *taq* polymerase[21] and the RNA polymerase thus making such nucleoside modifications interesting for future applications within the RNA chemistry field.[22] Some of the here reported complexes have already been tested with respect to their interaction with L-cystein and L-methionine.[23]

2.2. Synthesis of *cis*-platinum compounds 11, 12, 13 and 14

The prepared ferrocenyl ligands **2**, **3**, **6** and **10** were transformed to their corresponding *cis*-platinum complexes. These reactions were initiated by dissolving compounds **2**, **3**, **6**, or **10** in CH_2Cl_2, followed by addition of (1,5-cyclooctadiene)platinum(II)chloride, [$PtCl_2$(cod)] (Scheme 4). The reaction mixture was stirred for 1–2 h followed by reduction of the reaction volume of about 15–20%, whereupon crystals could be obtained by addition of ether. Before reacting ligand **10** with [$PtCl_2$(cod)], 1% methanol, calculated on the total reaction volume, was added to the reaction mixture in order to properly dissolve the ligand.



Scheme 3. Synthesis of the nucleoside containing ferrocenyl complex **10**.



Scheme 4. Reaction illustrating production of the platinum complexes **11**, **12**, **13** and **14**.

Comparison of the ^{31}P NMR spectra for the ferrocenyl complexes and their corresponding platinum complexes indicates that the bidentate ligands are bound to platinum as typical ^{195}Pt satellites could be observed on each ^{31}P signal and their coupling constants are of expected size. The *cis*-platinum complexes have also been verified by CV experiments, see below (Section 2.3).

2.3. Cyclic voltammetry

Cyclic voltammetry (CV) is a very powerful technique for characterising redox active compounds.[24] The ferrocene molecule is known to be redox active and it has been suggested that its biological activity (antineoplastic activity) could be connected with its redox processes in vivo[25] and following CV was chosen as one of the techniques to characterise compounds **11**, **12**, **13** and **14**. To compare the electrochemical behaviour of the platinated compounds, CV was also run on ferrocene (see Supplementary material data), 1,1′-bis(diphenylphosphino)ferrocene (dppf) and [$PtCl_2$(dppf)] and their corresponding CV voltammograms A and B, respectively, are shown in Figure 1. Since the CV voltammograms for the substituted complexes **11**, **12** and **13** were more or less identical to each other, only voltammogram of compound **13** is illustrated (Fig. 1C). The nucleoside containing compound **14** showed a somewhat different electrochemical behaviour shown in Figure 1D.

The CV of dppf contains two sets of redox reactions, those of the ferrocene moiety (1–2 in Fig. 1A) and those of the phosphino groups (3–4 in Fig. 1A). The $i_{p,c}/i_{p,a}$ ratio of the ferrocene redox reaction is highly sweep rate dependent (a ratio of 0.28 and of 0.18 at 100 and 50 mV/s, respectively) due to a fast chemical electron transfer from the ferrocene to the phosphino groups. The complex redox behaviour of dppf has been reported by Pilloni et al.[26]

The CV of platinated dppf, [$PtCl_2$(dppf)], contains only one set of redox waves (Fig. 1B) with a considerably higher formal potential ($E^{0'}$) in comparison with that of uncoordinated dppf ($E^{0'}=390$ mV vs dppf). The coordination of $PtCl_2$ to dppf results in blocking of the intramolecular ferrocene reduction, resulting in a reversible redox action ($\Delta E_p=60$ mV) with a $i_{p,c}/i_{p,a}$ ratio closer to unity than for dppf.

Modification of the cyclopentdienyl ring resulted in an increased $i_{p,c}/i_{p,a}$ ratio. Zanello et al.[27] have previously shown that modifications of the cyclopentadienyl ring of non-platinated dppf can, depending on the electron donating ability of the substituent, result in a partial stabilisation of the dppf monocation, observed as an increase in the $i_{p,c}/i_{p,a}$ ratio. The three substituted compounds **11**, **12** and **13** showed no significant difference in electrochemical behaviour (CV voltammogram for compound **13** is illustrated in Fig. 1C).

The nucleoside containing complex **14** showed different redox behaviour, that is, the peak current of the reduction wave of the ferrocene moiety is larger for the corresponding oxidation (Fig. 1D). The narrow shape of the reduction peak indicates that the oxidised species could be absorbed. The reduction peak current was proportional to the sweep rate ($R^2=0.999$) whereas the oxidation peak current was proportional to the square root of the sweep rate ($R^2=0.997$). This result suggests that the oxidised species might be adsorbed on the platinum electrode whereas the reduced specie is dissolved.[24]

2.4. DNA platination rates

To estimate the reactivity of this series of compounds towards DNA targets, a preliminary study of the reactivity of compound **14** was performed. Two types of oligomers were used as targets, one containing the GG sequence, which is preferred by cisplatin in vivo, d(T_7GGT_7), and the other containing the slightly more reactive phosphorothioate group d($T_6p(S)T_6$).[28,29] The kinetics for platination of the

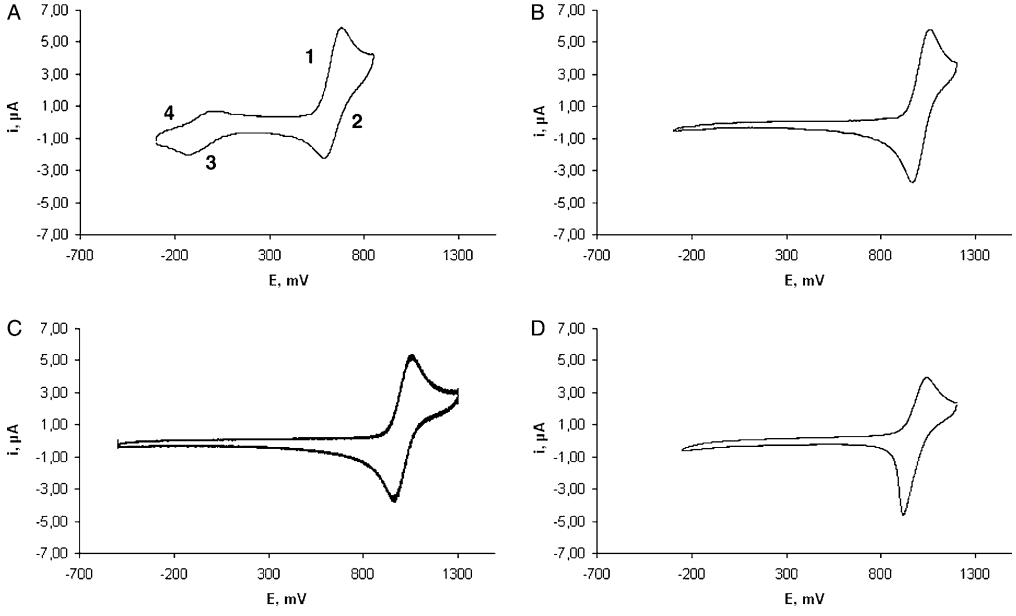


Figure 1. CV voltammograms of dppf (A), [$PtCl_2$(dppf)] (B), compound **10** (C) and nucleoside containing compound **14** (D).

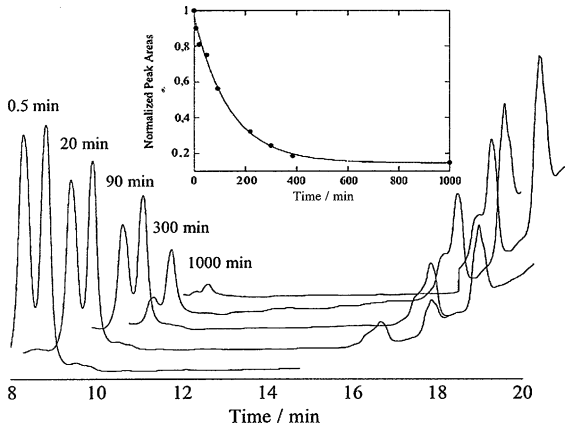


Figure 2. Selected HPLC chromatograms at different reaction times illustrating the platination of $d(T_6p(S)T_6)$. The two diastereomers of the unplatinated oligonucleotides are eluting at $t_r \approx 8$ and $t_r \approx 9$ min, and the product peaks start to elute at $t_r \approx 16$ min. The inserted graph displays the fit of a single exponential function to normalised, integrated peak areas versus time for the unplatinated oligonucleotide. Reaction conditions: $[Pt(II)] = 1.0 \times 10^{-5}$ M, $[d(T_6p(S)T_6)] = 2.0 \times 10^{-6}$ M, $[Na^+] = 10.0$ mM.

oligonucleotides was evaluated by the observed decrease in HPLC peak areas of the unplatinated reactant. The time course for the decline of the integrated area of the DNA-fragments were all found to follow first-order kinetics. Figure 2 shows typical HPLC chromatograms, illustrating the decrease of $d(T_6p(S)T_6)$ during the reaction with compound **14**, the inset shows a fit of a single exponential function to the normalised integrated peak areas. The platination rate was found to be twice as high for the phosphorothioate containing oligonucleotide compared to the G-N7 target in $d(T_7GGT_7)$. The obtained observed first-order rate constants were determined to $k_{obs} = (1.4 \pm 0.1) \times 10^{-4}\ s^{-1}$ and $(7.2 \pm 0.5) \times 10^{-5}\ s^{-1}$ for $d(T_6p(S)T_6)$ and $d(T_7GGT_7)$ respectively, all in agreement with the more pronuced nucleophilicity exhibited by the phosphorothiophate compared with G-N7. Thus, these reactions have half-lives of 1.4 and 2.7 h for the reactions with G-N7 and p(S), respectively, that is, indicating a slightly higher reactivity of **14** compared with cisplatin.[30,31]

3. Conclusions

We here report a successful synthetic pathway for the construction of several unique dppf-based platinum compounds with chemical modifications introduced in the ferrocenyl moiety. So far, the majority of chemical modifications have been focused on changing the properties of the phosphine groups. The limiting factor for many of the produced *cis*-platinum compounds is their poor aqueous solubility, lack of selectivity and high toxicity. By modulating the chemical properties we hope to construct new unique *cis*-platinum complexes with retained or improved in vivo activity. One such compound identified in this study is the nucleoside containing complex **14**, which show improved water solubility and thus allows for facile kinetics studies with DNA models systems. Its reactivity is similar to cisplatin with a reaction half-life in the hour range.

4. Experimental

4.1. General

Analytical thin-layer chromatography (TLC) was performed by using silica gel 60 F_{254} plates purchased from Merck and 5-iodouridine **7** was purchased from Aldrich. Column chromatography was carried out using Matrex silica gel 60A/35–70. The compounds were visualised on the TLC plates by three different methods: (1) using UV-light; (2) using a solution of *p*-methoxybenzaldehyde (10 mL), concentrated sulfuric acid (50 mL) and ethanol (95%, 950 mL) and (3) using a ninhydrin solution. Melting points were taken on a Sanyo Gallenkamp melting point apparatus (MPD.350.BM3.5) and are uncorrected. IR spectra were recorded on a Shimadzu 8300 FTIR instrument and $KBr_{(s)}$ was used as matrix. NMR spectra were recorded on a Bruker ARX300 or a DRX400 spectrometer and all chemical shifts (δ) are relative to the residual peak of the deuterated solvent and given in parts per million, apart from compound **9**, where ^{13}C NMR shifts are given relative to 3-(trimethylsilyl)-propanesulfonic acid sodium salt (D_2O) as external reference. Chemical shifts in ^{31}P NMR spectra are reported in parts per million relative to external 85% H_3PO_4 at 0.00 ppm. To enable determination of the various peaks, phosphorus decoupled ^{13}C NMR was run on compounds **3**, **5**, **6** and **10**. For the platinated compounds NMR experiments such as COSY, HMQC and HMBC were carried out. All solvents used in the synthetic procedures were distilled prior to use.

4.2. Synthesis

4.2.1. *N*,*N*-Dimethyl-1-[1′,2-bis(diphenylphosphino) ferrocenyl]ethylamine (2). *n*-BuLi (1.6 M in hexane, 5.84 mL, 9.3 mmol) was slowly added to a solution of racemic (+/−)-*N*,*N*-dimethyl-1-ferrocenylethylamine **1** (1.99 g, 7.74 mmol) dissolved in dry diethyl ether (12 mL) over a period of 20 min. The reaction flask was equipped with a septum, whereupon slowly filled with argon followed by setting the temperature of the reaction mixture to 25 °C. The reaction mixture was stirred for 1 h at room temperature, whereupon a mixture of *N*,*N*, *N*′,*N*′-tetramethylethylenediamine (1.4 mL, 9.3 mmol) and *n*-BuLi (1.6 M in hexane, 6.32 mL, 10.1 mmol) was added over a period of 15 min. The reaction mixture was kept at room temperature for 5 h followed by cooling to −15 °C. Chlorodiphenylphosphine (4.19 mL, 23.3 mmol) was slowly added and the reaction mixture was allowed to reach room temperature followed by gentle stirring overnight. Saturated $NaHCO_3$ (aq) was added with stirring, the two phases were separated, and the aqueous phase was extracted with toluene (3×60 mL). The combined organic phases were dried over Na_2SO_4, filtered and the product was isolated by evaporation under reduced pressure. The crude product was purified by silica gel column chromatography using toluene–ether–Et_3N (89/10/1) as eluent. The resulting product was isolated as red crystals in 56% yield (2.72 g). ^1H NMR spectrum was in agreement with the literature.[16] ^{31}P NMR ($CDCl_3$, ppm): δ −16.93 (s), −23.01 (s); mp 151.3–152.0 °C.

4.2.2. 1-[1′,2-Bis(diphenylphosphino)ferrocenyl]ethylacetate (3). *N*,*N*-Dimethyl-1-[1′,2-bis(diphenylphosphino)-ferrocenyl]ethylamine **2** (0.577 g, 0.922 mmol) and acetic anhydride (3 mL) were mixed together in a glass tube, degassed and heated to 100 °C for 2 h. The reaction mixture was slowly cooled to room temperature followed by further cooling to −20 °C, whereupon orange crystals started to precipitate. The product was isolated by filtration and dried under reduced pressure overnight resulting in 90% yield (532 mg) of **3**. ^{1}H NMR spectrum was in agreement with the literature,[16] ^{13}C NMR (100.61 MHz, CD_2Cl_2, ppm): δ 18.6, 20.3, 68.6 (d, J_{P-C}=9.1 Hz), 71.6 (d, J_{P-C}=2.7 Hz), 72.1 (d, J_{P-C}=2.1 Hz), 73.7 (d, J_{P-C}=9.9 Hz), 73.8 (d, J_{P-C}=2.6 Hz), 74.0 (d, J_{P-C}=10.4 Hz), 74.5 (d, J_{P-C}=4.6 Hz), 75.6 (d, J_{P-C}=18.9 Hz), 77.7 (d, J_{P-C}=14.5 Hz), 77.8 (d, J_{P-C}=16.4 Hz), 93.1 (d, J_{P-C}=24.5 Hz), 128.4, 128.5 (d, J_{P-C}=6.0 Hz), 128.69 (d, J_{P-C}=7.0 Hz), 128.72 (d, J_{P-C}=7.0 Hz), 128.73 (d, J_{P-C}=6.0 Hz), 129.0, 129.2, 129.9, 133.0 (d, J_{P-C}=19.1 Hz), 133.7 (d, J_{P-C}=19.1 Hz), 134.1 (d, J_{P-C}=20.1 Hz), 135.6 (d, J_{P-C}=21.1 Hz), 137.1 (d, J_{P-C}=9.1 Hz), 139.1 (d, J_{P-C}=10.1 Hz), 139.8 (d, J_{P-C}=10.1 Hz), 140.2 (d, J_{P-C}=10.1 Hz), 169.9; ^{31}P NMR ($CDCl_3$, ppm): δ −17.39 (s), −24.99 (s); mp 159.4–160.4 °C.

4.2.3. 1-[1′,2-Bis(diphenylphosphino)ferrocenyl]ethylamine (4). A mixture of 1-[1′,2-bis(diphenylphosphino)-ferrocenyl]ethylacetate **3** (423 mg, 0.660 mmol) and saturated ammonia–methanol (5 mL) was heated to 100 °C in a sealed glass tube. The mixture was stirred for 7 h followed by cooling to room temperature, whereupon 20 mL of toluene was added carefully. The reaction mixture was washed with 1 M NaOH (2×15 mL), and the organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using toluene–EtOH–Et_3N (98/1/1) as eluent, and **4** was isolated in a 87% yield (342 mg). ^{1}H NMR spectrum was in agreement with the literature,[16] ^{31}P NMR ($CDCl_3$, ppm): δ −18.48 (s), −25.89 (s).

4.2.4. *N*-[1-[1′,2-Bis(diphenylphosphino)ferrocenyl]-ethyl]succinamic acid (5). 1-[1′,2-Bis(diphenylphosphino) ferrocenyl]ethylamine **4** (559 mg, 0.936 mmol) was dissolved in dry CH_2Cl_2 (12 mL) followed by the addition of succinic anhydride (936 mg, 9.36 mmol) and Et_3N (0.390 mL, 2.80 mmol), whereupon the mixture was stirred under argon overnight. Prior to washing with 1 M HCl (2×20 mL) and water (3×20 mL), CH_2Cl_2 (10 mL) was added to the reaction mixture. The combined organic phases were dried over Na_2SO_4, filtered, and the solvent was removed by evaporation under reduced pressure. The resulting crude product was purified by silica gel column chromatography using CH_2Cl_2–MeOH (96/4) as eluent giving **5** as dark red crystals in an 81% yield (530 mg); IR (KBr, cm^{-1}): 3365, 3052, 1729, 1620, 1430; ^{1}H NMR ($CDCl_3$, ppm): δ 1.36 (d, 3H, J=6.6 Hz, CHCH_3), 1.41–1.47, 1.80–2.00, 2.15–2.40 (m, 4H, COCH_2CH_2-CO), 3.50–3.70, 4.05–4.55 (m, 7H, C_5H_4FeC_5H_3), 5.19 (m, 1H, CHCH$_3$), 5.65 (br s, NHCO), 7.10–7.80 (m, 20H, PC_6H_5); ^{13}C NMR (100.61 MHz, D_6-DMSO, ppm): δ 20.2, 28.9, 29.2, 42.0 (d, J_{P-C}=9.1 Hz), 70.6 (d, J_{P-C}=1.8 Hz), 70.9 (d, J_{P-C}=3.6 Hz), 71.9 (d, J_{P-C}=4.7 Hz), 72.7 (d, J_{P-C}=9.5 Hz), 72.9, 74.0 (d, J_{P-C}=4.9 Hz), 74.7 (d, J_{P-C}=20.4 Hz), 75.4 (d, J_{P-C}=11.4 Hz), 76.0 (d, J_{P-C}=8.8 Hz), 96.3 (d, J_{P-C}=26.2 Hz), 127.5, 127.8 (d, J_{P-C}=5.0 Hz), 128.1 (d, J_{P-C}=7.0 Hz), 128.2 (d, J_{P-C}=7.0 Hz), 128.3 (d, J_{P-C}=6.0 Hz), 128.4, 128.7, 129.2, 131.8 (d, J_{P-C}=18.1 Hz), 132.6 (d, J_{P-C}=19.1 Hz), 133.2 (d, J_{P-C}=20.1 Hz), 134.8 (d, J_{P-C}=22.1 Hz), 136.8 (d, J_{P-C}=9.1 Hz), 137.9 (d, J_{P-C}=10.1 Hz), 139.0 (d, J_{P-C}=11.1 Hz), 139.7 (d, J_{P-C}=11.1 Hz), 168.3, 173.7; ^{31}P NMR ($CDCl_3$, ppm): δ −17.28 (s), −25.15 (s); mp 175.0–175.5 °C; HRMS (FAB$^+$) *m*/*z* calculated for $C_{40}H_{37}FeNO_3P_2$: 697.1598. Found: 697.1590.

4.2.5. *N*-[1-[1′,2-Bis(diphenylphosphino)ferrocenyl]-ethyl]succinamic acid methylester (6). Chlorotrimethylsilane (0.450 mL, 3.52 mmol) was slowly added to a solution of *N*-[1-[1′,2-bis(diphenylphosphino)ferrocenyl]ethyl]succinamic acid **5** (460 mg, 0.659 mmol) in dry MeOH (6 mL) and CH_2Cl_2 (3 mL). The reaction mixture was stirred overnight under argon followed by removal of the solvents by evaporation under reduced pressure. The crude product was purified by silica gel column chromatography using two different solvent systems starting with heptane–EtOAc–EtOH (69/30/1) and, in later fractions, EtOAc–EtOH (99/1) to give **6** in 74% yield (348 mg); IR (KBr, cm^{-1}): 3374, 3062, 1724, 1663, 1173; ^{1}H NMR ($CDCl_3$, ppm): δ 1.33 (d, 3H, J=6.7 Hz, CHCH_3), 1.55–2.60 (m, 4H, COCH_2CH_2CO), 3.64 (s, 3H, OCH_3), 3.50–3.60, 4.10–4.60 (m, 7H, C_5H_4FeC_5H_3), 5.15 (m, 1H, CHCH$_3$), 5.75 (br d, 1H, J=6.4 Hz, NHCO), 7.10–7.70 (m, 20H, PC_6H_5); ^{13}C NMR (100.61 MHz, CD_2Cl_2, ppm): δ 21.1, 29.5, 30.5, 44.7 (d, J_{P-C}=7.0 Hz), 52.0, 71.8 (d, J_{P-C}=2.3 Hz), 72.2 (d, J_{P-C}=2.9 Hz), 73.4 (d, J_{P-C}=4.6 Hz), 73.77 (d, J_{P-C}=8.7 Hz), 73.81 (d, J_{P-C}=4.4 Hz), 74.7 (d, J_{P-C}=4.1 Hz), 75.8 (d, J_{P-C}=20.7 Hz), 76.0 (d, J_{P-C}=10.7 Hz), 77.5 (d, J_{P-C}=8.6 Hz), 96.1 (d, J_{P-C}=24.3 Hz), 128.66 (d, J_{P-C}=6.0 Hz), 128.69 (d, J_{P-C}=6.0 Hz), 128.73 (d, J_{P-C}=7.0 Hz), 128.8 (d, J_{P-C}=7.0 Hz), 128.9, 129.2, 129.9, 132.9 (d, J_{P-C}=19.1 Hz), 133.5 (d, J_{P-C}=19.1 Hz), 134.2 (d, J_{P-C}=20.1 Hz), 135.5 (d, J_{P-C}=21.1 Hz), 137.0 (d, J_{P-C}=8.0 Hz), 139.0 (d, J_{P-C}=10.1 Hz), 140.0 (d, J_{P-C}=11.1 Hz), 140.4 (d, J_{P-C}=10.1 Hz), 169.2, 173.6; ^{31}P NMR ($CDCl_3$, ppm): δ −17.06 (s), −24.67 (s); mp 186–187 °C; HRMS (FAB$^+$) *m*/*z* calculated for $C_{41}H_{39}FeNO_3P_2$: 711.1755. Found: 711.1757.

4.2.6. 5-(3″-Trifluoroacetamidopropynyl)uridine (8). 5-Iodouridine **7** (373 mg, 1.01 mmol) was dissolved in dry DMF (5 mL) followed by the addition of CuI (38 mg, 0.20 mmol), Et_3N (0.280 mL, 2.0 mmol), *N*-propargyl trifluoroacetamide[32] (453 mg, 3.00 mmol), and $Pd(PPh_3)_4$ (116 mg, 0.10 mmol). The reaction mixture was stirred overnight under argon atmosphere at room temperature, whereupon the solvent was removed by evaporation under reduced pressure. The crude product was purified by using silica gel column chromatography using CH_2Cl_2–MeOH (9/1) as eluent resulting in **8** as orange crystals in 80% yield (318 mg). ^{1}H NMR spectrum was in agreement with the literature. ^{1}H NMR (D_4-MeOH, ppm): δ 3.73 (dd, 1H, J=12.2, 2.7 Hz), 3.86 (dd, 1H, J=12.2, 2.5 Hz), 4.01 (m, 1H), 4.15 (m, 2H), 4.26 (s, 2H), 5.87 (d, 1H, J=3.8 Hz), 8.39 (s, 1H).

4.2.7. 5-(3″-Aminopropyin-1-yl)uridine (9). 5-(3″-Trifluoroacetamidopropynyl)uridine **8**[19] (305 mg, 0.776 mmol) was stirred in ammonium hydroxide solution (10 mL, 25–30% NH_3 in H_2O) for 15 h at 4 °C followed by the removal of the solvent by evaporation under reduced pressure. The crude product was purified by silica gel column chromatography using CH_2Cl_2–MeOH–Et_3N (69/30/1) as eluent resulting in a white solid product in 77% yield (178 mg); IR (KBr, cm^{-1}): 3384, 3071, 1691, 1663, 1610, 1278, 1107, 1083; ^1H NMR (D_2O, ppm): δ 3.70 (dd, 1H, J=4.0, 12.9 Hz, uridine 5′-H), 3.77 (s, 2H, CH_2NH$_2$), 3.82 (dd, 1H, J=2.7, 12.9 Hz, uridine 5′-H), 4.02 (m, 1H), 4.09 (m, 1H), 4.19 (m, 1H), 5.77 (d, 1H, J=3.7 Hz, uridine 1′-H), 8.07 (s, 1H, uridine 6-H); ^{13}C NMR (100.61 MHz, D_2O, ppm): δ 32.8, 63.2, 71.7, 76.7, 80.2, 86.6, 90.0, 92.7, 101.2, 147.4, 156.6, 171.7; mp 185 °C; HRMS (FAB$^+$) m/z calculated for $C_{12}H_{15}N_3NaO_6$: 320.0859 [M+Na]$^+$. Found: 320.0859 [M+Na]$^+$.

4.2.8. 5-{*N*-[1-[1′,2-Bis(diphenylphosphino)ferrocenyl]-ethyl]-*N*′-[prop-2-yn-3-yl]succinamide}uridine (10). *N*,*N*′-Dicyclohexylcarbodiimid (76 mg, 0.37 mmol, 1 equiv) was added to a solution of **5** (20 mL, 253 mg, 0.363 mmol) and 2,3,4,5,6-pentafluorophenol (86 mg, 0.47 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was stirred overnight, whereupon the solvent was removed by evaporation under reduced pressure. After removal of the solvent, dry DMF (20 mL) was added together with compound **9** (140 mg, 0.472 mmol) and diisopropylethylamine (125 μL). The reaction mixture was stirred for additional 16 h followed by removal of the solvent by evaporation under reduced pressure. The crude product was purified by silica gel column chromatography using CH_2Cl_2–MeOH (93/7) as eluent producing orange crystals of compound **10** in 78% yield (276 mg); IR (KBr, cm^{-1}): 3403, 3062, 1691, 1648, 1534, 1430, 1278, 1093; ^1H NMR (D_3-MeOD, ppm): δ 1.15–1.32 and 1.73–2.18 (m, 4H, COCH_2CH_2CO), 1.38 (d, 3H, J=6.7 Hz, CHCH_3), 3.50–3.68 (m, 2H, ferrocene), 3.70–3.95 (m, 2H, uridine 5′-H), 4.02 (m, 1H, uridine 4′-H), 4.06 (m, 2H, CH_2NHCO), 4.10–4.20 (m, 5H), 4.45–4.55 (m, 2H, ferrocene), 5.17 (m, 1H, CH$_3$C*H*NH), 5.88 (m, 1H, uridine 1′-H), 7.04–7.45 (m, 20H, PPh), 8.40 (s, 1H, uridine 6-H); ^1H NMR (D_6-DMSO, ppm): δ 1.15–1.28 and 1.65–2.10 (m, 4H, COCH_2CH_2CO), 1.30 (d, 3H, J=6.7 Hz, CHCH_3), 3.40–3.55 (m, 2H, ferrocene), 3.55–3.75 (m, 2H, uridine 5′-H), 3.86 (m, 1H), 3.95–4.25 (m, 7H), 4.40–4.53 (m, 2H, ferrocene), 4.90–5.05 (m, 1H, C*H*CH$_3$), 5.09 (d, 1H, J=5.0 Hz, O*H*), 5.23 (t, 1H, J=4.5 Hz, O*H*), 5.42 (d, 1H, J=5.3 Hz, O*H*), 5.75 (d, 1H, J=4.5 Hz, uridine 1′-H), 6.90–7.50 (m, 21H, PPh and CHN*H*CO), 8.15 (t, 1H, J=5.3 Hz, CH$_2$N*H*CO), 8.24 (s, 1H, uridine 6-H), 11.64 (br s, 1H, uridine 3-H); ^{13}C NMR (100.61 MHz, D_3-MeOD, ppm): δ 20.3, 30.5, 31.3, 31.8, 44.7 (d, J_{P-C}=9.1 Hz), 62.1, 71.2 (d, J_{P-C}=3.6 Hz), 72.4, 72.5 (d, J_{P-C}=4.8 Hz), 74.1 (d, J_{P-C}=4.8 Hz), 74.6, 74.7 (d, J_{P-C}=10.5 Hz), 75.2, 75.4 (d, J_{P-C}=4.8 Hz), 76.2, 76.3 (d, J_{P-C}=18.1 Hz), 77.7 (d, J_{P-C}=10.9 Hz), 78.4 (d, J_{P-C}=8.1 Hz), 86.6, 90.2, 91.1, 96.7 (d, J_{P-C}=25.2 Hz), 100.2, 129.3, 129.4 (d, J_{P-C}=6.0 Hz), 129.7, 130.0, 130.6, 133.7 (d, J_{P-C}=19.1 Hz), 134.4 (d, J_{P-C}=20.1 Hz), 134.8 (d, J_{P-C}=20.1 Hz), 136.5 (d, J_{P-C}=21.1 Hz), 138.4 (d, J_{P-C}=8.0 Hz), 140.0 (d, J_{P-C}=11.1 Hz), 140.8 (d, J_{P-C}=10.1 Hz), 141.4 (d, J_{P-C}=10.1 Hz), 145.7, 151.6, 164.6, 171.9, 174.3; ^{31}P NMR (D_3-MeOD, ppm): δ −17.02 (s), −24.40 (s); ^{31}P NMR (D_6-DMSO, ppm): δ −18.02 (s), −24.10 (s); HRMS (FAB$^+$) m/z calculated for $C_{52}H_{51}FeN_4O_8P_2$: 977.2532 [M+H]. Found: 977.2517 [M+H]; mp 157–158 °C.

4.2.9. [PtCl$_2$(P-P)] {P-P=*N*,*N*-dimethyl-1-[1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine} (11). [PtCl$_2$(cod)] (252 mg, 0.674 mmol) was added to a solution of *N*,*N*-dimethyl-1-[1′,2-bis(diphenylphosphino)ferrocenyl]-ethylamine **2** (425 mg, 0.679 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was stirred under argon for 2 h, whereupon the reaction mixture was concentrated to a volume of about 13 mL. After concentration, dry diethyl ether (80 mL) was added with stirring resulting in precipitation of yellow crystals. The crystals were collected, washed with ether and dried under reduced pressure overnight at room temperature to give **11** in a 95% yield (571 mg). ^1H NMR spectrum was in agreement with the literature;[33] ^{31}P NMR (CD_2Cl_2, ppm): δ 16.08 (d, J_{PP}=9.4 Hz, ^{195}Pt satellites J_{PtP}=3851 Hz), 9.28 (d, J_{PP}=9.4 Hz, ^{195}Pt satellites J_{PtP}=3736 Hz).

4.2.10. [PtCl$_2$(P-P)] {P-P=1-[1′,2-bis(diphenylphosphino)ferrocenyl]ethylacetate} (12). 1-[1′,2-Bis(diphenylphosphino)ferrocenyl]ethylacetate **3** (583 mg, 0.910 mmol) was dissolved in dry CH_2Cl_2 (20 mL) followed by the addition of [PtCl$_2$(cod)] (337 mg, 0.901 mmol). The reaction mixture was stirred for 2 h under argon, whereupon concentrated to about 10 mL. The concentrated solution was kept at room temperature with stirring and dry Et_2O (80 mL) was carefully added resulting in precipitation of a slightly orange product. The product was isolated by filtration, washed with ether and dried under reduced pressure producing a crystalline product of **12** in 97% yield (792 mg); IR (KBr, cm^{-1}): 3071, 1729, 1430, 1221; ^1H NMR (CD_2Cl_2, ppm): δ 1.47 (d, 3H, J=6.2 Hz, CHCH_3), 1.67 (s, 3H, COCH_3), 3.54, 3.91, 4.25–4.4, 4.75 (m, 7H, $C_5H_4FeC_5H_3$), 7.07 (q, 1H, J=6.3 Hz, C*H*CH$_3$), 7.14–8.30 (m, 20H, PC$_6H_5$); ^{13}C NMR (100.62 MHz, CD_2Cl_2); δ 18.5, 21.8, 69.0 (d, J_{P-C}=2.0 Hz), 72.1 (d, J_{P-C}=7.2 Hz), 72.8 (d, J_{P-C}=6.8 Hz), 74.0 (d, J_{P-C}=7.5 Hz), 74.2 (dd, J_{P-C}=64.5 Hz, $J_{P'-C}$=2.7 Hz), 74.6 (d, J_{P-C}=10.0 Hz), 74.8 (d, J_{P-C}=7.0 Hz), 77.6 (dd, J_{P-C}=65.8 Hz, $J_{P'-C}$=3.9 Hz), 78.9 (d, J_{P-C}=5.4 Hz), 79.9 (d, J_{P-C}=8.3 Hz), 93.0 (d, J_{P-C}=13.0 Hz), 127.1 (d, J_{P-C}=11.6 Hz), 128.5 (d, J_{P-C}=11.6 Hz), 128.6 (d, J_{P-C}=11.6 Hz), 128.8 (d, J_{P-C}=10.9 Hz), 130.9 (d, J_{P-C}=2.9 Hz), 131.0 (d, J_{P-C}=67.9 Hz), 131.3 (d, J_{P-C}=61.9 Hz), 131.65 (d, J_{P-C}=2.9 Hz), 131.7 (d, J_{P-C}=69.0 Hz), 131.9 (d, J_{P-C}=2.9 Hz), 132.3 (d, J_{P-C}=71.8 Hz), 132.5 (d, J_{P-C}=2.4 Hz), 135.79 (d, J_{P-C}=11.2 Hz), 135.84 (d, J_{P-C}=10.0 Hz), 136.0 (d, J_{P-C}=10.2 Hz), 137.0 (d, J_{P-C}=12.3 Hz), 170.1; ^{31}P NMR (CD_2Cl_2, ppm): δ 14.42 (d, J_{PP}=9.80 Hz, ^{195}Pt satellites J_{PtP}=3817 Hz), 9.63 (d, J_{PP}=9.80 Hz, ^{195}Pt satellites J_{PtP}=3717 Hz); HRMS (FAB$^+$) m/z calculated for $C_{38}H_{34}Cl_2FeO_2P_2Pt$: 905.0408. Found: 905.0410.

4.2.11. [PtCl$_2$(P-P)] {P-P=*N*-[1-[1′,2-bis(diphenylphosphino)ferrocenyl]ethyl]succinamic acid methylester} (13). [PtCl$_2$(cod)] (151 mg, 0.404 mmol) was added to a solution of *N*-[1-[1′,2-bis(diphenylphosphino)ferrocenyl]-ethyl]succinamic acid methylester **6** (289 mg, 0.406 mmol)

in dry CH_2Cl_2 (20 mL) and the reaction mixture was stirred for 2 h under argon. The crude reaction mixture was reduced to a total volume of ca. 5 mL under reduced pressure, and orange crystals started to precipitate after addition of dry Et_2O (50 mL). The produced crystals were washed with ether, collected by filtration and dried under reduced pressure to give **13** in 92% yield (367 mg); IR (KBr, cm^{-1}): 3488, 3336, 3052, 1724, 1667, 1530, 1430; ^1H NMR (CD_2Cl_2, ppm): δ 1.88 (d, 3H, $J=6.9$ Hz, $CHCH_3$), 1.92–2.50 (m, 4H, $COCH_2CH_2CO$), 3.64 (s, 3H, OCH_3), 3.45–3.60, 4.15–5.05 (m, 7H, $C_5H_4FeC_5H_3$), 6.77 (m, 1H, $CHCH_3$), 6.93 (br s, 1H, NHCO), 6.97–8.40 (m, 20H, PC_6H_5); ^{13}C NMR (100.61 MHz, CD_2Cl_2, ppm): δ 17.7, 29.4, 31.1, 46.5 (d, $J_{P-C}=3.0$ Hz), 52.0, 69.8 (d, $J_{P-C}=67.3$ Hz), 71.5 (d, $J_{P-C}=7.2$ Hz), 72.6 (d, $J_{P-C}=7.1$ Hz), 73.4 (d, $J_{P-C}=7.2$ Hz), 74.3 (d, $J_{P-C}=9.2$ Hz), 76.4 (d, $J_{P-C}=8.1$ Hz), 76.5 (d, $J_{P-C}=67.6$ Hz), 77.7 (d, $J_{P-C}=4.3$ Hz), 79.9 (d, $J_{P-C}=9.8$ Hz), 98.0 (d, $J_{P-C}=14.1$ Hz), 127.5 (d, $J_{P-C}=12.1$ Hz), 128.4 (d, $J_{P-C}=12.1$ Hz), 128.5 (d, $J_{P-C}=11.1$ Hz), 129.4 (d, $J_{P-C}=11.1$ Hz), 129.7 (d, $J_{P-C}=59.4$ Hz), 130.8 (d, $J_{P-C}=3.0$ Hz), 131.3 (d, $J_{P-C}=3.0$ Hz), 131.8 (d, $J_{P-C}=67.4$ Hz), 132.5 (d, $J_{P-C}=3.0$ Hz), 132.6 (d, $J_{P-C}=2.0$ Hz), 132.7 (d, $J_{P-C}=70.4$ Hz), 133.6 (d, $J_{P-C}=67.4$ Hz), 134.2 (d, $J_{P-C}=10.1$ Hz), 134.4 (d, $J_{P-C}=11.1$ Hz), 135.9 (d, $J_{P-C}=10.1$ Hz), 136.7 (d, $J_{P-C}=12.1$ Hz), 171.3, 173.6; ^{31}P NMR (CD_2Cl_2, ppm): δ 16.20 (s, ^{195}Pt satellites $J_{PtP}=3801$ Hz), 10.63 (s, ^{195}Pt satellites $J_{PtP}=3748$ Hz); mp 271.5–272.5 °C; HRMS (FAB^+) *m/z* calculated for $C_{41}H_{39}Cl_2FeNO_3P_2Pt$: 976.0779. Found: 976.0774.

4.2.12. [$PtCl_2$(P-P)] (P-P=10) (14). [$PtCl_2$(cod)] (30 mg) was added to a solution of **10** (78 mg, 0.080 mmol) in a mixture of dry CH_2Cl_2–MeOH (99/1) (5 mL). The reaction mixture was stirred for 2 h under argon, whereupon the reaction volume was reduced to about 2 mL. After addition of dry Et_2O (10 mL), yellow crystals started to precipitate, which were filtrated and carefully washed with Et_2O and dried under reduced pressure at room temperature to give **14** in 93% yield (92 mg); IR (KBr, cm^{-1}): 3393, 3052, 1691, 1530, 1430, 1278, 1093; ^1H NMR (D_6-DMSO, ppm): δ 0.97 (d, 3H, $J=6.4$ Hz, $CHCH_3$), 1.75–2.23 (m, 4H, $COCH_2$-CH_2CO), 3.52–3.70 (m, 2H, uridine 5′-H), 3.86 (m, 1H, uridine 4′-H), 3.93 (m, 1H, ferrocene), 3.97 (m, 1H, uridine 3′-H), 4.05 (m, 3H, CH_2NH and uridine 2′-H), 4.09–4.15 and 4.27–4.70 (m, 6H, ferrocene), 5.03–5.13 (m, 2H, $CHCH_3$ and OH), 5.20 (t, 1H, $J=4.8$ Hz, OH), 5.40 (d, 1H, $J=5.4$ Hz, OH), 5.75 (m, 1H, uridine 1′-H), 7.22 (d, 1H, $J=7.1$ Hz, CHNHCO), 7.27–8.12 (m, 20H, PPh), 8.17 (s, 1H, uridine 6-H), 8.28 (t, 1H, $J=5.4$ Hz, CH_2NH), 11.65 (s, 1H, uridine 3-H); ^{13}C NMR (100.61 MHz, D_6-DMSO, ppm): δ 19.9, 27.3, 28.4, 30.1, 42.9, 60.4, 69.4, 71.2 (d, $J_{P-C}=7.2$ Hz), 71.6 (dd, $J_{P-C}=65.4$ Hz, $J_{P'-C}=2.0$ Hz), 72.5 (d, $J_{P-C}=7.5$ Hz), 73.2 (d, $J_{P-C}=11.3$ Hz), 73.6, 73.8 (d, $J_{P-C}=7.5$ Hz), 73.98 (d, $J_{P-C}=6.3$ Hz), 74.01, 75.9 (dd, $J_{P-C}=70.4$ Hz, $J_{P'-C}=3.8$ Hz), 77.1 (d, $J_{P-C}=7.5$ Hz), 78.6 (d, $J_{P-C}=7.5$ Hz), 84.8, 88.0, 89.6, 95.0 (d, $J_{P-C}=12.6$ Hz), 98.1, 126.9 (d, $J_{P-C}=11.3$ Hz), 127.9 (d, $J_{P-C}=11.3$ Hz), 128.0 (d, $J_{P-C}=10.1$ Hz), 128.6 (d, $J_{P-C}=66.7$ Hz), 130.2 (d, $J_{P-C}=66.7$ Hz), 130.5 (d, $J_{P-C}=3.0$ Hz), 130.7 (d, $J_{P-C}=3.0$ Hz), 131.3 (d, $J_{P-C}=3.6$ Hz), 131.4 (d, $J_{P-C}=3.1$ Hz), 131.9 (d, $J_{P-C}=62.9$ Hz), 133.9 (d, $J_{P-C}=10.1$ Hz), 135.09 (d, $J_{P-C}=12.5$ Hz), 135.11 (d, $J_{P-C}=9.1$ Hz), 135.7 (d, $J_{P-C}=11.1$ Hz), 143.7, 149.6, 161.4, 169.3, 171.0; ^{31}P NMR (D_6-DMSO, ppm): δ 16.04 (d, $J_{PP}=9.5$ Hz, ^{195}Pt satellites $J_{PtP}=3894$ Hz), 12.95 (d, $J_{PP}=9.5$ Hz, ^{195}Pt satellites $J_{PtP}=3800$ Hz); HRMS (FAB^+) *m/z* calculated for $C_{52}H_{50}ClFeN_4O_8P_2Pt$: 1206.1790 [M−Cl]. Found: 1206.1799 [M−Cl].

4.3. Cyclic voltammetry

Cyclic voltammetry measurements were carried out at room temperature using a Gamry FAS2 Femtostat (Gamry Instruments, Warminster, USA) using a 2 mm Pt disk working electrode, an Ag/AgCl (3 M LiCl in ethanol) reference electrode (Radiometer) and a Pt-wire counter electrode. Prior to experiments, the Pt-working electrode was mechanically polished with a 0.1 μm alumina suspension and electrochemically cleaned in 0.5 M sulphuric acid. Experiments performed in N_2 saturated dichloromethane using 0.1 M tetrabutylammonium perchlorate as supporting electrolyte and a sample concentration of 500 μM.

4.4. Kinetic investigation by HPLC measurement

4.4.1. Chemicals. The oligonucleotides $d(T_6p(S)T_6)$ and $d(T_7GGT_7)$ were bought from Scandinavian Gene Synthesis AB. They were received in aqueous solutions and were kept frozen at −80 °C. Concentrations of the oligomers were determined by absorption measurements at 260 nm using calculated extinction coefficients. Spectra were recorded using a Nanodrop 3.0.0. spectrophotometer at ambient conditions. The kinetic measurements were performed in aqueous solution with 10 mM $NaClO_4$ (Merck p.a.), pH 6.2. The non-ionic surfactant Triton X-100 (Sigma) was added to the solution in 0.05% v/v, in order to avoid precipitation of the Pt(II)-complexes. Aqueous solutions were prepared using Millipore water, (18 MΩ, ELGA PURELAB Ultragenetic) and stored at room temperature, the pH was determined by use of a Methrom 744 pH meter.

4.4.2. HPLC measurements. The HPLC analysis was carried out on a LaChrome (Merck Hitachi) chromatograph system with a D-7000 interface and a D-7400 UV/vis detector set at 260 nm and at 30 °C. Separation of platinated from unreacted oligonucleotides was obtained by using reversed phase technique, a C18 YMC Hydrosphere column (250⇔4.6 mm I.D., 5 μm particle diameter), equipped with guard, was employed. 0.10 M ammonium acetate buffer (Merck) pH 6.0 was used as the mobile phase with different acetonitrile (LAB-Scan, HPLC grade) gradients, 10–25% for 15 min, 0.8 mL/min flow for separation of $d(T_6p(S)T_6)$. The chromatograms were evaluated by use of an on-line HPLC System Manager Software working under Microsoft Windows NT Workstation version 4.0.

4.4.3. Kinetic measurements. Stock solutions of compound **14** were made in DMSO (Aldrich), kept at −20 °C. The platination reactions were initiated by addition of appropriate amount of oligonucleotides to the thermostated aqueous solution containing the platinum compound (the final DMSO concentration was less than 0.25% v/v). The reactions were performed at 25 °C, the concentrations of the reactants were; [oligonucleotide]$=2.0\times10^{-6}$ M and [Pt(II)]$=1.0\times10^{-5}$ M. Aliquots were withdrawn at different time intervals and directly quenched by eight-fold

dilutions. The samples were stored in liquid nitrogen at −196 °C and injected on HLPC directly after thawing. The time-dependent decrease of the integrated peak areas of the nonreacted oligonucleotides was used to follow the kinetics. The observed first-order rate constant, k_{obs}, was determined by a fit of single exponential function to the experimental data points. The measurements were performed three times and averaged.

Acknowledgements

We are grateful to FLÄK (Forskarskolan i Läkemedelsvetenskap), Lund University, Crafoordska Stiftelsen, Schybergs Stiftelse, The Swedish Cancer Society (contract no. 040607) and The Swedish Research Council (contract no. 40446101 and 40447601) for their financial support. We are also grateful to Dr. Ola Wendt, Roger Johansson and Dr. Karl-Erik Bergquist for their kind help with the ^{13}C NMR experiments.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.057.

References and notes

1. Rosenberg, B.; Camp, L. V.; Krigas, T. *Nature* **1965**, *205*, 698–699.
2. Rosenberg, B.; VanCamp, L.; Trosko, J. E.; Mansour, V. H. *Nature* **1969**, *222*, 385–386.
3. Reedijk, J. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 3611–3616.
4. Zhang, C. X.; Lippard, S. J. *Curr. Opin. Chem. Biol.* **2003**, *7*, 481–489.
5. Boulikas, T.; Vougiouka, M. *Oncol. Rep.* **2003**, *10*, 1663–1682.
6. Bertrand, J.-C. *DNA Repair in Cancer Therapy*; Humana: Totowa, NJ, 2004; pp 51–72.
7. Barnes, K. R.; Lippard, S. J. In Sigel, A., Sigel, H., Eds.; Metal Ions in Biological Systems; Marcel Dekker: New York, 2004; Vol. 42, pp 143–177.
8. Takahara, P. M.; Rosenzweig, A. C.; Frederick, C. A.; Lippard, S. J. *Nature* **1995**, *377*, 649–652.
9. Takahara, P. M.; Frederick, C. A.; Lippard, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 12309–12321.
10. Papsai, P.; Aldag, J.; Persson, T.; Elmroth, S. K. C. Manuscript submitted.
11. Brabec, V.; Kasparkova, J. *Drug Resist. Updat.* **2002**, *5*, 147–161.
12. Kelland, L. R. *Am. J. Cancer* **2002**, *1*, 247–255.
13. Lokich, J. *Cancer Invest.* **2001**, *19*, 756–760.
14. Scarcia, V.; Furlani, A.; Longato, B.; Corain, B.; Pilloni, G. *Inorg. Chim. Acta* **1988**, *153*, 67–70.
15. Mason, R. W.; McGrouther, K.; Ranatunge-Bandarage, P. R.; Robinson, B. H.; Simpson, J. *Appl. Organomet. Chem.* **1999**, 163–173.
16. Hayashi, T.; Miese, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1138–1151.
17. Rausch, M. D.; Ciappenelli, D. J. *J. Organomet. Chem.* **1967**, *10*, 127–136.
18. Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffman, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389–5393.
19. Hobbs, J. F. W. *J. Org. Chem.* **1989**, *54*, 3420–3422.
20. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470.
21. Lee, S. E.; Sidorov, A.; Gourlain, T.; Mignet, N.; Thorpe, S. J.; Brazier, J. A.; Dickman, M. J.; Hornby, D. P.; Grasby, J. A.; Williams, D. M. *Nucleic Acids Res.* **2001**, *29*, 1565–1573.
22. Vaish, N. K.; Fraley, A. W.; Szostak, J. W.; McLaughlin, L. W. *Nucleic Acids Res.* **2000**, *28*, 3316–3322.
23. Puxty, G.; Bjelosevic, H.; Persson, T.; Elmroth, S. K. C. *Dalton Trans.* **2005**, *18*, 3032–3038.
24. Bard, A. J.; Faulkner, L. R. *Electrochemical methods—Fundamentals and Applications*; Wiley: New York, 1980; pp 519–532.
25. Osella, D.; Ferrali, M.; Zanello, P.; Laschi, F.; Fontani, M.; Nervi, C.; Cavigiolio, G. *Inorg. Chim. Acta* **2000**, *306*, 42–48.
26. Pilloni, G.; Longato, B.; Corain, B. *J. Organomet. Chem.* **1991**, *420*, 57–65.
27. Zanello, P.; Opromolla, G.; Giorgi, G.; Sasso, G.; Togni, A. *J. Organomet. Chem.* **1996**, *506*, 61–65.
28. Elmroth, S. K. C.; Lippard, S. J. *J. Am. Chem. Soc.* **1994**, *116*, 3633–3634.
29. Elmroth, S. K. C.; Lippard, S. J. *Inorg. Chem.* **1995**, *34*, 5234–5243.
30. Miller, S. E.; House, D. A. *Inorg. Chim. Acta* **1989**, *161*, 131–137.
31. Miller, S. E.; House, D. A. *Inorg. Chim. Acta* **1991**, *187*, 125–132.
32. Cruickshank, K. A.; Stockwell, D. L. *Tetrahedron Lett.* **1988**, *29*, 5221–5224.
33. Cullen, W. R.; Evans, S. V.; Han, N. F.; Trotter, J. *J. Inorg. Chem.* **1987**, *26*, 514–519.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 4528–4534
Tetrahedron

Efficient synthesis of antisense phosphorothioate oligonucleotides using a universal solid support

R. Krishna Kumar, Andrei P. Guzaev, Claus Rentel and Vasulinga T. Ravikumar*

Isis Pharmaceuticals, 2282 Faraday Avenue, Carlsbad, CA 92008, USA

Received 28 December 2005; revised 10 February 2006; accepted 15 February 2006

Available online 7 March 2006

Abstract—It is demonstrated that solid support containing a novel universal linker could be efficiently used to synthesize both phosphorothioate oligodeoxyribonucleotides and second-generation 2′-*O*-methoxyethyloligoribonucleotides with high yield and quality as judged by ion-pair-liquid chromatography–electrospray mass spectroscopy, ^{31}P NMR and reversed phase HPLC. Analysis of oligonucleotides shows quality being superior to that produced with standard succinyl-linker solid supports, without contamination of materials resulting from linker or support backbone decomposition.

1. Introduction

Synthesis of oligonucleotides and their analogs have undergone revolutionary changes in the last several years.[1–3] Currently, for small- as well as large-scale, the most widely used approach both by academic institutions and by pharmaceutical companies is the solid-supported synthesis utilizing β-cyanoethyl protected phosphoramidites of various nucleosides. The synthesis is performed in automated DNA/RNA synthesizer machines using controlled pore glass (CPG) or Amersham Biosciences' HL30 or PS200 polymeric solid support. The 3′-nucleoside is linked to solid support generally through a succinyl-linker to give support-bound nucleoside. The synthesis consists of stepwise coupling of individual monomeric units followed by oxidation of resulting phosphite triester with iodine to give the phosphate triester. In case of phosphorothioate analogs sulfurization is performed and the reagent of choice is phenylacetyl disulfide (PADS)[4,5] or 3*H*-1,2-benzodithiole-3-one-1,2-dioxide (Beaucage reagent).[6,7] Thus, four solid supports are required for synthesis of oligodeoxyribonucleotides. The advancement of antisense therapeutics has resulted in use of RNA–DNA–RNA chimeric molecules wherein the wings consists of 2′-*O*-alkyl RNA nucleotides (2′-*O*-methoxyethyl or 2-*O*-methyl).[8,9] This has necessitated the need to have a large number of pre-derivatized polymer supports. To obviate this need, several research groups have proposed the concept of a universal solid support. Gough et al. were the first to propose a universal support containing a linker, 3-anisoyl-2′-(3′-*O*-benzoyluridine-5′-*O*-succinyl, attached to CPG.[10] Since then several groups have reported various analogs of universal linkers.[11–26] These supports employ nucleosidic material, which does not get incorporated into oligonucleotide chains and hence goes to waste. Alternatively, some non-nucleoside-based universal supports have also been proposed, but cleavage of oligomers is either tedious or involves use of salts or other conditions. In addition, in our hands, evaluation of at least three of reported universal linker procedures when repeated and analyzed carefully by ion-pair-liquid chromatography–electrospray mass spectroscopy (a technique known to reveal small amounts ($<1\%$) of adducts or linker molecules), showed the quality of oligonucleotides is not the same as compared to standard method and was contaminated with the pendent linker molecule. Also, there was considerable (ca. 10%) amount of oligonucleotide still attached to solid support making it an inefficient approach. These limitations have so far, outweighed the added convenience of one support material for every sequence, and pre-derivatized supports are still predominantly preferred.

Herein, we have redesigned the vicinal diol-based linker system so that the linker remains firmly bound to support during the deprotection and cleavage steps of DNA synthesis. Thus, any DNA molecule that is released from support is not contaminated with linker molecule.

2. Results and discussion

Early on we realized that a major drawback in design of various universal linker molecules is the presence of a hydroxyl group that was derivatized with a cleavable group

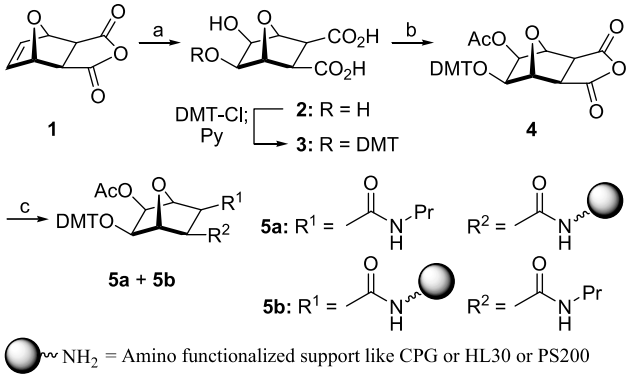
Keywords: Oligonucleotide; Succinate; Detritylation; Universal solid support.
* Corresponding author. Tel.: +1 760 603 2412; fax: +1 760 603 4655; e-mail: vravikumar@isisph.com

0040–4020/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tet.2006.02.040

such as succinyl or oxalyl. Instead, if the linker molecule possesses a non-hydroxyl functionality (e.g., carboxyl) that could be directly attached/coupled to amino-derivatized solid support to form an amide bond, then after oligomerization, the first step during ammonia deprotection is the unmasking of the protecting group on neighbouring hydroxyl group followed by intra-molecular attack on phosphate/phosphorothioate group similar to base-catalyzed hydrolysis of RNA leading to release of oligonucleotide. Thus, any oligonucleotide released from solid support has to be of good quality since the linker molecule will be still attached to solid support. In addition, if synthesis were to be efficient we have to demonstrate that there is no measurable amount of oligonucleotide still attached to solid support. Thus both quality and quantity (yield) issues could be addressed successfully if the molecule is designed appropriately.

2.1. Synthesis of universal linker and loading to support

In our earlier initial communication, we proposed a novel compound **4** as an efficient and high quality yielding universal linker molecule.[27] Synthesis and loading of this molecule **4** is shown in Scheme 1. The synthesis starts with bis-hydroxylation of olefin **1** according to literature procedure. No significant changes were made to this procedure after several attempts were made to improve yield and product obtained was used further without any additional purification. Chemoselective protection of diol **2** with 4,4′-dimethoxytrityl chloride happened to be tricky. The molecule was highly soluble in water in spite of having a large lyphophilic DMT group (possibly due to presence of two carboxyl and one hydroxyl groups) and care should be taken to obtain reasonable yield (22%). The overall yield of two steps starting from olefin **1** was low ($<10\%$) but due to inexpensive nature of starting materials, it did not discourage us from scaling up this molecule. We were able to scale up approximately 0.5 kg in a single batch. Treatment of the DMT compound **3** with acetic anhydride in pyridine gave the acetoxy protected cyclic anhydride **4** as colorless foam in almost quantitative yield. Loading of the universal linker molecule **4** to solid support was carried out in pyridine with amino-derivatized support to give the appropriate loading. The free carboxyl group generated during ring opening during loading is capped by forming an amide bond with *n*-propyl amine using HATU and HOBt coupling condition. A loading of 90 μmol/g was obtained while using HL30 support (recommended loading level by manufacturer).



Scheme 1. Synthesis of universal linker loaded support: (a) (i) OsO_4/H_2O_2/H_2O/acetone/*t*BuOH; 30 °C, 24 h; (ii) DMT chloride, pyridine; rt, 20 h; (b) (i) Ac_2O/NMI/Py; (c) (i) Py, rt; (ii) HATU/HOBT/MeCN/Py; (iii) *n*$PrNH_2$/MeCN; (iv) Ac_2O/NMI/Py.

2.2. Synthesis of phosphorothioate oligodeoxyribonucleotide

To demonstrate this methodology, a 20-mer phosphorothioate oligodeoxyribonucleotide [PS-d(GTTCTCGCTGG TGAGTTTCA), ISIS 3521] was chosen as an example. Three syntheses were carried out (standard nucleoside containing succinate linked support as control and universal linker attached support in duplicate). The results are summarized in Table 1.

2.3. Investigation on yield of oligonucleotide

To determine if any oligonucleotide was still attached to support leading to loss of yield, the support after cleaving and washing thoroughly to remove the synthesized oligonucleotide, was incubated with aqueous methylamine at 55 °C for 14 h. The solution after filtration of solid support was analyzed by HPLC and also by UV measurement. No detectable level of oligonucleotide was observed. Subsequently, the support was dried thoroughly under high vacuum and then tested for presence of DMT group by the usual acid treatment (*p*-toluene sulphonic acid in CH_3CN). No orange color was observed. This clearly indicates that release of oligonucleotide is quantitative (Scheme 2).

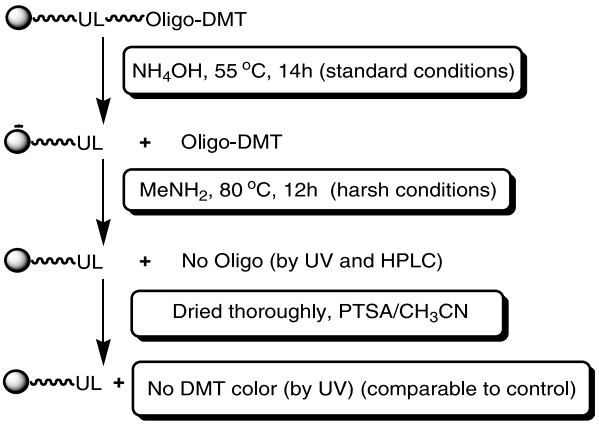
2.4. Investigation on increased level of $(n-1)$-mer

The quality of an oligonucleotide could be measured and quantitated by various analytical methods. Depending upon the technique used, full or partial information could be obtained. Strong anion exchange chromatography, mass spectrometry, and ^{31}P NMR spectroscopy may be used for quantitative assessment of PO-content. Capillary gel electrophoresis (CGE) could be used for quantitation of deletion sequences [$(n-1)$-mers]. For an analytical method to be good, it should have been demonstrated for its necessary accuracy, precision, linearity, range, selectivity and ruggedness for use in routine testing. In our laboratories, we use state-of-the-art ion-pair high performance liquid chromatography–mass spectroscopy (IP-LC–MS) technique as a specific, accurate, and sensitive means of quantitating oligonucleotides containing deletion sequences, depurinated sequences and 3′-terminal phosphorothioate monoester within a matrix of PS-oligonucleotides. Removal of deletionmers [$(n-1)$-mers; internal and terminal] on preparative scale using chromatographic separation technology is difficult to achieve without significant yield loss. Incomplete detritylation, potential re-tritylation (due to reversible reaction), incomplete coupling followed by incomplete capping and some other unknown mechanisms are a potential source of formation of $(n-1)$-mers. The extent of $(n-1)$-mer formation is frequently used as a quality measure of the performance of detritylation conditions.

Table 1. Comparison of oligonucleotides synthesized using standard succinate and universal linker supports

Support used for synthesis	Crude yield (mg/μmol)	Crude full length (%) (RP HPLC)	Purified full length (%) (IP-LC–MS)	(Depurinated species) (%) (IP-LC–MS)	P═S:P═O (^{31}P NMR)	P═S:P═O (IP-LC–MS)
dA succinate (**0849-149**)	6.2	70	82.4	5.1	99.66:0.34	99.59:0.41
Universal linker (**0849-150**)	5.9	77	86.6	2.2	99.62:0.38	99.64:0.36
Universal linker (**0849-151**)	6.4	77	87.2	2.3	99.60:0.40	99.61:0.39

Depurinated species include *n*-G, *n*-A/*n*-G+H_2O, *n*-A+H_2O, 3′-TPT.



Scheme 2. Investigation of any oligonucleotide attached to support leading to yield loss.

Analyses of the synthesized phosphorothioate oligonucleotides by IP-LC–MS clearly indicate that removal of DMT group from the secondary hydroxyl group of the universal linker molecule is slow as shown by increased levels of dA (as compared to oligonucleotide synthesized using succinate loaded support) (Table 2). We reasoned that all other cycles and conditions being equal, the increased level of dA could come from inefficient detritylation during the first cycle. This kind of precise information would not have been possible with other kinds of techniques. In addition, we have shown earlier that increased depurination occurs when base-protected deoxyadenosine has an electron withdrawing group attached at 3′-position (succinate group) as compared to having a phosphate/thioate group. A majority of this 3′-terminal depurinated species undergoes elimination followed by fragmentation during ammonia incubation step leading to formation of 3′-terminal phosphorothioate monoester (3′-TPT).[28] This possibility is eliminated or substantially reduced while using universal linker molecule (Table 2). We also confirmed that increased levels of dA is not due to inefficient coupling as use of large excess of phosphoramidite synthon (15 equiv), extended contact time (20 min), use of recycling during coupling and various other efforts did not lead to any measurable improvement.

Table 2. IP-LC–MS analysis of oligonucleotide synthesized using standard succinate and universal linker supports

Species	**0829-149** (%)	**0829-150** (%)	**0829-151** (%)
n [ISIS 3521]	84.6	84.8	85.1
P═O	7.0	5.5	4.9
n-dG	1.2	1.0	1.3
n-dA	**0.5**	**4.9**	**4.9**
T	2.0	1.4	1.6
n-dC	0.7	0.8	0.8
n-G	0.2	0.1	0.1
n-A/*n*-G+H_2O	0.7	0.7	0.5
n-A+H_2O	**2.2**	**0.5**	**0.5**
3′-TPT	**0.9**	**0.3**	**0.3**
Sum	100.0	100.0	100.0

2.5. Optimization on first detritylation step

There are at least two ways of removing the DMT group from the universal linker molecule efficiently viz., use of excess deblock solution and extending the contact time. After several experiments aimed at optimized detritylation condition, we found that efficient removal of DMT group could be achieved by using the same volume of acid solution but slowing down the delivery pump to double the contact time. Alternatively, the detritylation cycle could be repeated one more time (twice the deblock volume and time). With this optimized detritylation condition, we resynthesized the phosphorothioate oligonucleotide (ISIS 3521), purified and analyzed by ^{31}P NMR, RP-HPLC and IP-LC–MS. Comparable results were achieved between the two oligonucleotides synthesized (Table 3).

Table 3. IP-LC–MS analysis of oligonucleotide synthesized using optimized detritylation cycle for universal linker support (**0830-10**= using nucleoside-loaded support; **0830-11**=using universal linker loaded support)

Species	**0830-10** (%)	**0830-11** (%)
n [ISIS 3521]	85.8	90.0
P═O	6.8	6.0
n-dG	0.4	0.3
n-dA	**0.5**	**0.6**
T	0.9	0.5
n-dC	0.5	0.4
n-G	0.4	0.2
n-A/*n*-G+H_2O	1.0	0.7
n-A+H_2O	**2.4**	**0.7**
3′-TPT	**1.3**	**0.6**
Sum	100.0	100.0

2.6. Synthesis of 2′-*O*-methoxyethyl modified RNA chimera phosphorothioate oligonucleotides

Due to instability of wild-type DNA, phosphorothioate oligonucleotides, where one of the non-bridging oxygens of the internucleotide phosphate is formally replaced by a sulfur atom, are currently the modification of choice for design and development of therapeutic drugs. To further increase the therapeutic value of these phosphorothioate drugs, several nucleoside modifications have been investigated. Of these, 2′-*O*-methoxyethyl (MOE) modified oligoribonucleotide chimera has been selected in our laboratories (at Isis Pharmaceuticals) and multiple drugs are in various stages of human clinical trials against a variety of diseases.

Table 4. Comparison of oligonucleotides synthesized using succinate and universal linker supports

Support used for synthesis	Crude yield (mg/μmol)	Crude full length (%) (RP HPLC)	Purified full length (%) (IP-LC–MS)	(*n*−1) (%) (IP-LC–MS)	P═S:P═O (IP-LC–MS)
MOE meC succninate (**0830-45**)	6.76	77	91.1	2.9	3.8
Universal linker (**0830-40**)	7.60	74	90.0	3.0	4.0
Universal linker (**0830-43**)	7.13	70	91.2	3.2	2.9

To demonstrate the applicability of universal linker molecule for synthesis of MOE oligonucleotides, a 20-mer phosphorothioate, [PS-MOE-(GCTCC)-d(TTCCAC-TGAT)-MOE-(CCTGC)-3′] (ISIS 113715) where deoxycytidine and MOE cytidine have 5-methyl substitution was chosen as an example. For control experiment, MOE meC succinate loaded PS200 Primer support (200 μmol/g) was used. Similar cycle conditions were employed for oligonucleotide synthesis like phosphorothioate oligodeoxyribonucleotide including optimized extended condition for the first cycle involving removal of DMT group from the universal linker molecule. The results are summarized in Table 4. In addition, a portion of crude material obtained from each synthesis was purified by C_{18} reversed phase HPLC, the final DMT removed and then analyzed by ion-pair liquid chromatography–electrospray mass spectrometry (IP-LC–MS) (Table 5). The level of *n*-MOE meC (first base attached to support) and *n*-MOE meU (since both deletionmers have same mass) compare well between three experiments indicating that overall quality of oligonucleotide obtained using universal linker attached support is good with no detectable levels of any 3′-modifications. The sample was analyzed by ^{31}P NMR, analytical RP-HPLC, and IP-LC–MS.

Table 5. IP-LC–MS analysis of oligonucleotides synthesized using MOE meC succinate and universal linker supports

Species	**0830-45** (%)	**0830-40** (%)	**0830-43** (%)
n [ISIS 113715]	93.2	92.9	94.0
P═O	3.8	4.0	2.9
n-dG	0.0	0.1	0.1
n-dA	0.1	0.1	0.1
n-T/*n*-5medC	0.3	0.4	0.4
n-MOE G	0.5	0.2	0.3
n-MOE meU/*n*-MOE meC	0.8	1.0	1.3
n-G	0.0	0.1	0.1
n-A/*n*-G+H_2O	0.8	0.7	0.6
n-A+H_2O	0.3	0.4	0.2
3′-TPT	0.2	0.1	0.0
Sum	100.0	100.0	100.0

Subsequently, multiple oligonucleotides (both deoxy and MOE) were synthesized at different scales, various supports and different synthesizers (Amersham Biosciences Akta 10 and Akta 100 DNA/RNA synthesizer); yield and quality were found to be equivalent or slightly better compared to succinate loaded supports.

2.7. Mechanism of release of oligonucleotide from support

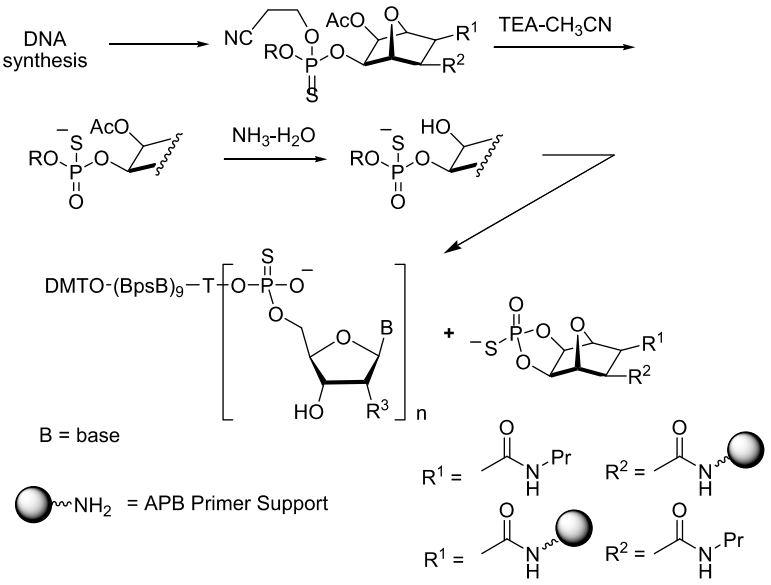
A reasonable mechanism for release of oligonucleotide is depicted in Scheme 3. At the end of oligonucleotide synthesis, treatment of the support with triethylamine:acetonitrile removes the cyanoethyl group and generates the phosphate/phosphorothioate diester charged backbone. Subsequent treatment with concentrated aqueous ammonium hydroxide, removes the acetyl protection from the vicinal hydroxyl group. Intra-molecular attack on adjacent phosphate/phosphorothioate center followed by cyclization releases the 3′-hydroxyl oligonucleotide (Scheme 3).

2.8. Economic and quality impact of using universal linker solid support

There are both direct and indirect cost savings while using universal linker loaded solid support. While it is difficult to precisely quantify the savings, overall there is definitely substantial economic benefit by switching over to one inventory of this solid support instead of at least eight different (four deoxy and four MOE) supports. In addition, while using succinate loaded supports, in particular containing 5-methyl MOE cytidine nucleoside, we have observed instability of the benzoyl group as evidenced by formation of longer formation, possibly arising out of branching from the exocyclic amine group.[29] Currently, we don't know if this happens during loading protocol or upon storage of the support at room temperature. We do not observe this longer formation while using universal linker loaded support. Besides these benefits, one major advantage for therapeutic applications is that this universal linker loaded solid supports are no longer considered as starting materials but rather as raw materials. Eliminating a starting material in drug development is a considerable advantage towards cost reduction (both direct and indirect costs) and more than compensates the additional cost involved in performing one more cycle containing an amidite as compared to nucleoside-loaded supports.

3. Summary and conclusions

A novel, conformationally pre-organized non-nucleosidic universal solid support for oligonucleotide synthesis has been developed. The solid support featured two chemically equivalent hydroxy groups locked in *syn*-periplanar orientation and orthogonally protected with 4,4′-dimethoxytrityl and acetyl groups. The solid support was extensively tested in preparation of phosphorothioate analogs containing 2′-deoxy and 2′-*O*-methoxyethylnucleoside residues at the 3′-terminus. Upon completion of oligonucleotide chain assembly, the support-bound oligonucleotide material was treated with concentrated ammonium hydroxide, which removed the *O*-acetyl protection. The deprotected hydroxyl group then affected the transesterification of a phosphorothioate linkage between the solid support and the 3′-terminal nucleoside residue to result in a facile release of the oligonucleotide to solution. In addition, the solid support containing this universal linker molecule is stable at room



Scheme 3. Mechanism for release of oligonucleotide from support.

temperature for extended period of time (at least 1 year) as shown by consistent good quality of oligonucleotides produced with it. Extended detritylation condition to remove the DMT group further indicates that this group is very stable.

4. Experimental

4.1. Materials and methods

Anhydrous acetonitrile (water content $<0.001\%$) was purchased from Burdick and Jackson (Muskegon, MI). 5′-*O*-Dimethoxytrityl-3′-*N*,*N*-diisopropylaminoe-3′-*O*-(2-cyanoethyl) phosphoramidites (T, dA^{bz}, dC^{bz}, dG^{ibu}) were purchased from Amersham Pharmacia Biotech, Milwaukee, WI. Toluene was purchased from Gallade, Escondido, CA. Dichloroacetic acid was purchased from Clariant Life Sciences. All other reagents and dry solvents were purchased from Aldrich and used without further purification. Primer support HL30 and PS200 was obtained from Amersham Biosciences, Uppsala, Sweden. 1*H*-Tetrazole was purchased from American International Chemical, Natick, MA. Phenylacetyl disulfide (PADS) was purchased from Acharya Chemicals, Dombivli, India. ^{31}P NMR spectra were recorded on a Unity-200 spectrometer (Varian, Palo Alto, CA) operating at 80.950 MHz. Capillary gel electrophoresis was performed on a eCAP ssDNA 100 Gel Capillary (47 cm) on a P/ACE System 5000 using Tris/borate/7 M urea buffer (all Beckman), running voltage 14.1 kV, temperature 40 °C. Thin-layer chromatography was performed on silica gel 60F-254 (Merck) plates and compounds were detected under shorter-wavelength UV light.

4.1.1. Preparation of universal linker 1α,2α,3α,4α,5α,6α)-5,6-dihydroxy-7-7-oxabicyclo[2.2.1]hetane-2,3-dicarboxylic acid (2). The title compound was synthesized by bis-hydroxylation of (3α*R*,4*S*,7*R*,7α*S*)-rel-3α,4,7,7α-tetrahydro-4,7-epoxyisobenzofuran-1,3-dione, **1** with hydrogen peroxide in presence of osmium tetroxide (OsO_4) as described in literature and used without any additional purification.[30]

4.1.2. (1α,2α,3α,4α,5α,6α)-5-Hydroxy-6-(4,4′-dimethoxytrityloxy)-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid (3). 4,4′-Dimethoxytrityl chloride (38.75 g, 114.5 mmol) was added in aliquots to a solution of compound **2** (16.95 g, 77.5 mmol) in anhydrous pyridine (200 mL) over a period of 6 h. The reaction mixture was stirred overnight at room temperature. The solvent was evaporated, and the residue taken up in ethyl acetate (1 L) and 1 M aqueous triethylammonium acetate (100 mL). The organic solution was washed with 1 M aqueous triethylammonium acetate (120 mL), diluted with methanol (100 mL), dried over sodium sulfate, and evaporated. The residue was dissolved in ethyl acetate (250 mL) and treated with ether (750 mL). A colorless amorphous solid, which precipitates was collected, washed with ether, and dried to give pure product as a free acid (27.5 g, 56%). ^{1}H NMR (pyridine-d_5): δ 7.87 (2H, m); 7.72 (2H, m); 7.66 (2H, m); 7.34 (2H, m); 7.25 (1H, m); 6.96 (4H, m); 5.35 (1H, d, $J=1.2$ Hz); 4.39 (1H, d, $J=6.4$ Hz); 4.23 (1H, d, $J=6.4$ Hz); 3.85 (1H, d, $J=1.2$ Hz); 3.68 (3H, s); 3.65 (3H, s); 3.26 (1H, d, $J=9.2$ Hz); 3.05 (1H, d, $J=9.2$ Hz). ^{13}C NMR (100.573 MHz, DMSO-d_6): δ 172.1, 171.9, 158.5, 145.7, 136.7, 136.2, 130.0, 129.9, 129.1, 128.1, 127.9, 127.8, 126.9, 87.4, 83.6, 82.1, 76.3, 74.5, 55.3, 46.8, 46.5. HRESMS: calcd for $C_{29}H_{27}O_9$ (M^-), 519.1655; found, 519.1663.

4.1.3. (1α,2α,3α,4α,5α,6α)-5-Acetoxy-6-(4,4′-dimethoxytrityloxy)-7-oxabicyclo[2.2.1]heptane 2,3-dicarbanhydride (4). Compound **3** (1.57 g, 3.0 mmol) was treated with acetic anhydride (3.0 g) and pyridine (15 mL) for 3 h at room temperature. The mixture was concentrated and co-evaporated with pyridine (5×15 mL) to give the title compound as colorless foam. Due to instability nature of molecule (being an anhydride), further purification was not attempted and was used as such in the next step. ^{1}H NMR (pyridine-d_5): δ 7.73 (2H, m); 7.60–7.55 (overlaps with a solvent peak, m); 7.40 (2H, m); 7.30 (1H, m); 7.00 (4H, m);

5.71 (1H, d, J=6.4 Hz); 5.21 (1H, s); 4.52 (1H, d, J=6.4 Hz); 3.91 (1H, d, J=7.2 Hz); 3.74 (3H, s); 3.73 (3H, s); 3.67 (1H, s); 3.63 (1H, d, J=7.2 Hz); 2.26 (3H, s). ^{13}C NMR (100.573 MHz, DMSO-d_6): δ 176.0, 173.3, 158.5, 145.4, 136.6, 136.2, 130.1, 129.9, 129.1, 128.3, 127.8, 127.8, 126.9, 87.4, 83.6, 82.1, 76.3, 74.5, 55.3, 46.8, 46.5, 20.9. IP-LC–MS: calcd for $C_{30}H_{27}O_9$ (M^-), 531.161; found, 531.204.

4.2. Loading of universal linker molecule (4) to HL30 solid support

Amino-derivatized HL30 primer support (4.0 g, 0.51 mmol) was gently shaken with compound **4** (1.39 g, 2.55 mmol) in pyridine (17 mL) for 4 h. The suspension was filtered, and solid support was washed with pyridine (3×20 mL). The solid support was additionally washed with ethyl acetate, dried, and capped by treating with a mixture of Ac_2O–pyridine–*N*-methylimidazole–THF (10/10/10/70, v/v/v/v) for 3 h at room temperature. Finally, the support was washed with acetonitrile (CH_3CN), ethyl acetate and dried. Loading of **5** (94±0.4 μmol/g) was determined by the standard DMT assay.

4.3. Capping of solid support

The solid support from previous step (1.0 g) was treated with 0.2 M HATU and 0.15 M HOBT in CH_3CN–pyridine (4/1, 6 mL) for 5 min. The liquid phase was removed, and solid support was treated with 0.5 M *n*-propylamine in CH_3CN (5 mL) for 15 min. The solid support was then washed with CH_3CN (5×10 mL) and capped with a mixture of Ac_2O–pyridine–*N*-methylimidazole–THF (10/10/10/70, v/v/v/v) for 8 h at room temperature. Finally, the solid support **5** was washed with CH_3CN (50 mL), ethyl acetate (50 mL) and dried. Loading of **5** (90±0.4 μmol/g) was determined by standard DMT assay.

4.4. Loading of universal linker molecule (4) to PS200 and controlled pore glass solid supports

Loading of universal linker molecule (**4**) to amino-derivatized supports like PS200 and controlled pore glass (CPG) were similar to the above described protocol for HL30 except that reagents were adjusted accordingly to obtain loadings of 200±5 and 45±5 μmol/g, respectively.

4.5. Oligonucleotide synthesis

All syntheses were performed on a Amersham Biosciences OligoPilot II DNA/RNA synthesizer at approximately 160 μmol scale in a 6.33 mL fixed column using β-cyanoethyl phosphoramidite synthons (1.75 equiv, 0.2 M in CH_3CN). 1*H*-Tetrazole (0.45 M in CH_3CN) was used as activator and phenylacetyl disulfide (PADS) (0.2 M in 3-picoline/CH_3CN 1:1, v/v) as sulfur transfer reagent.[31] 3% Dichloroacetic acid in toluene was used for removal of acid-labile dimethoxytrityl group[32,33] Capping reagents were made to the recommended Amersham Biosciences receipe: Cap A: *N*-methylimidazole–CH_3CN (1/4 v/v), Cap B: acetic anhydride–pyridine–CH_3CN (2/3/5, v/v/v). Solid supports loaded with universal linker molecule at recommended loading levels were used. Amidite and tetrazole solutions were prepared using anhydrous CH_3CN (ca. 10 ppm) and were dried further by addition of activated 4 Å molecular sieves (~50 g/L). Details of synthesis cycle are given in Table 6. At the end of each synthesis, the support was thoroughly dried to determine the crude weight yield, treated with a solution of triethylamine–CH_3CN (1/1, v/v) at room temperature for 2 h to remove the β-cyanoethyl protecting groups,[34] then treated with 30% aqueous ammonium hydroxide solution for 12 h at 55 °C to effect release from support and base deprotection. Yield (expressed in mg of oligonucleotide/μmol of support),[35] ^{31}P NMR and analytical RP-HPLC (full length determination) data were collected for each synthesis. The crude material obtained from each synthesis was purified by C_{18} reversed phase HPLC, the final DMT removed and then analyzed by ion-pair liquid chromatography–electrospray mass spectrometry (IP-LC–MS). The final product after lyophilization was obtained as a colorless hygroscopic solid (yield: 0.56–0.62 g).

Table 6. Synthesis parameters of cycle used on pharmacia OligoPilot II synthesizer

Step	Reagent	Volume (mL)	Time (min)
Detritylation	3% Dichloroacetic acid/toluene	72	1.5
Coupling	Phosphoramidite (0.2 M), 1*H*-tetrazole (0.45 m) in acetonitrile	10, 15	5
Sulfurization	PADS (0.2 M) in 3-picoline–CH_3CN (1/1, v/v)	36	3
Capping	Ac_2O/pyridine/CH_3CN, NMI/CH_3CN	24, 24	2

4.6. HPLC analysis and purification of oligonucleotides

Analysis and purification of oligonucleotides by reversed phase high performance liquid chromatography (RP-HPLC) was performed on a Waters Novapak C_{18} column (3.9×300 mm) using a Waters HPLC system (600E System Controller, 996 Photodiode Array Detector, 717 Autosampler). For analysis an acetonitrile (A)/0.1 M triethylammonium acetate gradient was used: 5–35% A from 0 to 10 min, then 35–40% A from 10 to 20 min, then 40–95% A from 20 to 25 min, flow rate=1.0 mL/min/50% A from 8 to 9 min, 9 to 26 min at 50% flow rate=1.0 mL/min, t_R(DMT-off) 10–11 min, t_R(DMT-on) 14–16 min. The DMT-on fraction was collected and was evaporated in vacuum, redissolved in water and the DMT group was removed as described below.

4.7. Dedimethoxytritylation

An aliquot (30 μL) was transferred into an Eppendorff tube (1.5 mL), and acetic acid (50%, 30 μL) was added. After 30 min at room temperature sodium acetate (2.5 M, 20 μL) was added, followed by cold ethanol (1.2 mL). The mixture was vortexed and cooled in dry ice for 20 min. The precipitate was spun down with a centrifuge, the supernatant was discarded and the precipitate was rinsed with ethanol and dried under vacuum.

4.8. MS sample preparation

HPLC-purified and dedimethoxytritylated oligonucleotide was dissolved in 50 μL water, ammonium acetate (10 M,

5 μL) and ethanol were added and vortexed. The mixture was cooled in dry ice for 20 min and after centrifugation the precipitate was isolated. This procedure was repeated two more times to convert the oligonucleotide to the ammonium form.

4.9. IP-HPLC–MS analysis

HPLC with UV and MS detection was performed using an HPLC system consisting of a binary pump, a degasser, a column oven and a variable wavelength UV detector. After passing through the UV detector, the column eluate was introduced directly into a single quadrupole, electrospray mass spectrometer. Samples were separated using a C_{18} column (3 μm, 2×150 mm) and eluted at 0.2 mL/min with a gradient of CH_3CN in 5 mM tributylammonium acetate (TBAA) as the ion-pairing agent.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.040. Supplementary material contains copies of ^{31}P (D_2O) NMR, reversed-phase HPLC and IP-LC–MS analysis of phosphorothioate oligonucleotides (ISIS 3521 and ISIS 113715) made using standard nucleoside succinate loaded support and universal linker loaded support.

References and notes

1. Beaucage, S. L.; Iyer, R. P. *Tetrahedron* **1992**, *48*, 2223–2311.
2. Beaucage, S. L.; Iyer, R. P. *Tetrahedron* **1993**, *49*, 1925–1963.
3. Beaucage, S. L. In *Oligonucleotide Synthesis In Comprehensive Natural Product Chemistry*; Barton, D. H. R., Nakanishi, K., Kool, E. T., Eds.; DNA and Aspects of Molecular Biology; Pergamon, 1999; p 105.
4. Cheruvallath, Z. S.; Wheeler, P. D.; Cole, D. L.; Ravikumar, V. T. *Nucleosides Nucleotides* **1999**, *18*, 485–492.
5. Cheruvallath, Z. S.; Carty, R. L.; Moore, M. N.; Capaldi, D. C.; Krotz, A. H.; Wheeler, P. D.; Turney, B. J.; Craig, S. R.; Gaus, H. J.; Scozzari, A. N.; Cole, D. L.; Ravikumar, V. T. *Org. Proc. Res. Dev.* **2000**, *4*, 199–204.
6. Iyer, R. P.; Egan, W.; Regan, J. B.; Beaucage, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 1253–1254.
7. Iyer, R. P.; Phillips, L. R.; Egan, W.; Regan, J. B.; Beaucage, S. L. *J. Org. Chem.* **1990**, *55*, 4693–4699.
8. Altmann, K.-H.; Dean, N. M.; Fabbro, D.; Freier, S. M.; Geiger, T.; Haner, R.; Husken, D.; Martin, P.; Monia, B. P.; Muller, M.; Natt, F.; Nicklin, P.; Phillips, J.; Pieles, U.; Sasmor, H.; Moser, H. E. *Chimia* **1996**, *50*, 168–176.
9. A number of second-generation phosphorothioate oligonucleotides are in various stages of pre-clinical and clinical trials against APOB-100, PTP-1B, VLA4, TRPM2, survivin, STAT-3. eIF-4E, etc. for the treatment of a variety of diseases such as cancer, psoriasis, diabetes, asthma, arthritis, multiple sclerosis, etc.
10. Gough, G. R.; Brunden, M. J.; Gilham, P. T. *Tetrahedron Lett.* **1983**, *24*, 5321–5324.
11. deBear, J. S.; Hayes, J. A.; Koleck, M. P.; Gough, G. R. *Nucleosides Nucleotides* **1987**, *6*, 821–830.
12. Schwartz, M. E.; Breaker, R. R.; Asteriadis, G. T.; Gough, G. R. *Tetrahedron Lett.* **1995**, *36*, 27–30.
13. Lyttle, M. H.; Hudson, D.; Cook, R. M. *Nucleic Acids Res.* **1996**, *24*, 2793–2798.
14. Lyttle, M. H.; Dick, D. J.; Hudson, D.; Cook, R. M. *Nucleosides Nucleotides* **1999**, *18*, 1809–1824.
15. Scheuer-Larsen, C.; Rosenbohm, C.; Joergensen, T. J. D.; Wengel, J. *Nucleosides Nucleotides* **1997**, *16*, 67–80.
16. Kumar, P.; Gupta, K. C. *Nucleic Acids Res.* **1999**, *27*, e2.
17. Nelson, P. S.; Muthini, S.; Vierra, M.; Acosta, L.; Smith, T. H. *Biotechniques* **1997**, *22*, 752–756.
18. Kumar, P.; Mahajan, S.; Gupta, K. C. *J. Org. Chem.* **2004**, *69*, 6482–6485.
19. Kumar, P.; Gupta, K. C. *React. Funct. Polym.* **1999**, *41*, 197–204.
20. Azhayev, A. V. *Tetrahedron* **1999**, *55*, 787–800.
21. Kumar, P.; Gupta, K. C. *Helv. Chim. Acta.* **2003**, *86*, 59–64.
22. Kumar, P.; Dhawan, R.; Chandra, R.; Gupta, K. C. *Nucleic Acids Res.* **2002**, *30*, e130.
23. Scheuer-Larson, C.; Rosenbohm, C.; Jorgensen, T. J. D.; Wengel, J. *Nucleosides Nucleotides* **1997**, *16*, 67–80.
24. Nelson, P. S.; Muthini, S.; Kent, M. A.; Smith, T. H. *Nucleosides Nucleotides* **1997**, *16*, 1951–1959.
25. Azhayev, A. V.; Antopolsky, M. L. *Tetrahedron* **2001**, *57*, 4977–4986.
26. Zheng, X.; Gaffney, B. L.; Jones, R. A. *Nucleic Acids Res.* **1997**, *25*, 3980–3983.
27. Guzaev, A. P.; Manoharan, M. *J. Am. Chem. Soc.* **2003**, *125*, 2380–2381.
28. Ravikumar, V. T.; Kumar, R. K.; Capaldi, D. C.; Turney, B.; Rentel, C.; Cole, D. L. *Org. Proc. Res. Dev.* **2003**, *7*, 259–266.
29. Kurata, C.; Bradley, K.; Gaus, H.; Luu, N.; Cedillo, I.; Ravikumar, V. T.; Van Sooy, K.; McArdle, J. V.; Capaldi, D. C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 607–614.
30. Daniels, R.; Fischer, J. L. *J. Org. Chem.* **1963**, *28*, 320–322.
31. Krotz, A. H.; Gorman, D.; Mataruse, P.; Foster, C.; Godbout, J. D.; Coffin, C. C.; Scozzari, A. N. *Org. Proc. Res. Dev.* **2004**, *8*, 852–858.
32. Krotz, A. H.; Cole, D. L.; Ravikumar, V. T. *Bioorg. Med. Chem.* **1999**, *7*, 435–439.
33. Krotz, A. H.; Carty, R. L.; Moore, M. N.; Scozzari, A. N.; Cole, D. L.; Ravikumar, V. T. *Green Chem.* **1999**, 277–281.
34. Capaldi, D. C.; Gaus, H.; Krotz, A. H.; Arnold, J.; Carty, R. L.; Moore, M. N.; Scozzari, A. N.; Lowery, K.; Cole, D. L.; Ravikumar, V. T. *Org. Proc. Res. Dev.* **2003**, *7*, 832–838.
35. Experience has taught us that yields expressed in terms of weight/μmol of support are more reliable than those expressed in terms of optical density/μmol.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 4535–4539

Enzymatic enantioselective reduction of α-ketoesters by a thermostable 7α-hydroxysteroid dehydrogenase from *Bacteroides fragilis*

Dunming Zhu, Jennifer Elisabeth Stearns, Monica Ramirez and Ling Hua*

Department of Chemistry, Southern Methodist University, Dallas, TX 75275, USA

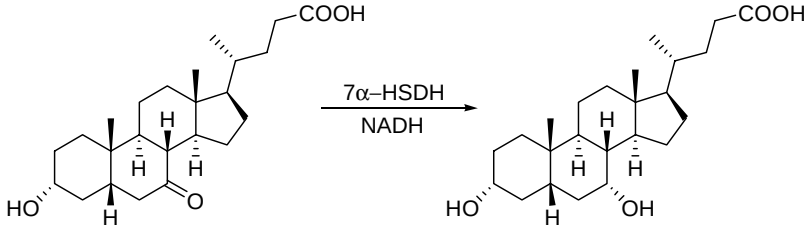
Received 28 December 2005; revised 10 February 2006; accepted 15 February 2006

Available online 10 March 2006

Abstract—A thermostable 7α-hydroxysteroid dehydrogenase (7-HSDH) from *Bacteroides fragilis* ATCC 25285 was cloned and over-expressed in *E. coli*, and its substrate specificity and stereoselectivity toward reduction of various ketones were examined. This alcohol dehydrogenase was active toward a series of aromatic and bulky aliphatic α-ketoesters. The substituents at the phenyl ring of aromatic α-ketoesters greatly affected the activity, but their effects on enantioselectivity were minimal. The synthetic application of this enzyme was then demonstrated through the preparation of a few α-hydroxy carboxylic acid esters of pharmaceutical interest.

1. Introduction

Optically pure α-hydroxy carboxylic acids and their derivatives are important intermediates in the synthesis of pharmaceuticals and other fine chemicals. Many approaches have been developed to obtain enantiomerically-enriched α-hydroxy carboxylic acid esters.[1] This includes (dynamic) kinetic resolution of racemic α-hydroxy esters,[2,3] hydrolysis of optically pure cyanohydrin, which in turn can be obtained via several asymmetric synthetic methods.[4–6] Another straightforward method to enantiomerically pure α-hydroxy carboxylic acid esters is the asymmetrical reduction of prochiral α-ketoesters that could be performed either chemically[7–10] or enzymatically.[1,11–13] Because of environmentally benign reaction conditions and unparallel selectivity, biocatalytic reduction has attracted more and more attention from both academia and industry. Recently, great efforts have been made to develop enzyme catalysts for the enantioselective reduction of ketones and varied levels of success have been achieved.[14–16] However, most research has been focused on the enantioselective reduction of aryl ketones and β-ketoesters.[17–20] Studies on enzymatic reduction of α-ketoesters have been only scarcely reported.[14,21,22] Especially biocatalytic reduction of aromatic α-ketoesters has been very limited and much less successful than that of their small counterparts.[23] Hydroxysteroid dehydrogenases normally reduce 3,7,12-oxo group of sterically bulky steroids in vivo.[24] These dehydrogenases belong to short-chain dehydrogenase family and their synthetic application has been largely unexplored.[25] Recently, a thermostable 7α-hydroxysteroid dehydrogenase from *Bacteroides fragilis* ATCC 25285 has been cloned,[26] and it reduces sterically demanding native substrate 7-keto-lithocholic acid to cheno-deoxycholic acid in gastrointestinal tract (Scheme 1).



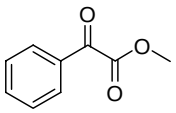
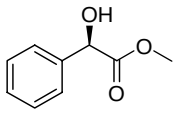
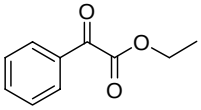
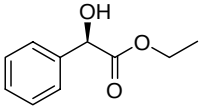
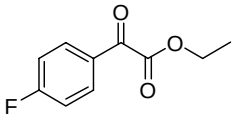
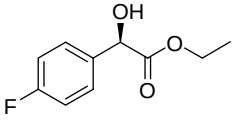
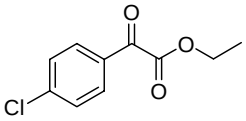
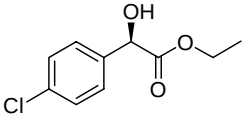
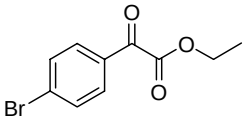
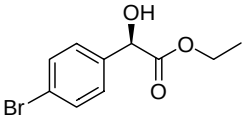
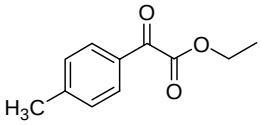
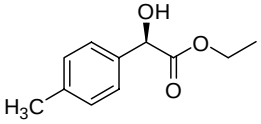
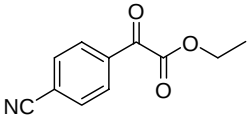
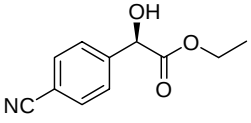
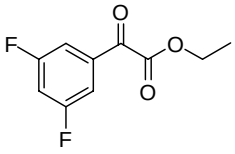
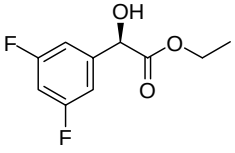
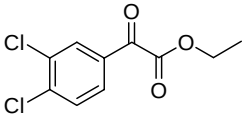
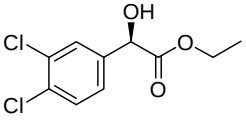
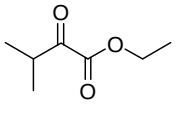
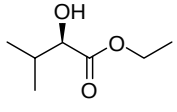
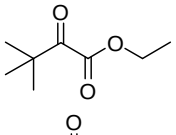
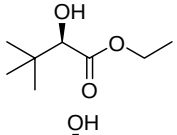
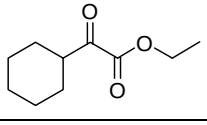
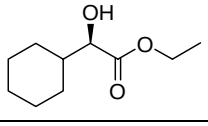
Scheme 1.

Keywords: α-Ketoesters; Dehydrogenase; Enzyme.
* Corresponding author. Tel.: +1 214 768 1609; fax: +1 214 768 4089; e-mail: lhua@smu.edu

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.041

We reasoned that this enzyme might be useful in the reduction of bulky ketones such as aromatic α-ketoesters. Therefore, we have cloned and over-expressed this 7α-hydroxysteroid dehydrogease in *E. coli* and examined its substrate specificity and stereoselectivity toward reduction of various ketones including aromatic and aliphatic α-ketoesters. This NADH-dependent alcohol dehydrogenase was found to be active toward a series of

Table 1. The activity and enantioselectivity of 7α-hydroxysteroid dehydrogenase toward various α-ketoesters

Entry	α-Ketoester	Relative activity[a]	Product[b]	ee (%)[c]
1		100		98
2		354		>99
3		421		95
4		209		99
5		163		99
6		85		99
7		788		99
8		364		98
9		172		99
10		22		97
11		63		>99
12		823		>99

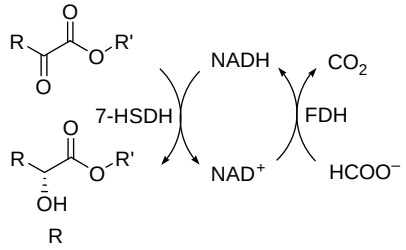
[a] The relative activity for methyl benzoylformate was defined as 100.
[b] The absolute configuration was determined by comparison with authentic standards, or the reported optical rotation.
[c] The ee value was determined by chiral HPLC or GC analysis.

aromatic α-ketoesters and aliphatic α-ketoester with bulky groups such as *tert*-butyl and cyclohexyl groups. The substituents at the phenyl ring of aromatic α-ketoesters greatly affected the enzyme activity, but exerted less effect on enantioselectivity of the reduction. This enzyme was then applied to the synthesis of a few pharmaceutical important α-hydroxy carboxylic acid esters.

2. Results and discussion

The 7α-hydroxysteroid dehydrogenase gene from *B. fragilis* ATCC 25285 was cloned and expressed in *E. coli* and the recombinant enzyme was purified sequentially by heat treatment, PEI treatment and fractional ammonium sulfate precipitation of cell-free extract (see Section 4). The obtained 7α-hydroxysteroid dehydrogenase was assayed for activity toward various ketones by spectrophotometrically measuring the oxidation of NADH at 340 nm at room temperature. The results are presented in Table 1. Surprisingly, while this dehydrogenase showed almost no activity toward a series of acetophenone derivatives and β-ketoesters (data not shown), it was very active for the reduction of aromatic and bulky aliphatic α-ketoesters using NADH as co-factor. This suggested that a carboxylic group adjacent to the carbonyl group might be necessary for being the substrate of 7α-hydroxysteroid dehydrogenase from *B. fragilis* ATCC 25285. From Table 1 it can be seen that the substituent at *para*-position of phenyl ring of aromatic α-ketoesters greatly affected the activity. For example, the fluoro- and cyano-group at *para*-position showed higher activity than ethyl benzoylformate, while chloro-, bromo- and methyl-substituents decreased the activity. The ester group also exerted some effects on the enzyme activity with ethyl ester being more active than methyl counterpart. Among the tested aliphatic α-ketoesters, ethyl 2-cyclohexyl-2-oxoacetate showed highest activity. Interestingly, this alcohol dehydrogenase was more active for the reduction of ethyl 3,3-dimethyl-2-oxo-butyrate than that of less bulky ethyl 3-methyl-2-oxo-butyrate, and showed almost no activity for the reduction of ethyl pyruvate (data not shown). Thus 7α-hydroxysteroid dehydrogenase from *B. fragilis* ATCC 25285 took more sterically demanding carbonyl compounds as substrates. This is probably due to the spacious active site cavity for its native substrate 7-ketolithocholic acid. The steric crowdness of the bulky non-native substrates might fit better to the enzyme's active site for the hydride transfer from NADH to the carbonyl group of substrates, while the less bulky substrates failed to accomplish this hydride transfer.

The enantioselectivity for reduction of various aromatic and aliphatic α-ketoesters catalyzed by 7α-hydroxysteroid dehydrogenase from *B. fragilis* was evaluated using NADH as co-factor, which was regenerated with a recycling system comprising formate dehydrogenase and sodium formate (Scheme 2). The results are summarized in Table 1. From the results it can be seen that both aromatic and aliphatic α-ketoesters were reduced to the (*R*)-enantiomer of the corresponding α-hydroxy carboxylic acid esters in high enantioselectivity with up to >99% ee. The substituent on phenyl ring of aromatic α-ketoesters had minimal effect on the enzyme enantioselectivity.



Scheme 2. Reduction of α-ketoesters catalyzed by 7α-hydroxysteroid dehydrogenase from *B. fragilis*.

Many of the α-hydroxy carboxylic acid esters listed in Table 1 are important intermediates in the synthesis of many pharmaceuticals. For example, optically active 2-hydroxy-3-methylbutyrate is an important chiral synthon in the preparation of a potent, selective and cell-penetrable inhibitor of caspase 3.[27] (*R*)-2-Hydroxy-3,3-dimethylbutyrate is a key component P3 of thrombin inhibitor identified by Merck.[28] Optically pure 3,5-difluoromandelate has recently been used to synthesize amino alcohol dipeptides designed to inhibit β-amyloid peptide (Aβ) formation, which is related to Azheimer's desease.[29,30] The results in Table 1 showed that 7α-hydroxysteroid dehydrogenase from *B. fragilis* ATCC 25285 had synthetic potential for the preparation of these α-hydroxyesters in optically pure form. Therefore, the reductions of ethyl 3-methyl-2-oxobutyrate, ethyl 3,3-dimethyl-2-oxobutyrate and ethyl (3,5-diflurophenyl)-glyoxylate were performed in 1 mmol scale. Ethyl (*R*)-2-hydroxy-3-methylbutyrate, ethyl (*R*)-2-hydroxy-3,3-dimethylbutyrate and ethyl (*R*)-2-hydroxy-2-(3,5-diflurophenyl)acetate were indeed obtained in isolated yields of 85–94%. The enantiomeric purities of the product α-hydroxyesters were from 97 up to >99%.

3. Conclusion

A thermostable recombinant 7α-hydroxysteroid dehydrogenase from *B. fragilis* ATCC 25285 was produced by overexpression of the 7-HSDH gene in *E. coli*. This alcohol dehydrogenase catalyzed the reduction of aromatic and sterically demanding aliphatic α-ketoesters to the corresponding α-hydroxyesters in essentially optically pure form. The synthetic application of 7α-hydroxysteroid dehydrogenase was then demonstrated by the preparation of ethyl (*R*)-2-hydroxy-3-methylbutyrate, ethyl (*R*)-2-hydroxy-3,3-dimethylbutyrate and ethyl (*R*)-2-hydroxy-2-(3,5-diflurophenyl)acetate.

4. Experimental

The chiral HPLC analysis was performed on an Agilent 1100 series high-performance liquid chromatography system with (*S*,*S*)-Whelk-O 1 column (25 cm×4.6 mm, Regis Technologies Inc.). The chiral GC analysis was performed on a Hewlett Packard 5890 series II plus gas chromatograph equipped with autosampler, EPC, split/splitless injector, FID detector and CP-Chirasil-Dex CB chiral capillary column (25 m×0.25 mm) (Table 2). The 7α-hydroxysteroid dehydrogenase activities toward the reduction of α-ketoesters (Table 1) were assayed using

Table 2. Details of chiral HPLC and GC analysis

α-Hydroxyester	Method[a]	Retention time (min)	
		t_R	t_S
Methyl 2-hydroxy-2-phenylacetate	A	10.2	11.0
Ethyl 2-hydroxy-2-phenylacetate	A	9.8	10.7
Ethyl 2-hydroxy-2-(4-fluorophenyl)acetate	A	8.4	8.9
Ethyl 2-hydroxy-2-(4-chlorophenyl)acetate	A	8.9	9.5
Ethyl 2-hydroxy-2-(4-bromophenyl)acetate	A	9.4	10.0
Ethyl 2-hydroxy-2-(4-methylphenyl)acetate	A	11.6	12.3
Ethyl 2-hydroxy-2-(4-cyanophenyl)acetate	A	21.6	22.6
Ethyl 2-hydroxy-2-(3,5-diflurophenyl)acetate	B	9.2	9.7
Ethyl 2-hydroxy-2-(3,4-dichlorophenyl)acetate	A	8.8	9.6
Ethyl 2-hydroxy-3-methylbutyrate	C	22.0	22.3
Ethyl 2-hydroxy-3,3-dimethylbutyrate	D	11.2	11.8
Ethyl 2-hydroxy-2-cyclohexylacetate	E	15.6	15.9

[a] (A) HPLC, flow rate 1.0 ml/min, hexane/isopropanol (0.1% HOAc)=95:5; (B) HPLC, flow rate 1.0 ml/min, hexane/isopropanol (0.1% HOAc)=99:1; (C) GC, 60 °C for 2 min, 1 °C/min to 90 °C, 90 °C for 5 min; (D) GC, 80 °C for 2 min, 1 °C/min to 110 °C, 110 °C for 5 min; (E) GC, 90 °C for 2 min, 1 °C/min to 120 °C, 120 °C for 5 min, α-hydroxyl group was acylated as trifluoroacetate.

SpectraMax M2 microplate reader (Molecular Devices). Methyl phenylglyoxylate, ethyl phenylglyoxylate, ethyl (4-cyanophenyl)glyoxylate, ethyl (3,4-dichlorophenyl)glyoxylate, ethyl (3,5-difluorophenyl)glyoxylate, and ethyl 3-methyl-2-oxobutyrate were purchased from Aldrich or Acros. All the other α-ketoesters were prepared by Friedel–Crafts acylation of substituted benzene with ethyl oxalyl chloride in the presence of anhydrous $AlCl_3$,[31] or reaction of diethyl oxalate with the corresponding Grignard reagents.[10] The racemic α-hydroxyester standards were prepared by reduction of α-ketoesters with sodium borohydride. Methyl and ethyl (*S*)-mandelate were purchased from Aldrich. (*R*) or (*S*) enantiomers of other α-hydroxyesters were prepared by following the literature methods.[28,32,33]

4.1. Gene expression and purification of 7α-hydroxysteroid dehydrogenase

Plasmid pBPC-1 (from James P. Coleman) containing 7-HSDH gene from *B. fragilis* ATCC 25285 was used as template for PCR amplification. The PCR fragment was cloned into pTXB1 expression vector at the *Nde* I and *Bam*H I sites to give JS2.2 and the cloned 7-HSDH gene was confirmed by DNA sequencing. The plasmid JS2.2 was transformed into Rosetta2(DE3)pLysS for expression. Overnight culture (20 ml) was diluted into 1 l of LB media containing 100 μg/ml of ampicillin and 34 μg/ml of chloramphenicol and propagated until OD_{595} reached 0.6–1.0 at 37 °C. The cells were then induced with 0.1 mM of IPTG and continuing grown at 30 °C for 5 h. The cells were harvested and lysed in 10 mM of potassium phosphate (pH 7.0) by homogenizer. The cell-free extract was heat-treated in a water-bath for 30 min at 55–60 °C and centrifuged at 20,000*g* for 30 min. The heat-treated lysate was then mixed with equal volume of PEI solution (0.25% polyethyleneimine MW 40–60 K, 6% NaCl, 100 mM Borax, pH 7.4) to remove lipids.[34] The PEI-treated supernatant was precipitated with 45% ammonium sulfate. The resulting precipitate was collected after centrifugation and dissolved in potassium phosphate buffer (10 mM, pH 7.0). The lysate was dialysed by gel filtration into potassium phosphate buffer (10 mM, pH 7.0), and then lyophilized as powder.

4.2. Activity assay of 7α-hydroxysteroid dehydrogenase

The activity of 7α-hydroxysteroid dehydrogenase toward the reduction of α-ketoesters (Table 1) was determined by spectrophotometrically measuring the oxidation of NADH at 340 nm ($\varepsilon=6.22\ mM^{-1}\ cm^{-1}$) in the presence of excess α-ketoesters. The activity was measured at room temperature in 96-well plate, in which each well contained α-ketoester (6.25 mM), NADH (0.25 mM) in potassium phosphate buffer (100 mM, pH 7.0, 190 μl). The reaction was initiated by the addition of 7α-hydroxysteroid dehydrogenase (10 μl solution containing 18 μg of enzyme). The specific activity was defined as the number of micromolar of NADH converted in 1 min by 1 mg of enzyme ($\mu mol\ min^{-1}\ mg^{-1}$). The specific activity for methyl benzoylformate was 0.32 $\mu mol\ min^{-1}\ mg^{-1}$ and its relative activity was defined as 100.

4.3. Enantioselectivity of reduction of α-ketoesters catalyzed by 7α-hydroxysteroid dehydrogenase

The enantioselectivity of the enzymatic reduction of α-ketoesters was studied using an NADH recycle system. The general procedure was as follows: sodium formate (3.4 mg), formate dehydrogenase (0.4 mg), NADH (0.4 mg), 7α-hydroxysteroid dehydrogenase (0.2 mg) and α-ketoester solution in DMSO (50 μl, 0.25 M) were mixed in a potassium phosphate buffer (1 ml, 100 mM, pH 7.0) and the mixture was shaken overnight at room temperature. The mixture was extracted with methyl *tert*-butyl ether (1 ml). The organic extract was dried over anhydrous sodium sulfate and was subjected to chiral HPLC or GC analysis to determine the enantiomeric excess. The absolute configuration of product α-hydroxyesters was identified by comparing the chiral HPLC or GC data with the standard samples, or by comparing the optical rotation of the product alcohols with the literature data.

4.4. Preparation of ethyl (*R*)-2-hydroxy-3-methylbutyrate, ethyl (*R*)-2-hydroxy-3,3-dimethylbutyrate, and ethyl (*R*)-2-hydroxy-2-(3,5-difluorophenyl)acetate

Sodium formate (4 mmol), formate dehydrogenase (40 mg), NADH (10 mg), 7α-hydroxysteroid dehydrogenase (10 mg) and ethyl 3-dimethyl-2-oxo-butyrate (1 mmol) were mixed in a potassium phosphate buffer (50 ml, 100 mM, pH 7.0) and the mixture was stirred at room temperature. After 24 h, GC analysis indicated that reduction was complete. The reaction mixture was extracted with ethyl ether (30 ml×2). The organic extract was dried over anhydrous Na_2SO_4 and removal of the solvent gave ethyl (*R*)-2-hydroxy-3-methylbutyrate as clear oil (124 mg, 85% yield). ^1H and ^{13}C NMR ($CDCl_3$) were in accordance with literature data.[35] $[\alpha]_D^{22}$ −9.4 (*c* 1.0, $CHCl_3$); lit.[35] $[\alpha]_D^{25}$ −10.5 (*c* 0.5, $CHCl_3$).

Similar procedures were followed for the preparation of other two α-hydroxyesters. Ethyl (*R*)-2-hydroxy-3,3-dimethylbutyrate (145 mg, 91% yield). ^1H and ^{13}C NMR ($CDCl_3$) were in accordance with literature data.[28] $[\alpha]_D^{22}$

−31.3 (*c* 1.0, $CHCl_3$); lit.[36] $[\alpha]_D^{22}$ +27.7 (*c* 3.4, $CHCl_3$) for (*S*)-enantiomer. Ethyl (*R*)-2-hydroxy-2-(3,5-difluorophenyl)acetate (203 mg, 94% yield). ^1H NMR (400 MHz, $CDCl_3$) δ ppm 1.27 (t, 3H, J=7.2 Hz), 3.58 (s, 1H), 4.21–4.34 (m, 2H), 5.15 (s, 1H), 6.78 (m, 1H), 7.03 (m, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ ppm 14.4, 63.2, 72.2, 104.1 (t, $^2J_{C-F}$=25 Hz), 109.8 (d, $^2J_{C-F}$=19 Hz), 109.9 (d, $^2J_{C-F}$=19 Hz), 142.5, 163.3 (d, $^1J_{C-F}$=247 Hz), 163.4 (d, $^1J_{C-F}$=247 Hz), 173.0. $[\alpha]_D^{22}$ −81.2 (*c* 1.0, $CHCl_3$).

Acknowledgements

We thank Professor James P. Coleman at East Carolina University for providing us the plasmid of 7α-hydroxysteroid dehydrogenase from *B. fragilis* ATCC 25285, and Southern Methodist University for start-up support.

References and notes

1. Groger, H. *Adv. Synth. Catal.* **2001**, *343*, 547–558.
2. Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2002**, *124*, 2870–2871.
3. Radosevich, A. T.; Musich, C.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 1090–1091.
4. Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8106–8107.
5. Glieder, A.; Weis, R.; Skranc, W.; Poechlauer, P.; Dreveny, I.; Majer, S.; Wubbolts, M.; Schwab, H.; Gruber, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 4815–4818.
6. Casas, J.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Org. Lett.* **2002**, *4*, 2589–2592.
7. Ramachandran, P. V.; Pitre, S.; Brown, H. C. *J. Org. Chem.* **2002**, *67*, 5315–5319.
8. Liu, P.-N.; Gu, P.-M.; Deng, J.-G.; Tu, Y.-Q.; Ma, Y.-P. *Eur. J. Org. Chem.* **2005**, 3221–3227.
9. Szori, K.; Sutyinszki, M.; Felfoldi, K.; Bartok, M. *Appl. Catal. A: Gen.* **2002**, *237*, 275–280.
10. Carpentier, J.-F.; Mortreux, A. *Tetrahedron: Asymmetry* **1997**, *8*, 1083–1099.
11. Milagre, H. M. S.; Milagre, C. D. F.; Moran, P. J. S.; Santana, M. H. A.; Rodrigues, J. A. R. *Enzyme Microb. Technol.* **2005**, *37*, 121–125.
12. Ishihara, K.; Nakajima, N.; Yamaguchi, H.; Hamada, H.; Uchimura, Y. S. *J. Mol. Catal. B: Enzym.* **2001**, *15*, 101–104.
13. Ishihara, K.; Yamaguchi, H.; Hamada, H.; Nakajima, N.; Nakamura, K. *J. Mol. Catal. B: Enzym.* **2000**, *10*, 429–434.
14. Kaluzna, I. A.; Matsuda, T.; Sewell, A. K.; Stewart, J. D. *J. Am. Chem. Soc.* **2004**, *126*, 12827–12832.
15. Nakamura, K.; Yamanaka, R.; Matsuda, T.; Harada, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2659–2681.
16. Patel, R. N. *Curr. Opin. Biotechnol.* **2001**, *12*, 587–604.
17. Zhu, D.; Mukherjee, C.; Hua, L. *Tetrahedron: Asymmetry* **2005**, *16*, 3275–3278.
18. Zhu, D.; Rios, B. E.; Rozzell, J. D.; Hua, L. *Tetrahedron: Asymmetry* **2005**, *16*, 1541–1546.
19. Kaluzna, I. A.; Feske, B. D.; Wittayanan, W.; Ghiviriga, I.; Stewart, J. D. *J. Org. Chem.* **2005**, *70*, 342–345.
20. Zhu, D.; Mukherjee, C.; Rozzell, J. D.; Kambourakis, S.; Hua, L. *Tetrahedron* **2006**, *62*, 901–905.
21. Ishihara, K.; Yamaguchi, H.; Omori, T.; Uemura, T.; Nakajima, N.; Esaki, N. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 2120–2127.
22. Yamaguchi, H.; Nakajima, N.; Ishihara, K. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 588–597.
23. Ishihara, K.; Yamaguchi, H.; Nakajima, N. *J. Mol. Catal. B: Enzym.* **2003**, *23*, 171–189.
24. Tanaka, N.; Nonaka, T.; Nakamura, K. T.; Hara, A. *Curr. Org. Chem.* **2001**, *5*, 89–111.
25. Bianchini, E.; Chinaglia, N.; Dean, M.; Giovannini, P. P.; Medici, A.; Pedrini, P.; Poli, S. *Tetrahedron* **1999**, *55*, 1391–1398.
26. Bennett, M. J.; McKnight, S. L.; Coleman, J. P. *Curr. Microbiol.* **2003**, *47*, 475–484.
27. Mellon, C.; Aspiotis, R.; Black, C. W.; Bayly, C. I.; Grimm, E. L.; Giroux, A.; Han, Y.; Isabel, E.; McKay, D. J.; Nicholson, D. W.; Rasper, D. M.; Roy, S.; Tam, J.; Thornberry, N. A.; Vaillancourt, J. P.; Xanthoudakis, S.; Zamboni, R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3886–3890.
28. Nelson, T. D.; LeBlond, C. R.; Frantz, D. E.; Matty, L.; Mitten, J. V.; Weaver, D. G.; Moore, J. C.; Kim, J. M.; Boyd, R.; Kim, P.-Y.; Gbewonyo, K.; Brower, M.; Sturr, M.; McLaughlin, K.; McMasters, D. R.; Kress, M. H.; McNamara, J. M.; Dolling, U. H. *J. Org. Chem.* **2004**, *69*, 3620–3627.
29. Prasad, C. V. C.; Vig, S.; Smith, D. W.; Gao, Q.; Polson, C. T.; Corsa, J. A.; Guss, V. L.; Loo, A.; Barten, D. M.; Zheng, M.; Felsenstein, K. M.; Roberts, S. B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3535–3538.
30. Garofalo, A. W.; Wone, D. W. G.; Phuc, A.; Audia, J. E.; Bales, C. A.; Dovey, H. F.; Dressen, D. B.; Folmer, B.; Goldbach, E. G.; Guinn, A. C.; Latimer, L. H.; Mabry, T. E.; Nissen, J. S.; Pleiss, M. A.; Sohn, S.; Thorsett, E. D.; Tung, J. S.; Wu, J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3051–3053.
31. Hu, S.; Neckers, D. C. *J. Org. Chem.* **1996**, *61*, 6407–6415.
32. Miyazawa, T.; Kurita, S.; Ueji, S.; Yamada, T. *Biocatal. Biotransform.* **2000**, *17*, 459–473.
33. Tsuboi, S.; Nishiyama, E.; Furutani, H.; Utaka, M.; Takeda, A. *J. Org. Chem.* **1987**, *52*, 1359–1362.
34. Milburn, P.; Bonnerjea, J.; Hoare, M.; Dunnill, P. *Enzyme Microb. Technol.* **1990**, *12*, 527–532.
35. Inoue, K.; Makino, Y.; Itoh, N. *Tetrahedron: Asymmetry* **2005**, *16*, 2539–2549.
36. Brown, H. C.; Cho, B. T.; Park, W. S. *J. Org. Chem.* **1988**, *53*, 1231–1238.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 4540–4548
Tetrahedron

Synthesis of β-hydroxy sulfones via opening of hydrophilic epoxides with zinc sulfinates in aqueous media

Nataliya Chumachenko* and Paul Sampson*

Department of Chemistry, Kent State University, Kent, OH 44242, USA

Received 24 December 2005; revised 13 February 2006; accepted 15 February 2006

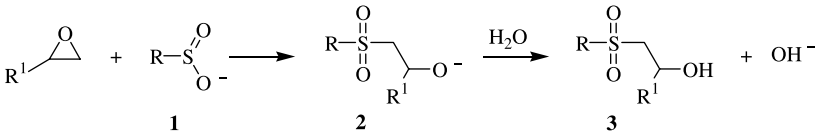
Abstract—Reaction of hydrophilic epoxides (ethylene oxide and propylene oxide) with readily accessible zinc sulfinates in aqueous solution under essentially neutral conditions afforded β-hydroxy sulfones in good yields. This method avoids the need for organic solvents and produces ZnO as the only major reaction byproduct. 2-(Methylsulfonyl)ethanol, a common reagent for the protection of various functional groups, was obtained by this methodology from ethylene oxide in 78% yield. Reaction of various simple zinc alkane- and benzenesulfinates with propylene oxide proceeded regioselectively in 63–67% yield. The corresponding opening of these epoxides with zinc 1,3-butadiene-1-sulfinate afforded 1-butadienyl β-hydroxyalkyl sulfones in 30% yield. Mechanistic studies revealed that the yields of these products were limited by their consumption in competing intra- and intermolecular Michael addition processes.

1. Introduction

S-Alkylation of sulfinate anions with alkyl halides is an established method for the synthesis of aliphatic sulfones.[1–7] However, the preparation of β-hydroxy sulfones by opening epoxides with sulfinate ions has been much less thoroughly investigated. There are two specific problems inherent to this transformation: (i) the low solubility of sulfinate salts in organic solvents necessitates the use of water as a cosolvent; (ii) the generation of a basic alkoxide adduct (**2**) leads to a progressive increase in the basicity of the reaction medium (Scheme 1). This, in turn, promotes side reactions involving the starting epoxide. In addition, the newly formed β-hydroxy sulfone product **3**, if hydrophilic, is prone to decomposition in strongly basic aqueous medium.

In an early report, direct opening of two simple symmetrical epoxides by sodium *p*-toluenesulfinate in aqueous alcohol was reported to proceed in 50–55% yield,[8] however, we were unable to reproduce these results. The necessity of adjusting pH during the reaction was recognized, yet, even with careful portionwise addition of acid to the reaction mixture while opening simple monosubstituted epoxides, the isolated yields of β-hydroxy sulfone products were low (25–40%).[9] Lewis acid catalysis with magnesium nitrate was used[10] to open propylene oxide with simple sodium arenesulfinates. However, good yields (64–83%) of products were observed only if propylene oxide was used as the solvent. Lower yields (23–42%) were noted when stoichiometric amounts of longer chain 1,2-epoxyalkanes were employed, and these reactions failed completely when using other epoxides or when employing sulfinates bearing an electron-withdrawing arene substituent.

More recently, the use of two-phase reaction systems in the presence of tetra-*n*-butylammonium chloride or bromide,[7] montmorillonite clay,[11] or polyethylene glycol 4000[12] have been exploited. Under all these protocols the aqueous phase

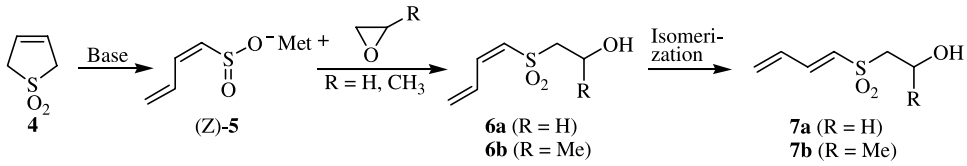


1 **2** **3**

Scheme 1.

Keywords: Zinc sulfinate; β-Hydroxy sulfone; Epoxide; Butadiene sulfone; Butadienyl sulfones.
* Corresponding authors. Tel.: +1 330 672 0034; fax: +1 330 672 3816 (P.S.); e-mail: psampson@kent.edu

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.043



Scheme 2.

still became strongly basic during the reaction; however, the decomposition of unreacted epoxide and β-hydroxy sulfone product was prevented by their partitioning into the organic phase. These protocols frequently provided good yields of β-hydroxy sulfone products but only when hydrophobic epoxides (such as cyclohexene oxide) were used. To the best of our knowledge, besides sodium arenesulfinates, only polyfluoroalkanesulfinate anions have been employed to date in epoxide ring opening reactions.[13,14]

As part of a study aimed at the development of new sulfonyl tethers for intramolecular Diels–Alder cycloaddition reactions,[15] we needed to synthesize several 1-(*E*)-butadienyl β-hydroxyalkyl sulfones (**7**). An epoxide opening reaction with butadiene-1-sulfinate anion (*Z*)-**5**, readily accessible via treatment of commercially available and inexpensive 2,5-dihydrothiophene-1,1-dioxide (butadiene sulfone, **4**) with base[1–3,16–18] seemed an attractive entry to this type of compounds (Scheme 2). S-Alkylation of both (*Z*)-1,3-butadiene-1-sulfinate ((*Z*)-**5**) and (*Z*)-2-methyl-1,3-butadiene-1-sulfinate anions has been reported,[1–5,19] however, to best of our knowledge, epoxide opening reactions with alkene-1-sulfinate salts have not been explored. Our need to use hydrophilic epoxides and the anticipation that both **6** and **7** would be quite water-soluble and would prove unstable under strongly basic conditions, made problematic the use of the previously developed two-phase systems described above. Thus, designing a reliable method for opening epoxides (including hydrophilic epoxides) with various sulfinate salts under essentially neutral reaction conditions became necessary.

In the present paper, we report that zinc sulfinates are, indeed, effective nucleophiles for the ring opening of ethylene oxide and propylene oxide under essentially neutral conditions in a simple one-phase aqueous reaction, providing an attractive new entry to the synthesis of base-sensitive β-hydroxy sulfones and β-hydroxy sulfones derived from water-soluble epoxides and sulfinate anions.

2. Results and discussion

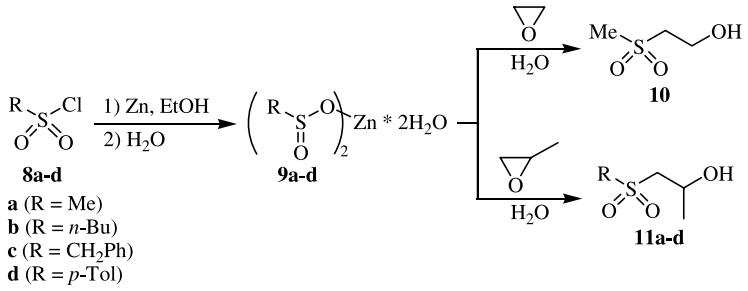
2.1. Synthesis of simple Zn sulfinates and their reactions with epoxides

As a first step, we decided to evaluate the applicability of some of the previously reported two-phase reaction systems for opening hydrophilic epoxides. We treated sodium methanesulfinate with propylene oxide[20] in the presence of Bu_4NBr under the conditions described by Crandall and Pradat.[7] The resulting reaction mixture was strongly basic (pH 14 for the aqueous phase). The ^1H NMR spectrum of the crude reaction product showed that only 20% of the desired β-hydroxy sulfone was formed along with 35% of propylene glycol. When the reaction was performed in the presence of montmorillonite clay,[11] formation of a strongly basic aqueous phase (pH 14) was again observed. Workup gave 31% of crude β-hydroxy sulfone, which was approximately 80% pure by ^1H NMR analysis. The slightly better yield of the desired product under these conditions could originate from partial neutralization of base formed during the reaction by acidic sites in the montmorillonite clay. We presumed that high yields for these two-phase methods might be expected only if (i) the starting epoxide resides primarily in the organic layer (i.e., is hydrophobic), and (ii) the β-hydroxy sulfone product is relatively stable under strongly basic conditions and/or also preferentially partitions into the organic layer.

We considered that epoxide opening with sulfinate anion **1** might be achieved in aqueous medium if we used metal sulfinates $(RSO_2)_nMet$ for which the corresponding metal hydroxides $Met(OH)_n$ are insoluble in water and would thus precipitate from the reaction medium, effectively maintaining neutral reaction conditions in solution. Ideally, the metal sulfinates should be readily available and inexpensive. To make large-scale synthesis possible, the corresponding metal hydroxides should precipitate in a form that can be removed by simple filtration. After considerable experimental work, we have found that zinc sulfinates fulfill all the above requirements. Zinc sulfinates can be conveniently prepared by direct reduction of sulfonyl chlorides with zinc powder.[21–23] In most reported cases, however, after the reduction is finished, the reaction mixture has been either acidified to obtain the corresponding sulfinic acids[21] or treated with excess aq $NaOH/Na_2CO_3$ solution to produce the corresponding sodium sulfinates.[22] Only in two cases have zinc arenesulfinates $Zn(O_2SAr)\cdot nH_2O$[23] and $Zn(O_2SCH_2NHC_6H_5)\cdot nH_2O$[24] been isolated, albeit in low to moderate yields.

In our hands, Zn reduction of commercially available sulfonyl chlorides **8a–d** afforded the respective Zn sulfinates **9a–d** as crystalline dihydrates[25] (Scheme 3, Table 1) in excellent to good yields. The reaction of Zn sulfinates **9a–c** with ethylene oxide or propylene oxide provided good yields of the desired β-hydroxy sulfones **11a–c** and **10** (Table 1) after a straightforward workup, which did not require column chromatography.

2-(Methylsulfonyl)ethanol (**10**) (Table 1, entry 1) is widely used in protecting various functional groups;[26] given the straightforward nature of the chemistry involved, we believe that that our method could be adapted to produce **10** on a very large scale. Given the low cost of the reagents used (methylsulphonyl chloride, zinc powder, ethanol, ethylene oxide and water) and the minimal amount of waste generated (ethanolic $ZnCl_2$ solution and clean ZnO), this



Scheme 3.

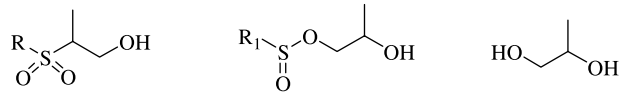
Table 1. Regioselective opening of epoxides using zinc sulfinates **9a–d**

Entry	RSO_2Cl	Yield of Zn salt (%)	Epoxide used (equiv)	Reaction conditions	Molar ratio of **11/12/13/14**[a,b]	β-Hydroxy sulfone product	Isolated yield (%)
1	**8a**	**9a** (90)	Ethylene oxide (1.3)	2 h, 70 °C	—	**10**	82[c]
2	**8a**	**9a** (92)	Propylene oxide (1.4)	2 h, 75 °C	86/8/6/21	**11a**	65[d]
3	**8b**	**9b** (92)	Propylene oxide (1.6)	12 h, 70 °C	85/8/7/34	**11b**	67[d]
4	**8b**	**9b** (92)	Propylene oxide (1.6)	4 h, 80 °C, ultrasound	85/8/7/42	**11b**	64[d]
5	**8c**	**9c** (91)	Propylene oxide (2.0)	7 h, 70 °C	85/8/7/85	**11c**	63[e]
6	**8d**	**9d** (78)	Propylene oxide (1.7)	16 h, 70 °C	93/7/0/93	**11d**	41[e]
7	n/a	**9d** (n/a)[f]	Propylene oxide (1.7)	4 h, 75 °C	93/7/0/20	**11d**	64[e]

[a] Determined through NMR analysis of the crude reaction product.
[b] **14** is generated via hydrolysis of excess propylene oxide in situ.
[c] Isolated yield after distillation.
[d] Isolated yield after purification by distillation followed by crystallization.
[e] Isolated yield after purification by crystallization.
[f] Obtained in situ from commercially available sodium *p*-toluenesulfinate and zinc chloride (0.5 equiv).

approach for the synthesis of **10** is quite environmentally friendly.

In most cases, the synthesis of **11a–c** was accompanied by the formation of less than 15% of two byproducts (Fig. 1): the corresponding regioisomeric sulfones **12a–c**, formed as a result of propylene oxide opening at the more substituted epoxy carbon, and sulfinate esters **13a–c** (as 1:1 diastereomeric mixtures), resulting from O-attack of the sulfinate anion on the epoxide. The structures of **12a–c** and **13a–c** were tentatively assigned from their mixtures with **11a–c** using NMR analysis.[27] Interestingly, in the case of *p*-tolyl sulfone **11d** we did not observe the formation of the corresponding sulfinate ester **13d**.[28]



12a-d **13a-d** **14**

Figure 1.

The isolation of the desired β-hydroxy sulfone products was rather simple: after removal of ZnO by filtration, the resulting aqueous solution was concentrated under reduced pressure and the residue was distilled (for **10**, **11a** and **11b**) or recrystallized from water (**11c** and **11d**.) While distilled 2-(methylsulfonyl)ethanol (**10**) was essentially pure, distilled **11a** and **11b** were sometimes contaminated with 5–9% of the regioisomer **12**. Optional recrystallization from toluene afforded **11a** and **11b** with up to 99% purity.

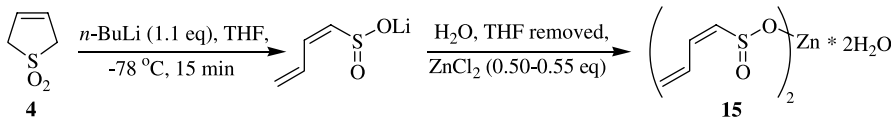
However, only 41% yield was obtained in the case of Zn *p*-toluenesulfinate **9d** (Table 1, entry 6), presumably due to the very limited solubility of **9d** in water. For less water-soluble sulfinate salts **9b–d**, we considered that it might be possible to facilitate reaction in the heterogeneous mixture using ultrasonication. Unfortunately, this approach had little impact on the reaction of **9b** (Table 1, compare entries 3 and 4), and so it was not investigated further.

We observed that the reactivity of zinc sulfinate salts was significantly enhanced if these salts were freshly prepared by an ion-exchange reaction from sodium sulfinates and $ZnCl_2$. Thus, we treated commercially available Na *p*-toluenesulfinate with $ZnCl_2$ (0.5 equiv) and immediately added propylene oxide to the resulting white slurry. To our delight, the reaction was completed in 4 h to give 64% isolated yield of the desired sulfone **11d** (Table 1, entry 7).

It is important to note that, during all these reactions, the pH of the solution was well controlled by the formation of insoluble ZnO (a solution pH of around 6.5 was observed at the end of the reaction).

2.2. Epoxide opening with zinc (*Z*)-buta-1,3-diene-1-sulfinate

Given that we had successfully developed a practical approach for the synthesis of β-hydroxy sulfones **10** and **11a–d** using simple Zn sulfinate salts **9a–d**, we were now in a position to explore the preparation of the more challenging 1-butadienyl β-hydroxyalkyl sulfones **6** and **7** required for our Diels–Alder studies (see Scheme 2). The presence of an unsaturated sulfone moiety, which provides a potent Michael acceptor motif, was recognized as a significant challenge to the successful execution of these studies. This work required the use of Zn (*Z*)-buta-1,3-diene-1-sulfinate



Scheme 4.

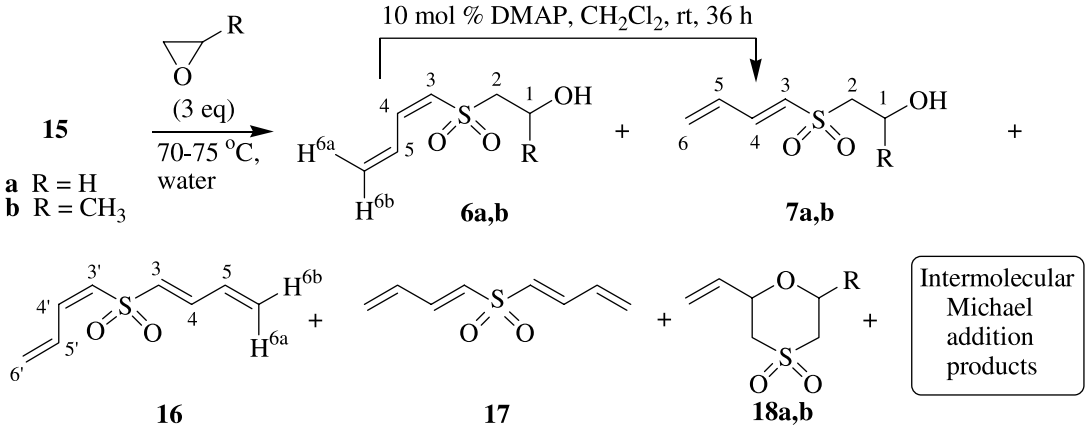
(**15**), which we anticipated would be accessible from commercially available 2,5-dihydrothiophene-1,1-dioxide (butadiene sulfone, **4**). Treatment of butadiene sulfone (**4**) with *n*-BuLi followed by addition of water and removal of the THF in vacuo afforded a clear solution of Li (*Z*)-buta-1,3-diene-1-sulfinate. This solution was treated with $ZnCl_2$ to afford Zn (*Z*)-buta-1,3-diene-1-sulfinate (**15**) as a white precipitate (Scheme 4).

Zinc sulfinate **15** could be isolated as a stable white solid dihydrate in 70–75% yield and was characterized by ^1H and ^{13}C NMR spectroscopy, and elemental analysis. However, we observed that excessive washing of **15** with water significantly decreased its reactivity toward epoxide opening chemistry (see later).

In practice, the Zn sulfinate **15** was prepared in situ and then allowed to react directly with added epoxide (3 equiv, 70–75 °C). ^1H NMR analysis of the crude product obtained from the reaction of **15** with propylene oxide showed the presence of a mixture of (*Z*)-butadienyl sulfone **6b**, (*E*)-butadienyl sulfone **7b**, (*E*,*Z*)-bis-butadienyl sulfone (**16**) and (*E*,*E*)-bis-butadienyl sulfone (**17**) (see Scheme 5 and Table 2, entry 1). Unfortunately, the desired products **6b** and **7b** were not separable by column chromatography. Similar results were obtained on reaction with ethylene oxide (Table 2, entry 7), however, a small amount of cyclization product **18a** was also observed.

To our delight, when mixtures of products **6** and **7** were treated with DMAP in dichloromethane, quantitative (*Z*)- to (*E*)-isomerization occurred to cleanly afford the desired (*E*)-1-butadienyl β-hydroxyalkyl sulfones **7a** and **7b** in ca. 30% overall yields from butadiene sulfone (**4**).

A series of experiments were run with varying amounts of $ZnCl_2$ and for various reaction times (see Table 2). The pH values shown in Table 2 were measured at the end of



Scheme 5.

Table 2. Preparation of butadienyl sulfones **6** and **7** (75 °C, water)

Entry	R	Equiv $ZnCl_2$	Time (h)	pH[a]	Approximate product ratio[b]				Yield **6**+**7** (%)[c]
					6	**7**	*cis*-**18**	*trans*-**18**	
1	CH_3	0.50–0.52	1.7	8.3–8.6	1	1	0	0	25[d]
2	CH_3	0.50–0.52	3	8.3–8.6	1	3.5	Traces	0	30
3	CH_3	0.50–0.52	5	8.3–8.6	1	7	0.2	0.1	23[e]
4	CH_3	0.49–0.50	3	10.2	1	3.5	0.6	0.3	30
5	CH_3	0.49–0.50	5	10.2	1	7	4.4	1.2	—
6	CH_3	0.35	3	14	0	0.2	4.8	1	—
7	H	0.50–0.52	3	8.3–8.6	1	3.3	0.4	n/a	30
8	CH_3	0.50[f]	2	6.5	1	0	0	0	20[d,g]
9	CH_3	0.50[f]	8	6.5	1	0	0	0	13[d,g]
10	CH_3	0.50[f,h]	9	6.5	1	0	0	0	13[d,g]

[a] Measured at the end of the reaction prior to workup.
[b] Measured by ^1H NMR analysis of the crude product. Bis-butadienyl sulfones **16** and **17** are not included; the ratio of **16**/**17** closely paralleled the ratio of **6**/**7**.
[c] Isolated yield after purification by column chromatography.
[d] Large amounts of intermolecular Michael addition products were seen in the crude ^1H NMR spectrum.
[e] Trace amounts of intermolecular Michael addition products were seen in the crude ^1H NMR spectrum.
[f] Compound **15** was thoroughly washed with water and dried before use.
[g] Isolated as a 3:1 inseparable mixture of **6** and buta-1,3-diene-1-sulfinate ester.
[h] LiOH (0.1 equiv) was added.

the indicated reaction time. If the reactions corresponding to entries 1–5 were interrupted after 1–1.5 h, the pH of the reaction medium was around 6.5. Importantly, the amount of ZnO precipitate formed in runs 1–3 was the same and corresponded to a quantitative recovery of Zn based on initially added $ZnCl_2$. This means that Zn sulfinate **15** was consumed and the formation of ZnO completed after 1.7 h. As long as Zn sulfinate **15** was present in the reaction medium, the pH of the solution was well controlled by the formation of insoluble ZnO and remained essentially neutral (pH 6.5). After all Zn sulfinate **15** had been consumed, the pH increased, with smaller amounts of added $ZnCl_2$ resulting in higher final solution pH levels (compare entries 2, 4 and 6 in Table 2).

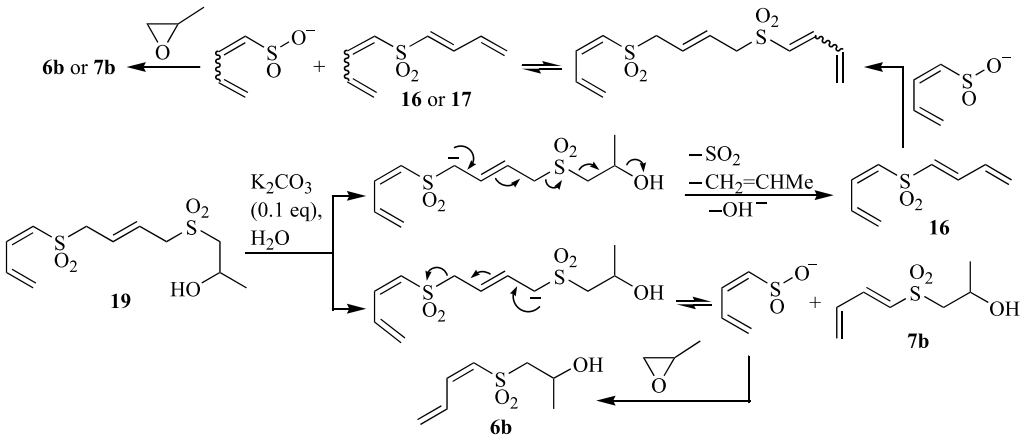
Attempts to purify zinc salt **15** before use through thorough washing with water and drying resulted in incomplete conversion—a significant amount of **15** remained unreacted (see entries 8 and 9). In these runs, low yields of (*Z*)-butadienyl sulfone **6b** contaminated with *O*-alkylated (buta-1,3-diene-1-sulfinate ester) byproducts were observed (entries 8 and 9). The higher reactivity of **15** formed in situ does not appear to correlate with the possible presence of Li^+ ions in the crude Zn sulfinate salt—the addition of 10 mol% LiOH had no impact on the reaction (entry 10).

The accumulated data allowed us to draw the following important conclusions about the reaction mechanism:

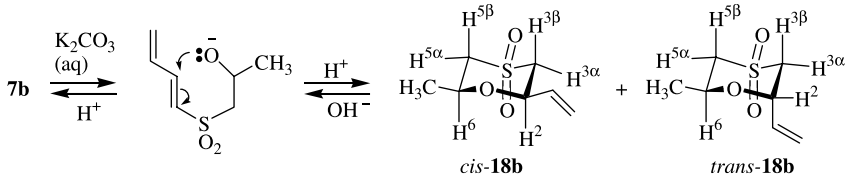
1. The formation of oligomeric intermolecular Michael addition byproducts is reversible under basic conditions (pH 8.3 and higher). At very short reaction times (1–1.5 h or less), the pH of the reaction solution (6.5) allows for accumulation of intermolecular Michael addition products. Beyond this point, the reaction becomes slightly basic (pH 8.3–8.6), which allows for the gradual conversion of these intermolecular Michael addition products (via a retro-Michael process) to afford bis-butadienyl sulfones **16** and **17**, and (*E*)-β-hydroxy sulfone **7b**. As a result, longer reaction times lead to the recovery of smaller amounts of intermolecular Michael addition products (compare entries 1 and 3). Since the only source of (*E*)-β-hydroxy sulfone **7b** is from this base-mediated retro-Michael process, the ratio of **7b** to **6b** increases with longer reaction times (compare entries 1–3). This is also supported by the complete absence of **7b** when the reaction medium remains completely non-basic (see entries 8–10), precluding retro-Michael reactions. To further support this conclusion, we subjected the (*E*,*Z*)-dimer **19** (one of the intermolecular Michael addition byproducts isolated from the reaction mixture in the run presented in Table 2, entry 1) to an aqueous solution of propylene oxide in the presence of a base (Scheme 6). The resulting crude reaction mixture contained 31% of dimers **19** (now as a mixture of (*E*,*Z*)- and (*E*,*E*)-stereoisomers), 7% of the product **6b**, 40% of the product **7b**, along with 32% of the bis-butadienyl sulfones **16** and **17**. Compounds **16** and **17** were commonly present as byproducts in reaction runs 1–7 represented in Table 2. It seemed logical that the formation of **16** and **17** (being essentially irreversible due to loss of SO_2 and propylene) was the major cause of the moderate yields obtained for the desired products **6** and **7** during reaction runs 1–7. Compounds **16** and **17**, as well as (*E*)-β-hydroxy sulfone **7b**, were completely absent during the reaction runs 8–10 (Table 2), where the pH of the reaction mixture never became basic and the decomposition of the intermolecular Michael addition byproducts did not occur.

2. Cyclized byproducts **18** were formed via base-mediated intramolecular Michael-type cyclization from initially produced butadienyl β-hydroxyalkyl sulfones **6** and **7**. This conclusion is supported by the fact that the combined yield of **6** and **7** reached a maximum after about 3 h, and then the formation of the cyclized byproducts **18** became noticeable (Table 2, entries 1, 2, 3 and 7). Using less than 0.50 equiv $ZnCl_2$ resulted in a higher solution pH at the end of the reaction, which correlated with the increasing formation of the cyclized byproducts **18**. Several additional experiments showed, that under basic conditions, **6b**, **7b**, *cis*-**18b** and *trans*-**18b** could equilibrate (Scheme 7, Table 3).

3. *O*-Alkylated (buta-1,3-diene-1-sulfinate ester) byproducts, observed when Zn sulfinate **15** had not been completely consumed before the workup (entries 8–10), are absent in the runs corresponding to entries 1–7 because of hydrolysis of these byproducts under the slightly basic conditions at the end of the reaction. When the mixtures of *S*-alkylated and *O*-alkylated products obtained in the runs



Scheme 6.



Scheme 7.

Table 3. Equilibration of **7b** in the presence of 0.2 equiv of aq K_2CO_3

Entry	Reactants	Conditions		Product ratio[a]		
		Time (h)	Temperature (°C)	**7b**	*cis*-**18b**	*trans*-**18b**
1	**7b**	5	75	11	71	18
2	**7b**	9	75	4	82	14
3	*cis*-**18b**:*trans*-**18b** 1:1	10	80	6	92	2

[a] Measured by ^{1}H NMR analysis of the crude product. The stereochemistry of the *cis*- and *trans*-diastereomers of **18** was assigned based on a careful analysis of their ^{1}H NMR spectra.[29,30]

corresponding to entries 8 and 9 were treated with saturated aqueous $NaHCO_3$ at rt, complete hydrolysis of the *O*-alkylated products was observed after 4 h, and clean sulfone **6b** was separated.

Unfortunately we were unable to efficiently suppress byproduct formation by changing the reaction conditions and isolated yields of the desired 1-butadienyl β-hydroxyalkyl sulfone products **6** and **7** remained at 30%. Nevertheless, the low cost of the reagents involved and our ability to quantitatively isomerize **6** to **7** before the separation of **7**, make this method an attractive entry for the preparation of (*E*)-1-butadienyl β-hydroxyalkyl sulfones **7** on a multigram scale.

3. Conclusion

A series of β-hydroxy sulfones **10** and **11a–d** were synthesized in good yields under neutral aqueous conditions by the nucleophilic opening of ethylene oxide or propylene oxide with simple zinc sulfinates **9a–d**. These Zn sulfinate salts were readily accessible by reduction of the corresponding sulfonyl chlorides **8a–d** or from the corresponding sodium or lithium sulfinate salts. These reactions favored S-attack of the sulfinate anion over O-attack and, in the case of propylene oxide, proceeded with high regioselectivity. This method allows easy and environmentally friendly access to β-hydroxy sulfones and represents a significant improvement over previously available epoxide ring opening reactions with sulfinate nucleophiles.

The corresponding opening of these epoxides with zinc (*Z*)-buta-1,3-diene-1-sulfinate **15**, followed by DMAP-mediated isomerization, afforded (*E*)-1-butadienyl β-hydroxyalkyl sulfones **7a**,**b** in 30% isolated yield. Detailed mechanistic studies revealed that the yields of these products were limited by their consumption in competing intra- and intermolecular Michael addition processes. Nevertheless, in spite of these competing side reactions, this method provides a convenient and inexpensive one-pot approach for the preparation of sensitive (*E*)-butadienyl β-hydroxyalkyl sulfones **7a**,**b** from commercially available butadiene sulfone (**4**). Currently, we are exploring the utility of compounds such as **7a**,**b** as building blocks for intramolecular Diels–Alder cycloaddition chemistry using sulfone tethers. Preliminary studies along these lines have already been reported[15b] and full details of this chemistry will be forthcoming in due course.

4. Experimental

4.1. General

Unless otherwise indicated, ^{1}H NMR spectra were recorded on a Bruker AMX 300 NMR spectrometer at 300 MHz, using TMS as an internal reference. ^{13}C NMR spectra were recorded on the same spectrometer at 75 MHz, with $CDCl_3$ or DMSO-d_6 as an internal reference. Indicated NMR spectra were recorded on a Bruker AVANCE 400 NMR spectrometer at 400 MHz (^{1}H) and 100 MHz (^{13}C), respectively. TLC analysis was performed using silica coated plates (Sorbent Technologies). Flash column chromatography was conducted on silica gel Premium Rf Grade (40–75 μm (200×400 mesh), Sorbent Technologies). The glass pressure vessel (150 mL) was purchased from Chemglass and used with magnetic stirring. Commercial reagents and solvents (Acros) (including anhydrous EtOH and CH_2Cl_2) were used as received. THF was freshly distilled from Na/benzophenone. Deionized water was used for aqueous reactions. Unless otherwise stated, no effort was made to exclude air. Commercially available 2.5 M *n*-BuLi solution in hexanes (Aldrich) was used. Melting points were determined using a Thomas-Hoover apparatus and are uncorrected. Combustion analyses were conducted by Chemisar Laboratories Inc., Ontario, Canada.

In the absence of solvent, compounds **6a**,**b**, **7a**,**b**, **16**, **17** and **19** are prone to very fast polymerization. 2,6-Di-*tert*-butyl-4-methylphenol (ca. 0.1 g per 100 mL) was added to the fractions containing these compounds before their concentration. The removal of solvents was performed in vacuo at 0–5 °C; the oily residue was immediately diluted with dichloromethane and stored at −5 °C. As a result,

combustion analysis data could not be obtained for these compounds.

The yields of compounds **6a**,**b**, **7a**,**b**, **16**, **17** and **19** were calculated by ^{1}H NMR analysis using 2,6-di-*tert*-butyl-4-methylphenol as an internal standard. To evaluate the reliability of these calculations, in several cases the solvent was removed in high vacuo and the isolated yield was compared with that established by use of an internal standard. These yields were always in good agreement (no more than 1% deviation).

4.2. General procedure for preparation of zinc sulfinate salts—zinc methanesulfinate dihydrate (9a)

Anhydrous ethanol (80 mL) containing zinc powder (9.35 g, 143 mmol, 1.11 equiv) was heated to reflux with stirring. Mesyl chloride (**8a**) (10.0 mL, 129 mmol, 1.00 equiv) was added dropwise over 10 min through the condenser, so as to maintain even boiling. The first portion of mesyl chloride should be added very carefully, making sure that the reaction initiates, otherwise the reaction mixture effervesces vigorously. Additional anhydrous ethanol (10 mL) was used to wash the condenser. No precipitate was formed while the zinc almost totally dissolved. The reaction mixture was refluxed for 15 min. It was then allowed to cool over 30 min with stirring and was filtered. The residual zinc powder (0.44 g, 6.7 mmol, 0.05 equiv) recovered on the filter was washed with ethanol (10 mL). Upon the addition of water (10 mL) with stirring to the combined filtrates (ca. 100 mL), a white precipitate slowly formed. Crystallization was continued for 30 min at rt, then for 1 h at 0 °C. The resulting white crystalline solid was filtered, washed with ice-cold ethanol (2×10 mL) and was allowed to air-dry at rt overnight. The title compound **9a** was obtained as a white solid (15.5 g, 59.5 mmol, 92%, mp 117–118 °C (dec); after drying (0.1 mmHg, at 60 °C) mp 133 °C). ^{1}H NMR (DMSO-d_6) δ 2.26 (s, 6H, CH_3), 3.42 (s, 4H, H_2O); ^{13}C NMR (DMSO-d_6) δ 48.8. Anal. Calcd for $C_2H_{10}O_6S_2Zn$: C, 9.25; H, 3.88; S, 24.70; Zn, 25.19. Found: C, 9.01; H, 3.85; S, 24.97; Zn, 25.03.

4.3. Synthesis of β-hydroxy sulfones 10 and 11

4.3.1. General procedure for preparation of β-hydroxy sulfones—(methylsulfonyl)ethanol (10).[31] A suspension of zinc methanesulfinate **9a** (15.2 g, 58.7 mmol, 1.00 equiv) and ethylene oxide (7.80 mL, 156 mmol, 2.66 equiv) in water (150 mL) was heated in a glass pressure vessel at 70 °C with magnetic stirring for 2 h. The reaction mixture was filtered while still hot. The filtered ZnO precipitate was washed with water (2×10 mL). The combined filtrates were concentrated in vacuo to remove most of the water. The crude product was distilled (bp 140–145 °C at 0.1 mmHg) to give the title compound **10** as a colorless oil (11.4 g, 92.1 mmol, 78%). ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 3H, CH_3), 3.28 (t, J=5.4 Hz, 2H, SO_2CH_2), 4.07 (t, J=5.4 Hz, 2H, O–CH_2); ^{13}C NMR ($CDCl_3$) δ 42.8, 56.4, 56.9.

4.3.2. 1-(Methylsulfonyl)propan-2-ol (11a).[32] The reaction was performed according to general procedure Section 4.3.2 using zinc methanesulfinate (**9a**) (8.31 g, 32.0 mmol, 1.00 equiv) and propylene oxide (6.10 mL, 87.2 mmol, 2.73 equiv) in water (80 mL) at 75 °C for 2 h 30 min. The crude product was distilled (bp 117–121 °C at 0.1 mmHg) to give 7.30 g (52.9 mmol, 83%) of **11a** contaminated with approx 6–7% of propylene glycol (**14**). Crystallization of the distillate from toluene (270 mL) gave clean **11a** (5.20 g, 37.6 mmol, 59%), mp 67–69 °C. Concentration of the mother liquor in vacuo to ca. 100 mL gave an additional crop of clean **11a** (0.53 g, 3.84 mmol, 6%). The combined yield of **11a** was 65%. ^{1}H NMR ($CDCl_3$) δ 1.33 (d, J=6.4 Hz, 3H, O–CHCH_3), 3.00–3.12 (m, 1H, $SO_2CH_AH_BCH$), 3.05 (s, 3H, CH_3SO_2), 3.21 (dd, J=14.5, 9.9 Hz, 1H, $SO_2CH_AH_BCH$), 4.36–4.47 (m, 1H, O–CHCH$_3$); ^{13}C NMR ($CDCl_3$) δ 23.4, 42.7, 62.1, 63.0.

^{1}H NMR analysis of the crude reaction mixture before distillation showed the presence of **11a**, **12a**, **13a** and propylene glycol in an 86/8/6/21 ratio.

2-(Methylsulfonyl)propan-1-ol (**12a**)[27] (assigned from the mixture with **11a** and **13a**): ^{1}H NMR ($CDCl_3$) δ 1.39 (d, J=7.2 Hz, 3H, SO_2–CHCH_3), 2.99 (d, J=0.4 Hz, 3H, CH_3SO_2), 3.14–3.24 (masked) (m, 1H, SO_2–CHCH$_3$), 3.94–3.96 (m, 2H, CHCH_AH_BOH); ^{13}C NMR ($CDCl_3$) δ 10.4, 40.4, 60.8, 61.7.

2-Hydroxypropyl methanesulfinate (**13a**) (obtained as a 1:1 mixture of diastereomers; assigned from the mixture with **11a** and **12a**): ^{1}H NMR ($CDCl_3$) δ 1.20 (d, J=6.4 Hz)/1.21 (d, J=6.4 Hz) (3H total, O–CHCH_3), 2.71 (s)/2.71(s), separated by 1 Hz (3H total, CH_3SO), 3.90–4.12 (m, 3H, SO–O–CH_AH_BCH); ^{13}C NMR ($CDCl_3$) δ 18.7/19.0, 44.2, 66.3/66.4, 74.2/74.5.

4.3.3. Preparation of 1-(4-methylphenylsulfonyl)propan-2-ol (11d)[9,33] **from sodium *p*-toluenesulfinate** A solution of commercially available sodium *p*-toluenesulfinate hydrate (0.9% water) (2.92 g, 16.2 mmol, 1.00 equiv) in water (40 mL) was placed in a 150 mL glass pressure vessel and was treated with aq $ZnCl_2$ (20 mL of an aq solution containing 1.10 g (8.1 mmol, 0.50 equiv) of $ZnCl_2$) with magnetic stirring. A white precipitate formed. Propylene oxide (1.90 mL, 27.2 mmol, 1.68 equiv) was added and the reaction mixture was heated at 75 °C with magnetic stirring for 4 h, and was then filtered while still hot. The filtered ZnO precipitate was washed with water (2×20 mL) and the combined filtrates (ca. 100 mL) were allowed to crystallize for 3 h to afford the title compound **11d** as a white crystalline solid (1.66 g, 7.75 mmol, 48%). The mother liquor was concentrated in vacuo and coevaporated with toluene (2×20 mL). This afforded a colorless oil, which was treated with dichloromethane (40 mL) and the insoluble solid residue (0.84 g) was filtered out. The filtrate was concentrated in vacuo to afford a colorless oil (1.65 g). ^{1}H NMR analysis of this oil showed the presence of **11d**, **12d**, and propylene glycol in an 81/19/95 ratio. Crystallization from water (40 mL) gave an additional crop of clean title compound **11d** (0.560 g, 2.61 mmol, 16%). The combined yield of **11d** was 64%. ^{1}H NMR ($CDCl_3$) δ 1.24 (d, J=6.4 Hz, 3H, O–CHCH_3), 2.45 (s, 3H, CH_3-Ar), 3.14 (dd, J=14.3, 2.8 Hz, 1H, $SO_2CH_AH_BCH$), 3.27 (dd, J=14.3, 8.6 Hz, 1H, $SO_2CH_AH_BCH$), 4.30 (dqd, J=9.0, 6.4, 2.8 Hz, 1H, O–CHCH$_3$), 7.39 (d, J=8.5 Hz, 2H, Ar), 7.80 (d, J=8.4 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$) δ 21.8, 22.7, 62.5, 63.5, 128.1, 130.3, 136.3, 145.4.

2-(4-Methylphenylsulfonyl)propan-1-ol (**12d**) (assigned from the mixture with **11d**): ^{1}H NMR ($CDCl_3$) δ 1.24 (d, $J=6.4$ Hz, 3H, O–CHCH_3, coincides with **11d**), 2.45 (s, 3H, CH_3-Ar, coincides with **11d**), 3.21–3.37 (masked by **11d**) (m, 1H, SO_2–CHCH$_3$), 3.73 (dd, $J=12.1$, 5.0 Hz, 1H, CHCH_AH$_B$OH), 3.98 (dd, $J=12.1$, 6.2 Hz, 1H, CHCH$_A$-H_BOH), 7.39 (app. d, $J=8.5$ Hz, 2H, Ar, coincides with **11d**), 7.76 (app. d, $J=8.3$ Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$) δ 11.4, 18.9, 61.3, 61.8, 128.9, 130.0, 134.1, 139.7.

4.4. Synthesis of 1,3-butadienyl sulfone derivatives

4.4.1. Zinc (*Z*)-buta-1,3-diene-1-sulfinate dihydrate (15). 2,5-Dihydrothiophene-1,1-dioxide (butadiene sulfone, **4**) (4.73 g, 40.0 mmol, 1.00 equiv) was dissolved in anhydrous THF (120 mL) under argon, and cooled in a dry ice/acetone bath. *n*-BuLi (2.5 M in hexanes, 16.00 mL, 40.0 mmol, 1.00 equiv) was added dropwise over 25 min, maintaining the reaction temperature below −68 °C. Initially a yellow solution was observed and then a cream precipitate formed. The addition of *n*-BuLi was stopped after a bright red coloration had developed in the reaction mixture. The reaction mixture was allowed to warm up to −50 °C, and then water (30 mL) and hydroquinone (ca. 0.05 g) were added. The precipitate immediately dissolved, and the red coloration disappeared. The organic solvents were removed in vacuo, resulting in a light yellow aqueous solution (ca. 30 mL) of lithium (*Z*)-buta-1,3-diene-1-sulfinate. The solution was cooled in ice, and a solution of $ZnCl_2$ (2.705 g, 19.85 mmol) in water (5 mL) was added dropwise with stirring. The reaction mixture was left in an ice bath for 20 min, and then the resulting white precipitate was filtered, washed with ice-cold water (20 mL) followed by dichloromethane (20 mL) and dried in vacuo. The title compound **15** was obtained as a cream solid (4.80 g, 14.3 mmol, 72%), mp 128–130 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.43 (s, 4H, H_2O), 5.26 (br d, $J=10.0$ Hz, 2H, H$_{cis}$H$_{trans}$C=CH), 5.34 (br d, $J=16.8$ Hz, 2H, H_{cis}H$_{trans}$C=CH), 6.02 (br d, $J=$ 10.0 Hz, 2H, =CH–SO_2), 6.26 (dd, $J=11.2$, 10.4 Hz, 2H, CH=CH–SO_2), 6.94 (dddd, $J=16.8$, 11.2, 10.1, 1.0 Hz, 2H, CH_2=CH); ^{13}C NMR (DMSO-d_6) δ 121.8, 131.2, 131.6, 146.6. Anal. Calcd for $C_8H_{14}O_6S_2Zn$: C, 28.62; H, 4.20; S, 19.10; Zn, 19.48. Found: C, 28.04; H, 4.33; S, 18.61; Zn, 19.01.

4.4.2. 1-((*E*)-Buta-1,3-diene-1-sulfonyl)ethanol (7a). The light yellow aqueous solution (ca. 30 mL) of Li (*Z*)-buta-1,3-diene-1-sulfinate (40.0 mmol) obtained in experiment Section 4.4.1 was added dropwise with stirring and cooling in ice to the glass pressure vessel containing $ZnCl_2$ (2.67–2.84 g, 19.6–20.8 mmol, 0.49–0.52 equiv) in water (60 mL). A white precipitate of zinc (*Z*)-buta-1,3-diene-1-sulfinate was formed. Ethylene oxide (6 mL, 120 mmol, 3 equiv) was added, and the solution was heated with stirring for 3 h at 70–75 °C. The resulting reaction mixture was cooled to rt and filtered. The precipitate was washed with water (3×20 mL) and the combined aqueous filtrate was extracted with dichloromethane (4×100 mL). The combined dichloromethane extracts (ca. 400 mL) were treated with 2,6-di-*tert*-butyl-4-methylphenol (0.200 g, 0.908 mmol), dried ($MgSO_4$), filtered, concentrated to a volume of ca. 150 mL and treated with DMAP (0.500 g, 4.09 mmol). The resulting solution was kept at rt for 36 h, and was then subjected to column chromatography (silica, EtOAc/hexanes 1.5:1) to afford the title compound **7a** as a colorless oil (1.95 g, 12.0 mmol, 30%). ^{1}H NMR ($CDCl_3$) δ 3.22 (t, $J=6.0$ Hz, 1H, OH), 3.26–3.31 (m, 2H, H^2), 4.02–4.10 (m, 2H, H^1), 5.68 (br d, $J=10.0$ Hz, 1H, H^{6b}), 5.77 (br d, $J=16.9$ Hz, 1H, H^{6a}), 6.47 (dd, $J=14.9$, 0.6 Hz, 1H, H^3), 6.48 (dddd, $J=16.9$, 10.9, 10.0, 0.6 Hz, 1H, H^5), 7.21 (br dd, $J=15.0$, 10.8 Hz, 1H, H^4); ^{13}C NMR ($CDCl_3$) δ 56.4, 57.4, 129.0 (two signals coincide), 132.5, 144.3.

4.4.3. 1-((*E*)-Buta-1,3-diene-1-sulfonyl)propan-2-ol (7b). The title compound **7b** was prepared from propylene oxide (8.4 mL, 120 mmol, 3 equiv) according to the procedure described above for **7a**, as a colorless oil (2.14 g, 12.1 mmol, 30%). ^{1}H NMR ($CDCl_3$) δ 1.31 (d, $J=6.4$ Hz, 3H, CH_3), 3.09 (dd, $J=14.4$, 2.8 Hz, 1H, H^2), 3.17 (dd, $J=$ 14.5, 8.7 Hz, 1H, H^2), 3.21 (d, $J=2.8$ Hz, 1H, OH), 4.39 (app. dqt $J=9.0$, 6.3, 2.8 Hz, 1H, H^1), 5.69 (br d, $J=$ 10.0 Hz, 1H, H^{6b}), 5.77 (br d, $J=16.7$ Hz, 1H, H^{6a}), 6.43 (br d, $J=15.0$ Hz, 1H, H^3), 6.47 (dddd, $J=16.9$, 10.8, 10.0, 0.5 Hz, 1H, H^5), 7.22 (br dd, $J=15.0$, 10.9 Hz, 1H, H^4); ^{13}C NMR ($CDCl_3$) δ 22.9, 62.4, 62.7, 128.7, 129.4, 132.4, 144.8.

Acknowledgements

We thank Kent State University for financial support and Yehor Novikov for valuable discussions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.043. Synthetic procedures, ^{1}H and ^{13}C NMR data for compounds **9b–d**, **11b**,**c**, **11d** (synthesis from **8d**), **6a**,**b**, **16**, **17**, **18a**, *cis*-**18b**, *trans*-**18b** and **19**; partial ^{1}H and ^{13}C NMR data for compounds **12b**,**c**, **13b**,**c**; copies of ^{1}H and ^{13}C NMR spectra of compounds **9b**, **15**, **6a**,**b**, **7a**,**b**, **17**, a mixture of **16/17** (1/1.35), **18a**, *cis*-**18b**, *trans*-**18b** and **19**.

References and notes

1. Polunin, E. V.; Zaks, I. M.; Moiseenkov, A. M.; Semenovskii, A. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1979**, *3*, 641–643.
2. Krug, R. C.; Rigney, J. A.; Tichelaar, G. R. *J. Org. Chem.* **1962**, *27*, 1305–1309.
3. Chabardes, P.; Julia, M.; Menet, A. Ger. Offen 2,319,518, 1973; U.S. Patent 3,890,393, 1975; *Chem. Abstr.* **1974**, *80*, 27403x.
4. Burger, J. J.; Chen, T. B. R. A.; De Waard, E. R.; Huisman, H. O. *Tetrahedron* **1980**, *36*, 723–726.
5. Naf, F.; Decorzant, R.; Escher, S. D. *Tetrahedron Lett.* **1982**, *23*, 5043–5046.
6. Solladie, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 6, pp 133–170; and references cited therin.
7. Crandall, J. K.; Pradat, C. *J. Org. Chem.* **1985**, *50*, 1327–1329 and references cited therein.
8. Culvenor, C. C. J.; Davies, W.; Heath, N. S. *J. Chem. Soc.* **1949**, 278–282.

9. Culvenor, C. C. J.; Davies, W.; Savige, W. E. *J. Chem. Soc.* **1949**, 2198–2206.
10. Still, I. W. J.; Ablenas, F. J. *Synth. Commun.* **1982**, *12*, 1103–1110.
11. Biswas, G. K.; Bhattacharyya, P. *Synth. Commun.* **1991**, *21*, 569–573.
12. Maiti, A. K.; Bhattacharyya, P. *Tetrahedron* **1994**, *50*, 10483–10490.
13. Zhu, S. Z.; Qin, C. Y.; Xu, B. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1996**, *113*, 259–262.
14. Brace, N. O. *J. Fluorine Chem.* **2000**, *102*, 21–41. Sodium 2-(perfluorooctyl)-ethanesulfinate ($R_FCH_2CH_2SO_2Na$, 1 equiv) reacts with cyclohexene oxide (1 equiv) in ethanol–water (1/1) to give the corresponding β-hydroxy sulfone product, albeit with low (27%) conversion.
15. (a) Chumachenko, N.; Sampson, P. *Abstracts of Papers*, 28th ACS National Meeting, Philadelphia, PA, Aug 22–26, 2004; ORGN 621. (b) Chumachenko, N.; Sampson, P.; Hunter, A. D.; Zeller, M. *Org. Lett.* **2005**, *7*, 3203–3206.
16. Crumbie, R. L.; Ridley, D. D. *Aust. J. Chem.* **1981**, *34*, 1017–1026.
17. Opening of related 3-methyl-2,5-dihydrothiophene-1,1-dioxide to produce 2-methyl-(*Z*)-butadienyl sulfones has also been reported. This transformation was achieved on treatment with BuLi in THF,[1] ethylmagnesium bromide in ether,[2] phenyl- and 2,6-dimethylphenylmagnesium iodide in ether/toluene,[2] potassium *tert*-butoxide in isopropanol[3] or $LiN(SiMe_3)_2$ in THF.[18]
18. Polunin, E. V.; Kharchevnikov, A. P.; Kashin, A. N. *Zh. Org. Khim.* **1995**, *31*, 775–778.
19. (*Z*)-Buta-1,3-diene-1-sulfinate salt **5** was *S*-alkylated with benzyl bromide and methyl iodide in refluxing methanol in 10–25% yield,[1] with benzyl chloride in refluxing ethanol in 13% yield[2] and with allyl bromide in DMSO (no yield given).[5] In the patent literature, Julia[3] prepared four allyl dienyl sulfones by reaction of potassium 2-methylbuta-1,3-diene-1-sulfinate with β-vinyl-ionol in AcOH (71%), geranyl bromide in DMSO/MeOH (50%), 1-chloro-3-methyl-2-butene in DMSO (85%), 1-bromo-3-methyl-2-butene in THF (70%) and 1,4-dibromo-2-methyl-2-butene in DMSO/MeOH (56%). Burger[4] employed the same potassium salt in reaction with five more allylic halides (38–97% yield), benzyl halide (81% yield) and methyl halide (29% yield) in DMSO at rt.
20. Both Crandall[7] and Bhattacharyya[11] used a 1.5/1 ratio of *p*-toluenesulfinate/epoxide in their studies, presumably to avoid problems associated with the rapid hydrolysis of the epoxide during the latter stages of their reactions (pH 14). Since we needed to employ valuable sulfinate salts and inexpensive epoxides in future studies, we employed a 1/1.37 ratio of sulfinate/epoxide. This also allowed direct comparison with our studies using Zn sulfinates (see Section 2).
21. (a) Konieczny, M. T.; Horowska, B.; Kunikowski, A.; Konopa, J.; Wierzba, K.; Yamada, Y.; Asao, T. *Synthesis* **2001**, 1363–1367. (b) Hanefeld, W.; Landwehr, J. *Pharmazie* **1995**, *50*, 344–351.
22. (a) Whitmore, F. C.; Hamilton, F. H.; Thurman, N. *J. Am. Chem. Soc.* **1923**, *45*, 1066–1068. (b) Mase, N.; Watanabe, Y.; Ueno, Y.; Toru, T. *J. Org. Chem.* **1997**, *62*, 7794–7800.
23. Cookson, P. G.; Deacon, G. B. *Aust. J. Chem.* **1971**, *24*, 1599–1610.
24. Bazlen, M. *Chem. Ber.* **1927**, *60*, 1470–1479.
25. Interestingly, Zn methanesulfinate and Zn butanesulfinate did not precipitate from the reaction mixture unless water was added. They were isolated as the corresponding dihydrates **9a** and **9b**. In contrast, Zn phenylmethanesulfinate and Zn *p*-toluenesulfinate precipitated directly from the ethanol solution. The precipitates contained some solvating ethanol, which was substituted by water on drying in air to produce the corresponding dihydrates **9c** and **9d**.
26. For example, 2-(methylsulfonyl)ethanol (**10**) is used in the synthesis of urethane-protected amines and amino acids (a) Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; p 540. (b) Henklein, P.; Heyne, H.-U.; Halatsch, W.-R.; Niedrich, H. *Synthesis* **1987**, 166–167. (c) Tamura, N.; Natsugari, H.; Kawano, Y.; Matsushita, Y.; Yoshioka, K.; Ochiai, M. *Chem. Pharm. Bull.* **1987**, *35*, 996–1015, protected phosphate esters. (d) Bradshaw, B.; Dinsmore, A.; Ajana, W.; Collison, D.; Garner, C. D.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3239–3244, and protected phenols. (e) Rogers, J. F.; Green, D. M. *Tetrahedron Lett.* **2002**, *43*, 3585–3587.
27. Out of all observed byproducts (**12a–d** and **13a–d**), only 2-(methylsulfonyl)propan-1-ol (**12a**) has been previously described in the literature: Alcudia, F.; Brunet, E. R.; Garcia Ruano, J. L.; Rodriguez, J. H.; Sanchez, F. *J. Chem. Res., Miniprint* **1982**, 2826–2850.
28. However, if the reaction of Zn sulfinate **9d** was interrupted after 1 h 30 min, small pairs of resonances were observed in the ^{13}C NMR spectrum of the reaction mixture at 66.0/66.2 and 70.40/70.46 ppm. By comparison with the sulfinate esters **13a–c** obtained earlier, we tentatively attribute these signals to the C1 and C2 carbons of the 2-hydroxypropyl fragments in the two diastereomers of **13d**.
29. The ^1H NMR spectrum of *cis*-**18b** shows strong support for a predominant conformation having both the vinyl and methyl substituents equatorial. The assignment of the axial protons $H^{3\beta}$ and H^6 was based on the large coupling constants observed for the pairs $H^2/H^{3\beta}$ and $H^{5\beta}/H^6$ (11.2–11.0 Hz); consequently, small coupling constants were observed for the pairs $H^2/H^{3\alpha}$ and $H^{5\alpha}/H^6$ (1.9–2.0 Hz). Equatorial protons $H^{3\alpha}$ and $H^{5\alpha}$ demonstrate strong W coupling (3.5 Hz). Similar patterns were observed for the ^1H NMR spectrum of **18a**.
30. The ^1H NMR spectrum of *trans*-**18b** shows that, as might be expected, two major conformations are present in $CDCl_3$ solution. The coupling constants of H^6 with the two protons H^5 became closer (7.1, 2.9 Hz), while the coupling between H^2 and the two H^3 protons are now very similar (5.7, 4.4 Hz). W-Coupling is now observed for both pairs of *syn*-protons H^3 and H^5 (2.3, 1.7 Hz).
31. Haynes, R. K.; Schober, P. A. *Aust. J. Chem.* **1987**, *40*, 1249–1265.
32. Alcudia, F.; Garcia Ruano, J. L.; Rodriguez, J.; Sanchez, F. *Can. J. Chem.* **1979**, *57*, 2426–2433.
33. (a) Kader, A. T.; Stirling, C. J. M. *J. Chem. Soc.* **1962**, 3686–3692. (b) (*S*)-(+) enantiomer: Kozikowski, A. P.; Mugrage, B. B.; Li, C. S.; Felder, L. *Tetrahedron Lett.* **1986**, *27*, 4817–4820.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 4549–4562

Syntheses of the cylindrospermopsin alkaloids

Ryan E. Looper,[a] Maria T. C. Runnegar[b] and Robert M. Williams[a,*]

[a]*Department of Chemistry, Colorado State University, Fort Collins, CO 80523, USA*
[b]*Research Center for Liver Diseases, University of Southern California Medical Center, Los Angeles, CA 90033, USA*

Received 14 December 2005; revised 14 February 2006; accepted 15 February 2006

Available online 13 March 2006

Abstract—An intramolecular 1,3-dipolar cycloaddition has efficiently constructed the A-ring portions of the cylindrospermopsin alkaloids. A nitro-aldol addition of an elaborated nitroalkane to a pyrimidine aldehyde followed by an intramolecular reductive guanidinylation has enabled the syntheses of all three alkaloids in this family in 18–19 steps. We report the first asymmetric synthesis of cylindrospermopsin, unambiguously assigning its absolute configuration.

1. Introduction

Among the many toxic metabolites produced by cyanobacteria, the hepatotoxins pose the greatest threat to human health.[1] The peptidal toxins, microcystin-LR (**1**, LD_{50} = 50 μg/kg) is an example of the cyclic hepta-peptides first isolated from *Microcytis aeruginosa* (Fig. 1).[2] This family of toxins has been implicated in the elevated occurrence of liver cancer in China, where surface water is relied upon.[3] They are also the only toxins implicated in human fatalities, tragically in the death of 60 people who received microcystin contaminated water at a hemodialysis center in Carauru, Brazil.[4] These peptides have been shown to be highly liver specific due to their active uptake into

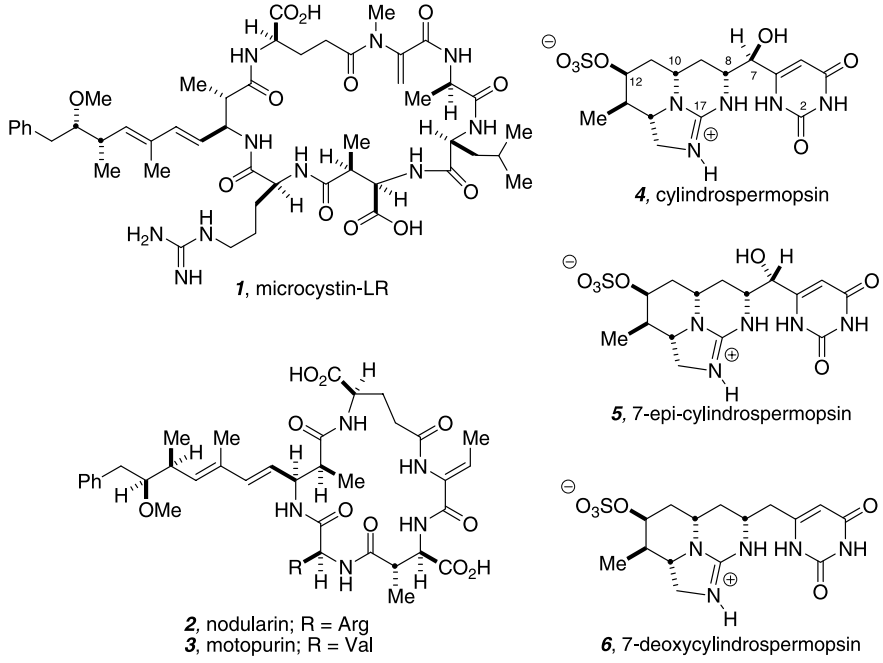


Figure 1. Hepatotoxic cyanobacterial metabolites.

Keywords: Cycloaddition; Guanidine; Alkaloid; Cyanobacteria; Hepatotoxin.
* Corresponding author. Tel.: +1 970 491 6747; fax: +1 970 491 3944; e-mail: rmw@chem.colostate.edu

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.044

hepatocytes via members of the organic anion transporting polypeptide family.[5] More importantly they have been shown to be potent inhibitors of the protein phosphatases PP1 and PP2A.[6] Nodularin (**2**) and motopurin (**3**) are related cyclic pentapeptides, with **3** remaining one of the most potent inhibitors of these phosphatases ($IC_{50}<1.0$ nM).[7] Inhibition of these enzymes is thought to cause hyperphosphorylation of cytoskeletal proteins leading to the disruption of the hepatic architecture resulting in cell death of hepatocytes and liver hemorrhage.

Cylindrospermopsin (**4**) was isolated as the principal hepatotoxin from *Cylindrospermopsis raciborskii* in 1992 after suspicion of its involvement in an outbreak of hepatoenteritis that hospitalized 150 people on Palm Island, Australia.[8,9] It has since been isolated in Japan from *Umezakia natans*[10] and Israel from *Aphanizomenon ovalisporum*.[11] Following the discovery of the parent compound, 7-*epi*-cylindrospermopsin (**5**) was isolated from *A. ovalisporum* as a toxic min or metabolite.[12] 7-Deoxy-cylindrospermopsin (**6**) was initially isolated from *C. raciborskii* and has recently been co-isolated with **4** in China from *Raphidiopsis curvata*.[13] Cylindrospermopsin has been shown to be a potent hepatotoxin ($LD_{50}=$ 0.2 mg/kg in mice), **4** is equipotent with **5** while **6** was thought to be non-toxic.[9,13a,14] Unlike **1**–**3**, the cylindrospermopsins do not inhibit PP1 or PP2A. Their toxicity appears to result at least in part from the inhibition of protein synthesis. The translation step of protein synthesis is inhibited by the cylindrospermopsins, but the mechanism of this inhibition is not yet known.[15] Cylindrospermopsin has also been shown, in vitro, to be a non-competitive inhibitor ($K_I=10$ μM) of the uridine monophosphate (UMP) synthase complex, although in vivo assays do not support a general inhibition of UMP synthesis.[16]

The threat posed to global public health by these molecules in drinking water and the isolation of *C. raciborskii* in several regions of the United States has prompted the NIH's national toxicology program (NTP) and the EPA's unregulated contaminant monitoring rule (UCMR) to elect **4** for toxicological and environmental evaluation.[17]

The intriguing biogenesis[18] and challenging structural features of the cylindrospermopsin alkaloids have garnered intense synthetic investigation.[19] Snider and co-workers completed the first racemic total synthesis of cylindrospermopsin 8 years after its discovery.[19h] Their accomplishments however, failed to illuminate the missasigned stereocenter at C7, elegantly corrected by Weinreb in a racemic but highly stereocontrolled synthesis of **5** validating the illustrated structures.[19j,k] Shortly thereafter Hansen and White were able to complete an asymmetric total synthesis of **5**, confirming the absolute stereochemistry as 7*S*, 8*R*, 10*S*, 12*S*, 13*R*, 14*S*.[19l,n]

2. Synthetic considerations

At the onset of this project little was known about the mechanism of action of this family of hepatotoxins. This encouraged us to develop an efficient and flexible synthesis of **4**. We were intrigued by the observations that while **4** and **5** are toxic and **6** is not. Cytochrome P450 oxidation had been purported to mediate their toxicity.[14c] We thought that an oxidation event at C7 or C8 may produce the enol-guanidine **7** (Fig. 2), alternatively C15 oxidation may generate the guanidinimine **8**. Both of these intermediates are potentially redundant through extensive tautomerization, and both are electrophilic intermediates, perhaps responsible for the observation that oxidized metabolites of **4** may alkylate DNA.[14d] These considerations helped guide our synthetic investigations. We envisaged a late stage guanidine installation via a reductive guanidinylation of the nitronol **9**. This nitro-aldol disconnection might lead to both the *anti* and *syn* C7 diastereomers required for the synthesis of **4** and **5**, respectively.[20] Further, diastereomers at C8 would allow us to test the possibility that a C7/C8 oxidation event generates an identical metabolite (i.e., **7**).

The three contiguous stereocenters in the A-ring were to be created through an intramolecular nitrone dipolar cycloaddition producing **10**.[21] The ultimate starting point of the synthesis would then be either antipode of the simple crotyl glycine derivative **11**. This was desirable as the absolute configurations of **4**–**6** were unknown and could not be discerned from their biogenesis. Although the absolute configuration of **4** has been inferred, it was confounding that **4** isolated from *C. raciborskii* and that isolated from

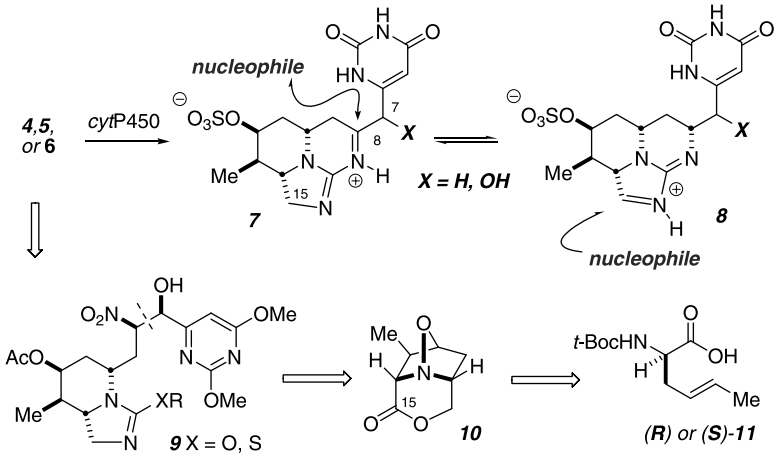


Figure 2. Synthetic strategy.

A. ovalisporum were characterized with opposite signs of optical rotation.

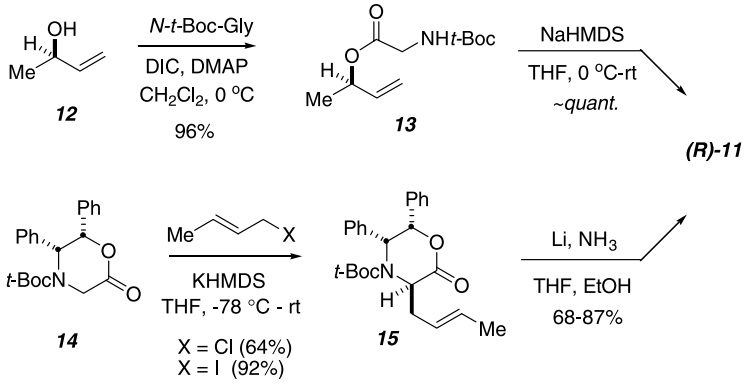
3. Results and discussion

3.1. Synthesis of a common precursor

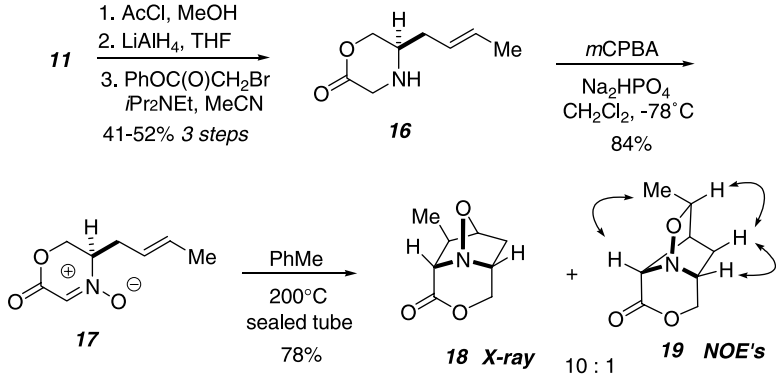
We investigated two strategies to obtain **11** (Scheme 1). The first began with *rac*- or (*R*)-3-buten-2-ol (**12**), which was coupled to *N*-Boc-Gly to give the ester **13**. Enolate-Claisen rearrangement of **13** gave good yields of **11** and was used to generate large quantities of racemic material for initial synthetic explorations.[22] Rearrangement of the optically pure ester through the chelated *Z*-enolate gave (*R*)-**11** in 92:8 er, with sodium being the most effective counterion. Unfortunately attempts to generate a non-chelated *E*-enolate and thus (*S*)-**11**, were ineffective merely eroding the selectivity for the *R*-enantiomer. Alternatively, the oxazinone **14** could be alkylated with crotyl iodide to give **15** as a single diastereomer.[23] Removal of the auxiliary with lithium in ammonia gave (*R*)-**11** in >99:1 er.[24] Similar results were obtained for the synthesis of (*S*)-**11**. Able to deliver both antipodes with higher optical purity, the oxazinone became the preferred method for the preparation of **11**.

Removal of the *t*-Boc group in **11** with concomitant methyl ester formation followed by reduction with lithium aluminumhydride gave the optically pure crotylglycinol (Scheme 2). This was then transformed into the free morpholinone **16** in a one-pot procedure by treatment with α-bromophenyl acetate.[25] It was found imperative that the aminoalcohol be distilled prior to use, trace amounts of water effect the annulation dramatically, and the use of the hygroscopic hydrochloride salt results in considerably lower yields. By introducing the lactone, we were confident that we could obviate dipole isomerization, which leads to diminished selectivity.[26] Oxidation of the secondary amine was most conveniently effected by treatment with purified *m*CPBA in dichloromethane to give an 84% yield of the oxazinone-*N*-oxide **17**.[27] Pleasingly, exposure of **17** to elevated temperatures gave the tricyclic isoxazolidine **18** in 78% isolated yield as a 10:1 mixture contaminated with **19**, arising from *endo*-approach of the alkene to the dipole. While treatment of **17** with scandium triflate can produce the tricycle as an improved 12:1 mixture, the reaction takes up to 3 days to reach completion at ambient temperatures. The relative stereochemistry of **18** was secured by X-ray crystallography.[19i]

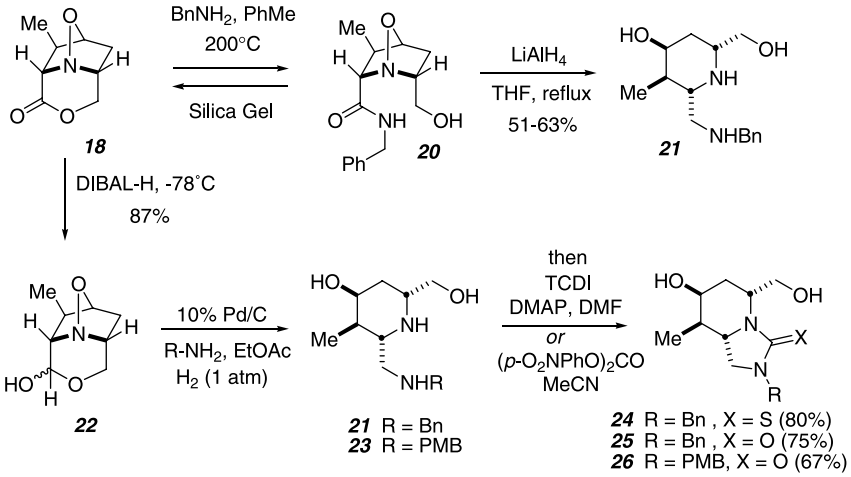
Having established the stereochemistry in the A-ring, we needed to install N16 (Scheme 3). The lactone in **18** could be opened with benzylamine to give **20**, however, purification on silica gel returned **18**. To obviate this reactivity the intermediate amide and *N*,*O*-bond could be reduced with lithium aluminum hydride to afford the diaminodiol **21**. While benzylamine proved a convenient way to introduce a protected nitrogen, we were concerned about its orthogonality with the nitro group. *para*-Methoxybenzylamine cleanly underwent the addition to **18**, but to our surprise we were unable to effect the reduction of this more electron rich amide. We then examined a preemptive oxidation state change for C15. Thus **18** was reduced with diisobutylaluminum hydride to give the lactol



Scheme 1. Preparation of crotyl glycine.



Scheme 2. Construction of the A-ring.

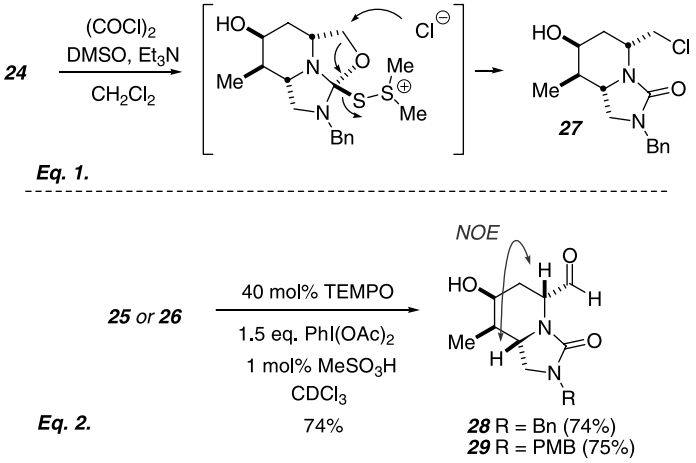


Scheme 3. N16 introduction.

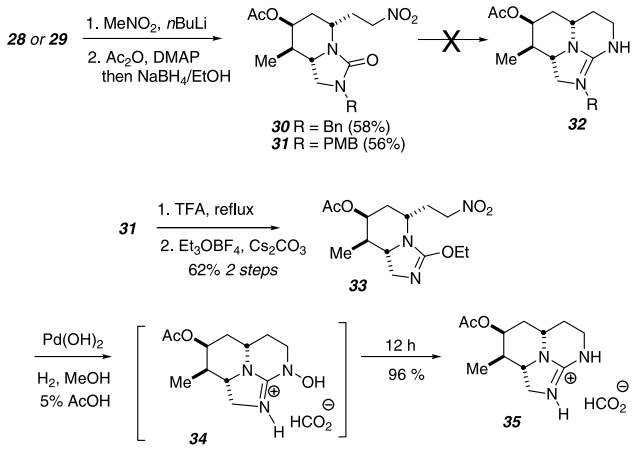
22 in 87% yield. Reductive amination of **22** with either $BnNH_2$ or $PMBNH_2$ proceeded smoothly to afford **21** or **23**, respectively. To aid purification, these diaminodiols were immediately converted to the thiourea using 1,1′-thiocarbonyldiimidazole or the urea using bis-*p*-nitrophenylcarbonate giving **24**–**26** in good yields.

Attempts to selectively oxidize the primary alcohol in the thiourea were unsuccessful. Interestingly, this system suffers from similar reactivity, used productively, in both Weinreb's and White's syntheses.[19j,1] Treatment of **24** with oxalyl chloride and DMSO surprisingly returned the chloromethyl urea **27**, presumably from preferential activation of the thiourea (Scheme 4, Eq. 1). This was also observed when treating **27** with mercuric chloride and the correspoding acetoxymethyl urea was observed when treating the thiourea with Dess–Martin periodinane or $PhI(OAc)_2$/TEMPO. Efforts to introduce productive nucleophiles (i.e., a C1–N synthon) such as cyanide or nitromethane enolates in the presence or mercuric salts failed, prompting us to rely on the ureas. Attempts to oxidize the hydroxymethyl group in **25** utilizing Swern, Dess–Martin, or Ley oxidations actually showed selectivity for the secondary alcohol. Initial experiments utilizing the hindered nitroxyl oxidant, TEMPO, were promising but many of the reported conditions resulted in epimerization of the sensitive ureidoaldehyde.[28] Using $PhI(OAc)_2$ as the reoxidant proved promising as it produced no epimerization, however, the reaction failed to surpass ~30% conversion by ^1H NMR.[29] We were able to show that the rate of oxidation or conversion was independent of the concentration of TEMPO, $PhI(OAc)_2$, or substrate. This suggested that disproportionation of the nitroxyl radical to the active oxoammonium salt may be the problematic step. This equilibrium should be affected by the addition of acid,[30] and indeed the addition of 1 mol% methanesulfonic acid resulted in complete conversion of the primary alcohol by ^1H NMR and ~75% isolated yields.[31] Our concerns that the aldehyde would epimerize to the more stable axial configuration, avoiding pseudo A[1,3] strain with the urea, were negated by NOE correlations in **28**.

Homologation of the aldehydes **28** or **29** by the addition of lithiated nitromethane provided an inseparable (~1.7:1) diastereomeric mixture of nitroalcohols (Scheme 5). Treatment of this mixture with acetic anhydride served both to protect the secondary alcohol and dehydrate the nitroalcohol. Fortunately this provided a single diastereomer of the nitroalkene, assuring us that epimerization of the aldehyde had not occurred. This nitroalkene was reduced



Scheme 4. Oxidation of the ureas.



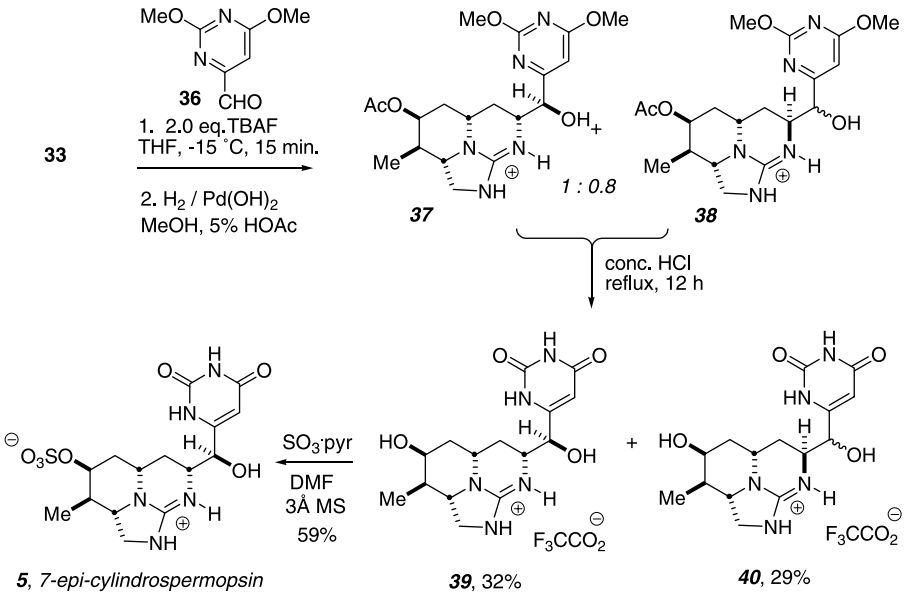
Scheme 5. Successful reductive guanidinylation.

in situ with sodium borohydride to give the homologated nitroalkanes **30** and **31** in reasonable yield for the two steps. Reduction of the nitro group in **30** provided an amine that failed to cyclize to the guanidine **32**. Attempts to force this guanidinylation with heat, Lewis acids or protic acids were unsuccessful. This forced us to pursue the deprotection of the *p*-methoxybenzyl group in **31**, anticipating the activation of the urea as an *O*-alkylisourea. Refluxing **31** in neat trifluoroacetic acid[32] cleanly provided the free urea that could be *O*-alkylated with methyl or ethyl Meerwein's salts in the presence of an inorganic base. The *O*-Me isourea could be synthesized, however, this proved to be unstable, returning the urea after nucleophilic displacement of the methyl group.[33] A slightly more sterically hindered *O*-ethyl isourea was superior and stable to subsequent reaction conditions. Hydrogenolysis of **33** cleanly gave the tricyclic guanidine **35** in 96% isolated yield. Interestingly, the intermediate *N*-hydroxy guanidine **34** could be isolated if the reduction was interrupted after 0.5 h and conducted without the addition of protic acid. Conducting the reduction in the presence of acetic acid accelerated the reduction of **34**, rendering it virtually undetectable.

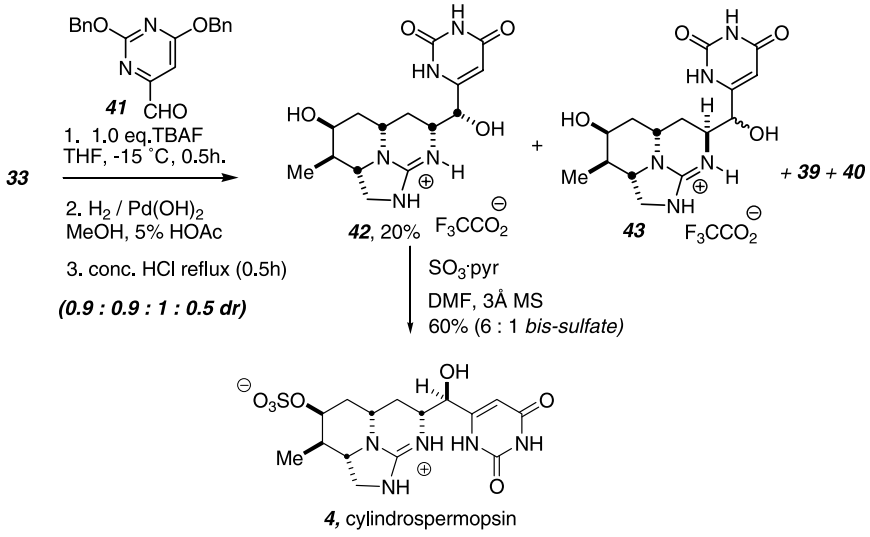
3.2. Synthesis of 7-*epi*-cylindrospermopsin

Having a substrate that successfully participated in the reductive guandinylation we were poised to construct the C7–C8 bond. Initial attempts to effect the nitro-aldol led to disappointing selectivities, yielding equimolar amounts of all four C7–C8 diastereomers. It was found imperative that the nitro-aldol reaction be quenched with AcOH and reduced. Treatment of **33** and 2,6-dimethoxypyrimidine-4-carbaldehyde (**36**)[34] with 2 equiv of tetra-*n*-butylammonium fluoride for short reaction times gave the best selectivities after reductive guanidinylation giving a 1:0.8 (**37**:**38**) mixture favoring the diastereomer required for the synthesis of 7-*epi*-cylindrospermopsin (Scheme 6). If the nitro-aldol products are purified without an acid quench, a ~1:1:1:1 mixture of diastereomers is formed, indicating that the reaction is indeed highly reversible. Thus, all reactions were quenched with 20% AcOH in THF and immediately subjected to reductive guanidinylation. At this stage the diastereomeric dimethoxypyrimidines were inseparable. Acidic hydrolysis of the pyrimidines gave a separable mixture of **39** (32% yield from **33**) and **40** (29%), isolated as their trifluoroacetate slats after purification.[19m] The use of sulfultrioxide–pyridine complex in DMF with 3 Å molecular sieves reproducibly gave **5** in 59% yield also as previously obtained as a ~2:1 mixture with its bis-sulfate.[19j–l] Synthetic **5** had spectroscopic properties identical to those reported. The optical rotation also agreed well: $[\alpha]_D^{25}$ −12.5 (*c* 0.04, H_2O); lit. $[\alpha]_D^{24}$ −20.5 (*c* 0.04, H_2O).[12]

Attempts to control this nitro-aldol process through the use of chiral Lewis acids that have been employed in the asymmetric additions of nitromethane or silylnitronates to aldehydes proved futile.[35] This is in part due to the extreme electrophilicity of the pyrimidine aldehyde **36**, which commonly underwent rapid disproportionation, returning the corresponding pyrimidinemethanol.[36] Cinchonidinium fluoride catalysts also provided equimolar mixtures and typically <10% conversion.[37]



Scheme 6. Synthesis of 7-*epi*-cylindrospermopsin.



Scheme 7. Synthesis of cylindrospermopsin.

3.3. Synthesis of cylindrospermopsin

At this juncture we were intrigued by the possibility of conducting our reductive guanidinylation sequence while simultaneous unmasking the uracil. The di-benzyloxypyrimidine aldehyde **41** was synthesized (Scheme 7).[38] Treatment of **33** with **41** and 1.0 equiv TBAF for 0.5 h followed by reductive guanidinylation gave an extremely clean mixture of diastereomers by ^{1}H NMR, indicating that the benzyl groups are efficiently cleaved under the reducing conditions. Although we had experienced partial cleavage of the acetate group under hydrogenolysis conditions at higher hydrogen pressures, we were unable to drive this cleavage to completion. Thus it remained necessary to expose the mixture to concd HCl briefly (0.5 h). At this stage we could correlate all the diastereomers, with **42** and **43** being identical to the racemic diastereomers synthesized by Snider and Xie. Although this 3-step reaction sequence produces a ~1:1:1:0.5 mixture of **42**:**43**:**39**:**40** the overall chemical yield is excellent with **42** isolated in 20% yield after HPLC purification. Sulfonation, again with sulfur trioxide–pyridine complex, gives cylindrospermopsin in 60% yield, representing the first asymmetric synthesis of **4**.

Interestingly, synthetic cylindrospermopsin carrying the 7*R*, 8*R*, 10*S*, 12*S*, 13*R*, 14*S* configuration exhibits an $[\alpha]_D^{25}$ +7.7 (*c* 0.05, H_2O). The natural material first isolated from *C. raciborskii* displays an opposite rotation; $[\alpha]_D^{25}$ −30.1 (*c* 0.1, H_2O).[9] From *A. ovalisporum*, however, the optical rotation is consistent with synthetic **4**; $[\alpha]_D^{25}$ +12.5 (*c* 0.6, H_2O).[12] It would seem unlikely that the two metabolites would carry opposite absolute configurations as the polyketide synthetases involved in their biogenesis are highly conserved.[39] To reconcile these differences in optical rotation, Circular dichroism (CD) spectra were obtained in water of natural **4** obtained from *C. raciborskii* and compared to that of synthetic **4** at ~44 μg/mL (Fig. 3). Natural cylindrospermopsin displayed a Cotton effect at 264 nm ($\Delta\varepsilon = -6.949$) and 228 nm ($\Delta\varepsilon = -4.243$). Synthetic **4** showed identical Cotton effects at 264 nm ($\Delta\varepsilon = -8.797$) and 229 nm ($\Delta\varepsilon = -4.432$). Although it is unclear what caused the erroneous optical rotation for **4** isolated from *C. raciborskii* it is now clear that cylindrospermopsin does indeed carry the 7*R*, 8*R*, 10*S*, 12*S*, 13*R*, 14*S* configuration from both organisms (*C. raciborskii* and *A. ovalisporum*).

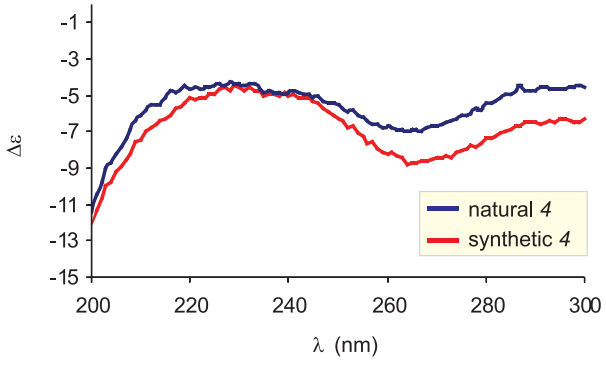
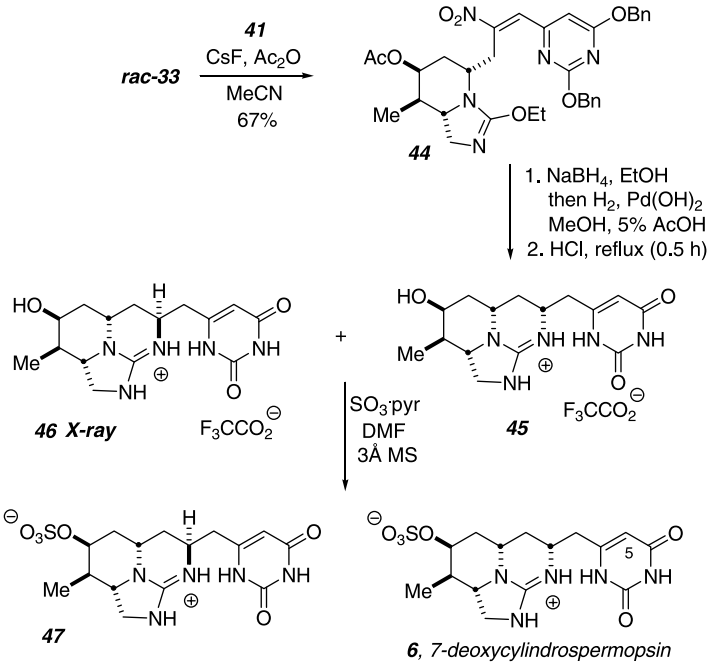


Figure 3. CD spectra of natural and synthetic **4**.

3.4. Synthesis of 7-deoxycylindrospermopsin

Having completed the syntheses of the two oxygenated cylindrospermopsin alkaloids we next focused on the synthesis of **6** (Scheme 8).[19o] We were intrigued that **6** was thought to exist as a mixture of unconjugated uracil tautomers, as the ^{1}H NMR spectrum lacked the vinyllic uracil proton, yet it displayed a $\lambda_{max} = 263$ nm, consistent with the presence of a fully conjugated uracil.[13]

Treatment of the racemic isourea (*rac*-**33**) with the aldehyde **41**, acetic anhydride, and cesium fluoride affords the nitroalkene **44** in 67% yield. Although fluoride promoted coupling and subsequent acetic anhydride mediated eliminations of nitroalcohols are known, they generally require two distinct steps and require a molar excess of the nitroalkane partner.[40] This sequence generates **44** in a single operation with only 1 equiv of both the aldehyde and the nitroalkane, making this protocol amenable to complex molecule synthesis. The nitoalkene is thought to carry the *E* geometry around the tri-substituted double bond. It was



Scheme 8. Synthesis of 7-deoxycylindrospermopin.

hoped that **44** could be directly reduced to **45** [via the intermediate ene-guanidine]. However, subjection of **44** to the reductive guanidinylation conditions returns a complex mixture, containing products arising from hydrolysis of the intermediate enamine prior to ring closure. To circumvent this hydrolysis, **44** was subjected to a one-pot conjugate reduction/reductive guanidinylation sequence giving a 1:1 mixture of diastereomers. Again the acetates could be cleaved by brief heating in HCl to give **45** and **46**. The relative stereochemistry of these uracils was secured by X-ray analysis of **46**.[41] Again, the reductive guanidinylation sequence was clean enough that sulfonation could be executed immediately, also uncomplicated by the need to selectively sulfonate the C12 hydroxyl group. Thus racemic **6** and **47** were obtained in 66% combined yield over the three steps. Co-HPLC-injection of synthetic **6** and natural 7-deoxycylindrospermopsin produced a single peak, corroborating both the structure of **6** and its natural occurrence. Further the ^{1}H NMR spectrum of **6** (Fig. 4) clearly shows the vinyllic uracil proton at 5.72 ppm. To reconcile these differences, we compared the spectrum that led to the elucidation of 5′s structure.[13a] However, it is clear that the natural material is a mixture of compounds, and we could not conclude whether **16** was a minor component of that mixture.

3.5. Inhibition of protein synthesis

Having completed the total syntheses of all the cylidrospermosin alkaloids, we were able to examine the feasibility of our biomechanistic hypothesis for the intermediacy of **7** or **8**. While synthetic **4** was a potent inhibitor of protein synthesis in hepatocytes (4% of control at 3.3 μM), the C8 diastereomer (**38**) required a concentration of 320 μM to achieve the same level of inhibition.[14] Two orders of magnitude less toxic, this suggests that they are not processed through a common metabolic intermediate. Most significantly, our synthetic **6** also proved to be a potent inhibitor of protein synthesis, contrary to previous results.[19o] Protein synthesis was completely inhibited at 12 μM, in vitro, and at 10 μM in whole cells; displaying potency within an order of magnitude of **4**. Resembling intoxication by **4**, synthetic **6** also inhibits the synthesis of glutathione (GSH).[15c] The deoxygenated C8 diastereomer **47**, also required a 100-fold increase in concentration to elicit these effects. These results suggest that substitution at C7 is not requisite for the toxicity of these alkaloids, and that a common oxidized metabolite at C8 is not involved. In agreement with previous studies, intermediates lacking the uracil (i.e., **35**) showed greatly diminished toxicity.[14] However, the *N*-hydroxyguanidine **34** was shown to inhibit protein synthesis on a dose dependent manner at millimolar concentrations, whereas, **35** did not.

4. Conclusion

The synthetic approach detailed herein has provided an efficient and flexible route to these natural products. This strategy has enabled the first enantioselective synthesis of cylindrospermopsin and corroborated the absolute configuration of this natural product. It also permitted the first synthesis of 7-deoxycylindrospermopsin and corrected both structural and toxicological misconceptions. We are further exploiting this synthetic strategy, guided by the preliminary toxicological data, to investigate alternative N18 or C15 oxidation events and their manifestation in the toxicity of the cylindrospermopsin alkaloids.

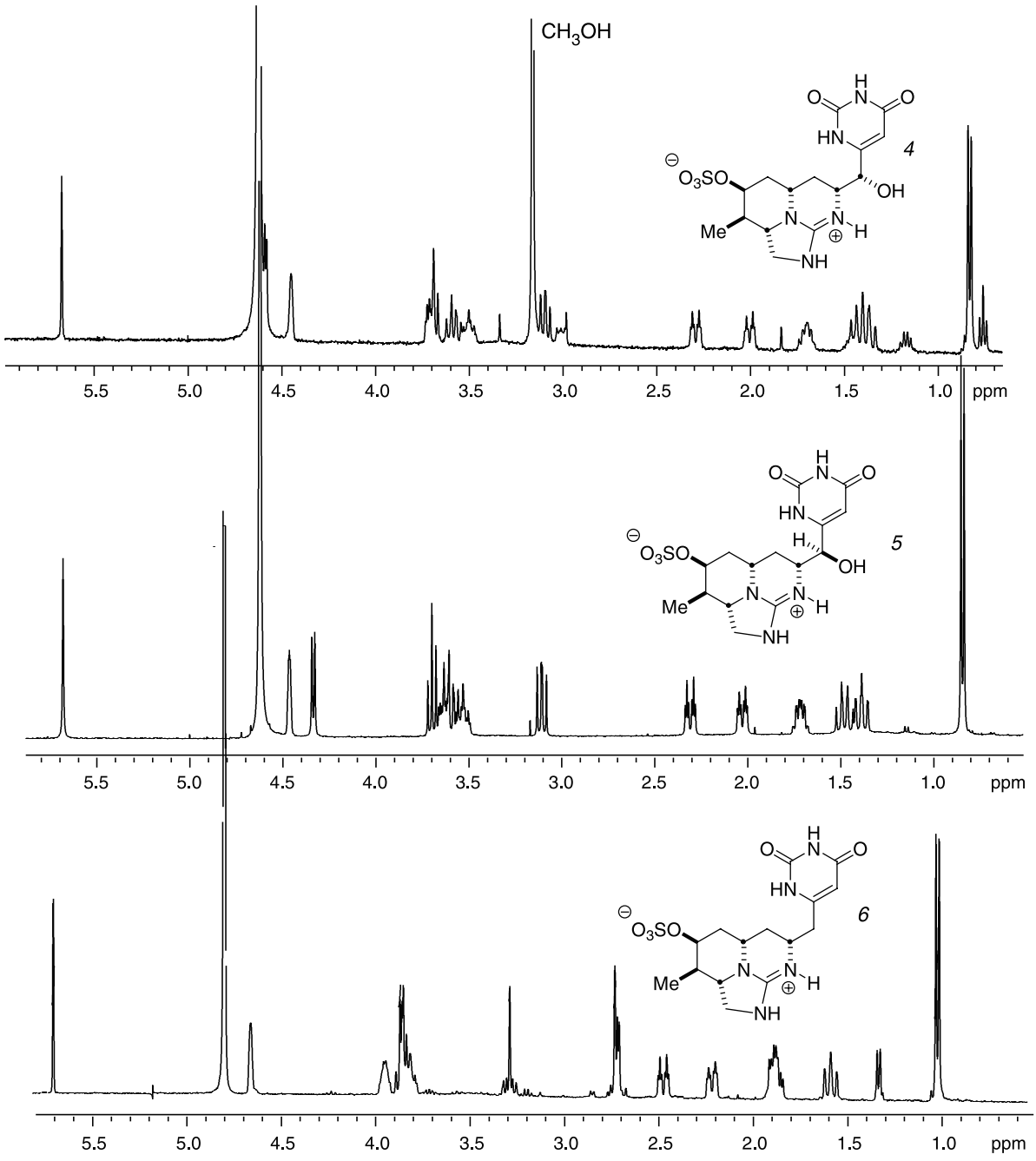


Figure 4. ^{1}H NMR of the synthetic cylindrospermopsins in D_2O (CH_3OH used as internal reference); (1) **4**, (2) **5**, (3) **6**.

5. Experimental

5.1. General

Dichloromethane, diisopropylamine, triethylamine, and *N*,*N*-diisopropylethylamine were distilled from CaH_2 immediately prior to use. Tetrahydrofuran, diethylether, toluene, and dimethylformamide were degassed with argon and passed through a solvent purification system (Meyer of Glass Contour) containing either alumina or molecular sieves. Flash chromatography was performed on Merk silica gel Kieselgel 60 (230–400 mesh) from EM science with the indicated solvent. ^{1}H NMR spectra were recorded on Varian 300, 400, or 500 MHz spectrometers. The chemical shifts (δ) of proton resonances are reported relative to $CHCl_3$, DMSO-d_5, HOD, or HD_2COD, and *J*-values reported in Hertz.[42] ^{13}C NMR spectra were recorded at 75, 100, or 125 MHz. The chemical shifts of carbon resonances are reported relative to the deuterated solvent peak, except those in D_2O, which are referenced to methanol. IR spectra were recorded on a Nicolet Avatar 320-FT IR spectrometer (Dep = deposited). Mass spectra were obtained on a Fisons VG Autospec. Optical rotations were obtained with a 2 mL, 1 dm cell on a Rudolf Research Autopol III polarimeter operating at 589 nm. $CHCl_3$ was distilled from $CaCl_2$ for optical rotations where indicated. HPLC data was obtained on a Waters 600 HPLC system Interfaced with Varian Dynamax Integration software using the indicated column and eluent conditions. Melting points are uncorrected.

5.1.1. 3-(*R*)-But-2-enyl-2-oxo-5-(*R*),6-(*S*)-diphenyl-morpholine-4-carboxylic acid *tert*-butyl ester (15). To a solution of NaI (6.00 g, 40.0 mmol) in MeCN (30 mL) under an argon atmosphere was added TMSCl (5.08 mL, 40.0 mmol) dropwise over 10 min. H_2O (0.36 mL, 20.0 mmol) was then added followed by crotyl alcohol (3.40 mL, 40.0 mmol). After 30 min the reaction was diluted with H_2O (100 mL) and extracted 3×50 mL hexanes. The combined organics were washed with satd $Na_2S_2O_3$, brine, and dried ($MgSO_4$). The organics were then concentrated under aspirator pressure to ~1/4 volume. To this solution, under an argon atmosphere, was added the oxazinone **14** (5.66 g, 16.0 mmol) and THF (100 mL). The mixture was cooled to −78 °C and a 0.5 M solution of KHMDS in PhMe (32.0 mL, 16.0 mmol) was added dropwise over 10 min. After 0.5 h the reaction was quenched with satd NH_4Cl and diluted with Et_2O. The organics were washed with satd $Na_2S_2O_3$, brine, and dried (Na_2SO_4). Concentration of the organics afforded a white solid, which was recrystallized from EtOH/H_2O. The white solid was dried at 60 °C to constant mass giving the crotyloxazinone (5.97 g, 92%, mp 138–141 °C). $[\alpha]_D^{25}$ +13.2 (*c* 1.00, $CHCl_3$). Optical purity was determined by HPLC, Chiracel OD-H column eluting with 97:3 hexanes/*i*PrOH at 1 mL/min; (* indicates minor rotamer): 3(*S*), 5(*S*), 6(*R*) t_R=5.78*, 6.26 min; 3(*R*), 5(*R*), 6(*S*) t_R=7.66*, 9.35 min.[43] ^{1}H NMR ($CDCl_3$, 400 MHz, 273 K): (mixture of rotamers, * indicates minor rotamer where discernable) δ 7.28–7.10 (m, 6H), 7.05 (t, *J*=7 Hz, 2H), 6.94 (d, *J*=7 Hz, 2H), 6.55 (t, *J*=8 Hz, 2H), 6.00* (br d, *J*=2 Hz, 1H), 5.92 (br d, *J*=3 Hz, 1H), 5.7–5.5 (m, 2H), 5.19* (d, *J*=2 Hz, 1H), 5.05 (app t, *J*=7 Hz, 1H), 4.96 (d, *J*=3 Hz, 1H), 4.88* (dd, *J*=6, 8 Hz, 1H), 2.80 (br t, *J*=6 Hz, 2H), 1.70 (overlapping d, *J*=5 Hz, 3H), 1.43* (s, 9H), 1.08 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz, 273 K): (major rotamer) δ 169.5, 153.9, 136.8, 134.7, 130.7, 128.7, 128.3, 127.9, 127.8, 127.7, 126.7, 125.2, 81.3, 79.1, 61.5, 57.2, 37.7, 28.0, 18.2. IR (Dep. $CDCl_3$): 2975 (w), 1752, 1700 (both s), 1388, 1166, 700 (all m). HRMS (FAB+): Calcd for $C_{25}H_{29}NO_4$ (*m*/*z*) 407.2097; Found (*m*/*z*) 407.2094.

5.1.2. 2-(*R*)-*tert*-Butoxycarbonylamino-hex-4-(*E*)-enoic acid ((*R*)-11). A flame dried flask fitted with a CO_2 condenser was charged with flattened lithium metal (660 mg, 95.7 mmol) under argon. Ammonia (50 mL) was condensed into the flask at −78 °C and the blue slurry stirred for 15 min. A solution of the oxazinone **15** (3.00 g, 7.36 mmol) in THF (10 mL) and EtOH (1.29 mL, 22.08 mmol) was added dropwise over 5 min. The cooling bath was removed and the mixture allowed to reflux at −33 °C for 0.5 h. The reaction was quenched by the careful addition of NH_4Cl and the ammonia allowed to evaporate. The resulting residue was taken up in satd $NaHCO_3$ (100 mL) and extracted Et_2O (2×50 mL). The aqueous layer was acidified to pH 2 with $NaHSO_4$ and extracted 3× CH_2Cl_2 (50 mL). The combined organics were washed with brine and dried (Na_2SO_4). Concentration gave the acid as a light yellow oil (1.12 g, 67%), which was used without further purification. Note: smaller reaction scale (~1 mmol) resulted in increased ~80% yields. $[\alpha]_D^{25}$ −4.30 (*c* 1.0, $CHCl_3$). Optical purity can be determined by HPLC on the free amino acid after hydrolysis with concd aqueous HCl, Crownpak CR column eluting with aqueous $HClO_4$ (pH 1) at 0.8 mL/min: 2(*R*) t_R=3.95 min.; 2(*S*) t_R=5.71 min. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.25 (br s, 1H), 5.60 (dq, *J*=15.0, 6.3 Hz, 1H), 5.40–5.24 (m, 1H), 5.00 (d, *J*=7.7 Hz, 1H), 4.34 (br m, 1H), 2.58–2.40 (m, 2H), 1.66 (dd, *J*=6.3, 0.9 Hz, 3H), 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.2, 155.7, 130.5, 124.5, 80.5, 52.2, 35.4, 28.6, 18.3. IR (Dep. $CDCl_3$): 3330 (m, br); 2978 (m); 1716 (s, br); 1508 (m); 1165 (s). HRMS (FAB+): Calcd for $C_{11}H_{20}NO_4$ [M+H]: (*m*/*z*) 230.1392; Found (*m*/*z*) 230.1393.

5.1.3. *tert*-Butoxycarbonylamino-acetic acid 1-methyl-allyl ester (13). To a solution of 3-buten-2-ol (**12**, 2.00 g, 27.7 mmol), 4-dimethylamino pyridine (10 mol%, 346 mg, 2.77 mmol), and *N*-*tert*-butoxycarbonyl glycine (5.35 g, 30.5 mmol) in CH_2Cl_2 (50 mL) was added diisopropylcarbodiimide (4.78 mL, 30.5 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred for 2 h and filtered through Celite with CH_2Cl_2 (100 mL). The combined organics were washed with 10% HCl, satd $NaHCO_3$, brine, and dried (Na_2SO_4). The concentrated organics were purified by flash chromatography (6:1 hexanes/EtOAc) to give the ester as a colourless oil (6.12 g, 96%). If the ester was derived from (*R*)-(−)-3-buten-2-ol $[\alpha]_D^{25}$ +17.9 (*c* 1.50, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.83 (ddd, *J*=17.3, 10.5, 6.6 Hz, 1H), 5.40 (qd (app quintet), *J*=6.6, 6.6 Hz, 1H), 5.25 (dd, *J*=17.2, 1.2 Hz, 1H), 5.15 (dd, *J*=10.5, 1.2 Hz, 1H), 5.00 (br s, 1H), 3.90 (app d, *J*=3.9 Hz, 2H), 1.45 (s, 9H), 1.33 (d, *J*=6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.7, 155.8, 137.2, 116.2, 80.1, 72.4, 42.8, 28.5, 20.1. IR (Dep. $CDCl_3$): 3381 (m); 2980 (m); 1751 (s, sh); 1719 (s); 1520 (m); 1368 (m); 1168 (s). HRMS (FAB+): Calcd for $C_{11}H_{20}NO_4$ [M+H]: (*m*/*z*) 230.1393; Found (*m*/*z*) 230.1392.

5.1.4. *rac*-2-*tert*-Butoxycarbonylamino-hex-4-(*E*)-enoic acid (11). To a solution of ester **13** (2.72 g, 11.9 mmol) in THF (30 mL) under an Ar atmosphere was added a 1 M solution of sodium bis(trimethylsilyl)amide in THF (2.2 equiv, 26.1 mL, 26.1 mmol) at 0 °C. The mixture was allowed to warm to rt. After 2 h the reaction was quenched with satd NH_4Cl (5 mL) and brought to pH 2 by the addition of 10% HCl. The mixture was extracted with Et_2O (3× 50 mL), the combined organics were washed with brine and dried (Na_2SO_4). Concentration gave **11** as a light yellow oil (2.69 g, 99%). All spectral characteristics agreed with (*R*)-**11**.

5.1.5. 5-(*R*)-But-2-enyl-morpholin-2-one (16). Acetyl chloride (1.39 mL, 19.5 mmol) was added dropwise to MeOH (40 mL) at 0 °C and the solution stirred for 15 min. A solution of the acid **11** (1.49 g, 6.49 mmol) in MeOH (3 mL) was added and the mixture allowed to reach rt and stirred an additional 12 h. The mixture was concentrated in vacuo and further concentrated after the addition of Et_2O (2×20 mL) and PhMe (1×50 mL). The crude solid was slurried in THF (50 mL) and $LiAlH_4$ (500 mg, 13.2 mmol) added in portions over 0.5 h at 0 °C. After stirring at rt for an additional 3 h the reaction was quenched by the sequential addition of H_2O (0.5 mL), 15% NaOH (0.5 mL), and H_2O (1.5 mL). The mixture was filtered through Celite with THF and concentrated. The crude oil was purified by Kugelhror distillation, collecting material between 80 and 100 °C

(0.5 mmHg) to give the amino alcohol as a clear oil (487 mg, 65%). $[\alpha]_D^{22}$ −14.3 (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 5.45 (dq, J=15, 6 Hz, 1H), 5.31 (dddq, J=15, 6, 6, 1.5 Hz, 1H), 3.59 (dd, J=11, 4 Hz, 1H), 3.24 (dd, J=11, 8 Hz, 1H), 2.78 (dddd, J=8, 6, 6, 4 Hz, 1H), 2.60 (br s, 3H), 2.06 (ddd, J=13, 6, 6 Hz, 1H), 1.86 (ddd, J=13, 6, 6 Hz, 1H), 1.61 (dd, J=6, 1.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 128.3, 127.4, 66.2, 52.6, 37.5, 18.2. IR (Dep. $CDCl_3$): 3335 (s), 1573, 1435, 1051, 968 (all m). HRMS (FAB+): Calcd for $C_6H_{13}NO$ [M+H]: (*m*/*z*) 116.1075; Found (*m*/*z*) 116.1080.

A solution of the amino alcohol (395 mg, 3.43 mmol) and *i*Pr_2NEt (745 mg, 3.46 mmol, 1.01 equiv) in MeCN (40 mL) was added dropwise over 1 h to a solution of bromophenyl acetate in MeCN (131 mL, final concd to be 0.02 M). The mixture was stirred for an additional 4 h and concentrated. Purification on silica with a Na_2CO_3 pre-pad eluting with 5% *i*PrOH/EtOAc gave the morpholinone **16** as a colourless oil (335 mg, 63%). $[\alpha]_D^{22}$ −49.6 (*c* 1.00, $CHCl_3$). ^1H NMR (CD_3OD, 300 MHz): δ 5.58 (dq, J=15.0, 6.3 Hz, 1H), 5.43 (ddd, J=15.0, 6.6, 1.5 Hz, 1H), 4.38 (dd, J=10.9, 3.7 Hz, 1H), 4.07 (dd, J=10.9, 10.9 Hz, 1H), 3.62 (ABq, dd, J=18.1, 18.1 Hz, 2H), 3.04 (m, 1H), 2.14 (dd, J=6.6, 6.6 Hz, 2H), 1.68 (dd, J=6.3, 1.2 Hz, 3H). ^{13}C NMR (CD_3OD, 75 MHz): δ 170.8, 130.1, 126.9, 75.0, 52.2, 48.2, 35.6, 18.3. IR (Dep. CD_3OD): 3400 (br s), 2964 (s), 1636, 1404 (both m), 1063 (vs). HRMS (FAB+): Calcd for $C_8H_{14}NO_2$ [M+H]: 156.1025; Found 156.1025.

5.1.6. 5-(*R*)-But-2-enyl-4-oxy-5,6-dihydro-[1,4]oxazin-2-one (17). A solution of the oxazinone **16** (260 mg, 1.67 mmol) in CH_2Cl_2 (1 mL) was added dropwise over 5 min to a solution of purified *m*CPBA (636 mg, 3.69 mmol) and Na_2HPO_4 (1.18 g) in CH_2Cl_2 at −78 °C. The reaction was allowed to proceed for 0.5 h and quenched with satd $Na_2S_2O_3$. The mixture was partitioned between H_2O and Et_2O and the organics further washed with 9% Na_2CO_3, brine, and dried (Na_2SO_4). The crude oil was purified on silica eluting with 1:1 hexanes/EtOAc to afford the nitrone as a colorless oil (236 mg, 84%). $[\alpha]_D^{25}$ +4.00 (*c* 4.00, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.14 (s, 1H), 5.66 (dq, J=15.0, 6.5 Hz, 1H), 5.46–5.30 (m, 1H), 4.58 (dd, J=12.3, 3.9 Hz, 1H), 4.43 (dd, J=12.3, 3.9 Hz, 1H), 3.92 (dddd, J=9.3, 3.9, 3.9, 3.9 Hz, 1H), 2.82–2.70 (m, 1H), 2.61–2.49 (m, 1H), 1.69 (d, J=6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.2, 132.3, 124.7, 123.3, 68.1, 65.6, 32.8, 18.3. IR (Dep. $CDCl_3$): 1715, 1556 (both s), 1209 (m), 1061, 968 (both w). HRMS (FAB+): Calcd for $C_8H_{12}NO_3$ [M+H]: 170.0818; Found 170.0817.

5.1.7. 2-(*S*)-Methyl-5-(*S*),9-(*R*)-dioxa-8-(*S*)-aza-tricyclo[5.2.1.0.^{3,8}]decan-4-one (18) The nitrone **17** (60 mg, 0.35 mmol) was dissolved in dry toluene (7 mL) to be 0.05 M. This solution was heated in a sealed tube at 200 °C (sand bath temperature) for 2.5 h. The mixture was then cooled and the solvent removed in vacuo. The crude organics were purified on silica eluting with 1:1 hexanes/EtOAc to afford the tricyclic isoxazolidine **18** (47 mg, 78%) as a colourless oil, which solidified upon standing. An analytical sample was recrystallized from pet. ether/CH_2Cl_2 (mp 78–80 °C). $[\alpha]_D^{25}$ +3.6 (*c* 0.52, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 4.56 (dd, J=12.3, 2.7 Hz, 1H), 4.53 (d, J=6.9 Hz, 1H), 4.45 (dd, J=12.3, 1.2 Hz, 1H), 3.58 (burried m, 1H), 3.58 (d, J=3.6 Hz, 1H), 2.30 (ddd, J=11.7, 10.8, 5.4 Hz, 1H), 2.08 (qd, J=6.9, 3.7 Hz, 1H), 1.56 (dd, J=12.0, 6.0 Hz, 1H), 1.22 (d, J=7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.9, 85.1, 70.4, 65.1, 57.7, 51.7, 34.7, 19.7. IR (Dep. $CDCl_3$): 2966 (w), 1746 (vs), 14548, 1404 (both w), 1227 (m), 1117 (w), 988 (m). HRMS (FAB+): Calcd for $C_8H_{12}NO_3$ [M+H]: 170.0817; Found 170.0812.

Compound **19**. ^1H NMR ($CDCl_3$, 400 MHz): δ 4.49 (buried dd, J=10.8, 1.6 Hz, 1H), 4.00 (dd, J=10.8, 2 Hz, 3.89 (br s, 1H), 3.80 (q, J=6 Hz), 3.82–3.78 (buried m, 1H), 2.98 (d, J=4.8 Hz), 1.87 (ddd, J=12.4, 4.8, 3.2 Hz, 1H), 1.58 (dd, J=12.4, 1.6 Hz, 1H), 1.15 (d, J=6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz, 2:1 mixture): δ 168.4, 81.0, 70.9, 67.9, 61.9, 50.4, 29.5, 20.4.

5.1.8. 2-(*S*)-Methyl-5(*S*),9-(*R*)-dioxa-8-aza-tricyclo-[5.2.1.0.^{3,8}]decan-4-ol (22) To a solution of the isoxazolidine (167 mg, 0.99 mmol) in CH_2Cl_2 (20 mL) at −78 °C under argon was added DIBAL-H (1 M/toluene, 0.99 mL, 0.99 mmol) over 0.5 h. The mixture was stirred for an additional 1 h, quenched with water (0.2 mL), allowed to warm to rt, and stirred for 2 h. The mixture was filtered through Celite and concentrated. The resulting solid was recrystallized from $CHCl_3$/pentane to give the lactol as white prisms (147 mg, 87%). ^1H NMR ($CDCl_3$, 400 MHz): [~2:1 mixture of anomers] δ 5.28 (s), 4.93 (d, J=2.4 Hz), 4.39 (app d, J=5.2 Hz), 4.34 (dd, J=12.4, 2.0 Hz), 3.88 (dd, J=12.8, 1.2 Hz), 3.69 (dd, J=12.4, 1.2 Hz), 3.64 (dd, J=12.4, 0.8 Hz), 3.35 (ddd, J=10.8, 4.4, 2.0 Hz), 3.25 (ddd, J=10.4, 4.4, 2.4 Hz), 3.04 (dd, J=4.4, 2.4 Hz), 2.96 (d, J=4.4 Hz), 2.14–2.01 (m), 1.99 (qd, J=6.8, 4.4 Hz), 1.79 (qd, J=6.8, 4.4 Hz), 1.58 (dd, J=11.2, 4.8 Hz), 1.51 (dd, J=11.2, 4.8 Hz), 1.07 (d, J=7.2 Hz), 1.05 (buried d, J=7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): [~2:1 mixture of anomers] δ 92.2, 86.9, 86.9, 73.9, 73.1, 62.1, 59.9, 59.2, 58.2, 44.5, 40.3, 36.1, 35.9, 19.9, 19.0. IR (Dep. $CDCl_3$): 3406, 3131 (br, s), 2965, 2930 (both s), 1452, 1124, 1092, 985, 710 (all m). HRMS (FAB+): Calcd for $C_8H_{14}NO_3$ [M+H]: 172.0974; Found 172.0976.

5.1.9. 7(*S*)-Hydroxy-5(*R*)-hydroxymethyl-2(*S*)-(4-methoxy-benzyl)-8(*S*)-methyl-hexahydro-imidazo[1,5-*a*]-pyridin-3-one (26). To a solution of the lactol (15 mg, 0.88 mmol) in EtOAc (3 mL) was added *p*-methoxybenzyl amine (17 mg, 0.12 mmol). The solution was degassed with argon and then 10% Pd/C (15 mg) was added. The solution was then purged with H_2 and stirred under a hydrogen atmosphere for 12 h. The mixture was filtered and concentrated. The crude oil was dissolved in MeCN (5 mL) and cooled to 0 °C. A solution of bis-*p*-nitrophenyl carbonate (32 mg, 0.11 mmol) in MeCN (5 mL) was added dropwise over 15 min. After stirring an additional 0.5 h the mixture was concentrated, taken up in EtOAc (20 mL) and the organics washed 3×9% Na_2CO_3, 1×brine and dried (Na_2SO_4). The crude material was purified on silica gel eluting with EtOAc/5% *i*PrOH to give the urea **26** as a clear oil (19 mg, 67%). $[\alpha]_D^{25}$ +37.7 (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.18 (d, J=8.4 Hz, 2H), 6.86 (d, J=8.4 Hz, 2H), 5.80 (dd, J=9, 5 Hz, 1H), 4.4 (1/2ABq, J=15 Hz, 1H), 4.19 (1/2ABq, J=15 Hz, 1H), 3.94 (br dd,

J=2.4, 2.4 Hz, 1H), 3.90–3.72 (buried m, 3H), 3.80 (s, 3H), 3.51 (dddd, J=9, 5, 3, 3 Hz, 1H), 3.45 (ddd, J=10, 9, 9 Hz, 1H), 3.28 (dd, J=9, 9 Hz, 1H), 2.76 (dd, J=9, 9 Hz, 1H), 1.82 (d, J=3 Hz, 1H), 1.72 (ddd, J=14, 3, 3 Hz, 1H), 1.62 (ddd, J=12, 12, 2 Hz, 1H), 1.48 (ddd, J=14, 6, 3 Hz, 1H), 0.89 (d, J=6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 160.8, 159.0, 129.4, 114.0, 68.2, 64.8, 55.4, 54.4, 53.3, 47.9, 47.6, 40.0, 36.4. IR (Dep. $CDCl_3$): 3385, 2933 (both m), 1664, 1513, 1246 (all s). HRMS (FAB+): Calcd for $C_{17}H_{24}N_2O_4$ [M+H]: 322.1814; Found: 321.1811.

5.1.10. 7(*S*)-Hydroxy-2(*S*)-(4-methoxy-benzyl)-8(*S*)-methyl-3-oxo-octahydro-imidazo[1,5-*a*]pyridine-5(*R*)-carbaldehyde (29). To a solution of the diol **26** (211 mg, 0.66 mmol) in $CDCl_3$ (3 mL) was added $PhI(OAc)_2$ (318 mg, 0.99 mmol) and TEMPO (41 mg, 0.26 mmol). Methanesulfonic acid (0.63 mg, 7 μmol, 1 mol%) was then added as a solution in $CDCl_3$. The mixture was stirred for 3 h, diluted with EtOAc (30 mL) and the organics washed with satd $Na_2S_2O_3$, satd $NaHCO_3$, brine, and dried (Na_2SO_4). The resulting oil was purified on silica gel eluting with EtOAc/5% *i*PrOH) to give the aldehyde as a white foam (156 mg, 75%). $[\alpha]_D^{25}$ +84.8 (*c* 1.13, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.81 (d, J=2.1 Hz, 1H), 7.16 (d, J=8.1 Hz, 2H), 6.86 (d, J=8.1 Hz, 2H), 4.36 (1/2ABq, J=15 Hz, 1H), 4.20 (1/2ABq, J=15 Hz, 1H), 4.00 (br s, 1H), 3.82 (buried m, 1H), 3.79 (s, 3H), 3.40 (ddd, J=10.5, 9, 9 Hz, 1H), 3.28 (dd, J=9, 9 Hz, 1H), 2.86 (dd, J=9, 9 Hz, 1H), 1.90 (br d, J=13.5 Hz, 1H), 1.64 (dd, J=12, 12 Hz, 1H), 1.54 (br dd, J=9, 9 Hz, 1H), 0.90 (d, J=6.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.3, 160.4, 158.9, 129.4, 128.7, 114.0, 67.9, 57.4, 55.4, 53.3, 47.9, 47.3, 38.4, 32.9, 13.4. IR (Dep. $CDCl_3$): 3431, 2878 (both m), 1727, 1682, 1513, 1448, 1246 (all s). HRMS (FAB+): Calcd for $C_{17}H_{22}N_2O_4$ [M+H]: 319.1657; Found: 319.1664.

5.1.11. (5*S*,7*S*,8*R*,8a*S*)-2-(4-Methoxybenzyl)-8-methyl-5-(2-nitroethyl)-3-oxo-octahydroimidazo[1,5-*a*]pyridin-7-yl acetate (31). A solution of nitromethane in THF (10:1, 20 mL) under argon was cooled to 0 °C. A 1.6 M solution of *n*BuLi (3.5 mL, 5.66 mmol) was added slowly (caution! highly exothermic) over 20 min. The mixture was stirred an additional 15 min and a solution of the aldehyde **29** (180 mg, 0.57 mmol) in THF added. The reaction was allowed to proceed for 12 h, quenched with satd NH_4Cl and extracted with EtOAc (3×10 mL). The combined organics were washed brine and dried (Na_2SO_4). The crude oil was purified on silica eluting with 1:1 hexanes/EtOAc then EtOAc/5% *i*PrOH to give the diastereomeric nitro alcohol (183 mg, 84%). To a solution of the nitroalcohol (41 mg, 0.11 mmol) and *N*,*N*-dimethylaminopyridine (3 mg, 0.025 mmol, 20 mol%) in CH_2Cl_2 under an argon atmosphere was added acetic anhydride (0.10 mL, 1.1 mmol). After stirring for 12 h the mixture was concentrated, taken up in EtOH (3 mL) and added dropwise to a slurry of $NaBH_4$ (101 mg, 2.67 mmol) in EtOH (5 mL). The mixture was stirred for 2 h and quenched by the addition of 50% AcOH/H_2O (0.4 mL). The mixture was concentrated under reduced pressure and partitioned between H_2O and EtOAc. The aqueous phase was extracted again with EtOAc and the combined organics washed with satd $NaHCO_3$, brine, and dried (Na_2SO_4). The crude oil was purified on silical gel eluting with 1:1 hexanes/EtOAc to give the nitroalkane **31** as a colorless oil (40 mg, 87%). $[\alpha]_D^{25}$ +15.2 (*c* 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12 (d, J=8 Hz, 2H), 6.87 (d, J=8 Hz, 2H), 5.12 (br d, J=6.8, 3 Hz, 1H), 4.72 (ddd, J=13.6, 8.4, 5.6 Hz, 1H), 4.61 (ddd, J=13.6, 5.6, 5.6 Hz), 4.23 (s, 2H), 3.78 (s, 3H), 3.43 (dddd, J=10.8, 10.8, 3, 3 Hz, 1H), 3.28 (ddd, J=9, 8, 5.6 Hz, 1H), 3.18 (dd, J=8, 8 Hz, 1H), 2.78 (dd, J=8, 5 Hz, 1H), 2.41 (dd, J=13.6, 8, 5, 5 Hz, 1H), 2.05 (s, 3H), 1.83 (ddd, J=12, 3, 3 Hz, 1H), 1.70–1.60 (m, 2H), 0.78 (d, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 159.7, 159.1, 129.5, 129.0, 114.2, 73.7, 71.5, 56.1, 55.5, 48.8, 47.3, 46.6, 36.8, 36.4, 29.6, 21.3, 13.3. IR (Dep. $CDCl_3$): 2937 (m), 1737, 1693, 1550, 1513 (all s), 1442, 1374, 1351 (all m), 1242 (s). HRMS (FAB+): Calcd for $C_{20}H_{28}N_3O_6$ [M+H]: 406.1978; Found: 406.1969.

5.1.12. (5*S*,7*S*,8*R*,8a*S*)-3-Ethoxy-8-methyl-5-(2-nitroethyl)-1,5,6,7,8,8a-hexahydroimidazo[1,5-*a*]pyridin-7-yl acetate (33). The protected urea **31** (25 mg, 0.062 mmol) was dissolved in trifluoroacetic acid (1.5 mL). The mixture was refluxed for 1 h and concentrated under reduced pressure. The purple residue was taken up in EtOAc (10 mL) and washed H_2O, satd $NaHCO_3$, brine, and dried (Na_2SO_4). The crude residue was purified on silica gel eluting with EtOAc/5% *i*PrOH to give the urea (14 mg, 80%) as a white solid. $[\alpha]_D^{25}$ +17.3 (*c* 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.14 (dd, J=6, 3 Hz, 1H), 4.80 (br s, 1H), 4.76–4.54 (m, 2H), 3.52–3.38 (m, 3H), 3.1–2.9 (m, 2H), 2.37 (dddd, J=15, 6, 6, 3 Hz, 1H), 2.09 (s, 3H), 1.86 (ddd, J=12, 3, 3 Hz, 1H), 1.84–1.78 (buried m, 1H), 1.66 (ddd, J=12, 3, 3 Hz, 1H), 0.87 (d, J=6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.5, 161.6, 73.6, 71.5, 58.8, 48.5, 42.5, 36.5, 36.6, 29.4, 21.2, 13.2. IR (Dep. $CDCl_3$): 3269, 2939 (both w), 1736, 1698, 1550 (all s), 1436, 1374 (both m), 1242 (s). HRMS (FAB+): Calcd for $C_{12}H_{20}N_3O_5$ [M+H]: 286.1403; Found: 286.1409.

To a solution of the urea (58 mg, 0.20 mmol) under argon in CH_2Cl_2 (10 mL) was added Cs_2CO_3 (650 mg, 2.0 mmol) and triethyloxonium tetrafluoroborate (386 mg, 2.0 mmol). The reaction was stirred at rt for 15 h and quenched by the addition of aqueous 9% Na_2CO_3 (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organics were washed with brine and dried (Na_2SO_4). After concentration the crude mixture was purified on silica gel with 10% MeOH/CH_2Cl_2 to give the isourea **33** as a clear oil (49 mg, 78%). $[\alpha]_D^{25}$ +6.2 (*c* 1.00, $CHCl_3$). ^{1}H NMR (CD_3OD, 400 MHz): δ 5.22 (app br dd, J=8.0, 2.8 Hz, 1H), 4.61 (ddd, J=7.6, 7.6, 2.4 Hz, 1H), 4.21 (q, J=7.2 Hz, 2H), 3.59–3.46 (m, 2H), 3.55 (buried dd, J=11.6, 4.0 Hz, 1H), 3.25 (dd, J=11.6, 4.8 Hz, 1H), 2.66 (dddd, J=18, 8, 8, 8 Hz, 1H), 2.37 (dddd, J=18, 8, 8, 6 Hz, 1H), 2.08 (s, 3H), 1.94–1.79 (m, 2H), 1.65 (ddd, J=14, 12, 2 Hz, 1H), 1.32 (q, J=7.2 Hz, 3H), 0.85 (d, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 163.3, 73.0, 71.9, 65.4, 63.8, 52.5, 48.6, 36.2, 35.5, 30.3, 21.2, 14.6, 13.0. IR (Dep. $CDCl_3$): 2963 (m), 1735 (s), 1622, 1550, 1436, 1372, 1334 (all m), 1228 (s). HRMS (FAB+): Calcd for $C_{14}H_{24}N_3O_5$ [M+H]: 314.1715; Found: 314.1710.

5.1.13. 7-*epi*-Cylindrospermopsin diol (37). To a solution of **33** (8.0 mg, 26 μmol) and pyrimidine aldehyde **36** (5.2 mg, 31 μmol) in THF at −15 °C was added a 1 M

solution of tetra-*n*-butylammonium fluoride (51 μL, 51 μmol). The reaction was allowed to proceed for 0.5 h and quenched with Twenty percentage AcOH/THF (0.5 mL). The mixture was concentrated and the crude oil dissolved in 5% AcOH/MeOH (5.1 mL, to be 5 mM) and the solution purged with argon. 20% $Pd(OH)_2$ on carbon (32 mg) was added and the solution purged with hydrogen. After stirring for 12 h under an H_2 atmosphere the mixture was filtered through a 0.45 μm Acrodisc® and concentrated. Purification (to remove 6-hydroxymethyl pyrimidine and TBAF) by PTLC eluting with 20% MeOH/CH_2Cl_2 with 1% HCO_2H afforded an inseparable mixture (1:0.8) of the two C-7 diastereomers after stripping the silica with 20% abs EtOH/CH_2Cl_2. This mixture was then refluxed in concd HCl for 8 h and concentrated. Purification of the uracils was achieved by HPLC using a Waters Symmetry® C-18 colum (4.6×250 mm) eluting with 4% MeOH/H_2O with 1% TFA at 1.5 mL/min, monitoring at 263 nm to give 7-*epi*-cylindrospermopsin diol as a white solid (3.0 mg, 32%, t_R=19.05 min) and the other C8 diastereomer also as a white crystalline solid (2.7 mg, 29%, t_R=23.53 min).

Compound **37**. ^1H and ^{13}C NMR agreed with those previously reported.[19m] $[\alpha]_D^{25}$ −11.7 (*c* 0.06, H_2O); (lit. $[\alpha]_D^{24}$ −8.3 (*c* 0.06, H_2O));[12] **38**: $[\alpha]_D^{25}$ +70.0 (*c* 0.20, H_2O). ^1H NMR (D_2O, 400 MHz): δ 5.80 (s, 1H), 4.62 (d, *J*=4.4 Hz, 1H), 4.04 (br s, 1H), 3.88–3.74 (m, 3H), 3.28 (app t, *J*=8.4 Hz, 1H), 2.26 (ddd, *J*=14, 4, 3 Hz, 1H), 2.07 (ddd, *J*=14, 4, 4 Hz, 1H), 1.87 (ddd, *J*=15, 10, 6 Hz, 1H), 1.78–1.68 (m, 1H), 1.52 (app t, *J*=13 Hz, 1H), 0.97 (d, *J*=7 Hz, 3H). HRMS (FAB+): Calcd for $C_{15}H_{22}N_5O_4$ [M+H]: 336.1672; Found: 336.1672.

5.1.14. 7-*epi*-Cylindrospermopsin (5). 7-*epi*-Cylindrospermopsin diol **37** (2.6 mg, 7.0 μmol) was co-concentrated with MeCN (2×5 mL) and PhMe (2×5 mL). The resulting solid was dried under vacuum for 0.5 h and placed under argon. DMF (0.4 mL) and activated, powdered 3 Å molecular sieves (6 mg) were added and the mixture stirred for 15 min. To this solution was added solid SO_3·pyr (11 mg, 70 μmol) and the mixture was stirred for 1 h. MeOH (0.1 mL) was added and the solvents removed in vacuo. The mixture was taken up in MeOH and filtered through a 0.45 μm Acrodisc®. Purificataion by HPLC on a Waters Symmetry® C-18 colum (4.6×250 mm) eluting with 2% MeOH/H_2O with 1% TFA at 1.5 mL/min, monitoring at 263 nm gave 7-*epi*-cylindrospermopsin **5** (t_R=9.22 min) as a white solid after lyophilization (1.7 mg, 59%). This was preceded by its bis sulfate (t_R=6.54 min) as a ~2:1 mixture. $[\alpha]_D^{25}$ −12.5 (*c* 0.04, H_2O); (lit. $[\alpha]_D^{24}$ −20.5 (*c* 0.04, H_2O),[3] ^1H and ^{13}C NMR spectra agree with those reported.[12] HRMS (FAB+): Calcd for $C_{15}H_{22}N_5O_7S$ [M+H]: 416.1240; Found: 416.1247.

5.1.15. 2,4-Bis(benzyloxy)-6-bromopyrimidine (41). To a solution of benzyl alcohol (0.11 mL, 1.03 mmol) in THF (0.5 mL) under an argon atmosphere at 0 °C was added a 1.6 M solution of *n*BuLi in hexanes (0.62 mL, 0.99 mmol). The mixture was stirred 10 min and DMF (5 mL) added. A solution of the tribromopyrimidine in DMF (1 mL) was added and the mixture stirred at 0 °C for 3 h. The reaction was quenched with satd NH_4Cl and diluted with H_2O (10 mL). The aqueous phase was extracted with Et_2O (3×10 mL) and the combined organics washed with brine and dried (Na_2SO_4). The crude oil was purified on silica gel eluting with 15:1 hexanes/EtOAc to give the dibenzyloxypyrimidine as a clear oil (137 mg, 80%). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.47–7.32 (m, 10H), 6.66 (s, 1H), 5.43 (s, 2H), 5.40 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.1, 163.8, 152.3, 135.9, 135.6, 128.7, 128.6, 128.5, 128.4, 128.3, 128.3, 105.5, 70.1, 69.1. IR (Dep. $CDCl_3$): 2952 (w), 1549, 1404, 1323 (all s), 1130, 1003 (both m). HRMS (FAB+): Calcd for $C_{18}H_{16}N_2O_2^{81}Br_1$ [M+H]: 373.0375; Found 373.0363. Calcd for $C_{18}H_{16}N_2O_2Br_1$ [M+H]: 371.0395; Found 371.0383.

5.1.16. Cylindrospermopsin (4). To a solution of **33** (4.5 mg, 14 μmol) and **41** (5.5 mg, 17 μmol) in THF (120 μL) at −15 °C was added a 1 M solution of TBAF (14 μL, 14 μmol). The solution was stirred for 0.5 h and quenched with 20% AcOH/THF (0.2 mL). The mixture was concentrated and taken up in 5% AcOH/THF (3 mL) and $Pd(OH)_2$ (20%/C, 5 mg) added. The solution was purged with H_2 and stirred under an H_2 atmosphere for 12 h. The mixture was taken up in MeOH and filtered through a 0.45 μm Acrodisc®. Purificataion by HPLC on a Waters Symmetry® C-18 colum (4.6×250 mm) eluting with 8% MeOH/H_2O with 1% TFA at 1.5 mL/min, monitoring at 263 nm gave cylindrospermopsin diol (**42**) (t_R=9.47 min) as a white solid after lyophilization (1.3 mg, 20%). $[\alpha]_D^{25}$ +7.7 (*c* 0.13, H_2O). Compound **42** (1.3 mg, 2.89 μmol) was co-concentrated with MeCN (2×5 mL) and PhMe (2×5 mL). The resulting solid was dried under vacuum for 0.5 h and placed under argon. DMF (0.3 mL) and activated, powdered 3 Å molecular sieves (6 mg) were added and the mixture stirred for 15 min. To this solution was added solid SO_3·pyr (4.6 mg, 29 μmol) and the mixture stirred for 1 h. MeOH (0.1 mL) was added and the solvents removed in vacuo. The mixture was taken up in MeOH and filtered through a 0.45 μm Acrodisc®. Purification by HPLC on a Waters Symmetry® C-18 colum (4.6×250 mm) eluting with 4% MeOH/H_2O with 1% TFA at 1.5 mL/min, monitoring at 263 nm gave cylindrospermopsin **4** (t_R=8.14 min) as a white solid after lyophilization (0.7 mg, 60%). This was preceded by its bis sulfate (t_R=5.32 min) as a ~6:1 mixture. ^1H and ^{13}C NMR agreed with those previously reported.[9,12,19h] $[\alpha]_D^{25}$ +8.0 (*c* 0.05, H_2O).

5.1.17. 5-((*E*)-3-(2,6-Bis(benzyloxy)pyrimidin-4-yl)-2-nitroallyl)-3-ethoxy-8-methyl-1,5,6,7,8,8a-hexahydroimidazo[1,5-*a*]pyridin-7-yl acetate (44). To a solution of the isourea **33** (23 mg, 73 μmol) and the pyrimidine aldehyde (26 mg, 81 μmol, 1.1 equiv) in CH_2Cl_2 (1 mL) under argon was added Ac_2O (34 μL, 0.35 mmol, 5 equiv). CsF (110 mg, 0.73 mmol) was then added as a solid in one portion. The reaction was diluted with MeCN (3 mL) and the mixture stirred for 4 h. The reaction was concentrated under reduced pressure, taken up in CH_2Cl_2 and filtered to remove the cesium salts. This mixture was again concentrated and purified on silica gel eluting with 10% MeOH/CH_2Cl_2 to give the nitroalkene as a yellow oil (30 mg, 67%) as a single geometric isomer. This compound is unstable, decomposing overnight at rt. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.68 (s, 1H), 7.48–7.30 (m, 10H), 6.58 (s, 1H), 5.52–5.40 (m, 4H), 4.98 (br 2, *J*=3.2 Hz), 4.28–4.18 (m, 3H), 4.00 (dd, *J*=14, 5 Hz, 1H), 3.66 (ddd, *J*=15, 10, 5 Hz, 1H), 3.55

(dd, J=10, 8 Hz, 1H), 3.40–3.30 (m, 1H), 3.12 (dd, J=10, 8 Hz, 1H), 1.98 (s, 3H), 1.78–1.64 (m, 1H), 1.62–1.60 (m, 2H), 1.25 (t, J=7.2 Hz, 3H), 0.76 (d, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.3, 170.6, 165.0, 164.3, 159.8, 155.2, 136.2, 135.7, 130.4, 128.9, 128.7, 128.5, 128.4, 127.8, 106.9, 71.6, 69.8, 69.1, 65.3, 64.1, 52.9, 50.2, 36.7, 35.4, 31.1, 21.2, 14.7, 13.0. HRMS (FAB+): Calcd for $C_{33}H_{38}N_5O_7$ [M+H]: (m/z) 616.2771; Found: (m/z) 616.2795.

5.1.18. 7-Deoxycylindrospermopsin diol (45). A solution of the nitroalkene **44** (18 mg, 29.2 μmol) in EtOH (0.5 mL) was added dropwise to a slurry of $NaBH_4$ (5 mg, 146 μmol) in EtOH (0.5 mL) over 20 min. After stirring for 1.5 h the reaction was quenched by the addition of 1:1 H_2O/AcOH (0.1 mL) and concentrated. The concentrate was diluted with 5% AcOH:MeOH (5.8 mL, to be 5 mM) and purged with argon. $Pd(OH)_2$ (20%/C, 6 mg) was added and the mixture stirred under a hydrogen atmosphere for 12 h, filtered through a 0.45 μm Acrodisc® and concentrated. The residue was dissolved in concd HCl and refluxed for 1 h and concentrated. Purification of the uracils was achieved by HPLC using a Waters Symmetry® C-18 colum (4.6× 250 mm) eluting with 8% MeOH/H_2O with 1% TFA at 1.5 mL/min, monitoring at 263 nm to give 7-deoxy-cylindrospermopsin diol **45** as a white solid (3.7 mg, 38%, t_R=22.1 min) preceded by the C8 diastereomer **46** also obtained as a white crystalline solid (4 mg, 38%, t_R= 12.6 min). A small sample of **45** (~1 mg) was recrystallized from methanol (layered with pentane) to give X-ray quality crystals. Compound **45** (8*S**): ^{1}H NMR (D_2O, 500 MHz): δ 5.68 (s, 1H), 4.03 (br s, 1H), 3.92 (m, 1H), 3.82 (dd, J=9, 9 Hz, 1H), 3.78 (dd, J=9, 9 Hz, 1H), 3.72 (dddd, J=11, 11, 4, 4 Hz, 1H), 3.25 (m, 1H), 2.71 (dd, J=14, 5.5 Hz, 1H), 2.67 (dd, J=14, 9 Hz, 1H), 2.16 (dt, J=14, 4, 4 Hz, 1H), 2.06 (dt, J=15, 3 Hz, 1H), 1.83 (ddd, J=15, 11, 5 Hz, 1H), 1.72 (ddq, J=14, 7, 3 Hz, 1H), 1.55 (ddd, J=14, 14, 1.5 Hz, 1H), 0.95 (d, J=7 Hz, 3H). HRMS (FAB+): Calcd for $C_{15}H_{22}N_5O_3$ [M+H]: (m/z) 320.1723; Found: (m/z) 320.1723. Compound **46** (8*R**): ^{1}H NMR (D_2O, 500 MHz): δ 5.72 (s, 1H), 4.00 (br s, 1H), 3.86 (buried m, 1H), 3.82 (dd, J=9.0, 9.0 Hz, 1H), 3.74 (dd, J=10, 10 Hz, 1H), 3.61 (ddt, J=11, 11, 3.5 Hz, 1H), 3.23 (dd, J=10, 10 Hz, 1H), 2.73 (app d, J=5 Hz, 1H), 2.26 (dt, J=15, 5, 5 Hz, 1H), 2.07 (dt, J=15, 3, 3, Hz, 1H), 1.70 (ddq, J=9, 6.5, 2.5 Hz, 1H), 1.50 (app q, J=11 Hz, 2H), 0.95 (d, J= 6.5 Hz, 3H). HRMS (FAB+): Calcd for $C_{15}H_{22}N_5O_3$ [M+H]: (m/z) 320.1723; Found: 320.1712.

5.1.19. 7-Deoxycylindrospermopsin (6). Alternatively a mixture of the C12-hydroxy uracils (3.2 mg, 7.9 μmol) can be directly sulfonated by treatment with SO_3·pyr (19 mg, 120 μmol) in DMF (300 μL). Purification of the uracils after concentration was achieved by HPLC using a Waters Symmetry® C-18 colum (4.6×250 mm) eluting with 8% MeOH/H_2O with 1% TFA at 1.5 mL/min, monitoring at 263 nm to give 7-deoxy-cylindrospermopsin **6** as a white solid (1 mg, 33%, t_R=8.25 min) preceded by the C8 diastereomer **47** also obtained as a white crystalline solid (1 mg, 33%, t_R=4.91 min). Compound **6**: ^{1}H NMR (D_2O, 400 MHz): δ 5.74 (s, 1H), 4.63 (br s, 1H), 3.92–3.85 (burried m, 1H), 3.86 (dd, J=8.9, 8.9 Hz, 1H), 3.78 (dd, J=10.7, 10.7 Hz, 1H), 3.70 (dddd, J=11.3, 11.3, 3.8, 3.8 Hz, 1H), 3.26 (dd, J=10.8, 8.9 Hz, 1H), 2.76 (app d, J= 6.8 Hz, 2H), 2.48 (ddd, J=14.3, 3.8, 3.8 Hz, 1H), 2.32 (ddd, J=13.2, 3.6, 3.6 Hz, 1H), 1.87 (ddd, J=8.9, 6.8, 2 Hz, 1H), 1.55 (app dd, J=13.2, 11.3 Hz, 1H), 1.01 (d, J=6.8 Hz, 3H). Calcd for $C_{15}H_{22}N_5O_6S$ [M+H]: (m/z) 400.1296; Found: 400.1282.

Acknowledgements

This work was supported by the National Institutes of Health Grant #GM068011 (to R.M.W) and Grant #DK51788 (to M.T.C.R) and the National Science Foundation #CHE0202827 (to R.M.W). We are grateful to Array Biopharma for fellowship support to R.E.L. We thank Dr. Andrew Humpage for providing a sample of natural 7-deoxycylidrospermopsin and Dr. Glenn Shaw for providing us with spectra of 6. We thank Dr. Chris Rithner for helpful NMR discussions and are indebted to Prof. Alan Kennan and Dr. Nathan Schnarr for assistance with CD measurements.

References and notes

1. Carmichael, W. W.; Falconer, I. R. In *Algal Toxins in Seafood and Drinking Water*; Falconer, I. R., Ed.; Academic: London, 1993; pp 187–209.
2. Rinehart, K. L.; Harada, K.; Namikoshi, M.; Chen, C.; Harvis, C. A.; Munro, M. H. G.; Blunt, J. W.; Mulligan, P. E.; Beasely, V. R.; Dahlem, A. M.; Carmichael, W. W. *J. Am. Chem. Soc.* **1988**, *110*, 8557–8558.
3. Nishiwaki-Matsushima, R.; Ohta, T.; Nishiwaki, S.; Suganuma, M.; Kohyama, K.; Ishikawa, T.; Carmichael, W. W. *J. Cancer Res. Clin. Oncol.* **1992**, *118*, 420–424.
4. Jochimson, E. M.; Charmichael, W. W.; An, J. S.; Cardo, D. M.; Cookson, S. T.; Holmes, C. E. M.; Antunes, M. B.; Fihlo, D.; Lyra, T. M.; Barreto, V. S. T.; Azevedo, S. M. F. O.; Jarvis, W. R. *N. Eng. J. Med.* **1998**, *338*, 873–878.
5. Fischer, W. J.; Altheimer, S.; Cattori, V.; Meier, P. J.; Dietrich, D. R. *Toxicol. Appl. Pharmacol.* **2005**, *203*, 257–263.
6. MacKintosh, C.; Beattie, K. A.; Klumpp, S.; Cohen, P.; Codd, G. A. *FEBS Lett.* **1990**, *264*, 187–192.
7. Rinehart, K. L.; Harada, K.; Namikoshi, M.; Chen, C.; Harvis, C. A.; Munro, M. H. G.; Blunt, J. W.; Mulligan, P. E.; Beasely, V. R.; Dahlem, A. M.; Carmichael, W. W. *J. Am. Chem. Soc.* **1988**, *110*, 8557–8558 and references therein.
8. Hawkins, P. R.; Runnegar, M. T. C.; Jackson, A. R. B.; Falconer, I. R. *Appl. Environ. Microbiol.* **1985**, *50*, 1292–1295.
9. Ohtani, I.; Moore, R. E.; Runnegar, M. T. C. *J. Am. Chem. Soc.* **1992**, *114*, 7941–7942.
10. Harada, K.; Ohtani, I.; Iwamoto, K.; Suzuki, M.; Watanabe, M. F.; Watanabe, M.; Terao, K. *Toxicon* **1994**, *32*, 73–84.
11. Banker, R.; Carmeli, S.; Hadas, O.; Teltsch, B.; Porat, R.; Sukenik, A. *J. Phycol.* **1997**, *33*, 613–616.
12. Banker, R.; Teltsch, B.; Sukenik, A.; Carmeli, S. *J. Nat. Prod.* **2000**, *63*, 387–389.
13. (a) Norris, R. L.; Eaglesham, G. K.; Pierens, G.; Shaw, G. R.; Smith, M. J.; Chiswell, R. K.; Seawright, A. A.; Moore, M. R. *Environ. Toxicol.* **1999**, *14*, 163–165. (b) Li, R. H.; Carmichael, W. W.; Brittain, S.; Eaglesham, G. K.; Shaw, G. R.; Liu, Y. D.; Watanabe, M. M. *J. Phycol.* **2001**, *37*, 1121–1126.

14. Runnegar, M. T.; Xie, C.; Snider, B. B.; Wallace, G. A.; Weinreb, S. M.; Kuhlenkamp, J. *Toxicol. Sci.* **2002**, *67*, 81.
15. (a) For a review see: Griffiths, D. J.; Saker, M. L. *Environ. Toxicol.* **2003**, *18*, 78–93. (b) Terao, K.; Ohmori, S.; Igarashi, K.; Ohtani, I.; Watanabe, M. F.; Harada, K. I.; Ito, E.; Watanabe, M. *Toxicon* **1994**, *32*, 833–843. (c) Runnegar, M. T.; Kong, S. M.; Zhong, Y. Z.; Lu, S. C. *Biochem. Pharmacol.* **1995**, *49*, 219–225. (d) Humpage, A. R.; Fenech, M.; Thomas, P.; Falconer, I. R. *Mutat. Res.* **2000**, *472*, 155–161.
16. Reisner, M.; Carmeli, S.; Werman, M.; Sukenik, A. *Toxicol. Sci.* **2004**, *82*, 620–627.
17. Information available at: http://www.epa.gov/safewater/standard/ucmr/, 2001 and http://ntpserver.niehs.nih.gov/htdocs/Results_status/ResstatC/M000072, 2004.
18. Burgoyne, D. L.; Hemscheidt, T. K.; Moore, R. E.; Runnegar, M. T. *J. Org. Chem.* **2000**, *65*, 152–156.
19. (a) Heintzelman, G. R.; Parvez, M.; Weinreb, S. M. *Synlett* **1993**, 551–552. (b) Harvey, B. B. T. C. *Tetrahedron Lett.* **1995**, *36*, 4587–4590. (c) Heintzelman, G. R.; Weinreb, S. M.; Parvez, M. *J. Org. Chem.* **1996**, *61*, 4594–4599. (d) Snider, B. B.; Xie, C. Y. *Tetrahedron Lett.* **1998**, *39*, 7021–7024. (e) McAlpine, I. J.; Armstrong, R. W. *Tetrahedron Lett.* **2000**, *41*, 1849–1853. (f) Keen, S. P.; Weinreb, S. M. *Tetrahedron Lett.* **2000**, *41*, 4307–4310. (g) Djung, J. F.; Hart, D. J.; Young, E. R. R. *J. Org. Chem.* **2000**, *65*, 5668–5675. (h) Xie, C. Y.; Runnegar, M. T. C.; Snider, B. B. *J. Am. Chem. Soc.* **2000**, *122*, 5017–5024. (i) Looper, R. E.; Williams, R. M. *Tetrahedron Lett.* **2001**, *42*, 769–771. (j) Heintzelman, G. R.; Fang, W. K.; Keen, S. P.; Wallace, G. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **2001**, *123*, 8851–8853. (k) Heintzelman, G. R.; Fang, W. K.; Keen, S. P.; Wallace, G. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **2002**, *124*, 3939–3945. (l) White, J. D.; Hansen, J. D. *J. Am. Chem. Soc.* **2002**, *124*, 4950–4951. (m) Looper, R. E.; Williams, R. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2930–2933. (n) White, J. D.; Hansen, J. D. *J. Org. Chem.* **2005**, *7*, 1963–1977. (o) Looper, R. E.; Runnegar, M. T. C.; Williams, R. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3879–3881.
20. For a review see: Luzio, F. A. *Tetrahedron* **2001**, *57*, 915–945.
21. For reviews on the 1,3-DC reaction: (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, 863–909. (b) Confalone, P. N.; Huie, E. M. In Kende, A. S., Ed.; Organic Reactions; Wiley: New York, 1988; Vol. 36, pp 3–173.
22. Kazmaier, U. *Agnew. Chem., Int. Ed. Engl.* **1994**, *33*, 998–999.
23. (a) Williams, R. M.; Im, M. N. *J. Am. Chem. Soc.* **1991**, *113*, 9276–9286. (b) Williams, R. M. *Aldrichim. Acta* **1992**, *25*, 11–25. (c) Williams, R. M. In Hassner, A., Ed.; Advances in Asymmetric Synthesis; JAI: Greenwich, CT, 1995; Vol. 1, pp 45–94. (d) Lactone **14** and the corresponding antipode are commercially available from Aldrich Chemical Co.; **11**: catalog #33-184-8; the antipode of **14** is catalog #33,181-3
24. For an analogous preparation of (*R*)-allylglycine see: Williams, R. M.; Sinclair, P. J.; DeMong, D. E. *Org. Synth.* **2003**, *80*, 31.
25. Dellaria, J. F.; Santasiero, B. D. *J. Org. Chem.* **1989**, *54*, 3916.
26. (a) Tamura, O.; Gotanda, K.; Terashima, R.; Kikuchi, M.; Miyawaki, T.; Sakamoto, M. *Chem. Commun.* **1996**, 1861–1862. (b) Baldwin, S. W.; Young, B. G.; McPhail, A. T. *Tetrahedron Lett.* **1998**, *39*, 6819–6822.
27. Traylor, T. G.; Miksztal, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 2770.
28. For a review see: De Nooy, A. E. J.; Besemer, A. C.; van Bekkum, H. *Synthesis* **1996**, 1153–1174.
29. De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974–6977.
30. Ma, Z.; Bobbitt, J. M. *J. Org. Chem.* **1991**, *56*, 6110–6114.
31. *p*-TsOH and AcOH as well as $CDCl_3$, which presumably contains trace amounts of HCl were not as effective as co-catalysts. The reaction can be run concentrated (0.5–1 M) and was routinely run in $CDCl_3$ to allow careful monitoring to ensure selective oxidation of the primary alcohol. Commercial $CHCl_3$ is stabilized with ethanol and is unsuitable for the oxidation unless distilled from $CaSO_4$ prior to use.
32. Brooke, G. M.; Mohammed, S.; Whiting, M. C. *J. Chem. Soc., Chem. Commun.* **1997**, 1511.
33. Treatment of the *O*-Me isourea with benzene thiol quantitatively returned the urea with concomitant formation of mehthylphenyl sulfide.
34. Langley, B. W. *J. Am. Chem. Soc.* **1956**, *75*, 2136–2141.
35. (a) Colvin, E. W.; Seebach, D. *Chem. Commun.* **1978**, 689–691. (b) Sasi, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420. (c) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693.
36. Hemiacetal formation occurs immediately in CD_3OD.
37. Corey, E. J.; Zhang, F.-Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 1931–1934.
38. Stogryn, E. L. *J. Heterocycl. Chem.* **1974**, *11*, 251.
39. Schembri, M. A.; Neilan, B. A.; Saint, C. P. *Environ. Toxicol.* **2001**, *16*, 413–421.
40. Wollenberg, R. H.; Miller, S. J. *Tetrahedron Lett.* **1978**, *35*, 3219–3222.
41. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. ID: CCDC 258351.
42. Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512–7515.
43. Clayden, J.; Pink, J. H. *Angew. Chem., Int. Ed.* **1998**, 1937–1939.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 4563–4572

Palladium-catalyzed carbonylative cyclization of Baylis–Hillman adducts. An efficient approach for the stereoselective synthesis of 3-alkenyl phthalides

Fernando Coelho,[a,*] Demetrius Veronese,[a] Cesar H. Pavam,[a] Vanderlei I. de Paula[b] and Regina Buffon[b,*]

[a]*Laboratory of Synthesis of Natural Products and Drugs, IQ/DQO, PO Box 6154, 13084-971 Campinas, SP, Brazil*
[b]*IQ/DQI, UNICAMP, PO Box 6154, 13084-971 Campinas, SP, Brazil*

Received 9 December 2005; revised 10 February 2006; accepted 15 February 2006

Available online 10 March 2006

Abstract—A palladium-mediated carbonylative cyclization reaction of Baylis–Hillman adducts is disclosed. This simple, efficient and straightforward sequence leads to the formation of an array of 3-alkenylphthalides with different substitution patterns on the aromatic ring, with good chemical yields and selectivities.

1. Introduction

Natural products play a pivotal role in modern drug discovery. Among the class of oxygen heterocycles, benzoannulated lactones (phthalides or 3*H*-isobenzofuran-1-one) are commonly found in many naturally occurring substances,[1–6] as well as some of their synthetically related compounds and show a broad spectrum of biological effects.[7]

Particularly, the 3-alkylated phthalides are present in some natural products such as vermistatin (**1**),[8] (−)-hidrastine (**2**) and fuscinarin (**3**),[9,10] alcyopterosin E (**4**),[11] isoochracinic (**5**) and herbaric (**6**) acids (Fig. 1).[7,12] Phthalides, such as the

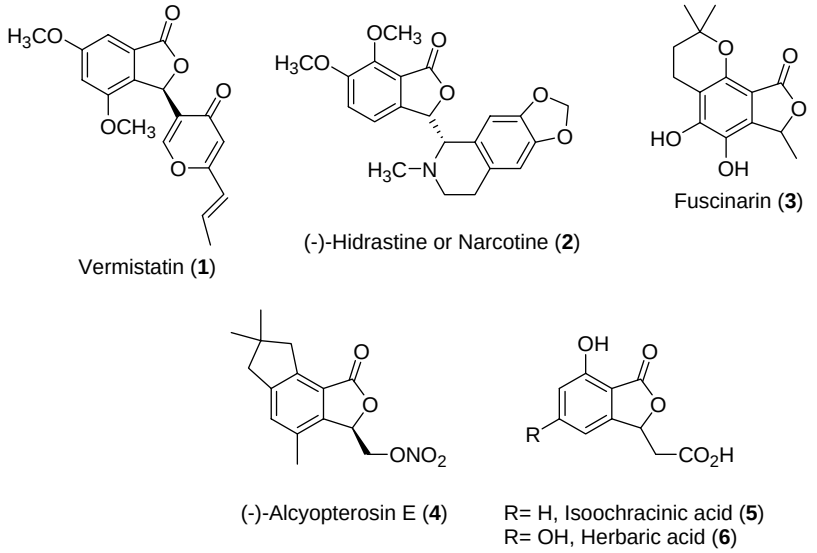


Figure 1. Some naturally occuring 3-substituted phthalides, which exhibited relevant biological activity.

Keywords: Baylis–Hillman adducts; Phthalides; Cyclization; Palladium.
* Corresponding authors. Tel.: +55 19 3788 3085; fax: +55 19 3788 3023 (F.C.); Tel.: +55 19 3788-3090; fax: +55 19 3788-3023 (R.B.); e-mail addresses: coelho@iqm.unicamp.br; buffon@iqm.unicamp.br

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.045

aforementioned, possess a wide range of biological activity. (−)-Hidrastine (**2**) is active at the human opioid receptor known as CCR5, while fuscinarin (**3**) interferes with HIV entry into cells. Vermistatin (**1**) and alcyopterosin E (**4**) are both cytotoxic.

Besides its biological activities, phthalides are versatile starting materials for the synthesis of a variety of structures, including key intermediates in the synthesis of functionalized naphtalenes and anthracenes, which in turn are used as synthons for tricyclic and tetracyclic linear aromatic natural products.[13–18]

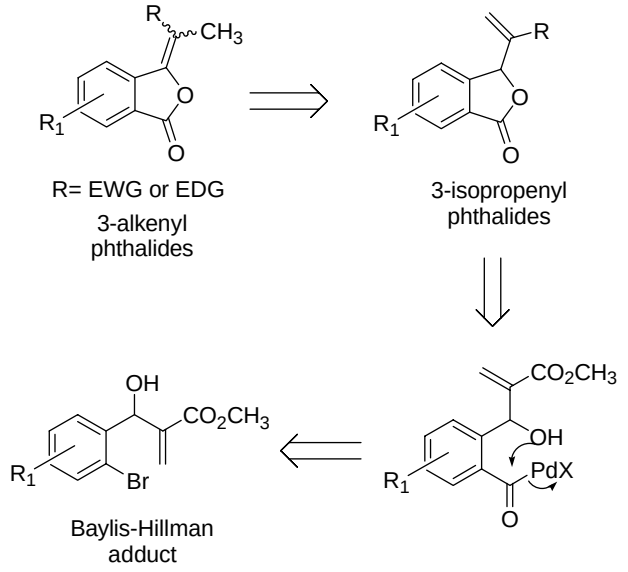
Due to its biological and synthetic importance, several methods have been developed for the synthesis of phthalides.[19–22] Classical methods for their preparation are based on the chloromethylation of benzoic acids, which unfortunately often result in low yields and are not suitable for the regioselective preparation of substituted phthalides.[23–25] To circumvent these difficulties, useful approaches based on the reduction of phthalic anhydrides or the oxidation of diols have been developed, however, the regioselectivity of the products obtained from these methods are frequently problematic.[26–28] Strategies based on the solid phase-synthesis have already been used as alternative for the preparation of this important class of compounds.[29]

More recently, palladium-catalyzed carbonylation reactions[30] of several halogenated substrates have been reported as a convenient route for the synthesis of phthalides using either CO gas[31] or $Mo(CO)_6$[32] as carbonylation source. The use of supercritical CO_2 as solvent has also been successfully combined with palladium-mediated carbonylations to prepare phthalides.[33]

The Baylis–Hillman (BH) reaction is a useful and general σ C–C bond-forming reaction, providing a straightforward single-step synthetic method to form densely functionalized precursors (α-methylene-β-hydroxy derivatives).[34,35] The versatility of these multifunctionalized compounds have made these adducts valuable synthetic intermediates[36] and has also stimulated their utilization as substrates for chemical transformations mediated by palladium, especially for Heck reactions.[37,38]

Owing to its highly synthetic versatility, Baylis–Hillman adducts are also employed as substrates for the preparation of phthalides. Kim et al.[39] described the utilization of Baylis–Hillman adducts generated from 2-carboxyaldehyde as substrates for the synthesis of phthalides. Despite its elegance, the method has some drawbacks with respect to the preparation of phthalides having different substituents on the aromatic ring. The scope of the method was demonstrated only by varying the acrylates used in the Baylis–Hillman reaction.

In an ongoing research program based on the biological evaluation of 3-alkenylphthalides as antiproliferative agents, we needed to prepare some particular derivatives of this class of compounds. In a preliminary approach, we were interested in exploring a palladium-catalyzed carbonylative cyclization of Baylis–Hillman adducts as an alternative to prepare the required phthalides. An oxidative addition of a Pd catalyst to the C–Br bond followed by a CO insertion would give an acyl–palladium intermediate (Scheme 1). The secondary hydroxyl group of the Baylis–Hillman adduct could then effect a nucleophilic addition on the acyl–palladium complex to give a free lactone (phthalide), as depicted in Scheme 1.



Scheme 1. Retrosynthetic proposition for the synthesis of phthalides from Baylis–Hillman adducts mediated by palladium.

From our point of view, the impressive list of biological effects associated with phthalides (also for 3-alkenylphthalides)[40] promptly justify the development of alternative strategies for the preparation of these compounds.

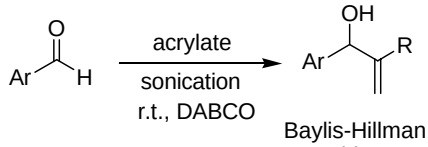
A palladium-mediated carbonylation of an *o*-brominated Baylis–Hillman adduct could tolerate different substituents on the aromatic ring as well as different types of acrylates. Besides, *o*-brominated substituted aldehydes could be prepared using directed ortho metallation reactions, through the trapping of the aryl–lithium intermediates with bromine.[41] As far as we know, Baylis–Hillman adducts has never been used before as substrates for a palladium-catalyzed carbonylation reaction[42] having as aim the preparation of 3-alkenyl phthalides.

In this communication, we describe an efficient and direct approach for the preparation of phthalides based on a palladium-mediated cyclocarbonylation reaction of Baylis–Hillman adducts.

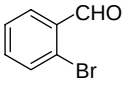
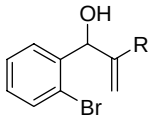
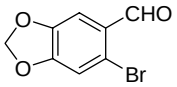
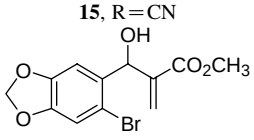
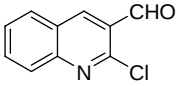
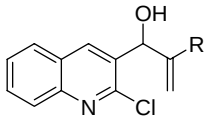
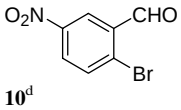
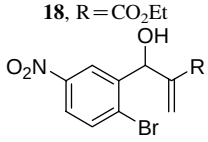
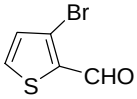
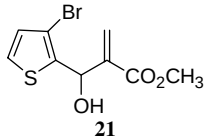
2. Results and discussions

We started our work by preparing the Baylis–Hillman adducts, using a method we recently developed.[43] The results are summarized in Table 1. Most aldehydes we used are commercially available, although aldehyde **10** had to be prepared from the corresponding carboxylic acid, according to a method described by Brown et al.[44]

Table 1. Results for the preparation of Baylis–Hillman adducts



Ar= *o*-brominated aromatic substituent

Aldehyde	Product[a]	Time (h)[b]	Yield (%)[c]
 **7**	 **12**, R=CO_2Me	18	89
	13, R=CO_2Et	17	92
	14, R=CO_2n-Bu	96	85
	15, R=CN	7	93
 **8**	 **16**	96	76
 **9**	 **17**, R=CO_2Me	1	≤99
	18, R=CO_2Et	15	97
 **10**[d]	 **19**, R=CO_2Me	2	92
	20, R=CO_2Et	3	91
 **11**	 **21**	18	98

[a] All reactions were carried out using an excess of acrylate (methyl, ethyl, *n*-butyl and acrylonitrile) in the presence of DABCO (0.65 equiv). For the preparation of Baylis–Hillman adducts **12**, **13**, **16** and **17**, *N*-butyl-2-methyl-imidazolium hexafluorate [(bmim)PF_6] (7 mol%) was used as co-catalyst.

[b] For total conversion.

[c] Yields refer to isolated and purified products.

[d] 5-Nitro-2-bromobenzaldehyde was prepared from the corresponding carboxylic acid by reduction with borane, followed by treatment of the intermediate trialkoxyboroxine with PCC in dichloromethane to afford the required aldehyde in 61% overall yield.[44]

After that, our work aimed at finding or developing a set of reaction conditions that would use the Baylis–Hillman adducts to produce the required 3-alkenylphthalides. Recently, Littke and Fu[45] described mild conditions for the Heck reaction of aryl chlorides and bromides. Since the initial step of the palladium-catalyzed carbonylative cyclization process, as well as in the Heck reaction, is an oxidative addition of the C–halogen bond to a Pd catalyst, we started our work testing the experimental conditions proposed by Littke and Fu.[45]

Solutions of Baylis–Hillman adducts (**12**–**21**) in anhydrous dioxane were treated with $Pd_2(dba)_3$/P(*t*Bu)$_3$ in the presence of dicyclohexylmethylamine (Cy_2NMe), at 70–90 °C under CO (2 atm) pressure. To our delight, the reactions worked quite nicely to provide the expected 3-alkenylphthalides (**22**–**32**) as the sole detectable products in few hours. The results are summarized in Table 2.

Analysis of the data shown in Table 2 revealed that the carbonylation cyclization procedure works well with different Baylis–Hillman adducts. In most cases, the phthalides were obtained with good to excellent yields. The presence of electron-withdrawing (see entries 8 and 9) or electron-donating groups (see entry 5) has no influence on the rate and efficiency of the procedure. Baylis–Hillman adducts prepared from heteroaromatic aldehydes work equally well as substrates for this palladium-mediated carbonylative process (entries 6 and 7), although the yield is lower when a sulfur-containing Baylis–Hillman adduct was used (see entry 10). Moreover, we observed some restrictions with respect to the acrylates. Cyanide derivatives might deactivate palladium(0) in the catalytic cycle,[46] which perhaps could explain the moderate yield achieved in the preparation of the corresponding phthalide (entry 4).

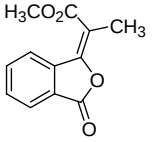
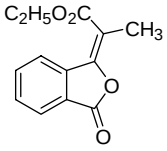
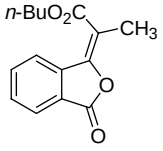
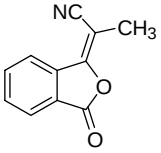
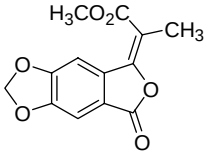
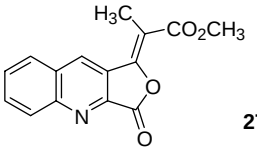
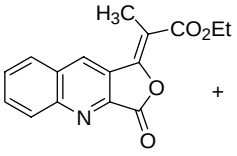
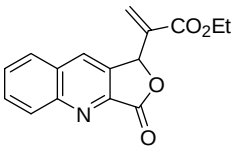
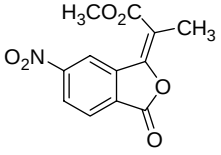
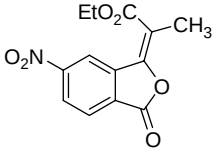
In most cases, the only afforded product was that in which the double bond was totally conjugated (tetrasubstituted alkene). Probably a palladium–hydride intermediate is responsible for double bond isomerization, leading to the formation of the most stable alkene. The only exception was observed when Baylis–Hillman adduct **18**, prepared from the reaction between ethyl acrylate and 2-chloro-3-quinolinecarboxyaldehyde, was employed as substrate. In this particular case, we observed the formation of 3-isopropenyl phthalide (**29**), which could be considered as a Baylis–Hillman adduct in which the conformation was partially restricted, in 60% yield.

The formation of this unusual product is particularly interesting, because it constitutes evidence that the formation of the 3-alkenylphthalides (with a tetrasubstituted double bond) may go through this intermediate, with an in situ palladium-catalyzed double bond isomerization step being responsible for the formation of the enol–lactones, as expected (see Scheme 2). The presence of large substituents would hamper re-coordination of the palladium species, preventing the isomerization step and thus favoring the formation of phthalide **29**.

The configuration of the double bond was deduced from NOE experiments. The aromatic proton adjacent to the double bond of the phthalide was irradiated and an increment was observed in the spectra. For the *Z* configuration an increment in the absorption of the vinylic methyl group was observed (increments ranged from 0.3 to 0.45%).[39] Otherwise, for the *E* configurations increments in the absorption of the alkyl residue of the ester group were observed (increments ranged form 0.3–0.4%) (Fig. 2).

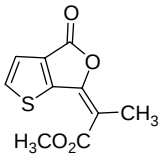
In most cases, the *E* isomer was exclusively or almost exclusively formed. The degree of stereoselectivity might vary depending on the Baylis–Hillman adduct employed, and an inversion in the stereoselectivity *Z*/*E* could also be

Table 2. Palladium-catalyzed carbonylative cyclization of Baylis–Hillman adducts

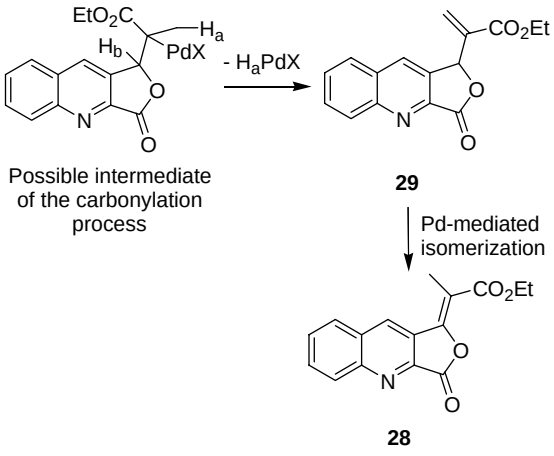
Entry	BH adducts	Phthalides[a]	Time (h)	%[b,c]
1	**12**	 **22** (*E*/*Z* ≥ 95:5)	15	94
2	**13**	 **23** (*E*/*Z* 88:12)	5[b]	96
3	**14**	 **24** (*E*/*Z* ≥ 95:5)	78	68[d]
4	**15**	 **25** (*E*/*Z* ≥ 95:5)	15	59
5	**16**	 **26** (*E*/*Z* ≥ 95:5)	15	96
6	**17**	 **27** (*E*/*Z* 5:95)	15	98
7	**18**	 +  **28** (*E*/*Z* ≥ 5:95) **29**	18	82;[e] 22 (**28**); 60 (**29**)
8	**19**	 **30** (*E*/*Z* ≥ 95:5)	16	76
9	**20**	 **31** (*E*/*Z* 95:5)	25	71

(*continued on next page*)

Table 2 (*continued*)

Entry	BH adducts	Phthalides[a]	Time (h)	%[b,c]
10	**21**	 **32** (*E*/*Z* 85:15)[f]	72	29[d]

[a] The double bond configurations were determined using NOE experiments, in which the aromatic proton adjacent to the phthalide double bond was irradiated.[39] In some cases the isomer distribution could also be observed by ^{1}H NMR.
[b] All reactions were carried out in the presence of $Pd_2(dba)_3$ (1 or 2 mol%)/P(^{t}Bu$_3$), Cy_2NCH_3 and CO (2 atm) at 70–90 °C.
[c] Yields refer to isolated and purified products.
[d] Yield based on the recovered starting material.
[e] Global yield (mixture of products).
[f] We assume the stereochemistry of the majoritary product as being *E* or *Z* based on NOE experiments. We observed an increment of only 0.1% on proton adjacent to the sulfur atom when the methylic ester was irradiated. No increment was observed when vinylic methyl was irradiated.



Scheme 2. Palladium–hydride elimination and double bond isomerization of **29**.

observed (see entry 7, Table 2). Apparently, the stereoselectivity observed has no direct relationship with the size of the ester residue exhibited by the acrylate.

In summary, we disclosed herein a stereoselective, straightforward and high yielding method to prepare phthalides, in only one step, from Baylis–Hillman adducts. The method tolerates different types of substituents in the aromatic ring, as expected for a palladium-mediated procedure. The method can be easily scaled up, since experiments in a scale of 1 g were carried out without any significant alterations in either chemical yield or product quality. In this particular aspect, we believe that the disclosed approach could be used for the stereoselective preparation of several phthalides.

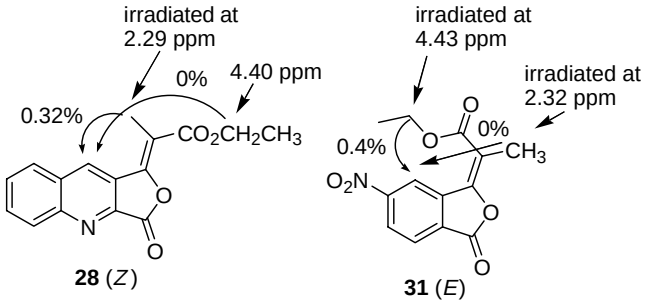


Figure 2. Exemplifying the procedure for determination of the configuration of the tetrasubstituted double bond of phthalides.

Due to its operational simplicity this approach could be considered as a valuable, broadly applicable alternative for the preparation of this class of compounds, since *o*-brominated Baylis–Hillman adducts are readily accessible from the corresponding *o*-brominated aromatic aldehydes. This simplicity could be seen as an advantage of our approach, since some palladium-mediated methods reported for the synthesis of phthalides require the preparation of elaborated starting materials.

Additional work describing the biological profile of these phthalides and their synthetic utility are underway in our laboratory and the results will be disclosed in due course. Although palladium-mediated carbonylative methodology for the preparation of phthalides have already been reported,[31] as far as we know, this is the first report describing a successful palladium-mediated carbonylative cyclization from Baylis–Hillman adducts.

3. Experimental

3.1. General

The following procedures are representative for all the Baylis–Hillman adducts and phthalides prepared in this work. All the reagents were purchased from specialized suppliers with analytical purity and were utilized without previous purification, unless noted. The dioxane was refluxed over CaH_2 under an argon atmosphere for 48 h and distilled at ambient pressure prior to use. After, this solvent was degasified through external ultrasound irradiation in a water bath cleaner (81 W, 40 kHz), over activated molecular sieves 4 Å and under continuous positive pressure of argon during about 5 h. The ^{1}H and ^{13}C spectra were recorded on a Varian GEMINI BB-300 at 300 and 75.4 MHz, respectively, or on an Inova instrument at 500 and 125 MHz, respectively. The mass spectra were recorded using a HP model 5988A GC/MS with a High-Resolution Autospec-Micromass/EBE. IR were obtained with a Nicolet model Impact 410. Melting points were

measured in open capillary tubes using an Electrothermal apparatus model 9100, and are uncorrected. Only the spectral data of the unknown Baylis–Hillman adducts are enclosed.

3.1.1. General procedure for the preparation of the Baylis–Hillman adducts. A mixture of the aromatic aldehyde (1–2 mmol), an excess of acrylate (methyl, ethyl, butyl or acrylonitrile −20 equiv, used as reagent and solvent) and DABCO (0.65 equiv) was sonicated (1000 W, 25 kHz) for a certain period of time (for details, see Table 1 in text). The ultrasound bath temperature was constantly monitored and kept at 30–40 °C during the reaction, through ice addition or by using a refrigerated circulator. After the reaction time, the mixture was evaporated under reduced pressure in order to remove the excess of acrylate. The residue was diluted with ethyl acetate (30 mL). The organic solution was washed with 10% aqueous HCl (2×10 mL), saturated $NaHCO_3$ (20 mL), brine (20 mL), and dried over Na_2SO_4 or $MgSO_4$. After filtration and solvent removal, the residue was filtered through a pad of gel of silica.

3.1.1.1. Ethyl 2-[(2-bromophenyl)(hydroxy)methyl]-acrylate (13). Yield: 92%; for chromatographic purification: ethyl acetate–hexane (20/80); colorless viscous oil; IR (Film, υ_{max}): 3473, 2987, 1720, 1630, 1466, 1430, 1266, 1135, 1025, 759 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.35 (m, 1H), 7.17 (m, 1H), 6.37 (s, 1H), 5.95 (s, 1H), 5.58 (s, 1H), 4.23 (q, J=7.0 Hz, 2H), 3.13 (broad s, 1H, exchangeable with D_2O), 1.28 (t, J=7.0 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.3, 141.2, 140.3, 133.0, 129.6, 128.7, 128.0, 127.1, 123.5, 71.9, 61.5, 14.6; HRMS (70 eV, *m/z*) Calcd for $C_{12}H_{13}BrO_3$ 285.13382; Found 285.13375.

3.1.1.2. Butyl 2-[(2-bromophenyl)(hydroxy)methyl]-acrylate (14). Yield: 85%; for chromatographic purification: ethyl acetate–hexane (20/80); tinged yellow viscous oil; IR (Film, υ_{max}): 3444, 2958, 1719, 1634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.32 (m, 1H), 7.15 (m, 1H), 6.35 (broad s, 1H), 5.93 (broad s, 1H), 5.61 (s, 1H), 4.14 (m, 2H), 3.37 (broad s, 1H, exchangeable with D_2O), 1.61 (quintet, J=7.5 Hz, 2H), 1.31 (sextet, J=7.5 Hz, 2H), 0.90 (t, J=7.5 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.2, 140.8, 139.8, 132.5, 129.0, 128.1, 127.4, 126.4, 123.0, 71.2, 64.8, 30.4, 19.0, 13.6; HRMS (ESI, *m/z*) Calcd for $C_{14}H_{17}BrNaO_3$ $[M+Na]^+$335.0253; Found 335.0323.

3.1.1.3. 2-[(2-Bromophenyl)(hydroxy)methyl]acrylo-nitrile (15). Yield: 93%; eluent for chromatographic purification: ethyl acetate–hexane (30/70); white solid, mp 48–50 °C; IR (neat, υ_{max}): 3444, 3064, 2950, 2234, 1466, 1437 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (m, 2H), 7.41 (m, 1H), 7.23 (m, 1H), 6.07 (broad s, 2H), 5.74 (m, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 138.4, 133.5, 131.9, 130.8, 128.7, 128.6, 125.0, 123.1, 117.0, 73.1; HRMS (70 eV, *m/z*) Calcd for $C_{10}H_8NBrO$ 236.97892; Found 236.97314.

3.1.1.4. Methyl 2-[(2-chloroquinolin-3-yl)(hydroxy)-methyl]acrylate (17). Yield: >99%; eluent for chromatographic purification: ethyl acetate–hexane (30/70); white solid, mp 69–71 °C; IR (neat, υ_{max}) 3209, 1715, 1491, 1331, 1298, 1147, 1060, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.22 (d, J=8.4 Hz, 1H), 8.03 (d, J=8.4 Hz, 1H), 7.94 (ddd, J=1.5, 8.4 Hz, 1H), 7.76 (ddd, J=1.5, 8.4 Hz, 1H), 6.60 (s, 1H), 6.25 (s, 1H), 5.84 (s, 1H), 4.0 (s, 3H), 1.89 (broad s, exchangeable with D_2O); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.8, 149.2, 147.1, 140.1, 137.0, 132.6, 130.6, 128.1, 127.8, 127.7, 127.2, 127.1, 69.2, 52.2; HRMS (70 eV, *m/z*) Calcd for $C_{14}H_{12}ClNO_3$ 277.0506; Found 277.0497.

3.1.1.5. Ethyl 2-[(2-chloroquinolin-3-yl)(hydroxy)-methyl]acrylate (18). Yield: 97%; eluent for chromatographic purification: ethyl acetate–hexane (30/70); yellow solid, mp 75–77 °C; IR (neat, υ_{max}): 3378, 3064, 2978, 1711, 1621, 1589, 1143 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.02 (d, J=8.5 Hz, 1H), 7.85 (d, J=8.2 Hz, 1H), 7.73 (m, 1H), 7.57 (m, 1H), 6.40 (s, 1H), 6.05 (s, 1H), 5.63 (s, 1H), 4.24 (q, J=7.2 Hz, 2H), 3.60 (broad s, exchangeable with D_2O, 1H), 1.29 (t, J=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 149.2, 147.0, 140.3, 137.0, 132.6, 130.5, 128.1, 127.8, 127.4, 127.2, 127.1, 69.3, 61.3, 14.0; HRMS (70 eV, *m/z*) Calcd for $C_{15}H_{14}ClNO_3$ 291.06622; Found 291.05665.

3.1.1.6. Methyl 2-[(2-bromo-5-nitrophenyl)(hydroxy)-methyl]acrylate (19). Yield: 92%; white solid, mp 81–84 °C; eluent for chromatographic purification: ethyl acetate–hexane (30/70); IR (Film, υ_{max}): 3452, 3105, 1723, 1629, 1523, 1343 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, J=2.9 Hz, 1H), 8.03 (dd, J=2.9, 8.8 Hz, 2H), 7.73 (d, J=8.8 Hz, 1H), 6.39 (s, 1H), 5.94 (s, 1H), 5.56 (s, 1H), 3.81 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.4, 147.3, 142.0, 139.5, 133.6, 129.8, 127.7, 123.7, 123.5, 71.1, 52.4; HRMS (70 eV, *m/z*) Calcd for $C_{11}H_9NO_5Br$ 314.97423; Found 314.97939.

3.1.1.7. Ethyl 2-[(2-bromo-5-nitrophenyl)(hydroxy)-methyl]acrylate (20). Yield: 91%; tinged yellow viscous oil; eluent for chromatographic purification: ethyl acetate–hexane (30/70); IR (Film, υ_{max}): 3444, 3109, 1711, 1634, 1527, 1339 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.42 (d, J=2.7 Hz, 1H), 8.03 (dd, J=2.7, 8.8 Hz, 1H), 7.72 (d, J=8.8 Hz, 1H), 6.39 (s, 1H), 5.94 (s, 1H), 5.57 (s, 1H), 4.25 (q, J=7.5 Hz, 2H), 3.22 (broad s, exchangeable with D_2O, 1H), 1.29 (t, J=7.5 Hz, 3H); ^{13}C NMR (125.4 MHz, $CDCl_3$) δ 166.4, 147.6, 142.3, 139.8, 133.7, 130.0, 127.5, 123.7, 123.6, 71.1, 61.4, 14.0; HRMS (70 eV, *m/z*) Calcd for $C_{12}H_{12}BrNO_5$ 328.9899; Found 328.9880.

3.1.1.8. Methyl 2-[(3-bromo-2-thienyl)(hydroxy)-methyl]acrylate (21). Yield: 98%; eluent for chromatographic purification: ethyl acetate–hexane (30/70); pale yellow viscous oil; IR (Film, υ_{max}): 3436, 3113, 2949, 1711, 1629, 1442, 1266, 1147, 1029, 874, 714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J=5.5 Hz, 1H), 6.93 (d, J=5.5 Hz, 1H), 6.36 (s, 1H), 5.85 (s, 1H), 5.82 (s, 1H), 3.77 (s, 3H), 3.24 (broad s, exchangeable with D_2O, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.3, 139.7, 139.2, 129.9, 126.8, 125.4, 109.0, 68.4, 52.1; HRMS (ESI, *m/z*) Calcd for $C_9H_9BrNaO_3S$ $[M+Na]^+$298.9348; Found 298.9445.

3.1.2. General procedure for the cyclocarbonylation reactions—synthesis of phthalides. In a dry Fisher-Porter flask equipped with a magnetic stirrer was deposited

1.0 mol% (2.0 mol% for Baylis–Hillman adducts **14** and **21**) of $Pd_2(dba)_3$. The reactor was then closed and the internal atmosphere exchanged by argon. Then, there was injected into the flask, sequentially, under magnetic stirring and an argon atmosphere, 1.0 mL of anhydrous and degasified 1,4-dioxane, 1.1 equiv of Cy_2NMe and 4.0 mol% (8.0 mol% when Baylis–Hillman adducts **14** and **21**) of a 0.1 mol L^{-1} solution of P(*t*Bu)$_3$ in 1,4-dioxane, previously and freshly prepared in a dry box. This catalytic mixture was stirred for 5 min at room temperature (rt) under argon, until the purple color changed to red-brown. In other dry flask a solution of the Baylis–Hillman adduct (1.12 mmol) in 2.0 mL of anhydrous and degasified 1,4-dioxane, under argon, was prepared. This solution was then injected into the Fisher-Porter reactor, and the reaction mixture was stirred at rt under argon for 15 min. At this point, the color changed to a pale yellow. Finally, the reactor was pressurized with carbon monoxide (CO, 2 atm). The temperature was raised to 70–90 °C with a silicon oil bath, and the mixture stirred under these conditions for the required time. Initially, the color of the system changed from pale yellow to orange-brown. In the final hours of the reaction, a gray precipitate forms, indicating the deactivation of the catalyst (Pd black along with the salt $Cy_2NMeH^+Br^-$). After, the mixture was cooled to rt and the reactor carefully opened. The mixture was then filtered and the residue was washed with ethyl acetate (10 mL). The combined solutions were washed with a 10% solution of HCl (10 mL) and with water (10 mL) and brine (10 mL). The organic phase was separated, dried over a pad of Na_2SO_4, filtered and the solvent was removed under reduced pressure. The residue obtained was then purified by silica gel column chromatography (elution with ethyl acetate/hexane–10:90) to provide the corresponding phthalide.

3.1.2.1. Methyl (2*E*)-2-(3-oxo-2-benzofuran-1(3*H*)-ylidene)propanoate (22). White solid, mp 133–135 °C (lit.[39] 133–136 °C); IR (neat, υ_{max}): 2958, 2917, 2851, 1781, 1708, 1634, 1246, 1062, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.58 (d, J=8.1 Hz, 1H), 7.95 (d, J=8.1 Hz, 1H), 7.75 (m, 1H), 7.62 (m, 1H), 3.91 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.6, 151.9, 136.8, 134.9, 131.0, 126.5, 125.4, 112.6, 70.1, 52.3, 29.7, 14.8; HRMS (70 eV, *m*/*z*) Calcd for $C_{12}H_{10}O_4$ 218.05791; Found 218.05437.

3.1.2.2. Ethyl (2*E*)-2-(3-oxo-2-benzofuran-1(3*H*)-ylidene)propanoate (23). Diastereoisomeric mixture (*E*)+(*Z*); tinged yellow solid, mp 70–72 °C (lit.[39] 69–70 °C); IR (neat, υ_{max}): 2958, 2925, 2847, 1793, 1711, 1621, 1470, 1237, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.56 (d, J=8.2 Hz, 1H), 8.02 (d, J=7.6 Hz, 1H, minoritary diastereoisomer), 7.95 (d, J=7.6 Hz, 1H, majoritary diastereoisomer), 7.91 (d, J=7.9 Hz, 1H, minoritary diastereoisomer), 7.78–7.72 (m, 2H), 7.67–7.59 (m, 2H), 7.44–7.42 (m, 2H), 4.37 (q, J=7.0 Hz, 2H), 2.39 (s, 3H, minoritary diastereoisomer), 2.28 (s, 3H, majoritary diastereoisomer), 1.44 (t, J=7.0 Hz, 3H, minoritary diastereoisomer), 1.39 (t, J=7.0 Hz, 3H, majoritary diastereoisomer); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 143.8, 137.3, 135.3, 131.4, 130.9, 129.4, 128.8, 126.9, 126.6, 126.5, 125.9, 125.7, 125.1, 113.4, 62.0, 61.8, 30.1, 15.3, 14.6; HRMS (70 eV, *m*/*z*) Calcd for $C_{13}H_{12}O_4$ 232.07356; Found 232.07346.

3.1.2.3. Butyl (2*E*)-2-(3-oxo-2-benzofuran-1(3*H*)-ylidene)propanoate (24). Yield: 68% (based on recovered starting material—see Table 2); tinged yellow viscous oil; IR (neat, υ_{max}) 2949, 2933, 2868, 1789, 1719, 1634, 1466, 1237, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, J=8.4 Hz, 1H), 7.92 (d, J=7.6 Hz, 1H), 7.69 (ddd, J=1.1, 7.5 Hz, 1H), 7.59 (m, 1H), 4.29 (t, J=7.0 Hz, 2H), 2.26 (s, 3H), 1.71 (quintet, J=7.0 Hz, 2H), 1.45 (sextet, J=7.0 Hz, 2H), 0.97 (t, J=7.0 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 167.2, 165.8, 151.6, 136.8, 134.8, 130.9, 126.4, 126.1, 125.2, 112.9, 65.2, 30.5, 19.1, 14.8, 13.6; HRMS (ESI, *m*/*z*) Calcd for $C_{15}H_{16}NaO_4$ $[M+Na]^+$283.0941; Found 283.1046.

3.1.2.4. (2*E*)-2-(3-Oxo-2-benzofuran-1(3*H*)-ylidene)-propanenitrile (25). Yield: 63% (based on recovered starting material—see Table 2); white solid, mp 142–144 °C (lit.[19] 143–144 °C); IR (neat, υ_{max}) 2953, 2917, 2847, 2214, 1805, 1646, 1466, 1207, 1127, 1041, 980, 767, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, J=8.0 Hz, 1H), 7.99 (d, J=7.0 Hz, 1H), 7.84 (m, 1H), 7.7 (m, 1H), 2.32 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 164.0, 155.3, 136.0, 135.4, 131.9, 125.9, 125.0, 123.6, 118.0, 88.7, 14.8; HRMS (70 eV, *m*/*z*) Calcd for $C_{11}H_7NO_2$ 185.0477; Found 185.0440.

3.1.2.5. Methyl (2*E*)-2-(7-oxofuro[3,4-*f*][1,3]benzodioxol-5(7*H*)-ylidene)propanoate (26). Yield: 96%; white solid, mp 109–110 °C; IR (neat, υ_{max}): 2987, 2920, 1769, 1712, 1479, 1307, 1283, 1277, 1091, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.20 (s, 1H), 6.18 (s, 2H), 3.98 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 167.4, 164.9, 153.8, 150.4, 133.1, 127.3, 121.3, 111.3, 106.4, 103.7, 102.9, 52.3, 14.8; HRMS (70 eV, *m*/*z*) Calcd for $C_{13}H_{10}O_6$ 262.04774; Found 262.04352.

3.1.2.6. Methyl (2*Z*)-2-(3-oxofuro[3,4-*b*]quinolin-1(3*H*)-ylidene)propanoate (27). IR (neat, υ_{max}): 2933, 2855, 1785, 1719, 1617, 1454, 1372, 1241, 1196, 1119, 1057 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.59 (s, 1H), 8.31 (d, J=8.8 Hz, 1H), 8.03 (d, J=8.1 Hz, 1H), 7.88 (m, 1H), 7.72 (m, 1H), 3.93 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 166.8, 162.7, 150.4, 149.2, 143.8, 142.7, 136.3, 132.8, 131.8, 129.3, 129.0, 113.1, 52.0, 14.0; HRMS (70 eV, *m*/*z*) Calcd for $C_{15}H_{11}NO_4$ 269.06881; Found 269.06656.

3.1.2.7. Ethyl (2*Z*)-2-(3-oxofuro[3,4-*b*]quinolin-1(3*H*)-ylidene)propanoate (28). Yield: 22%; tinged yellow solid, mp 196–198 °C; IR (neat, υ_{max}): 2962, 2917, 1805, 1711, 1634, 1609, 1372, 1294, 1233 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.36 (d, J=9.0 Hz, 1H), 8.08 (d, J=9.0 Hz, 1H), 7.89 (m, 1H), 7.74 (m, 1H), 4.40 (q, J=7.0 Hz, 2H), 2.32 (s, 3H), 1.43 (t, J=7.0 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.8, 163.2, 150.6, 149.7, 144.2, 136.7, 132.1, 130.7, 129.6, 129.5, 129.4, 126.2, 114.0, 61.5, 14.4, 14.3; HRMS (ESI, *m*/*z*) Calcd for $C_{16}H_{13}NNaO_4$ $[M+Na]^+$306.0737; Found 306.0828.

3.1.2.8. Ethyl 2-(3-oxo-1,3-dihydrofuro[3,4-*b*]-quinolin-1-yl)acrylate (29). Yield: 60%; white solid, mp

162–164 °C; IR (neat, υ_{max}): 2982, 2921, 2847, 1772, 1711, 1629, 1376, 1335, 1286, 1123 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.34 (d, $J=8.5$ Hz, 1H), 7.93 (d, $J=8.0$ Hz, 1H), 7.83 (m, 1H), 7.69 (m, 1H), 6.47 (broad s, 2H), 6.08 (broad s, 1H), 4.21 (m, 2H), 2.32 (s, 3H), 1.24 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 167.4, 164.3, 149.7, 144.2, 136.7, 136.1, 136.0, 131.3, 130.9, 130.8, 129.2, 129.0, 128.1, 128.0, 76.5, 61.5, 14.0; HRMS (ESI, *m/z*) Calcd for $C_{16}H_{13}NNaO_4$ $[M+Na]^+$306.0737; Found 306.0808.

3.1.2.9. Methyl (2*E*)-2-(6-nitro-3-oxo-2-benzofuran-1(3*H*)-ylidene)propanoate (30). Yield: 76%; tinged yellow solid, mp 155–157 °C; IR (neat, υ_{max}): 3133, 3096, 2966, 1809, 1707, 1644, 1618, 1544, 1441 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.51 (d, $J=1.8$ Hz, 1H), 8.44 (dd, $J=1.8$, 8.4 Hz, 1H), 8.09 (d, $J=8.4$ Hz, 1H), 3.95 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.8, 163.6, 152.3, 150.3, 137.7, 130.4, 126.3, 125.9, 122.6, 115.7, 52.7, 15.0; HRMS (70 eV, *m/z*) Calcd for $C_{12}H_9NO_6$ 263.04298; Found 263.04145.

3.1.2.10. Ethyl (2*E*)-2-(6-nitro-3-oxo-2-benzofuran-1(3*H*)-ylidene)-propanoate (31). Yield: 71%; pale yellow solid, mp 141–144 °C; IR (neat, υ_{max}): 3133, 3101, 2962, 2921, 2843, 1809, 1711, 1642, 1540, 1343 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.50 (d, $J=1.8$ Hz, 1H), 8.45 (dd, $J=1.8$, 8.4 Hz, 1H), 8.11 (d, $J=8.4$ Hz, 1H), 4.43 (q, $J=6.9$ Hz, 2H), 2.32, (s, 3H), 1.43 (t, $J=6.9$ Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 166.4, 163.6, 152.2, 149.9, 137.7, 130.4, 126.3, 125.8, 122.4, 116.1, 62.0, 15.1, 14.1; HRMS (70 eV, *m/z*) Calcd for $C_{13}H_{11}NO_6$ 277.05864; Found 277.04955.

3.1.2.11. Methyl (2*E*)-2-(4-oxothieno[2,3-*c*]furan-6(4*H*)-ylidene)-propanoate (32). Yield: 29% (based on recovered starting material—see Table 2); light yellow viscous oil; IR (neat, υ_{max}): 3105, 2953, 2917, 2855, 1777, 1695, 1638, 1433, 1323, 1266, 1053 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, $J=5.19$ Hz, 1H), 7.32 (d, $J=5.19$ Hz, 1H), 3.89 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 160.6, 150.6, 149.0, 137.0, 120.8, 108.3, 52.3, 12.6; HRMS (ESI, *m/z*) Calcd for $C_{10}H_8NaO_4S$ $[M+Na]^+$247.0035; Found 247.0094.

Acknowledgements

We thank FAPESP (04/09745-0 and 02/03461-3) and CNPq for financial support, for a fellowship to C.H.P. (FAPESP 02/10872-0) and for research fellowships to F.C. and R.B. (CNPq). We thank also Prof. Carol H. Collins for helpful suggestions about English grammar and style.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.045. Spectra (^1H and ^{13}C NMR, and HRMS) of almost all compounds (unknown Baylis–Hillman adducts and phthalides) are available. For some compounds IR spectra is also available.

References and notes

1. van Wassenhove, F.; Dirinck, P.; Vulsteke, G.; Schamp, N. *HortScience* **1990**, *25*, 556–559.
2. Rickborn, B. *Adv. Theor. Interesting Mol.* **1989**, *1*, 1–134.
3. Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093–2135.
4. Bird, W. C.; Cheeseman, G. W. H. In *Comprehensive Heterocyclic Chemistry*; Katrizky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; pp 89–153.
5. Parisot, D.; Devys, M.; Ferezou, J. P.; Barbier, M. *Phytochemistry* **1983**, *22*, 1301–1303.
6. Curtis, P. J.; Grove, J. F. *Nature* **1947**, *160*, 574–575.
7. For some additional examples of phthalides, which could show remarkable biological activities, see: (a) MacLean, D. B. In *Phthalideisoquinoline Alkaloids and Related Compounds*; Brossi, A., Ed.; The Alkaloids; Academic: Orlando, 1985; Vol. 24, pp 253–286. (b) Zhou, J.; Gupta, K.; Yao, J.; Ye, K.; Panda, D.; Giannakakaou, P.; Joshi, H. C. *J. Biol. Chem.* **2002**, *277*, 39777–39785. (c) Shode, F. O.; Mahomed, A. S.; Rogers, C. B. *Phytochemistry* **2002**, *61*, 955–957. (d) Arnone, A.; Assante, G.; Nasini, G.; de Pava, O. V. *Phytochemistry* **1990**, *29*, 613–616. (e) Wild, D.; Toth, G.; Humpf, H. U. *J. Agric. Food Chem.* **2002**, *50*, 3999–4002. (f) Arnone, A.; Assante, G.; Nasini, G.; Strada, S.; Vercesi, A. *J. Nat. Prod.* **2002**, *65*, 48–50. (g) Puder, C.; Zeeck, A.; Beil, W. *J. Antibiot.* **2000**, *53*, 329–336. (h) Brady, S. F.; Wagenaar, M. M.; Singh, M. P.; Janso, J. E.; Clardy, J. *Org. Lett.* **2000**, *2*, 4043–4046. (i) Kosaka, M.; Sekiguchi, S.; Naito, J.; Uemura, M.; Kuwahara, S.; Watanabe, M.; Harada, N.; Hiroi, K. *Chirality* **2005**, *17*, 218–232. (j) For an example for the synthesis of isoochracinic acid, see: Trost, B. M.; Rivers, G. T.; Gold, J. M. *J. Org. Chem.* **1980**, *45*, 1835–1838.
8. Arai, M.; Tomoda, H.; Okuda, T.; Wang, H.; Tabata, N.; Masuma, R.; Yamaguchi, Y.; Omura, S. *J. Antibiot.* **2002**, *55*, 172–180.
9. Chatterjee, P.; Franklin, M. R. *Drug Metab. Dispos.* **2003**, *31*, 1391–1397.
10. Yoganathan, K.; Rossant, C.; Ng, S.; Huang, Y.; Butler, M. S.; Buss, A. D. *J. Nat. Prod.* **2003**, *66*, 1116–1117.
11. (a) Palermo, J. A.; Rodriguez, B.; Maria, F.; Spagnuolo, C.; Seldes, A. M. *J. Org. Chem.* **2000**, *65*, 4482–4486. (b) For the synthesis of this phthalide, see: Witulski, B.; Zimmermann, A.; Gowans, N. D. *Chem. Commun.* **2002**, 2984–2985.
12. Holler, U.; Gloer, J. B.; Wicklow, D. T. *J. Nat. Prod.* **2002**, *65*, 876–882.
13. Larock, R. C. *Heterocycles* **1982**, *18*, 397–410.
14. (a) Snieckus, V. *Heterocycles* **1980**, *14*, 1649–1676. (b) Dodsworth, D. J.; Caliagno, M. P.; Ehramann, U. E.; Sammes, P. G. *Tetrahedron Lett.* **1980**, *21*, 5075–5078. (c) de Silva, S. O.; Watanabe, M.; Snieckus, V. *J. Org. Chem.* **1979**, *44*, 4802–4808.
15. Franck, R. W.; John, T. V. *J. Org. Chem.* **1980**, *45*, 1170–1172.
16. Hauser, F. M.; Rhee, R. P.; Prasanna, S.; Weinreb, S. M.; Dodd, J. H. *Synthesis* **1980**, 72–74.
17. Larock, R. C.; Fellows, C. A. *J. Org. Chem.* **1980**, *45*, 363–365.
18. Kraus, G. A.; Pezzanite, J. O.; Sugimoto, H. *Tetrahedron Lett.* **1979**, 853–856.
19. (a) Everaere, K.; Scheffler, J.-L.; Mortreux, A.; Carpentier, J.-F. *Tetrahedron Lett.* **2001**, *42*, 1899–1901 and references cited therein. (b) Napolitano, E.; Spinelli, G.; Fiaschi, R.; Marsili, A. *Synthesis* **1985**, 38–40. (c) Holland, H. L.; Maclean, D. B.; Rodrigo, R. G. A.; Manske, R. F. H. *Tetrahedron Lett.* **1975**, *49*,

4323–4326. (d) Watanabe, M.; Morimoto, H.; Furukawa, S. *Heterocycles* **1993**, *36*, 2681–2686. (e) Ross Kelly, T.; Bell, S. H.; Oshashi, N.; Armstrong-Chong, R. J. *J. Am. Chem. Soc.* **1988**, *110*, 6471–6480 and references cited therein.
20. Zimmer, H.; Barry, R. D. *J. Org. Chem.* **1962**, *27*, 3710–3711.
21. Shapiro, S. L.; Geiger, K.; Freedman, L. *J. Org. Chem.* **1960**, *25*, 1860–1865.
22. Shriner, R. L.; Keyser, L. S. *J. Org. Chem.* **1940**, *5*, 200–203.
23. Bhattacharjee, D.; Popp, F. D. *J. Heterocycl. Chem.* **1980**, *17*, 315–320.
24. Buehler, I. C.; Powers, T. A.; Michels, J. G. *J. Am. Chem. Soc.* **1944**, *66*, 417–418.
25. Edwards, G. A.; Perkin, W. H., Jr.; Stoyle, F. W. *J. Chem. Soc., Chem. Commun.* **1925**, *127*, 195–199.
26. Elderfield, R. C.; Heterocyclic Compounds; Wiley: New York, 1951; Vol. 2; p 571.
27. (a) McAlees, A. J.; McCrindle, R.; Sneddon, D. W. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2030–2036. (b) McAlees, A. J.; McCrindle, R.; Sneddon, D. W. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2037–2038.
28. Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750–6755.
29. Knepper, K.; Ziegert, R. E.; Bräse, S. *Tetrahedron* **2004**, *60*, 8591–8603.
30. For some recent examples concerning the utilization of palladium-mediated carbonylation in organic synthesis see: (a) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. *Carbonylation: Direct Synthesis of Carbonyl Compounds*; Plenum: New York, 1991. (b) Tkatchenko, I. In Wilkinson, G., Stone, G. F. A., Abel, E. W., Eds.; Comprehensive Organometallic Chemistry; Pergamon: Oxford, 1982; Vol. 8, pp 101–223. (c) Negishi, E. I.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365–393. (d) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635–662. (e) Pfeffer, M. *Recl. Trav. Chim. Pays-Bas.* **1990**, *109*, 567–576. (f) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081–1119. (g) Larock, R. C. *J. Organomet. Chem.* **1999**, 111–124. (h) Långström, B.; Karini, F. *Org. Biomol. Chem.* **2003**, *1*, 541–546. (i) Uozumi, Y.; Arii, T.; Watanabe, T. *J. Org. Chem.* **2001**, *66*, 5272–5274. (j) Långström, B.; Karini, F. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2111–2115. (k) Rahman, O.; Kihlberg, T.; Långström, B. *Org. Biomol. Chem.* **2004**, *2*, 1612–1616. (l) Gagnier, S. V.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 4804–4807 and references cited therein. (m) Cho, C. S.; Baek, D. Y.; Shim, S. C. *J. Heterocycl. Chem.* **1999**, *36*, 1101–1102 and references cited therein. (n) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, P. *Tetrahedron* **1994**, *50*, 437–452. (o) Torii, S.; Okumoto, H.; Xu, L. H. *Tetrahedron Lett.* **1990**, *31*, 7175–7178. (p) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **1990**, *68*, 9423–9432.
31. For some examples concerning the palladium-mediated synthesis of phthalides, see: (a) Lee, Y.; Fujiwara, Y.; Ujita, K.; Nagatomo, M.; Ohta, H.; Shimizu, I. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1437–1443. (b) Bouyssi, D.; Balme, G. *Synlett* **2001**, 1191–1193. (c) Orito, K.; Miyazawa, M.; Kanbayashi, R.; Tokuda, M.; Suginome, H. *J. Org. Chem.* **1999**, *64*, 6583–6596. (d) Orito, K.; Miyazawa, M.; Suginome, H. *Synlett* **1994**, 245–246. (e) Crisp, G.; Meyer, A. G. *J. Org. Chem.* **1992**, *57*, 6972–6975. (f) Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193–4198. (g) Yamamoto, Y.; Ishii, J.-I.; Nishiyama, H.; Itoh, K. *J. Am. Chem. Soc.* **2005**, *127*, 9625–9631. (h) Kawasaki, T.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 2653–2658 and references cited therein. (i) Mukhopadhyay, R.; Kundu, N. G. *Tetrahedron* **2001**, *57*, 9475–9480. (j) Shim, S. C.; Lee, D. Y.; Jiang, L. H.; Kim, T. J.; Cho, S.-D. *J. Heterocycl. Chem.* **1995**, *32*, 363–365. (k) Uozomi, Y.; Mori, E.; Mori, M.; Shibasaki, M. *J. Organomet. Chem.* **1990**, *399*, 93–102. (l) Caviocchioli, M.; Decortiat, S.; Bouyssi, D.; Goré, J.; Balme, G. *Tetrahedron* **1996**, *52*, 11463–11478 and references cited therein. (m) Miyamoto, M.; Minami, Y.; Ukaji, Y.; Kinoshita, H.; Inomota, K. *Chem Lett.* **1994**, 1149–1152. (n) Ciattini, P. G.; Mastropietro, G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1993**, *23*, 3763–3766. (o) Izumi, T.; Itou, O.; Kodera, K. *J. Chem. Technol. Biotechnol.* **1996**, *67*, 89–95. (p) Lee, D. Y.; Cho, C. S.; Jang, L. H.; Wu, X.; Shim, S. C.; Oh, D. H. *Synth. Commun.* **1997**, *27*, 3449–3455. (q) Shim, S. C.; Lee, D. Y.; Jiang, L. H.; Kim, T. J.; Cho, S.-D. *J. Heterocycl. Chem.* **1995**, *32*, 363–365. (r) Kundu, N. G.; Pal, M. *J. Chem. Soc., Chem. Commun.* **1993**, 86–88.
32. Wu, X.; Mahanlingam, A. K.; Wan, Y.; Alterman, M. *Tetrahedron Lett.* **2004**, *45*, 4635–4638.
33. Kyaki, Y.; Noguchi, Y.; Iwasa, S.; Ikariya, T.; Noyori, R. *Chem. Commun.* **1999**, 1235–1236.
34. For comprehensive reviews on the Baylis–Hillman reaction see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891. (b) Almeida, W. P.; Coelho, F. *Quim. Nova* **2000**, *23*, 98–101; *Chem. Abstr.* **2000**, *132*, 236562e. (c) Ciganek, E. *Org. React.* **1997**, *51*, 201–350. (d) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001–8062.
35. For some new insights into the mechanism of the Baylis–Hillman reaction, see: (a) Santos, L. S.; Pavam, C. H.; Almeida, W. P.; Coelho, F.; Eberlin, N. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4330–4333. (b) Price, K. E.; Broadwater, S. J.; Walker, B. J.; McQuade, D. T. *J. Org. Chem.* **2005**, *70*, 3980–3987. (c) Aggarwal, V. K.; Fulford, S. Y.; Llyod-Jones, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1706–1708.
36. For some examples of the utilization of Baylis–Hillman adducts as intermediates for total synthesis, see: (a) Mateus, C. R.; Coelho, F. *J. Braz. Chem. Soc.* **2005**, *16*, 386–396. (Available free-of-charge at http://jbcs.sbq.org.br/online/2005/vol16_n3A/11-238-04.pdf). (b) Silveira, G. P. C.; Coelho, F. *Tetrahedron Lett.* **2005**, *46*, 6477–6481. (c) Porto, R. S.; Coelho, F. *Synth. Commun.* **2004**, *34*, 3037–3046. (d) Almeida, W. P.; Coelho, F. *Tetrahedron Lett.* **2003**, *44*, 937–940. (e) Feltrin, M. A.; Almeida, W. P. *Synth. Commun.* **2003**, *33*, 1141–1146. (f) Rossi, R. C.; Coelho, F. *Tetrahedron Lett.* **2002**, *43*, 2797–2800. (g) Mateus, C. R.; Feltrin, M. P.; Costa, A. M.; Coelho, F.; Almeida, W. P. *Tetrahedron* **2001**, *57*, 6901–6908. (h) Iwabuchi, Y.; Furukawa, M.; Esumi, T.; Hatakeyama, S. *Chem. Commun.* **2001**, 2030–2031. (i) Iwabuchi, Y.; Sugihara, T.; Esumi, T.; Hatakeyama, S. *Tetrahedron Lett.* **2001**, *42*, 7867–7871. (j) Masunari, A.; Trazzi, G.; Ishida, E.; Coelho, F.; Almeida, W. P. *Synth. Commun.* **2001**, *31*, 2100–2109. (k) Ameer, F.; Drewes, S. E.; Houston-McMillan, M. S.; Kaye, P. T. *S. Afr. J. Chem.* **1986**, *39*, 57–63; *Chem. Abstr.* **1986**, 105, 114809 (l) Hofmann, H. M. R.; Rabe, J. *Helv. Chim. Acta* **1984**, *67*, 413–415.
37. For reviews, see: (a) Heck, R. F. *Org. React.* **1982**, *27*, 345–390. (b) Heck, R. F. In *Vinyl Substitutions with Organopalladium Intermediates*; Trost, B. M., Fleming, I., Eds.; Comprehensive Organic Synthesis; Pergamon: Oxford, 1991; Vol. 4, pp 833–863. (c) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427–436.

38. To some examples concerning the utilization of Baylis–Hillman adducts for palladium-mediated methods, see: (a) Basavaiah, D.; Muthukumaran, K. *Tetrahedron* **1998**, *54*, 4943–4948. (b) Kumareswaran, R.; Vankar, Y. D. *Synth. Commun.* **1998**, *28*, 2291–2302. (c) Sundar, N.; Bhat, S. V. *Synth. Commun.* **1998**, *28*, 2311–2316. (d) Kulkarni, B. A.; Ganesan, A. *J. Comb. Chem.* **1999**, *1*, 373–378. (e) Roy, O.; Riahi, A.; Hénin, F.; Muzart, J. *Tetrahedron* **2000**, *56*, 8133–8140. (f) Pachamuthu, K.; Vankar, Y. D. *Tetrahedron Lett.* **1998**, *39*, 5439–5442. (g) Park, J. B.; Ko, S. H.; Kim, B. G.; Hong, W. P.; Lee, K.-J. *Bull. Korean Chem. Soc.* **2004**, *25*, 27–28. (h) Navarre, L.; Darses, S.; Genet, J.-P. *Chem. Commun.* **2004**, 1108–1109.
39. Lee, K. Y.; Kim, J. M.; Kim, J. N. *Synlett* **2003**, 357–360 and references cited therein.
40. Liu, Z.; Song, Y.; Wang, W.; Chen, W.; Wang, X. *Zhongcaoyao* **1982**, *13*, 1117–1123; *Chem. Abstr.* **1982**, *97*, 174444.
41. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–993 and references cited therein.
42. Baylis–Hillman adduct has already been used as substrate for a palladium-mediated carbonylative reaction on the terminal double bond, see: Wang, S.-Z.; Yamamoto, K.; Yamada, H.; Takahashi, T. *Tetrahedron* **1992**, *48*, 2333–2348.
43. (a) Coelho, F.; Almeida, W. P.; Veronese, D.; Mateus, C. R.; Lopes, E. C. S.; Silveira, G. P. C.; Rossi, R. C.; Pavam, C. H. *Tetrahedron* **2002**, *58*, 7437–7447. (b) Almeida, W. P.; Coelho, F. *Tetrahedron Lett.* **1998**, *39*, 8609–8612.
44. Brown, H. C.; Rao, C. G.; Kulkarni, S. U. *Synthesis* **1979**, 704–705.
45. Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989–7000.
46. (a) Sundermeier, M.; Mutyala, S.; Zapf, A.; Spannenberg, A.; Beller, M. *J. Organomet. Chem.* **2003**, *684*, 50–55. (b) You, J.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8003–8007 and references cited therein.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 4573–4583

Surveying approaches to the formation of carbon–carbon bonds between a pyran and an adjacent ring

Jeffrey D. Frein and Tomislav Rovis*

Department of Chemistry, Colorado State University, Fort Collins, CO 80523, USA

Received 14 November 2005; revised 14 February 2006; accepted 15 February 2006

Available online 13 March 2006

Abstract—We have examined several methods for the stereoselective formation of carbon–carbon bonds between contiguous rings where a stereogenic center is already present. The approaches investigated were a [1,3] oxygen to carbon rearrangement of cyclic vinyl acetals, an intermolecular enolsilane addition into an in situ generated oxocarbenium ion, an intramolecular conjugate addition of tethered alkoxy enones, and epimerization of several α-pyranyl cycloalkanones. These routes have been found to be complementary in several cases and have enabled formation of both the trans:*anti* and cis:*anti* stereoisomers in good to excellent yields and varying diastereoselectivities. We have proven C2–C2′ relative stereochemistry of 1–2 via a chemical correlation.

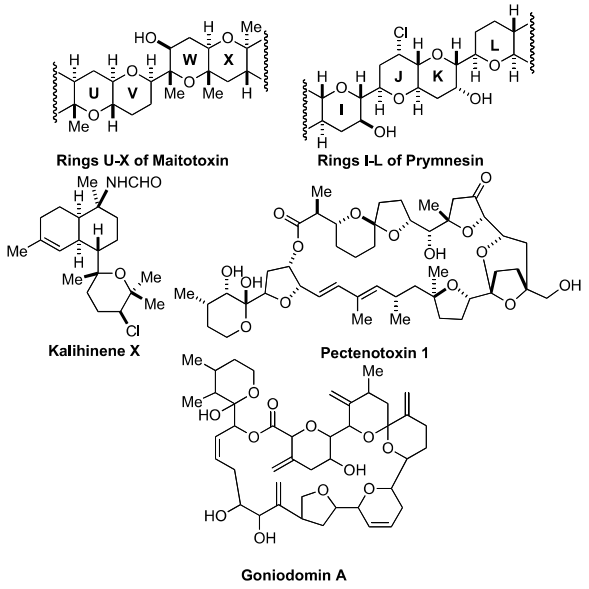
1. Introduction

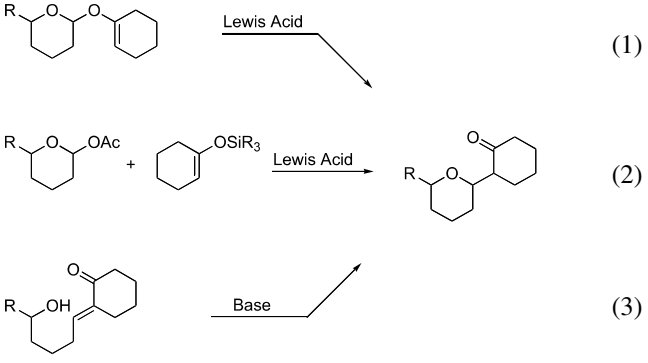
Among the largest and most complicated non-biopolymer molecules discovered to date are maitotoxin, prymnesin and ciguatoxin, along with other members of the polyether ladder toxin family.[1] These molecules are characterized by sections of fused oxacycles connected to each other by carbon linkers. Only a handful of total syntheses have emerged to date, including Nicolaou's synthesis of brevetoxin[2] and Hirama's recent synthesis of ciguatoxin.[3] No syntheses have yet appeared of the largest members of this family, maitotoxin and prymnesin. At least a part of the reason for this is the comparative complexity of subsections of maitotoxin, compelling and challenging targets in their own right. We became interested in the problem of how to connect subsections of these molecules once they are assembled. Arguably, the most obvious bond disconnections involve the single C–C bonds that connect the fused oxacycle subsections to each other.[4] An approach to these types of bonds must address the key issue of controlling stereochemistry at both ends, a problem that is shared by various other natural product targets as well.

We chose to conduct an in-depth study of various approaches to this type of ring juncture. Prime among these was our intention to apply our recently developed stereoretentive O to C rearrangement to this problem.[5] In doing so, we hoped to take advantage of the relative facility of controlling stereochemistry in the formation of a C–O bond and induce it to rearrange to a C–C bond, having already paid the entropic price of bringing two fragments together in the formation of the 'easy' bond. The question that we needed to address was our ability to control the second stereocenter in the rearrangement (Eq. 1).[6] Second, we hoped to contrast these results with selectivities obtained in the more classical Lewis acid induced intermolecular enolsilane addition to an in situ generated oxocarbenium ion (Eq. 2). This method is comparable to the rearrangement method without having to address the issue of creating the oxocarbenium ion and enolate via an intramolecular event, although it lacks the possibility of providing the cis adduct via a stereoretentive process. Last, we wanted to exploit an intramolecular conjugate addition of an alkoxide into an α,β-unsaturated ketone (Eq. 3).

Keywords: Stereoretentive process; Lewis acid; Oxocarbenium ions; [1,3]rearrangement.
* Corresponding author. Tel.: +1 970 491 7208; fax: +1 970 491 1801; e-mail: rovis@lamar.colostate.edu

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.042





Other groups have exploited various methods for the formation of these carbon–carbon linkers.[7] Suzuki and co-workers have reported a $BF_3 \cdot OEt_2$ mediated 1,3-oxygen to carbon rearrangement of vinyl acetals resulting in pyranyl aldehydes in good yields (85–89%) and modest to good C2–C2′ diastereoselectivities (3:2–3:1).[6i] In addition, Ley and co-workers have shown a $SnCl_4$ mediated oxygen to carbon rearrangement of silyl enol ethers derived from lactols.[6e,f] This rearrangement affords exclusively the trans orientation across the pyran ring with the resultant contiguous stereocenters (C2–C2′) in poor to modest diastereoselectivities (1:1–3:1) and in good yields (79–90%).[6e,f] Also, Ley and co-workers have shown the use of the oxygen to carbon rearrangement for the formation of various mono- and bi-cyclic ethers.[6g,h]

As stated above, recently we have developed a Lewis acid-mediated highly stereoretentive [1,3] rearrangement of vinyl acetals, wherein the selectivity is controlled by tight ion pairing of the resulting oxocarbenium ion and Lewis acid coordinated enolate intermediate.[5] Should the generated ions escape the solvent cage prior to recombination, the trans product would predominate. However, if recombination occurs faster, the cis product would result. In many cases, either isomer may be prepared by simple choice of Lewis acid system—$BF_3 \cdot OEt_2$ proved to be trans selective while $Me_3Al/BF_3 \cdot OEt_2$ afforded products of stereoretention, with a crossover study providing conclusive evidence. We envisioned the chosen Lewis acid would have the ability to control the recombination of the intermediates and possibly form a single diastereomer in a highly selective manner (Fig. 1).

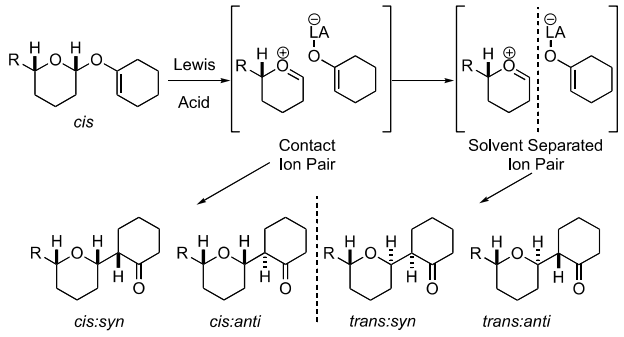


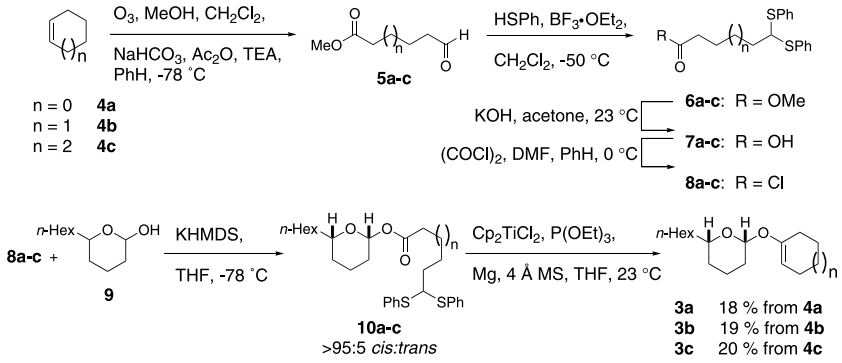
Figure 1.

2. Results and discussion

We chose to begin our investigations with simple enolates and oxocarbenium ions devoid of electronic or steric features, which might dictate selectivity in the bond forming event.[8] The requisite cyclic vinyl acetals **3a–c** were prepared by ozonolysis of the corresponding cycloalkenes **4a–c** using Schreiber's conditions.[9] The resulting aldehyde–methyl esters **5a–c** were treated with $BF_3 \cdot OEt_2$ and thiophenol to yield the thioacetal–methyl esters **6a–c**. Hydrolysis of **6a–c** and treatment with $(COCl)_2$ resulted in the acyl chloride–thioacetals **8a–c**. Using conditions reported by Ley,[6d] **8a–c** were treated with lactol **9** and KHMDS at −78 °C yielding the *cis*-tetrahydropyran esters **10a–c** in high cis:trans selectivity (>95:5). **10a–c** were cyclized via Takeda's titanocene(II)-promoted intramolecular carbonyl olefination of esters to yield the desired cyclic vinyl acetals **3a–c** (Scheme 1).[10]

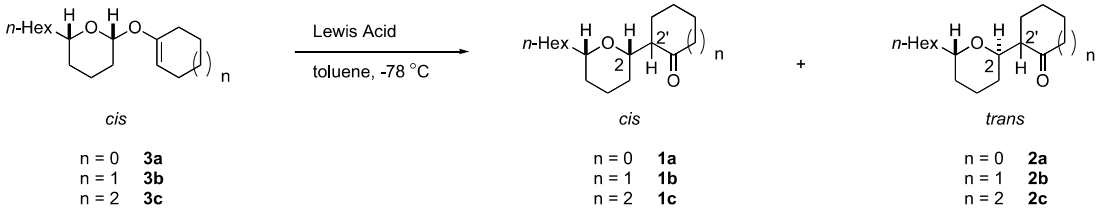
Our intitial screening of Lewis acids that would induce the rearrangement began with $BF_3 \cdot OEt_2$ (Table 1). From our previous work, we expected the strong Lewis acid would allow the complexed enolate to escape from the solvent cage prior to recombination and thus form the kinetically favored trans-isomer.[5a] Under these conditions, the rearrangements of **3a–c** resulted in extremely high trans:cis selectivities (entries 1, 5, and 9; Table 1).[11] Moreover, we were pleased that **3a** and **3b** (entries 1 and 5; Table 1) also had relatively good *anti*:*syn* selectivity for the C2–C2′ bond, (79:21 and 82:18, respectively). Unfortunately, further investigations aimed at identifying a Lewis acid capable of forming the opposite C2–C2′ stereochemistry were unsuccessful.

From our previous findings, we knew that the use of Me_3Al–$BF_3 \cdot OEt_2$ (4/1) results in a highly stereoretentive rearrangement.[5a] These conditions proved unsuccessful with the trisubstituted alkenes in this study (entries 3, 6, and 10; Table 1) which we interpret as due to the increased steric requirement of the trisubstituted alkene. However, adjustment of the acidity of the Lewis acid to Et_2AlCl provided a partial solution, potentially due to a slightly more reactive



Scheme 1.

Table 1.



Entry	*n*	Lewis acid	cis:trans[a]	cis (*anti*:*syn*)[a]	trans (*anti*:*syn*)[a]	Yield (%)[b]
1	0	$BF_3 \cdot OEt_2$	<1:>99	NA	79:21	90
2	0	$FeCl_3$	16:84	74:26	81:19	87
3	0	$Me_3Al/BF_3 \cdot OEt_2$[c]	40:60	62:38	71:29	75
4	0	Et_2AlCl	70:30	69:31	78:22	86
5	1	$BF_3 \cdot OEt_2$	4:96	>99:<1	82:18	88
6	1	$Me_3Al/BF_3 \cdot OEt_2$[c]	55:45	72:28	58:42	81
7	1	Et_2AlCl	92:8	63:37	86:14	84
8	1	Me_2AlCl	78:22	79:21	75:25	75
9	2	$BF_3 \cdot OEt_2$	2:98	52:48	52:48	92
10	2	$Me_3Al/BF_3 \cdot OEt_2$[c]	38:62	69:31	52:48	68
11	2	Et_2AlCl	72:28	58:42	57:43	90
12	2	Et_2AlCl/PPh_3[d]	89:11	55:45	52:48	88

[a] Ratios were determined by GC analysis.
[b] Isolated yield.
[c] Reaction conducted using 4 equiv Me_3Al and 1 equiv $BF_3 \cdot OEt_2$.
[d] Reaction conducted using 1.5 equiv Et_2AlCl and 1.65 equiv PPh_3.

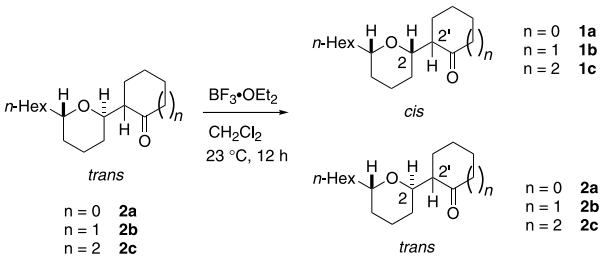
enolate intermediate. The Et_2AlCl mediated rearrangement presumably proceeds via tight ion-pairing and results in modest to good cis:trans selectivities for entries 4, 7, and 11 in Table 1 (70:30, 92:8, and 72:28, respectively).

Previous work had established that the cis-isomer is thermodynamically preferred, relative to the trans-isomer, due to reduced diaxial interactions and Ley has exploited this aspect to access the cis-isomer by epimerizing the trans-isomer with TMSOTf at 23 °C.[6c,d,12] As a result, our attention was focused on the ability to epimerize the stereocenter at the anomeric carbon (C2) in the reaction products. Treatment of the *trans*-ketone **2a–c** (products of entries 1, 3, and 5, respectively, in Table 3) with $BF_3 \cdot OEt_2$ at room temperature resulted in a highly efficient method for the epimerization to the *cis*-ketones **1a–c** (Table 2). All entries showed high cis:trans selectivity and **1a** exhibited good C2–C2′ diastereoselectivity (entry 1).

Our attention next focused on forming products **1a–c** and **2a–c** via a Lewis acid mediated intermolecular substitution reaction of an anomeric acetate (**11**) and enolsilanes (**12a–c**). The results of this substitution study, shown in Table 3, are comparable to the results from the [1,3] O to C rearrangement and the epimerization studies (Tables 1 and 2, respectively). Compound **1a** illustrates a higher selectivity for the cis isomer than in the two previous methods (entry 2; Table 3). While the C2–C2′ selectivities for the cis isomer of **1b** and **1c** (entries 4 and 6, respectively) were disappointing, the room temperature enolsilane addition afforded the α-pyranyl cyclopentanone (**1a**) with good stereoselectivity for the formation of the cis:*anti* diastereomer (entry 2). The enolsilane addition to the oxocarbenium ion derived from **11** at −78 °C yielded the α-pyranyl cycloalkanones (**2a–c**) in high trans:cis diastereoselectivities with modest C2–C2′ diastereoselectivities (entries 1, 3, and 5; Table 3).

Finally, our attention shifted to forming these bonds via an intramolecular conjugate addition. These types of reactions have been employed previously in the synthesis of substituted pyran compounds using a variety of bases including catalytic amounts of KO*t*-Bu.[13] Under these conditions (Table 4), the selectivities observed were comparable to the selectivities obtained in the previously

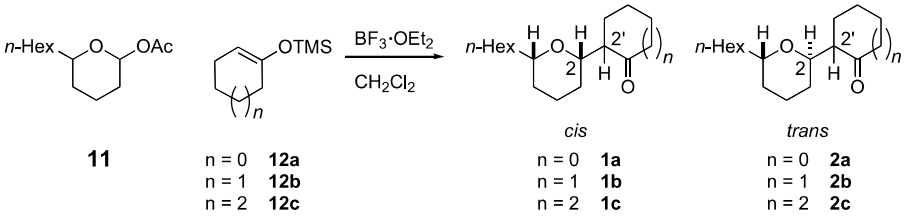
Table 2.



Entry	*n*	cis:trans[a]	cis (*anti*:*syn*)[a]	trans (*anti*:*syn*)[a]	Yield (%)[b]
1	0	93:7	80:20	92:8	98
2	1	97:3	50:50	79:21	96
3	2	99:1	50:50	50:50	97

[a] Ratios were determined by GC analysis.
[b] Isolated yield.

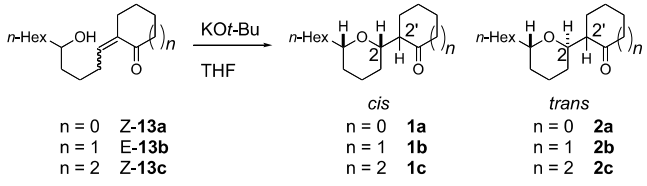
Table 3.



Entry	*n*	Temperature (°C)	Time (h)	cis:trans[a]	cis (*anti*:*syn*)[a]	trans (*anti*:*syn*)[a]	Yield (%)[b]
1	0	−78	1	4:96	64:36	64:36	90
2	0	23	12	98:2	76:24	64:36	86
3	1	−78	1	3:97	70:30	77:23	94
4	1	23	12	98:2	52:48	66:34	87
5	2	−78	1	<1:>99	37:63	57:43	92
6	2	23	12	99:1	52:48	66:34	92

[a] Ratios were determined by GC analysis.
[b] Isolated yield.

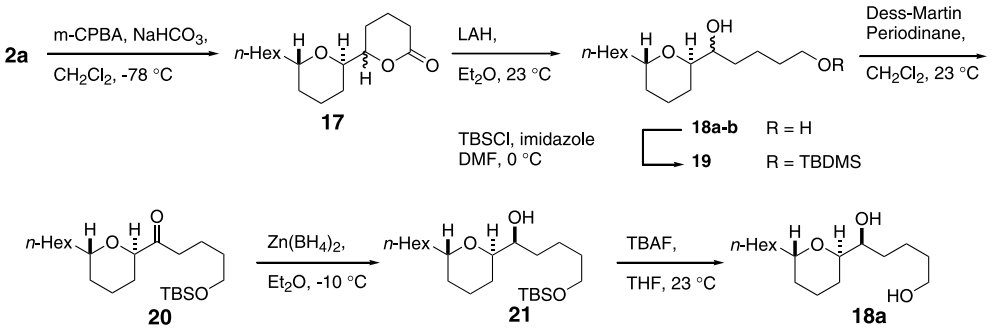
Table 4.



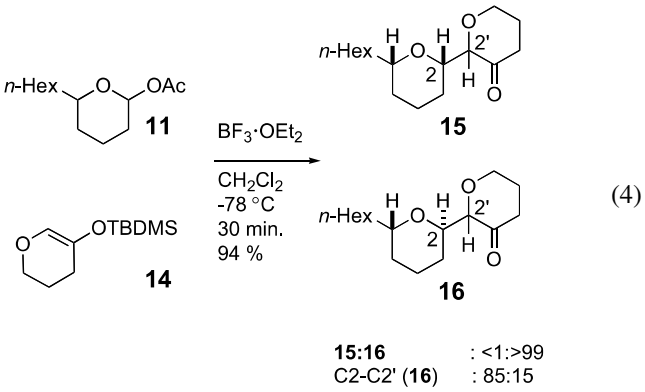
Entry[a]	*n*	Temperature (°C)	Time (min)	cis:trans[b]	cis (*anti*:*syn*)[b]	trans (*anti*:*syn*)[b]	Yield (%)[c]
1	0	−78	30	16:84	74:26	81:19	83
2	0	0	10	96:4	77:23	94:6	88
3	1	−78	30	18:82	60:40	74:26	84
4	1	0	10	98:2	55:45	60:40	86
5	2	−78	30	48:52	55:45	62:38	85
6	2	0	10	89:11	52:48	55:45	90

[a] Starting materials used as >95:5 isomerically enriched favoring the defined olefin isomer.
[b] Ratios of C2/C2′ isomers, determined by GC analysis.
[c] Isolated yield.

listed methods (Tables 1–3). Stereoselectivities in the synthesis of the cis isomer were good to excellent in all the systems that were explored (entries 2, 4, and 6; Table 4). In addition, the C2–C2′ selectivities were poor to modest for systems **1a–c** (entries 2, 4, and 6, respectively). The selectivity towards the trans isomers (**2a–c**) were modest at best for all three substrates and the C2–C2′ selectivities were poor to good (entries 1, 3, and 5; Table 4). In all entries, the yields of the conjugate addition products were good (84–90%).



Scheme 2.



(4)

With these results in hand, we wanted to apply this technique to a system containing a heteroatom in both ring segments. Therefore, enolsilane **14** was prepared according to methods reported by Gallagher and co-workers.[14b] When acetal **11** and enolsilane **14** were treated with $BF_3 \cdot OEt_2$ at −78 °C, the trans-isomers **15** (Eq. 4) were the only observed diastereomers.[15] A control experiment was performed in order to determine whether the more bulky silyl group (TBS / TMS) caused a significant change in the diastereoselectivity observed for the all carbon system (**1b** and **2b**); no significant change in diastereoselectivity was observed at either −78 or 23 °C.[16]

Determination of C2–C2′ stereochemistry was not trivial due to our inability to separate the C2–C2′ diastereomers formed from the reaction products. As a result, we resorted to a chemical correlation to prove stereochemistry (Scheme 2). First, a Baeyer–Villiger oxidation of ketone **2a** affords the lactone **17**. The reduction of **17** with LAH yielded the two diastereomeric diols **18a** and **18b** (3:1), separable by column chromatography on silica gel. The major isomer **18a** was then mono-protected with TBDMSCl and oxidized with Dess–Martin periodinane yielding the ketone **20**. Chelate controlled reduction of **20** with $Zn(BH_4)_2$ resulted in a single diastereomer, **21**.[17] $Zn(BH_4)_2$ delivers the hydride in a manner, which leaves a *syn* relationship between C2 and C2′ (Fig. 2). Following the deprotection of **21** with TBAF and a comparison of spectroscopic data, it was established that the major isomer was that shown as **18a**, corresponding to the rearrangement product *anti* **2a**. This route was also performed on substrates **1a** and **2b**. The assignment of stereochemistry in **1b–c** and **2c** was based on analogies derived from predictable GC retention times of the product diastereomers. Thus, all reactions resulted in the *anti* isomer (C2–C2′) as the major product. We propose that the C2–C2′ *anti* selectivity is a result of the recombination of the oxocarbenium ion and Lewis acid complexed enolate in the lowest energy staggered conformation when the two hydrogen atoms are *anti*-periplanar (Fig. 3). cis:trans Selectivity in the rearrangement is a result of the recombination from either a contact (cis) or solvent separated (trans) ion pair. The cis:trans selectivity in the intermolecular oxocarbenium/enolsilane addition mirror this model (Fig. 3). The epimerization studies reflect thermodynamic (cis) stability.

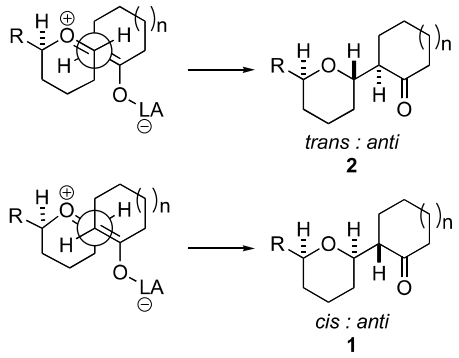


Figure 3.

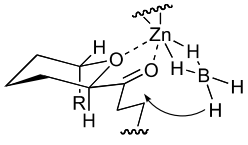
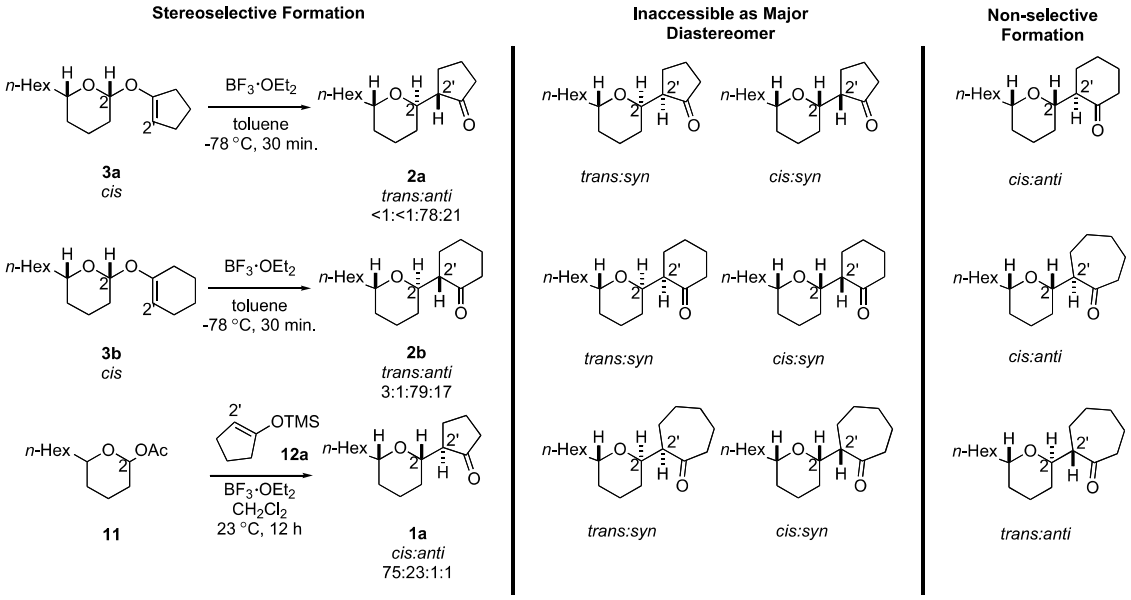


Figure 2.

3. Conclusions

In summary, we have investigated the formation of carbon–carbon bonds between adjacent rings via a stereoretentive rearrangement of cyclic vinyl acetals, an intermolecular addition of an enolsilane into an oxocarbenium ion, and an intramolecular conjugate addition of an ω-hydroxy-α,β-unsaturated ketones. Furthermore, we have shown that the product ratios obtained from the epimerization studies (Table 2) are indeed at their equilibrium positions, as justified by the similar results shown in Tables 3 and 4. The [1,3] oxygen to carbon rearrangement proved the best route for synthesizing the trans:*anti* diastereomer for substrates **2a**



[a]Ratios represented as: (*cis:anti*):(*cis:syn*):(*trans:anti*):(*trans:syn*).

Figure 4.

and **2b** in 70% yield for each of the desired diastereomers (Fig. 4). The enolsilane addition into an in situ generated oxocarbenium ion afforded the cis:*anti* diastereomer in 65% yield for substrate **1a** (Fig. 4). The synthesis of substrates **1b**, **1c**, and **2c** proceeded in a non-selective manner and unfortunately, the synthesis of the C2–C2′ *syn* diastereomers in all cases proved to be stereoselectively inaccessible by these approaches. The most promising result that we have identified is the selective assembly of bis-pyrans such as **16**, of particular relevance to key subsections of the polyether ladder toxins. Efforts at elaborating these substrates to probe the behavior of fully functionalized substrates are ongoing.

4. Experimental

4.1. General

4.1.1. General procedure for the synthesis of cyclic vinyl acetals. A 500 mL, three necked, round bottomed flask with a glass tube to admit ozone, a calcium chloride drying tube, and a glass stopper is charged with 5.109 g (75.0 mmol) of cyclopentene **4a**, 250 mL of CH_2Cl_2, 50 mL of MeOH, and 2.0 g of anhydrous $NaHCO_3$. After the apparatus is cooled to ca. −78 °C, ozone is bubbled through the solution as it is stirred (flow rate =4.0 lpm; 50 V). Ozone addition is stopped when the solution turns blue. Argon is passed through until the blue color is discharged and then the cold bath is removed. The solution is filtered into a 1-L, round-bottomed flask and 80 mL of benzene is added. The volume is reduced to approximately 50 mL by rotary evaporation. After dilution with 225 mL of CH_2Cl_2 the flask is cooled to 0 °C and 16 mL (113 mmol) of TEA and 21.24 mL (225 mmol) of Ac_2O are added via syringe, and the solution is stirred under an argon atmosphere at 0 °C for 15 min. The ice bath is removed and stirring is continued for 4 h. The solution is washed with 150 mL portions of aq 0.1 N HCl, 10% aq NaOH, and H_2O. The organic layer is dried over $MgSO_4$, filtered, and concentrated to provide 9.85 g (89%) of aldehyde–methyl ester **5a** as colorless oil.

A 250 mL round bottomed flask was charged with 1.68 g (12.9 mmol) of **5a** and 40 mL of CH_2Cl_2 then cooled to −50 °C. Next, 2.91 g (26.45 mmol) of PhSH and 4.58 g (32.25 mmol) of $BF_3\cdot OEt_2$ were added successively. The mixture was stirred at −50 °C for 30 min, then poured into a little ice-water and extracted with CH_2Cl_2. The organic layer was washed successively with 30 mL portions of 7% aq KOH, H_2O, and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated to yield 4.22 g (98%) of thioacetal–methyl ester **6a** as a yellow oil.

A 50 mL round bottomed flask was charged with thioacetal–methyl ester **6a** (4.22 g, 12.69 mmol), 3.56 g (63.46 mmol) of KOH, and 40 mL of acetone. The mixture was stirred overnight and then acidified with concd HCl to pH 4. The reaction mixture was extracted with EtOAc (3×50 mL) and washed with 100 mL H_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to yield a black oil. The crude product was purified by standard acid/base workup to yield 3.6 g (89%) of thioacetal-acid **7a**.

A 25 mL round bottomed flask was charged with 1.0 g (3.14 mmol) of thioacetal-acid **7a**, five drops of dry DMF, and 10.0 mL of benzene, then cooled to 0 °C and 1.24 g (9.73 mmol) of $(COCl)_2$ was added dropwise. After addition, the reaction mixture was allowed to warm to room temperature and stirred for 2 h. Excess reagents and solvent were removed by rotary evaporation and the residue was twice treated with 10 mL of benzene and concentrated by rotary evaporation. Reaction yielded 1.04 g (98%) of thioacetal–acyl chloride **8a** as a yellow oil.

To a stirred solution of lactol **9** (0.547 g, 2.94 mmol) in 10 mL THF at −78 °C was added a solution of KHMDS in toluene (0.5 M, 5.94 mL, 2.97 mmol) dropwise, and the reaction mixture was warmed to 0 °C over 5 min before

cooling to −78 °C. A solution of thioacetal–acyl chloride **8a** (1.04 g, 3.09 mmol) in 5 mL THF was added dropwise, and the reaction mixture was stirred for 2 h at −78 °C before quenching with satd aq NH_4Cl (20 mL). Next, distilled water (20 mL) was added and the aqueous layer was extracted with Et_2O (3×25 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to yield a yellow oil. Purification by flash column chromatography, eluting with 15% EtOAc in hexanes with 1% TEA, provided 1.10 g (76%) of ester **10a** as a yellow oil in >95:5 cis:trans diastereoselectivity.

Finely powdered 4 Å MS (400 mg), Mg turnings (120 mg, 4.94 mmol), and Cp_2TiCl_2 (1.03 g, 4.12 mmol) were placed in a flask and dried by heating with a heat gun under reduced pressure (2–3 mmHg). During this procedure care was taken not to sublime Cp_2TiCl_2. After cooling, THF (5 mL) and $P(OEt)_3$ (1.37 g, 8.24 mmol) were added successively with stirring at room temperature under argon. Within 15 min, the reaction mixture turned dark green and then dark brown with slight evolution of heat. After 3 h, the ester **10a** (0.5 g, 1.03 mmol) in 10 mL THF was added to the reaction mixture dropwise over 20 min. After stirring for 3 h, the reaction was quenched by addition of aq 1 M NaOH (20 mL) and then the insoluble materials were filtered off through Celite and washed with Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O (3×30 mL). The combined organic extracts were washed with aq 1 M NaOH, stirred with deactivated charcoal, and dried over $MgSO_4$. The slurry was then filtered and concentrated. The residue was purified by flash column chromatography, eluting with 25% EtOAc in hexanes containing 1% TEA, to afford 138 mg (32%) of cyclic vinyl acetal **3a** as a colorless oil.

4.1.2. General procedure for rearrangement of cyclic vinyl ethers. To a flame dried 5 mL round bottomed flask was added 5.0 mg (0.019 mmol) of cyclic vinyl ether **3b** and 1.0 mL of toluene. The reaction mixture was cooled to −78 °C and $BF_3\cdot OEt_2$ (2.7 μL, 0.021 mmol) was added dropwise. The reaction was allowed to stir until **3b** was completely consumed as seen by TLC, then quenched with 2 mL of satd aq Na_2CO_3 and separated layers. The aqueous layer was extracted with EtOAc (3×3 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 4.4 mg (88%) of a 2:98 (cis:trans) mixture of ketones **1b** and **2b**.

4.1.3. General procedure for the epimerization of *trans*-ketone (2) to *cis*-ketone (1). To a flame dried 5 mL round bottomed flask containing 100 mg (0.438 mmol) of ketone **2b** and 5.0 mL of CH_2Cl_2 was added dropwise at room temperature 124 mg (0.876 mmol) of $BF_3\cdot OEt_2$. The mixture was stirred for 12 h and quenched with 7.0 mL of satd aq Na_2CO_3. The layers were separated and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield 96 mg (96%) of a 98:2 (cis:trans) mixture of ketones **1b** and **2b**.

4.1.4. General procedure for the intermolecular enolsilane addition reaction. To a flame dried 5 mL round bottomed flask was added 22.8 mg (0.10 mmol) of lactol **11**, 25.5 mg (0.15 mmol) of silyl enol ether **12b**, and 1.0 mL of CH_2Cl_2. The reaction was then cooled to −78 °C and 19 μL (0.15 mmol) of $BF_3\cdot OEt_2$ was added dropwise. After 1 h at −78 °C, the reaction was quenched by the addition of 1.0 mL satd aq Na_2CO_3 and extracted with Et_2O (3×10 mL). The organics were combined and washed with H_2O, then satd aq $NaHCO_3$. The organic layer was then dried over $MgSO_4$, filtered, and concentrated to yield 21.2 mg (94%) of 3:97 (cis:trans) mixture of ketones **1b** and **2b**.

4.1.5. General procedure for the conjugate addition. To a flame dried 5 mL round bottomed flask was added 10.0 mg (0.036 mmol) of hydroxy-ketone **13a** and 0.5 mL of THF. The reaction was cooled to 0 °C and 1.0 mg (0.0072 mmol) of KO*t*Bu was added. After 10 min, the reaction was quenched with 0.5 mL of satd aq NH_4Cl and extracted with Et_2O (3×10 mL). The organic layers were combined and washed with brine, dried over $MgSO_4$, filtered and concentrated to afford 8.8 mg (88%) of 96:4 (cis:trans) mixture of ketones **1a** and **2b**.

4.1.6. Determination of C2–C2′ stereochemistry. A 25 mL round bottomed flask was charged with 370 mg (1.63 mmol) of ketone **2a**, 3.3 mL of aq 0.5 M $NaHCO_3$ (1.63 mmol), and 6.0 mL of CH_2Cl_2. *m*-CPBA (564 mg, 3.27 mmol, purity 77% max) was added portionwise at room temperature and the reaction was allowed to stir overnight. The reaction was quenched by addition of 15% aq Na_2SO_3 (5 mL) and stirred at room temperature for 1 h. The layers were separated and the organic layer was washed with 5 mL portions of H_2O, 5% aq $NaHCO_3$, H_2O, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to yield 255 mg (55%) of lactone **17**.

To a 125 mL round bottomed flask charged with 255 mg (0.908 mmol) of lactone **17** and 30.0 mL of Et_2O was added portionwise 111 mg (2.937 mmol) of LAH. The reaction was stirred for 12 h, then cooled to 0 °C and added to the reaction flask 0.111 mL of H_2O, 0.111 mL of 15% aq NaOH, and 0.333 mL of H_2O (Fieser workup).[18] The reaction was allowed to stir until the gray solution turned clear. The precipitate was filtered off and the filtered solution was then concentrated to afford a crude oil. The crude oil was purified by flash column chromatography using 90% EtOAc in hexanes as eluant to yield 146 mg (56%) of diol **18a** and 50.6 mg (19%) of diol **18b**.

A 25 mL round bottomed flask was charged with 40 mg (0.140 mmol) of diol **18a** and 2.0 mL of dry DMF. The reaction was cooled to 0 °C and then successively added 11.4 mg (0.168 mmol) of imidazole and 21.9 mg (0.145 mmol) of TBDMSCl. After 15 min, the reaction was diluted with 5.0 mL of Et_2O and 5.0 mL of H_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 50 mg (89%) of alcohol **19**.

A 5 mL round bottomed flask was charged with 50 mg (0.125 mmol) of alcohol **19**, trace amount of $NaHCO_3$, 84.4 mg (0.200 mmol) of Dess–Martin periodinane, and 1.0 mL of DCM and stirred for 12 h at room temperature.

The reaction mixture was diluted with 2.0 mL satd aq $NaHCO_3$ and 2.0 mL of satd aq $Na_2S_2O_3$, then extracted with Et_2O (3×5 mL). The combined organics were washed with 5 mL portions of H_2O and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford 48 mg (96%) of ketone **20**.

To a stirred solution of 20.0 mg (0.0502 mmol) of ketone **20** in ether (1.0 mL) was added dropwise a 0.14 M solution of $Zn(BH_4)_2$[19] in ether at −10 °C, and the mixture was stirred at the same temperature for 0.5 h. After quenching with satd aq NH_4Cl (2.0 mL), the resulting mixture was dried over $MgSO_4$, filtered through a pad of Celite, and concentrated to yield 19 mg (94%) of alcohol **21**.

A 5 mL round bottomed flask was charged with 20 mg (0.050 mmol) of alcohol **21**, a solution of TBAF in THF (1.0 M, 0.10 mmol, 0.1 mL), and 0.5 mL of THF. The reaction was allowed to stir at room temperature for 12 h, then quenched with 1.0 mL satd aq $NaHCO_3$. The aqueous layer was extracted with EtOAc (3×5 mL) and the combined organic layers were washed with 10.0 mL brine, and dried over $MgSO_4$. The slurry was filtered and concentrated to afford 14.0 mg (97%) of diol **18a**.

4.2. Compound characterization

4.2.1. α-Pyranyl-cycloalkonones (1a–c, 2a–c).

4.2.1.1. (2′*S,6′*S**)-2-(6-Hexyl-tetrahydro-pyran-2-yl)-cyclopentanone (1a).** Following the general procedure afforded **1a**, a yellow oil, as a mixture of C2–C2′ diastereomers: R_f=0.429 (15% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (2H, d, J=11.3 Hz), 3.56 (1H, ddd, J=10.9, 3.4, 1.9 Hz), 3.19 (2H, m), 0.95–2.33 (46H, m), 0.84 (3H, t, J=7.0 Hz), 0.84 (3H, t, J=9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.0, 219.9, 78.5, 78.2, 77.9, 76.8, 53.8, 53.3, 39.6, 39.5, 36.6, 32.0, 31.6, 31.5, 29.9, 29.5, 29.4, 27.7, 26.4, 25.6, 25.5, 24.4, 23.8, 22.8, 21.3, 21.2, 14.3; IR (NaCl, neat) 2931, 2857, 1738 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{29}O_2$, 253.2168. Found 253.2177.

4.2.1.2. (2′*R,6′*S**)-2-(6-Hexyl-tetrahydro-pyran-2-yl)-cyclopentanone (2a).** Following the general procedure afforded **2a**, a yellow oil, as a mixture of C2–C2′ diastereomers: R_f=0.365 (15% EtOAc/hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78–3.94 (2H, m), 3.56–3.67 (1H, m), 1.10–2.38 (47H, m), 0.82–0.94 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.1, 219.4, 73.3, 72.4, 69.9, 69.6, 52.8, 51.9, 39.5, 32.7, 32.2, 31.1, 29.7, 29.0, 28.9, 27.7, 26.4, 26.3, 26.0, 25.3, 23.0, 21.2, 21.0, 19.0, 14.5; IR (NaCl, neat) 2931, 2857, 1738 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{29}O_2$, 253.2168. Found 253.2177.

4.2.1.3. (2′*S,6′*S**)-2-(6-Hexyl-tetrahydro-pyran-2-yl)-cyclohexanone (1b).** Following the general procedure afforded **1b**, a yellow oil, as a mixture of C2–C2′ diastereomers: R_f=0.429 (15% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (1H, ddd, J=11.2, 6.2, 1.5 Hz); 3.51 (1H, ddd, J=10.2, 9.0, 1.3 Hz), 3.22 (2H, m), 2.20–2.49 (6H, m), 0.95–2.40 (44H, m), 0.80–0.90 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 212.1, 78.5, 78.3, 76.5, 76.0, 56.7, 56.1, 42.9, 42.0, 36.8, 36.6, 32.1, 31.7, 30.5, 30.0, 29.5, 29.4, 29.2, 28.5, 28.2, 28.0, 25.8, 25.6, 24.4, 24.0, 23.8, 22.8, 14.3; IR (NaCl, neat) 2931, 2858, 1711 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{31}O_2$, 267.2324. Found 267.2331.

4.2.1.4. (2′*R,6′*S**)-2-(6-Hexyl-tetrahydro-pyran-2-yl)-cyclohexanone (2b).** Following the general procedure afforded **2b**, a yellow oil, as a mixture of C2–C2′ diastereomers: R_f=0.341 (15% EtOAc/hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.11 (1H, ddd, J=10.6, 8.1, 3.3 Hz), 3.92 (1H, ddd, J=9.9, 5.9, 4.0 Hz), 3.69 (1H, m), 3.51 (1H, m), 2.53–2.66 (2H, m), 2.37–2.49 (1H, m), 2.20–2.32 (4H, m), 2.07–2.20 (1H, m), 1.45–2.00 (20H, m), 1.13–1.40 (22H, m), 0.77–0.88 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.6, 212.1, 72.4, 71.8, 69.1, 69.0, 54.2, 53.0, 42.9, 41.5, 33.8, 32.8, 30.4, 30.2, 29.8, 29.7, 29.7, 29.4, 28.9, 27.3, 26.1, 24.4, 23.3, 23.0, 19.0, 18.8, 14.4; IR (NaCl, neat) 2931, 2858, 1710 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{31}O_2$, 267.2324. Found 267.2331.

4.2.1.5. (2′*S,6′*S**)-2-(6-Hexyl-tetrahydro-pyran-2-yl)-cycloheptanone (1c).** Following the general procedure afforded **1c**, a yellow oil, as a mixture of C2–C2′ diastereomers: R_f=0.455 (15% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51 (1H, ddd, J=12.7, 6.1, 1.6 Hz), 3.18 (1H, m), 2.30–2.62 (3H, m), 2.16–2.19 (1H, m), 1.00–1.98 (23H, m), 0.85 (3H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.8, 215.4, 79.3, 79.0, 78.3, 58.5, 58.4, 44.4, 44.4, 36.7, 36.5, 32.1, 31.9, 31.7, 30.0, 29.7, 29.6, 29.5, 28.8, 28.5, 28.1, 27.4, 26.2, 25.7, 25.6, 25.4, 24.9, 23.9, 22.8, 14.3; IR (NaCl, neat) 2930, 2856, 1702 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{33}O_2$, 281.2481. Found 281.2486.

4.2.1.6. (2′*R,6′*S**)-2-(6-Hexyl-tetrahydro-pyran-2-yl)-cycloheptanone (2c).** Following the general procedure afforded **2c**, a yellow oil, as a mixture of C2–C2′ diastereomers: R_f=0.417 (15% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (2H, ddd, J=15.0, 6.7, 2.6 Hz), 3.72 (1H, m), 3.61 (1H, m), 2.68–2.81 (2H, m), 2.20–2.65 (7H, m), 2.06–2.18 (1H, m), 1.12–1.98 (44H, m), 0.80–0.92 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.8, 214.5, 72.4, 72.2, 72.0, 71.4, 56.5, 55.5, 44.1, 42.2, 33.1, 32.9, 32.2, 32.2, 30.3, 30.1, 29.9, 29.7, 29.6, 28.8, 27.7, 27.6, 26.9, 26.0, 25.0, 24.7, 23.0, 19.1, 18.8, 14.5; IR (NaCl, neat) 2930, 2856, 1702 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{33}O_2$, 281.2481. Found 281.2486.

4.2.2. Cyclic vinyl acetals (3a–c).

4.2.2.1. (2*R,6*S**)-2-(Cyclopent-1-enyloxy)-6-hexyl-tetrahydro-pyran (3a).** Following the general procedure afforded **3a** as a yellow oil: R_f=0.309 (25% EtOAc/hex with 1% TEA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (1H, d, J=9.4 Hz), 3.89 (1H, m), 3.37 (1H, m), 1.06–1.88 (22H, m), 0.84 (3H, t, J=6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.4, 92.1, 69.0, 36.4, 36.2, 33.1, 32.0, 31.3, 30.6, 30.0, 29.6, 25.6, 22.8, 22.3, 17.7, 14.3; IR (NaCl, neat) 2932, 2858 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{29}O_2$, 253.2168. Found 253.2176.

4.2.2.2. (2*R,6*S**)-2-(Cyclohex-1-enyloxy)-6-hexyl-tetrahydro-pyran (3b).** Following the general procedure afforded **3b** as a yellow oil: R_f=0.283 (25% EtOAc/hex with 1% TEA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65 (1H, d, J=9.2 Hz), 3.89 (1H, m), 3.37 (1H, m), 1.05–1.89 (24H, m), 0.84 (3H, t, J=6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ

96.7, 92.1, 69.0, 36.4, 36.2, 33.1, 32.0, 31.3, 30.6, 30.0, 29.5, 25.7, 25.6, 22.8, 22.3, 17.7, 14.3; IR (NaCl, neat) 2932, 2858 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{31}O_2$, 267.2324. Found 267.2329.

4.2.2.3. (2*R,6*S**)-2-(Cyclohept-1-enyloxy)-6-hexyl-tetrahydro-pyran (3c).** Following the general procedure afforded **3c** as a yellow oil: R_f=0.278 (25% EtOAc/hex with 1% TEA); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (1H, m), 3.88 (1H, m), 3.37 (1H, m), 1.05–1.89 (26H, m), 0.84 (3H, t, J=6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 96.4, 92.1, 69.0, 36.4, 36.2, 33.1, 32.0, 31.4, 30.6, 30.0, 29.6, 29.5, 25.7, 25.6, 22.8, 22.3, 17.7, 14.3; IR (NaCl, neat) 2931, 2858 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{33}O_2$, 281.2481. Found 281.2489.

4.2.3. Hydroxy ketones (13a–c).

4.2.3.1. 2-(5-Hydroxy-undecylidene)-cyclopentanone (13a). Compound **13a** was prepared from the Horner–Wadsworth–Emmons reaction of undecanoic δ-lactol and diethyl 2-oxocyclohexylphosphonate and was isolated as the *Z* isomer as a yellow oil: R_f=0.138 (25% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.5 (1H, dddd, J=2.8, 2.8, 7.5, 10.2 Hz), 3.55 (1H, m), 2.54 (2H, t, J=7.0 Hz), 2.29 (2H, t, J=7.7 Hz), 2.13 (2H, q, J=7.0 Hz), 1.90 (2H, quint., J=7.7 Hz), 1.19–1.67 (15H, m), 0.84 (3H, t, J=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5, 137.7, 136.1, 71.9, 38.8, 37.8, 37.2, 32.0, 29.8, 29.5, 26.9, 25.8, 24.7, 22.8, 20.0, 14.3; IR (NaCl, neat) 3430, 2929, 2857, 1718, 1647 cm^{-1}; HRMS (EI+) Calcd for $C_{16}H_{28}O_2$, 252.2089. Found 252.2084.

4.2.3.2. 2-(5-Hydroxy-undecylidene)-cyclohexanone (13b). Compound **13b** was prepared via the ring opening of **1b** with Me_2BBr and Et_3N and was isolated as the *E* isomer as a yellow oil:[20] R_f=0.142; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (1H, t, J=4.3 Hz), 3.55 (1H, m), 2.39 (2H, m), 2.32 (2H, m), 2.15 (2H, m), 1.94 (2H, m), 1.25–1.65 (15H, m), 0.86 (3H, t, J=5.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 145.3, 140.0, 72.1, 38.8, 37.7, 37.4, 32.0, 29.7, 29.6, 28.9, 26.2, 25.8, 25.6, 23.4, 22.8, 14.3; IR (NaCl, neat) 3431, 2928, 2856, 1666 cm^{-1}; HRMS (EI+) calcd for $C_{17}H_{30}O_2$, 266.2246. Found 266.2248.

4.2.3.3. 2-(5-Hydroxy-undecylidene)-cycloheptanone (13c). Compound **13c** was prepared from the Horner–Wadsworth–Emmons reaction of undecanoic δ-lactol and diethyl 2-oxocycloheptylphosphonate and was isolated as the *Z* isomer as a yellow oil: R_f=0.150 (25% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (1H, t, J=7.46 Hz), 3.55 (1H, m), 2.56 (2H, m), 2.39 (2H, m), 2.13 (2H, m), 1.20–1.76 (21H, m), 0.85 (3H, t, J=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.0, 140.9, 139.0, 71.9, 43.5, 37.7, 37.3, 32.0, 31.6, 30.0, 29.5, 28.1, 27.3, 25.8, 25.4, 25.1, 22.8, 14.3; IR (NaCl, neat) 3433, 2927, 2855, 1686, 1616 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{33}O_2$, 281.2481. Found 281.2482.

4.2.4. Bipyranyl ketone (16).

4.2.4.1. (2′*R,6′*S**)-6′-Hexylhexahydro-2*H*, 2′*H*-2,2′-bipyran-3(4*H*)-one (16).** Following the general procedure afforded **16** as a yellow oil: R_f=0.175 (15% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (1H, ddd, J=11.7, 5.5, 5.5 Hz, major), 4.09 (1H, m, minor), 4.01 (1H, m, major), 3.91 (d, 1H, J=3.6 Hz, minor), 3.78–3.85 (2H, m), 3.70 (1H, d, J=3.2 Hz, major), 3.62 (1H, ddd, J=11.6, 8.1, 5.1 Hz, major), 2.50–2.64 (1H, m), 2.35–2.46 (1H, m), 2.02–2.27 (1H, m), 1.86–2.00 (1H, m), 1.52–1.80 (7H, m), 1.38–1.50 (1H, m), 1.06–1.38 (13H, m), 0.84 (3H, t, J=6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3, 208.1, 85.1, 85.0, 73.3, 73.1, 69.6, 69.1, 64.4, 64.8, 37.9, 37.2, 31.8, 30.9, 30.4, 29.2, 29.1, 28.2, 28.4, 26.9, 25.9, 25.6, 25.5, 25.2, 23.8, 22.6, 18.6, 18.2, 14.1; IR (NaCl, neat) 2930, 2857, 1723 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{29}O_3$, 269.2117. Found 269.2113.

4.2.5. Determination of C2–C2′ stereochemistry (17–21).

4.2.5.1. (2′*R,6′*S**)-6′-Hexyl-octahydro-[2,2′]-bipyranyl-6-one (17).** Following the general procedure **17** was isolated as a yellow oil: R_f=0.179 (25% EtOAc/hex) major isomer, R_f=0.120 (25% EtOAc/hex) minor isomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 (1.5H, ddd, J=3.5, 8.0, 11.11 Hz), 4.19–4.25 (1.25H, m), 3.87 (1H, m), 3.55–3.67 (4H, m), 2.50–2.61 (2.75H, m), 2.36–2.48 (2.75H, m), 1.18–2.11 (60H, m), 0.85 (3H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 171.6, 82.8, 80.6, 73.2, 72.8, 72.4, 70.7, 32.9, 32.0, 31.0, 30.0, 29.9, 29.7, 29.5, 28.7, 26.4, 26.1, 26.0, 24.6, 23.8, 22.8, 18.7, 18.6, 18.4, 14.3; IR (NaCl, neat) 2931, 2857, 1736, 1241, 1049 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{29}O_3$, 269.2117. Found 269.2113.

4.2.5.2. 1-(*S)-(6-(*S**)-Hexyl-tetrahydro-pyran-2-(*R**)-yl)-pentane-1,5-diol (18a).** Following the general procedure **18a** was isolated as a clear oil: R_f=0.242 (90% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (1H, m), 3.55–3.64 (3H, m), 3.42 (1H, dddd, J=4.1, 4.1, 8.8, 13.3 Hz), 2.25 (1H, s), 1.82 (1H, s), 1.18–1.79 (22H, m), 0.85 (3H, t, J=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.1, 73.0, 72.4, 62.9, 32.8, 32.0, 31.9, 31.2, 29.5, 29.1, 26.2, 24.9, 22.8, 22.3, 18.3, 14.3; IR (NaCl, neat) 3344, 2930, 2858, 1077, 1037 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{33}O_3$, 273.2430. Found 273.2427.

4.2.5.3. 1-(*R)-(6-(*S**)-Hexyl-tetrahydro-pyran-2-(*R**)-yl)-pentane-1,5-diol (18b).** Following the general procedure **18b** was isolated as a clear oil: R_f=0.328 (90% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (1H, ddd, J=4.3, 4.3, 8.8 Hz), 3.61 (2H, t, J=6.0 Hz), 3.54 (1H, ddd, J=2.5, 8.4, 10.3 Hz), 3.34 (1H, ddd, J=2.7, 7.8, 10.7 Hz), 2.77 (1H, s), 1.83 (1H, s), 1.18–1.75 (22H, m), 0.84 (3H, t, J=6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.7, 72.4, 72.0, 62.9, 32.9, 32.6, 32.4, 32.0, 29.5, 29.4, 26.7, 26.0, 22.8, 21.9, 18.6, 14.3; IR (NaCl, neat) 3402, 2932, 2858, 1040 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{33}O_3$, 273.2430. Found 273.2441.

4.2.5.4. 5-(*t*-Butyl-dimethyl-silanyloxy)-1-(*S)-(6-(*S**)-hexyl-tetrahydro-pyran-2-(*R**)-yl)-pentan-1-ol (19).** Following the general procedure **19** was isolated as a clear oil: R_f=0.424 (25% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (1H, m), 3.54–3.62 (3H, m), 3.42 (1H, ddd, J=4.3, 4.3, 8.8 Hz), 2.01 (1H, d, J=3.9 Hz), 1.18–1.79 (22H, m), 0.86 (9H, s), 0.85 (3H, t, J=7.2 Hz), 0.01 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.1, 72.4, 63.4, 33.0, 32.2, 32.0, 31.3, 29.5, 29.1, 26.2, 24.8, 22.8, 22.4, 18.4, 18.3, 14.3, −5.1; IR (NaCl, Neat) 3434, 2930, 2857, 1100,

1040 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{47}O_3Si$, 387.3294. Found 387.3296.

4.2.5.5. 5-(*t*-Butyl-dimethyl-silanyloxy)-1-(6-(*S)-hexyl-tetrahydro-pyran-2-(*R**)-yl)-pentan-1-one (20).** Following the general procedure **20** was isolated as a clear oil: R_f=0.282 (10% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (1H, dd, J=4.3, 4.3 Hz), 3.58 (2H, t, J=6.4 Hz), 3.42 (1H, m), 2.59 (1H, ddd, J=1.8, 1.8, 6.2 Hz), 2.53 (1H, ddd, J=1.8, 1.8, 6.2 Hz), 1.92 (1H, m), 1.20–1.67 (19H, m), 0.86 (9H, s), 0.85 (3H, t, J=6.0 Hz), 0.01 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.8, 78.5, 74.4, 63.1, 38.4, 35.3, 32.6, 32.0, 30.7, 29.6, 26.2, 25.8, 25.2, 22.8, 20.2, 19.7, 18.5, 14.3, −5.1; IR (NaCl, neat) 2930, 2857, 1717, 1101 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{45}O_3Si$, 385.3138. Found 385.3128.

4.2.5.6. 5-(*t*-Butyl-dimethyl-silanyloxy)-1-(*S)-(6-(*S**)-hexyl-tetrahydro-pyran-2-(*R**)-yl)-pentan-1-ol (21).** Following the general procedure **19** was isolated as a clear oil: R_f=0.424 (25% EtOAc/hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (1H, m), 3.54–3.62 (3H, m), 3.42 (1H, ddd, J=4.3, 4.3, 8.8 Hz), 2.01 (1H, d, J=3.9 Hz), 1.18–1.79 (22H, m), 0.86 (9H, s), 0.85 (3H, t, J=7.2 Hz), 0.01 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 73.1, 72.4, 63.4, 33.0, 32.2, 32.0, 31.3, 29.5, 29.1, 26.2, 24.8, 22.8, 22.4, 18.4, 18.3, 14.3, −5.1; IR (NaCl, Neat) 3434, 2930, 2857, 1100, 1040 cm^{-1}; HRMS (FAB+) calcd for $C_{22}H_{47}O_3Si$, 387.3294. Found 387.3296.

Acknowledgements

Financial support has been provided by the National Institute of General Medical Sciences (GM65407). We thank Merck Research Laboratories, GlaxoSmithKline, Amgen, Boehringer Ingelheim, and Eli Lilly for unrestricted support. T.R. is a fellow the Alfred P. Sloan Foundation. T.R. thanks the Monfort Family Foundation for a Monfort Professorship.

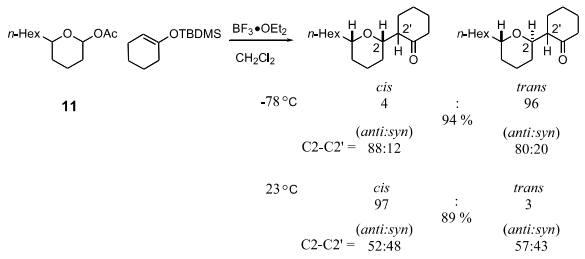
Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2006.02.042

References and notes

1. (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897–1909. (b) Marmsäter, F. P.; West, F. G. *Chem. Eur. J.* **2002**, *8*, 4346–4353.
2. Nicolaou, K. C.; Yang, Z.; Shi, G.; Gunzner, J. L.; Agrios, K. A.; Gärtner, P. *Nature* **1998**, *392*, 264–270.
3. Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904–1907.
4. For examples of total synthesis or synthetic studies for natural products, see: (a) Sakamoto, Y.; Matsuo, G.; Matsukura, H.; Nakata, T. *Org. Lett.* **2001**, *3*, 2749–2752. (b) Nicolaou, K. C.; Postema, M. H. D.; Yue, E. W.; Nadin, A. *J. Am. Chem. Soc.* **1996**, *118*, 10335–10336. (c) Trost, B. M.; Rhee, Y.-H. *Org. Lett.* **2004**, *6*, 4311–4313. (d) Sasaki, M.; Shida, T.; Tachibana, K. *Tetrahedron Lett.* **2001**, *42*, 5725–5728. (e) Fujiwara, K.; Kobayashi, M.; Yamamoto, F.; Aki, Y.; Kawamura, M.; Awakura, D.; Amano, S.; Okano, A.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2005**, *46*, 5067–5069. (f) Halim, R.; Brimble, M. A.; Merten, J. *Org. Lett.* **2005**, *7*, 2659–2662. (g) Bondar, D.; Liu, J.; Müller, T.; Paquette, L. A. *Org. Lett.* **2005**, *7*, 1813–1816. (h) Peng, X.; Bondar, D.; Paquette, L. A. *Tetrahedron* **2004**, *60*, 9589–9598. (i) Evans, D. A.; Rajapakse, H. A.; Hemaka, A.; Stenkamp, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4569–4573. (j) Paquette, L. A.; Peng, X.; Bondar, D. *Org. Lett.* **2002**, *4*, 937–940. (k) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *3*, 1949–1952. (l) Awakura, D.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 1733–1736. (m) Amano, S.; Fujiwara, K.; Murai, A. *Synlett* **1997**, 1300–1302.
5. (a) Zhang, Y.; Reynolds, N. T.; Manju, K.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 9720–9721. (b) Zhang, Y.; Rovis, T. *Tetrahedron* **2003**, *59*, 8979–8987.
6. (a) For other examples of O–C rearrangements see: (a) Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1455–1458. (b) Ferrier, R. J.; Middleton, S. *Chem. Rev.* **1993**, *93*, 2779–2831. (c) Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2665–2667. (d) Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans.1* **2000**, 2385–2394. (e) Dixon, D. J.; Ley, S. V.; Tate, E. W. *Synlett* **1998**, 1093–1095. (f) Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3125–3126. (g) Buffet, M. F.; Dixon, D. J.; Edwards, G. L.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1815–1827. (h) Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1829–1836. (i) Takahashi, M.; Suzuki, H.; Moro-Oka, Y.; Ikawa, T. *Tetrahedron Lett.* **1982**, *23*, 4031–4034.
7. For examples of reductive coupling using SmI_2 see: (a) Hung, S.-C.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1996**, *35*, 2671–2674. (b) Vlahov, I. R.; Vlahova, P. I.; Linhardt, R. J. *J. Am. Chem. Soc.* **1997**, *119*, 1480–1481. (c) Miquel, N.; Doisneau, G.; Beau, J.-M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4111–4114. (d) Chiara, J. L.; Sesmilo, E. *Angew. Chem., Int. Ed.* **2002**, *41*, 3242–3246. (e) Aurrecoechea, J. M.; Gil, J. H.; Lopez, B. *Tetrahedron* **2003**, *59*, 7111–7121. For an example of insertion into B–C bonds using glycosylidene carbenes see: (f) Wenger, W.; Vasella, A. *Helv. Chim. Acta* **2000**, *83*, 1542–1560. For examples of nucleophilic addition into oxocarbenium ions see: (g) Hoffman, M. G.; Schmidt, R. R. *Liebigs Ann. Chem.* **1985**, 2403–2419. (h) Kunz, H.; Müller, B.; Weissmüller, J. *Carbohydr. Res.* **1987**, *171*, 25–34. (i) Palmacci, E. R.; Seeberger, P. H. *Org. Lett.* **2001**, *3*, 1547–1550.
8. (a) Shenoy, S. R.; Woerpel, K. A. *Org. Lett.* **2005**, *7*, 1157–1160. (b) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168–169. (c) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521–15528.
9. Schreiber, S. L.; Claus, R. E. *Org. Synth.* **1984**, *64*, 150–156.
10. Rahim, M. A.; Sasaki, H.; Saito, J.; Fujiwara, T.; Takeda, T. *Chem. Commun.* **2001**, 625–626.
11. The rearrangement of **3a–c** with 1.1 equiv of $BF_3{\cdot}OEt_2$ at 23 °C resulted in modest selectivities.

12. Bergman, E. D.; Ginsburg, D.; Pappo, R. *Org. React.* **1959**, *10*, 179–563.
13. (a) Bhattacharjee, A.; Soltani, O.; De Brabander, J. K. *Org. Lett.* **2002**, *4*, 481–484. (b) Evans, D. A.; Ripin, D. H. B.; Halstead, D. P.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 6816–6826. (c) Evans, D. A.; Carreira, E. M. *Tetrahedron Lett.* **1990**, *31*, 4703–4706. For other examples see: (d) Ramirez, M. A.; Padron, J. M.; Palazon, J. M.; Martin, V. S. *J. Org. Chem.* **1997**, *62*, 4584–4590. (e) Schneider, C.; Schuffenhauer, A. *Eur. J. Org. Chem.* **2000**, 73–82.
14. (a) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2075–2088. (b) Cox, P.; Lister, S.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3151–3157.
15. At 23 °C, this reaction also provided trans-isomer as the major adduct (<1:>99; cis:trans). Efforts to epimerize trans to cis have so far met with failure. cis C2–C2′ diastereoselectivity deteriorated to 75:25 (*anti*:*syn*) at 23 °C.
16. The resultant diastereomers obtained are comparable with entries 3 and 4 in Table 3.



17. (a) Nakata, T.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 2653–2656. (b) Takahashi, S.; Kubota, A.; Nakata, T. *Tetrahedron* **2003**, *59*, 1627–1638.
18. Paquette, L. A., Ed.; Encyclopedia of Reagents for Organic Synthesis; Wiley: New York, 1995; Vol. 5, p 3009.
19. Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338–344.
20. Abel, S.; Linker, T.; Giese, B. *Synlett* **1991**, 171–172.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 4584–4589
Tetrahedron

An efficient and convergent synthesis of the potent and selective H_3 antagonist ABT-239

Yi-Yin Ku,[a,*] Yu-Ming Pu,[a] Tim Grieme,[a] Padam Sharma,[a] Ashok V. Bhatia[a] and Marlon Cowart[b]

[a]*Process R&D, Abbott Laboratories, North Chicago, IL 60064-4000, USA*
[b]*Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Laboratories, North Chicago, IL 60064-4000, USA*

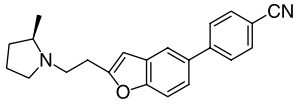
Received 14 November 2005; revised 9 February 2006; accepted 15 February 2006

Available online 15 March 2006

Abstract—An efficient and convergent process for the preparation of a potent and selective H_3 receptor antagonist, ABT-239, **1A** was accomplished with an overall yield of 64%. The key step in the synthesis is a Sonogashira coupling/cyclization reaction of 1-but-3-ynyl-2-(*R*)-methylpyrrolidine (**9**) with 4′-hydroxy-3′-iodo-biphenyl-4-carbonitrile (**3**). Additionally, the key amine component 2-(*R*)-methylpyrrolidine (**7**) was effectively synthesized from the readily available Boc-L-prolinol with a simple catalytical hydrogenolysis as the key step. This column chromatography-free process is highlighted by several simple work-up and purification procedures and is amendable to the large-scale preparation of **1A**.

1. Introduction

Histamine H_3 receptor antagonists have been demonstrated to modulate the release of a variety of neurotransmitters,[1] and antagonists of this receptor have been shown effective in animal models of ADHD (attention-deficit hyperactivity disorder).[2] In addition, H_3 antagonists, unlike stimulants, do not increase locomotive activity in animals and are thus expected to have low abuse potential. Because H_3 receptors function as both auto- and heteroreceptors to modulate the release of several neurotransmitters, H_3 antagonists have the potential to provide greater efficacy, or at least have a different pharmacological profile than drugs that target a single neurotransmitter. Based on studies in animal models, H_3 receptor antagonists have also been proposed to have potential benefits in treating disorders of cognition, attention, pain, allergic rhinitis and obesity. In spite of their projected medical utility, no H_3 antagonists have achieved clinical approval as a drug for human use. Due in part to suggestions that some of imidazole-based H_3 antagonists have potential to inhibit cytochrome-P450 enzymes leading to drug–drug interactions,[3] non-imidazole H_3 antagonists have received increasing attention as potential drug candidates.[1] One example of this class, ABT-239, **1A**[4a] is a potent and highly selective H_3 antagonist, that has been shown to be very efficacious in a variety of animal models of CNS disease. This, coupled with the favorable CNS safety profile, PK, and drug-likeness has led to the need for more advanced studies. In order to further evaluate its effectiveness and profile in extended studies, a highly efficient and convergent three-step chromatography-free process was developed for the preparation of **1A** in high purity.



ABT-239
1 = Free base
1A =Tartrate salt

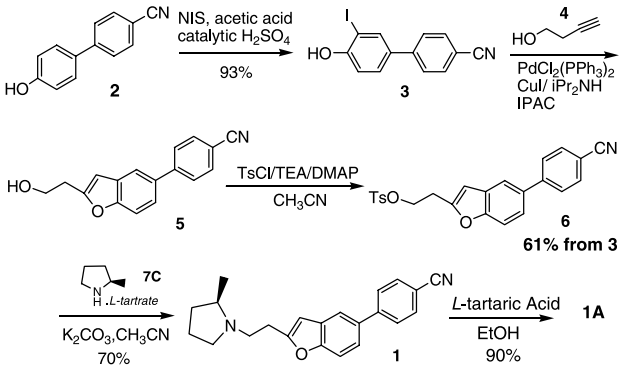
2. Results and discussion

Preparation of **1A**, was initially accomplished by a four-step process in 36% overall yield (Scheme 1)[5] starting with commercially available 4′-hydroxy-biphenyl-4-carbonitrile **2**. The chiral 2-(*R*)-methylpyrrolidine **7C** was obtained via classical resolution with L-tartaric acid.

Although the process was used to provide a sufficient amount of **1** for the initial toxicology evaluations, there were several drawbacks to the synthesis. For example, a side product was produced by an E2 elimination occurring during the final displacement reaction, producing an olefinic

Keywords: H_3 receptor antagonist; ABT-239; Sonogashira coupling; 2-(*R*)-Methylpyrrolidine.
* Corresponding author. Tel.: +1 847 937 4843; fax: +1 847 938 5932; e-mail: yiyin.ku@abbott.com

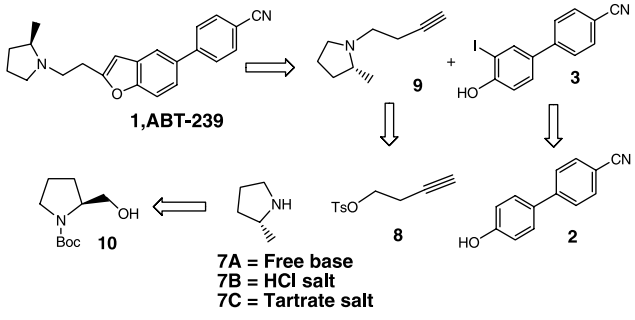
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.046



Scheme 1.

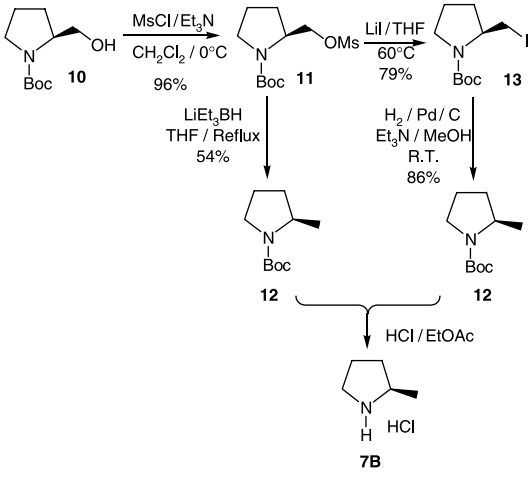
by-product in about 25% yield; even more significant was that the undesired elimination was even more severe on scales larger than a few grams.

Another drawback to the original synthetic route was that the resolution process that led to 2-(*R*)-methylpyrrolidine **7C** was tedious, requiring a minimum of four rounds of diastereoselective crystallization of an L-tartrate salt to increase the enantiomeric excess to an acceptable (>98% ee) level. These drawbacks motivated us to develop a more efficient process for **1**, as well as a more practical alternative synthesis for 2-(*R*)-methylpyrrolidine **7A**. A short, more practical process was envisioned, as outlined in Scheme 2. The retrosynthetic analysis to ABT-239, **1** suggests that it could be prepared by the Pd-catalyzed Sonogashira–Stevens coupling of **9** and **3** followed by a subsequent in situ cyclization to the benzofuran. The 1-but-3-ynyl-2-(*R*)-methylpyrrolidine **9** would arise from the displacement reaction of the commercially available tosylate **8** with 2-(*R*)-methylpyrrolidine **7A**, while the iodophenol derivative **3** can be easily obtained from 4′-hydroxy-biphenyl-4-carbonitrile **2** by selective ortho-iodination.[5]



Scheme 2.

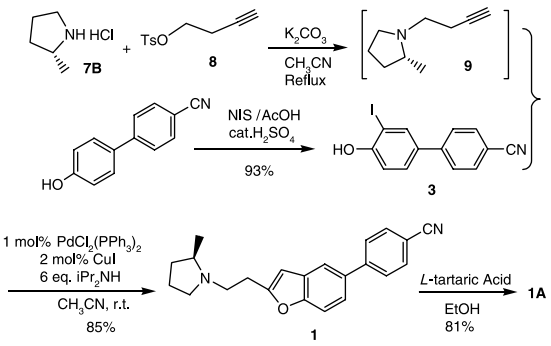
Chiral 2-(*R*)-methylpyrrolidine **7A** has been incorporated into many biologically active compounds[6] and their preparations have been the subject of a number of recent reports.[7] However, a careful literature search revealed a lack of practical and cost-effective processes for the large-scale preparation of 2-(*R*)-methylpyrrolidine **7** in high ee%. The intramolecular hydroamination of alkenes catalyzed by chiral metal complexes remains the most promising approach,[7a–c] however, the chiral purity of 2-methylpyrrolidine is normally moderate. The most recent report uses yttrium complexes of axially chiral bis(thiolate) ligands to obtain the chiral 2-methylpyrrolidine in 73% ee.[7a] Other approaches also have drawbacks. For example, in one of the syntheses, a large excess of a highly toxic tin hydride Bu_3SnH was required for the reductive de-chlorination of Boc-protected 2-chloromethylpyrrolidine.[7i] In another synthesis, 1 equiv of an expensive chiral auxiliary reagent was used for the condensation of γ-chloroketone with (*R*)-phenylglycinol.[7d] On the other hand, **7C** has been prepared by a classical resolution of racemic 2-methylpyrrolidine with L-tartaric acid in ethanol.[8] Indeed, we were able to use this process in our earlier synthetic route, but were unsatisfied with the four crystallizations required to achieve 98% ee due to considerable loss of material with a low overall yield of 31%. Several alternative approaches were considered to develop a more practical process for **7**. We were particularly interested in the strategies employing the 'chiral pool', which is one of the most attractive approaches for the synthesis of chiral compounds, provided that suitable precursors can be selected.[9] Considering the fact that Boc-L-prolinol **10** is readily available and inexpensive, its use as a chiral starting material was thought to provide a superior route to obtain chiral 2-(*R*)-methylpyrrolidine **7A** in the required high ee%. First the Boc-L-prolinol **10** was converted to the mesylate **11** in excellent yield (96%) under the standard conditions of $MsCl/Et_3N/CH_2Cl_2/0$ °C (Scheme 3). Direct conversion of the methanesulfonyloxymethyl group to the methyl group was attempted with several reduction conditions including the use of $LiAlH_4$,[10a] or $NaBH_3CN/BF_3\cdot OEt_2$[10b] and Super Hydride. Among the reagents evaluated, Super Hydride was most effective in producing the target *N*-Boc-2-(*R*)-methylpyrrolidine **12**, with a 54% yield under reflux conditions (Scheme 3). Concerns over the rigorous reaction conditions coupled with the hazardous nature of the Super Hydride, led us to consider other possibilities, particularly the use of an iodide intermediate **13**. The mesylate **11** was converted to the iodide **13** in 79% yield under conditions of LiI/THF/60 °C. Conventionally, de-iodination is accomplished via a free radical reaction;[11] however, hazardous and toxic tin reagents are often required. We were delighted to find that iodide **13** was conveniently de-iodinated by a simple hydrogenation procedure, with hydrogen gas under ambient pressure in the presence of 5% Pd on carbon, to obtain **12** in



Scheme 3.

86% yield and >99% ee. The hydrogenolytic de-iodination of simple alkyl iodides by catalytic hydrogenation has not often been reported. In our hands, the conditions are ideal with respect to cost, convenience and environmental impact, and may be applicable to other simple alkyl iodides. Deprotection of the Boc group was carried out using HCl in EtOAc in essentially quantitative yield to obtain the HCl salt of 2-(*R*)-methylpyrrolidine **7B**. With a highly practical and cost-effective route to 2-(*R*)-methylpyrrolidine in hand, efforts were next focused on developing a more efficient process for ABT-239, **1** with a particular focus on overcoming the problem of the undesired elimination reaction present in the original synthesis.

The tandem Sonogashira–Stevens coupling/cyclization reactions of *o*-halophenols with substituted 1-alkynes are the most commonly used and most efficient methodology for 2-substituted benzo[*b*]furans,[12] which are prevalent in many biologically important compounds.[13] However, the use of this methodology for the preparation of β-ethylamine-benzo[*b*]furans such as **1** has not been well documented.[14] In a series of close benzofuran analogs of **1A**, this type of process previously gave very low (<20%) and variable yields of products.[15] In our earlier synthesis of **1**, the key intermediate **5** was prepared in 85% yield using a standard protocol with $PdCl_2(PPh_3)_2$ and CuI as catalysts, and iPr_2–NH as base (Scheme 1). To increase the efficiency of the route, it was proposed that Sonogashira–Stevens coupling of 1-but-3-ynyl-2-(*R*)-methyl-pyrrolidine **9** with 4′-hydroxy-3′-iodo-biphenyl-4-carbonitrile **3** and subsequent spontaneous cyclization could provide the desired final product **1** in fewer number of linear steps. The use of the synthetic intermediate **9** in the synthesis also circumvented the main shortcoming of the earlier linear synthetic route, in which a substantial amount (~25%) of olefinic elimination by-product was formed in the final displacement reaction of the tosylate **6** with 2-(*R*)-methylpyrrolidine.[5] Thus, 1-but-3-ynyl-2-(*R*)-methylpyrrolidine **9** was prepared by a displacement reaction of the commercially available toluene-4-sulfonic acid but-3-ynyl ester **8** with 2-(*R*)-methylpyrrolidine **7A**, which was in turn conveniently generated in situ from its HCl salt **7B** in acetonitrile in the presence of K_2CO_3. The displacement of the tosylate proceeded well, with the desired product **9** obtained in high yield (98%) (Scheme 4). When the tartaric salt of 2-(*R*)-methylpyrrolidine **7C** was used, similar results were obtained. In both reactions, no elimination by-products were observed.



Scheme 4.

The 1-but-3-ynyl-2-(*R*)-methyl-pyrrolidine **9** in CH_3CN was then subjected to the Sonogashira reaction conditions with iodophenol **3**, followed by a simple filtration to remove the excess K_2CO_3 and inorganic salts produced. The coupling–cyclization went smoothly under the protocol, employing 1 mol% $PdCl_2(PPh_3)_2$, 2 mol% CuI in CH_3CN in the presence of 6 equiv of i-Pr_2NH at room temperature. The desired product **1** was obtained in 85% yield (Scheme 4).

The iodophenol **3** was prepared in high yield (93%) by the optimized conditions previously reported,[5] using 0.95 equiv of *N*-iodosuccinimide and 0.5 equiv of sulfuric acid in acetic acid at ambient temperature.

The development of an effective and practical column chromatography-free purification and isolation procedure was essential for this new convergent route to be used for large-scale preparations. To support advanced profiling, the final product **1A** had to meet or exceed the product quality specifications established in the earlier synthesis. Extrapolating from the experience gained from the initial process, upon completion of the final reaction the solvent was switched from acetonitrile to toluene. The desired product **1** was readily extracted into a mixture of water–*N*-methylpyrrolidinone–methanesulfonic acid (70/20/10 by volume), thereby leaving all the neutral by-products in the organic layers; the aqueous layers were extracted twice with isopropyl acetate to ensure removal of non-basic organic impurities. The free base **1** was then extracted back to the organic layer with isopropyl acetate, after a pH adjustment of the aqueous phase to ~14 with 50% NaOH. The free base **1** in isopropyl acetate was then suspended with silica gel (equal weight of product) and further purified by crystallization after being converted to the desired L-tartaric salt **1A**. The final product **1A** was obtained in high purity (99% p.a.) with acceptable metal residual levels (Pd and Cu <10 ppm by ICP) in 81% recovery.

3. Conclusions

In summary, we have developed an efficient and convergent process for the preparation of ABT-239, **1** (Scheme 4) in high purity (99%) with an improved overall yield of 65 versus 36% in the earlier linear route. The convergent process is highlighted by the Sonogashira coupling/cyclization reaction of 1-but-3-ynyl-2-(*R*)-methyl-pyrrolidine **9** with 4′-hydroxy-3′-iodo-biphenyl-4-carbonitrile **3** to produce the final product **1**, demonstrating the feasibility of the Sonogashira–Stevens reaction for the large-scale synthesis of β-ethylamine-benzo[*b*]furan derivatives. The new process successfully overcomes the drawbacks of a troublesome elimination side reaction that plagued the key step of an earlier large-scale process to **1**. Additionally, 2-(*R*)-methylpyrrolidine was effectively synthesized from the readily available Boc-L-prolinol **10** in good overall yield (65%) and excellent ee% (>99%). The synthesis of this intermediate featured a highly effective de-iodination procedure enabled by catalytic hydrogenation, a process, which may be applicable to other alkyl iodide compounds. This column chromatography-free process involved several simple work-up and purification procedures and is amendable to the large-scale preparation of ABT-239, **1**.

4. Experimental

4.1. General

The NMR spectra were recorded at a Varian 400 MHz instrument at 400 MHz for ^{1}H and 100 MHz for ^{13}C. The electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) mass spectra were obtained using a Hewlett Packard 1100, LC–MS, HPLC-mass spectrometer and fast atom bombardment (FAB) mass spectra were obtained using a JEOL SX102A spectrometer. All the reactions were performed under a positive pressure of nitrogen. Commercial grade anhydrous solvents and reagents were used without further purification. All reactions were monitored by HPLC (Zorbax SB-C8, 4.6 mm×25 cm column) with purities being determined by peak area % at the UV detector wavelength of 215 and 230 nm. The HPLC assay yields of the reaction mixture were determined using quantitative HPLC analysis by comparison to a know amount of analytical pure reference standards and potency refers to a wt% assay by HPLC versus a purified standard. The enantiomeric purity of the product was determined by the chiral HPLC analysis using a Chiral Pak-AD column, 10 μm, 250 mm×4.6 mm (Chiralcel Technologies) at the UV detector wavelength of 223. The enantiomeric purity of 2-(*R*)-methylpyrrolidine was determined by chiral derivatization using Cbz valine anhydride to prepare the diastereomeric derivative. The elemental analysis was performed by Quantitative Technologies Inc.

4.1.1. 2-(*S*)-Methanesulfonyloxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (11). A solution of 2-(*S*)-hydroxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (99.5 g 0.49 mol) in dichloromethane (500 mL) was cooled to 0 °C. Triethylamine (139 mL, 101 g, 1 mol) was added to the cold solution dropwise maintaining the reaction temperature below 0 °C. Methanesulfonyl chloride (58 mL, 85.8 g, 0.75 mol) was then added dropwise to the reaction mixture maintaining the reaction temperature below 0 °C. The resulting reaction mixture was stirred at room temperature for 12 h (HPLC indicated that all the starting material was consumed). The reaction mixture was quenched with 1 M H_3PO_4 (300 mL) and mixed for 15 min. The organic layer was separated and washed with 1 M aqueous H_3PO_4 (2×300 mL), followed by saturated aqueous $NaHCO_3$ (4×250 mL), dried over $MgSO_4$, filtered, and concentrated to obtain the product **11** (132 g, 95.6% yield). The spectral data was consistent with those reported.[16]

4.1.2. 2-(*S*)-Iodomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester 13. A solution of 2-(*S*)-methanesulfonyloxy-methyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (27.9 g, 0.10 mol) in anhydrous tetrahydrofuran (600 mL) was cooled to 0 °C. Lithium iodide (144 g, 1 mol) was added to the cold reaction mixture as a solid in portions maintaining the reaction temperature below 30 °C. The reaction mixture was then stirred at 62 °C for 4 h (HPLC indicated that all the starting material was consumed) and quenched with 10% aqueous sodium thiosulfate (300 mL). Ethyl acetate (600 mL) was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (2×100 mL), dried over $MgSO_4$, filtered, and concentrated to obtain the product **13** (26.3 g, 79% yield). The spectral data was consistent with those reported.[17]

4.1.3. 2-(*R*)-Methyl-pyrrolidine-1-carboxylic *tert*-butyl ester 12. A heterogeneous reaction mixture of 2-(*S*)-iodomethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester **13** (25 g, 0.08 mol), triethylamine (11.2 mL, 8.12 g, 0.08 mol) in methanol (250 mL) and 5% palladium on carbon (2.5 g, 10 wt%, Pd/C) was allowed to react at room temperature under a blanket of hydrogen gas overnight (HPLC indicated that all the starting material was consumed). The reaction mixture was filtered and the filtrate was concentrated and the residue was dissolved in distilled water (100 mL) and ethyl acetate (100 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×50 mL). The combined organic layer was washed with 1 M aqueous H_3PO_4 (2×100 mL) followed by saturated $NaHCO_3$ (2×100 mL), dried over $MgSO_4$, filtered, and concentrated to obtain the product **12** (12.78 g, 86% yield). The spectral data was consistent with those reported.[18]

4.1.4. HCl salt of (*R*)-2-methyl-pyrrolidine 7B. 2-(*R*)-Methyl-pyrrolidine-1-carboxylic *tert*-butyl ester (12 g, 65 mmol) was dissolved in ethyl acetate (120 mL) and HCl gas was then bubbled through for 5 min until the pH of the reaction mixture was below 1. The reaction mixture was mixed at room temperature for 2 h (HPLC indicated that all the starting material was consumed). The reaction mixture was concentrated to one-fourth of the original volume, and methyl *tert*-butyl ether (200 mL) was added to the mixture, the mixture was then concentrated to ~50 mL. The solid was filtered, and dried at 40 °C overnight with nitrogen bleeding to obtain the HCl salt as a white solid (7.5 g, 96% yield). The spectral data was consistent with those reported.[19] The ee% was determined as follows: add 12.0 mg of 2-(*R*)-methylpyrrolidine hydrochloric acid, 62.0 mg of Cbz-valine anhydride, 1 mL dichloromethane, and 0.1 mL of triethylamine to a 4 mL vial. Stir for 10 min. An aliquot was assayed by normal HPLC (Zorbax SB-C8, 4.6 mm×25 cm column) with the enantiomeric purity being determined by peak area % of the two diastereomers at the UV detector wavelength of 215 nm. The ee% was determined to be >99%.

4.1.5. 1-But-3-ynyl-2*R*-methyl-pyrrolidine 9. To a 250 mL RB-flask was charged potassium carbonate powder (18.4 g, 133.2 mmol, 325 mesh), (*R*)-2-methylpyrrolidine HCl salt **7B** (10.7 g, 88.8 mmol), and CH_3CN (150 mL) and 3-butynyl *p*-toluenesulfonate **8** (15.7 mL, 88.8 mmol). The mixture was heated to reflux and stirred for 6 h or until all the tosylate was consumed as indicated by GC. The reaction mixture was cooled to room temperature, filtered, washed with CH_3CN (50 mL). The resulting filtrate (~200 mL) was assayed to contain ~12 g of the product by GC analysis using a pure and racemic standard 1-but-3-ynyl-2-methyl-pyrrolidine, which was prepared from racemic 2-methylpyrrolidine and 3-butynyl *p*-toluenesulfonate, and fractionally distilled. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (d, J=6.1 Hz, 3H), 1.40 (m, 1H), 1.6–1.8 (m, 2H), 1.90 (m, 1H),

1.98 (t, $J=2.7$ Hz, 1H), 2.15 (q, $J=8.8$ Hz, 1H), 2.3–2.5 (m, 4H), 3.0 (m, 1H), 3.14 (td, $J=8.6$, 2.8 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 18.7, 19.3, 21.9, 32.9, 52.9, 53.9, 59.7, 68.8, 83.0; GC–MS m/z 138 ($M^+ + 1$).

4.1.6. 4′-Hydroxy-3′-iodo-biphenyl-4-carbonitrile 3. To a reaction vessel provided with a mechanical stirrer and dropping funnel were charged 4′-hydroxy-biphenyl-4-carbonitrile **2** (215 g, 1.1 mol), glacial acetic acid (1.8 kg, ~1.7 L), and concentrated sulfuric acid (53.3 g, 0.54 mol). *N*-Iodosuccinimide (240 g, 97%, 1.04 mol) was added portion-wise at the internal temperature of ~20 °C. The suspension was agitated overnight (20 h) or until **2** was less than 4% by HPLC. The reaction mixture was diluted with water (3.4 kg, 3.4 L), and mixed at 20 °C for 1 h. The product was collected by filtration, washed with water (3.2 kg), and heptane (1.5 kg), dried at 55 °C under vacuum with a nitrogen bleed for 48 h to give 327 g (93% yield) of **3** as an off-white solid. The product was used directly in the next step without further purification. An analytical sample was obtained by crystallizing from methanol; mp: 166–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.99 (3H, s), 7.62 (dd, $J=8.4$, 2.3 Hz, 1H), 7.79 (d, $J=8.4$ Hz, 2H), 7.85 (d, $J=8.4$ Hz, 2H), 8.05 (d, $J=2.3$ Hz, 1H), 10.70 (s, br, 1H); ^{13}C NMR (400 MHz, DMSO-d_6), δ 85.3, 108.8, 114.9, 118.5, 126.3, 127.9, 130.5, 132.2, 136.6, 142.5, 156.8; CI-MS (NH_3): m/z 339 ($M+NH_4^+$).

4.1.7. 4-{2-[2-(2-Methylpyrrolidin-1-yl)-ethyl]-benzofuran-5-yl}-benzonitrile L-tartrate 1A. A solution of 1-but-3-ynyl-2(*R*)-methyl-pyrrolidine **9** (12.0 g, 87.5 mmol) in CH_3CN (200 mL) was purged with nitrogen. To this solution were added 4′-hydroxy-3′-iodo-biphenyl-4-carbonitrile **3** (18.7 g, 58.3 mmol), CuI (220 mg, 1.16 mmol), $PdCl_2$–$(Ph_3P)_2$ (409 mg, 0.58 mmol), followed by *i*-Pr_2NH (35.0 g, 345 mmol) under N_2. The resulting mixture was stirred at room temperature overnight under nitrogen or until all the starting material 4′-hydroxy-3′-iodo-biphenyl-4-carbonitrile was consumed monitored by HPLC. The reaction mixture was concentrated to about 100 mL volume, and toluene (400 mL) and 5% $NaHCO_3$ aqueous solution were added. The mixture was stirred for ~10 min, and filtered through a layer of Celite to remove some solid impurities. The filtrate was washed with 5% $NaHCO_3$ (2×400 mL). The organic layer was extracted with mixture of solvents of CH_3SO_3H–NMP–H_2O (10/20/70 by volume) (300 and 100 mL), respectively. The combined aqueous layer was washed with isopropyl acetate (200 mL). Isopropyl acetate (400 mL) was added, and the resulting mixture was cooled to ~5 °C, and then basified to pH~13 at the internal temperature < 25 °C with 50% NaOH. The upper organic phase was separated, and the lower aqueous solution was extracted with IPAC (100 mL). The combined organic solution was washed with 5% $NaHCO_3$ (2×400 mL), then 25% brine (200 mL). The organic layer was assayed to contain 16 g of free base **1** by HPLC. Activated carbon, Darco KB-B (1.5 g), and silica gel (15.0 g) were added, and the mixture was stirred at room temperature for 1 h and filtered through a layer of Celite. The filtrate was concentrate to one-fourth of the original volume, and isopropyl acetate (200 mL) was added. The solution was filtered to remove inorganic salt, and concentrated to dryness to give the free base 4-{2-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-benzofuran-5-yl}-benzonitrile **1**. 2-Propanol (150 mL) and absolute EtOH **3A** (60 mL) were added. The resulting solution was heated to ~60 °C, and a solution of L-tartaric acid (7.5 g, 50.0 mmol) in absolute ethanol **3A** (90 mL) added slowly at 60 °C. The resulting solution was seeded with ~0.5 g of **1A**, and cooled very slowly to room temperature (approximately ~2 °C/h). The slurry was stirred at room temperature overnight, it was then cooled to 0 °C for 2 h. The solid was filtered and dried at 65 °C in a vacuum oven overnight to give 19.6 g of 4-{2-[2-(2-methyl-pyrrolidin-1-yl)-ethyl]-benzofuran-5-yl}-benzonitrile L-tartrate **1A** as a white solid (81% recovery and 70% isolated overall yield). Mp 152–154 °C; 98% pure by HPLC (PA), ee=98.2% by chiral HPLC; Pd<10 ppm, Cu<10 ppm. Mp: 166–167 °C (lit.[5] 166–167 °C). The spectral data was consistent with those reported.[5]

References and notes

1. For reviews, see: Leurs, R.; Blandina, P.; Tedford, C.; Timmerman, H. *Trends Pharmacol. Sci.* **1998**, *19*, 177. (b) *The Histamine H3 Receptor: A Target for New Drugs*; Leurs, R., Timmerman, H., Eds.; Pharmacochemistry Library; Elsevier: Amsterdam, The Netherlands, 1998; Vol. 30.
2. (a) Fox, G. B.; Pan, J. B.; Radek, R. J.; Lewis, A. M.; Bitner, R. S.; Esbenshade, T. A.; Faghih, R.; Bennani, Y. L.; Williams, M.; Yao, B. B.; Decker, M. W.; Hancock, A. A. *J. Pharmacol. Exp. Ther.* **2003**, *305*, 897. (b) Bjenning, C.; Liu, W.; Rimvall, K. *International Congress Series*, **2001**, 1224 (Histamine Research in the New Millennium), 451–452.
3. (a) Liedtke, S.; Flau, K.; Kathmann, M.; Schlicker, E.; Stark, H.; Meier, G.; Schunack, W. *Nauyn-Schmiedeberg's Arch. Pharm.* **2003**, *367*, 43. (b) McLeod, R. L.; Rizzo, C. A.; West, R. E., Jr.; Aslanian, R.; McCormick, K.; Bryant, M.; Hsieh, Y.; Korfmacher, W.; Mingo, G. G.; Varty, L.; Williams, S. M.; Shih, N.-Y.; Egan, R. W.; Hey, J. A. *J. Pharmacol. Exp. Ther.* **2003**, *305*, 1037. (c) Lin, J. H.; Lu, A. Y. H. *Clin. Pharmacokinet.* **1998**, *35*, 361.
4. (a) Cowart, M.; Pratt, J. K.; Stewart, A. O.; Bennani, Y. L.; Esbenshade, T. A.; Hancock, A. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 689. (b) Altenbach, R. J.; Black, L. A.; Chang, S.-J.; Cowart, M. D.; Faghih, R.; Gfesser, G. A.; Ku, Y. Y.; Liu, H.; Lukin, K. A.; Nersesian, D. L.; Pu, Y. M.; Sharma, P. N.; Bennani, Y. L.; Curtis, M. P. PCT Int. Appl. WO 2004043458 A1, 2004, pp 229. (c) Stark, H. *Expert Opin. Ther. Patents* **2003**, *13*, 851.
5. Pu, Y. M.; Grieme, T.; Gupta, A.; Bhatia, A. V.; Cowart, M.; Ku, Y. Y. *Org. Process Res. Dev.* **2005**, *9*, 45.
6. (a) Dininno, F. P.; Chen, H. Y.; Tan, Q., PCT Int. Appl. WO 2004091488, 2004, pp 113. (b) Whitten, J. P.; Schwaebe, M. K.; Moran, T., PCT Int. Appl. WO 2004091627, 2004, pp 37. (c) Bamford, M. J.; Dean, D. K.; Wilson, D. M. PCT Int. Appl. WO 2004089373, 2004, pp 45. (b) Ringdahl, B. *Eur. J. Pharmacol.* **1987**, *140*, 13.
7. (a) Kim, J. Y.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 1737. (b) Hong, S.; Tian, S.; Metz, M. V.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 14768. (c) Gribkov, D. V.; Hultzsch, K. C. *Chem. Commun.* **2004**, 730. (d) Gross, K. M.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 315. (e) Andres, J. M.; Herraiz-Sierra, I.;

Pedrosa, R.; Perez-Encabo, A. *Eur. J. Org. Chem.* **2000**, 1719. (f) Donner, B. G. *Tetrahedron. Lett.* **1995**, *36*, 1223. (g) Elworthy, T. R.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 6089. (h) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708. (i) Nijhuis, W. H. N.; Verboom, W.; El-Fadl, A. A.; Hummel, G. J. V.; Reinhoudt, D. N. *J. Org. Chem.* **1989**, *54*, 209.

8. (a) Karrer, P.; Ehrhart, K. *Helv. Chim. Acta* **1951**, *34*, 2202. (b) Kuil, L. A.; Veldhuizen, Y. S. J.; Grove, D. M.; Zwikker, L. J. W.; Jenneskens, L. W.; Drenth, W.; Smeets, W. J. J.; Spek, A. L.; Koten, G. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 267.
9. Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis*; Wiley Interscience: New York, 1987.
10. (a) Maier, C. A.; Wuensch, B. *J. Med. Chem.* **2002**, *45*, 4923–4930. (b) Krow, G. R.; Henz, K. J.; Szczepanski, S. W. *J. Org. Chem.* **1985**, *50*, 1888.
11. (a) Keusenkothen, P. F.; Smith, M. B. *Tetrahedron. Lett.* **1989**, *30*, 3369–3372. (b) Takahata, H.; Takamatsu, T.; Yamazaki, T. *J. Org. Chem.* **1989**, *54*, 4812.
12. (a) Pal, M.; Subramanian, V.; Yeleswarapu, K. R. *Tetrahedron. Lett.* **2003**, *44*, 8221–8225. (b) Uozumi, Y.; Kobayashi, Y. *Heterocycles* **2003**, *59*, 71–74. (c) Dai, W. M.; Lai, K. W. *Tetrahedron Lett.* **2002**, *43*, 9377. (d) Smith, L. R.; Mahoney, N.; Molyneux, R. J. *J. Nat. Prod.* **2003**, *66*, 169–176. (e) Bates, C. G.; Saejueng, P.; Murphy, J. M.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 4727–4729. (f) Inoue, M.; Carson, M. W.; Frontier, A. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 1878–1889. (g) Kundu, N. G.; Pal, M.; Mahanty, J. S.; De, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2815–2820. (h) Cacchi, S.; Fabrizi, G.; Moro, L. *Tetrahedron. Lett.* **1998**, *39*, 5101–5104. (i) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432–1434. (j) Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 297–299. (k) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron* **2001**, *57*, 8017–8028.
13. Donnelly, D. M. X.; Meegan, M. J. In Katritzky, A. R., Ed.; Comprehensive Heterocyclic Chemistry; Pergamon: New York, 1984; Vol. 4.
14. Frackenpohl, J.; Braje, W. M.; Hoffmann, H. M. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 47–65.
15. Cowart, M.; Faghih, R.; Curtis, M. P.; Gfesser, G. A.; Bennani, Y. L.; Black, L. A.; Pan, L.; Marsh, K. C.; Sulivan, J. P.; Esbenshade, T. A.; Fox, G. B.; Hancock, A. A. *J. Med. Chem.* **2005**, *48*, 38.
16. Braghiroli, D.; Avallone, R.; Bella, M. D. *Tetrahedron: Asymmetry* **1997**, *8*, 2209.
17. Park, S. H.; Kang, H. J.; Ko, S.; Park, S.; Chang, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2621.
18. Elworthy, T. R.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 6089.
19. Kim, M.-J.; Lim, I.-T.; Choi, G.-B.; Whang, S.-Y.; Ku, B.-C.; Choi, J.-Y. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 71.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 62 (2006) 4590–4596

Direct determination of the stereoisomer constitution by 2D-HPLC and stereochemistry–pheromone activity relationship of the copulation release pheromone of the cowpea weevil, *Callosobruchus maculatus*

Arata Yajima,[a] Kazuaki Akasaka,[b] Tomonori Nakai,[a] Hiroki Maehara,[a] Tomoo Nukada,[a] Hiroshi Ohrui[b] and Goro Yabuta[a,*]

[a]*Department of Fermentation Science, Faculty of Applied Biological Science, Tokyo University of Agriculture, Sakuragaoka 1-1-1, Setagaya-ku, Tokyo 156-8502, Japan*
[b]*Graduate School of Life Science, Tohoku University, Tsutsumidori-Amamiya 1-1, Aoba-ku, Sendai 981-8555, Japan*

Received 10 January 2006; accepted 13 February 2006

Available online 10 March 2006

Abstract—The copulation release pheromone of the cowpea weevil, *Callosobruchus maculatus*, was re-isolated from about 30,000 virgin female. The natural pheromone was confirmed to be stereochemically impure by Ohrui–Akasaka-2D-HPLC methodology. The structure–activity relationship of the pheromone was also clarified.

1. Introduction

Insect pheromones are extremely important compounds to communicate with each other in the insect kingdom. Because of the strong activity, an insect usually produces only a nanogram or a picogram order of the pheromone. In 1961, Butenandt and co-workers identified the sex pheromone of the silkworm moss, *Bombix mori*, after extensive studies as bombykol.[1] Since then, various pheromone structures were clarified during the past half century. In the pheromone chemistry, a common problem is always the scarcity of the natural pheromone material. To supplement the scarcity, a great number of the insect population was used to obtain a sufficient amount of the pheromone sample. Needless to say, there is an inevitable need to sacrifice the insects, but we must minimize the usage number of insect population. Thus, it is important to establish a highly sensitive analytical method. Gas chromatography–mass spectrometry (GC–MS), one of the most sensitive analytical methods, is suitable for the pheromone structure determination, because pheromones are volatile compounds in most cases. However, the determination of the absolute configuration of a pheromone is often difficult by GC, because the effective chiral stationary phase for GC is limited and some pheromone is not volatile enough for GC analysis. The development of an alternative analytical method is important to determine the absolute configuration in insect pheromone chemistry.

The most prevailing chiral discrimination reagent of an alcohol is α-methoxy-α-trifuluoromethylphenylacetic acid (MTPA).[2] In most cases, it is possible to determine the absolute configuration of the chiral alcohol by NMR spectroscopy or HPLC analysis with an UV detector. This is called Mosher's method. From 1993 to 2003, Ohrui, Akasaka and co-workers reported alternative powerful chiral discrimination reagents for alcohols or branched fatty acids.[3] These reagents are applicable for alcohols or acids having chiral centers remote from the functional group. Moreover, since the Ohrui–Akasaka method uses a fluorescence detector instead of an UV detector in the HPLC analysis, an fmol order of the material is enough.[3e] We presumed that the Ohrui–Akasaka method might become a powerful tool for insect pheromone chemistry owing to its high sensitivity.

The cowpea weevil, *Callosobruchus maculatus*, is a serious cosmopolitan pest of stored products such as cowpea, azuki or other pulses.[4] During the course of the pest-management program of the cowpea weevil, *C. maculatus*, Ohsawa and

Keywords: Copulation release pheromone; Cowpea weevil; *Callosobruchus maculatus*; 2-(2,3-Anthracenedicarboximide)-1-propyl ester.
* Corresponding author. Tel.: +81 3 5477 2562; fax: +81 3 5477 2622; e-mail: yabta@nodai.ac.jp

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.059

co-workers identified the copulation release pheromone from the acidic fraction of the crude extracts of ca. 3000 females.[5] The pheromone induced protrusion of the genital organ in the presence of the neutral fraction of the extracts. The structure of the pheromone was proposed to be 2,6-dimethyloctane-1,8-dioic acid (**1**) on the basis of the GC–MS spectrum of the partially purified corresponding methyl ester (**1a**) (Fig. 1). Since a pure sample of **1** was unavailable due to the scarcity of the material and the incorporation of other acids, such physical properties as IR, NMR or $[\alpha]_D$ of the natural product were unavailable. Recently, we reported the synthesis of the four stereoisomers of 2,6-dimethyloctane-1,8-dioic acid (**1**).[6] The synthetic four isomers were distinguishable by the Ohrui–Akasaka method. This means that it is possible to determine the absolute configuration of the natural product by a simple comparison of the retention times of the Ohrui–Akasaka ester of the synthetic **1** with that of the natural **1**. In order to determine the absolute configuration of the natural product and clarify the biological activity–structure relationship, there was urgent need to re-isolate the natural pheromone. This paper describes the re-isolation, the determination of the stereoisomer constitution and the stereochemistry–pheromone activity relationship of the copulation release pheromone of the cowpea weevil, *C. maculatus*.

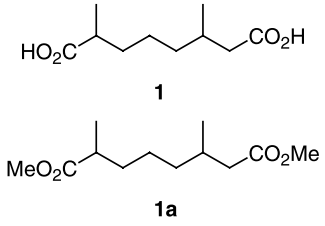


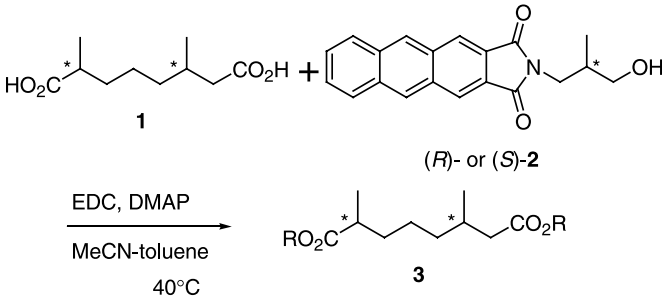
Figure 1. Structure of the copulation release pheromone of *Callosobruchus maculatus* (**1**).

2. Results and discussion

The re-isolation of the copulation release pheromone was carried out according to Ohsawa's procedure.[5] A laboratory-maintained colony was reared on azuki bean under dark condition. Newly emerged adults were sexed and kept separately. Several hundred virgin females were kept in a petri dish with a pile of filter papers as shelters. After 20–27 days, the pheromone was extracted with ether from the filter papers. The extracts were collected from 31,461 females. The concentrated extracts were dissolved in ether and the solution was fractioned into the neutral, acidic and basic fractions. The obtained acidic compounds were filtered through a silica gel column to remove such highly polar compounds as proteins to give 7.1 mg of crude material. The crude material was divided in three portions, and each portion was used for (1) GC–MS analysis, (2) the determination of the absolute configuration and (3) bioassay, respectively.

In order to confirm the existence of the pheromone component, 2,6-dimethyl-1,8-octanedioic acid (**1**), a portion of the crude extract was dissolved in ether and treated with diazomethane. The resulting solution was subjected to GC–MS analysis. Although many peaks were observed in the chromatogram, the retention time and the MS spectrum of one of the peaks agreed with that of the synthetic authentic sample.[6]

Next, we set out to determine the absolute configuration of the natural pheromone by the Ohrui–Akasaka method. Although it was suspected whether the separation would be possible or not, the unpurified crude extract was directly subjected to the analysis. The second portion of the crude extract (ca. 1 mg estimated to be ~50 nmol) was condensed with (*R*)- or (*S*)-2-(2,3-anthracenedicarboximide)-1-propanol (2A1P-OH, **2**)[3a–c] in the presence of *N*-(3-dimethylamino)propyl-*N*′-ethylcarbodiimide (EDC) and *N*,*N*-dimethylaminopyridine (DMAP) at 40 °C to give diester [(*R*)-*nat*-**3** and (*S*)-*nat*-**3**] (Scheme 1). The reaction mixture was developed on TLC, and the band with the same R_f value of the authentic sample was extracted. The authentic samples were prepared from synthetic (2*R*,6*R*)- and (2*S*,6*R*)-2,6-dimethyloctane-1,8-dioic acid (**1**) with (*R*)- and (*S*)-2A1P-OH (**3**) to give the four stereoisomer equivalents [(*R*)-*RR*-**3**, (*R*)-*SR*-**3**, (*S*)-*RR*-**3** and (*S*)-*SR*-**3**]. In the preliminary experiment, there were many peaks on the chromatogram of (*R*)-*nat*-**3** and (*S*)-*nat*-**3**. Because of that, the assignments of each peak by a simple comparison of the retention times were difficult. In order to achieve the complete separation of the peaks, we examined a two-dimensional HPLC (2D-HPLC) analysis. The 2D-HPLC often improves the separation by using two columns with different property.[7] For the first column, Develosil ODS-HG-3, a reverse phase column with MeOH as a mobile phase, was used at 0 °C, and Develosil ODS-A-3 with MeOH/MeCN/THF=2:2:1 (v/v/v) as a mobile phase was used for the second column at −35 °C. Develosil ODS-HG-3 is endcapped with trimethylsilyl group, but A-3 is not. Due to the different property, the analyses with HG-3 or A-3 gave different chromatographic patterns. Because of that, the two columns were suitable for 2D-HPLC analysis.



Scheme 1. Preparation of 2A1P-O ester of **1**.

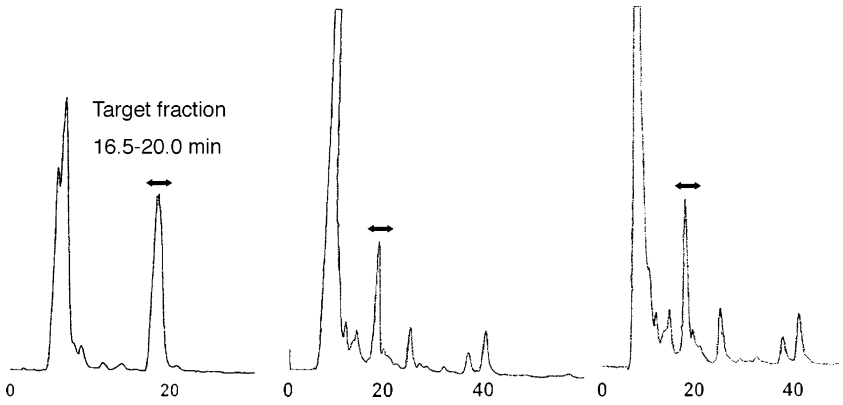


Figure 2. HPLC separation of **3** without the second column; standard (left), (*S*)-*nat*-**3** (center), and (*R*)-*nat*-**3** (right).

In the preliminary experiment, the analysis of the authentic samples gave a broad peak at 16.5–20.0 min without using the second column (Fig. 2). The analyses of (*R*)-*nat*-**3** and (*S*)-*nat*-**3** also gave the same peak with other peaks. To avoid re-incorporation with an impurity in the second column, only the separated target fraction, with retention time of 16.5–20.0 min, was directly injected into the second column by using a six-way bulb. Figure 3 shows the chromatograms on the 2D conditions with the assignments of each peak. The assignments were rationalized by considering the peaks of (*R*)-*RR*-**3** and (*R*)-*SR*-**3** to be those of (*S*)-*SS*-**3** and (*S*)-*RS*-**3**, respectively. The Ohrui–Akasaka ester derivative of the natural product, (*S*)-*nat*-**3**, was next subjected to analysis (the center chart of Fig. 3). To our surprise, there were four peaks on the chromatogram. There should be a single peak if the natural product consisted of a single stereoisomer. The careful assignments of each peak clarified that three of the peaks (peaks 1, 2 and 4) were in perfect accordance with the authentic samples. But one of the peaks (peak 5) originated from an unidentified impurity. The small shoulder peak at 55 min, which might be peak 3, was included in peak 5. This result indicates that the natural product is a mixture of at least (2*R*,6*S*)-**1**, (2*S*,6*S*)-**1** and (2*S*,6*R*)-**1**. We also examined the analysis of the (*R*)-2A1P-O ester of the natural product [(*R*)-*nat*-**3**] (the right chart of Fig. 3). By inverting the stereochemistry of the chiral discrimination reagent, the retention times of each component were shifted under the same 2D analytical condition. A careful comparison proved that the peaks 1, 3 and 4 were in perfect accordance with the authentic samples. Since (*R*)-2A1P derivatives were used, the peaks 1, 3 and 4 were considered to be the equivalents of (2*S*,6*R*)-, (2*S*,6*S*)- and (2*R*,6*S*)-isomers. Although the small shoulder peak of (2*R*,6*R*)-isomer at 51.5 min was included, peak 6 was an impurity because the retention time was not agreed with that of any authentic samples. The peak ratios of each component are shown in Table 1. Obviously, (*S*)- and (*R*)-2A1P-O esters of the natural product gave almost the same results. Since it cannot be considered that this accordance is a coincidence, we concluded that the natural product is constituted of (2*S*,6*R*)-, (2*S*,6*S*)- and (2*R*,6*S*)-isomers with a small amount of (2*R*,6*R*)-isomer. And the

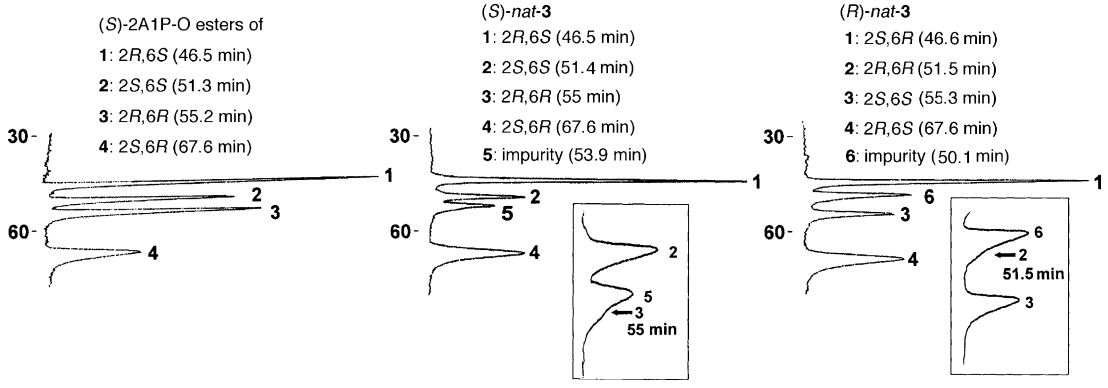
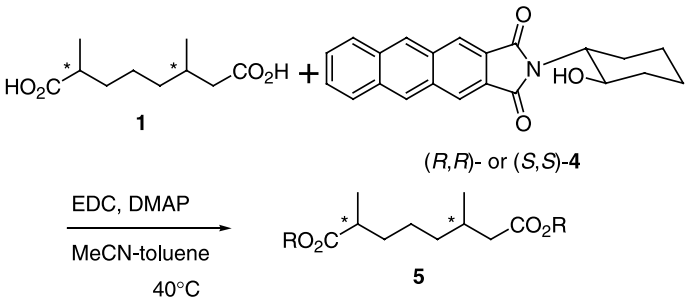


Figure 3. 2D-HPLC separations of the standard **3** (left), (*S*)-*nat*-**3** (center) and (*R*)-*nat*-**3** (right).

Table 1. Peak area ratios of (*S*)-*nat*-**3** and (*R*)-*nat*-**3**

Stereochemistry of **1**	(*S*)-*nat*-**3**		(*R*)-*nat*-**3**	
	Retention time (min)	Peak area ratio (%)	Retention time (min)	Peak area ratio (%)
2*R*,6*S*	46.5 (Peak 1)	43.7	67.6 (Peak 4)	43.2
2*R*,6*S*	51.4 (Peak 2)	17.5	55.3 (Peak 4)	18.7
2*R*,6*R*	55.0 (Peak 3)[a]	Trace	51.5 (Peak 2)[a]	Trace
2*S*,6*R*	67.6 (Peak 4)	38.9	46.6 (Peak 1)	38.1

[a] As shoulder peak.



Scheme 2. Preparation of 2Acyclo-O ester of **1**.

ratio of the stereoisomers of the natural product was estimated to be (2*R*,6*S*):(2*S*,6*R*):(2*S*,6*S*):(2*R*,6*R*)= 43:38:18:trace.

To support this conclusion, an alternative analysis was examined. Instead of 2A1P-OH (**2**), (1*R*,2*R*)- and (1*S*,2*S*)-2-(2,3-anthracenedicarboximide)-1-cyclohexanol (2ACyclo-OH, **4**)[3f] were used for the analysis (Scheme 2). These are more powerful chiral discrimination reagents than 2A1P-OH due to their more fixed cyclohexane ring system. In the same manner as described above, (1*R*,2*R*)- and (1*S*,2*S*)-2ACyclo-OH (**4**) were condensed with the natural product to give esters [(1*R*,2*R*)-*nat*-**5** and (1*S*,2*S*)-*nat*-**5**]. The esters were also prepared from synthetic (2*R*,6*R*)-**1** and (2*S*,6*R*)-**1** with (1*R*,2*R*)- and (1*S*,2*S*)-2ACyclo-OH (**4**) to give the four authentic stereoisomer equivalent [(1*R*,2*R*)-*RR*-**5**, (1*R*,2*R*)-*SR*-**5**, (1*S*,2*S*)-*RR*-**5** and (1*S*,2*S*)-*SR*-**5**]. With the samples in hand, 2D-HPLC analysis was carried out. Develosil ODS-A-3 with MeOH as the mobile phase was used for the first column at 20 °C, and Develosil C-30-UG-3 with MeOH/MeCN/THF=2:2:1 (v/v/v) as the mobile phase was used for the second column at 0 °C. Since the separation of the four stereoisomers was relatively easy with 2ACyclo-O esters, the separation sequence was reversed. That is to say, the stereoisomers were separated on the first column, then impurities were separated from the target component on the second column. Figure 4 shows the chromatograms of the authentic, (1*R*,2*R*)-*nat*-**5** and (1*S*,2*S*)-*nat*-**5** without the second column. Each stereoisomer was eluted at 18.7–20.5 min (peak 1), 21.5–23.5 min (peak 2), 25.2–27.5 min (peak 3) and 33.5–37.5 min (peak 4), respectively. Although the four stereoisomers were separated under this condition, some impurity was inseparable. Then, each component was directly injected into the second column by a six-way bulb, to give peaks at 36.3 min (peak 5), 46.4 min (peak 6), 52.3 min (peak 7) and 74.7 min (peak 8), respectively. For example, (1*S*,2*S*)-2ACyclo-O ester of (2*R*,6*S*)-**1** [(1*S*,2*S*)-*RS*-**5**] initially gave peak 1 and finally gave peak 5. Similarly, all the stereoisomers were assigned by a comparison with the standard samples. Table 2 summarizes the retention times of the stereoisomers. In order to confirm the existence of each stereoisomer, (1*R*,2*R*)-*nat*-**5** and (1*S*,2*S*)-*nat*-**5** were analyzed. Figure 5 shows the final chromatograms of (1*R*,2*R*)-*nat*-**5** and (1*S*,2*S*)-*nat*-**5**. Obviously, all the stereoisomers of **5** were observed in the analyses. Since these analyses were carried out with the aim of detecting the peaks, the peak ratio was incorrect. But the estimated amounts of the peaks were as follows: (2*R*,6*S*) ≈ (2*S*,6*R*) > (2*S*,6*S*) ≫ (2*R*,6*R*). The peak of (2*R*,6*R*)-isomer was much smaller than other peaks, and estimated to be about 10% of (2*S*,6*R*)- or (2*R*,6*S*)-isomers. These results were in good accordance with the first

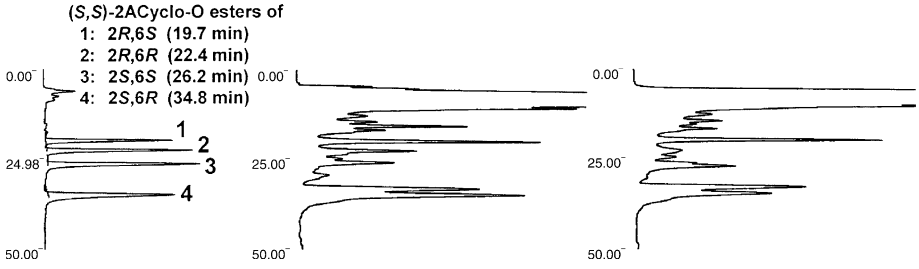


Figure 4. HPLC separation of **5** without the second column; standard (left), (1*R*,2*R*)-*nat*-**5** (center) and (1*S*,2*S*)-*nat*-**5** (right).

Table 2. Retention time of (1*S*,2*S*)- and (1*R*,2*R*)-2ACyclo-O ester derivative of **1**

Stereochemistry of **1**	(1*S*,2*S*)-2ACyclo-O ester		(1*R*,2*R*)-2ACyclo-O ester	
	Initial retention time (min)	Final retention time (min)	Initial retention time (min)	Final retention time (min)
2*R*,6*S*	18.7–20.5 (Peak 1)	36.3 (Peak 5)	33.5–37.5 (Peak 4)	74.6 (Peak 8)[a]
2*R*,6*R*	21.5–23.5 (Peak 2)	46.4 (Peak 6)	25.2–27.5 (Peak 3)	52.3 (Peak 7)
2*S*,6*S*	25.2–27.5 (Peak 3)	52.4 (Peak 7)	21.5–23.5 (Peak 2)	46.5 (Peak 6)
2*S*,6*R*	33.5–37.5 (Peak 4)	74.7 (Peak 8)[a]	18.7–20.5 (Peak 1)	36.3 (Peak 5)

[a] With shoulder peak.

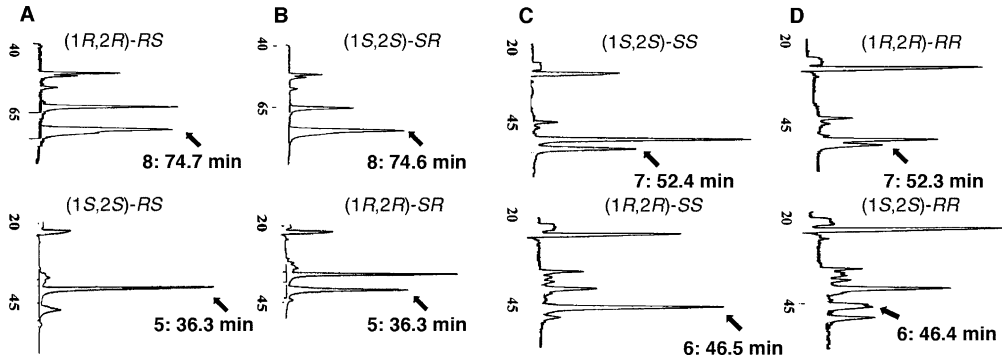


Figure 5. Detection of 2,6-dimethyloctane-1,8-dioic acid (**1**) in the crude extracts by 2D-HPLC of (1*S*,2*S*)- and (1*R*,2*R*)- 2ACyclo-O ester derivatives; **A**: (2*R*,6*S*)-isomer, **B**: (2*S*,6*R*)-isomer, **C**: (2*S*,6*S*)-isomer, **D**: (2*R*,6*R*)-isomer.

analyses using 2A1P-O ester derivatives. It cannot be considered that these two results with 2A1P-O and 2Acyclo-O ester derivatives are coincidental.

Since 2,6-dimethyl-1,8-octanedioic acid (**1**) has a carbonyl group next to a chiral center, an accidental enolization of the carbonyl group leads to racemization at C-2. However, in our previous synthetic studies, no racemization was observed with the isolation or the purification conditions.[6] Moreover, the observed major stereoisomers of the natural product were (2*S*,6*R*)- and (2*R*,6*S*)-isomer, namely, not the diastereomers but the enantiomers. Thus, our sample of the stereoisomeric mixture of **1** should not be an artifact, and we concluded that the natural product is constituted of all the stereoisomers. In other words, the natural product is enantiomerically impure.

Most insect pheromones are enantiomerically pure, and the stereochemistry of the pheromone is often strictly recognized.[8,9] However, the stereochemistry–pheromone activity relationships are complicated.[9] Since the natural copulation release pheromone of *C. maculates* was proven to be enantiomerically impure, we became interested in clarifying the stereochemistry–pheromone activity relationship of **1**. With the possible four stereoisomers of **1** in hand, we prepared a pseudo-natural product by mixing the synthetic stereoisomers in the determined ratio: (2*R*,6*S*):(2*S*,6*R*):(2*S*,6*S*):(2*R*,6*R*)=43:38:18:trace. Bioassays of the synthetic four isomers, the pseudo-natural product and the third portion of the crude extract were carried out by a modified Ohsawa's procedure.[5] As a female dummy, Ohsawa used a glass rod (2 mm OD and 150 mm in length); however, some males of *C. maculatus* were very responsive to the size of the glass rod. In our experiments, some males were not prompted to extrude their genital organ with an enough sample concentration due to the unfitness of the size of their body to the glass rod. To avoid this disfavored confusion, we examined a dead body of a male with an appropriate size instead of a glass rod. To our surprise, some males were active against a dead male body without any pheromone sample. They held the male dead body and drummed him with their antenna, but the extruding genital organ action was not observed. However, by washing the male dead body with diethyl ether, methanol and again diethyl ether, the washed body was totally inactive against any male. This indicates that the copulation release activity of *C. maculatus* is induced by multi components. A waxy compound at the dead male body surface might induce the behavior. In fact, Ohsawa reported the importance of the co-existence of a neutral compound such as hydrocarbons with **1** for the pheromone activity of *C. maculatus*. By using the male dead body certification, we examined the stereochemistry–pheromone activity relationships. Figure 6 shows the results of the dose-behavioral response tests at 1–25 μg/ml sample against male weevils. The neutral fraction of the extract was used for the co-factor of the pheromone with each sample. There was an inclination for the more contained isomer in the natural product, to be more active. Almost all male weevils were induced copulation release behavior by the pseudo-natural product at 25 μg/ml. The acidic fraction of the extract was also subjected to the bioassay. But correct activity was not determined, because the sample was not pure. The activity of the crude acidic fraction was about a half of that of the pseudo-natural product (data not shown).

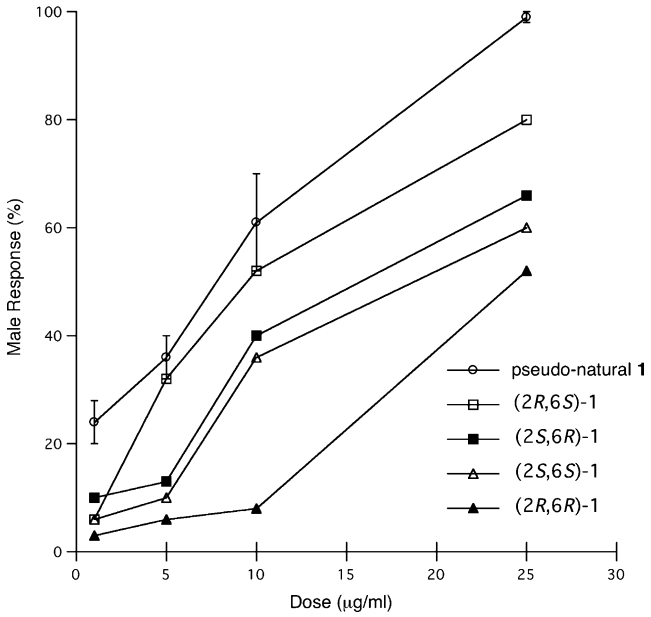


Figure 6. Dose-behavioral response curves of *C. maculatus* males to 2,6-dimethyloctane-1,8-dioic acid (**1**). The percentage of males that give full copulatory responses to treated decoys was recorded. The washed dead male decoys, solvent controls and the neutral extract controls were totally inactive.

3. Conclusion

The copulation release pheromone of the weevil, *C. maculatus*, was re-isolated from 31,461 virgin females. In the acidic fraction of the crude extract, we confirmed the existence of 2,6-dimethyl-1,8-octanedioic acid (**1**) by the GC–MS spectrum of the corresponding dimethylester. The constitution of the stereoisomers of the natural product was determined by the Ohrui–Akasaka method with the corresponding 2A1P-O or 2ACyclo-O ester. The analyses were performed with the unpurified extract under 2D-HPLC conditions. With these analyses, the direct determination of the constitution of the stereoisomers of the natural product was achieved. The natural pheromone was clarified to be enantiomerically impure, and the constitution of the natural product was determined to be 2*R*,6*S*:2*S*,6*R*:2*S*,6*S*:2*R*,6*R*=43:38:18:trace. The prepared pseudo-natural product by mixing the synthetic four isomers was the most active against male weevil. Since the Ohrui–Akasaka method needs an fmol level of the sample material[3f] and avoids any structure rearrangement of the sample sometimes observed in GC analysis, this methodology would be a powerful tool for the insect pheromone chemistry. Indeed, the analyses were performed with less than 50 nmol of the crude natural product. It is possible to cut down the amount of the material. To the best of our knowledge, this is the first example of the determination of the absolute configuration and the constitution of the stereoisomers of natural insect pheromone by 2D-HPLC analyses and the Ohrui–Akasaka method.

4. Experimental

4.1. General

Mass spectra were recorded with Shimadzu GCMS-QP 2000A. Column chromatography was carried out using silica gel (Wakogel C-200).

4.1.1. Collection and purification procedure of the pheromone from the weevil, *C. maculates*. The collection was carried out according to Ohsawa's procedure.[5] A laboratory-maintained colony of *C. maculattus* was reared on azuki bean (*Vigna angularis*, Dainagon) at 27 °C, 60% rh under dark. Newly emerged adults were sexed, and a group of several hundred virgin females was kept in a petri dish (90 mm ID×60 mm height) with a pile of filter papers (40×20 cm) corrugated in 1 cm section as shelters. After 20–27 days under the same condition, the filter papers were Shoxhlet-extracted with ether for 1 day. The extracts were combined and the solvent was evaporated in vacuo. The extracts were collected from 31,461 females. The extracts were dissolved in ether, and the solution was fractionated into neutral, acidic and basic fractions using 5% NaOH aq and 5% HCl aq. The resulting acidic compounds were filtered through a short silica gel (1 g) column with hexane–ethyl acetate (30/1 to 0/100) as eluting solvent to give 7.1 mg of crude material. The crude material was divided in three portions.

4.1.2. Preparation of the dimethylester derivative of the natural product. A portion of the crude extract was concentrated in vacuo, and the residue was dissolved in ether. The solution was cooled to 0 °C and added ethereal diazomethane solution prepared from nitrosomethylurea and potassium hydroxide until the yellowish color was attained. The mixture was concentrated in vacuo to give crude dimethylester derivative of the natural product. The crude product was subjected to GC–MS analysis. GC–MS analysis; column: DB-5 (30 m×0.25 mm), carrier gas He (1.3 ml/min), 100 °C (2 min)–220 °C (4 °C/min), t_R=14.2, m/z=199 ($M-CH_3O^+$), 171, 166, 157, 143, 139, 125, 111, 97, 88, 83, 74, 69, 59, 55 (100), 43, 41. The retention time and MS spectrum were identical with those of the synthetic authentic sample.[6]

4.1.3. Preparation and HPLC analysis of bis-2-(2,3-anthracenedicarboximide)-1-propyl ester derivatives (3). To a portion of the crude extract (ca. 1 mg, ~50 nmol) in MeCN–toluene (1/1), (*R*)- or (*S*)-2-(2,3-anthracenedicarboximide)-1-propanol (2A1P-OH, excess amount), 4-*N*,*N*-dimethylaminopyridine (DMAP, excess amount) and 2-(3-dimethylaminopropyl)-1-ethylcarbodiimide hydrochloride (EDC, excess amount) was successively added. The mixture was stirred at 40 °C overnight. An aliquot was then loaded onto silica gel TLC plate (10 cm length, Silicagel 60 F_{254}, Art-5744, Merck) and developed with hexane–EtOAc (4/1, v/v). The target spot detected by fluorescence was collected, packed in a Pasteur pipette and eluted with EtOAc–EtOH (4/1, v/v). After evaporation of the solvent with N_2 gas stream, the residue was dissolved in MeOH, and directly used for 2D-HPLC analysis. The prepared (*R*)-*nat*-**3** or (*S*)-*nat*-**3** was separated on two reverse-phase columns (the first column: Develosil ODS-HG-3, 4.6 mm i.d.×150 mm, the second column: Develosil ODS-A-3, 4.6 mm i.d.×150 mm, Nomura Chemical Co., Aichi, Japan). The detection was carried out by monitoring the fluorescence intensity at 462 nm (excitation at 298 nm). The separation was performed with two different solvent systems; for the first column: MeOH at a flow rate 0.4 ml/min at 0 °C, for the second column: MeOH/MeCN/THF=2:2:1 (v/v/v) at a flow rate 0.5 ml/min at −35 °C; t_R[(*S*)-*RS*]=46.5, t_R[(*S*)-*SS*]=51.3, t_R[(*S*)-*RR*]=55.2, t_R[(*S*)-*SR*]=67.6, t_R[(*R*)-*RS*]=67.6, t_R[(*R*)-*SS*]=55.3, t_R[(*R*)-*RR*]=51.5, t_R[(*R*)-*SR*]=46.6.

4.1.4. Preparation and HPLC analysis of bis-2-(2,3-anthracenedicarboximide)-1-cyclohexyl ester derivatives (5). In the same manner as 2A1P-O esters, (1*R*,2*R*)- and (1*S*,2*S*)-2-(2,3-anthracenedicarboximide)-1-cyclohexyl (2ACyclo-O) esters were prepared from the crude extract to give crude (1*R*,2*R*)-*nat*-**5** or (1*S*,2*S*)-*nat*-**5**. The crude **5** was directly subjected to 2D-HPLC analysis. The prepared (1*R*,2*R*)-*nat*-**5** or (1*S*,2*S*)-*nat*-**5** was separated on two reverse-phase columns (the first column: Develosil ODS-A-3, 4.6 mm i.d.×150 mm, the second column: Develosil C-30-UG-3, 4.6 mm i.d.×150 mm, Nomura Chemical Co., Aichi, Japan). The detection was carried out by monitoring the fluorescence intensity at 462 nm (excitation at 298 nm). The separation was performed with two different solvent systems; for the first column: MeOH at a flow rate 0.4 ml/min at 20 °C, for the second column: MeOH/MeCN/THF=2:2:1 (v/v/v) at a flow rate 1.0 ml/min at 0 °C; t_R[(1*S*,2*S*)-*RS*]=36.3, t_R[(1*S*,2*S*)-*SS*]=52.4, t_R[(1*S*,2*S*)-*RR*]=46.4,

t_R[(1*S*,2*S*)-*SR*]=74.7, t_R[(1*R*,2*R*)-*RS*]=74.6, t_R[(1*R*,2*R*)-*SS*]=46.4, t_R[(1*R*,2*R*)-*RR*]=52.3, t_R[(1*R*,2*R*)-*SR*]=36.3.

4.2. Procedure of the bioassay

Bioassays were carried out by modified Ohsawa's procedure. A newly emerged male was put into a glass vial (20 mm ID and 40 mm in height) covered with a cap. The insect was conditioned for 20 h under the same condition as in the mass rearing. The test sample solution was prepared from the ethereal solution of **1** and the natural neutral components of the extract. The adjusted solution of **1** was combined with the equal volume of the 50 μg/ml natural neutral components in ether. A dead male washed with ether, methanol and ether successively was used as a female dummy. The female dummy was pricked with a pin and treated with the ethereal test sample solution. After the solvent evaporation, the female dummy was introduced into the male vial. If he holds the dummy, drumming with his antennae and extruding his genital organ toward it within 20 s, the sample was judged to have copulation release activity. Each sample was tested using fifty males. Solvent controls and the neutral components of the extract controls were also tested for fifty males. The results of the bioassays were shown in Figure 5. The washed dead male decoys, solvent controls and the neutral extract controls were totally inactive.

Acknowledgements

We wish to acknowledge valuable discussions on the natural pheromone and measurement of GC–MS spectra with Prof. K. Ohsawa and Prof. S. Yajima (Tokyo University of Agriculture).

References and notes

1. Butenandt, A.; Hecker, E. *Angew. Chem.* **1961**, *73*, 349–353.
2. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.
3. (a) Akasaka, K.; Ohrui, H.; Meguro, H. *Analyst* **1993**, *118*, 765–768. (b) Akasaka, K.; Ohrui, H.; Meguro, H.; Umetsu, T. *Anal. Sci.* **1997**, *13*, 461–466. (c) Akasaka, K.; Ohrui, H. *Tetrahedron Lett.* **1997**, *38*, 6853. (d) Akasaka, K.; Imaizumi, K.; Ohrui, H. *Enantiomer* **1998**, *3*, 169–174. (e) Akasaka, K.; Imaizumi, K.; Ohrui, H. *Bunseki Kagaku* **1999**, *48*, 1085–1094. (f) Akasaka, K.; Ohrui, H. *Biosci., Biotechnol., Biochem.* **1999**, *63*, 1209–1215. (g) Ohrui, H.; Terashima, K.; Imaizumi, K.; Akasaka, K. *Proc. Jpn. Acad., Ser. B* **2002**, *78*, 69–72. (h) Imaizumi, K.; Terashima, H.; Akasaka, K.; Ohrui, H. *Anal. Sci.* **2003**, *19*, 1243–1249.
4. Phillips, T. W.; Phillips, J. K.; Webster, F. X.; Tang, R.; Burkholder, W. E. *J. Chem. Ecol.* **1996**, *22*, 2233–2249.
5. Nojima, S.; Ohsawa, K.; Yamamoto, I. Private communication and to be submitted.
6. Nakai, T.; Yajima, A.; Akasaka, K.; Kaihoku, T.; Ohtaki, M.; Nukada, T.; Ohrui, H.; Yabuta, G. *Biosci., Biotechnol., Biochem.* **2005**, *69*, 2401–2408.
7. Erni, F.; Frei, R. W. *J. Chromatogr.* **1978**, *149*, 561–569.
8. Silverstein, R. M. *J. Chem. Ecol.* **1988**, *14*, 1981–2004.
9. Mori, K. *Biosci., Biotechnol., Biochem.* **1996**, *60*, 1925–1932.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 62 (2006) 4597–4602

Stable nitroxyl radicals with triple bonds: 4-acetylenyl-3-imidazoline-3-oxide-1-oxyls

Sergei F. Vasilevsky,[a,*] Svetlana V. Klyatskaya,[a] Olga L. Korovnikova,[a] Svetlana A. Amitina,[b] Dmitri V. Stass,[a,c] Igor A. Grigor'ev[b,c,*] and José Elguero[d,*]

[a]*Institute of Chemical Kinetics and Combustion, Siberian Branch of the Russian Academy of Science, 630090 Novosibirsk, Russian Federation*
[b]*Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Science, 630090 Novosibirsk, Russian Federation*
[c]*Novosibirsk State University, 630090 Novosibirsk, Russian Federation*
[d]*Instituto de Química Médica (CSIC), Juan de la Cierva 3, E-28006 Madrid, Spain*

Received 9 January 2006; revised 10 February 2006; accepted 13 February 2006

Available online 20 March 2006

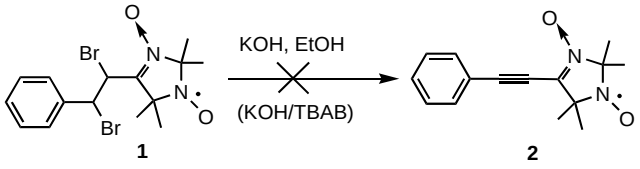
Abstract—Cross-coupling reaction of 1-hydroxy-2,2,5,5-tetramethyl-4-[2-(*p*-iodophenyl)vinyl]-3-imidazoline-3-oxide with copper(I) salts of 1-aryl(hetaryl)alkynes leads to the corresponding 2,2,5,5-tetramethyl-4-[2-(*p*-aryl(hetaryl)ethynylphenyl)vinyl]-3-imidazoline-3-oxide-1-oxyls in high yields.

1. Introduction

A recent extension of the spin-labeling methodology in physicochemical studies consists of the preparation of model systems to gain insight into the phenomenon of spin catalysis,[1] that is, the effect of the 'external' spin on the evolution of a correlated spin system. A reasonable way to accomplish this is the augmentation of a photo- or radiation generated spin-correlated radical pair with a third spin—the spin of a stable radical moiety introduced in the precursor of one of the pair partners. Recently,[2] we have reported the synthesis and physicochemical study of a series of aromatic charge acceptors and luminophores containing a stable 2-imidazoline radical fragment, which under X-irradiation in non-polar solvents, produced biradical ions that are partners in spin-correlated radical ion pairs. An important outcome of this study was the realization that the exchange coupling between the two unpaired spins of the short-lived biradical ion was too strong and must be reduced to allow for more quantitative studies going beyond the mere observation of the effect. In the present paper, we report the synthesis of a series of acetylenic derivatives of 3-imidazoline-1-oxyls. In this way, as opposed to 2-imidazoline radicals, the NO fragment bearing the unpaired electron is isolated from the substituent by single bonds within the radical itself, thus providing the desired attenuation of 'electron spin conductivity' outside the radical moiety of the spin-labeled molecule.

We have already published a preliminary communication devoted to the synthesis of acetylene-containing nitroxides of the 3-imidazoline series.[3] In this work, we will report the synthesis of these compounds and provide additional examples of the preparation of spin-labeled acetylenyl nitroxides as well as their diamagnetic derivatives, in full detail with all spectral and analytical data.

Our attempts to use the classical method for the synthesis of the desired acetylenes,[4] dehydrobromination of the corresponding 1,2-dibromoethane, were unsuccessful. Reaction of **1** with either KOH in boiling EtOH, KOH in the presence of TBAB (tetrabutylammonium bromide), or KOH in DMSO in a wide interval of temperatures (20–100 °C) led to a large number of by-products, from which acetylene **2** could not be isolated (Scheme 1).



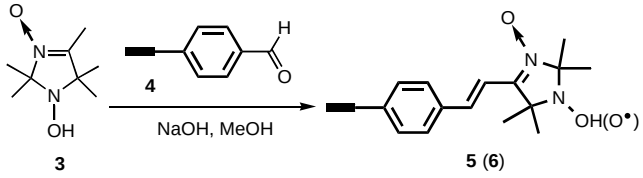
1 2

Scheme 1. Attempts of dehydrobromination of dibromoethane **1**.

Keywords: Acetylenes; 3-Imidazoline nitroxides; Cross-coupling reaction; Copper acetylides.
* Corresponding authors. Fax: +7 383 3307350 (S.F.V.); fax: +34 91 5644853 (J.E.);
e-mail addresses: vasilev@ns.kinetics.nsc.ru; grig@nioch.nsc.ru; iqmbe17@iqm.csic.es

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.02.036

For the preparation of a series of both diamagnetic and paramagnetic acetylenic derivatives of 3-imidazoline-3-oxide-1-oxyl we thought of using the key ethynyl derivatives **5** (**6**). These compounds are obtained by condensation of 1-hydroxy-2,2,4,5,5-pentamethyl-3-imidazoline-3-oxide **3** with *p*-ethynyl benzaldehyde **4** (Scheme 2).

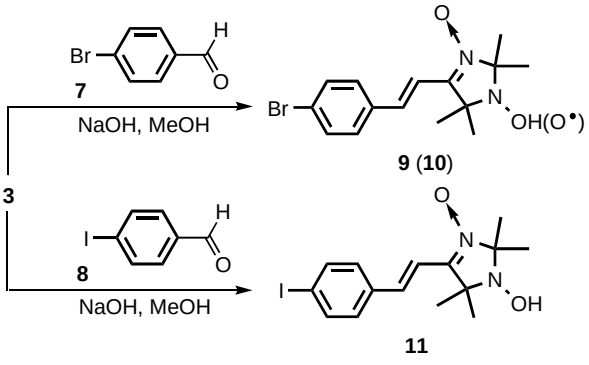


Scheme 2. Condensation of hydroxylamine **3** with the aldehyde **4**.

However, we observed strong polymerization and the mixture of hydroxylamine **5** and nitroxyl **6** was isolated in low yields (2.4 and 3.0%, respectively).

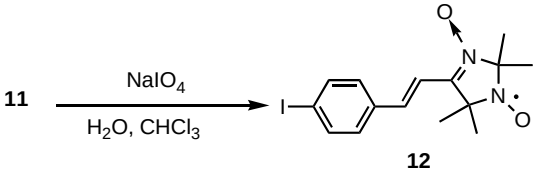
Then we tried another approach to the synthesis of acetylenic derivatives of 3-imidazoline-3-oxide-1-oxyl, based on the Sonogashira cross-coupling reaction[5] of the corresponding iodo(bromo)-imidazolines with acetylenyl-arenes, a reaction that has been successfully applied to the preparation of a series of acetylenyl derivatives of 2-imidazoline nitroxides.[6]

The starting halogeno-arylimidazolines were synthesized by condensation of 2,2,4,5,5-pentamethyl-imidazoline **3** with *p*-bromobenzaldehyde **7** or *p*-iodobenzaldehyde **8**. In the case of the bromo derivative **7** both para- (**10**, 10%) and diamagnetic (**9**, 36%) (bromophenyl)vinylimidazolines were isolated. On the other hand, only the iodo derivative **11** was isolated in 28% yield in the case of iodoaldehyde **8** (Scheme 3).



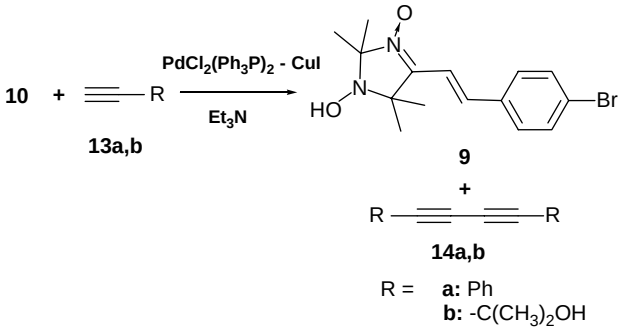
Scheme 3. Condensation of imidazoline **3** with *p*-halogeno benzaldehydes **7** and **8** in the presence of NaOH.

The paramagnetic iodo derivative **12** was synthesized by oxidation of **11** in the presence of $NaIO_4$. It is necessary to emphasize that this is the first successful application of the system $NaIO_4$–H_2O–$CHCl_3$ for preparing 3-imidazoline nitroxyls. The yield of the desired radical **12** was 72% (Scheme 4).



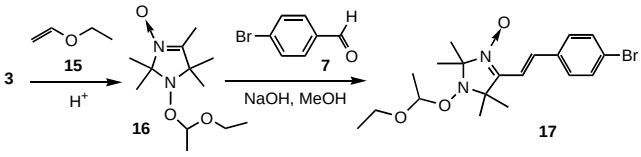
Scheme 4. Oxidation of hydroxylamine **11** into nitroxyl **12** in the presence of $NaIO_4$.

However, we failed to perform cross-coupling of the spin-labeled bromo derivative **10** with both phenylacetylene **13a** and 2-methylbut-3-yn-2-ol **13b**. In both cases the reaction resulted in the obtention of diamagnetic derivatives **9**, accompanied by formation of the homo-coupling product of 1-alkynes—1,4-disubstituted-1,3-diynes **14a**,**b** (Scheme 5). Even the use of the more active, for cross-coupling reactions, iodo compounds **11** or **12**, was unsuccessful.



Scheme 5. Cross-coupling of bromonitroxyl **10** with terminal acetylenes **13a** and **13b**.

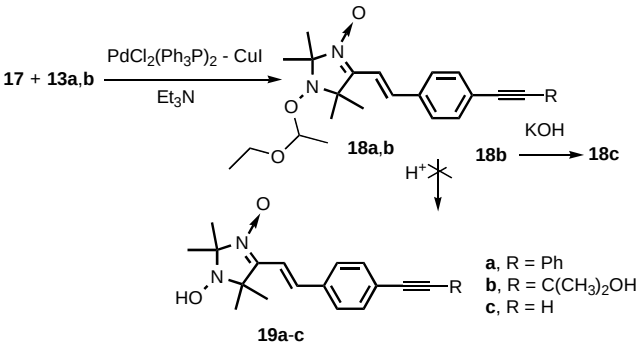
We tried to avoid these complications by protecting the hydroxyl group in the starting halogen derivatives with ethyl vinyl ether **15**.[7] The starting bromide was prepared as shown below (Scheme 6).



Scheme 6. Protection of the hydroxy group in hydroxylamine **3** followed by condensation of **16** with *p*-bromobenzaldehyde **7**.

In case of success, this way could open a route to the synthesis of the diamagnetic acetylenyl-3-imidazolines and the corresponding paramagnetic derivatives. This is important because the study of the phenomenon of spin catalysis requires the determination of quantum yields of luminescence of both dia- and paramagnetic compounds.[8]

Thus protected bromo-imidazoline **17** reacted with terminal acetylenes **13a**,**b** under standard conditions [$Pd(PPh_3)_2Cl_2$–CuI–NEt_3, 55–80 °C] to afford the desired diamagnetic cross-coupling products **18a**,**b** in 60–70% yield (Scheme 7). The mono substituted acetylene derivative **18c** was obtained by alkaline cleavage of **18b**.



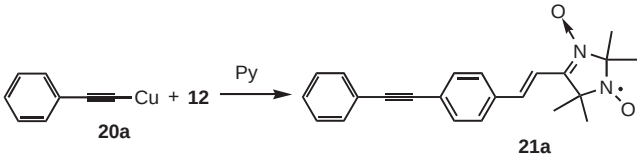
Scheme 7. Cross-coupling of acetal **17** with terminal acetylenes **13a**,**b** followed by attempts to eliminate the protecting group and the cleavage of carbinol **18b**.

Next we tried to remove the protecting group, followed by oxidation of the hydroxyl group. However, deprotection of the acetal group from the acetylenic derivatives in the presence of trace amounts of HCl led only to the formation of a gum.

We suppose that the successful application of cross-coupling in the 2-imidazoline series and the negative result of the same reaction for 3-imidazolines is related to stronger oxidative properties of the nitroxide group in 3-imidazoline-3-oxide-1-oxyls as compared with 2-imidazoline-3-oxide-1-oxyl derivatives.[9] On the other hand, this result is connected also with the low reactivity of the bromine atom in the aryl moiety due to +M-effect of the *N*-oxide fragment.[10] This effect of the N–O group for 3-imidazolines is confirmed by the data from ^{13}C NMR spectra.[11]

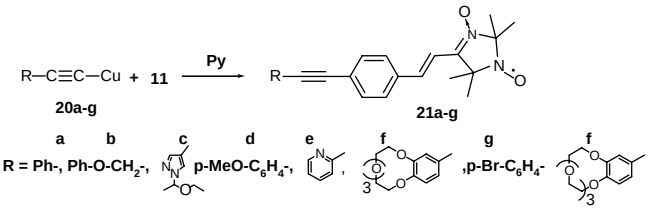
For this reason, and taking into account the difference in the mechanisms of Cu- and Pd-catalyzed cross-coupling reaction of alk-1-ynes,[12] we supposed that the described difficulties could be overcome by using the acetylide synthesis to obtain the desired products.

As a model, the copper salt of phenylacetylene **20a** was allowed to react with paramagnetic iodo-imidazoline **12** in boiling pyridine to afford product **21a** in 83% yield (Scheme 8).



Scheme 8. Cross-coupling of paramagnetic iodo-imidazoline **12** with the copper salt of phenylacetylene **20a**.

It is important to note that the diamagnetic analogue, the iodo-imidazoline **11** was also successfully used in the cross-coupling reaction affording the radical **21a**. The transformation of the reaction products directly into radicals **21a**–**g** probably takes place during the work-up of the reaction mixture (Scheme 9). We observed similar transformations in the condensation of 1-hydroxy-2,2,4,5,5-pentamethyl-3-imidazoline-3-oxide **3** with *p*-bromobenzaldehyde **7**.



Scheme 9. Cross-coupling of diamagnetic iodo-imidazoline **11** with the copper salt of phenylacetylenes **20a**–**g**.

The series of acetylenic nitroxides **21a**–**e**, were obtained in good yields (90–95%), and even in the worst case of low reactive crown ether **20f** or the bromo derivative **20g** the yields of **21f**,**g** were 50 and 60%.

Thus, new methods for the acetylide synthesis of aryl(hetaryl)ethynylphenyl-3-imidazoline nitroxides have been developed.

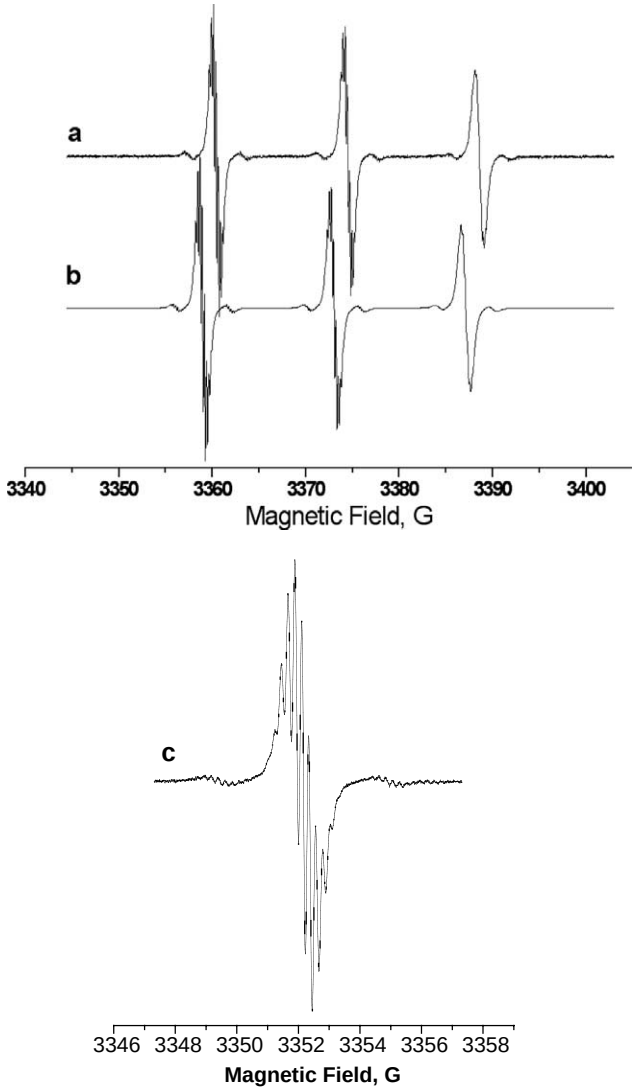


Figure 1. (a) X-band CW ESR spectrum of 10^{-5} M **21d** in degassed toluene, room temperature, microwave power 2 mW, modulation 0.1 G 100 kHz, single scan of 40 min; (b) simulation (shifted), $A_N = 4.09$ G, $A(^{13}C)_{(CH_3)} = 5.71$ G, $A_{H(CH_3)}(12H) = 0.23$ G; (c) expanded view of the low-field line. The structure from minor coupling with 12 methyl hydrogens is clearly seen both for the main line and for the ^{13}C satellites.

ESR spectra of the nitroxides are typical for 3-imidazoline radicals with spin density localized mostly at the NO fragment (Fig. 1). All spectra show a dominant triplet at N atom in the first position with splitting of about 14.1 G (in toluene) and weaker satellites from ^{13}C nuclei of the four methyl groups in natural abundance (splitting about 5.7 G). Minor splittings of 0.23 G from 12 nearly equivalent methyl protons are also neatly resolved (Fig. 1c).

2. Conclusions

A synthetic approach to acetylenic derivatives of 3-imidazoline nitronyl nitroxide radicals (NNR) has been found. Unlike nitronyl nitroxides of the 2-imidazoline series, Sonogashira cross-coupling reaction is unsuitable for the synthesis of 3-imidazoline nitroxides. It was found that coupling reaction of Cu(I)-salts of 1-alkynes with the corresponding iodo-containing 3-imidazolines leads to disubstituted spin-labeled acetylenes in good yield. We have investigated the cross-coupling of copper acetylides with both spin-labeled **12** and diamagnetic **11** iodo-imidazolines. In both cases cross-coupling leads to paramagnetic derivatives **21a–g** in 50–90% yields. ESR-spectra of the prepared compounds are typical for 3-imidazoline radicals with spin density localized mostly at the nitroxyl fragment.

3. Experimental

3.1. General

Melting points were determined with a hot-stage microscope. Column chromatography was performed on Al_2O_3. The R_f values were measured on aluminium backed TLC plates of silica gel 60 F254 (Merck, 0.2 mm) with the indicated eluent. ^1H NMR spectra were recorded on a Bruker DRX 400 (9.4 T, 200.13 MHz) spectrometer. Chemical shifts (δ in parts per million) are given from internal $CHCl_3$ (7.24). Coupling constants (J in Hertz) were accurate to ± 0.2 Hz for ^1H. Mass spectra (HRMS) were measured on a Finnigan SSQ-710 at 70 eV using electron impact modes. The IR-spectra were recorded on a Bruker IFS 66 spectrometer (potassium bromide). CW ESR spectra were taken in degassed solutions on a Bruker EMX CW ESR spectrometer, all hyperfine coupling constants and field offsets from standard DPPH line are given in Gauss with accuracy ± 0.02 G, except for the couplings with methyl carbon-13 for which the accuracy is ± 0.1 G, concentration of radicals 10^{-5}–10^{-4} M in the indicated solvent. Compounds **1**,[13] **3**,[9] **4**[6] and **7**[8] were prepared by previously reported methods. Copper(I) acetylides (**20a–g**) were prepared according to the published procedure[12] from the corresponding acetylenes. Commercial ethoxyethene **15** was used freshly distilled over sodium and pyridine over NaOH; phenylacetylene was used freshly distilled. Compound **16** and $PdCl_2(PPh_3)_2$ were used without additional purification.

3.1.1. 4-[2-(*p*-Iodophenyl)vinyl]-2,2,5,5-tetramethyl-3-imidazoline-3-oxide-1-oxyl (12). A mixture of **11** (0.11 g, 0.28 mmol) and $NaIO_4$ (0.09 g, 4.2 mmol) in chloroform (7 mL) and water (7 mL), was stirred at room temperature for 2–2.5 h till absence of **11** (TLC-control). The organic layer was separated and dried over K_2CO_3 and evaporated to dryness under reduced pressure. Purification of the crude product by column chromatography on Al_2O_3 (elution with chloroform) and following recrystallization gave 80 mg (72%) compounds **12**, mp 180.5–182.0 °C (from mixture of hexane–benzene). IR, cm^{-1}: $\nu_{max}=1306$ (N→O), 1362 (N–˙O). HRMS, *m/z* (%): 384.8 $[M]^+$ (16.84), 337.8 (73.54), 295.0 (19.22), 240.8 (21.97), 170.0 (99.63), 155.9 (57.73), 141.0 (69.80), 129.0 (50.06), 115.0 (49.39). Found: *m/z* 385.03914 $[M]^+$. $C_{15}H_{18}IN_2O_2$. Calcd: $M=385.04148$. ESR, G: $g_{iso}=2.0060$ ($\Delta H_{DPPH}=4.05$ G), $A_N=14.10$ $A_{H(CH_3)}(12H)=0.23$, $A(^{13}C)=5.78$. Solvent: toluene.

3.1.2. 1-(*O*-Ethoxyethyl)-2,2,4,5,5-pentamethyl-3-imidazoline-3-oxide (16). A solution of imidazoline **3** (6.1 g, 35.3 mmol) and freshly distilled ethoxyethene **15** (5.1 mL, 52.9 mmol) in benzene (7 mL) was stirred at 45–50 °C in the presence of traces of HCl for 3.5–4 h till absence of **3** (TLC-control). The reaction mixture was neutralized and dried over K_2CO_3, filtered through $A1_2O_3$, and concentrated under reduced pressure. The final yellowish oil was purified by vacuum distillation to give 8.2 g (95%) of the title compound as a colorless oil, bp 110–111 °C/0.5 Torr, $n_D^{17}=1.4750$. ^1H NMR ($CDCl_3$) δ 1.09–1.53 (m, 18H, –CH–*CH*$_3$, –OCH_2–*CH*$_3$, 2,2,5,5-*CH*$_3$), 1.90 (s, 3H, 4-*CH*$_3$), 3.52–3.75 (two q, 2H, –*OCH*$_2$–CH_3, $J=5$ Hz), 4.77 (q, 1H, –*CH*–CH_3, $J=9$ Hz). Anal. Calcd for $C_{12}H_{24}N_2O_3$: C, 58.98; H, 9.86; N,11.46. Found: C, 58.35; H, 9.48; N, 10.97.

3.1.3. 1-Hydroxy-4-[2-(*p*-ethynylphenyl)vinyl]-2,2,5,5-tetramethyl-3-imidazoline-3-oxide (5) and 4-[2-(*p*-ethynylphenyl)vinyl]-2,2,5,5-tetramethyl-3-imidazoline-3-oxide-1-oxyl (6). A solution of NaOH (440 mg, 11 mmol), imidazoline derivative **3** (1.72 g, 10 mmol), and aldehyde **4** (1.3 g, 10 mmol) in MeOH (7 mL) was stirred at 45–50 °C in argon atmosphere for 3.5–4 h till absence of aldehyde (TLC-control). $CHCl_3$ (30 mL) and water (40 mL) were then added. The organic layer was separated and dried over K_2CO_3 and evaporated to dryness under reduced pressure. Purification of the mixture of **5** and **6** (420 mg, 15%) by column chromatography on Al_2O_3 (elution with chloroform) followed by recrystallization gave the corresponding compounds **5** and **6**.

For **5** the yield was 68 mg (2.4%), mp 169.0–171.0 °C (from mixture of benzene–hexane). IR, cm^{-1}: $\nu_{max}=1295$ (N→O), 2105 (–C≡C–), 3251 (C≡C–H), 3441 (br, OH). ^1H NMR ($CDCl_3$) δ, 1.48 (s, 6H, 2,2-*CH*$_3$), 1.59 (s, 6H, 5,5-*CH*$_3$), 3.15 (s, 1H, *H*–C≡C), 4.77 (s br, 1H, *OH*), 6.65 (d, –*CH*=CH-Ar, $J=16$ Hz), 7.49 (s, 4H, H_{Ar}), 8.38 (d, –CH=*CH*-Ar, $J=16$ Hz). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.65; H, 6.96; N, 9.98.

For **6** the yield was 85 mg (3%), mp 182.0–184.0 °C (from mixture of benzene–hexane). IR, cm^{-1}: $\nu_{max}=1275$ (N→O), 1355 (N–˙O), 2104 (–C≡C–); 3250 (≡C–H). Anal. Calcd for $C_{17}H_{19}N_2O_2$: C, 72.06; H, 6.76; N, 9.89. Found: C, 72.25; H, 6.55; N, 9.86. ESR, G: $g_{iso}=2.0058$ $A_N=13.81$ $A_{H(CH_3)}(12H)=0.24$, $A(^{13}C)=5.74$. Solvent: *n*-hexane.

3.1.4. 1-Hydroxy-4-[2-(*p*-bromophenyl)vinyl]-2,2,5,5-tetramethyl-3-imidazoline-3-oxide (9) and 4-[2-(*p*-bromophenyl)vinyl]-2,2,5,5-tetramethyl-3-imidazoline-3-

oxide-1-oxyl (10). For **9** the yield was 1.67 g (49%), mp 153.0–154.0 °C (from mixture of hexane–benzene). IR, cm^{-1}: $\nu_{max}=1320$ (N→O), 3241 (br, OH). ^1H NMR ($CDCl_3$) δ, 1.44 (s, 6H, 2,2-CH_3), 1.58 (s, 6H, 5,5-CH_3), 5.29 (s br, 1H, *OH*), 6.61–6.65 (d, 1H, –*CH*═CH-Ar, $J=16$ Hz), 7.35–7.49 (d, d, 4H, H_{Ar}), 8.30–8.34 (d, 1H, –CH═*CH*-Ar, $J=16$ Hz). HRMS, *m/z* (%): 338.0 $[M]^+$ (7.90), 265.0 (8.19), 237.0 (8.97), 236.0 (8.40), 157.0 (15.24), 156.0 (100.0), 141.1 (30.46), 115.1 (9.83), 74.1 (10.60). Found: *m/z* 338.06344 $[M]^+$. $C_{15}H_{19}BrN_2O_2$. Calcd: $M=338.06299$.

For **10** the yield was 480 mg (14%), mp 189.5–192.0 °C (from mixture of benzene–hexane). IR, cm^{-1}: $\nu_{max}=1279$ (N→O), 1363 (N–˙O). HRMS, *m/z* (%): 337.0 $[M]^+$ (6.14), 291.8 (51.08), 290.0 (25.81), 247.9 (14.43), 236.9 (2.73), 170.1 (100.0), 156.0 (56.52), 141.1 (58.93), 115.1 (32.81), 102.1 (26.81). Found: *m/z* 337.05547 $[M]^+$. $C_{15}H_{18}BrN_2O_2$. Calcd: $M=337.05521$. ESR: $g_{iso}=2.0059$ ($\Delta H_{DPPH}=3.97$ G), $A_N=13.86$ G, $A_{H(CH_3)}(12H)=0.22$ G, $A(^{13}C)=5.62$ G. Solvent: toluene.

3.1.5. 1-Hydroxy-4-[2-(*p*-iodophenyl)vinyl]-2,2,5,5-tetramethyl-3-imidazoline-3-oxide (11). The yield of compound **11** was 2.15 g (28%), mp 175 (decomp.) °C (from ethylacetate). IR, cm^{-1}: $\nu_{max}=1310$ (N→O), 3233 (br, OH). ^1H NMR ($CDCl_3$) δ, 1.44 (s, 6H, 2,2-CH_3), 1.55 (s, 6H, 5,5,-CH_3), 5.46 (s br, 1H, *OH*), 6.64 (d, 1H, –*CH*═CH-Ar, $J=8$ Hz), 7.22 (d, 2H, 2,6-H_{Ar}, $J=4$ Hz), 7.65 (d, 2H, 3,5-H_{Ar}, $J=4$ Hz), 8.27 (d, –CH═*CH*-Ar, $J=8$ Hz). Anal. Calcd for $C_{15}H_{19}IN_2O_2$: C, 46.65; H, 4.96; N, 7.25; I, 32.86. Found: C, 47.00; H, 5.40; N, 6.92; I, 32.39.

3.1.6. 1-(*O*-Ethoxyethyl)-4-[2-(*p*-bromophenyl)vinyl]-2,2,5,5-tetramethyl-3-imidazoline-3-oxide (17). The yield of compound **17** was 1.50 g (36%, viscous liquid). IR, cm^{-1}: $\nu_{max}=1298$ (N→O). ^1H NMR ($CDCl_3$) δ, 1.15–1.54 (m, 18H, 2,2,5,5-CH_3, –OCH_2–CH_3, –CH–CH_3), 3.54–3.85 (m, 2H, –CH_2–CH_3), 4.79 (q, 1H, –*CH*–CH_3, $J=9$ Hz), 6.39–6.47 (d, 1H, –*CH*═CH-Ar, $J=16$ Hz), 7.31–7.43 (q, 4H, H_{ar}), 8.30–8.38 (d, 1H, –CH═*CH*-Ar, $J=16$ Hz). HRMS, *m/z* (%): 409.9 $[M]^+$ (12.41), 339.8 (63.51), 337.8 (64.89), 156.0 (58.47), 140.9 (40.75), 98.0 (41.37), 73.0 (100.0), 56.0 (35.40), 45.0 (89.33). Found: *m/z* 410.12611 $[M]^+$. $C_{19}H_{27}BrN_2O_3$. Calcd: $M=410.12054$.

3.1.7. 1-(*O*-Ethoxyethyl)-2,2,5,5-tetramethyl-4-{2-[4-(*p*-phenylethynyl)phenyl)vinyl}-3-imidazoline-3-oxide (18a). A mixture of the halogen compound **17** (171 mg, 0.4 mmol), alkyne **13a** (43 mg, 0.43 mmol), $PdCl_2(PPh_3)_2$ (40 mg) and CuI (20 mg) and Et_3N or piperidine (10 mL) was stirred under argon stream at 80 °C for 3 h. The solvent was removed with an oil pump (0.1 Torr) at 20 °C, the residue was dissolved in benzene, the solution was filtered through a thin-layer of Al_2O_3 and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography on Al_2O_3, and the solvent was distilled off. Purification of the crude product by column chromatography on Al_2O_3 (elution with chloroform) and following crystallization gave the corresponding compound **18a**. The yield of compound **18a** was 125 mg (72%), mp 138–140 °C (from hexane). IR, cm^{-1}: $\nu_{max}=1325$ (N→O), 2220 (–C≡C–). ^1H NMR ($CDCl_3$) δ, 1.12–1.16 (m, 6H, –CH–CH_3, –OCH_2–CH_3), 1.26–1.43 (m, 12H, 2,2,5,5-CH_3), 3.45–3.75 (m, 2H, –OCH_2–CH_3), 4.74 (q, 1H, –*CH*–CH_3), 6.41–6.49 (d, –*CH*═CH-Ar, $J=16$ Hz), 7.21–7.41 (m, 9H, H_{ar}), 8.31 (d, 1H, –CH═*CH*-Ar, $J=16$ Hz). Anal. Calcd for $C_{27}H_{32}N_2O_3$: C, 74.97; H, 7.46; N, 6.48. Found: C, 74.83; H, 7.28; N, 6.30.

3.1.8. 1-(*O*-Ethoxyethyl)-2,2,5,5-tetramethyl-4-{2-[*p*-(3-methyl-3-hydroxybutyn-1-yl)phenyl]vinyl}-3-imidazoline-3-oxide (18b). The yield of compound **18b** was 580 mg (48%) obtained from 1.23 g (3.0 mmol) of **17**, mp 104.0–106.0 °C (from hexane). IR, cm^{-1}: $\nu_{max}=1278$ (N→O), 2220 (–C≡C–), 3406 (br, OH). ^1H NMR ($CDCl_3$) δ, 1.18 (t, 3H, –OCH_2–CH_3, $J=6$ Hz), 1.21 (d, 3H, –CH–CH_3, $J=7$ Hz), 1.31–1.65 (m, 18H, 2,2,5,5-CH_3, –C(CH_3)OH), 2.035 (s br, –C(CH_3)*OH*), 3.51–3.91 (two q, 2H, –OCH_2–CH_3, $J=6$ Hz), 4.80–4.91 (q, 1H, –*CH*–CH_3, $J=7$ Hz), 6.54–6.65 (d, –*CH*═CH-Ar, $J=16$ Hz), 7.32–7.47 (dd, 4H, H_{ar}), 8.37–8.48 (d, –CH═*CH*-Ar, $J=16$ Hz). HRMS, *m/z* (%): 414.1 $[M]^+$ (10.04), 343.0 (25.46), 342.1 (77.46), 295.2 (14.03), 239.0 (17.93), 98.0 (19.81), 73.0 (100.0), 56.1 (13.72), 45.1 (82.62). Found: *m/z* 414.25148 $[M]^+$. $C_{24}H_{34}N_2O_4$. Calcd: $M=414.25184$.

3.1.9. 1-(*O*-Ethoxyethyl)-2,2,5,5-tetramethyl-4-[2-(*p*-ethynylphenyl)vinyl]-3-imidazoline-3-oxide (18c). A mixture of **18b** (150 mg, 0.36 mmol) and KOH (130 mg, 0.33 mmol) in 10 mL of toluene was stirred at 80–85 °C for 14 h till absence of alcohol (TLC-control). The reaction mixture was filtered off through Al_2O_3 (elution with chloroform), and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography on Al_2O_3 (elution with chloroform) and following recrystallization gave 74 mg (62%) of compound **18c**, mp 93.0–94.5 °C (from mixture of hexane–benzene). IR, cm^{-1}: $\nu_{max}=1325$ (N→O), 2099 (–C≡C–), 3221 (C≡C–H), ^1H NMR ($CDCl_3$) δ, 1.18–1.25 (t, 3H, –OCH_2–CH_3, $J=4$ Hz), 1.31–1.34 (d, 3H, –CH–CH_3, $J=3$ Hz), 1.43–1.65 (m, 12H, 2,2,5,5-CH_3), 3.13 (s, 1H, C≡C–*H*), 3.50–3.92 (two q, 2H, –OCH_2–CH_3, $J=4$ Hz), 4.80–4.92 (q, 1H, –*CH*–CH_3, $J=3$ Hz), 6.55–6.63 (d, –*CH*═CH-Ar, $J=16$ Hz), 7.43–7.45 (s br, 4H, H_{ar}), 8.42–8.53 (d, –CH═*CH*-Ar, $J=16$ Hz). HRMS, *m/z* (%): 356.0 $[M]^+$ (1.07), 355.9 (3.78), 283.8 (58.09), 268.8 (4.17), 236.8 (9.31), 180.8 (11.41), 164.8 (15.12), 72.9 (100.0), 45.1 (86.33). Found: *m/z* 356.20998 $[M]^+$. $C_{21}H_{28}N_2O_3$. Calcd: $M=356.20999$.

3.1.10. 2,2,5,5-Tetramethyl-4-{2-[4-(*p*-phenylethynyl)phenyl]vinyl}-3-imidazoline-3-oxide-1-oxyl (21a). A mixture of copper(I) salt of acetylenes **20a** (60 mg, 0.36 mmol) and diamagnetic (**11**) or spin-labeled iodide (**12**) (130 mg, 0.33 mmol) in 10 mL of pyridine was stirred at 80–85 °C in argon atmosphere for 3.5–4 h till absence of iodide (TLC-control). Then $CHCl_3$ (30 ml) and water (40 mL) were added. The organic layer was separated, the water layer was extracted with $CHCl_3$ (2×25 mL), and the combined organic layers were washed with 25% NH_{3aq} (2×15 mL), dried over K_2CO_3, filtered off and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography on Al_2O_3 (elution with chloroform) and following recrystallization gave 100 mg (85%) of nitroxide **21a**, mp 197.5–198.5 °C (from benzene). IR, cm^{-1}: $\nu_{max}=1315$ (N→O), 1364 (N–˙O), 2216 (C≡C). Anal. Calcd for $C_{23}H_{23}N_2O_2$: C, 76.85; H, 6.45; N, 7.79.

Found: C, 76.63 H, 6.51 N, 7.87 ESR: $g_{iso}=2.0058$ ($\Delta H_{DPPH}=3.79$ G), $A_N=14.05$ G, $A_{H(CH_3)}(12H)=0.23$ G, $A(^{13}C)=5.66$ G. Solvent: toluene.

From spin-labeled iodide **12**: the yield of compound **21a** was 50 mg (85%) obtained from 65 mg (0.165 mmol) of **12**, mp 197.5–198.5 °C (from benzene).

3.1.11. 2,2,5,5-Tetramethyl-4-{2-[4-(3-phenoxyprop-1-ynyl)phenyl]vinyl}-3-imidazoline-3-oxide-1-oxyl (21b). The yield of compound **21b** was 120 mg (92%), mp 161.5–163.5 °C (from mixture of benzene–hexane). IR, cm^{-1}: $\nu_{max}=1318$ (N→O), 1360 (N–˙O), 2225 (C≡C). HRMS, *m/z* (%): 389.0 [M^+] (24.15), 222.0 (27.09), 221.0 (15.41), 207.9 (11.70), 194.9 (39.90), 94.0 (11.80), 73.1 (43.77), 72.0 (63.66), 67.0 (14.59). Found: *m/z* 389.18652 [M^+]. $C_{24}H_{25}N_2O_3$. Calcd: $M=389.18650$. ESR: $g_{iso}=2.0059$ ($\Delta H_{DPPH}=4.00$ G), $A_N=14.13$ G, $A_{H(CH_3)}(12H)=0.23$ G, $A(^{13}C)=5.81$ G. Solvent: toluene.

3.1.12. 4-{2-[*p*-(*N*-Ethoxyethyl-1*H*-pyrazol-4-ylethynyl)-phenyl]vinyl}-2,2,5,5-tetramethyl-3-imidazoline-3-oxide-1-oxyl (21c). The yield of compound **21c** was 111 mg (80%), mp 169.0–170.0 °C (from benzene). IR, cm^{-1}: $\nu_{max}=1310$ (N→O), 1351 (N–˙O), 2214 (C≡C). Anal. Calcd for $C_{24}H_{29}N_4O_3$: C, 68.39; H, 6.93; N, 11.39. Found: C, 66.35; H, 7.07; N, 12.09. ESR: $g_{iso}=2.0060$ ($\Delta H_{DPPH}=4.10$ G), $A_N=14.11$ G, $A_{H(CH_3)}(12H)=0.23$ G, $A(^{13}C)=5.93$ G. Solvent: toluene.

3.1.13. 2,2,5,5-Tetramethyl-4-{2-[4-(*p*-methoxyphenyl ethynyl)phenyl]vinyl}-3-imidazoline-3-oxide-1-oxyl (21d). The yield of compound **21d** was 120 mg (92%), mp 172.0–173.0 °C (from mixture of benzene–hexane). IR, cm^{-1}: $\nu_{max}=1295$ (N→O), 1343 (N–˙O), 2212 (C≡C). Anal. Calcd for $C_{24}H_{25}N_2O_3$: C, 74.01; H, 6.47; N, 7.19. Found: C, 74.15; H, 6.58; N, 7.12. ESR: $g_{iso}=2.0058$ ($\Delta H_{DPPH}=3.71$ G), $A_N=14.09$ G, $A_{H(CH_3)}(12H)=0.23$ G, $A(^{13}C)=5.71$ G. Solvent: toluene.

3.1.14. 2,2,5,5-Tetramethyl-4-{2-[*p*-(2-pyridinylethynyl) phenyl]vinyl}-3-imidazoline-3-oxide-1-oxyl (21e). The yield of compound **21e** was 84 mg (90%) obtained from 100 mg (0.239 mmol) of **11**, mp 179.5–180.0 °C (from mixture of benzene–hexane). IR, cm^{-1}: $\nu_{max}=1283$ (N→O), 1365 (N–˙O), 2221 (C≡C). Anal. Calcd for $C_{22}H_{22}N_3O_2$: C, 73.31; H, 6.15; N, 11.66. Found: C, 73.33; H, 6.60; N, 11.20. ESR: $g_{iso}=2.0059$ ($\Delta H_{DPPH}=4.05$ G), $A_N=13.81$ G, $A_{H(CH_3)}(12H)=0.23$ G, $A(^{13}C)=5.60$ G. Solvent: toluene.

3.1.15. 2,2,5,5-Tetramethyl-4-{2-[*p*-(2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-pentaoxabenzocyclopentadecen-15-yl-ethynyl)phenyl]vinyl}-3-imidazoline-3-oxide-1-oxyl (21f). The yield of compound **21f** was 90 mg (50%), mp 178.5–180.0 °C (from mixture of benzene–hexane). IR, cm^{-1}: $\nu_{max}=1253$ (N→O), 1363 (N–˙O), 2205 (C≡C). HRMS, *m/z* (%): 549.2 $[M]^+$ (15.31), 534.1 (31.71), 504.1 (24.31), 502.2 (45.38), 448.3 (12.07), 447.3 (35.54), 343.1 (11.61), 295.2 (18.03), 189.2 (6.38), 180.1 (23.58), 163.1 (33.76), 98.2 (28.67). Found: *m/z* 549.25942 $[M]^+C_{31}H_{37}N_2O_7$. Calcd: $M=549.26006$. ESR: $g_{iso}=2.0059$ ($\Delta H_{DPPH}=4.10$ G), $A_N=3.74$ G, $A_{H(CH_3)}(12H)=0.22$ G, $A(^{13}C)=5.57$ G. Solvent: toluene.

3.1.16. 2,2,5,5-Tetramethyl-4-{2-[4-(*p*-bromophenyl-ethynyl)phenyl]vinyl}-3-imidazoline-3-oxide-1-oxyl (21g). The yield of compound **21g** was 100 mg (69%), mp 192.5–193.5 °C (from benzene). IR, cm^{-1}: $\nu_{max}=1314$ (N→O), 1361 (N–˙O), 2212 (C≡C). HRMS, *m/z* (%): 437.0 $[M]^+$ (6.34), 410.1 (7.24), 407.0 (35.07), 394.0 (39.32), 391.9 (100.00), 350.9 (37.18), 349.9 (45.67), 294.9 (37.56), 257.1 (9.18), 239.1 (50.58), 176.0 (23.43), 150.0 (11.40), 135.1 (30.55), 98.1 (24.57). Found: *m/z* 437.08795 $C_{23}H_{22}N_2O_2Br$. Calcd: $M=437.08651$. ESR: $g_{iso}=2.0057$ ($\Delta H_{DPPH}=3.6$ G), $A_N=14.09$ G, $A_{H(CH_3)}(12H)=0.23$ G, $A(^{13}C)=5.72$ G. Solvent: toluene.

Acknowledgements

This work was supported by RFBR grant No 02-03-32265, grant CRDF REC No 008-XI. The Chemical Service Center of SB RAS. D.V.S. is grateful to the Science Support Foundation for awarding a personal scholarship.

References and notes

1. Buchachenko, A. L.; Berdinsky, V. L. *Chem. Rev.* **2002**, *102*, 603–612.
2. Sviridenko, F. V.; Stass, D. V.; Kobzeva, T. V.; Tretyakov, E. V.; Klyatskaya, S. V.; Mshvidobadze, E. V.; Vasilevsky, S. F.; Molin, Yu. N. *J. Am. Chem. Soc.* **2004**, *126*, 2807–2819.
3. Vasilevsky, S. F.; Klyatskaya, S. V.; Korovnikova, O. L.; Stass, D. V.; Amitina, S. A.; Grigor'ev, I. A.; Elguero, J. *Tetrahedron Lett.* **2004**, *45*, 7741–7743.
4. Klein, J.; Gurfinkel, E. *Tetrahedron* **1970**, *26*, 2127–2131.
5. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467–4470. (b) Brandsma, L.; Vasilevsky, S. F.; Verkruijsse, H. D. *Application of Transition Metal Catalysts in Organic Synthesis*; Springer: Berlin, New York, 1998.
6. Klyatskaya, S. V.; Tretyakov, E. V.; Vasilevsky, S. F. *Izv. Akad. Nauk, Ser. Khim.* **2002**, 122–127. *Russ. Chem. Bull., Int. Ed.* **2002**, *51*, 128–133.
7. Vasilevsky, S. F.; Klyatskaya, S. V.; Tretyakov, E. V.; Elguero, J. *Hererocycles* **2003**, *60*, 879–886.
8. Tretyakov, E. V.; Novikova, T. V.; Korolev, V. V.; Usov, O. M.; Vasilevsky, S. F.; Molin, Yu. N. *Izv. Akad. Nauk, Ser. Khim.* **2000**, 1415–1420. *Russ. Chem. Bull., Int. Ed.* **2000**, *49*, 1409–1414.
9. *Imidazoline Nitroxides*; Volodarsky, L. B., Ed.; Synthesis and Properties; CRC: Boca Raton, Florida, 1988; Vol. 1; pp 171–214.
10. Volodarsky, L. B.; Grigor'ev, I. A.; Grigor'eva, L. N.; Kirilyuk, I. A. *Tetrahedron Lett.* **1984**, *25*, 5809–5812.
11. Grigor'ev, I. A.; Martin, V. V.; Schukin, G. I.; Mamatyuk, V. I.; Volodarsky, L. B. *Khim Geter. Soed.* **1985**, *2*, 247–251 (Russ. Ed.). Grigor'ev, I. A.; Martin, V. V.; Schukin, G. I.; Mamatyuk, V. I.; Volodarsky, L. B. *Khim. Geter. Soed.* **1985**, *2*, 205–209.
12. Tretyakov, E. V.; Knight, D. W.; Vasilevsky, S. F. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3713–3720.
13. *An Atlas of IR Spectra of Aromatic and Heterocyclic Compounds*; Koptyug, V. A., Ed.; Institute of Organic Chemistry of Siberian Branch of Russian Academy of Sciences; Novosibirsk: Russia, 1979; Vol. 17.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 62 (2006) 4603–4614

Studies towards the biomimetic synthesis of pyridomacrolidin

Nageswara Rao Irlapati,[a] Jack E. Baldwin,[a] Robert M. Adlington,[a,*] Gareth J. Pritchard[b] and Andrew R. Cowley[a]

[a]*Chemistry Research Laboratory, Department of Chemistry, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK*
[b]*Department of Chemistry, Loughborough University, Loughborough, Leicestershire LE11 3TU, UK*

Received 16 December 2005; revised 11 January 2006; accepted 26 January 2006

Available online 28 February 2006

Abstract—A possible biomimetic synthesis of pyridomacrolidin has been proposed and experimentally supported by carrying out a model study. Regio and stereospecific [3+2] cycloaddition of an in situ generated unusual di-*tert*-butylated acyl nitrone with *Z*-2-cyclodecenone and subsequent aromatisation was the key step in our proposed biomimetic synthesis. Finally a pyridomacrolidin analogue was prepared via Friedel–Crafts di-de-*t*-butylation of the cycloadduct.

1. Introduction

As part of our ongoing program towards the biomimetic synthesis of pyridone natural products we became particularly interested in a biomimetic synthesis of pyridomacrolidin **2**. Pyridovericin **1** and pyridomacrolidin **2** are novel metabolites isolated in 1998 by Nakagawa and co-workers from the entomopathogenic fungus *Beauveria bassiana* (Fig. 1).[1]

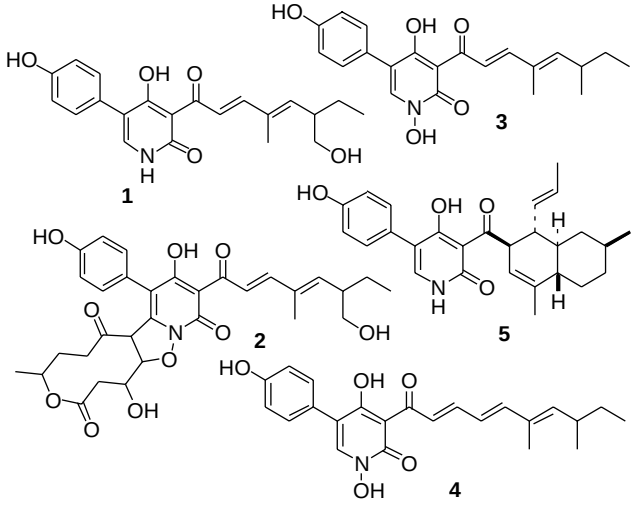


Figure 1. Pyridovericin **1**, pyridomacrolidin **2**, and related fungal metabolites.

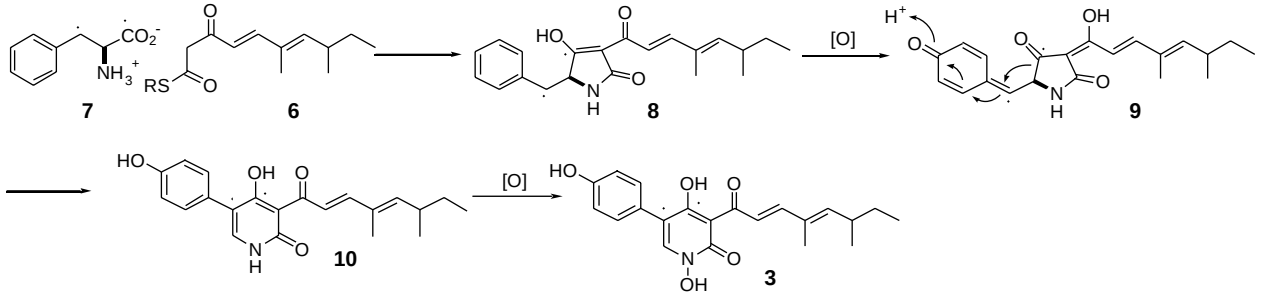
Structurally both pyridovericin **1** and pyridomacrolidin **2** contain the same *p*-hydroxyphenyl pyridone unit present in the related fungal metabolites tenellin **3**,[2] bassianin **4**,[3] and ilicicolin *H* **5**.[4] Chemically this class of compounds has elicited a significant amount of interest as demonstrated by the significant synthetic work already published.[5,6]

Biologically, pyridovericin **1** and pyridomacrolidin **2** have been shown to inhibit the protein tyrosine kinase (PTK) activity at concentrations of 100 μg/mL. PTK inhibitors are of potential use as therapeutic agents against a variety of proliferative and inflammatory diseases.[7] In common with several compounds found to inhibit PTKs, pyridovericin **1** and pyridomacrolidin **2** contain a *p*-hydroxyphenyl moiety, which presumably mimics tyrosine. Interest in these type of compounds has largely focused on the determination of the biosynthetic pathway for the generation of tenellin **3**, bassianin **4**, and ilicicolin H **5**.[8–10] Biosynthetically, it has been shown through a series feeding experiments that tenellin **3**, originates from a polyketide chain **6** and the aromatic amino acid L-phenylalanine **7**. Mechanistically, it has been proposed that L-phenylalanine **7** combines with the polyketide **6** unit to generate the acyltetramic acid intermediate **8**. Oxidation of acid **8** could then generates the transient *p*-quinonemethide intermediate **9**, which could undergo a ring expansion to generate the 2-pyridone **10**. Finally, oxidation of the newly formed pyridone unit **10** could generate tenellin **3** (Scheme 1).[7,9]

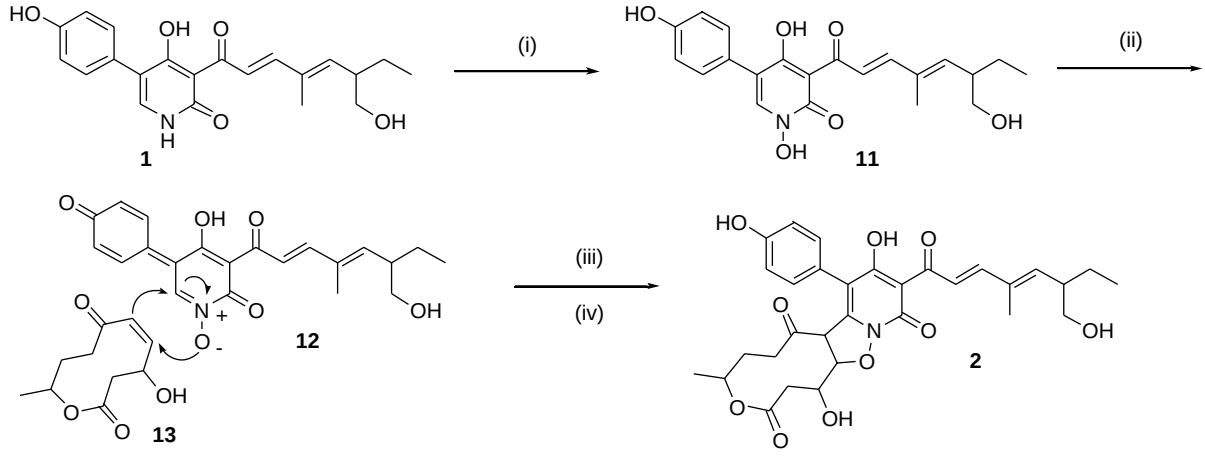
Although it is believed that the biosynthesis of pyridovericin **1** presumably follows a similar pathway as that of tenellin **3**, the biosynthesis of pyridomacrolidin **2** has not yet been

Keywords: [3+2] Cycloaddition; Pyridovericin; Pyridomacrolidin; Cephalosporolide B; Regio- and stereospecific; Friedel–Crafts dealkylation.
* Corresponding author. Tel.: +44 1865 275 626; fax: +44 1865 275 632; e-mail: robert.adlington@chem.ox.ac.uk

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.01.090



Scheme 1. Proposed biosynthesis of tenellin **3**.

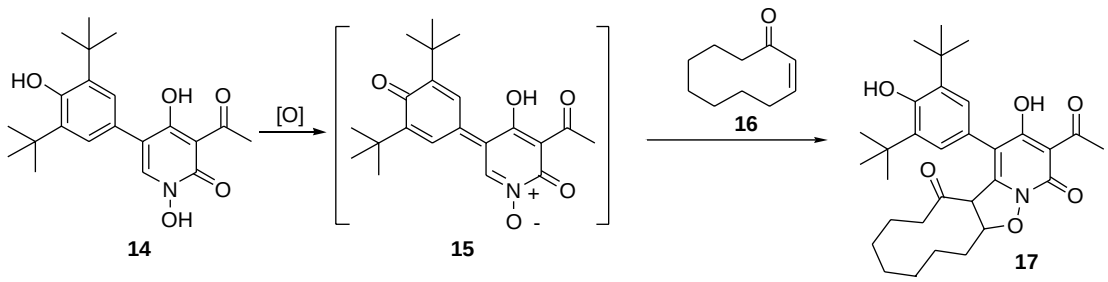


Scheme 2. Proposed biosynthesis of pyridomacrolidin **2**.

elucidated. However, it is possible to propose a biomimetic formation of pyridomacrolidin **2** from the pyridovericin **1** (which was co-isolated from the same fungus) via a number of simple steps (Scheme 2), namely, (i) oxidation of pyridovericin **1** to *N*-hydroxypyridovericin **11**, (ii) further oxidation to the novel acyl nitrone intermediate **12**, (iii) 1,3-dipolar cycloaddition[11] with cephalosporolide B **13**, and (iv) rearomatisation to form pyridomacrolidin **2**. Cephalosporolide B is itself a natural product, isolated independently from the fungus *Cephalosporium aphidicola*,[12] although it has not yet been isolated from *B. bassiana*.

2. Results and discussion

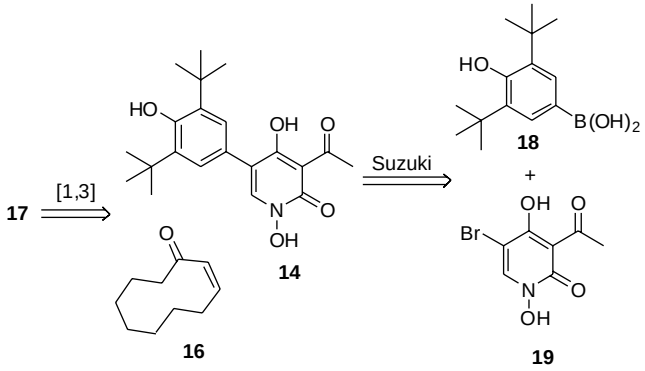
Herein, we would like to describe full details of our studies towards the biomimetic synthesis of pyridomacrolidin **2**, by reporting a model study of an unusual oxidative cyclisation, which supports such an approach to pyridomacrolidin **2**.[13] Although, 1,3-dipolar cycloadditions of nitrones with enones is well documented,[14] as far as we are aware, hitherto, such reactions have not been demonstrated from a nitrone (such as **12**) derived from the oxidation of a 5-(4-hydroxyphenyl)-*N*-hydroxy-2-pyridone (such as **11**). As initial attempts to oxidatively generate and trap unsubstituted quinonoid species similar to **12** were unsuccessful, probably due to competing additions to this highly electron deficient system as well as solubility problems, we chose to block the phenolic *ortho* positions by sterically hindering groups. The introduction of the bulky *t*-butyl groups not only increased the solubility but also provided a protective effect to minimize possible competing side reactions. Moreover, to simplify our task the C-3 side chain of the *N*-hydroxy-2-pyridone **11** was replaced by an acetyl group. Accordingly, compound **14** was targeted for oxidation to produce the corresponding nitrone **15**, from which [3+2] cycloaddition with the simple *Z*-2-cyclodecenone **16**,[15] similar to the desired enone **13** could be attempted. Subsequent aromatisation would afford the cyclised adduct **17**, a pyridomacrolidin analogue (Scheme 3).



Scheme 3.

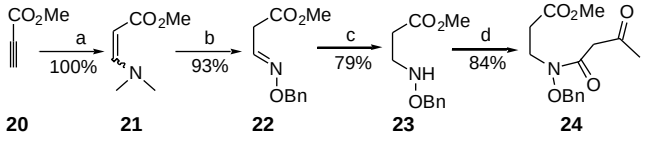
2.1. Total synthesis of di-*t*-butylated-*N*-hydroxy-2-pyridone 14

A retrosynthetic analysis reduced the target compound **14** to a Suzuki cross-coupling between boronic acid **18** and bromide **19** (Scheme 4). The bromide **19** itself should be available following (modification of) methodology developed by Williams et al.[5d]



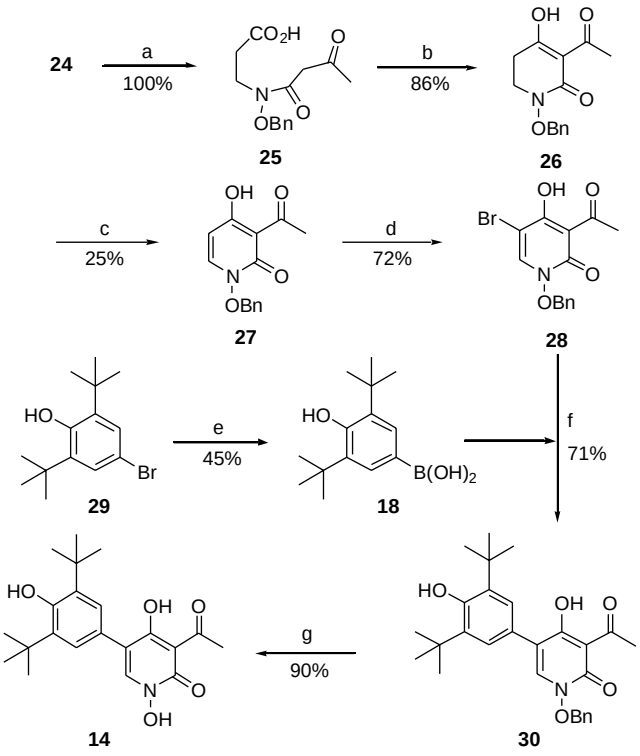
Scheme 4. Retrosynthetic scheme.

The enamine **21**[16] was prepared by passing dimethylamine gas into an ice cooled solution of methyl propiolate **20** in diethyl ether for 1 h, which on subsequent reflux with *O*-benzylhydroxylamine in xylene containing a catalytic amount of camphorsulphonic acid for 24 h afforded the oxime **22**.[17] Sodium cyanoborohydride reduction of the oxime **22** in ethanolic HCl provided the amine **23**. Acylation of the resulting amine **23** with diketene, conducted in anhydrous THF containing triethylamine and a catalytic amount of 4-(dimethylamino)-pyridine, provided the amide **24** in overall good yield (62%) over four steps (Scheme 5).



Scheme 5. Reagents and conditions: (a) $(CH_3)_2NH$, Et_2O, rt, 1 h; (b) H_2NOBn, xylene, cat. CSA, reflux, 24 h; (c) $NaCNBH_3$, EtOH·HCl, rt, 12 h; (d) diketene, cat. DMAP, Et_3N, THF, 0 °C, 30 min.

Ester hydrolysis of the amide **24** was achieved with lithium hydroxide in THF/H_2O (1:1) at rt for 2 h in quantitative yield. The resultant crude carboxylic acid **25** was treated with *N*,*N*′-carbonyldiimidazole (CDI), which after intramolecular cyclisation followed by the addition of sodium hydride yielded the 5,6-dihydropyridone **26**. Unlike the Williams chemistry precedent[5d] attempted oxidation of pyridone **26** with several oxidants (MnO_2, DDQ, *p*-chloranil, Pd/C, H_2SO_4, PhSeCl/LDA then H_2O_2) met with failure. After considerable experimentation, oxidation was achieved with lead tetraacetate[18] in 25% yield [(plus recovered **26** (40%)] to provide pyridone **27**, which on bromination[19] afforded the crucial Suzuki coupling partner **28** in good yield. The phenylboronic acid **18** required for the Suzuki coupling was prepared by the transmetallation of the commercially available 4-bromo-2,6-di-*t*-butylphenol **29** with *t*-butyl lithium and quenching of the organolithium species with triisopropyl borate, followed by acid hydrolysis. Coupling of the bromide **28** and boronic acid **18** was carried out under standard Suzuki conditions in toluene/ethanol (4:1) to yield the *N*-protected pyridone **30** in 44%. The yield of the reaction was later improved to 71% when the solvent was replaced by THF. Deprotection of benzyl group with 10% palladium on carbon in dioxane furnished the *N*-hydroxy-2-pyridone **14** in excellent yield (Scheme 6).

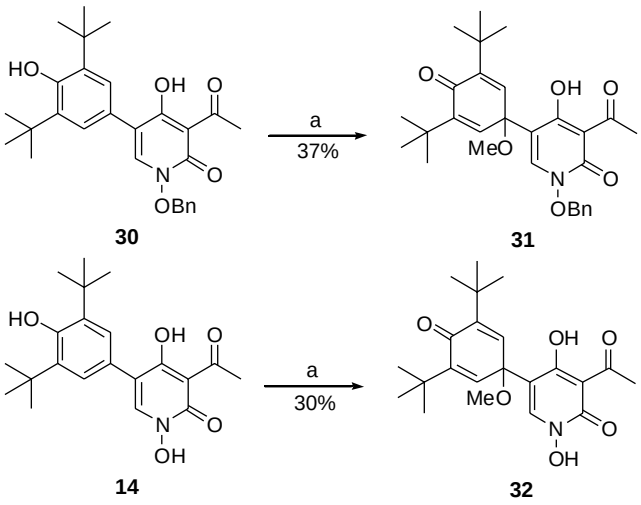


Scheme 6. Reagents and conditions: (a) LiOH, THF, H_2O, rt, 2 h; (b) CDI, THF, 12 h; NaH, rt, 5 h; (c) $Pb(OAc)_4$, benzene, 70 °C, 20 h; (d) Br_2, DCM, reflux, 12 h; (e) *t*-BuLi, $B(OCH(CH_3)_2)_3$, THF, rt, 12 h; (f) $Pd(PPh_3)_4$, 2 M Na_2CO_3, THF, reflux, 12 h; (g) 10% Pd/C, dioxane, H_2, rt, 2 h.

2.2. Oxidation of *N*-hydroxy-2-pyridone 14—[3+2] cycloaddition

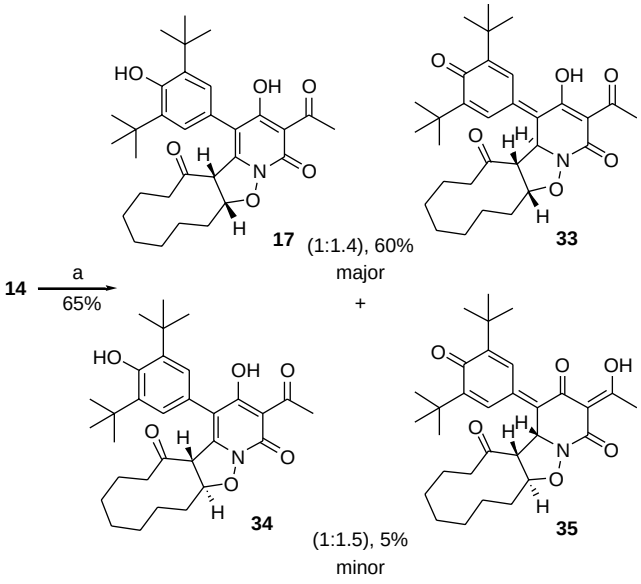
At this stage, in order to find a suitable oxidant, a few model oxidations were conducted on pyridone analogues **14** and **30**. When oxidation of benzyl-protected pyridone **30** was carried out with iodobenzene diacetate[20] in methanol there was obtained the cyclohexadienone **31** in moderate yield. Likewise oxidation of *N*-hydroxy-2-pyridone **14** in methanol gave a similar cyclohexadienone **32** in moderate yield (Scheme 7).

The results of the above oxidation revealed the feasibility of the oxidation of the di-*t*-butylated system, when the oxidation products were trapped by the nucleophilic solvent methanol. We anticipated that if the oxidation could be carried out in the presence of a dipolarophile **16** and in the absence of a nucleophilic solvent, the *N*-hydroxy-2-pyridone **14** after oxidation could undergo [3+2] cycloaddition in situ. Accordingly, oxidation of the *N*-hydroxy-2-pyridone **14** in the presence of *Z*-2-cyclodecenone **16** with



Scheme 7. Reagents and conditions: (a) $PhI(OAc)_2$, MeOH, 40 °C, 24 h.

iodobenzene diacetate in DCM at reflux temperature was attempted. Encouragingly, the unstable nitrone **15** formed by the oxidation of hydroxy pyridone **14** underwent [3+2] cycloaddition with enone **16** smoothly to give cyclized products, phenol **17** and quinone methide **33** each with a cis-ring junction in a combined 60% yield. A detailed examination of the crude reaction mixture led us to the discovery of yet two more cyclised products, namely phenol **34** and quinone methide **35** each with a trans ring junction in a 5% combined yield (Scheme 8).[13b]



Scheme 8. Reagents and conditions: (a) $PhI(OAc)_2$, *Z*-2-cyclodecenone **16**, DCM, reflux, 24 h.

2.3. Regio- and stereochemistry

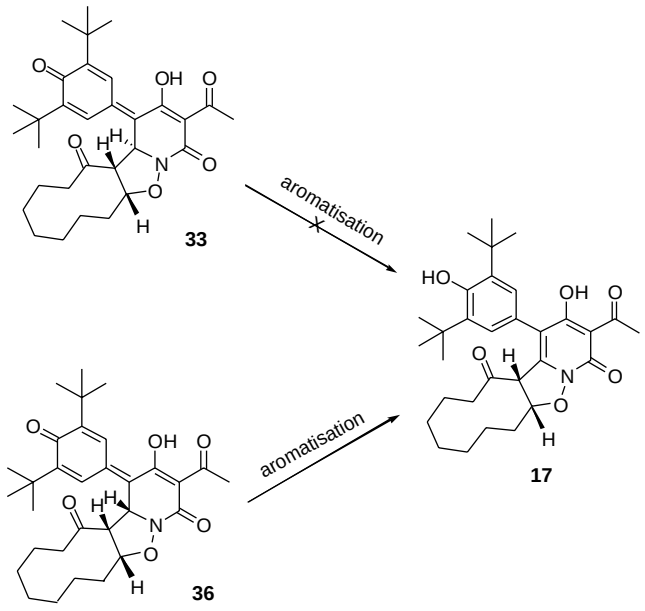
The structures and relative stereochemistry of the major cyclised products **17** and **33** were established by extensive NMR coupling experiments. The stereochemistry at the ring junction was determined as cis based on 1D quantitative NOE[13b] (strong NOE corroboration between the ring junction hydrogens; 11.3% for **17** and 11.0% for **33**), thus retaining the geometry of the enone. Later the structures and relative stereochemistry were unambiguously confirmed by single crystal crystallography.[13] It is clear from the crystal structures that the nitrogen in quinone methide **33** is pyramidal whereas in phenol **17** it is planar. The crystallographic data (of **17** and **33**) also revealed the presence of an intramolecular hydrogen bond between the hydroxyl group at the C-4 of the pyridone ring and the carbonyl oxygen of the neighbouring acetyl group.

The structures and relative stereochemistry of the minor cyclised products were established by NMR coupling experiments. The stereochemistry at the ring junction was determined as trans based on 1D quantitative NOE corroborations (weak NOE corroboration between the ring junction hydrogen; 1.2% for **34** and 2.3% for **35**). The structure and relative stereochemistry of the phenol **34** was further established by single crystal crystallography.[13b] The formation of these products can be rationalized by a two step radical or ionic mechanism. As either mechanisms are non-concerted, the formation of both *syn* and *anti* adducts are possible.

It is noteworthy that there was no evidence for formation of regioisomers arising from the reversed regiochemical pathway for the addition to the double bond, that is, the oxygen of the nitrone was added to the β-carbon of the enone in all cycloadducts. The stereochemistry of the major cyclised products (**17** and **33**) retained the geometry of the enone. No evidence of isomerisation of the enone **16** (>98% *Z*) was observed under the reaction conditions via analysis of recovered unreacted enone. This is consistent with the reaction following a concerted mechanism as the major pathway. The coupling constant of the major cis-fused phenol **17** ($J=7.0$ Hz) rather than the trans-fused phenol **34** ($J=10.5$ Hz) matches closer to the corresponding coupling constant $J=5.9$ Hz of pyridomacrolidin **2**.[1b] So the nitrone **15** derived from *N*-hydroxy-2-pyridone **14** underwent regio- and highly stereospecific [3+2] cycloaddition with enone **16** providing sound evidence for our biomimetic proposal of the pyridomacrolidin formation.

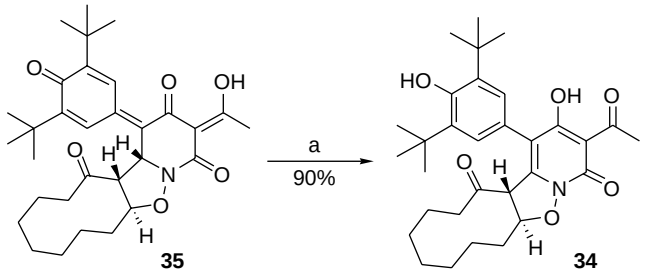
2.4. Equilibration of quinone methides 33 and 35—*exo* and *endo* mode of cycloaddition

The two cyclised products resulted from major cis fusion, **17** and **33** are in fact tautomers. Various attempts to equilibrate the two cyclised products **17** and **33** separately, in aprotic solvent, for example, DCE and protic solvent, for example, *t*-butanol, under acidic condition, for example, trifluoroacetic acid in *t*-butanol (reflux for 24 h), and under basic condition, for example, Hunig's base in *t*-butanol (reflux for 24 h) were unsuccessful. From these results, we rationalized that the products **17** and **33** were generated by means of [3+2] cycloaddition of nitrone **15** with enone **16** in two different modes, that is, *exo* and *endo* cycloaddition pathways providing two different quinone methide adducts **33** and **36** (Scheme 9).



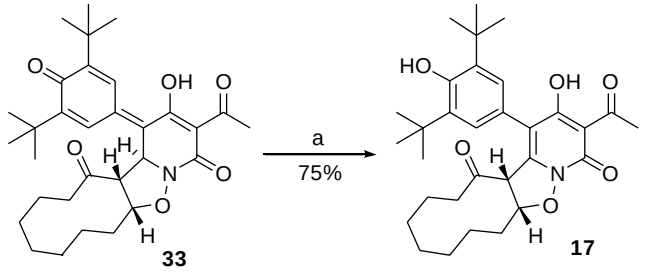
Scheme 9.

It is clear from the crystal structure of quinone methide **33** that it is *exo*. From this observation, we propose that an *endo* quinone methide **36** is formed in situ in the reaction, which subsequently undergoes further aromatization under reaction conditions to provide phenol **17**, while the *exo* adduct **33** remains intact. In this regard the activation energies associated with the aromatisation of **33** and **36** are likely to be different. On the other hand, the *trans* quinone methide **35** could be cleanly transformed into the *trans* phenol **34** by refluxing in *t*-butanol (Scheme 10).



Scheme 10. Reagents and conditions: *t*-butanol, reflux, 24 h.

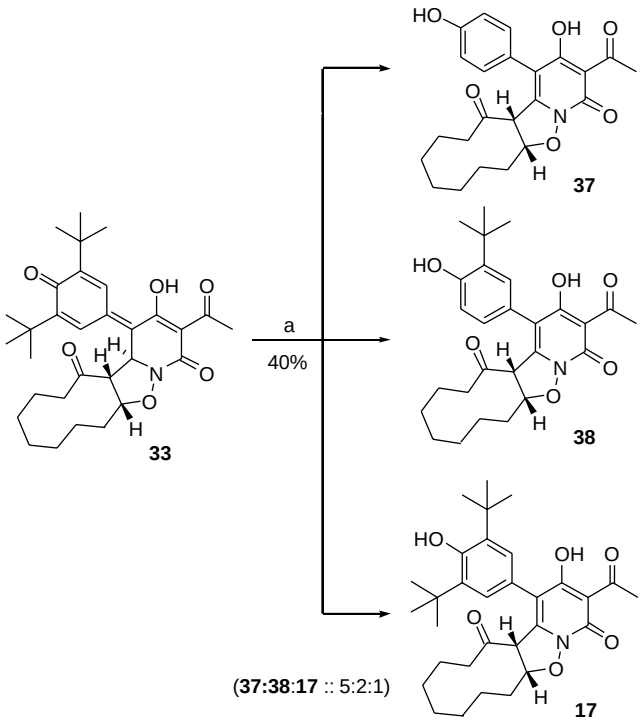
We also attempted the equilibration of *exo* quinone methide **33** using Lewis acid conditions. To our delight quinone methide **33** on treatment with aluminium chloride (2 equiv) in refluxing DCE cleanly transformed into phenol **17** (Scheme 11).



Scheme 11. Reagents and conditions: $AlCl_3$, DCE, reflux, 24 h.

2.5. Friedel–Crafts di-de-*tert*-butylation

Next, we focused our attention towards the removal of *tert*-butyl groups on the phenyl ring of **33** and **17** to produce a true pyridomacrolidin analogue. When *exo* quinone methide **33** was treated with excess of $AlCl_3$ in toluene at 95 °C for 2 days, encouragingly it underwent aromatization and subsequent dealkylation[21] giving the natural product analogue **37** along with mono dealkylated product **38** and phenol **17** in moderate yield (Scheme 12).



Scheme 12. Reagents and conditions: $AlCl_3$, toluene, 95 °C, 2 days.

Phenol **17**, when subjected to the same reaction conditions also underwent dealkylation at a slower rate but in low yield leaving most of the starting material unreacted. Though a few variations of the reaction conditions (use of *t*-butyl cation acceptors like phenol or use of nitromethane[22]) and reagents (Nafion H^+,[23] $AlBr_3$, H_3PO_4[24]) were employed it was not possible to improve the overall yield. Likewise the reaction carried out in anisole in place of toluene with an excess of $AlCl_3$ also found no further improvement.[25] Similarly, although the reaction with a catalytic amount of nitromethane in toluene with excess of $AlCl_3$ was found to be clean, it gave no appreciable improvement in terms of yield. This moderate yield of dealkylation is acceptable if we consider the presence of different functionalities, which survive these rather harsh reaction conditions. The structure of the de-alkylated product **37** was characterized by 2D NMR and was unambiguously determined by single-crystal crystallography (Fig. 2).

2.6. Reactivity of isopropylated-*N*-hydroxy-2-pyridone 43 in oxidative cyclisation

We also investigated the effect of isopropyl groups at C-2 and C-6 of the phenyl ring in our biomimetic oxidative

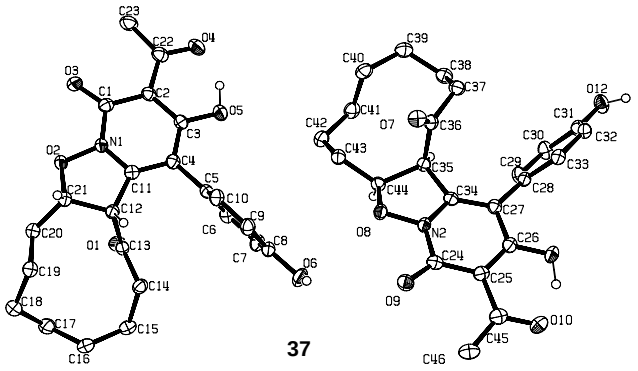
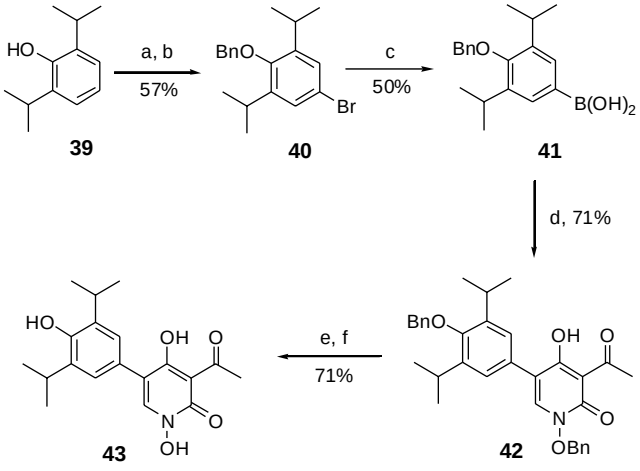


Figure 2. Crystal structure of di-de-*tert*-butylated phenol **37**.

cyclisation. The corresponding *N*-hydroxy-2-pyridone **43** was synthesized by following the methodology in analogy to the synthesis of di-*t*-butylated *N*-hydroxy-2-pyridone **14** from the readily available 2,6-di-isopropylphenol **39** (Scheme 13).



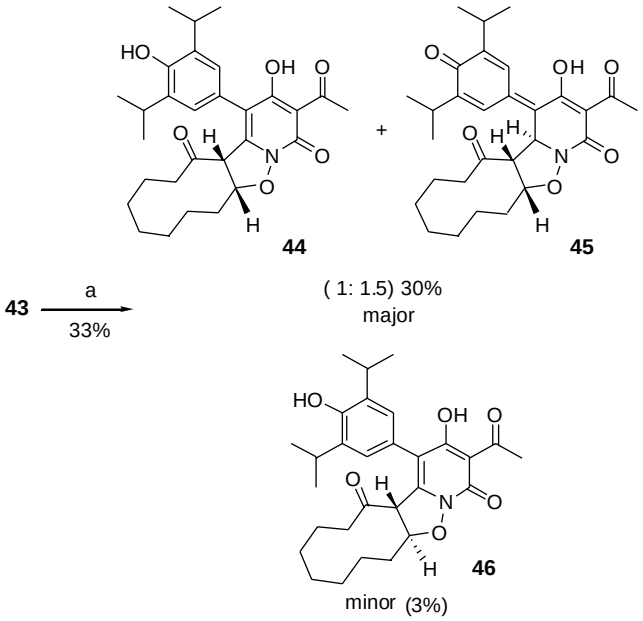
Scheme 13. Reagents and conditions: (a) Br_2, AcOH, rt, 6 h; (b) BnBr, NaH, THF, 40 °C, 12 h; (c) (i) *t*-BuLi, $(MeO)_3B$, THF, rt, overnight; (ii) satd NH_4Cl; (d) $Pd(PPh_3)_4$, Na_2CO_3, toluene: EtOH (4/1), reflux, 12 h; (e) 10% Pd/C, H_2, dioxane, rt, 2 h; (f) 1 M BBr_3 in DCM, DCM, −78 °C, 1 h.

Oxidative cyclisation of isopropylatedpyridone **43** with *Z*-2-cyclodecenone **16** under previously optimised reaction conditions afforded the cyclised products **44**–**46** in 33% combined yield with major products possessing cis ring fusion (Scheme 14).

The structure and relative stereochemistry of all the cyclised products were established by extensive proton coupling experiments and the structure and relative stereochemistry of the phenol **44** was further determined by single crystal crystallography (Fig. 3).

3. Conclusion

We have demonstrated an unusual oxidative cyclisation of the di-*t*-butylated and di-isopropylated *N*-hydroxy-2-pyridones **14** and **43** with *Z*-2-cyclodecenone **16**. This provides strong evidence for our proposed biomimetic



Scheme 14. Reagents and conditions: (a) *Z*-2-cyclodecenone **16**, $PhI(OAc)_2$, DCM, reflux, 24 h.

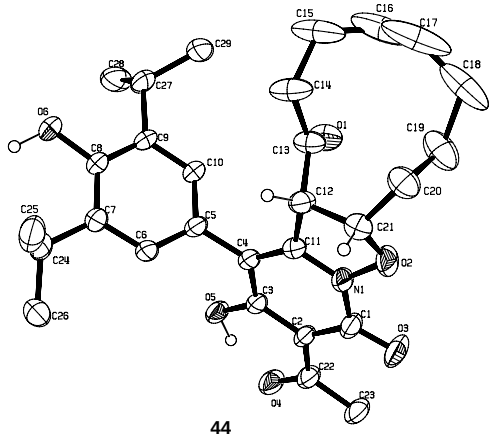


Figure 3. Crystal structure of di-isopropylated phenol **44**.

route to pyridomacrolidin **2** (Scheme 2). The successful oxidative cyclisation with *t*-butylated pyridone **14** in 65% yield and with isopropylated pyridone **43** in 33% yield compared to failure to undergo cycloaddition with unsubstituted pyridone (each with *Z*-2-cyclodecenone **16**) suggests that *t*-butyl or isopropyl groups play a crucial role in allowing the system to undergo oxidation and consecutive cycloaddition. The effect of these alkyl groups is most likely attributable to their ability to prevent possible side reactions of the nitrone intermediate, which might result in its decomposition. It may well be that in an in vivo enzyme mediated oxidation the structure of enzyme binding pocket provides a similar protective effect on the proposed key intermediate **12**. The Friedel–Crafts di-de-*t*-butylation of the phenol **17** in a *tert*-butyl cation acceptor solvent like toluene has been achieved to produce a close pyridomacrolidin **2** analogue.

4. Experimental

4.1. General methods

Melting points were recorded using a Cambridge Instruments Gallen™ III Kofler Block melting apparatus or a Buchi 510 capillary apparatus and are uncorrected. NMR spectra were recorded on a Bruker AMX-500, Bruker AV-400, Bruker DPX-400 or Varian Gemini DPX-200 spectrometers. The following abbreviations are used: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Proton assignments are supported by ^{1}H–^{1}H COSY when necessary. Data are reported in the following manner: chemical shift (multiplicity, coupling constant, integration if appropriate). Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) are given in hertz to the nearest 0.5 Hz.

^{13}C NMR spectra were recorded at 50.3, 100.6 and 125.8 MHz using Varian Gemini 200, Bruker AV-400 or Bruker AMX-500 instruments. Carbon spectra assignments are supported by DEPT-135 spectra, ^{13}C ^{1}H (HMQC and HMBC) correlations when necessary. Chemical shifts are quoted in ppm and are referenced to the appropriate residual solvent peak.

IR-spectra were recorded as a thin film on a Perkin-Elmer Paragon 1000 Fourier Transform spectrometer with internal referencing. Strong (s) medium (m) and weak (w) absorption bands are reported in wavenumbers (cm^{-1}).

High resolution mass spectrometry was measured on a Waters 2790-Micromass LCT electrospray ionisation mass spectrometer and on a VG autospec chemical ionisation mass spectrometer. Thin layer chromatography (TLC) was performed using Merck aluminium foil backed sheets precoated with Kieselgel $60F_{254}$. Column chromatography was carried out on Sorbsil™ C60 (40–63 μm, 230–400 mesh) silica gel.

All solvents and reagents were purified by standard techniques reported in Perrin, D. D.; Amarego, W. L. F. Purification of Laboratory Chemicals, 3rd ed., Pergamon, Oxford, 1988 or used as supplied from commercial sources as appropriate. Solvents were removed under reduced pressure using a Buchi R110 or R114 rotavapor fitted with a water or dry ice condenser as necessary. Final traces of solvent were removed from samples using an Edwards E2M5 high vacuum pump with pressures below 1 mm Hg.

All experiments were carried out under inert atmosphere unless otherwise stated.

4.1.1. 3-Acetyl-5-[(3′,5′-di-*t*-butyl-4′-hydroxy)phenyl]-1,4-dihydroxy-2(1*H*)-pyridone 14. A mixture of 3-acetyl-*N*-benzyloxy-5-[(3′,5′-di-*tert*-butyl-4′-hydroxy)phenyl]-4-hydroxy-2(1*H*)-pyridone **30** (120 mg, 0.26 mmol, 1.0 equiv) and 10% palladium on carbon (120 mg) in dioxane (5 mL) was stirred under a hydrogen (balloon) atmosphere at 25 °C for 2 h. The reaction mixture was filtered, the solid residue was washed with dioxane (20 mL) and the combined filtrates evaporated under vacuum. The crude product was purified by flash column chromatography [silica gel, 3% ethyl acetate in DCM (silica gel having been pre-washed by being allowed to stand as a slurry in 50% aqueous nitric acid for 24 h followed by rinsing with doubly distilled water until the aqueous filtrates were neutral. Subsequent trituration with reagent grade acetone was followed by drying in vacuum at 25 °C for 24 h)] gave 87 mg (90%) of the desired title compound **14** as a yellow solid, mp 255 °C. ν_{max} (neat)/cm^{-1} 3635w, 3094w, 2958m, 1644s, 1610m, 1547w, 1433m, 1414m, 1237m, 1142m, 909w; δ_H (250 MHz, $CDCl_3$) 1.49 (s, 18H), 2.85 (s, 3H), 5.37 (s, 1H), 7.27 (s, 2H), 7.89 (s, 1H); δ_C (62.5 MHz, $CDCl_3$) 30.6, 32.1, 34.8, 106.3, 114.1, 123.0, 126.4, 134.1, 136.4, 154.4, 157.9, 171.8, 205.9; *m/z* (ESI-) 372 [$(M-H)^-$, 100%]; HRMS: found 372.1805 $(M-H)^-$. $C_{21}H_{26}NO_5$ requires 372.1811.

4.1.2. 3,5-Di-*tert*-butyl-4-hydroxyphenylboronic acid 18. To a −78 °C cooled solution of 4-bromo-2,6-di-*tert*-butyl phenol (1.00 g, 3.51 mmol, 1.0 equiv) in THF (25 mL) was added dropwise a 1.5 M solution of *tert*-butyl lithium in hexanes (7.0 mL, 10.5 mmol, 3.0 equiv). The reaction mixture was stirred for 1 h at 25 °C and then cooled down to −78 °C prior to the addition of tri-isopropyl borate (2.43 mL, 10.5 mmol, 3.0 equiv). The reaction was left overnight at 25 °C prior to the addition of saturated ammonium chloride solution (50 mL). The resulting mixture was stirred at 25 °C for 2 h and the layers separated. The aqueous layer was extracted with ethyl acetate (3× 25 mL) and the combined organic layers were washed with brine (25 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum and the crude product was purified by recrystallization (30% ethyl acetate in hexane) to yield 400 mg (45%) of the title compound **18** as a white solid, mp >250 °C. ν_{max} (neat)/cm^{-1} 3424brm, 2959m, 1599m, 1481m, 1417s, 1343m, 1231s, 1155m, 1122m, 778m; δ_H (400 MHz, $CDCl_3$) 1.55 (s, 18H), 5.64 (s, 1H), 8.13 (s, 2H); δ_C (100.6 MHz, $CDCl_3$) 30.1, 34.2, 132.7, 135.1, 157.9; *m/z* (ESI-) 249 [$(M-H)^-$, 100%]; HRMS: found 249.1658 $(M-H)^-$. $C_{14}H_{22}BO_3$ requires 249.1662.

4.1.3. Methyl-3-(*O*-benzyloxyimino)-propanoate 22.[17] To a solution of methyl-3-(*N*,*N*′-dimethylamino)-2-propeonate **21**[16] (5.52 g, 42.7 mmol) in xylene (50 mL) was added *O*-benzylhydroxylamine (5.26 g, 42.8 mmol, 1.0 equiv) followed by a catalytic amount of camphorsulphonic acid (248 mg, 1.07 mmol, 0.025 equiv). The resulting solution was heated at reflux for 24 h. After cooling to rt (25 °C), the solvent was removed under vacuum, and the crude product was purified by flash column chromatography (silica gel, 10% diethyl ether in 30–40 petroleum ether) to yield the 8.26 g (93%) of the known[17] methyl-3-(*O*-benzyloxyimino)-propanoate **22** as a (1:1.5) mixture of inseparable isomers as a clear oil. ν_{max} (neat)/cm^{-1} 3032m, 2953m, 1743s, 1455m, 1437s, 1350m, 1256m, 1200m, 1172m; δ_H (400 MHz, $CDCl_3$) 3.27 (d, J=6.5 Hz, 0.8H), 3.44 (d, J=5.0 Hz, 1.2H), 3.72 (s, 1.2H), 3.73 (s, 1.8H), 5.09 (s, 0.8H), 5.15 (s, 1.2H), 7.03 (t, J=5.0 Hz, 0.4H), 7.29–7.39 (m, 5H), 7.57 (t, J=6.5 Hz, 0.6H); δ_C (100.6 MHz, $CDCl_3$) 31.3, 34.9, 52.1, 52.2, 75.9, 76.1, 127.9, 128.0, 128.2 (2C), 128.4 (2C), 137.3, 137.5, 143.6, 144.1, 169.6; *m/z* (APCI+) 208 (MH^+, 100%).

4.1.4. Methyl-3-(*O*-benzyloxyamino)-propanoate 23. To a solution of methyl-3-(*O*-benzyloxyimino)-propanoate **22**[17] (8.26 g, 39.9 mmol, 1.0 equiv) in ethanol (80 mL) containing bromothymol blue indicator was added 1 N hydrochloric acid (40 mL) until a yellow precipitate formed. Sodium cyanoborohydride (3.77 g, 60.0 mmol, 1.5 equiv) was then added portionwise to the above reaction mixture at 0 °C. The reaction was then brought to rt, and stirred overnight. The reaction mixture was diluted with water (80 mL) and the aqueous layer extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum. The crude product was purified by flash column chromatography (silica gel, 30% diethyl ether in 30–40 petroleum ether) to yield 6.63 g (79%) of the title compound **23** as a clear oil. ν_{max} (neat)/cm^{-1} 2951m, 1736s, 1496w, 1438m, 1364m, 1176m, 1018m; δ_H (400 MHz, $CDCl_3$) 2.59 (t, J=7.0 Hz, 2H), 3.08 (t, J=7.0 Hz, 2H), 3.67 (s, 3H), 4.68 (s, 2H), 7.38 (s, 5H); δ_C (100.6 MHz, $CDCl_3$) 32.0, 47.4, 51.6, 76.1, 127.8, 128.3 (2C), 137.7, 172.9; *m/z* (APCI+) 210 (MH^+, 100%).

4.1.5. Methyl-3-(*N*-benzyloxy-*N*-(3-oxo-butyryl)amino)-propanoate 24. To a solution of methyl-3-(*O*-benzylhydroxylamino)propanoate **23** (6.64 g, 31.7 mmol, 1.0 equiv) in THF (65 mL) was added 4-(dimethylamino)pyridine (390 mg, 3.20 mmol, 0.1 equiv), followed by triethylamine (4.42 mL, 31.7 mmol, 1.0 equiv) at 25 °C under argon. Diketene (3.65 mL, 47.6 mmol, 1.5 equiv) was added in small portions over 30 min via syringe pump to the above reaction mixture at −78 °C. After stirring for 30 min at −78 °C, the reaction mixture was warmed to 0 °C, stirred for an additional 30 min and the resulting orange solution was diluted with saturated aqueous ammonium chloride solution (50 mL) and extracted with ethyl acetate (3× 100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum and the crude product was purified by flash column chromatography (silica gel, 50% diethyl ether in 30–40 petroleum ether) to yield 7.80 g (84%) of the desired title compound **24** as a mixture of inseparable tautomers as a syrupy oil. ν_{max} (neat)/cm^{-1} 2952m, 1736s, 1664s, 1438m, 1361m, 1175m; δ_H (400 MHz, $CDCl_3$) 1.95 (s, 0.5H), 2.15 (s, 2.5H), 2.60 (t, J=7.0 Hz, 0.2H), 2.64 (t, J=7.0 Hz, 1.8H), 3.45 (s, 1.8H, keto tautomer), 3.63, 3.64 (2×s, 3H), 3.94 (t, J=7.0 Hz, 0.2H), 4.01 (t, J=6.5 Hz, 1.8H), 4.81, 4.82 (2×s, 2H), 5.40 (s, 0.2H, enol tautomer), 7.33–7.42 (m, 5H); δ_C (100.6 MHz, $CDCl_3$) 22.2, 30.1, 31.5, 31.9, 41.2, 41.5, 49.0, 51.7, 51.8, 76.4, 87.2, 128.6, 128.7, 128.9 (2C), 129.1, 129.4, 133.8, 169.6, 171.9, 201.3; *m/z* (ESI+) 294 (MH^+, 100%); HRMS: found 294.1345 (MH^+). $C_{15}H_{20}NO_5$ requires 294.1341.

4.1.6. 3-(*N*-Benzyloxy-*N*-(3-oxo-butyryl)amino)-propanoic acid 25. To a solution of methyl-3-(*N*-benzyloxy-*N*-(3-oxo-3-butyryl)amino)-propanoate **24** (7.80 g, 26.6 mmol, 1.0 equiv) in a 1:1 mixture of THF and H_2O (150 mL) was added lithium hydroxide monohydrate (5.59 g, 133 mmol, 5 equiv) and the reaction was stirred at 25 °C for 2 h. The reaction mixture was diluted with ethyl acetate (100 mL) and the organic layer was extracted with water (3×100 mL). The combined aqueous extracts were acidified with 1 N hydrochloric acid (50 mL, pH 2.0) and re-extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum to yield 7.42 g (100%) of the title compound **25** as a mixture of inseparable tautomers as a gum. The crude product was used for next step without further purification ν_{max} (Neat)/cm^{-1} 3450m, 3034m, 1723s, 1654brs, 1418m, 1185w; δ_H (400 MHz, $CDCl_3$) 1.98 (s, 0.5H), 2.14 (s, 2.5H), 2.64 (t, J=7.0 Hz, 0.35H), 2.69 (t, J=7.0 Hz, 1.65H), 3.46 (s, 1.80H), 3.93 (t, J=7.0 Hz, 0.35H), 4.00 (t, J=6.5 Hz, 1.65H), 4.82, 4.83 (2×s, 2H), 5.40 (s, 0.2H), 7.18–7.59 (m, 5H); δ_C (100.6 MHz, $CDCl_3$) 30.1, 31.4, 31.8, 41.0, 48.9, 76.5 76.6, 87.2, 128.7, 128.8, 128.9, 129.1, 129.2, 129.4, 134.5, 135.2, 169.6, 176.4, 189.1, 191.2, 201.5; *m/z* (ESI+) 280 (MH^+, 100%); HRMS: found 280. 1192 (MH^+). $C_{14}H_{18}NO_5$ requires 280.1185.

4.1.7. 3-Acetyl-*N*-benzyloxy-5,6-dihydro-4-hydroxy-2(1*H*)-pyridone 26. To a solution of 3-(*N*-benzyloxy-*N*-(3-oxobutyryl)amino)propanoic acid **25** (7.42 g, 26.6 mmol, 1.0 equiv) in THF (75 mL) at 0 °C was added portionwise 1,1′-carbonyl diimidazole (5.17 g, 31.9 mmol, 1.2 equiv) and the resulting mixture was stirred at 25 °C for 12 h. The reaction mixture was cooled to 0 °C and sodium hydride (2.76 g, 69.2 mmol, 2.6 equiv, 60% dispersion in oil) was added portionwise. The resulting mixture was stirred at 25 °C for 5 h. Water (50 mL) was added to the above reaction mixture, which was then acidified with 1 N hydrochloric acid (pH 2.0, 50 mL). The aqueous layer was extracted with ethyl acetate (3×100 mL) and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum to afford the crude product, which was purified by flash column chromatography (silica gel, 50% diethyl ether in 30–40 petroleum ether) to yield 6.0 g (86%) of the desired title compound **26** as a white solid and as a (1:1) mixture of tautomers, mp 56–57 °C. ν_{max} (neat)/cm^{-1} 2960m, 1671s, 1555s, 1449m, 1224w; δ_H (400 MHz, $CDCl_3$) 2.52 (t, J= 6.5 Hz, 1H), 2.53 (s, 1.5H), 2.65 (t, J=6.5 Hz, 1H), 2.67 (s, 1.5H), 3.39 (t, J=6.5 Hz, 1H), 3.44 (t, J=6.5 Hz, 1H), 4.99 (s, 1H), 5.03 (s, 1H), 7.34–7.41 (m, 2.5H), 7.42–7.49 (m, 2.5H); δ_C (100.6 MHz, $CDCl_3$) 24.4, 26.8, 33.5, 33.8, 45.7, 46.0, 76.7, 102.1, 105.7, 128.4, 128.6, 128.7, 129.1, 129.6, 129.7, 134.8, 135.6, 165.5, 172.1, 190.3, 192.1, 194.4, 199.5; *m/z* (ESI-) 260 [$(M-H)^-$, 100%]; HRMS: found 260.0928 $(M-H)^-$. $C_{14}H_{14}NO_4$ requires 260.0923.

4.1.8. 3-Acetyl-*N*-benzyloxy-4-hydroxy-2(1*H*)-pyridone 27. To a solution of 3-acetyl-*N*-benzyloxy-5,6-dihydro-4-hydroxy-2(1*H*)-pyridone **26** (1.00 g, 3.83 mmol, 1.0 equiv) in benzene (15 mL) was added lead tetraacetate (1.70 g, 3.83 mmol, 1.0 equiv) and the reaction mixture was stirred at 70 °C for 20 h. After cooling to 25 °C, the reaction mixture was filtered and the solid residue was washed with ethyl acetate (50 mL). The combined filtrates were evaporated under vacuum and the crude product was purified by flash column chromatography (silica gel, 20% diethyl ether in 30–40 petroleum ether and 30% ethyl acetate in 30–40 petroleum ether) to afford 250 mg (25%) of the desired title compound **27** as a white solid, mp 105 °C, and 400 mg (40%) of unreacted 3-acetyl-*N*-benzyloxy-5,6-dihydro-4-hydroxy-2(1*H*)-pyridone **26** as a white solid. ν_{max}

(neat)/cm^{-1} 2960m, 1664s, 1613s, 1551m, 1468m, 1386m, 1355m, 1220w, 1165w, 960w; δ_H (400 MHz, $CDCl_3$) 2.80 (s, 3H), 5.22 (s, 2H), 5.69 (d, $J=8.0$ Hz, 1H), 7.18 (d, $J=8.0$ Hz, 1H), 7.41 (s, 5H); δ_C (100.6 MHz, $CDCl_3$) 31.6, 78.9, 98.3, 108.4, 128.9, 129.5, 130.1, 133.4, 142.1, 154.1, 175.6, 204.8; *m/z* (ESI-) 258 [$(M-H)^-$, 100%]; HRMS: found 258.0769 $(M-H)^-$. $C_{14}H_{12}NO_4$ requires 258.0766.

4.1.9. 3-Acetyl-*N*-benzyloxy-5-bromo-4-hydroxy-2(1*H*)-pyridone 28. To a solution of 3-acetyl-*N*-benzyloxy-4-hydroxy-2(1*H*)-pyridone **27** (800 mg, 3.09 mmol, 1.0 equiv) in DCM (10 mL) was added dropwise a solution of bromine (0.17 mL, 3.39 mmol, 1.1 equiv) in DCM (0.5 mL) and the resulting mixture was heated at reflux for 12 h. The reaction mixture was cooled down to 25 °C before the addition of water (20 mL). The phases were separated and the aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum to afford the crude product which was purified by flash column chromatography (silica gel, 20% diethyl ether in 30–40 petroleum ether) to yield 750 mg (72%) of the desired title compound **28** as a white solid, mp 122 °C. ν_{max} (neat)/cm^{-1} 3082m, 1673s, 1599s, 1528m, 1454m, 1381m, 1223m, 968.5m; δ_H (400 MHz, $CDCl_3$) 2.79 (s, 3H), 5.21 (s, 2H), 7.41 (s, 5H), 7.52 (s, 1H); δ_C (100.6 MHz, $CDCl_3$) 31.1, 79.4, 90.1, 107.9, 128.9, 129.8, 130.0, 132.9, 142.5, 157.6, 172.7, 205.7; *m/z* (ESI-) 338, 336 $(M-H)^-$, 100%]; HRMS: found 335.9871 [$M(^{79}Br)-H]^-$ $C_{14}H_{11}BrNO_4$ requires 335.9871.

4.1.10. 3-Acetyl-*N*-benzyloxy-5-[(3′,5′-di-*t*-butyl-4′-hydroxy)phenyl]-4-hydroxy-2(1*H*)-pyridone 30. To a solution of 3,5-di-*tert*-butyl-4-hydroxyphenylboronic acid **18** (156 mg, 0.62 mmol, 1.0 equiv) and 3-acetyl-*N*-benzyloxy-5-bromo-4-hydroxy-2(1*H*)-pyridone **28** (214 mg, 0.63 mmol, 1.0 equiv) in THF (1.25 mL) was added 2 M aqueous sodium carbonate solution (1.25 mL) followed by tetrakis(triphenylphosphine)palladium(0) (37 mg, 0.03 mmol, 0.05 equiv). The reaction mixture was then heated at reflux for 12 h before cooling to 25 °C and partitioned in a 1:1 mixture of ethyl acetate/water (30 mL). The phases were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum and the crude residue was purified by flash column chromatography (silica gel, 3% ethyl acetate in DCM) to yield 205 mg (71%) of the desired title compound **30** as a yellow solid, mp 230–232 °C. ν_{max} (neat)/cm^{-1} 3632w, 2957m, 1663s, 1608m, 1536m, 1436m, 1414m, 1376w, 1226m, 1120m; δ_H (400 MHz, $CDCl_3$) 1.42 (s, 18H), 2.86 (s, 3H), 5.29 (s, 2H+OH), 6.95 (s, 2H), 7.21 (s, 1H), 7.39–7.44 (m, 5H); δ_C (100.6 MHz, $CDCl_3$) 30.1, 31.6, 34.2, 78.6, 108.1, 113.3, 122.1, 125.8, 128.9, 129.7, 130.2, 134.0, 135.8, 140.6, 153.8, 158.1, 173.8, 206.1; HRMS: found 462.2271 $(M-H)^-$. $C_{28}H_{32}NO_5$ requires 462.2280.

4.1.11. 3-Acetyl-*N*-benzyloxy-5-[(3′,5′-di-*tert*-butyl-1′-methoxy-4′-oxo)-2,5-cyclohexadienyl]-4-hydroxy-2(1*H*)-pyridone 31. To a clear solution of 3-acetyl-*N*-benzyloxy-5-[(3′,5′-di-*tert*-butyl-4′-hydroxy)phenyl]-4-hydroxy-2(1*H*)-pyridone **30** (14 mg, 0.03 mmol, 1.0 equiv) in MeOH (2 mL) was added iodobenzene diacetate (11 mg, 0.033 mmol, 1.1 equiv) and the reaction mixture was stirred at 40 °C for 24 h. After cooling to rt (25 °C), the solvent was removed under vacuum and the residue was dissolved in ethyl acetate (5 mL). The organic layer was washed with water (5 mL), brine (5 mL) dried ($MgSO_4$), filtered and the filtrate was evaporated under vacuum. The crude product was purified by flash column chromatography (silica gel, 15% ethyl acetate in 30–40 petroleum ether) to yield 5.5 mg (37%) of quinone methide **31** as a yellow solid, mp 224–225 °C. ν_{max} (neat)/cm^{-1} 2956m, 1731m, 1668s, 1650m, 1635m, 1611m, 1457w; δ_H (400 MHz, $CDCl_3$) 1.23 (s, 18H), 2.77 (s, 3H), 3.15 (s, 3H), 5.26 (s, 2H), 6.02 (s, 2H), 7.32–7.45 (m, 5H), 7.73 (s, 1H); *m/z* (ESI-) 492 [$(M-H)^-$, 100%]; HRMS: found 492.2388 $(M-H)^-$. $C_{29}H_{34}NO_6$ requires 492.2386.

4.1.12. 3-Acetyl-5-[(3′,5′-di-*tert*-butyl-1′-methoxy-4′-oxo)-2,5-cyclohexadienyl]-1,4-dihydroxy-2(1*H*)-pyridone 32. To a solution of 3-acetyl-5-[(3′,5′-di-*tert*-butyl-4′-hydroxy)phenyl]-1,4-dihydroxy-2(1*H*)-pyridone **14** (10 mg, 0.027 mmol, 1.0 equiv) in MeOH (2 mL) was added iodobenzene diacetate (9 mg, 0.028 mmol, 1.05 equiv) and the reaction mixture was stirred at 40 °C for 24 h. After cooling to rt (25 °C), the solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (5 mL). The organic layer was washed with water (5 mL), brine (5 mL) dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum and the crude product was purified by flash column chromatography (silica gel, 3–5% methanol in DCM) to yield 3.2 mg (30%) of quinone methide **32** as a yellow solid, mp 235–237 °C. ν_{max} (neat)/cm^{-1} 2956m, 1731m, 1668s, 1650m, 1635m, 1611m, 1457w; δ_H (200 MHz, $CDCl_3$) 1.21 (s, 18H), 2.72 (s, 3H), 3.24 (s, 3H), 5.28 (s, 1H), 6.12 (s, 2H), 8.33 (s, 1H); *m/z* (ESI-) 402 [$(M-H)^-$, 100%]; HRMS: found 402.1921 $(M-H)^-$. $C_{22}H_{28}NO_6$ requires 402.1917.

4.1.13. Preparation of de-*tert*-butylated phenols 37 and 38. To a solution of toluene (2 mL) containing *exo*-quinone methide **33**[13] (20 mg, 0.038 mmol) was added aluminium chloride (23 mg, 0.172 mmol, 4.5 equiv) and stirred the reaction at 95 °C for 2 days. After cooling to rt, the reaction mixture was poured into crushed ice, 1 N hydrochloric acid was added (0.3 mL) and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum. The crude product was purified by flash column chromatography [silica gel, 0.2–1% methanol in DCM as a gradient elution, (Silica gel had been prewashed by being allowed to stand as a slurry in 50% aqueous nitric acid for 24 h followed by rinsing with doubly distilled water until the aqueous filtrates were neutral. Subsequent trituration with reagent grade acetone was followed by drying in vacuum at 25 °C)] to yield 4 mg (25%) of di-dealkylated phenol **37** as a pale brown solid recrystallized from 10% methanol in benzene, mp 202–203 °C, 1.7 mg (10%) of mono-dealkylated phenol **38** as a pale brown solid, mp 196–197 °C and 1.0 mg (5%) of phenol **17**[13] as a pale yellow solid. The structure of phenol **37** was determined by single-crystal crystallography.

Di-de-t-butylated phenol **37**. ν_{max} (neat)/cm^{-1} 3243brm, 2938m, 1704w, 1647s, 1612s, 1541w, 1516m, 1428m, 1272m, 1263m; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 1.05–1.11 (m, 2H), 1.17–1.28 (m, 1H), 1.30–1.80 (m, 9H), 2.02–2.11 (m, 2H), 2.81 (s, 3H), 4.72–4.78 (m, 1H), 4.94 (d, J=7.0 Hz, 1H), 5.72 (brs, 1H), 6.96 (d, J=8.5 Hz, 2H), 7.18 (d, J=8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 22.4, 22.8, 22.9, 23.0, 24.5, 26.8, 31.4, 45.5, 55.9, 84.3, 107.1, 107.8, 116.1, 122.8, 131.3, 144.9, 154.3, 156.3, 173.1, 204.9, 205.4; *m/z* (ESI+) 412 (MH^+, 100%); HRMS: found 412.1755 (MH^+). $C_{23}H_{26}NO_6$ requires 412.1760.

Monode-alkylated phenol **38**. ν_{max} (neat)/cm^{-1} 3243brm, 2939m, 1705w, 1648s, 1613s, 1541w, 1515m, 1428m, 1272m, 1263m; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.05–1.11 (m, 2H), 1.17–1.28 (m, 1H), 1.30–1.80 (m, 18H), 2.02–2.13 (m, 2H), 2.82 (s, 3H), 4.75–4.79 (m, 1H), 4.89 (d, J=7.5 Hz, 1H), 5.02 (s, 1H), 6.77 (d, J=8.0 Hz, 1H), 7.01 (dd, J=8.0, 2.0 Hz, 1H), 7.15 (d, J=2.0 Hz, 1H,); *m/z* (ESI-) 466 [$(M-H)^-$, 100%); HRMS: found 466.2231 $(M-H)^-$. $C_{27}H_{32}NO_6$ requires 466.2230.

4.1.14. 4-Benzyloxy-3,5-di-isopropylbromobenzene 40. To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 176 mg, 4.41 mmol, 1.2 equiv) in THF (10 mL) at 0 °C was added dropwise a solution of 4-bromo-2,6-di-isopropylphenol[26] (0.94 g, 3.67 mmol, 1.0 equiv). After stirring for 1 h at 25 °C, the reaction mixture was cooled down to 0 °C prior to the addition of benzyl bromide (0.46 mL, 3.85 mmol, 1.05 equiv). The resulting mixture was stirred at 40 °C for 12 h. The reaction mixture was cooled to rt before the addition of water (20 mL) and the aqueous layer was extracted with diethyl ether (3×15 mL). The combined organic layers were washed with water (2×10 mL), brine (10 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum. The crude product was purified by flash column chromatography (silica gel, 2% diethyl ether in 30–40 petroleum ether) to yield 1.10 g (86%) of title compound **40** as a clear oil. ν_{max} (neat)/cm^{-1} 2963s, 1574m, 1497m, 1456s, 1325s, 1184s; δ_H (400 MHz, $CDCl_3$) 1.25 (d, J=7.0 Hz, 12H), 3.39 (septet, J=7.0 Hz, 2H), 4.83 (s, 2H), 7.27 (s, 2H), 7.41 (t, J=7.0 Hz, 1H), 7.47 (t, J=7.0 Hz, 2H), 7.52 (d, J=7.0 Hz, 2H); δ_C (100.6 MHz, $CDCl_3$) 23.9, 26.8, 76.5, 118.1, 127.3, 127.4, 128.1, 128.4, 137.3, 144.4, 152.2.

4.1.15. 4-Benzyloxy-3,5-di-isopropylphenylboronic acid 41. To a −78 °C cooled solution of 4-benzyloxy-3,5-di-isopropylbromobenzene **40** (1.00 g, 2.89 mmol, 1.0 equiv) in THF (25 mL) was added dropwise a 1.5 M solution of *tert*-butyl lithium in hexanes (4.04 mL, 6.06 mmol, 2.1 equiv). The reaction mixture was brought to 25 °C and after stirring for 1 h at 25 °C, the reaction mixture was cooled to −78 °C prior to the addition of trimethyl borate (0.97 mL, 8.67 mmol, 3.0 equiv). The reaction was left overnight at 25 °C prior to the addition of saturated ammonium chloride solution (50 mL). The resulting mixture was stirred at 25 °C for 2 h and the aqueous layer was extracted with ethyl acetate (3×25 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum. The crude product was purified by recrystallization (30% ethyl acetate in hexane) to yield 450 mg (50%) of the title compound **41** as a white solid, mp >250 °C. ν_{max} (neat)/cm^{-1} 3377brm, 2961s, 1600m, 1360s, 1316s, 1295s, 1181s, 1022m; δ_H (400 MHz, $CDCl_3$) 1.36 (d, J=7.0 Hz, 12H), 3.49 (septet, J=7.0 Hz, 2H), 4.90 (s, 2H), 7.40 (t, J=7.0 Hz, 1H), 7.47 (t, J=7.0 Hz, 2H), 7.53 (d, J=7.0 Hz, 2H), 8.07 (s, 2H); δ_C (100.6 MHz, $CDCl_3$) 24.1, 26.6, 76.4, 127.4, 128.0, 128.6, 131.7, 137.4, 141.5, 157.2; *m/z* (ESI-) 311 [$(M-H)^-$, 100%]; HRMS: found 311.1824 $(M-H)^-$. $C_{19}H_{24}BO_3$ requires 311.1819.

4.1.16. 3-Acetyl-*N*-benzyloxy-5-[(4′-benzyloxy-3′,5′-di-isopropyl)phenyl]-4-hydroxy-2(1*H*)-pyridone 42. To a solution of 4-benzyloxy-3,5-di-isopropylphenylboronic acid **41** (92 mg, 0.29 mmol, 1.0 equiv), and 3-acetyl-*N*-benzyloxy-5-bromo-4-hydroxy-2-pyridone **28** (98 mg, 0.29 mmol, 1.0 equiv) in 4:1 mixture of toluene/ethanol (1.25 mL) was added a 2 M aqueous sodium carbonate solution (1.25 mL), followed by tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.014 mmol, 0.05 equiv). The resulting mixture was heated at reflux for 12 h before being cooled to rt and partitioned in a 1:1 mixture of ethyl acetate/water (20 mL). The phases were separated, and the organic layer was washed with brine (10 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum. The crude product was purified by flash column chromatography (silica gel, 3% ethyl acetate in DCM) to yield 110 mg (71%) of the title compound **42** as a yellow gum. ν_{max} (neat)/cm^{-1} 2963s, 1668s, 1609s, 1536m, 1454m, 1413m, 1377m, 1308m, 1223m; δ_H (400 MHz, $CDCl_3$) 1.26 (d, J=7.0 Hz, 12H), 2.89 (s, 3H), 3.42 (septet, J=7.0 Hz, 2H), 4.83 (s, 2H), 5.33 (s, 2H), 6.90 (s, 2H), 7.21 (s, 1H), 7.38–7.51 (m, 10H); δ_C (100.6 MHz, $CDCl_3$) 24.1, 26.6, 31.6, 76.5, 78.8, 107.9, 112.6, 124.9, 127.4, 127.9, 128.0, 128.5, 129.0, 129.8, 130.5, 133.7, 137.5, 141.0, 142.0, 153.0, 158.1, 174.0, 206.1; HRMS: found 524.2434 $(M-H)^-$. $C_{33}H_{34}NO_5$ requires 524.2437.

4.1.17. 3-Acetyl-1,4-dihydroxy-5-[(3′,5′-di-isopropyl-4′-hydroxy)phenyl]-2(1*H*)-pyridone 43. A mixture of 3-acetyl-*N*-benzyloxy-5-(4′-benzyloxy-3′,5′-di-isopropylphenyl)-4-hydroxy-2(1*H*)-pyridone **42** (100 mg, 0.19 mmol, 1.0 equiv) and 10% palladium on carbon (100 mg) in dioxane (5 mL) was stirred under hydrogen (balloon) atmosphere at 25 °C for 2 h. The reaction mixture was filtered, the solid residue was washed with dioxane (20 mL) and the combined filtrates were evaporated under vacuum to yield 80 mg (96%) of the 3-acetyl-*N*-hydroxy-5-(4′-benzyloxy-3′,5′-di-isopropylphenyl)-4-hydroxy-2(1*H*)-pyridone as a yellow solid, mp 202–203 °C. The crude product was used as such for next step without further purification. ν_{max} (neat)/cm^{-1} 3174m, 2963m, 1648s, 1613s, 1429s, 1323m, 1248m, 1212w, 1123m, 722m; δ_H (400 MHz, $CDCl_3$) 1.27 (d, J=7.0 Hz, 12H), 2.83 (s, 3H), 3.48 (septet, J=7.0 Hz, 2H), 4.87 (s, 2H), 7.23 (s, 2H), 7.39 (t, J=7.0 Hz, 1H, 7.45 (t, J=7.0 Hz, 2H), 7.53 (d, J=7.0 Hz, 2H), 7.94 (s, 1H); δ_C (100.6 MHz, $CDCl_3$) 22.7, 24.1, 26.7, 76.5, 107.9, 112.6, 125.0, 127.3, 127.9, 128.0, 128.6, 133.9, 137.5, 142.2, 153.2, 158.1, 174.0, 206.1; *m/z* (ESI-) 434 [$(M-H)^-$, 100%]; HRMS: found 434.1964 $(M-H)^-$. $C_{26}H_{28}NO_5$ requires 434.1967.

To a −78 °C cooled solution of 3-acetyl-1,4-dihydroxy-5-(4′-benzyloxy-3′,5′-di-isopropylphenyl)-2(1*H*)-pyridone (60 mg, 0.14 mmol, 1.0 equiv) in DCM was added 1 M boron

tribromide in DCM (0.70 mL, 0.70 mmol, 5.0 equiv) and the reaction mixture was stirred at the same temperature for 1 h. Methanol (100 μL) was added to the reaction mixture, which was then stirred for 10 min at the same temperature. The reaction was then further quenched by the sequential addition of water (5 mL) and ethyl acetate (5 mL). The phases were separated and the aqueous layer extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum. The crude residue was purified by flash column chromatography [silica gel, 1% methanol in DCM, (silica gel having been prewashed by being allowed to stand as a slurry in 50% aqueous nitric acid for 24 h followed by rinsing with doubly distilled water until the aqueous filtrates were neutral. Subsequent trituration with reagent grade acetone was followed by drying in vacuum at 25 °C)] to yield 35 mg (74%) of the title compound **43** as a yellow solid, mp 201 °C. ν_{max} (neat)/cm^{-1} 3467m, 3166m, 2961m, 1648s, 1602s, 1548m, 1432m, 1416s, 1260w, 1198m, 1146m, 1127m, 723w; δ_H (250 MHz, $CDCl_3$) 1.32 (d, J=7.0 Hz, 12H), 2.85 (s, 3H), 3.20 (septet, J=7.0 Hz, 2H), 5.33 (s, 1H), 7.18 (s, 2H), 7.91 (s, 1H); δ_C (100.6 MHz, $CDCl_3$) 22.7, 27.2, 31.7, 106.0, 113.5, 123.7, 124.5, 133.8, 134.5, 150.2, 157.4, 171.5, 205.5; *m/z* (ES-) 344 [$(M-H)^-$, 100%)]; HRMS: found 344.1497 $(M-H)^-$. $C_{19}H_{22}NO_5$ requires 344.1498.

4.1.18. Oxidative cyclisation of di-isopropylated *N*-hydroxy-2-pyridone 43 with *Z*-2-cyclodecenone 16 (44–46). To a mixture of 3-acetyl-1,4-dihydroxy-5-[(3′,5′-di-isopropyl)-4′-hydroxy)phenyl]-2(1*H*)-pyridone **43** (140 mg, 0.41 mmol, 1.0 equiv) and *Z*-2-cyclodecenone[15] (65.4 mg, 0.43 mmol, 1.05 equiv) in DCM (0.026 M) was added iodobenzene diacetate (145 mg, 0.45 mmol, 1.1 equiv) all at once. Immediately the reaction turned to a dark colour. After stirring for 2 h at 25 °C, the reaction was refluxed for 24 h. During the reflux, the colour of the reaction turned into reddish yellow. After cooling to 25 °C, water (5 mL) was added to the reaction mixture and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and filtered. The filtrate was evaporated under vacuum. The crude product was purified by flash column chromatography [silica gel, 10–30% EtOAc in 30–40 petroleum ether to collect phenol and quinone methides, followed by second purification with DCM for quinone methide and 0–3% EtOAc in DCM as a gradient elution for phenols, (silica gel having been pre-washed by being allowed to stand as a slurry in 50% aqueous nitric acid for 24 h followed by rinsing with doubly distilled water until the aqueous filtrates were neutral. Subsequent trituration with reagent grade acetone was followed by drying in vacuum at 25 °C for 24 h)] to give 36 mg (18%) of *cis*-quinone methide **45** as a reddish-yellow solid, mp 146 °C, 24 mg (12%) of *cis*-phenol **44** as pale yellow solid, re-crystallized from ethyl acetate, mp 262–264 °C, and 5.5 mg (3%) of *trans*-phenol **46** as a pale yellow solid, mp 185–187 °C. *cis*-Quinone methide **45** was equilibrated into *cis*-phenol **44** by treating with aluminium chloride (2 equiv) in DCE at reflux for 24 h.

cis-Phenol **44**. ν_{max} (neat)/cm^{-1} 3398br, 2959s, 2874m, 1706w, 1654s, 1611m, 1541m, 1438m, 1419m, 1297w, 1201w, 1151m: δ_H (400 MHz, $CDCl_3$) 0.98–1.10 (m, 2H), 1.12–1.22 (m, 3H), 1.22–1.31 (d, J=7.0 Hz, 12H), 1.32–1.71 (m, 7H), 2.02–2.12 (m, 2H), 2.80 (s, 3H), 3.16–3.27 (m, 2H), 4.71–4.81 (m, 1H), 4.88 (d, J=7.0 Hz, 1H), 5.10 (s, 1H), 6.94 (s, 2H); δ_C (100.6 MHz, $CDCl_3$) 22.1, 22.6, 22.8, 23.1 (2C), 24.4, 27.1, 27.2, 31.5, 45.7, 55.7, 84.1, 107.1, 108.8, 123.1, 134.7, 145.0 (2C), 150.3, 154.3, 173.2, 205.1, 205.5; HRMS: found 494. 2534 $(M-H)^-$. $C_{29}H_{36}NO_6$ requires 494.2543.

cis-Quinone methide **45**. ν_{max} (neat)/cm^{-1} 2962s, 2873m, 1688s, 1620s, 1558m, 1439s, 1387m, 1361m, 1289m, 1078w; δ_H (400 MHz, $CDCl_3$) 0.88–1.01 (m, 1H), 1.02–1.21 (m, 14H), 1.29–1.51 (m, 4H), 1.66–1.70 (m, 2H), 1.82–1.87 (m, 1H), 1.96–2.08 (m, 2H), 2.18–2.26 (m, 1H), 2.49 (dd, J=16.0, 10.5 Hz, 1H), 2.77 (s, 3H), 3.06–3.19 (m, 2H), 3.67 (ca. t, J=9.0 Hz, 1H), 4.29 (ca. t, J=9.0 Hz, 1H), 5.32 (d, J=9.0 Hz, 1H), 6.97 (d, J=2.5 Hz, 1H), 8.41 (d, J=2.5 Hz, 1H); δ_C (100.6 MHz, $CDCl_3$) 21.5, 22.0, 22.3, 23.2, 24.3, 24.6, 25.1, 27.2, 27.3, 27.4, 28.8, 48.3, 61.6, 66.0, 85.7, 107.0, 126.3, 128.5, 129.7, 141.1, 148.5, 150.4, 167.9, 182.1, 185.5, 204.3, 209.5; HRMS: found 494.2540 $(M-H)^-$. $C_{29}H_{36}NO_6$ requires 494.2543.

trans-Phenol **46**. ν_{max} (neat)/cm^{-1} 3400m, 2959s, 2871m, 1711m, 1654s, 1613m, 1542m, 1468s, 1436m, 1295m, 1202m, 1152m, 975m; δ_H (500 MHz, $CDCl_3$) 0.82–0.98 (m, 3H), 1.20–1.31 (m, 6H), 1.27 (d, J=7.0 Hz, 12H), 1.40–1.61 (m, 2H), 1.89–1.98 (m, 2H), 2.28–2.38 (m, 1H), 2.80 (s, 3H), 3.12–3.22 (br m, 2H), 4.64 (d, J=10.5 Hz, 1H), 4.72 (dt, J=10.5, 2.5, Hz, 1H), 4.93 (s, 1H), 6.79 (s, 1H), 6.87 (s, 1H); δ_C (125.8 MHz, $CDCl_3$) 23.4, 23.8, 24.3, 25.4, 25.9, 29.8, 30.6, 30.7, 31.8, 34.7, 34.9, 44.1, 64.1, 87.6, 107.4, 109.4, 122.6, 127.4, 129.7, 136.6, 137.2, 147.0, 154.7, 154.8, 174.1, 205.9, 208.2; HRMS: found $(M-H)^-$ 494.2545. $C_{29}H_{36}NO_6$ requires 494.2543.

4.2. X-ray crystallographic studies

Crystals were grown as described in preparations. Single crystals were mounted on glass fibres using perfluoro-polyether oil and cooled rapidly to 150 K in a stream of cold N_2 using an Oxford Cryosystems Cryostream unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated Mo K_α radiation, λ=0.71073 Å). Intensity data were processed using the DENZO-SMN package.

Space groups were assigned by examination of the systematic absence of the intensity data. The structures were solved using the direct-methods program SIR92, which located all non-hydrogen atoms of the organic molecules. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The hydroxyl hydrogen atoms of the organic molecules were located in a difference Fourier map and their coordinates and isotropic thermal parameters subsequently refined. CH hydrogen atoms were positioned geometrically after each cycle of refinement. 3-Term Chebychev polynomial weighting schemes were applied. The crystal structures are shown as thermal ellipsoid plots (ORTEP-3)[27] at 40% probability.

4.3. Supplementary material

Crystallographic data for compounds **37** and **44** have been deposited with Cambridge Crystallographic Data Centre (Deposition numbers CCDC 292547 and 292548, respectively). Copies of this data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (deposit@ccdc.cam.ac.uk).

Acknowledgements

NRI is indebted to Dr. Reddy's Research Foundation (DRF), Hyderabad, India for their support and financial assistance.

References and notes

1. (a) Takahashi, S.; Kakinuma, N.; Uchida, K.; Hashimoto, R.; Yanagishima, T.; Nakagawa, A. *J. Antibiot.* **1998**, *51*, 596–598. (b) Takahashi, S.; Kakinuma, N.; Uchida, K.; Hashimoto, R.; Yanagishima, T.; Nakagawa, A. *J. Antibiot.* **1998**, *51*, 1051–1054.
2. ElBayouni, S. H.; Brewer, D.; Vining, L. C. *Can. J. Bot.* **1968**, *46*, 441–448.
3. Wat, C.-K.; McInnes, A. G.; Smith, D. G.; Wright, J. C. L.; Vining, L. C. *Can. J. Chem.* **1977**, *55*, 4090–4098.
4. Matsumoto, M.; Minato, H. *Tetrahedron Lett.* **1976**, *17*, 3827–3830.
5. (a) Williams, D. R.; Lowder, P. D.; Gu, Y. G. *Tetrahedron Lett.* **1997**, *38*, 327–330. (b) Buck, J.; Madeley, J. P.; Adeley, J. P.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1992**, 67–73. (c) Rigby, J. H.; Qabar, M. *J. Org. Chem.* **1989**, *54*, 5852–5853. (d) Williams, D. R.; Sit, S. Y. *J. Org. Chem.* **1982**, *47*, 2846–2851. (e) Zhang, Q. S.; Curran, D.P. *Abstracts of Papers*, 222nd National Meeting of the American Chemical Society, Chicago, IL, Aug 26–30, 2001; American Chemical Society: Washington, DC; Orgn-519. (f) Zhang, Q.; Rivkin, A.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 5774–5781.
6. (a) Baldwin, J. E.; Adlington, R. M.; Conte, A.; Irlapati, N. R.; Marquez, R.; Pritchard, G. J. *Org. Lett.* **2002**, *4*, 2125–2127. (b) Irlapati, N. R.; Adlington, R. M.; Conte, A.; Pritchard, G. J.; Marquez, R.; Baldwin, J. E. *Tetrahedron* **2004**, *60*, 9307–9317.
7. Levitzki, A.; Gazit, A. *Science* **1995**, *267*, 1782–1788.
8. McInnes, A. G.; Smith, D. G.; Wat, C.-K.; Vining, L. C.; Wright, J. L. C. *J. Chem. Soc., Chem. Commun.* **1974**, *8*, 281–282.
9. Tanable, M.; Urano, S. *Tetrahedron* **1983**, *39*, 3569–3574.
10. Leete, E.; Kowanko, N.; Newmark, R. A.; Vining, L. C.; McInnes, A. G.; Wright, J. L. C. *Tetrahedron Lett.* **1975**, *16*, 4103–4106.
11. Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; Wiley-Interscience: New York, 1984.
12. Ackland, M. J.; Hanson, J. R.; Hitchcock, P. B.; Ratcliff, A. H. *J. Chem. Soc., Perkin Trans. 1* **1985**, *4*, 843–847.
13. (a) Irlapati, N. R.; Baldwin, J. E.; Adlington, R. M.; Pritchard, G. J.; Cowley, A. R. *Org. Lett.* **2003**, *5*, 2351–2354. (b) Irlapati, N. R.; Baldwin, J. E.; Adlington, R. M.; Pritchard, G. J.; Cowley, A. R. *Tetrahedron* **2005**, *61*, 1773–1784.
14. See for example: (a) Iwasa, s.; Tsushima, s.; Shimada, T.; Nishiyama, H. *Tetrahedron Lett.* **2001**, *42*, 6715–6717. (b) Fourets, O.; Cauliez, P.; Simonet, J. *Tetrahedron Lett.* **1998**, *39*, 565–566. (c) Gothelf, K. V.; Jorgensen, K. A. *J. Org. Chem.* **1994**, *59*, 5687–5691. (d) Joucla, M.; Tonnard, F.; Gree, D.; Hamelin, J. *J. Chem. Res. (S).* **1978**, 240–241. (e) Joucla, M.; Hamelin, J.; Carrie, R. *Bull. Chem. Soc. Fr.* **1973**, *11*, 3116–3118. (f) Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; Wiley-Interscience: New York, 1984; Chapters 1, 9, 12.
15. Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y. L. *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258.
16. Kurtz, A. N.; Billups, W. E.; Greenlee, R. B.; Hamil, H. F.; Pace, W. T. *J. Org. Chem.* **1965**, *30*, 3141–3147.
17. Macchia, M.; Menchini, E.; Nencetti, S.; Orlandini, E.; Rossello, A.; Belfore, M. S. *II Farmaco* **1996**, *51*, 25.
18. Daniel, L.; Jean-Charles, L.; Max, R. *Tetrahedron Lett.* **1985**, *26*, 1295–1296.
19. Japanese Patent 5-78324, 1993.
20. Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677–680.
21. (a) US patent 4,405,528, 1983. (b) Boy, P.; Combellas, C.; Fielding, S.; Thiebault, A. *Tetrahedron Lett.* **1991**, *32*, 6705–6708.
22. Masashi, T.; Haruo, Y.; Takehiko, Y. *Synthesis* **1978**, 399–400.
23. (a) George, A. O.; Surya Prakash, G. K.; Pradeep, S. I.; Masashi, T.; Takehiko, Y. *J. Org. Chem.* **1987**, *52*, 1881–1884. (b) George, A. O.; Pradeep, S. I.; Surya Prakash, G. K. *Synthesis* **1986**, 513–531.
24. Fukata, G.; Itoh, T.; Tashiro, M. *Heterocycles* **1982**, *19*, 1487–1495.
25. Lewis, N.; Morgan, I. *Synth. Commun.* **1988**, *18*, 1783–1793.
26. Jay, E. W.; Arlene, J. D.; Zenan, L. US Patent 6,110,962, 2000.
27. Johnson, C. K.; Burnett, M. K. ORTEP-3 v. 1.0.2, 1998.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 4615–4621

4-Formylazetidin-2-ones, synthon for the synthesis of (2*R*,3*S*) and (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid (AHDA)

Nilesh M. Shirode and Abdul Rakeeb A. S. Deshmukh*

Division of Organic Chemistry (Synthesis), National Chemical Laboratory, Pune 411 008, India

Received 24 October 2005; revised 3 January 2006; accepted 19 January 2006

Abstract—An efficient synthesis of 3-amino-2-hydroxydecanoic acid (AHDA), a nonproteinogenic amino acid, using enantiopure 3-benzyloxy-4-formylazetidin-2-one as a building block is described. Both the enantiomers of AHDA have been synthesized from the corresponding enantiomer of 3-benzyloxy-4-formylazetidin-2-one in good yield and optical purity.

1. Introduction

Apart from the antibacterial agents,[1–3] azetidin-2-ones are increasingly used as synthons for the synthesis of variety of pharmaceutically useful products.[4] This is mainly because of the strain energy associated with the four membered azetidinone ring, that is responsible for selective bond cleavage, giving a variety of transformation products. Moreover, there are many methods available to prepare them in reasonable quantities required for synthetic purpose. One such synthon, 4-formylazetidin-2-one, has wide applications as a building block[5,6] for the synthesis of monobactams, isocephams, carbapenems and several other non-β-lactam compounds like α-hydroxy aspartate and hydroxybutanoic acids. As a part of our research program on asymmetric synthesis of β-lactams, we have developed an efficient method for the synthesis of enantiomerically pure 4-formylazetidin-2-ones[7a] and used them as building blocks for the synthesis of 4-aminopiperidin-2-ones,[8] important intermediates for the synthesis of biologically useful compounds.

2. Results and discussion

In continuation of our efforts towards the synthesis of substituted β-lactams via the Staudinger reaction[9] and their utility as synthons[7c,8,10] for the synthesis of various biologically important compounds, we were interested in the synthesis of 3-amino-2-hydroxydecanoic acid (AHDA) from the 4-formyl-β-lactam synthon. (2*S*,3*R*)-3-Amino-2-hydroxydecanoic acid (**1b**) is an unusual novel amino acid, which has been suggested as the N-terminal component of the recently isolated angiotensin-converting enzyme inhibitor microginin (**2**)[11] (Figs. 1 and 2).

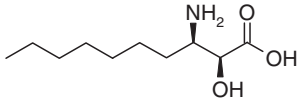


Figure 1. (2*S*,3*R*)-3-Amino-2-hydroxydecanoic acid (**1b**).

Microginin is a small linear peptide isolated from the blue-green alga *Microcystis aeruginosa* and its structure was established on the basis of degradation studies, spectral data and total synthesis.[11,12] It was shown that a linear α-hydroxy-β-aminodecanoic acid is at the N-terminal of the peptide chain. Subsequently it was also found that AHDA is common to other linear peptides isolated from the same species.[11b,c] There are several approaches[12,13] for the synthesis of AHDA. In most cases, asymmetric functionalization of alkenes[13c–e] via either asymmetric epoxidation or asymmetric dihydroxylation is the common strategy. There are few reports using 'chiral pool' strategies[13f,g] wherein a chiral starting material is used for the synthesis. The Lewis acid catalyzed addition of ketene acetals to chiral imines[13b] is another approach for the synthesis of α-hydroxy-β-amino acids.

Although β-amino acids are easily accessible by hydrolysis of the corresponding azetidin-2-ones,[4b,14] surprisingly there is no report on the synthesis of AHDA starting from an azetidin-2-one synthon. Therefore, we planned our

Keywords: Stereoselective synthesis; Azetidin-2-ones; Amino acids; Wittig reaction; Staudinger reaction.
* Corresponding author. Fax: +91 20 25893153/25893355; e-mail: aras.deshmukh@ncl.res.in

0040–4020/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tet.2006.01.082

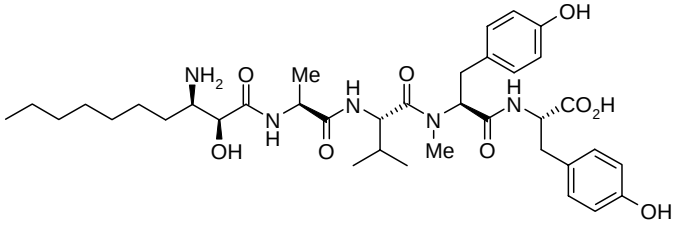
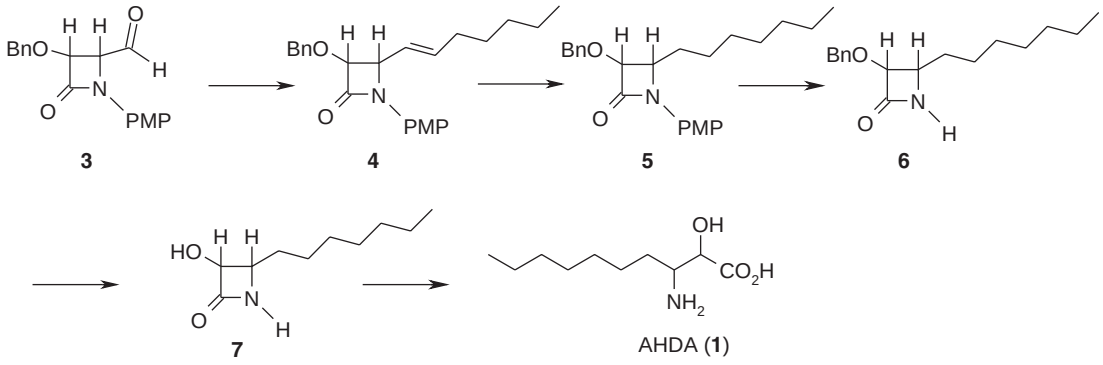


Figure 2. Microginin (**2**).

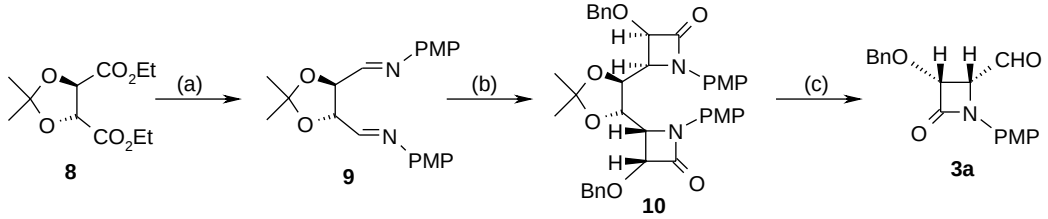


Scheme 1.

synthesis from suitably substituted 4-formylazetidin-2-one. Our synthesis is based on the application of well-defined stereochemistry at both the stereocentres of *cis*-3-benzyloxy-4-formylazetidin-2-one ring, which is required for the synthesis of natural AHDA. The synthesis involves Wittig olefination of *cis*-3-benzyloxy-4-formylazetidin-2-one, followed by hydrogenation and careful hydrolysis of the azetidinone ring to get the desired AHDA (Scheme 1). The Scheme is simple and it can be applied for the synthesis of both the enantiomers of AHDA, since both the enantiomers of starting *cis*-4-formylazetidin-2-one can be prepared in reasonable yields and good optical purities. Also by following the synthetic protocol, one can easily prepare other analogues of AHDA.

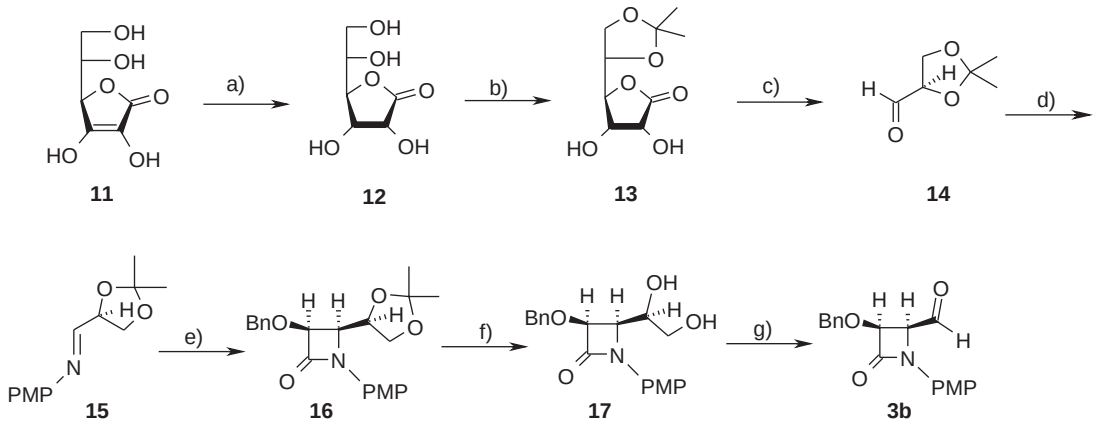
Enantiomerically pure (3*R*,4*R*)-3-benzyloxy-4-formylazetidin-2-one (**3a**) was prepared from L-diethyl tartrate using a synthetic method developed by our group.[7a] C_2-Symmetry of natural tartaric acid has been exploited to achieve the synthesis of 2 mol of *cis*-4-formylazetidin-2-ones from 1 mol of diethyl tartrate acetonide (Scheme 2). Alternatively enantiopure **3a** can also be prepared from D-mannitol diacetonide in four steps.[15] The other enantiomer (3*S*,4*S*)-3-benzyloxy-4-formylazetidin-2-one (**3b**) was also synthesized (Scheme 3) from L-glyceraldehyde acetonide, which was easily prepared from L-ascorbic acid in three steps.[16]

Having both the enantiomers in hand, we initially started our work with (3*R*,4*R*)-3-benzyloxy-4-formylazetidin-2-one (**3a**) since it can be easily prepared in large quantities from L-diethyl tartrate.[7a] The aldehyde **3a**, on Wittig olefination reaction with the Wittig reagent derived from triphenylphosphine and *n*-1-bromohexane, gave olefin **4a** in good yield. The olefin **4a** on catalytic hydrogenation with Pd/C (10%) gave 4-heptanyl-β-lactam **5a**, in very good yield (90%). A small amount of debenzylated compound **18a** (6%) was also obtained along with **5a**, which was separated by flash column chromatography. The oxidative removal of the *p*-methoxyphenyl (PMP) group from **5a** was achieved by cerric ammonium nitrate (CAN)[17] to get (3*R*,4*S*)-3-benzyloxy-4-heptanyl-azetidin-2-one (**6a**) in 85% yield. The benzyl group was removed by transfer hydrogenation[18] using Pd/C (10%) to afford 3-hydroxy-β-lactam **7a** in quantitative yield. Hydrolysis of **7a** was achieved by heating with 3 M HCl at 60 °C for 6 h and the product was purified by ion-exchange chromatography (Dowex 50 W×2-400) using 5% NH_4OH as the eluent to afford pure (2*R*,3*S*)-AHDA (**1a**) in 70% yield (Scheme 4).



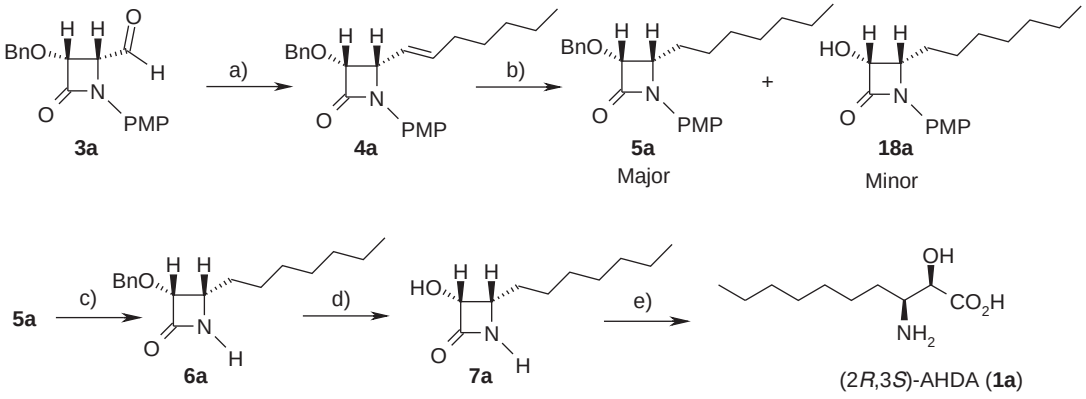
Reagents and conditions: (a) DIBAL-H, PMP-NH_2, toluene, -78°C to rt, 15 h (b) $BnOCH_2COCl$, Et_3N, CH_2Cl_2, –23°C to rt, 14 h (c) i) 2.5 M $HClO_4$, THF, rt, 4-8 h; ii) $NaIO_4$, acetone-H_2O, rt, 4-12 h

Scheme 2.



Reagents and conditions: a) H_2, Pd/C (10%), 50 Psi, 50 °C, H_2O, 95% b) 2-Methoxypropene, DMF, PTSA, 24 h, rt, 70% c) $NaIO_4$, H_2O, 0 °C to rt, 2h d) PMP-NH_2, CH_2Cl_2, 2 h, rt e) $BnOCH_2COCl$, Et_3N, CH_2Cl_2, 0 °C to rt, 12h, 50% f) PTSA, THF/H_2O, reflux, 18h, 98% g) $NaIO_4$, Acetone/H_2O, 85%.

Scheme 3.



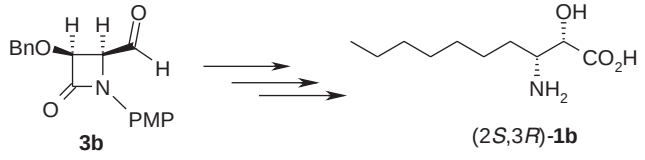
Reagents and conditions: a) $CH_3(CH_2)_5PPh_3^+ Br^-$, *n*-BuLi, 0 °C, 6h, dry THF, 75% b) H_2, Pd/C (10%), 50 psi, 6h, EtOAc, 90% c) CAN, CH_3CN/H_2O, 0 °C, 25 min, 85% d) $HCOONH_4$, Pd/C (10%), MeOH, reflux, 6h, 95% e) 3M HCl, 60 °C, 6h, Ion-exchange resin, Dowex 50W x 2-400, 5% NH_4OH, 70%.

Scheme 4.

The other enantiomer, (2*S*,3*R*)-AHDA (**1b**) was also synthesized (Scheme 5) from (3*S*,4*S*)-3-benzyloxy-4-formyl-azetidin-2-one (**3b**) by following a similar synthetic protocol as shown in Scheme 4. The spectral data and the specific rotations are comparable with that of the reported in the literature.[12ab,13a]

3. Conclusion

In conclusion, we have accomplished the synthesis of both the enantiomers of 3-amino-2-hydroxydecanoic acid (AHDA), from corresponding enantiomer of 4-formyl-3-benzyloxyazetidin-2-one. (2*S*,3*R*)-AHDA is a nonproteinogenic amino acid, an important constituent of natural product microginin (**2**).



Scheme 5.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions on Brüker AC 200, AV 400 spectrometers, and chemical shifts are reported in ppm downfield from tetramethylsilane for ^1H NMR. Infrared spectra were recorded on Perkin-Elmer Infrared Spectrophotometer, Model 599-B or Shimadzu FTIR-8400 using sodium chloride optics. Melting points were determined on a Thermonik Campbell melting point apparatus and are uncorrected. The microanalyses were performed on a Carlo-Erba, CHNS-O EA 1108

elemental analyzer. Optical rotations were recorded on ADP 220 polarimeter Bellingham + Stanley Ltd. under standard conditions. Mass spectra were recorded on API QSTAR PULSAR using electron spray ionization (ESI) method.

4.1.1. (3*R*,4*S*)-3-Benzyloxy-4-hept-1-enyl-1-(4-methoxyphenyl)-azetidin-2-one (4a). To a solution of a *n*-hexyltriphenylphosphonium bromide (1.538 g, 3.6 mmol) in anhydrous THF at 0 °C was added *n*-butyl lithium (2.20 mL, 3.3 mmol, 1.5 M, colour change from yellow to orange red was observed). Reaction mixture was stirred at this temperature for 45 min. A solution of azetidin-2-one **3a** (0.934 g, 3 mmol) in anhydrous THF (20 mL) was added drop-wise at 0 °C to the reaction mixture and then allowed to warm up to room temperature. After 6 h, the reaction mixture was quenched with saturated solution of NH_4Cl (5 mL). The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (20 mL), washed with water (10 mL) and then with saturated brine solution (5 mL) to afford the crude **4a**, which was then purified by flash column on silica gel (EtOAc/pet ether 1:9 as eluent), to get *E*/*Z* isomeric mixture of **4a** (0.853 g, 75%) as a viscous oil. The geometrical isomers were difficult to separate by flash column chromatography and used as such for further reaction. [Found C, 75.65; H, 7.52; N, 3.80. $C_{24}H_{29}NO_3$ requires C, 75.95; H, 7.72; N, 3.69%]; ν_{max} ($CHCl_3$) 1747 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.94 (m, 3H), $CH_3(CH_2)_6$), 1.28–1.51 (m, 6 H, =CH–CH_2 (CH_2)$_3$–CH_3), 2.08–2.40 (m, 2H, CH=CH–CH_2), 3.79 (s, 3H, Ar-OCH_3), 4.54–4.95 (m, 4H, C3*H*, C4*H*, OCH_2Ph), 5.56–5.68 (m, 1H, CH=C*H*–CH_2–(CH_2)$_3$–CH_3), 5.83–6.06 (m, 1H, C*H*=CH–CH_2–(CH_2)$_3$–CH_3), 6.85 (d, J=9.1 Hz, 2H, Ar), 7.28–7.43 (m, 7H, Ar); δ_C (75.48 MHz) 14.0, 22.5, 27.9, 28.5, 29.1, 31.2, 31.6, 32.4, 55.4, 55.5, 60.9, 72.6, 72.7, 82.2, 82.4, 114.4, 118.6, 118.7, 124.0, 124.3, 128.0, 128.4, 131.1, 137.0, 137.5, 138.8, 156.4, 163.5; MS (*m*/*z*): 380 ($M^+ + 1$).

4.1.2. (3*R*,4*S*)-3-Benzyloxy-4-heptyl-1-(4-methoxyphenyl)azetidine-2-one (5a) and (3*R*,4*S*)-4-heptyl-3-hydroxy-1-(4-methoxyphenyl)-azetidine-2-one (18a). Compound **4a** (0.760 g, 2 mmol) was dissolved in EtOAc (20 mL) and Pd/C (10%) (70 mg) was added. The mixture was hydrogenated at 50 psi of H_2 in a Parr hydrogenator for 6 h at room temperature. The catalyst was removed by filtration through Celite and washed with EtOAc. The solvent was distilled off under reduced pressure and the crude product was purified by flash column chromatography on silica gel (EtOAc/pet ether 15:85 as eluent) to afford compound **5a**; (0.688 g, 90%) as viscous oil. [Found C, 75.47; H, 8.35; N, 3.61. $C_{24}H_{31}NO_3$ requires C, 75.57; H, 8.21; N, 3.67%]; R_f (40% EtOAc/pet ether) 0.56; $[\alpha]_D^{30}$ +112.38 (*c* 1.05, $CHCl_3$); ν_{max} ($CHCl_3$) 1742 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.89 (t, J=6.5 Hz, 3H, $(CH_2)_6CH_3$), 1.2–1.5 (m, 10H, $CH_2(CH_2)_5CH_3$), 1.83–1.94 (m, 2H, $CH_2(CH_2)_5CH_3$), 3.80 (m, 3H, Ar-OCH_3), 4.11–4.19 (m, 1H, C4*H*), 4.74–4.80 (m, 2H, C3*H*, CH_aH_bPh), 4.98 (d, J= 11.9 Hz, 1H, CH_aH_bPh), 6.89 (d, J=9.1 Hz, 2H, Ar), 7.28–7.43 (m, 7H, Ar); δ_C (50.32 MHz) 13.7, 22.2, 25.3, 27.0, 28.7, 29.3, 31.3, 54.9, 57.5, 72.7, 80.7, 114.1, 118.3, 127.3, 127.4, 128.0, 130.5, 137.1, 156.0, 164.4; MS (*m*/*z*): 382 ($M^+ + 1$).

The compound **18a** (0.035 g, 6%) was obtained as a white crystalline solid; mp 105–107 °C; [Found C, 70.20; H, 8.70; N, 4.93. $C_{17}H_{25}NO_3$ requires C, 70.06, H, 8.66; N, 4.81%]; R_f (40% EtOAc/pet ether) 0.27; $[\alpha]_D^{30}$ +107.50 (*c* 0.4, $CHCl_3$); ν_{max} ($CHCl_3$) 1724, 3365 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.89 (t, J=6.8 Hz, 3H, $(CH_2)_6CH_3$), 1.28–1.50 (m, 10H, CH_2 (CH_2)$_5CH_3$), 1.80–2.00 (m, 2H, $CH_2(CH_2)_5CH_3$), 2.88 (br s, 1H, O*H*), 3.81 (s, 3H, Ar-OCH_3), 4.14–4.20 (m, 1H, C4*H*), 5.05 (d, J=5.2 Hz, 1H, C3*H*), 6.85 (d, J=9.0 Hz, 2H, Ar), 7.32 (d, J=9.0 Hz, 2H, Ar); δ_C (50.32 MHz) 13.9, 22.5, 25.7, 27.1, 29.1, 29.6, 31.7, 55.4, 59.1, 75.1, 114.4, 119.0, 130.5, 156.5, 167.2; MS (*m*/*z*): 292 ($M^+ + 1$).

4.1.3. (3*R*,4*S*)-3-Benzyloxy-4-heptylazetidin-2-one (6a). A solution of **5a** (0.572 g, 1.5 mmol) in acetonitrile (15 mL) was cooled to 0 °C and treated with a solution of CAN (2.469 g, 4.51 mmol) in water (20 mL) over 3 min. The reaction mixture was stirred at −5 to 0 °C for 25 min and diluted with water (110 mL). The mixture was extracted with EtOAc (3×25 mL). The organic extracts were washed with 5% $NaHCO_3$ (2×25 mL) and the aqueous extracts back washed with EtOAc (10 mL). The combined organic layer was washed with 10% sodium sulfite (until the aqueous layer remained colourless), 5% $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was then dried over anhydrous Na_2SO_4, evaporated under reduced pressure to yield the crude product **6a**, which was then purified by flash column chromatography on silica gel (EtOAc/pet ether 3:7 as eluent) to get pure **6a** (0.351 g, 85%) as a white solid; mp 53–55 °C; [Found C, 74.13; H, 8.93; N, 4.95. $C_{17}H_{25}NO_2$ requires C, 74.13; H, 9.17; N, 5.08%]; R_f (40% EtOAc/pet ether) 0.18; $[\alpha]_D^{30}$ +40.57 (*c* 0.30, $CHCl_3$); ν_{max} ($CHCl_3$) 1757 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.89 (t, J=6.4 Hz, 3H, $CH_3(CH_2)_6$), 1.05–1.45 (m, 10 H, $CH_2(CH_2)_5CH_3$), 1.50–1.75 (m, 2H, $CH_2(CH_2)_5CH_3$), 3.67–3.77 (m, 1H, C4*H*), 4.66–4.72 (m, 2H, C3H, CH_aH_bPh,), 4.87 (d, J=11.9 Hz, 1H, CH_aH_bPh), 6.21 (br s, 1H, N–*H*), 7.25–7.45 (m, 5H, Ar); δ_C (50.32 MHz) 13.8, 22.3, 25.7, 28.9, 29.2, 29.4, 29.7, 31.5, 55.0, 72.5, 82.2, 127.4, 127.6, 128.1, 137.1, 169.4; MS (*m*/*z*): 276 ($M^+ + 1$).

4.1.4. (3*R*,4*S*)-4-Heptyl-3-hydroxyazetidin-2-one (7a). To a solution of **6a** (0.275 g, 1 mmol) in methanol (10 mL), 10% Pd/C (30 mg) was added followed by ammonium formate (0.315 g, 5 mmol) and the reaction mixture was heated at reflux under argon for 6 h. After completion of the reaction (TLC), the reaction mixture was allowed to cool to room temperature and filtered through Celite. The solvent was distilled off under reduced pressure and the residue was dissolved in CH_2Cl_2 (20 mL), washed with water (5 mL), brine (5 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave crude product, which was then purified by flash column chromatography on silica gel (EtOAc/pet ether 6:4 as eluent) to get pure **7a** (0.176 g, 95%) as a white solid, mp 112–113 °C; [Found C, 64.91; H, 10.40; N, 7.77. $C_{10}H_{19}NO_2$ requires C, 64.81; H, 10.36; N, 7.56%]; R_f (60% EtOAc/pet ether) 0.22; $[\alpha]_D^{30}$ +40 (*c* 0.25, $CHCl_3$); ν_{max} ($CHCl_3$) 1751 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 0.88 (t, J=6.3 Hz, 3H, $CH_3(CH_2)_6$), 1.15–1.65 (m, 12H, $(CH_2)_6CH_3$), 3.65–3.85 (m, 1H, C4*H*), 4.55–4.85 (m, 1H, C3*H*), 4.91 (br s, 1H, O*H*), 6.80 (br s, 1H, N–*H*); δ_C

(50.32 MHz) 14.1, 22.6, 25.9, 29.2, 29.5, 29.7, 31.7, 56.7, 76.5, 172.0; MS (*m*/*z*): 186 ($M^+ + 1$).

4.1.5. (2*R*,3*S*)-3-Amino-2-hydroxydecanoic acid (1a). A solution of **7a** (93 mg, 0.5 mmol) in 3 M HCl (5 mL) was heated at 60 °C for 6 h. After completion of the reaction (TLC), the solution was cooled to room temperature and extracted with CH_2Cl_2 (3 mL). The aqueous layer was evaporated to dryness under reduced pressure and the residue was further subjected to ion exchange chromatography (Dowex 50 W×2-400) using 5% NH_4OH as the eluent to afford **1a** (71 mg, 70%) as a white solid, mp 220–223 °C (dec), lit. mp 152–156 °C (dec);[12a] [Found C, 59.28; H, 10.53; N, 7.10. $C_{10}H_{21}NO_3$ requires C, 59.07; H, 10.43; N, 6.89%]; $[\alpha]_D^{30}$ −6.2 (*c* 0.40, 1 M HCl); δ_H (200 MHz, D_2O) 0.84 (t, *J*=6.7 Hz, 3H, C*H*$_3$(CH$_2$)$_6$), 1.19–1.45 (m, 10H, CH$_2$(C*H*$_2$)$_5$-CH$_3$), 1.50–1.83 (m, 2H, C*H*$_2$(CH$_2$)$_5$CH$_3$), 3.38–3.50 (m, 1H, C3*H*), 4.08 (d, *J*=3.8 Hz, 1H, C2*H*); δ_C (50.32 MHz, DMSO-d_6) 14.0, 22.1, 24.7, 28.4, 28.7, 29.1, 31.2, 52.7, 69.3, 172.9; MS (*m*/*z*): 204 (M+1).

4.1.6. (3*S*,4*R*)-3-Benzyloxy-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-1-(4-methoxyphenyl)azetidine-2-one (16). To a stirred solution of 5,6-*O*-isopropylidene-L-gulono-1,4-lactone **13** (10.90 g, 50 mmol) in water (150 mL), $NaIO_4$ (21.37 g, 100 mmol) was added portion-wise at 0 °C, over 30 min, at pH 5.5 (adjusted by addition of 2 M NaOH). The suspension was further stirred at room temperature for 2 h, and filtered through filter paper to get a crude aqueous solution of L-(*S*)-glyceraldehyde acetonide (**14**), which was then cooled to 10 °C under argon and vigorously stirred with a solution of *p*-anisidine (5.72 g, 46.5 mmol) in CH_2Cl_2 (150 mL) for 30 min. The organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2 (2×50 mL). The combined organic layers dried over anhydrous Na_2SO_4 under argon. The organic layers were collected and reduced in volume to 30 mL. To this solution dry triethylamine (6.22 g, 61.5 mmol) was added and the reaction mixture was then cooled to 0 °C. A solution of benzyloxyacetyl chloride (8.59 g, 46.5 mmol) in dry CH_2Cl_2 (100 mL) was added drop-wise to the above reaction mixture. The reaction mixture was further stirred for 12 h at room temperature and then washed with water (3×15 mL), 1 N hydrochloric acid (10 mL), saturated $NaHCO_3$ (25 mL), water (25 mL) and brine solution (20 mL). The organic phase dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/pet ether 15:85 as eluent) to get a pure product **16** (8.90 g, 50%) as a white solid, mp 117 °C; [Found C, 68.98; H, 6.73; N, 3.61. $C_{22}H_{25}NO_5$ requires C, 68.90; H, 6.58; N, 3.65%]; R_f (30% EtOAc/pet ether) 0.57; $[\alpha]_D^{30}$ = −113.4 (*c* 0.70, $CHCl_3$); ν_{max} ($CHCl_3$) 1735 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.35 (s, 3H, C*H*$_3$), 1.54 (s, 3H, C*H*$_3$), 3.73–3.89 (m, 1H, OC*H*CH$_2$), 3.75 (s, 3H, Ar-OC*H*$_3$), 4.10–4.50 (m, 3H, C4*H*, OC*H*$_2$CHO), 4.70–4.80 (m, 2H, C3*H*, OC*H*$_a$H$_b$Ph), 5.00 (d, *J*=11.8 Hz, 1H, OCH$_a$*H*$_b$Ph), 6.85 (d, *J*=9.2 Hz, 2H, Ar), 7.30–7.45 (m, 5H, Ar), 7.70 (d, *J*=9.2 Hz, 2H, Ar); δ_C (50.32 MHz) 24.8, 26.5, 55.3, 61.6, 66.9, 73.1, 79.6, 109.6, 113.8, 119.4, 127.8, 128.1, 128.4, 131.1, 136.6, 156.3, 164.8; MS (*m*/*z*): 383 ($M^+ + 1$).

4.1.7. (3*S*,4*S*)-3-Benzyloxy-1-(4-methoxyphenyl)-4-oxoazetidin-2-carbaldehyde (3b). A mixture of azetidin-2-one **16** (3.83 g, 10 mmol) and PTSA (0.570 g, 3 mmol) in THF (40 mL) and water (15 mL) was refluxed for 24 h. After completion of reaction (TLC), the reaction mixture was neutralized with $NaHCO_3$ and the solvent was removed under reduced pressure. The residue was dissolved in EtOAc (25 mL) and the organic layer was washed with saturated brine solution (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to afford diol **17**, which was then dissolved in acetone (50 mL) and water (25 mL) and cooled to 0 °C. To the cooled diol solution, $NaIO_4$ (2.60 g, 12 mmol) was added in portions. After completion of addition, the reaction mixture was stirred at room temperature for 1 h. After completion of reaction (TLC), the solid was filtered off and washed with acetone. The solvent was removed and the residue was dissolved in CH_2Cl_2 (30 mL), washed with water (2×10 mL), saturated $NaHCO_3$ (2×10 mL), brine solution (15 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to afford **3b** (2.65 g, 85%) as a white solid, mp 157–158 °C; [Found C, 69.33; H, 5.58; N, 4.63. $C_{18}H_{17}NO_4$ requires C, 69.43; H, 5.51; N, 4.50%]; R_f (30% EtOAc/pet ether) 0.28; $[\alpha]_D^{30}$ = −176.19 (*c* 0.42, $CHCl_3$); ν_{max} ($CHCl_3$) 1753 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.79 (s, 3H, Ar-OC*H*$_3$), 4.51 (dd, *J*=5.3, 3.7 Hz, 1H, C4*H*), 4.71 (d, *J*=11.3 Hz, 1H, OC*H*$_a$H$_b$Ph), 4.84 (d, *J*=11.3 Hz, 1H, OCH$_a$*H*$_b$Ph), 5.05 (d, *J*=5.3 Hz, 1H, C$_3$*H*), 6.88 (d, *J*=9.1 Hz, 2H, Ar), 7.26 (d, *J*=9.1 Hz, 2H, Ar), 7.30–7.50 (m, 5H, Ar), 9.72 (d, *J*=3.7 Hz, 1H, C*H*O); δ_C (50.32 MHz) 55.5, 63.2, 73.5, 82.6, 114.6, 118.1, 128.3, 128.5, 128.6, 130.5, 135.8, 156.9, 162.9, 198.9; MS (*m*/*z*): 312 ($M^+ + 1$).

4.1.8. (3*R*,4*S*)-3-Benzyloxy-4-hept-1-enyl-1-(4-methoxyphenyl)azetidin-2-one (4b). Following the similar procedure described for **4a**, an inseparable mixture of *E* and *Z* isomers of **4b** was obtained from **3b** as a viscous oil.

4.1.9. (3*S*,4*R*)-3-Benzyloxy-4-heptyl-1-(4-methoxyphenyl)azetidine-2-one (5b) and (3*S*,4*R*)-4-heptyl-3-hydroxy-1-(4-methoxyphenyl)azetidine-2-one (18b). Following the similar procedure described for **5a** and **18a**, compound **5b** and **18b** were prepared from **4b**.

Compound **5b** was obtained as viscous oil, [Found C, 75.57; H, 8.35; N, 3.61. $C_{24}H_{31}NO_3$ requires C, 75.57; H, 8.21; N, 3.67%]; $[\alpha]_D^{30}$ −113.42 (*c* 0.80, $CHCl_3$); MS (*m*/*z*): 382 ($M^+ + 1$); spectral data same as for **5a**.

Compound **18b** was obtained as white crystals, mp 106–107 °C; [Found C, 70.33; H, 8.79; N, 4.95. $C_{17}H_{25}NO_3$ requires C, 70.06, H, 8.66; N, 4.81%]; $[\alpha]_D^{30}$ −110.30 (*c* 0.52, $CHCl_3$); MS (*m*/*z*): 292 ($M^+ + 1$); spectral data same as for **18a**.

4.1.10. (3*S*,4*R*)-3-Benzyloxy-4-heptylazetidin-2-one (6b). Following the similar procedure described for **6a**, compound **6b** was prepared from **5b**. It was obtained as a white solid, mp 55–56 °C; [Found C, 74.18; H, 9.09; N, 4.96. $C_{17}H_{25}NO_2$ requires C, 74.13; H, 9.17; N, 5.08%]; $[\alpha]_D^{30}$ −38.57 (*c* 0.7, $CHCl_3$); MS (*m*/*z*): 276 ($M^+ + 1$); spectral data same as for **6a**.

4.1.11. (3*S*,4*R*)-4-Heptyl-3-hydroxyazetidin-2-one (7b). Following the similar procedure described for **7a**, compound **7b** was prepared from **6b**. It was obtained as a white crystalline solid, mp 111–113 °C; [Found C, 64.97; H, 10.33; N, 7.73. $C_{10}H_{19}NO_2$ requires C, 64.81; H, 10.36; N, 7.56%]; $[\alpha]_D^{30}$ −40.5 (*c* 0.25, $CHCl_3$); (*m*/*z*): 186 ($M^+ + 1$); spectral data same as for **7a**.

4.1.12. (2*S*,3*R*)-3-Amino-2-hydroxydecanoic acid (1b). Following the similar procedure described for **1a**, compound **1b** was prepared from **7b**. It was obtained as a white solid, mp 219–220 °C (dec), lit. mp 218.4–219.7 °C (dec);[9a] [Found C, 59.33; H, 10.48; N, 6.95. $C_{10}H_{21}NO_3$ requires C, 59.07; H, 10.43; N, 6.89%]; $[\alpha]_D^{30}$ +6.5 (*c* 0.47, 1 N HCl), lit. $[\alpha]_D^{22}$ +7.3 (*c* 0.34, 1 N HCl),[13a] $[\alpha]_D^{25}$ +5.4 (*c* 0.59, 1 M HCl);[12b] MS (*m*/*z*): 204 ($M^+ + 1$); spectral data same as for **1a**.

Acknowledgements

Authors thank D.S.T., New Delhi, for financial support and N.M.S. thanks UGC, New Delhi, for research fellowship.

References and notes

1. For reviews on β-lactam antibiotics, see: (a) Dürkheimer, W.; Blumbach, J.; Lattrell, R.; Scheunemann, K. H. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 180–202. (b) Morin, R. B., Gorman, M., Eds.; Chemistry and Biology of β-Lactam Antibiotics; Academic: New York, 1982; Vols. 1–3. (c) Coulton, S.; Hunt, E. In Lukacs, G., Ed.; Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products; Springer: Berlin, 1993; Vol. 2, p 621. (d) Southgate, R. *Contemp. Org. Synth.* **1994**, *1*, 417–431.
2. *The Chemistry of β-lactams*; Page, M. I., Ed.; Chapman and Hall: London, 1992.
3. For comprehensive general reviews, see: (a) Koppel, G. A. In Hasner, A., Ed.; Small Ring Heterocycles; Wiley: New York, 1983; Vol. 42, p 219. (b) Backes, J. In *Houben-Weyl, Methoden der Organischem Chemie*; Muller, E., Bayer, O., Eds.; Thieme: Stuttgart, 1991; p 31; Band E16B. (c) de Kimpe, N. In Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Padwa, A., Eds.; Comprehensive Heterocyclic Chemistry II; Pergamon: Oxford, 1996; Vol. 1B, p 507.
4. (a) Ojima, I. In *The Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993; p 197; and references cited therein. (b) Palomo, C.; Aizpurua, J.; Ganboa, I. In *Enantioselective Synthesis of Beta-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997; pp 279–357; and references cited therein. (c) For a review on this subject see: Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377–386. (d) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226–240. (e) Alcaide, B.; Almendros, P. *Synlett* **2002**, 381–393.
5. (a) Nagahara, T.; Kametani, T. *Heterocycles* **1987**, *25*, 729–806. (b) Thomas, R. C. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, 1990; p 553. (c) Palomo, C. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Berlin, 1990; p 565. (d) Palomo, C.; Arrieta, A.; Cossio, F. P.; Aizpurua, J. M.; Mielgo, A.; Aurrekoetxea, N. *Tetrahedron Lett.* **1990**, *31*, 6429–6432. (e) Palomo, C.; Cabre, F.; Ontoria, J. M. *Tetrahedron Lett.* **1992**, *33*, 4819–4822. (f) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Ponzini, F. *J. Org. Chem.* **1993**, *58*, 4746–4748.
6. Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226–240.
7. (a) Jayaraman, M.; Deshmukh, A. R. A. S.; Bhawal, B. M. *J. Org. Chem.* **1994**, *59*, 932–934. (b) Jayaraman, M.; Nandi, M.; Sathe, K. M.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron: Asymmetry* **1993**, *4*, 609–612. (c) Jayaraman, M. J.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron* **1996**, *52*, 8989–9004.
8. Krishnaswamy, D.; Govande, V. V.; Deshmukh, A. R. A. S. *Synthesis* **2003**, *12*, 1903–1908.
9. (a) Govande, V. V.; Arun, M.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Synth. Commun.* **2000**, *30*, 4177–4182. (b) Joshi, S. N.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron: Asymmetry* **2000**, *11*, 1477–1485. (c) Krishnaswamy, D.; Bhawal, B. M.; Deshmukh, A. R. A. S. *Tetrahedron Lett.* **2000**, *41*, 417–419. (d) Thiagarajan, K.; Puranik, V. G.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron* **2000**, *56*, 7811–7816. (e) Karupaiyan, K.; Puranik, V. G.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron* **2000**, *56*, 8555–8560. (f) Bhawal, B. M.; Joshi, S. N.; Krishnaswamy, D.; Deshmukh, A. R. A. S. *J. Indian Inst. Sci.* **2001**, *81*, 265–276. (g) Joshi, S. N.; Puranik, V. G.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Tetrahedron: Asymmetry* **2001**, *12*, 3073–3076. (h) Arun, M.; Govande, V. V.; Deshmukh, A. R. A. S.; Bhawal, B. M. *Indian J. Chem.* **2002**, *41B*, 856–857. (i) Krishnaswamy, D.; Govande, V. V.; Gumaste, V. K.; Bhawal, B. M.; Deshmukh, A. R. A. S. *Tetrahedron* **2002**, *58*, 2215–2225. (j) Patil, R. T.; Parveen, G.; Gumaste, V. K.; Bhawal, B. M.; Deshmukh, A. R. A. S. *Synlett* **2002**, 1455–1458. (k) Joshi, S. N.; Phalgune, U. D.; Bhawal, B. M.; Deshmukh, A. R. A. S. *Tetrahedron Lett.* **2003**, *44*, 1827–1830. (l) Arun, M.; Joshi, S. N.; Puranik, V. G.; Bhawal, B. M.; Deshmukh, A. R. A. S. *Tetrahedron* **2003**, *59*, 2309–2316. (m) Shinkre, B. A.; Puranik, V. G.; Bhawal, B. M.; Deshmukh, A. R. A. S. *Tetrahedron: Asymmetry* **2003**, *14*, 453–459. (n) Jayanthi, A.; Gumaste, V. K.; Deshmukh, A. R. A. S. *Synlett* **2004**, 979–982. (o) Shaikh, A. L.; Puranik, V. G.; Deshmukh, A. R. A. S. *Tetrahedron* **2005**, *61*, 2441–2451.
10. (a) Jayaraman, M.; Puranik, V. G.; Bhawal, B. M. *Tetrahedron* **1996**, *52*, 9005–9016. (b) Srirajan, V.; Deshmukh, A. R. A. S.; Puranik, V. G.; Bhawal, B. M. *Tetrahedron: Asymmetry* **1996**, *7*, 2733–2738. (c) Deshmukh, A. R. A. S.; Bhawal, B. M.; Krishnaswamy, D.; Govande, V. V.; Shinkre, B. A.; Jayanthi, A. *Curr. Med. Chem.* **2004**, *11*, 1889–1920. (d) Shirode, N. M.; Kulkarni, K. C.; Gumaste, V. K.; Deshmukh, A. R. A. S. *ARKIVOC (i)* **2005**, 53–64.
11. (a) Okino, T.; Matsuda, H.; Murakami, M.; Yamaguchi, K. *Tetrahedron Lett.* **1993**, *34*, 501–504. (b) Ishida, K.; Kato, T.; Murakami, M.; Watanabe, M.; Watanabe, M. F. *Tetrahedron* **2000**, *56*, 8643–8656. (c) Ishida, K.; Matsuda, H.; Murakami, M. *Tetrahedron* **1998**, *54*, 13475–13484.
12. (a) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1994**, *50*, 11303–11314. (b) Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goodwin, C. J. *Tetrahedron: Asymmetry* **1995**, *6*, 165–176.

13. (a) Wee, A. G. H.; McLeod, D. D. *J. Org. Chem.* **2003**, *68*, 6268–6273. (b) Ha, H. J.; Ahn, Y.-G.; Woo, J.-S.; Lee, G. S.; Lee, W. K. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1667–1672. (c) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1999**, *64*, 2852–2859. (d) Sugimura, H.; Miura, M.; Yamada, N. *Tetrahedron: Asymmetry* **1997**, *8*, 4089–4099. (e) Righi, G.; Chionne, A.; D'Achille, R.; Bonini, C. *Tetrahedron: Asymmetry* **1997**, *8*, 903–907. (f) Jefford, C. W.; Mcnulty, J.; Lu, Z. H.; Wang, J. B. *Helv. Chim. Acta* **1996**, *79*, 1203–1216. (g) Tuch, A.; Saniere, M.; Merrer, Y. L.; Depezay, J. *Tetrahedron: Asymmetry* **1996**, *7*, 2901–2909. (h) Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goodwin, C. J. *Tetrahedron: Asymmetry* **1994**, *5*, 203–206.

14. Palomo, C.; Aizpurua, J.; Ganboa, I.; Oiarbide, M. *Synlett* **2001**, 1813–1826.
15. (a) Banik, B. K.; Manhas, M. S.; Kaluza, Z.; Barakat, K. J.; Bose, A. K. *Tetrahedron Lett.* **1992**, *33*, 3603–3606. (b) Wagle, D. R.; Garai, C.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeyer, T. M.; Hegde, V. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1988**, *53*, 4227–4236.
16. (a) Andrews, G. C.; Crawford, T. C.; Bacon, B. E. *J. Org. Chem.* **1981**, *46*, 2977–2979. (b) Hubschwerlen, C. *Synthesis* **1986**, 962–964.
17. Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765–2768.
18. Bieg, T.; Szeja, W. *Synthesis* **1985**, 76–77.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron
Tetrahedron 62 (2006) 4622

Corrigendum

Corrigendum to: "A glycal approach towards an efficient and stereodivergent synthesis of polyhydroxypyrrolidines" [Tetrahedron 62 (2006) 1877]

Vipin Kumar and Namakkal G. Ramesh*

Department of Chemistry, Indian Institute of Technology-Delhi, Hauz Khas, New Delhi 110016, India

Available online 10 March 2006

An error has been noticed in the proton NMR spectral data of compound **3**. The correct data is given below. We regret the oversight.

Compound **3**; δ_H (300 MHz, D_2O): 4.17 (1H, br t), 3.99 (1H, br t), 3.92–3.71 (4H, m), 3.50 (1H, quintet, $J=5.0$ Hz), 3.00 (1H, q, $J=5.0$ Hz).

DOI of original article: 10.1016/j.tet.2005.11.037
* Corresponding author. Tel.: +91 11 26596584; fax: +91 11 26581102/26582037; e-mail: ramesh@chemistry.iitd.ac.in

doi:10.1016/j.tet.2006.02.058