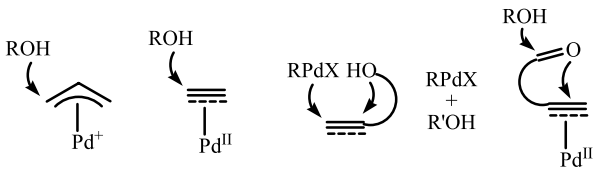
ELSEVIER

Tetrahedron

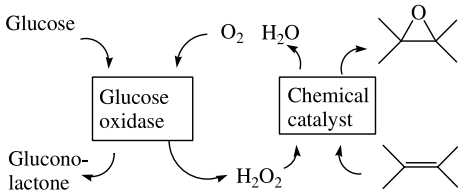
Tetrahedron Vol. 61, No. 25, 2005

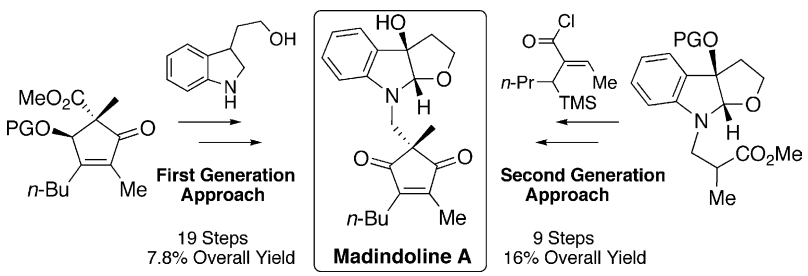
Contents

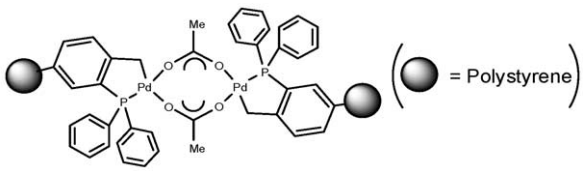
REPORT

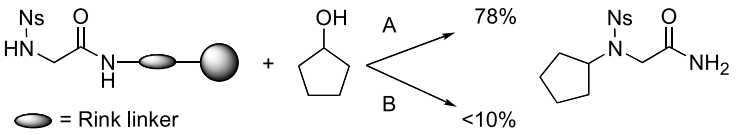


ARTICLES

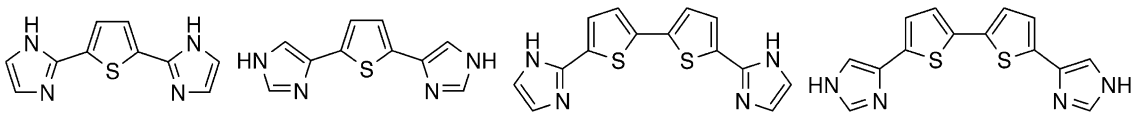


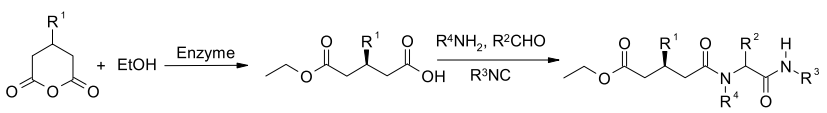


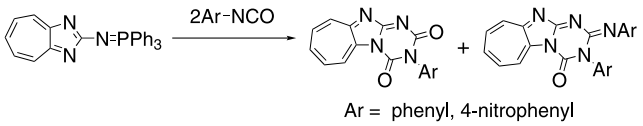


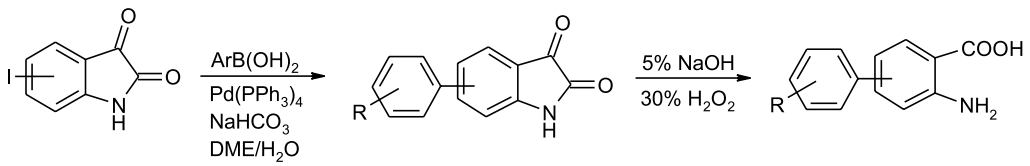


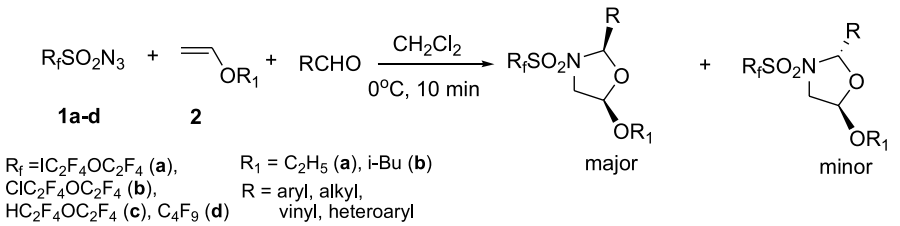
A. PPh_3, DEAD, iPr_2EtN; B. PEt_3, DEAD, iPr_2EtN

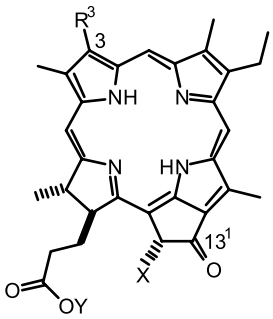


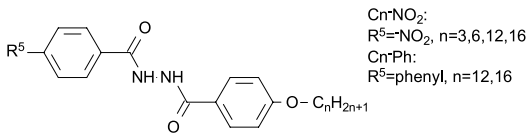


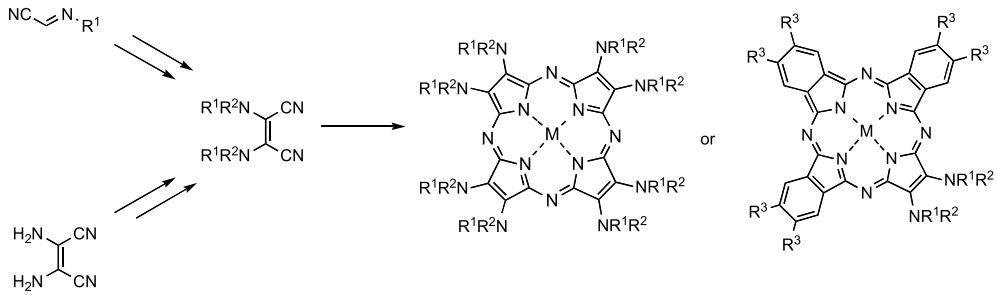


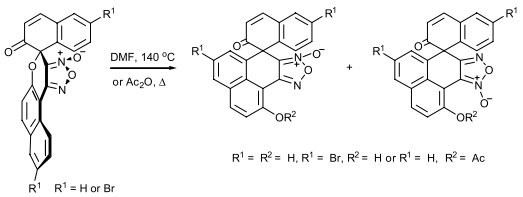


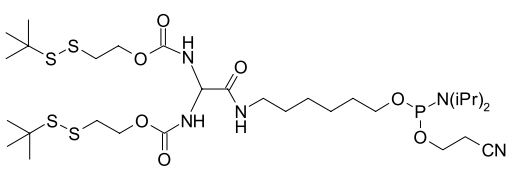


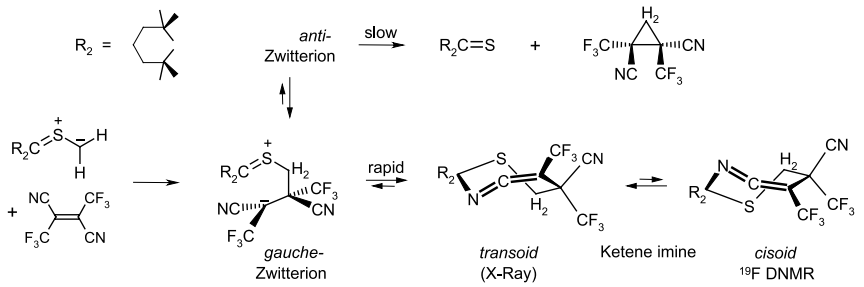












OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Image representing a porphyrazine, a class of molecules with diverse potential applications from optical recording media to the diagnosis and treatment of cancers. We are grateful to Murray Robertson (Visual Elements, Glasgow) for designing the cover and the attendant video (http://www.certainerrors.co.uk/wip/synthesis/tetra 01.html). *Tetrahedron* **2005**, *61*, 6115–6130.

Indexed/Abstracted in: AGRICOLA, Beilstein, BIOSIS Previews, CAB Abstracts, Chemical Abstracts, Chemical Engineering and Biotechnology Abstracts, Current Biotechnology 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
ELSEVIER
Tetrahedron 61 (2005) 5955–6008

Tetrahedron report number 721

Palladium-catalysed reactions of alcohols. Part C: Formation of ether linkages☆

Jacques Muzart*

Unité Mixte de Recherche 'Réactions Sélectives et Applications', CNRS, Université de Reims Champagne-Ardenne, B.P. 1039, 51687 Reims Cedex 2, France

Received 17 March 2005

Contents

☆ See Refs. 1 and 2.

Keywords: Palladium; Alcohols; Etherification; Heterocyclisation; Oxypalladation; η^3-Allylpalladium.
Abbreviations: atm, atmosphere; BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; cat., catalytic; COD, 1,5-cyclooctadiene; conv, conversion; Cy, cyclohexyl; dba, dibenzylidene acetone; DBU, 1,8-diazabicyclo[5.4.0]undec-7ene; de, diastereoisomeric excess; DMA, *N*,*N*-dimethylacetamide; dppe, 1,2-bis(diphenylphosphino)ethane; dppb, 1,4-bis(diphenylphosphino)butane; dppf, 1,1′-bis(diphenylphosphino)ferrocene; dppp, 1,3-bis(diphenylphosphino)propane; dr, diastereoisomeric ratio; ee, enantiomeric excess; equiv, equivalent; MS, molecular sieves; phenan, phenanthroline; Py, pyridine; rt, room temperature; THP, tetrahydropyranyl; tol-BINAP, 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl; Ts, 4-methylphenylsulfonyl; TON, turnover number; TPPTS, tris(3-sulfanatophenylphosphine) trisodium.
* Tel.: +33 3 2691 3237; fax: +33 3 2691 3166; e-mail: jacques.muzart@univ-reims.fr

doi:10.1016/j.tet.2005.04.002

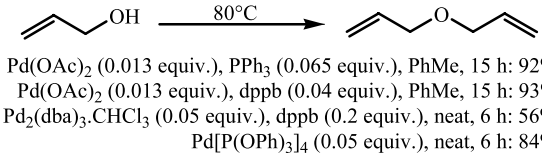
1. Introduction

The literature contains an impressive number of Pd-catalysed reactions using alcohols as substrates or reagents, and we are attempting to cover this topic with a series of reviews. The oxidation reactions of alcohols to the corresponding carbonyl compounds have been the subject of Part A,[1] while Part B has summarised the formation of C–C and C–N bonds from unsaturated alcohols.[2] The present review is devoted to the formation of C–O bonds, the oxygen atom coming from an alcohol, and is organised, as previously, according to, firstly, the type of reaction and, secondly, the nature of the substrate. The next review, Part D, will complete the series, with, mainly, a description of the rearrangement, cleavage, carbonylation and carboxylation reactions. As mentioned in Part B, the reports concerning phenols, and those where the hydroxy group is recovered unmodified at the end of the process, are beyond the scope of these reviews.

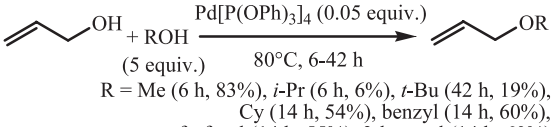
2. Addition of alcohols to η^3-allylpalladium intermediates

2.1. η^3-Allylpalladium intermediates from allylic alcohols

2.1.1. Intermolecular reactions. The homocoupling of allylic alcohols (Eq. 1)[3–6] and the dehydrative allylation of primary and secondary alcohols (Eq. 2)[4,6,7] to afford ethers are mediated by various palladium catalysts, the concomitant formation of some 1,3-butadiene from crotyl alcohol indicating an η^3-allylpalladium intermediate.[6]

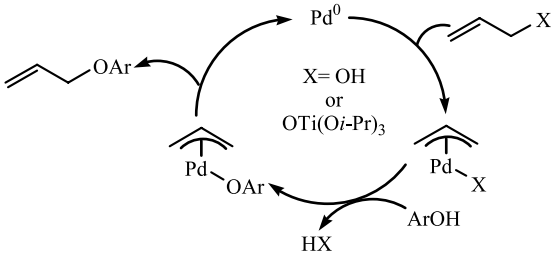


$Pd(OAc)_2$ (0.013 equiv.), PPh_3 (0.065 equiv.), PhMe, 15 h: 92%
$Pd(OAc)_2$ (0.013 equiv.), dppb (0.04 equiv.), PhMe, 15 h: 93%
$Pd_2(dba)_3.CHCl_3$ (0.05 equiv.), dppb (0.2 equiv.), neat, 6 h: 56%
$Pd[P(OPh)_3]_4$ (0.05 equiv.), neat, 6 h: 84% (1)

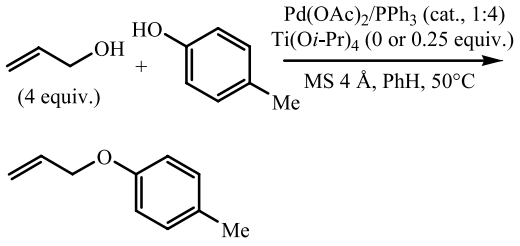


R = Me (6 h, 83%), *i*-Pr (6 h, 6%), *t*-Bu (42 h, 19%), Cy (14 h, 54%), benzyl (14 h, 60%), furfuryl (14 h, 55%), 3-butenyl (14 h, 60%) (2)

The Pd-catalysed etherification of allylic alcohols with phenols is promoted by titanium^{IV} isopropoxide (Eq. 3), and the proposal of a transient allyl titanate leading to an η^3-allylpalladium intermediate (Scheme 1) is supported by the formation of the diallyl ether and allyl isopropyl ether in the absence of a phenol.[8]



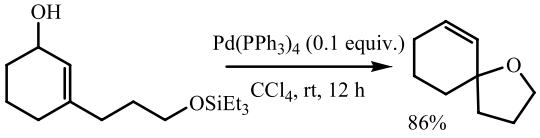
Scheme 1.



(3)

$Pd(OAc)_2$ (0.025 equiv.), without $Ti(O\textit{i}\text{-}Pr)_4$, 7 h: 26%
$Pd(OAc)_2$ (0.01 equiv.), $Ti(O\textit{i}\text{-}Pr)_4$ (0.25 equiv.), 1 h: 93%

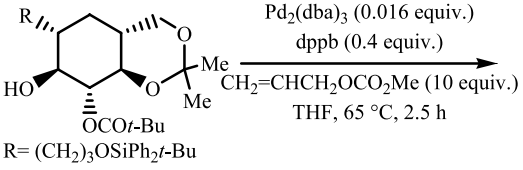
2.1.2. Intramolecular reactions. A variety of furan rings, in particular spirotetrahydrofurans, have been obtained by the exposure to $Pd(PPh_3)_4$ of carbon tetrachloride solutions of allylic alcohols substituted in the β-position by a triethylsilyloxyalkyl chain (Eq. 4). Godleski et al. suggest an unusual mechanism (Scheme 2): PPh_3 liberated from the complex would react with CCl_4 to form the known $PPh_3Cl^+CCl_3^-$ salt, which would be trapped by the hydroxy group to provide $HCCl_3$ and an oxyphosphonium ion; the reaction of this ion with Pd^0 would give the η^3-allylpalladium complex, while Cl^- would deprotect the triethylsilyl ether, thus allowing the cyclisation step. The problem with this mechanism is the regeneration of PPh_3 from $OPPh_3$; a reduction by Et_3SiCl was suspected, but control experiments showed too slow a reaction at room temperature to be operative.[9]



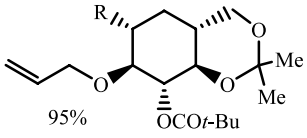
(4)

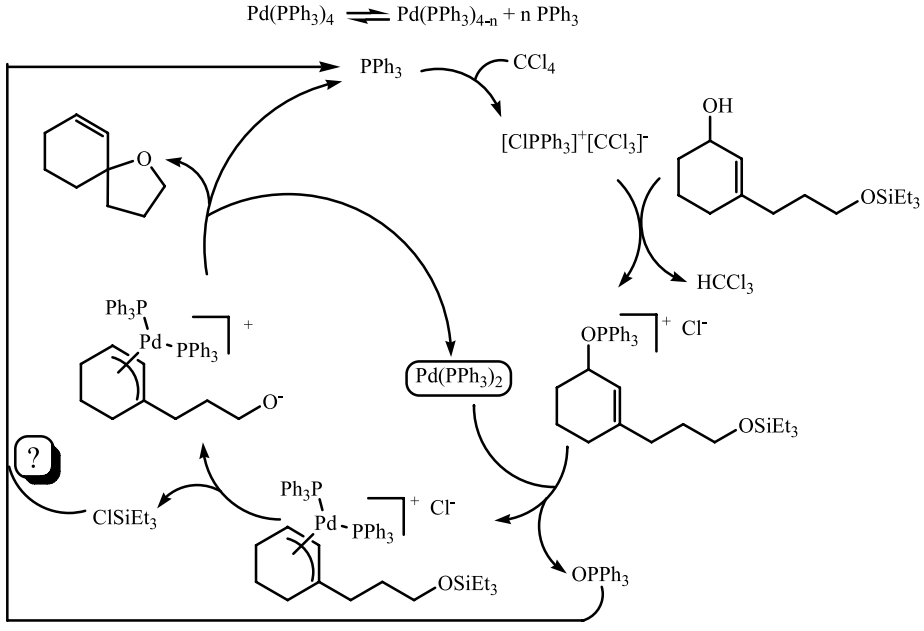
2.2. η^3-Allylpalladium intermediates from allylic alcohol derivatives

2.2.1. Intermolecular reactions. In 1970, Hata et al. reported the formation of ethers via the Pd-assisted intermolecular displacement between allylic alcohol derivatives and methanol or benzyl alcohol.[10–12] This allylic etherification has been subsequently abundantly documented using allylic acetates or carbonates, and various alcohols or lactols such as partially protected carbohydrates (Eqs. 5–9),[13–21] and asymmetric allylations have been carried out in the presence of chiral ligands with low to moderate enantioselectivities.[20,21] The rate of coupling can be increased by the addition of small amounts of tributyltin alkoxide (Eq. 9).[20,22] The addition of the alcohol may, however, be an unwanted reaction, as, for example, the Pd-catalysed cross-coupling of allylic acetates with arylboronic acids carried out in methanol, which led to the allylic methyl ether as a side product.[23]

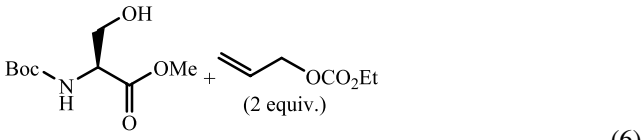


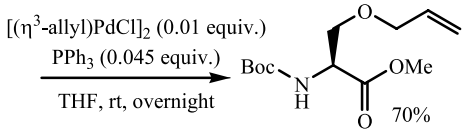
(5)



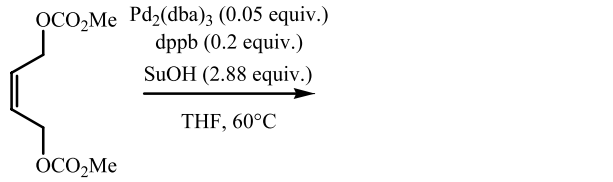


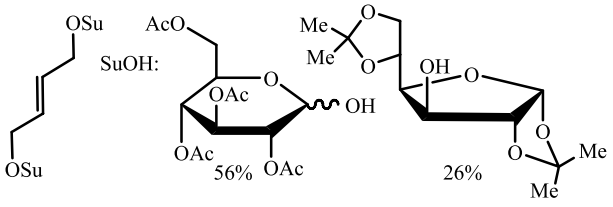
Scheme 2.



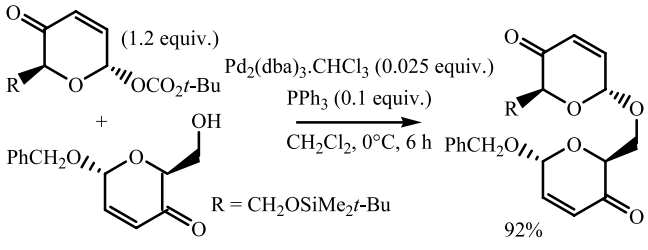


(6)

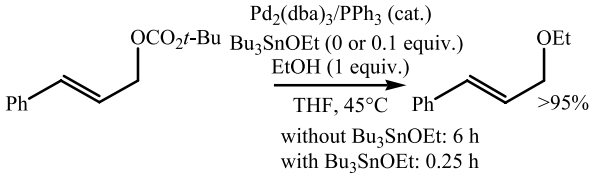




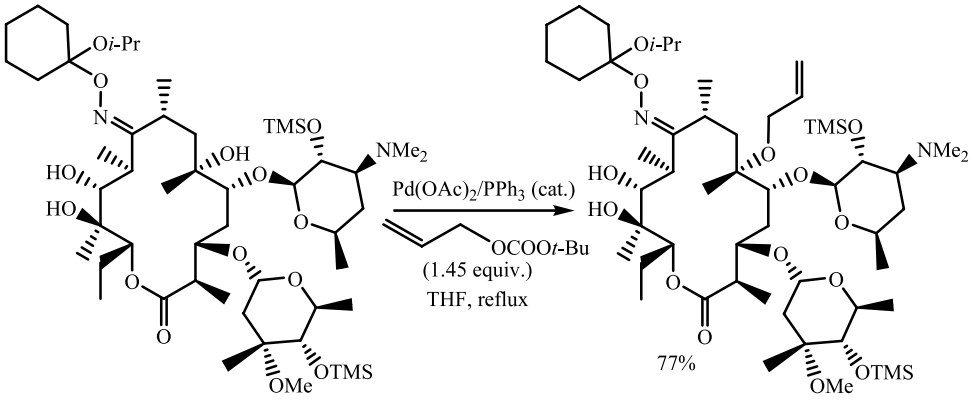
(7)



(8)



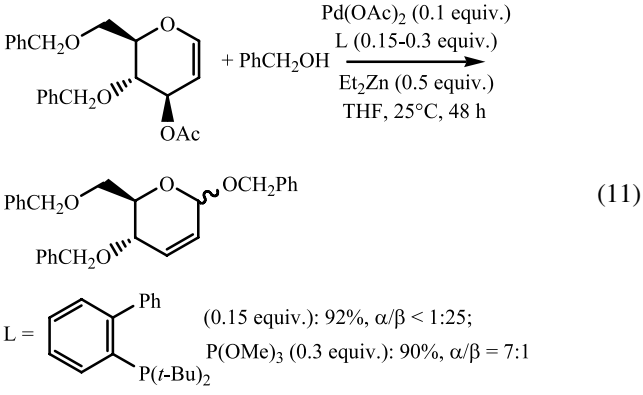
(9)



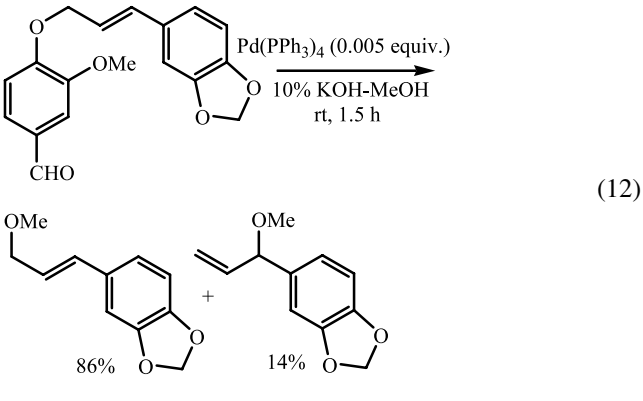
(10)

Allyl *tert*-butyl carbonate has been used for the *O*-allylation of polyhydroxylated macrolides, such as erythromycin (Eq. 10)[19] and tylosin[24] derivatives, with a selectivity towards the different hydroxyls attributed to the large size of the *tert*-butoxy group, and it has been pointed out that water was detrimental to these reactions by competing as a nucleophile.[19,25]

Diethylzinc and dimethylzinc are able to promote the reaction of various alcohols with allylic acetates at room temperature.[26–28] The *O*-glycosylation of benzyl alcohol and monosaccharides with glycal was thus attained, the choice of ligand giving selective access to the α- or β-linked product (Eq. 11). According to Lee et al., the role of Zn^{II} in these reactions is the activation of both the acceptor for the nucleophilic addition and the leaving group for the ionisation.[27]



(11)

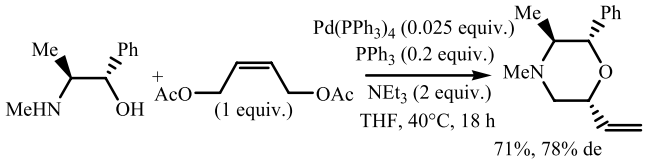


(12)

Although heating is usually required to form η^3-allylpalladium intermediates from allyl aryl ethers,[29] Hara et al.

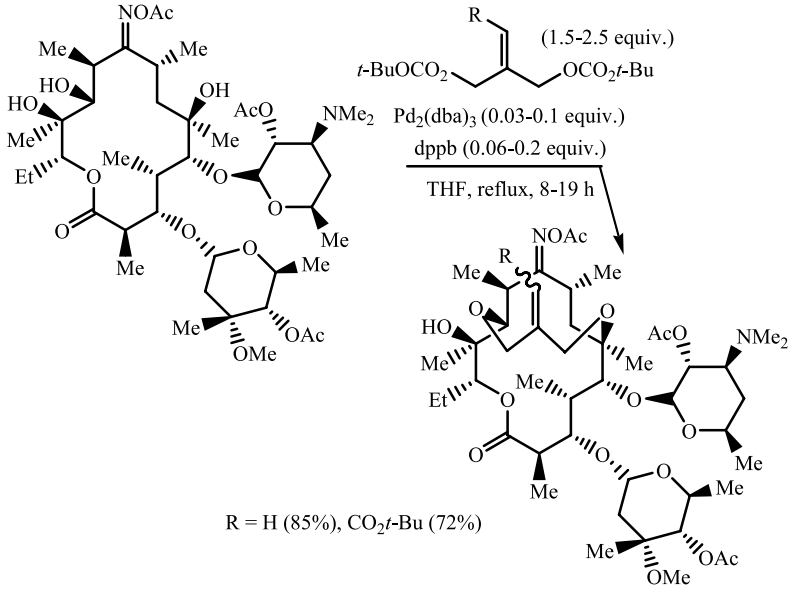
efficiently synthesised allyl methyl ethers from *O*-[3-(3,4-methylenedioxyphenyl)-2-propenyl]-vanillin and methanol at room temperature (Eq. 12).[30]

The β-aminoalcohols are bifunctional nucleophiles, which afford vinyl morpholines by a domino reaction with 2-butene-1,4-diol derivatives,[31] via the successive nucleophilic additions of the nitrogen and hydroxy moieties on η^3-allylpalladium intermediates. The use of chiral ligands or enantiopure aminoalcohols leads to enantioselective[32] or diastereoselective[33] cyclisations, respectively (Eq. 13).



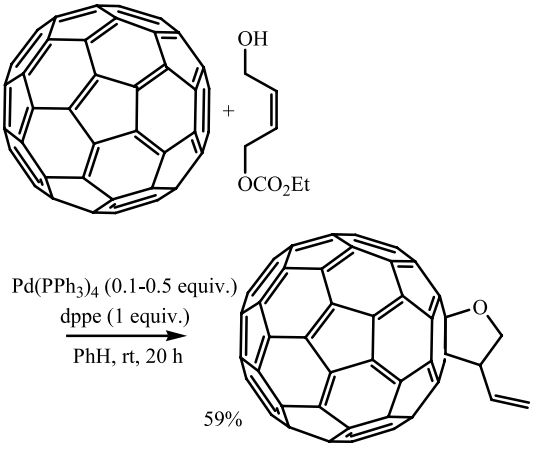
(13)

Wang et al. have synthesised an erythromycin A-derived macrolide via Pd-catalysed cascade inter- and intramolecular dialkylations (Eq. 14).[34]



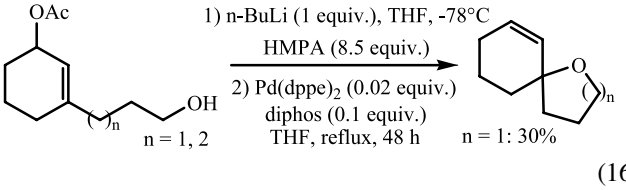
(14)

The [3+2] cycloaddition of 60-fullerene with (*Z*)-$HOCH_2$-$CH{=}CHCH_2OCO_2Et$ (Eq. 15) would involve the addition of the η^3-allylpalladium alkoxide as shown in Scheme 3.[35]

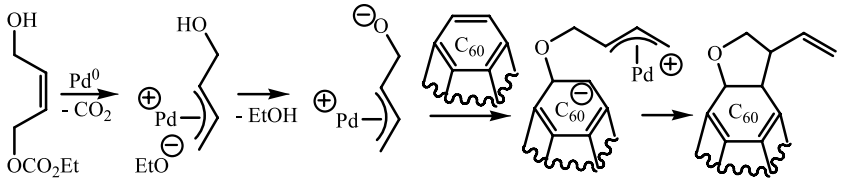


(15)

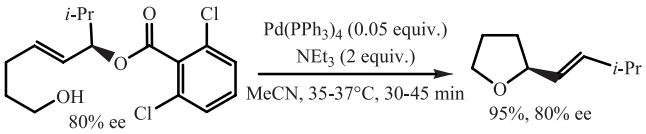
2.2.2. Intramolecular reactions. In 1983, three Pd-catalysed intramolecular heteroannelations were disclosed almost simultaneously: (i) spirotetrahydrofurans(pyrans) were obtained with low yields via the addition of a preformed alcoholate to an in situ-formed η^3-allylpalladium complex (Eq. 16),[9] (ii) vinyltetrahydrofurans(pyrans) were isolated as side products of the Pd-catalysed deamination of allylic amines bearing a 4-hydroxyalkyl substituent in the β-position,[36] and (iii) a 2-alkenyltetrahydrofuran was efficiently synthesised, with a complete transfer of the chirality, using 2,6-dichlorobenzoate as the leaving group (Eq. 17).[37]



(16)

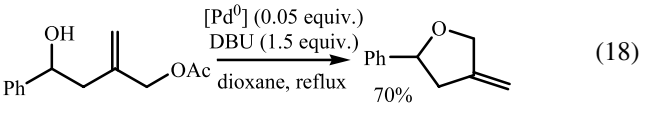


Scheme 3.

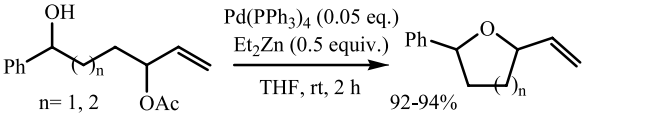


(17)

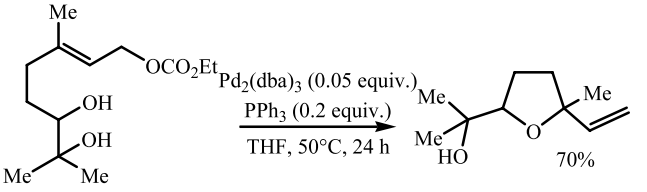
Subsequently, a number of furan (Eqs. 18–20)[26,38–42] and pyran (Eqs. 21 and 22)[39,40,43–45] rings have been obtained via intramolecular additions of hydroxy groups to in situ-formed η^3-allylpalladium complexes,[46] but the process has a low efficiency with a tertiary alcohol as the nucleophilic species.[39]



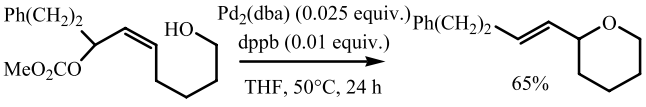
(18)



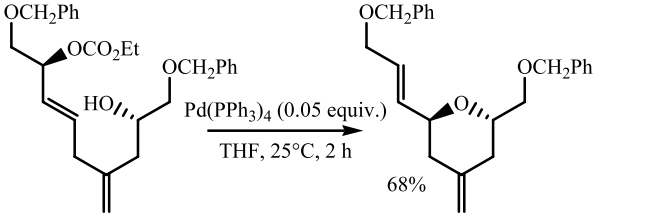
(19)



(20)



(21)



(22)

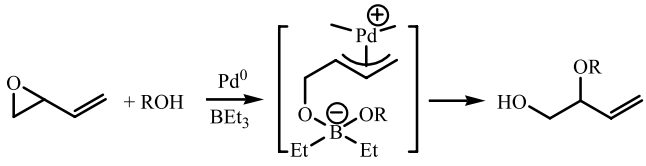
Low enantioselectivities have been reported in the presence of chiral ligands such as (*R*)-Binap, (*S*,*S*)-Chiraphos, (*S*,*S*)-Diop or (*S*,*S*)-BDPP,[40] while Trost's pocket ligands have allowed desymmetrisations leading to bis-oxanes with up to 98% ee from *meso*-tetraol bis-(allylic acetates) (Eq. 23),[47] and to tetrahydrofuran (Eq. 24)[48] or bis-tetrahydrofuran[49] cores with up to 97% ee from diol bis(allylic acetates).

Wang e t al. have synthesised a 6,11-*O*-bridged 9-keto-erythromycin from the selective intramolecular addition of a tertiary hydroxy group to an allylic *t*-butyl carbonate moiety (Eq. 25).[34]

Cyclic carbonates have been obtained with fair to high yields from alkyl 4-hydroxybut-2-enyl-carbonates in a sealed flask (Eq. 26).[50] Without a sealed flask, the process was less efficient and led, sometimes, to epoxides except for the reactions carried out under a carbon dioxide atmosphere (Eq. 27)[51] (see Part D of this series of reviews).

2.3. η^3-Allylpalladium intermediates from vinyl epoxides

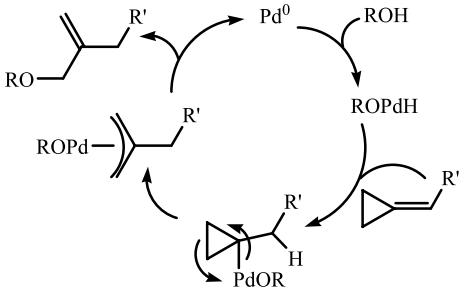
The Pd-catalysed addition of alcohols to vinyl epoxides affords a mixture of the two corresponding hydroxylated allylic ethers,[52] the reaction becoming regioselective by the addition of catalytic amounts of triethylborane,[53] and enantioselective by the use of chiral ligands (Eqs. 28 and 29).[53–59] The boron co-catalyst would enhance the nucleophilicity of the alcohol via the formation of an 'ate' complex which, furthermore, induces the regioselectivity of the substitution (Scheme 4).[55] Nevertheless, intramolecular reactions, leading efficiently to 2-vinyl-3-hydroxytetrahydro(furan)pyrans in the absence of boron species, have been documented (Eqs. 30 and 31).[41,59,60]



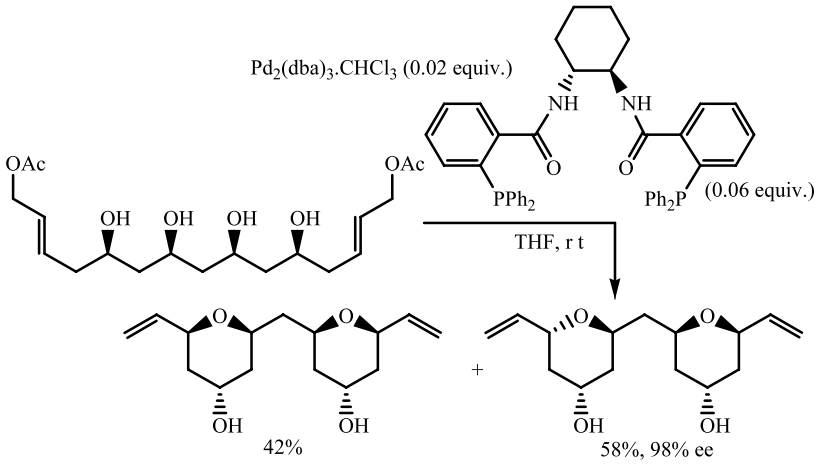
Scheme 4.

2.4. η^3-Allylpalladium intermediates from alkylidene cyclopropanes

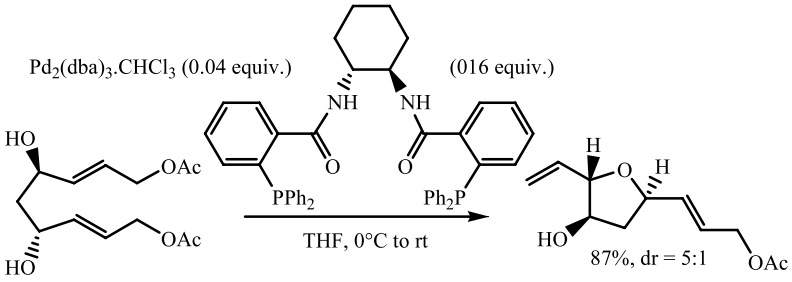
The reaction of primary, secondary or tertiary alcohols with alkylidene cyclopropanes led to the corresponding allylic ethers, the efficiency of this hydroalkoxylation depending greatly on the nature of the alcohol (Eq. 32). The proposed mechanism, which involves, as the first step, the insertion of Pd^0 into the RO–H bond (Scheme 5), rather than the palladium-mediated activation of the alkylidene cyclopropane, has been substantiated by deuterium-labelling experiments.[61,62]



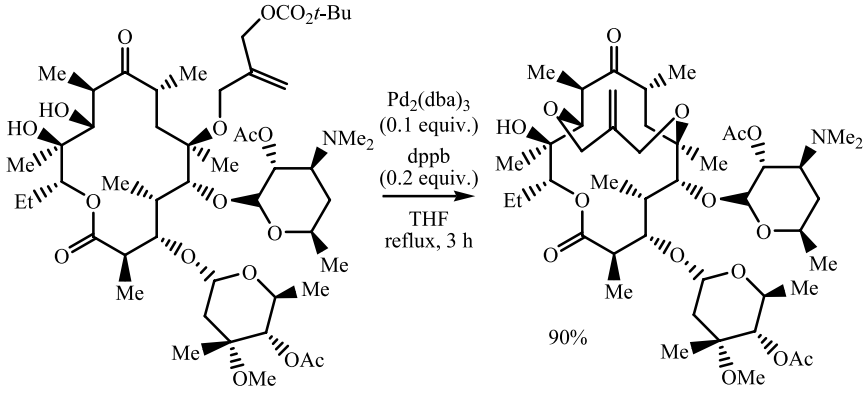
Scheme 5.


Pd2(dba)3.CHCl3 (0.02 equiv.)
(0.06 equiv.)
THF, r t
42%
58%, 98% ee

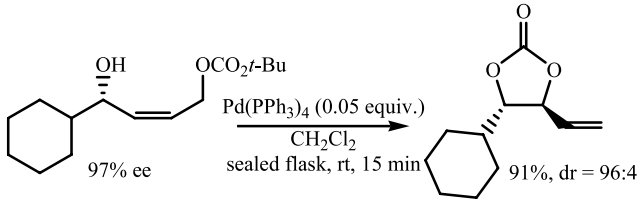
(23)


Pd2(dba)3.CHCl3 (0.04 equiv.)
(016 equiv.)
THF, 0°C to rt
87%, dr = 5:1

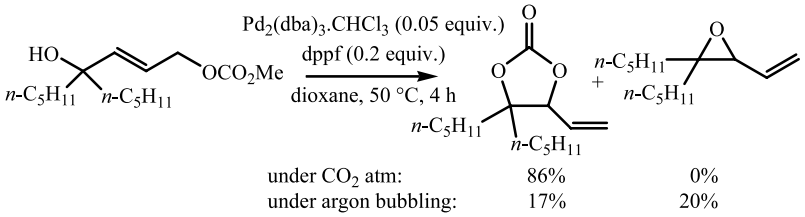
(24)


Pd2(dba)3
(0.1 equiv.)
dppb
(0.2 equiv.)
THF
reflux, 3 h
90%

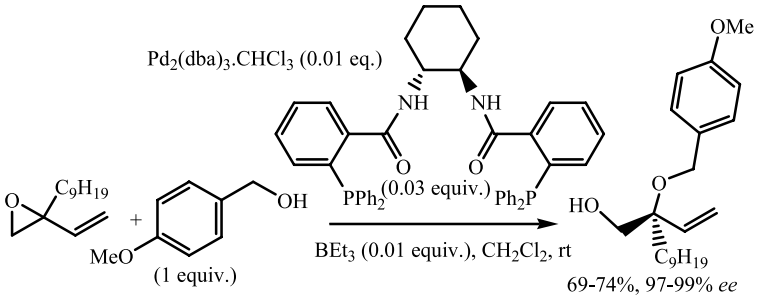
(25)


Pd(PPh3)4 (0.05 equiv.)
CH2Cl2
sealed flask, rt, 15 min
97% ee
91%, dr = 96:4

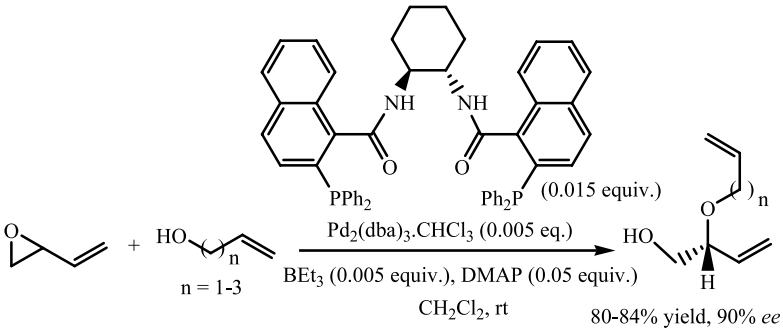
(26)


Pd2(dba)3.CHCl3 (0.05 equiv.)
dppf (0.2 equiv.)
dioxane, 50 °C, 4 h
under CO2 atm: 86% 0%
under argon bubbling: 17% 20%

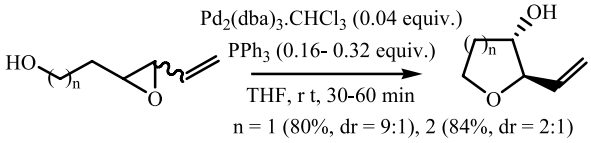
(27)



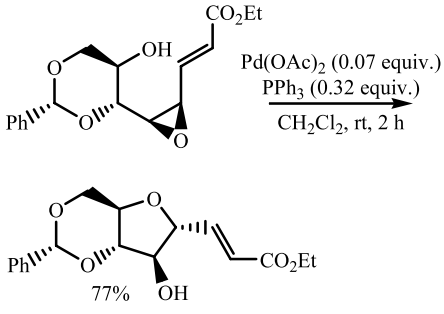
(28)



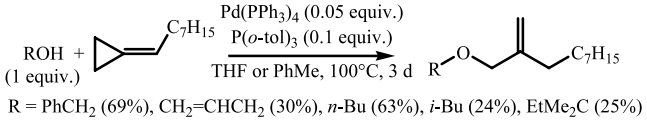
(29)



(30)



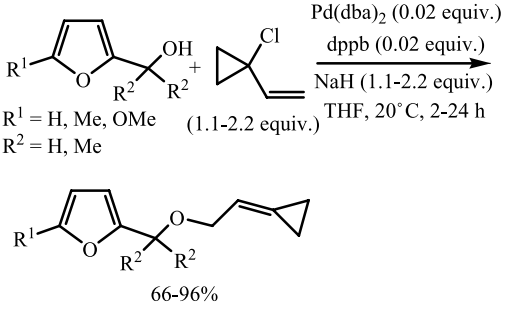
(31)



(32)

2.5. η^3-Allylpalladium intermediates from allylic chlorides

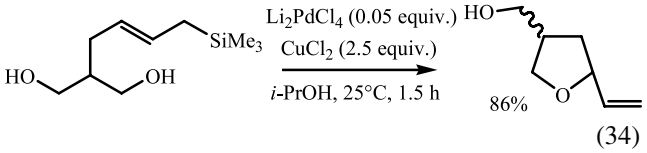
Furfuryl derivatives with an ether linkage to a methylenecyclopropane moiety have been synthesised via the substitution of 1-chloro-1-vinylcyclopropane with furfurols (Eq. 33).[63]



(33)

2.6. η^3-Allylpalladium intermediates from allylsilanes

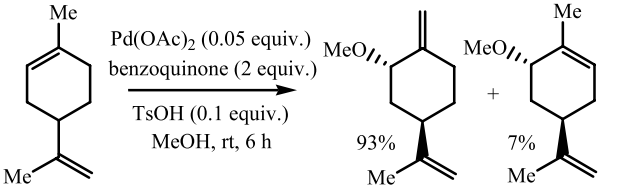
Szabó et al. employed allylsilanes to form the η^3-allylpalladium intermediates, and carried out the Pd-catalysed cyclisation in *i*-PrOH of allylsilanes containing hydroxy groups, in the presence of an excess of $CuCl_2$ (Eq. 34) or 2,3-dichloro-5,6-dicyanobenzoquinone.[42,64] These additives have a dual role, as an oxidising agent for the regeneration of the Pd^{II} catalyst, and as an activating agent of the η^3-allylpalladium intermediate[65] towards nucleophilic attack. The alcoholic solvent facilitates the palladadesilylation step, in leading to alkylsiloxanes, and may also act as a weak base that assists in the deprotonation of the hydroxy group. It seems interesting to point out that the nucleophilic attack by the internal hydroxyl was much faster than that by the external alcohol.



(34)

2.7. η^3-Allylpalladium intermediates from alkenes

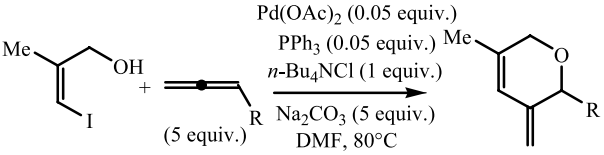
The allylic methoxylation of the endocyclic double bond of limonene, which has been carried out effectively (Eq. 35), probably involves η^3-allylpalladium intermediates.[66]



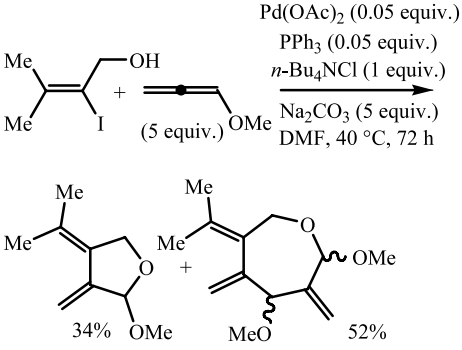
(35)

2.8. η^3-Allylpalladium intermediates from 1,2-dienes

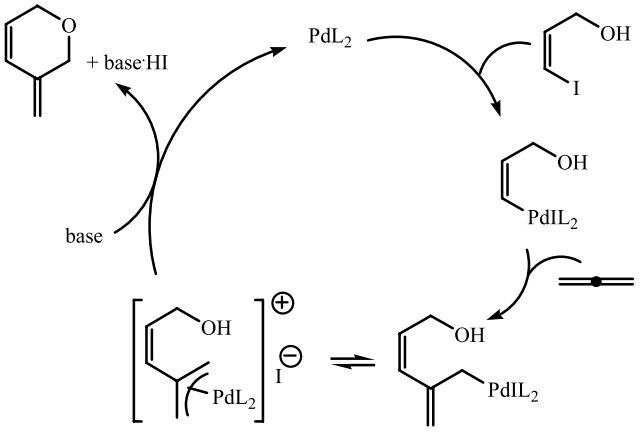
2.8.1. From allenes. The annelation of allenes with vinylic iodides bearing a hydroxyalkyl group provides five-, six- or seven-membered heterocycles (Eqs. 36–38) via the addition of the vinylpalladium iodide to the allene affording a cationic η^3-allylpalladium intermediate, from which the final adduct is produced (Scheme 6).[67–69]



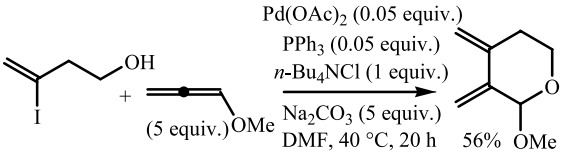
(36)



(37)

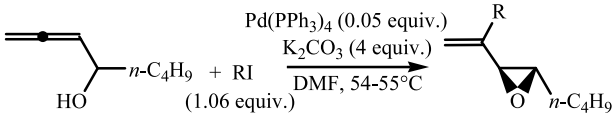


Scheme 6.

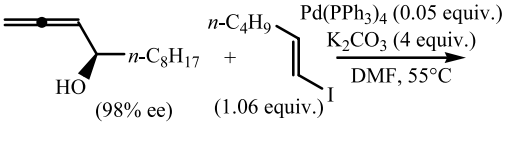


(38)

2.8.2. From allenols. In contrast to Tsuji et al., who synthesised β-disubstituted-α,β-unsaturated carbonyl compounds from 1,2-dien-4-ols and aryl or alkenyl halides (see Eq. 46 in Part B[2]),[70] Ma et al. have obtained substituted vinylic oxiranes (Eq. 39), the optically active allenols leading to the corresponding adducts without loss of chirality (Eq. 40).[71,72] In fact, Kang et al. have previously obtained epoxides from the Pd-catalysed reaction of secondary 1,2-dien-4-ols with hypervalent iodonium salts such as diphenyliodonium tetrafluoroborate, demonstrating the decisive role of the nature of the base and the C-4 substituent on the course of the reaction, the cyclic carbonates being obtained in some cases (Eqs. 41–43).[73]

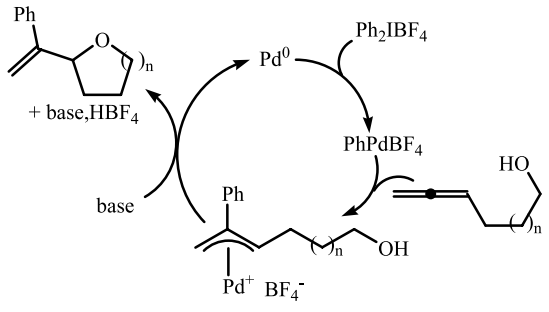


(39)

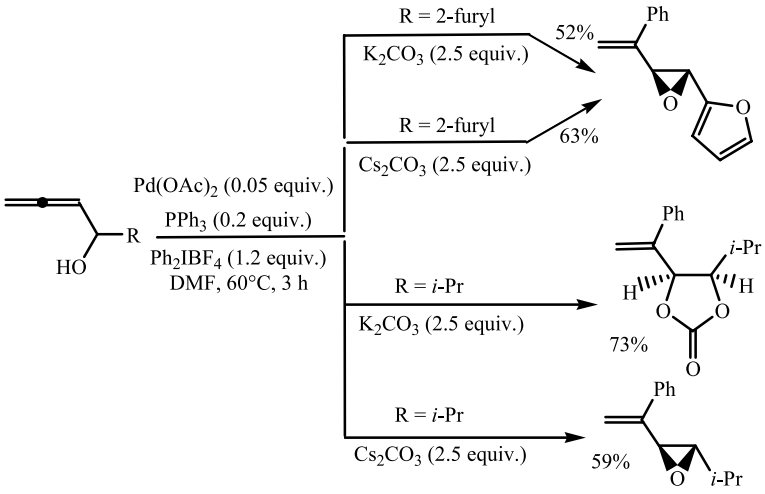


(40)

Kang et al. have also used hypervalent iodonium salts for the arylation of 1,2-dien-6(or 7)-ols to obtain 2-(2-styrenyl)-tetrahydrofuran(pyran)s (Eq. 44).[74] Kang's team seems to prefer a mechanism involving an η^3-allylpalladium intermediate (Scheme 7), rather than the nucleophilic addition of the hydroxy group to the allene moiety activated by $PhPdBF_4$,[73,74] this latter possibility corresponding to the mechanism depicted in Scheme 24, path b (see Section 3.3.5).



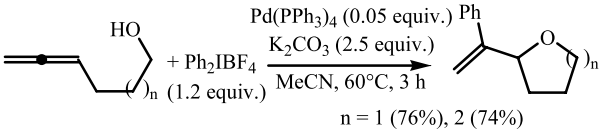
Scheme 7.



(41)

(42)

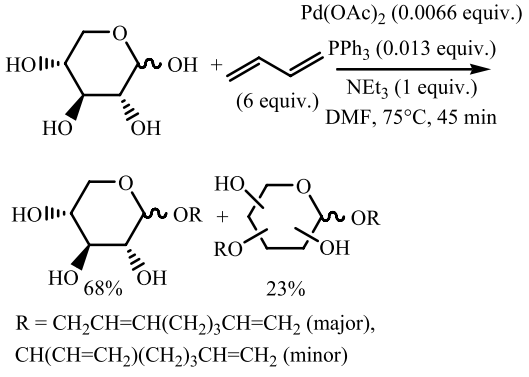
(43)



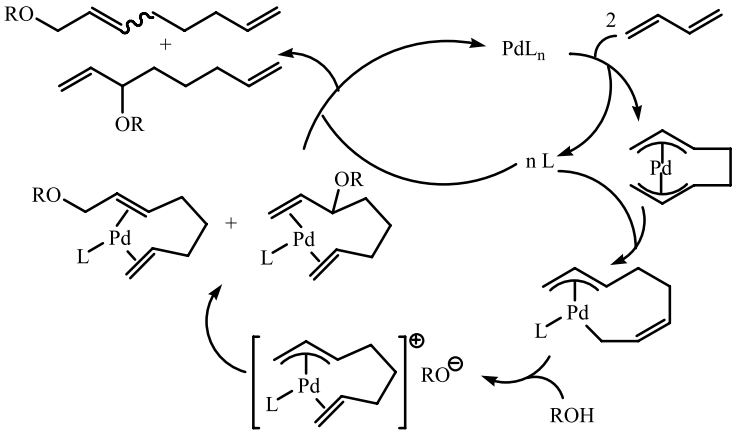
(44)

2.9. η^3-Allylpalladium intermediates from 1,3-dienes

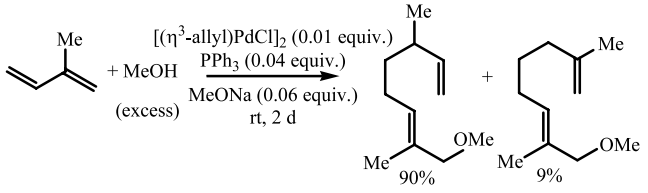
2.9.1. Intermolecular reactions. Since its discovery in 1967,[75,76] the telomerisation of 1,3-dienes with alcohols has been the subject of intensive research, because this process leads to functionalised compounds, which are useful as building blocks for fine chemicals and industrial preparations.[77] Many studies have been carried out with butadiene and methanol; mixtures of linear and branched isomers containing two butadiene units and the alkoxy functionality are usually produced,[78–80] via the simplified reaction course shown in Scheme 8. A variety of alkanols,[80,81] ethylene glycol,[82,83] and polyols,[84] especially carbohydrates (Eq. 45),[85–89] these latter substrates affording non-ionic surfactants,[90] have also been used. The telomerisation of other 1,3-dienes with alcohols has been less studied; isoprene has led to terpenoic ethers (Eq. 46),[91,92] which were obtained optically active in the presence of chiral ligands.[93]



(45)

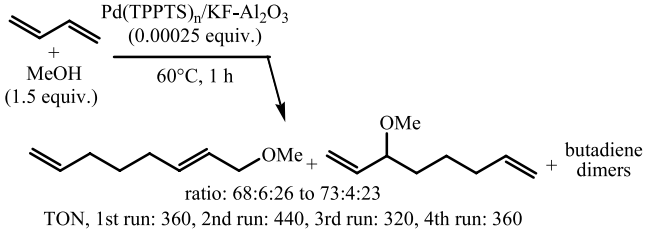


Scheme 8.



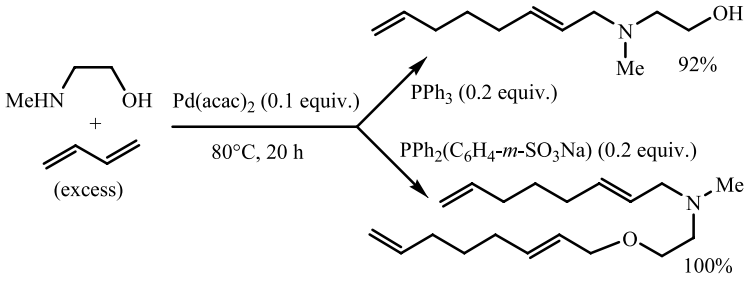
(46)

A number of studies have been carried out to control the chemo- and regioselectivity,[94,95] and to obtain better[95,96] and/or recyclable catalysts (Eq. 47),[80,97–101] with, in addition, the use of aqueous biphasic systems,[83,87] water,[87,89b,102–103] or ionic liquids[104] as solvents.



(47)

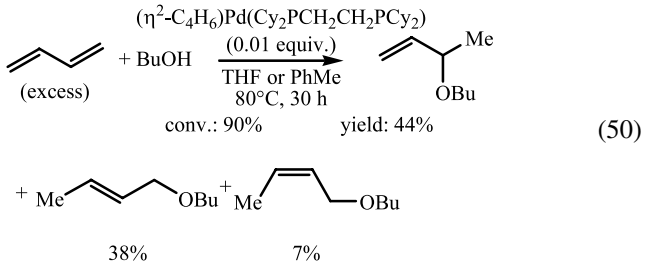
The telomerisation of butadiene with aminoalcohols affords mainly *N*-(octadienyl)-aminoalcohols (Eq. 48), but the use of a hydrophilic phosphine can promote the etherification (Eq. 49).[105]



(48)

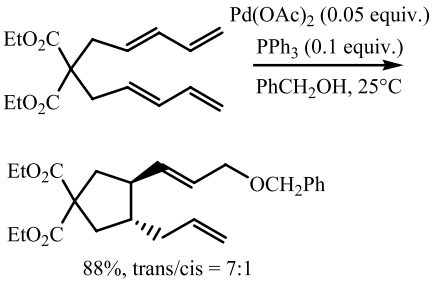
(49)

Although the intermolecular reaction of alcohols with 1,3-butadiene leads generally to octadiene derivatives, 1:1 adducts are sometimes produced as minor compounds[106] and this reactive pathway becomes highly selective with $(\eta^2\text{-}C_4H_6)Pd(R_2PC_2H_4PR_2)$ as the catalysts (Eq. 50).[107] In contrast, alkoxy ethers containing up to six butadiene units have been obtained, using either cationic η^3-allylpalladium complexes[108] or cationic cyclopalladated complexes.[109] A Japanese patent has recently claimed the selective synthesis of 2-cyclopentenyl methyl ether, via the ammonium tetrachloropalladate-catalysed addition of methanol to cyclopentadiene at 40 °C.[110]



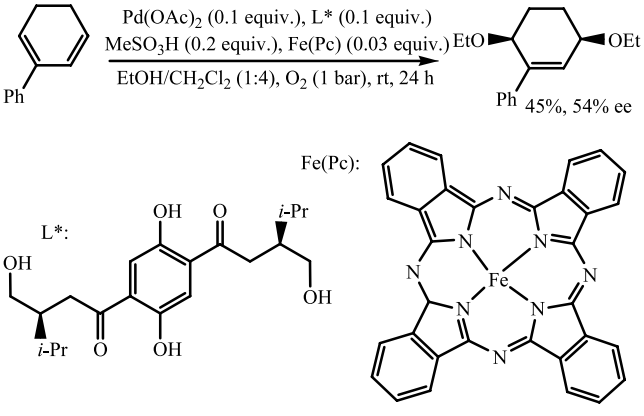
(50)

Takacs et al. have stereoselectively prepared functionalised ring systems, via the carbocyclisation of tetraenes with benzyl alcohol as the trapping reagent (Eq. 51).[111]

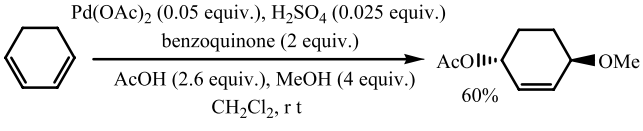


(51)

The intermolecular 1,4-dialkoxylation of cyclic 1,3-dienes has been particularly studied by Bäckvall's team,[112,113] who proposed an enantioselective procedure based on the use of a chiral hydroquinone derivative as the ligand (Eq. 52).[114,115] When the 1,3-diene is treated with a mixture of a primary, secondary or tertiary alcohol and acetic or benzoic acid, the corresponding 1-acyloxy-4-alkoxy product can be obtained with a high chemo- and stereoselectivity (Eq. 53);[113,116] the accepted mechanism involves coordination of the diene to palladium, followed by *trans* attack of the alcohol at one extremity of the diene, to afford a 4-alkoxy-substituted η^3-allylpalladium complex having an acyloxy ligand, the *cis*-migration of this ligand producing the final adduct.



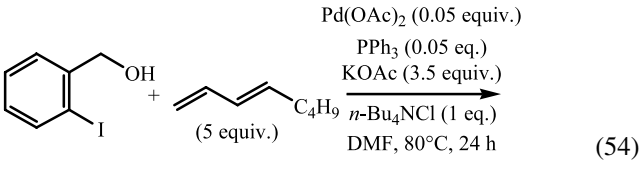
(52)



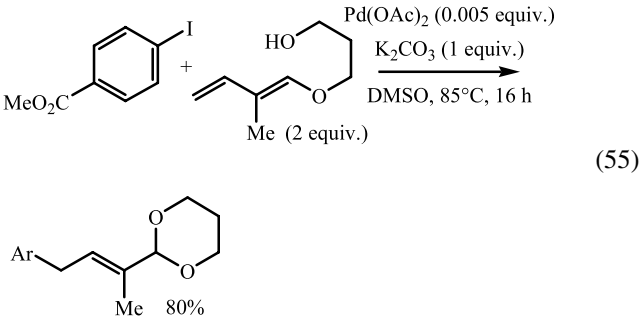
(53)

Oxygen heterocycles have been obtained through domino

reactions involving Heck arylation of an 1,3-diene leading to an η^3-allylpalladium complex, the attack on which by a hydroxy group affords the annelation product (Eqs. 54 and 55).[117,118]

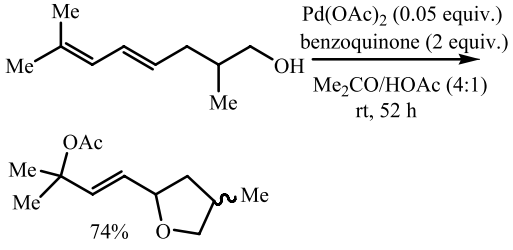


(54)

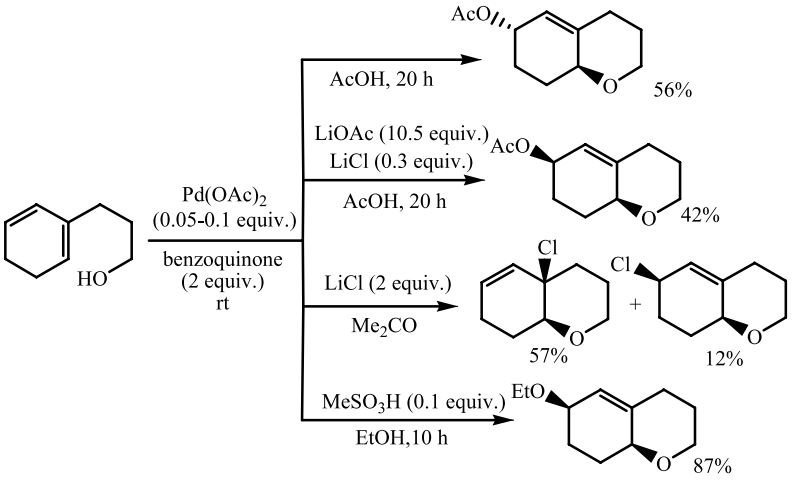


(55)

2.9.2. Intramolecular reactions. The intramolecular Pd-catalysed addition of a hydroxy group to conjugated dienes led to heteroannelation products bearing a chloro, acetoxy, hydroxy or alkoxy substituent (Eqs. 56–69). The reaction conditions have an important influence on the nature, stereo- and regioselectivity of the introduced substituent,[119–126] and also on the reproducibility of the results.[127]



(56)

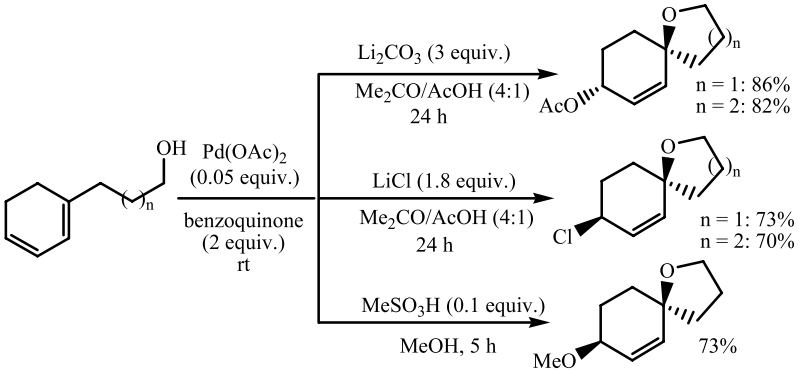


(57)

(58)

(59)

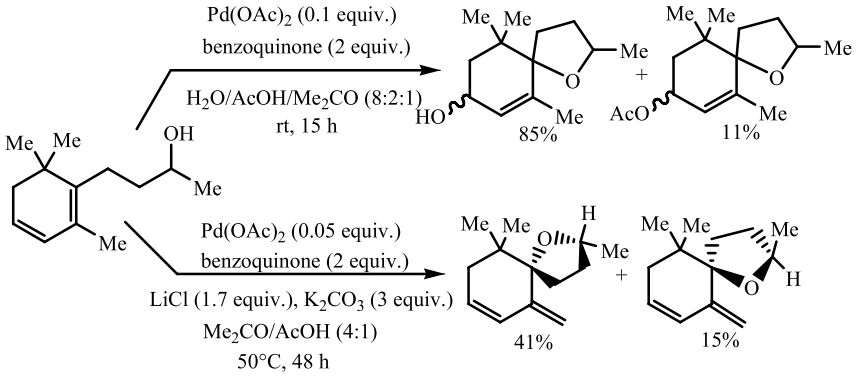
(60)



(61)

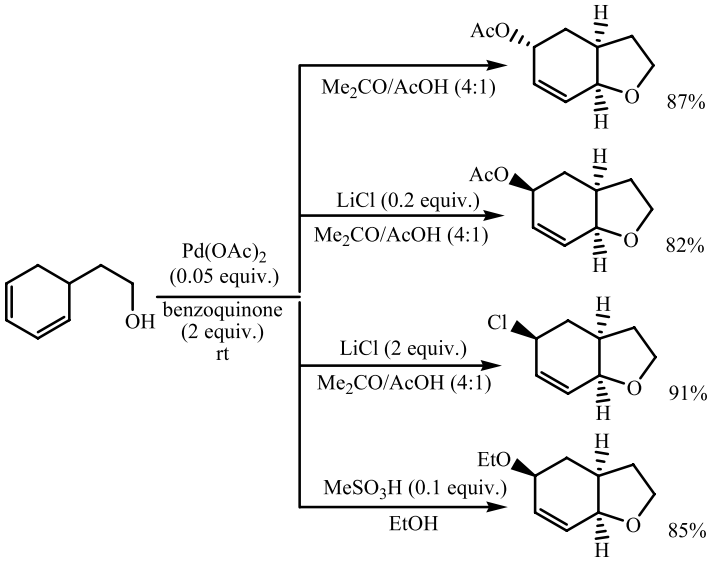
(62)

(63)



(64)

(65)



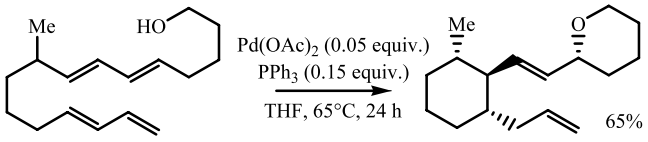
(66)

(67)

(68)

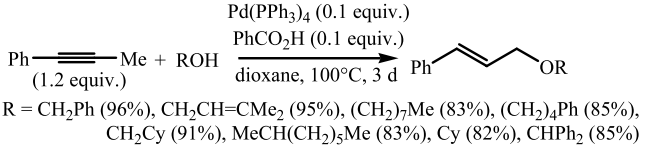
(69)

The intramolecular diene-to-diene coupling with intramolecular trapping provides two rings, via the stereoselective addition of carbon and oxygen across an internal diene subunit (Eq. 70).[128]



(70)

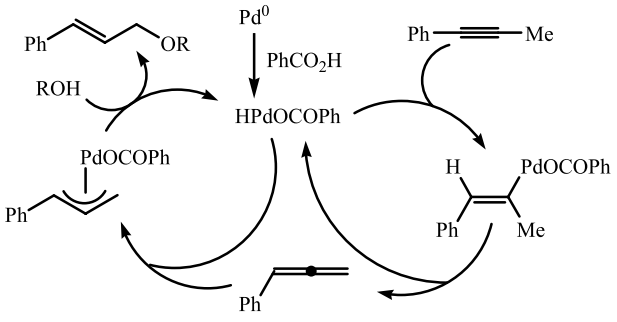
molecular allylations of alcohols with alkynes under microwave activation and solvent-free conditions (Eq. 74).[132]



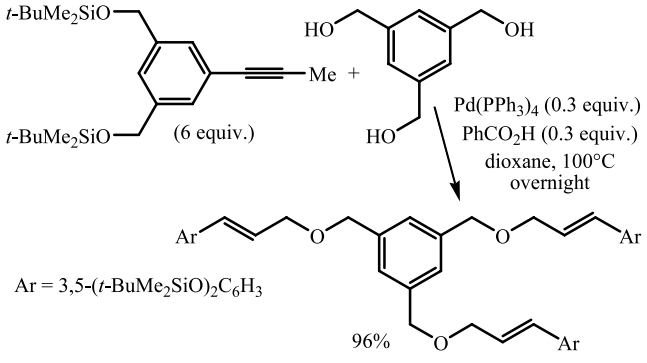
(71)

2.10. η^3-Allylpalladium intermediates from alkynes

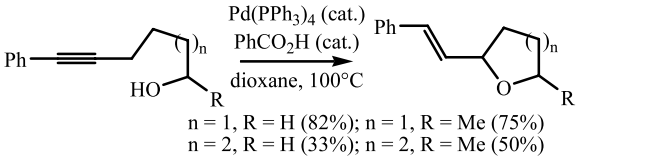
According to Yamamoto et al., the hydroalkoxylation of internal alkynes catalysed by a mixture of $Pd(PPh_3)_4$ and benzoic acid (Eq. 71) involves, firstly, the isomerisation of the substrate to the corresponding allene (Scheme 9). This process led to dendritic molecules from polyols (Eq. 72), and to five- or six-membered cyclic ethers from the intramolecular reaction of hydroxyalkynes (Eq. 73).[129] A similar procedure was reported by Zhang et al.,[130,131] while, subsequently, a dramatically reduced reaction time was observed by Yamamoto et al. in carrying out the inter-



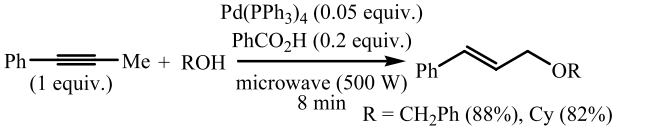
Scheme 9.



(72)

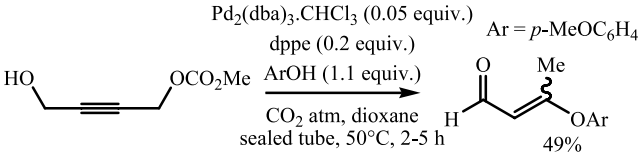


(73)

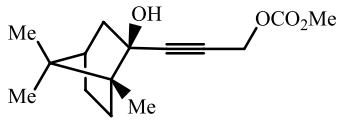


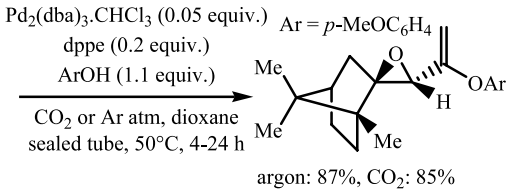
(74)

The Pd^0-catalysed addition of *p*-methoxyphenol to 4-methyloxycarbonyloxy-2-butyn-1-ol, leading to the corresponding α,β-unsaturated aldehyde (Eq. 75), which would occur as shown in Scheme 10, path a, is not a general reaction[133] (see Part D of this series of reviews). When the hydroxy group of the substrate is tertiary, the reaction may evolve towards the formation of an epoxide (Eqs. 76 and 77) and a small amount of a dihydrofuran; these reactive pathways (Scheme 10, paths b and c) are also not general,[133,134] and can be greatly dependent on the nature of the ligand[135] (see Part D).

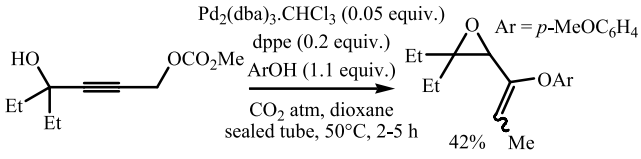


(75)





(76)

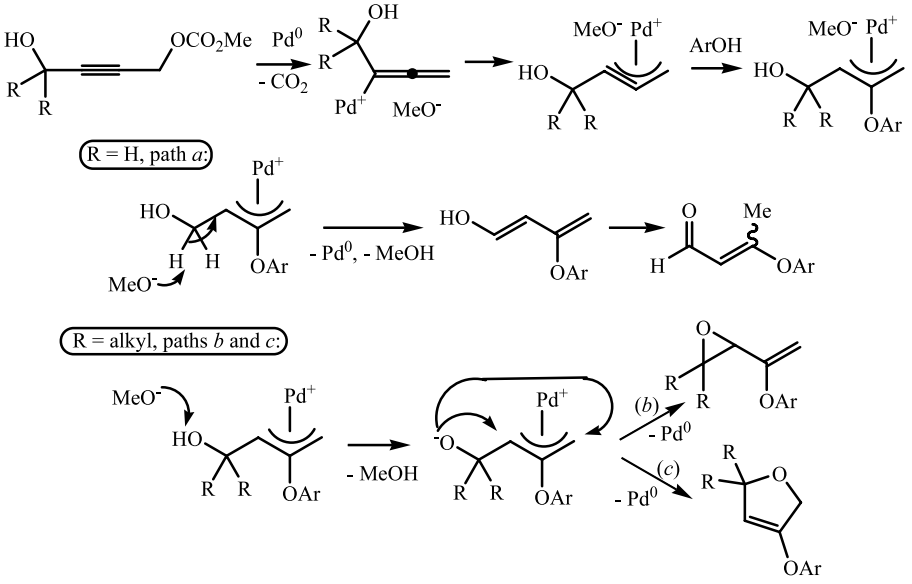


(77)

3. Oxypalladation of unsaturated carbon–carbon bonds

3.1. Oxypalladation of alkenes

The formation of acetaldehyde from ethylene, water and $PdCl_2$, discovered in 1894 by Phillips,[136] has led to the Wacker process,[137] which requires only catalytic amounts of the palladium compound. The activation of the C=C bond by coordination to Pd^{II}, and the regeneration of the catalyst, are the key steps of this process; its most extensive application in organic synthesis is the specific oxidation of terminal alkenes into methyl ketones.[138] Alcohols instead of water have been used,[139] and it has been assumed that they

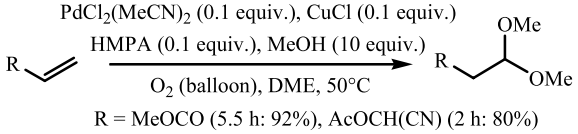


Scheme 10.

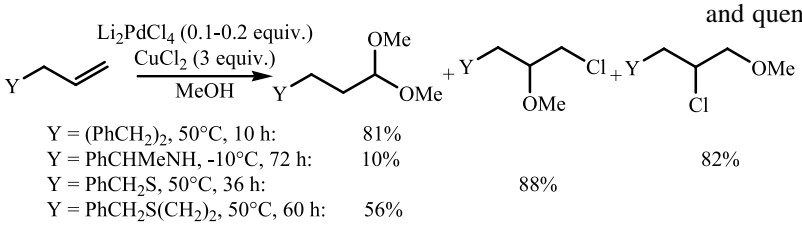
attack, primarily externally, the (η^2-olefin)palladium complexes.[140] Nevertheless, as with water,[141] the stereochemistry, *syn* or *anti*, of the oxypalladation of olefins with alcohols can be greatly dependent on the additives.[142]

3.1.1. Intermolecular addition of alcohols to alkenes. The intermolecular Pd^{II}-catalysed reaction of an alcohol with a C=C bond can lead to a variety of compounds, as summarised in Scheme 11.

In 1969, Lloyd et al. disclosed that terminal olefins and cyclohexene were oxidised to ketones by catalytic amounts of $PdCl_2$ and $CuCl_2$ in oxygenated alcoholic solvents with, sometimes, the possibility to isolate the intermediate ketal, in particular with ethylene glycol as the solvent.[143] The $PdCl_2$/benzoquinone catalytic system has also been used, cyclopentene producing cyclopentanone and slight amounts of both cyclopentenyl ethyl ether and 1,1-diethoxycyclopentane in anhydrous ethanol.[144,145] The cleavage of the ethers and ketals is probably due to the Lewis acid properties of the metal salts and to the presence of traces of water. Nevertheless, high yields of acetals have been obtained from various terminal alkenes (Eq. 78),[146–151] but the course of these reactions can be strongly influenced by the presence and the nature of an allylic heteroatom (Eq. 79).[152] The literature also contains examples of the formation of ketals from terminal[152] and non-terminal alkenes.[147]

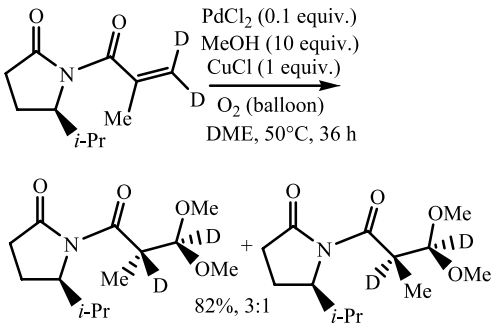


(78)



(79)

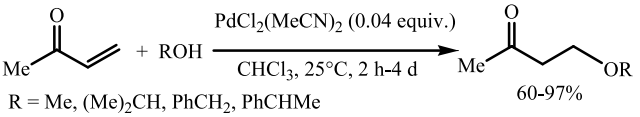
The diastereoselective acetalisation of chiral methacrylamides with methanol involves a *trans*-methoxypalladation, followed by a 1,2-stereoselective hydride migration, as determined using a deuteriated substrate (Eq. 80).[153,154]



(80)

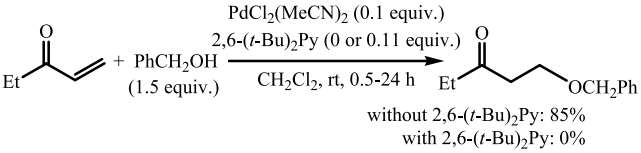
More recently, the acetalisation of acrylate esters and acrylonitrile has been carried out in supercritical carbon dioxide[155] or using supported Pd^{II} catalysts.[156]

The Pd^{II}-catalysed hydroalkoxylation is effective for terminal alkenes activated by a carbonyl or acetal group (Eq. 81), but is not observed from acrylonitrile and unfunctionalised alkenes such as styrene or 1-hexene;[157–159] the catalytic cycle proposed by Abu-Omar et al. is shown in Scheme 12.



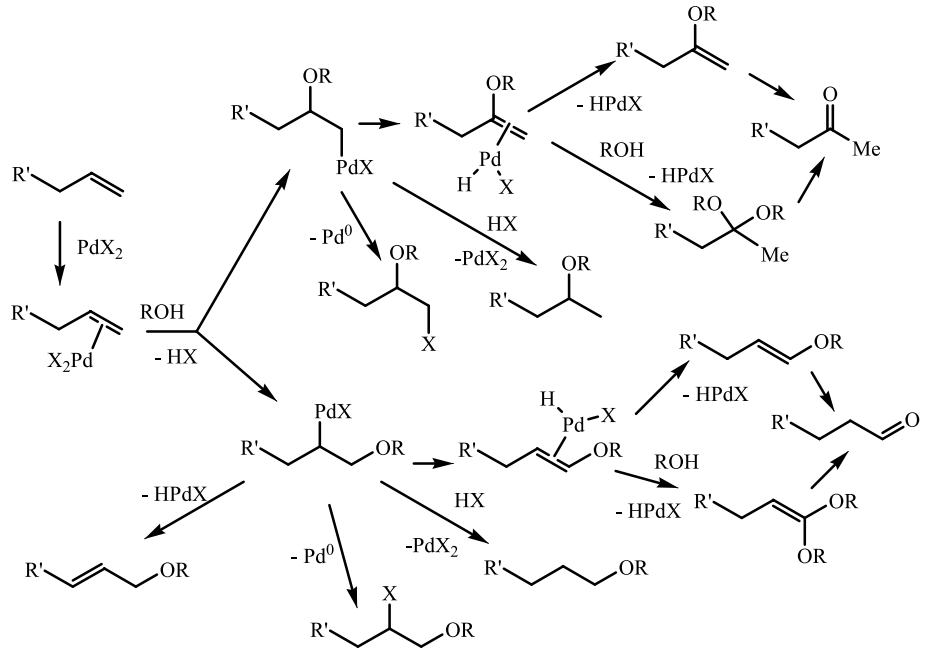
(81)

Hosokawa's and Abu-Omar's teams proposed that these hetero-Michael addition reactions are initiated by Pd^{II} activation of the olefinic double bond.[153,154,158] The Lewis acid properties of $PdCl_2$ additionally permit an activation of the carbonyl group via its coordination to the metal atom. In contrast to these suggestions, Spencer et al. have assumed that these reactions are catalysed by H^+, rather than Pd^{II}, i.e. by a Brønsted acid, rather than by interactions of the conjugated system with $PdCl_2$;[160] this proposal was asserted on the basis of the failure of the reaction in the presence of 2,6-di-*tert*-butylpyridine (Eq. 82). According to Spencer et al., residual moisture or water released through acetal formation would hydrolyse $PdCl_2$ to afford HOPdCl and H^+. Thus, an additive with Brønsted basic properties such as 2,6-di-*t*-butylpyridine, that would be unable to coordinate to metal ions due to the bulky *tert*-butyl groups, traps H^+ and quenches the reaction.[160,161]

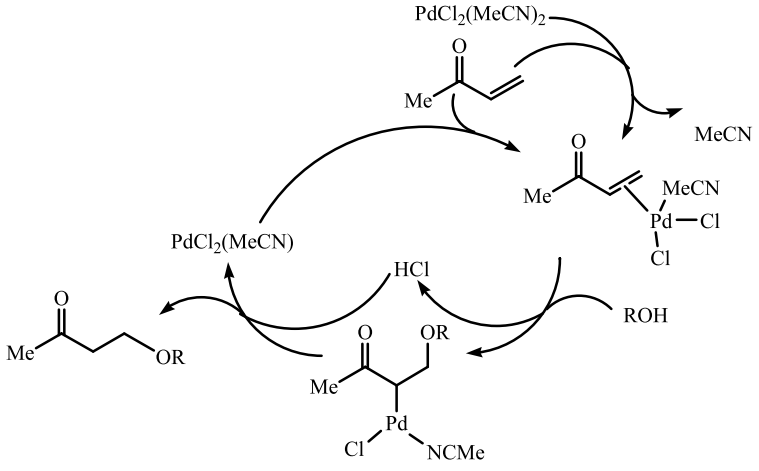


(82)

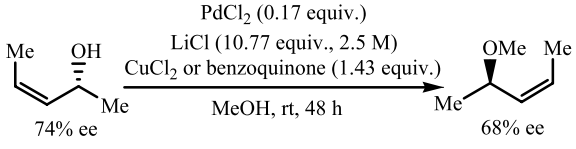
In the presence of chloride anions, the reaction between an alkanol and an allylic alcohol under Pd^{II} catalysis produces an allylic ether through the formal elimination of palladium hydroxide (Eq. 83),[162,163] or a β-keto ether (Eq. 84),[162,164] the course of the reaction depending on [Cl^-], as studied meticulously by Henry et al. using optically active substrates.[163,165] Nevertheless, Hosokawa et al. have observed that the PdOH elimination can occur even in the absence of a high [Cl^-], provided that the allylic alcohol bears a COOR group at the α-position (Eq. 85).[166]



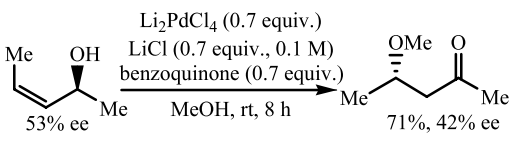
Scheme 11.



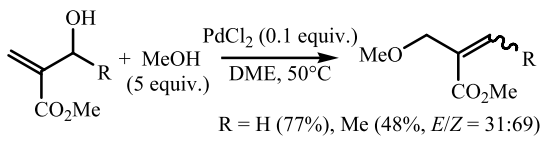
Scheme 12.



(83)

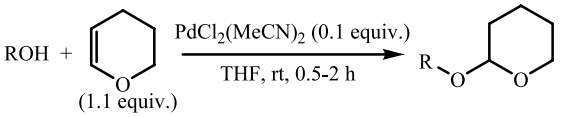


(84)



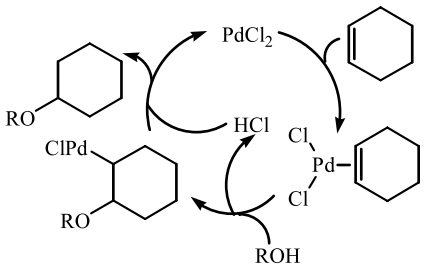
(85)

The tetrahydropyranylation of alcohols is catalysed by palladium chloride at room temperature, and this method is compatible with the presence of various functional groups (Eq. 86).[167,168] As a possible mechanism, we suspect oxypalladation of the dihydropyran, followed by protolysis of the resultant alkylpalladium with the in situ-produced HCl (Scheme 13), but, according to the proposal of Spencer et al. (vide infra),[160] the whole reaction could be catalysed by H^+.



(86)

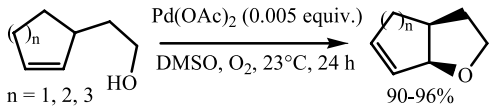
3.1.2. Intramolecular reactions of alkenols. A variety of oxygen-containing heterocycles have been obtained from the intramolecular Pd-catalysed reaction of alcohols having



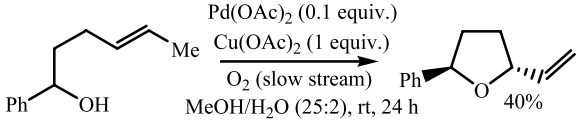
Scheme 13.

an olefinic bond in the 4,5- or 5,6-position.[169] This heteroannelation involves the attack of the oxygen nucleophile onto the Pd^{II}–olefin complex to produce an η^1-alkylpalladium complex, which evolves towards the final product through a β-H elimination.

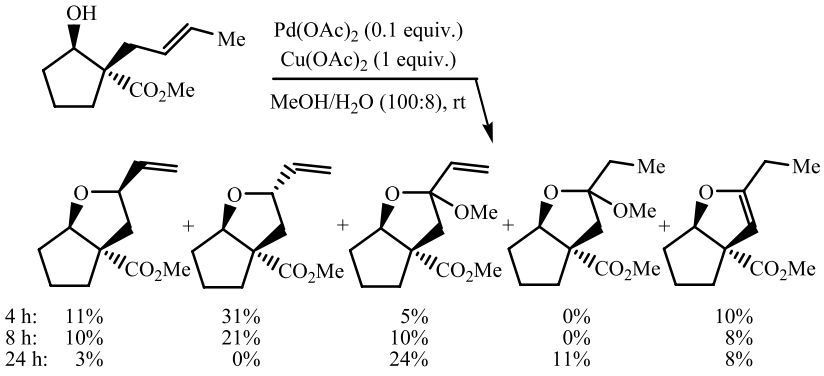
With DMSO as the solvent, the reaction requires sometimes the addition of 8–10 equiv of acetic acid.[170] The regeneration of the catalyst with oxygen in DMSO does not require a copper salt as additive to be efficient (Eq. 87).[171–173] The use of *p*-benzoquinone instead of oxygen was detrimental to the selectivity in decreasing the yield of the allylic ether to the profit of the corresponding homoallylic ether.[171] In aqueous methanol, the heteroannelations were carried out in the presence of stoichiometric amounts of copper acetate (Eq. 88),[174,175] and may afford some ketals (Eq. 89).[176]



(87)

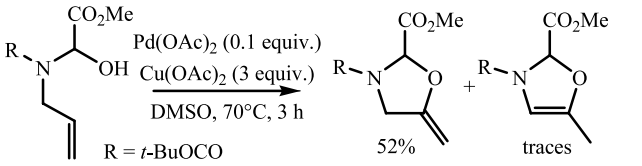


(88)

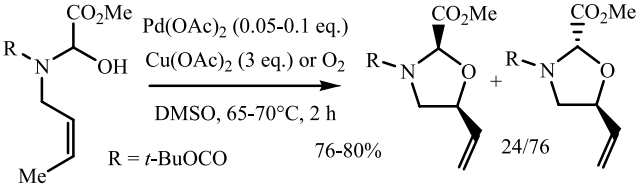


(89)

Oxazolidines have been obtained through the $Pd(OAc)_2$-catalysed intramolecular Wacker-type reaction of allylic carbamates bearing a hydroxy group (Eqs. 90 and 91),[177,178] the annelation not being observed with $PdCl_2$ as the catalyst.[179] The solvent, DMSO, has a unique role in leading to sulfoxide-stabilised giant palladium clusters,[180] and the catalytic species are regenerated by either $Cu(OAc)_2$ or O_2.

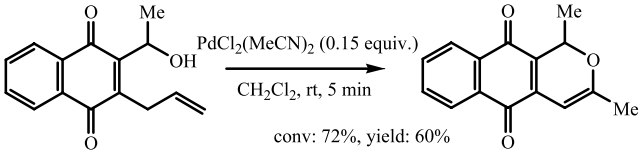


(90)



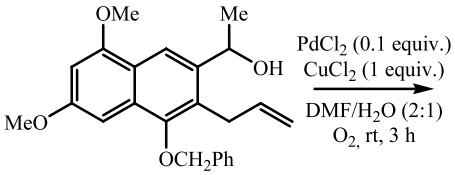
(91)

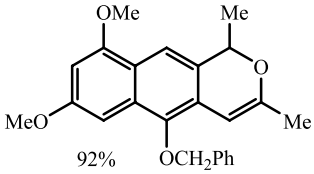
Since the above experiments require Cu^{II} and/or O_2 for the regeneration of the active catalyst, the efficiency of the Pd^{II}-catalysed cyclisation of 1,3-dimethylbenzoisochromenequinone reported by Giles et al. is surprising, because no re-oxidant of palladium was mentioned (Eq. 92).[181,182] Actually, an effective synthesis of a benzoisochromene was subsequently reported, with $CuCl_2$ and O_2 as additives, by one of the authors (Eq. 93).[183] For these reactions, the Pd^{II}-catalysed migration of the C=C bond could precede the oxidation step.[184]



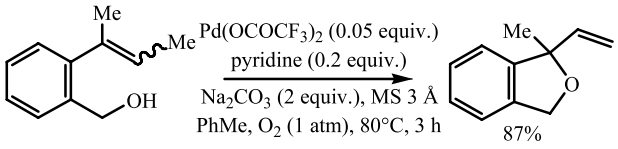
(92)

The heteroannelation was also obtained under basic conditions, using $Pd(OCOCF_3)_2$/pyridine in oxygenated toluene (Eq. 94). It has been proposed that the addition of the hydroxy group to the alkene activated by η^2-coordination to palladium affords an oxonium ion, which is deprotonated by the base, the subsequent β-hydride elimination producing HPdX in liberating the heterocycle. Under these conditions, the regeneration of the active catalytic species by oxygen is assumed.[185] Sasai et al. have also used $Pd(OCOCF_3)_2$ as catalyst, but with chiral ligands under neutral conditions and *p*-benzoquinone as co-oxidant, to carry out the asymmetric 6-*endo* cyclisation of alkenyl alcohols (Eq. 95).[186]

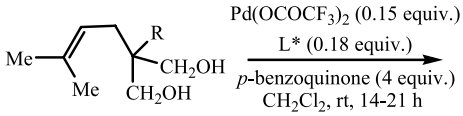


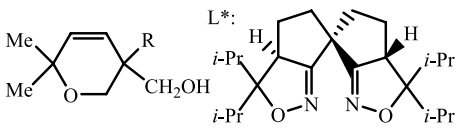


(93)



(94)





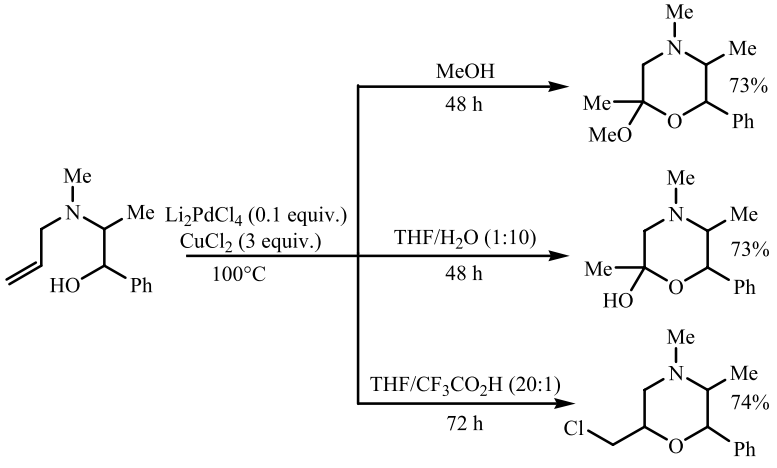
(95)

R = Me (70%, 70% ee), Et (86%, 70% ee), CH_2Ph (81%, 63% ee)

By slightly varying the reaction conditions with $CuCl_2$ as the re-oxidant, Dai et al. have obtained three different types of morpholine derivatives from the intramolecular addition of an hydroxyl group to an allylic amine moiety (Eqs. 96–98).[187] To explain the high diastereoselectivities obtained from chiral substrates, the authors suggest the coordination of both the nitrogen atom and the double bond to a bimetallic complex (Scheme 14).

When the η^1-alkylpalladium intermediate obtained from the intramolecular oxypalladation cannot undergo a β-H elimination, it can be trapped by an alkene to afford a chain extension, as reported by Semmelhack et al., who have carried out the heteroannelation of substituted 1,4- and 1,5-hydroxyalkenes in DMF (Eq. 99) with a regeneration of the catalyst more efficient with $CuCl/O_2$ than with *p*-benzoquinone or $CuCl_2/O_2$. In the case of styrene, which is reluctant to react as a trapping agent, catalytic amounts of acetic acid were added to get an appropriate reaction rate.[188] Working in CH_2Cl_2 with *p*-benzoquinone as re-oxidant and chiral ligands, Sasai et al. have applied such domino reactions, but with intramolecular trappings, to the synthesis of optically active 6-*endo* cyclised products (Eq. 100).[186,189]

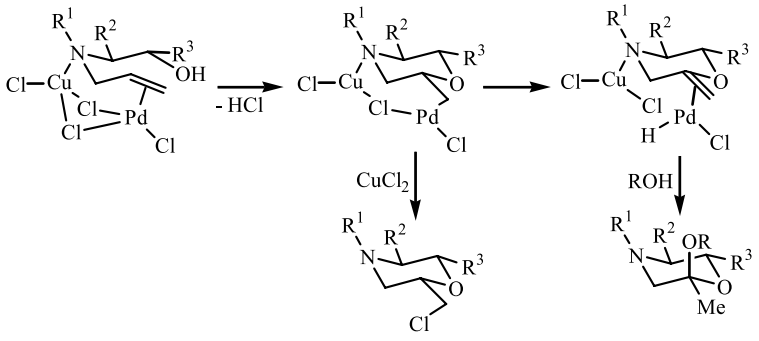
Even when a β-H elimination is possible, carbon monoxide can react with the η^1-alkylpalladium intermediate, as reported in particular by Semmelhack et al. (Eqs. 101 and 102).[170,190–200]



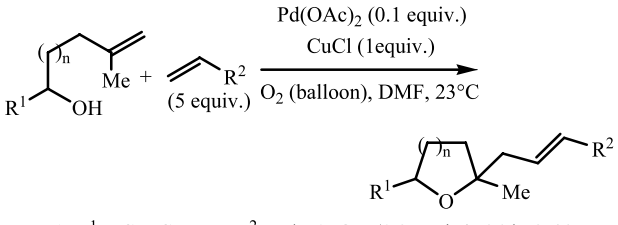
(96)

(97)

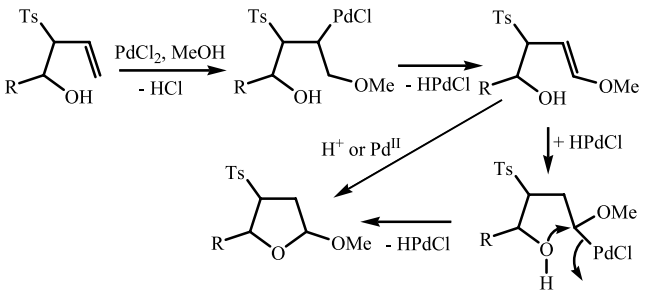
(98)



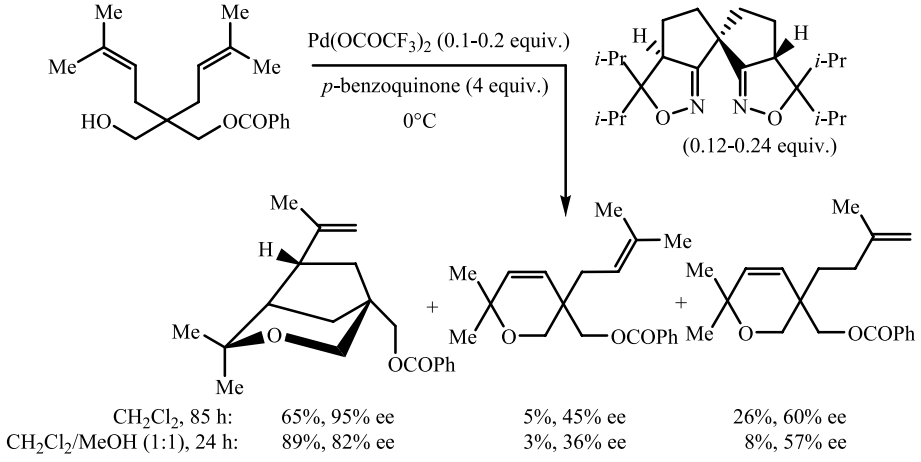
Scheme 14.



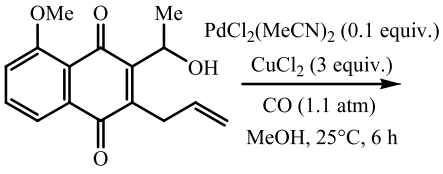
(99)

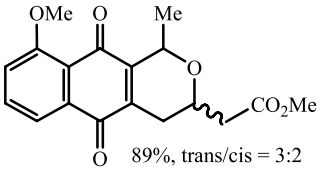


Scheme 15.

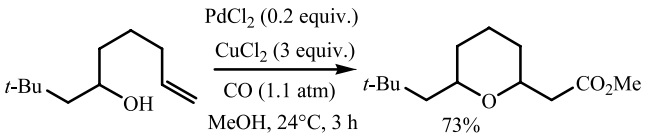


(100)



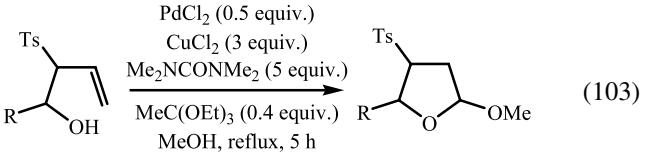


(101)

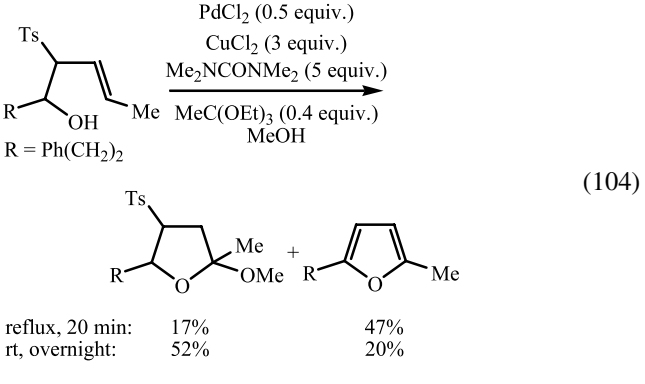


(102)

Inomata et al. have disclosed the cycloacetalisation of 2-tosyl-3-butenols in methanol (Eq. 103).[148] On the basis of Baldwin's rule, the authors suspected that the O–C bond formation by intramolecular addition to the C=C bond activated by coordination to Pd^{II}, i.e. a 5-*endo-trig* cyclisation, was unlikely. Thus, the oxypalladation of the C=C bond with methanol leading to the corresponding enol ether was proposed as the key step, and a possible reaction mechanism is depicted in Scheme 15. When the substrate bore a substituent in the 4-position, some furan derivative was produced (Eq. 104).

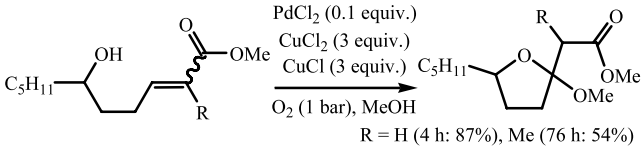


(103)



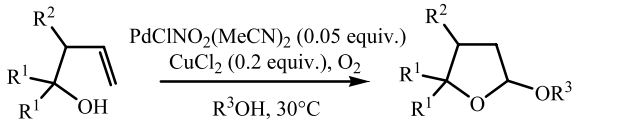
(104)

In carrying out the heteroannelation of ε-hydroxy-α,β-unsaturated esters in MeOH, Sturgess et al. have obtained masked β-ketoesters, the regeneration of the catalyst being assumed with O_2 and a mixture of CuCl and $CuCl_2$ (Eq. 105).[201]



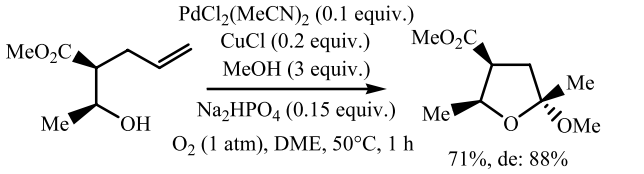
(105)

Having previously observed that, in *t*-butanol with oxygen and a $PdClNO_2(MeCN)_2/CuCl_2$ system as catalyst, 1-alkenes are oxidised preferentially to aldehydes rather than methyl ketones, while allyl alcohol led to a 70/30 mixture of 3-*t*-butoxypropanal and 3-*t*-butoxy-2-propen-1-ol,[202] Feringa et al. have oxidised primary and tertiary homoallylic alcohols to cyclic acetals under such conditions, isopropanol instead of *t*-butanol also being effective (Eq. 106).[203] In contrast to other reports,[204] in particular that of Inomata,[148] a substituent[204] or a coordinating group[148] on the allylic position is not required to regioselectively achieve the oxidation at the terminal carbon.



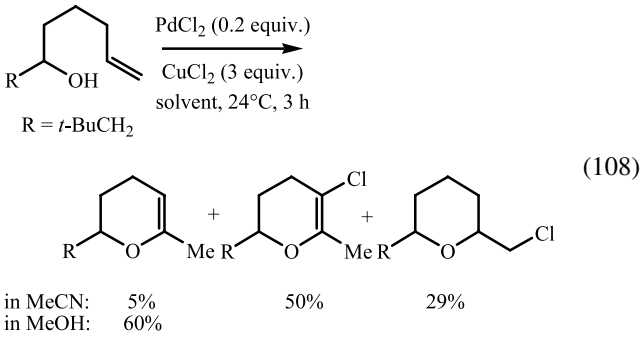
(106)

The Pd^{II}-catalysed cyclisation of terminal 5-hydroxyalkenes in the presence of alcohols led also to α-alkoxytetrahydrofurans,[148,203] and diastereoselective cycloacetalisations have been observed (Eq. 107).[205–207] With these substrates, the reaction would involve, firstly, the 5-*exo*-*trig* cyclisation and, subsequently, the alkoxylation of the intermediate *exo*-methylene (Scheme 16).



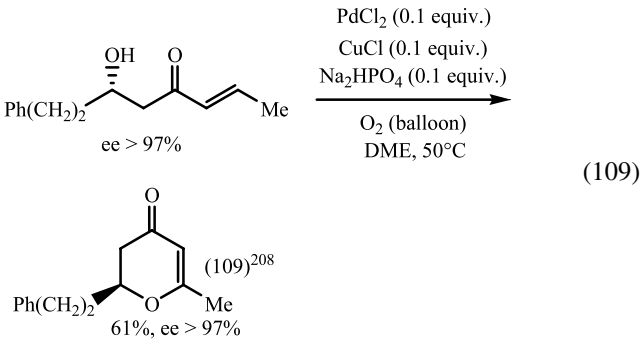
(107)

With a 6-hydroxyalkene as substrate, the ketalisation under Semmelhack's conditions was, however, not observed, as shown in Eq. 108, since a dihydropyran was produced in methanol, the selectivity of the reaction being very sensitive to the nature of the solvent.[193]



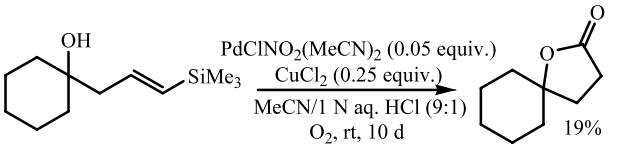
(108)

The oxidative cyclisation of β′-hydroxyenones provides 2,3-dihydro-4*H*-pyran-4-ones, with no detectable racemisation when the substrate was optically active (Eq. 109). The regeneration of the active catalyst was best achieved by oxygen and catalytic amounts of both CuCl and Na_2HPO_4.[208] Oxygen can also be used as the sole oxidant but, in this case, the presence of 0.1 equiv of Na_2HPO_4 is essential.[206]



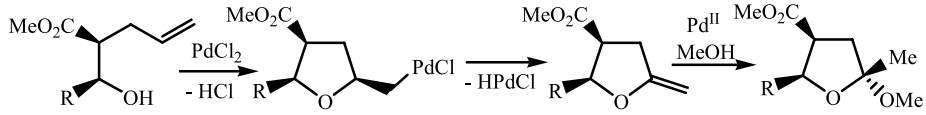
(109)

The formation of a γ-butyrolactone from (*E*)-1-[3-(trimethylsilyl)allyl]-1-cyclohexanol in an aqueous medium (Eq. 110) is due to the *trans*-hydroxypalladation of the silylated dihydrofuran intermediate (see Scheme 30 for a similar reaction), as demonstrated from 1-substituted-4-(trimethylsilyl)-3-butyn-1-ols.[209]

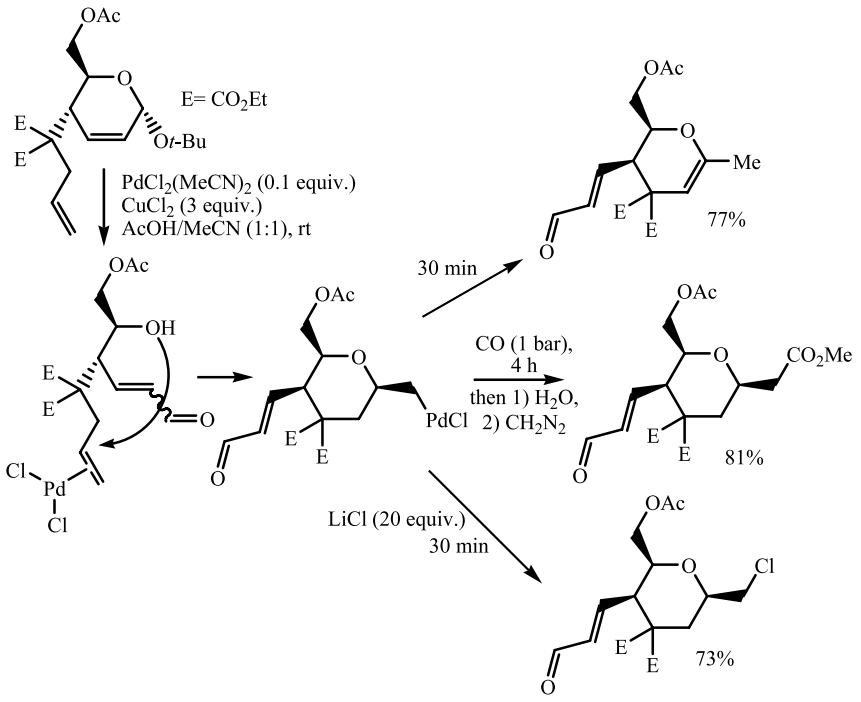


(110)

Holzapfel et al. have carried out the intramolecular oxypalladation of alkenes using the in situ formation of the hydroxy group mediated by the acidic cleavage of a cyclic unsaturated acetal substituted by an unsaturated chain, this affording a dihydropyran. In addition, the σ-alkylpalladium intermediate has either been trapped by carbon monoxide or substituted by a chloride anion (Scheme 17).[210]

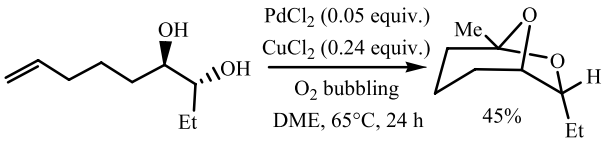


Scheme 16.

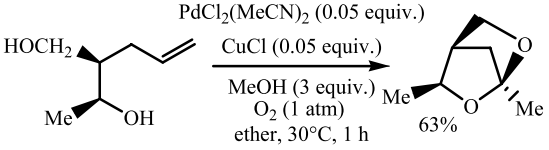


Scheme 17.

3.1.3. Intramolecular reactions of alkenediols. A number of di- and tri-oxabicyclo[x.y.1] systems (x, $y=2$ or 3),[211–214] in particular beetle pheromones[215] such as brevicomins (Eq. 111)[211,216–219] and frontalin,[220–222] have been synthesised from unsaturated diols, the regeneration of the Pd^{II} catalyst being achieved either by stoichiometric amounts of $CuCl_2$,[211–213,215,217–219,221,222] or catalytic amounts of this salt associated with a stream of oxygen.[214,216,223,224] The two alkoxylations can be intramolecular, even in the presence of methanol (Eq. 112).[205]

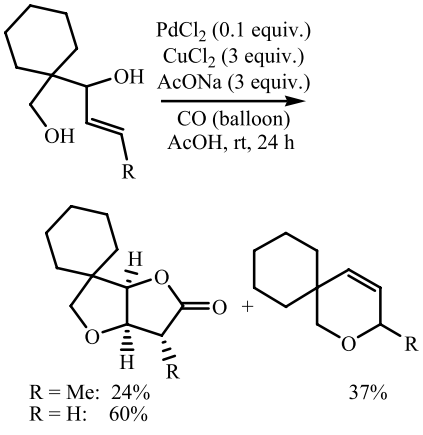


(111)

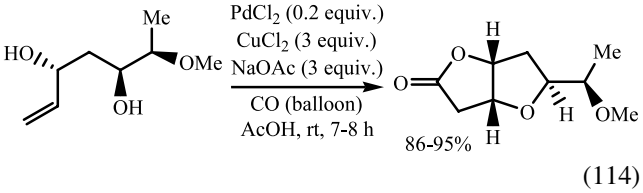


(112)

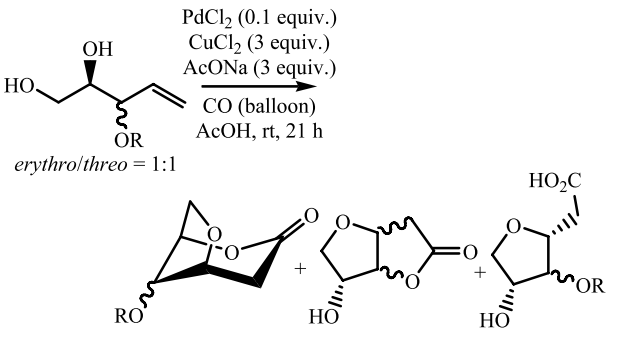
Using catalytic amounts of $PdCl_2$ and excesses of both $CuCl_2$ and AcONa in acetic acid, Tamaru et al. have reported that the oxycarbonylation of 4-penten-1,3-diols led selectively to bicyclic lactones when the C=C bond was terminal, the acylpalladium intermediate being trapped by the second hydroxy group (Eq. 113). The oxycarbonylation of an internal olefin is ineffective or leads mainly to the dihydropyran derivative (Eq. 113).[225] We suspect that (i) the dihydropyran is produced from a 6-*endo-trig* heterocyclisation followed by the PdOH elimination and (ii) $PdCl_2$ was used rather than $Pd(OAc)_2$ because, in acetic acid containing sodium acetate, $Pd(OAc)_2$ reacts with CO to give Pd^0, CO_2 and Ac_2O.[179,226] A variety of unsaturated polyols[170,197,198,200,227–231] have been cyclized using a similar procedure (Eq. 114 and 115).[170,230a] The oxycarbonylation has also been carried out without AcONa, using THF instead of AcOH, but it seems that, with this solvent, $Pd(OAc)_2$ is the preferred catalyst (Eq. 116),[232] $PdCl_2$ mediating an OH/Cl exchange (Eq. 117).[233]



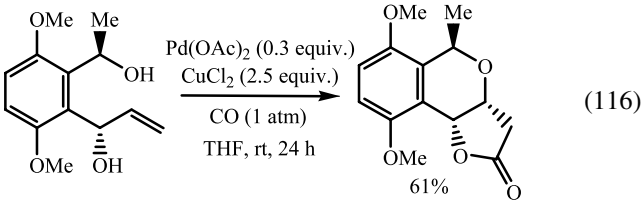
(113)



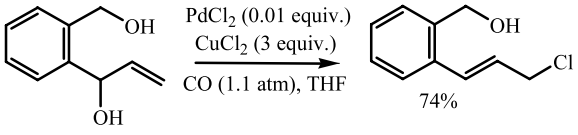
(114)



(115)

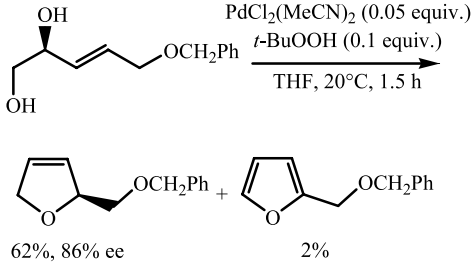


(116)



(117)

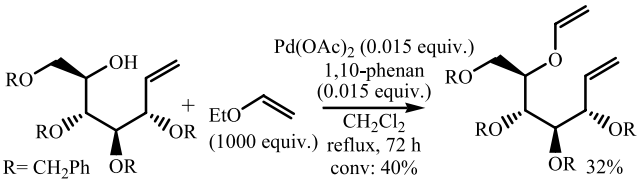
Optically active dihydrofurans and small quantities of furans have been obtained as the main products via, apparently, the 5-*endo-trig* cyclisation of homochiral 3-ene-1,2-diols (Eq. 118).[234] In fact, rather than a Wacker-type reaction, the formation of the dihydrofurans would involve the chloropalladation of the double bond and the nucleophilic substitution of the resultant alkyl chloride (Scheme 18).



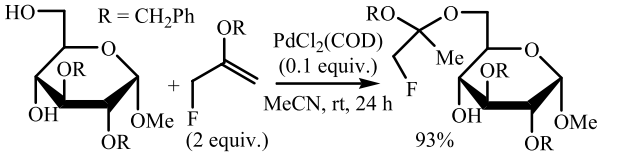
(118)

3.2. Oxypalladation of vinyl ethers

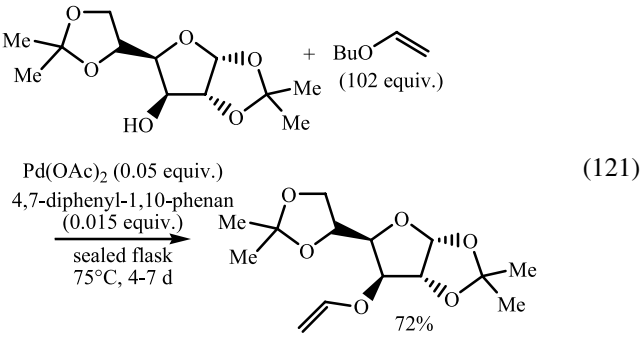
The Pd^{II}-catalysed vinyl interchange between vinyl ethers and alcohols, disclosed more than 30 years ago,[235,236] has been applied to the etherification of various alcohols[237–240] including sterols[241] and sugars[237,238,242] (Eqs. 119–121). These reactions are sometimes carried out under an oxygen atmosphere[242,243] or with trifluoroacetic acid as additive.[244]



(119)

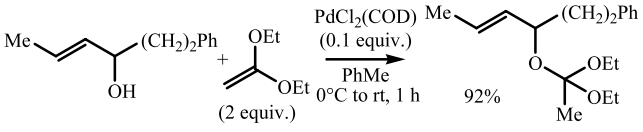


(120)

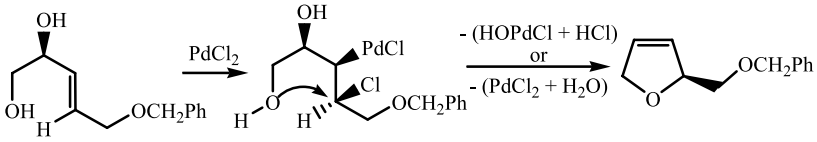


(121)

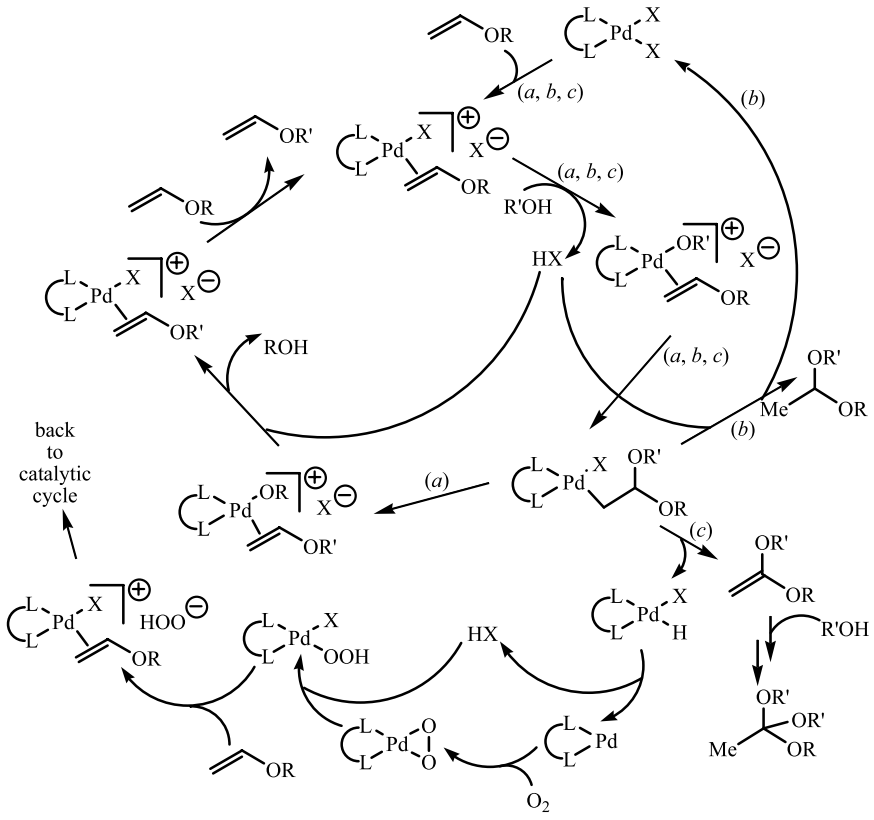
The catalyst system is often obtained by coordination of a phenanthroline to $Pd(OAc)_2$, but it has recently been shown that the use of $Pd(OCOCF_3)_2$ instead of $Pd(OAc)_2$ substantially shortens the reaction times.[240] In agreement with the mechanism proposed for the vinyl transfer (Scheme 19, path a),[240,242] the reaction course can switch to afford an acetal (Scheme 19, path b),[236,245] or an *ortho* ester via a ketene acetal (Scheme 19, path c).[242] Mixed *ortho* esters have been efficiently obtained from the addition of primary or secondary allylic alcohols to ketene acetals (Eq. 122).[246]



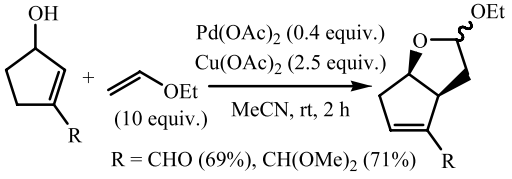
(122)



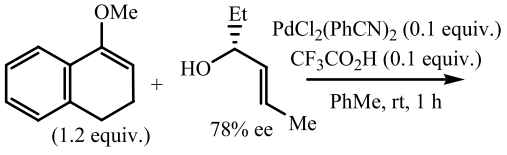
Scheme 18.

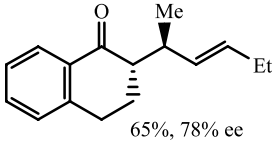


Scheme 19.



(123)



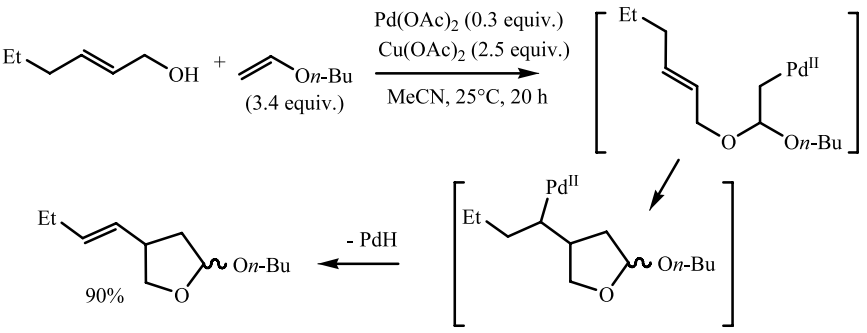


(124)

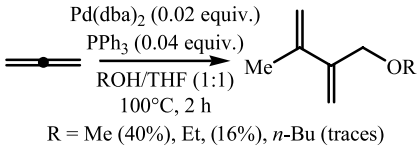
The nucleophilic addition of an allylic alcohol to vinyl ethers can lead to domino reactions, affording either tetrahydrofuran derivatives[247–250] (Scheme 20 and Eq. 123) or Claisen rearrangement products[244,251,252] (Eq. 124). These reaction courses are not a general rule,[240] however, and the Claisen rearrangement can require an elevated reaction temperature.[253]

3.3. Oxypalladation of cumulenes

3.3.1. Intermolecular reactions of alcohols with allene and 1-methoxyallene. The Pd-catalysed dimerisation of allene in the presence of alcohols affords 4-alkoxy-2-methyl-3-methylene-1-butenes, with an efficiency decreasing with the steric hindrance of the alcohol (Eq. 125).[254]

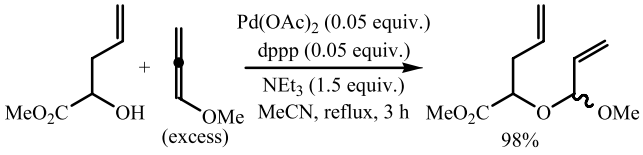


Scheme 20.



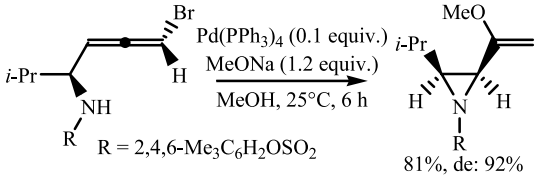
(125)

The oxypalladation of methoxyallene reported by Rutjes et al. (Eq. 126) would occur via attack of the alcohol onto the complex formed by the coordination of Pd^{II} with the more electron-rich oxygen-substituted double bond of the substrate, the protonolysis of the resultant vinylpalladium species leading to the acetal and to regeneration of the Pd^{II} catalyst.[255]



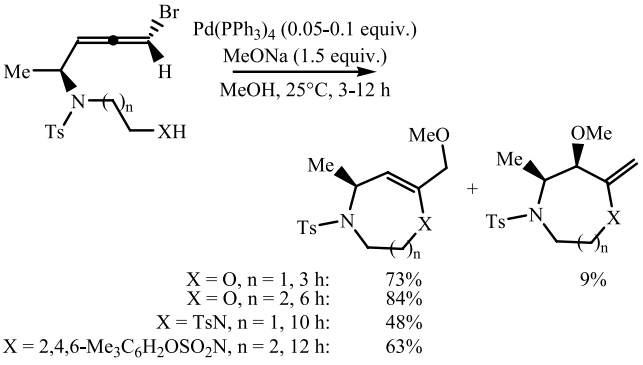
(126)

3.3.2. Addition of alcohols to 1-bromoallenes. The 1-bromoallenes are equivalent to allyl dications, and Tanaka et al. have used this property for the intramolecular aziridination of a bromoallene bearing a protected amino group at the α-position. The use of sodium methoxide in methanol and a palladium catalyst has led to the formation of both C–N and C–O bonds (Eq. 127). According to the authors, the reaction involves an intermediate η^3-allylpalladium bearing a methoxy group on the central carbon atom, and the subsequent nucleophilic addition of the nitrogen atom.[256]

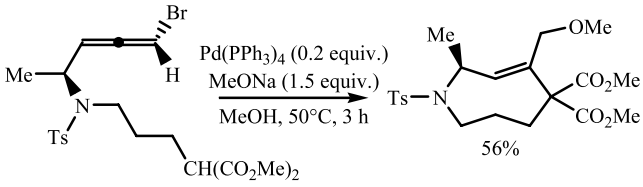


(127)

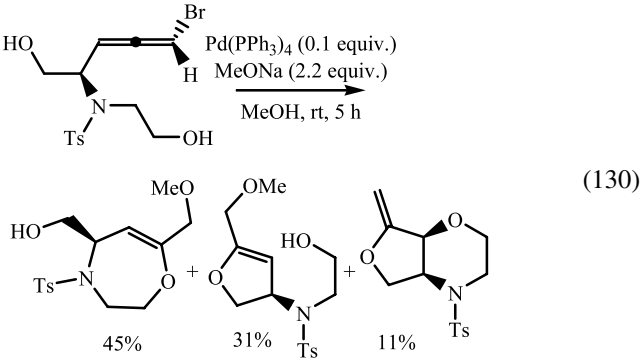
Tanaka et al. have synthesised medium-sized heterocycles via the cyclisation of bromoallenes bearing an oxygen, nitrogen or carbon functionality (Eqs. 128 and 129).[256–258] (Eqs. 128 and 129). The proposed reaction course (Scheme 21) involves intramolecular nucleophilic addition to a η^3-propargylpalladium complex to produce an η^3-allylpalladium intermediate reacting with methanolate (path a).[257] The generation of the η^3-allylpalladium through a palladacyclobutene, which is protonated by MeOH, has subsequently been suggested (path b).[258] The cyclisation of a bromoallene bearing two oxygen nucleophiles has also been described (Eq. 130). It seems useful to note that the formation of these heterocycles, in particular the eight-membered ring, is sensitive to the substitution, and that the reaction can affect only the bromoallenyl moiety, as illustrated in Eq. 131.



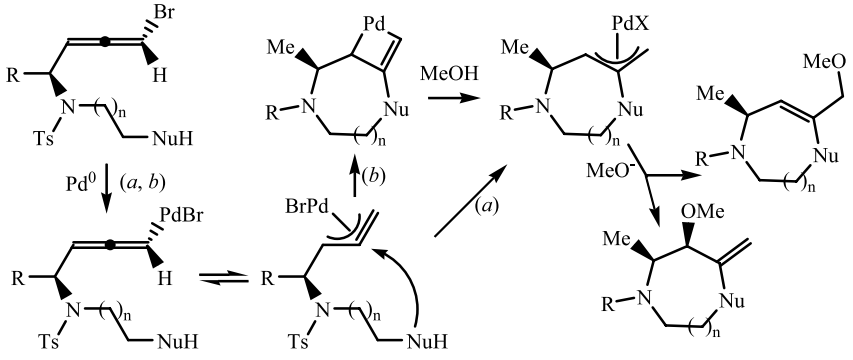
(128)



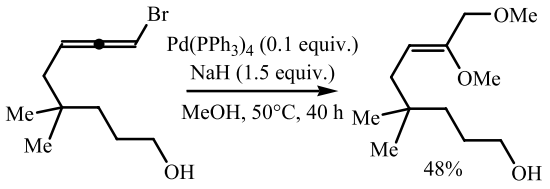
(129)



(130)

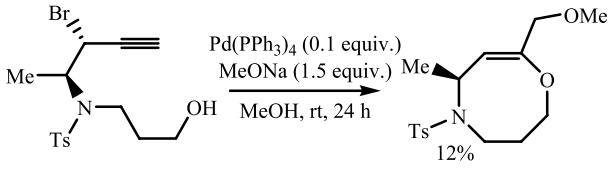


Scheme 21.



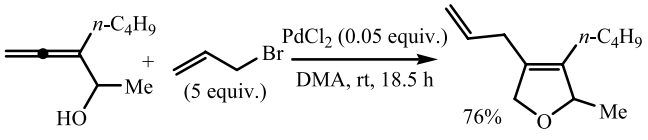
(131)

Although propargylic bromides and bromoallenes can have the same reactivity in the presence of a Pd catalyst,[259] the efficiency of the heterocyclisation is much lower from a propargylic bromide bearing an oxygen functionality[256] than from the corresponding bromoallene (cf. Eqs. 128 and 132).

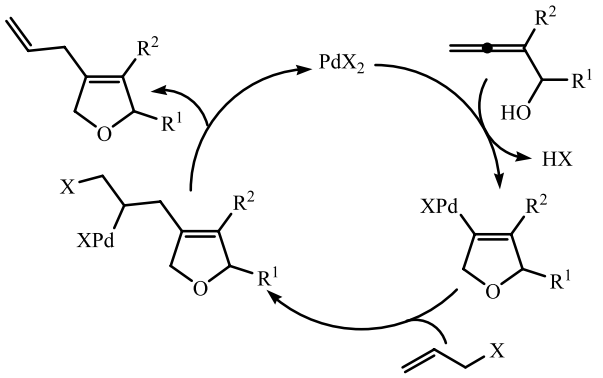


(132)

3.3.3. 1,2-Dien-4-ols. In contrast to the Pd^0-catalysed reaction of 1,2-dien-4-ols with aryl or vinyl halides, which leads to either, β-disubstituted-α,β-unsaturated carbonyl compounds (see Eq. 46 in Part B[2])[70] or substituted vinylic oxiranes (Eqs. 39 and 40),[71,72] the reaction with allylic halides under Pd^{II} catalysis affords 4-(2-alkenyl)-2,5-dihydrofurans (Eq. 133).[72,260,261] While the Pd^0 catalysis involves the addition of the organopalladium halide to the allenic moiety to give an η^3-allylpalladium intermediate, the Pd^{II} catalysis involves the oxypalladation of the allenic moiety, followed by a Heck-type reaction, and regeneration of the Pd^{II} catalyst through β-halide elimination (Scheme 22). A catalytic system has also been obtained using 4-bromo-1,2-butadiene to trap the vinylpalladium intermediate.[261]

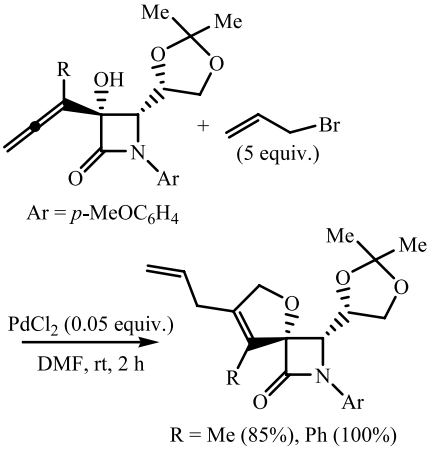


(133)

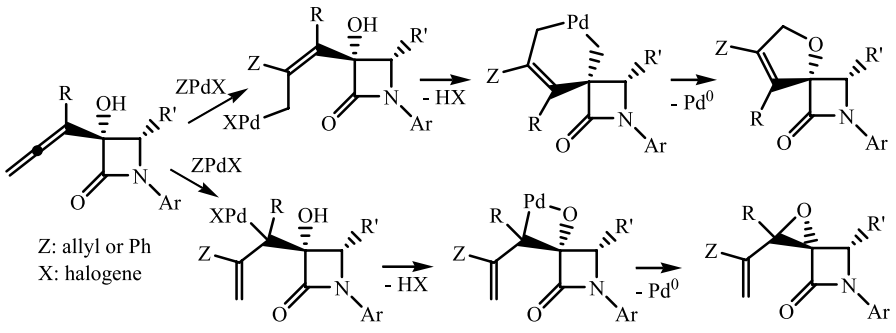


Scheme 22.

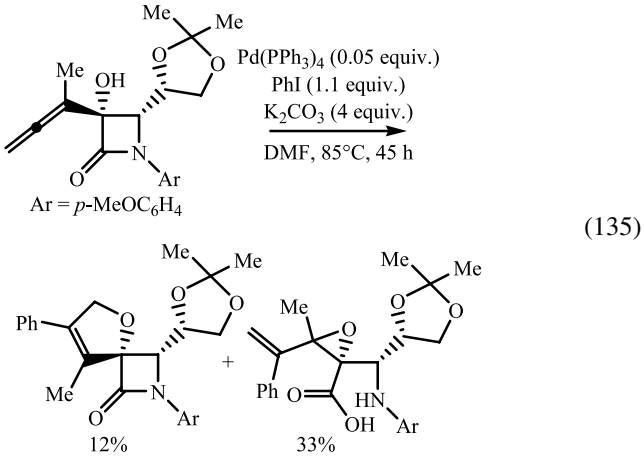
While the reaction of 1-allenylcyclobutanols with aryl- and vinylpalladium species can lead to cleavage of the C–OH bond (see Part D of this series of reviews),[262] the addition of allyl bromide or phenyl iodide to 3-hydroxy-3-(1,2-alkadienyl)-2-azetidinones does not induce such a cleavage, but leads to spiranic systems (Eqs. 134 and 135).[263] The formation of these compounds can be explained as shown in Scheme 23, the ring strain of the spirocyclic oxirane-β-lactam inducing the opening of the β-lactam nucleus.[263]



(134)

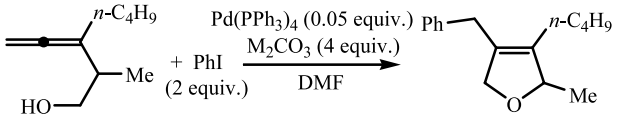


Scheme 23.



(135)

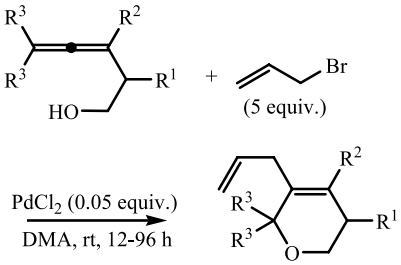
3.3.4. 1,2-Dien-5-ols. The oxypalladation of 3-substituted-1,2-dien-5-ols in the presence of aryl iodides can afford 2,3-dihydrofurans. According to Ma et al., this process requires a substituent in the 3-position, and its efficiency depends strongly on the nature of the base (Eq. 136) and solvent.[264]



M = Na (80°C, 17 h: trace), K (70°C, 10 h: 56%), Cs (70°C, 4 h: 67%)

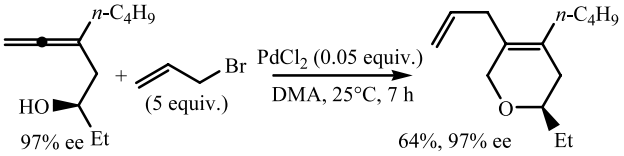
(136)

At room temperature and in the absence of a base, but with a Pd^{II} catalyst and allyl bromide instead of a Pd^0 catalyst and an aryl iodide, the same team has obtained 4-allyl-5,6-dihydro-2*H*-pyrans (Eq. 137)[261] and, interestingly, no racemisation was detected from an optically active substrate (Eq. 138).[265]



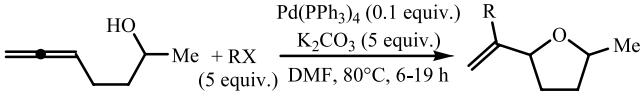
(137)

R^1 = Me, R^2 = *n*-C_4H_9, R^3 = H: 63%
R^1 = H, R^2 = *n*-C_4H_9, R^3 = H: 61%
R^1 = Me, R^2 = Ph, R^3 = H: 78%
R^1 = Me, R^2 = H, R^3 = Me: 64%



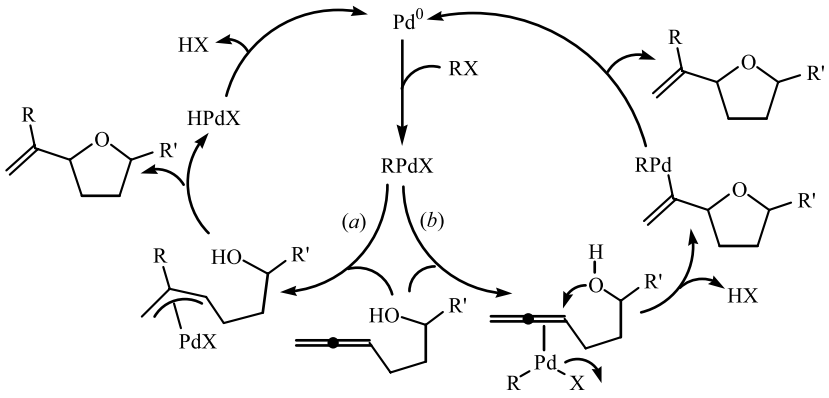
(138)

3.3.5. 1,2-Dien-6-ols. In Section 2.8.2, it has been postulated, according to the authors,[71–74] that the reaction of allenols with aryl and alkenyl halides could involve the addition of RPdX (R = Ar, alkenyl) to the allene to afford an η^3-allylpalladium intermediate. Instead of such a mechanism (Scheme 24, path a), Walkup et al., who obtained substituted 2-vinyltetrahydrofurans from 1,2-dien-6-ols (Eq. 139), proposed oxypalladation of the allene as the key step (Scheme 24, path b).[266] The formation of 2-(2-tetrahydrofuranyl)acrylates when the reaction is carried out without RX, but under a CO atmosphere in MeOH (Eq. 140), is in agreement with this proposal.[267,268]

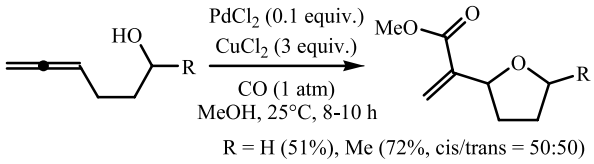


RX = PhBr (14%), PhI (60%), PhCH=CHBr (41%)

(139)

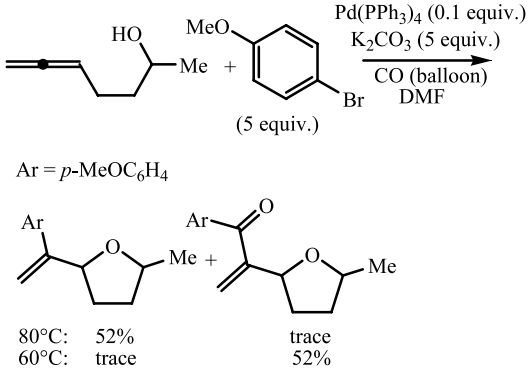


Scheme 24.



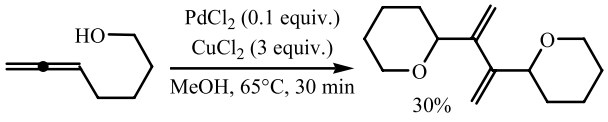
(140)

In the presence of both CO and an arylating reagent, and in DMF instead of methanol, the domino reaction evolves towards the formation of arylated adducts,[266] with a temperature-dependent CO insertion (Eq. 141).[269]

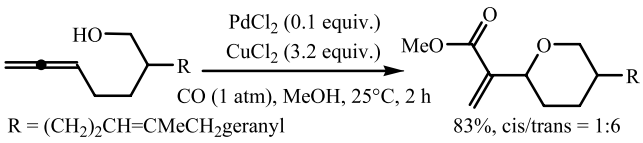


(141)

3.3.6. 1,2-Dien-7-ols. Gallagher et al. have obtained a dimer from hepta-1,2-dien-7-ol under Pd^{II} catalysis in methanol (Eq. 142), and a tetrahydropyranylacrylate when the reaction was carried out under CO.[270] This cyclisation/methoxycarbonylation procedure has subsequently been used as the key step of the synthesis of rhopaloic acid A (Eq. 143).[271]

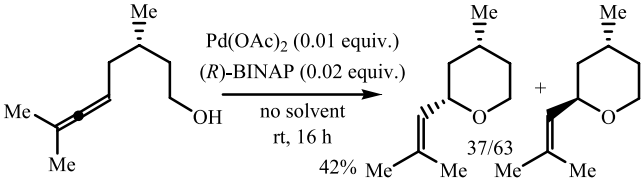


(142)



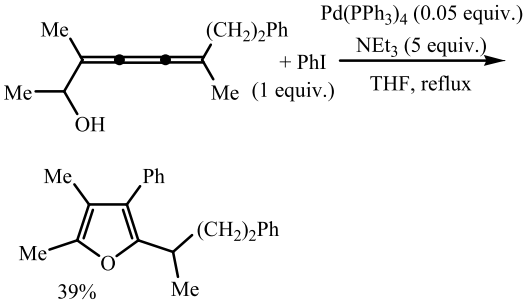
(143)

Optically active rose oxides have been synthesised from (3*R*)- and (3*S*)-3,7-dimethyl-6,7-octadien-1-ol using chiral Pd catalysts (Eq. 144).[272]



(144)

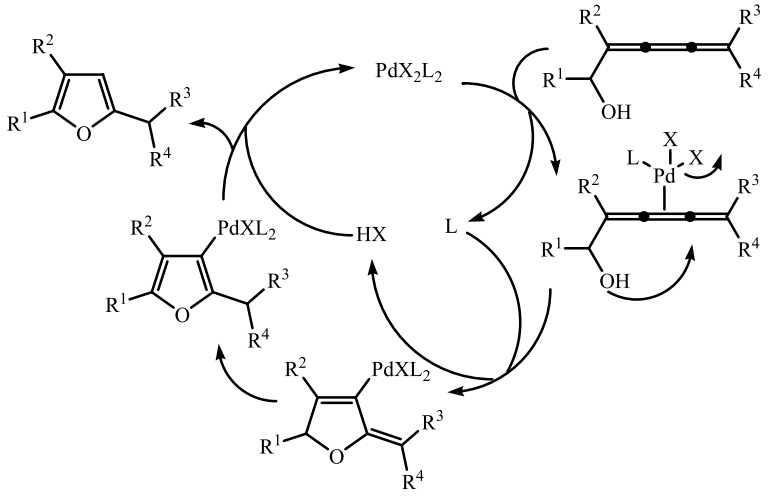
3.3.7. 1,2,3-Trien-5-ols. Aurrecoechea et al. have obtained tri- or tetrasubstituted furans, via the Pd^{II}- or Pd^{0}-catalysed cyclisation of butatrienyl carbinols, in the absence (Scheme 25)[273] or presence (Eq. 145 and Scheme 26)[274,275] of an arylating agent, respectively.



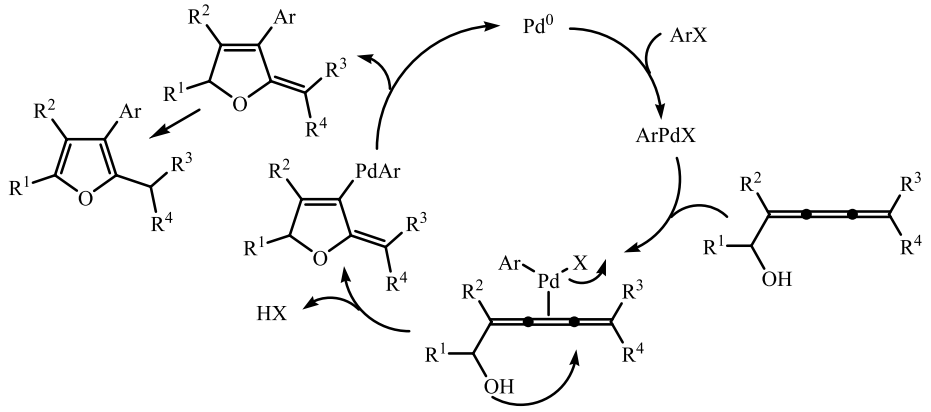
(145)

3.4. Oxypalladation of alkynes

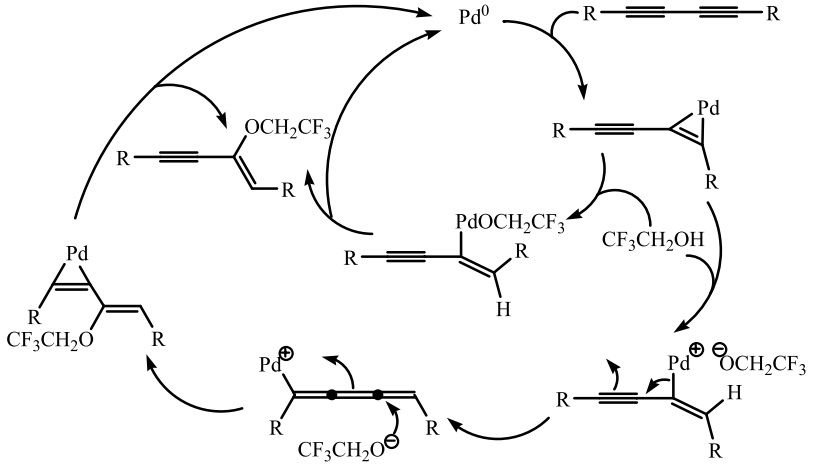
3.4.1. 1,3-Diynes. Yamamoto's team, who disclosed the Pd^{0}/$PhCO_2H$-catalysed hydroalkoxylation of internal alkynes leading to allylic ethers (Section 2.10), has also



Scheme 25.

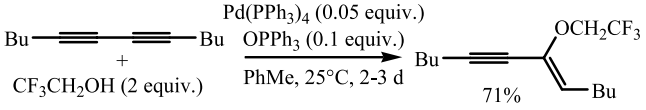


Scheme 26.



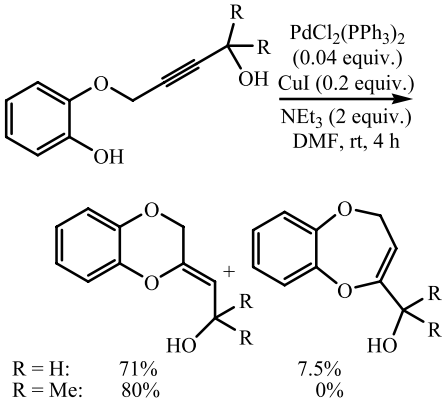
Scheme 27.

carried out the hydroalkoxylation of conjugated diynes using $Pd(PPh_3)_4/OPPh_3$ as catalyst.[276] This different procedure led to the alkoxylated enyne (Eq. 146) and did not work from mono-alkynes. The requirement, for an effective reaction, of both an electron-rich Pd^0 catalyst and an acidic alcohol led the authors to propose the two plausible mechanisms shown in Scheme 27.



(146)

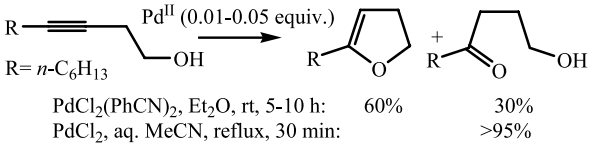
3.4.2. 2-Yn-1-ols. Exomethylene benzo- and naphthodioxans have been prepared via the intramolecular addition of a phenoxy group to the triple bond of a propargylic alcohol activated by coordination to a Pd^{II} catalyst (Eq. 147).[277]



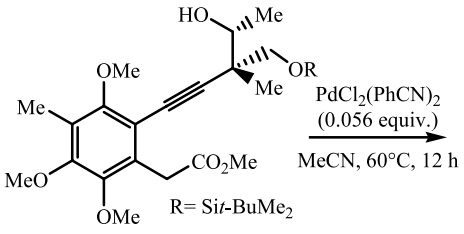
(147)

3.4.3. 3-Yn-1-ols. At room temperature in anhydrous diethyl ether, 3-decyn-1-ol cyclised in a 5-*endo-dig* manner to afford mainly the corresponding dihydrofuran while, in refluxing aqueous acetonitrile, the hydrolysed product of this vinylic ether was exclusively isolated (Eq 148).[278] The process has been used to synthesise a polyfunctionalised dihydrofuran, which is an intermediate of the synthesis of furaquinocin D (Eq. 149).[279] We presume that the formation of the dihydrofurans occurs via the protolysis of vinylpalladium intermediates by in situ-produced hydrochloric acid (Scheme 28), and that the synthesis of 1,6-dioxaspiro-[4.4]non-3-en-2-one from 7-hydroxyhept-4-ynoic acid (Eq. 150)[280] also involves a dihydrofuran as an

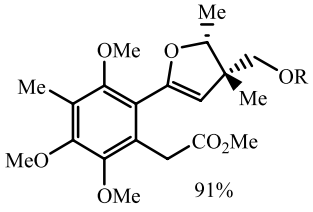
intermediate.

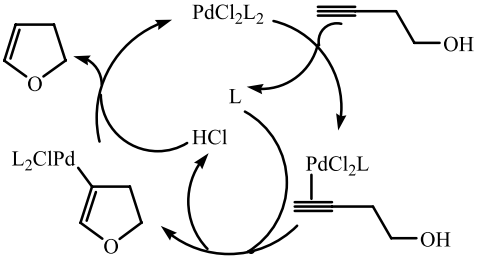


(148)

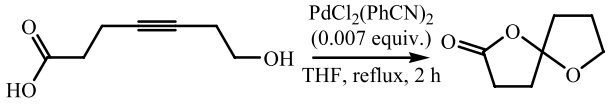


(149)



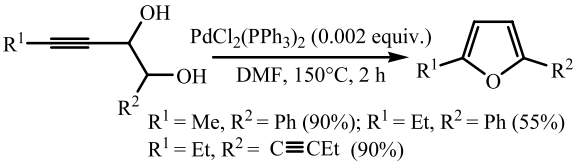


Scheme 28.

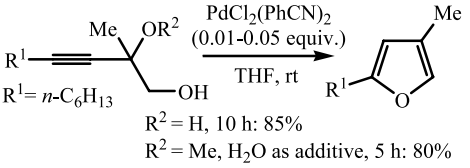


(150)

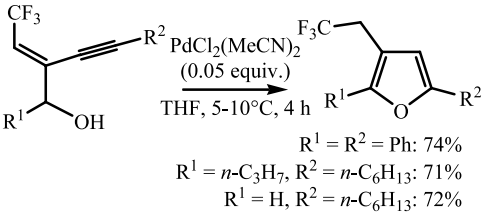
Furans have been obtained from 3-alkyn-1,2-diols (Eqs. 151 and 152),[281,282] 2-methoxy-3-alkyn-1-diols (Eq. 152)[282] and 2-(1,1,1-trifluoroethylene)-3-alkyn-1-diols (Eq. 153).[283] All these substrates require catalysis by Pd^{II} to cyclise[284] and, in addition, water or diluted HCl when 2-methoxy-3-alkyn-1-diols are used as the starting materials (Eq. 152).



(151)



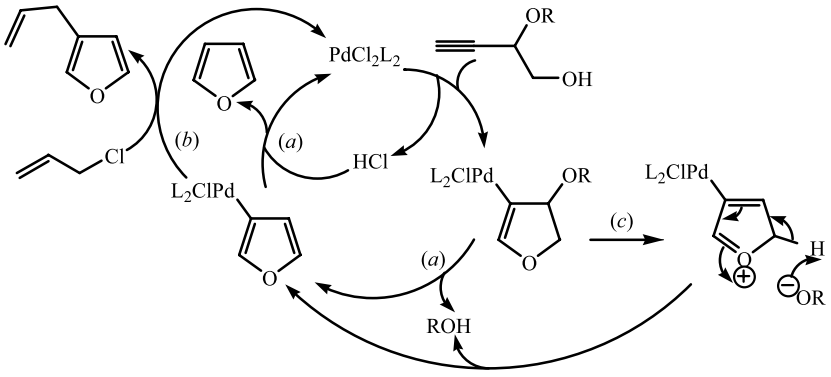
(152)



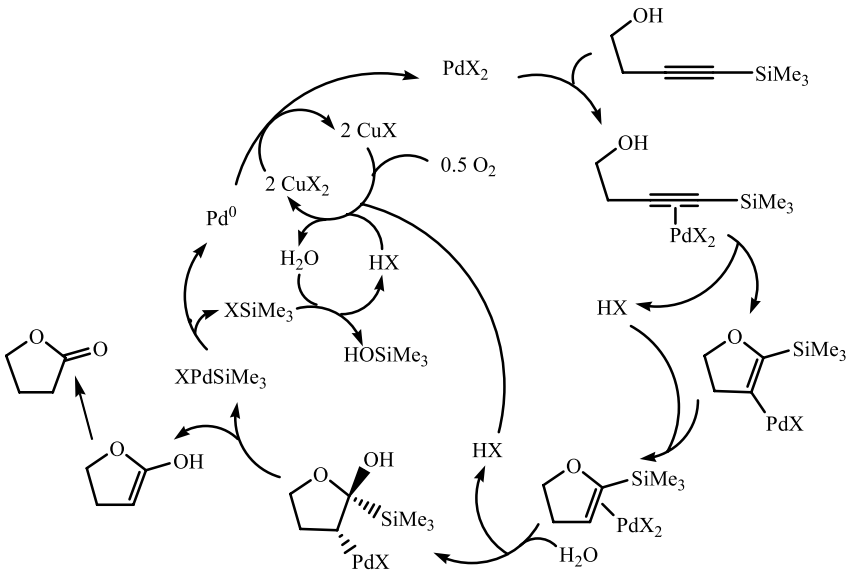
(153)

Utimoto et al. proposed the mechanism shown in Scheme 29, path a for the reaction depicted in Eq. 152, and they trapped the intermediary 3-furylpalladium with allylic chlorides, thus synthesising 3-allylfurans (Scheme 29, path b).[282] Utimoto et al. did not provide an explanation for the elimination of ROH (Scheme 29, path a), and we suggest the formation of an oxonium intermediate (Scheme 29, path c).

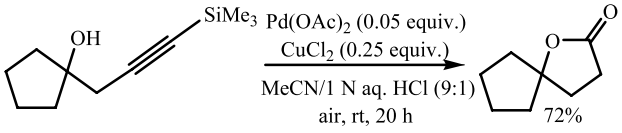
When the triple bond of the secondary or tertiary homopropargylic alcohol is substituted by a trimethylsilyl group, the reaction in an aqueous medium leads to a γ-butyrolactone instead of stopping at the level of the dihydrofuran (Eq. 154).[285,286] With these substrates, the 5-*endo-dig* ring closure is followed by a *trans*-hydroxypalladation, i.e. a Wacker-type reaction, and a β-$SiMe_3$ elimination (Scheme 30), as demonstrated by Goré et al. in carrying out the reaction in the presence of deuterated water.[209] The use of this method for the synthesis of a multifunctionalised substrate bearing a distant *t*-butyldimethylsilyl ether group has led to the expected lactone, but with cleavage of this silyl ether (Eq. 155).[287]



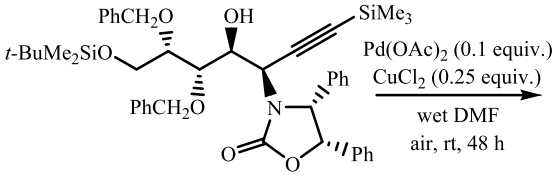
Scheme 29.



Scheme 30.

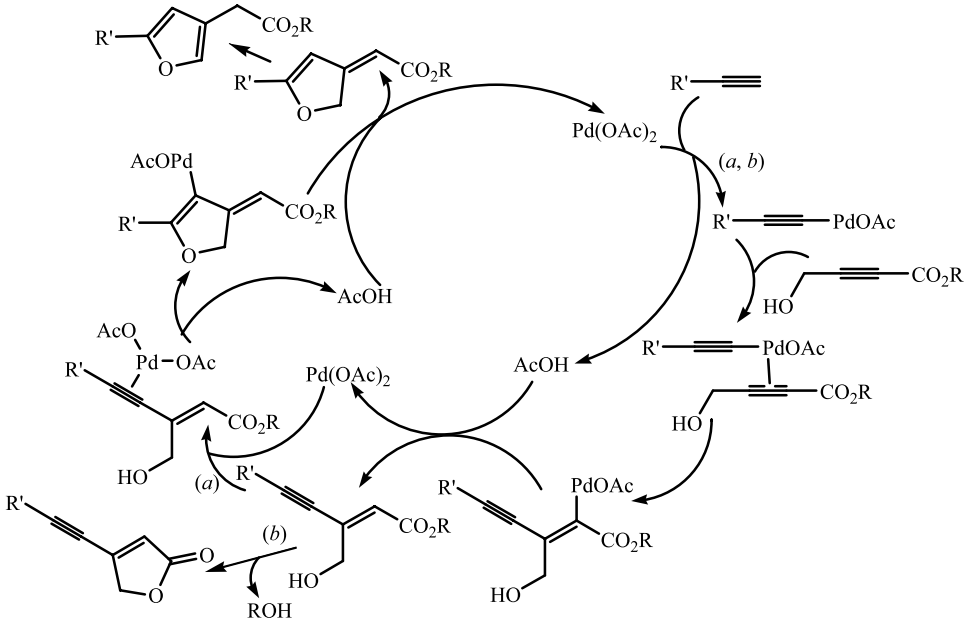


(154)

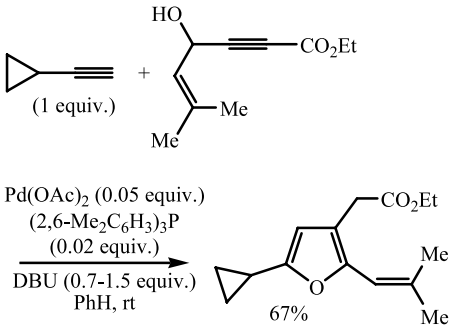


(155)

Trost et al. have synthesised furans from the coupling of propargylic alcohols with alkynes (Eq. 156), a key step being the oxypalladation of the triple bond of an in situ-produced homopropargylic alcohol (Scheme 31, path a). In modifying the experimental conditions with the addition of tri-*n*-butyltin acetate to serve as a transesterification catalyst, the γ-hydroxy α,β-unsaturated ester intermediate led to a butenolide instead of a furan (Scheme 31, path b).[288]

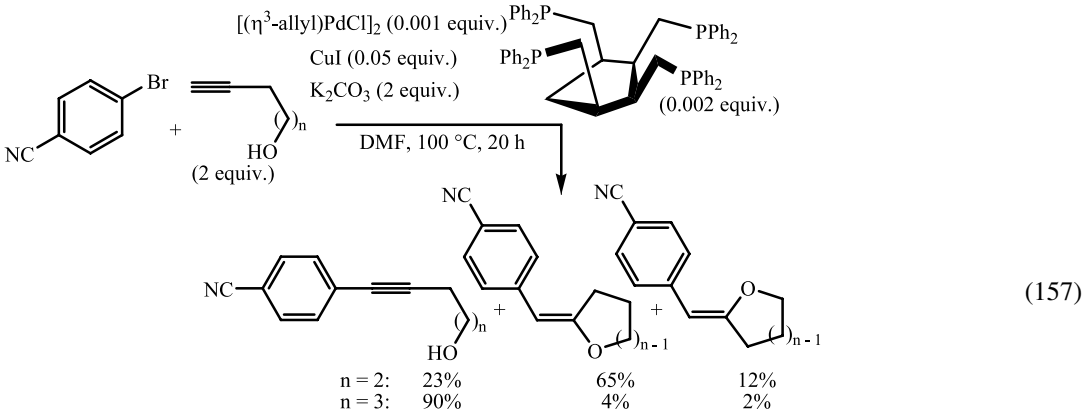


Scheme 31.

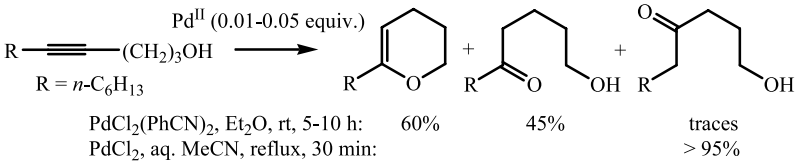


(156)

The Sonogashira reaction of aryl bromides with pent-1-yn-5-ol and hex-1-yn-6-ol can, in some cases, evolve towards the cyclisation products (Eq. 157).[289]

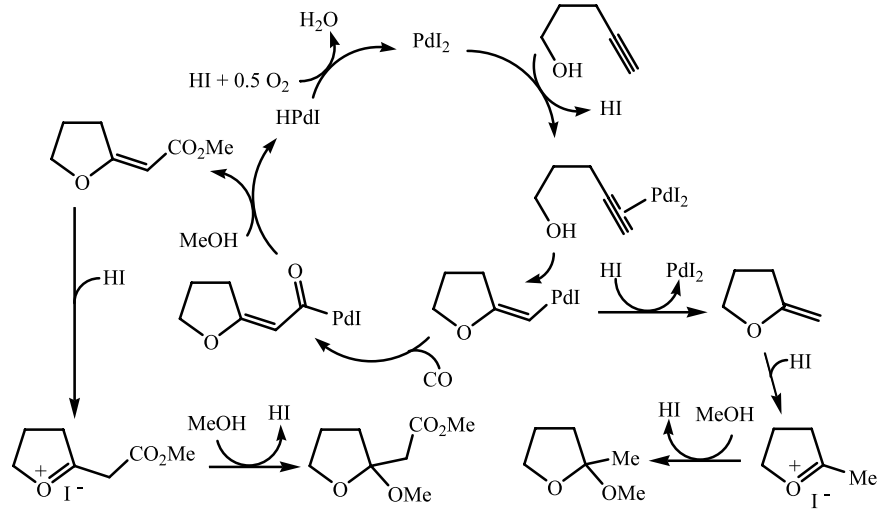


(157)



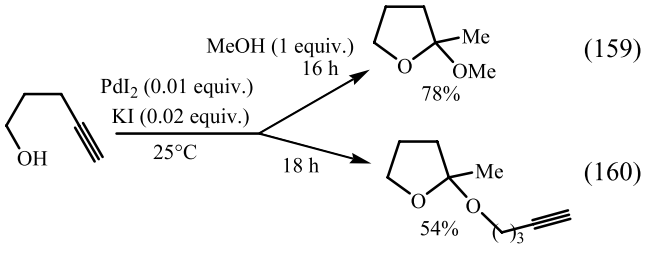
3.4.4. 4-Yn-1-ols. At room temperature in anhydrous diethyl ether, 4-undecyn-1-ol cyclised predominantly in a 6-*endo-dig* manner to afford a mixture of the corresponding dihydropyran and its hydrolysed product, while the 5-*exo-dig* cyclisation, followed by hydrolysis, was preferred in refluxing aqueous acetonitrile (Eq. 158).[278]

Gabriele at al. have carried out the 5-*exo-dig* cyclisation–alkoxylation and the 5-*exo-dig* cyclisation–alkoxycarbonylation of 4-yn-1-ols in the presence of PdI_2 and KI (Eqs. 159–161).[290,291] According to these authors,[290] the acetals woud be obtained from the acid-mediated addition of methanol to enol ethers (Scheme 32). This is in agreement with Kato et al., who have improved the cyclisation–alkoxycarbonylation procedure using milder experimental conditions and *p*-benzoquinone to regenerate the catalyst (Eq. 162),[292] the re-oxidation step effectively trapping the protons liberated in the course of the domino reaction and, consequently, preventing the acetalisation process. Subsequently, the Japonese team has disclosed the Pd^{II}/chiral bisoxazolines-catalysed



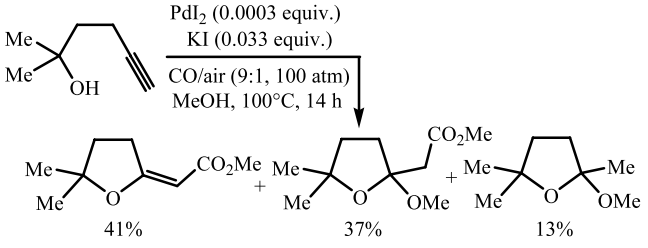
Scheme 32.

asymmetric cyclisation–alkoxycarbonylation of cyclic-2-methyl-2-propargyl-1,3-diols with ee up to 65% (Eq. 163).[293]

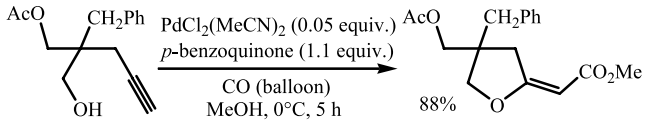


(159)

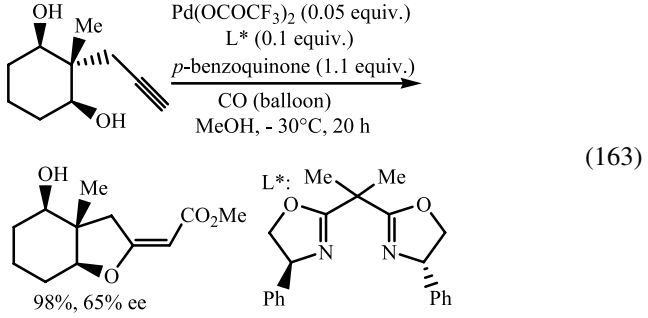
(160)



(161)

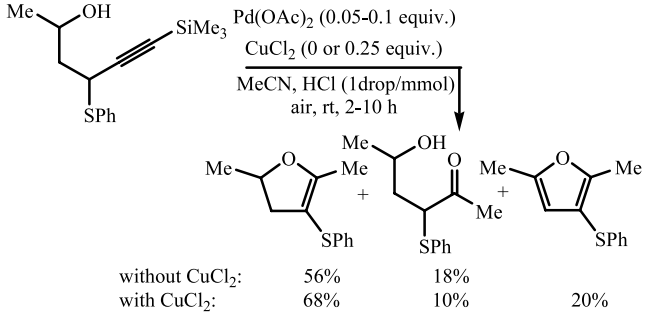


(162)



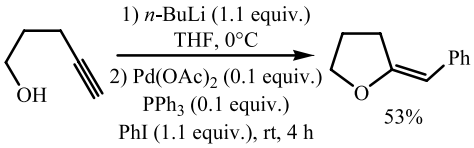
(163)

A procedure similar to that of Goré (Eq. 154 and Scheme 30),[209,285,286] applied to silyl-substituted bis(homo)propargylic alcohols, led mainly to dihydrofurans (Eq. 164), the nucleophilic attack of the hydroxy taking place in the β-position relative to the silicon atom.[294]

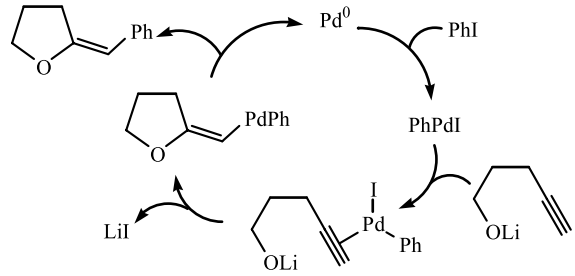


(164)

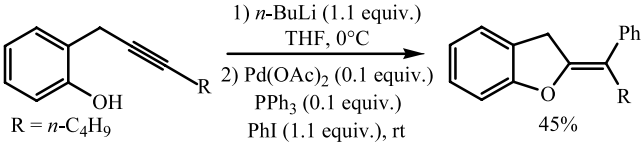
Stereodefined 2-alkylidenetetrahydrofurans have been synthesised from phenyl iodide and the alcoholates of 4-alkyn-1-diols (Eq. 165), through the *trans*-phenoxypalladation of the triple bond, as shown in Scheme 33.[295,296] The assertion of a *trans*-oxypalladation, rather than either a *cis*-oxypalladation or a Heck-type reaction followed by alcoholysis of the resultant vinylpalladium species, has been assumed by the formation of the *E*-isomer from 2-(2-heptynyl)phenol and phenyl iodide (Eq. 166).[295]



(165)

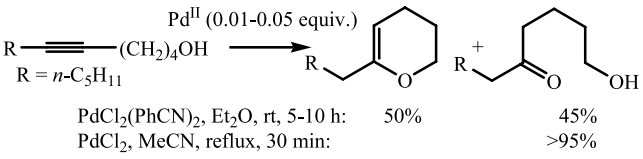


Scheme 33.



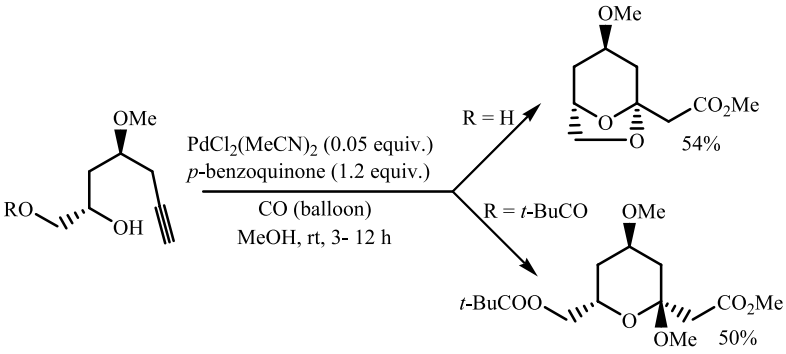
(166)

3.4.5. 5-Yn-1-ols. At room temperature in anhydrous diethyl ether, 5-undecyn-1-ol cyclised in a 6-*exo*-*dig* manner to afford, after migration of the C=C bond, the corresponding dihydropyran and its hydrolysed product (Eq. 167). This latter compound is selectively obtained in refluxing aqueous acetonitrile (Eq. 167),[278] and this procedure has been used to produce a key intermediate of the synthesis of (*R*)-muscone.[297]



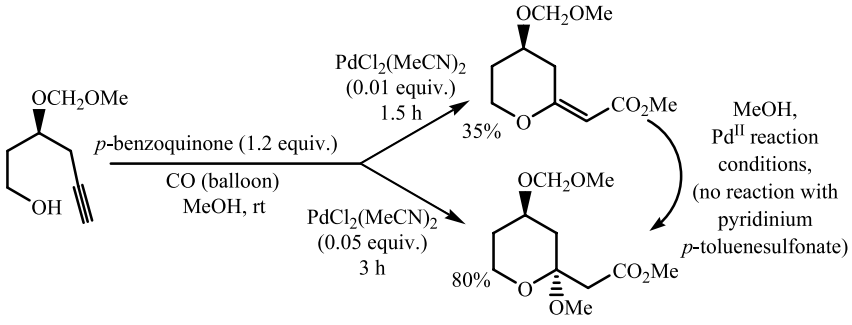
(167)

Marshall et al. have obtained substituted ketopyranose subunits of polyketide natural products via the intramolecular alkoxycarbonylation of 5-alkyn-1-ols (Eqs. 168 and 169). On decreasing both the quantity of the catalyst and the reaction time, the reaction stops at the level of the unsaturated ester (Scheme 34), while the use of $CuCl_2$ instead of *p*-benzoquinone as re-oxidant of the palladium species led to decomposition products.[298] With *p*-benzoquinone, the protons produced in the addition steps are consumed in the course of the Pd^{II} regeneration, ensuring a weakly acidic reaction environment, while HCl is produced with $CuCl_2$.



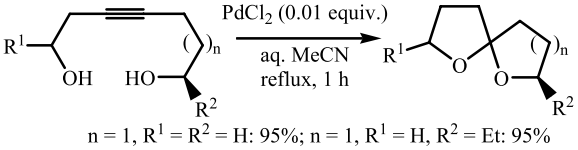
(168)

(169)

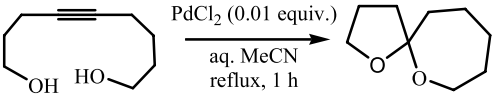


Scheme 34.

3.4.6. 3-Yn-1,7(or 8)-diols and 4-yn-1,8-diols. Utimoto has synthesised spiroacetals from acetylenes containing two hydroxyl groups at appropriate positions (Eqs. 170 and 171). Interestingly, a chiral centre was not touched during this process (Eq. 170).[278]

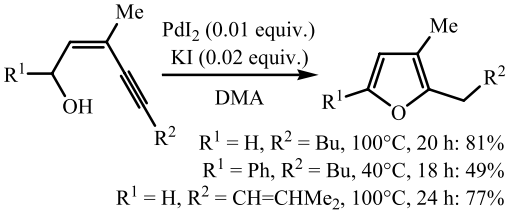


(170)

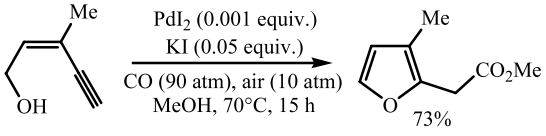


(171)

3.4.7. 2-En-4-yn-1-ols. Gabriele et al. used 0.002–0.01 equiv of K_2PdI_4 at 25–100 °C to synthesise furans via the cycloisomerisation of (*Z*)-2-en-4-yn-1-ols (Eq. 172), and they suggested the *anti-exo-dig* intramolecular attack of the hydroxyl on the triple bond coordinated to Pd^{II}, leading to an oxonium intermediate (Scheme 35).[291,299,300] A similar mechanism would explain the formation of furan-2-acetic esters when the reaction was carried out under a CO/air pressure in MeOH (Eq. 173).[301,302]

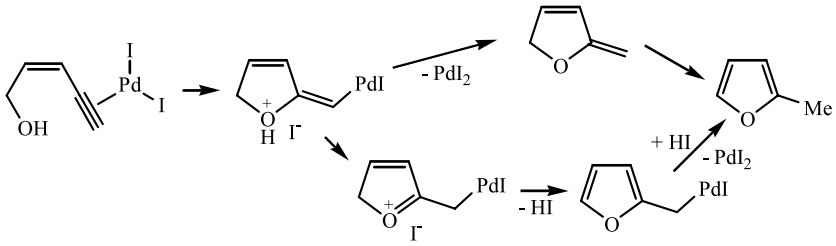


(172)

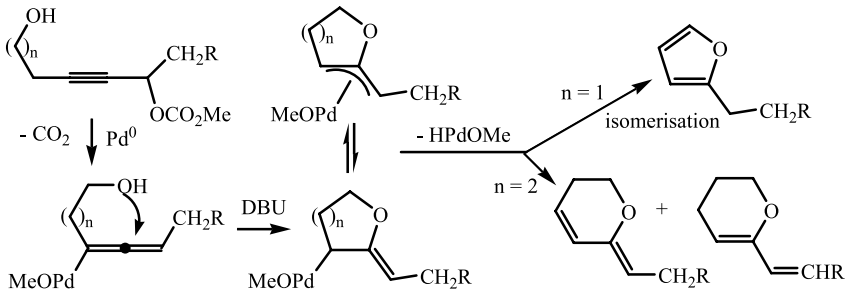


(173)

The PdI_2/KI procedure was used by the Italian team for the cycloisomerisation of 2-alkynylbenzyl alcohols and, interestingly, the same substrate can selectively lead, in several cases, to either the 1,3-dihydroisobenzofuran (5-*exo-dig* cyclisation mode) or the 1*H*-isochromene (6-*endo-dig* cyclisation mode) derivative on changing the polarity of the solvent (Eq. 174).[303] The ratio between the two

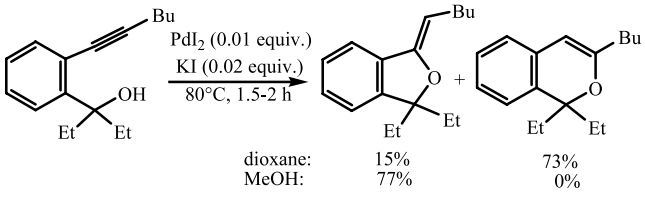


Scheme 35.

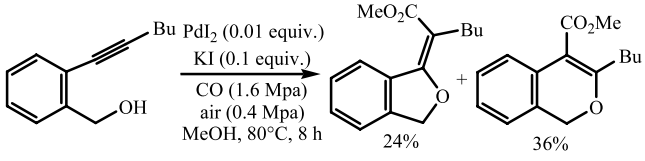


Scheme 36.

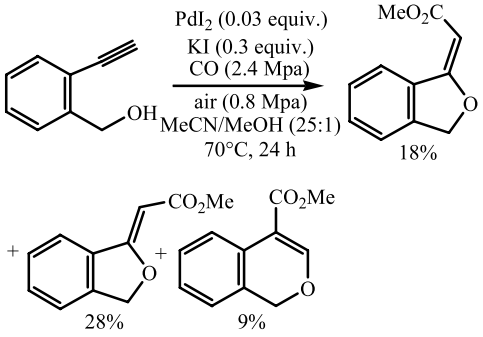
cyclisation modes also depends on the substitution pattern of the substrate.[303] Costa, Gabriele et al. succeeded in trapping the vinylpalladium intermediates by carbonylation (Eqs. 175 and 176), and the formation of the isomeric 1-(methoxycarbonyl)methylene-1,3-dihydroisobenzofurans (Eq. 176) has been attributed to the alcohol addition/elimination involving the exocyclic double bond.[304]



(174)

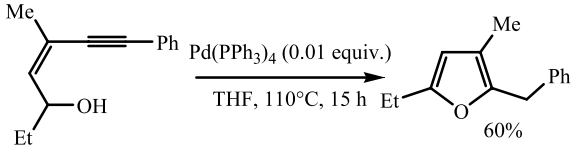


(175)



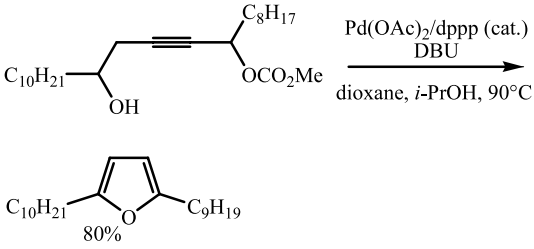
(176)

In contrast to the above cyclisations performed with a Pd^{II} catalyst, Dixneuf et al. used a Pd^0 catalyst to synthesise 2-benzyl-3-methyl-4-ethylfuran from the corresponding 2-en-4-yn-1-ol (Eq. 177).[305]

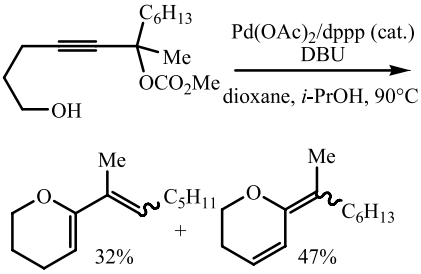


(177)

3.4.8. Hydroxylated propargylic carbonates. Unsaturated heterocycles have been obtained from propargylic carbonates bearing an hydroxyalkyl chain (Eqs. 178 and 179), via the intramolecular nucleophilic addition of the hydroxy group to the central atom of an allenylpalladium intermediate (Scheme 36).[306]



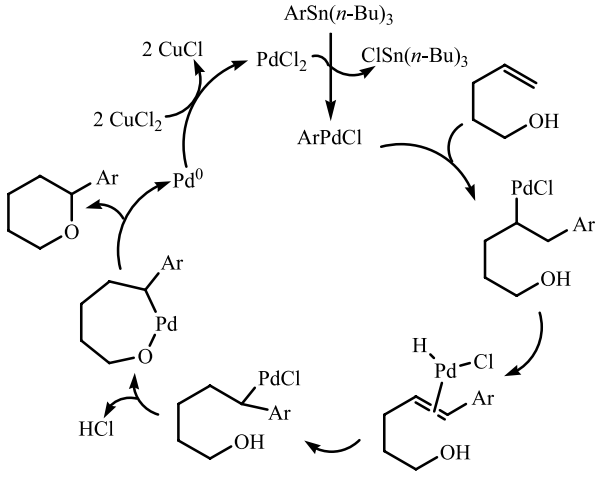
(178)



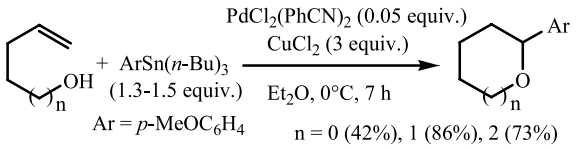
(179)

4. Addition of organopalladium intermediates to double bonds of alkenols

The Pd-catalysed addition of phenylmercuric chloride or, especially, arylstannanes to 3-, 4- and 5-alkenols affords mainly the corresponding arylated cyclo ethers (Eq. 180),[307] presumably via the pathways summarised in Scheme 37.

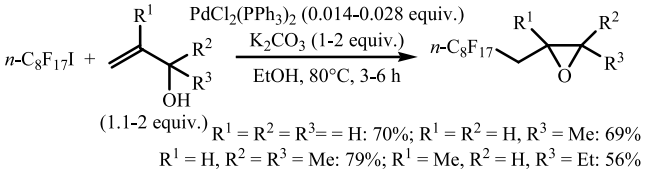


Scheme 37.

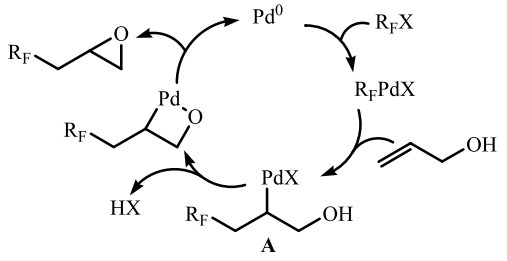


(180)

Fuchikami et al. have obtained polyfluoroalkylmethyl-substituted oxiranes from the reaction of polyfluoroalkyl halides with allylic alcohols (Eq. 181), and proposed the reaction steps shown in Scheme 38.[308] The formation of the oxopalladacycle intermediate from **A**, rather than the double bond via the β-H elimination, would be due to interactions between the palladium centre and fluorine atoms.

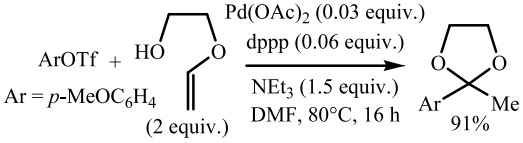


(181)



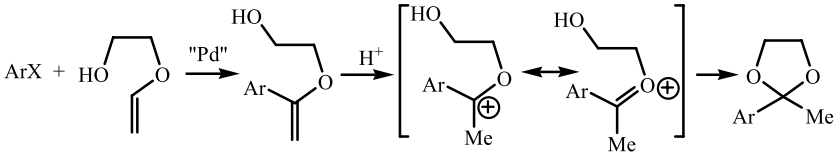
Scheme 38.

Hallberg et al. have disclosed the synthesis of cyclic ketals of acetophenones from hydroxyalkyl vinyl ethers and aryl halides or triflates (Eq. 182), and a set of experiments has supported a domino reaction involving a Heck arylation, followed by an acid-catalysed, rather than a Pd^{II}-promoted cyclisation (Scheme 39; $HNEt_3^+X^-$ can provide H^+). With aryl halides, the addition of stoichiometric amounts of TlOAc was required for a regioselective arylation.[309]

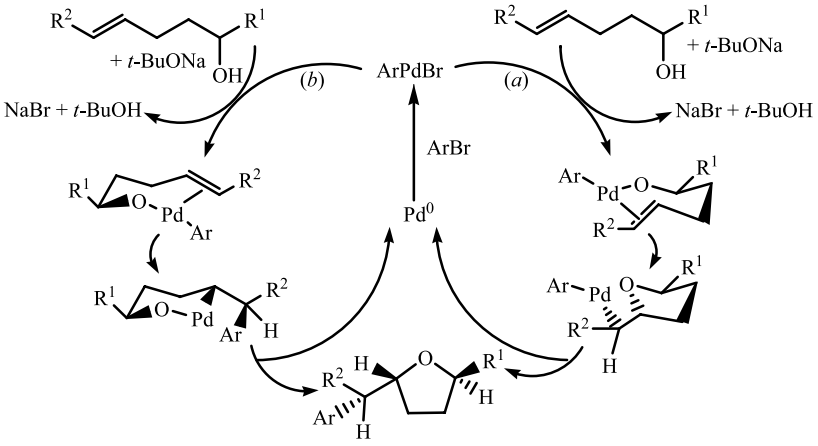


(182)

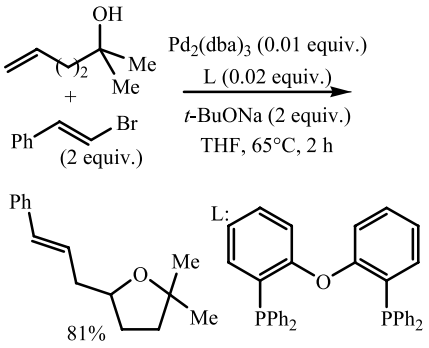
While Larock et al. have obtained the Heck adduct from the reaction of 4-penten-1-ol with phenyl iodide (see Eq. 43 in Part B[2]),[310] Wolfe et al. have achieved the synthesis of tetrahydrofurans from vinyl or aryl bromides and primary, secondary or tertiary 5-hydroxy-alkenes (Eqs. 183 and 184).[311] Surprisingly, the use of aryl iodides and electron-deficient bromides afforded low yields of the expected products. From their analysis of the regio- and stereo-selectivity of the arylation (Eq. 184), the authors assumed that the reaction proceeds through an Ar-Pd-alkoxy intermediate, followed by the insertion of the double bond into either the Pd–O (Scheme 40, path a) or Ar-Pd (Scheme 40, path b) bond.[311] Thus, the reaction mechanism is neither the usual *trans*-oxypalladation, nor the Heck-type reaction which involves the insertion of the olefin into the Ar-Pd bond of the Ar-Pd–halogen species.



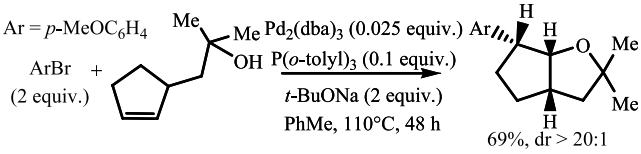
Scheme 39.



Scheme 40.



(183)

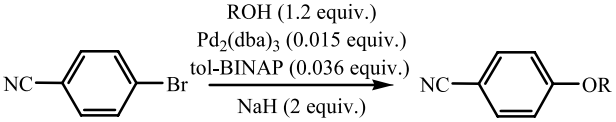


(184)

5. Reaction of organopalladium intermediates with alcohols

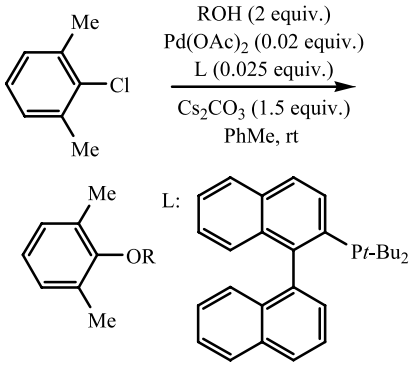
5.1. Intermolecular reactions

In contrast to the $Pd(PPh_3)_4$-catalysed reductions of aryl halides with either sodium methoxide or a mixture of methanol and sodium hydroxide (see Part D of this series of reviews)[312] and to the Pd-catalysed oxidations of alcohols using aryl halides in a basic medium,[1,313] the use of $Pd_2(dba)_3$ or $Pd(OAc)_2$ with biphenyl ligands as the catalytic system, in a basic toluene solution, allows the intermolecular C–O bond formation, as discovered by Buchwald et al. (Eqs. 185 and 186).[314–316] Hartwig et al. have simultaneously reported that the association of $Pd_2(dba)_3$ or $Pd(PPh_3)_4$ with (phosphino)ferrocenyl ligands catalyses the formation of ethers from the reaction of aryl halides with NaOR (R = *t*-Bu, $SiMe_2$*t*-Bu or Ar).[317,318] Aryl-alkoxypalladium complexes have been isolated[318–320] but, whether the formation of alkoxypalladium intermediates involves oxygen coordination of the alcohol and then deprotonation, or deprotonation and then coordination, remains an open question,[321] even if enhancing the acidity of the alcohol by complexation to Pd^{II} seems to be required for deprotonation with some bases.[322]



R = Me (70°C: 81%), *i*-Pr (50°C: 80%), CH_2Ph (70°C: 71%)

(185)



(186)

R = *n*-Bu (39 h: 90%), *t*-Bu (38.5 h: 88%)
Et (29 h: 93%), $PhCH_2$ (44.5 h: 95%)

Bidentate ligands, such as DPEphos or Xantphos, work better than the Buchwald's monophosphine ligands for the $Pd(OAc)_2$- and $Pd_2(dba)_3$-catalysed etherifications of bromoporphyrins (Eq. 187) and their zinc complexes by a variety of alcohols.[323]

Jing et al. have obtained a number of benzodioxanes from the reaction of 1,2-dihalogenoaryls with 1,2-diols (Eq. 188), including the synthesis of a highly functionalised intermediate (Eq. 189) leading to isoamericanol A and isoamericanin A.[324]

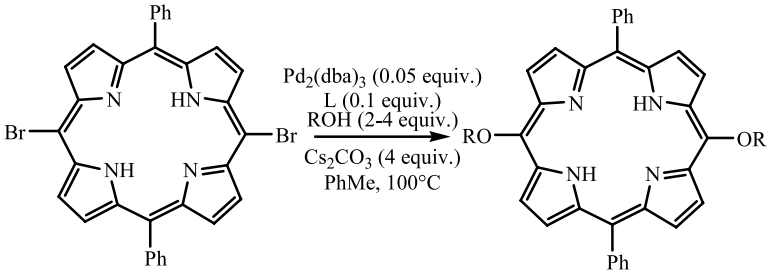
Russian workers have reported yields of $\leq$98% for the alcoholysis of 1-chloroadamantane with alcohols using $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ as catalysts at 120–160 °C;[325] this reaction probably involves adamantylpalladium chloride as an intermediate and some di-1-diadamanthyl ether has sometimes been observed.

The etherification of sp^2 (Eq. 190) and sp^3 (Eq. 191) C–H bonds of aromatic hetero compounds by various alcohols has been disclosed, by Sanford et al., using $PhI(OAc)_2$ to regenerate the active catalyst. Since no product was formed using typical oxidants of Pd^0 such as $Cu(OAc)_2$ and benzoquinone, the authors suggested a catalytic cycle involving Pd^{II} and Pd^{IV} intermediates.[326]

5.2. Intramolecular reactions

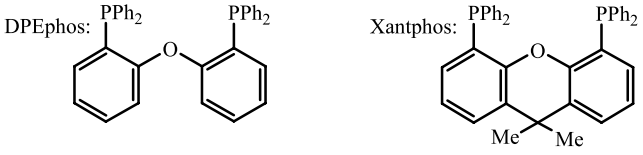
Trost et al. have briefly reported the synthesis of a substituted tetrahydrofuran from the intramolecular alcoholysis of an in situ-formed alkylpalladium iodide (Scheme 41).[327]

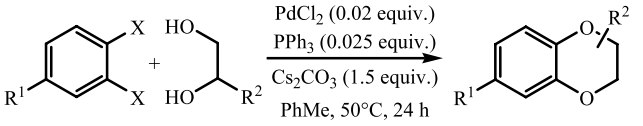
Buchwald's and Hartwig's teams have disclosed the synthesis of oxygen heterocycles via the intramolecular C–O bond-forming reaction of aryl halides substituted in the *o*-position by an alkyl chain bearing a primary or secondary hydroxy group (Eq. 192), the reported experimental conditions restricting the oxidation–dehalogenation processes.[318,328–330] Interestingly, the formation of chiral benzodioxanes (Eq. 193), benzoxazines (Eq. 194) and indolodioxanes (Eq. 195) was attained from optically active substrates, with only slight racemisation.[328,329,331]



(187)

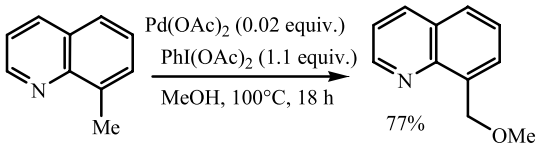
R = Et (DPEphos, 47 h: 50%), $MeCH(CH_2)_2Me$ (Xantphos, 39 h: 30%), *n*-Bu (Xantphos, 39 h: 66%), CF_3CH_2 (DPEphos, 48 h: 33%)





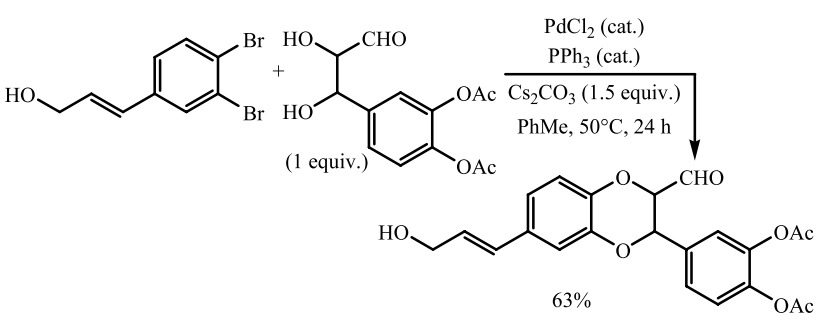
X = Cl, $R^1 = R^2$ = H (63%); X = Br, $R^1 = R^2$ = H (65%)
X = Br, R^1 = H, R^2 = Me (60%); X = Br, R^1 = CN, R^2 = H (60%)
X = Br, $R^1 = CO_2Me$, R^2 = H (61%)

(188)

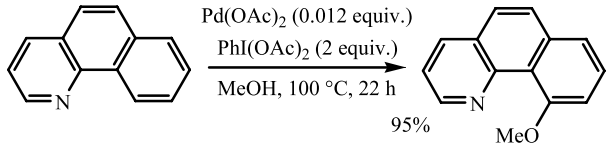


(191)

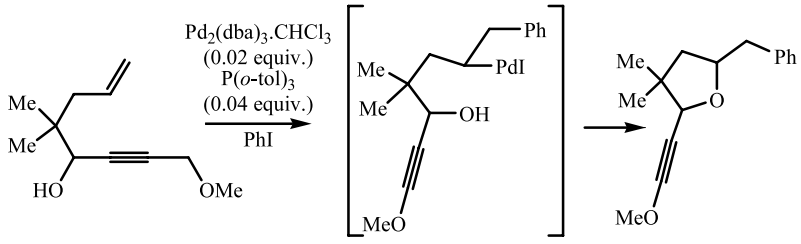
Under Buchwald's conditions, oxygen heterocycles were usually obtained at lower temperatures and with lower quantities of catalyst from primary than secondary alcohols.[328,329] Nevertheless, the intramolecular heterocyclisation was also effective from tertiary alcohols[317b,321,330] and, according to Hartwig et al., even at room temperature (Eq. 196).[318]



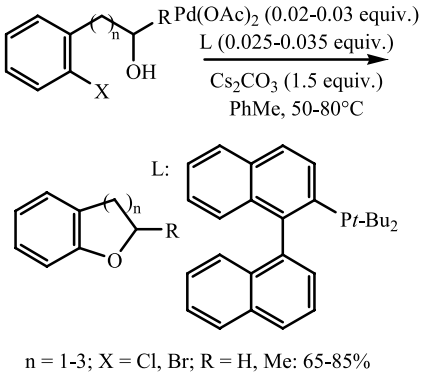
(189)



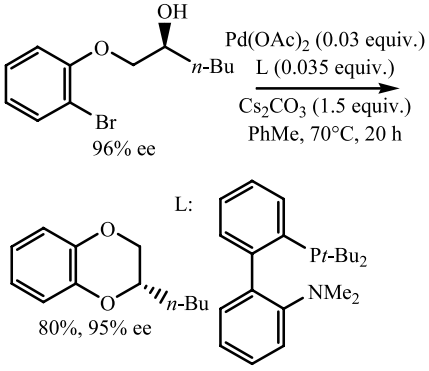
(190)



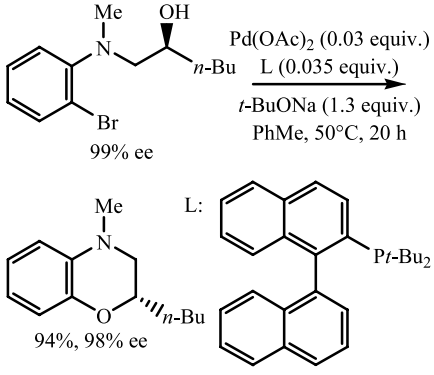
Scheme 41.



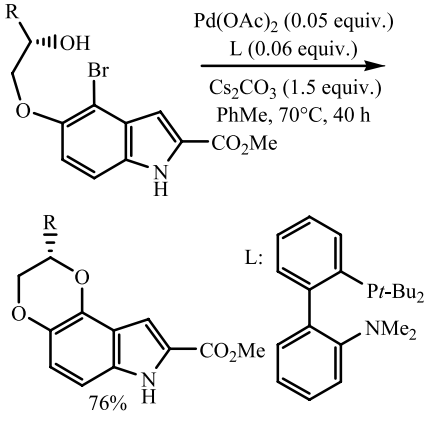
n = 1-3; X = Cl, Br; R = H, Me: 65-85% (192)



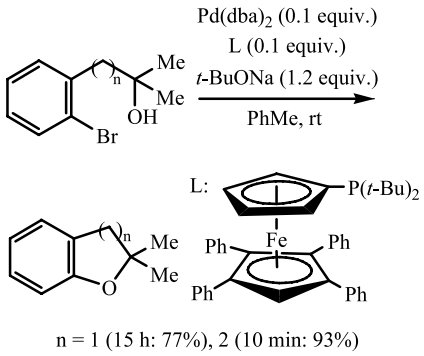
(193)



(194)

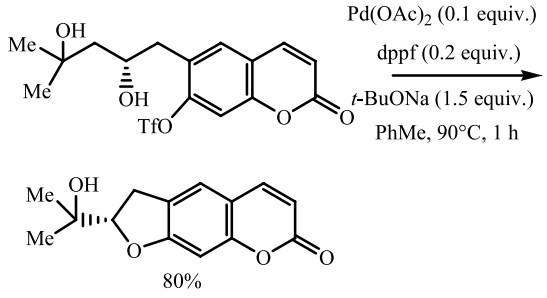


R = CH_2OSiMe_2t-Bu (195)

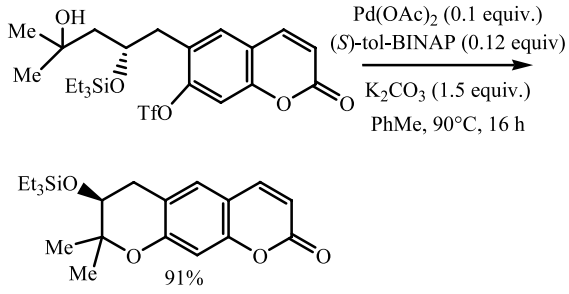


n = 1 (15 h: 77%), 2 (10 min: 93%) (196)

The Buchwald–Hartwig heterocyclisation was used for the synthesis of homochiral natural dihydropyranocoumarin intermediates using hydroxy triflates as substrates instead of hydroxy halides (Eqs. 197 and 198).[332]



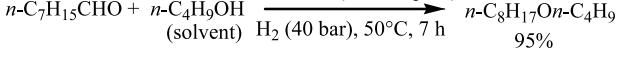
(197)



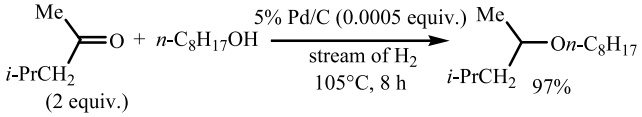
(198)

6. Reaction of alcohols with aldehydes or ketones

Unsymmetical ethers have been obtained from the reaction at 25–160 °C of alcohols with aldehydes (Eq. 199) or ketones in the presence of heterogeneous Pd^0 catalysts and hydrogen (Eq. 200),[333–337] with an efficiency depending on the pH[338] and on the nature of the palladium support.[339] According to Lemaire et al,[334,335] the hemiketal or hemiacetal initially formed[340] would produce the ether by either hydrogenolysis or dehydration, the dehydration affording the corresponding enol ether, its double bond subsequently being hydrogenated.

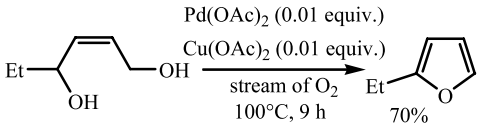


(199)



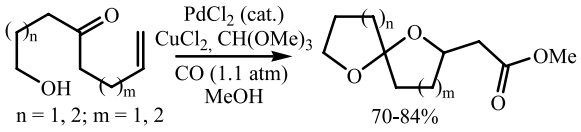
(200)

Couturier et al. obtained furans from *Z*-2-butene-1,4-diols (Eq. 201).[341] Since this method led also to 1,4-diones, we suspect a reaction involving the oxidation of one hydroxyl to the corresponding carbonyl group, followed by the formation of the hemiketal (maybe through the intramolecular attack of an alkoxypalladium) and then dehydration.



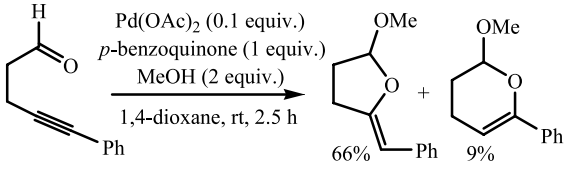
(201)

Yadav et al. isolated spiroacetals from a domino reaction of hydroxyenones involving (i) intramolecular addition of the hydroxy group to the carbonyl to afford a hemiketal, (ii) oxypalladation of the double bond by the hemiketal, (iii) insertion of carbon monoxide into the C–Pd bond, and (iv) methoxylation of the acylpalladium (Eq. 202).[342]

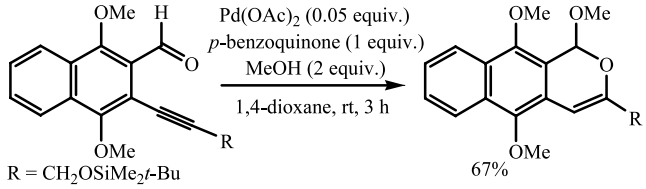


(202)

Yamamoto et al. synthesised cyclic alkenyl ethers via the $Pd(OAc)_2$-catalysed reaction between carbon-tethered acetylenic aldehydes and MeOH, EtOH or *i*-PrOH (Eq. 203).[343] The large increase in the chemical yield in the presence of 1 equiv of benzoquinone, which was, however, recovered in 83% yield, has suggested that this quinone acts as a ligand rather than as an oxidizing agent.[65] Switching from $Pd(OAc)_2$ to $PdCl_2$ led to a low conversion and to traces of the cyclic ether, while the use of Pd^0 catalysts was totally ineffective. This heteroannelation procedure has provided a six-membered product leading to the synthesis of a potent antitumour agent (Eq. 204).[344] As a possible mechanism, Yamamoto et al. assumed that $Pd(OAc)_2$ acts simultaneously as a Lewis acid catalyst and as a transition metal catalyst towards the substrate to promote, firstly, the addition of the alcohol and, secondly, the cyclisation reaction (Scheme 42, path a).[343] Such a proposal is of interest, but recent reports[345] suggest to us an alternative mechanism, which would involve an oxonium salt intermediate formed by the addition of the carbonyl to the palladium-activated alkyne (Scheme 42, path b). Nevertheless, the Yamamoto mechanism, which involves a hemiacetal intermediate, could explain the inefficiency of the $PdCl_2$ catalyst; indeed, the literature reports various examples of deacetalisation by $PdCl_2(MeCN)_2$,[346,347] while $Pd(OAc)_2$ seems to be less efficient.[247,346,348] Thus, $PdCl_2$ would induce a 'no reaction reaction'[349] due to the instability of the hemiacetal. Whatever the correct mechanism, it is interesting to highlight that the oxidation state of palladium is maintained all along the process.

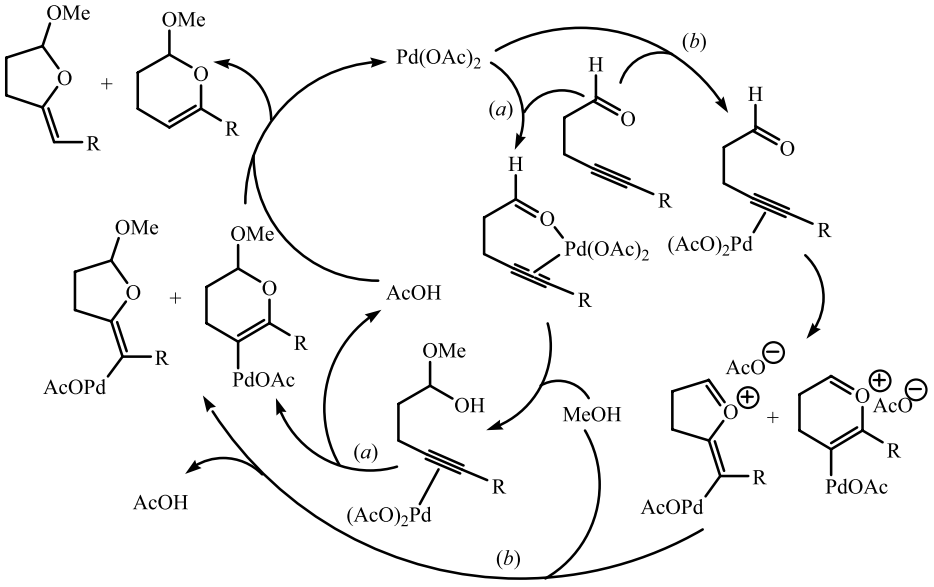


(203)

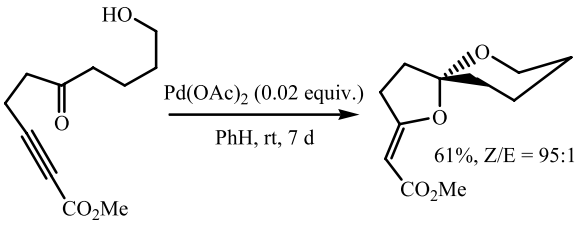


(204)

In fact, a similar reaction, but with intramolecular attack of the hydroxy group, was previously carried out by Toshima et al. (Eq. 205), the selective formation of the *Z*-isomer indicating a *trans*-oxypalladation.[350]

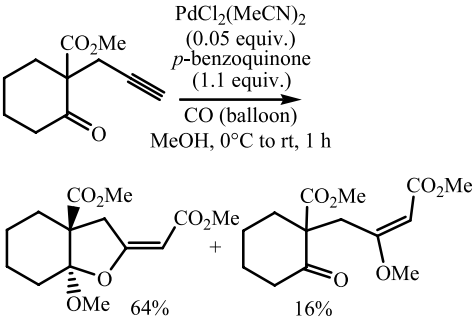


Scheme 42.

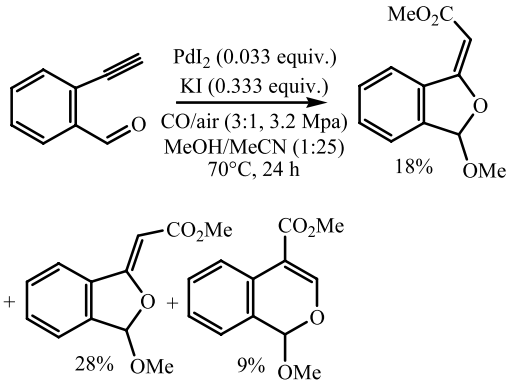


(205)

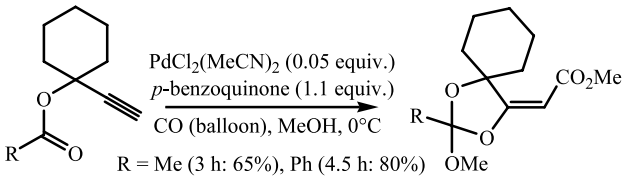
Subsequently, these intermolecular alcohol/carbonyl-alkyne reactions have been performed under a carbon monoxide atmosphere by the teams of Kato (Eq. 206)[351] and Costa (Eq. 207).[304] The experimental conditions led to carbonylation of the vinylpalladium intermediate, and a re-oxidant is required because the Pd^{II} catalyst is reduced in the course of the process. Kato et al. used *p*-benzoquinone, and proposed a mechanistic scheme (Scheme 43) which has some similarities with Scheme 42, path b. Costa et al. used their well-known PdI_2/KI catalyst with air, and suggested a mechanism connected with Scheme 42, path a. In addition, Kato et al. obtained similar reactions from tertiary propargylic acetates and benzoates (Eq. 208).[352,353]



(206)

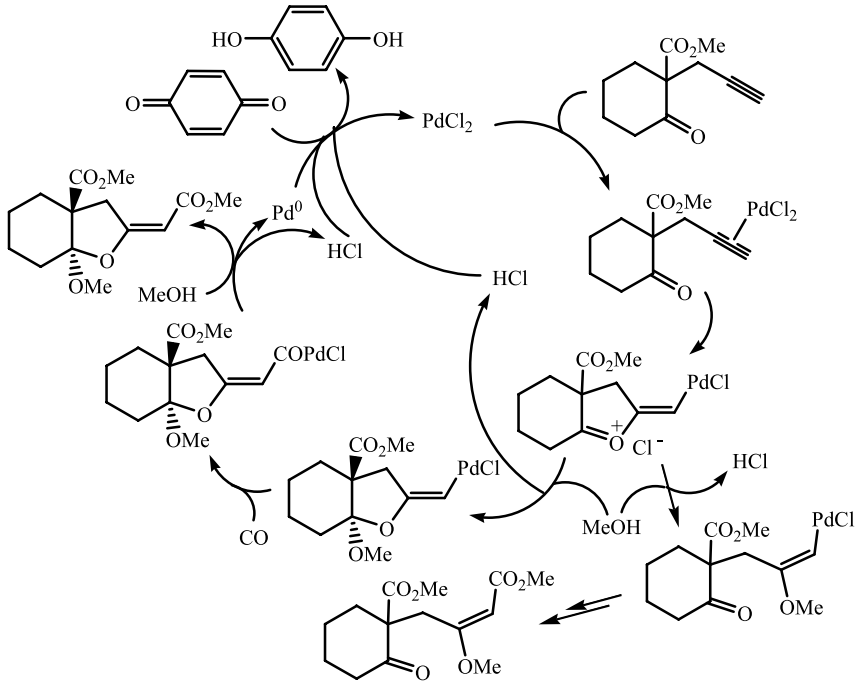


(207)

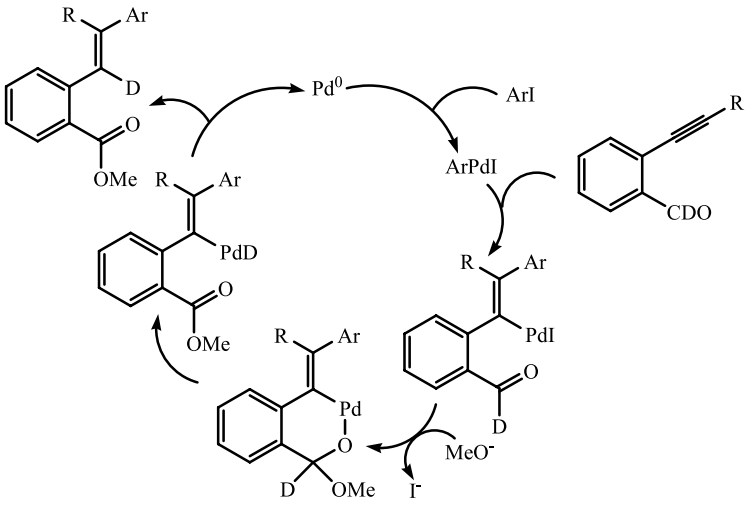


(208)

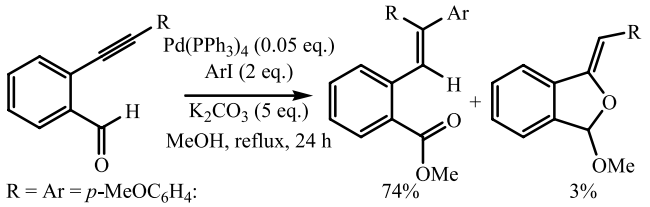
Recently, Wu et al., reacting 2-alkynylbenzaldehydes with aryl iodides and a Pd^0 catalyst in basic methanol, obtained two types of compounds, a hydroarylation–esterification adduct and/or an acetal (Eq. 209). The mechanism of the formation of the hydroarylation–esterification adduct, supported by experiments with a deuterium-labelled substrate, implies a β-hydrogen elimination from a cyclic oxypalladium complex (Scheme 44).[354] As for the acetal, we suggest pathways as in Scheme 42 with $ArPd^{II}I$ as the catalyst.



Scheme 43.



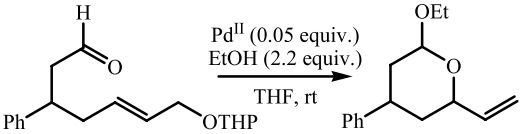
Scheme 44.



R = Ar = *p*-$MeOC_6H_4$: 74% 3%
R = *p*-$MeOC_6H_4$, Ar = 2-pyridinyl: 88%

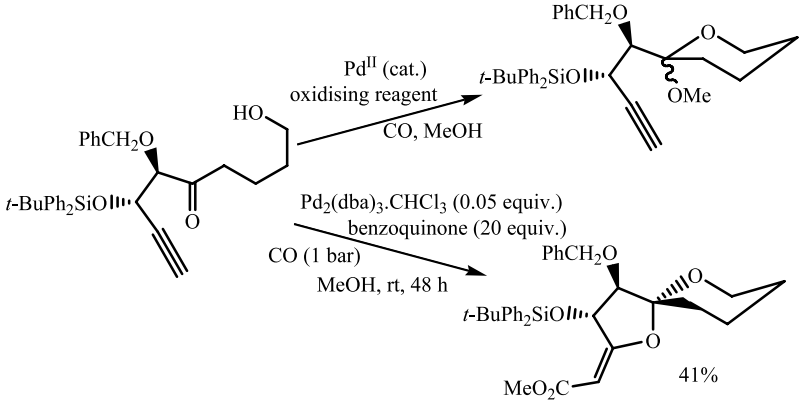
(209)

Mukai et al. tested the MeOH/hydroxy-carbonyl-alkyne/CO reaction: the expected cascade process did not succeed with a Pd^{II} catalyst (Eq. 210), but arose using a Pd^0 catalyst and an oxidising reagent (Eq. 211). According to the authors, only a minimal amount of the active Pd^{II} species has to be present in the reaction vessel to avoid the reaction of the hemiacetal with methanol.[355] The *E*-stereochemistry of the double bond of the spiroacetal is in agreement with the *trans*-oxypalladation of the triple bond.



$PdCl_2(PhCN)_2$, 16 h: 70%
$PdCl_2(MeCN)_2$, 16 h: 29%
$PdBr_2(PhCN)_2$, 40 h: 56%
$[(\eta^3\text{-allyl})PdCl]_2$ or $Pd(OAc)_2$, 24 h: 0%

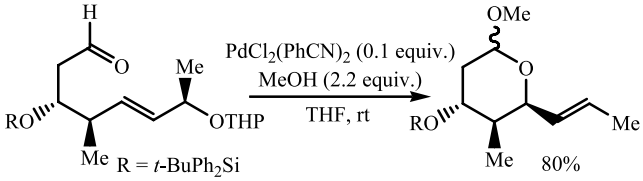
(212)



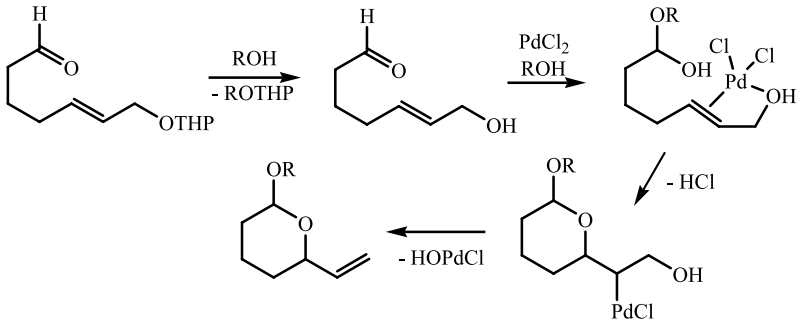
(210)

(211)

Hirai et al. have disclosed the cascade reactions illustrated in Eqs. 212 and 213 for the construction of 2-alkenyl-tetrahydropyrans with a palladium dihalide as catalyst.[356,357] According to the authors, the first step of the reaction is the conversion of the allylic ether group into the corresponding allylic alcohol.[358] Indeed, the cyclisation succeeded using directly the allylic alcohol and was faster than from the allylic ether. The second step of the reaction is the formation of the hemiacetal that adds to the palladium-activated C=C bond, leading, finally, to the product, as depicted in Scheme 45. The oxypalladation, rather than the addition to an η^3-allylpalladium intermediate, was retained, because no cyclisation product was obtained from the corresponding allyl methyl carbonate.[356]



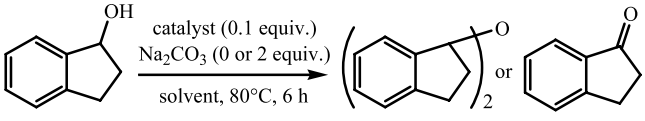
(213)



Scheme 45.

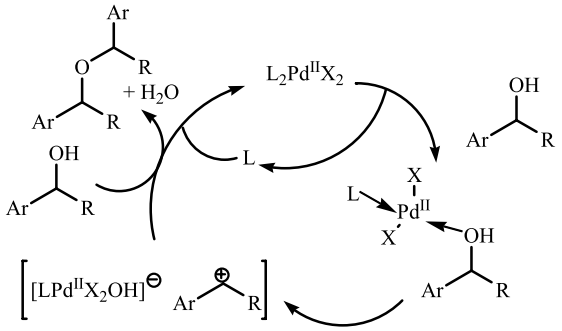
7. Carbocation intermediates

Palladium^{II} catalysts can mediate the self-condensation of alcohols to afford symmetrical ethers,[359] and we have shown the critical role of the coordination environment of palladium on the course of the catalytic reaction of secondary benzylic alcohols, since either oxidation or etherification was selectively obtained, depending on the Lewis acid properties of the catalyst (Eq. 214).[360] Our suggestion of the involvement of carbocation intermediates (Scheme 46) is in agreement with the subsequent work of Abu-Omar et al., who obtained a diastereoisomeric and racemic mixture of bis-*sec*-phenylethyl ether from (*S*)-*sec*-phenylethyl alcohol.[361]



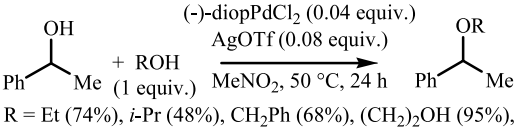
$PdCl_2(MeCN)_2$, Na_2CO_3, $ClCH_2CH_2Cl$:	98%	0%
$(n\text{-}Bu_4N)_2PdCl_4$, Na_2CO_3, $ClCH_2CH_2Cl$:	0%	92%
$PdCl_2(MeCN)_2$, $PhCF_3$:	97%	0%

(214)



Scheme 46.

Instead of undergoing self-condensation, secondary benzylic alcohols (Eq. 215)[361,362] and tertiary alcohols[363] can afford disymmetric ethers, under Pd catalysis, by reacting with other primary or secondary alcohols.

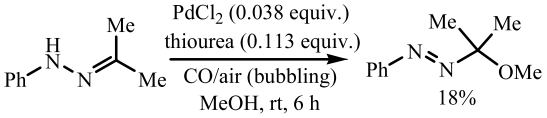


R = Et (74%), *i*-Pr (48%), CH_2Ph (68%), $(CH_2)_2OH$ (95%), $(CH_2)_2SH$ (34%), CHPhCOPh (36%)

(215)

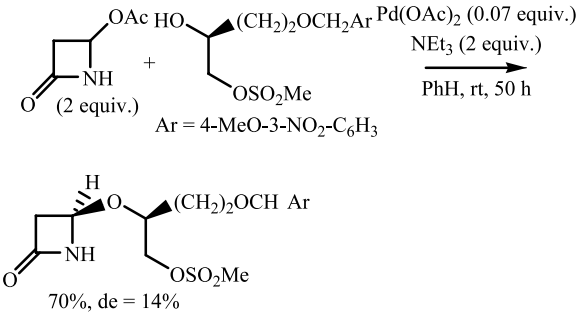
8. Miscellaneous etherifications

Aliphatic phenylhydrazones react with methanol, leading to (phenylazo)alkyl methyl ethers in low yields (Eq. 216).[364]



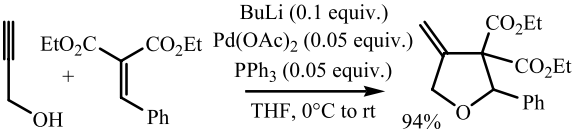
(216)

The condensation reaction between 4-acetoxy-2-azetidinone and various alcohols has been mediated by catalytic amounts of $Pd(OAc)_2$. The use of a chiral alcohol leads to a diastereoselective reaction (Eq. 217),[365–367] while the use of an enantiomerically pure azetidinone has no advantage, because the substitution proceeds via a planar intermediate.[366]



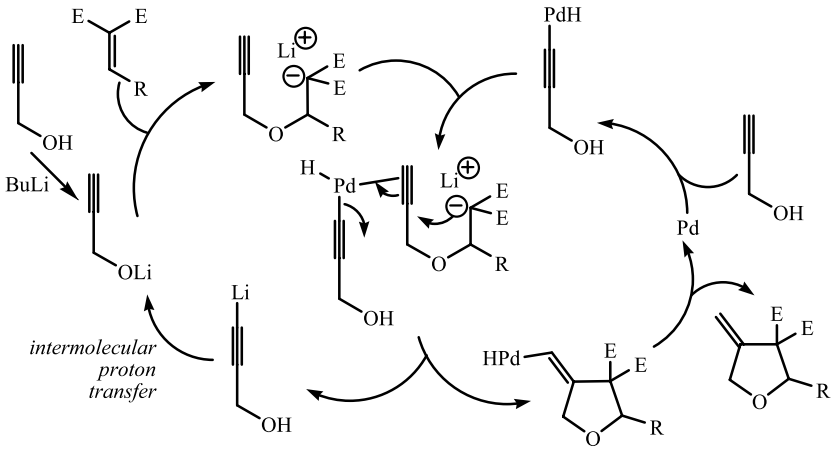
(217)

Highly functionalised 3-methylenetetrahydrofurans have been isolated by Balme et al. from sequential Michael addition/carbocyclisation reactions of propargyl alcohol with activated alkenes (Eq. 218). Scheme 47 has been proposed to explain the use of only catalytic amounts of the base.[368,369]

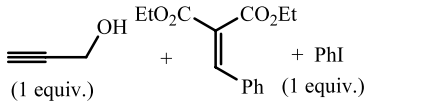


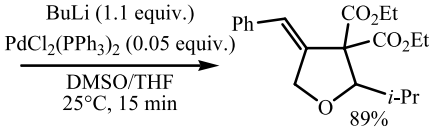
(218)

Three-component reactions affording 3-arylidene- or 3-alkenylidene-tetrahydrofurans have been subsequently carried out by Balme's team, using propargylic alcohols, Michael acceptors and aryl (or 1-alkenyl) halides or triflates with a Pd catalyst and a stoichiometric amount of base (Eq. 219).[370–372] A similar strategy has been reported by Lu et al.[373] The use of allylic instead of propargylic alcohols leads to tetrahydrofurans (Eq. 220).[374]

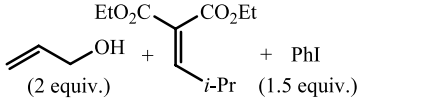


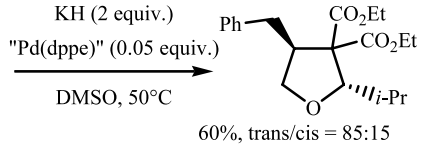
Scheme 47.





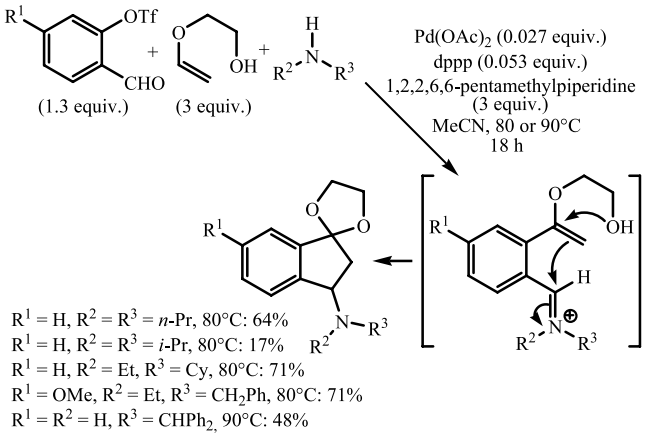
(219)





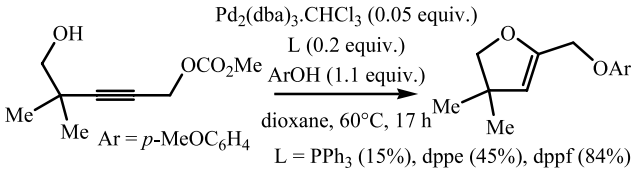
(220)

Another three-component annulation process has been recently reported by Hallberg et al. to prepare masked 3-aminoindan-1-ones from a set of salicyclic aldehyde triflates, ethylene glycol vinyl ether, and α-phenylbenzylamine or various secondary nucleophiles amines. The invoked reaction route involves the initial internal Heck arylation of the vinylic ether, the formation of an iminiumm ion, and the subsquent cascade cyclisation (Scheme 48).[375]

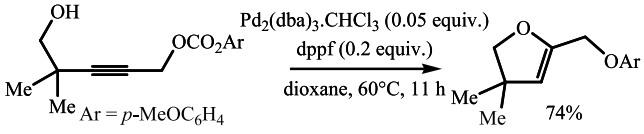


Scheme 48.

The efficiency of the synthesis of substituted 2,3-dihydrofurans from the Pd^0-catalysed reaction of phenols with 5-methoxycarbonyloxy-3-pentyn-1-ols depends on the nature of the ligands (Eq. 221).[376] The mechanism proposed by Yoshida et al. involves the nucleophilic addition of the phenol to a π-propargylic complex (Scheme 49, path a);[376] we suggest a palladium vinylcarbene complex as another plausible intermediate (Scheme 49, path b). The Japanese team has shown that the nucleophile can be a latent species released from the carbonate moiety (Eq. 222).



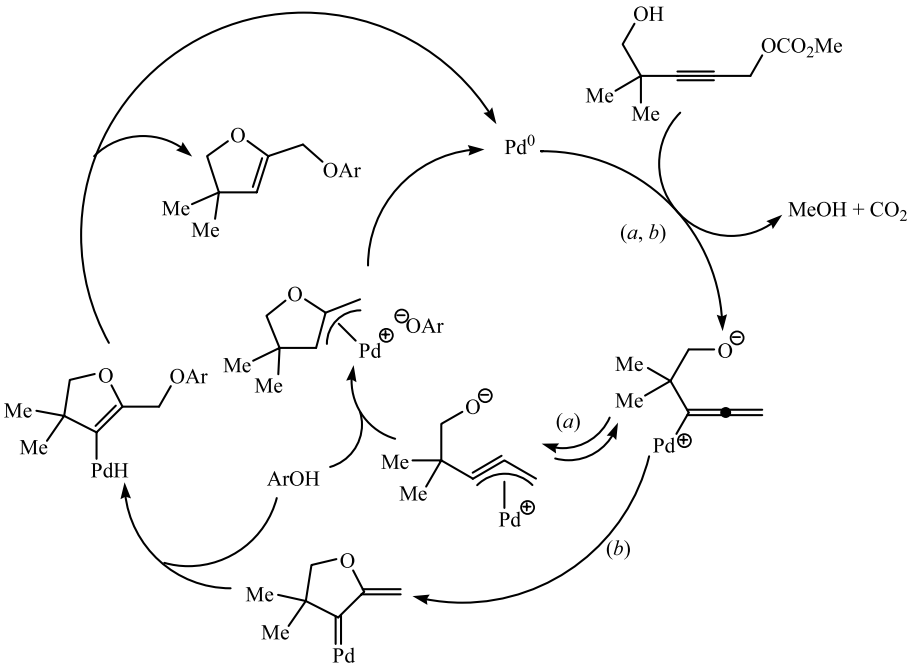
(221)



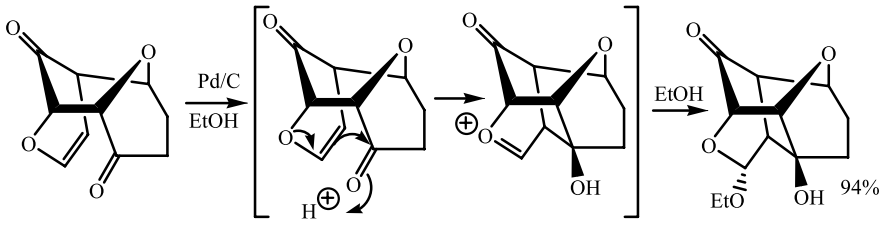
(222)

The unusual transannular cyclisation depicted in Scheme 50 was ascribed to the acidic nature of the reaction medium.[377] Thus, we suspect that its efficiency depends on the purity of the catalyst.[378]

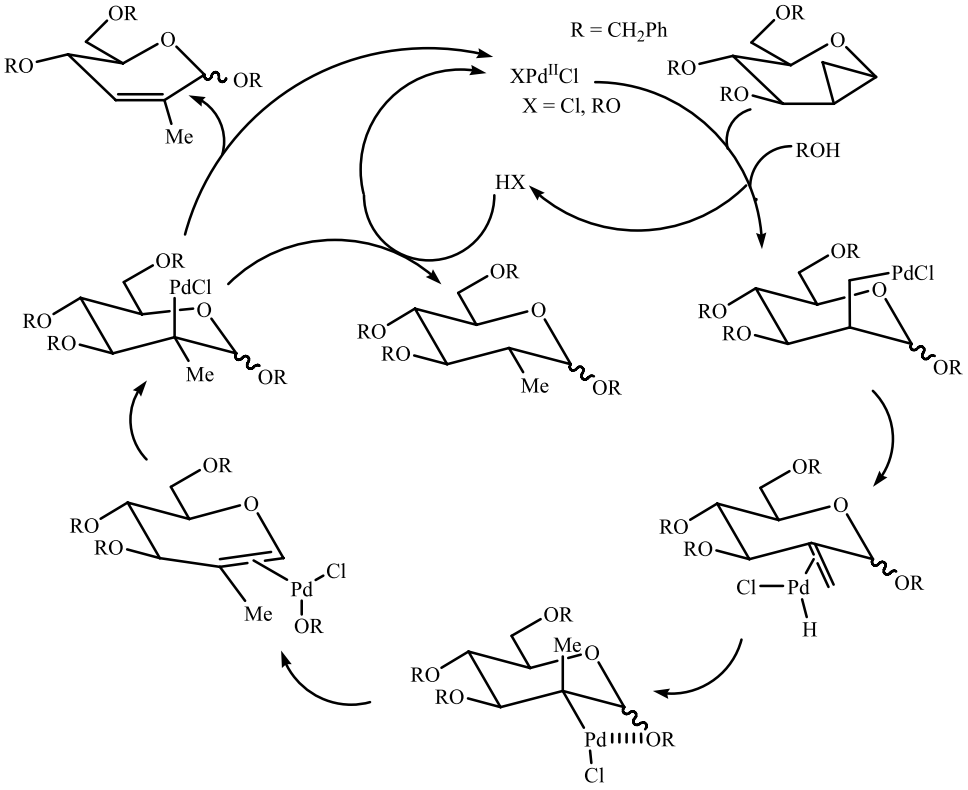
The Pd^{II}-catalysed ring opening of 1,2-cyclopropanated sugars with benzyl alcohol affords 2,3-unsaturated glycals containing a 2-*C*-alkyl substituent as the main product (Eq. 223), the catalyst serving as Lewis acid for this Ferrier-type rearrangement (Scheme 51).[379]



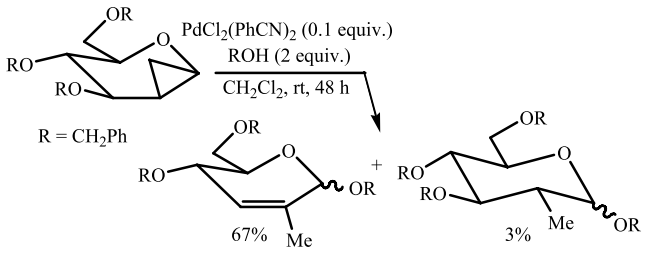
Scheme 49.



Scheme 50.

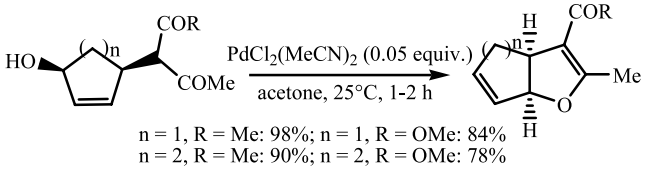


Scheme 51.

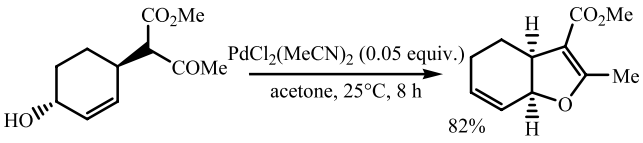


(223)

Tenaglia et al. have reported the formation of the bicyclic systems shown in Eq. 224, via the $PdCl_2(MeCN)_2$-catalysed intramolecular reactions of an allylic alcohol with a β-diketone or a β-ketoester.[380] The mechanism of these formally 5-enol *endo-exo-trig* ring closures remains undetermined. Nevertheless, the French team has also obtained such a bicyclic system from the *trans*-1,4-disubstituted cyclohex-2-ene, as depicted in Eq. 225.[381] Consequently, Tenaglia suggests oxopalladation of the C=C bond by the enol, and protonation of the hydroxy group, the elimination of which (as water) regenerates the Pd^{II} catalyst (Scheme 52). Interestingly, this procedure has been used for the synthesis of tricyclic spiroketals (Scheme 53).[380]



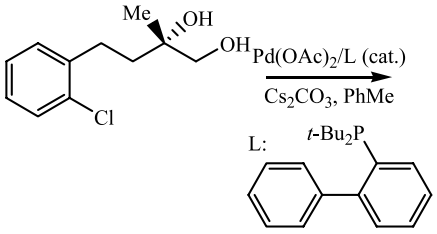
(224)



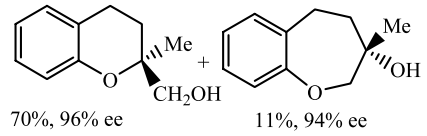
(225)

Note added in proof

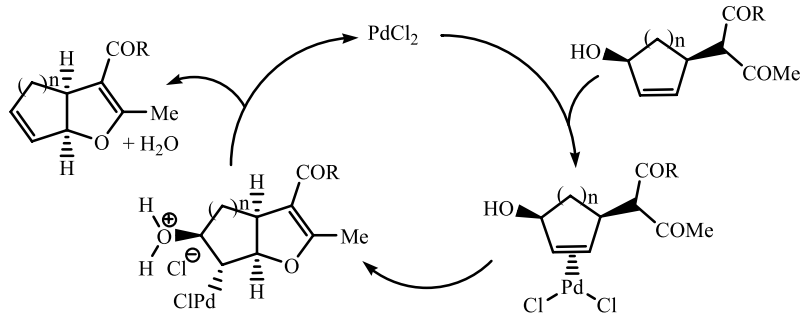
Palucki et al. have reported the enantioselective synthesis of oxygen heterocycles via the intramolecular C–O bond-forming reaction of an aryl chloride substituted in the *o*-position by an alkyl chain bearing two hydroxy groups (Eq. 226).[382]



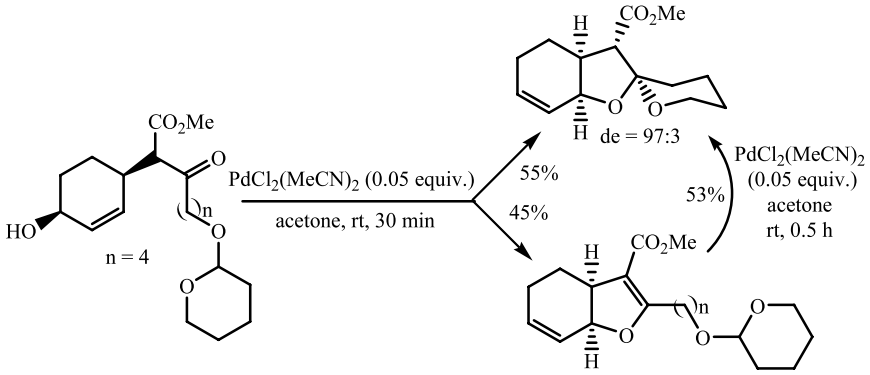
(226)



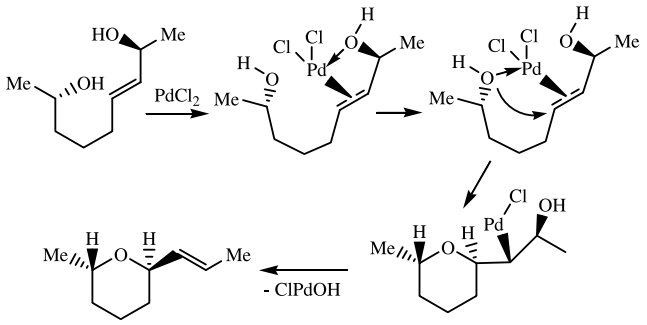
Ueneshi et al. have reported the stereospecific formation of tetrahydro- and 3,6-dihydro[2*H*]pyran rings from the intramolecular oxypalladation of homochiral 2-ene-1,7-ols and 4-ene-1,3-ols respectively (Eqs 227 and 228).[383] In contrast to the processes depicted in Section 3.1.3., the



Scheme 52.

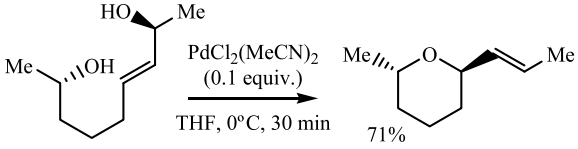


Scheme 53.

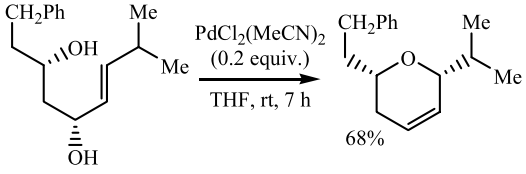


Scheme 54.

reaction was carried out in the absence of re-oxidants of palladium. To explain the 1,3-chirality transfer, the authors suggest a Wacker-type reaction (Scheme 54), rather than the intermediate chloropalladation of the double bond (Scheme 18).

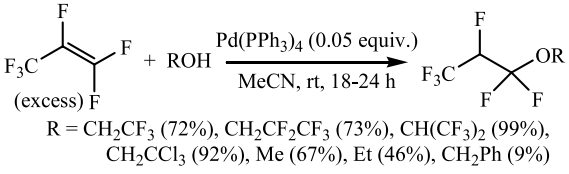


(227)



(228)

The hydroalkoxylations of hexafluoropropene disclosed by Matsukawa et al. are the first examples of the Pd-catalysed synthesis of saturated ethers by the addition of an alcohol to a C=C bond (Eq. 229).[384]



(229)

Acknowledgements

I am grateful to Dr. A. Tenaglia (Marseille University) for correspondence, and to my spouse for the careful reading of, and linguistic improvements in, the manuscript.

References and notes

1. Muzart, J. Part A: Palladium-catalysed oxidation of primary and secondary alcohols. *Tetrahedron* **2003**, *59*, 5789–5816.
2. Muzart, J. Part B: Palladium-catalysed reactions of alcohols: formation of C–C and C–N bonds from unsaturated alcohols. *Tetrahedron* **2005**, *61*, 4179–4212.
3. (a) Yamamoto, T.; Akimoto, M.; Yamamoto, A. *Chem. Lett.* **1983**, 1725–1726. (b) Kayaki, Y.; Koda, T.; Ikariya, T. *Eur. J. Org. Chem.* **2004**, 4989–4993.
4. Yamamoto, T.; Akimoto, M.; Saito, O.; Yamamoto, A. *Organometallics* **1986**, *5*, 1559–1567.
5. Bricourt, H.; Carpentier, J.-F.; Mortreux, A. *J. Mol. Catal. A: Chem.* **1998**, *136*, 243–251.
6. Kayaki, Y.; Koda, T.; Ikariya, T. *J. Org. Chem.* **2004**, *69*, 2595–2597.
7. Tsukamoto, H.; Sato, M.; Kondo, Y. *Chem. Commun.* **2004**, 1200–1201.
8. Satoh, T.; Ikeda, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1997**, *62*, 4877–4879.
9. Stanton, S. A.; Felman, S. W.; Parkhurst, C. S.; Godleski, S. A. *J. Am. Chem. Soc.* **1983**, *105*, 1964–1969.
10. Hata, G.; Takahashi, K.; Miyake, A. *J. Chem. Soc., Chem. Commun.* **1970**, 1392–1393.
11. Takahashi, K.; Miyake, A.; Hata, G. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 230–236.
12. 1-Methoxy-1,3-diphenylpropene can be obtained from 1-acetoxy-1,3-diphenylpropene and aqueous methanol even in the absence of a metal-catalyst: Chevrin, C.; Le Bras, J.; Hénin, F.; Muzart, J. *Tetrahedron Lett.* **2003**, *44*, 8099–8102.
13. Lakhmiri, R.; Lhoste, P.; Krycka, B.; Sinou, D. *J. Carbohydr. Chem.* **1993**, *12*, 223–235.
14. Oguri, H.; Hishiyama, S.; Sato, O.; Oishi, T.; Hirama, M.; Murata, M.; Yasumoto, T.; Harada, N. *Tetrahedron* **1997**, *53*, 3057–3072.
15. (a) Sugiura, M.; Yagi, Y.; Wei, S.-Y.; Nakai, T. *Tetrahedron Lett.* **1998**, *39*, 4351–4354. (b) Hamada, Y.; Seto, N.; Takayanagi, Y.; Nakano, T.; Hara, O. *Tetrahedron Lett.* **1999**, *40*, 7791–7794. (c) Comely, A. C.; Eelkema, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2003**, *125*, 8714–8715. (d) Babu, R. S.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 12406–12407. (e) Plata, D. J.; Leanna, M. R.; Rasmussen, M.; McLaughlin, M. A.; Condon, S. L.; Kerdesky, F. A. J.; King, S. A.; Peterson, M. J.; Stoner, E. J.; Wittenberger, S. J. *Tetrahedron* **2004**, *60*, 10171–10180.
16. Zumpe, F. L.; Kazmaier, U. *Synthesis* **1999**, 1785–1791.
17. Sinou, D.; Lhoste, P.; Pichon, N.; Kryczka, B.; Porwanski, S.; Zawisza, A. *J. Carbohydr. Chem.* **2002**, *21*, 545–558.
18. Babu, R. S.; Zhou, M.; O'Doherty, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 3428–3429.
19. Stoner, E. J.; Peterson, M. J.; Allen, M. S.; DeMattei, J. A.; Haight, A. R.; Leanna, M. R.; Patel, S. R.; Plata, D. J.; Premchandran, R. H.; Rasmussen, M. *J. Org. Chem.* **2003**, *68*, 8847–8852.
20. Frappa, I.; Krycka, B.; Lhoste, P.; Porwanski, S.; Sinou, D. *J. Carbohydr. Chem.* **1997**, *16*, 891–910.
21. Haight, A. R.; Stoner, E. J.; Peterson, M. J.; Grover, V. K. *J. Org. Chem.* **2003**, *68*, 8092–8096.
22. For the reaction of stannyl ethers with η^3-allylpalladium intermediates, see: (a) Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2931–2934. (b) Holzapfel, C. W.; Huyser, J. J.; van der Merwe, T. L.; van Heerden, F. R. *Heterocycles* **1991**, *32*, 1445–1450.
23. Bouyssi, D.; Gerusz, V.; Balme, G. *Eur. J. Org. Chem.* **2002**, 2445–2448.
24. Phan, L. T.; Jian, T.; Chen, Z.; Qiu, Y.-L.; Wang, Z.; Beach,

T.; Polemeropoulos, A.; Or, Y. S. *J. Med. Chem.* **2004**, *47*, 2965–2968.
25. Instead of acting as a nucleophile towards the η^3-allyl-palladium, water could mediate the palladium-catalysed 'hydrolysis' of allyl *tert*-butyl carbonate through the formation of allyl hydrogen carbonate, leading finally to allyl alcohol and carbon dioxide: (a) Lüssem, B.; Gais, H.-J. *J. Am. Chem. Soc.* **2003**, *125*, 6066–6067. (b) Lüssem, B.; Gais, H.-J. *J. Org. Chem.* **2004**, *69*, 4041–4052.
26. Kim, H.; Lee, C. *Org. Lett.* **2002**, *4*, 4369–4371.
27. Kim, H.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 1336–1337.
28. Ohi, K. *Kagaku to Kogyo (Tokyo, Japan)* **2004**, *57*, 962. *Chem. Abstr. 141*, 314494
29. (a) Hata, G.; Takahashi, K.; Miyake, A. *J. Chem. Soc., Chem. Commun.* **1970**, 1392–1393. (b) Muzart, J.; Genêt, J. P.; Denis, A. *J. Organomet. Chem.* **1987**, *326*, C23–C28.
30. Ishizaki, M.; Yamada, M.; Watanabe, S.; Hoshino, O.; Nishitani, K.; Hayashida, M.; Tanaka, A.; Hara, H. *Tetrahedron* **2004**, *60*, 7973–7981.
31. (a) Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 3388–3390. (b) Audouze, K.; Nielsen, E.Ø.; Peters, D. *J. Med. Chem.* **2004**, *47*, 3089–3104.
32. (a) Uozumi, Y.; Tanahashi, A.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 6826–6832. (b) Hayashi, T.; Uozumi, Y.; Tanahashi, A.; Kyoi, T., Jpn. Kokai Tokkyo Koho JP 05,255,285, 1993; *Chem. Abstr.* **1994**, *120*, 164205. (c) Yamazaki, A.; Achiwa, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1021–1024. (d) Nakano, H.; Yokoyama, J.; Fujita, R.; Hongo, H. *Tetrahedron Lett.* **2002**, *43*, 7761–7764. (e) Ito, K.; Imahayashi, Y.; Kuroda, T.; Eno, S.; Saito, B.; Katasuki, T. *Tetrahedron Lett.* **2004**, *45*, 7277–7281.
33. Thorey, C.; Wilken, J.; Hénin, F.; Martens, J.; Mehler, T.; Muzart, J. *Tetrahedron Lett.* **1995**, *36*, 5735–5736.
34. Wang, G.; Niu, D.; Qiu, Y.-L.; Phan, L. T.; Chen, Z.; Polemeropoulos, A.; Or, Y. S. *Org. Lett.* **2004**, *6*, 4455–4458.
35. Shen, C. K. F.; Chien, K.-M.; Liu, T.-Y.; Lin, T.-I.; Her, G.-R.; Luh, T.-Y. *Tetrahedron Lett.* **1995**, *36*, 5383–5384.
36. Chalk, A. J.; Wertheimer, V.; Magennis, S. A. *J. Mol. Catal.* **1983**, *19*, 189–200.
37. Stork, G.; Poirier, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1073–1074.
38. Trost, B. M.; Bonk, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 1778–1781.
39. Fournier-Nguefack, C.; Lhoste, P.; Sinou, D. *Tetrahedron* **1997**, *53*, 4353–4362.
40. Fournier-Nguefack, C.; Lhoste, P.; Sinou, D. *J. Chem. Res. (S)* **1998**, 105. *(M)* **1998**, 0614–0634.
41. Trost, B. M.; Tenaglia, A. *Tetrahedron Lett.* **1988**, *29*, 2927–2930.
42. Mascári, I.; Szabó, K. L. *Tetrahedron Lett.* **2000**, *41*, 1119–1122.
43. Keinan, E.; Seth, K. K.; Lamed, R. *J. Am. Chem. Soc.* **1986**, *108*, 3474–3480.
44. Smith, A. B., III; Ohta, M.; Clark, W. M.; Leahy, J. W. *Tetrahedron Lett.* **1993**, *34*, 3033–3036.
45. Hansen, E. C.; Lee, D. *Tetrahedron Lett.* **2004**, *45*, 7151–7155.
46. The treatment of $Ph(CH_2)_2CH(OCO_2Me)CH{=}CH(CH_2)_2$-OH with $Pd_2(dba)_3$/dppb in THF at 50 °C afforded a mixture of hydroxydienes instead of the cyclic ether;[40] see also: Coste-Manière, I. C.; Zahra, J. P.; Waegell, B. *Tetrahedron Lett.* **1988**, *29*, 1017–1020.
47. Lucas, B. S.; Burke, S. D. *Org. Lett.* **2003**, *5*, 3915–3918.
48. Jiang, L.; Burke, S. D. *Org. Lett.* **2002**, *4*, 3411–3414.
49. Burke, S. D.; Jiang, L. *Org. Lett.* **2001**, *3*, 1953–1955.
50. Georges, Y.; Allenbach, Y.; Ariza, X.; Campagne, J.-M.; Garcia, J. *J. Org. Chem.* **2004**, *69*, 7387–7390.
51. Yoshida, M.; Ohsawa, Y.; Ihara, M. *J. Org. Chem.* **2004**, *69*, 1590–1597.
52. Godleski, S. A. PCT Int. Appl. WO 89 02,883. *Chem. Abstr.* **1989**, *111*, 173607.
53. Trost, B. M.; Tang, W. *Org. Lett.* **2001**, *3*, 3409–3411.
54. Trost, B. M.; Tang, W.; Schulte, J. L. *Org. Lett.* **2000**, *2*, 4013–4015.
55. Trost, B. M.; Brown, B. S.; Mc Earchern, E. J.; Kuhn, O. *Chem. Eur. J.* **2003**, *9*, 4442–4451.
56. Trost, B. M.; Andersen, N. G. *J. Am. Chem. Soc.* **2002**, *124*, 14320–14321.
57. Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2943.
58. Kato, N.; Tomita, D.; Maki, K.; Kanai, M.; Shibasaki, M. *J. Org. Chem.* **2004**, *69*, 6128–6130.
59. Suzuki, T.; Sato, O.; Hirama, M. *Tetrahedron Lett.* **1990**, *31*, 4747–4750.
60. Harvey, J. E.; Raw, S. A.; Taylor, R. J. K. *Org. Lett.* **2004**, *6*, 2611–2614.
61. Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3365–3367.
62. Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 270–275.
63. Heiner, T.; Michalski, S.; Gerke, K.; Kuchta, G.; Buback, M.; de Meijere, A. *Synlett* **1995**, 355–357.
64. Mascári, I.; Szabó, K. L. *Chem. Eur. J.* **2001**, *7*, 4097–4106.
65. Bäckvall et al. have effectively shown the coordination of quinones to palladium species: (a) Bäckvall, J.-E.; Gogoll, A. *Tetrahedron Lett.* **1988**, *29*, 2243–2246. (b) Grennberg, A.; Bäckvall, J.-E.; Gogoll, A. *Organometallics* **1993**, *12*, 1790–1793.
66. El Firdoussi, L.; Benharref, A.; Allaoud, S.; Karim, A.; Castanet, Y.; Mortreux, A.; Petit, F. *J. Mol. Catal.* **1992**, *72*, L1–L5.
67. Larock, R. C.; Zenner, J. M. *J. Org. Chem.* **1995**, *60*, 482–483.
68. Larock, R. C.; He, Y.; Leong, W. W.; Han, X.; Refvik, M. D.; Zenner, J. M. *J. Org. Chem.* **1998**, *63*, 2154–2160.
69. Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111–124.
70. Shimizu, I.; Sugiura, T.; Tsuji, J. *J. Org. Chem.* **1985**, *50*, 537–539.
71. Ma, S.; Zhao, S. *J. Am. Chem. Soc.* **1999**, *121*, 7943–7944.
72. Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701–712.
73. Kang, S.-K.; Yamaguchi, T.; Pyun, S.-J.; Lee, Y.-T.; Baik, T.-G. *Tetrahedron Lett.* **1998**, *39*, 2127–2130.
74. Kang, S.-K.; Baik, T.-G.; Kulak, A. N. *Synlett* **1999**, 324–326.
75. Takahashi, S.; Shibano, T.; Hagihara, N. *Tetrahedron Lett.* **1967**, 2451–2453.
76. Smutny, E. J. *J. Am. Chem. Soc.* **1967**, *89*, 6793–6794.
77. (a) Tsuji, J. *Acc. Chem. Res.* **1973**, *6*, 8–15. (b) Keim, W.; Behr, A.; Röper, M. In Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Comprehensive organometallic chemistry; Pergamon: Oxford, 1982; Vol. 8, pp 371–462. (c) Behr, A. In Mortreux, A., Petit, F., Eds.; Industrial applications of homogeneous catalysis; Reidel: Dordrecht, 1988; pp 141–175. (d) Tsuji, J. Palladium reagents and catalysis: innovations in organic synthesis; Wiley: Chichester, 1995; pp

423–449. (e) Takacs, J. M. In Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Comprehensive organometallic chemistry II; Elsevier: Oxford, 1995; Vol. 12, pp 785–796.
78. (a) Jacobsen, G. B.; Pelt, H. L.; Schaart, B. J., PCT Int. Appl. WO 9109822; *Chem. Abstr. 115*, 158514. (b) National Distillers and Chemical Corp. Jpn. Kokai Tokkyo Koho JP 62063538, 1987; *Chem. Abstr.* **1987**, 533904. (c) Ishino, H.; Iwasaki, H. PCT Int. Appl. WO 65,006, 2004; *Chem. Abstr. 141*, 156682.
79. Vollmüller, F.; Mägerlein, W.; Klein, S.; Krause, J.; Beller, M. *Adv. Synth. Catal.* **2001**, *343*, 29–33.
80. Jackstell, R.; Gómez Andreu, M.; Frisch, A.; Selvakumar, K.; Zapf, A.; Klein, H.; Spannenberg, A.; Röttger, D.; Briel, O.; Karch, R.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 986–989.
81. Takahasi, S.; Shibano, T.; Hagihara, N. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 454–460.
82. (a) Behr, A.; Urschey, M. *Adv. Synth. Catal.* **2003**, *345*, 1242–1246. (b) Behr, A.; Urschey, M. *J. Mol. Catal. A: Chem.* **2003**, *197*, 101–113.
83. Behr, A.; Urschey, M.; Brehme, V. A. *Green Chem.* **2003**, *5*, 198–204.
84. Hill, K.; Axt, S. D.; Weese, K. J., PCT Int. Appl. WO 9302032; *Chem. Abstr. 119*, 94948.
85. (a) Gruber, B.; Weese, K. J.; Hoagland, S. M.; Mueller, H.-P.; Hill, K.; Behr, A. PCT Int. Appl. WO 13531, 1990; *Chem. Abstr.* **1991**, *115*, 137003. (b) Hill, K.; Weese, K. J., Ger. Offen. DE 92-4242467; *Chem. Abstr.* **1994**, *120*, 301648. (c) Pennequin, I.; Mortreux, A.; Petit, F.; Mentech, J.; Thiriet, B., Brev. Fr., FR 92 08116; *Chem. Abstr. 121*, 205887. (d) Muzart, J.; Hénin, F.; Estrine, B.; Bouquillon, S. 2001, Fr Patent 0116363; PCT Int. Appl. WO 03 053987; *Chem Abstr.* **2003**, *139*, 54601.
86. (a) Hill, K.; Gruber, K. J.; Weese, K. J. *Tetrahedron Lett.* **1994**, *35*, 4541–4542. (b) Desvergnes-Breuil, V.; Pinel, C.; Gallezot, P. *Green Chem.* **2001**, *3*, 175–177. (c) Donzé, C.; Pinel, C.; Gallezot, P.; Taylor, P. L. *Adv. Synth. Catal.* **2002**, *344*, 906–910.
87. Pennequin, I.; Meyer, J.; Suisse, I.; Mortreux, A. *J. Mol. Catal. A: Chem.* **1997**, *120*, 139–142.
88. Hénin, F.; Bessmertnykh, A.; Serra-Muns, A.; Muzart, J.; Bailla, H.; Eur *J. Org. Chem.* **2004**, 511–520.
89. (a) Estrine, B.; Bouquillon, S.; Hénin, F.; Muzart, J. *Eur. J. Org. Chem.* **2004** 2914–2922. (b) Estrine, B.; Bouquillon, S.; Hénin, F.; Muzart, J. *Green Chem.*, **2005**, *7*, 219–223. (c) Bessmertnykh, A., Hénin, F., Muzart, J. *J. Mol. Catal. A: Chem.*, in press.
90. For a review on carbohydrates based surfactants, see: von Rybinski, W.; Hill, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 1328–1345.
91. Yagi, H.; Tanaka, E.; Ishiwatari, H.; Hidai, M.; Uchida, Y. *Synthesis* **1977**, 334–335.
92. Behr, A.; Keim, W. *Chem. Ber.* **1983**, *116*, 862–873.
93. Hidai, M.; Mizuta, H.; Yagi, H.; Nagai, Y.; Hata, K.; Uchida, Y. *J. Organomet. Chem.* **1982**, *232*, 89–98.
94. (a) Patrini, R.; Lami, M.; Marchionna, M.; Benvenuti, F.; Raspolli Galletti, A. M.; Sbrana, G. *J. Mol. Catal. A: Chem.* **1998**, *129*, 179–189. (b) Benvenuti, F.; Carlini, C.; Marchionna, M.; Patrini, R.; Raspolli Galletti, A. M.; Sbrana, G. *J. Mol. Catal. A: Chem.* **1999**, *140*, 139–155. (c) Benvenuti, F.; Carlini, C.; Lami, M.; Marchionna, M.; Patrini, R.; Raspolli Galletti, A. M.; Sbrana, G. *J. Mol. Catal. A: Chem.* **1999**, *144*, 27–40. (d) Basato, M.; Crociani, L.; Benvenuti, F.; Raspolli Galletti, A. M.; Sbrana, G. *J. Mol. Catal. A: Chem.* **1999**, *145*, 313–316. (e) Harkal, S.; Jackstell, R.; Nierlich, F.; Ortmann, D.; Beller, M. *Org. Lett.* **2005**, *7*, 541–544.
95. Vollmüller, F.; Krause, J.; Klein, S.; Mägerlein, W.; Beller, M. *Eur. J. Inorg. Chem.* **2000**, 1825–1832.
96. (a) Jackstell, R.; Frisch, A.; Beller, M.; Röttger, D.; Malaun, M. *J. Mol. Catal. A: Chem.* **2002**, *185*, 105–112. (b) Jackstell, R.; Harkal, S.; Jiao, H.; Spannenberg, A.; Borgmann, C.; Röttger, D.; Nierlich, F.; Elliot, M.; Niven, S.; Cavell, K.; Navarro, O.; Viciu, M. S.; Nolan, S. P.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 3891–3900.
97. Pittman, C. U., Jr.; Ng, Q. *J. Organomet. Chem.* **1978**, *153*, 85–97.
98. (a) Kaneda, K.; Kurosaki, H.; Terasawa, M.; Imanaka, T.; Teranishi, S. *J. Org. Chem.* **1981**, *46*, 2356–2362. (b) Kaneda, K.; Higuchi, M.; Imanaka, T. *Chem. Express* **1988**, *3*, 335–338.
99. (a) Benvenuti, F.; Carlini, C.; Raspolli Galletti, A. M.; Sbrana, G,; Marchionna, M.; Patrini, R. *J. Mol. Catal. A: Chem.* **1999**, *137*, 49–63. (b) Benvenuti, F.; Carlini, C.; Marchionna, M.; Patrini, R.; Raspolli Galletti, A. M.; Sbrana, G. *J. Mol. Catal. A: Chem.* **1999**, *139*, 177–187.
100. (a) Estrine, B.; Blanco, B.; Bouquillon, S.; Hénin, F.; Moreno-Mañas, M.; Muzart, J.; Pena, C.; Pleixats, R. *Tetrahedron Lett.* **2001**, *42*, 7055–7057. (b) Moreno-Mañas, M.; Pleixats, R.; Spengler, J.; Chevrin, C.; Estrine, B.; Bouquillon, S.; Hénin, F.; Muzart, J.; Pla-Quintana, A.; Roglans, A. *J. Org. Chem.* **2003**, 274–283.
101. Estrine, B.; Soler, R.; Damez, C.; Bouquillon, S.; Hénin, F.; Muzart, J. *Green Chem.* **2003**, *5*, 686–689.
102. Kuntz, E. U.S. US 4,142,060, 1978; *Chem. Abstr.* **1978**, *88*, 152026.
103. Estrine, B., PhD Thesis, Reims, 2002.
104. Magna, L.; Chauvin, Y.; Niccolai, G. P.; Basset, J.-M. *Organometallics* **2003**, *22*, 4418–4425.
105. Groult, A.; Guy, A. *Tetrahedron* **1983**, *39*, 1543–1550.
106. Commereuc, D.; Chauvin, Y. *Bull. Soc. Chim. Fr.* **1974**, 652–656.
107. Jolly, P. W.; Kokel, N. *Synthesis* **1990**, 771–773.
108. Grenouillet, P.; Neibecker, D.; Poirier, J.; Tkatchenko, I. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 767–768 and cited references.
109. Camargo, M.; Dani, P.; Dupont, J.; de Souza, J.; Pfeffer, M.; Tkatchenko, I. *J. Mol. Catal. A: Chem.* **1996**, *109*, 127–131.
110. (a) Watanabe, K.; Ogoshi, N. Jpn. Kokai Tokkyo Koho JP, 323369, 2004; *Chem. Abstr. 141*, 410639.
111. Takacs, J. M.; Zhu, J. *J. Org. Chem.* **1989**, *54*, 5193–5195.
112. Bäckvall, J.-E.; Hopkins, R. B.; Greenberg, H.; Mader, M. M.; Awasthi, A. K. *J. Am. Chem. Soc.* **1990**, *112*, 5160–5166.
113. Aranyos, A.; Szabó, K. J.; Bäckvall, J.-E. *J. Org. Chem.* **1998**, *63*, 2523–2529.
114. Thorarensen, A.; Palmgren, A.; Itami, K.; Bäckvall, J.-E. *Tetrahedron Lett.* **1997**, *38*, 8541–8544.
115. Itami, K.; Palmgren, A.; Thorarensen, A.; Bäckvall, J.-E. *J. Org. Chem.* **1998**, *63*, 6466–6471.
116. Hupe, E.; Itami, K.; Aranyos, A.; Szabó, K. J.; Bäckvall, J.-E. *Tetrahedron* **1998**, *54*, 5375–5384.
117. Larock, R. C.; Berrios-Peña, N.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447–3450.
118. Deagostino, A.; Prandi, C.; Venturello, P. *Org. Lett.* **2003**, *5*, 3815–3817.

119. Bäckvall, J.-E. *New J. Chem.* **1990**, *14*, 447–452.
120. Andersson, P. G.; Bäckvall, J.-E. *J. Org. Chem.* **1991**, *56*, 5349–5353.
121. Bäckvall, J.-E.; Andersson, P. G. *J. Org. Chem.* **1991**, *56*, 2274–2276.
122. Bäckvall, J.-E.; Andersson, P. G. *J. Am. Chem. Soc.* **1992**, *114*, 6374–6381.
123. Andersson, P. G.; Nilsson, Y. I. M.; Bäckvall, J.-E. *Tetrahedron* **1994**, *50*, 559–572.
124. Koroleva, E. B.; Bäckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett.* **1995**, *36*, 5397–5400.
125. Nilsson, Y. I. M.; Aranyos, A.; Andersson, P. G.; Bäckvall, J.-E.; Parrain, J.-L.; Ploteau, C.; Quintard, J.-P. *J. Org. Chem.* **1996**, *61*, 1825–1829.
126. Itami, K.; Palmgren, A.; Bäckvall, J.-E. *Tetrahedron Lett.* **1998**, *39*, 1223–1226.
127. Verboom, R. C.; Persson, B. A.; Bäckvall, J.-E. *J. Org. Chem.* **2004**, *69*, 3102–3111.
128. Takacs, J. M.; Chandramouli, S. V. *J. Org. Chem.* **1993**, *58*, 7315–7317.
129. Kadota, I.; Lutete, L. M.; Shibuya, A.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6207–6210.
130. Zhang, W.; Haight, A. R.; Hsu, M. C. *Tetrahedron Lett.* **2002**, *43*, 6575–6578.
131. Apparently, Zhang et al.[130] were not aware of the Yamamoto's report.[129]
132. Patil, N. T.; Khan, N.; Yamamoto, Y. *Tetrahedron Lett.* **2004**, *45*, 8497–8499.
133. Yoshida, M.; Fujita, M.; Ishii, T.; Ihara, M. *J. Am. Chem. Soc.* **2003**, *125*, 4874–4881.
134. Yoshida, M.; Ihara, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 616–619.
135. Yoshida, M.; Fujita, M.; Ihara, M. *Org. Lett.* **2003**, *5*, 3325–3327.
136. Phillips, F. C. *Am. Chem. J.* **1894**, *16*, 255–277.
137. Smidt, J.; Hafner, W.; Jira, R.; Sedlmeier, J.; Sieber, R.; Rüttinger, R.; Kojer, H. *Angew. Chem.* **1959**, *71*, 176–182.
138. Tsuji, J. *Synthesis* **1984**, 369–384.
139. Henry, P. M. *Palladium catalyzed oxidation of hydrocarbons*; Reidel: Dordrecht, 1980; pp 133–147.
140. (a) Stille, J. K.; Divakaruni, R. *J. Organomet. Chem.* **1979**, *169*, 239–248. (b) Bäckvall, J.-E.; Ãkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411–2416.
141. Henry, P. M. *Palladium catalyzed oxidation of hydrocarbons*; Reidel: Dordrecht, 1980; pp 41–84.
142. Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036–3037.
143. Lloyd, W. G.; Luberoff, B. J. *J. Org. Chem.* **1969**, *34*, 3949–3952.
144. Takehira, K.; Hayakawa, T.; Orita, H. *Chem. Lett.* **1985**, 1835–1838.
145. Methyl nitrites in methanol have been used with $PdCl_2$ as catalyst to obtain ketals from olefins in the absence of a re-oxidant: Uchiumi, S.; Ataka, K.; Matsuzaki, T. *J. Organomet. Chem.* **1999**, *576*, 279–289.
146. (a) Hosokawa, T.; Ohta, T.; Murahashi, S.-I. *J. Chem. Soc., Chem. Commun.* **1983**, 848–849. (b) Hosokawa, T.; Ohta, T.; Kanayama, S.; Murahashi, S.-I. *J. Org. Chem.* **1987**, *52*, 1758–1764. (c) Hosokawa, T.; Ataka, Y.; Murahashi, S.-I. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 166–169.
147. Hosokawa, T.; Aoki, S.; Murahashi, S.-I. *Synthesis* **1992**, 558–561.
148. Igarashi, S.; Haruta, Y.; Ozawa, M.; Nishide, Y.; Kinoshita, H.; Inomata, K. *Chem. Lett.* **1989**, 737–740.
149. Izumi, T.; Nishimoto, Y.; Kohei, K.; Kasahara, A. *J. Heterocycl. Chem.* **1990**, *27*, 1419–1424.
150. Hosokawa, T.; Murahashi, S.-I. *Acc. Chem. Res.* **1990**, *23*, 49–54.
151. Hosokawa, T.; Murahashi, S.-I. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 1009–1020.
152. Lai, J.-Y.; Shi, X.-X.; Dai, L.-X. *J. Org. Chem.* **1992**, *57*, 3485–3487.
153. Hosokawa, T.; Yamanaka, T.; Murahashi, S.-I. *J. Chem. Soc., Chem. Commun.* **1993**, 117–119.
154. Hosokawa, T.; Yamanaka, T.; Itotani, M.; Murahashi, S.-I. *J. Org. Chem.* **1995**, *60*, 6159–6167.
155. Jia, L.; Jiang, H.; Li, J. *Chem. Commun.* **1999**, 985–986.
156. Kishi, A.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2000**, *2*, 523–525.
157. Hosokawa, T.; Shinohara, T.; Ooka, Y.; Murahashi, S.-I. *Chem. Lett.* **1989**, 2001–2004.
158. Miller, K. J.; Kitagawa, T. T.; Abu-Omar, M. M. *Organometallics* **2001**, *20*, 4403–4412.
159. Methyl ethers have been obtained as side products of the Pd-catalysed hydrocarbomethoxylation of 2-phenylpropene and acenaphthylene: (a) Hayashi, T.; Tanaka, M.; Ogata, I. *J. Mol. Catal.* **1984**, *26*, 17–30. (b) Gironès, J.; Duran, J.; Polo, A.; Real, J. *Chem. Commun.* **2003**, 1776–1778.
160. Wabnitz, T. C.; Yu, J.-Q.; Spencer, J. B. *Chem. Eur. J.* **2004**, *10*, 484–493.
161. Asymmetric Michael reactions catalysed by chiral palladium complexes, leading to C–C and C–N bonds with up to 83 and 98% ee, respectively, have been, however, reported: (a) Takenaka, K.; Uozumi, Y. *Org. Lett.* **2004**, *6*, 1833–1835. (b) Hamashima, Y.; Somei, H.; Shimura, Y.; Tamura, T.; Sodeoka, M. *Org. Lett.* **2004**, *6*, 1861–1864.
162. Dumiao, C. M.; Francis, J. W.; Henry, P. M. *Organometallics* **1991**, *10*, 1400–1405.
163. Hamed, O.; Henry, P. M.; Thompson, C. *J. Org. Chem.* **1999**, *64*, 7745–7750.
164. Hamed, O.; Henry, P. M. *Organometallics* **1997**, *16*, 4903–4909.
165. Hamed, O.; Henry, P. M.; Thompson, C. *J. Org. Chem.* **1997**, *62*, 7082–7083.
166. Hosokawa, T.; Sugafuji, T.; Yamanaka, T.; Murahashi, S.-I. *J. Organomet. Chem.* **1994**, *470*, 253–255.
167. Wang, Y.-G.; Wu, X.-X.; Jiang, Z.-Y. *Tetrahedron Lett.* **2004**, *45*, 2973–2976.
168. Wang et al. have also reported the deprotection of tetrahydropyranyl ethers with the same catalyst in refluxing aqueous acetonitrile.[167]
169. (a) Heumann, A.; Jens, K.-J.; Réglier, M. In Karlin, K. D., Ed.; Progress in inorganic chemistry; Wiley: New York, 1994; Vol. 42, pp 483–576. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2309.
170. Semmelhack, M. F.; Epa, W. R.; Cheung, A. W.-H.; Gu, Y.; Kim, C.; Zhang, N.; Lew, W. *J. Am. Chem. Soc.* **1994**, *116*, 7455–7456.
171. Rönn, M.; Bäckvall, J.-E.; Andersson, P. G. *Tetrahedron Lett.* **1995**, *36*, 7749–7752.
172. Sharma, G. V. M.; Chander, A. S.; Krishnudu, K.; Krishna, P. R. *Tetrahedron Lett.* **1998**, *39*, 6957–6960.
173. For a theoretical study of the reaction between Pd^0 and oxygen, see: Landis, C. R.; Morales, C. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2004**, *126*, 16302–16303.

174. Hosokawa, T.; Hirata, M.; Murahashi, S.-I.; Sonoda, A. *Tetrahedron Lett.* **1976**, 1821–1824.
175. Hosokawa, T.; Murahashi, S.-I. *Heterocycles* **1992**, *33*, 1079–1100.
176. Peçanha, E. P.; Fraga, C. A. M.; Barreiro, E. J. *Heterocycles* **1998**, *48*, 2621–2630.
177. van Benthem, R. A. T. M.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1992**, *57*, 6083–6085.
178. van Benthem, R. A. T. M.; Hiemstra, H.; Michels, J. J.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1994**, 357–359.
179. Hiemstra, H.; van Benthem, R. A. T. M. *Bull. Soc. Chim. Belg.* **1994**, *103*, 559–563.
180. van Benthem, R. A. T. M.; Hiemstra, H.; van Leeuwen, P. W. N. M.; Gens, J. W.; Speckamp, W. N. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 457–460.
181. Giles, R. G. F.; Green, I. R.; Taylor, C. P. *Tetrahedron Lett.* **1999**, *40*, 4871–4872.
182. Giles, R. G. F.; Green, I. R.; Taylor, C. P. *Arkivoc* **2001**, *7*, 166–174.
183. Mmutlane, E. M.; Michael, J. P.; Green, I. R.; de Koning, C. B. *Org. Biomol. Chem.* **2004**, *2*, 2461–2470.
184. de Koning, C. B.; Green, I. R.; Michael, J. P.; Oliveira, J. R. *Tetrahedron* **2001**, *57*, 9623–9634.
185. Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892–2895.
186. Arai, M. A.; Kuraishi, M.; Arai, T.; Sasai, H. *J. Am. Chem. Soc.* **2001**, *123*, 2907–2908.
187. Lai, J.-Y.; Shi, X.-X.; Gong, Y.-S.; Dai, L.-X. *J. Org. Chem.* **1993**, *58*, 4775–4777.
188. Semmelhack, M. F.; Epa, W. R. *Tetrahedron Lett.* **1993**, *34*, 7205–7208.
189. (a) Sasai, H. 227th ACS National Meeting March 28–April 1, 2004, Abstract no. 607. (b) Kato, T.; Marubayashi, K.; Takizawa, S.; Sasai, H. *Tetrahedron: Asymmetry* **2004**, *15*, 3693–3697.
190. (a) Semmelhack, M. F. *Pure Appl. Chem.* **1981**, *53*, 2379–2388. (b) Semmelhack, M. F.; Kim, C. R.; Zhang, N.; Bodurow, C.; Sanner, M.; Dobler, W.; Meier, M. *Pure Appl. Chem.* **1990**, *623*, 2035–2400.
191. Semmelhack, M. F.; Keller, L.; Sato, T.; Spiess, E. *J. Org. Chem.* **1982**, *47*, 4382–4384.
192. (a) Semmelhack, M. F.; Zask, A. *J. Am. Chem. Soc.* **1983**, *105*, 2034–2043. (b) Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496–1498. (c) Semmelhack, M. F.; Zhang, N. *J. Org. Chem.* **1989**, *54*, 4483–4485.
193. Semmelhack, M. F.; Kim, C. R.; Dobler, W.; Meier, M. *Tetrahedron Lett.* **1989**, *30*, 4925–4928.
194. Holmes, C. P.; Bartlett, P. A. *J. Org. Chem.* **1989**, *54*, 98–108.
195. McCormick, M.; Monahan, R., III; Soria, J.; Goldsmith, D.; Liotta, D. *J. Org. Chem.* **1989**, *54*, 4485–4487.
196. White, J. D.; Hong, J.; Robarge, L. A. *Tetrahedron Lett.* **1999**, *40*, 1463–1466.
197. Tamaru, Y.; Yoshida, Z. *J. Organomet. Chem.* **1987**, *334*, 213–223.
198. Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321–3408.
199. Chiusoli, G. P. *Transition Met. Chem.* **1991**, *16*, 553–564.
200. (a) Jäger, V.; Gracza, T.; Dubois, E.; Hasenöhrl, T.; Hümmer, W.; Kautz, B. K.; Lieberknecht, A.; Remen, L.; Shaw, D.; Stahl, U.; Stephan, O. In Helmchen, G., Dibo, J., Flubacher, D., Wiese, B., Eds.; Organic synthesis via organometallics, OSM 5; Vieweg: Braunschweig/Wiesbaden, 1997; pp 331–360.
201. Auclair, S. X.; Morris, M.; Sturgess, M. A. *Tetrahedron Lett.* **1992**, *33*, 7739–7742.
202. Feringa, B. L. *J. Chem. Soc., Chem. Commun.* **1986**, 909–910.
203. Meulemans, T. M.; Kiers, N. H.; Feringa, B. L.; van Leeuwen, P. W. N. M. *Tetrahedron Lett.* **1994**, *35*, 455–458.
204. Nokami, J.; Ogawa, H.; Miyamoto, S.; Mandai, T.; Wakabayashi, S.; Tsuji, J. *Tetrahedron Lett.* **1988**, *29*, 5181–5184.
205. Hosokawa, T.; Nakajima, F.; Iwasa, S.; Murahashi, S.-I. *Chem. Lett.* **1990**, 1387–1390.
206. The probable role of Na_2HPO_4 is to act as a base: Gouverneur, V. Personal communication April, 15, 2004.
207. See Eq. 89 for the reaction of non-terminal 4-hydroxyalkenes in the presence of methanol.[176]
208. (a) Reiter, M.; Ropp, S.; Gouverneur, V. *Org. Lett.* **2004**, *6*, 91–94. (b) Baker-Glenn, C.; Hodnett, N.; Reiter, M.; Ropp, S.; Ancliff, R.; Gouverneur, V. *J. Am. Chem. Soc.* **2005**, *127*, 1481–1486.
209. Compain, P.; Goré, J.; Vatèle, J.-M. *Tetrahedron* **1996**, *52*, 10405–10416.
210. Holzapfel, C. W.; Marais, L. *J. Chem. Res. (S)* **1999**, 190–191. *(M)* **1999**, 0960–0968.
211. Byrom, N. T.; Grigg, R.; Kongkathip, B. *J. Chem. Soc., Chem. Commun.* **1976**, 216–217.
212. Kongkathip, B.; Kongkathip, N. *Tetrahedron Lett.* **1984**, *25*, 2175–2176.
213. Page, P. C. B.; Rayner, C. M.; Sutherland, I. O. *Tetrahedron Lett.* **1986**, *27*, 3535–3538.
214. Perlmutter, P.; Selajerern, W.; Vounatsos, F. *Org. Biomol. Chem.* **2004**, *2*, 2220–2228.
215. Dauphin, G.; Fauve, A.; Veschambre, H. *J. Org. Chem.* **1989**, *54*, 2238–2242.
216. Byrom, N. T.; Grigg, R.; Kongkathip, B.; Reimer, G.; Wade, A. R. *J. Chem. Soc., Perkin Trans 1* **1984**, 1643–1653.
217. Mori, K.; Seu, Y.-B. *Tetrahedron* **1985**, *41*, 3429–3431.
218. Mori, K.; Seu, Y.-B. *Liebigs Ann. Chem.* **1986**, 205–209.
219. Page, P. C. B.; Rayner, C. M.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1988**, 356–358.
220. Hosokawa, T.; Makabe, Y.; Shinohara, T.; Murahashi, S.-I. *Chem. Lett.* **1985**, 1529–1530.
221. Kongkathip, B.; Sookkho, R.; Kongkathip, N. *Chem. Lett.* **1985**, 1849–1850.
222. Kroutil, W.; Osprian, I.; Mishitz, M.; Faber, K. *Synthesis* **1997**, 156–158.
223. The formation of the ketal from the hydroxyalkyl vinyl ether intermediate could be mediated by acid rather than palladium: (a) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 7858–7862. (b) Kondolff, I.; Doucet, H.; Santelli, M. *Synlett* **2004**, 1561–1564.
224. For the formation of ketodiols from 1,2-diol-3-enes, see: Kang, S.-K.; Jung, K.-Y.; Chung, J.-U.; Namkoong, E.-Y.; Kim, T.-H. *J. Org. Chem.* **1995**, *60*, 4678–4679.
225. Tamaru, Y.; Kobayashi, T.; Kawamura, S.; Ochiai, H.; Hojo, M.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 3207–3210.
226. Moiseev, I. I.; Stromnova, T. A.; Vargaftik, M. N. *J. Mol. Catal.* **1994**, *86*, 71–94.
227. (a) Gracza, T.; Hasenöhrl, T.; Stahl, U.; Jäger, V. *Synthesis* **1991**, 1108–1118. (b) Gracza, T.; Jäger, V. *Synlett* **1992**, 191–193. (c) Gracza, T.; Jäger, V. *Synthesis* **1994**, 1359–1368.

228. (a) Paddon-Jones, G. C.; Moore, C. J.; Brecknell, D. J.; König, W. A.; Kitching, W. *Tetrahedron Lett.* **1997**, *38*, 3479–3482. (b) Paddon-Jones, G. C.; Hungerford, N. L.; Hayes, P.; Kitching, W. *Org. Lett.* **1999**, *1*, 1905–1907.
229. Boukouvalas, J.; Fortier, G.; Radu, I. I. *J. Org. Chem.* **1998**, *63*, 913–917.
230. (a) Babjak, M.; Zálupský, P.; Gracza, T. *Arkivoc* **2005**, *5*, 45–47. (b) Babjak, M.; Kapitán, P.; Gracza, T. *Tetrahedron* **2005**, *61*, 2471–2479.
231. Heumann, A.; Réglier, M. *Tetrahedron* **1996**, *52*, 9289–9346.
232. Kraus, G. A.; Li, J.; Gordon, M. S.; Jensen, J. H. *J. Org. Chem.* **1995**, *60*, 1154–1159.
233. Semmelhack, M. F.; Bodurow, C.; Baum, M. *Tetrahedron Lett.* **1984**, *25*, 3171–3174.
234. Saito, S.; Hara, T.; Takahashi, N.; Hirai, M.; Moriwake, T. *Synlett* **1992**, 237–238.
235. (a) Hayden, P. Brit. Pat. GB 1119657, 1968; *Chem. Abstr. 93*, 149792; (b) Takagi, K.; Motohashi, T. Jpn. Kokai Tokkyo Koho JP 72-87803, 1974; *Chem. Abstr. 81*, 119951.
236. (a) McKeon, J. E.; Fitton, P.; Griswold, A. A. *Tetrahedron* **1972**, *28*, 227–232. (b) McKeon, J. E.; Fitton, P. *Tetrahedron* **1972**, *28*, 233–238.
237. Mukaiyama, T.; Ohshima, M.; Murakami, M. *Chem. Lett.* **1984**, 265–266.
238. Mukaiyama, T.; Ohshima, M.; Nagaoka, H.; Murakami, M. *Chem. Lett.* **1984**, 615–618.
239. Peczuh, M. W.; Snyder, N. L. *Tetrahedron Lett.* **2003**, *44*, 4057–4061.
240. Bosch, M.; Schlaf, M. *J. Org. Chem.* **2003**, *68*, 5225–5227.
241. Weintraub, P. M.; King, C.-H.R. *J. Org. Chem.* **1997**, *62*, 1560–1562.
242. Handerson, S.; Schlaf, M. *Org. Lett.* **2002**, *4*, 407–409.
243. Takagi, K., Motobashi, C. Jpn. Tokkyo Koho JP 72-87802; *Chem. Abstr*., **1980**, *93*, 149792.
244. Sugiura, M.; Nakai, T. *Tetrahedron Lett.* **1996**, *37*, 7991–7994.
245. Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845–1848.
246. Ohshima, M.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1984**, 1535–1536.
247. (a) Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 809–812. (b) Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2050–2054.
248. Larock, R. C.; Stinn, D. E. *Tetrahedron Lett.* **1989**, *30*, 2767–2770.
249. Kraus, G. A.; Thurston, J. *J. Am. Chem. Soc.* **1989**, *111*, 9203–9205.
250. Evans, M. A., Morken, J. P., 227th, *ACS National Meeting* March 28–April 1, 2004, Abstract no. 604.
251. (a) Mikami, K.; Takahashi, K.; Nakai, T. *Tetrahedron Lett.* **1987**, *28*, 5879–5882. (b) Mikami, K.; Takahashi, K.; Nakai, T.; Uchimaru, T. *J. Am. Chem. Soc.* **1994**, *116*, 10948–10954.
252. Sugiura, M.; Yanagisawa, M.; Nakai, T. *Synlett* **1995**, 447–448.
253. Ohshima, M.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1984**, 1535–1536.
254. Inoue, Y.; Ohtsuka, Y.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3345–3346.
255. Rutjes, F. P. J. T.; Kooistra, T. M.; Hiemstra, H.; Shoemaker, H. E. *Synlett* **1998**, 192–194.
256. Ohno, H.; Hamaguchi, H.; Ohata, M.; Tanaka, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 1749–1753.
257. Ohno, H.; Hamaguchi, H.; Ohata, M.; Kosaka, S.; Tanaka, T. *Heterocycles* **2003**, *61*, 65–68.
258. Ohno, H.; Hamaguchi, H.; Ohata, M.; Kosoka, S.; Tanaka, T. *J. Am. Chem. Soc.* **2004**, *126*, 8744–8754.
259. Trieu, N. D.; Elsevier, C. J.; Vrieze, K. *J. Organomet. Chem.* **1987**, *325*, C23–C26.
260. Ma, S.; Gao, W. *Tetrahedron Lett.* **2000**, *41*, 8933–8936.
261. Ma, S.; Gao, W. *J. Org. Chem.* **2002**, *67*, 6104–6112.
262. (a) Nemoto, H.; Yoshida, M.; Fukumoto, K. *J. Org. Chem.* **1997**, *62*, 6450–6451. (b) Yoshida, M.; Sugimoto, K.; Ihara, M. *Tetrahedron Lett.* **2000**, *41*, 5089–5092. (c) Yoshida, M.; Sugimoto, K.; Ihara, M. *Tetrahedron* **2002**, *58*, 7839–7846.
263. Alcaide, B.; Almendros, P.; Martínez-del Campo, T.; Rodríguez-Acebes, T. *Tetrahedron Lett.* **2004**, *45*, 6429–6431.
264. Ma, S.; Gao, W. *Synlett* **2002**, 65–68.
265. Xu, D.; Lu, Z.; Li, Z.; Ma, S. *Tetrahedron* **2004**, *60*, 11879–11887.
266. Walkup, R. D.; Guan, L.; Mosher, M. D.; Kim, S. W.; Kim, Y. S. *Synlett* **1993**, 88–90.
267. Walkup, R. D.; Park, G. *Tetrahedron Lett.* **1987**, *28*, 1023–1026.
268. (a) Walkup, R. D.; Park, G. *Tetrahedron Lett.* **1988**, *29*, 5505–5508. (b) Walkup, R. D.; Park, G. *J. Am. Chem. Soc.* **1990**, *112*, 1597–1603.
269. Walkup, R. D.; Guan, L.; Kim, Y. S.; Kim, S. W. *Tetrahedron Lett.* **1995**, *36*, 3805–3808.
270. Gallagher, T.; Davies, I. W.; Jones, S. W.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Shaw, R. W.; Vernon, P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 433–440.
271. Snider, B. B.; He, F. *Tetrahedron Lett*. **1997**, *38*, 5453–5454.
272. Yamamoto, T.; Matsuda, H.; Utsumi, Y.; Hagiwara, T.; Kanisawa, T. *Tetrahedron Lett.* **2002**, *43*, 9077–9080.
273. Aurrecoechea, J. M.; Pérez, E.; Solay, M. *J. Org. Chem.* **2001**, *66*, 564–569.
274. (a) Aurrecoechea, J. M.; Pérez, E. *Tetrahedron Lett.* **2001**, *42*, 3839–3841. (b) Aurrecoechea, J. M.; Pérez, E. *Tetrahedron Lett.* **2003**, *44*, 3263–3266.
275. Aurrecoechea, J. M.; Pérez, E. *Tetrahedron* **2004**, *60*, 4139–4149.
276. Camacho, D. H.; Saito, S.; Yamamoto, Y. *Tetrahedron Lett.* **2002**, *43*, 1085–1088.
277. Basak, A.; Bhattacharya, G.; Mallik, U. K.; Khamrai, U. K. *Synth. Commun.* **1997**, *27*, 367–373.
278. Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845–1852.
279. Saito, T.; Morimoto, M.; Akiyama, C.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1995**, *117*, 10757–10758.
280. Tu, Y. Q.; Byriel, K. A.; Kennard, C. H. L.; Kitching, W. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1309–1315.
281. Galaj, S.; Guichon, Y.; Pascal, Y. L. *C.R. Acad. Sci. Paris, Série C* **1979**, *288*, 541–543.
282. Wakabayashi, Y.; Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1985**, *41*, 3655–3661.
283. Qing, F. L.; Gao, W.-Z.; Ying, J. *J. Org. Chem.* **2000**, *65*, 2003–2006.
284. Stoichiometric amounts of $Pd(OAc)_2$ are sometimes used for cyclisations leading to dihydropyrans: (a) Riediker, M.; Schwartz, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 5842–5844. (b) Gleason, M. M.; McDonald, F. E. *J. Org. Chem.* **1997**, *62*, 6432–6435.
285. Compain, P.; Vatèle, J.-M.; Goré, J. *Synlett* **1994**, 943–945.
286. Compain, P.; Goré, J.; Vatèle, J.-M. *Tetrahedron Lett.* **1995**, *36*, 4059–4062.

287. Achmatowicz, M.; Hegedus, L. S. *J. Org. Chem.* **2004**, *69*, 2229–2234.
288. Trost, B. M.; McIntosh, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 7255–7256.
289. Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2004**, *45*, 1603–1606.
290. Gabriele, B.; Salerno, G.; De Pascali, F.; Costa, M.; Chiusoli, G. P. *J. Organomet. Chem.* **2000**, *593-594*, 409–415.
291. (a) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *J. Organomet. Chem.* **2003**, *687*, 219–228. (b) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *Curr. Org. Chem.* **2004**, *8*, 919–946. (c) Gabriele, B.; Salerno, G.; Costa, M. *Synlett* **2004**, 2468–2483.
292. Kato, K.; Nishimura, A.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2001**, *42*, 4203–4205.
293. Kato, K.; Nishimura, A.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, *43*, 643–645.
294. Schabbert, S.; Schaumann, E. *Eur. J. Org. Chem.* **1998**, 1873–1878.
295. Luo, F.-T.; Schreuder, I.; Wang, R.-T. *J. Org. Chem.* **1992**, *57*, 2213–2215.
296. Luo, F. T.; Wang, R. T.; Schreuder, I. *Youji Huaxue* **1993**, *13*, 297–298. *Chem. Abstr.* **1994**, *120*, 163831.
297. Fehr, C.; Galindo, J.; Etter, O. *Eur. J. Org. Chem.* **2004**, 1953–1957.
298. Marshall, J. A.; Yanik, M. M. *Tetrahedron Lett.* **2000**, *41*, 4717–4721.
299. Gabriele, G.; Salerno, G. *J. Chem. Soc., Chem. Commun.* **1997**, 1083–1084.
300. Gabriele, G.; Salerno, G.; Lauria, E. *J. Org. Chem.* **1999**, *64*, 7687–7692.
301. Gabriele, G.; Salerno, G.; De Pascali, F.; Scianò, G. T.; Costa, M.; Chiusoli, G. P. *Tetrahedron Lett.* **1997**, *38*, 6877–6880.
302. Gabriele, G.; Salerno, G.; De Pascali, F.; Costa, M.; Chiusoli, G. P. *J. Org. Chem.* **1999**, *64*, 7693–7699.
303. Gabriele, G.; Salerno, G.; Fazio, A.; Pitelli, R. *Tetrahedron* **2003**, *59*, 6251–6259.
304. Bacchi, A.; Costa, M.; Della Cà, N.; Fabbricatore, M.; Fazio, A.; Gabriele, B.; Nasi, C.; Salerno, G.; Eur *J. Org. Chem.* **2004**, 574–585.
305. Seiller, B.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1995**, *51*, 13089–13102.
306. Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589–2612.
307. Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 735–737.
308. Fuchikami, T.; Shibata, Y.; Urata, H. *Chem. Lett.* **1987**, 521–524.
309. Larhed, M.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 7858–7862.
310. Larock, R. C.; Leung, W.-Y.; Stolz-Dunn, S. *Tetrahedron Lett.* **1989**, *30*, 6629–6632.
311. (a) Wolfe, J. P.; Rossi, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 1620–1621. (b) Hay, M. B.; Hardin, A. R.; Wolfe, J. P. *J. Org. Chem.* **2005**, *70*, 3099–3107.
312. Zask, A.; Helquist, P. *J. Org. Chem.* **1978**, *43*, 1619–1620.
313. (a) Tamaru, Y.; Yamamoto, Y.; Yamada, Y.; Yoshida, Z. *Tetrahedron Lett.* **1979**, 1401–1404. (b) Tamaru, Y.; Inoue, K.; Yamada, Y.; Yoshida, Z. *Tetrahedron Lett.* **1981**, *22*, 1801–1802. (c) Tamaru, Y.; Yamada, Y.; Inoue, K.; Yamamoto, Y.; Yoshida, Z. *J. Org. Chem.* **1983**, *48*, 1286–1292. (d) Choudary, B. M.; Lakshmi Kantam, M. L. *J. Mol. Catal.* **1986**, *36*, 343–347. (e) Choudary, B. M.; Prabhakar Reddy, N. P.; Lakshmi Kantam, M. L.; Jamil, Z. *Tetrahedron Lett.* **1985**, *26*, 6257–6258. (f) Choudary, B. M.; Shobha Rani, S. S.; Subba Rao, Y. V.; Lakshmi Kantam, M. L. *J. Chem. Soc., Perkin Trans. 1* **1991**, *2274*, 2275. (g) Bei, X.; Hagemeyer, A.; Volpe, A.; Saxton, R.; Turner, H.; Guram, A. S. *J. Org. Chem.* **2004**, *69*, 8626–8633. (h) Bessmertnykh, A.; Hénin, F.; Muzart, J. *Carbohydr. Res.* **2004**, *339*, 1377–1380.
314. Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395–3396.
315. Torraca, K. E.; Huang, Y.; Parrish, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 10770–10771.
316. As pointed out by Buchwald et al.,[314] the substitution of aryl bromides occurs, in some cases, in DMF without catalyst, but lower yields are generally obtained.
317. (a) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109–13110. (b) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224–3225.
318. (a) Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 10718–10719. (b) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553–5556.
319. Widenhoefer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6504–6511.
320. Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852–860.
321. Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333–10334.
322. Blackburn, T. F.; Schwartz, J. *J. Chem. Soc., Chem. Commun.* **1977**, 157–158.
323. Gao, G.-Y.; Colvin, A. J.; Chen, Y.; Zhang, X. P. *Org. Lett.* **2003**, *5*, 3261–3264.
324. Jing, X.; Shi, Y.; Liu, Y.; Han, Y.; Yan, C.; Wang, L. *Synth. Commun.* **2004**, *34*, 1723–1727.
325. (a) Khusnutdinov, R. I.; Shchadneva, N. A.; Malikov, A. I.; Dzhemilev, U. M. *Neftekhimiya* **2000**, *40*, 458–461. *Chem. Abstr. 135*: 210769. (b) Dzhemilev, U. M; Khusnutdinov, R. I.; Shchadneva, N. A.; Malikov, A. I. Russian Patent RU 2145593 C1, 2000; *Chem. Abstr. 135*, 210774.
326. Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300–2301.
327. Trost, B. M.; Pfrengle, W.; Urabe, H.; Dumas, J. *J. Am. Chem. Soc.* **1992**, *114*, 1923–1924.
328. Torraca, K. E.; Kuwabe, S.-I.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12907–12908.
329. Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202–12206.
330. Cacchi, S.; Fabrizi, G.; Goggiamani, A. *J. Mol. Catal. A: Chem.* **2004**, *214*, 57–64.
331. Chae, J.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 3336–3339.
332. Nemoto, T.; Ohshima, T.; Shibasaki, M. *Tetrahedron* **2003**, *59*, 6889–6897.
333. Nishimura, S.; Itaya, T. *J. Chem. Soc., Chem. Commun.* **1967**, 422–423.
334. Bethmont, V.; Fache, F.; Lemaire, M. *Tetrahedron Lett.* **1995**, *36*, 4235–4236.
335. Fache, F.; Bethmont, V.; Jacquot, L.; Lemaire, M. *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 231–238.
336. (a) Fujii, Y.; Okutsu, T.; Furugaki, H.; Kita, K., Jpn. Kokai Tokkyo Koho JP 09 67,288, 1997; *Chem. Abstr. 126*, 293089; (b) Fujii, Y.; Uno, M.; Tamura, H.; Kita, K. Jpn. Kokai Tokkyo Koho JP 09 316,017, 1997; *Chem. Abstr. 128*, 75107.

337. Fujii, Y.; Furugaki, H.; Yano, S.; Kita, K. *Chem. Lett.* **2000**, 926–927.
338. Fujii, Y.; Furugaki, H.; Kita, K. Jpn. Kokai Tokkyo Koho JP 09 67,289; *Chem. Abstr.* **1997**, *126*, 293090.
339. Fujii, Y.; Furugaki, H.; Kita, K. Jpn. Kokai Tokkyo Koho JP, 09 67,290; *Chem. Abstr*. **1997**, *126*, 293091.
340. 1,1-Diethoxy-4-methylcyclohexanone has been detected by gas chromatography from the reaction of 4-methylcyclohexanone with ethanol.[333]
341. Camus, F.; Hasiak, B.; Martin, M.; Couturier, D. *Synth. Commun.* **1982**, *12*, 647–650.
342. Yadav, J. S.; Rao, E. S.; Rao, C. S.; Choudary, B. M. *J. Mol. Catal.* **1989**, *49*, L61–L63.
343. Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764–765.
344. Mondal, S.; Nogami, T.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **2003**, *68*, 9496–9498.
345. (a) Miki, K.; Yokoi, T.; Nishino, F.; Kato, Y.; Washitake, Y.; Ohe, K.; Uemura, S. *J. Org. Chem.* **2004**, *69*, 1557–1564. (b) Zhu, J.; Germain, A. R.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2004**, *43*, 1239–1243. (c) Sato, K.; Yudha, S. S.; Asao, N.; Yamamoto, Y. *Synthesis* **2004**, 1409–1412.
346. Lipshutz, B. H.; Pollart, D.; Montforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705–708.
347. (a) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Synlett* **1992**, 1005–1006. (b) Antony, N. J.; Clarke, T.; Jones, A. B.; Ley, S. V. *Tetrahedron Lett.* **1987**, *28*, 5755–5758. (c) Shimizu, I.; Ishikawa, T. *Tetrahedron Lett.* **1994**, *35*, 1905–1908. (d) Schmeck, C.; Hegedus, L. S. *J. Am. Chem. Soc.* **1994**, *116*, 9927–9934. (e) Bujons, J.; Roura, L.; Messguer, A. *Synlett* **1994**, 437–438. (f) Molander, G. A.; Rönn, M. *J. Org. Chem.* **1999**, *64*, 5183–5187.
348. (a) Tadano, K.; Miyake, A.; Ogawa, S. *Tetrahedron* **1991**, *47*, 7259–7270. (b) Ohira, S.; Fujiwara, H.; Maeda, K.; Habara, M.; Sakaedani, N.; Akiyama, M.; Kuboki, A. *Tetrahedron Lett.* **2004**, *45*, 1639–1641.
349. For the introduction of this expression and its use, see: (a) Berson, J. E.; Willcott, M. R. *J. Org. Chem.* **1965**, *30*, 3569–3572. (b) Baldwin, J. E.; Dunmire, D. A. *J. Org. Chem.* **2000**, *65*, 6791–6794. (c) Aït-Mohand, S.; Hénin, F.; Muzart, J. *Organometallics* **2001**, *20*, 1683–1686.
350. Toshima, H.; Aramaki, H.; Furumoto, Y.; Inamura, S.; Ichihara, A. *Tetrahedron* **1998**, *54*, 5531–5544.
351. Kato, K.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, *43*, 4915–4917.
352. Kato, K.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett.* **2002**, *43*, 6587–6590.
353. These results of the Kato team contrast with those of Okumoto et al., who observed only a reaction at the level of the triple bond leading to γ-acetoxy-β-methoxy-α,β-unsaturated esters: Okumoto, H.; Nishihara, S.; Nakagawa, H.; Suzuki, A. *Synlett* **2000**, 217–218.
354. Wei, L.-L.; Wei, L.-M.; Pan, W.-B.; Wu, M.-J. *Synlett* **2004**, 1497–1502.
355. Miyakoshi, N.; Mukai, C. *Org. Lett.* **2003**, *5*, 2335–2338.
356. Miyazawa, M.; Hirose, Y.; Narantsetseg, M.; Yokoyama, H.; Yamaguchi, S.; Hirai, Y. *Tetrahedron Lett.* **2004**, *45*, 2883–2886.
357. Miyazawa, M.; Narantsetseg, M.; Yokoyama, H.; Yamaguchi, S.; Hirai, Y. *Heterocycles* **2004**, *63*, 1017–1021.
358. This alcoholysis in the presence of Lewis acid catalysts, such as palladium dihalides, has some similarity with a simultaneous report describing the $PdCl_2(MeCN)_2$-catalysed hydrolysis of various tetrahydropyranyl ethers in refluxing wet acetonitrile.[167] In the presence of water, the cleavage could be, however, due to HCl, this Brønstedt acid being produced from the hydrolysis of $PdCl_2(MeCN)_2$.[160]
359. Derdar, F.; Martin, J.; Martin, C.; Brégeault, J.-M.; Mercier, J. *J. Organomet. Chem.* **1988**, *338*, C21–C26.
360. Bouquillon, S.; Hénin, F.; Muzart, J. *Organometallics* **2000**, *19*, 1434–1437.
361. Miller, K. J.; Abu-Omar, M. M. *Eur. J. Org. Chem.* **2003**, 1294–1299.
362. Gabriele, B.; Mancuso, R.; Salerno, G.; Veltri, L. *Chem. Commun.* **2005**, 271–273.
363. (a) Kerby, M. C.; Vaughan, D. E. W. U.S. US 5,364,980, 1994; *Chem. Abstr.* **1995**, *122*, 55587. (b) Knifton, J. F.; Dai, P. S. E. U.S. US 5,364,981, 1994. *Chem. Abstr.* **1995**, *122*, 55588.
364. Chiusoli, G. P.; Venturello, C. *Organometal. Chem. Synth.* **1970/1971**, *1*, 203–204.
365. De Bernardo, S.; Tengi, J. P.; Sasso, G. J.; Weigele, M. *J. Org. Chem.* **1985**, *50*, 3457–3462.
366. Hoppe, D.; Hilpert, T. *Tetrahedron* **1987**, *43*, 2467–2474.
367. (a) Arribas, E.; Carreiro, C.; Valdeolmillos, A. M. *Tetrahedron Lett.* **1988**, *29*, 1609–1612. (b) Kaluza, Z.; Furman, B.; Krajewski, P.; Chmielewski, M. *Tetrahedron* **2000**, *56*, 5553–5562.
368. Marat, X.; Monteiro, N.; Balme, G. *Synlett* **1997**, 845–847.
369. Monteiro, N.; Balme, G. *J. Org. Chem.* **2000**, *65*, 3223–3226.
370. Bottex, M.; Cavicchioli, M.; Hartmann, B.; Monteiro, N.; Balme, G. *J. Org. Chem.* **2001**, *66*, 175–179.
371. (a) Garçon, S.; Vassiliou, S.; Cavicchioli, M.; Hartmann, B.; Monteiro, N.; Balme, G. *J. Org. Chem.* **2001**, *66*, 4069–4073. (b) Lomberget, T.; Bossharth, E.; Bouyssi, D.; Monteiro, N.; Balme, G. *Synthesis* **2004**, 2407–2410.
372. Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101–4111.
373. (a) Liu, G.; Lu, X. *Tetrahedron Lett.* **2002**, *44*, 467–470. (b) Doe, M.; Shibue, T.; Haraguchi, H.; Morimoto, Y. *Org. Lett.* **2005**, *7*, 1765–1768.
374. Cavicchioli, M.; Sixdenier, E.; Derrey, A.; Bouyssi, D.; Balme, G. *Tetrahedron Lett.* **1997**, *38*, 1763–1766.
375. Arefalk, A.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2005**, *70*, 938–942.
376. (a) Yoshida, M.; Morishita, Y.; Fujita, M.; Ihara, M. *Tetrahedron Lett.* **2004**, *45*, 1861–1864. (b) Yoshida, M.; Morishita, Y.; Fujita, M.; Ihara, M. *Tetrahedron* **2005**, *61*, 4381–4393.
377. Krishna, U. M.; Deodhar, K. D.; Trivedi, G. K.; Mobin, S. M. *J. Org. Chem.* **2004**, *69*, 967–969.
378. (a) Sajiki, H.; Ikawa, T.; Hattori, K.; Hirota, K. *Tetrahedron Lett.* **2003**, *44*, 7407–7410. (b) Ikawa, T.; Sajiki, H.; Hirota, K. *Tetrahedron* **2004**, *60*, 6189–6195.
379. Beyer, J.; Skaanderup, P. R.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 9575–9583.
380. Tenaglia, A.; Kammerer, F. *Synlett* **1996**, 576–578.
381. Tenaglia, A. *Personal communication* January 10, 2005.
382. Palucki, M.; Yasuda, N. *Tetrahedron Lett.* **2005**, *46*, 987–990.
383. Uenishi, J.; Ohmi, M.; Ueda, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1299–1303.
384. Matsukawa, Y.; Mizukado, J.; Quan, H.-d.; Tamura, M.; Sekiya, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1128–1130.

Biographical sketch

Jacques Muzart was born in 1946, in Vienne la Ville, a small village in the Argonne area, 200 km east of Paris. He studied chemistry at the Université de Champagne-Ardenne and received his degrees (Doctorat de 3ème cycle—1972, Doctorat d'Etat—1976) for his work with Jean-Pierre Pète on photochemical rearrangements of α,β-epoxyketones and β-diketones. He was appointed at the Centre National de la Recherche Scientifique (CNRS) in 1971 as Stagiaire de Recherche and spent 15 months (1977–1978) as a postdoctoral fellow of National Science Foundation working with Elias J. Corey at Harvard University on natural product synthesis. On his return to Reims, he mainly studied the photoreactivity of η^3-allylpalladium complexes and anionic activation by supported reagents. In 1988, he was promoted to Directeur de Recherche CNRS. His research interests concentrate on transition metal-catalysis with particular emphasis on oxidations, asymmetric reactions and mechanisms. For the last few years, he has also been involved in the valorisation of agricultural by-products and in the use of water and molten salts as solvents for Organic Synthesis.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 61 (2005) 6009–6014
Tetrahedron

A chemoenzymic approach to the epoxidation of alkenes in aqueous media

Kit-Ho Tong, Kwok-Yin Wong and Tak Hang Chan*

Department of Applied Biology and Chemical Technology and the Open Laboratory for Chirotechnology, Institute of Molecular Technology for Drug Discovery and Synthesis, The Hong Kong Polytechnic University, Hung Hom, Hong Kong SAR; State Key Laboratory of Chinese Medicine and Molecular Pharmacology, Shenzhen, China

Received 24 February 2005; revised 21 April 2005; accepted 25 April 2005

Abstract—Hydrogen peroxide, generated insitu by the enzymic oxidation of glucose using glucose oxidase, is coupled to a catalytic system of sodium bicarbonate/manganese sulfate to epoxidize alkenes in aqueous media.

1. Introduction

Epoxides are an important class of compounds and often made by the epoxidation of alkenes.[1] Industrially, with the exception of ethylene, which is directly oxidized by oxygen, most alkenes are epoxidized by peroxides or peracids in organic solvents. Recently, because of the concern for the environment, organic reactions conducted in aqueous media instead of organic solvents have gained considerable attention.[2] In this connection, hydrogen peroxide has been promoted as a green oxidant because the oxidation reactions can often be carried out in aqueous media and give water as the only by-product.[3,4] Some recent examples of alkene epoxidation with hydrogen peroxide include, as catalyst, the use of silica-supported titanium,[5] methyltrioxorhenium,[6,7] sodium tungstate,[8] iron complexes,[9] sodium bicarbonate[10] together with manganese (II) salts.[11] The last example is particularly interesting since, under the catalytic conditions, epoxidation of alkenes was facile, and the conditions were considered scalable. Possible limitations of the manganese/carbonate catalyzed reaction were that the hydrogen peroxide solution had to be added slowly (1.2–4.1 mL/h), via a syringe system, to the reaction system, otherwise the yield of the epoxide was much reduced, and organic co-solvents were required for the epoxidation of lipophilic alkenes.[11]

Hydrogen peroxide is produced commercially by the anthraquinone (AQ) process. However, the process can hardly be considered green. It involves the sequential hydrogenation and oxidation of an alkyl-anthraquinone dissolved in a mixture of organic solvents (usually a mixture of an aromatic hydrocarbon and a polar organic compound),[3] followed by liquid–liquid extraction in the recovery of product.[12] Each process cycle requires replacement of solvents and anthraquinone makeup. Aromatic hydrocarbon solvents are generally to be avoided because they contribute to volatile organic contaminants (VOC) and are potentially toxic. Another concern in the use of hydrogen peroxide is the danger of transportation because of the hazardous nature of neat hydrogen peroxide. It is usually handled as a 30% aqueous solution, adding to the bulk and weight of transportation. Methods for the alternative production of hydrogen peroxide are being explored actively. These include the use of a membrane catalyst,[13] liquid carbon dioxide as the solvent in the AQ process[14] or electrochemical reduction of oxygen.[15–17]

One way to circumvent the production and transportation of hydrogen peroxide is to use microbial/enzymic epoxidation of alkenes. Microbial epoxidation of alkenes had been reported previously but the yields of epoxides tended to be low, and accompanied by hydrolysis side products.[18] The use of peroxidases and hydrogen peroxide for the epoxidation of alkenes had also been reported but suffered from the easy degradation of the peroxidases.[19] More recently, the combined co-immobilization of glucose oxidase and peroxidases has been explored to alleviate the operational instability of the peroxidases.[20] A general problem in using purely enzymic system is the limitation of substrate specificity and product inhibition of the enzymes. Here, we report a chemoenzymic approach for the epoxidation of

Keywords: Epoxidation; Immobilized enzyme; Glucose oxidase.
* Corresponding author. Tel.: +86 852 2766 5605; fax: +86 850 2364 9932; e-mail: bcchanth@polyu.edu.hk

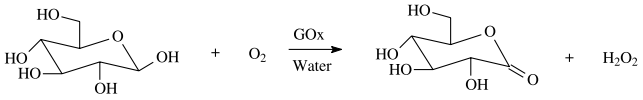
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.04.055

alkenes by combining the insitu enzymic generation of hydrogen peroxide with the broad substrate generality of a catalytic chemical system.

2. Results and discussions

2.1. Preliminary studies

Glucose oxidase (GOx, EC: 1.1.3.4) is a flavoenzyme which catalyzes the oxidation of β-D-glucose by oxygen to δ-D-gluconolactone and hydrogen peroxide (Eq. 1).



(1)

GOx is readily available commercially because of its applications in food industry and in biosensors for the detection of glucose. In most preparations of GOx, catalase, which catalyzes the decompostion of hydrogen peroxide, is also present in low concentration and therefore, cannot be used for the production of hydrogen peroxide. Recently, a catalase-free preparation of GOx with high activity (>300 unit/mg) has become available and is therefore, suitable for hydrogen peroxide generation using glucose as the substrate.

Because glucose is likely to be present in excess in the enzymic generation of hydrogen peroxide, we examined first, the potential effect of glucose on the chemical catalytic system for epoxidation. Using 4-styrenesulfonic acid, sodium salt (**1a**) as the alkene and sodium bicarbonate (1 M) as the catalyst in a pH 7.0 buffer solution, hydrogen peroxide (0.15 M) epoxidation of the alkene was examined in the presence of varying concentrations of glucose. It was found that glucose did have a retarding effect on the bicarbonate catalyzed epoxidation reaction (Fig. 1). On the other hand, there was no noticeable difference between 0.1 M and 0.2 M glucose concentrations. When the concentration was increased to 0.3 M or higher, the retardation effect became significant. This suggests that a reasonable concentration of glucose should not exceed 0.2 M for the chemoenzymic epoxidation.

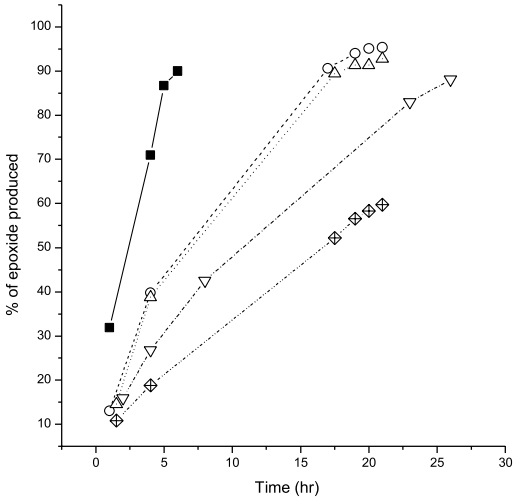


Figure 1. The effect of glucose on the bicarbonate catalyzed epoxidation of **1a** with hydrogen peroxide. The reaction was monitored by ^{1}H NMR and the percentage yield was determined by ^{1}H NMR using internal standard. (-■- without GO, - -○- - 0.1 M GO, ···△··· 0.2 M GO, · · ▽ · · 0.3 M GO and ···⊕··· 0.5 M GO).

We therefore, used a pH 7.0 phosphate buffer (10 mL) solution containing glucose (0.2 M) and the GOx enzyme (175 unit/mL), oxygen was bubbled into the mixture at a flow rate of 0.1 mL/min and hydrogen peroxide generation was followed by electrochemical monitoring. It was found that hydrogen peroxide was produced to an optimal concentration of 0.025 M in 6.5 h (Fig. 2). The concentration of H_2O_2 started to level off after that time even though the glucose was still far from depleted, suggesting that product inhibition of the enzyme was beginning to occur. This also suggests that it is preferable to have the alkene epoxidation completed within that timeframe before enzyme inhibition occurs.

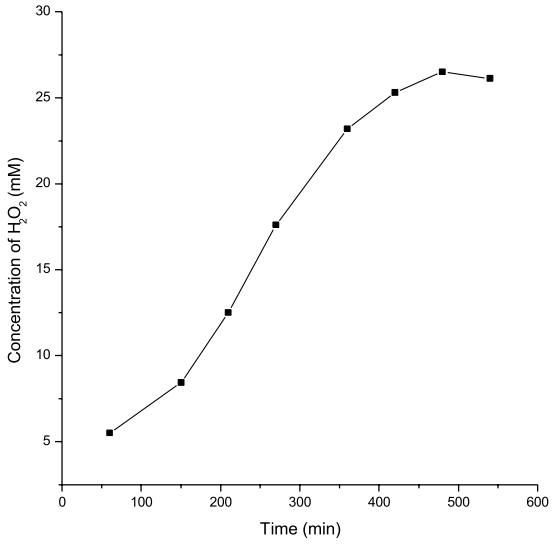
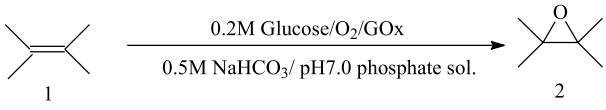


Figure 2. The generation of hydrogen peroxide by glucose oxidase (175 unit/mL) and 0.2 M glucose in 10 ml pH 7.0 phosphate buffer solution with an oxygen flow of 0.1 mL/min.

2.2. Epoxidation of aqueous soluble alkenes

Using 0.2 M glucose, 0.5 M $NaHCO_3$ and 0.05 M **1a** as the substrate in pH 7.0 phosphate buffer solution and GOx (175 unit/mL) as the standard condition, with oxygen bubbling at a flow rate of 0.1 mL/min, the epoxidation was followed by ^{1}H NMR. The yield of the epoxide (**2a**) was however moderate, at about 15% even after prolonged reaction time. Increasing the amount of glucose in the reaction mixture did not improve the yield (Eq. 2).



(2)

More recently, it has been reported that catalytic amount of manganese sulfate greatly accelerates epoxidation of alkenes in the hydrogen peroxide/aqueous sodium

bicarbonate process.[11] We found that under the chemoenzymic conditions as described above, by adding a catalytic amount of manganese sulfate (0.1 mol%), the epoxidation of 4-styrenesulfonic acid, sodium salt (**1a**) was completed in a short time (less than 3 h) with excellent yields of the epoxide **2a** (>90%, entry 1, Table 1). Other water-soluble alkenes, such as 4-vinylbenzoic acid (**1b**, entry 2) and 3-methyl-2-buten-1-ol (**1c**, entry 3) were also epoxidized in high yields under similar conditions.

2.3. Epxidation of lipophilic alkenes

We have also examined the chemoenzymic approach for the epoxidation of lipophilic alkenes. It is known that glucose oxidase is quite robust and not deactivated by the presence of *t*-butanol.[20] We examined first, the effect of *t*-butanol on the epoxidation of **1a**. It was found that both the rates of conversion of the alkene to the epoxide were substantially lower as the concentration of *t*-butanol increased,[20] but only modestly affected in 10% solution (Fig. 3, curve B–D; and entries 4–6, Table 1). Thus, using aqueous 10% *t*-butanol solution as the media and the same reaction conditions, styrene (**1d**) was epoxidised with oxygen/glucose/GOx and Mn^{2+}/HCO_3^- to give 45% conversion of styrene to the corresponding epoxide in 90% yield, after 3 h (entry 7).

It would be preferable to be able to avoid the use of organic co-solvent completely. It is known that the glucose oxidase enzyme is not affected by sodium dodecyl sulfate (SDS) at 10 mM concentration at pH 6–7 even after prolonged incubation.[21] We examined therefore, the effect of 5 mM SDS on the epoxidation of **1a** in aqueous media under identical conditions (Fig. 3, curve E). It is clear that the presence of SDS did not affect the rate or yield of the epoxidation reaction under the chemoenzymic conditions. We applied therefore, the SDS (5 mM) conditions to the epoxidation of styrene (**1d**) and styrene epoxide was

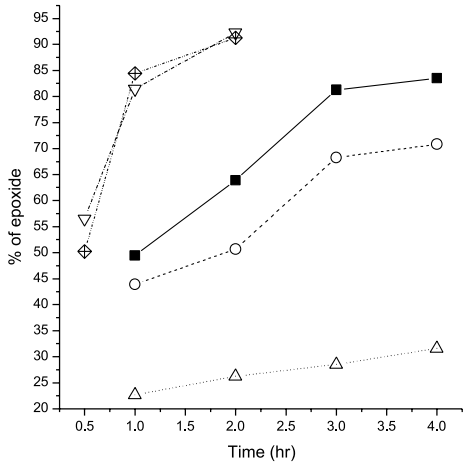
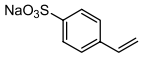
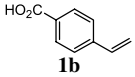
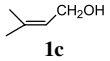
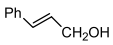


Figure 3. The effect of *t*-butanol and SDS on the chemenzymic epoxidation of 4-styrenesulfonic acid, sodium (**1a**). The reaction was monitored by ^{1}H NMR and the percentage yield was determined by ^{1}H NMR. (· · ▽ · · Curve A: without SDS and *t*-butanol, -■- Curve B: 10% *t*-butanol, - - ○ - - Curve C: 20% *t*-butanol, ···△··· Curve D: 30% *t*-butanol, ···◈··· and Curve E: 5 mM SDS).

Table 1. Chemoenzymic epoxidation of alkenes

Entry	Alkene (**1**)	Time (h)	Additive	Conversion of **1** (%)	Yield of **2** (%)[a]
1	 **1a**	3	—	>99	93(81)
2	 **1b**	3	—	>99	91(83)
3	 **1c**	8	—	>99	81
4	**1a**	3	10% *t*-BuOH	80	90
5	**1a**	3	20% *t*-BuOH	68	91
6	**1a**	3	30% *t*-BuOH	30	90
7	 **1d**	3	10% *t*-BuOH	45	90
8	 **1d**	3	5 mM SDS	65	91
9	 **1e**	3	5 mM SDS	>90	71(56)
10	 **1f**	8	5 mM SDS	20	>99
11	 **1g**	6	5 mM SDS	95	60[b]
12	 **1h**	8	5 mM SDS	32	90

[a] Yields were calculated based on converted alkene **1** and were determined by ^{1}H NMR or GC using an internal standard. Isolated yield was given in parenthesis.

[b] *trans*-3-Phenylpropenal was observed in 35% yield.

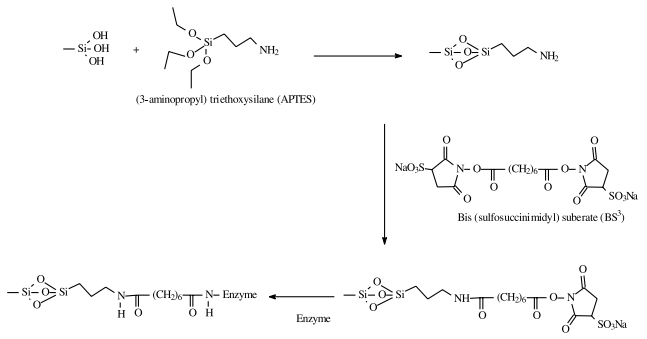
obtained in 91% yield, now with 65% conversion, after 3 h (entry 8). We had the same results when we used 8 mM SDS which is the critical micelle concentration. Operationally, the SDS conditions are quite simple to handle and can be used readily for the preparative scale epoxidation of alkenes.

We have also applied the same reaction conditions to the epoxidation of α-methylstyrene (**1e**), cyclooctene (**1f**), cinnamyl alcohol (**1g**) and 1,2-dihydronaphthalene (**1h**). The results are summarized in Table 1 (entries 9–12). In the case of cinnamyl alcohol (**1g**), oxidation of the allylic alcohol to the corresponding aldehyde was observed as a competitive reaction. It should be noted that in the epoxidation of lipophilic alkenes, the oxygen was not bubbled through the reaction mixture because the volatile alkenes would be carried away by the oxygen with subsequent reduction of yield. The reaction mixture was simply stirred in an atmosphere of oxygen. This may have contributed to the lower conversion of some of the alkenes within the reaction time studied.

2.4. Enzyme immobilization

We have also explored the use of immobilized glucose oxidase for the reaction and the possible recovery and recycling of the enzyme. We have examined two methods of immobilization: (a) sol gel formation[22–24] and (b) immobilized glucose oxidase on silica gel surface using the approach outlined in Scheme 1.[25–27] In the first, approach, the enzyme was physically dispersed in the sol gel. The advantage is that the enzyme is readily accessible to the substrate in the aqueous reaction mixture. The use of such a method of immobilization gave indeed good epoxidation of **1a** to the corresponding epoxide (Fig. 4). The sol gel was recovered from the aqueous phase followed by washings. However, on recycling of the sol-gel immobilized enzyme, the activity dropped dramatically and became essentially inactive after the third cycle (Fig. 4). We attributed the loss of the enzymic activity to the removal of the enzyme from the sol gel during the washing process.

We therefore, examined the other immobilization method where the glucose oxidase is chemically anchored onto silica gel (Scheme 1). In this method of immobilization, the enzyme is less accessible, and thus, larger amount of enzyme (4500 units) was required to achieve the epoxidation of **1a** to the product epoxide in three hours. On the other hand, the immobilized enzyme could be recovered easily



Scheme 1. Immobilization of glucose oxidase on silica gel.

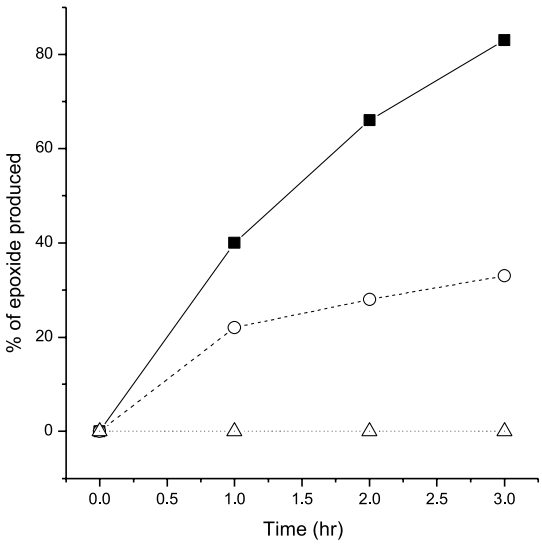


Figure 4. Epoxidation of **1a** by chemoenzymic system using enzyme immobilized in sol-gel. Yield was determined by HPLC versus an internal standard. (-■- 1st cycle, - -○- - 2nd cycle and ···△··· 3rd cycle).

and retained its activity. It was found that the immobilized GOx can be re-used 8 times with excellent yields of epoxide (Fig. 5). The immobilized GOx was very stable and can be kept for 4 weeks at −4 without loss of activity.

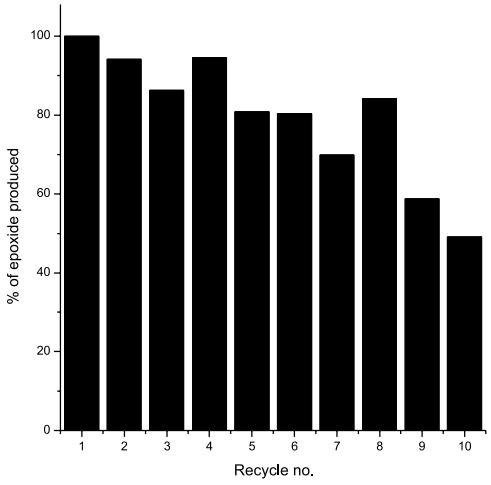


Figure 5. Recycling of enzyme in the epoxidation of **1a** by chemoenzymic system using enzyme immobilized on silica gel. Yield was determined by HPLC versus an internal standard.

3. Conclusions

A chemoenzymic approach for the insitu generation of hydrogen peroxide in the epoxidation of alkenes was investigated. Water-soluble alkenes were oxidized with oxygen/glucose/GOx and Mn^{2+}/HCO_3^- and the yields of epoxides were excellent (~90%). The effect of *t*-butanol or SDS on the chemoenzymic oxidation system was studied. By using SDS, lipophilic alkenes were also epoxidized with glucose/GOx and Mn^{2+}/HCO_3^- without the need for organic co-solvent. Moreover, immobilized GOx was explored and it was found that chemically immobilized GOx on silica gel was stable and could be re-used 8 times with no significant loss of activity. By the combined use of

enzymic generation of hydrogen peroxide with a chemical catalyst, one can take advantage of the easy modifications of the chemical system and the broad substrate generality as demonstrated in the present study for the epoxidation of alkenes. The system may be adaptable to other abiotic catalytic systems for different chemical transformations using hydrogen peroxide.

4. Experimental

4.1. Materials

All chemicals were purchased from Aldrich and used as received. Glucose oxidase (catalase free) was purchased from Biocatalyst Limited.

4.2. Instrumentation

^{1}H NMR spectral measurements were carried out on a Bruker DPX-400 MHz NMR spectrometer. Differential pulse voltammetry (DPV) was carried out on a Bioanalytical System BAS100B electrochemical analyzer.

4.3. Epoxidation of the 4-styrenesulfonic acid, sodium salt (1a) in the presence of varying concentrations of glucose

An aqueous solution of the alkene (0.1 mmol, **1a**), $NaHCO_3$ (1 M) and hydrogen peroxide (0.15 M) was mixed with glucose (0.0.1–0.5 M) in 500 μL pH 7.0 phosphate buffer D_2O solution. The reaction was monitored with ^{1}H NMR by the disapperance of the vinyl proton signals at 6.2 ppm or the appearance of the epoxide signals at 2.4 ppm.

4.4. Electrochemical determination of hydrogen peroxide concentration.[28,29]

Platinum was used as the working electrode. It was first, polished with 0.05 μm alumina followed by ultrasonic cleaning and thorough rinsing with distilled water. The electrode was then activated in 1.0 M sulfuric acid by scanning the potential between 1.3 and −0.25 V versus SCE at a scan rate of 200 mV/s. The platinum electrode was considered as being activated if the cyclic voltammogram exhibited the characteristic hydrogen adsorption and desorption fine structure as well as the oxide formation and removal profile.[30]

A solution of glucose was mixed with glucose oxidase (175 unit/mL) in a pH 7.0 phosphate buffer solution (10 mL) to make up a 0.2 M glucose solution. The mixture was bubbled with oxygen gas. DPV was carried out at different time intervals to monitor the hydrogen peroxide generated by the enzyme. Calibration curve was constructed using known concentrations of hydrogen peroxide under similar conditions.

4.5. Chemoenzymic epoxidation of water-soluble alkenes

A mixture of alkene (**1a**–**1c**, 0.1 mmol), $NaHCO_3$ (0.5 M), glucose (0.2 M), glucose oxidase (175 units/mL) and $MnSO_4$ (0.1 mol %) was dissolved in a pH 7.0 phosphate buffer solution (2.0 mL) which was prepared using D_2O as solvent. The mixture was bubbled with oxygen gas at a flow rate of 0.1 mL/min throughout the reaction. The reaction was monitored by ^{1}H NMR and the percentage yield was determined by NMR.

4.6. Epoxidation of 1a in the presence of varying concentrations of *t*-butanol

A solution of the alkene **1a** (0.1 mmol), $NaHCO_3$ (0.5 M), glucose (0.2 M), $MnSO_4$ (1 mol %) and GOx (175 unit/mL) was mixed with different concentrations of *t*-butanol in a pH 7.0 phosphate buffer solution in D_2O (15 mL). The mixture was bubbled with oxygen gas at a flow rate of 0.1 mL/min throughout the reaction. The reaction was monitored by ^{1}H NMR.

4.7. Epoxidation of 1a in the presence SDS

A solution of the alkene **1a** (0.1 mmol), $NaHCO_3$ (0.5 M), glucose (0.2 M), $MnSO_4$ (1 mol %), SDS (5 mM) and GOx (175 unit/mL) was mixed in a pH 7.0 phosphate buffer solution in D_2O (15 mL). The mixture was bubbled with oxygen gas at a flow rate of 0.1 mL/min throughout the reaction. The reaction was monitored by ^{1}H NMR.

4.8. Chemoenzymic epoxidation of water-insoluble alkenes

A solution of the alkene (**1d**–**1h**, 0.1 mmol), $NaHCO_3$ (0.5 M), glucose (0.2 M), $MnSO_4$ (1 mol %) and GOx (175 unit/mL) was mixed in a pH 7.0 phosphate buffer solution in water (20 mL) containing 10% *tert*-butyl alcohol or SDS (5 mM). The reaction mixture was simply stirred in an atmosphere of oxygen. When the reaction was completed, water (20 mL) was added and the mixture was extracted with diethyl ether (5×20 mL). The organic layer was then washed with brine (2×15 mL), dried over sodium sulfate, filtered, and the diethyl ether was removed by a rotary evaporator to give the desired product. The percentage yields were determined by GC or ^{1}H NMR with internal standard.

4.9. Immobilization of glucose oxidase in sol-gel

A solution of tetramethoxysilane (300 μL) in hydrochloric acid (0.1 M, 10 μL) was mixed vigorously with distilled water (700 μL) for 3 h. A pH 7.0 phosphate buffer solution (200 μL) was added to neutralize the excess acid. The enzyme GOx (2900 unit) was then added and well mixed. The sol-gel was then put into refrigerator for 2 days at 4 °C for condensation.

4.10. Immobilization of glucose oxidase on silica gel

A quantity of silica gel (1.0 g, Merck grade 10184, 70–230 mesh, pore size 100 A, surface area 300 m^2/g) was activated under vacuum at about 80 °C for 2 days. After cooling, 3-(aminopropyl)-triethoxysilane (4 mL) was added in chloroform (60 mL) and the mixture was stirred for 1 days. The solid was filtered off, washed with chloroform (10 mL) and dried in air. The solid was then mixed with bis(sulfosuccinimidyl) suberate (1.5 mL, 0.57 mg/mL) in a

pH 7.0 phosphate buffer solution (20 mL). After 20 min, the solid was filtered off and washed with the buffer solution (5 mL). It was then mixed with GOx (4500 units) in a pH 7.0 phosphate buffer solution (20 mL). After 30 min, the solid was filtered off and washed with the buffer solution. The immobilized GOx was kept under −4 °C.

4.11. Epoxidation of 1a with immobilized enzyme

4.11.1. Immobilization of glucose oxidase in sol-gel. A solution of the alkene **1a** (0.1 mmol), $NaHCO_3$ (0.5 M), glucose (0.2 M), $MnSO_4$ (1 mol %) and the sol-gel immobilized GOx (2900 units) was mixed in a pH 7.0 phosphate buffer solution in D_2O (2 mL) for 3 h with stirring under oxygen. After the reaction, the immobilized GOx was filtered and washed with pH 7.0 phosphate buffer solution in D_2O. The yield was determined by ^1H NMR with internal standard.

4.11.2. Immobilization of glucose oxidase on silica gel. A solution of the alkene **1a** (0.1 mmol), $NaHCO_3$ (0.5 M), glucose (0.2 M), $MnSO_4$ (1 mol%) and the silica-gel immobilized GOx (4500 units) was mixed in a pH 7.0 phosphate buffer solution in water (20 mL, the larger volume of water was required to allow smooth stirring of the solid silica-gel) and the mixture was allowed to react for 7 h with stirring under oxygen. After the reaction, the immobilized GOx was separated by centrifugation and washed with a pH 7.0 phosphate buffer solution. The yield was determined by HPLC with internal standard. The recovered silica-gel immobilized GOx could be stored at −4 °C and reused for the epoxidation reaction.

Acknowledgements

This work was supported by the Areas of Excellence Scheme established under the University Grants Committtee of the Hong Kong Special Administrative Region, China (Project No. AoE/P-10/01). We thank the Hong Kong Polytechnic University for financial support. T.H.C. acknowledges the support of McGill University for the granting of a leave.

References and notes

1. Sienel, G.; Rieth, R.; Rowbottom, K. T. *Ullmann's Encyclopedia of Organic Chemicals*; Wiley-VCH: Weinheim, 1999.
2. Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; Wiley-Interscience: New York, 1997.
3. Strukul, E. G. *Catalytic Oxidations with Hydrogen Peroxide as Oxidant*; Kluwer Academic: Dordrecht, Ntherlands, 1992.
4. Grigoropoulou, G.; Clark, J. H.; Elings, J. A. *Green Chem.* **2003**, *5*, 1–7.
5. Capel-Sanchez, M. C.; Campos-martin, J. M.; Fierro, J. L. G.; de Frutos, M. P.; Polo, A. P. *Chem. Commun.* **2000**, 855–856.
6. Romao, C. C.; Kuhn, F. E.; Herrmann, W. A. *Chem. Rev.* **1997**, *97*, 3197–3246.
7. Herrmann, W. A.; Kuhn, F. E. *Acc. Chem. Res.* **1997**, *30*, 169–180.
8. Sato, K.; Aoki, M.; Ogawa, M.; Hashimoto, T.; Noyori, R. *J. Org. Chem.* **1996**, *61*, 8310–8311.
9. White, M. C.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 7194–7195.
10. (a) Yao, H. R.; Richardson, D. E. *J. Am. Chem. Soc.* **2000**, *122*, 3220–3221. (b) Richardson, D. E.; Yao, H.; Frank, K. M.; Bennett, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 1729–1739.
11. (a) Lane, B. S.; Burgess, K. *J. Am. Chem. Soc.* **2001**, *123*, 2933–2934. (b) Lane, B. S.; Vogt, M.; DeRose, V. J.; Burgess, K. *J. Am. Chem. Soc.* **2002**, *124*, 11946–11954.
12. Kabisch, G.; Richter, E. U.S. Patent 70-69151, 1959.
13. Choudhary, V. R.; Gaikwad, A. G.; Sansare, S. D. *Angew. Chem. Int. Ed.* **2001**, *40*, 1776–1779.
14. Hancu, D.; Beckman, E. J. *Green Chem.* **2001**, *3*, 80–86.
15. Harrington, T.; Pletcher, D. *J. Electrochem. Soc.* **1999**, *146*, 2983–2989.
16. White, J. H.; Schwartz, M.; Sammells, A. F. US Patent 5,645,700, 1997.
17. Kinoshita, K. *Electrochemical Oxygen Technology*; Wiley-Interscience: , 1992.
18. Drauz, K.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis, a Comprehensive Handbook*; VCH: Weinheim, 1995.
19. (a) VanDeurzen, M. P. J.; Seelbach, K.; VanRantwijk, F.; Kragl, U.; Sheldon, R. A. *Biocatal. Biotransform.* **1997**, *15*, 1–16. (b) The alternative of using hydrogen peroxide/dimethyl carbonate with lipase for the epoxidation of alkenes has been reported. gen. Klaas, M. R.; Warwel, S. *Org. Lett.* **1999**, *1*, 1025–1026.
20. van de Velde, F.; Lourenco, N. D.; Bakker, M.; van Rantwijk, F.; Sheldon, R. A. *Biotechnol. Bioeng.* **2000**, *69*, 286–291.
21. Jones, M. N.; Manley, P.; Wilkinson, A. *J. Biochem.* **1982**, *203*, 285–291.
22. Dunn, B.; Miller, J. M.; Dave, B. C.; Valentine, J. S.; Zink, J. I. *Acta Mater.* **1998**, *46*, 737–741.
23. Li, J.; Chia, L. S.; Goh, N. K.; Tan, S. N.; Ge, H. *Sens. Actuator B-Chem.* **1997**, *40*, 135–141.
24. Lin, J.; Brown, C. W. *Trac-Trends Anal. Chem.* **1997**, *16*, 200–211.
25. Prado, A. G. S.; Airoldi, C. *J. Colloid Interface Sci.* **2001**, *236*, 161–165.
26. Liu, C. J.; Yu, W. Y.; Li, S. G.; Che, C. M. *J. Org. Chem.* **1998**, *63*, 7364–7369.
27. Rhee, W.M. Eur. Pat. Appl. Patent EP 96-102366, 1996.
28. Gerlache, M.; Senturk, Z.; Quarin, G.; Kauffmann, J. M. *Electroanalysis* **1997**, *9*, 1088–1092.
29. Johnston, D. A.; Cardosi, M. F.; Vaughan, D. H. *Electroanalysis* **1995**, *7*, 520–526.
30. Bard, A. J.; Faulkner, L. R. *Electrochemical Methods, Fundamental and Applications*; Wiley: New York, 1980; pp 538–540.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 6015–6039

Determination of the absolute stereochemistry and asymmetric total synthesis of madindolines A and B: a practical improvement to a second-generation approach from the first-generation

Tomoyasu Hirose, Toshiaki Sunazuka, Daisuke Yamamoto, Naoto Kojima, Tatsuya Shirahata, Yoshihiro Harigaya, Isao Kuwajima and Satoshi Ōmura*

The Kitasato Institute, and Kitasato Institute for Life Sciences and Graduate School of Infection Control Sciences and School of Pharmaceutical Sciences, Kitasato University and CREST, The Japan Science and Technology Corporation (JST), 5-9-1 Shirokane, Minato-Ku, Tokyo 108-8642, Japan

Received 7 April 2005; accepted 20 April 2005

Abstract—In this report, we describe an efficient, highly convergent, stereocontrolled first total synthesis and a second-generation synthesis of madindolines A **1** and B **2**, potent selective inhibitors of interleukin 6. The key steps include (1) asymmetric oxidative ring-closure reaction of tryptophol **3** to construct a chiral 3a-hydroxyfuroindoline **4** using the modified Sharpless asymmetric epoxidation condition, (2) highly diastereoselective acylation to build up the quaternary carbon center, and (3) intramolecular acylation of ester **32** with allylsilanes to produce the full substituted cyclopentenedione units. Our first synthetic route defines for the first time both their relative and absolute configurations. Moreover, a more efficient second-generation synthesis was designed, which is suitable for gram-scale preparation of these compounds.

1. Introduction

Interleukin 6 (IL-6) is a multifunctional cytokine involved in the regulation of differentiation and antibody production. In addition, uncontrolled IL-6 activity plays a central role in a variety of serious diseases,[1] including cancer cachexia,[2] Castleman's disease,[3] rheumatoid arthritis,[4] hypercalcemia,[5] and multiple myeloma.[6] Because no effective therapeutic agents for these diseases have been developed, a low molecular weight compound that modulates the function of IL-6 has been sought.

In 1996, we reported the isolation of the novel indole alkaloids from the culture broth of *Streptomyces nitrosporeus* K93-0711, madindolines A (+)-**1** and B (+)-**2** (Fig. 1), as selective inhibitors of IL-6.[7,8] The biological activity profiles of (+)-**1** and (+)-**2** were exceptional. Both (+)-**1** and (+)-**2** specifically inhibited the growth of the IL-6-dependent MH60 cell line (IC_{50} values of 8 and 30 μM, respectively),[7] but they did not affect the IL-6-independent MH60 cell line. More detailed biological studies showed that (+)-**1** dose-dependently suppressed

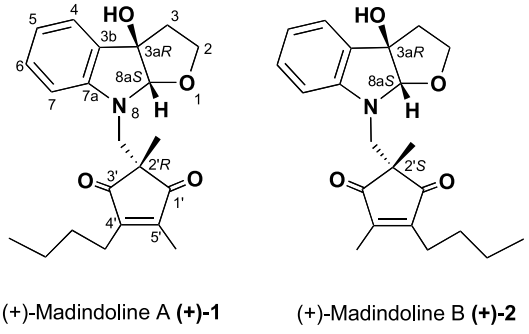


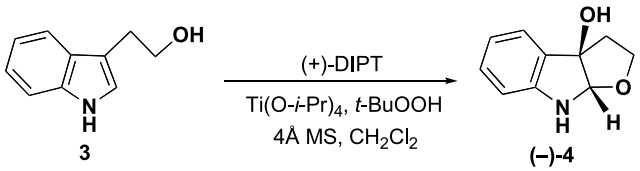
Figure 1. Structures of (+)-madindoline A (**1**) and B (**2**).

IL-6 and IL-11-induced osteoclastogenesis.[9] Moreover, oral administration of (+)-**1** to ovariectomized (OVX) mice significantly suppressed the decrease in bone mass and increase in serum Ca^{2+} level after ovariectomy.[9] This suppression mechanism was distinct from that of 17β-estradiol.[9] However, further studies on their biological properties were not possible, because the madindolines were no longer available from natural sources due to mutation of the bacterial strain. Thus, the madindolines have been only available via total synthesis.

Keywords: Interleukin 6; Madindolines; Tryptophol.
* Corresponding author. Tel.: +81 3 5791 6101; fax: +81 3 5791 6380.; e-mail: omura-s@kitasato.or.jp

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.04.056

Table 1. Results of asymmetric oxidative ring-closure of tryptophol (**3**)



Entry	Reagents[a] (equiv)		Concentration of **3** in CH_2Cl_2 (M)	Temp. (°C)	Time (h)	Scales for **3**	Yield[b] (%)	ee of Product[c] (%ee)
	$Ti(O\text{-}i\text{-}Pr)_4$	(+)-DIPT						
1	1.0	1.2	0.4	−20	3	500 mg	36	69
2	1.0	1.2	0.01	−20	6	70 mg	72	99
3	1.0	1.2	0.01	−20	5	1.0 g	67	73
4	0.25	0.30	0.01	−20	48	70 mg	37	28
5	1.0	1.2	0.1	−40	4	1.0 g	60	84
6	1.8	2.0	0.1	−40	2	1.0 g	56	>99
7	1.8	2.0	0.1	−40	2	7.5 g	55	99

[a] All reactions were carried out with *t*-BuOOH (2.5 equiv) in 4 Å-molecular sieves.
[b] Yields were based on pure materials isolated by chromatography on SiO_2.
[c] The ee of the product was determined by HPLC analysis (column, DAICEL Chiralcel (46×250 mm); UV at 254 nm; 0.35 ml/min; 0 °C; solvent, 9% 2-propanol in hexane, rt=70.5 min).

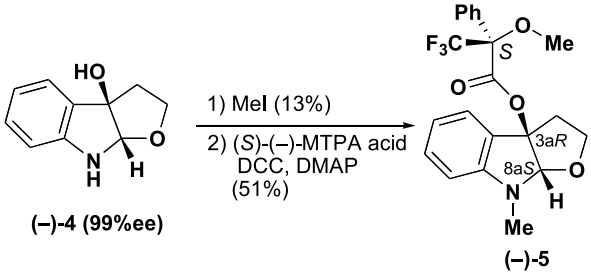
Madindolines are comprised of an unusual 3a-hydroxyfuroindoline ring connected at the nitrogen via a methylene bridge to the cyclopentene-1,3-dione ring. The planar structures of **1** and **2** were assigned by detailed 1- and 2-D NMR studies, in conjunction with IR, UV and mass data, but the relative and absolute configurations have remained undefined.[8] Due to the promising biological activity and novel structures of madindolines, we have focused on the total synthesis of these compounds to determine their stereochemistry and to supply the materials. So far, four total syntheses of madindolines, including our first- and second-generation syntheses, have been reported.[10] Herein, we report the development of our total syntheses of madindolines.

2. Results and discussion

2.1. Asymmetric synthesis of both enantiomers of 3a-hydroxyfuroindoline

Before we embarked upon the first total synthesis and determination of the absolute stereochemistry of madindolines, it was necessary to demonstrate that optically pure 3a-hydroxyfuroindoline **4** can be easily prepared from commercially available compounds. Based on our observation that *m*-CPBA oxidation of tryptophol **3** afforded racemic 3a-hydroxyfuroindoline **4** in 75% yield, we expected that asymmetric oxidative ring closure of **3** would be possible by a combination of suitable asymmetric inducers with an oxidative reagent. Thus, we tried to establish the protocol by taking advantage of the Sharpless asymmetric epoxidation.[11] In the initial attempts we examined the reaction under the standard Sharpless epoxidation conditions, the results of which are summarized in Table 1. To obtain high enantioselectivities, a low concentration of the substrate **3** with a stoichiometric oxidant is required for relatively small-scale production, but for large scale reactions, a short reaction time and a lower temperature is preferred rather than the dilute conditions. For instance, dilute and stoichiometric conditions for a small scale (70 mg) reaction generated highly optically active (−)-**4** in 72% yield (entry 2); however, the catalytic protocol proved less effective (e.g., 37% yield; 28% ee; entry 4), and the reaction with 0.1 M at −40 °C for a large scale production (7.5 g) gave (−)-**4** in 55% yield without a decrease in enantioselectivity (entry 7). We suspect that this is caused by difficulty in maintaining the temperature within the reaction mixture when dilute conditions are used for large scale production. Finally, use of (+)-DIPT instead of (−)-DIPT afforded the enantiomer (+)-**4** with high enantioselectivity and with a similarly good yield. Thus, the reaction protocol can provide both enantiomers of 3a-hydroxyfuroindoline with high optical purities.

Based on the proposed mechanism by Saito et al. for the preparation of racemic **4** using singlet oxygen,[12] this oxidative ring-closure likely occurs by an electrophilic attack of the peroxide at the 3-position of the indole ring, followed by ring closure between the imine carbon and the primary alcohol. To determine the absolute stereochemistry, (−)-**4** was treated with MeI followed by esterification with (−)-MTPA to produce ester (−)-**5**[13] as a light yellow crystal (Scheme 1). Single-crystal X-ray diffraction for (−)-**5** was performed to confirm the stereochemistry of (−)-**4**[14] (Fig. 2).



Scheme 1. Synthesis of (−)-**5**.

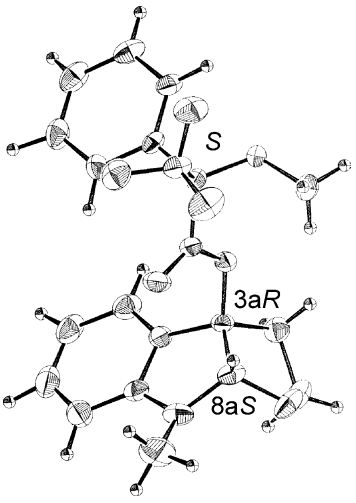
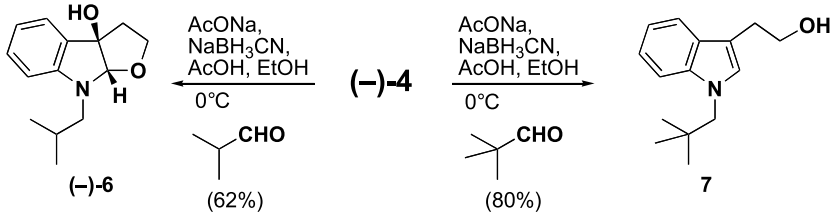


Figure 2. ORTEP plot of the X-ray structure of (−)-**5**.

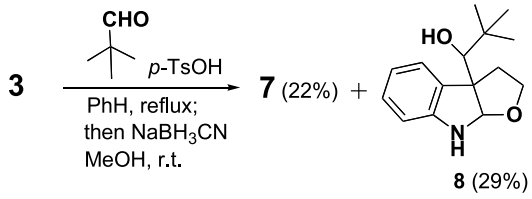
2.2. *N*-Alkylation of a model system

Next, we tried to establish the reaction conditions for coupling (−)-**4** to cyclopenten-1,3-dione units to construct the whole madindoline skeleton. We examined reductive amination[15] of simple aldehydes with (−)-**4** (Scheme 2). Amination of 2-methylpropanal with (−)-**4** provided the *N*-isobutylindoline (−)-**6**[13] in moderate yield (62%), whereas pivaroylaldehyde, carrying a quaternary center at the α-position like a real coupling partner, did not produce the desired product but rather the undesired *N*-*t*-butyltryptophol **7**[13] in high yield (80%). Moreover, all attempts of *N*-alkylation of (−)-**4** with a simple alkylhalide were unsuccessful under the conditions tested and produced mixtures of undesired products.

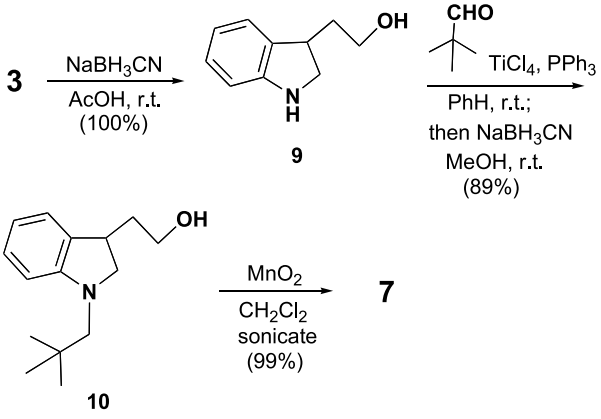
These results led us to try coupling with tryptophol **3**, the precursor of (−)-**4**, with a suitable aldehyde under reductive amination conditions.[15] However, due to the high nucleophilicity of the 3-position of indole, standard reductive amination conditions furnished the undesired



Scheme 2. Reductive amination of simple aldehydes with furoindoline (−)-**4**.



Scheme 3. Reductive amination of pivaroyl aldehyde with tryptophol (**3**).



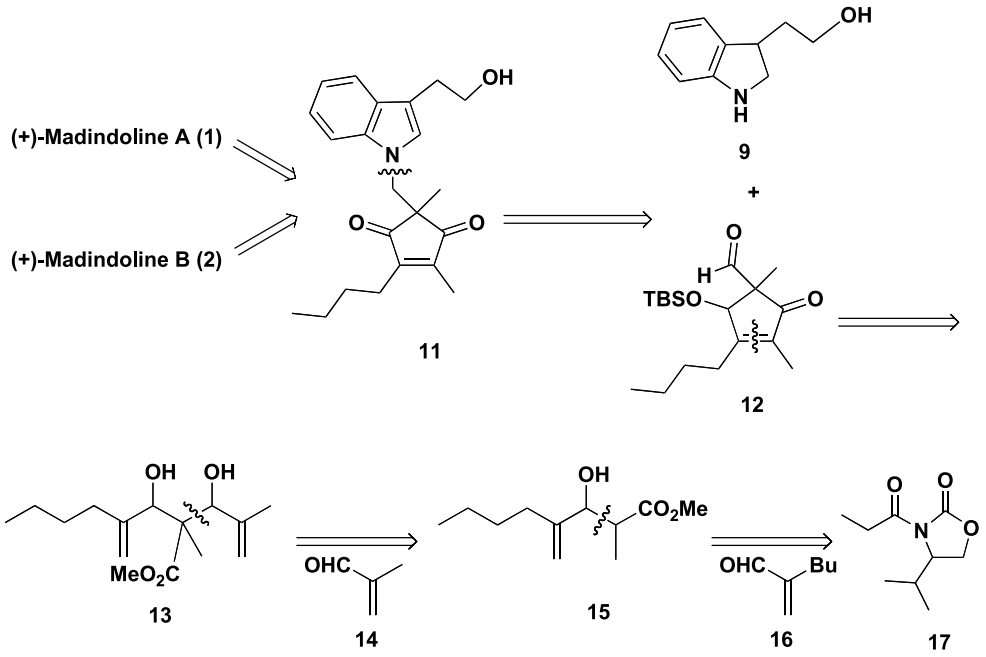
Scheme 4. Reductive amination with indoline.

furoindoline **8**[13] in 29% yield together with the desired *N*-alkylated indole **7** in 22% yield (Scheme 3).

To circumvent this problem, the indole moiety was reduced to indoline **9**[13,16] in 100% yield to remove the nucleophilicity at the C3-position. Reductive amination[17] was then carried out to produce *N*-alkylated indoline **10**[13] in good yield (89%). Oxidation of **10** with MnO_2[16] led to the desired product **7** in excellent yield (99%) (Scheme 4). With this ability to convert indoline to indole, we could design a coupling reaction between the indole unit and sterically hindered aldehyde.

2.3. Retrosynthetic analysis of madindoline A and B for the first generation

Scheme 5 outlines our retrosynthetic strategy for madindolines. Having secured a viable asymmetric protocol to access the 3a-hydroxyfuroindoline ring and an *N*-alkylation protocol to yield *N*-alkyl indole, we envisioned the total synthesis of **1** and **2** to entail reductive coupling of aldehyde **12** with 3-(2-ethanol)-indoline **9** and oxidation of the indoline unit, followed by the stereocontrolled introduction of the 3a-hydroxyfuroindoline ring exploiting the Sharpless protocol. The synthetic strategy for the cyclic aldehyde **12** depends on the efficient ring formation from the linear diene **13** with Grubbs's ring-closing olefin metathesis reaction.[18] We reasoned that **13** could be prepared from double-stereoselective aldol reactions. Importantly, this strategy

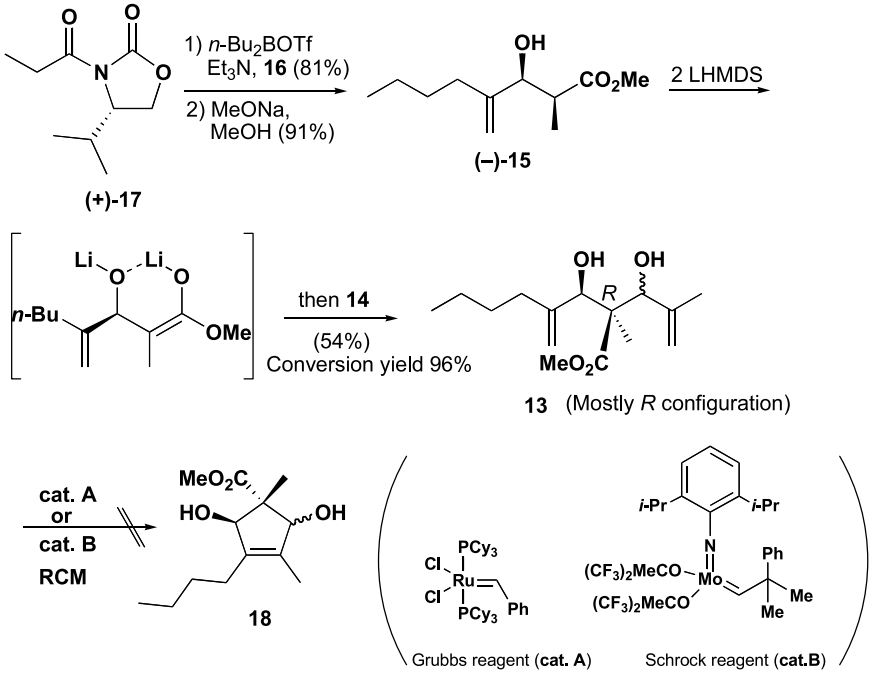


Scheme 5. Retrosynthesis of madindolines.

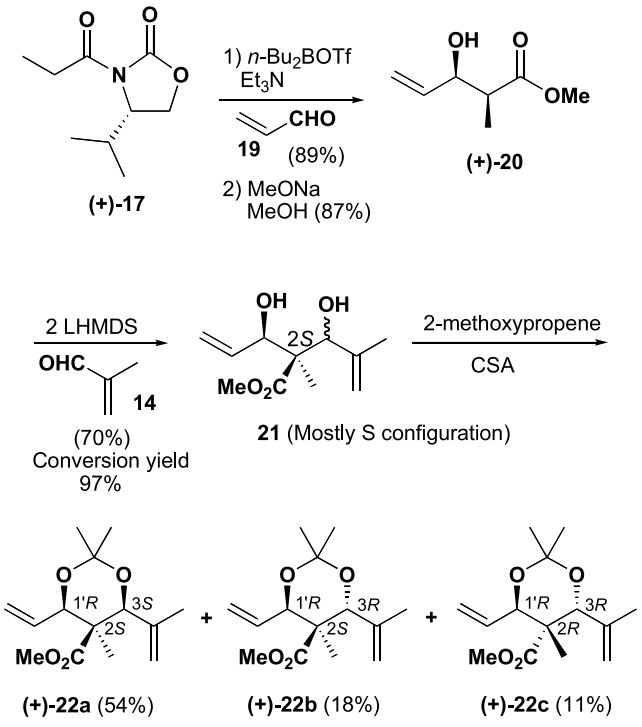
was promising for controlled access to each of the possible stereoisomers of the madindoline skeleton, thereby permitting establishment of the relative and absolute configurations of **1** and **2**.

2.4. Synthesis of the cyclopentene core

The construction of the required cyclopentene core began with the Evans asymmetric aldol reaction of oxazolidinone (+)-**17**[19,20] with 2-butylacrolein **16** to produce the aldol product in 81% yield with >99% de, which was followed by methanolysis under basic conditions (MeONa in MeOH), furnishing the β-hydroxyester (−)-**15**[13] in 91% yield (Scheme 6). Aldol reaction based on the Fráter's protocol[21] of (−)-**15** with methacrolein **14** furnished diene **13**[13] as an inseparable mixture (mainly the *R* configuration) in 54% (96% based on recovered SM) yield. However, the ring-closing olefin metathesis (RCM) using first generation Grubbs reagent (cat. **A**)[18] or Schrock reagent (cat. **B**)[18a] to form cyclopentene **18** was unsuccessful. When the RCM was attempted with cat. **A** in any solvents, only the unreacted starting material and some unstable carbene complexes were observed. In the case of cat. **B**, substrate **13** could not survive under the reaction conditions. We



Scheme 6. Preparation of diene **13** and RCM.



Scheme 7. Preparation of diene **21**.

expected that this RCM reaction would be suppressed by high steric hindrance between the methyl and butyl groups on the double bonds. To avoid this problem, we planned to introduce the butyl function on the double bond of cyclopentene after the RCM reaction.

To produce a cyclopentene substrate without a butyl group, stereoselective double aldol reactions from (+)-**17** with acrolein **19** and methacrolein **14** were carried out by a series of reactions analogous to Scheme 6. The aldol reaction of (+)-**17** with acrolein **19** proceeded in 89% yield with >99% de (Scheme 7); methanolysis afforded (+)-**20**[13] in 87% yield. Aldol reaction based on the Fráter's protocol with methacrolein **14** furnished diene **21**[13] in 70% (97% based on recovered SM) yield as a hardly separable diastereomeric mixture. To establish the relative stereochemistries of the components in **21**, the mixture was converted to the corresponding 1,3-acetonides **22a–c**,[13,22] which were separated by flash chromatography. NOE analysis permitted stereochemical assignment (Fig. 3).

Hydrolysis[23] of the major acetonide (+)-**22a** followed by RCM of (+)-**21a** (0.2 >equiv Grubbs catalyst, CH_2Cl_2, 40 °C) furnished cyclopentene (−)-**23**[13] in 69% yield. Selective protection of the less hindered allylic alcohol with TBSOTf (86% yield) followed by MnO_2 oxidation provided

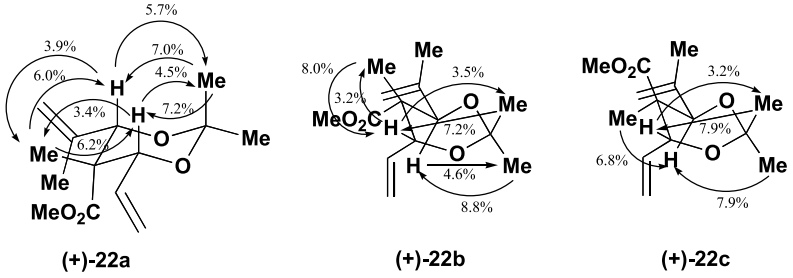
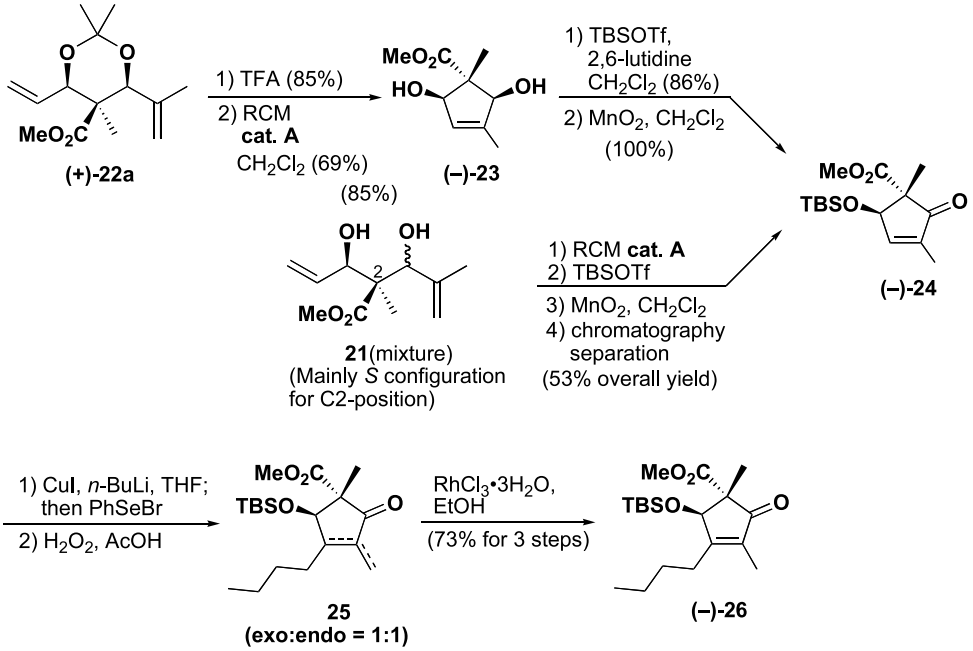
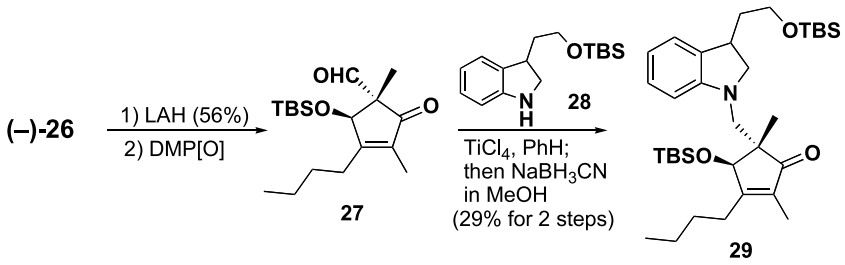


Figure 3. NOE analysis of (+)-**22a–c**.



Scheme 8. Synthesis of cyclopentenone (−)-**26**.



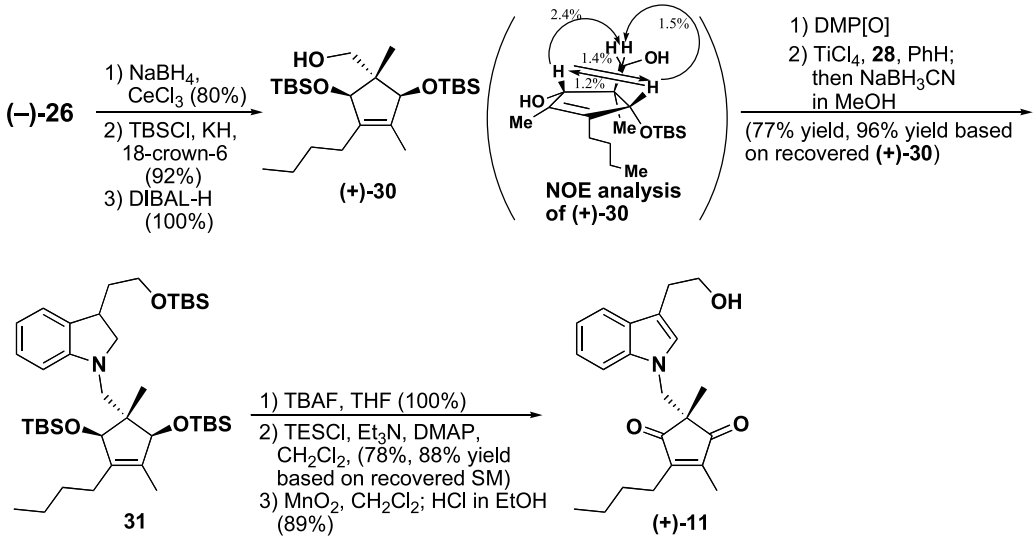
Scheme 9. Reductive amination **1**.

(−)-**24**[13] in quantitative yield (Scheme 8). For material advancement, the diastereomeric mixture of diene **21** was subjected directly to the RCM, and selective protection of the less hindered hydroxyl group, oxidation and flash chromatography separation provided (−)-**24** as a single diastereomer in 53% overall yield. Subsequent conjugate addition with *n*-Bu_2CuLi,[24] followed by phenylselenylation of the derived enolate with PhSeBr, and oxidative elimination using H_2O_2 under acidic conditions furnished a 1:1 mixture of *exo*/*endo* olefin isomers. Treatment of the mixture with $RhCl_3$[25] in aqueous EtOH converted the *exo* congener to the *endo* cyclopentenone (−)-**26**[13] in 73% overall yield from (−)-**24**.

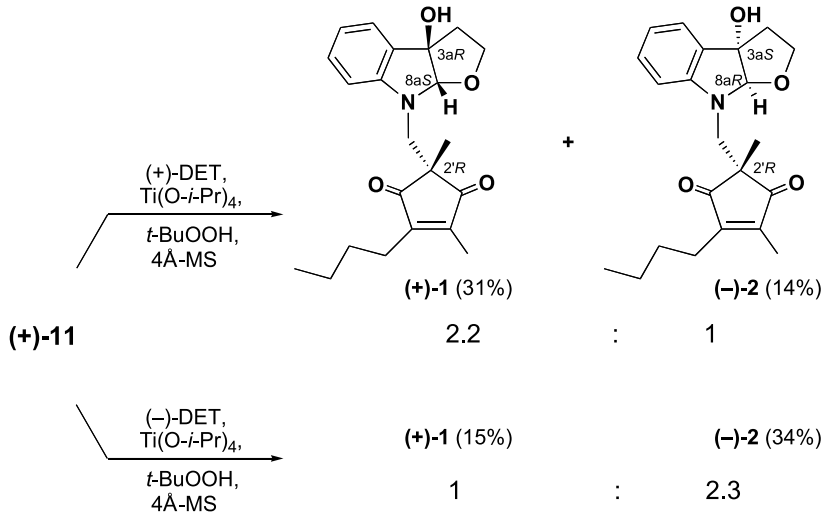
2.5. Fragment coupling and completion of total synthesis of the madindolines A and B

Having prepared the madindoline cyclopentene fragment (−)-**26**, the following steps were carried out to couple the indoline unit with the cyclopentene fragment and, thus, complete the total synthesis. As previously discussed, failure in the coupling of 3a-hydroxyfuroindoline with cyclopentene-dione led us to focus on the use of 3-(2-ethanol)-indoline as a precursor of 3a-hydroxyfuroindoline. To obtain the coupling partner, reduction of (−)-**26** with $LiAlH_4$, followed by Dess–Martin oxidation[26] provided ketoaldehyde **27** (Scheme 9). However, **27** was found to be very unstable due to deformylation. Therefore, **27** was subjected to the reductive amination with indoline **28** without purification. Several reaction conditions were attempted for this reductive amination. However, all of them resulted in poor yields, and the best result obtained by $TiCl_4$ treatment in PhH and $NaBH_3CN$ reduction in MeOH gave the desired product **29** in only 16% overall yield from (−)-**26**.[13]

This difficulty was probably associated with the instability of the aldehyde function due to the ketone group at the α-carbon. To avoid this problem, (−)-**26** was subjected to stereoselective reduction of the ketone group with $NaBH_4$ and $CeCl_3$,[27] silylation of the resulted allylic alcohol with TBSCl in the presence of KH and 18-crown-6,[28] and DIBAL-H reduction of the ester group to produce the primary alcohol (+)-**30**[13] (74% for the three steps), which is the precursor of the aldehyde. NOE analysis of (+)-**30** allowed stereochemical assignment (Scheme 10). To this end, the Dess–Martin oxidation[26] of (+)-**30** proceeded smoothly. The intermediate of an iminium salt was generated from aldehyde and **28** with $TiCl_4$ in PhH, and then the solution of $NaBH_3CN$ in MeOH was directly added to the iminium solution to furnish the desired *N*-alkylindoline **31**[13] as a diastereomeric mixture in 77% yield from (+)-**30** (96% based on recovered (+)-**30**). Finally, all protecting groups were removed by TBAF in THF, followed, in turn, by selective TES protection of the primary hydroxy group with TESCl and Et_3N, oxidation



Scheme 10. Reductive amination **2** and preparation of *N*-alkylindole (+)-**11**.



Scheme 11. Oxidative ring closing reaction of (+)-**11**.

of indoline and allyl alcohols with MnO_2, and acid hydrolysis of TES ether, producing indole (+)-**11**[13] in 69% yield from **31**.

In the final stage, we attempted the oxidative ring-closure reaction of (+)-**11** under a modified Sharpless asymmetric epoxidation protocol using (+)-diethyl tartrate (DET). This yielded (+)-madindoline A (+)-**1** and (−)-madindoline B (−)-**2** in 45% yield in a 2.2:1 ratio (Scheme 11). The (−)-DET ligand was also attempted and produced (+)-**1** and (−)-**2** in 49% yield with 1:2.3 ratio. In the case of this substrate, high diastereoselectivity was not observed. This was presumably due to steric hindrance by the bulky substitution on the nitrogen that interferes with the access of the Sharpless catalyst to the reaction site.

The synthetic crystalline (+)-madindoline A (+)-**1** was identical in all respects with natural (+)-**1** [400 MHz ^{1}H and 100 MHz ^{13}C NMR, IR, HRMS, optical rotation, mp, mmp, and TLC]. Synthetic (−)-madindoline B (−)-**2** was also identical with natural (+)-madindoline B (+)-**2** in all respects, except for the chiroptical properties {$[\alpha]_D^{25}$ −82.3 (*c* 0.62 MeOH); natural, $[\alpha]_D^{24}$ +25.6 (*c* 0.3 MeOH)}. Thus, (−)-madindoline B (−)-**2** is the enantiomer of natural (+)-**2**.

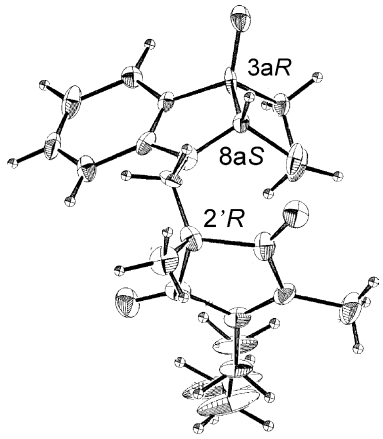


Figure 4. ORTEP plot for synthetic (+)-**1**.

Furthermore, confirmation of the relative and absolute stereochemistry in (+)-**1** and (+)-**2** was achieved by single crystal X-ray analysis of synthetic (+)-**1**[29] as shown in Figure 4. Based on these results, we were able to reveal the absolute stereochemistries of madindolines as shown in Figure 1, and show that these compounds are diastereomers of the C2′ position. In summary, the first asymmetric total synthesis of madindolines A and B has been achieved via a 19 linear sequence in 7.8% overall yield from commercially available materials.

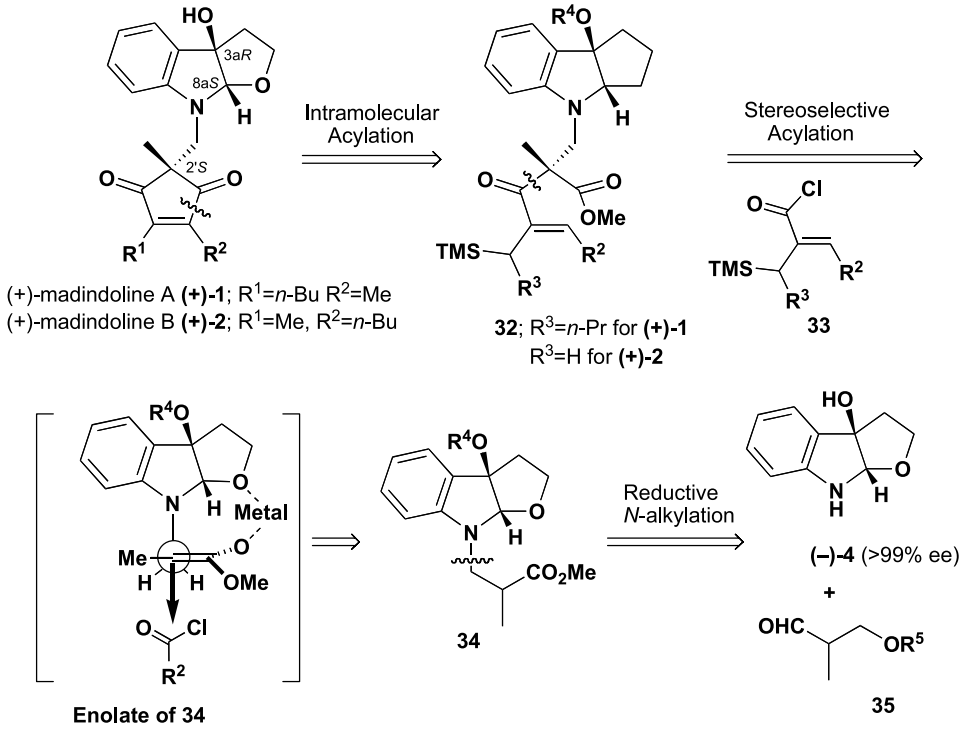
2.6. Synthetic strategy of (+)-madindolines for the second generation

As described above, we have achieved the first total synthesis and determined the absolute stereochemistries of madindoloines A and B. However, this first synthesis requires too many steps, especially for construction of the fully substituted cyclopentenedione core. In addition, the final oxidative ring-closure is not highly stereoselective. In this section, we report a more efficient and practical total synthesis of (+)-madindolines A (+)-**1** and B (+)-**2**. The retrosynthesic analysis of the second generation is outlined in Scheme 12.

The key reaction is the diastereoselective acylation of ester **34** with the α,β-unsaturated acid chloride **33**. We predicted that the lithium enolate of compound **34** would coordinate with oxygen of the furan ring on the chiral 3a-hydroxyfuroindoline to make a rigid conformation and that diastereoselective acylation would occur, producing **32**. Further, at the final stage, we expected that intramolecular acylation would occur with allylsilane compound **32**, directly yielding (+)-madindolines A (+)-**1** and B (+)-**2**. The chiral 3a-hydroxyfuroindoline (−)-**4** is available as an enantiomerically pure substrate by asymmetric oxidative ring-closure reaction of tryptophol **3**, which was developed in the first-generation synthesis.

2.7. Synthesis of *N*-alkyl-3a-hydroxyfuroindoline ester

First, we started with the known compound (+)-**36**[30] to



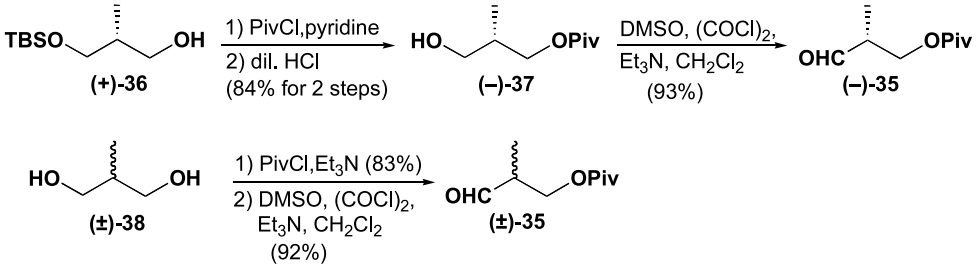
Scheme 12. Retrosynthetic analysis of (+)-madindolines A and B.

synthesize the enantiomerically pure aldehyde (−)-**35**, thus providing simple NMR spectra for all intermediates after the reductive amination sequence (Scheme 13). Pivaloyl protection of the hydroxy group of (+)-**36** followed by acid hydrolysis of the TBS protection furnished alcohol (−)-**37**[13] in 84% yield for two steps. Next, (−)-**37** was oxidized under Swern conditions to produce aldehyde (−)-**35**[13] in 93% yield without epimerization at the α-position. For material advancement on large-scale synthesis, we also prepared the racemic aldehyde (±)-**35**, because either epimer will generate the same enolate at the enolation stage of **34**. Actually, (±)-**35** was provided in high yield (76% for two steps) from the commercially available diol (±)-**38** via mono pivaloyl protection and Swern oxidation.

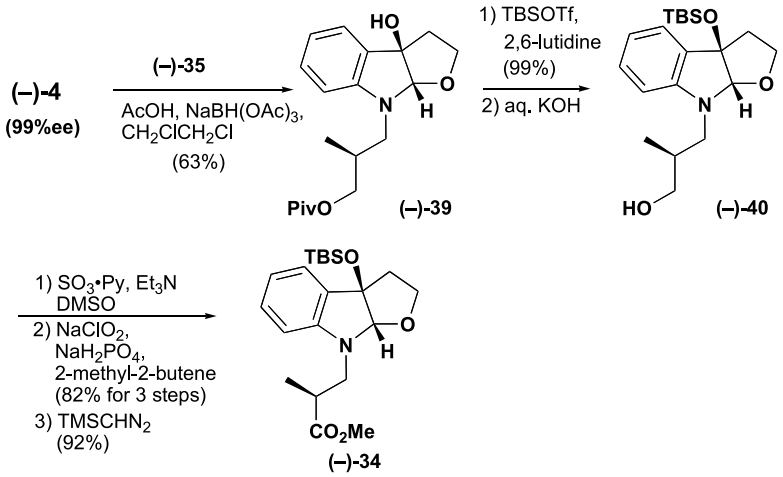
Next, reductive amination[31] of 3a-hydroxyfuroindoline (−)-**4** with aldehyde (−)-**35** using acetic acid in dichloroethane, followed by iminium reduction with sodium triacetoxyborohydride[32] provided the desired *N*-alkyl-3a-hydroxyfuroindoline (−)-**39**[13] in 63% yield on multi-gram scale (Scheme 14). Silylation of the tertiary alcohol with TBSOTf in the presence of 2,6-lutidine and hydrolysis of the pivaloyl ester under basic conditions generated the primary alcohol (−)-**40**.[13] SO_3·Pyridine oxidation of (−)-**40** provided an aldehyde, followed by successive sodium chlorite oxidation and esterification using TMS-diazomethene furnished methyl ester (−)-**34**[13] as a single diastereomer and enantiomer in 75% overall yield for the five steps. For material advancement, the same procedure was applied for synthesis of a diastereomeric mixture of **34** starting from the racemic aldehyde (±)-**35** and (−)-**4**, which generated **34** in good yield.

2.8. Construction of the quaternary carbon center in a model system

Reaction conditions to construct the required quaternary carbon center were examined by coupling methacrolein **14**, a simple aldol partner, to the methyl ester (−)-**34** for confirming the selectivity and the generation of the enolate of (−)-**34**, and the results are summarized in Table 2. To establish the conditions to form a rigid enolate (Scheme 12), we selected a few kinds of metal amines as the base. The best result, high yield and high selectivity at the quaternary carbon center was obtained using 2.5 equiv of LDA (entry 3). On the other hand, KDA as a base (entry 5) or LDA with



Scheme 13. Preparation of aldehyde **35**.



Scheme 14. Synthesis of methyl ester (−)-**34**.

HMPA (entry 6) did not match with this diastereoselective aldol reaction in both chelation ability of the metal and basicity. In all cases, selectivity of the quaternary carbon center was determined by ^{1}H NMR measurements of the oxidation product (−)-**42**.[13] Based on our hypothesis of the enolate structure shown in Scheme 12, the configuration shown in Table 2 is expected to be produced predominantly as the stereochemistry of the quaternary center.

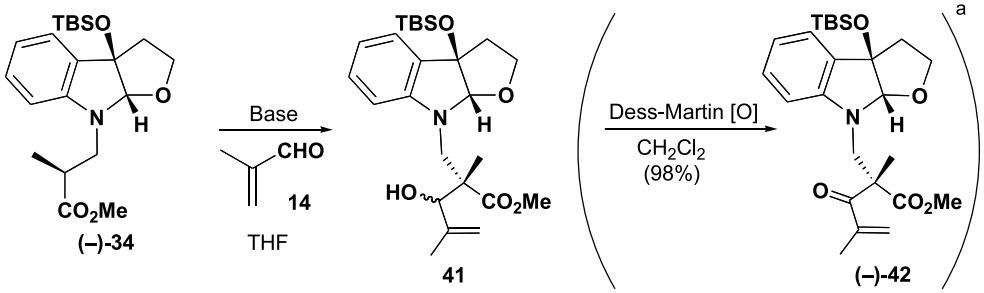
2.9. Preparation of allylsilane 33

Two kinds of allylsilanes (**33a** and **33b**), were synthesized by practical methods (Scheme 15) as building blocks for (+)-**1** and (+)-**2**. For a building block of (+)-**2**, alkylation of **43** with iodomethyltrimethylsilane,[33] followed by the Wittig–Horner reaction[34] with valeraldehyde led to the corresponding unsaturated ester **44**[13] as 3:1=*Z*:*E* isomeric mixture in 82% yield for the two steps. Hydrolysis of ethyl ester **44**, followed by chlorination with thionyl chloride generated (*Z*)-α,β-unsaturated acyl chloride **33b** as a single isomer[35] in 72% yield. For the synthesis of another allylsilane **33a**, Michael addition of trimethylsilyllithium to the ethyl 1-hexenoate **45**,[36] followed by aldol reaction of the derived enolate with acetaldehyde produced the β-hydroxyester **46**[13] in 72% yield as a diastereomeric mixture. Mesylation of **46**, followed by basic hydrolysis resulted in the corresponding unsaturated acid, which was treated with thionyl chloride to afford the (*Z*)-α,β-unsaturated acid chloride **33a** as a single isomer[35] in 96% yield for the three steps.

2.10. Diastereoselective acylation and completion of the synthesis

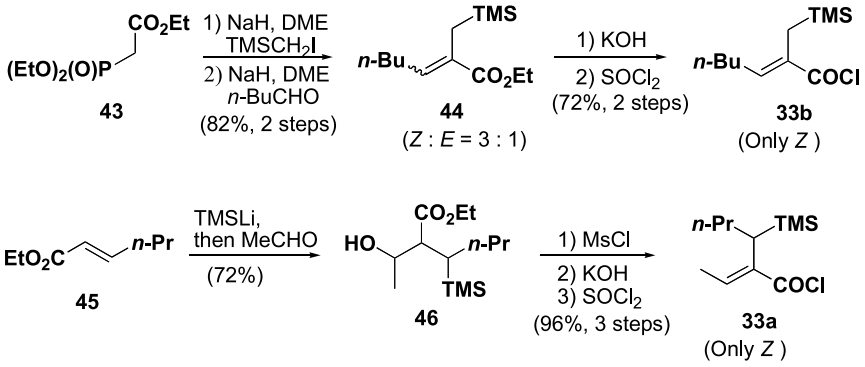
The final stages of the synthesis involved diastereoselective acylation of ester **34** carrying a 3a-hydroxyfuroindoline moiety with the acyl chloride **33a–b** and intramolecular acylation promoted by allyl silane. The ester (−)-**34** was treated with 2.5 equiv LDA followed by treatment with acyl chloride **33b** to afford the desired compound (−)-**32b**[13] as a

Table 2. Diastereoselective aldol reaction for the construction of the quaternary carbon center

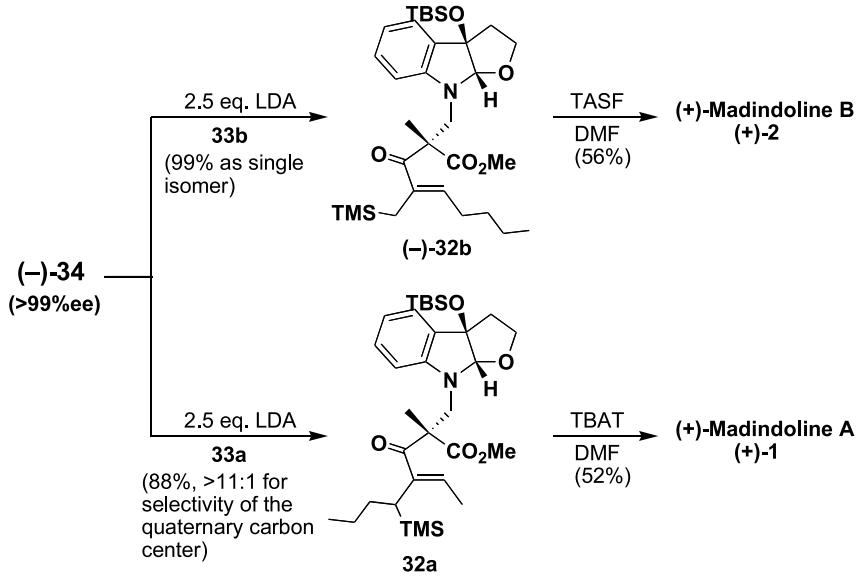


Entry	Reagents (equiv)	Temp. and time (for enolation)	Results	Selectivity to quaternary center[a]
1	LDA (1.1)	−78 °C; 2 h	No reaction	—
2	LDA (1.1)	−78 °C; 30 min 0 °C; 1 h	Complex	—
3	LDA (2.5)	−78 °C; 2 h	96%[b]	22:1
4	LTMP (2.5)	−78 °C; 2 h	95%[b]	17:1
5	KDA (2.5)	−78 °C; 2 h	37%[b]	2:1
6	LDA (2.5), HMPA	−78 °C; 2 h	34%[b]	2:1

[a] Stereochemistry of the quaternary carbon was not determined, and the ratio of selectivity was elucidated by ^{1}H NMR measurements of the oxidized ketone product of **41**.
[b] Yields were based on pure materials isolated by chromatography on SiO_2.



Scheme 15. Preparation of allylsilanes.



Scheme 16. The end games for total synthesis of (+)-madindolines A and B.

single isomer, in 99% yield (Scheme 16). The diastereomeric mixture of **34** for the α-methyl group, which was prepared from racemic aldehyde (±)-**35** by the same route as for (−)-**34**, was also subjected to this reaction, and produced the desired (−)-**32b** as a single diastereomer in 99% yield. Finally, an intramolecular endo cyclization of allylsilane (−)-**32b** using tris(dimethylamino)sulfur(trimethylsilyl)difluoride (TASF),[37] directly led to (+)-madindoline B (+)-**2** in 56% yield. The synthetic (+)-**2** was identical in all respects to a sample of the natural (+)-**2** (^{1}H and ^{13}C NMR, IR, HRMS, optical rotation, mp and mobility TLC). In addition, the absolute stereochemistry in (+)-**2** was confirmed by X-ray analysis of synthetic (+)-**2**[38] (Fig. 5).

On the other hand, in the total synthesis of (+)-madindoline A (+)-**1**, the stereoselective acylation of (−)-**34** with acyl chloride **33a** predominantly (>11:1 for selectivity of the quaternary carbon center) afforded the desired compound **32a**[13] in 88% yield. The diastereomeric mixture **34** also gave the desired **32a** under the same conditions. The intramolecular endo cyclization of allylsilane **32a** with triphenyldifluorosilicate (TBAT)[39] directly led to (+)-madindoline A (+)-**1** in 52% yield. The synthetic (+)-**1** was also identical in all respects with a sample of the natural (+)-**1** (^{1}H and ^{13}C NMR, IR, HRMS, optical rotation, mp and mobility TLC).

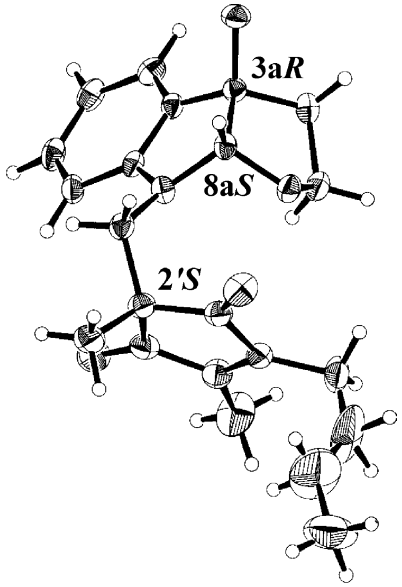
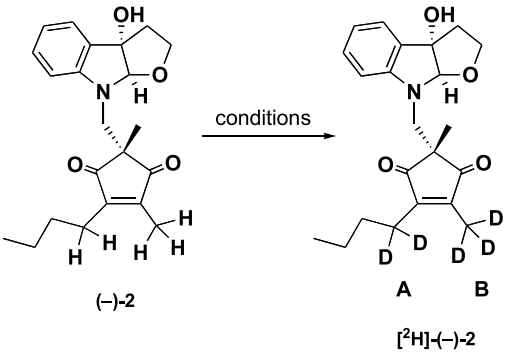


Figure 5. ORTEP plot of synthetic (+)-**2**.

Table 3. Deuteration of (−)-**2**



Entry	Reagents	Temp.	Time	Deuteration rates[a]		Recovered yield[b]
				A-position	B-position	
1	NaOMe (20 equiv) in CD_3OD	rt	7 h	90%	71%	95%
2	NaOMe (70 equiv), D_2O (50 equiv) in THF	rt	30 min	—		Complex
3	0.5 N NaOD in MeOH·D_2O(3:5)	rt	22 h	0%	49%	84%
4	1.0 N NaOD in MeOH·D_2O(3:5)	rt	22 h	0%	43%	73%
5	0.5 N KOD in *t*-BuOH·D_2O(3:5)	rt	20 h	86%	63%	71%

[a] The deuteration rate was determined by ^1H NMR.
[b] The recovered yields were based on pure materials isolated by chromatography on SiO_2.

2.11. Preparation of tritiated (+)-madindoline A [^{3}H]-(+)-1

Since madindolines are nonpeptidal low-molecular specific inhibitors of IL-6, studies on their action mechanism to IL-6 functions are expected to provide significant information about IL-6 dependent diseases as well as possible therapeutic uses of the compounds. After completion of the total syntheses of madindolines, we attempted to prepare of radioactively labeled madindoline A to facilitate the studies on its mode of action.[9]

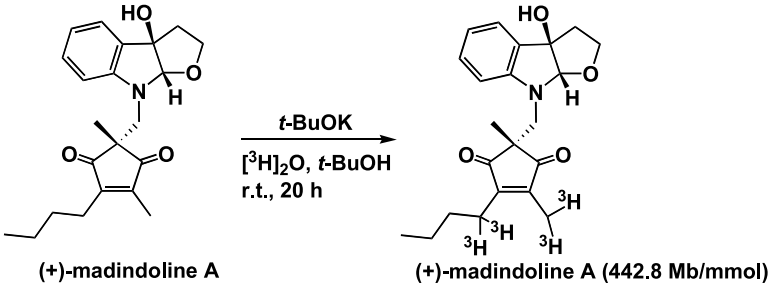
We tested deuteration of (−)-**2** with D_2O under a basic condition, prior to the preparation of tritiated (+)-**1** with ^3H_2O. The results are summarized in Table 3.

The conditions providing the highest deuteration rate with a good recovered yield were NaOMe in CD_3OD or 0.5 N NaOH in *t*-BuOH·D_2O (entry 1 or 5). Therefore, we chose the conditions of entry 5 to prepare the tritiated madindoline A ([^{3}H]-(+)-**1** 442.8 Mb/mmol) as shown in Scheme 17. In our recent paper,[9] we revealed the binding site of (+)-**1** in the complex of gp130, IL-6 and IL-6 receptor (IL-6R) by the use of [^{3}H]-(+)-**1**. IL-6 has three topological binding sites (sites I, II, and III),[40–42] whereas gp130 has two binding sites (sites 1 and 2).[43,44] IL-6 binds to the IL-6R via its site I and then to gp130 site 2 via site II, forming a trimeric IL-6/IL-6R/gp130 complex.[40] The trimeric complex then induces homodimerization of gp130 and forms a hexameric complex. We found that (+)-**1** binds to gp130 and inhibits the actions of IL-6 activity without inhibiting the formation of the IL-6/IL-6R/gp130 complex.[9]

2.12. Conclusion

In summary, in the first-generation synthesis, we completed the first asymmetric total synthesis of madindolines A and B via an efficient and convergent strategy (19 linear steps, 7.8% overall yield). The synthetic route not only provides access to these unique natural products, but also enabled us to define their relative and absolute stereochemistries for the first time. In the second-generation synthesis, we achieved a highly convergent total synthesis of (+)-madindolines A and B by exploiting the 3a-hydroxyfuroindoline function to permit rapid and efficient construction of the quaternary carbon center of madindolines with high selectivity. Importantly, the syntheses of (+)-**1** and **2** are highly efficient, proceeding in 16 and 19% overall yield for nine linear steps, respectively, stereocontrolled, and amenable to gram-scale production.

We also confirmed that synthetic (+)-madindoline A (+)-**1**



Scheme 17. Preparation of [^{3}H]-(+)-madindoline A.

markedly inhibited osteoclastogenesis in vitro and inhibited bone resorption in OVX mice in vivo, and the use of tritiated [^{3}H]-(+)-madindoline A revealed the mode of action for manifestation of inhibitory activity.[9] We believe that madindolines can serve as lead compounds for development of new drugs to treat refractory diseases known to involve IL-6.

3. Experimental

3.1. General

Dry THF, toluene, ethyl ether and CH_2Cl_2 were purchased from Kanto Chemical Co. Precoated silica gel plates with a fluorescent indicater (Merck 60 F254) were used for analytical and preparative thin layer chromatography. Flash column chromatography was carried out with Merk silica gel 60 (Art. 1.09385). ^{1}H and ^{13}C NMR spectra were measured on JEOL JNM-EX270 (270 MHz) or Varian VXR-300 (300 MHz) or Varian XL-400 (400 MHz) or Varian UNITY-400 (400 MHz). All infrared spectra were measured on a Horiba FT-210 spectrometer. Melting points were measured on a Yanagimoto Micro Melting Apparatus. High- and low-resolution mass spectra were measured on a JEOL JMS-DX300 and JEOL JMS-AX505 HA spectrometer. Elemental analysis data were measured on a Yanaco CHN CORDER MT-5. Single crystal X-ray spectra were measured on a Rigaku Automatic Four Cricle Diffractometer: AFC-5S. Melting points were measured on a Yanagimoto Micro Apparatus. Liquid chromatographic preparation was conducted on a Jasco PU-980 with Senshu Pak-PEGASIL ODS.

3.2. First generation synthesis

3.2.1. Asymmetric synthesis of (−)-3a-hydroxyfuroindoline (−)-4. *70 mg scale*. To a mixture of activated 4 Å molecular sieves (300 mg) in CH_2Cl_2 (42.5 ml) at −5 °C was added titanium(IV) isopropoxide (128 μl, 0.44 mmol) and (+)-diisopropyl tartrate (111 μl, 0.52 mmol) and the mixture was stirred for 30 min. The solution was cooled to −20 °C and stirred. After 30 min, *tert*-butylhydroperoxide (5.0 M in decane, 217 μl, 1.09 mmol) was added dropwise over 5 min, and the resulting mixture was stirred for 15 min at −20 °C. A solution of **3** (70 mg, 0.44 mmol) in CH_2Cl_2 (1.0 ml) was then added to reaction mixture over 5 min. After stirring for 6 h (all SM was consumed completely at this time), the reaction mixture was quenched with Et_2O (6 ml) and saturated aqueous Na_2SO_4 (0.5 ml), warmed to room temperature and stirred 2 h further. The resultant mixture was filtered through a celite, washing with $CHCl_3$ (3×10 ml). Preparative TLC (hexane/EtOAc=2:3) furnished (−)-**4** (53 mg, 0.30 mmol, 72% yield, 99% ee) as a colorless needle.

7.5 g scale. To a mixture of activated 4 Å molecular sieves (9.0 g) in CH_2Cl_2 (411 ml) at −5 °C was added titanium(IV) isopropoxide (24.7 ml, 83.7 mmol) and (+)-diisopropyl tartrate (19.8 ml, 93.1 mmol) and the mixture was stirred for 30 min. The reaction flask was equipped with −40 °C cooled bath and stirred. After 30 min, *tert*-butylhydroperoxide (5.0 M in decane, 23.3 ml, 116 mmol) was added dropwise over 5 min, and the resulting mixture was stirred for 15 min at −40 °C. A solution of **3** (7.5 g, 46.5 mmol) in CH_2Cl_2 (54 ml) was then added to reaction mixture over 5 min. After stirring for 1.5 h, the reaction mixture was quenched with Et_2O (315 ml) and saturated aqueous Na_2SO_4 (26.2 ml), warmed to 30 °C with water bath and stirred 2 h further. At this time, SM was not consumed completely, and it was not recovered from reaction mixture. The resultant mixture was filtered through a celite, washing with Et_2O (3×1 l), and the filtrate was concentrated to give crude oil. Flash chromatography (only $CHCl_3$) furnished (−)-**4** (4.5 g, 25.4 mmol, 55% yield, 99% ee) as a colorless needle: mp 65–67 °C; $[\alpha]_D^{25}$ −144 (*c* 0.84, $CHCl_3$); IR (KBr) 3435 (s), 3366 (m), 1614 (m), 1473 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (ddd, *J*=7.5, 1.5, 0.5 Hz, 1H), 7.12 (ddd, *J*=8.0, 7.2, 1.5 Hz, 1H), 6.80 (ddd, *J*=7.5, 7.2, 1.0 Hz, 1H), 6.59 (ddd, *J*=8.0, 1.0, 0.5 Hz, 1H), 5.34 (s, 1H), 4.56 (broad s, 1H), 4.01 (ddd, *J*=9.0, 7.5, 2.5 Hz, 1H), 3.63 (ddd, *J*=11.0, 9.0, 5.5 Hz, 1H), 2.70 (broad s, 1H), 2.42 (ddd, *J*=12.0, 11.0, 7.5 Hz, 1H), 2.32 (ddd, *J*=12.0, 5.5, 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5, 130.3, 130.1, 124.1, 119.8, 109.5, 99.4, 89.3, 67.3, 40.8, HRMS (EI) *m/z* 177.0783 [(M)$^+$, Calcd for $C_{10}H_{11}NO_2$: 177.0790]; Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N. 7.91, Found: C, 67.46; H, 6.31; N. 7.70.

3.2.2. *N*-Methyl-3a-hydroxyfuroindoline. At room temperature, (−)-**4** (100 mg, 0.57 mmol) was diluted MeI·THF (1/2 v/v, 2.8 ml) and the mixture was warmed to 40 °C and stirred for 13 h. The resultant mixture was concentrated to afford crude products. Preparative TLC (hexane/EtOAc=1:2) furnished *N*-methyl-3a-hydroxyfuroindoline (14 mg, 13% yield) as a brown oil: $[\alpha]_D^{22}$ −85.5 (*c* 1.12, $CHCl_3$); IR (KBr) 3413, 1612, 1495 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.27 (ddd, *J*=7.6, 1.3, 0.7 Hz, 1H), 7.21 (ddd, *J*=8.0, 7.2, 1.3 Hz, 1H), 6.73 (ddd, *J*=7.6, 7.2, 1.0 Hz, 1H), 6.43 (ddd, *J*=8.0, 1.0, 0.7 Hz, 1H), 5.20 (s, 1H), 4.08, 3.61 (m, each 1H), 2.92 (s, 3H), 2.45, 2.32 (m, each 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 150.9, 130.4, 130.2, 123.6, 117.7, 105.9, 104.9, 87.8, 67.4, 41.1, 31.2; HRMS (FAB, NBA, PEG200 matrix) *m/z*: 192.1019 [(M+H)$^+$, Calcd for $C_{11}H_{14}O_2N$: 192.1025].

3.2.3. 3a-[(*S*)-α-Methoxy-α-trifluoromethylphenyl-acetoxy]-*N*-methylfuroindoline (−)-5. At room temperature a solution of *N*-methyl-3a-hydroxyfuroindoline (10 mg, 0.053 mmol) in THF (1.1 ml) was treated with *(S)*-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (31 mg, 0.13 mmol) and dicyclohexylcarbodiimide (66 mg, 0.32 mmol). A white precipitate formed immediately. The resultant mixture was warmed to 80 °C, stirred for 4.5 h, quenched with H_2O (3 ml), and extracted with dichloromethane (3×5 ml). The combined extracts were dried over sodium sulfate, filtered and concentrated. Preparative TLC (2/1= hexanes/EtOAc) gave (−)-**5** (11 mg, 51% yield) as a light yellow crystal: mp: 100–102 °C ($CHCl_3$); $[\alpha]_D^{24}$ −143.0 (*c* 1.07, $CHCl_3$); IR (KBr) 1747, 1612, 1495, 1454 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.43–7.33 (complex m, 5H), 7.23 (t, *J*=7.6 Hz, 1H), 7.22 (d, *J*=7.6 Hz, 1H), 6.88 (t, *J*=7.6 Hz, 1H), 6.47 (d, *J*=7.6 Hz, 1H), 5.60 (s, 1H), 4.06, 3.59 (m, each 1H), 3.51 (s, 3H), 2.99 (s, 3H), 2.63 (m, 2H); HRMS (FAB, NBA, PEG400 matrix) *m/z*: 407.1342 [(M)$^+$, Calcd for $C_{21}H_{20}O_4NF_3$: 407.1344].

3.2.4. *N*-Isopropyl-3a-hydroxyfuroindoline (−)-6. At 0 °C, a solution of (−)-**4** (25 mg, 0.14 mmol) and isobutylaldehyde (64 μl, 0.14 mmol) in EtOH (0.21 ml) was treated with AcONa (58 mg, 0.71 mmol) and AcOH (0.11 ml), then added $NaBH_3CN$ (151 mg, 2.4 mmol, portionwise over 30 min), and the resultant mixture was stirred for 20 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (2.5 ml). The resultant mixture was extracted with $CHCl_3$ (3×6 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Preparative TLC (hexane/EtOAc=1:1) provided (−)-**6** (21 mg, 62% yield) as a light brown solid and *N*-isobutylindole (7.9 mg, 26%) as a light brown oil. (−)-**6**: mp: 53–55 °C ($CHCl_3$); $[\alpha]_D^{20}$ −96.3 (*c* 0.60, $CHCl_3$); IR (KBr) 3392, 1610, 1489, 1466 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.27 (d, J=7.6 Hz, 1H), 7.17 (t, J=7.6 Hz, 1H), 6.70 (t, J=7.6 Hz, 1H), 6.44 (d, J=7.6 Hz, 1H), 5.23 (s, 1H), 4.03, 3.59 (m, each 1H), 3.11 (dd, J=14.2, 7.9 Hz, 1H), 2.99 (dd, J=14.2, 6.9 Hz, 1H), 2.44, 2.32 (m, each 1H), 2.21 (s, 1H), 2.06 (m, 1H), 0.96, 0.94 (d, J=6.6 Hz, each 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 151.2, 130.3, 129.8, 123.7, 117.3, 105.9, 104.6, 87.9, 67.0, 53.8, 41.3, 28.0, 20.5, 20.4; HR-MS (FAB, NBA, PEG200 matrix) *m/z*: 233.1416 $[(M)^+$, Calcd for $C_{14}H_{19}O_2N$: 233.1416]; *N*-isobutylindole: IR (KBr) 3400, 1468, 1481 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.61 (dd, J=7.9, 1.0 Hz, 1H), 7.32 (d, J=8.2 Hz, 1H), 7.22 (ddd, J=8.2, 7.3, 1.0 Hz, 1H), 7.11 (dd, J=7.9, 7.3 Hz, 1H), 6.97 (s, 1H), 3.90 (t, J=6.3 Hz, 2H), 3.88 (d, J=7.3 Hz, 2H), 3.03 (t, J=6.3 Hz, 2H), 2.19 (m, 1H), 0.93 (d, J=6.6 Hz, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 136.8, 127.8, 126.9, 121.5, 118.9, 118.8, 110.3, 109.7, 62.7, 54.0, 29.5, 28.7, 20.3, 20.3; HR-MS (FAB, NBA, PEG200 matrix) *m/z*: 217.1464 $[(M)^+$, Calcd for $C_{14}H_{19}ON$: 217.1467].

3.2.5. *N*-Neopentyl indole 7. At 0 °C, a solution of (−)-**4** (23 mg, 0.13 mmol) and pivalaldehyde (70 μl, 0.65 mmol) in EtOH (0.21 ml) was treated with AcONa (53 mg, 0.65 mmol) and AcOH (0.11 ml), then added $NaBH_3CN$ (138 mg, 2.2 mmol, portionwise over 30 min), and the resultant mixture was stirred for 20 min. The reaction was quenched with saturated aqueous $NaHCO_3$ (2.5 ml). The resultant mixture was extracted with $CHCl_3$ (3×6 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Preparative TLC (hexane/EtOAc=1:1) provided **7** (24 mg, 80% yield) as a light yellow oil: IR (KBr) 3415, 3055, 1466, 1481 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.61 (dd, J=7.9, 1.3 Hz, 1H), 7.35 (dd, J=8.3, 1.0 Hz, 1H), 7.22 (ddd, J=8.3, 6.9, 1.3 Hz, 1H), 7.11 (ddd, J=7.9, 6.9, 1.0 Hz, 1H), 6.97 (s, 1H), 3.90 (dd, J=6.6, 6.3 Hz, 2H), 3.87 (s, 2H), 3.04 (dd, J=6.6, 6.3 Hz, 2H), 1.24 (broad s, 1H), 1.02 (s, 9H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 137.7, 128.1, 127.4, 121.5, 118.7, 118.6, 110.3, 110.3, 62.7, 57.7, 34.3, 28.6, 28.2; HREIMS *m/z*: 231.1637 $[(M)^+$, Calcd for $C_{15}H_{21}NO$: 231.1623]; Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.06. Found: C, 77.50; H, 9.11; N, 6.13.

3.2.6. Reductive amination of 3. A solution of **3** (33 mg, 0.20 mmol) and pivalaldehyde (67 μl, 0.61 mmol) in benzene (10.3 ml) was treated with *p*-TsOH·H_2O (12 mg, 0.61 μmol), warmed to 95 °C, and stirred for 10 min. The solution was then cooled to room temperature and concentrated. The crude mixture was dissolved in dry MeOH (2.0 ml), and added bromocresol green (2 mg) and $NaBH_3CN$ (39 mg, 0.61 mmol) at room temperature. pH was kept below 4 by addition of concd HCl solution while stirring. After stirring for 2 h, the reaction mixture was cooled to room temperature, and concentrated to give crude products. The mixture was diluted with $CHCl_3$ (20 ml), 5% KOH aq solution (4 ml) and H_2O (7 ml), and stirred. The organic layer was separated, and aqueous layer was extracted with $CHCl_3$ (3×25 ml). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Preparative TLC (hexane/EtOAc=2:1) provided **7** (10 mg, 22% yield) as a light yellow oil and **8** (15 mg, 29%) as a light yellow oil. Compound **8**. ^1H NMR (270 MHz, $CDCl_3$) δ 7.84 (broad s, 1H), 7.54 (dd, J=7.6, 1.3 Hz, 1H), 7.36 (dd, J=7.6, 1.3 Hz, 1H), 7.19 (ddd, J=7.6, 6.9, 1.3 Hz, 1H), 7.13 (ddd, J=7.6, 6.9, 1.3 Hz, 1H), 4.50 (s, 1H), 3.65, 4.29 (m, each 1H), 2.68, 2.95 (m, each 1H), 1.24 (s, 1H), 1.11 (s, 9H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 136.1, 134.0, 127.2, 122.1, 119.9, 118.6, 111.2, 81.6, 65.5, 46.4, 36.6, 26.8, 23.1.

3.2.7. 3-(2-Hydroxyethyl)-indoline 9. A solution of 2-(3-indole)-ethanol **3** (1.00 g, 6.21 mmol) in acetic acid (36.5 ml) was cooled to 0 °C and $NaBH_3CN$ (1.95 g, 31.0 mmol) was added. The reaction mixture was warmed to room temperature, stirred for 3.5 h, and then quenched with H_2O (150 ml) and $NaHCO_3$ (50 g). The mixture was extracted with $CHCl_3$ (3×200 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (1.0% MeOH/$CHCl_3$) provided **9** (1.01 g, 6.20 mmol, 100% yield) as a brown oil: IR (KBr) 3338 (s), 3049 (s), 1606 (s), 1487 (m), 1464 (m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.10 (d, J=7.9 Hz, 1H), 7.06 (dd, J=7.9, 7.3 Hz, 1H), 6.76 (dd, J=7.6, 7.3 Hz, 1H), 6.68 (d, J=7.6 Hz, 1H), 3.74–3.55 (complex m, 2-H, 3H), 3.44 (m, 1H), 3.28 (dd, J=8.6, 5.9 Hz, 1H), 3.10 (bs, 1H), 2.09 (m, 1H), 1.79 (m, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 151.0, 132.4, 127.5, 124.0, 119.1, 109.9, 60.6, 53.5, 39.0, 37.0; HRMS (EI) *m/z*: 163.0998 $[M^+$; Calcd for $C_{10}H_{13}NO$: 163.0997]; Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.94; H, 8.05; N, 8.41.

3.2.8. *N*-(2,2-Dimethylpropyl)-3-(2-hydroxyethyl)-indoline 10. At 0 °C, to a solution of **9** (249 mg, 1.52 mmol), pivalaldehyde (55 μl, 0.51 mmol) and Ph_3P (73 mg, 0.28 mmol) in benzene (2.5 ml) was added $TiCl_4$ (1.0 M in toluene, 278 μl, 0.28 mmol). The solution was stirred for 1 h, and the mixture was then added to a solution of $NaBH_3CN$ (96 mg, 1.52 mmol) in methanol (5.1 ml) and stirred for 1 h. The solution was quenched with H_2O (10 ml) and 5% KOH aq solution (8 ml), extracted with $CHCl_3$ (3×25 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (6% EtOAc/hexanes) provided **10** (105 mg, 89% yield based on pivalaldehyde) as a yellow oil: IR (KBr) 3373, 3050, 1606, 1489, 1460 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.09 (1H, dd, J=7.9, 7.3 Hz, 1H), 7.07 (1H, d, J=7.6 Hz, 1H), 6.67 (1H, td, J=7.6, 7.3 Hz, 1H), 6.47 (1H, d, J=7.9 Hz, 1H), 3.73 (m, 2H), 3.62 (td, J=8.9, 8.6 Hz, 1H), 3.39 (m, 1H), 3.23 (1H, dt, J=8.6, 6.3 Hz, 1H), 2.79 (s, 1H,), 2.10, 1.83 (m, each 1H), 1.00 (s, 9H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 153.9, 132.3, 127.9, 123.7, 117.2, 106.9, 64.0, 63.7, 61.1, 38.0, 37.5, 34.1, 28.4; HREIMS *m/z*: 233.1788 $[M]^+$, Calcd for $C_{15}H_{23}NO$: 233.1780 [M]; Anal.

Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 76.98; H, 9.67; N, 6.12.

3.2.9. *N*-(2,2-Dimethylpropyl)-3-(2-hydroxyethyl)-indole 7. At room temperature a solution of **10** (171 mg, 0.73 mmol) in CH_2Cl_2 (14.7 ml) was treated with manganese(IV) dioxide (868 mg, 10.0 mmol), and the solution was sonicated (38 kHz) for 2 h. The reaction mixture was filtered and concentrated. The flash chromatography (6% EtOAc/hexanes) afforded **7** (168 mg, 99% yield) as a yellow oil.

3.2.10. [(2*S*,3*R*),4*S*]-3-(3-Hydroxy-2-methyl-4-methyl-ideneoctanoyl)-4-isopropyl-2-oxazolidinone. To a solution of imide (+)-**17** (107 mg, 0.58 mmol) in CH_2Cl_2 (1.2 ml) at −78 °C was added Et_3N (137 μl, 0.98 mmol), followed by *n*-Bu_2BOTf (1.0 M in CH_2Cl_2, 870 μl, 0.87 mmol). The solution was stirred for 1 h at −78 °C and for 45 min at 0 °C. After the solution was recooled to −78 °C, 2-butylacrolein (1.0 M in CH_2Cl_2, 750 μl, 0.75 mmol) was added. The reaction mixture was warmed to 0 °C, stirred for 45 min, and then quenched with methanol (4.5 ml), pH 7.0 phosphate buffer (1.5 ml) and 30% aqueous H_2O_2 (0.45 ml), and stirred for 20 min further. The resultant mixture was extracted with $CHCl_3$ (3×6 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (20% EtOAc/hexanes) provided [(2*S*,3*R*),4*S*]-3-(3-hydroxy-2-methyl-4-methyl-ideneoctanoyl)-4-isopropyl-2-oxazolidinone (139 mg, 81% yield) as a colorless solid: $[\alpha]_D^{24}$ +49.1 (*c* 1.29, $CHCl_3$); IR (KBr) 3496, 1782 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.18, 4.98 (s, each 1H), 4.46 (m, 1H), 4.42 (bs, 1H), 4.28 (dd, J=17.2, 9.2 Hz, 1H), 4.22 (dd, J=9.2, 3.0 Hz, 1H), 3.96 (dq, J=6.9, 3.0 Hz, 1H), 3.10 (bs, 1H), 2.35 (m, 1H), 1.98 (m, 2H), 1.38 (m, 4H), 1.18 (d, J=6.9 Hz, 3H), 0.92 (d, J=6.9 Hz, 3H), 0.90 (t, J=7.3 Hz, 3H), 0.88 (d, J=6.9 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 177.7, 153.4, 147.9, 110.5, 72.8, 63.4, 58.3, 40.1, 32.5, 30.1, 28.3, 22.5, 17.9, 14.7, 13.9, 10.5; HRMS (FAB, NBA, NaI matrix) *m/z*: 320.1840 $[(M+Na)^+$, Calcd for $C_{16}H_{27}O_4NNa$: 320.1838].

3.2.11. (2*S*,3*R*)-3-Hydroxy-2-methyl-4-methylidene-octanoic acid methyl ester (−)-15. A solution of [(2*S*,3*R*),4*S*]-3-(3-hydroxy-2-methyl-4-methylidene-octanoyl)-4-isopropyl-2-oxazolidinone (20 mg, 0.0068 mmol) in methanol (0.68 ml) was cooled to 0 °C and sodium methoxide (4.1 mg, 0.075 mmol) was added. The reaction mixture was stirred for 15 min at 0 °C and quenched with saturated aqueous NH_4Cl (2 ml). The mixture was then extracted with $CHCl_3$ (3×5 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (5% EtOAc/hexanes) provided (−)-**15** (12 mg, 91% yield) as a colorless liquid: $[\alpha]_D^{24}$ −8.1 (*c* 1.21, $CHCl_3$); IR (KBr) 3485, 1736, 1647 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.13, 4.96 (s, each 1H), 4.45 (bs, 1H), 3.71 (s, 3H), 2.69 (m, 1H), 2.47 (bs, 1H), 1.98 (m, 2H), 1.40 (m, 4H), 1.12 (d, J=7.3 Hz, 3H), 0.91 (t, J=7.3 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 176.2, 148.3, 110.3, 73.9, 51.8, 42.3, 32.1, 29.9, 22.4, 13.9, 10.1.

3.2.12. [(1ξ),2*R*,3*R*]-3-Hydroxy-2-(1-hydroxy-2-methyl-2-propenyl)-2-methyl-4-methylideneoctanoic acid methyl ester (13). To a solution of LHMDS (1.0 M in THF, 0.48 ml, 0.48 mmol) at −78 °C was added (−)-**15** (42 mg, 0.21 mmol) in THF (0.42 ml) over 15 min. The solution was warmed to −20 °C and stirred for 30 min. After the solution was recooled to −78 °C, methacrolein (52 μl, 0.62 mmol) was added. The reaction was stirred for 12 min at −78 °C and then quenched with saturated aqueous NH_4Cl (2.0 ml), warmed to room temperature and stirred 5 min further. The resultant mixture was extracted with EtOAc (3×8 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (25% EtOAc/hexanes) furnished **13** (30 mg, 54% yield, 96% based on recovered (−)-**15**) as a colorless oil and recovered (−)-**15** (18 mg, 44%). For main product of **13**: IR (KBr) 3467, 1697, 1643 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.03, 5.01 (s, each 1H), 4.97, 4.93 (s, each 1H), 4.39 (d, J=5.6 Hz, 1H), 4.25 (d, J=6.6 Hz, 1H), 3.73 (s, 3H), 3.72 (bd, J=5.6 Hz, 1H), 3.33 (bd, J=6.6 Hz, 1H), 2.11, 1.93 (m, each 1H), 1.67 (s, 3H), 1.31 (m, 4H), 0.97 (s, 3H), 0.89 (t, J=6.9 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 177.1, 148.7, 143.6, 115.7, 113.6, 79.9, 79.2, 53.1, 52.2, 32.1, 30.6, 22.5, 18.4, 14.9, 14.0; HRMS (FAB, NBA, PEG 200 matrix) *m/z*: 271.1911 $[(M+H)^+$, Calcd for $C_{15}H_{27}O_4$: 271.1909].

3.2.13. [(2*S*,3*R*),4*S*]-3-(3-Hydroxy-2-methyl-4-pentenoyl)-4-isopropyl-2-oxazolidinone. To a solution of imide (+)-**17** (100 mg, 0.541 mmol) in CH_2Cl_2 (1.1 ml) at −78 °C was added Et_3N (90.6 μl, 0.650 mmol), followed by *n*-Bu_2BOTf (1.0 M in CH_2Cl_2, 596 μl, 0.596 mmol). The solution was stirred for 1 h at −78 °C and for 45 min at 0 °C. After the solution was recooled to −78 °C, 90% acrolein (52.3 μl, 0.704 mmol) in CH_2Cl_2 (0.70 ml) was added. The reaction mixture was stirred for 30 min at −78 °C and then quenched with methanol (1.1 ml), pH 7.0 phosphate buffer (1.2 ml) and 30% aqueous H_2O_2 (0.6 ml), warmed to 0 °C and stirred 20 min further. The resultant mixture was extracted with $CHCl_3$ (3×10 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (20% EtOAc/hexanes) provided [(2*S*,3*R*),4*S*]-3-(3-hydroxy-2-methyl-4-pentenoyl)-4-isopropyl-2-oxazolidinone (116.6 mg, 0.484 mmol, 89% yield) as a colorless solid: mp 42–44 °C; $[\alpha]_D^{26}$ +125.0 (*c* 0.74, MeOH); IR (KBr) 3453 (s), 1780 (s), 1697 (S), 1387 (s), 1302 (m), 1230 (s), 1205 (s), 989 (m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.81 (ddd, J=17.2, 10.6, 5.3 Hz, 1H), 5.31 (dd, J=17.2, 1.7 Hz, 1H), 5.18 (dd, J=10.6, 1.7 Hz, 1H), 4.45 (m, 2H), 4.26 (dd, J=13.5, 9.2 Hz, 1H), 4.19 (dd, J=9.2, 3.3 Hz, 1H), 3.85 (dq, J=7.3, 3.6 Hz, 1H), 3.05 (bs, 1H), 2.32 (m, 1H), 1.21 (d, J=7.3 Hz, 3H), 0.90 (d, J=7.3 Hz, 3H), 0.86 (d, J=6.9 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 176.9, 153.5, 137.3, 116.1, 72.2, 63.3, 58.2, 42.4, 28.3, 17.8, 14.2, 11.2; HRMS (FAB, NBA matrix) *m/z* 242.1393 $[(M+H)^+$; Calcd for $C_{12}H_{20}O_4N$: 242.1392]. Anal. Calcd for $C_{12}H_{19}O_4N$: C, 59.73; H, 7.94; N, 5.81. Found: C, 59.51; H, 7.82; N, 5.80.

3.2.14. (2*S*,3*R*)-3-Hydroxy-2-methyl-4-pentenoic acid methyl ester (+)-20. To a solution of [(2*S*,3*R*),4*S*]-3-(3-hydroxy-2-methyl-4-pentenoyl)-4-isopropyl-2-oxazolidinone (3.99 g, 16.6 mmol) in methanol (166 ml) at 0 °C was added sodium methoxide (984 mg, 18.2 mmol). The reaction mixture was stirred for 30 min at 0 °C and quenched with saturated aqueous NH_4Cl (100 ml). The mixture was

then extracted with $CHCl_3$ (3×300 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (6.7% EtOAc/hexanes) provided (+)-**20** (2.07 g, 14.4 mmol, 87% yield) as a colorless liquid: $[\alpha]_D^{24}$ +30.0 (*c* 0.94, MeOH); IR (KBr) 3434 (s), 2929 (s), 1728 (m), 1639 (m), 1461 (m), 1105 (m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.82 (ddd, J=17.2, 10.6, 5.6 Hz, 1H), 5.32 (dd, J=17.2, 1.3 Hz, 1H), 5.19 (dd, J=10.6, 1.3 Hz, 1H), 4.39 (m, 1H), 3.69 (s, 3H), 2.72 (bs, 1H), 2.63 (dq, J=7.3, 4.3 Hz, 1H), 1.16 (d, J=7.3 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 116.3, 137.3, 175.7, 11.2, 44.6, 51.3, 73.1.

3.2.15. [(1*R*),2*S*,3ξ]-3-Hydroxy-2-(1-hydroxy-2-propenyl)-2,4-dimethyl-4-pentenoic acid methyl ester (21). To a solution of LHMDS (1.0 M in THF, 1.68 ml, 1.68 mmol) at −78 °C was added (+)-**20** (121 mg, 0.842 mmol) in THF (1.68 ml) over 15 min. The solution was warmed to −20 °C and stirred for 30 min. After the solution was recooled to −78 °C, methacrolein (83.6 µl, 1.01 mmol) in THF (1.68 ml) was added. The reaction was stirred for 12 min at −78 °C and then quenched with saturated aqueous NH_4Cl (5.0 ml), warmed to room temperature and stirred 5 min further. The resultant mixture was extracted with EtOAc (3×15 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (33% EtOAc/hexanes) furnished **21** (126 mg, 0.589 mmol, 70% yield, 97% based on recovered (+)-**20** and recovered (+)-**20** (33.5 mg, 0.233 mmol, 28%).

3.2.16. Isopropylidene acetal (+)-22a–c. To a solution of **21** (109 mg, 0.509 mmol) and camphorsulfonic acid (59.1 mg, 0.254 mmol) in CH_2Cl_2 (5.1 ml) at 0 °C was added 2-methoxypropene (146 µl, 1.53 mmol). The reaction mixture was stirred for 15 min at 0 °C and quenched with saturated aqueous $NaHCO_3$ (2.5 ml). The mixture was then extracted with $CHCl_3$ (3×10 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (1.0% EtOAc/hexanes) provided (+)-**22c** (14.1 mg, 0.0555 mmol, 11% yield) as a colorless liquid, (1.0% EtOAc/hexanes) provided (+)-**22b** (22.6 mg, 0.0890 mmol, 18% yield) as a colorless liquid and (5.0% EtOAc/hexanes) provided (+)-**22a** (70.1 mg, 0.276 mmol, 54% yield) as a colorless liquid. (+)-**22c**: $[\alpha]_D^{25}$ +65.3 (*c* 1.16, MeOH); IR (KBr) 2929 (m), 1730 (s), 1643 (m), 1381 (m), 1225 (s), 1016 (m), 989 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.66 (ddd, J=17.4, 10.7, 5.8 Hz, 1H), 5.26 (d, J=17.4 Hz, 1H), 5.16 (d, J=10.7 Hz, 1H), 5.03 (s, 1H), 4.98 (d, J=5.8 Hz, 1H), 4.90 (s, 1H), 3.91 (s, 1H), 3.63 (s, 3H), 1.74 (s, 3H), 1.47 (s, 3H), 1.39 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 142.1, 133.9, 116.6, 112.9, 101.7, 79.2, 72.8, 54.4, 51.6, 24.7, 23.4, 20.4, 17.0,; MS (FAB, NBA matrix) m/z 255 $[M+H]^+$. (+)-**22b**: $[\alpha]_D^{25}$ +59.4 (*c* 0.67, MeOH); IR (KBr) 2933 (m), 1732 (s), 1647 (m), 1381 (w), 1225 (s), 1095 (m), 991 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.70 (ddd, J=17.3, 10.5, 6.3 Hz, 1H), 5.31 (d, J=17.3 Hz, 1H), 5.18 (d, J=10.5 Hz, 1H), 5.02 (s, 1H), 4.89 (s, 1H), 4.82 (s, 1H), 3.89 (d, J=6.3 Hz, 1H), 3.69 (s, 3H), 1.54 (s, 3H), 1.47 (s, 3H), 1.40 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 141.2, 132.9, 117.5, 111.6, 101.8, 77.5, 74.1, 53.0, 51.9, 24.4, 24.0, 20.3, 15.5; MS (FAB, NBA matrix) m/z 255 $[M+H]^+$. (+)-**22a**: $[\alpha]_D^{25}$ +11.9 (*c* 0.36, MeOH); IR (KBr) 2949 (m), 1716 (s), 1647 (w), 1385 (m), 1228 (s), 1088 (m), 987 (w) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.71 (ddd, J=17.3, 10.5, 7.2 Hz, 1H), 5.34 (d, J=17.3 Hz, 1H), 5.26 (d, J=10.5 Hz, 1H), 5.01 (s, 1H), 4.99 (s, 1H), 4.18 (s, 1H), 4.12 (d, J=7.2 Hz, 1H), 3.68 (s, 3H), 1.68 (s, 3H), 1.54 (s, 3H), 1.52 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 141.3, 133.5, 119.5, 115.9, 98.8, 79.9, 77.5, 51.3, 46.4, 29.8, 18.9 (2 C), 18.4; MS (FAB, NBA matrix) m/z 255 $[M+H]^+$.

3.2.17. [(1*R*),2*S*,3*S*]-3-Hydroxy-2-(1-hydroxy-2-propenyl)-2,4-dimethyl-4-pentenoic acid methyl ester (21). To a solution of (+)-**22a** (51.3 mg, 0.202 mmol) in $THF \cdot H_2O$ (4/1 v/v, 0.84 ml) at 0 °C was added trifluoroacetic acid (0.17 ml). The reaction mixture was warmed to room temperature. The reaction mixture was stirred for 15 h and quenched with saturated aqueous $NaHCO_3$ (2.5 ml). The mixture was then extracted with $CHCl_3$ (3×10 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (33% EtOAc/hexanes) provided **21** (single isomer) (36.9 mg, 0.172 mmol, 85% yield) as a colorless oil: $[\alpha]_D^{25}$ +13.1 (*c* 2.31, MeOH); IR (KBr) 3454 (s), 2926 (w), 1699 (s), 1643 (s), 1456 (m), 1331 (m), 1252 (s), 980 (m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.84 (ddd, J=17.2, 10.2, 6.6 Hz, 1H), 5.35 (d, J=17.2 Hz, 1H), 5.26 (d, J=10.2 Hz, 1H), 4.96 (s, 1H), 4.92 (s, 1H), 4.45 (d, J=6.6 Hz, 1H), 4.20 (s, 1H), 3.73 (s, 3H), 3.68 (bs, 1H), 2.95 (bs, 1H), 1.67 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 177.0, 144.0, 136.2, 118.7, 116.0, 79.7, 76.5, 54.0, 52.7, 18.9, 14.6; HRMS (FAB, NBA matrix) m/z 215.1283 $[(M+H)^+$; Calcd for $C_{11}H_{19}O_4$: 215.1283].

3.2.18. (1*R*,2*S*,3*S*)-1,3-Dihydroxy-2-methoxycarbonyl-2,4-dimethyl-4-cyclopentene (−)-23. At room temperature a solution of **21** (from (+)-**22a**) (59.7 mg, 0.279 mmol) in CH_2Cl_2 (5.6 ml) was treated with Grubbs reagent first (46.0 mg, 0.056 mmol). The reaction mixture was warmed to 40 °C and stirred for 5 h. A solution was then cooled to room temperature and quenched with saturated aqueous NaCl (3.0 ml). The mixture was then extracted with $CHCl_3$ (5×10 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (2.0% MeOH/$CHCl_3$) provided (−)-**23** (69.4 mg, 0.194 mmol, 69% yield) as a colorless crystal: mp 99–100 °C; $[\alpha]_D^{25}$ −4.9 (*c* 1.28, MeOH); IR (KBr) 3435 (s), 2947 (w), 1736 (s), 1454 (w), 1435 (w), 1257 (s), 1161 (w), 1055 (m), 1007 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.68 (s, 1H), 4.79 (s, 1H), 4.65 (s, 1H), 3.72 (s, 3H), 2.31 (bs, 1H), 2.23 (bs, 1H), 1.79 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 177.3, 143.4, 127.4, 80.1, 78.0, 59.1, 52.3, 13.6, 12.7; HRMS (FAB, PZG200 matrix) m/z 187.0976 $[(M+H)^+$; Calcd for $C_9H_{15}O_4$: 187.0970].

3.2.19. (1*R*,2*S*,3*S*)-1-(*tert*-Butyldimethylsiloxy)-3-hydroxy-2-methoxycarbonyl-2,4-dimethyl-4-cyclopentene. At −78 °C a solution of (−)-**23** (7.0 mg, 0.0376 mmol), and 2,6-lutidine (8.8 µl, 0.0753 mmol) in CH_2Cl_2 (0.75 ml) was treated with TBSOTf (14.3 µl, 0.0621 mmol), and the solution was stirred for 80 min, quenched with H_2O (1.0 ml), and warmed to room temperature and stirred 5 min further. The mixture was then extracted with $CHCl_3$

(3×5 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (10% EtOAc/hexanes) provided (1*R*,2*S*,3*S*)-1-(*tert*-butyldimethylsiloxy)-3-hydroxy-2-methoxycarbonyl-2,4-dimethyl-4-cyclopentene (9.7 mg, 0.0323 mmol, 86% yield) as a colorless crystal: mp 55–56 °C; $[\alpha]_D^{25}$ −31.4 (*c* 1.11, MeOH); IR (KBr) 3464 (s), 2933 (m), 1703 (s), 1458 (w), 1257 (s), 1119 (m), 1066 (s), 837 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.41 (s, 1H), 4.82 (s, 1H), 4.60 (d, J=8.6 Hz, 1H), 3.70 (s, 3H), 1.79 (s, 3H), 1.68 (bd, J=8.6 Hz, 1H), 1.16 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 177.1, 142.5, 128.8, 81.0, 78.0, 59.6, 52.0, 25.6 (3 C), 18.1, 13.6, 12.6, −4.8 (2 C); HRMS (FAB, NBA+NaI matrix) *m/z* 323.1658 $[(M+Na)^+$; Calcd for $C_{15}H_{28}O_4SiNa$: 323.1655].

3.2.20. (2*S*,3*S*)-3-(*tert*-Butyldimethylsiloxy)-2-methoxycarbonyl-2,5-dimethyl-4-cyclopentene-1-one (−)-24. At room temperature a solution of (1*R*,2*S*,3*S*)-1-(*tert*-butyldimethylsiloxy)-3-hydroxy-2-methoxycarbonyl-2,4-dimethyl-4-cyclopentene (352 mg, 1.17 mmol) in CH_2Cl_2 (3.9 ml) was treated with manganese(IV) dioxide (2.04 g, 23.4 mmol), and the solution was sonicated (38 kHz) for 2.5 h. After a solution was filtered, and concentrated and provided (−)-**24** (348 mg, 1.17 mmol, 100% yield) as a colorless oil: $[\alpha]_D^{25}$ −102.0 (*c* 0.81, MeOH); IR (KBr) 2931 (m), 1750 (s), 1716 (s), 1639 (m), 1255 (s), 1126 (m), 1086 (s), 845 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.07 (s, 1H), 5.08 (s, 1H), 3.71 (s, 3H), 1.82 (s, 3H), 1.28 (s, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 204.4, 172.1, 157.2, 139.9, 74.8, 59.9, 52.5, 25.7 (3 C), 18.0, 16.3, 10.0, −4.4, −4.9; HRMS (FAB, NaI matrix) *m/z* 321.1497 $[(M+Na)^+$; Calcd for $C_{15}H_{26}O_4SiNa$: 321.1498].

3.2.21. (2*S*,3*R*)-4-(*n*-Butyl)-3-(*tert*-butyldimethylsiloxy)-2-methoxycarbonyl-2,5-dimethyl-4-cyclopentene-1-one (−)-26. To a solution of copper (I) iodide (87.7 mg, 0.461 mmol) in THF (1.9 ml) at −40 °C was added *n*-BuLi (1.53 M in hexane, 602 μl, 0.921 mmol). The solution was stirred for 10 min, and added to a solution of (−)-**24** (110 mg, 0.368 mmol) in THF (1.0 ml) and stirred for 10 min, and added to a solution of phenylselenenyl bromide (148 mg, 0.626 mmol) and DMPU (75.7 μl, 0.626 mmol) in THF (1.0 ml) and stirred for 20 min at −40 °C and then quenched with saturated aqueous NH_4Cl (7.5 ml), warmed to room temperature and stirred 5 min further. The resultant mixture was extracted with AcOEt (3×15 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. The crude product was diluted THF (3.7 ml) and cooled to 0 °C, and AcOH (0.14 ml) and 30% aqueous solution H_2O_2 (0.25 ml, 2.21 mmol) was added to the mixture. The reaction mixture was stirred for 10 min and then quenched with saturated aqueous $NaHCO_3$ (3.0 ml). The mixture was extracted with Et_2O (3×10 ml). Drying over Na_2SO_4 of organic layer followed by removal of the solvent gave crude enone **25** (mixture of *exo*/*endo*=1:1), which was pure enough for the next operation.

At room temperature a solution of enone in ethanol·H_2O (1/1 v/v) (3.7 ml) was treated with $RhCl_3 \cdot 3H_2O$ (35.0 mg, 0.133 mmol), and the solution was warmed to 100 °C and stirred for 2 h. After a solution was cooled to room temperature and extracted with $CHCl_3$ (3×10 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (12.5% EtOAc/hexanes) provided (−)-**26** (95.5 mg, 0.270 mmol, 73% yield) as a light yellow oil: $[\alpha]_D^{25}$ −59.2 (*c* 0.51, MeOH); IR (KBr) 2933 (m), 1747 (s), 1711 (s), 1653 (m), 1253 (s), 1086 (s), 839 (m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.05 (s, 1H), 3.72 (s, 3H), 2.39 (m, 2H), 1.73 (s, 3H), 1.49 (m, 2H), 1.39 (m, 2H), 1.25 (s, 3H), 0.95 (t, J=6.9 Hz, 3H), 0.92 (s, 9H), 0.13 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 203.6, 172.5, 133.8, 76.5, 60.1, 52.4, 29.8, 27.4, 25.7 (3 C), 23.0, 18.0, 16.8, 13.9, 8.2, −4.5 (2 C); HRMS (FAB, NaI matrix) *m/z* 377.2120 $[(M+Na)^+$; Calcd for $C_{19}H_{34}O_4SiNa$: 377.2124]; Anal. Calcd for $C_{19}H_{34}O_4Si$: C, 64.36; H, 9.67. Found: C, 64.23; H, 9.56.

3.2.22. (1*R*,2*R*,3*S*)-5-(*n*-Butyl)-1-(*tert*-butyldimethylsiloxy)-3-hydroxy-2-hydroxymethyl-2,4-dimethyl-4-cyclopentene. At 0 °C a solution of (−)-**26** (17 mg, 0.048 mmol) in THF (0.48 ml) was treated with LAH (10 mg, 0.29 mmol). The solution was stirred for 105 min and then quenched with saturated aqueous Na_2SO_4 (0.2 ml) and brine (3 ml). The resultant mixture was extracted with Et_2O (3×5 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Preparative TLC (33% EtOAc/hexanes) provided (1*R*,2*R*,3*S*)-5-(*n*-butyl)-1-(*tert*-butyldimethylsiloxy)-3-hydroxy-2-hydroxymethyl-2,4-dimethyl-4-cyclopentene (8.8 mg, 56% yield) as a colorless solid: mp: 113–116 °C; $[\alpha]_D^{24}$ −3.4 (*c* 0.53, $CHCl_3$); IR (KBr) 3317 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.26 (s, 1H), 4.11 (s, 1H), 3.53, 3.46 (d, J=10.5 Hz, each 1H), 2.03 (m, 2H), 1.72 (bs, 1H), 1.69 (s, 3H), 1.57 (bs, 1H), 1.30 (m, 4H), 0.90 (s, 3H), 0.90 (q, J=6.0 Hz, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ: 140.1, 134.5, 81.2, 78.6, 68.7, 52.0, 30.8, 26.0, 25.3, 22.9, 18.2, 14.0, 12.4, 11.2, −4.0, −4.4; HRMS (FAB, NBA, NaI matrix) *m/z*: 351.2326 $[(M+Na)^+$, Calcd for $C_{18}H_{36}O_3SiNa$: 351.2331].

3.2.23. 3-(2-*tert*-Butyldimethylsiloxyethyl)-indoline 28. At room temperature a solution of 3-(2-hydroethyl)-indoline **9** (71.9 mg, 0.441 mmol), DMAP (2.7 mg, 0.022 mmol) and TBSCl (79.7 mg, 0.529 mmol) in CH_2Cl_2 (2.2 ml) was treated with triethylamine (92.2 μl, 0.661 mmol), and the solution stirred for 2 h 20 min, quenched with H_2O (3.0 ml) and extracted with $CHCl_3$ (3×8 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (33% EtOAc/hexanes) provided **28** (109 mg, 0.392 mmol, 89% yield) as a light brown oil: IR (KBr) 3381 (s), 1608 (s), 1489 (m), 1464 (m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.16 (d, J=7.3 Hz, 1H), 7.08 (t, J=7.3 Hz, 1H), 6.78 (dd, J=7.6, 7.3 Hz, 1H), 6.68 (d, J=7.6 Hz, 1H), 3.77 (complex m, 2-H, 3H), 3.45 (m, 1H), 3.28 (dd, J=8.2, 7.9 Hz, 1H), 2.13 (m, 1H), 1.81 (m, 1H), 0.98 (s, 9H), 0.15(s, 3H), 0.14 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 151.7, 133.3, 127.8, 124.2, 118.9, 109.8, 61.8, 54.1, 39.5, 37.5, 26.3, 18.7, −4.9; HRMS (FAB, S-GTG, PEG200 matrix) *m/z*: 277.1862 ($[M]^+$, Calcd for $C_{16}H_{27}NOSi$: 277.1862).

3.2.24. [(2*S*,3*R*),3ξ]-1-[4-(*n*-Butyl)-3-(*tert*-butyldimethylsiloxy)-2,5-dimethyl-1-oxo-2-(4-cyclopentenyl)methyl]-3-(2-hydroxyethyl)indoline 29. At room temperature a solution of (1*R*,2*R*,3*S*)-5-(*n*-butyl)-1-(*tert*-butyldimethyl-

siloxy)-3-hydroxy-2-hydroxymethyl-2,4-dimethyl-4-cyclopentene (5.8 mg, 0.018 mmol) in CH_2Cl_2 (0.88 ml) was treated with Dess–Martin periodinane (23 mg, 0.053 mmol), and the solution stirred for 45 min, and then added $TiCl_4$ (1.0 M in toluene, 14 μl, 0.014 mmol). The solution was stirred for 15 min, and added to a solution of $NaBH_3CN$ (3.3 mg, 0.053 mmol) in methanol (0.18 ml) and stirred for 5 min. The solution was quenched with H_2O (2 ml), extracted with $CHCl_3$ (3×15 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Preparative TLC (17% EtOAc/hexanes) provided **29** (3.0 mg, 29% yield) as a brown oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.03 (complex m, 2H), 6.67 (m, 1H), 6.51 (m, 1H), 4.82 (bs, 1H), 3.65 (complex m, 3H), 3.20 (complex m, 4H), 2.38 (m, 2H), 2.08 (m, 2H), 1.73 (s, 3H), 1.34 (complex m, 4H), 1.04, 1.02 (s, each 3/2H), 0.93 (s, 9H), 0.91 (m, 3H), 0.90 (s, 9H), 0.21, 0.18, 0.13, 0.11 (s, each 3/2H), 0.05, 0.04 (s, each 3H).

3.2.25. (1*R*,2*R*,3*S*)-5-(*n*-Butyl)-3-(*tert*-butyldimethylsiloxy)-3-hydroxy-2-methoxycarbonyl-2,4-dimethyl-4-cyclopentene. At 0 °C a solution of (−)-**26** (429 mg, 1.21 mmol) and $CeCl_3\cdot 7H_2O$ (587 mg, 1.58 mmol) in methanol (12.1 ml) was treated with $NaBH_4$ (179 mg, 4.74 mmol). The solution was warmed to room temperature, and stirred for 1 h and then quenched with saturated aqueous Na_2SO_4 (8.0 ml). The resultant mixture was extracted with $CHCl_3$ (3×50 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (10% EtOAc/hexanes) provided (1*R*,2*R*,3*S*)-5-(*n*-butyl)-3-(*tert*-butyldimethylsiloxy)-3-hydroxy-2-methoxycarbonyl-2,4-dimethyl-4-cyclopentene (347 mg, 0.975 mmol, 80% yield) as a colorless solid: mp 64–66 °C; $[\alpha]_D^{26}$ −3.9 (*c* 0.47, MeOH); IR (KBr) 3489 (s), 2931 (s), 1705 (s), 1680 (w), 1458 (m), 1257 (s), 1111 (m), 1086 (s), 1057 (m), 866 (m), 839 (m) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.84 (s, 1H), 4.54 (d, J=8.6 Hz, 1H), 3.70 (s, 3H), 2.03 (m, 2H), 1.68 (s, 3H), 1.57 (bd, J=8.6 Hz, 1H), 1.31 (m, 4H), 1.11 (s, 3H), 0.90 (t, J=6.9 Hz, 3H), 0.90 (s, 9H), 0.09 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 177.4, 139.8, 133.2, 81.8, 79.8, 58.6, 51.9, 30.5, 25.8 (3 C), 25.2, 22.8, 18.1, 14.0, 12.2, 11.1, −4.0, −4.9; HRMS (FAB, PZG400+NaI matrix) *m*/*z* 379.2283 [(M+Na)$^+$; Calcd for $C_{19}H_{36}O_4SiNa$: 379.2281].

3.2.26. (1*S*,2*R*,3*R*)-4-(*n*-Butyl)-1,3-bis(*tert*-butyldimethylsiloxy)-2-methoxycarbonyl-2,5-dimethyl-4-cyclopentene. To a solution of KH (35 wt% dispersion in mineral oil, 212 mg, 1.85 mmol) and 18-crown-6 (4.9 mg, 0.0185 mmol) in THF (3.7 ml) at 0 °C was added (1*R*,2*R*,3*S*)-5-(*n*-butyl)-3-(*tert*-butyldimethylsiloxy)-3-hydroxy-2-methoxycarbonyl-2,4-dimethyl-4-cyclopentene (329 mg, 0.924 mmol) in THF (9.2 ml). The solution was stirred for 5 min at 0 °C. To a reaction mixture was added TBSCl (223 mg, 1.48 mmol) in THF (7.4 ml). The reaction was warmed to room temperature and stirred for 11.5 h. The reaction was carefully quenched with H_2O (5.0 ml), extracted with $CHCl_3$ (3×30 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (2.0% EtOAc/hexanes) provided (1*S*,2*R*,3*R*)-4-(*n*-butyl)-1,3-bis(*tert*-butyldimethylsiloxy)-2-methoxycarbonyl-2,5-dimethyl-4-cyclopentene (399 mg, 0.849 mmol, 92% yield) as a colorless oil: $[\alpha]_D^{25}$ +3.4 (*c* 0.88, MeOH); IR (KBr) 2933 (s), 1726 (m), 1468 (m), 1072 (s), 870 (m), 839 (m) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.82 (s, 1H), 4.69 (s, 1H), 3.69 (s, 3H), 2.04 (m, 1H), 1.93 (m, 1H), 1.57 (s, 3H), 1.28 (m, 4H), 1.01 (s, 3H), 0.89 (s, 18H), 0.88 (t, J=6.9 Hz, 3H), 0.04 (s, 6H), −0.06 (s, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 178.3, 137.1, 132.9, 82.0, 80.9, 60.7, 51.7, 30.8, 25.8 (6 C), 25.3, 22.9, 18.1 (2 C), 14.0, 11.3 (2 C), −4.3, −4.6, −4.7, −4.9; HRMS (FAB, NBA matrix) *m*/*z* 469.3144 [(M−H)$^+$; Calcd for $C_{25}H_{49}O_4Si_2$: 469.3169].

3.2.27. (1*S*,2*R*,3*R*)-4-(*n*-Butyl)-1,3-bis(*tert*-butyldimethylsiloxy)-2-hydroxymethyl-2,5-dimethyl-4-cyclopentene (+)-30. To a solution of (1*S*,2*R*,3*R*)-4-(*n*-butyl)-1,3-bis(*tert*-butyldimethylsiloxy)-2-methoxycarbonyl-2,5-dimethyl-4-cyclopentene (23.6 mg, 0.0502 mmol) in CH_2Cl_2 (0.5 ml) at −78 °C was added diisobutylaluminum hydride (0.98 M in hexane, 154 μl, 0.151 mmol). The solution was stirred for 15 min at −78 °C and then quenched with saturated aqueous NH_4Cl (0.1 ml) and Na_2SO_4 (200 mg). The resultant mixture was warmed to room temperature and stirred for 10 min. After a solution was filtered, and concentrated. Flash chromatography (10% EtOAc/hexanes) provided (+)-**30** (22.2 mg, 0.0502 mmol, 100% yield) as a colorless oil: $[\alpha]_D^{25}$ +5.8 (*c* 0.81, MeOH); IR (KBr) 3431 (s), 2933 (s), 1468 (w), 1254 (m), 1068 (s), 893 (w), 837 (s), 773 (m) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.49 (s, 1H), 4.39 (s, 1H), 3.50 (s, 2H), 2.06 (m, 1H), 1.96 (m, 1H), 1.58 (s, 3H), 1.30 (m, 4H), 0.91 (s, 18H), 0.89 (t, J=7.0 Hz, 3H), 0.72 (s, 3H), 0.10 (s, 3H), 0.09 (s, 6H), 0.08 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −4.3, −4.2 (2 C), 137.8, 133.7, 76.5, 77.6, 65.3, 53.8, 31.1, 26.0 (6 C), 25.3, 23.0, 18.3 (2 C), 14.1, 12.7, 11.7, −4.0; HRMS (FAB, NBA matrix) *m*/*z* 441.3200 [(M−H)$^+$; Calcd for $C_{24}H_{49}O_3Si_2$: 441.3220].

3.2.28. [(1*S*,2*R*,3*R*),3ξ]-1-[-4-(*n*-Butyl)-1,3-bis(*tert*-butyldimethylsiloxy)-2,5-dimethyl-2-(4-cyclopentenyl)-methyl]-3-[2-(*tert*-butyldimethylsiloxy)]indoline 31. At room temperature a solution of (+)-**30** (42.3 mg, 0.0957 mmol) in CH_2Cl_2 (1.9 ml) was treated with Dess–Martin periodinane (101 mg, 0.239 mmol), and the solution stirred for 40 min quenched with H_2O (1.5 ml). The resultant mixture was extracted with $CHCl_3$ (3×5 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. The crude product was eluted by Flash chromatography (20% EtOAc/hexanes) provided aldehyde, which was pure enough for the next operation.

To a solution of aldehyde and **28** (79.5 mg, 0.287 mmol) in benzene (4.8 ml) at room temperature was added $TiCl_4$ (1.0 M in toluene, 115 μl, 0.155 mmol). The solution was stirred for 15 min, and added to a solution of $NaBH_3CN$ (18.0 mg, 0.287 mmol) in methanol (4.8 ml) and stirred for 10 min. The solution was quenched with H_2O (2 ml) and 5% KOH aqueous solution (3 ml), extracted with $CHCl_3$ (3×15 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (5.0% EtOAc/hexanes) provided **31** (51.7 mg, 0.0738 mmol, 77% yield, 96% based on recovered (+)-**30**) and recovered (+)-**30** (8.5 mg, 0.0192 mmol, 19%).

Aldehyde. ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.71 (s, 1H), 4.71

(s, 1H), 4.59 (s, 1H), 2.03 (m, 2H), 1.60 (s, 3H), 1.30 (m, 4H), 1.05 (s, 3H), 0.89 (s, 18H), 0.89 (t, J=7.0 Hz, 3H), 0.06 (s, 6H), 0.03 (s, 6H).

Compound **31**. Light yellow oil; IR (KBr) 2929 (s), 1606 (m), 1487 (m), 1471 (m), 1462 (m), 1255 (s), 1063 (s), 870 (m), 835 (s) 773 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.05 (m, 2H), 6.67 (dd, J=7.3, 7.3 Hz, 1H), 6.33 (d, J=7.9 Hz, 1/2H), 6.32 (d, J=7.9 Hz, 1/2H), 4.18 (s, 1/2H), 4.11 (s, 1/2H), 4.04 (s, 1/2H), 4.00 (s, 1/2H), 3.75 (dd, J=6.3, 5.9 Hz, 2H), 3.69 (m, 1H), 3.32 (m, 1H), 3.06 (m, 1H), 2.88 (d, J=14.2 Hz, 1H), 2.72 (d, J=14.2 Hz, 1H), 2.08 (m, 4H), 1.67 (s, 3H), 1.35 (m, 4H), 1.03 (s, 3H), 0.92 (s, 9H), 0.91 (s, 9H), 0.89 (s, 9H), 0.87 (t, J=7.0 Hz, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3/2H), 0.02 (s, 3H), 0.01 (s, 3H), −0.01 (s, 3/2H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 153.7, 139.8 (1/2 C), 139.7 (1/2 C), 135.6 (1/2 C), 135.4 (1/2 C), 132.8, 127.4, 123.3 (1/2 C), 123.2 (1/2 C), 117.3, 106.5, 83.3 (1/2 C), 83.2 (1/2 C), 80.9 (1/2 C), 80.6 (1/2 C), 64.0, 61.4, 60.9 (1/2 C), 60.8 (1/2 C), 50.9 (1/2 C), 50.8 (1/2 C), 38.0, 37.1, 30.7, 26.0 (9 C), 25.6 (1/2 C), 25.5 (1/2 C), 22.8, 18.4, 18.3, 18.1, 14.1 (2 C), 12.6 (1/2 C), 12.5 (1/2 C), −3.1, −3.7, −3.8, −3.9, −4.0, −4.1; HRMS (FAB, NBA matrix) m/z 702.5126 $[(M+H)^+$; Calcd for $C_{40}H_{76}O_3NSi_3$: 702.5133].

3.2.29. [(1*S*,2*R*,3*R*),3ξ]-1-[4-(*n*-Butyl)-1,3-dihydroxy-2,5-dimethyl-2-(4-cyclopentenyl)methyl]-3-(2-hydroxy)-indoline. At room temperature a solution of **31** (7.6 mg, 0.0108 mmol) in THF (0.54 ml) was treated with tetra-*n*-butylammonium fluoride (1.0 M in THF, 52.4 μl, 0.0542 mmol). The reaction mixture was warmed to 60 °C and stirred for 4 h. After a solution was cooled to room temperature and quenched with H_2O (1.0 ml). The mixture was then extracted with $CHCl_3$ (3×5 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (50% $CHCl_3$/acetone) furnished [(1*S*,2*R*,3*R*),3ξ]-1-[4-(*n*-butyl)-1,3-dihydroxy-2,5-dimethyl-2-(4-cyclopentenyl)methyl]-3-(2-hydroxy)indoline (3.9 mg, 0.0108 mmol, 100% yield) as a light green oil: IR (KBr) 3450 (s), 2929 (m), 1606 (m), 1489 (m), 1462 (m), 1261 (m), 1041 (m), 1014 (m), 744 (m) cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 7.01 (d, J=7.6 Hz, 1H), 6.99 (dd, J=7.6, 7.3 Hz, 1H), 6.60 (dd, J=7.6, 7.3 Hz, 1H), 6.43 (d, J=7.6 Hz, 1H), 4.21 (s, 1H), 4.08 (s, 1/2H), 4.07 (s, 1/2H), 3.65 (t, J=6.6 Hz, 2H), 3.63 (m, 1H), 3.29 (m, 1H), 3.17 (m, 1H), 2.96 (d, J=14.5 Hz, 1H), 2.89 (d, J=14.5 Hz, 1H), 2.17 (t, J=6.6 Hz, 2H), 1.98 (m, 1H), 1.70 (s, 3H), 1.68 (m, 1H), 1.37 (m, 4H), 0.94 (s, 3H), 0.90 (t, J=7.3 Hz, 3H); ^{13}C NMR (67.5 MHz, CD_3OD) δ 154.9, 140.3 (1/2 C), 140.2 (1/2 C), 136.1, 133.8, 128.5, 124.3, 118.4, 107.5, 81.9 (1/2 C), 81.8 (1/2 C), 79.9 (1/2 C), 79.8 (1/2 C), 64.5, 61.0, 59.2 (1/2 C), 59.1 (1/2 C), 52.9, 39.0, 38.3 (1/2 C), 38.2 (1/2 C), 31.2, 26.4 (1/2 C), 26.3 (1/2 C), 23.9 (1/2 C), 23.8 (1/2 C), 14.6 (1/2 C), 14.5 (1/2 C), 14.4, 11.6; HRMS (FAB, NaI matrix) m/z 382.2329 $[(M+Na)^+$; Calcd for $C_{22}H_{33}O_3NNa$: 382.2358].

3.2.30. [(1*S*,2*R*,3*R*),3ξ]-1-[-4-(*n*-Butyl)-1,3-dihydroxy-2,5-dimethyl-2-(4-cyclopentenyl)methyl]-3-(2-triethylsiloxyethyl)indoline. At room temperature a solution of [(1*S*,2*R*,3*R*),3ξ]-1-[-4-(*n*-butyl)-1,3-dihydroxy-2,5-dimethyl-2-(4-cyclopentenyl)methyl]-3-(2-hydroxy)indoline (106.4 mg, 0.296 mmol), DMAP (1.8 mg, 0.0148 mmol) and triethylamine (82.7 μl, 0.593 mmol) in CH_2Cl_2 (9.9 ml) was treated with TESCl (84.6 μl, 0.504 mmol), and the solution was stirred for 2.5 h, quenched with H_2O (3.0 ml) and extracted with $CHCl_3$ (3×10 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (50% EtOAc/hexanes) provided [(1*S*,2*R*,3*R*),3ξ]-1-[4-(*n*-butyl)-1,3-dihydroxy-2,5-dimethyl-2-(4-cyclopentenyl)methyl]-3-(2-triethylsiloxyethyl)indoline (110 mg, 0.232 mmol, 78% yield, 88% based on recovered SM) and recovered SM (12.3 mg, 0.0343 mmol, 12%). *Product*. Light brown oil; IR (KBr) 3460 (s), 2931 (m), 1628 (w), 1606 (m), 1489 (m), 1460 (m), 1261 (m), 1097 (m), 1041 (w), 1009 (m), 744 (s) cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 7.00 (d, J=7.0 Hz, 1H), 6.98 (dd, J=7.6, 7.3 Hz, 1H), 6.59 (dd, J=7.6, 7.0 Hz, 1H), 6.43 (d, J=7.3 Hz, 1H), 4.07 (s, 1H), 4.02 (s, 1H), 3.73 (m, 2H), 3.62 (m, 1H), 3.29 (m, 1H), 3.18 (m, 1H), 2.95 (d, J=14.2 Hz, 1H), 2.88 (d, J=14.2 Hz, 1H), 2.17 (t, J=7.3 Hz, 2H), 2.06 (m, 1H), 1.70 (s, 3H), 1.70 (m, 1H), 1.32 (m, 4H), 0.98 (t, J=7.9 Hz, 9H), 0.94 (s, 3H), 0.89 (t, J=6.9 Hz, 3H), 0.62 (q, J=7.9 Hz, 6H); ^{13}C NMR (67.5 MHz, CD_3OD) δ 154.9, 140.4, 136.2 (1/2 C), 136.1 (1/2 C), 133.8, 128.5, 124.3, 118.4, 107.5 (1/2 C), 107.4 (1/2 C), 82.0 (1/2 C), 81.9 (1/2 C), 79.5, 64.6 (1/2 C), 64.5 (1/2 C), 62.1, 59.3, 52.8, 39.2, 38.5, 31.3, 26.4, 23.9 (1/2 C), 23.8 (1/2 C), 14.6 (1/2 C), 14.5 (1/2 C), 14.4, 11.6, 7.1 (3 C), 5.3 (3 C); HRMS (FAB, NaI matrix) m/z 496.3225 $[(M+Na)^+$; Calcd for $C_{28}H_{47}O_3NSiNa$: 496.3223].

3.2.31. (2′*R*)-1-[4-(*n*-Butyl)-2,5-dimethyl-1,3-dioxo-2-(4-cyclopentenyl)methyl]-3-(2-hydroxyethyl)indoline (+)-11. At room temperature a solution of [(1*S*,2*R*,3*R*),3ξ]-1-[4-(*n*-butyl)-1,3-dihydroxy-2,5-dimethyl-2-(4-cyclopentenyl)methyl]-3-(2-triethylsiloxyethyl)indoline (94.3 mg, 0.199 mmol) in CH_2Cl_2 (19.9 ml) was treated with manganese(IV) dioxide (1.73 g, 19.9 mmol), and the solution was sonicated (38 kHz) for 32 h. The reaction mixture was filtered and concentrated to afford crude product. At 0 °C the product was diluted 0.5% concd HCl in EtOH (10 ml), and stirred for 5 min at 0 °C and then quenched with $CHCl_3$ (5 ml) and saturated aqueous $NaHCO_3$ (3.0 ml). The mixture was extracted with $CHCl_3$ (3×10 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (50% EtOAc/hexanes) provided (+)-**11** (62.8 mg, 0.178 mmol, 89% yield) as a yellow oil.

Diketone TES ether. ^1H NMR (270 MHz, $CDCl_3$) δ 7.42 (d, J=7.9 Hz, 1H), 7.15 (dd, J=8.3, 6.3 Hz, 1H), 7.14 (d, J=8.3 Hz, 1H), 6.99 (dd, J=7.9, 6.3 Hz, 1H), 6.53 (s, 1H), 4.39 (d, J=14.5 Hz, 1H), 4.31 (d, J=14.5 Hz, 1H), 3.73 (m, 2H), 2.85 (dd, J=8.6, 6.9 Hz, 2H), 2.12 (m, 1H), 1.97 (m, 1H), 1.67 (s, 3H), 1.21 (s, 3H), 0.96 (t, J=7.9 Hz, 9H), 0.94 (m, 4H), 0.66 (q, J=7.5 Hz, 4H), 0.62 (t, J=7.9 Hz, 3H), 0.60 (q, J=7.5 Hz, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 4.8 (3 C), 6.8 (3 C), 9.1, 13.7, 16.1, 22.5, 23.5, 28.8, 29.1, 49.9, 51.4, 63.5, 110.5, 112.7, 118.7, 119.2, 122.0, 126.4, 127.9, 135.6, 155.4, 159.6, 205.1, 206.1.

Compound (+)-**11**. $[\alpha]_D^{25}$ +51.7 (*c* 0.64, MeOH); IR (KBr) 3417 (m), 2929 (m), 1691 (s), 1630 (w), 1464 (m), 1381 (m), 1047 (w), 743 (m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ

7.44 (d, J=7.9 Hz, 1H), 7.20 (dd, J=8.6, 7.9 Hz, 1H), 7.18 (d, J=8.6 Hz, 1H), 7.02 (dd, J=7.9, 7.9 Hz, 1H), 6.61 (s, 1H), 4.41 (d, J=14.5 Hz, 1H), 4.34 (d, J=14.5 Hz, 1H), 3.79 (dd, J=6.6, 6.3 Hz, 2H), 2.88 (dd, J=6.6, 6.3 Hz, 2H), 2.15 (m, 1H), 2.00 (m, 1H), 1.69 (s, 3H), 1.22 (s, 3H), 0.89 (m, 2H), 0.76 (m, 2H), 0.67 (t, J=6.9 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 206.0, 205.1, 159.6, 155.5, 135.9, 127.7, 127.0, 122.3, 119.4, 118.7, 112.0, 110.6, 62.7, 51.3, 49.8, 29.1, 28.4, 23.6, 22.5, 16.3, 13.7, 9.1; HRMS (FAB, NaI matrix) m/z 376.1899 [$(M+Na)^+$; Calcd for $C_{22}H_{27}O_3NNa$: 376.1889].

3.2.32. (+)-Madindoline A (+)-1 and (−)-madindoline B (−)-2. *By the use of (+)-diethyl tartrate*. To a solution of activated 4 Å molecular sieves (165 mg) in CH_2Cl_2 (11.8 ml) at −5 °C was added titanium(IV) isopropoxide (46.7 μl, 0.158 mmol) and (+)-diethyl tartrate (32.5 μl, 0.190 mmol) and stirred for 30 min. The solution was cooled to −20 °C, and was added *tert*-butylhydroperoxide (5.0 M in decane, 158 μl, 0.790 mmol) and stirred for 15 min at −20 °C. To the solution was added a solution of (+)-**11** (55.8 mg, 0.158 mmol) in CH_2Cl_2 (4.0 ml). The solution was stirred for 3 days and then quenched with Et_2O (7 ml), and saturated aqueous Na_2SO_4 (0.5 ml), warmed to room temperature and stirred 2 h further. The resultant mixture was filtered through a celite, washing with $CHCl_3$ (3×15 ml). The filtrate was added to silica gel (Silica gel 60, 0.040–0.063 mm, Merck, 24 ml), and the solvent was removed under vacuo. After suspending on silica gel for 2 h, the mixture was eluted with 10% MeOH/$CHCl_3$ (3×20 ml) and concentrated. Flash chromatography (11% acetone/$CHCl_3$) furnished *(+)-madindoline A* (+)-**1** (18.0 mg, 0.0488 mmol, 31% yield, 34% based on recovered (+)-**11**), *(−)-madindoline B* (−)-**2** (8.1 mg, 0.020 mmol, 14% yield, 15% based on recovered (+)-**11**) and recovered (+)-**11** (5.1 mg, 0.0144 mmol, 9%). *(+)-madindoline A* (+)-**1**. Light yellow crystal; mp 82–84 °C; mmp 82–85 °C; $[\alpha]_D^{21}$ + 69.6 (*c* 0.30, MeOH); IR (KBr) 3412 (s), 2926 (m), 1740 (w), 1695 (s), 1610 (m), 1487 (m), 1383 (m), 1283 (w), 754 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 1H), 7.19 (m, 1H), 6.75 (dt, J=7.3, 0.5 Hz, 1H), 6.63 (d, J=8.0 Hz, 1H), 4.93 (s, 1H), 3.85 (m, 1H), 3.70 (d, J=14.2 Hz, 1H), 3.46 (d, J=14.2 Hz, 1H), 3.15 (m, 1H), 2.38 (m, 1H), 2.36 (m, 1H), 2.33 (dd, J=12.0, 8.0 Hz, 1H), 2.17 (ddd, J=12.0, 5.0, 1.5 Hz, 1H), 2.00 (s, 3H), 1.29 (m, 2H), 1.19 (m, 2H), 1.12 (s, 3H), 0.76 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.4, 206.3, 157.7, 156.5, 130.6, 129.5, 150.5, 123.5, 119.1, 108.1, 106.2, 88.0, 66.6, 53.6, 50.6, 41.1, 29.9, 23.6, 22.7, 17.3, 13.6, 9.4; HRMS (FAB, NBA matrix) m/z 370.2044 [$(M+H)^+$; Calcd for $C_{22}H_{28}O_4N$: 370.2018]. *(−)-Madindoline B* (−)-**2**. Light yellow oil; $[\alpha]_D^{29}$ −82.3 (*c* 0.03, MeOH); IR (KBr) 3429 (s), 2931 (m), 1740 (w), 1695 (s), 1610 (m), 1489 (m), 1383 (m), 1283 (m), 754 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (m, 2H), 6.74 (dt, J=7.2, 1.0 Hz, 1H), 6.62 (d, J=8.0 Hz, 1H), 4.91 (s, 1H), 3.84 (ddd, J=12.0, 7.8, 1.5 Hz, 1H), 3.68 (d, J=14.9 Hz, 1H), 3.48 (d, J=14.9 Hz, 1H), 3.16 (ddd, J=12.0, 9.1, 5.0 Hz, 1H), 2.46 (m, 1H), 2.37 (m, 1H), 2.33 (ddd, J=12.0, 7.9, 1.5 Hz, 1H), 2.19 (ddd, J=12.0, 5.0, 1.5 Hz, 1H), 1.94 (s, 3H), 1.39 (m, 2H), 1.26 (m, 2H), 1.13 (s, 3H), 0.86 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.6, 205.9, 160.3, 153.7, 150.4, 130.5, 129.4, 123.5, 118.9, 107.8, 105.0, 87.9, 66.7, 52.1, 50.5, 41.2, 29.5, 24.0, 22.9, 17.5, 13.8, 9.1; HRMS (FAB, NBA matrix) m/z 370.2022 [$(M+H)^+$; Calcd for $C_{22}H_{28}O_4N$: 370.2018].

By the use of (−)-diethyl tartrate. To a solution of activated 4 Å molecular sieves (15 mg) in CH_2Cl_2 (0.90 ml) at −5 °C was added titanium(IV) isopropoxide (4.3 μl, 0.0144 mmol) and (−)-diethyl tartrate (3.0 μl, 0.0173 mmol) and stirred for 30 min. The solution was cooled to −20 °C, and was added *tert*-butylhydroperoxide (5.0 M in decane, 14.4 μl, 0.0722 mmol) and stirred for 15 min at −20 °C. To the solution was added a solution of (+)-**11** (5.1 mg, 0.0144 mmol) in CH_2Cl_2 (0.54 ml). The solution was stirred for 3 days and then quenched with Et_2O (1 ml), and saturated aqueous Na_2SO_4 (0.06 ml), warmed to room temperature and stirred 2 h further. The resultant mixture was filtered through a celite, washing with $CHCl_3$ (3× 5 ml). The filtrate was added to silicagel (Silica gel 60, 0.040—0.063 mm, Merck, 2.4 ml), and the solvent was removed under vacuo. After suspending on silica gel for 2 h, the mixture was eluted with 10% MeOH/$CHCl_3$ (3×10 ml) and concentrated. Flash chromatography (11% acetone/$CHCl_3$) furnished *(+)-madindoline A* (+)-**1** (0.8 mg, 2.17 mmol, 15% yield, 16.3% based on recovered (+)-**11**), *(−)-madindoline B* (−)-**2** (1.8 mg, 4.88 mmol, 34% yield, 37% based on recovered (+)-**11**) and recovered (+)-**11** (0.4 mg, 1.13 mmol, 8%).

3.3. Second generation synthesis

3.3.1. (*S*)-2-Methyl-3-trimethylacetoxy-1-propanol (−)-37. At room temperature a solution of (+)-**36** (3.0 g, 14.8 mmol) in pyridine (14.8 ml) was treated with trimethylacetyl chloride (2.2 ml, 17.8 mmol), and the solution was stirred for 2 h, quenched with H_2O (30 ml). The mixture was extracted with $CHCl_3$ (60 ml). The extract was washed with H_2O (20 ml) and 1.0 N HCl in H_2O (30 ml), and then dried over Na_2SO_4, filtered and concentrated. Crude product was not measured and was used in next step without purification.

Crude TBS ether was diluted with 1% concd HCl aqueous solution in MeOH (29.6 ml), and the resultant mixture was stirred for 30 min at room temperature. H_2O (30 ml) was added to dilute the reaction mixture, and the resulting mixture was extracted with CH_2Cl_2 (3×60 ml). The combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc=4:1) provided (−)-**37** (2.2 g, 12.5 mmol, 84% yield) as a colorless oil: $[\alpha]_D^{24}$ −12.0 (*c* 0.30, $CHCl_3$); IR (KBr) 3440(s), 2972(s), 1732(s), 1481(m), 1286(s), 1169(s), 1036(m) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.09 (1H, dd, J=11.0, 5.3 Hz), 4.01 (1H, dd, J=11.0, 6.3 Hz), 3.50 (1H, dd, J=11.2, 6.1 Hz), 3.44 (1H, dd, J=11.2, 6.6 Hz), 1.96 (1H, m), 1.18 (9H, s), 0.93 (3H, d, J=6.9 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 180.0, 66.8, 65.2, 39.6, 36.5, 28.3 (3C), 14.4; HRMS (FAB, NBA, PEG200+NaI matrix) m/z: 197.1158 [$(M+Na)^+$; Calcd for $C_9H_{18}O_3Na$: 197.1154].

3.3.2. (*R*)-2-Methyl-3-trimethylacetoxy-1-propanal (−)-35. To a solution of oxalyl chloride (4.91 ml, 56.3 mmol) in CH_2Cl_2 (75 ml) at −78 °C was added DMSO (6.57 ml,

92.5 mmol). The solution was stirred for 15 min, and then added to a solution of (−)-**37** (7.0 g, 40.2 mmol) in CH_2Cl_2 (25.5 ml) and stirred for 15 min at −78 °C. Et_3N (25.2 ml, 181 mmol) was then added, the resultant mixture was stirred for 10 min at 0 °C, quenched with H_2O (100 ml) and Et_2O·hexane (1/1=v/v) (200 ml). The organic layer was separated, washed with H_2O (1×150 ml), saturated aqueous NH_4Cl (2×150 ml) and saturated aqueous NaCl (1×150 ml), and then dried over Na_2SO_4, filtered. Evaporation of the solvent afforded (−)-**35** (6.42 mg, 93% yield) as a colorless oil: $[\alpha]_D^{25}$ −16.0 (*c* 0.65, $CHCl_3$); IR (KBr) 2972(m), 1732(s), 1286(m), 1163(s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 9.70 (1H, d, J=1.3 Hz), 4.26 (2H, d, J=5.9 Hz), 2.71 (1H, m), 1.18 (9H, s), 1.16 (3H, d, J=6.9 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 202.0, 178.3, 63.4, 45.9, 38.8, 27.1 (3C), 10.4; HRMS (FAB, NBA, PEG200+NaI matrix) *m/z*: 195.1004 [$(M+Na)^+$; Calcd for $C_9H_{16}O_3Na$: 195.0997].

3.3.3. (±)-2-Methyl-3-trimethylacetoxy-1-propanol (±)-37. To a solution of 2-methyl-1,3-propanediol (−)-**38** (1.5 ml, 16.9 mmol) in CH_2Cl_2 (16.9 ml) was added Et_3N (2.4 ml, 16.9 mmol) and PivCl (2.5 ml, 20 mmol) at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 24 h. The reaction was quenched with H_2O (30 ml). The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (3×30 ml). The combined organic layers were washed with brine (50 ml), dried over Na_2SO_4, filtered and concentrated. Flash chromatography (50% EtOAc/hexane) furnished ()-**37** (2.4 g, 83%) as a colorless oil.

3.3.4. (±)-2-Methyl-3-trimethylacetoxy-1-propanal (±)-35. According to the procedure for preparation of (−)-**35**. Oxidation of (±)-**37** afforded (±)-**35** (92% yield) on 10 g scale.

3.3.5. [(2*S*),3a*R*,8a*S*]-3a-Hydroxy-8-(2-methyl-3-trimethylacetoxypropyl)-3,3a,8,8a-tetrahydro-2*H*-furo-[2,3-*b*]indole (−)-39. At room temperature a solution of (−)-**4** (4.5 g, 25.4 mmol) and (−)-**35** (5.7 g, 33.0 mmol) in CH_2ClCH_2Cl (127 ml) was treated with AcOH (2.2 ml, 38.1 mmol) and $NaBH(OAc)_3$ (7.0 g, 33.0 mmol), and the resultant mixture was stirred for 30 min, and then quenched with saturated aqueous $NaHCO_3$ (150 ml). The resultant mixture was extracted with $CHCl_3$ (3×100 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc=5:1) provided (−)-**39** (5.3 g, 63% yield) as a light brown oil: $[\alpha]_D^{27}$ −39.7 (*c* 2.13, $CHCl_3$); IR (KBr) 3431(s), 2972(m), 1728(s), 1612(m), 1491(s), 1288(m), 1165(s), 1030(m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.28 (1H, d, J=7.6 Hz), 7.18 (1H, dd, J=7.9, 7.3 Hz), 6.72 (1H, dd, J=7.6, 7.3 Hz), 6.43 (1H, d, J=7.9 Hz), 5.24 (1H, s), 4.06 (1H, dd, J=11.2, 5.3 Hz), 4.05 (1H, m), 3.93 (1H, dd, J=11.2, 5.9 Hz), 3.59 (1H, m), 3.22 (2H, d, J=7.6 Hz), 2.45 (1H, m), 2.32 (1H, m), 2.30 (1H, m), 1.22 (9H, s), 1.02 (3H, d, J=6.9 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 178.5, 150.9, 130.4, 130.0, 123.9, 117.8, 105.9, 104.3, 88.0, 67.2, 66.8, 48.9, 41.2, 38.9, 32.9, 27.2 (3C), 15.3; HRMS (FAB, NBA, PEG200+NaI matrix) *m/z*: 333.1944 [$(M)^+$; Calcd for $C_{19}H_{27}NO_4$: 333.1940].

3.3.6. [(2*S*),3a*R*,8a*S*]-3a-(*tert*-Butyldimethylsilyloxy)-8-(2-methyl-3-trimethylacetoxypropyl)-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole. At 0 °C a solution of (−)-**39** (5.2 g, 15.6 mmol), and 2,6-lutidine (3.64 ml, 31.2 mmol) in CH_2Cl_2 (156 ml) was treated with TBSOTf (5.38 ml, 23.4 mmol), and the solution was stirred for 80 min at 0 °C, quenched with H_2O (100 ml). The mixture was then extracted with CH_2Cl_2 (3×100 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc=10:1) provided [(2*S*),3a*R*,8a*S*]-3a-(*tert*-butyldimethylsilyloxy)-8-(2-methyl-3-trimethylacetoxypropyl)-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole (6.9 g, 99% yield) as a light yellow oil: $[\alpha]_D^{27}$ −58.4 (*c* 1.66, $CHCl_3$); IR (KBr) 2956(s), 1730(s), 1612(s), 1489(s), 1288(m), 1255(m) 1034(m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.19 (1H, d, J=7.6 Hz), 7.15 (1H, dd, J=7.9, 7.3 Hz), 6.69 (1H, dd, J=7.6, 7.3 Hz), 6.41 (1H, d, J=7.9 Hz), 5.17 (1H, s), 4.05 (2H, m), 4.00 (1H, m), 3.50 (1H, m), 3.23 (2H, d, J=7.3 Hz), 2.45 (1H, m), 2.30 (1H, m), 2.30 (1H, m), 1.24 (9H, s), 1.03 (3H, d, J=6.6 Hz), 0.86 (9H, s), −0.15 (3H, s), −0.20 (3H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 178.4, 151.1, 130.3, 129.8, 124.7, 117.4, 105.7, 103.8, 89.5, 66.9, 66.9, 49.1, 43.4, 38.9, 33.1, 27.3 (3C), 25.6 (3C), 18.0, 15.3, −3.1, −3.6; HRMS (FAB, NBA, PEG200+NaI matrix) *m/z*: 447.2814 [$(M)^+$; Calcd for $C_{25}H_{41}NO_4Si$: 447.2805].

3.3.7. [(2*S*),3a*R*,8a*S*]-3a-(*tert*-Butyldimethylsilyloxy)-8-(2-carboxypropyl)-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole. [(2*S*),3a*R*,8a*S*]-3a-(*tert*-butyldimethylsilyloxy)-8-(2-methyl-3-trimethylacetoxypropyl)-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole (9.4 g, 21.0 mmol) was diluted 3.0 N KOH in EtOH/H_2O (2/1 v/v)(210 ml), and the resultant mixture was stirred for 17.5 h at room temperature. The mixture was then diluted with H_2O (200 ml) and resultant mixture was extracted with Et_2O (3×300 ml). The combined extracts were dried over Na_2SO_4, filtered and concentrated. The crude alcohol (−)-**40** was used for the next step without purification.

To a solution of (−)-**40** in CH_2Cl_2 (105 ml) at 0 °C was added DMSO (22.4 ml, 315 mmol), Et_3N (14.7 ml, 105 ml) and SO_3·Py (8.7 g, 54.7 mmol). The solution was stirred for 110 min at room temperature, and then quenched with H_2O (200 ml). The resultant mixture was extracted with CH_2Cl_2 (3×200 ml), dried over Na_2SO_4, and filtered. Evaporation of the solvent afforded the crude aldehyde, which was used for next step without further purification.

At room temperature to a solution of the crude aldehyde and 2-methyl-2-butene in *t*BuOH (210 ml) was added a solution of $NaClO_2$ (19.0 g, 210 mmol) and NaH_2PO_4 (37.7 g, 273 mmol) in H_2O (105 ml). The solution was stirred for 10 min at room temperature and then quenched with saturated aqueous NH_4Cl (250 ml). The resultant mixture was extracted with $CHCl_3$ (3×500 ml) and combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography ($CHCl_3$/MeOH=1:0∼50:1) provided [(2*S*),3a*R*,8a*S*]-3a-(*tert*-butyldimethylsilyloxy)-8-(2-carboxypropyl)-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole (6.5 g, 82% yield, 3 steps) as a light orange oil: $[\alpha]_D^{27}$ −78.3 (*c* 1.69, $CHCl_3$); IR (KBr) 2954(s), 1711(s), 1610(s), 1491(s), 1466(m), 1257(m), 1142(s) 1034(m) cm^{-1}; ^1H

NMR (270 MHz, $CDCl_3$) δ 7.19 (1H, d, J=6.9 Hz), 7.16 (1H, dd, J=7.9, 7.6 Hz), 6.71 (1H, dd, J=7.6, 6.9 Hz), 6.48 (1H, d, J=7.9 Hz), 5.22 (1H, s), 3.98 (1H, m), 3.57 (1H, dd, J=14.2, 7.6 Hz), 3.45 (1H, m), 3.41 (1H, dd, J=14.2, 6.9 Hz), 2.96 (1H, m), 2.45 (1H, m), 2.29 (1H, m), 1.27 (3H, d, J=6.9 Hz), 0.85 (9H, s), −0.23 (3H, s), −0.26 (3H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 181.7, 151.1, 130.6, 130.4, 125.1, 118.2, 106.4, 103.1, 89.9, 67.5, 49.0, 43.8, 40.1, 26.1 (3C), 18.4, 15.7, −3.2, −3.4; HRMS (FAB, NBA matrix) m/z: 377.1994 [$(M)^+$; Calcd for $C_{20}H_{31}NO_4Si$: 377.2022].

3.3.8. [(2*S*),3a*R*,8a*S*]-3a-(*tert*-Butyldimethylsilyloxy)-8-(2-methoxycarbonylpropyl)-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole (−)-34. At room temperature a solution of [(2*S*),3a*R*,8a*S*]-3a-(*tert*-butyldimethylsilyloxy)-8-(2-carboxypropyl)-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole (1.2 g, 3.18 mmol) in benzene/MeOH (10/1 v/v) (32 ml) was added $TMSCHN_2$ (2.0 M in hexane, 1.9 ml, 3.8 mmol) and the solution was stirred for 30 min at room temperature. The resultant mixture was concentrated in vacuo. Flash chromatography (hexane/EtOAc=50:1) provided (−)-**34** (1.14 g, 92% yield) as a light yellow oil: $[\alpha]_D^{27}$ −79.5 (*c* 1.17, $CHCl_3$); IR (KBr) 2931(m), 1741(s), 1610(m), 1491(s), 1464(m), 1317(m), 1257(m), 1142(s), 1038(s) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.18 (1H, d, J=7.3 Hz), 7.15 (1H, dd, J=7.9, 7.6 Hz), 6.69 (1H, dd, J=7.6, 7.3 Hz), 6.46 (1H, d, J=7.9 Hz), 5.19 (1H, s), 4.00 (1H, m), 3.65 (3H, s), 3.56 (1H, dd, J=14.2, 7.9 Hz), 3.43 (1H, m), 3.38 (1H, dd, J=14.2, 6.6 Hz), 2.93 (1H, m), 2.44 (1H, m), 2.28 (1H, m), 1.23 (3H, d, J=7.3 Hz), 0.85 (9H, s), −0.18 (3H, s), −0.20 (3H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 175.8, 150.7, 130.1, 129.8, 124.6, 117.5, 105.8, 102.5, 89.5, 66.9, 51.6, 48.7, 43.4, 39.5, 25.6 (3C), 17.9, 15.4, −3.3, −3.9; HRMS (FAB, NBA matrix) m/z: 391.2180 [$(M)^+$; Calcd for $C_{21}H_{33}NO_4Si$: 391.2179].

3.3.9. [(2*S*,3ξ),3a*R*,8a*S*]-3a-(*tert*-Butyldimethylsilyloxy)-8-(3-hydroxy-2-methoxycarbonyl-2,4-dimethyl-4-pentenyl)-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole 41. To a solution of LDA (0.5 M in THF, 0.60 ml, 0.30 mmol) at −78 °C was added (−)-**34** (47 mg, 0.12 mmol) in THF (0.60 ml) dropwise. The solution was stirred for 2 h, and then a solution of **14** (30 μl, 0.36 mmol) in THF (0.73 ml) was added. The reaction was stirred for 6 min at −78 °C and then quenched with saturated aqueous NH_4Cl (2 ml), warmed to room temperature and stirred 5 min further. The resultant mixture was extracted with EtOAc (3×10 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Preparative TLC (hexane/EtOAc=5:1) furnished **41** (54 mg, 96% yield) as a light yellow oil: IR (KBr) 3437, 1734, 1610, 1487, 1464 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.19 (complex 2H), 6.78–6.48 (complex m, 2H), 5.10–4.63 (complex m, 3H), 4.15–3.45 (complex m, 5H), 3.72, 3.70, 3.65, 3.64 (s, total 3H), 2.38 (m, 2H), 1.73, 1.67, 1.57 (s, total 3H), 1.29, 1.26, 1.24 (s, total 3H), 0.91, 0.85, 0.81, 0.75 (s, total 9H), −0.14, −0.15, −0.19, −0.20, −0.21 (s, total 6H); HRMS (FAB, NBA, NaI matrix) m/z: 484.2493 [$(M+Na)^+$, Calcd for $C_{25}H_{39}O_5NSiNa$: 484.2495].

3.3.10. [(2*S*),3a*R*,8a*S*]-3a-(*tert*-Butyldimethylsilyloxy)-8-(2-methoxycarbonyl-2,4-dimethyl-3-oxo-4-pentenyl)-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole (−)-42. At room temperature a solution of **41** (7.6 mg, 0.017 mmol) in CH_2Cl_2 (0.83 ml) was treated with Dess–Martin periodinane (21 mg, 0.049 mmol), and the solution was stirred for 35 min quenched with H_2O (2 ml). The resultant mixture was extracted with $CHCl_3$ (3×5 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Preparative TLC (17% EtOAc/hexanes) provided (−)-**42** (7.4 mg, 98%) as a light yellow oil: $[\alpha]_D^{26}$ −86.0 (*c* 0.57, $CHCl_3$); IR (KBr) 1739, 1676, 1610, 1486, 1464 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.18 (d, J=7.6 Hz, 1H), 7.14 (dd, J=7.9, 7.3 Hz, 1H), 6.71 (dd, J=7.6, 7.3 Hz, 1H), 6.13 (d, J=7.9 Hz, 1H), 5.72, 5.70 (s, each 1H), 5.08 (s, 1H), 4.14 (d, J=15.2 Hz, 1H), 3.96, (m, 1H), 3.65 (s, 3H), 3.64 (d, J=15.2 Hz, 1H), 3.39 (m, 1H), 2.43, 2.26 (m, each 1H), 1.90 (s, 3H), 1.59 (s, 3H), 0.86 (s, 9H), −0.16, −0.17 (s, each 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 198.6, 174.0, 151.8, 142.7, 130.3, 129.8, 124.6, 123.7, 118.1, 106.5, 102.9, 89.6, 66.7, 58.0, 52.5, 52.5, 43.8, 25.7, 20.7, 19.2, 18.0, −3.2, −3.8; HR-MS (FAB, NBA, NaI matrix) m/z: 482.2390 [$(M+Na)^+$, Calcd for $C_{25}H_{37}O_5NSi$: 482.2339].

3.3.11. 3-Trimethylsilyl-2-diethylphosphonopropionic acid ethyl ester. To a solution of NaH (84 mg, 2.10 mmol, 60% in mineral oil) in DME (2.0 ml) at 0 °C was added a solution of $(EtO)_2P(O)CH_2CO_2Et$ **43** (400 μl, 2.00 mmol) dropwise. After being stirred for 30 min at room temperature, (iodomethyl)trimethylsilane (359 μl, 2.40 mmol) was added, and mixture was warmed to 70 °C for 2 h 20 min. Saturated aqueous NH_4Cl (5 ml) was added to quench the reaction, and the aqueous mixture was extracted with $CHCl_3$ (3×10 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc=2:1) provided 3-trimethylsilyl-2-diethylphosphonopropionic acid ethyl ester (596 mg, 1.92 mmol, 96% yield) as a colorless oil: IR (KBr) 2981(m), 1736(s), 1323(m), 1252(s), 1055(s), 1028(s) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.12 (6H, m), 2.91 (1H, m), 1.29 (6H, t, J=6.9 Hz), 1.25 (3H, t, J=6.9 Hz), 1.22 (1H, m), 1.00 (1H, m), −0.03 (9H, s); HRMS (FAB, NBA matrix) m/z: 311.1441 [$(M+H)^+$; Calcd for $C_{12}H_{28}O_5PSi$: 311.1444].

3.3.12. 2-Trimethylsilylmethyl-2-heptenoic acid ethyl ester 44 (*Z*:*E*=3:1). To a solution of 3-trimethylsilyl-2-diethylphosphonopropionic acid ethyl ester (85 mg, 0.27 mmol) in DME (1.4 ml) at 0 °C was added NaH (14 mg, 0.36 mmol, 60% in mineral oil). After being stirred for 15 min at room temperature, valeraldehyde (38 μl, 0.36 mmol) was added, and mixture was stirred for 7 min. Saturated aqueous NH_4Cl (3 ml) was added to quench the reaction, and the aqueous mixture was extracted with $CHCl_3$ (3×7 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc=100:1) provided **44** (56 mg, 0.23 mmol, 85% yield, *Z*: *E*=3: 1) as a colorless oil: IR (KBr) 2958(m), 1713(s), 1248(s), 1173(m) cm^{-1}.

Z-isomer. ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.60 (1H, t, J=7.3 Hz), 4.16 (2H, q, J=7.3 Hz), 2.09 (2H, m), 1.80 (2H, bs), 1.38 (4H, m), 1.28 (3H, t, J=7.3 Hz), 0.91 (3H, t, J=6.9 Hz), −0.01 (9H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.5, 139.7, 131.0, 61.4, 32.0, 29.9, 23.6, 18.3, 15.3, 15.0, 0.0 (3C)

E-isomer. ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.65 (1H, t, J= 7.6 Hz), 4.16 (2H, q, J=7.3 Hz), 2.38 (2H, m), 1.71 (2H, bs), 1.38 (4H, m), 1.28 (3H, t, J=7.3 Hz), 0.88 (3H, t, J= 7.3 Hz), −0.03 (9H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.6, 140.2, 130.2, 61.0, 33.0, 30.4, 25.1, 23.5, 15.3, 15.0, −0.6 (3C); MS (FAB, NBA matrix) *m/z*: 243 $[M+H]^+$.

3.3.13. 2-Trimethylsilylmethyl-2-heptenoic acid. At room temperature **44** (54 mg, 0.22 mmol, *Z*: *E*=3: 1) was dissolved in 20% H_2O–EtOH solution and KOH (38 mg, 0.67 mmol) was added. The mixture was warmed to 85 °C and stirred for 3 h 20 min. After being cooled to room temperature, the reaction mixture was diluted with saturated aqueous NH_4Cl (2 ml) and $CHCl_3$ (5 ml), and then neutralized with 1.0 N aqueous HCl solution. The mixture was extracted with $CHCl_3$ (3×5 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc=3:1) provided **2**-trimethylsilylmethyl-2-heptenoic acid (35 mg, 0.16 mmol, 72% yield, *Z*: *E*=5.5: 1) as a colorless oil: IR (KBr) 2958(m), 1684(s), 1248(m) cm^{-1}

Z-isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (1H, t, J= 7.3 Hz), 2.12 (2H, m), 1.80 (2H, bs), 1.38 (4H, m), 0.91 (3H, t, J=7.3 Hz), 0.01 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 141.5, 129.3, 30.8, 29.0, 22.5, 16.9, 13.9, −1.1 (3C).

E-isomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (1H, t, J= 7.5 Hz), 2.48 (2H, m), 1.74 (2H, bs), 1.38 (4H, m), 0.90 (3H, t, J=7.0 Hz), 0.00 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 142.9, 128.3, 31.9, 29.6, 23.7, 22.4, 13.9, −1.7 (3C); HRMS (FAB, NBA, PEG200+NaI matrix) *m/z*: 237.1275 $[(M+Na)^+$; Calcd for $C_{11}H_{22}O_2SiNa$: 237.1287].

3.3.14. (*Z*)-2-Trimethylsilylmethyl-2-heptenoyl chloride 33b. At room temperature 2-trimethylsilylmethyl-2-heptenoic acid (66.3 mg, 0.31 mmol) was dissolved in $SOCl_2$ (0.77 ml) and the mixture was warmed to 80 °C and stirred for 4 h. The resultant mixture was concentrated, which was afforded **33b** (77 mg, 0.31 mmol, 100% yield) as a light brown oil. The product was not measured and was used in next step.

3.3.15. 2-(1-Hydroxyethyl)-3-trimethylsilylhexanoic acid ethyl ester 46. To a solution of hexamethyldisilane (1.21 ml, 5.9 mmol) in HMPA (4.7 ml) at 0 °C was added MeLi (1.14 M in Et_2O, 4.11 ml, 4.7 mmol). After being stirred for 15 min at 0 °C, the solution was diluted with THF (23.4 ml) and cooled to −78 °C. A solution of **45** (500 mg, 3.52 mmol) in THF (7.0 ml) was added, and mixture was stirred for 5 min. Acetaldehyde (593 µl, 10.6 mmol) was then added, and the resultant mixture was stirred for 7 min at −78 °C and then quenched with saturated aqueous NH_4Cl (10 ml), warmed to room temperature and stirred for 5 min further. The resultant mixture was extracted with AcOEt (100 ml) and the extracts was washed with H_2O (3× 30 ml). The AcOEt solution was dried over Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc= 20:1) provided **46** (660 mg, 2.54 mmol, 72% yield) as a colorless oil: IR (KBr) 3448(s), 2958(m), 1730(s), 1377(m), 1248(s) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 4.12 (2H, m), 4.07 (1H, m), 2.50 (1H, m), 1.46 (1H, m), 1.41 (4H, m), 1.26 (3H, m), 1.18 (3H, d, J=6.6 Hz), 0.86 (3H, t, J=6.9 Hz), 0.06 (9/11H, s), 0.04 (18/11H, s), 0.01 (36/11H, s), −0.01 (36/11H, s); MS (FAB, NBA matrix) *m/z*: 261 $[M+H]^+$.

3.3.16. 2-(1-Methanesulfonyloxyethyl)-3-trimethylsilylhexanoic acid ethyl ester. At room temperature a solution of **46** (401 mg, 1.54 mmol) and *i*Pr_2NEt (672 µl, 3.86 mmol) in CH_2Cl_2 (7.7 ml) was treated with MsCl (239 µl, 3.08 mmol), and the reaction mixture was stirred for 10 min, quenched with H_2O (10 ml), extracted with $CHCl_3$ (3×15 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc=15:1) provided 2-(1-methanesulfonyloxyethyl)-3-trimethylsilylhexanoic acid ethyl ester (501 mg, 1.48 mmol, 96% yield) as a light yellow oil: IR (KBr) 2958(m), 1732(s), 1358(m), 1249(m), 1178 (s) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.07 (1H, m), 4.13 (2H, m), 3.02 (1H, s), 2.97 (1/2H, s), 2.95 (3/2H, s), 2.78 (1H, m), 1.50 (1H, m), 1.45 (4H, m), 1.29 (3H, m), 1.28 (3H, m), 0.91 (3H, t, J=7.3 Hz), 0.06 (9H, s); HRMS (FAB, NBA matrix) *m/z*: 361.1501 $[(M+Na)^+$; Calcd for $C_{14}H_{30}O_5SSiNa$: 361.1481].

3.3.17. 2-Ethylidene-3-trimethylsilylhexanoic acid. At room temperature 2-(1-methanesulfonyloxyethyl)-3-trimethylsilylhexanoic acid ethyl ester (49 mg, 0.146 mmol) was dissolved in 1.5 N KOH in 20% H_2O–EtOH. The mixture was warmed to 85 °C and stirred for 39 h. After being cooled to room temperature, the reaction mixture was diluted with H_2O (2 ml) and $CHCl_3$ (3 ml), and then neutralized with 1.0 N aqueous HCl solution. The mixture was extracted with $CHCl_3$ (3×5 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc=3:1) provided 2-ethylidene-3-trimethylsilylhexanoic acid (31 mg, 0.146 mmol, 100% yield, *Z*: *E*=4: 1) as a light yellow oil: IR (KBr) 2956(m), 1684(s), 1248(m) cm^{-1}.

Z-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (1H, q, J= 7.2 Hz), 2.03 (1H, m), 1.78 (3H, d, J=7.2 Hz), 1.78 (1H, m), 1.47 (1H, m), 1.34 (1H, m), 1.13 (1H, m), 0.86 (3H, t, J=7.2 Hz), 0.01 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 137.5, 134.8, 30.4, 28.1, 22.9, 14.7, 13.9, −1.5 (3C);

E-isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (1H, q, J= 7.3 Hz), 2.03 (1H, m), 2.03 (3H, d, J=7.3 Hz), 1.78 (1H, m), 1.47 (1H, m), 1.35 (1H, m), 1.15 (1H, m), 0.87 (3H, t, J=7.5 Hz), −0.02 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 134.9, 133.8, 32.1, 31.5, 21.8, 16.1, 13.9, −2.7 (3C);HRMS (FAB, NBA matrix) *m/z*: 214.1375 $[(M)^+$; Calcd for $C_{11}H_{22}O_2Si$: 214.1389].

3.3.18. (*Z*)-2-Ethylidene-3-trimethylsilylhexanoic acid ethyl ester 33a. At room temperature 2-ethylidene-3-trimethylsilylhexanoic acid (58.6 mg, 0.27 mmol) was dissolved in $SOCl_2$ (0.68 ml) and the mixture was warmed to 80 °C and stirred for 4 h. The resultant mixture was concentrated, which was afforded **33a** (68 mg, 0.27 mmol, 100% yield) as a light brown oil. The product was not measured and was used in next step.

3.3.19. (*Z*)-[(2*S*),3a*R*,8a*S*]-3a-(*tert*-Butyldimethylsilyloxy)-8-(2-methoxycarbonyl-2-methyl-4-trimethylsilylmethyl-3-oxo-4-nonenyl)-3,3a,8,8a-tetrahydro-2*H*-

furo[2,3-*b*]indole (−)-32b. To a solution of LDA (0.5 M in THF, 0.79 ml, 0.39 mmol) at −78 °C was added (−)-**34** (60.6 mg, 0.155 mmol) in THF (0.77 ml) dropwise. The solution was stirred for 2 h, and then a solution of **33b** (77 mg, 0.31 mmol) in THF (0.62 ml) was added. The reaction was stirred for 5 min at −78 °C and then quenched with H_2O (3 ml) and saturated aqueous NH_4Cl (3 ml), warmed to room temperature and stirred 5 min further. The resultant mixture was extracted with EtOAc (3×10 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Preparative TLC (hexane/EtOAc=8:1) furnished (−)-**32b** (90 mg, 0.154 mmol, 99% yield) as a light yellow oil: $[\alpha]_D^{27}$ −104.0 (*c* 0.85, $CHCl_3$); IR (KBr) 2954(s), 1738(s), 1662(s), 1610(m), 1487(s), 1466(m), 1250(s), 1140(s), 1045(m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.17 (1H, d, *J*=7.3 Hz), 7.13 (1H, dd, *J*=7.9, 7.3 Hz), 6.71 (1H, dd, *J*=7.3, 7.3 Hz), 6.44 (1H, d, *J*=7.9 Hz), 6.29 (1H, t, *J*=7.3 Hz), 5.04 (1H, s), 4.13 (1H, d, *J*=15.2 Hz), 3.97 (1H, m), 3.63 (3H, s), 3.61 (1H, d, *J*=15.2 Hz), 3.40 (1H, m), 2.42 (1H, m), 2.25 (1H, m), 2.14 (2H, m), 1.84 (1H, d, *J*=13.5 Hz), 1.75 (1H, d, *J*=13.5 Hz), 1.61 (3H, s), 1.36 (4H, m), 0.91 (3H, t, *J*=6.9 Hz), 0.86 (9H, s), 0.00 (9H, s), −0.14 (3H, s), −0.16 (3H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 199.0, 175.5, 153.0, 140.5, 138.6, 131.6, 130.7, 125.4, 118.9, 107.5, 103.6, 90.6, 67.6, 58.4, 54.1, 53.0, 44.9, 31.8, 30.3, 26.6 (3C), 23.4, 22.6, 18.9, 17.8, 14.8, 0.0 (3C), −2.3, −2.9; HRMS (FAB, NBA matrix) *m/z*: 587.3465 $[(M)^+$; Calcd for $C_{32}H_{53}NO_5Si_2$: 587.3462].

3.3.20. (+)-Madindoline B (+)-2. At room temperature a solution of (−)-**32b** (8.5 mg, 0.0145 mmol) in DMF (1.45 ml) was treated with tris(dimethylamino)sulfur(trimethylsilyl)difluoride (19.9 mg, 0.0724 mmol). The reaction mixture was stirred for 30 min, and then quenched with H_2O (3 ml), extracted with $CHCl_3$ (3×6 ml), and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Preparative TLC ($CHCl_3$/acetone=9:1) furnished *(+)-madindoline B* (+)-**2** (3.0 mg, 0.0081 mmol, 56% yield) as a light yellow crystal; mp 115–116 °C; $[\alpha]_D^{27}$ +85.3 (*c* 0.45, MeOH); IR (KBr) 3429(s), 2931(m), 1738(w), 1692(s), 1612(m), 1489(m), 1383(m), 1282 (m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.19 (1H, m), 7.19 (1H, m), 6.74 (1H, dt, *J*=7.2, 1.0 Hz), 6.62 (1H, d, *J*=8.2 Hz), 4.91 (1H, s), 3.84 (1H, ddd, *J*=12.0, 7.8, 1.5 Hz), 3.69 (1H, d, *J*=14.8 Hz), 3.48 (1H, d, *J*=14.8 Hz), 3.16 (1H, ddd, *J*=12.0, 9.1, 5.0 Hz), 2.46 (1H, m), 2.37 (1H, m), 2.33 (1H, ddd, *J*=12.0, 7.9, 1.5 Hz), 2.19 (1H, ddd, *J*=12.0, 5.0, 1.5 Hz), 1.94 (3H, s), 1.39 (2H, m), 1.26 (2H, m), 1.13 (3H, s), 0.86 (3H, t, *J*=7.0 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 206.6, 205.6, 160.3, 153.7, 150.4, 130.5, 129.4, 123.5, 119.0, 107.8, 105.1, 87.9, 66.7, 52.1, 50.5, 41.2, 29.5, 24.0, 22.9, 17.5, 13.8, 9.1; HRMS (FAB, NBA matrix) *m/z*: 369.1943 $[(M)^+$; Calcd for $C_{22}H_{27}NO_4$: 369.1940].

3.3.21. (*Z*)-[(2*S*),3a*R*,8a*S*]-3a-(*tert*-Butyldimethylsilyloxy)-8-(4-ethylidene-2-methoxycarbonyl-2-methyl-5-trimethylsilyl-3-oxo-octanyl)-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole 32a. *For small scale*. To a solution of LDA (0.5 M in THF, 0.70 ml, 0.34 mmol) at −78 °C was added (−)-**34** (53.5 mg, 0.137 mmol) in THF (0.69 ml) dropwise. The solution was stirred for 2 h, and then a solution of **33a** (68 mg, 0.27 mmol) in THF (0.55 ml) was added. The reaction was stirred for 6 min at −78 °C and then quenched with H_2O (3 ml) and saturated aqueous NH_4Cl (2 ml), warmed to room temperature and stirred 5 min further. The resultant mixture was extracted with EtOAc (3×7 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Preparative TLC (hexane/EtOAc=8:1) furnished **32a** (70 mg, 0.120 mmol, 88% yield) as a light yellow oil: IR (KBr) 2954(s), 1740(s), 1664(s), 1610(s), 1487(s), 1466(m), 1248(s), 1142(s), 1045(m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.17 (1H, d, *J*=7.3 Hz), 7.14 (1H, dd, *J*=7.9, 7.6 Hz), 6.70 (1H, dd, *J*=7.6, 7.3 Hz), 6.48 (1H, d, *J*=7.9 Hz), 6.46 (1H, d, *J*=6.9 Hz), 5.00 (1H, s), 4.07 (1H, d, *J*=15.2 Hz), 3.96 (1H, m), 3.65 (1H, d, *J*=15.2 Hz), 3.64 (3H, s), 3.40 (1H, m), 2.43 (1H, m), 2.26 (1H, m), 1.76 (3H, d, *J*=6.9 Hz)1.61 (3H, s), 1.61 (1H, m), 1.61 (1H, m), 1.43 (1H, m), 1.25 (1H, m), 1.14 (1H, m), 0.87 (9H, s), 0.86 (3H, t, *J*=6.9 Hz), 0.01 (9H, s), −0.14 (3H, s), −0.15 (3H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 200.3, 175.8, 153.4, 145.3, 135.7, 131.3, 131.0, 125.7, 119.1, 107.8, 103.1, 90.9, 68.0, 59.1, 53.4, 53.2, 45.2, 31.6, 30.0, 26.8 (3C), 24.0, 22.7, 19.1, 16.0, 15.2, 0.0 (3C), −2.0, −2.7; HRMS (FAB, NBA matrix) *m/z*: 588.3554 $[(M+H)^+$; Calcd for $C_{32}H_{54}NO_5Si_2$: 588.3541].

For large scale. Following the procedure described above for the preparation of **32a**, C-acylation of (−)-**34** (1.94 g, 4.96 mmol) and 2.0 equiv of **33a** gave **32a** (2.45 g, 84%). Total 9.5 g of **32a** was prepared in this manner.

3.3.22. (+)-Madindoline A (+)-1. *For small scale*. At 70 °C a solution of **32a** (9.5 mg, 0.0145 mmol) in DMF (1.62 ml) was treated with tetrabutylammonium triphenyldifluorosilicate (48.1 mg, 0.0809 mmol). The reaction mixture was stirred for 1 h 45 min, and then cooled to room temperature and quenched with H_2O (2 ml), extracted with $CHCl_3$ (3×6 ml), and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Preparative TLC ($CHCl_3$/acetone=9:1) furnished *(+)-madindoline A* (+)-**1** (3.1 mg, 0.0084 mmol, 52% yield) as a light yellow crystal; mp 83–86 °C; $[\alpha]_D^{26}$ +65.1(*c* 1.56, MeOH); IR (KBr) 3400(s), 2933(m), 1740(w), 1695(s), 1605(m), 1487(m), 1382(m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.20 (1H, m), 7.19 (1H, m), 6.76 (1H, dt, *J*=7.3, 0.5 Hz), 6.63 (1H, d, *J*=7.9 Hz), 4.93 (1H, s), 3.85 (1H, m), 3.70 (1H, d, *J*=14.5 Hz), 3.46 (1H, d, *J*=14.5 Hz), 3.16 (1H, m), 2.39 (1H, m), 2.37 (1H, m), 2.34 (1H, dd, *J*=12.0, 8.0 Hz), 2.18 (1H, ddd, *J*=12.0, 5.0, 1.5 Hz), 2.00 (3H, s), 1.29 (2H, m), 1.19 (2H, m), 1.13 (3H, s), 0.77 (3H, t, *J*=6.9 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 206.4, 206.3, 157.7, 156.6, 150.5, 130.5, 129.5, 123.5, 119.1, 108.0, 106.2, 87.9, 66.6, 53.7, 50.6, 41.1, 29.9, 23.5, 22.7, 17.3, 13.6, 9.4; HRMS (FAB, NBA matrix) *m/z*: 370.2017 $[(M+H)^+$; Calcd for $C_{22}H_{28}NO_4$: 370.2018].

For large scale. Following the procedure described above for the preparation of (+)-madindoline A, cyclization and deprotection of **32a** (2.06 g, 3.51 mmol) with 5.0 equiv of TBAT (10.4 g, 17.6 mmol) gave *(+)-madindoline A* (544 mg, 1.47 mmol, 42%). Total 2.1 g of *(+)-madindoline A* was prepared in this manner.

3.4. Preparation of radioactive (+)-1

To a solution of (+)-madindoline A (4.2 mg, 0.011 mmol) in *t*-BuOH (0.3 ml) at room temperature was added $[^3H]_2O$ (37 GBq(1 Ci)/g, 0.5 ml), followed by *t*-BuOK (45 mg, 0.40 mmol). The solution was stirred for 20 h at room temperature and quenched with saturated aqueous NH_4Cl (5.0 ml). The mixture was then extracted with $CHCl_3$ (3× 7 ml) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. HPLC (PEGASIL-B ODS 20ϕ× 250 mm column; mobile phase, 50% CH_3CN/H_2O; Flow rate, 9.0 ml/min; Detection, UV at 210 nm) provided [^{3}H]-(+)-madindoline A (4.2 mg, 442.8 MBq/mmol) as a light yellow crystal.

Acknowledgements

We are grateful to Professor Amos B. Smith, III for his helpful suggestions. This work was supported by the Ministry of Education, Science, Sports and Culture, Japan and the Japan Keirin Association, the Grant of the 21st Century COE Program, and a Kitasato University Research Grant for Young Researchers (T.S.). We also thank the JSPS for a predoctoral fellowship to T.H.

References and notes

1. (a) Kishimoto, T.; Akira, S.; Taga, T. *Science* **1992**, *258*, 593–597. (b) Hirano, T. *Int. Rev. Immunol.* **1998**, *16*, 249–284 and references cited therein.
2. Strassmann, G.; Masui, Y.; Chizzonite, R.; Fong, M. *J. Immunol.* **1993**, *150*, 2341–2345.
3. Yoshizaki, K.; Matsuda, T.; Nishimoto, N.; Kuritani, T.; Taeho, L.; Aozasa, K.; Nakahata, T.; Kawai, H.; Tagoh, H.; Komori, T.; et al *Blood* **1989**, *74*, 1360–1367.
4. Takagi, N.; Mihara, M.; Moriya, Y.; Nishimoto, N.; Yoshizaki, K.; Kishimoto, T.; Takeda, Y.; Ohsugi, Y. *Arthritis Rheum.* **1998**, *41*, 2117–2121.
5. de la Mata, J.; Uy, H. L.; Guise, T. A.; Story, B.; Boyce, B. F.; Mundy, G. R.; Roodman, G. D. *J. Clin. Invest.* **1995**, *95*, 2846–2852.
6. Zhang, X. G.; Bataille, R.; Jourdan, M.; Saeland, S.; Banchereau, J.; Mannoni, P.; Klein, B. *Blood* **1990**, *76*, 2599–2605.
7. Hayashi, M.; Kim, Y.-P.; Takamatsu, S.; Enomoto, A.; Shinose, M.; Takahashi, Y.; Tanaka, H.; Komiyama, K.; Omura, S. *J. Antibiot.* **1996**, *49*, 1091–1095.
8. Takamatsu, S.; Kim, Y.-P.; Enomoto, A.; Hayashi, M.; Tanaka, H.; Komiyama, K.; Omura, S. *J. Antibiot.* **1997**, *50*, 1069–1072.
9. Hayashi, M.; Fukami, A.; Rho, M.-C.; Sekiguchi, Y.; Sunazuka, T.; Hirose, T.; Komiyama, K.; Omura, S. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 14728–14733.
10. (a) Sunazuka, T.; Hirose, T.; Shirahata, T.; Harigaya, Y.; Hayashi, M.; Komiyama, K.; Omura, S.; Smith, A. B., III *J. Am. Chem. Soc.* **2000**, *122*, 2122–2123. (b) Hosokawa, S.; Sekiguchi, K.; Enemoto, M.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 6429–6433. (c) Hosokawa, S.; Sekiguchi, K.; Hayase, K.; Hirukawa, Y.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 6435–6439. (d) Hosokawa, S.; Kobayashi, S. *J. Synth. Org. Chem., Jpn.* **2001**, *59*, 1103–1108. (e) Hirose, T.; Sunazuka, T.; Shirahata, T.; Yamamoto, D.; Harigaya, Y.; Kuwajima, I.; Omura, S. *Org. Lett.* **2002**, *4*, 501–503. (f) McComas, C. C.; Perales, J. B.; Van Vranken, D. L. *Org. Lett.* **2002**, *4*, 2337–2340.
11. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.
12. Racemic 3a-hydroxyfuroindoline (±)-**4** had been prepared previously by photosensitized oxygenation of tryptophol **3**; see: Saito, I.; Imuta, M.; Nakada, A.; Matsugo, S.; Matsuura, T. *Photochem. Photobiol.* **1978**, *28*, 531 and references cited therein.
13. The structural assignment to each new compound is in accord with its IR, ^{1}H and ^{13}C NMR, and high-resolution mass spectra.
14. Compound (−)-**5**, $C_{21}H_{20}NO_4F_3$, MW 407.39 was obtained as clear colorless crystals, space group *P*1, $a=10.858(2)$ Å, $b=11.320(2)$ Å, $c=8.507(2)$ Å, $Z=2$, $D_{calcd}=1.380$ g/cm^3, No. of observations ($I>0.00\sigma(I)$) 3370; *R* 0.076; *Rw* 0.077. Crystallographic data of (−)-**5** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 267697. Copies of the data can be obtained, free of charge, on application to CDCC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
15. Lance, C. F. *Synthesis* **1975**, 135 and references cited therein.
16. Flaugh, M. E.; Mullen, D. L.; Fuller, R. W.; Mason, N. R. *J. Med. Chem.* **1988**, *31*, 1746–1753.
17. White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *55*, 619–630.
18. (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2036–2056 and references cited therein. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388.
19. Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001–7031.
20. The absolute stereochemistry of **17** was randomly selected.
21. Fráter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269–1277.
22. Gelas, J.; Horton, D. *Heterocycles* **1981**, *16*, 1587–1601.
23. Leblanc, Y.; Fitzsimmons, B. J.; Adams, J.; Perez, F.; Rokach, J. *J. Org. Chem.* **1986**, *51*, 789–793.
24. Borrelli, S.; Paquette, L. A. *J. Am. Chem. Soc.* **1996**, *118*, 727–740.
25. (a) Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102–7104. (b) Clive, D. L. J.; Joussef, A. C. *J. Org. Chem.* **1990**, *55*, 1096–1098.
26. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
27. Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.
28. Braish, T. F.; Fuchs, P. L. *Synth. Commun.* **1986**, *16*, 111–115.
29. Synthetic (+)-**1**, $C_{22}H_{27}NO_4$, MW 369.46 was obtained as clear light yellow crystals, space group $P2_1$, $a=7.884(10)$ Å, $b=8.786(7)$ Å, $c=14.915(10)$ Å, $Z=2$, $D_{calcd}=1.21$ g/cm^3, No. of observations ($I>0.00\sigma(I)$) 1593; *R* 0.137; *Rw* 0.080. Crystallographic data of (+)-**1** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 267698. Copies of the data can be obtained, free of charge, on application to CDCC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
30. (a) Marshall, A. J.; Trometer, D. J. *Tetrahedron Lett.* **1987**, *28*,

4985–4988. (b) Mori, K.; Koseki, K. *Tetrahedron* **1988**, *44*, 6013–6020.
31. Michael addition of (−)-**4** to methyl methacrylate or acrylate to afford **34** was unsuccessful under several conditions.
32. Ramanjulu, J. M.; Joullie, M. M. *Synth. Commun.* **1996**, *26*, 1379–1384.
33. Hosomi, A.; Hashimoto, H.; Sakurai, H. *Tetrahedron Lett.* **1980**, *21*, 951–954.
34. Martin, H.; Hoffmann, R.; Rabe, J. *J. Org. Chem.* **1985**, *50*, 3849–3859.
35. Because (*E*)-isomers changed to more thermodynamically stable (*Z*)-isomers during the reactions.
36. Still, W. C. *J. Org. Chem.* **1985**, *41*, 3063–3064.
37. (a) Fujita, M.; Obayashi, M.; Hiyama, T. *Tetrahedron* **1988**, *44*, 4135–4145. (b) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436–6437.
38. Synthetic (+)-**2**, $C_{22}H_{27}NO_4$, MW 369.46 was obtained as clear light yellow crystals, space group $P2_1$, $a=7.635(1)$ Å, $b=8.999(2)$ Å, $c=14.713(1)$ Å, $Z=2$, $D_{calcd}=1.214$ g/cm^3, No. of observations ($I>0.00\sigma(I)$) 1861; R 0.068; Rw 0.068. Crystallographic data of (+)-**2** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 267699. Copies of the data can be obtained, free of charge, on application to CDCC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
39. (a) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996**, *61*, 6901–6905. (b) Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166–5167.
40. Ciapponi, L.; Graziani, R.; Paonessa, G.; Lahm, A.; Ciliberto, G.; Savino, R. *J. Biol. Chem.* **1995**, *270*, 31249–31254.
41. Paonessa, G.; Graziani, R.; De Serio, A.; Savino, R.; Ciapponi, L.; Lahm, A.; Salvati, A. L.; Toniatti, C.; Ciliberto, G. *EMBO J.* **1995**, *14*, 1942–1951.
42. Barton, V. A.; Hall, M. A.; Hudson, K. R.; Heath, J. K. *J. Biol. Chem.* **2000**, *275*, 36197–36203.
43. Barton, V. A.; Hudson, K. R.; Heath, J. K. *J. Biol. Chem.* **1999**, *274*, 5755–5761.
44. Kurth, I.; Horsten, U.; Pflanz, S.; Dahmen, H.; Kuster, A.; Grotzinger, J.; Heinrich, P. C.; Muller-Newen, G. *J. Immunol.* **1999**, *162*, 1480–1487.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 61 (2005) 6040–6045
Tetrahedron

Preparation of polystyrene-supported soluble palladacycle catalyst for Heck and Suzuki reactions

Fen-Tair Luo,[a,*] Cuihua Xue,[a,b] Sheng-Li Ko,[a] Yu-Der Shao,[c] Chien-Jung Wu[a] and Yang-Ming Kuo[c]

[a]*Institute of Chemistry, Academia Sinica, Nankang, Taipei 115, Taiwan*
[b]*The Faculty of Chemistry, Sichuan University, Chengdu 610064, China*
[c]*Institute of Applied Chemistry, Chinese Culture University, Taipei 111, Taiwan*

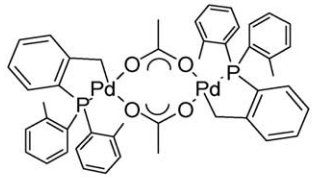
Received 26 January 2005; revised 19 April 2005; accepted 20 April 2005

Available online 17 May 2005

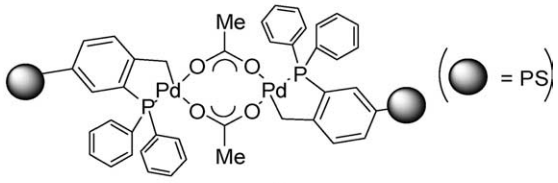
Abstract—A polystyrene-supported palladium complex soluble in tetrahydrofuran and *N*,*N*-dimethylacetamide and precipitated in diethyl ether or acetonitrile was prepared from two routes as an excellent and recyclable palladacycle catalyst for carbon–carbon bond formation in Heck and Suzuki reactions to give high yields of the desired products.

1. Introduction

The advantage of using soluble polymers to recover catalysts and ligands has its origins in the synthetic approaches to peptide and oligonucleotide synthesis that were developed in the labs of Merrifield and Letsinger in the 1960s.[1,2] Although soluble polymers were common 40 years ago, but they did not receive as much attention for using as catalyst supports as was the case for their cross-linked, insoluble analogues. However, the uses of soluble polymer systems have substantially expanded in recent years due to the point that soluble polymers are no longer uncommon as supports for catalysts and ligands.[3–5] On the other hand, palladacycles have been known for over 20 years; yet they have been used as catalysts recently.[6–10] Nitrogen-, phosphorus-, and sulfur-containing palladacycles are emerging as a new family of palladium catalyst precursors, and they have recently, become the most simple and efficient catalyst in applying to Heck-Mizoroki, Suzuki-Miyaura and Sonogashira reactions.[11] Herrmann and his co-workers have demonstrated that Herrmann's palladacycle catalyst **1** is thermally stable and efficient catalyst for Heck-Mizoroki, Suzuki-Miyaura, and Sonogashira reactions.[12–15] It also had been shown to have high reactivity toward arylation of olefins with aryl chlorides.[16] Although the palladacycle catalyst, as Herrmann reported, have high reactivity to promote a lot of reactions, only a few reports on the recovery of palladacycle catalysts were reported in the literature.[17–23] In addition, phosphorus-containing polystyrene was generally used as the ligand to trap and reuse Pd catalysts after the reaction.[24–30] In this paper, we summarized two synthetic routes for the synthesis of a polystyrene-supported palladacycle catalyst **2** which can be used as an efficient recyclable palladium catalyst for running Heck-Mizoroki and Suzuki-Miyaura reaction.[31]



1



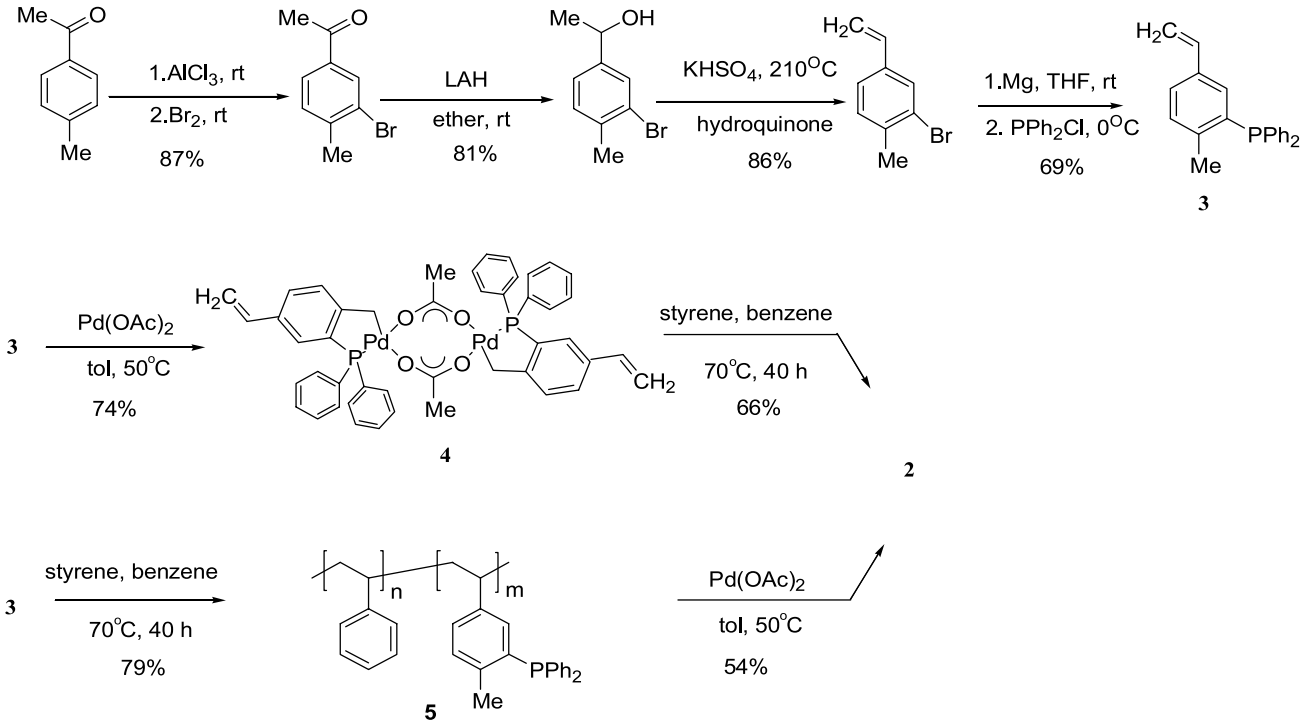
2

2. Results and discussion

The two synthetic routes of the polystyrene-supported palladacycle catalyst are shown in Scheme 1. In the first

Keywords: Supported catalyst; Heck reaction; Suzuki reaction; Recyclable catalyst; Polystyrene-bound catalyst; Palladacycle catalyst.
* Corresponding author. Tel.: +886 2 27898576; fax: +886 2 27888199; e-mail: luoft@chem.sinica.edu.tw

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.04.036

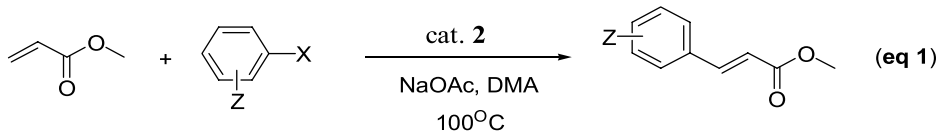


Scheme 1. Two routes for the synthesis of polystyrene-supported pallacycle catalyst **2**.

route, *trans*-di(μ-acetato)-bis[2-(diphenylphosphino)-4-vinylbenzyl]dipalladium(II) **4** was synthesized from 3-(diphenylphosphino)-4-methylstyrene **3** by heating with palladium acetate in toluene at 50 °C.[32] Compound **3** was prepared in moderate yield by bromination ($Br_2/AlCl_3$)[33] of 4-methylaceto-phenone followed by the reduction (LAH/ether), dehydration ($KHSO_4$)[34] and coupling with chloro-diphenylphosphine (Mg/THF; $ClPPh_2$).[35] Considering the proper space around the palladium in the catalyst, the palladacycle precursor **4** was copolymerized with 6 equiv of styrene at 70 °C (Route 1) to give polystyrene-supported palladacycle catalyst **2**. Alternatively, the phosphine-containing monomer **3** was copolymerized with 6 equiv of styrene at 70 °C to form the phosphine-bound polystyrene **5**, which was then heating with Pd(II) acetate in toluene at 50 °C (Route 2) to form polystyrene-supported palladacycle catalyst **2**. The exterior deep dark brown color and their ^{31}P NMR and ^{1}H NMR spectral data are the same for the catalyst **2** obtained from Route 1 and Route 2. The total yields for two routes via **4** and **5** for the preparation of polystyrene-supported palladacycle catalyst **2** were 21 and 18%, respectively, on the basis of atomic absorption analysis of palladium in **2**. The phosphorous-containing compounds were analyzed by solution phase ^{31}P NMR in $CDCl_3$. The chemical shift of phosphous in **3** appeared at −12 ppm as a singlet, while it was shifted to 17 ppm as a singlet in **4**. On the other hand, the methyl protons in **3** appeared at 2.36 ppm as a singlet, while the methylene protons in **4** appeared at 3.63 ppm as a broad singlet in ^{1}H NMR spectrum. The signal of catalyst **2** in ^{31}P NMR spectrum was observed at 53 ppm before and after Heck reaction, while the signal of catalyst **4** in ^{31}P NMR spectrum observed at 17 ppm before Heck reaction but appeared at 17 ppm along with a new peak at 53 ppm after Heck reaction (the peaks ratio at 17 and 53 ppm is about 7:3). The peak at 53 ppm in ^{31}P NMR spectrum became the sole peak after six times recycling of the catalyst **4**. Thus, the catalyst **4** was polymerized completely under the reaction conditions. On the other hand, the chemical shift of phosphorus in **5** appeared at −12 ppm as a singlet. Gel permeation chromatography analysis (mobile phase: THF, polystyrene standards) indicated that M_w of catalyst **2** prepared from Route 1 and Route 2 was 1.434×10^4 and 1.529×10^4 g/mol, respectively. Atomic absorption spectrophotometer analysis showed that palladium was containing at 86.39 and 82.91 mg of Pd per gram of **2** prepared from Route 1 and Route 2, respectively.

To test the applicability of polystyrene-supported palladacycle catalyst **2** obtained from the above two routes, we examined the Heck reaction of methyl acrylate and various aryl halide in the presence of NaOAc in *N*,*N*-dimethylacetamide as shown in Table 1. Under various reaction conditions, all the desired products were isolated in more than 90% yields. Thus, the polystyrene-supported catalyst **2** can easily promote the Heck reaction of aryl bromides- and iodides-containing with either electron-rich or electron-withdrawing group (Eq. 1), which produced only one major product as determined from GC and crude ^{1}H NMR spectral analysis. The polystyrene-supported catalyst **2** prepared with other ratio of styrene (mole ratio of styrene/**4**=3 and 9) were also synthesized and were run as the catalyst in the above Heck reaction. Gel permeation chromatography analysis (mobile phase: THF, polystyrene standards) indicated that M_w of catalyst **2** prepared from mole ratio of styrene/**4**=3 and 9 was 1.126×10^4 and 1.578×10^4 g/mol, respectively. No obvious difference was observed in the results of the above Heck reaction among these polystyrene-supported catalysts prepared from different ratio of styrene/**4**. Thus, the reactivity of catalyst

Table 1. Heck reaction of using polystyrene-supported catalyst **2**



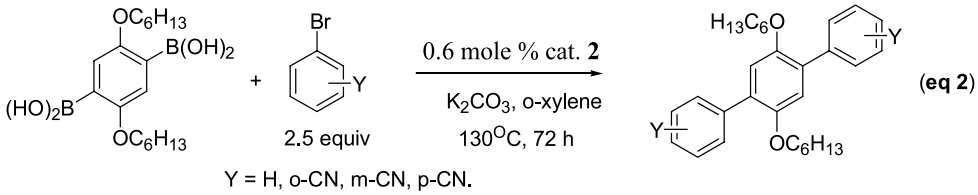
Entry	Haloarene	Catalyst **2** (equiv)	Temp (°C)	Time (h)	Iso. Yield (%)	
					Route 1	Route 2
1	Iodobenzene	0.02	100	8	>99	99
2	Bromobenzene	0.05	130	48	97	98
3	4-Bromotoluene	0.05	130	48	95	93
4	4-Bromoanisole	0.05	130	48	92	92
5	2-Bromobenzaldehyde	0.002	100	10	>99	99
6	4-Bromobenzonitrile	0.02	100	10	>99	98

2 was proved to be similar to Herrmann's palladacycle catalyst **1**. Furthermore, we also found that the reactivity of polystyrene-supported palladacycle catalyst **2** obtained from two different precursors were similar to each other based on the yields of the above model Heck reaction, although the catalyst **2** obtained from Route 2 gave a little lower yields than that from Route 1.

The polystyrene-supported catalyst **2** was soluble in tetrahydrofuran, *N*,*N*-dimethylacetamide, *N*,*N*-dimethylformamide, toluene, chloroform, dichloromethane and not very soluble in methanol, acetonitrile, hexane, and diethyl ether. Diethyl ether and acetonitrile were used here, to precipitate our new catalyst **2**. Salt removal was skipped due to the palladacycle catalyst, which can be deactivated easily by water. Probably, the phosphine ligand may form phosphine oxide in the presence of water. The Heck reaction of 4-bromobenzonitrile and methyl acrylate (1.5 equiv) with 2 mol% of catalyst **2** and NaOAc (1.5 equiv) in *N*,*N*-dimethylacetamide at 100 °C was proceeded as the model reaction. The results showed that the yield of the product can be isolated more than 80% after recycled four times with diethyl ether as the solvent to precipitate our polystyrene-supported catalyst **2**. Using acetonitrile as the solvent may drop the yield of the product below 60% after the 2nd run. The reactivity of Herrmann's catalyst **1** diminished thoroughly after recycled two times in the model reaction. We also found that the yield can be kept more than 99% after recycling 6 times, using Et_3N instead of NaOAc as the base in the model Heck reaction. The ^1H NMR and IR spectra of the recycled palladium catalysts showed no difference before and after recycling five times. The elemental analysis for the repeating unit ($C_{142}H_{138}O_4P_2Pd$) in the polystyrene-supported palladium catalyst found C, $82.12\pm0.5\%$ and H, $6.70\pm0.5\%$ before and after recycling one to three times clearly indicated the composition of the copolymer. Atomic absorption spectrophotometer analysis showed that palladium was containing at 85.43, 80.78, 74.13 mg of Pd per gram of polymer after recycling one to three times, respectively.

We also tested the applicability of catalyst **2** in Suzuki-Miyaura cross-coupling reaction. Thus, the cross-coupling of 2,5-dihexyloxy-1,4-benzenediboronic acid, prepared in 79% yield from the lithium–halogen exchange reaction of 2,5-dibromo-1,4-dihexyloxybenzene with *n*-butyllithium followed by the treatment of trimethylborate and dilute acid (2 N HCl), with 2.5 equiv of bromoarene with or without cyano groups at *o*-, *m*-, or *p*-positions in the presence K_2CO_3 as the base and catalyst **2**, prepared from Route 1 and Route 2, in *o*-xylene could give *p*-terphenyls in fair to good yields (72 to 88%) as shown in Table 2. The results showed that the activities of the catalyst **2** prepared

Table 2. Suzuki reaction of using polystyrene-supported catalyst **2**



Entry	Haloarene	Iso. Yield (%)	
		Route 1	Route 2
1	Bromobenzene	85	88
2	2-Bromobenzenecarbonitrile	72	78
3	3-Bromobenzenecarbonitrile	74	83
4	4-Bromobenzenecarbonitrile	76	84

from Route 1 and Route 2 were similar. Attempts to change the base as Et_3N or other solid bases (K_3PO_4, Cs_2CO_3) in the above Suzuki-Miyaura cross-coupling reaction gave very low yields (<20%).

3. Conclusion

We have synthesized via two routes in six steps with high yields to a new polystyrene-supported palladacycle catalyst **2** which was successfully employed in the carbon–carbon bond formation to give good yields in the Heck-Mizoroki and Suzuki-Miyaura model studies. The simple precipitation and filtration process to recycle the catalyst after our model reactions for these reactions were noteworthy. Our catalyst exhibited a high reactivity as Herrmann's palladacycle catalyst and, in addition, to its high reactivity, it gave us a promising solution to lower the reaction cost by its good recyclabilities in Heck-Mizoroki reaction of using pertinent organic bases.

4. Experimental

4.1. General

4.1.1. Synthesis of 3-bromo-4-methylacetophenone. Anhydrous aluminum chloride (30 g, 225 mmol) and one magnetic stirrer bar were put into a 100 mL of two necked round bottomed flask equipped with one septum at one neck and a pressure-equalizer dropping funnel at the other neck. Then, the flask was flushed with nitrogen through the septum. 4-Methylacetophenone (13.3 mL, 100 mmol) was added slowly from the dropping funnel to the stirred solid over a period of 10 min. The flask was stirred continuously for another 30 min after completion of the addition. Bromine (5.7 mL, 110 mmol) was added, dropwise, to the stirred, molten mass over a period of 5 min. The reaction was completed when the stirred mass solidified and no more hydrogen bromide was emitted. The solidified mass was dropped, portionwise, into 3 N HCl aqueous solution (250 mL). The dark oil at the bottom of the solution was extracted by ether (3×30 mL). The organic layer was then washed by saturated NH_4Cl aqueous solution (50 mL), dried over with $MgSO_4$, and concentrated to get the crude product. The crude product was further purified by distillation at low pressure [118 °C (3 mm Hg)] to give 18.53 g (87% yield) of the desired product. Mp 38–40 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H), 2.58 (s, 3H), 7.33 (d, J=4.7 Hz, 1H), 7.79 (dd, J=4.7, 0.99 Hz, 1H), 8.12 (d, J=0.99 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.19, 26.52, 123.21, 127.08, 130.87, 132.32, 136.46, 143.53, 196.4; IR (neat) 3024, 1684, 1599, 1383, 1521, 1039, 958, 907, 831 cm^{-1}; MS m/z 212 (M^+), 199, 197, 171, 169, 89; HRMS calcd for C_9H_9OBr: 211.9837, found: 211.9840.

4.1.2. Synthesis of 1-(3-bromo-4-methyl-phenyl)ethanol. LAH (6.45 g, 170 mmol) and one magnetic stirrer bar were added into a 250 mL of round bottomed flask, which was then closed with one septum and dried under vacuum followed by filling with nitrogen. One part of dry ether (50 mL) was first injected into the stirred LAH. The mixture of 3-bromo-4-methylacetophenone (38 g, 180 mmol) in dry ether (50 mL) was injected into the flask dropwisely. Stirring was continued after the completion of addition of 3-bromo-4-methylacetophenone until no more gas was generated. The mixture was poured into 2 N HCl aqueous solution (240 mL), extracted with EAC (4×30 mL), washed over saturated NH_4Cl aqueous solution (50 mL), dried over anhydrous $MgSO_4$, and concentrated at low pressure. The crude product was further purified by distillation at low pressure [130 °C (4 mm Hg)] to give 31.35 g (81% yield) of the desired product as clear and pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (t, J=6.4 Hz, 3H), 1.76 (s, 1H), 2.38 (s, 3H), 4.84 (q, J=6.4 Hz, 1H), 7.20 (s, 2H), 7.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.54, 25.16, 69.33, 124.30, 124.93, 129.34, 130.82, 136.88, 145.27; IR (neat) 3024, 2997, 2927, 1605, 1562, 1494, 1452, 1381, 1331, 1255, 1091, 1038, 1009, 908, 822, 733 cm^{-1}; MS m/z 214 (M^+), 199, 197, 171, 169, 119, 91; HRMS calcd for $C_9H_{11}OBr$: 213.9993, found: 213.9995.

4.1.3. Synthesis of 3-bromo-4-methyl-styrene. $KHSO_4$ (0.55 g, 34 mmol), hydroquinone (0.142 g, 1.3 mmol), and 1-(3-bromo-4-methyl-phenyl)ethanol (17.2 g, 80 mmol) were delivered into a 25 mL round bottomed flask, equipped with a distillation equipment. The mixture was kept stirring. The system was vacuumed at 3 mm Hg. The dehydration and distillation processes [102 °C (3 mm Hg)] were proceeded at the same time. The isolated product was obtained in 13.6 g (86% yield) as clear and golden yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 5.23 (d, J=10.9 Hz, 1H), 5.69 (d, J=17.6 Hz, 1H), 6.60 (dd, J=10.9, 17.6 Hz, 1H), 7.16 (d, J=7.8 Hz, 1H), 7.21 (d, J=7.8 Hz, 1H), 7.57 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.63, 114.32, 125.04, 125.09, 129.92, 130.76, 135.30, 137.11, 137.22 ppm; IR (neat) 3091, 3063, 3016, 2985, 2964, 1899, 1833, 1701, 1629, 1602, 1554, 1492, 1450, 1380, 1304, 1278, 1205, 1037, 989, 914, 833, 854, 826 cm^{-1}; MS m/z 197 (M^++1) 171, 169, 117, 115, 91, 89; HRMS calcd for C_9H_9Br: 195.9888, found: 195.9887.

4.1.4. Synthesis of 3-(diphenylphosphino)-4-methyl-styrene 3. Mg (0.72 g, 30 mmol) was added into a 50 mL of round bottomed flask, which was dried and filled with nitrogen. Dry THF (10 mL) was injected first and then stirred with Mg. Half mixture of 3-bromo-4-methyl-styrene (3.94 g, 20 mmol) in dry THF (10 mL) was injected dropwisely. After an exothermic reaction starts, the rest of the mixture was injected. The Grignard reagent was reversely added into the mixture of chlorodiphenylphosphine (5.25 g, 25 mmol) in dry THF (10 mL) at 0 °C. After completion of the addition, the temperature was raised to the room temperature. After stirring for another 20 h, the mixture was poured into a saturated NH_4Cl aqueous solution (10 mL) at 0 °C and extracted with dry THF (3×20 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated to 5 mL only. Hexane was added into the organic solution to deposit the by-products. After filtration and concentration, the residue was purified by a flash column chromatography (hexane/EAC=4:1). The isolated product was 2.42 g (39% yield). Mp 48–49 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H), 5.06 (d, J=10.9 Hz, 1H), 5.42 (d, J=17.6 Hz, 1H), 6.48 (q, J=10.9, 17.6 Hz, 1H), 6.79 (q, J=2.1, 5.8 Hz, 1H), 7.20–7.34 (m,

11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 21.1, 113.0, 126.2, 128.5, 128.6, 128.8, 130.2, 130.3, 130.7, 133.9, 134.1, 135.1, 136.0, 136.3, 136.5, 141.7 ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ −12.34 ppm; IR (neat) 3057, 3016, 2974, 1957, 1900, 1819, 1629, 1589, 1479, 1435, 1380, 1306, 1262, 1179, 1152, 1093, 1028, 992, 911, 830, 699 cm^{-1}; MS *m/z* 302 (M^+) 223, 183, 165, 152, 115, 78; HRMS calcd for $C_{21}H_{19}P$: 302.1224, found: 302.1227.

4.1.5. Synthesis of *trans*-di(μ-acetato)-bis[3-(diphenylphosphino)-4-styryl]dipalladium (II) 4. $Pd(OAc)_2$ (0.225 g, 1 mmol) was solvated in stirring dry toluene (20 mL) in a 50 mL round bottomed flask. The mixture of 3-(diphenylphosphino)-4-methyl-styrene **3** (0.333 g, 1.1 mmol) and dry toluene (4 mL) was injected into the flask. After that, the mixture was heated at 50 °C for 5 min, and then cooled slowly to the room temperature. The mixture was concentrated to one third of the original volume. Hexane (25 mL) was added to the mixture for precipitation of the product. The recrystallization was proceeded repeatedly in the system of toluene/hexane or dichloromethane/hexane. The isolated product was 0.34 g (74% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.61 (s, 6H), 3.63 (br s, 4H), 5.06 (d, J=11.1 Hz, 2H), 5.42 (d, J=17.6 Hz, 2H), 6.48 (q, J=11.1, 17.6 Hz, 2H), 7.1–7.8 (m, 26H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 17.41 ppm. IR ($CHCl_3$) ν 3058, 2921, 2860, 1653, 1561, 1435 cm^{-1}. Anal. Calcd for $C_{46}H_{42}O_4P_2Pd_2$: C, 59.18; H, 4.53. Found: C, 59.33; H, 4.68.

4.1.6. Synthesis of phosphine-bound polystyrene 5. 3-(Diphenylphosphino)-4-methyl-styrene **3** (0.33 g, 1.1 mmol) was added to a test tube and flushed with nitrogen. A mixture of styrene (0.68 g, 6.6 mmol) and benzene (2 mL) was injected into the test tube. Then, a mixture of AIBN (0.18 g, 0.1 mmol) and benzene (10 mL) was injected into the stirring test tube. The reaction mixture was then heated at 70 °C for 40 h. The mixture was concentrated to dryness. The dry solid was repeatedly washed by the solvent (THF/hexane=1:30). The isolated polymer was 0.8 g (79% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.1–1.7 (m, phenylC*H*C*H*$_2$), 2.2–2.4 (br s, Ar-C*H*$_3$), 6.2–6.7 (m, Ar-*H*), 6.8–7.3 (m, Ar-*H*) ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ −12.23 ppm; IR ($CHCl_3$) ν 3023, 2924, 2846, 1653, 1561, 1492, 1452, 756, 699 cm^{-1}. Anal. Calcd for $C_{69}H_{68}P$ (repeating unit): C, 89.28; H, 7.38. Found: C, 89.60; H, 7.84.

4.1.7. Synthesis of polystyrene-supported palladacycle catalyst 2. *trans*-Di(μ-acetato)-bis[3-(diphenylphosphino)-4-styryl]dipalladium(II) **4** (93 mg, 0.1 mmol) was added to a test tube and flushed with nitrogen. A mixture of styrene (62 mg, 0.6 mmol) and benzene (2 mL) was injected into the test tube. Then, a mixture of AIBN (18 mg, 0.01 mmol) and benzene (1 mL) was injected into the stirring test tube. The reaction mixture was then heated at 70 °C for 40 h. The mixture was concentrated to dryness. The dry solid was repeatedly washed by the solvent (THF/hexane=1:15). The isolated polymer was 0.11 g (66% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.1–2.0 (m, phenylC*H*C*H*$_2$), 2.2–2.4 (br s, Ar-C*H*$_3$), 6.3–6.7 (m, Ar-*H*), 6.8–7.4 (m, Ar-*H*) ppm; ^{31}P NMR (121 MHz, $CDCl_3$) δ 53.01 ppm. IR ($CHCl_3$) ν 3027, 2921, 2858, 1447, 912, 743 cm^{-1}; Gel permeation chromatography analysis (mobile phase: THF, polystyrene standards) indicated that M_w of catalyst **2** prepared from Route 1 and Route 2 was 1.434×10^4 and 1.529×10^4 g/mol, respectively. Atomic absorption spectrophotometer analysis showed that palladium was containing at 86.39 and 82.91 mg of Pd per gram of polymer prepared from Route 1 and Route 2, respectively.

4.1.8. Typical procedure for use of polystyrene-supported palladacycle catalyst 2 in the Heck reaction. Polystyrene-supported palladacycle catalyst **2** (30 mg, 24 μmol Pd), iodobenzene (0.20 g, 1 mmol), methyl acrylate (0.13 g, 1.5 mmol), sodium acetate (0.12 g, 1.5 mmol), and *N*,*N*-dimethylacetamide (3 mL) were sequentially added into a 15 mL septum-sealed test tube under nitrogen atmosphere. The mixture was then heated at 100 °C for 8 h. After cooling to the room temperature, the mixture was added 8 mL of dry ether to precipitate the polystyrene-supported palladacycle catalyst. After the catalyst was further precipitated by a centrifuge, the upper liquid layer of the reaction mixture was transferred via a syringe into another 20 mL round bottom flask. Repeat the above precipitation procedure one more time. The combined liquid layer was concentrated under reduced pressure. Saturated ammonium chloride solution (5 mL) was then added to the oil mixture. The organic product was extracted three times by ethyl acetate (10 mL×3), dried over magnesium sulfate, filtrated, and concentrated to give the crude product. The crude product was further purified by column chromatography (silica gel, hexane/EAC=4:1) to give 0.16 g (99% yield) of *trans*-methyl cinnamate.[36]

4.1.9. Typical procedure for the use of polystyrene-supported palladacycle catalyst 2 from Route 1 in the Suzuki-Miyaura reaction for the preparation of 2,5-dihexyloxy-1,4-di-phenylbenzene. *o*-Xylene (5 mL) was added to a mixture of 2,5-dihexyloxy-1,4-benzenediboronic acid (0.44 g, 1 mmol), bromobenzene (0.39 g, 2.5 mmol), and K_2CO_3 (0.83 g, 6 mmol) in a 10 mL round-bottomed flask under nitrogen atmosphere. A solution of catalyst **2** (0.007 g) in 1 mL of *o*-xylene was added into the above mixture at 130 °C. The mixture was cooled to room temperature after it was stirred and heated for 72 h. The mixture was added 16 mL of dry diethyl ether to precipitate the polystyrene-supported palladacycle catalyst. After the catalyst was further precipitated by a centrifuge, the upper liquid layer of the reaction mixture was transferred via a syringe into another 20 mL round bottom flask. Repeat the above precipitation procedure one more time. The combined organic layer was dried over $MgSO_4$, filtrated, and concentrated before recrystallized by EAC and MeOH to give 0.37 g (85% yield) of the desired product. Mp 67–68 °C; R_f=0.9 (hexane/EAC=4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (t, J=7 Hz, 6H), 1.26–1.36 (m, 12H), 1.65–1.68 (m, 4H), 3.90 (t, J=6.4 Hz, 4H), 6.98 (s, 2H), 7.32 (t, J=7.1 Hz, 2H), 7.41 (t, J=7.5 Hz, 4H), 7.60 (d, J=7.75 Hz, 4H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.96, 22.56, 25.72, 29.33, 31.45, 69.70, 116.44, 126.88, 127.89, 129.53, 130.91, 138.46, 150.31 ppm; IR ν 1484.8, 1400.4, 1211.4, 1054.1, 763.9, 698.1 cm^{-1}; MS *m/z* 430 (M^+), 347, 262; HRMS Calcd for $C_{30}H_{38}O_2$: 430.2872, found: 430.2869.

4.1.10. 2-[4-(2-Cyanophenyl)-2,5-dihexyloxyphenyl]-benzenecarbonitrile. Following the procedure as described for the preparation of 2,5-dihexyloxy-1,4-diphenylbenzene by using 2,5-dihexyloxy-1,4-benzenediboronic acid (0.37 g, 1 mmol), 2-bromobenzene-carbonitrile (0.45 g, 2.5 mmol), catalyst **2** (0.007 g), and K_2CO_3 (0.83 g, 6 mmol) to obtain 0.35 g (72% yield) of the desired product. Mp 129–131 °C; R_f=0.6 (*n*-hexane/EAC=4/1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.83 (t, J=7 Hz, 6H), 1.21–1.28 (m, 12H), 1.64–1.67 (m, 4H), 3.94 (t, J=6.5 Hz, 4H), 6.94 (s, 2H), 7.44 (t, J=7.6 Hz, 2H), 7.56 (d, J=7.7 Hz, 2H), 7.64 (t, J=7.7 Hz, 2H), 7.74 (d, J=7.6 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.88, 22.47, 25.53, 29.05, 31.35, 69.19, 113.21, 115.51, 118.61, 127.42, 128.52, 131.11, 132.17, 132.74, 142.17, 149.80 ppm; IR ν 2228.1, 1513.9, 1390.7, 1215.4, 1035.9, 762.8 cm^{-1}; MS *m/z* 480.2 (M^+), 412.0, 395.2, 313.1; HRMS Calcd for $C_{32}H_{36}O_2N_2$: 480.2777, found: 480.2786.

4.1.11. 3-[4-(3-Cyanophenyl)-2,5-dihexyloxyphenyl]-benzenecarbonitrile. Following the procedure as described for the preparation of 2,5-dihexyloxy-1,4-diphenylbenzene by using 2,5-dihexyloxy-1,4-benzenediboronic acid (0.37 g, 1 mmol), 3-bromobenzene-carbonitrile (0.45 g, 2.5 mmol), catalyst **2** (0.007 g), and K_2CO_3 (0.83 g, 6 mmol) to give 0.35 g (74% yield) of the desired product. Mp 100–103 °C; R_f=0.525 (*n*-hexane/EAC=4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (t, J=7.5 Hz, 6H), 1.26–1.68 (m, 12H), 1.67–1.71 (m, 4H), 3.94 (t, J=6 Hz, 4H), 6.94 (s, 2H), 7.52 (t, J=7.7 Hz, 2H), 7.63 (d, J=7.7 Hz, 2H), 7.7 (d, J=7.7 Hz, 2H), 7.89 (s, 2H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.96, 22.53, 25.75, 29.17, 31.40, 69.58, 112.21, 115.48, 118.93, 128.77, 129.21, 130.57, 133.14, 133.89, 139.29, 150.16 ppm; IR ν 2232.1, 1478.3, 1397.7, 1216.6, 1037.7, 785.9 cm^{-1}; MS *m/z* 480.2 (M^+), 397.1, 325.1, 312.1; HRMS Calcd for $C_{32}H_{36}O_2N_2$: 480.2777, found: 480.2772.

4.1.12. 4-[4-(4-Cyanophenyl)-2,5-dihexyloxyphenyl]-benzenecarbonitrile. Following the procedure as described for the preparation of 2,5-dihexyloxy-1,4-diphenylbenzene by using 2,5-dihexyloxy-1,4-benzenediboronic acid (0.37 g, 1 mmol), 4-bromobenzene-carbonitrile (0.45 g, 2.5 mmol), catalyst **2** (0.007 g), and K_2CO_3 (0.83 g, 6 mmol) to give 0.37 g (76% yield) of the desired product. Mp 152–154 °C; R_f=0.68 (*n*-hexane/EAC=4:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (t, J=7 Hz, 6H), 1.25–1.33 (m, 12H), 1.67–1.68 (m, 4H), 3.93 (t, J=6 Hz, 4H), 6.93 (s, 2H), 7.69 (s, 8H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.89, 22.48, 25.65, 29.11, 31.31, 69.56, 110.70, 115.55, 118.96, 129.82, 130.13, 131.70, 142.80, 150.18 ppm; IR ν 2226.4, 1647.6, 1601.0, 1214.5, 776.0 cm^{-1}; MS *m/z* 480.2 (M^+), 397.1, 325.1, 312.1; HRMS Calcd for $C_{32}H_{36}O_2N_2$: 480.2777, found: 480.2772.

Acknowledgements

The authors thank the National Science Council and Academia Sinica for financial supports.

References and notes

1. Merrifield, R. B. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 799.
2. Letsinger, R. L.; Mahadevan, V. *J. Am. Chem. Soc.* **1966**, *88*, 5319.
3. Clapham, B.; Reger, T. S.; Janda, K. D. *Tetrahedron* **2001**, *57*, 4637.
4. Toy, P. H.; Janda, K. D. *Acc. Chem. Res.* **2000**, *33*, 546.
5. Bergbreiter, D. E. *Curr. Opin. Drug Discovery Dev.* **2001**, *4*, 736.
6. Brody, M. S.; Finn, M. G. *Tetrahedron Lett.* **1999**, *40*, 415.
7. Ohiff, M.; Ohiff, A.; van der Boom, M. E.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119*, 11687.
8. Albisson, D. A.; Bedford, R. B.; Scully, P. N. *Tetrahedron Lett.* **1998**, *39*, 9393.
9. Beller, M.; Riermeier, T. M. *Tetrahedron Lett.* **1996**, *37*, 6535.
10. Miyazaki, F.; Yamaguchi, K.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 7379.
11. Dupont, J.; Pfeffer, M.; Spencer, J. *Eur. J. Inorg. Chem.* **2001**, *15*, 1917.
12. Herrmann, W. A.; Brossmer, C.; Ofele, K.; Reisinger, C. P.; Priermeie, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844.
13. Beller, M.; Fischer, H.; Herrmann, W. A.; Ofele, K.; Brossmer, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1848.
14. Herrmann, W. A.; Reisinger, C.-P.; Ofele, K.; Brossmer, C.; Beller, M.; Fischer, H. *J. Mol. Catal. A* **1996**, *108*, 51.
15. Herrmann, W. A.; Bohm, V. P. W.; Reisinger, C.-P. *J. Organomet. Chem.* **1999**, *576*, 23.
16. Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 481.
17. Bergbreiter, D. E.; Osburn, P. L.; Wilson, A.; Sink, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 9058.
18. Bergbreiter, D. E.; Liu, Y.-S.; Osburn, P. L. *J. Am. Chem. Soc.* **1998**, *120*, 4250.
19. Bergbreiter, D. E.; Osburn, P. L.; Liu, Y.-S.; Osburn, P. L. *J. Am. Chem. Soc.* **1999**, *121*, 9531.
20. Bergbreiter, D. E. *Catal. Today* **1998**, *42*, 389.
21. Nowotny, M.; Hanefeld, U.; Koningsveld, H.; Maschmeyer, T. *Chem. Commun.* **2000**, 1877.
22. Rocaboy, C.; Gladysz, J. A. *Org. Lett.* **2002**, *4*, 1993.
23. Herrmann, W. A.; Bohm, V. P. W. *J. Organomet. Chem.* **1999**, *572*, 141.
24. Benvenuti, F.; Carlini, C.; Marchionna, M.; Galletti, A. M. R.; Sbrana, G. *J. Mol. Catal. A* **1999**, *145*, 221.
25. Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 3820.
26. Inada, K.; Miyaura, N. *Tetrahedron* **2000**, *56*, 8661.
27. Jang, S.-B. *Tetrahedron Lett.* **1997**, *38*, 1793.
28. Jang, S.-B. *Tetrahedron Lett.* **1997**, *38*, 4421.
29. Villemin, D.; Goussu, D. *Heterocycles* **1989**, *29*, 1255.
30. McNamara, C. A.; Dixon, M. J.; Bradley, M. *Chem. Rev.* **2002**, *102*, 3275.
31. Lin, C.-A.; Luo, F.-T. *Tetrahedron Lett.* **2003**, *44*, 7565.
32. Albisson, D. A.; Bedford, R. B.; Lawrence, S. E.; Scully, P. N. *Chem. Commun.* **1998**, 2095.
33. Pearson, D. E.; Pope, H. W.; Hargrove, W. W.; Stamper, W. E. *J. Org. Chem.* **1958**, *23*, 1412.
34. Huyser, E. S.; Kim, L. *J. Org. Chem.* **1968**, *33*, 94.
35. Rabinowitz, R.; Marcus, R. *J. Org. Chem.* **1961**, *26*, 4157.
36. Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 61 (2005) 6046–6055
Tetrahedron

Fukuyama–Mitsunobu alkylation in amine synthesis on solid phase revisited: N-alkylation with secondary alcohols and synthesis of curtatoxins

Christian A. Olsen,[a,*] Matthias Witt,[b] Steen H. Hansen,[c] Jerzy W. Jaroszewski[a] and Henrik Franzyk[a,*]

[a]*Department of Medicinal Chemistry, The Danish University of Pharmaceutical Sciences, Universitetsparken 2, DK-2100 Copenhagen, Denmark*
[b]*Bruker Daltonik GmbH, Fahrenheitstrasse 4, D-28359 Bremen, Germany*
[c]*Department of Analytical Chemistry, The Danish University of Pharmaceutical Sciences, Universitetsparken 2, DK-2100 Copenhagen, Denmark*

Received 14 January 2005; revised 29 March 2005; accepted 15 April 2005

Available online 17 May 2005

Abstract—The Fukuyama–Mitsunobu amination strategy has emerged as an efficient means of N-alkylation of peptides and sulfonamides, as well as a method for synthesis of polyamines on solid phase. Here, an array of reagent combinations for solid-phase alkylation with secondary alcohols was examined in various solvents. The classical reagents DEAD–PPh_3 as well as DEAD–PEt_3 proved applicable for a single alkylation step. Sharply dropping yields in successive alkylation steps were identified as the most serious limitation of the use of Fukuyama–Mitsunobu reaction in SPS of polyamines using primary and in particular secondary alcohols.

1. Introduction

Polyamines and their derivatives play important roles in biochemistry and their pharmacological significance continues to increase. Simple polyamines such as spermidine (**1**) and spermine (**2**) are ubiquitous in eukaryotic cells, where they conduct important roles in cellular physiology, for example, in cell proliferation and DNA synthesis.[1] Relatively simple *n*-alkylated analogs of **2** have been shown to possess anticancer activity in various cell lines.[2] Polyamine-based cationic lipids have proved to be efficient gene-delivery agents.[3] Moreover, certain polyamine derivatives have been shown to interact with ion channels in the central nervous system (CNS).[4] Thus, polyamine neurotoxins isolated from venoms of spiders and wasps antagonize various classes of ionotropic receptors such as nicotinic acetylcholine receptors (nAChRs) and ionotropic glutamate receptors (iGluRs).[5] A variety of polyamine neurotoxins with closely related structures have been isolated from venoms of the funnel web spiders *Hololena curta*[6] and *Agelenopsis aperta*.[7] Some of these indole-containing toxins, known as curtatoxins, are shown in Figure 1. Compounds **4** and **6**, for instance, were isolated from both venom mixtures (which explains the two different names assigned to each of these compounds). Only the *H. curta* venom contains long-chain non-hydroxylated toxins such as compound **5**. The structurally similar wasp toxin component, philanthotoxin-433 (**7**),[8] has been the subject of extensive structure–activity relationship (SAR) studies on various receptor types.[9]

In order to obtain pure natural toxins in useful quantities as well as unnatural analogs for biological studies, efficient synthetic strategies are necessary. Since solution-phase methods for polyamine synthesis[10] often require extensive use of protecting groups as well as tedious purification steps, the development of solid-phase synthesis (SPS) methodologies has received considerable attention in recent years. The subsequent attachment of the amino acid and/or acyl residues to the polyamines may be achieved by well-established solid-phase peptide synthesis (SPPS) protocols. The synthetic strategies for construction of polyamines on solid phase may be classified into three major groups: (1) simple S_N2 alkylation reactions;[11] (2) methods based on reduction of intermediary imines[12] or amides;[13] and (3) Fukuyama amination reactions.[14] In the latter approach,

Keywords: Solid-phase synthesis; Fukuyama–Mitsunobu alkylation; Amines; Spider toxins.
* Corresponding authors. Tel.: +45 35306499; fax: +45 35306041 (C.A.O.); e-mail addresses: cao@dfuni.dk; hf@dfuni.dk

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.04.027

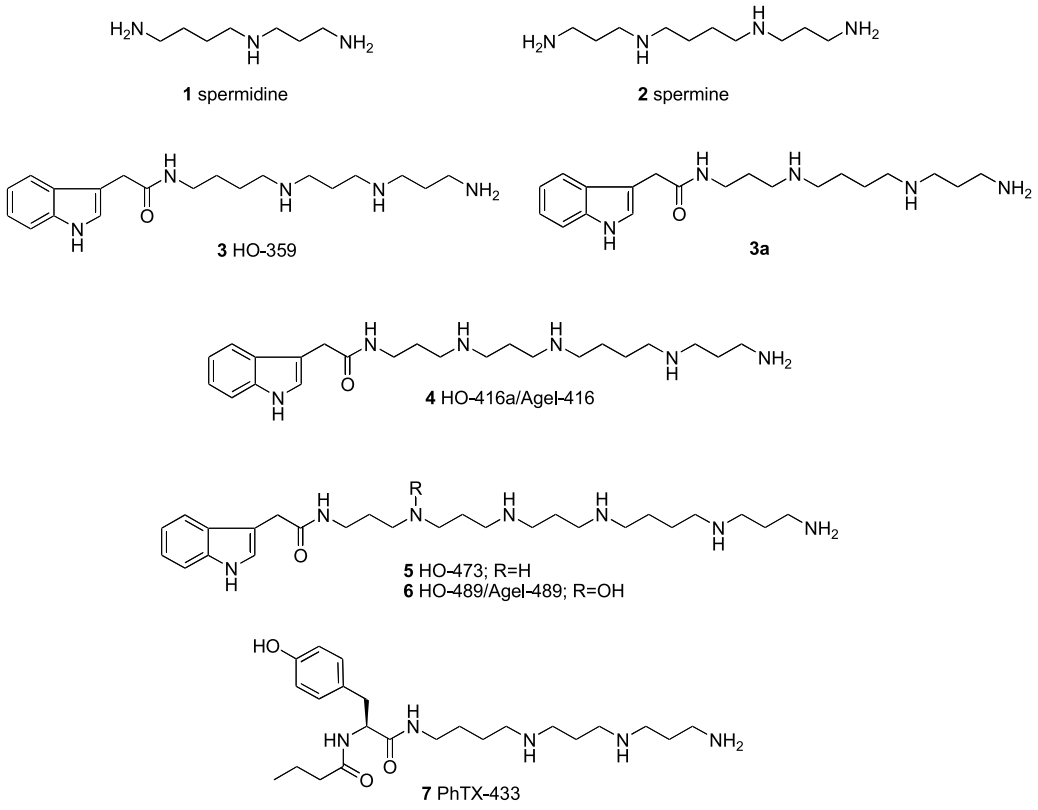


Figure 1. Structures of polyamines and acylpolyamine neurotoxins isolated from venom mixtures of spiders and wasps. The numerals in the names of **3**–**6** denote the molecular masses. In PhTX-433 (**7**) the digits denote the number of methylene groups that separate the amino functionalities, starting from the tyrosine end.

alkylation of secondary sulfonamides is achieved with alkyl halides under mildly basic conditions or with alcohols under Mitsunobu conditions.[15] Fukuyama and co-workers have applied the alkyl bromide approach in mixed solution/solid-phase total syntheses of several spider and wasp toxins. Ns-Protected acylpolyamines (corresponding to **4**[16] and **6**[16b]) were prepared in solution, and the syntheses were completed after anchoring of the terminal amino group to a solid support. Furthermore, two Fukuyama-type approaches based entirely on SPS have been employed in the total synthesis of philanthotoxins,[17] and two SPS Ns-strategies for site-selective N-methylation in peptide synthesis were reported by Miller and Scanlan.[18] The Fukuyama–Mitsunobu conditions have recently emerged as a versatile and general SPS method used, for instance, in N-alkylation of peptides,[19] peptide nucleic acid (PNA) monomer synthesis,[20] preparation of N-alkylated sulfonamides,[21] and in synthesis of polyamine neurotoxins.[22]

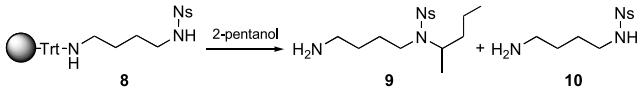
Although a relatively large amount of work has already been devoted to SPS of amines using Fukuyama–Mitsunobu alkylation, we addressed two important issues in order to define the scope and limitations of this strategy. The first issue concerns investigation of alkylation conditions suitable for SPS employing sterically hindered alcohols as building blocks (application of secondary alcohols is also challenging in solution-phase Mitsunobu reactions[23]). The second issue concerns the number of consecutive chain elongation steps that are possible to carry out in a satisfactory overall yield, that is, the length limit of polyamines obtainable by this method. The latter question is of interest, since the Fukuyama–Mitsunobu method has been optimized to give >99% yield in a single alkylation step,[22c] yet the overall yields of philanthotoxins obtained after two alkylations only amounted to 23–40%.[22c,e] Accordingly, the present work reports on the use of Fukuyama–Mitsunobu protocols for the SPS of curtatoxins, which contain polyamine moieties of different lengths, and thus constitutes an interesting test case.

2. Results and discussion

2.1. Screening of SPS reagent combinations for N-alkylation with secondary alcohols

Numerous combinations of solvents, bases, azo reagents and phosphines[24] have previously been applied in Mitsunobu reactions, and it was decided to select a range of reagents for a combinatorial screening in order to identify suitable conditions for Fukuyama–Mitsunobu SPS alkylations with secondary alcohols. Bycroft and co-workers[22a] as well as Hone and Payne[22b] have employed the traditional reagent pair diethyl azocarboxylate (DEAD) and PPh_3 in their original reports on polyamine SPS using Fukuyama–Mitsunobu amination, and hence these reagents were included in the present investigation. The two azo reagents used under Tsunoda conditions, that is, 1,1′-(azodicarbonyl)dipiperidide (ADDP) and *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD),[25] were likewise included, since both of these reagents in combination with PMe_3 were previously found to give acceptable to good yields in alkylation of

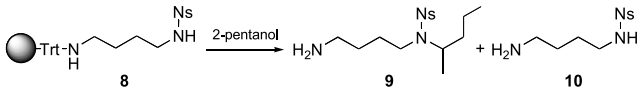
Table 1. Effect of reagent combinations on the yield of single Fukuyama–Mitsunobu solid-phase alkylations with a secondary alcohol in CH_2Cl_2–THF (1:1)[a]



Yields	No base			*i*Pr$_2$EtN		
	TMAD %[a]/%[b]	ADDP %[a]/%[b]	DEAD %[a]/%[b]	TMAD %[a]/%[b]	ADDP %[a]/%[b]	DEAD %[a]/%[b]
PMe_3	46/49	37/39	19/14	51/52	49/53	21/16
PEt_3	60/71	29/47	71/60	71/74	38/54	69/71
PPh_3	24/30	Trace	70/92	14/19	Trace	68/93

[a] Yields estimated from ^{1}H NMR.
[b] Product purities calculated from RP-HPLC as ratios {[9]/([9]+[10])}×100.

Table 2. Effect of various solvents on the yield of single Fukuyama–Mitsunobu solid-phase alkylations with a secondary alcohol[a]



PPh_3, DEAD, *i*Pr$_2$EtN			PEt_3, DEAD, *i*Pr$_2$EtN		
THF–PhMe 1:1	CH_2Cl_2–PhMe 1:1	PhMe	THF–PhMe 1:1	CH_2Cl_2–PhMe 1:1	PhMe
>95%	>95%	76%	53%	82%	38%

[a] Product purities calculated from RP-HPLC as ratios {[9]/([9]+[10])}×100.

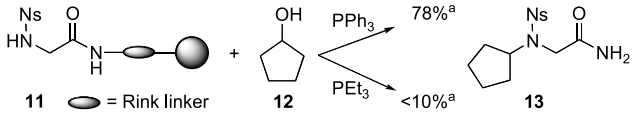
sulfonamides with secondary alcohols in solution.[26] Thus, the phosphines selected were the traditional PPh_3 and the least sterically hindered trialkylphosphine, PMe_3, along with PEt_3. All three phosphines have recently been reported to give acceptable to high conversion in C–C bond formation reactions with secondary benzylic alcohols.[27] Tributylphosphine, which previously has been widely used, was omitted in the present study due to the recently reported lack of reactivity in combination with ADDP and TMAD in solution-phase reactions.[26]

The above-mentioned phosphines and azo reagents comprise nine reagent combinations. The presence of base in Fukuyama–Mitsunobu reactions has previously been reported to enhance the tolerance towards steric bulk of the alcohol (using imidazole[28]) as well as to increase the reaction rate (using *i*Pr$_2$EtN[20]). Hence, the effect of the presence of *i*Pr$_2$EtN was also investigated (Table 1).

In the initial N-alkylation experiments described below we relied on the findings by Strømgaard et al.[22c] concerning the effect of solvent, concentration, order of reagent addition, and the number of repetitions. However, longer reaction times were applied (2×3 and 16 h), as this was found advantageous in our previous solution-phase experiments with secondary alcohols.[26] The results of ^{1}H NMR and RP-HPLC analyses of the product mixtures are shown in Table 1. Subsequently, the two best reagent combinations were further tested in additional solvent mixtures (Table 2).

The general observations about the SPS alkylation of sulfonamide **8** with 2-pentanol that emerged from these investigations are as follows: (1) triphenylphosphine worked well in combination with DEAD; (2) triethylphosphine combinations generally afforded acceptable conversions; (3) the presence of base did not increase the conversion significantly; (4) the reagent pairs DEAD/PPh_3, DEAD/PEt_3 and TMAD/PEt_3 (with and without base) all proved quite efficient in the alkylation. The reagent combinations containing PMe_3 proved not to be superior as opposed to previous solution-phase studies.[26,27] However, acceptable yields were only obtained with this phosphine when combined with ADDP or TMAD, paralleling the previous solution-phase experiments.[26] The RP-HPLC evaluation of the influence of the solvent showed good yields for 1:1 mixtures of THF–PhMe and CH_2Cl_2–PhMe (Table 2), but the ^{1}H NMR spectra of all of the six crude products revealed the presence of more impurities than observed in CH_2Cl_2–THF (1:1). Thus, the latter solvent combination was applied in the subsequent experiments.

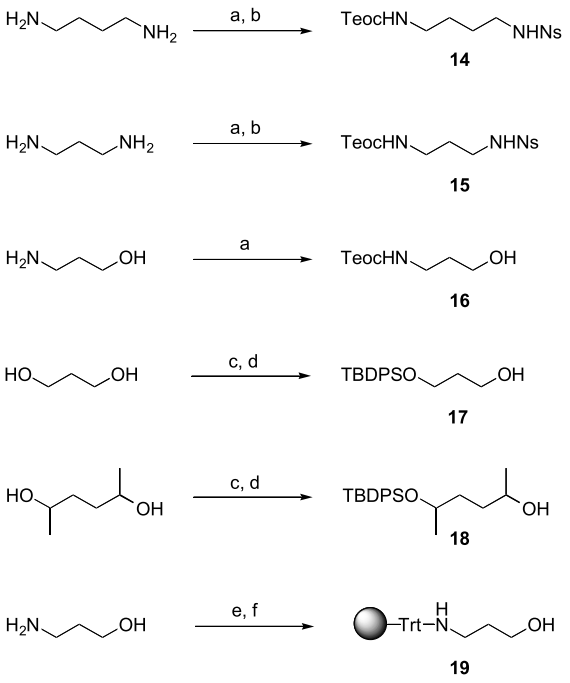
N-Alkylation of the sulfonamide (Ns-derivative) of resin-bound glycine (**11**) with a secondary alcohol (cyclopentanol) was subsequently performed with the most promising reagent combinations found in the above screening. A good yield (78%) was obtained when using PPh_3 as the phosphine, while PEt_3 did not furnish a satisfactory yield (Scheme 1). The two phosphines gave similar conversions in the investigation shown in Tables 1 and 2, which suggests that optimal conditions for N-alkylation is likely to be sensitive to the type of substrate and/or linker used.



Scheme 1. Resin **11** was alkylated with cyclopentanol (**12**) under Fukuyama–Mitsunobu conditions (DEAD/PPh_3/*i*Pr$_2$EtN or DEAD/PEt_3/*i*Pr$_2$EtN in CH_2Cl_2–THF (1:1), and the product (**13**) was cleaved with TFA–CH_2Cl_2 (95:5). [a]Isolated yields after vacuum liquid chromatography (VLC) based on the original resin loading.

2.2. Building block synthesis

The possibility of synthesizing long-chain polyamines (pentaamines or higher homologs) on solid phase using

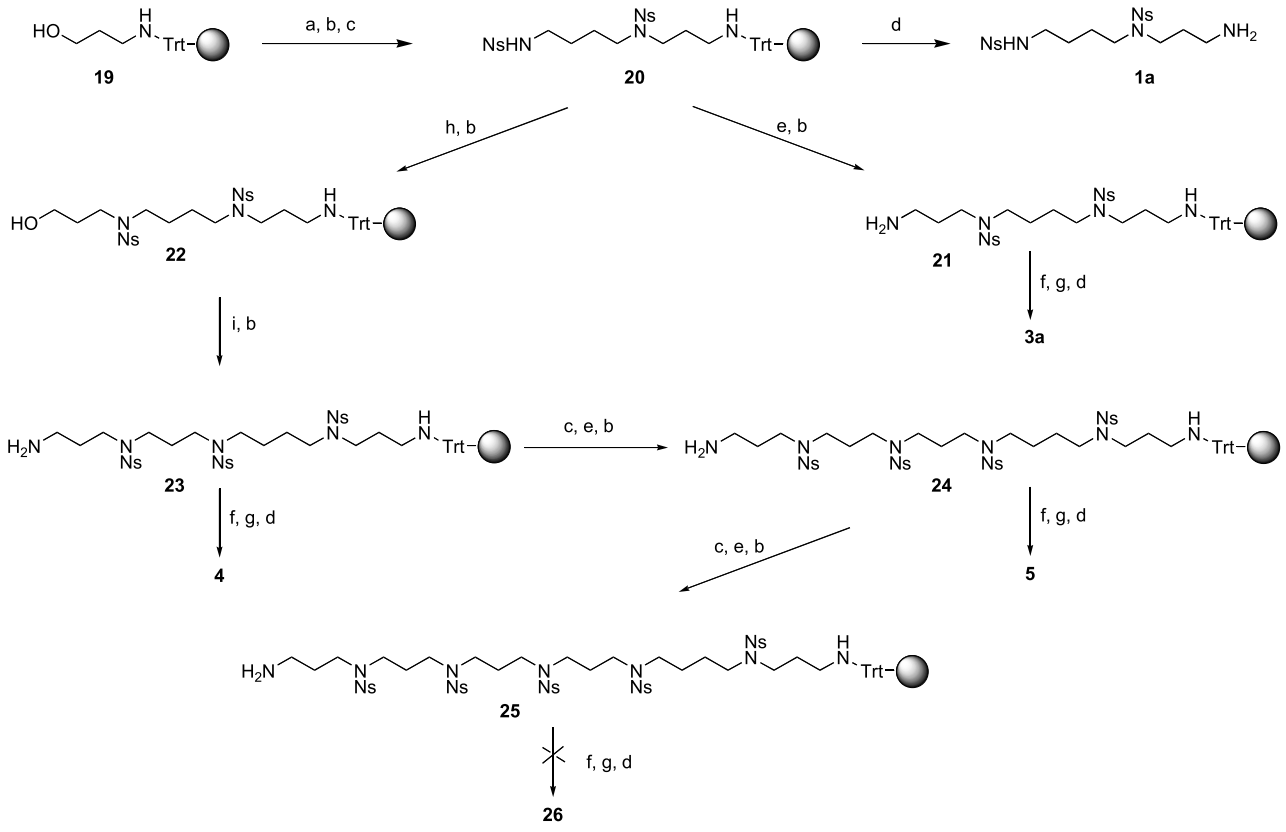


Scheme 2. Reagents and conditions: (a) 2-(trimethylsilyl)ethyl *p*-nitrophenyl carbonate, MeOH, CH_2Cl_2; (b) NsCl, *i*Pr_2EtN, CH_2Cl_2; (c) NaH (1 equiv), THF, 30 min; (d) TBDPS-Cl (1 equiv); (e) TMS-Cl, CH_2Cl_2, 40 °C, then Et_3N at room temperature followed by trityl chloride resin; (f) TBAF, DMF, 50 °C.

the Fukuyama–Mitsunobu approach was examined with curtatoxin analogs as the example. For this purpose, chain elongation building blocks **14**–**18** were prepared along with resin **19**, necessary for synthesis of **3**–**5** and their branched analogs. The diamine building blocks were mono-(2-trimethylsilylethoxy)carbonyl (Teoc) protected and Ns-activated, as previously described.[26] Thus, compounds **14** and **15** were obtained in 70–73% overall yield. Compound **16** was obtained in 80% yield by treatment of 3-amino-1-propanol with (2-trimethylsilyl)ethyl *p*-nitrophenyl carbonate in MeOH–CH_2Cl_2 (1:1), and the crude product was used without further purification. Diols were mono-protected as the *tert*-butyldiphenylsilyl (TBDPS) ethers under the conditions described by Wacowich-Sgarbi and Bundle,[29] affording **17** and **18** in 77 and 73% yield, respectively. It was decided to start from resin **19** shown in Scheme 2. In order to avoid the potential risk of resin cross-linking upon loading with an unprotected amino alcohol, the loading was accomplished with temporarily *O*-trimethylsilyl (TMS) protected 3-aminopropanol, employing similar conditions as used for attachment of amino acids via the N-terminal onto polystyrene trityl resins.[30]

2.3. SPS of curtatoxins using multiple Fukuyama–Mitsunobu amination steps

An efficient SPS strategy for the preparation of pentaamine spider toxins was recently reported by Bienz and co-workers.[11c]



Scheme 3. Reagents and conditions: (a) **14**, PMe_3, ADDP, CH_2Cl_2–THF 1:1; (b) TBAF, DMF, 50 °C; (c) NsCl, *i*Pr_2EtN, CH_2Cl_2; (d) TFA, CH_2Cl_2 1:1; (e) **16**, PMe_3, ADDP, CH_2Cl_2–THF 1:1; (f) indol-3-ylacetic acid, DIC, HOBt; (g) DBU, 2-mercaptoethanol; (h) **17**, PMe_3, ADDP, CH_2Cl_2–THF 1:1; (i) **15**, PMe_3, ADDP, CH_2Cl_2–THF 1:1.

In their case, the polyamine was constructed from the center by bromide displacement reactions. In the present work, however, the aim was to test the efficiency of the Fukuyama–Mitsunobu SPS method for preparation of long-chain polyamines. The sequence shown in Scheme 3 was carried out starting with 500 mg of resin **19**. After the initial Fukuyama–Mitsunobu alkylation with **14** under modified Tsunoda conditions (PMe_3, ADDP),[22e] removal of the Teoc group, and subsequent treatment with NsCl, resin **20** was obtained, which was extensively washed and dried in vacuo.

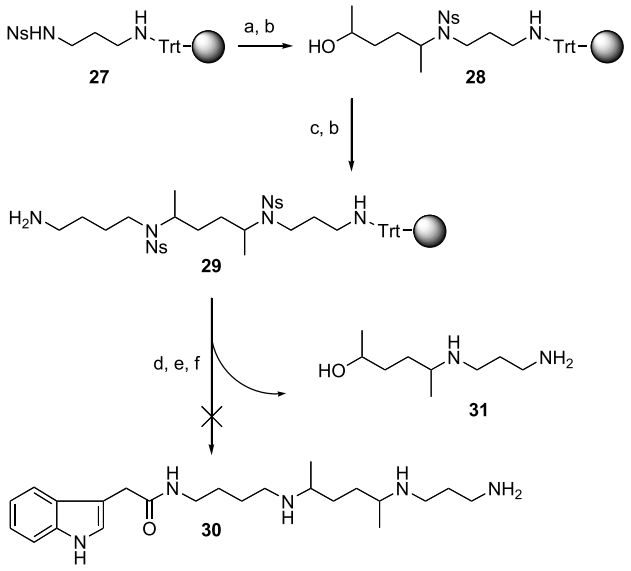
One-fifth of resin **20** was then treated with TFA–CH_2Cl_2 (1:1) to give the dinosylated spermidine derivative **1a** in order to determine the yield after a single alkylation step.

The isolated yield of **1a** was 67% after this 6-step reaction sequence (including the resin loading and cleavage), corresponding to an average yield per step of $>93\%$.

Another one-fifth of the original resin was elongated with the *N*-Teoc-protected aminoalcohol (**16**), and the Teoc group was removed to give resin **21**. The terminal primary amino group was acylated with indol-3-ylacetic acid under activation with DIC and HOBt, the Ns groups were removed, and the resin was treated with TFA–CH_2Cl_2 to furnish **3a** (12% isolated yield).

The remaining three fifths of the original resin were elongated with mono-protected diol **17** to give resin **22**, which was further elongated with the building block **15** to give **23**. Resin **23** was then divided into three equal portions for the acylation to give **4**, and for chain elongations to give **24** and **25**, respectively, as shown in Scheme 3. Thus, the theoretical yields of **1a**, **3a**, **4**, **5**, and **26** represented the same molar amounts, as they were designed to arise from one fifth each of the starting resin **19**. The Ns groups in the fully protected resin-bound products were removed by two treatments with DBU and 2-mercaptoethanol in DMF,[18] for 24 h[16] and for 1 h, respectively, in order to complete the deprotection as indicated by a colorless drain [the absence of the yellow 2-(2-nitrophenylthio)ethanol].[18] The products (**4**, **5**, and **26**) were released from the solid support with TFA–CH_2Cl_2 (1:1) and purified by reversed-phase vacuum liquid chromatography (VLC), a method previously reported to be appropriate for isolation of acylpolyamines.[31] Neither the yields nor the purities were satisfactory after the RP-VLC purification, however, and ^1H NMR spectra demonstrated the presence of relatively complex mixtures, with only minor resonances from the indole moiety present. The samples were therefore analyzed by reversed-phase HPLC and LC–MS.

For compound **4**, the LC–MS analysis was satisfactory. This was not the case for compound **5**, however, and the polyamine **26** was apparently not formed in appreciable amounts after five Fukuyama–Mitsunobu coupling steps (see Supporting Information for chromatograms and MS spectra). The same negative result was obtained when performing five consecutive elongations using the Strømgaard approach (*N*-Teoc protected amino alcohols and ADDP–PBu_3).[22c]



Scheme 4. Reagents and conditions (a) **18**, PPh_3, DEAD, CH_2Cl_2–THF 1:1; (b) TBAF, DMF, 50 °C; (c) **14**, PPh_3, DEAD, CH_2Cl_2–THF 1:1; (d) indol-3-ylacetic acid, DIC, HOBt; (e) DBU, 2-mercaptoethanol; (f) TFA–CH_2Cl_2 1:1.

The optimized conditions developed for alkylation with secondary alcohols were applied in order to prepare di-*C*-methyl branched curtatoxin analog **30** (Scheme 4). Initially, resin **27**[22e] was elongated with the mono protected diol (**18**) using PPh_3 and DEAD in CH_2Cl_2–THF (1:1), and the Teoc group was removed to give resin **28**. The diamine building block **14** was then introduced employing the same Mitsunobu conditions, designed to give resin **29**.

The remaining sequence aimed towards **30** was performed as described above, but no well-defined product could be isolated by RP-VLC. Furthermore, LC–MS analysis of the obtained fractions revealed no traces of **30**, while the most polar fraction contained the diamino alcohol **31**, which indicated that the first alkylation had taken place partially. Thus, the decrease in yield as observed in consecutive alkylations with primary alcohols appears to be even more pronounced when using secondary alcohols.

As shown in Table 3, good isolated yields were obtained after a single alkylation reaction with both primary and secondary alcohols. However, in both cases the isolated yields dropped significantly after the second consecutive alkylation step. We hypothesize that the low yield generally observed in the second SPS Fukuyama–Mitsunobu alkylation step may arise from interference of deposited byproducts and/or excess reagents in the resin pores. This

Table 3. Isolated yields obtained in polyamine solid-phase synthesis using polystyrene trityl resin as shown in Table 1, Schemes 3 and 4

	1st Alkylation	2nd Alkylation	3rd Alkylation
Primary alcohol	67%[a]	12%[a]	Trace
Secondary alcohol	59%[b]	0%[c]	n.p.[d]

[a] Isolated yields obtained in the experiments shown in Scheme 3.
[b] Isolated yield of compound **9** (Table 1).
[c] Yield of **30** (Scheme 4).
[d] Not performed.

explanation seems plausible when considering the problems often encountered with isolation of products from Mitsunobu reactions in general, a subject very recently reviewed by Dembinski[32] as well as by Dandapani and Curran.[33]

3. Conclusions

The experiments described in the present paper show that the Fukuyama–Mitsunobu amination reaction is a versatile but also a limited method for SPS of secondary amines. Superior reagent combinations for Fukuyama–Mitsunobu alkylation of resin-bound 2-nitrobenzenesulfonamides with secondary alcohols have been established by examining a combinatorial array of selected phosphine-reagents and azo reagents, with or without addition of a base. Also, resin-bound Ns-activated glycine was successfully alkylated with a secondary alcohol (cyclopentanol) in good yield, which shows that these results may find extended use in the synthesis of novel peptide analogs. Furthermore, systematic elongation sequences targeting long-chain polyamines (up to a heptaamine), showed that the Fukuyama–Mitsunobu amination method employing primary alcohols is practically limited to two chain elongation steps in SPS, if acceptable yields are to be obtained. However, when using a secondary alcohol, only one alkylation step was feasible under the conditions employed in the present work. Sharply dropping yields in successive alkylation steps are thus the most serious limitation of the use of the Fukuyama–Mitsunobu reaction in SPS of polyamines.

4. Experimental

4.1. Chemicals and instruments

Unless otherwise stated, starting materials were obtained from commercial suppliers and used without further purification. Trityl resins (100–200 mesh, 1% divinylbenzene) were obtained from Novabiochem (Läufelingen, Switzerland) and IRIS Biotech (Marktredwitz, Germany). The Rink amide resin was from IRIS Biotech (Marktredwitz, Germany). Indol-3-ylacetic acid was purchased from Lancaster (Morecambe, England). Tetrahydrofuran (THF) was distilled under N_2 from sodium/benzophenone prior to use. Dry dichloromethane was distilled from P_2O_5 and kept over 4 Å molecular sieves. Water for reversed-phase high-performance liquid chromatography (HPLC) was filtered through a 0.22 μm membrane filter (Millipore, Millipak40). ^{1}H NMR spectra were recorded at 400.14 or 600.13 MHz on a Bruker Avance 400 or Avance 600 spectrometer, respectively, and ^{13}C NMR spectra were recorded at 100.6 MHz on a Bruker Avance 400 spectrometer, using $CDCl_3$ or CD_3OD as solvents and TMS as internal standard. Coupling constants (J values) are given in hertz (Hz). Multiplicities of ^{1}H NMR signals are reported as follows: s, singlet; d, doublet; t, triplet; p, pentet; m, multiplet; br, broad signal. VLC was performed using Merck silica gel 60H, 5–40 μm (average size 15 μm), or Merck LiChroprep RP-18 (40–63 μm) stationary phase. Analytical HPLC was performed on a Shimadzu HPLC-system consisting of an SCL-10A VP controller, an SIL-10AD VP autoinjector, an LC-10AT VP Pump, an SPD-M10A VP diode array detector, and a CTO-10AC VP column oven, using a Phenomenex Luna C18(2) 3 μm column (150×4.6 mm) eluted at a rate of 0.8 mL/min. The system was controlled by Class VP 6 software, and elution was performed with eluent A (MeCN–H_2O–TFA 10:90:0.1) containing 0% of eluent B (MeCN–H_2O–TFA 90:10:0.1) at t=0–5 min, rising linearly to 40% of B during t=5–35 min, and rising linearly to 100% of B during t=35–40 min. LC–MS was performed using a ThermoFinnigan TSQ Quantum Ultra instrument. The preparative HPLC system consisted of a Waters model 590 pump, a Waters Lambda-Max model 481 spectrophotometric detector operating at 215 nm, and a Phenomenex Luna C18(2) 5 μm column (250×21.2 mm). The chromatograph operated isocratically at a flow-rate of 9 mL/min, using water–acetonitrile–TFA 85:15:0.1 as the mobile phase. High-resolution mass spectrometry (HRMS) measurements for exact mass determination were performed on a Bruker APEX Qe Fourier transform mass spectrometer equipped with a 7-tesla superconducting magnet and an external electrospray ion source (Apollo source). The spectra were externally calibrated with a CID (collision induced dissociation) spectrum of LHRH (luteinizing hormone releasing hormone) free acid. The samples were introduced into the electrospray ion source using a 250 μL syringe with a syringe pump flow of 2 μL/min.

4.2. General procedures

4.2.1. SPS Fukuyama–Mitsunobu alkylation of resin-bound 2-nitrobenzenesulfonamides (Tables 1 and 2, Schemes 1, 3, and 4). The vacuum dried *N*-nosyl-functionalized resin (typically ~0.1 mmol) was suspended in THF (0.5 mL), and then a secondary alcohol or a monoprotected diol (5 equiv) in CH_2Cl_2 (0.5 mL), a phosphine (6 equiv, ~0.6 mL, 1.0 M in THF) and an azo reagent (5 equiv) in CH_2Cl_2 (0.5 mL) were added. The mixture was shaken at room temperature under N_2 for 3 h. The resin was drained and washed with DMF, MeOH and CH_2Cl_2 (3×5 mL, 5 min each time) and flushed with N_2 for 15 min, after which the procedure was repeated twice. In the final repetition the reaction time was 16 h.

4.2.2. SPS Fukuyama–Mitsunobu alkylation of resin-bound amino alcohols (Schemes 3 and 4). A vacuum-dried resin-bound alcohol (typically ~0.1 mmol) was suspended in THF (0.5 mL), and then *N*-nosyl activated primary amine (5 equiv) in CH_2Cl_2 (0.5 mL), phosphine (6 equiv, ~0.6 mL, 1.0 M in THF) and an azo reagent (5 equiv) in CH_2Cl_2 (0.5 mL) were added. The mixture was shaken at room temperature under N_2 for 3 h. The resin was drained and washed with DMF, MeOH and CH_2Cl_2 (3×5 mL, 5 min each time) and flushed with N_2 for 15 min, after which the procedure was repeated twice. In the final repetition the reaction time was 16 h.

4.2.3. Nosylation of resin-bound amines (Schemes 1 and 3). The resin was dried in vacuo and NsCl (5 equiv) in CH_2Cl_2 was added under a stream of N_2. iPr$_2$EtN (7 equiv) was added, and the mixture was shaken at room temperature for 15 h. Then the resin was washed with DMF, MeOH and CH_2Cl_2 (3×5 mL, 5 min each time) and dried in vacuo before the next chain-elongation step.

4.2.4. Removal of TBDPS or Teoc groups (Schemes 3 and 4)**.** The resin was treated with TBAF·$3H_2O$ (5 equiv) in DMF (3 mL) for 30 min at 50 °C, and washed with DMF, MeOH and CH_2Cl_2 (3×5 mL, 5 min each time).

4.2.5. Introduction of the indol-3-ylacetic acid residue (Schemes 3 and 4)**.** The resin was suspended in dry DMF (1 mL). DIC (5 equiv), HOBt (5 equiv), and indol-3-ylacetic acid (5 equiv) in dry DMF (1 mL) were added and the mixture was shaken at room temperature under N_2 for 4 h. The resulting resin was drained and washed with DMF, CH_2Cl_2 and DMF (3×5 mL, 5 min each time).

4.2.6. Removal of Ns groups on solid phase (Schemes 3 and 4)**.** The resin was treated twice with DBU (10 equiv) in DMF (1 mL) and 2-mercaptoethanol (20 equiv) in DMF (1 mL) for 20 and 1 h, respectively. The resin was drained and washed with MeOH between each repetition until a final colorless drain confirmed complete deprotection. The resin was washed with DMF, MeOH and CH_2Cl_2 (3×5 mL, 5 min each time).

4.2.7. Cleavage from the resins (Tables 1 and 2, Schemes 1, 3, and 4)**.** The products were cleaved by treatment with TFA–CH_2Cl_2 (4 mL, 1:1 for trityl linkers and 95:5 for Rink linker) at room temperature for 2 h. The drained solvent was combined with washings (MeOH (2×5 mL) and CH_2Cl_2 (2×5 mL) and concentrated in vacuo. The products were purified by reversed-phase VLC [H_2O–MeCN–TFA (95:5:0.1, 90:10:0.1, 85:15:0.1 and 80:20:0.1)] or preparative RP-HPLC.

4.2.8. Characterization of compounds 1a, 3a, 9, and 13. *Compound* **1a**. Yield: 44 mg (67%) of a yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (m, 2H, Ns), 7.83–7.76 (br m, 6H, Ns), 3.40 (t, J=7.2 Hz, 2H), 3.30 (t, J=6.6 Hz, 2H), 3.02 (t, J=6.6 Hz, 2H), 2.86 (t, J=7.2 Hz, 2H), 1.87 (p, J=7.2 Hz, 2H), 1.58 (m, 2H), 1.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.6, 135.5, 135.0 (2C), 134.8, 133.7, 133.6, 133.3, 131.5 (2C), 125.9, 125.6, 49.3, 46.2, 43.7, 38.6, 28.9, 27.8, 26.2. HRMS: *m/z* calcd for $[C_{19}H_{26}N_5O_8S_2]^+$ 516.1217, found 516.1217, ΔM 0.14 ppm.

Compound **3a**. Yield: 11 mg (12%) of a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.56 (d, J=7.9 Hz, 1H), 7.37 (d, J=8.1 Hz, 1H), 7.13 (dd, J=8.1 and 7.9 Hz, 1H), 7.04 (dd, J=8.1 and 7.9 Hz, 1H), 3.69 (s, 2H, CH_2CO), 3.11–3.03 (br m, 6H, 3×CH_2N), 2.98 (t, J=7.6 Hz, 2H, CH_2N), 2.81 (m, 4H, 2×CH_2N), 2.08 (m, 2H), 1.82 (p, J=6.6 Hz, 2H), 1.63 (m, 2H), 1.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 138.2, 128.4, 125.2, 122.8, 120.1, 119.3, 112.6, 109.4, 48.2, 48.0, 46.0 (2C), 37.8 (2C), 36.7, 33.9, 27.6, 25.3 (2C). HRMS: *m/z* calcd for $[C_{20}H_{34}N_5O]^+$ 360.2758, found 360.2759, ΔM 0.39 ppm.

Compound **9**. Yield: 12 mg (59%) of a yellow oil after RP-VLC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J=7.3 Hz, 1H, Ns), 7.80–7.72 (br m, 3H, Ns), 3.91 (m, 1H, CHNNs), 3.39 (t, J=7.8 Hz, 2H, CH_2NNs), 2.72 (t, J=7.3 Hz, 2H, CH_2NH$_2$), 1.65–1.26 (br m, 8H, 4×CH_2), 1.10 (d, J=6.1 Hz, 3H, CH_3CH), 0.84 (t, J=7.3 Hz, 3H, CH_3CH$_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 147.9, 135.1, 132.9, 131.9, 125.2, 55.3, 44.3, 41.7, 38.7, 30.4, 30.0, 20.7, 19.5, 14.1. HRMS: *m/z* calcd for $[C_{15}H_{26}N_3O_2S]^+$ 344.1639, found 344.1640, ΔM 0.32 ppm.

Compound **13**. Yield: 21 mg (78%) of a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J=7.3 Hz, 1H, Ns), 7.76–7.66 (br m, 3H, Ns), 6.53 (br s, 1H, NHCO), 5.73 (br s, 1H, NHCO), 4.33 (m, 1H, CHN), 3.93 (br s, 2H, H-α), 1.91–1.22 (br m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1, 134.3, 132.5, 132.1, 131.4, 124.5, 59.6, 46.7, 29.0 (2C), 23.2 (2C). HRMS: *m/z* calcd for $[C_{13}H_{17}N_3O_5SNa]^+$ 350.0781, found 350.0782, ΔM 0.37 ppm.

4.2.9. *N*-[(2-Nitrophenyl)sulfonyl]-N^1-[(2-trimethylsilyl)-ethoxycarbonyl]-1,4-butanediamine (14). (2-Trimethylsilyl)ethyl *p*-nitrophenyl carbonate (4.83 g, 17.05 mmol) in CH_2Cl_2 (25 mL) was added to a stirred solution of 1,4-butanediamine (3.97 g, 45 mmol, 2.6 equiv) in MeOH (25 mL), and the mixture was stirred for 16 h at room temperature. The methanol was removed in vacuo and then EtOAc (250 mL) was added. The organic phase was washed with 2 M aq NaOH (4×100 mL) and brine (2×100 mL), dried (Na_2SO_4), filtered, concentrated, and dried in vacuo to give a sufficiently pure product (2.89 g; 73%). ^{1}H NMR (400 MHz, CD_3OD): δ 4.11 (t, J=8.3 Hz, 2H, CH_2O), 3.10 (t, J=6.4 Hz, 2H, CH_2NHCO), 2.64 (t, J=6.4 Hz, 2H, CH_2NH$_2$), 1.49 (m, 4H, 2×CH_2), 0.98 (t, J=8.3 Hz, 2H, CH_2Si), −0.05 (br s, 9H, $(CH_3)_3$Si). ^{13}C NMR (100 MHz, CD_3OD): δ 159.8, 64.2, 42.7, 41.9, 31.4, 28.8, 19.2, −0.9 (3C). The crude material, *i*Pr$_2$EtN (2.80 mL), and NsCl (3.30 g) were dissolved in CH_2Cl_2 (40 mL) and the solution was stirred at room temperature. After 16 h the mixture was concentrated, the residue was loaded onto a VLC column (7×7 cm), and the column eluted with hexane–EtOAc (10:1, 6:1, 4:1, 2:1, and 1:1) to furnish **14** (4.39 g; 62% overall) as a pale yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (m, 1H, Ns), 7.86 (m, 1H, Ns), 7.74 (m, 2H, Ns), 5.38 (br t, 1H, $NHSO_2$), 4.57 (br t, 1H, NHCO), 4.13 (m, 2H, CH_2O), 3.12 (m, 4H, 2×CH_2N), 1.55 (m, 4H, 2×CH_2), 0.96 (t, J=7.2 Hz, 2H, CH_2Si), 0.02 [br s, 9H, $(CH_3)_3$Si]. ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.9, 148.0, 133.7, 133.6, 132.8, 125.4, 63.0, 43.4, 40.2, 27.1, 26.8, 17.8, −1.5 (3C).[26]

4.2.10. *N*-[(2-Nitrophenyl)sulfonyl]-N^1-[(2-trimethylsilyl)ethoxycarbonyl]-1,3-propanediamine (15). The procedure was as described above using 1,3-propanediamine as the starting material, to give **15** (2.15 g; 68% overall) as a pale yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (m, 1H, Ns), 7.84 (m, 1H, Ns), 7.74 (m, 2H, Ns), 5.95 (br s, 1H, $NHSO_2$), 4.99 (br s, 1H, NHCO), 4.13 (br t, J=8.2 Hz, 2H, CH_2O), 3.25 (q, J=6.4 Hz, 2H), 3.16 (q, J=6.4 Hz, 2H), 1.71 (p, J=6.4 Hz, 2H, CH_2), 0.96 (br t, J=8.2 Hz, 2H, CH_2Si), 0.02 [br s, 9H, $(CH_3)_3$Si]. ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 147.9, 133.8, 133.5, 132.7, 125.2, 63.0, 40.7, 37.3, 30.2, 17.6, −1.6 (3C). HRMS: *m/z* calcd for $[C_{15}H_{24}N_3O_6SSiNa]^+$ 426.1126, found 426.1127, ΔM 0.40 ppm.

4.2.11. *N*-[(2-Trimethylsilyl)ethoxycarbonyl]-3-amino-1-propanol (16). 3-Amino-1-propanol (552 μL, 2.4 mmol, 1.2 equiv) was dissolved in MeOH (20 mL), (2-trimethylsilyl)ethyl *p*-nitrophenyl carbonate (567 mg, 2.0 mmol) in

CH_2Cl_2 (20 mL) was added, and the mixture was stirred at room temperature for 16 h. Methanol was removed in vacuo, EtOAc (150 mL) was added, and the organic phase was washed with 2 M aq NaOH (4×75 mL), and brine (2×75 mL), dried (Na_2SO_4), filtered and concentrated. Drying in vacuo afforded compound **16** (1.23 g; 79%) as a colorless syrup. ^{1}H NMR (400 MHz, CD_3OD): δ 4.13 (t, J=8.3 Hz, 2H, CH_2O), 3.59 (t, J=6.3 Hz, 2H, CH_2OH), 3.18 (t, J=6.9 Hz, 2H, CH_2N), 1.69 (br p, $J\approx$6.7 Hz, 2H, CH_2), 0.98 (t, J=8.3 Hz, 2H, CH_2Si), 0.05 [br s, 9H, $(CH_3)_3Si$]. ^{13}C NMR (100 MHz, CD_3OD): δ 159.4, 63.7, 60.4, 38.6, 33.7, 18.6, −1.6 (3C).[34]

4.2.12. 3-(*tert*-Butyldiphenylsilyloxy)-1-propanol (17). A mixture of 1,3-propanediol (1.66 mL, 23.0 mmol) and NaH (920 mg, 23 mmol; 60% suspension in oil) in dry THF (20 mL) was stirred at room temperature under N_2 for 30 min. *tert*-Butyldiphenylsilylchloride (5.98 mL, 23.0 mmol) was added during 1 h, and stirring was continued for 16 h. The mixture was then diluted with EtOAc (200 mL), and washed with water (3×100 mL) and brine (2×100 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was purified by VLC (hexane–EtOAc 15:1, 8:1, and 6:1) to give **17** (5.58 g; 77%) as a clear syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (m, 4H, Ph), 7.41 (m, 6H, Ph), 3.85 (br t, J=7.2 Hz, 4H, 2×CH_2O), 1.82 (p, J=7.2 Hz, 2H, CH_2), 1.06 [br s, 9H, $(CH_3)_3C$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.6 (4C), 133.3 (2C), 129.8 (2C), 127.8 (4C), 63.2, 61.8, 34.4, 26.9 (3C), 19.1. HRMS: *m/z* calcd for $[C_{19}H_{26}O_2SiNa]^+$ 337.1594, found 337.1595, ΔM 0.27 ppm.

4.2.13. 5-(*tert*-Butyldiphenylsilyloxy)-2-hexanol (18). A mixture of 2,5-hexanediol (809 mg, 6.9 mmol) and NaH (280 mg, 6.9 mmol; 60% suspension in oil) in dry THF (10 mL) was stirred at room temperature under N_2 for 30 min. *tert*-Butyldiphenylsilylchloride (1.78 mL, 6.9 mmol) was added during 30 min, and stirring was continued for 16 h. The mixture was then diluted with EtOAc (100 mL), and washed with water (3×75 mL) and brine (2×75 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was purified by VLC (hexane–EtOAc 15:1, 8:1, and 6:1) to give **18** (1.78 g; 73%) as a clear syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (m, 4H, Ph), 7.39 (m, 6H, Ph), 3.88 (m, 1H, C*H*OH), 3.69 (m, 1H, CHOSi), 1.65–1.44 (br m, 4H, 2×CH_2), 1.14–1.04 (br m, 15H, 5×CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0 (2C), 135.9 (4C), 129.6 (2C), 127.5 (4C), 69.5/69.4* (1C), 68.3/68.0* (1C), 35.5/35.1* (1C), 34.7/34.5* (1C), 27.1 (3C), 23.4, 23.1/22.8* (1C), 19.2 (diastereoisomers). HRMS: *m/z* calcd for $[C_{22}H_{32}O_2Si]^+$ 357.2244, found 357.2244, ΔM 0.03 ppm.

4.2.14. Preparation of N-resin-bound 3-amino-1-propanol (19). 3-Amino-1-propanol (1.03 mL, 13.5 mmol, 10 equiv) was dissolved in dry CH_2Cl_2 (20 mL) and TMS-Cl (1.71 mL, 13.5 mmol, 10 equiv) was added. The mixture was stirred at 40 °C under N_2 for 1.5 h, and Et_3N (3 mL, 16 equiv) was added upon cooling to room temperature, followed by trityl chloride resin (1.0 g, 1.35 mmol/g, 1.35 mmol). The mixture was stirred at room temperature under N_2 overnight. The resin was drained, washed with MeOH and treated with 20% iPr$_2$EtN in MeOH (30 mL) for 30 min to cap unreacted trityl chloride functionalities. The resin was washed with DMF, MeOH and CH_2Cl_2 (3×5 mL), and then it was treated with TBAF (426 mg, 6.75 mmol, 5 equiv) in DMF (10 mL) at room temperature for 2 h. Finally the resin was drained, washed with DMF, MeOH and CH_2Cl_2 (3×5 mL), and freeze-dried to give the functionalized resin (**19**, 1.25 g, 1.283 mmol/g assuming that complete conversions had been achieved).

Acknowledgements

The authors gratefully acknowledge financial support to C. A. O. through the Novo Nordisk PhD Plus Prize and from the Danish Technical Research Council (Grant No. 26-00-0312). We also thank Ms. Maja Lambert and Dr. Cailean Clarkson for help with LC–MS, and Ms. Uraiwan Ngamrabiab Adamsen and Ms. Birgitte Simonsen for technical assistance. The Lundbeck Foundation and the Danish Medical Research Council (Grant No. 22-02-0340) are thanked for financial support to S. H. H. NMR equipment used in this work was acquired through grants from Apotekerfonden af 1991 (Copenhagen).

Supplementary data

Supplementary data associated with this article can be found at 10.1016/j.tet.2005.04.027

References and notes

1. Cohen, S. S. *A guide to polyamines*; Oxford University Press: New York, 1998.
2. (a) Bergeron, R. J.; McManis, J. S.; Liu, C. Z.; Feng, Y.; Weimar, W. R.; Luchetta, G. R.; Wu, Q.; Ortiz-Ocasio, J.; Vinson, T. J. R.; Kramer, D.; Porter, C. *J. Med. Chem.* **1994**, *37*, 3464–3476. (b) Reddy, V. K.; Valasinas, A.; Sarkar, A.; Basu, H. S.; Marton, L. J.; Frydman, B. *J. Med. Chem.* **1998**, *41*, 4723–4732. (c) Casero, R. A.; Woster, P. M. *J. Med. Chem.* **2001**, *44*, 1–26. (d) Valasinas, A.; Sarkar, A.; Reddy, V. K.; Marton, L. J.; Basu, H. S.; Frydman, B. *J. Med. Chem.* **2001**, *44*, 390–403.
3. (a) Byk, G.; Dubertret, C.; Escriou, V.; Frederic, G.; Jaslin, G.; Rangara, R.; Pitard, B.; Crouzet, J.; Wils, P.; Schwartz, B.; Scherman, D. *J. Med. Chem.* **1998**, *41*, 224–235. (b) Yingyongnarongkul, B.-e.; Howarth, M.; Elliott, T.; Bradley, M. *Chem. Eur. J.* **2004**, *10*, 463–473. (c) Yingyongnarongkul, B.-e.; Howarth, M.; Elliott, T.; Bradley, M. *J. Comb. Chem.* **2004**, *6*, 753–760.
4. (a) Scott, R. H.; Sutton, K. G.; Dolphin, A. C. *Trends Neurosci.* **1993**, *16*, 153–160. (b) Williams, K. *Biochem. J.* **1997**, *325*, 289–297. (c) Igarashi, K.; Kashiwagi, K. *Biochem. Biophys. Res. Commun.* **2000**, *271*, 559–564.
5. For recent reviews, see: (a) Strømgaard, K.; Andersen, K.; Krogsgaard-Larsen, P.; Jaroszewski, J. W. *Mini Rev. Med. Chem.* **2001**, *1*, 317–338. (b) Strømgaard, K.; Mellor, I. R.

Med. Res. Rev. **2004**, *24*, 589–620. (c) Mellor, I. R.; Usherwood, P. N. R. *Toxicon* **2004**, *43*, 493–508.
6. Quistad, G. B.; Reuter, C. C.; Skinner, W. S.; Dennis, P. A.; Suwanrumpha, S.; Fu, E. W. *Toxicon* **1991**, *29*, 329–336.
7. (a) Jasys, V. J.; Kelbaugh, P. R.; Nason, D. M.; Philips, D.; Rosnack, K. J.; Saccomano, N. A.; Stroh, J. G.; Volkmann, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 6696–6704. (b) Jasys, V. J.; Kelbaugh, P. R.; Nason, D. M.; Phillips, D.; Rosnack, K. J.; Forman, J. T.; Saccomano, N. A.; Stroh, J. G.; Volkmann, R. A. *J. Org. Chem.* **1992**, *57*, 1814–1820. (c) Adams, M. E. *Toxicon* **2004**, *43*, 509–525.
8. (a) Eldefrawi, A. T.; Eldefrawi, M. E.; Konno, K.; Mansour, N. A.; Nakanishi, K.; Eugene, O.; Usherwood, P. N. R. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 4910–4913. (b) Piek, T.; Fokkens, R. H.; Karst, H.; Kruk, C.; Lind, A.; van Marle, J.; Tong, Y. C. In *Neurotox 8: molecular basis of drug and pesticide action*; Lunt, G. G., Ed.; Elsevier: Amsterdam, 1988; pp 61–76.
9. (a) Nakanishi, K.; Goodnow, R., Jr.; Konno, K.; Niwa, M.; Bukownik, R.; Kallimopoulos, T.; Usherwood, P. N. R.; Eldefrawi, A. T.; Eldefrawi, M. E. *Pure Appl. Chem.* **1990**, *62*, 1223–1230. (b) Bruce, M.; Bukownik, R.; Eldefrawi, A. T.; Eldefrawi, M. E.; Goodnow, R., Jr.; Kallimopoulos, T.; Konno, K.; Nakanishi, K.; Niwa, M.; Usherwood, P. N. R. *Toxicon* **1990**, *28*, 1333–1346. (c) Goodnow, R., Jr.; Bukownik, R.; Nakanishi, K.; Usherwood, P. N. R.; Eldefrawi, A. T.; Anis, N. A.; Eldefrawi, M. E. *J. Med. Chem.* **1991**, *34*, 2389–2394. (d) Nakanishi, K.; Choi, S.-K.; Hwang, D.; Lerro, K.; Orlando, M.; Kalivretenos, A. G.; Eldefrawi, A. T.; Eldefrawi, M. E.; Usherwood, P. N. R. *Pure Appl. Chem.* **1994**, *66*, 671–678. (e) Choi, S.-K.; Kalivretenos, A. G.; Usherwood, P.; Nakanishi, K. *Chem. Biol.* **1995**, *2*, 23–32. (f) Nakanishi, K.; Huang, X.; Jiang, H.; Liu, Y.; Fang, K.; Huang, D.; Choi, S.-K.; Katz, E.; Eldefrawi, M. E. *Bioorg. Med. Chem.* **1997**, *5*, 1969–1988. (g) Huang, D.; Jiang, H.; Nakanishi, K.; Usherwood, P. N. R. *Tetrahedron* **1997**, *53*, 12391–12404. (h) Strømgaard, K.; Brierley, M. J.; Andersen, K.; Sløk, F. A.; Mellor, I. R.; Usherwood, P. N. R.; Krogsgaard-Larsen, P.; Jaroszewski, J. W. *J. Med. Chem.* **1999**, *42*, 5224–5234. (i) Bixel, M. G.; Krauss, M.; Liu, Y.; Bolognesi, M. L.; Rosini, M.; Mellor, I. R.; Usherwood, P.; Melchiorre, C.; Nakanishi, K.; Hucho, F. *Eur. J. Biochem.* **2000**, *267*, 110–120. (j) Bixel, M. G.; Krauss, M.; Weise, C.; Bolognesi, M. L.; Rosini, M.; Usherwood, P. N. R.; Melchiorre, C.; Hucho, F. *Farmaco* **2001**, *56*, 133–135. (k) Bixel, M. G.; Weise, C.; Bolognesi, M. L.; Rosini, M.; Brierley, M. J.; Mellor, I. R.; Usherwood, P.; Melchiorre, C.; Hucho, F. *J. Biol. Chem.* **2001**, *276*, 6151–6160. (l) Mellor, I. R.; Brier, T. J.; Pluteanu, F.; Strømgaard, K.; Saghyan, A.; Eldursi, N.; Brierley, M. J.; Andersen, K.; Jaroszewski, J. W.; Krogsgaard-Larsen, P.; Usherwood, P. N. R. *Neuropharmacology* **2002**, *44*, 70–80. (m) Brier, T. J.; Mellor, I. R.; Tikhonov, D.; Neagoe, I.; Shao, Z.; Brierley, M. J.; Strømgaard, K.; Jaroszewski, J. W.; Krogsgaard-Larsen, P.; Usherwood, P. N. R. *Mol. Pharmacol.* **2003**, *64*, 954–964. (n) Jørgensen, M. R.; Olsen, C. A.; Mellor, I. R.; Usherwood, P. N. R.; Witt, M.; Franzyk, H.; Jaroszewski, J. W. *J. Med. Chem.* **2005**, *48*, 56–70.
10. For recent reviews, see: (a) Karigiannis, G.; Papaioannou, D. *Eur. J. Org. Chem.* **2000**, 1841–1863. (b) Kuksa, V.; Buchan, R.; Lin, P. K. T. *Synthesis* **2000**, 1189–1207.
11. (a) Renault, J.; Lebranchu, M.; Lecat, A.; Uriac, P. *Tetrahedron Lett.* **2001**, *42*, 6655–6658. (b) Manov, N.; Bienz, S. *Tetrahedron* **2001**, *57*, 7893–7898. (c) Manov, N.; Tzouros, M.; Chesnov, S.; Bigler, L.; Bienz, S. *Helv. Chim. Acta* **2002**, *85*, 2827–2846. (d) Olsen, C. A.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *Org. Lett.* **2003**, *5*, 4183–4185. (e) Olsen, C. A.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *Org. Lett.* **2004**, *6*, 1935–1938. (f) Picard, S.; Le Roch, M.; Renault, J.; Uriac, P. *Org. Lett.* **2004**, *6*, 4711–4714.
12. (a) Chhabra, S. R.; Khan, A. N.; Bycroft, B. W. *Tetrahedron Lett.* **2000**, *41*, 1095–1098. (b) Jönsson, D. *Tetrahedron Lett.* **2002**, *43*, 4793–4796. (c) Jönsson, D.; Unden, A. *Tetrahedron Lett.* **2002**, *43*, 3125–3128.
13. (a) Paikoff, S. J.; Wilson, T. E.; Cho, C. Y.; Schultz, P. G. *Tetrahedron Lett.* **1996**, *37*, 5653–5656. (b) Nefvi, A.; Ostresh, J. M.; Meyer, J.-P.; Houghten, R. A. *Tetrahedron Lett.* **1997**, *38*, 931–934. (c) Ostresh, J. M.; Schoner, C. G.; Hamashin, V. T.; Nefvi, A.; Meyer, J.-P.; Houghten, R. A. *J. Org. Chem.* **1998**, *63*, 8622–8623. (d) Yu, Y.; Ostresh, J. M.; Houghten, R. A. *Org. Lett.* **2001**, *3*, 2797–2799. (e) Hall, D. G.; Laplante, C.; Manku, S.; Nagendran, J. *J. Org. Chem.* **1999**, *64*, 698–699. (f) Wang, F.; Manku, S.; Hall, D. G. *Org. Lett.* **2000**, *2*, 1581–1583. (g) Manku, S.; Laplante, C.; Kopac, D.; Chan, T.; Hall, D. G. *J. Org. Chem.* **2001**, *66*, 874–885. (h) Manku, S.; Wang, F.; Hall, D. G. *J. Comb. Chem.* **2003**, *5*, 379–391. (i) Olsen, C. A.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *J. Org. Chem.* **2004**, *69*, 6149–6152.
14. For reviews, see: (a) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353–359. (b) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373–6374.
15. Mitsunobu, O. *Synthesis* **1981**, 1–28.
16. (a) Hidai, Y.; Kan, T.; Fukuyama, T. *Tetrahedron Lett.* **1999**, *40*, 4711–4714. (b) Hidai, Y.; Kan, T.; Fukuyama, T. *Chem. Pharm. Bull.* **2000**, *48*, 1570–1576.
17. (a) Kan, T.; Kobayashi, H.; Fukuyama, T. *Synlett* **2002**, 1338–1340. (b) Andersen, T. F.; Strømgaard, K. *Tetrahedron Lett.* **2004**, *45*, 7929–7933.
18. (a) Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc.* **1997**, *119*, 2301–2302. (b) Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc.* **1998**, *120*, 2690–2691.
19. (a) Reichwein, J. F.; Liskamp, R. M. J. *Tetrahedron Lett.* **1998**, *39*, 1243–1246. (b) Reichwein, J. F.; Wels, B.; Kruitjzer, J. A. W.; Versluis, C.; Liskamp, R. M. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3684–3687. (c) Brouwer, A. J.; Liskamp, R. M. J. *J. Org. Chem.* **2004**, *69*, 3662–3668. (d) Lin, X. D.; Dorr, H.; Nuss, J. M. *Tetrahedron Lett.* **2000**, *41*, 3309–3313.
20. Viirre, R. D.; Hudson, R. H. E. *Org. Lett.* **2001**, *3*, 3931–3934.
21. Dankwarth, S. M.; Smith, D. B.; Porco, J. A., Jr.; Nguyen, C. H. *Synlett* **1997**, 854–856.
22. (a) Chhabra, S. R.; Khan, A. N.; Bycroft, B. W. *Tetrahedron Lett.* **2000**, *41*, 1099–1102. (b) Hone, N. D.; Payne, L. J. *Tetrahedron Lett.* **2000**, *41*, 6149–6152. (c) Strømgaard, K.; Andersen, K.; Ruhland, T.; Krogsgaard-Larsen, P.; Jaroszewski, J. W. *Synthesis* **2001**, 877–884. (d) Kromann, H.; Krikstolaityte, S.; Andersen, A. J.; Andersen, K.; Krogsgaard-Larsen, P.; Jaroszewski, J. W.; Egebjerg, J.; Strømgaard, K. *J. Med. Chem.* **2002**, *45*, 5745–5754. (e) Olsen, C. A.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *Synlett* **2004**, 473–476.
23. Hughes, D. L. In *Organic reactions*; Paquette, L. A., Ed.; Wiley: New York, 1992; Vol. 42, pp 335–656.
24. Valentine, D. H., Jr.; Hillhouse, J. H. *Synthesis* **2003**, 317–334.
25. (a) Tsunoda, T.; Yamamiya, Y.; Itô, S. *Tetrahedron Lett.* **1993**, *34*, 1639–1642. (b) Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Itô, S. *Chem. Lett.* **1994**, 539–542.
26. Olsen, C. A.; Jørgensen, M. R.; Witt, M.; Mellor, I. R.;

Usherwood, P. N. R.; Jaroszewski, J. W.; Franzyk, H. *Eur. J. Org. Chem.* **2003**, 3288–3299.
27. Hillier, M. C.; Desrosiers, J.-N.; Marcoux, J.-F.; Grabowski, J. *Org. Lett.* **2004**, *6*, 573–576.
28. Falck, J. R.; Lai, J.-Y.; Cho, S.-D.; Yu, J. *Tetrahedron Lett.* **1999**, *40*, 2903–2906.
29. Wacowich-Sgarbi, S. A.; Bundle, D. R. *J. Org. Chem.* **1999**, *64*, 9080–9089.
30. Barlos, P. *Liebigs Ann. Chem.* **1988**, 1079–1081.
31. Wellendorph, P.; Jaroszewski, J. W.; Hansen, S. H.; Franzyk, H. *Eur. J. Med. Chem.* **2003**, *38*, 117–122.
32. Dembinski, R. *Eur. J. Org. Chem.* **2004**, 2763–2772.
33. Dandapani, S.; Curran, D. P. *Chem. Eur. J.* **2004**, *10*, 3130–3138.
34. Kita, Y.; Haruta, J.-I.; Yasuda, H.; Fukunaga, K.; Shirouchi, Y.; Tamura, Y. *J. Org. Chem.* **1982**, *47*, 2697–2700.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 61 (2005) 6056–6063
Tetrahedron

Pluri-dimensional hydrogen-bonded networks of novel thiophene-introduced oligo(imidazole)s and physical properties of their charge-transfer complexes with TCNQ

Tsuyoshi Murata,[a] Yasushi Morita[a,b,*] and Kazuhiro Nakasuji[a,*]

[a]*Department of Chemistry, Graduate School of Science, Osaka University, Toyonaka, Osaka 560-0043, Japan*
[b]*PRESTO, JST, Honcho Kawaguchi, Saitama 332-0012, Japan*

Received 21 December 2004; revised 15 April 2005; accepted 15 April 2005

Available online 13 May 2005

Abstract—Novel π-extended oligo(imidazole)s composed of imidazole and thiophene ring systems, bis(imidazolyl)thiophenes **1**–**4**, were synthesized as new building blocks for electron-donor molecules having diverse hydrogen-bonding directionalities in order to explore hydrogen-bonded charge-transfer complexes and supramolecular assemblies. The cyclic voltammetry of these compounds showed increase of electron-donating ability compared with those of 2,2′- and 4,4′-biimidazoles. In the crystal structure, **1**, **2** and **3** exhibited multi-dimensional hydrogen-bonded networks via solvent molecules including the π–π interaction. Charge-transfer complexes of **1**, **2** and **4** with TCNQ were characterized as partial charge-transfer complexes with segregated stacks. The compressed pellets of the TCNQ complex of **2** showed a high electrical conductivity ($\sigma_{rt}=5.2\times10^{-2}$ S cm^{-1}) at room temperature with semiconducting behavior (activation energy, $E_a=71$ meV).

1. Introduction

The design of molecular building blocks exhibiting multi-dimensional networks with well-defined molecular aggregation by non-covalent interactions such as hydrogen-bonding (H-bonding), π–π interaction and coordination bond is an important issue for the development of molecule-based materials.[1] In this context, construction of charge-transfer (CT) complexes with H-bonding functionalities is a recent trend in the creation of new organic conductors.[2] Numerous attempts to construct H-bonded CT salts and complexes afforded the successful preparations of metallic CT salts of tetrathiafulvalene (TTF) derivatives with amido functionalities furnished by Batail and co-workers.[3] Furthermore, the introduction of H-bonding interaction into CT systems gives an effective methodology for the electronic modulation by controlling the electron-donating abilities as demonstrated by tetracyanoquinodimethane (TCNQ) complex of diamino-dibenzo-TTF[4] and for the realization of cooperative proton–electron transfer system.[5] Recently, we have disclosed novel potential of imidazole group as an H-bonding functionality in CT complex by regulating the donor–acceptor ratio, as exemplified by a chloranil complex of TTF derivative having imidazole moiety.[6]

2,2′-Biimidazole (2,2′-H_2Bim), having strong H-bonding and coordination sites, has attracted attention as a building block of molecular architectures[7] and assembled metal complexes.[8] Furthermore, 2,2′-H_2Bim system has been utilized as electron-donor molecule of H-bonded CT complexes from the interest in its possible redox properties coupled with multiple proton- and electron-transfer processes.[9] In order to explore H-bonded CT complexes and assembled metal complexes based on imidazole ring system, we have recently synthesized 4,4′-biimidazole (4,4′-H_2Bim) and oligo(imidazole)s composed only of imidazole moieties by linear ring assemblies.[10] In the studies of protonated salt of 4,4′-H_2Bim[10] and its metal complexes,[11] we demonstrated that the characteristic H-bonded structures inherent in 4,4′-H_2Bim system and proved a fundamental importance of directionality of H-bonding interaction in the construction of assembled structures (Chart 1).

Recently, we have also demonstrated that H-bonding directionality is profoundly affected by molecular modification of 4,4′-H_2Bim, giving rise to increasing the variation of H-bonded networks.[12] Importantly, a transformation of

Keywords: Oligo(imidazole); Hydrogen-bond; Thiophene; Molecular assembly; Charge-transfer complex; Organic conductor.
* Corresponding authors. Tel.: +81 6 6850 5393; fax: +81 6 6850 5395 (Y.M.); (K.N.); e-mail: morita@chem.sci.osaka-u.ac.jp

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.04.030

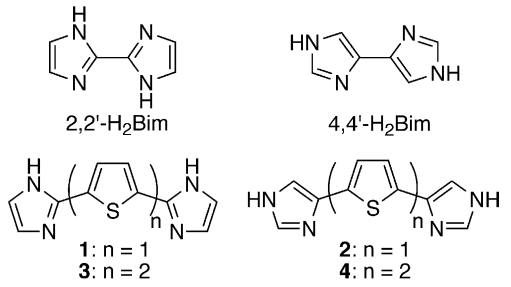
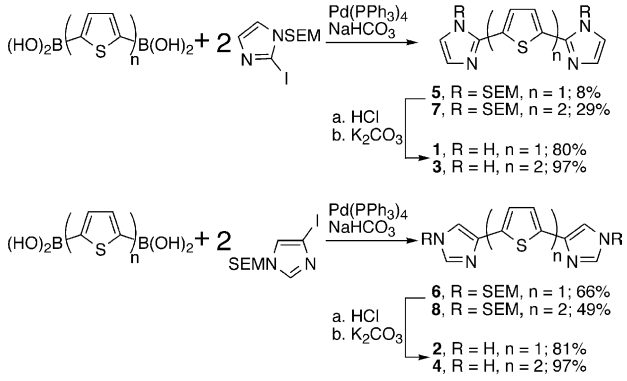


Chart 1.



Scheme 1.

molecular skeleton by an insertion of a spacer molecule into 2,2′- and 4,4′-H_2Bim systems could cause a dramatic change of the directionalities of the H-bondings, which can give an interesting chance to explore further H-bonded structure based on the H_2Bim system. Moreover, an extension of π-electronic systems of oligo(imidazole)s by aromatic ring system is expected to modulate electron-donating abilities. Thiophene-ring system is a planar and highly redox-active aromatic system, and has a high potential as a component molecular system for electronic and optical materials.[13] In this report, we have designed novel thiophene-introduced oligo(imidazole)s, bis(imidazolyl)-thiophenes, **1**–**4**, as new building blocks for electron-donor molecules in the H-bonded CT complexes. Their synthesis, cyclic voltammograms and pluri-dimensional H-bonded networks in crystal structure analysis of **1**–**3**, and physical properties of their TCNQ complexes were described. Emphasis lies on the directionalities of H-bonding networks induced by an electronic modulation and deformation of the molecular skeleton by introduction of thiophene-ring system into the 2,2′- and 4,4′-H_2Bim systems.

2. Results and discussion

2.1. Synthesis of bis(imidazolyl)thiophenes and their TCNQ complexes

Suzuki coupling reaction of 2,5-thiophenediboronic acid or 2,2′-bithiophene-5,5′-diboronic acid with *N*-SEM protected 2- or 4-iodoimidazole using Pd(0) catalyst gave the SEM-protected products **5**–**8** (SEM=[2-(trimethylsilyl)ethoxy]-methyl). The SEM protection groups of **5**–**8** were removed by the treatment with excess amount of HCl to afford bis(imidazolyl)thiophenes **1**–**4** (Scheme 1).[14] Single crystals of **1**, **2** and **3** suitable for X-ray analyses were obtained by the aerial evaporation of their MeOH solution. Data collection and refinement parameters for structural analyses are summarized in Table 1. TCNQ complexes of **1**–**4** were prepared by direct mixing method with TCNQ in MeCN–MeOH or MeOH–DMSO solution.

2.2. Cyclic voltammetry of bis(imidazolyl)thiophenes

In order to estimate electron-donating abilities of **1**–**4**, their electrochemical properties were studied. Due to existence of acidic N–H moieties, the cyclic voltammograms of **1**–**4** showed irreversible oxidation waves. Table 2 summarizes the oxidation peak potentials (E_p^{ox}) of **1**–**4**, including those of 2,2′- and 4,4′-H_2Bims, tetrathiafulvalene (TTF) and hydroquinone.

Table 1. Crystal data and structure refinement parameters for **1**·2H_2O, **2**·H_2O and **3**·2MeOH

	1·2H_2O	**2**·H_2O	**3**·2MeOH
Empirical formula	$C_{10}H_{12}N_4O_2S$	$C_{10}H_{10}N_4OS$	$C_{16}H_{18}N_4O_2S_2$
Formula weight	252.29	234.28	362.46
Temperature (K)	200	296	200
Crystal system	Orthorhombic	Orthorhombic	Monoclinic
Space group	$P2_12_12_1$	$C222_1$	$P2_1/c$
a (Å)	8.850(8)	8.968(1)	4.698(6)
b (Å)	13.17(1)	11.992(2)	12.994(10)
c (Å)	20.35(2)	10.321(1)	13.52(2)
α (°)	90	90	90
β (°)	90	90	95.74(4)
γ (°)	90	90	90
V (Å)^3	2372(15)	1110.0(2)	820(1)
Z	8	4	2
D_{calc} (g cm^{-1})	1.413	1.402	1.466
μ (Mo Kα) (cm^{-1})	2.69	2.75	3.42
2θ range (°)	6.1–55.0	6.8–55.0	6.3–54.8
Unique reflections	5395	746	1855
Observed data	2784 [$I>2\sigma(I)$]	616 [$I>2\sigma(I)$]	1333 [$I>2\sigma(I)$]
Refined parameters	307	74	109
R, R_w	—	0.033, 0.080	—
R_1, $_wR_2$	0.048, 0.088	—	0.047, 0.134
Goodness-of-fit	0.80	1.23	1.03

Table 2. Oxidation peak potentials (E_p^{ox}) of bis(imidazolyl)thiophenes **1**–**4**

	E_p^{ox} (V)		E_p^{ox} (V)
1	+0.33	2,2′-H_2Bim	+0.40
2	+0.20	4,4′-H_2Bim	+0.26
3	+0.28	TTF	−0.11
4	+0.21	Hydroquinone	+0.26

Experimental conditions: solvent, DMF; [**1**–**4**]=5 mM; [^{n}Bu$_4$NBF$_4$]=0.1 M; scan rate, 100 mV s^{-1}; reference electrode, Ag/AgNO$_3$ (0.01 M); counter electrode, Pt wire; working electrode, glassy carbon; the results were calibrated with ferrocene/ferrocenium couple.

The electron-donating abilities of **1**–**4** were evaluated to be weaker than that of TTF and comparable to that of hydroquinone. The lower E_p^{ox} values of **1**–**4** than analogous H_2Bim (2,2′-H_2Bim for **1** and **3**, 4,4′-H_2Bim for **2** and **4**) indicate the increase of the electron-donating abilities due to the π-extension by the introduction of thiophene-ring systems. The 2,2′-H_2Bim analogues **1** and **3** showed higher oxidation potential than 4,4′-H_2Bim analogues **2** and **4**. This tendency is similar to the relationship between connectivity of the molecular systems and oxidation potentials of 2,2′- and 4,4′-H_2Bim.

2.3. Crystal structures of 1·2H$_2$O, 2·H$_2$O and 3·2MeOH

2.3.1. Crystal structure of 1·2H$_2$O. Within a unit cell, two crystallographically independent **1** molecules (**1**-A and **1**-B) and four water molecules are found. A curved-shape molecular structure of **1**-A and -B is contrastive structural feature to the linear-shape molecule of 2,2′-H_2Bim system which construct one-dimensional chain by double complementary H-bonding (Fig. 1a).[7a] Imidazole rings in **1**-A and -B are twisted by ∼9° from thiophene ring. Both of **1**-A and -B possess the pseudo-rotation axes in their thiophene rings, and there are no noticeable differences in the geometries of **1**-A and -B molecules. However, their molecular symmetries are broken by crystallographically different environments and H-bondings with water molecules. **1**-A and -B molecules alternately stacked with face-to-face distance of 3.5 Å, to form π-stacking column along the *a*-axis (Fig. 1b–d). The N atoms at the inside of the curved-shape molecules bind water molecules by H-bondings, resulting in the formation of a channel structure along the *a*-axis (Fig. 1d and e). This channel structure is fulfilled with water molecules which construct a one-dimensional H-bonded chain (Fig. 1e). Direct N(3)–H···N(7) H-bonding interaction of N atoms at the outside of the curved-shape molecules connect the π-stacking columns. These H-bonding interactions build up a three-dimensional network of this crystal.

2.3.2. Crystal structure of 2·H$_2$O. The crystal of 4,4′-H_2Bim analogue **2** consists of one **2** molecule and a water molecule. Molecular structure of **2** possesses the rotation axis, and the imidazole ring is twisted by ∼31° from the central thiophene ring with *syn–syn* conformation (Fig. 2a). All nitrogen atoms on imidazole moiety interact with water molecules to construct a three-dimensional H-bonded

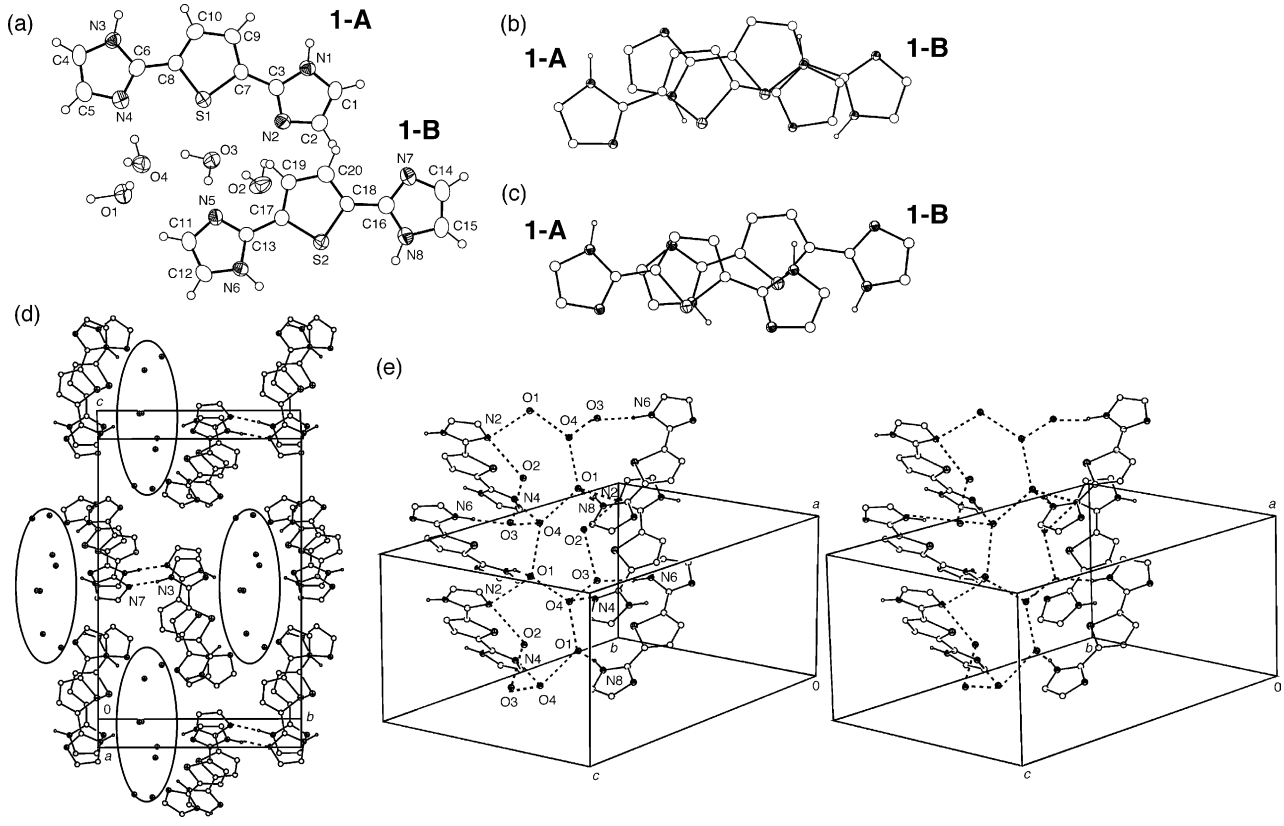


Figure 1. Crystal structure of **1**·2H$_2$O. ORTEP view of the molecular structure of **1** showing the atomic labelling scheme (a). Overlap modes in a π-stacking column (b) and (c). Perspective view nearly along the *a*-axis showing the π-stacking columns and channel structures (d). Stereoview of the crystal packing, showing one-dimensional chain of water molecules within a channel structure (e). The ellipses show the channel fulfilled by water molecules, and the dotted lines show H-bonding interactions. H-bonding distances (D···A in Å): N(3)···N(7), 2.81; N(1)···O(2), 2.77; N(2)···O(1), 2.93; N(2)···O(2), 2.89; N(4)···O(4), 2.75; N(5)···O(3), 2.76; N(6)···O(3), 2.87; N(8)···O(1), 2.83; O(1)···O(4), 2.79; O(2)···O(3), 2.83; O(3)···O(4), 2.78.

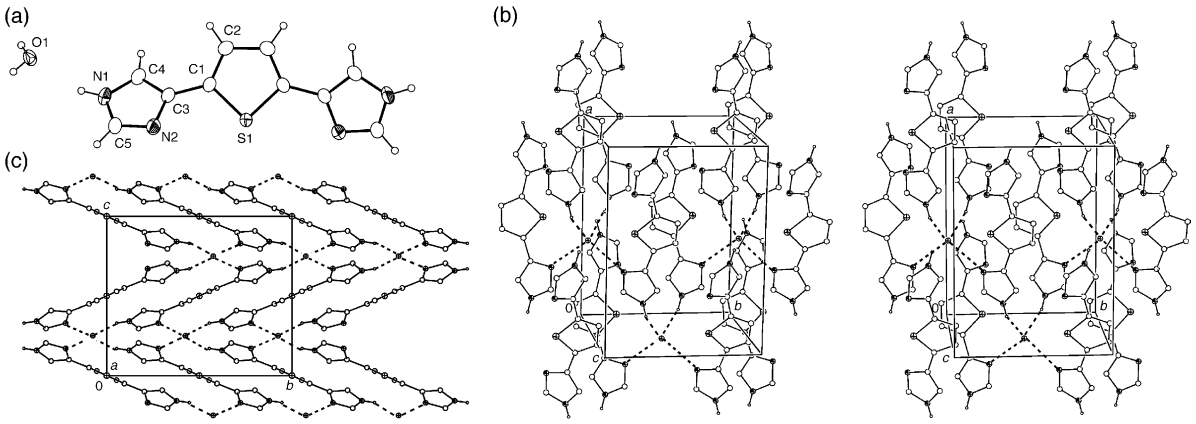


Figure 2. Crystal structure of **2**·H_2O. ORTEP view of the molecular structure of **2** showing the atomic labelling scheme (a). Stereoview of the crystal packing (b). Perspective view along the *a*-axis (c). Dotted lines show the H-bonding interactions. H-bonding distances (D···A in Å): N(1)···O(1), 2.87; N(2)···O(1), 2.81.

network (Fig. 2b and c). The closest N···O distances are 2.87 Å for N(1)···O(1) and 2.81 Å for N(2)···O(1). π–π Interaction was not found in this structure. In this crystal, the dihedral angle between two imidazole-rings in one **2** molecule is ∼59°, which is larger than those of 2,2′- and 4,4′-H_2Bim systems having nearly planar molecular structures.[7,10] The twisted structure of **2** changes the directionality of H-bonding interaction to construct the three-dimensional H-bonded network.

2.3.3. Crystal structure of 3·2MeOH. This crystal consists of one **3** molecule and two MeOH molecules. The molecule **3** possesses the inversion center on the central C–C bond of bithiophene skeleton, and the central bithiophene unit has a *anti*-conformation to give a linear-shape structure of **3**, which is similar to that of 2,2′-H_2Bim system (Fig. 3a). In the molecular structure of **3**, the bithiophene unit is planar, and imidazole ring is inclined by ∼14° from the bithiophene skeleton. The π–π interaction of **3** forms a uniform stacking column along the *a*-axis with 3.4 Å of interplanar distance (Fig. 3b and c). The directionalities of the H-bonding interactions of the two imidazole-rings in **3** are parallel to each other similarly to those of 2,2′-H_2Bim. The **3** molecules are connected by N(1)–H···O(1)–H···N(2) H-bondings via MeOH molecules to construct a two-dimensional sheet structure (Fig. 3c). The closest N···O distances are 2.71 Å for N(1)···O(1) and 2.73 Å for N(2)···O(1). This observation exhibits a striking contrast to that of 2,2′-H_2Bim system which shows one-dimensional chain structure by double complementary H-bondings.[7] This difference is probably derived from distance of two imidazole moieties and the steric effect of the bithiophene unit.

2.4. Physical properties of TCNQ complexes

In order to investigate structural and electronic effects of the H-bonding interactions in CT complexes, we have prepared the TCNQ complexes of **1**–**4**. Although TCNQ complex of 2,2′-H_2Bim is not obtained by the direct mixing method,[15] the preparation of TCNQ complexes of **1**–**4** were performed by the direct mixing method between **1**–**4** and TCNQ because of the increased electron-donating abilities of **1**–**4** compared to that of 2,2′-H_2Bim. Figures 4 and 5 show the IR and electronic spectra of CT complexes of **1**–**4** with TCNQ, respectively, and Table 3 summarizes their physical

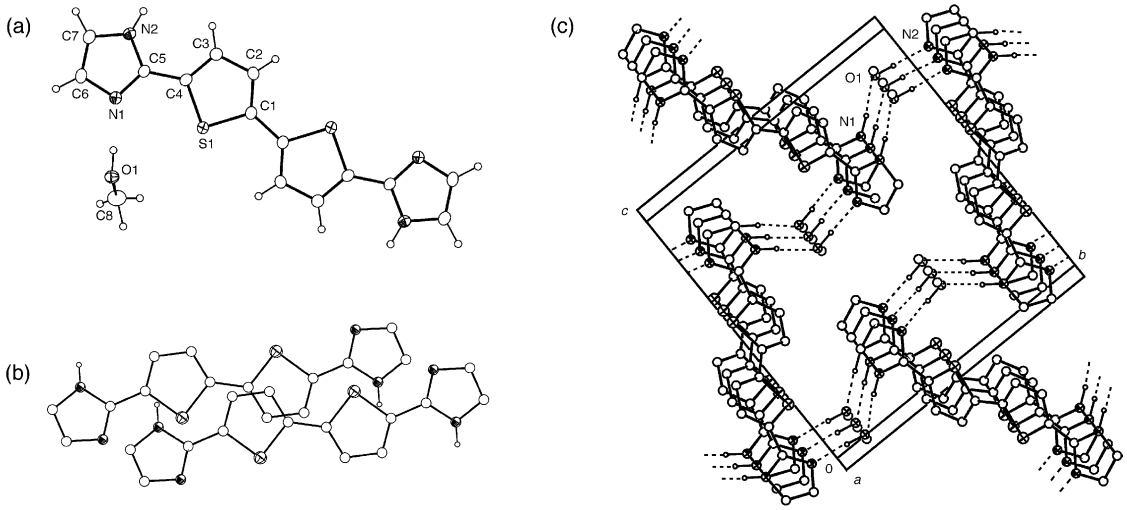


Figure 3. Crystal structure of **3**·2MeOH. ORTEP view of the molecular structure of **3** showing the atomic labelling scheme (a). Overlap mode in a π-stacking column (b). Molecular packing viewed along the *a*-axis showing the π-stacking column and two-dimensional H-bonded network (c). Dotted lines show the H-bonding interactions. H-bonding distances (D···A in Å): N(1)···O(1), 2.71; N(2)···O(1), 2.73.

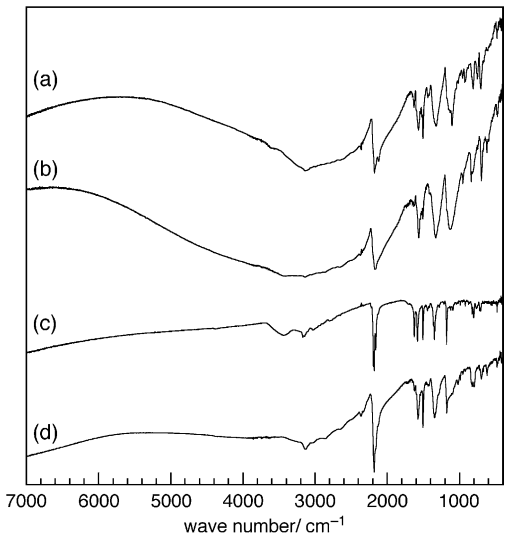


Figure 4. IR spectra of **1**-TCNQ (a), **2**-TCNQ (b), **3**-TCNQ (c) and **4**-TCNQ (d) complexes in KBr pellets.

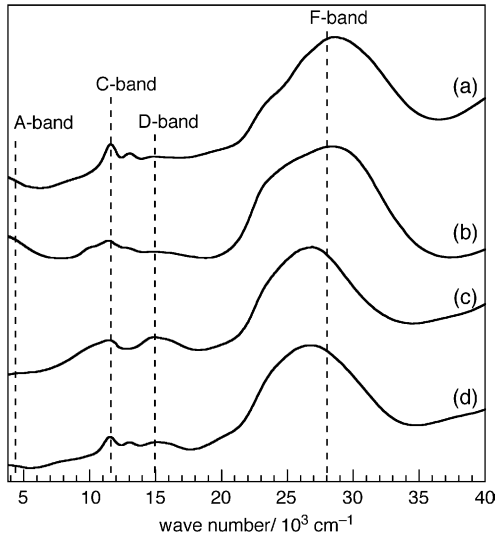


Figure 5. Electronic spectra of **1**-TCNQ (a), **2**-TCNQ (b), **3**-TCNQ (c) and **4**-TCNQ (d) complexes in KBr pellets.

properties. The broad and multiplet absorption bands spread over 3300–2500 cm^{-1} in the IR spectra of **3**- and **4**-TCNQ complexes are assigned to be N–H stretching frequencies of donor molecules. These bands may indicate a formation of intermolecular N–H···N≡C H-bonding between donor and acceptor molecules (Fig. 4c and d). In the case of **1**- and **2**-TCNQ complexes, N–H stretching absorption bands overlap with the strong CT bands at around 3000 cm^{-1} (Fig. 4a and b), hampering the elucidation of H-bonding natures in CT complexes in terms of IR spectra. The donor–acceptor ratio of **2**-TCNQ complex is estimated to be 1:3 from elemental analysis, and those of TCNQ complexes of **1**, **3** and **4** are 1:1. The ionicities of TCNQ moieties (ρ) in these TCNQ complexes of **1**–**4** are estimated to be 0.61, 0.61, 0.82 and 0.75 from the C≡N stretching frequency ($\nu_{C\equiv N}$), 2200, 2200, 2191 and 2194 cm^{-1}, respectively, in the IR measurement.[16] However, these ρ values remain somewhat ambiguous due to the possibility of the shift of CN stretching frequencies induced by the formation of H-bonding on TCNQ moieties and of the formation of dication (not monocation) of donor molecules. In the electronic spectra (Fig. 5), TCNQ complexes of **1**–**4** show the general resemblance of $TCNQ^{\cdot -}$ in the range of 10,000–40,000 cm^{-1}; these TCNQ complexes exhibit the C-band (intermolecular CT transition of $TCNQ^{\cdot -}$) at around 11500 cm^{-1}, the D-band at 15,000–17,000 cm^{-1} (intramolecular transition of $TCNQ^{\cdot -}$) and F-band (intramolecular transition of neutral TCNQ and $TCNQ^{\cdot -}$) at 26,000–29,000 cm^{-1}.[17] The absorption of **1**–**4** moieties are overlapped with the F-band, and observed as shoulder peaks. In addition, the CT bands are observed at lower energy region around 3000–4000 cm^{-1} (A-band) in **1**-, **2**- and **4**-TCNQ complexes. These bands are assignable to the intermolecular CT transition from $TCNQ^{\cdot -}$ to neutral TCNQ.[17] These results indicate that TCNQ complexes of **1**, **2** and **4** are partial CT complexes with segregated stacking columns.[17] On the other hand, **3**-TCNQ complex is assigned to be completely ionic complex from the larger ρ value and the absence of the A-band. The measurement of electrical conductivity for compressed pellet of the CT complex shows that **3**-TCNQ is an insulator, while TCNQ complexes of **1** and **4** are found to be low-conductive semiconductors with room temperature conductivities (σ_{rt}) of $\sim 10^{-6}$ S cm^{-1}. Interestingly, **2**-TCNQ complex exhibits a high conductivity with semiconductive behavior ($\sigma_{rt}=5.2\times10^{-2}$ S cm^{-1}, activation energy (E_a)= 71 meV). This σ_{rt} value is 10^4 orders higher than those of 2,2′-H_2Bim system.[18]

3. Conclusion

The π-extended oligo(imidazole)s composed of imidazole and thiophene-ring systems, bis(imidazolyl)thiophenes, were synthesized as novel electron-donor molecules for H-bonded CT complexes. In the crystal structures, neutral **1**,

Table 3. Stoichiometry, optical and conductivity data of TCNQ complexes of bis(imidazolyl)thiophenes **1**–**4**

	D:A:solvent[a]	$\nu_{C\equiv N}$[b]/cm^{-1}	ρ[c]	A-band[b], $\times10^3$ cm^{-1}	C-band[b], $\times10^3$ cm^{-1}	D-band[b], $\times10^3$ cm^{-1}	F-band[b], $\times10^3$ cm^{-1}	σ_{rt}[d]/S cm^{-1}	E_a/meV
1	1:1:1.7H_2O	2200	0.61	3.0	11.6	14.9	28.7	9.0×10^{-6}	154
2	1:3:3H_2O	2200	0.61	3.0	11.5	16.6	29.1	5.2×10^{-2}	71
3	1:1	2191	0.82	—[e]	11.5	14.9	26.8	$<10^{-7}$	—
4	1:1:0.7H_2O	2194	0.75	3.8	11.5	15.1	26.7	7.9×10^{-6}	215

[a] Component ratios were estimated by the elemental analysis.
[b] IR and electronic spectra were measured in KBr pellet.
[c] The ionicities of TCNQ (ρ) were estimated by the C≡N stretching frequencies ($\nu_{C\equiv N}$) of the IR spectrum on the basis of the Chappell's method.[16]
[d] Electrical conductivities were measured for compressed pellets using the two- or four-probe method.
[e] Not observed.

2 and **3** showed diverse and characteristic assembled structures depending on their H-bonding directionalities derived from their molecular structures and connectivities of imidazole moieties with thiophenes. The curved-shape of **1** molecule made two different H-bonding environments, inside and outside of molecular skeleton, and built up the channel structure. In the crystal structure of **2**, the *syn–syn* conformation and large dihedral angle of two imidazole-rings increased the dimensionality of the H-bonding interaction to construct the three-dimensional network. Furthermore, the two parallel H-bondings of **3** molecule having the linear-shape structure formed the two-dimensional H-bonded network. Notably, these H-bonded structures reveal their high potentials as building blocks for supramolecular assemblies. In addition, increased electron-donating abilities of **1**–**4** compared with those of 2,2′- and 4,4′-H_2Bim systems indicate a high potential of **1**–**4** as the promising candidates for the electron-donor molecules in H-bonded CT complexes. Actually, TCNQ complex of **2** was highly conductive semiconductor. These results show that the design of electron-donor molecules having diverse H-bonding directionalities is useful and interesting strategy for the construction of H-bonded CT complexes with intriguing functionalities. Further studies on π-extended oligo(imidazole)s are now carried out not only for the construction of conducting molecular assemblies with H-bonding interactions, serving for the realization of cooperative proton–electron transfer system,[5] but also for investigating a possibility as component molecular systems of electronic and optical materials.

4. Experimental

4.1. General

^{1}H NMR spectra were measured on a JEOL EX-270 spectrometer with Me_4Si or residual solvent as an internal standard. EI-MS spectra were recorded at 70 eV on a Shimadzu QP-5000. Infrared and electronic spectra were recorded using KBr plates on JASCO FT/IR-660M and Shimadzu UV/vis-NIR scanning spectrophotometer UV-3100 PC, respectively. Melting points were measured by a Yanaco micro melting point apparatus and were uncorrected. Elemental analyses were performed at the Analytical Center of Graduate School of Science, Osaka University. The direct current electrical-conductivity measurements were performed on the compressed powder pellets by a conventional two- or four-probe method using gold paint and gold wire. Cyclic voltammetric measurements were made with an ALS Electrochemical Analyzer Model 612A. Cyclic voltammogram was recorded with 3.0 mm diameter glassy plate carbon electrode and Pt wire counter electrode in DMF containing 0.1 M Bu_4NBF_4 as the supporting electrolyte at room temperature. The experiments employed an $Ag/AgNO_3$ reference electrode. The final results were calibrated with the ferrocene/ferrocenium couple. R_f values on TLC were recorded on E. Merck precoated (0.25 mm) silica gel 60 F_{254} and alumina F_{254} plates. The plates were sprayed with a solution of 10% phosphomolybdic acid in 95% EtOH and then heated until the spots become clearly visible. Silica gel 60 (100–200 mesh) was used for column chromatography. Recycle preparative gel permeation chromatography (GPC) was performed using tandemly connected two polystyrene gel columns (JAIGEL 1H, Japan Analytical Industry). 2,2′-Bithiophene-5,5′-diboronic acid,[19] *N*-[2′-(trimethylsilyl)ethoxy]methyl (SEM)-protected 2-iodoimidazole[20] and SEM-protected 4-iodoimidazole[10] were prepared by the reported procedures. DME were dried (Na-benzophenone ketyl) and distilled under argon prior to use. All reactions requiring anhydrous conditions were conducted under argon atmosphere.

4.2. Synthesis of bis(imidazolyl)thiophenes (1–4)

4.2.1. 2,5-Bis[1′-{[2″-(trimethylsilyl)ethoxy]methyl}-imidazol-2′-yl]thiophene (5). The SEM-protected 2-iodoimidazole (3.00 g, 9.25 mmol), 2,5-thiophenediboronic acid (800 mg, 4.66 mmol), and $Pd(PPh_3)_4$ (500 mg, 0.432 mmol) were placed in a 200 mL schlenk flask and suspended with DME (40 mL) and 1 M $NaHCO_3$ aqueous solution (30 mL). The mixture was stirred at 70 °C for 18 h under argon atomosphere. The reaction mixture was poured into H_2O (100 mL), and was extracted with ethyl acetate (100 mL). The organic layer was washed with a satd NaCl aqueous solution (100 mL) and dried over Na_2SO_4, then filtered and concentrated under reduced pressure. The residual oil was subjected to silica gel column chromatography with 3:1–0:1 mixture of hexane and ethyl acetate as eluant. The resulting mixture containing desired compound was subjected to GPC with $CHCl_3$ as eluant, to give the coupling product **5** (170 mg, 8%) as a pale yellow powder: mp 215–216 °C; R_f=0.21 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 18H), 0.95 (t, 4H, J=8.2 Hz), 3.61 (t, 4H, J=8.2 Hz), 5.40 (s, 4H), 7.09 (d, 2H, J=1.3 Hz), 7.13 (d, 2H, J=1.3 Hz), 7.53 (s, 2H); IR (KBr) 3103, 3085, 2952, 2893 cm^{-1}; EI-MS, *m/z* 476 (M^+, 100%). Anal. Calcd for $C_{22}H_{36}N_4O_2Si_2S$: C, 55.52; H, 7.61; N, 11.75. Found: C, 55.31; H, 7.44; N, 11.73%.

4.2.2. 2,5-Bis[1′-{[2″-(trimethylsilyl)ethoxy]methyl}-imidazol-4′-yl]thiophene (6). Following the same procedure as that for **5**, compound **6** was obtained as a white powder (66% yield): mp 89–90 °C; R_f=0.42 (10:1 ethyl acetate/MeOH); ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 18H), 0.93 (t, 4H, J=8.2 Hz), 3.53 (t, 4H, J=8.2 Hz), 5.27 (s, 4H), 7.21 (d, 2H, J=1.3 Hz), 7.24 (d, 2H, J=1.3 Hz), 7.58 (s, 2H); IR (KBr) 3098, 2952, 2916 cm^{-1}; EI-MS, *m/z* 476 (M^+, 100%). Anal. Calcd for $C_{22}H_{36}N_4O_2Si_2S$: C, 55.52; H, 7.61; N, 11.75. Found: C, 55.15; H, 7.59; N, 11.54%.

4.2.3. 5,5′-Bis[1″-{[2‴-(trimethylsilyl)ethoxy]methyl}-imidazol-2″-yl]-2,2′-bithiophene (7). Following the same procedure as that for **5**, compound **7** was obtained as a yellow powder (29% yield): mp 138–139 °C; R_f=0.24 (1:1 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$) δ −0.04 (s, 18H), 0.88 (t, 4H, J=8.1 Hz), 3.59 (t, 4H, J=8.1 Hz), 5.48 (s, 4H), 7.00 (d, 2H, J=1.2 Hz), 7.39 (d, 2H, J=4.0 Hz), 7.44 (d, 2H, J=4.0 Hz), 7.49 (d, 2H, J=1.2 Hz); IR (KBr) 3098, 2952, 2916, 2893 cm^{-1}; EI-MS, *m/z* 558 (M^+, 100%). Anal. Calcd for $C_{26}H_{38}N_4O_2Si_2S_2$: C, 55.87; H, 6.85; N, 10.02. Found: C, 55.66; H, 6.77; N, 10.01%.

4.2.4. 5,5′-Bis[1″-{[2‴-(trimethylsilyl)ethoxy]methyl}-imidazol-4″-yl]-2,2′-bithiophene (8). Following the same procedure as that for **5**, compound **8** was obtained as a

yellow powder (49% yield): mp 200–202 °C; R_f=0.53 (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ −0.02 (s, 18H), 0.87 (t, 4H, J=8.1 Hz), 3.51 (t, 4H, J=8.1 Hz), 5.34 (s, 4H), 7.19 (d, 2H, J=3.8 Hz), 7.23 (d, 2H, J=3.8 Hz), 7.69 (d, 2H, J=1.2 Hz), 7.84 (d, 2H, J=1.2 Hz); IR (KBr) 3124, 2954, 2893 cm^{-1}; EI-MS, m/z 558 (M^+, 100%). Anal. Calcd for $C_{26}H_{38}N_4O_2Si_2S_2$: C, 55.87; H, 6.85; N, 10.02. Found: C, 55.76; H, 6.71; N, 9.98%.

4.2.5. 2,5-Bis(2′-imidazolyl)thiophene (1). The SEM-protected bis(imidazolyl)thiophene **5** (112 mg, 0.23 mmol) was placed in a 50 mL round-bottomed flask and dissolved with EtOH (1 mL) and a 5 M HCl aqueous solution (2.5 mL). The reaction mixture was refluxed for 3 h. EtOH was removed by distillation under reduced pressure, and the residue was neutralized with a satd K_2CO_3 aqueous solution. The resulting powder was collected by filtration and washed with H_2O (3 mL), to give **1** (40.4 mg, 80%) as a white powder: mp >300 °C; ^{1}H NMR (DMSO-d_6, 80 °C) δ 6.96 (s, 2H), 7,24 (s, 2H), 7.45 (s, 2H), 12.60 (br s, 2H); IR (KBr) 3200–2300, 1588, 1524 cm^{-1}; UV (KBr) 222, 348 nm; EI-MS, m/z 216 (M^+, 100%). Anal. Calcd for $(C_{10}H_8N_4S)$ $(H_2O)_{0.2}$: C, 54.63; H, 3.85; N, 25.48. Found: C, 54.78; H, 3.74; N, 25.35%.

4.2.6. 2,5-Bis(4′-imidazolyl)thiophene (2). Following the same procedure as that for **1**, compound **2** was obtained as a white powder (81% yield): mp 251–253 °C; ^{1}H NMR (DMSO-d_6, 80 °C) δ 7.12 (s, 2H), 7.31 (s, 2H), 7.60 (s, 2H); IR (KBr) 3200–2300, 1647, 1602, 1525 cm^{-1}; UV (KBr) 348 nm; EI-MS, m/z 216 (M^+, 100%). Anal. Calcd for $(C_{10}H_8N_4S)$ $(H_2O)_{1.2}$: C, 50.49; H, 4.41; N, 23.55. Found: C, 50.64; H, 4.40; N, 23.58%.

4.2.7. 5,5′-Bis(2″-imidazolyl)-2,2′-bithiophene (3). Following the same procedure as that for **1**, compound **3** was obtained as a yellow powder (97% yield): mp >300 °C; ^{1}H NMR (DMSO-d_6, 80 °C) δ 6.97 (s, 2H), 7.23 (s, 2H), 7.31 (d, 2H, J=3.6 Hz), 7.46 (d, 2H, J=3.6 Hz); IR (KBr) 3300–2600, 1590, 1516 cm^{-1}; UV (KBr) 332, 374 nm; EI-MS, m/z 298 (M^+, 100%). Anal. Calcd for $(C_{14}H_{10}N_4S_2)(H_2O)_{0.2}$: C, 55.68; H, 3.47; N, 18.55. Found: C, 55.77; H, 3.30; N, 18.21%.

4.2.8. 5,5′-Bis(4″-imidazolyl)-2,2′-bithiophene (4). Following the same procedure as that for **1**, compound **4** was obtained as a brownish yellow powder (97% yield): mp >300 °C; ^{1}H NMR (DMSO-d_6, 80 °C) δ 7.13 (d, 2H, J=3.6 Hz), 7.17 (d, 2H, J=3.6 Hz), 7.41 (s, 2H), 7.63 (s, 2H); IR (KBr) 3200–2500, 1653, 1575, 1535 cm^{-1}; UV (KBr) 374 nm; EI-MS, m/z 298 (M^+, 100%). Anal. Calcd for $(C_{14}H_{10}N_4S_2)(H_2O)_{0.4}$: C, 54.70; H, 3.61; N, 18.23. Found: C, 55.09; H, 3.40; N, 17.85%.

4.3. Preparation of TCNQ complexes

4.3.1. TCNQ complex of 2,5-bis(2′-imidazolyl)thiophene [(1)(TCNQ)$(H_2O)_{1.7}$]. In a 30 mL round-bottomed flask, a solution of **1** (21.6 mg, 0.10 mmol) in MeOH (5 mL) and a solution of TCNQ (20.4 mg, 0.10 mmol) in MeCN (10 mL) were mixed at room temperature. After stirring at room temperature for 2 h, the mixture was concentrated under reduced pressure. The resulting powder was washed with MeCN (2 mL) and CH_2Cl_2 (10 mL), to give CT complex (30.0 mg) as a black powder: IR (KBr) 2200, 2179, 2120, 1629, 1570, 1505 cm^{-1}; UV (KBr) 348, 672, 764, 862, ~3300 nm. Anal. Calcd for $(C_{10}H_8N_4S)(C_{12}H_4N_4)$-$(H_2O)_{1.7}$: C, 58.58; H, 3.44; N, 24.84. Found: C, 58.38; H, 3.06; N, 24.41%.

4.3.2. TCNQ complex of 2,5-bis(4′-imidazolyl)thiophene [(2)(TCNQ)$_3$$(H_2O)_3$]. Following the same procedure as that for TCNQ complex of **1**, TCNQ complex of **2** was obtained as a deep green powder: IR (KBr) 2200, 2179, 2120, 1636, 1565, 1506 cm^{-1}; UV (KBr) 344, 604, 866, ~3300 nm. Anal. Calcd for $(C_{10}H_8N_4S)(C_{12}H_4N_4)_3(H_2O)_3$: C, 62.58; H, 2.97; N, 25.38. Found: C, 62.25; H, 2.89; N, 25.09%.

4.3.3. TCNQ complex of 5,5′-bis(2″-imidazolyl)-2,2′-bithiophene [(3)(TCNQ)]. Following the same procedure as that for TCNQ complex of **1**, TCNQ complex of **3** was obtained as a bluish green powder: IR (KBr) 2191, 2181, 2161, 1625, 1582, 1506 cm^{-1}; UV (KBr) 373, 672, 872 nm. Anal. Calcd for $(C_{14}H_{10}N_4S_2)(C_{12}H_4N_4)$: C, 62.14; H, 2.81; N, 22.30. Found: C, 62.78; H, 2.81; N, 22.61%.

4.3.4. TCNQ complex of 5,5′-bis(4″-imidazolyl)-2,2′-bithiophene [(4)(TCNQ)$(H_2O)_{0.7}$]. Following the same procedure as that for TCNQ complex of **1**, TCNQ complex of **4** was obtained as a black powder: IR (KBr) 2194, 2182, 2158, 2125, 1623, 1576, 1505 cm^{-1}; UV (KBr) 374, 662, 768, 872, ~2600 nm. Anal. Calcd for $(C_{14}H_{10}N_4S_2)(C_{12}$-$H_4N_4)(H_2O)_{0.7}$: C, 60.62; H, 3.01; N, 21.75. Found: C, 60.87; H, 2.81; N, 21.40%.

4.4. X-ray crystallographic study

X-ray crystallographic measurements for single crystals were made on Rigaku AFC7R for **2**·H_2O, and Rigaku Raxis-Rapid Imaging Plate for **1**·$2H_2O$ and **3**·2MeOH with graphite monochromated Mo Kα radiation (λ=0.7107 Å). Structures were determined by direct method using SIR-92 for **2**·H_2O, and SHELXS-86 for **1**·$2H_2O$ and **3**·2MeOH. Refinements of structures were carried out by full-matrix least squares on F^2. All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were included but not refined.

Crystallographic data for the structural analysis have been deposited with Cambridge Crystallographic Data Center, CCDC reference numbers 258743, 258744 and 258745. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1233 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research (No. 16350074) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan, by PRESTO-JST, by a grant of The Asahi Glass Foundation and by 21COE program 'Creation of Integrated EcoChemistry of Osaka University'.

References and notes

1. (a) Lehn, J.-M. *Supramolecular Chemistry-concepts and Perspective*; VCH: Weinheim, 1995. (b) Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; Wiley: Chichester, 2000.
2. (a) Bryce, M. R. *J. Mater. Chem.* **1995**, *5*, 1481–1495. (b) Batail, P.; Boubekeur, K.; Fourmigué, M.; Gabriel, J.-C. P. *Chem. Mater.* **1998**, *10*, 3005–3015. (c) Fourmigué, M.; Batail, P. *Chem. Rev.* **2004**, *104*, 5379–5418. (d) Morita, Y.; Maki, S.; Ohmoto, M.; Kitagawa, H.; Okubo, T.; Mitani, T.; Nakasuji, K. *Org. Lett.* **2002**, *4*, 2185–2188.
3. (a) Heuzé, K.; Fourmigué, M.; Batail, P.; Canadell, E.; Auban-Senzier, P. *Chem. Eur. J.* **1999**, *5*, 2971–2976. (b) Heuzé, K.; Mézière, C.; Fourmigué, M.; Batail, P.; Coulon, C.; Canadell, E.; Auban-Senzier, P.; Jérome, D. *Chem. Mater.* **2000**, *12*, 1898–1904.
4. Morita, Y.; Miyazaki, E.; Fukui, K.; Maki, S.; Nakasuji, K. To be submitted for publication.
5. Nakasuji, K.; Sugiura, K.; Kitagawa, T.; Toyoda, J.; Okamoto, H.; Okaniwa, K.; Mitani, T.; Yamamoto, H.; Murata, I.; Kawamoto, A.; Tanaka, J. *J. Am. Chem. Soc.* **1991**, *113*, 1862–1864.
6. Murata, T.; Morita, Y.; Fukui, K.; Sato, K.; Shiomi, D.; Takui, T.; Maesato, M.; Yamochi, H.; Saito, G.; Nakasuji, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 6343–6346.
7. (a) Cromer, D. T.; Ryan, R. R.; Storm, C. B. *Acta Crystallogr., Sect. C* **1987**, *43*, 1435–1437. (b) Bélanger, S.; Beauchamp, A. L. *Acta Crystallogr., Sect. C* **1996**, *52*, 2588–2590. (c) Ramírez, K.; Reyes, J. A.; Briceño, A.; Atencio, R. *CrystEngComm* **2002**, *4*, 212–218.
8. (a) Tadokoro, M.; Nakasuji, K. *Coord. Chem. Rev.* **2000**, *198*, 205–218. (b) Tadokoro, M.; Kanno, H.; Kitajima, T.; Umemoto, H.-S.; Nakanishi, N.; Isobe, K.; Nakasuji, K. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4950–4955.
9. (a) Akutagawa, T.; Saito, G.; Kusunoki, M.; Sakaguchi, K. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2487–2511. (b) Akutagawa, T.; Hasegawa, T.; Nakamura, T.; Inabe, T.; Saito, G. *Chem. Eur. J.* **2002**, *8*, 4402–4411. (c) Akutagawa, T.; Hasegawa, T.; Nakamura, T.; Saito, G. *CrystEngComm* **2003**, *5*, 54–57.
10. Morita, Y.; Murata, T.; Yamada, S.; Tadokoro, M.; Ichimura, A.; Nakasuji, K. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2598–2600.
11. Morita, Y.; Murata, T.; Fukui, K.; Tadokoro, M.; Sato, K.; Shiomi, D.; Takui, T.; Nakasuji, K. *Chem. Lett.* **2004**, *33*, 188–189.
12. (a) Murata, T.; Morita, Y.; Nishimura, Y.; Nakasuji, K. *Polyhedron*, in press. See also: (b) Zhang, W.; Landee, C. P.; Willett, R. D.; Turnbull, M. M. *Tetrahedron* **2003**, *59*, 6027–6034.
13. For recent overview, see: Mullen, K.; Wegner, G. *Electronic Materials: The Oligomer Approach*; Wiley-VCM: Weinheim, Germany, 1998.
14. Due to the highly hygroscopic nature of **1**–**4**, the elemental analyses do not always give the appropriate values. However, the elemental analyses of the corresponding SEM-protected derivatives can provide alternative characterization of **1**–**4**.
15. Murata, T.; Morita, Y.; Nakasuji, K. Unpublished result. See also Ref. 9a.
16. The ρ values of TCNQ complexes were deduced by the linear relation between ρ and $\nu_{C\equiv N}$ value as $\rho=(2227-\nu_{C\equiv N})/44$, see: Chappell, J. S.; Bloch, A. N.; Bryden, W. A.; Maxfield, M.; Poehler, T. O.; Cowan, D. O. *J. Am. Chem. Soc.* **1981**, *103*, 2442–2443.
17. (a) Torrance, J. B.; Scott, B. A.; Welber, B.; Kaufman, F. B.; Seiden, P. E. *Phys. Rev. B* **1979**, *19*, 730–741. (b) Conwell, E. M.; Howard, I. A.; Pouget, J. P.; Jacobsen, C. S.; Scott, J. C.; Zuppiroli, L. In *Semiconductors and semimetals*; Conwell, E. M., Ed.; Semiconductors and semimetals; Academic: New York, 1988; Vol. 27. (c) Tanaka, J.; Tanaka, M.; Kawai, T.; Takabe, T.; Maki, O. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2358–2373. (d) Torrance, J. B.; Scott, B. A.; Kaufman, F. B. *Solid State Commun.* **1975**, *17*, 1369–1373.
18. σ_{rt} values of TCNQ salts of 2,2′-H_2Bim; 5.9×10^{-8} S cm^{-1} for (2,2′-H_3Bim^+)(TCNQ), 8.3×10^{-7} S cm^{-1} for (2,2′-H_3Bim^+)$_2$(TCNQ)$_3$, 1.6×10^{-7} S cm^{-1} for (2,2(-H_4Bim^{2+})-(TCNQ)$_2$. See Ref. 9a.
19. Olinga, T.; Destri, S.; Porzio, W. *Macromol. Chem. Phys.* **1997**, *198*, 1091–1107.
20. Knapp, S.; Albaneze, J.; Schugar, H. J. *J. Org. Chem.* **1993**, *58*, 997–998.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 61 (2005) 6064–6072
Tetrahedron

One-pot enzymatic desymmetrization and Ugi MCR

Anna Fryszkowska,[a] Jadwiga Frelek[b] and Ryszard Ostaszewski[a,b,*]

[a]*Faculty of Chemistry, Warsaw University of Technology, Noakowskiego 3, 00-664 Warsaw, Poland*
[b]*Institute of Organic Chemistry PAS, Kasprzaka 44/52, 01-224 Warsaw, Poland*

Received 24 November 2004; revised 29 March 2005; accepted 15 April 2005

Available online 13 May 2005

Abstract—A new approach to the synthesis of chiral peptidomimetics is reported. It combines an enzymatic desymmetrization of 3-phenylglutaric anhydrides with a subsequent Ugi multi-component reaction in a one-pot, two-step procedure. NMR and CD spectroscopy was used to assign the configurations of obtained products. Our synthetic method is very efficient and it can easily be extended to other types of multi-component reactions and can be used for the preparation of chiral peptidomimetic libraries.

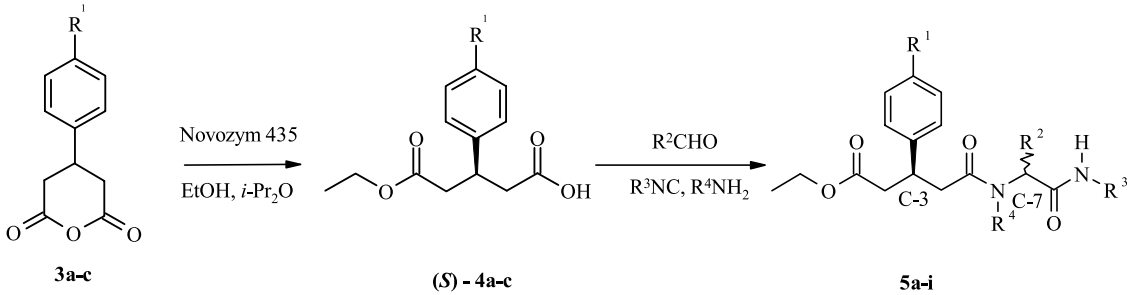
1. Introduction

Multi-component reactions (MCRs) are of great interest for medicinal chemistry.[1] MCRs can be efficiently used in the synthesis of chiral compounds.[2] They are also useful in peptidomimetic synthesis due to their ability to generate a large number of compounds efficiently in one or two synthetic steps.[3,4] Commonly used MCRs include the Ugi reaction.[5,6] These reactions are especially attractive as a one-pot tandem processes with other reactions.

Only a few examples can be found in the literature, in which one-pot, two-step and one-pot, three-step methodologies involving Ugi condensation were applied.[7–19] In the significant majority of these processes, the Ugi MCR is followed by a subsequent modification of the Ugi product, as acidic hydrolysis or hydroxyaminolysis[7] or post-condensation modifications leading to cyclic products.[8,9]

The generation of chiral combinatorial libraries by one-pot methodologies is much more challenging.[20] To gain access to the optically active reactants for MCRs at least one additional step is required. Routinely chiral compounds are obtained via stereoselective synthesis paths (including enzymatic resolution) or by chiral HPLC resolution of enantiomers. Unfortunately, constructing a combinatorial library for pharmaceutical purposes or asymmetric synthesis means that additional step(s) is/are involved.[21] In most cases, different types of chiral auxiliaries are used in these syntheses. This leads to substantial complication of the overall processes, since not all auxiliaries are cheap and readily available in both enantiomeric forms. Moreover, two additional steps are required for introduction and efficient removal of these groups. Recently, we announced a novel approach towards the synthesis of chiral combinatorial libraries.[22]

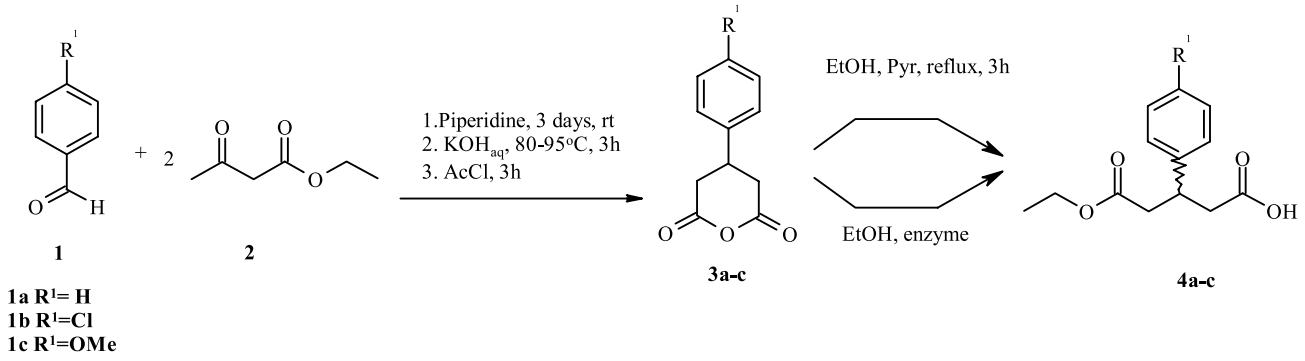
In this paper we present the results of our studies on the



Scheme 1. Combination of enzymatic desymmetrization with Ugi condensation.

Keywords: Enzyme; Desymmetrization; Peptidomimetic.
* Corresponding author. Tel.: +48 22 632 32 21; fax: +48 22 632 66 81; e-mail: rysza@icho.edu.pl

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.04.032



Scheme 2. The synthesis of monoesters **4**.

combination of multi-component reactions with enzymatic procedures (Scheme 1).

Our idea is based on the combination of enzymatic procedures with multi-component condensations as a one-pot, two-step reaction. We propose to use a *meso* reagent (**3**) as a substrate, which can be enzymatically desymmetrized into the desired optically active product (**4**). In this way, two steps: enzymatic reaction and subsequent reaction can be combined in one step. This two-step, one-pot approach is much simpler then the ones currently used, and application of chiral auxiliaries is omitted. We are unaware of precedent methodology combining an enzymatic procedure with an MCC.

2. Results

The 3-phenylglutaric anhydrides (**3**), required for the synthesis, were obtained according to the procedures described previously[23,24] from appropriate benzaldehydes (**1**) and ethyl acetylacetate (**2**) in yields of 41% for **3a**, 80% for **3b**, and 19% for **3c** (Scheme 2).

Since the carboxylic acid is one of the reactants in Ugi MCR, we decided to generate these chiral reagents from respective cyclic anhydrides **3**. Enzymatic desymmetrization of *meso*-anhydrides with alcohols is known in literature,[25–30] but it has been never applied for 3-phenylglutaric anhydrides.

For the preparation of chiral monoesters **4**, the following immobilized enzymes were used: Novozym 435 (CAL-B), Chirazyme L-2, c-f, c-3 lyso (CAL-B) and immobilized Amano PS lipase. Enzymes not only carried out the desymmetrization efficiently but the change of the enzyme provided access to different enantiomers (Table 1). The reactions reached full conversion within a few days and gave monoacids (**4**) in over 95% yields, while the same racemic esters were obtained in 91, 89, 63% for **4a**, **4b** and **4c**, respectively, according to the literature procedures.[23,24]

Absolute configurations of monoacids **4a** and **4b** were established by comparison to literature data (vide infra). We observed that while Novozym 435 and Chirazyme catalysed formation of (*S*)-**4a** monoacid (78 and 80% ee, respectively), the immobilized Amano PS lipase showed an opposite selectivity ((*R*)-enantiomer formed with 66% ee). Desymmetrization of anhydrides **3b** and **3c** led to the formation of respective monoacids with lower enantiomeric excess. According to our expectation, the enzyme changes the stereoselectivity and the kinetics of the desymmetrization reaction. An influence of substituent on phenyl ring is also observed. The presence of these substituents (4-Cl, for **4b** and 4-OMe, for **4c**) led to longer reaction time and lowered the optical purity.

Our initial idea of combination of Ugi four-component condensations with enzymatic desymmetrization was based on the assumption that both experimental procedures can be performed simultaneously, in the same solvent. Initially, we tried to perform the Ugi reaction in ethereal solvents, using racemic monoester **4a**, butylamine, 2-naphthaldehyde and ethyl isocyanoacetate as reagents (entry 1 in Table 2). The reaction did not occur. Addition of alcohol was necessary to complete the reaction. In the mixture of isopropyl ether and methanol (2:1, v/v) the reaction proceeded in 24 h and the desired product was obtained in 6% yield (entry 2 in Table 2). It is already known that aromatic aldehydes are not good substrates for Ugi reaction. For isovaleraldehyde, *n*-butylamine and benzyl isocyanate, the yield increased to 82% (entry 6 in Table 2). Interestingly, upon dilution of this

Table 1. Enzymatic desymmetrization of anhydrides **1**

Entry	Lipase	4a				4b				4c			
		Time (h)	Yield (%)	ee[20a] (%)	Conf.	Time (days)	Yield (%)	ee[20b] (%)	Conf.	Time (days)	Yield (%)	ee[20b] (%)	Conf.
1	Novozym 435	48	99	78	(*S*)	5	99	54	(*S*)	13	99	68	(*S*)
2	Chirazyme L-2	48	99	80	(*S*)	4	99	60	(*S*)	7	99	73	(*S*)
3	Amano PS immob.	48	95	66	(*R*)	4	99	14	(*R*)	7	99	52	(*S*)

Reagents and conditions: To the solution of anhydride **3** (0.05 mmol) in *iso*-propyl ether (1 mL) ethanol (0.075 mmol) was added, followed by respective lipase: Novozym 435–7.6 mg; Chirazyme L-2, c.-f., c-3, Amano PS—6.2 mg. The reaction was conducted until it reached full conversion and ee was determined by HPLC on Chiracel OD-H column.

Table 2. The synthesis of products **5a–i**

Entry	5	Acid 4	R^2	R^3	R^4	Solvent[a]	Ugi MCR		Enzymatic and Ugi reaction		
							Time (days)	Yield	Time (days)	Yield	$[\alpha]_D$ (benzene)
1	**5a**	**4a**	2-Naph	CH_2COOEt	*n*-Bu	A	4	0		—	
2	**5a**	**4a**	2-Naph	CH_2COOEt	*n*-Bu	B	1	6		—	
3	**5a**	(*S*)-**4a**	2-Naph	CH_2COOEt	*n*-Bu	B	1	6	2	6	
4	**5b**	(*S*)-**4a**	*p*-Br-Ph	Bn	*n*-Bu	B	17	32	15	31	−4.0 (*c* 1.29)
5	**5c**	(*S*)-**4a**	*i*-Bu	CH_2COOEt	*n*-Bu	B	9	49	9	49	−0.9 (*c* 1.30)
6	**5d**	**4a**	*i*-Bu	Bn	*n*-Bu	B	4	82		—	
7	**5d**	(*S*)-**4a**	*i*-Bu	Bn	*n*-Bu	B	5	81	2	65	−0.4 (*c* 1.31)
8	**5e**	(*S*)-**4b**	*i*-Bu	Bn	*n*-Bu	B	7	70	2	61	−4.9 (*c* 1.27)
9	**5f**	(*S*)-**4c**	*i*-Bu	Bn	*n*-Bu	B	7	72	2	78	−3.0 (*c* 1.28)
10	**5g**	(*S*)-**4a**	*i*-Bu	Bn	Bn	B	4	80	2	67	+9.0 (*c* 1.50)
11	**5h**	(*S*)-**4a**	*p*-Br-Ph	Bn	Bn	B	17	23	15	25	−13.8 (*c* 1.43)
12	**5i**	(*S*)-**4a**	2-Naph	CH_2COOEt	Bn	B	2	33		—	

[a] Solvents: A—*i*-Pr_2O, rt; B—*i*-Pr_2O/MeoH, 2:1, v/v, rt.

reaction mixture the yield of reaction decreased to 65% (concentrations of substrates are 0.042 and 0.170 M). Further, dilution decreased the yield to 44% and the reaction became poorly reproducible. In order to preserve reproducibility, all experiments were performed at concentration of substrates 0.1 M.

In the next experiments, we applied our two-step, one-pot approach based on combination of enzymatic desymmetrization of anhydrides **3** with subsequent Ugi MCR for the synthesis of compounds **5**. The same compounds were obtained in Ugi MCR with chiral or racemic acids **4**. The results are presented in Table 2.

In Ugi reaction with racemic acid **4a**, product **5a** was obtained in 6% yield (entry 3 in Table 2). The same yield was obtained when the reaction was repeated with chiral acid (*S*)-**4a** or when enzymatic desymmetrization was combined with Ugi MCR (entry 3 in Table 2). Better yields were obtained for *p*-bromobenzaldehyde as a substrate (entry 4 in Table 2) and our approach led to formation of the desired product in almost the same yield as for the two separate reactions. Optical rotation of compound **5b** proved that a chiral, nonracemic product **5c** was obtained. For isovaleraldehyde, the two-step approach leads to formation of a 1:1 diastereoisomeric mixture of products **5c** in 49% yield (entry 5 in Table 3). Our two-step but one-pot approach did not change the yield of reaction, and optical rotation of products proved that racemisation did not occur. It is interesting to note that Ugi reaction of racemic acid **4a** proceeds in 82% yield (entry 6 in Table 2). The same, but chiral product was obtained in lower, 67% yield, in two-step process. Our one-pot two-step process proceeds in 81% yield similar to that for Ugi reaction of racemic acid (entry 7 versus entry 6 in Table 3). Desymmetrization of 3-(4-chlorophenyl)-anhydride (**3b**) combined with Ugi condensation is also straightforward. The corresponding product **5e**, obtained in one-pot, two-step methodology, was formed in slightly lower yield (entry 8 in Table 3) in respect of the two-pot process.

It is evident from the data presented in Table 3, that the combination of enzymatic desymmetrization with Ugi MCR proceeds efficiently. In most cases, the yields of the one-pot, two-step procedure are similar to the yields of Ugi reaction performed on pure monoacid **4**.

We observed that all the products **5** consisted of a *syn*/*anti* diastereoisomeric mixture, in approximately 1:1 ratio on newly formed C-7 chiral centres, what was evident from NMR and HPLC data.

In the case of products **5c–f**, the diastereoisomers were separated by preparative TLC. Relative configurations at C-3 and C-7 carbons were assigned by ^{1}H NMR spectroscopy. The most distinctive ^{1}H NMR data of separated diastereoisomers of compounds **5c–f** are shown in Table 3.

The analysis of proton spectra led us to a conclusion that all less polar diastereoisomers of compounds **5c–f**-possess the same *anti* configuration, at C-3 and C-7 carbon atoms. Analogously, the more polar diastereoisomers possess relative *syn* configuration.

The most significant difference is observed for N*H* protons,

Table 3. The most distinctive ^{1}H NMR data for peptidomimetic **5c–f** diastereoisomers

Entry	Comp.	Chemical shifts δ (ppm) and coupling constant J_{gem} (Hz)			
		N*H*	NHCH_2R	CH_2CHPh	CH_3[a]
1	**5c** *anti*	6.55	3.76; 3.85 J_{gem}=18.0	2.66; 2.80 J_{gem}=15.4	0.84–0.96 (m)
2	**5c** *syn*	7.00	3.85; 3.98	2.60–2.80	0.79 (d, J=6.5)
3	**5d** *anti*	6.66	4.17; 4.33 J_{gem}=14.9	2.63; 2.75 J_{gem}=15.5	0.83–0.92 (m)
4	**5d** *syn*	6.95	4.35	2.64; 2.69	0.79 (d, J=6.5)
5	**5e** *anti*	6.67	4.18; 4.34 J_{gem}=14.8	2.63; 2.73 J_{gem}=16.6	0.84–0.92
6	**5e** *syn*	6.91	4.35	2.55–2.71	0.77 (d, J=6.5)
7	**5f** *anti*	6.68	4.17; 4.34 J_{gem}=14.9	2.59; 2.73 J_{gem}=15.4	0.82–0.92 (m)
8	**5f** *syn*	6.96	4.35	2.55–2.71	0.79 (d, J=6.5)

[a] For one of the CH_3 groups from *i*-Bu chain.

which are shifted downfield for all *syn* compounds ($\Delta\delta$ 0.28–0.45 ppm, Table 3). We postulate that intramolecular hydrogen bond formation can be responsible for this phenomenon. In case of opposite diastereoisomers such a bond is weakened due to steric repulsion. Spectral data suggest that the *syn* diastereoisomers can be folded analogously, as it is observed in β-turn mimetics,[31] while the *anti* diastereoisomers possess an open chain conformation.

2.1. Attempt to assign the absolute configurations by CD spectroscopy

An effort was also made to assign unambiguously the absolute configuration to compounds *syn*-**5d**, *anti*-**5d** and *syn*-**5c**, *anti*-**5c**. For this purpose, circular dichroism spectroscopy was chosen. UV and CD data of compounds **5c** and **5d** are presented in Table 4. As can be seen from the table, the less polar components of both reaction mixtures, namely compounds *syn*-**5c** and *syn*-**5d**, displayed the same shape of their CD curves in the 250–185 nm spectral range (Fig. 1).

Analogously, in the same spectral region (Table 4), CD curves of more polar components *anti*-**5d** and *anti*-**5c** are similar to each other, that is, the signs of particular Cotton effects (CEs) are the same with very similar amplitudes. In addition, their CD curves are in a mirror–image relationship to those of the less polar compounds. The only exception to this regularity presents the long-wavelength CE occurring at 268 nm being negative for all compounds investigated. This CE, associated with an electronic absorption observed at 257 nm, can be attributed to the ^1L_b benzene transition. According to the benzene sector rule, the negative sign of this CE points unambiguously to the (*S*) absolute configuration at the stereogenic centre contiguous to the benzene ring.[32] Thus, (3*S*,7*S*) configuration can be assumed for the *syn* diastereoisomer and (3*S*,7*R*) for the *anti* diastereoisomers. The presence of an additional phenyl substituent in compounds (3*S*,7*S*)-**5d** and (3*S*,7*R*)-**5d** (entries 1 and 2 in Table 4) does not affect this assignment because the sign of the ^1L_b CE depends exclusively upon the chirality of the chiral centre directly linked to the benzene ring. Thus, the configuration assignment made on the basis of the benzene sector rule corroborates nicely with the assignment previously done on the basis of NMR spectroscopy.

Independent determination of the absolute configuration at the second stereogenic centre, however, remains a much more difficult task. Different functional groups, present in the molecules, have their own contributions to the overall CD spectrum approximately at the same energy range. Thus, the most pronounced CE at ca. 230 nm poses a sum of contributions stemming from the amide, ester and phenyl groups. It has to be added that, due to the conformational mobility, different rotamers also contribute to the overall spectrum with their own CD. Therefore, the absolute configuration assignment to the second stereogenic centre (C-7) is impossible only on the basis of CD spectroscopy. Additional data is required to correlate the absolute configuration and the sign of the specific CD band. Nevertheless, on the basis of the same signs of the CE around 230 nm, we are able to state that the less and the more polar products have the same absolute configuration at the carbon atom directly attached to the tertiary amide nitrogen. Further study allowing the determination of the absolute configuration at this stereogenic centre is in progress in our laboratory.

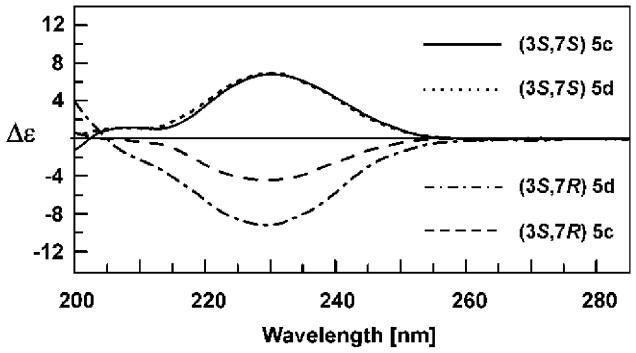


Figure 1. CD spectra of compounds (3*S*,7*S*)-**5d** (·····), (3*S*,7*S*)-**5c** (———), (3*S*,7*R*)-**5d** (–·–·–·–), and (3*S*,7*R*)-**5c** (– – – – – –) recorded in acetonitrile.

3. Conclusions

We developed a general, simple and efficient method for chiral peptidomimetic preparation. Combination of the enzymatic and Ugi reactions gave us access to the optically active compounds **5**. Both reactions can be performed separately or successively, without isolation of the intermediates. The latter approach evidently simplifies the overall process. In our opinion, the one-pot enzymatic desymmetrization followed by Ugi reaction can be readily extended to prepare chiral, Ugi-type combinatorial libraries starting from achiral substrates. This efficient process opens new options in organic chemistry. It can be easily extended to other types of reactions and used to generate chiral peptidomimetic libraries as well. According to our knowledge, this is the first example of combination of enzymatic procedures with multi-component conden-sations.

In enzymatic reactions, one can control the stereochemistry

Table 4. UV and CD data of compounds **5c** and **5d**—peptidomimetics obtained by Ugi reaction and diastereoisomers separations recorded in acetonitrile

Entry	Comp.	UV		CD			
		ε (λ)		$\Delta\varepsilon$ (λ)			
1	(3*S*,7*S*)-**5c** (*syn*)	280 (257)	15 900 (205^{sh})	+3.10 (193.0)	−0.46 (210.5)	−4.56 (228.5)	−0.05 (268.0)
2	(3*S*,7*R*)-**5c** (*anti*)	260 (257)	14 700 (205^{sh})	−0.69 (197.0)	+1.17 (207.0^{sh})	+6.92 (229.5)	−0.03 (268.0)
3	(3*S*,7*S*)-**5d** (*syn*)	450 (257)	24 500 (207^{sh})	+12.1 (191.5)	−2.40 (210.5^{sh})	−9.23 (229.5)	−0.03 (268.0)
4	(3*S*,7*R*)-**5d** (*anti*)	480 (257)	24 300 (207^{sh})	−1.68 (197.5)	+1.16 (209.5)	+6.96 (230.5)	−0.02 (268.0)

UV and CD values are given as ε (nm) and $\Delta\varepsilon$ (nm), respectively.

of C-3 carbon atom. Unfortunately, the C-7 center formed in the Ugi reaction cannot be controlled. The resulting mixtures of diastereoisomers can be readily separated using column chromatography.

An attempt was made to assign relative configuration in obtained products using NMR and CD spectroscopy. By proton NMR, the relative configurations of less polar diastereoisomers were assigned to be *anti*. Spectral data suggest that all more polar, *syn* diastereoisomers are folded, as it is analogously observed in β-turn mimetics. Currently, the absolute configurations of chiral products cannot be assigned using CD spectroscopy. Further studies into unambiguous configuration assignment by CD spectroscopy are in progress in our laboratory.

4. Experimental

4.1. General

NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard using a 200 MHz Varian Gemini 200 or a 500 MHz Bruker DRX 500 Avance spectrometers. Chemical shifts are reported in ppm and coupling constants (J) are given in Hertz (Hz). MS spectra were recorded on an API-365 (SCIEX) apparatus. IR spectra in $CHCl_3$ were recorded with a Perkin Elmer FT-IR Spectrum 2000 apparatus. Optical rotations were measured in 1 dm cell of 1 mL capacity using a Jasco DIP-360 polarimeter operating at 589 nm. HPLC analyses were performed on a LC-6A Shimadzu apparatus with an UV SPD-6A detector and a Chromatopac C-R6A analyser.

The determination of enantiomeric excess of monoesters **4** was performed on a Chiracel OD-H column 4.6 mm×250 mm (from Diacel Chemical Ind., Ltd) equipped with a pre-column (4 mm×10 mm, 5 μ). The determination of diastereoisomeric ratio of the Ugi products **5** was performed on a Kromasil SI 60 Å column (4.6 mm×250 mm) from Eka Chemicals.

CD spectra were measured using a JASCO J-715 spectropolarimeter in 1 cm and 1 mm cells in acetonitrile at concentrations approximately of 2×10^{-4} M. The elemental analyses were performed on a CHN Perkin–Elmer 240 apparatus. Melting points are uncorrected. All reactions were monitored by TLC on Merck silica gel plates 60 F_{254}. Preparative TLC was performed on 0.5 mm Kieselgel 60 F_{254} preparative plates. Column chromatography was performed on Merck silica gel 60/230–400 mesh.

Immobilized lipase Amano PS-C was purchased from Amano. Chirazyme L-2, c.-f., c-3, lyo. (*C. antarctica* lipase type B) was purchased from Roche. Novozym 435 was purchased from Novo Nordisk. All the chemicals were obtained from common chemical suppliers. The solvents were of analytical grade.

4.2. Chemistry

4.2.1. 3-Phenylglutaric acid anhydride (3a). The anhydride **3a** was obtained according to the literature procedures[23,24] in 40% yield as white crystals (EtOAc/hexane): mp 104–105 °C (lit. 104–105[33]); ^{1}H NMR δ 2.86 (dd, J=11.3, 17.2 Hz, 2H), 3.08 (dd, J=4.5, 17.2 Hz, 2H), 3.30–3.50 (m, 1H), 6.90–7.40 (m, 5H); ^{13}C NMR δ 34.7, 37.7, 126.8, 128.7, 129.9, 139.7, 166.6.

4.2.2. 3-(4-Chlorophenyl)glutaric acid anhydride 2b. The anhydride **3b** was prepared in 80% overall yield as white crystals (EtOAc/hexane): mp 126 °C (lit. 131–133[34]); R_f=0.36 ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^{1}H NMR δ 2.82 (dd, J=11.4, 17.2 Hz, 2H), 3.08 (dd, J=4.5, 17.2 Hz, 2H), 3.34–3.50 (m, 1H), 6.91 (d, J=8.4 Hz, 2H), 7.12 (d, J=8.8 Hz, 2H); ^{13}C NMR δ 34.2, 37.6, 37.8, 128.1, 128.2, 130.1, 134.6, 138.0, 166.0; Anal. Calcd for $C_{11}H_9ClO_3$: C, 58.81; H, 4.04. Found: C, 58.19; H, 4.05.

4.2.3. 3-(4-Methoxyphenyl)glutaric acid anhydride 3c. The anhydride **3c** was prepared in 19% overall yield as white crystals (EtOAc/hexane): 155–156 °C (lit. 155–157[35]); R_f=0.60 (hexane/EtOAc, 6:4); ^{1}H NMR δ 2.82 (dd, J=11.2, 17.0 Hz, 2H), 3.08 (dd, J=4.5, 17.0 Hz, 2H), 3.31–3.44 (m, 1H), 3.81 (s, 1H), 6.91 (d, J=8.4 Hz, 2H), 7.12 (d, J=8.8 Hz, 2H); ^{13}C NMR δ ^{13}C NMR δ 33.3, 37.3, 55.3, 114.7, 127.3, 131.0, 159.1, 166.0; Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.90; H, 5.44.

4.3. General procedure for chemical synthesis of 3-arylglutaric acid monoethyl esters (4)

Model racemic monoethyl esters **4** were obtained by the procedure described before[24] in 91% yield for **4a** yield 89% for **4b**, 63% for **4c**, respectively. Spectral and physical data are in accordance with data obtained for chiral monoesters **4** obtained in enzymatic reaction.

4.4. General procedure of synthesis of chiral monoesters of 3-arylglutaric acids (4) with Novozym 435 in *iso*-propyl ether

To the solution of anhydride (**3**, 0.5 mmol) dissolved in *iso*-propyl ether (10 mL), lipase (75.0 mg) and absolute ethanol (0.80 mmol) were added. The reaction was carried out at room temperature and its progress was monitored by TLC ($CHCl_3$/MeOH/HCOOH, 100:2:0.05). The enzyme was filtered off and residue was concentrated to give a monoester **4** as colourless oil. The product was recrystallized from Et_2O/hexane (or EtOAc/hexane).

4.4.1. (*S*)-3-Phenylglutaric acid monoethyl ester, (*S*)-4a. The reaction reached full conversion after 43 h to give (*S*)-**4a** in 99% yield as a colourless oil. After crystallisation (Et_2O/hexane), the ester was obtained as white crystals in 66% yield. Mp 58–59 °C (lit. 59–60[24]); $[\alpha]_D^{20}$ −9.5 (*c* 1.10, benzene) (lit. $[\alpha]_D^{25}$ 9.47 (*c* 1.1, benzene) for (*R*)-enantiomer)[36]; HPLC analysis [hexane/*i*-PrOH/CH_3COOH, 185:14:1; λ=226 nm; 1.0 ml/min; $t_R(S)$=8.26 min, $t_R(R)$=8.95 min)] 78% ee; R_f=0.24 ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.15 (t, J=7.1 Hz, 3H), 2.68–2.81 (m, 4H), 3.10–3.25 (m, 1H), 4.08 (q, J=7.1 Hz, 2H), 7.28 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.7, 38.6, 41.3, 61.1, 113.4, 127.8, 129.1, 142.8, 156.9, 172.1, 178.1; IR ($CHCl_3$) ν_{max}: 3513 (OH), 1727 (C=O) cm^{-1}; LSIMS (+), NBA, (*m/z*), 259

([M+Na]$^+$, 56%), 237 ([M+H]$^+$, 100%); LSIMS (+), NBA+NaOAc, (*m/z*), 281 ([M+2Na]$^+$, 100%), 259 ([M+Na]$^+$, 41%).

4.4.2. (*S*)-3-(4-Chlorophenyl)glutaric acid monoethyl ester, (*S*)-4b. The reaction reached full conversion after 4 days to give (*S*)-**4b** as an oil in 99% yield. After crystallisation, the ester was obtained as white crystals in 61% yield. Mp 56 °C (Et_2O/hexane); $[\alpha]_D^{20}$ −3.8 (*c* 0.90, $CHCl_3$); HPLC analysis [hexane/*i*-PrOH/CH_3COOH, 185:14:1; λ=226 nm; 1.0 ml/min; $t_R(S)$=9.0 min, $t_R(R)$=9.8 min]; R_f=0.27 ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.15 (t, *J*=7.1 Hz, 3H), 2.69 (m, 4H), 3.60 (m, 1H), 4.03 (q, *J*=7.1 Hz, 2H), 7.15 (d, *J*=8.6 Hz, 2H), 7.34 (d, *J*=8.6 Hz, 2H), 10.7 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.7, 38.0, 40.7, 41.1, 61.2, 115.1, 129.2, 129.3, 129.4, 133.3, 141.2, 171.8, 177.8; Anal. Calcd for $C_{13}H_{15}ClO_4$: C, 57.68; H, 5.59. Found: C, 57.59; H, 5.74.

4.4.3. (*S*)-3-(4-Methoxyphenyl)glutaric acid monoethyl ester, (*S*)-4c. The reaction reached full conversion after 19 days to give (*S*)-**4c** as an oil in 93% yield. After crystallisation (Et_2O/hexane), the ester was obtained as white crystals in 71% yield. Mp 75–77 °C (lit. 78[37]); $[\alpha]_D^{20}$ +8.3 (*c* 0.95, EtOH); HPLC analysis [hexane/*i*-PrOH/CH_3COOH 193:6:1; λ=226 nm; 0.7 ml/min; $t_R(S)$=26.5 min, $t_R(R)$=29.1 min] 69% ee; R_f=0.28 ($CHCl_3$/MeOH/HCOOH, 100:2:0.05); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.20 (t, *J*=7.2 Hz, 3H), 2.74 (m, 4H), 3.63 (m, 1H), 3.83 (s, 3H), 4.09 (q, *J*=7.2 Hz, 2H), 6.9 (d, *J*=7.0 Hz, 2H), 7.19 (d, *J*=7.2 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.6, 41.1, 41.1, 55.9, 60.9, 114.8, 129.4, 136.0, 159.4, 172.9, 174.8; Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.81. Found: C, 63.12; H, 6.81.

4.5. General procedure for synthesis of compounds 5

To a solution of monoester **4** (1.0 mmol) in *iso*-propyl ether/methanol mixture (2:1, v/v, 5 mL), aldehyde (1.1 mmol), amine (1.1 mmol) and isonitrile (1.0 mmol) were added subsequently at 0 °C. The reaction was allowed to warm up to room temperature and its progress was monitored by TLC. After the reaction was completed, the solvent was removed in vacuo and the residue was poured into 10 mL of EtOAc. The organic solution was washed consecutively with hydrochloric acid (1 M, 10 mL), sodium hydroxide (1 M, 10 mL), saturated sodium sulphite solution (10 mL) and brine (10 mL), and dried ($MgSO_4$). The solvent was evaporated and the product **5** was isolated by flash chromatography.

4.6. General experimental procedure for tandem enzymatic-Ugi reaction

To a solution of glutaric anhydride **3** (1.0 mmol) in 10 mL of *iso*-propyl ether, lipase (150 mg) and ethanol (1.50 mmol, 90 μL, 99.8% pure) were added. The reaction was carried out at room temperature and its progress was monitored by TLC. After all the substrate reacted, the enzyme was filtered off and washed with *iso*-propyl ether and concentrated to 1% of volume, then *iso*-propyl ether/methanol mixture (2:1, v/v, 5 mL) was added. Subsequently, the aldehyde (1.1 mmol), the amine (1.1 mmol) and the isonitrile (1.0 mmol) were added to the resulting solution cooled to 0 °C. The reaction was allowed to warm up to room temperature and its progress was monitored by TLC. When the reaction was completed, the solvent was removed in vacuo and the residue was poured into 10 mL of EtOAc. The organic solution was washed consecutively with hydrochloric acid (1 M, 10 mL), sodium hydroxide (1 M, 10 mL), saturated sodium sulphite solution (10 mL) and brine (10 mL), and dried ($MgSO_4$). The solvent was evaporated and the product was isolated by flash chromatography.

4.6.1. Compound 5a (*syn/anti* mixture). Yellow oil, R_f=0.24 (hexane/EtOAc/CH_3COOH, 7:3:0.17); ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.80–1.50 (m, 13H), 2.40–2.90 (m, 4H), 3.15–3.30 (m, 2H), 3.47 (q, *J*=7.0 Hz, 2H), 3.70–3.90 (m, 1H), 4.00–4.10 (m, 2H), 4.47 (m, 2H), 5.83 (s, 1H, rotamers), 6.07 (s, 1H, rotamers), 6.23 (m, 1H, NH_{anti}), 6.46 (m, 1H, NH_{syn}), 6.8–7.8 (m, 12H). MS (ESI): *m/z*=583 ([M+Na]$^+$, 100%); (ESI-MS HR: *m/z* Calcd for $C_{33}H_{40}N_2O_6Na$: 583.2779. Found: 583.2783.

4.6.2. Compound 5b (*syn/anti* mixture). Yellow oil; R_f=0.32 (hexane/EtOAc, 7:3); $[\alpha]_D^{32}$ −4.0 (*c* 1.29, benzene); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.71–0.81 (m, 3H), 1.12 (t, *J*=7.1 Hz, 3H), 1.00–1.50 (m, 4H), 2.68–2.90 (m, 4H), 3.10–3.30 (m, 2H), 3.68–3.90 (m, 1H), 3.93–4.15 (m, 2H), 4.44 (dd, *J*=5.9, 10.5 Hz, 2H), 5.62 (s, 1H, rotamers), 5.87 (s, 1H, rotamers), 6.45–6.60 (m, 1H, NH_{anti}), 6.83–6.90 (m, 1H, NH_{syn}), 7.04 (dd, *J*=8.6, 16.4 Hz, 2H), 7.15–7.30 (m, 10H), 7.37 (d, *J*=8.6 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ:13.5, 14.0, 19.9, 31.6, 38.6, 38.8, 39.3, 39.4, 40.4, 43.6, 46.5, 60.3, 61.2, 62.7, 122.0, 126.7, 126.8, 127.0, 127.3, 127.5, 127.6, 128.5, 130.5, 130.6, 131.5, 134.2, 137.9, 142.8, 169.2, 171.7, 172.1; MS (ESI): *m/z*=617 ([M+Na]$^+$, 100%), 615 ([M+Na]$^+$; 76%); ESI-MS HR: *m/z* Calcd for $C_{32}H_{37}N_2O_4NaBr$: 617.1829. Found: *m/z*: 617.1796.

4.6.3. Compound 5c (*syn/anti* mixture). Reaction time: 9 days. The product was purified by flash chromatography to give two fractions R_{f1}=0.26—*anti*-diastereoisomer and R_{f2}=0.15—*syn*-diastereoisomer (hexane/EtOAc, 7:3) in 49% total yield as viscous transparent oil. $[\alpha]_{D\,syn/anti}^{34}$ −0.9 (*c* 1.30, benzene).

4.6.4. Compound (3*S*,7*R*)-5c (*anti*-diastereoisomer). Transparent oil; R_f=0.26 (hexane/EtOAc, 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84–0.096 (m, 9H) 1.15 (t, *J*=7.1 Hz, 3H), 1.26 (t, *J*=7.1 Hz, 3H), 1.25–1.32 (m, 2H), 1.35–1.45 (m, 2H), 1.48–1.56 (m, 2H), 1.75–1.81 (m, 1H), 2.66 (dd, *J*=7.7, 15.4 Hz, 1H), 2.71–2.77 (m, 2H), 2.80 (dd, *J*=7.1, 15.4 Hz, 1H), 3.05–3.20 (m, 2H), 3.76 (dd, *J*=5.7, 18.0 Hz, 1H), 3.85 (dd, *J*=6.0, 18.0 Hz, 1H), 3.77–3.82 (m, 1H), 4.04 (dq, *J*=2.6, 7.1 Hz, 2H), 4.17 (q, *J*=7.1 Hz, 2H), 4.96 (t, *J*=7.0 Hz, 1H), 6.55 (br s, 1H), 7.17–7–21 (m, 1H), 7.22–7.30 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) 13.6, 14.0, 14.1, 20.2, 22.2, 22.5, 22.8, 24.7, 32.2, 36.7, 38.9, 39.7, 40.5, 41.1, 45.5, 60.4, 61.1, 126.8, 127.4, 128.5, 143.1, 169.4, 171.8, 172.7; MS (ESI): *m/z*=513 ([M+Na]$^+$, 64%), 491 ([M+H]$^+$, 100%), ESI-MS HR: *m/z* Calcd for $C_{27}H_{43}N_2O_6$: 491.3121. Found: *m/z*: 491.3134.

4.6.5. Compound (3*S*,7*S*)-5c (*syn* diastereoisomer). Transparent oil; R_f=0.15 (hexane/EtOAc, 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79 (d, J=6.5 Hz, 3H), 0.85 (d, J=6.6 Hz, 3H), 0.88–0.97 (m, 3H), 1.15 (t, J=7.1 Hz, 3H), 1.26 (t, J=7.1 Hz, 3H), 1.24–1.32 (m, 2H), 1.35–1.55 (m, 4H), 1.68–1.75 (m, 1H), 2.60–2.80 (m, 4H), 3.05–3.20 (m, 2H), 3.73–3.84 (m, 1H), 3.85 (d, J=5.3 Hz, 1H), 3.98 (d, J=6.3 Hz, 1H), 4.00–4.08 (m, 2H), 4.17 (q, J=7.1 Hz, 2H), 4.97 (t, J=7.4 Hz, 1H), 7.00 (t, J=5.3 Hz, 1H), 7.17–7.30 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.0, 14.1, 20.3, 22.1, 22.8, 24.5, 31.9, 36.5, 38.8, 39.6, 40.7, 41.1, 60.4, 61.1, 126.8, 127.2, 127.4, 128.5, 143.1, 169.5, 172.0, 172.1, 172.8; MS (ESI): m/z=513 ($[M+Na]^+$, 50%), 491 ($[M+H]^+$, 100%), ESI-MS HR: m/z Calcd for $C_{27}H_{43}N_2O_6$: 491.3121. Found: m/z: 491.3105.

4.6.6. Compound (3*S*,7*RS*)-5d. Reaction time: 2 days. The product was purified by flash chromatography (R_f=0.23, hexane/EtOAc, 8:2) and obtained as a colourless oil in 65% yield. The ^{1}H NMR spectrum was a superposition of 2 separate diastereoisomers. ESI-MS: m/z=517 ($[M+Na]^+$, 100%); ESI-MS HR: m/z Calcd for $[M+Na]^+$, $C_{30}H_{42}N_2O_4Na$: 517.3037. Found: 517.3028; $[\alpha]^{26}_{D\,syn/anti}$ −0.4 (*c* 1.31, benzene). The diastereoisomers (in 1.1:1 ratio) were separated by preparative TLC (R_f= 0.16 and 0.15, hexane/*i*-PrOH, 95:5; 6 times reversed).

4.6.7. Compound (3*S*,7*R*)-5d (*anti*-diastereoisomer). Transparent oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83–0.92 (m, 9H), 1.14 (t, 3H, J=7.1 Hz), 1.17–1.33 (m, 4H) 1.36–1.48 (m, 1H), 1.49–1.61 (m, 1H), 1.69–1.84 (m, 1H), 2.63 (dd, J=7.5, 15.5 Hz, 1H), 2.66–2.72 (m, 2H), 2.75 (dd, J=7.3, 15.5 Hz, 1H), 3.05–3.15 (m, 2H), 3.73 (quintet, 1H, J=7.3 Hz), 4.01 (dq, J=3.6, 7.1 Hz, 2H), 4.17 (dd, J=5.6, 14.9 Hz, 1H), 4.33 (dd, J=6.4, 14.9 Hz, 1H), 4.94 (br s, 1H), 6.66 (br s, 1H), 7.13–7.31 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.0, 20.2, 22.2, 22.9, 24.7, 32.0, 36.7, 38.8, 39.7, 40.5, 43.2, 45.2, 60.4, 126.8, 126.9, 127.1, 127.2, 127.3, 127.5, 127.7, 128.4, 128.5, 128.6, 138.4, 143.0, 171.4, 171.8, 172.5; ESI-MS: m/z=517 ($[M+Na]^+$, 100%); ESI-MS HR: m/z Calcd for $[M+Na]^+$, $C_{30}H_{42}N_2O_4Na$: 517.3037. Found: 517.3062.

4.6.8. Compound (3*S*,7*S*)-5d (*syn*-diastereoisomer). Transparent oil; R_f=0.23 (hexane/EtOAc, 8:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79 (d, J=6.5 Hz, 3H), 0.82–0.97 (m, 6H), 1.12 (t, J=7.1 Hz, 3H), 1.18–1.33 (m, 4H), 1.35–1.45 (m, 1H), 1.47–1.57 (m, 1H), 1.70–1.77 (m, 1H), 2.64 (dd, J=5.4, 7.3 Hz, 2H)), 2.69 (dd, J=7.3, 8.5 Hz, 2H), 3.05–3.15 (m, 2H), 3.75 (quintet, J=7.3 Hz, 1H), 3.98 (dq, J=4.3, 7.1 Hz, 2H), 4.35 (d, J=6.0 Hz, 2H), 4.94 (t, 1H, J=7.4 Hz), 6.95 (br s, 1H), 7.14–7.31 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.0, 20.2, 22.1, 22.2, 22.9, 24.6, 31.9, 36.6, 38.8, 39.5, 40.8, 43.3, 45.0, 60.4, 126.8, 127.1, 127.2, 127.7, 128.5, 128.6, 138.4, 140.1, 171.5, 172.0, 172.6; ESI-MS: m/z=518 517 ($[M+Na]^+$, 100%); ESI-MS HR: m/z Calcd for $[M+Na]^+$, $C_{30}H_{42}N_2O_4Na$: 517.3037. Found: 517.3020.

4.6.9. Compound (3*S*,7*RS*)-5e. Reaction time: 2 days. The product was purified by flash chromatography (R_f=0.41, hexane/EtOAc, 7:3) and obtained in 61% yield as colourless oil that solidified. ^{1}H NMR spectrum was superposition of two separated diastereoisomers. ESI-MS: m/z=552 ($[M+Na]^+$, 5%), 551 ($[M+Na]^+$, 100%); ESI-MS HR: m/z Calcd for $[M+Na]^+$, $C_{30}H_{41M2}O_4NaCl$: 551.2647. Found: 551.2650; $[\alpha]^{26}_{D\,syn/anti}$ −4.9 (*c* 1.27, benzene). The diastereoisomers (in 1.1:1 ratio) were separated by PTLC (R_f= 0.15 and 0.14, respectively, hexane/*i*-PrOH, 95:5; 8 times reversed).

4.6.10. Compound (3*S*,7*R*)-5e (*anti*-diastereoisomer). Colourless oil; R_f=0.41 (hexane/EtOAc, 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84–0.92 (m, 9H), 1.15 (t, 3H, J=7.1 Hz), 1.18–1.33 (m, 4H), 1.35–1.48 (m, 1H), 1.50–1.59 (m, 1H), 1.73–1.85 (m, 1H), 2.63 (dd, J=7.8, 15.6 Hz, 1H), 2.67–2.73 (m, 2H), 2.73 (dd, J=7.0, 15.6 Hz, 1H), 3.05–3.20 (m, 2H), 3.73 (quintet, J=7.3 Hz, 1H), 4.01 (dq, J=3.5, 7.1 Hz, 2H), 4.18 (dd, J=5.6, 14.8 Hz, 1H), 4.34 (dd, J=6.4, 14.8 Hz, 1H), 4.91 (t, J=6.0 Hz, 1H), 6.67 (br s, 1H), 7.13–7.19 (m, 4H), 7.20–7.30 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.1, 20.2, 22.2, 22.8, 24.7, 32.0, 36.7, 38.1, 39.4, 40.4, 43.2, 45.2, 60.5, 127.2, 127.6, 128.5, 128.6, 128.7, 132.6, 138.3, 141.6, 171.3, 171.5, 172.2; ESI-MS: m/z=552 ($[M+Na]^+$, 6%), 551 ($[M+Na]^+$, 100%); ESI-MS HR: m/z Calcd for $[M+Na]^+$, $C_{30}H_{41}N_2O_4NaCl$: 551.2647. Found: 551.2661.

4.6.11. Compound (3*S*,7*S*)-5e (*syn*-diastereoisomer). Colourless oil, R_f=0.41 (hexane/EtOAc, 7:3).^{1}H NMR (500 MHz, $CDCl_3$) δ 0.77 (d, J=6.5 Hz, 3H), 0.84–0.90 (m, 6H), 1.14 (t, J=7.1 Hz, 3H), 1.17–1.34 (m, 4H), 1.35–1.44 (m, 1H), 1.49–1.57 (m, 1H), 1.67–1.74 (m, 1H), 2.55–2.71 (m, 4H), 3.08–3.15 (m, 2H), 3.74 (quintet, J=7.3 Hz, 1H), 3.99 (dq, J=7.1, 4.5 Hz, 2H), 4.35 (d, J=5.9 Hz, 2H), 4.92 (t, J=7.3 Hz, 1H), 6.91 (br s, 1H), 7.13 (dd, J=1.8, 6.6 Hz, 2H), 7.19–7.27 (m, 5H), 7.28–7.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 13.9, 20.1, 22.0, 22.7,, 24.4, 31.8, 36.4, 38.0, 39.1, 40.5, 43.2, 44.7, 60.4, 127.1, 127.6, 128.3, 128.4, 128.5, 132.4, 138.2, 141.3, 171.2, 171.5, 172.1; ESI-MS: m/z=552 ($[M+Na]^+$, 6%), 551 ($[M+Na]^+$, 100%); ESI-MS HR: m/z Calcd for $[M+Na]^+$, $C_{30}H_{41}N_2O_4NaCl$: 551.2647. Found: 551.2630.

4.6.12. Compound (3*S*,7*RS*)-5f. Reaction time: 2 days. The product was purified by flash chromatography (R_f=0.36, hexane/EtOAc, 7:3) and obtained as colourless oil in 78% yield. ^{1}H NMR spectrum was superposition of two separated diastereoisomers. ESI-MS: m/z=547 ($[M+Na]^+$, 100%); ESI-MS HR: m/z Calcd for $[M+Na]^+$, $C_{31}H_{44}N_2NaO_4$: 547.3137. Found: 547.3139; $[\alpha]^{26}_{D\,syn/anti}$ −3.0 (*c* 1.28, benzene). The diastereoisomers (in 2.4:1 ratio) were separated by PTLC (R_f=0.15 and 0.14, hexane/*i*-PrOH, 95:5; 11 times reversed).

4.6.13. Compound (3*S*,7*R*)-5f (*anti*-diastereoisomer). Colourless oil; R_f=0.36 (hexane/EtOAc, 7:3); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82–0.92 (m, 9H), 1.14 (t, J=7.1 Hz, 3H), 1.18–1.35 (m, 4H) 1.36–1.47 (m, 1H), 1.50–1.59 (m, 1H), 1.75–1.83 (m, 1H), 2.59 (dd, J=7.7, 15.4 Hz, 1H), 2.62–2.69 (m, 2H), 2.73 (dd, J=7.2, 15.4 Hz, 1H), 3.10 (t, J=8.1 Hz, 2H), 3.73 (s, 3H), 3.68–3.80 (m, 1H), 4.01 (dq, J=7.3, 4.0 Hz, 2H), 4.17 (dd, J=5.7, 14.9 Hz, 1H), 4.34 (dd, J=5.9, 14.8 Hz, 1H), 4.94 (t, J=7.0 Hz, 1H), 6.68 (br s, 1H), 6.77–6.82 (m, 2H), 7.09–7.19 (m, 2H), 7.20–7.32 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.1, 20.2,

22.2, 22.9, 24.7, 32.1, 36.7, 38.1, 39.9, 41.0, 43.2, 45.3, 55.2, 60.4, 113.9, 127.1, 127.2, 127.5, 127.7, 128.2, 128.3, 128.4, 128.5, 135.0, 138.4, 158.4, 171.5, 171.9, 172.7.

4.6.14. Compound (3*S*,7*S*)-5f (*syn*-diastereoisomer). Colourless oil; R_f=0.36 (hexane/EtOAc, 7:3); $[\alpha]_D^{26}$ −0.4 (*c* 1.31, benzene); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.79 (d, 3H, *J*=6.5 Hz), 0.83–0.90 (m, 6H), 1.14 (t, 3H, *J*=7.1 Hz), 1.17–1.34 (m, 4H), 1.35–1.45 (m, 1H), 1.49–1.57 (m, 1H), 1.68–1.76 (m, 1H), 2.55–2.71 (m, 4H), 3.07–3.15 (m, 2H), 3.76 (s, 3H), 3.74–3.67 (m, 1H), 3.94–4.05 (m), 4.35 (d, *J*= 6.0 Hz, 2H), 4.93 (t, *J*=7.3 Hz, 1H), 6.80 (d, *J*=8.7 Hz, 2H), 6.96 (br s, 1H), 7.11 (d, *J*=8.7 Hz, 2H), 7.20–7.32 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 14.1, 20.3, 22.2, 22.9, 24.6, 32.0, 36.6, 38.1, 39.7, 41.0, 43.3, 45.0, 55.2, 60.4, 113.9, 127.2, 127.7, 128.2, 128.4, 128.5, 135.0, 138.4, 158.4, 171.5, 172.1, 172.8.

4.6.15. Compound (3*S*,7*RS*)-5g. Colourless oil; R_f=0.41 (hexane/EtOAc, 7:3); $[\alpha]_{D\,syn/anti}^{26}$ +9.0 (*c* 1.50, benzene); ^{1}H NMR (200 MHz, $CDCl_3$) (0.60–0.88 (m, 6H), 1.14 (dt, *J*=1.0, 7.1 Hz, 3H), 1.20–1.50 (m, 2H), 1.61–1.78 (m, 1H), 2.48–2.78 (m, 4H), 3.68–3.84 (m, 1H), 4.01 (dq, *J*=3.1, 7.1 Hz, 2H), 4.30–4.41 (m, 2H), 4.41–4.53 (m, 2H), 5.06 (dt, *J*=3.2, 7.0 Hz, 1H), 6.57 (t, *J*=5.7 Hz, 1H$_{anti}$), 6.95 (t, *J*=5.7 Hz, 1H$_{syn}$), 7.02–7.40 (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$) (14.1, 22.4, 22.6, 22.7, 25.0, 25.1, 36.9, 37.0, 38.6, 40.0, 40.1, 40.4, 40.7, 43.3, 48.3, 48.4, 56.0, 56.1, 60.3, 125.9, 126.7, 127.1, 127.2, 127.5, 127.9.128.3, 128.4, 128.6, 127.1, 137.2, 138.1, 142.7, 142.8, 170.3, 170.4, 171.5, 171.6, 173.7; MS (ESI): *m*/*z*= 551 ([M+Na]$^+$, 100%), 529 ([M+H]$^+$, 18%), ESI-MS HR *m*/*z* Calcd for $C_{33}H_{40}N_2O_4Na$: 551.2880. Found: *m*/*z:* 551.2877.

4.6.16. Compound (3*S*,7*RS*)-5h (*syn*/*anti* mixture). Yellow oil; R_f=0.20 (hexane/EtOAc, 7:3); $[\alpha]_{D\,syn/anti}^{26}$ +13.8 (*c* 1.43, benzene); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.09 (t, *J*=7.0 Hz, 3H), 2.48–2.85 (m, 4H), 3.68–3.90 (m, 1H), 4.01 (q, *J*=7.0 Hz, 2H), 4.30–4.70 (m, 4H), 5.63 (s, 1H, rotamers), 5.90 (s, 1H, rotamers), 6.23–6.38 (m, 1H$_{anti}$), 6.48–6.58 (m, 1H$_{syn}$), 6.80–7.50 (m, 19H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 32.0, 38.5, 39.4 39.9, 40.5, 43.6, 49.8, 50.5, 60.3, 60.4, 61.7, 63.0, 122.3, 122.4, 125.9, 126.6, 126.9, 127.1, 127.2, 127.4, 127.5, 128.3, 128.4, 128.7, 131.0, 131.4, 131.6, 136.4, 137.6, 142.6, 142.7, 171.6, 172.5, 172.8; MS (ESI): *m*/*z*=651 ([M+Na]$^+$, 100%), 649 ([M+Na]$^+$, 58%); ESI-MS HR *m*/*z* Calcd for $C_{35}H_{35}N_2O_4NaBr$: 651.1649. Found: 651.1651.

4.6.17. Compound (3*S*,7*RS*)-5i (*syn*/*anti* mixture). Yellow oil; R_f=0.33 (hexane/EtOAc/CH_3COOH, 7:3:0.17); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.03 (dt, *J*=2.0, 7.1 Hz, 3H), 1.17 (dt, *J*=2.1, 7.1 Hz, 3H), 2.4–2.8 (m, 4H), 3.7 (m, 1H), 3.92 (m, 2H), 4.1 (m, 4H), 4.47 (m, 2H), 5.83 (s, 1H, rotamers), 6.07 (s, 1H, rotamers), 6.23 (m, 1H$_{syn}$, 6.46 (m, 1H, 1H$_{anti}$, 6.8–7.8 (m, 17H); MS (ESI): *m*/*z*=617 ([M+Na]$^+$, 100%), ESI-MS HR *m*/*z* Calcd for $C_{36}H_{38}N_2O_6Na$: 617.2627. Found: (*m*/*z*): 617.2643.

Acknowledgements

This work was supported by Polish State Committee for Scientific Research, grant no. PBZ-MIN-007/P04/2003.

References and notes

1. Ripka, A. S. D.; Rich, H. *Curr. Opin. Chem. Biol.* **1998**, *2*, 441.
2. Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602.
3. Domling, A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 318.
4. Bienayme, H.; Hulme, C.; Oddon, G.; Schmidt, P. *Chem. Eur. J.* **2000**, *6*, 3321.
5. Obrecht, D.; Villalgordo, J. M. Solid-supported combinatorial and parallel synthesis of small-molecular-weight compound libraries.; Tetrahedron organic chemistry series; Pergamon: New York, 1998; Vol. 17; Chapters 1 and 4.
6. Ugi, I.; Karl, R.; Lohberg, S. The Passerini and Ugi reaction. In *Comprehensive organic chemistry*; Trost, B. M., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; pp 1083–1109.
7. Floyd, C. D.; Harnett, L. A.; Patel, S.; Sarglou, L.; Whittaker, M. *Synlett* **1998**, 637.
8. Bossio, R.; Marcos, C. F.; MarcaFini, S.; Pepino, R. *Synthesis* **1997**, 1389.
9. Bienayme, H.; Bouzid, K. *Tetrahedron Lett.* **1998**, *39*, 2735.
10. Hulme, C.; Ma, L.; Morrisette, M.; Burns, C. J. *Tetrahedron Lett.* **1998**, *39*, 1113.
11. Hulme, C.; Peng, J.; Lourdias, B.; Menard, P.; Krolikowski, P.; Kumar, V. *Tetrahedron Lett.* **1998**, *39*, 8047.
12. Hulme, C.; Peng, J.; Tang, S. Y.; Burns, C. J.; Morize, I.; Labaudiniere, R. *J. Org. Chem.* **1998**, *63*, 8021.
13. Hulme, C.; Ma, L.; Romano, J.; Morrisette, M. *Tetrahedron Lett.* **1999**, *40*, 7925.
14. Hulme, C.; Ma, L.; Romano, J.; Morton, G.; Tang, S. Y.; Cherrier, M. P.; Choi, S.; Salvino, J.; Labaudiniere, R. *Tetrahedron Lett.* **2000**, *41*, 1889.
15. Tempest, P.; Ma, V.; Thomas, S.; Kelly, M. G.; Hulme, C. *Tetrahedron Lett.* **2001**, *42*, 4959.
16. Nixej, T.; Kelly, M.; Semin, D.; Hulme, C. *Tetrahedron Lett.* **2002**, *43*, 3681.
17. Paulvannan, K. *Tetrahedron Lett.* **1999**, *40*, 1851.
18. Ugi, I.; Demharter, A.; Schmid, T. *Tetrahedron Lett.* **1996**, *52*, 11657.
19. Portlock, D. E.; Ostaszewski, R.; Naskar, D.; West, L. *Tetrahedron Lett.* **2003**, *44*, 603.
20. Jung, G. *Combinatorial chemistry*; Wiley-VCH: Weinheim, 1999; Chapters 1 and 4.
21. Molecular design and combinatorial compound libraries. Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Handbook of combinatorial chemistry; Wiley-VCH: Weinheim, 2002; Vol. 2, pp 725–743.
22. Ostaszewski, R.; Portlock, D. E.; Fryszkowska, A.; Jeziorska, K. *Pure Appl. Chem.* **2003**, *75*, 413.
23. Perregaard, J.; Moltzen, E. K.; Meier, E.; Sanchez, C. *J. Med. Chem.* **1995**, *38*, 1998.
24. Burger, A.; Hofstetter, A. *J. Org. Chem.* **1959**, *24*, 1290.
25. Bornscheuer, U. T.; Kazlauskas, R. J. *Hydrolases in organic synthesis*; Wiley-VCH: Weinheim, 1999; pp 116–117.
26. Yamamoto, K.; Nishioka, T.; Oda, J. *Tetrahedron Lett.* **1988**, *29*, 1717.

27. Yamamoto, Y.; Iwasa, M.; Sawada, S.; Oda, J. *Agric. Biol. Chem.* **1990**, *54*, 3269.
28. Ozegowski, R.; Kunath, A.; Schick, H. *Liebigs Ann. Chem.* **1994**, 1019.
29. Ozegowski, R.; Kunath, A.; Schick, H. *Liebigs Ann. Chem.* **1996**, 1443.
30. Ozegowski, R.; Kunath, A.; Schick, H. *Liebigs Ann. Chem.* **1995**, 1699.
31. Souers, A. J.; Ellman, J. A. *Tetrahedron* **2001**, *57*, 7431.
32. Smith, H. E. Circular dichroism of the benzene chromophore. In *Circular dichroism principles and applications*; Nakanishi, N., Berova, N., Woody, R. W., Eds.; VSH: New York, 2000; pp 397–429.
33. Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 142.
34. Koer, A. *Recl. Trav. Chim. Pays-Bas* **1974**, *93*, 147.
35. Jackson, J. G.; Kenner, J. *J. Chem. Soc., Chem. Commun.* **1928**, 1657.
36. Sato, M.; Nagashima, S.; Furuya, T.; Kaneko, C. *Chem. Pharm. Bull.* **1992**, *40*, 1972.
37. Chitre, L. J. *Univ. Bombay Sci.* **1935**, *4/2*, 94.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 6073–6081

Synthesis and properties of 3-arylcyclohepta[4,5]imidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*)-diones and related compounds: photo-induced autorecycling oxidation of some amines

Makoto Nitta,* Daisuke Ohtsuki, Yuhki Mitsumoto and Shin-ichi Naya

Department of Chemistry, Advanced Research Center of Science and Engineering, Waseda University, Shinjuku-ku, Tokyo 169-8555, Japan

Received 23 March 2005; revised 14 April 2005; accepted 14 April 2005

Available online 13 May 2005

Abstract—Novel 3-phenyl- and 3-(4-nitrophenyl)cyclohepta[4,5]imidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*)-diones and the corresponding imino derivatives **5a**,**b** and **6a**,**b** were synthesized in modest to moderate yields by the abnormal and normal aza-Wittig reaction of 2-(1,3-diazaazulen-2-ylimino)triphenylphosphorane with aryl isocyanates and subsequent heterocyclization reaction with a second isocyanate. The related cationic compound, 1-methyl-3-phenylcyclohepta[4,5]imidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*)-dionylium tetrafluoroborate **7a**, was also prepared. The electrochemical reduction of these compounds exhibited more positive reduction potentials as compared with those of the related compounds of 3,10-disubstituted cyclohepta[4,5]pyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione systems. In a search of the oxidizing ability, compounds **5a**, **6a**, and **7a** were demonstrated to oxidize some amines to give the corresponding imines in more than 100% yield under aerobic and photo-irradiation conditions, while even benzylamine was not oxidized under aerobic and thermal conditions at 100 °C. The oxidation reactions by cation **7a** are more efficient than that by **5a** and **6a**. Quenching of the fluorescence of **5a** was observed, and thus, the oxidation reaction by **5a** probably proceeds via electron-transfer from amine to the excited singlet state of **5a**. In the case of cation **7a**, the oxidation reaction is proposed to proceed via formation of an amine-adduct of **7a** and subsequent photo-induced radical cleavage reaction.

1. Introduction

The importance of fused pyrimidines, which are common sources for the development of new potential therapeutic agents,[1,2] is well known. Among these, flavins are known to play an important role as cofactors in a wide variety of biological redox reactions. Dehydrogenation reactions represent a major family of processes mediated by the subclass of flavoenzymes known as oxidase. Included in this group are the oxidative transformations of alcohols to carbonyl compounds, of amines to imines, and of fatty acid esters to their α,β-unsaturated analogs[3]. In this context, 5-deazaflavin (**1**) has been studied extensively in both enzymatic[4] and model systems[5,6] in the hope of gaining mechanistic insight into flavin-catalyzed reactions. On the basis of the above observations and our interest concerning the unique reactivity afforded by the vinyliminophosphoranes[7] and related compounds,[8] we have previously studied convenient preparations of 1,3-dialkylcyclohepta[4,5]pyrrolo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (**2**)[9] and 3.10-disubstituted cyclohepta[4,5]pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,10*H*)-diones (**3**) and derivatives,[10] which are the structural isomers of 5-deazaflavin (**1**) (Fig. 1). Cationic

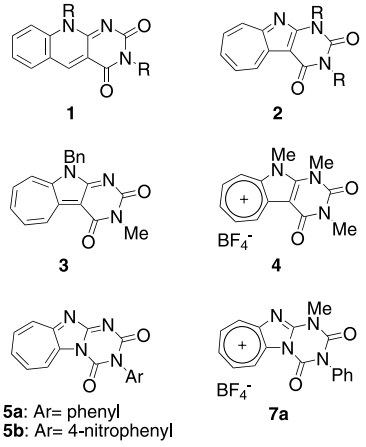
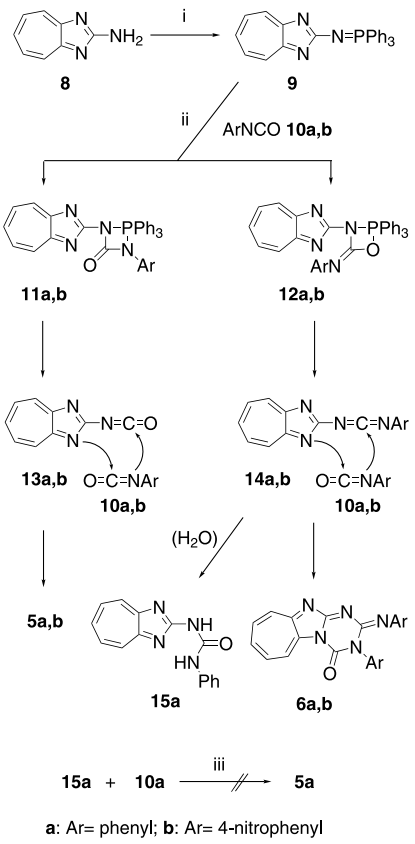


Figure 1.

Keywords: 3-Arylcyclohepta[4,5]imidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*)-diones; aza-Wittig reaction; X-ray analysis; Photo-induced autorecycling oxidation.
* Corresponding author. Tel.: +81 3 5286 3236; fax: +81 3 3208 2735; e-mail: nitta@waseda.jp

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.04.035



Scheme 1. Reagents and conditions: (i) PPh_3, DEAD, THF, rt, 4 h; (ii) benzene or toluene, reflux; (iii) $ZnCl_2$, dioxane, reflux, 50 h.

compounds **4** have also been prepared.[11] Compounds **3** and **4** have an appreciable oxidizing ability toward some alcohols and/or amines under photo-irradiation and aerobic conditions in an autorecycling process.[11,12] Thus, structural modifications of the uracil-annulated heteroazulenes such as **2**, **3**, and **4** are an interesting project in view of the exploration of novel functions. Much of the motivation for studying the properties of organic molecules stems from manipulation of the primary chemical structure. Although strategies for raising or lowering the HOMO and LUMO levels include conjugation length control, the introduction of an electron-withdrawing or donating group or element to the parent molecular skeleton is also an interesting project. Based on this concept, we studied here the synthesis, structural characteristics, and electrochemical properties of 3-arylcyclohepta[4,5]imidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*)-diones (**5a**,**b**) and related compounds **6a**,**b**, which involve the 1,3-diazaazulene and triazinedione skeletons instead of a 1-azaazulene and a pyrimidinedione ring system, along with cationic compound **7a** (Fig. 1). Photo-induced and thermal autorecycling oxidation of some amines to give the corresponding imines is studied as well. We describe here the results in detail.

2. Results and discussion

2.1. Synthesis

The aza-Wittig reaction of iminophosphoranes with isocyanate has proven to be one of the most useful methodologies for the synthesis of nitrogen-containing heterocycles.[7,8,13] We report herein an abnormal aza-Wittig reaction observed in the attempted program directed toward the synthesis of **5a**,**b** along with the corresponding imines **6a**,**b**. The abnormal aza-Wittig reaction involves the formation of an isocyanate instead of a carbodiimide intermediate, and reported studies on this reaction are very limited.[14] Starting from the 2-amino-1,3-diazaazulene (**8**),[15] the iminophosphorane (**9**) was prepared under Mitsunobu conditions using DEAD and triphenylphosphine (Scheme 1).[16] Treatment of the iminophosphorane (**9**) with phenyl and 4-nitrophenyl isocyanates (**10a**,**b**) afforded **5a**,**b** and **6a**,**b**, along with the known compound *N*-(1,3-diazaazulen-2-yl)-*N*′-phenylurea (**15a**).[17] Reaction conditions and the yields of the products are summarized in Table 1. The structures of new compounds **5a**,**b** and **6a**,**b** are confirmed on the basis of the ^{1}H (Table 2) and ^{13}C NMR spectra, IR, UV–vis, and mass spectral data, as well as elemental analyses. In addition, while single crystals of **5a**,**b** were not obtained, the structural characteristics of **6a**,**b** are revealed by the X-ray crystal analysis (vide infra). The proposed mechanistic pathways for the formation of **5a**,**b** and **6a**,**b** are outlined in Scheme 1. Both intermediates **11a**,**b** and **12a**,**b** can be formed upon treatment of **9** with **10a**,**b**. Breakdown of **11a**,**b** involving loss of triphenylphosphinimide results in the isocyanate intermediates **13a**,**b** as the abnormal aza-Wittig product. The isocyanates **13a**,**b** can undergo an intermolecular heterocyclization reaction with a second aryl isocyanates **10a**,**b** providing compounds **5a**,**b**. In contrast, intermediates **12a**,**b** can lead to the carbodiimides **14a**,**b** as the normal aza-Wittig product involving the loss of triphenylphosphine oxide. Subsequent heterocyclization of **14a**,**b** with a second aryl isocyanate **10a**,**b** results in the formation of compounds **6a**,**b**. The isocyanate **14a** reacts also with stray water to give the urea **15a**. The controlling factor for the abnormal and normal aza-Wittig reactions is still unclear. 2-Amino-1-azaazulene is known to react with **10a** to give *N*-(1-azaazulen-2-yl)-*N*′-phenylurea, which undergoes heterocyclization with a second **10a** to give 3-phenylcyclohepta[4,5]pyrrolo[1,2-*a*]-1,3,5-triazine-2,4-(3*H*)-dione.[18] In contrast, the urea **15a**, which was obtained upon treatment of **8** with **10a**, does not react with a second isocyanate **10a**, and the expected **5a** was not obtained even in the presence of $ZnCl_2$. Thus, the iminophosphorane (**9**) is a key synthon for the formation of the desired ring system of **5a**,**b**. In relation to the studies of the oxidizing ability of neutral and cationic compounds such as **3** and **4**, compound **5a** was converted to **7a** upon treatment of **5a** with MeI and followed by counter ion exchange reaction by using 42%

Table 1. Results for the reaction of **9** with aryl isocyanates **10a**,**b**

Isocyanate	Solvent[a]	Time/h	Product (yield/%)		
10a	Benzene	58	**5a** (9)	**6a** (55)	**15a** (11)
10a	Toluene	20	**5a** (28)	**6a** (52)	**15a** (14)
10b	Toluene	24	**5b** (13)	**6b** (57)	

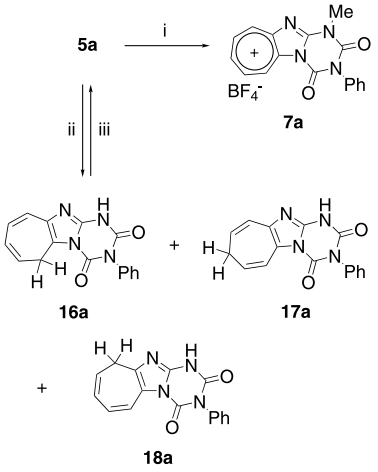
[a] Reaction was carried out under reflux.

Table 2. ^{1}H NMR spectral data (600 MHz) of **5a**,**b**, **6a**,**b**, and **7a** and reference compounds **3** and **4**

Compd		H5	H6	H7	H8	H9	Remaining signals
5a[a]	δ_H	9.17	8.19	8.06	8.32	8.45	7.36 (2H, d, J=8.2 Hz), 7.45 (1H, t, J=7.4 Hz), 7.52 (2H, d, J=8.2, 7.4 Hz)
	J	9.8	10.5	9.6	10.5		
5b[a]	δ_H	9.19	8.23	8.10	8.35	8.49	7.70 (2H, d, J=9.0 Hz), 8.39 (2H, d, J=9.0 Hz)
	J	9.8	9.8	9.2	10.5		
6a	δ_H	8.85	7.88	7.46	7.61	7.99	6.96 (1H, t, J=7.5 Hz), 7.04 (2H, d, J=8.3 Hz), 7.21 (2H, dd, J=8.3 Hz, 7.5), 7.41 (2H, d, J=8.1 Hz), 7.44 (1H, t, J=7.6 Hz), 7.54 (2H,dd, J=8.2, 7.6 Hz)
	J	11.2	10.8	10.1	9.8		
6b[a]	δ_H	9.00	7.84	7.92	7.99	8.19	7.13 (2H, d, J=8.9 Hz), 7.62 (2H, d, J=8.9 Hz), 8.12 (2H, d, J=8.9 Hz), 8.43 (2H, d, J=8.9 Hz)
	J	9.8	10.5	9.5	10.6		
7a[b]	δ_H	9.98–10.0	8.80–8.95			9.16	3.83 (3H, s), 7.44–7.48 (2H, m), 7.61–7.67 (2H, m)
	J	m	m		10.3		
3[c]	δ_H	9.29	7.66–7.90				5.69 (3H, s), 5.69 (2H, s), 7.26–7.3 (5H, m, Ph)
	J	10.6		m			
4[d]	δ_H	9.84–9.89	8.46–8.58			8.90–8.94	3.41 (3H, s), 3.94 (3H, s)
	J	m	m			m	

[a] Recorded in DMSO-d_6.
[b] Recorded in CD_3CN.
[c] Ref. 12.
[d] Ref. 11.

HBF_4 in Ac_2O in good yield. The spectroscopic data involving mass spectral data as well as the elemental analysis are in good accordance with the proposed structure. The redox ability of **5a** was also investigated. The reduction of **5a** with $NaBH_4$ was carried out to give a mixture of three regio-isomers **16a**, **17a**, and **18a**. The mixture of the regio-isomers was not separated, and thus, the structural assignment was based on the high resolution MS spectrum of the mixture and the ^{1}H NMR spectrum of each compounds, which was assigned independently by using the H–H Cosy spectrum. The mixture was oxidized by DDQ or under aerobic conditions to regenerate **5a**, and thus, the correlation of the compounds between **5a** and **16a**, **17a**, and **18a** was assessed (Scheme 2).



Scheme 2. Reagents and conditions: (i) (a) MeI, $(CH_2Cl)_2$, 100 °C, 3 h; (b) 42% aq. HBF_4, Ac_2O, 0 °C, 1 h; (ii) $NaBH_4$, MeOH, rt, 0.5 h; (iii) air, CH_2Cl_2, 7 days or DDQ, CH_2Cl_2, rt, 1 h.

2.2. Properties

The ^{1}H NMR spectra of two series of **5a**,**b** and **6a**,**b** resemble each other, respectively. Unambiguous proton assignment was successfully made, and the chemical shifts of the protons of the seven-membered ring and the aryl group and selected coupling constants are listed in Table 2, together with those of the reference compounds **3**[10] and cation **4**.[11] The chemical shifts of the seven-membered ring protons (H6–H9) of **5a** and **5b** are found in the appreciably lower field (δ 8.06–8.46 and δ 8.11–8.49) as compared with those (δ 7.66–7.90) of **3**. This feature is similarly observed in the chemical shifts of compounds **6a** (δ 7.46–7.99) and **6b** (δ 7.84–8.19). The chemical shifts of the seven-membered ring protons of cation **7a** are also listed and they are similar to those of cation **4**. In particular, the characteristic H5 signals appearing at around δ 9.0–9.9 in the ^{1}H NMR spectra of the compounds listed in Table 2 are due to the anisotropy effect of the oxygen atom of the triazinedione and pyrimidinedione moieties. The vicinal coupling constants of protons of the seven-membered ring of neutral compounds **5a**,**b** and **6a**,**b** suggest bond alternation in the cycloheptatriene moiety, while no significant bond alternation is observed in cation **7a** as well as **4**. The π-electron delocalization of cation **7a** is much enhanced as compared

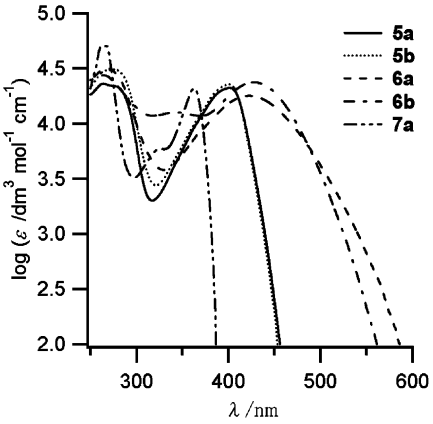


Figure 2. UV–vis spectra of **5a**,**b**, **6a**,**b** and **7a**.

with that of **5a**,**b** and **6a**,**b**. The UV–vis spectra of compounds **5a**,**b**, **6a**,**b** and cation **7a** in CH_3CN are shown in Figure 2. The two series of **5a**,**b** and **6a**,**b** are very similar to each other, respectively. On the other hand, the spectrum of cation **7a** exhibits a greater extent of blue-shift as compared with compound **5a**, suggesting the much lowering of the HOMO as compared with the LUMO by methylation.

Table 3. pK_{R+} values and reduction potentials[a] of **5a**,**b**, **6a**,**b**, **7a**[b] and reference compounds **3** and **4**

Compd	pK_{R+}	Reduction potential (V)[a] $E1_{red}$
5a	—	−1.15
5b	—	−1.12
6a	—	−1.24
6b	—	−1.14
7a	6.8	−0.66
3[b]	—	−1.37
4[c]	11.2	−0.87

[a] Peak potential in V versus $Ag/AgNO_3$.
[b] Ref. 10.
[c] Ref. 11.

The affinity of carbocation toward the hydroxide ion, expressed by the pK_{R+} value, is the common criterion of carbocation stability.[19] The value of cation **7a** was determined spectrophotometrically as 6.8 in buffer solutions prepared in 50% CH_3CN and indicated in Table 3, along with that of reference cation **4**. The value indicates that cation **7a** is much more unstable than reference compound **4**. The reduction potentials of **5a**,**b**, **6a**,**b**, and **7a** are determined by cyclic voltammetry (CV) in CH_3CN. The reduction waves of **5a**,**b**, **6a**,**b** and **7a** are irreversible under conditions of the CV measurements, and thus, their peak potentials are summarized in Table 3, together with those of the reference compounds **3**[10] and **4**.[11] As expected, the $E1_{red}$ of phenyl-substituted compounds **5a** and **6a** is more negative than that of 4-nitophenyl substituted derivatives **5b** and **6b**, respectively, due to the electron-withdrawing property of the 4-nitrophenyl group. The $E1_{red}$ of dicarbonyl compounds **5a**,**b** is more positive than that of the imino derivatives **6a**,**b**, respectively, due to the electron-withdrawing dicarbonyl function. The $E1_{red}$ of these compounds is less negative than that of the reference compound **3**. In contrast, the $E1_{red}$ of cation **7a** is much more positive than that of **5a**,**b** and **6a**,**b**, and the value is more positive than that of the reference compound **4**, suggesting an appreciable oxidizing property.

The X-ray structure analyses were carried out and the ORTEP drawings of **6a**,**b** are shown in Figure 3. The selected bond lengths and bent angles of the two aryl groups

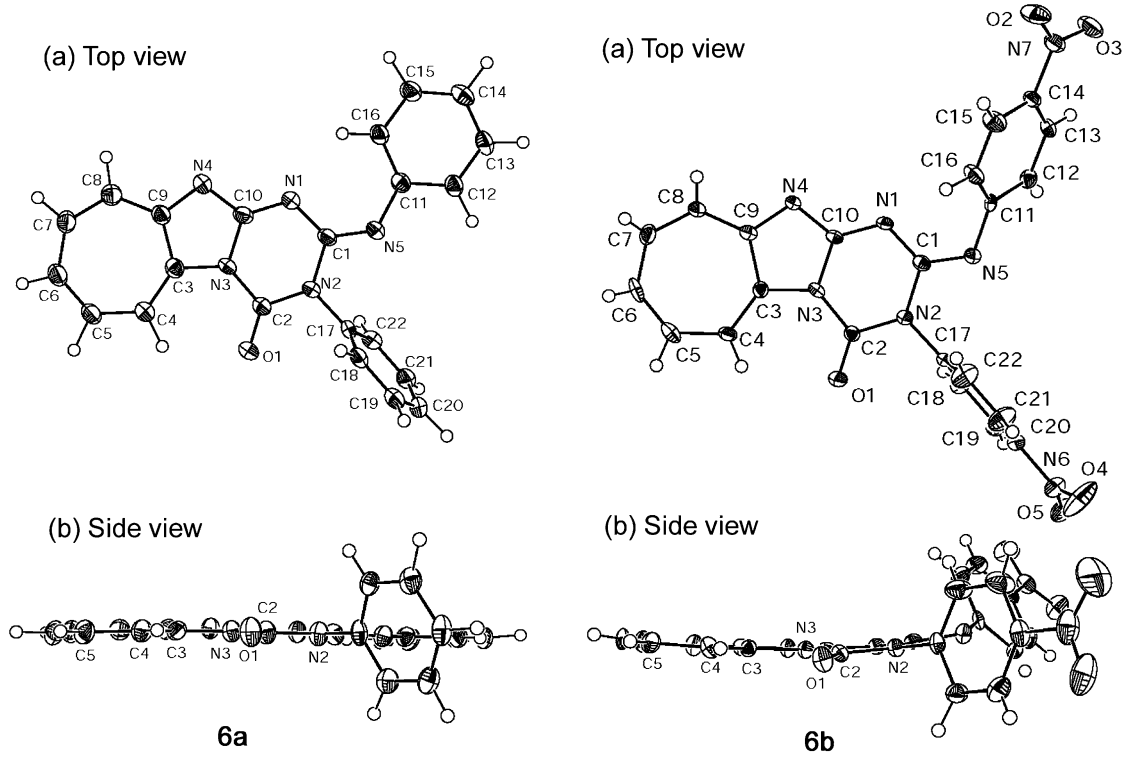


Figure 3. ORTEP drawings of **6a**,**b** with thermal ellipsoid plot (50% probability).

Table 4. Bond lengths of **6a**,**b** obtained by X-ray structure analysis

Compd.	Bond length[a]/Å												
	C3–C4	C4–C5	C5–C6	C6–C7	C7–C8	C8–C9	N4–C9	N4–C10	C3–N3	C10–N3	N1–C10	N1–C1	C1–N2
6a	1.38	1.40	1.35	1.41	1.37	1.40	1.34	1.34	1.38	1.39	1.30	1.35	1.43
6b	1.37	1.41	1.36	1.41	1.37	1.41	1.34	1.34	1.40	1.40	1.30	1.36	1.43

[a] Numbering is based on the ORTEP drawings in Figure 3.

from the plane of the 7–5–6 π-systems are summarized in Tables 4 and 5. The bond lengths of C3–C4, C5–C6, and C7–C8 are shorter than those of C4–C5 and C6–C7, suggesting bond-length alternation in the seven-membered ring as demonstrated by vicinal coupling constants of the ^{1}H NMR spectrum (Table 2). Electron delocalization in the triazine ring is not observed. Both 7–5–6 π-systems of **6a**,**b** are a nearly planar structure. The twisted angles of the aryl group against the plane of the 7–5–6 ring system are summarized in Table 5. The planes of the aryl group on the amide nitrogens of **6a**,**b** (N2Ar) are twisted 75.7 and 77.9°, respectively, against the plane of the 7–5–6 π-system. This is probably due to steric hindrance between the aryl group and the carbonyl-oxygen and imino-nitrogen. Remarkably, the twisted angle of N5Ar of **6a**,**b** is 2.5 and 58.7°, respectively (Table 1).

Table 5. Torsion angles of **6a**,**b** twisted angle/degree

Compd	N2Ar[a]	N5Ar[a]
6a	75.7	2.5
6b	77.9	58.7

[a] Numbering is based on the ORTEP drawings in Figure 3.

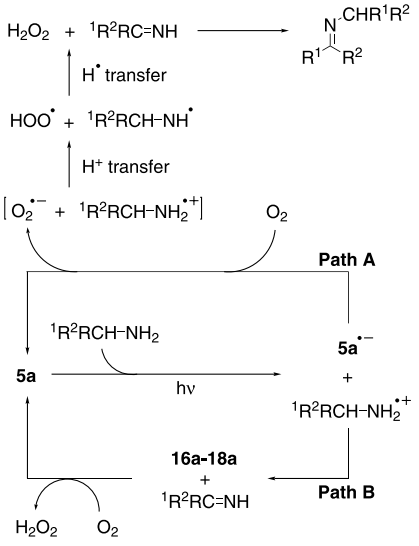
2.3. Photo-induced autorecycling oxidation

Compounds **3**,[12] **4**,[11] and related compounds[20] undergo photo-induced autorecycling oxidation toward some alcohols and some amines under aerobic conditions. In this context, we examined the oxidation of some amines by using **5a**, **6a**, and **7a** under aerobic and photo-irradiation (RPR100, 350 nm lamps) conditions. Although benzyl alcohol was not oxidized effectively by either **5a** or **7a**, we found that both compounds have oxidizing ability toward benzylamine, 1-phenylethylamine, hexylamine, and cyclohexylamine. In the amine oxidation, imine is produced at first; however, it reacts with another amine to result in the formation of another imine $R^1R^2C{=}N{-}CHR^1R^2$ and NH_3 (Scheme 3). Then the reaction mixture was diluted with ether and filtered and the filtrate was treated with 2,4-dinitrophenylhydrazine in 6% HCl to give 2,4-dinitrophenylhydrazone of the corresponding carbonyl compound. Direct irradiation of amines in the absence of **5a**, **6a**, and **7a** (named 'blank') gives the corresponding carbonyl compounds in low to modest yields under similar conditions. Thus, the yields are calculated by subtraction of the 'blank' yield from the total yield of the carbonyl compound in the presence of **5a** and **7a**, and the results are summarized in Table 6 (Entries 1–8). More than 100% yields are obtained based on **5a** and **7a**, and thus, autorecycling oxidation clearly proceeds. In contrast, oxidation reaction by using **6a** does not proceed effectively, and even benzylamine and 1-phenethylamine are oxidized in low yield as compared

Table 6. Photo-induced autorecycling oxidation of some amines by **5a**, **6a**, and **7a**[a]

Entry	Compd	Amines	Yield (%)[b,c]	Recycling no.
1	**5a**	$PhCH_2NH_2$	8322	83.2
2	**5a**	$PhCH(Me)NH_2$	6733	67.3
3	**5a**	Hexylamine	2000	20.0
4	**5a**	Cyclohexylamine	862	8.6
5	**7a**	$PhCH_2NH_2$	11 818	118.2
6	**7a**	$PhCH(Me)NH_2$	8457	84.6
7	**7a**	Hexylamine	3143	31.4
8	**7a**	Cyclohexylamine	909	9.1
9	**6a**	$PhCH_2NH_2$	909	9.1
10	**6a**	$PhCHMeNH_2$	400	4.0

[a] CH_3CN solution was irradiated by RPR100, 350 nm lamps.
[b] Isolated by converting to the corrresponding 2,4-dinitrophenylhydrazone.
[c] Based on the compound used; the yield is calculated by subtraction of the 'blank' yield from the total yield.



Scheme 3.

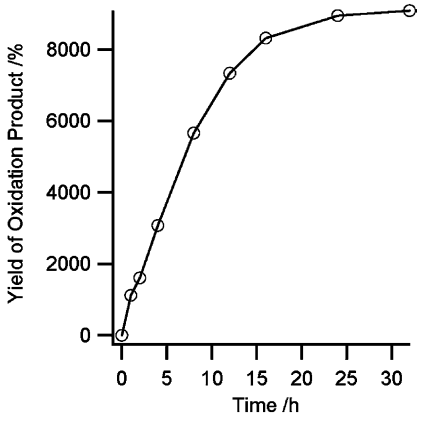


Figure 4. Time dependence of benzylamine oxidation by **5a**.

with that of **5a** and **7a** (Table 6, Entries 9 and 10). As the time of photo-irradiation is prolonged, the yield of oxidation product by **5a** is increased gradually. After 16 h irradiation, the yield is not increased appreciably (Fig. 4), suggesting plausible decomposition of **5a**. The attempted oxidation reaction of benzylamine by **5a** was not observed under thermal and aerobic conditions. In a previous study, the fluorescence spectrum of 1,3-dimethylcyclohepta[*b*]furo-[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dionylium tetrafluoroborate, which has oxidizing ability toward some alcohols, is quenched by addition of 1-phenylethanol, suggesting an interaction of the singlet excited state of the compound with the alcohol.[21] Thus, in a search of the mechanistic aspect of the photo-induced oxidation reaction, the fluorescence spectra of **5a** and **7a** were studied; the quantum yield (Φ) of that for **5a** was determined to be 0.075; however, no fluorescence spectra of **7a** was observed. The fluorescence spectrum of **5a** (Fig. 5) was quenched by adding benzylamine, while quenching of the fluorescence was not observed by addition of benzyl alcohol, suggesting interaction of the singlet excited state of **5a** with the amine.

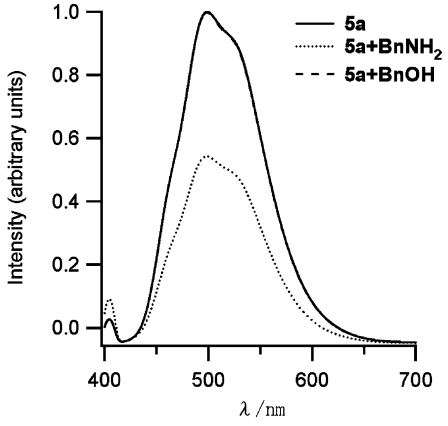


Figure 5. Fluorescence spectra of **5a**.

The postulated mechanistic pathways for the oxidation of amines ($R^1R^2CHNH_2$) are depicted in Scheme 3. The electron transfer from amines to the excited singlet state of **5a** would occur to produce a radical anion $\mathbf{5a}^{\cdot -}$ and $R^1R^2CHNH_2^{\cdot +}$. In the presence of oxygen, an electron transfer from $\mathbf{5a}^{\cdot -}$ to O_2 may give the radical ion pair [$R^1R^2CHNH_2^{\cdot +}$ $O_2^{\cdot -}$] and **5a**. Then a proton transfer from $R^1R^2CHNH_2^{\cdot +}$ to $O_2^{\cdot -}$ may occur, followed by formation of product $R^1R^2CH{=}NH$ and H_2O_2 (Path A).[22] On the other hand, there is an alternative pathway (Path B), in which a mixture of hydrogenated compounds **16a**, **17a**, and **18a** (Scheme 3) in addition to the imine are generated from $\mathbf{5a}^{\cdot -}$ and $R^1R^2CH{-}NH_2^{\cdot +}$ directly; the former compound is oxidized under aerobic conditions to regenerate **5a**. It is shown that the regeneration of **5a** by air oxidation of **16a**, **17a**, and **18a** is slow and seems to be ineffective to achieve an efficient autorecycling oxidation (Scheme 2, vide supra). Thus, Path A seems to be favorable. In the case of oxidation by **7a**, photo-induced homolytic cleavage of the initially formed amine-adduct of **7a**, which is detected by UV–vis spectra as shown in Figure 6, probably occurs to generate $\mathbf{7a}^{\cdot}$ and $R^1R^2CHNH_2^{\cdot +}$. An electron transfer from $\mathbf{7a}^{\cdot}$ to O_2 gives the radical ion pair [$R^1R^2CHNH_2^{\cdot +}$ $O_2^{\cdot -}$] and **7a**; the former ion pair would follow Path A.

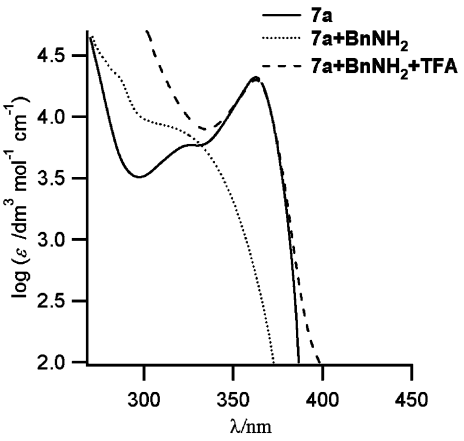


Figure 6. UV–vis spectra of **7a**.

3. Conclusion

Novel 3-phenyl- and 3-(4-nitropenyl)cyclohepta[4,5]-imidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*)-diones and the corresponding imino derivatives **5a**,**b**, **6a**,**b**, and 1-methyl-3-phenylcyclohepta[4,5]imidazo[1,2-*a*]-1,3,5-triazine-2,4-(1*H*,3*H*)-dionylium tetrafluoroborate **7a** were synthesized in modest to moderate yields. Compounds **5a**, **6a**, and **7a** were demonstrated to oxidize some amines to give the corresponding imines in more than 100% yield under aerobic and photo-irradiation conditions. Thus, oxidation reaction proceeds in a photo-induced autorecycling process.

4. Experimental

4.1. General

IR spectra were recorded on a HORIBA FT-710 spectrometer. UV–vis spectra were recorded on a Shimadzu UV-3101PC spectrometer. Mass spectra and high-resolution mass spectra were run on JMS-AUTOMASS 150 and JMS-SX102A spectrometers. Unless otherwise specified, ^1H NMR and ^{13}C NMR spectra were recorded on an AVANCE 600 spectrometer using $CDCl_3$ as the solvent, and the chemical shifts are given relative to internal $SiMe_4$ standard: *J*-values are given in Hz. Mps were recorded on a Yamato MP-21 apparatus and are uncorrected. Photo-irradiation was carried out by using RPR-100 fitted with 350 nm lamps though a Pyrex filter.

4.2. Preparation of 9

To a solution of **8** (435 mg, 3 mmol) and PPh_3 (786 mg, 3 mmol) in THF (30 mL) was added DEAD (1.5 mL, 3.3 mmol) at 0 °C, and the mixture was stirred at rt for 4 h. The reaction mixture was filtered, and the filtrate was concentrated. The resulting residue was crystallized from Et_2O to give **9** (1.17 g, 86%).

4.2.1. 2-(1,3-Diazaazulen-2-yl)iminotriphenylphosphorane (9). Pale yellow prisms; mp 212–213 °C (decomp.) (from AcOEt); ^{1}H NMR (600 MHz) δ 7.31 (1H, t, J=9.9 Hz, H-6), 7.44 (6H, ddd, J=7.8, 7.5, 2.9 Hz, *m*-Ph), 7.53 (3H, td, J=7.5, 1.7 Hz, *p*-Ph), 7.58 (2H, dd, J=10.7, 9.9 Hz, H-5 and H-7), 7.93 (6H, dd, J=7.8, 1.7 Hz, *o*-Ph), 7.94 (2H, d, J=10.7 Hz, H-4 and H-8); ^{13}C NMR (150.9 MHz) δ 124.6 (C-4 and C-8), 128.5 (J_{PC}=12.2 Hz, *m*-Ph), 128.8 (J_{PC}=100.1 Hz, *i*-Ph), 129.4 (C-6), 132.1 (J_{PC}=2.6 Hz, *p*-Ph), 133.4 (J_{PC}=10.1 Hz, *o*-Ph), 133.6 (C-5 and C-7), 165.1 (C-2); ^{31}P NMR (109.3 MHz) δ 16.97; IR ($CHCl_3$, cm^{-1}) 1549, 1470, 1438, 1364, 1114, 957, 926, 882; MS *m*/*z* 406 (M^++H); Anal. calcd for $C_{26}H_{21}N_3P$: C, 77.02; H, 4.97; N, 10.36. Found: C, 76.87; H, 4.95; N, 10.46.

4.3. Preparation of 5a and 6a

A solution of **9** (810 mg, 2.0 mmol) and **10a** (714 mg, 6.0 mmol) in a solvent (100 mL) indicated in Table 1 was refluxed for an adequate time. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2, the insoluble material was collected by filtration to give *N*-(1,3-diazaazuln-2-yl)-*N*′-phenylurea **15a**, and the filtrate was separated by column chromatography on SiO_2. The fractions eluted with AcOEt gave **6a**, and the fractions eluted with acetone gave **5a**. The results are summarized in Table 1.

4.3.1. 3-Phenylcyclohepta[4,5]imidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*)-dione (5a). Yellow needles; mp 228–230 °C (decomp.) (from CH_2CL_2/Et_2O); ^{13}C NMR (150.9 MHz, DMSO-d_6) δ 124.6, 128.2, 128.6, 128.9, 134.5, 135.6, 138.7, 139.0, 142.7, 145.1, 147.9, 155.0, 162.7, 166.3; IR (KBr, cm^{-1}) 1739, 1707; MS *m*/*z* 290 (M^+); Anal. calcd for $C_{16}H_{10}N_4O_2$–1/4H_2O: C, 65.19; H, 3.59; N, 19.01. Found: C, 65.20; H, 3.23; N, 19.14.

4.3.2. 3-Phenyl-2-phenyliminocyclohepta[4,5]imidazo[1,2-*a*]-1,3,5-triazine-4-one (6a). Dark red prisms; mp 222–223 °C (decomp) (from AcOEt); ^{13}C NMR (150.9 MHz) ^{13}C NMR (150.9 MHz) δ 122.2, 123.0, 123.1, 128.3, 128.5, 128.7, 129.5, 133.5, 135.7, 136.2, 137.9, 141.3, 146.1, 147.7, 148.0, 148.4, 159.7, 168.2; IR ($CHCl_3$, cm^{-1}) 1728; MS *m*/*z* 366 (M^++H); Anal. calcd for $C_{22}H_{15}N_5O$: C, 72.32; H, 4.14; N, 19.17. Found: C, 72.02; H, 4.12; N, 19.05.

4.4. Preparation of 5b and 6b

A solution of **9** (810 mg, 2.0 mmol) and **10b** (984 mg, 6.0 mmol) in toluene–dioxane (1/1; 100 mL) was refluxed for 24 h. After evaporation of the toluene, the residue was dissolved in CH_2Cl_2, the insoluble material was filtered and the filtrate was concentrated and separated by column chromatography on SiO_2. The fractions eluted with AcOEt afforded **6b**, and the fractions eluted with acetone gave **5b**. The results are summarized in Table 1.

4.4.1. 3-(4-Nitrophenyl)cyclohepta[4,5]imidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*)-dione (5b). Yellow powder; mp 249–252 °C (decomp.) (from AcOEt); ^{13}C NMR (150.9 MHz, DMSO-d_6) δ 124.5, 125.3, 130.7, 135.0, 139.4, 139.5, 141.8, 143.2, 145.2, 147.4, 147.9, 154.7, 163.0, 166.5; IR (KBr, cm^{-1}) 1746, 1683; MS *m*/*z* 336 (M^++H); Anal. calcd for $C_{16}H_9N_5O_4$–1/4CH_2Cl_2: C, 54.75; H, 2.69; N, 19.64. Found: C, 54.75; H, 2.80; N, 19.39.

4.4.2. 3-(4-Nitrophenyl)-2-(4-nitorophenyl)iminocyclohepta[4,5]imidazo[1,2-*a*]-1,3,5-triazine-4-one (6b). Red prisms; mp 258–260 °C (decomp.) (from $CHCl_3$); ^{13}C NMR (150.9 MHz, DMSO-d_6) δ 123.6, 123.8, 124.5, 124.9, 130.1, 134.6, 137.3, 138.4, 141.5, 142.1, 145.8, 147.2, 147.8, 149.3, 154.0, 160.1, 168.2, 175.2; IR ($CHCl_3$, cm^{-1}) 1734; MS *m*/*z* 456 (M^++H); Anal. calcd for $C_{22}H_{13}N_7O_5$–$CHCl_3$: C, 48.06; H, 2.46; N, 17.06. Found: C, 48.32; H, 2.58; N, 17.30.

4.5. Preparation of urea 15a

A solution of **8** (73 mg, 0.5 mmol) and **10a** (179 mg, 1.5 mmol), and $ZnCl_2$ (68 mg, 0.5 mmol) in dioxane (40 mL) was heated under reflux for 50 h. After evaporation of the solvent, the reaction mixture was washed with EtOH, the EtOH layer was concentrated to give **15a** (106 mg, 80%). A similar reaction in the absence of $ZnCl_2$ afforded **15a** (45 mg, 34%), which is identified on the basis of comparison of the physical data reported previously.[17]

4.6. Reaction of 15a with 10a

A mixture of **15a** (26 mg, 0.1 mmol) and **10a** (24 mg, 0.2 mmol) in the presence or absence of $ZnCl_2$ (14 mg, 0.1 mmol) in dioxane (40 mL) was heated under reflux for 50 h. The reaction mixture was concentrated and the residue was washed with EtOH. The collected EtOH solution was concentrated and **15a** was isolated in 83% (in the presence of $ZnCl_2$) and 76% (in the absence of $ZnCl_2$).

4.7. Preparation of 7a

A solution of **5a** (2.9 mg, 0.1 mL) and MeI (2 mL) in $(CH_2Cl)_2$ (4 mL) in a sealed tube was heated at 100 °C for 3 h. The solvent was evaporated and the residue was dissolved in Ac_2O (3 mL) and treated with 42% aq. HBF_4 (0.6 mL). To the solution was added ether (5 mL) and precipitates were collected by filtration to give **7a** (36 mg, 92%).

4.7.1. 1-Methyl-3-phenylcyclohepta[4,5]imidazo[1,2-*a*]-1,3,5-triazine-2,4(3*H*)-dionylium tetrafluoroborate (7a). Colorless needles; mp 289–291 °C (decomp.) (from CH_3CN/Et_2O.); ^{13}C NMR (150.9 MHz, CD_3CN) δ 32.1, 96.1, 128.7, 130.4, 130.7, 133.7, 134.8, 142.0, 145.0, 147.0, 147.2, 147.7, 148.2, 155.3, 162.8; IR ($CHCl_3$, cm^{-1}) 1726, 1084; MS *m*/*z* 305 (M^+−BF_4). HRMS calcd for $C_{17}H_{13}N_4O_2BF_4$: 305.1060 (M−BF_4). Found: 305.1021 (M^+−BF_4). Anal calcd for $C_{17}H_{13}N_4O_2BF_4$: C, 52.07; H, 3.34; N, 14.29. Found: C, 52.04, H, 3.53; N, 13.95.

4.8. Reduction of 5a

A solution of **5a** (29 mg, 0.1 mmol) and $NaBH_4$ (23 mg, 0.6 mmol) in MeOH (10 mL) was stirred at rt for 30 min. The reaction mixture was extracted with CH_2Cl_2 and the extract was dried over Na_2SO_4, and concentrated in vacuo.

The resulting residue afforded a mixture of **16a**, **17a**, and **18a** (100%) in a ratio of 6:3:1.

4.8.1. A mixture of 16a, 17a, and 18a. IR ($CHCl_3$, cm^{-1}) 1726, 1637, 1084; MS (FAB) m/z 293 ($M^+ + H$). HRMS calcd for $C_{16}H_{13}N_4O_2$: 293.1040 (M+H). Found: 293.1044 ($M^+ + H$).

4.8.2. Compound 16a. ^{1}H NMR (600 MHz) δ 3.73 (2H, d, J=6.4 Hz, H-6), 5.54 (1H, dt, J=10.4, 6.4 Hz, H-7), 6.11 (1H, dd, J=10.4, 6.1 Hz, H-8), 6.45 (1H, dd, J=11.5, 6.1 Hz, H-9), 6.90 (1H, d, J=1.5 Hz, H-10), 7.30–7.56 (5H, m, *o*-Ph, *m*-Ph and *p*-Ph); MS *m*/*z* 293 (M^+).

4.8.3. Compound 17a. ^{1}H NMR (600 MHz) δ 3.36 (2H, d, J=6.3 Hz, H-10), 5.48 (1H, dt, J=10.2, 6.3 Hz, H-10), 6.08–6.13 (1H, m, H-8), 6.40 (1H, dd, J=11.5, 6.1 Hz, H-7), 7.30–7.39 (1H, m, H-6), MS *m*/*z* 293 (M^+).

4.8.4. Compound 18a. ^{1}H NMR (600 MHz) δ 2.50 (2H, t, J=7.0 Hz, H-8), 5.36 (1H, dt, J=10.0, 7.0 Hz, H-7), 5.52–5.56 (1H, m, H-9), 6.87 (1H, d, J=10.0 Hz, H-10), 7.20 (1H, d, J=10.0 Hz, H-6), 7.30–7.56 (5H, m, *o*-Ph, *m*-Ph and *p*-Ph); MS *m*/*z* 293 (M^+).

4.9. Oxidation of a mixture of 16a, 17a, and 18a

A mixture of **16a**, **17a**, and **18a** (29 mg, 0.1 mmol) in CH_2Cl_2 (15 mL) was stirred under aerobic conditions for 7 day. The solution was dried over Na_2SO_4 and concentrated. The resulting residue was purified by TLC on SiO_2 (acetone) to give **5a** (17 mg, 59%).

A solution of **16a**, **17a**, and **18a** (29 mg, 0.1 mmol) and DDQ (27 mg, 0.12 mmol) in CH_2Cl_2 (15 mL) was stirred at rt for 1 h. The reaction mixture was extracted with CH_2Cl_2, and the extract was washed with aq. Na_2CO_3 and dried over Na_2SO_4. The CH_2Cl_2 was evaporated and the residue was purified by TLC on SiO_2 (acetone) to give **5a** (25 mg, 86%).

4.10. General procedure for the photo-induced auto-recycling oxidation of amines

To a solution of **5a** (0.005 mmol) and **7a** (0.005 mmol) in CH_3CN (16 mL) was added an amine (2.5 mmol) in a pyrex tube, and the mixture was irradiated by RPR-100, 350 nm lamps under aerobic conditions for 16 h. The reaction mixture was concentrated in vacuo and diluted with ether and filtered. The filtrate was treated with 2,4-dinitrophenylhydrazine in 6% HCl to give the 2,4-dinitrophenylhydrazone of the corresponding carbonyl compound. The results are summarized in Table 6. In the case of the benzylamine oxidation, nine samples are irradiated and time dependency of the yields of 2,4-dinitrophenylhydrazone was investigated as summarized in Figure 4.

4.11. Determination of pK_{R+} value of cation 7a

Buffer solutions of slightly different acidities were prepared by mixing aqueous solutions of potassium hydrogen phthalate (0.1 M) and HCl (0.1 M) (for pH 2.2–4.0), potassium hydrogen phthalate (0.1 M) and NaOH (0.1 M) (for pH 4.1–5.9), and KH_2PO_4 (0.1 M) and NaOH (0.1 M) (for pH 6.0–8.0) in various portions. For the preparation of sample solutions, 1 mL portions of the stock solution, prepared by dissolving 3–5 mg of compound **7a** in CH_3CN (20 mL), were diluted to 10 mL with the buffer solution (8 mL) and CH_3CN (1 mL). The UV–vis spectrum was recorded for cation **7a** in 20 different buffer solutions. Immediately after recording the spectrum, the pH of each solution was determined on a pH meter calibrated with standard buffers. The observed absorbance at the specific absorption wavelength (500 nm) of cation **7a** was plotted against pH to give a classical titration curve, whose midpoint was taken as the pK_{R+} value.

4.12. Cyclic voltammetry of 5a,b and 7a

The reduction potentials of **5a**,**b** and **7a** were determined by means of CV-27 voltammetry controller (BAS Co). A three-electrode cell was used, consisting of Pt working and an Ag/$AgNO_3$ reference electrode. Nitrogen was bubbled through a CH_3CN solution (4 mL) of each sample (1 mmol dm^{-3}) and Bu_4NClO_4 (100 mmol dm^{-3} to deaerate it. The measurements were made at a scan rate of 0.1 V s^{-1}, and the voltammograms were recorded on an X–Y recorder. Immediately after the measurements, ferrocene (0.2 mmol dm^{-3}) ($E_{1/2}$=+0.083 V) was added as the internal standard, and the observed peak potentials were corrected with reference to this standard.

4.13. X-ray structure determination of 6a[†]

Reddish prisms, $C_{22}H_{15}N_5O$, M=365.39, triclinic, space group $P-1$, a=7.059(3), b=10.399(5), c=11.990(7) Å, α=100.50(3)°, β=96.87(3)°, γ=105.17(2)°, V=822.2(7) Å^3, Z=2, D_c=1.476 g mL^{-1}, crystal dimensions 0.80×0.50×0.30 mm. Data were measured on a Rigaku RAXIS-RAPID radiation diffractomater with graphite monochromated Mo Kα radiation. Total 7445 reflections were collected, using the ω–2θ scan technique to a maximum 2θ value of 55.0°. The structure was solved by direct methods and refined by a full-matrix least-squares method using SIR92 structure analysis software, with 268 variables and 2897 observed reflections [$I>3.00\sigma(I)$]. The non-hydrogen atoms were refined anisotropically. The weighting scheme $w=[20.0000\times\sigma_c(F_0^2)+0.0010\times F_0^2+0.5000]^{-1}$ gave satisfactory agreement analysis. The final R and Rw values were 0.0810 and 0.0990. The maximum peak and minimum peak in the final difference map were 0.38 and −0.41 e$^-$/Å^3.

4.14. X-ray structure determination of 6b[‡]

Reddish prisms, $C_{23}H_{14}Cl_3N_7O_5$, M=574.77, monoclinic, space group $P2_1/n$, a=13.15(1), b=14.632(9), c=13.754(8) Å, β=114.06(5) °, V=2417.0(3) Å^3, Z=4, D_c=1.579 g mL^{-1}, crystal dimensions 0.80×0.40×0.20 mm. Data were measured on a Rigaku RAXIS-RAPID radiation diffractomater with graphite monochromated Mo Kα radiation. Total 21,037 reflections were collected, using the ω–2θ scan technique to a maximum 2θ value of 55.0°. The structure was solved by direct methods

[†] CCDC reference number 266692.
[‡] CCDC reference number 266693.

and refined by a full-matrix least-squares method using SIR92 structure analysis software, with 357 variables and 2922 observed reflections [$I>3.00\sigma(I)$]. The non-hydrogen atoms were refined anisotropically. The weighting scheme $w=[3.0000\times\sigma_c(F_0^2)+0.0010\times F_0^2+0.5000]^{-1}$ gave satisfactory agreement analysis. The final R and Rw values were 0.0690 and 0.0860. The maximum peak and minimum peak in the final difference map were 1.01 and -0.78 e$^-$/Å^3.

Acknowledgements

Financial support from a Waseda University Grant for Special Research Project and 21COE 'Practical Nano-Chemistry' from MEXT, Japan, is gratefully acknowledged. We thank the Materials Characterization Central Laboratory, Waseda University, for technical assistance with the spectral data, elemental analyses, and X-ray analysis.

References and notes

1. Brown, D. J. In Katritzky, A. R., Rees, C. W., Eds.; Comprehensive Heterocyclic Chemistry; Pergamon: Oxford, 1984; Vol. 3, pp 57–155.
2. Wamhoff, H.; Dzenis, J.; Hirota, K. *Adv. Heterocycl. Chem.* **1992**, *55*, 129–259.
3. Hamilton, G. A. In Kaiser, E. T., Kezdy, F. J., Eds.; Progress in Bioorganic Chemistry; Wiley: New York, 1971; Vol. 1, p 83.
4. Walsh, C. *Acc. Chem. Res.* **1986**, *19*, 216–221 and references therein.
5. Yoneda, F.; Tanaka, K. *Med. Res. Rev.* **1987**, *4*, 477–506 and references therein.
6. Yoneda, F.; Kokel, B. In Muller, F., Ed.; Chemistry and Biochemistry of Flavoenzymes; CRC: Boca Raton, 1991; Vol. 1, pp 121–169; and references therein.
7. (a) Nitta, M. *Rev. Heteroatom Chem.* **1993**, *9*, 87–121 and references therein. (b) Nitta, M.; Iino, Y.; Mori, S.; Takayasu, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1001–1007.
8. (a) Nitta, M.; Akie, T.; Iino, Y. *J. Org. Chem.* **1994**, *59*, 1309–1314. (b) Nitta, M.; Kanda, H. *Heterocycles* **2002**, *57*, 491–499.
9. Nitta, M.; Tajima, Y. *J. Chem. Res. (S)* **1999**, 372–373.
10. Nitta, M.; Tajima, Y. *Synthesis* **2000**, 651–654.
11. Naya, S.; Nitta, M. *Tetrahedron* **2003**, *59*, 7291–7299.
12. Naya, S.; Iida, Y.; Nitta, M. *Tetrahedron* **2004**, *60*, 459–467.
13. For reviews: (a) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353–1406. (b) Eguchi, S.; Matsushita, Y.; Yamashita, K. *Org. Prep. Proced. Int.* **1992**, *24*, 209. (c) Molina, P.; Vilaplana, M. J. *Synthesis* **1994**, 1197. (d) Wamhoff, H.; Richardt, G.; Stolben, S. *Adv. Heterocycl. Chem.* **1995**, *64*, 159–249.
14. (a) Bruche, L.; Garanti, L.; Zecchi, G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2177–2179. (b) Molina, P.; Alajarin, M.; Vidal, A. *Tetrahedron* **1990**, *46*, 1063–1073. (c) Yamamoto, H.; Ohnuma, M.; Nitta, M. *J. Chem. Res., (S)* **1999**, 173. *(M)* **1999**, 901–919.
15. Nozoe, T.; Mukai, T.; Takase, K.; Murata, I.; Matsumoto, K. *Proc. Jpn. Acad.* **1953**, *29*, 452–456.
16. Hoest, C. E.; Nefzi, A.; Houghten, R. A. *Tetrahedron Lett.* **2003**, 3705–3708.
17. Ishiguro, M.; Kitahara, T.; Tomino, K. Jpn. Kokai Tokkyo Koho JP04208267, 1992.
18. Abe, N.; Matsuda, H.; Sugihara, Y.; Kakehi, A. *J. Heterocycl. Chem.* **1996**, *33*, 1323–1331.
19. Freedman, H. H. In *Carbonium Ions*; Olah, G. A., Schleyer, P., Eds.; Wiley-Interscience: New York, 1973.
20. (a) Mitsumoto, Y.; Nitta, M. *J. Org. Chem.* **2004**, *69*, 1256–1261. (b) Naya, S.; Tokunaka, T.; Nitta, M. *J. Org. Chem.* **2004**, *69*, 4732–4740. (c) Naya, S.; Warita, M.; Mitsumoto, Y.; Nitta, M. *J. Org. Chem.* **2004**, *69*, 9184–9190 and references therein.
21. Naya, S.; Miyama, H.; Yasu, K.; Takayasu, T.; Nitta, M. *Tetrahedron* **2003**, *59*, 4929–4938.
22. Fukuzumi, S.; Kuroda, S. *Res. Chem. Intermed.* **1999**, *25*, 789–811.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 61 (2005) 6082–6087
Tetrahedron

Direct synthesis of new arylanthranilic acids via a Suzuki cross-coupling reaction from iodoisatins

Anne-Laure Gérard,[a] Vincent Lisowski[b] and Sylvain Rault[a,*]

[a]*Centre d'Etudes et de Recherche sur le Médicament de Normandie, UFR des Sciences Pharmaceutiques, 5 rue Vaubénard, 14032 Caen Cedex, France*

[b]*Laboratoire des Aminoacides, Peptides et Protéines (UMR-CNRS 5810), Faculté de Pharmacie, 15 avenue Charles Flahault, 34093 Montpellier Cedex 5, France*

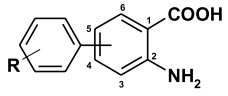
Received 23 February 2005; revised 30 March 2005; accepted 14 April 2005

Available online 13 May 2005

Abstract—Direct synthesis of new arylanthranilic acids via a Suzuki cross-coupling reaction with iodoisatins as key intermediates is described. A 'one pot' procedure is proposed.

1. Introduction

Anthranilic acids **I** are very important building-blocks to prepare compounds of pharmaceutical interest. Surprisingly, little work has yet to be developed on the synthesis of arylanthranilic acids which could exhibit interesting properties not only as new building-blocks but also as new bioactive compounds.



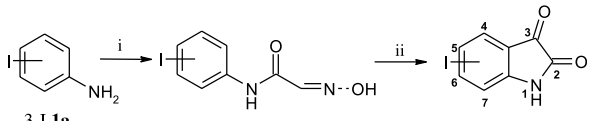
I

Concerning the synthesis of these aminoacids, it was only mentioned without description that 4-arylanthranilic acids have been obtained via a Suzuki cross-coupling reaction starting from methyl-4-bromoanthranilate[1] and further, only one example of Stille cross-coupling reaction has been described on 5-bromo-1-methylisatin.[2] Finally, some 5-arylisatins are obtained via a Suzuki cross-coupling reaction from 5-bromoisatin with some boronic acids.[3]

In a recent study[4] we have demonstrated that the best way to produce 3-phenylanthranilic acid was the cross-coupling reaction of phenylboronic acid, not with the 3-iodoanthranilic acid itself, but with 7-iodoisatin that can be considered as a biprotected aminoacid. We recently, showed the usefulness of this coupling in the synthesis of tripentones with antitubulin properties.[5] In this paper, we wish to present the first results concerning the enlargement of this methodology to the coupling of 4-, 5- and 6-iodoisatins with arylboronic acids in order to create a new library of arylanthranilic acids useable in parallel chemistry.[6,7]

2. Results and discussion

Starting from 3- **1a** or 4-iodoaniline **1b**, the corresponding 4- **3a**, 5- **3b** or 6-iodoisatins **3c** are obtained in two steps via the corresponding isonitrosoacetanilides.[8] So 4- and 6-iodoisatins are obtained from the non-regioselective ring closure of 3-iodoisonitroacetanilide **2a** and subsequently separated by their pH-dependant solubility in aqueous solution as previously described by Sadler.[9] 5-Iodoisatin is synthesized from **2b** according to Marvel.[8] (Scheme 1).



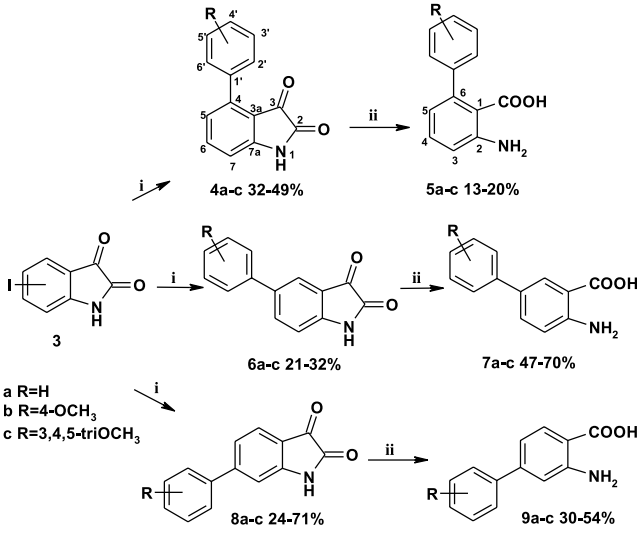
Scheme 1. Reagents and conditions: (i) $Cl_3CCH(OH)_2$, $NH_2OH{\cdot}HCl$, HCl cc., Na_2SO_4, H_2O; (ii) H_2SO_4 cc.

Starting either from 4-iodoisatin **3a**, 5-iodoisatin **3b** or from 6-iodoisatin **3c** the cross-coupling reaction[10] was effective and give, respectively, 4-arylisatins **4a–c**, 5-arylisatins **6a–c** and 6-arylisatins **8a–c**. The yields remained rather

Keywords: Suzuki; Arylisatin; Arylanthranilic acid.
* Corresponding author. Tel.: +33 2 31 56 59 10; fax: +33 2 31 93 11 88; e-mail: rault@pharmacie.unicaen.fr

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.04.022

disappointing mainly because of the poor solubility of arylisatins in usual solvents such as dioxan, DMF or DME, which makes their isolation difficult. Finally, 6-arylanthranilic acids **5a–c**, 5-arylanthranilic acids **7a–c** and 4-arylanthranilic acids **9a–c** (Scheme 2) were then obtained by oxidative cleavage in a 5% sodium hydroxide and 30% hydrogen peroxide aqueous solution (v/v).[11,12] The global yields of this route are summarised in Table 1.



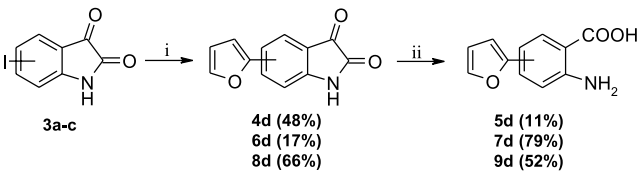
Scheme 2. Reagents and conditions: (i) Ar-B(OH)$_2$ (1.2 equiv), Pd(PPh$_3$)$_4$ (0.05 equiv), NaHCO$_3$ (2 equiv), DME/H$_2$O; (ii) NaOH 5%, H$_2$O$_2$ 30%.

Table 1. Overall yields of the two steps one-pot cross-coupling and oxidative cleavage

	Phenyl	4-OMephenyl
5-Arylanthranilic acid	62% (**7a**)	67% (**7b**)
4-Arylanthranilic acid	42% (**9a**)	13% (**9b**)

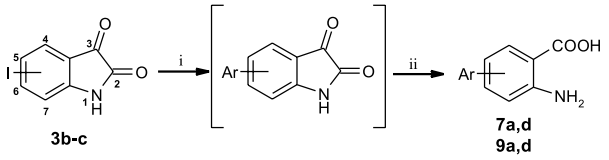
This sequence is also applicable with fragile heterocyclic boronic acids and, for example, we have prepared furylanthranilic acids **5d**, **7d** and **9d** from furylisatins **4d**, **6d** and **8d** (Scheme 3).

Since, we mainly wish to obtain anthranilic acids and considering that the essential reason for these poor yields was the purification of the arylisatins intermediates, we tried to find 'one-pot' conditions to produce arylanthranilic acids directly from iodoisatins (Scheme 4). We applied this methodology to 5- **3b** and 6-iodoisatins **3c** with phenylboronic acid and 4-methoxyphenylboronic acid. Satisfactorily we found that a slight modification of the cross-coupling reaction work up was able to produce the



Scheme 3. Reagents and conditions: (i) Ar-B(OH)$_2$ (1.2 equiv), Pd(PPh$_3$)$_4$ (0.05 equiv), NaHCO$_3$ (2 equiv), DME/H$_2$O; (ii) NaOH 5%, H$_2$O$_2$ 30%.

cleavage by adding hydrogen peroxide during the final washing steps. We thus, obtained the four arylanthranilic acids **7a–b** and **9a–b** with better yields than the two steps route (Table 1). The difficulty in purifying the intermediate arylisatins is thus, circumvented by this procedure which could be preferable to obtain arylanthranilic acids (Scheme 4).



Scheme 4. Reagents and conditions: (i) Ar-B(OH)$_2$ (1.2 equiv), Pd(PPh$_3$)$_4$ (0.05 equiv), NaHCO$_3$ (2 equiv), DME/H$_2$O; (ii) NaOH 5%, H$_2$O$_2$ 30%.

These results encourage us to pursue the study of the reactivity of these very potent scaffolds particularly in the field of parallel chemistry in the light of our recent results obtained with thiophenic bioisosters series.[6,7]

3. Experimental

3.1. General

Commercial reagents were used as received without additional purification. Melting points were determined on a Köfler melting point apparatus. IR spectra were taken with a Perkin–Elmer spectrum BX FT-IR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C (100 MHz) spectra were recorded on a JEOL Lambda 400 spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Mass spectra were recorded on a JEOL JMS GCMate with ionising potential of 70 eV and with pfk as internal standard for high-resolution procedure.

3.2. General procedure for the preparation of the arylisatins (4a–d, 6a–d and 8a–d).

To a solution mixture of iodoisatin **3a–c** (3 mmol, 1 equiv) in DME (50 mL) under argon was added Pd(PPh$_3$)$_4$ (0.15 mmol, 0.05 equiv) followed by the addition of arylboronic acid (3.6 mmol, 1.2 equiv) and sodium hydrogen carbonate (6 mmol, 2 equiv) in H$_2$O (10 mL). The reaction mixture was refluxed and the rate of the reaction, followed by TLC. After the starting aryl halide was consumed, the organic solvent is removed under reduced pressure. The residue, partially soluble in H$_2$O, is extracted with AcOEt and the organic layer is dried (MgSO$_4$) and evaporated. The crude products are purified by column chromatography (AcOEt/Cyclohexane, 1:2).

3.2.1. 4-Phenylisatin (4a). 32%, Orange solid. Mp 209 °C. IR (KBr): 3171, 1745, 1732, 1618, 1588, 1573, 1480, 1241, 1185, 910 and 800 cm^{-1}. ^{1}H NMR (DMSO-d$_6$): 7.59 (t, 1H, H$_6$, J=7.8 Hz), 7.54–7.42 (m, 5H, H$_{phenyl}$), 6.99 (d, 1H, H$_5$ or H$_7$, J=7.8 Hz), 6.87 (d, 1H, H$_5$ or H$_7$, J=7.8 Hz). ^{13}C NMR (DMSO-d$_6$): 183.04 (C-3), 159.10 (C-2), 151.56 (C-1′), 141.52 (C-7a), 137.90 (C-6), 136.36 (C-4), 128.87

(C-phenyl), 128.65 (C-phenyl), 128.08 (C-phenyl), 124.34 (C-5), 114.24 (C-3a), 111.13 (C-7). MS *m/z*: 223.1. $C_{14}H_9NO_2$ (223.23); calcd: C, 75.33; H, 4.06; N, 6.27; found: C, 75.27; H, 4.12; N, 6.31.

3.2.2. 4-(4-Methoxyphenyl)isatin (4b). 49%, red solid. Mp 214 °C. IR (KBr): 3335, 2921, 1754, 1719, 1612, 1519, 1469, 1303, 1252, 1194, 1101, 1026 and 789 cm^{-1}. ^1H NMR (DMSO-d_6): 11.09 (s, 1H, NH), 7.55 (t, 1H, H_6, J= 7.8 Hz), 7.50 (d, 2H, $H_{2'}$ and $H_{6'}$, J=8.3 Hz), 6.99 (d, 2H, $H_{3'}$ and $H_{5'}$, J=8.3 Hz), 6.98 (d, 1H, H_5 or H_7, J=7.8 Hz), 6.82 (d, 1H, H_5 or H_7, J=7.8 Hz), 3.80 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): 183.22 (C-3), 160.01 (C-2), 159.33 (C-4′), 151.67 (C-1′), 141.69 (C-7a), 138.02 (C-6), 130.55 (C-2′ and C-6′), 128.74 (C-4), 124.35 (C-5), 114.21 (C-3a), 113.71 (C-3′ and C-5′), 110.65 (C-7), 55.44 (OCH_3). MS *m/z*: 253.1. $C_{15}H_{11}NO_3$ (253.26); calcd: C, 71.14; H, 4.38; N, 5.53; found: C, 71.08; H, 4.29; N, 5.48.

3.2.3. 4-(3,4,5-Trimethoxyphenyl)isatin (4c). 32%, orange solid. Mp 231 °C. IR (KBr): 3242, 2922,1760, 1727, 1615, 1586, 1486, 1412, 1347, 1312, 1258, 1176, 1120, 987 and 797 cm^{-1}. ^1H NMR (DMSO-d_6): 11.12 (s, 1H, NH), 7.57 (t, 1H, H_6, J=7.8 Hz), 7.10 (d, 1H, H_5 or H_7, J=7.8 Hz), 6.88 (s, 2H, $H_{2'}$ and $H_{6'}$), 6.85 (d, 1H, H_5 or H_7, J=7.8 Hz), 3.78 (s, 6H, OCH_3), 3.70 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): 182.33 (C-3), 159.04 (C-2), 152.40 (C-3′ and C-5′), 151.43 (C-4), 141.54 (C-4′), 137.97 (C-7a), 137.65 (C-6), 131.54 (C-1′), 124.16 (C-5), 114.22 (C-3a), 110.90 (C-7), 106.57 (C-2′ and C-6′), 60.06 (OCH_3), 55.96 (OCH_3). MS *m/z*: 313.2. $C_{17}H_{15}NO_5$ (313.31); calcd: C, 65.17; H, 4.83; N, 4.47; found: C, 65.12; H, 4.94; N, 4.53.

3.2.4. 4-(2-Furyl)isatin (4d). 48%, red solid. Mp 241 °C. IR (KBr): 3302, 3124, 1754, 1731, 1616, 1567, 1490, 1475, 1250, 1190, 1027 and 923 cm^{-1}. ^1H NMR (DMSO-d_6): 11.16 (s, 1H, NH), 7.94 (d, 1H, H_{fur}, J=3.6 Hz), 7.90 (m, 1H, H_{fur}), 7.61 (t, 1H, H_6, J=7.9 Hz), 7.46 (d, 1H, H_5 or H_7, J=8 Hz), 6.79 (d, 1H, H_5 or H_7, J=7.8 Hz), 6.72 (m, 1H, H_{fur}). ^{13}C NMR (DMSO-d_6): 182.30 (C-3), 158.67 (C-2), 151.67 (C-7a), 149.25 (C-1′), 144.75 (C-fur), 138.39 (C-6), 129.05 (C-4), 119.27 (C-fur), 114.12 (C-5), 112,49 (C-fur), 111.48 (C-7), 110.68 (C-3a). MS *m/z*: 213.1. $C_{12}H_7NO_3$ (213.19); calcd: C, 67.61; H, 3.31; N, 6.57; found: C, 67.49; H, 3.23; N, 6.48.

3.2.5. 5-Phenylisatin (6a).[3] 26%, red solid. Mp 270 °C. IR (KBr): 3435, 3052, 1603, 1494, 1442, 1345, 1306, 1178, 1086, 1024 and 700 cm^{-1}. ^1H NMR (DMSO-d_6): 11.12 (s, 1H, NH), 7.90 (dd, 1H, H_6, J=8.0, 2.0 Hz), 7.76 (d, 1H, H_4, J=2 Hz), 7.64 (d, 2H, H_{phenyl}, J=7.0 Hz), 7.46 (m, 3H, H_{phenyl}), 6.99 (d, 1H, H_7, J=8.0 Hz). ^{13}C NMR (DMSO-d_6): 184.29 (C-3), 159.31 (C-2), 149.72 (C-7a), 138.68 (C-1′), 136.43 (C-6), 134.86 (C-5), 128.97 (C-phenyl), 127.44 (C-phenyl), 126.18 (C-phenyl), 122.40 (C-4), 118.30 (C-3a), 112.63 (C-7). MS *m/z*: 223.1.

3.2.6. 5-(4-Methoxyphenyl)isatin (6b). 21%, purple solid. Mp 242 °C. IR (KBr): 3257, 2957, 1762, 1728, 1622, 1603, 1478, 1412, 1340, 1245, 1170, 1110, 1019 and 829 cm^{-1}. ^1H NMR (DMSO-d_6): 11.08 (s, 1H, NH), 7.84 (dd, 1H, H_6, J=8, 1.8 Hz), 7.70 (d, 1H, H_4, J=1.8 Hz), 7.58 (d, 2H, $H_{2'}$ and $H_{6'}$, J=8.5 Hz), 6.99 (d, 2H, $H_{3'}$ and $H_{5'}$, J=8.5 Hz), 6.96 (d, 1H, H_5, J=8 Hz), 3.77 (s, 1H, OCH_3). ^{13}C NMR (DMSO-d_6): 184.46 (C-3), 159.55 (C-2), 158.90 (C-4′), 149.39 (C-7a), 135.93 (C-6), 134.68 (C-5), 131.09 (C-1′), 127.35 (C-4), 121.89 (C-7), 118.37 (C-3′ and C-5′), 114.40 (C-3a), 112.60 (OCH_3), 55.17 (OCH_3). MS *m/z*: 253.1. $C_{15}H_{11}NO_3$ (253.26); calcd: C, 71.14; H, 4.38; N, 5.53; found: C, 70.96; H, 4.29; N, 5.43.

3.2.7. 5-(3,4,5-Trimethoxyphenyl)isatin (6c). 32%, orange solid. Mp 113 °C. IR (KBr): 3471, 3289, 1739, 1625, 1582, 1482, 1411, 1348, 1242, 1121 and 986 cm^{-1}. ^1H NMR (DMSO-d_6): 11,11 (s, 1H, NH), 7.92 (dd, 1H, H_6, J=8, 1.7 Hz), 7.83 (d, 1H, H_4, J=1.7 Hz), 6.96 (d, 1H, H_7, J= 8 Hz), 6.88 (s, 2H, $H_{2'}$ and $H_{6'}$), 3.85 (s, 6H, OCH_3), 3.66 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): 184.42 (C-3), 159.64 (C-2), 153.24 (C-3′ and C-5′), 149.80 (C-4′), 137.09 (C-7a), 136.57 (C-6), 135.09 (C-5), 134.47 (C-1′), 122.75 (C-4), 118.30 (C-3a), 112.40 (C-7), 103.72 (C-2′ and C-6′), 60.02 (OCH_3), 55.98 (OCH_3). MS *m/z*: 313.4. $C_{17}H_{15}NO_5$ (313.31); calcd: C, 65.17; H, 4.83; N, 4.47; found: C, 65.02; H, 4.80; N, 4.35.

3.2.8. 5-(2-Furyl)isatin (6d). 17%, purple solid. Mp 214 °C. IR (KBr): 3285, 1757, 1730, 1621, 1503, 1477, 1282, 1200 and 1120 cm^{-1}. ^1H NMR (DMSO-d_6): 11.13 (s, 1H, NH), 7.89 (dd, 1H, H_6, J=8.2, 1.9 Hz), 7.78 (d, 1H, H_4, J= 1.9 Hz), 7.72 (s, 1H, H_{fur}), 6.97 (s, 1H, H_{fur}), 6.96 (d, 1H, H_7, J=8.2 Hz), 6.57 (s, 1H, H_{fur}). ^{13}C NMR (DMSO-d_6): 183.97 (C-3), 159.49 (C-2), 151.81 (C-1′), 149.39 (C-7a), 142.79 (C-fur), 132.74 (C-6), 125.41 (C-5), 119.36 (C-4), 118.34 (C-3a), 112.61 (C-fur), 112.12 (C-7), 105.48 (C-fur). MS *m/z*: 213.0. $C_{12}H_7NO_3$ (213.19); calcd: C, 67.61; H, 3.31; N, 6.57; found: C, 67.58; H, 3.30; N, 6.49.

3.2.9. 6-Phenylisatin (8a). 71%, orange solid. Mp 230 °C. (Lit.[13] 230–235 °C). IR (KBr): 3271, 2923, 1765, 1733, 1622, 1455, 1433, 1325, 1181, 1107 and 893 cm^{-1}. ^1H NMR (DMSO-d_6): 11.13 (s, 1H, NH), 7.70 (d, 2H, H_{phenyl}, J=8 Hz), 7.58 (d, 1H, H_4, J=7.8 Hz), 7.53–7.46 (m, 3H, H_{phenyl}), 7.35 (d, 1H, H_5, J=7.8 Hz), 7.09 (br s, 1H, H_7). ^{13}C NMR (DMSO-d_6): 183.70 (C-3), 159.77 (C-2), 151.38 (C-7a), 149.86 (C-6), 138.87 (C-1′), 129.17 (C-phenyl), 129.12 (C-phenyl), 127.05 (C-4), 125.30 (C-phenyl), 121.33 (C-5), 116.81 (C-3a), 110.06 (C-7). MS *m/z*: 223.1.

3.2.10. 6-(4-Methoxyphenyl)isatin (8b). 24%, red solid. Mp 250 °C. IR (KBr): 3408, 2962, 1757, 1706, 1627, 1597, 1568, 1392, 1258, 1179, 1115, 1017, 828 and 800 cm^{-1}. ^1H NMR (DMSO-d_6): 7.68 (d, 2H, $H_{2'}$ and $H_{6'}$, J=8 Hz), 7.54 (d, 1H, H_4, J=7.9 Hz), 7.32 (d, 1H, H_5, J=7.9 Hz), 7.06 (d, 2H, $H_{3'}$ and $H_{5'}$, J=8 Hz,), 7.06 (br s, 1H, H_7), 3.81 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): 183.50 (C-3), 160.26 (C-4′), 159.97 (C-2), 151.52 (C-6), 149.57 (C-7a), 131.00 (C-1′), 128.43 (C-2′ and C-6′), 125.36 (C-4), 120.59 (C-5), 116.17 (C-3a), 114.63 (C-3′ and C-5′), 109.68 (C-7), 55.32 (OCH_3). MS *m/z*: 253.2. $C_{15}H_{11}NO_3$ (253.26); calcd: C, 71.14; H, 4.38; N, 5.53; found: C, 71.23; H, 4.40; N, 5.22.

3.2.11. 6-(3,4,5-Trimethoxyphenyl)isatin (8c). 24%, orange solid. Mp 236 °C. IR (KBr): 3398, 3304, 1750, 1730, 1625, 1577, 1489, 1436, 1411, 1343, 1252, 1161, 1120, 983 and 800 cm^{-1}. ^1H NMR (DMSO-d_6): 8.01 (s, 1H, NH), 7.67 (d, 1H, H_4 or H_5, J=8 Hz), 7.32 (d, 1H, H_4 or H_5,

$J=8$ Hz), 7.08 (br s, 1H, H_7), 6.79 (s, 2H, $H_{2'}$ and $H_{6'}$), 3.94 (s, 6H, OCH_3), 3.91 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): 183.62 (C-3), 159.85 (C-2), 153.24 (C-3′ and C-5′), 151.27 (C-4′), 150.05 (C-7a), 138.46 (C-6), 134.58 (C-1′), 125.12 (C-4), 121.50 (C-5), 116.62 (C-3a), 110.20 (C-7), 104.63 (C-2′ and C-6′), 60.08 (OCH_3), 56.04 (OCH_3). MS *m/z*: 313.0. $C_{17}H_{15}NO_5$ (313.31); calcd: C, 65.17; H, 4.83; N, 4.47; found: C, 65.03; H, 4.91; N, 4.52.

3.2.12. 6-(2-Furyl)isatin (8d). 66%, dark red solid. Mp 252 °C. IR (KBr): 3427, 2923, 1743, 1731, 1614, 1442, 1337, 1261, 1111, 1015 and 881 cm^{-1}. ^1H NMR (DMSO-d_6): 11.19 (s, 1H, NH), 7.90 (d, 1H, H_7, $J=2$ Hz), 7.54 (d, 1H, H_4, $J=8$ Hz), 7.40 (dd, 1H, H_5, $J=8$, 2 Hz), 7.28 (d, 1H, H_{fur}, $J=3.4$ Hz), 7.14 (s, 1H, H_{fur}), 6.69 (m, 1H, H_{fur}). ^{13}C NMR (DMSO-d_6): 183.03 (C-3), 159.87 (C-2), 151.80 (C-7a), 151.45 (C-1′), 145.25 (C-fur), 138.57 (C-6), 125.60 (C-4), 117.60 (C-5), 116.38 (C-3a), 112.91 (C-fur), 110.54 (C-fur), 105.92 (C-7). MS *m/z*: 213.1. $C_{12}H_7NO_3$ (213.19); calcd: C, 67.61; H, 3.31; N, 6.57; found: C, 67.28; H, 3.24; N, 6.51.

3.3. General procedure for the preparation of the arylanthranilic acids (5a–d, 7a–d and 9a–d) from arylisatins

To a stirred suspension of arylisatin **4**, **6** and **8** (4.5 mmol, 1 equiv) in 5% sodium hydroxide (10 mL) is slowly added 30% hydrogen peroxide (10 mL) dropwise. The reaction mixture is stirred at 50 °C for 30 min and then allowed to reach room temperature. For compounds **7a–d** and **9a–d**, the filtered solution is acidified to pH 4 with 1 N hydrochloric acid and the product is then collected by filtration. For the other compounds, the filtered solution is acidified to pH 3. The acidified aqueous layer is then extracted with AcOEt (2×10 mL) and the organic layer is dried ($MgSO_4$) and evaporated. The residue is crystallised from CH_2Cl_2/*n*-hexane.

3.3.1. 6-Phenylanthranilic acid (5a). 13%, beige solid. Mp 112 °C. IR (KBr): 3391, 2962, 1693, 1604, 1462, 1384, 1261, 1100, 1024 and 800 cm^{-1}. ^1H NMR (DMSO-d_6): 7.36–7.24 (m, 5H, H_{phenyl}), 7.14 (t, 1H, H_4, $J=7.8$ Hz), 6.73 (d, 1H, H_3 or H_5, $J=8$ Hz), 6.45 (d, 1H, H_3 or H_5, $J=7.5$ Hz). ^{13}C NMR (DMSO-d_6): 170.23 (COOH), 148.04 (C-2), 142.52 (C-1′), 130.61 (C-4), 129.36 (C-6), 128.56 (C-phenyl), 127.94 (C-phenyl), 127.85 (C-phenyl), 126.66 (C-5), 117.83 (C-3), 114.90 (C-1). MS *m/z*: 213.1. $C_{13}H_{11}NO_2$ (213.24); calcd: C, 73.23; H, 5.20; N, 6.57; found: C, 73.19, H, 5.06; N, 6.49.

3.3.2. 6-(4-Methoxyphenyl)anthranilic acid (5b). 20%, beige solid. Mp 128 °C. IR (KBr): 3470, 3360, 1686, 1605, 1578, 1514, 1456, 1428, 1305, 1262, 1170, 1106, 1027 and 773 cm^{-1}. ^1H NMR (DMSO-d_6): 7.18 (d, 2H, $H_{2'}$ and $H_{6'}$, $J=7.2$ Hz), 7.11 (t, 1H, H_4, $J=7.8$ Hz), 6.91 (d, 2H, $H_{3'}$ and $H_{5'}$, $J=7.2$ Hz), 6.69 (d, 1H, H_3 or H_5, $J=7.8$ Hz), 6.44 (d, 1H, H_3 or H_5, $J=7.8$ Hz), 3.75 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): 170.41 (COOH), 158.29 (C-4′), 147.83 (C-2), 141.68 (C-1′), 134.72 (C-4), 130.52 (C-6), 128.95 (C-2′ and C-6′), 117.73 (C-5), 115.22 (C-1), 114.44 (C-3), 113.45 (C-3′ and C-5′), 55.06 (OCH_3). MS *m/z*: 243.1. $C_{14}H_{13}NO_3$ (243.26); calcd: C, 69.12; H, 5.39; N, 5.76; found: C, 69.02; H, 5.31; N, 5.70.

3.3.3. 6-(3,4,5-Trimethoxyphenyl)anthranilic acid (5c). 14%, beige solid. Mp 110 °C. IR (KBr): 3378, 2935, 1692, 1583, 1462, 1346, 1239, 1125, 999 and 808 cm^{-1}. ^1H NMR (DMSO-d_6): 7.10 (t, 1H, H_4, $J=8$ Hz), 6.70 (d, 1H, H_3 or H_5, $J=8.5$ Hz), 6.55 (s, 2H, $H_{2'}$ and $H_{6'}$), 6.53 (d, 1H, H_3 or H_5, $J=7.8$ Hz), 3.75 (s, 6H, OCH_3), 3.65 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): 170.47 (COOH), 152.35 (C-3′ and C-5′), 147.30 (C-2), 137.98 (C-4′), 130.30 (C-4), 129.95 (C-1′), 121.80 (C-6), 121.03 (C-1), 117.51 (C-5), 114.63 (C-3), 105.41 (C-2′ and C-6′), 59.98 (OCH_3), 55.76 (OCH_3). MS *m/z*: 303.3. $C_{16}H_{17}NO_5$ (303.32); calcd: C, 63.36, H; 5.65; N, 4.62; found: C, 63.41; H, 5.58; N, 4.59.

3.3.4. 6-(2-Furyl)anthranilic acid (5d). 11%, beige solid. Mp 134 °C. IR (KBr): 3075, 2920, 1657, 1561, 1502, 1380, 1368, 1256, 1212, 1018 and 928 cm^{-1}. ^1H NMR (DMSO-d_6): 7.66 (s, 1H, H_{fur}), 7.13 (t, 1H, H_4, $J=8$ Hz), 6.72 (d, 1H, H_3 or H_5, $J=7.5$ Hz), 6.71 (d, 1H, H_3 or H_5, $J=8$ Hz), 6.55 (d, 1H, H_{fur}, $J=3.2$ Hz), 6.51 (m, 1H, H_{fur}). ^{13}C NMR (DMSO-d_6): 170.11 (COOH), 153.43 (C-2), 147.17 (C-1′), 142.59 (C-fur), 130.44 (C-4), 129.76 (C-6), 115.52 (C-5), 115.46 (C-fur), 114.48 (C-1), 111.52 (C-3), 106.88 (C-fur). MS *m/z*: 203.1. $C_{11}H_9N0_3$ (203.20); calcd: C, 65.02; H, 4.46; N, 6.89; found: C, 64.89; H, 4.51; N, 6.94.

3.3.5. 5-Phenylanthranilic acid (7a). 47%, beige solid. Mp 206 °C. (Lit.[14] 203–205 °C, lit.[15] 200–202 °C). IR (KBr): 3438, 3393, 3031, 1665, 1622, 1584, 1482, 1421, 1301, 1234, 1170, 897, 824 and 759 cm^{-1}. ^1H NMR (DMSO-d_6): 7.96 (br s, 1H, H_6), 7.56 (m, 3H, H_{phenyl}), 7.38 (m, 2H, H_{phenyl}), 7.25 (d, 1H, H_3 or H_4, $J=7.3$ Hz), 6.83 (d, 1H, H_3 or H_4, $J=7.3$ Hz). ^{13}C NMR (DMSO-d_6): 169.95 (COOH), 151.38 (C-2), 140.23 (C-1′), 132.54 (C-6), 129.28 (C-phenyl), 129.25 (C-phenyl), 126.88 (C-5), 126.57 (C-4), 125.85 (C-phenyl), 117.53 (C-3), 110.27 (C-1). HRMS (EI^+) *m/z*: 213.0843 (M^+, 100, $C_{13}H_{11}NO_2$ required 213.0789).

3.3.6. 5-(4-Methoxyphenyl)anthranilic acid (7b). 54%, beige solid. Mp 250 °C. IR (KBr): 3492, 3391, 1683, 1624, 1584, 1555, 1489, 1414, 1233, 1165, 1024 and 812 cm^{-1}. ^1H NMR (DMSO-d_6): 11.07 (s, 2H, NH_2), 7.84 (dd, 1H, H_4, $J=8.2$, 1.8 Hz), 7.70 (d, 1H, H_6, $J=1.8$ Hz), 7.58 (d, 2H, $H_{2'}$ and $H_{6'}$, $J=8.5$ Hz), 6.99 (d, 2H, $H_{3'}$ and $H_{5'}$, $J=8.5$ Hz), 6.96 (d, 1H, H_3, $J=8.2$ Hz), 3.77 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): 169.53 (COOH), 157.94 (C-4′), 150.37 (C-2), 132.37 (C-5), 131.76 (C-1′), 128.20 (C-4), 126.50 (C-2′ and C-6′), 126.38 (C-6), 117.03 (C-7), 114.26 (C-3′ and C-5′), 109.92 (C-1), 55.08 (OCH_3). HRMS (EI^+) *m/z*: 243.0877 (M^+, 48.5, $C_{14}H_{13}NO_3$ required 243.0895).

3.3.7. 5-(3,4,5-Trimethoxyphenyl)anthranilic acid (7c). 70%, beige solid. Mp 220 °C. IR (KBr): 3468, 3356, 2945, 2833, 1682, 1626, 1584, 1493, 1430, 1242, 1129, 992 and 813 cm^{-1}. ^1H NMR (DMSO-d_6): 7.92 (d, 1H, H_6, $J=2.2$ Hz), 7.57 (dd, 1H, H_4, $J=8.5$, 2.2 Hz), 6.82 (d, 1H, H_3 $J=8.5$ Hz), 6.74 (s, 2H, $H_{2'}$ and $H_{6'}$), 3.82 (s, 6H, OCH_3), 3.65 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): 169.51 (COOH), 153.19 (C-3′ and C-5′), 150.79 (C-2), 136.38 (C-4′), 135.88 (C-1′), 132.39 (C-5), 128.76 (C-4), 126.88

(C-6), 116.93 (C-1), 109.80 (C-3), 103.12 (C-2′ and C-6′), 60.06 (OCH_3), 55.94 (OCH_3). HRMS (EI^+) *m/z*: 303.1116 (M^+, 100, $C_{16}H_{17}NO_5$ required 303.1106).

3.3.8. 5-(2-Furyl)anthranilic acid (7d). 79%, green solid. Mp 180 °C. IR (KBr): 3499, 3388, 2961, 1679, 1631, 1583, 1477, 1412, 1229, 1163, 1014 and 795 cm^{-1}. ^1H NMR (DMSO-d_6): 7.99 (d, 1H, H_6 $J=2.2$ Hz), 7.59 (s, 1H, H_{fur}), 7.56 (dd, 1H, H_4, $J=8.5$, 2.2 Hz), 6.79 (d, 1H, H_3, $J=$ 8.5 Hz,), 6.61 (d, 1H, H_{fur}, $J=3.4$ Hz), 6.48 (s, 1H, H_{fur}). ^{13}C NMR (DMSO-d_6): 169.25 (COOH), 153.30 (C-2), 150.85 (C-1′), 141.32 (C-fur), 129.50 (C-5), 126.03 (C-4), 117.67 (C-6), 116.95 (C-1), 111.74 (C-3), 109.48 (C-fur), 102.48 (C-fur). HRMS (EI^+) *m/z*: 203.0575 (M^+, 25.5, $C_{11}H_9NO_3$ required 203.0582).

3.3.9. 4-Phenylanthranilic acid (9a). 54%, white solid. Mp 234 °C. IR (KBr): 3493, 3383, 3028, 1670, 1621, 1591, 1543, 1415, 1312, 1259, 1224, 1115, 910, 859 and 758 cm^{-1}. ^1H NMR (DMSO-d_6): 7.75 (d, 1H, H_6, $J=7.6$ Hz), 7.59 (d, 2H, $H_{2'}$ and $H_{6'}$, $J=6.8$ Hz), 7.45–7.38 (m, 3H, $H_{3'}$, $H_{4'}$ and $H_{5'}$), 7.00 (br s, 1H, H_3), 6.79 (d, 1H, H_5, $J=7.6$ Hz). ^{13}C NMR (DMSO-d_6): 169.41 (COOH), 151.71 (C-2), 145.11 (C-1′), 139.65 (C-4), 131.89 (C-6), 128.88 (C-2′ and C-6′), 128.04 (C-4′), 126.59 (C-3′ and C-5′), 114.02 (C-5), 113.38 (C-3), 109.00 (C-1). HRMS (EI^+) *m/z*: 213.0844 (M^+, 17.0, $C_{13}H_{11}NO_2$ required 213.0789).

3.3.10. 4-(4-Methoxyphenyl)anthranilic acid (9b). 32%, beige solid. Mp 258 °C. IR (KBr): 3481, 3376, 1668, 1604, 1523, 1418, 1251, 1192, 1118, 1033 and 778 cm^{-1}. ^1H NMR (DMSO-d_6): 10.21 (s, 2H, NH_2), 7.71 (d, 1H, H_5 or H_6, $J=8.3$ Hz), 7.54 (d, 2H, $H_{2'}$ and $H_{6'}$, $J=7.3$ Hz), 7.01 (d, 2H, $H_{3'}$ and $H_{5'}$, $J=7.3$ Hz), 6.96 (br s, 1H, H_3), 6.75 (d, 1H, H_5 or H_6, $J=8.3$ Hz), 3.78 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): 169.36 (COOH), 159.37 (C-4′), 151.76 (C-2), 144.79 (C-4), 131,84 (C-1′), 131.81 (C-6), 127.75 (C-2′ and C-6′), 114.33 (C-3′ and C-5′), 113.31 (C-5), 113.05 (C-3), 108.22 (C-1), 55.19 (OCH_3). HRMS (EI^+) *m/z*: 243.0916 (M^+, 100, $C_{14}H_{13}NO_3$ required 243.0895).

3.3.11. 4-(3,4,5-Trimethoxyphenyl)anthranilic acid (9c). 30%, beige solid. Mp 188 °C. IR (KBr): 3446, 3362, 2937, 1674, 1588, 1516, 1455, 1403, 1305, 1231 and 1132 cm^{-1}. ^1H NMR (DMSO-d_6): 7.73 (d, 1H, H_6, $J=8$ Hz), 7.01 (d, 1H, H_3, $J=1.5$ Hz), 6.85 (s, 2H, $H_{2'}$ and $H_{6'}$), 6.81 (dd, 1H, H_5, $J=8$, 1.5 Hz), 3.83 (s, 6H, OCH_3), 3.68 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6): 169.25 (COOH), 153.12 (C-2), 151.62 (C-3′ and C-5′), 145.19 (C-4′), 137.74 (C-4), 135.41 (C-1′), 131.68 (C-6), 114.03 (C-5), 113.57 (C-3), 108.87 (C-1), 104.17 (C-2′ and C-6′), 59.73 (OCH_3), 55.96 (OCH_3). HRMS (EI^+) *m/z*: 303.1062 (M^+, 23.6, $C_{16}H_{17}NO_5$ required 303.1106).

3.3.12. 4-(2-Furyl)anthranilic acid (9d). 52%, green solid. Mp 204 °C. IR (KBr): 3486, 3383, 1668, 1623, 1595, 1541, 1483, 1418, 1320, 1264, 1233, 1215, 1167, 1011, 868 and 777 cm^{-1}. ^1H NMR (DMSO-d_6): 10.20 (s, 2H, NH_2), 7.75 (d, 1H, H_{fur}, $J=1.2$ Hz), 7.70 (d, 1H, H_6, $J=8.3$ Hz), 7.07 (d, 1H, H_3, $J=1.7$ Hz), 6.91 (d, 1H, H_{fur}, $J=3.4$ Hz), 6.84 (dd, 1H, H_5, $J=8.3$, 1.7 Hz), 6.60 (m, 1H, H_{fur}). ^{13}C NMR (DMSO-d_6): 169.16 (COOH), 152.47 (C-2), 151.72 (C-1′), 143.55 (C-fur), 134.61 (C-4), 131.86 (C-6), 112.17 (C-5), 110.32 (C-fur), 110.17 (C-3), 108.51 (C-1), 107.50 (C-fur). HRMS (EI^+) *m/z*: 203.0520 (M^+, 57.9, $C_{11}H_9NO_3$ required 203.0582).

3.4. General procedure for the one-pot preparation of the anthranilic acids (7a–b, 9a–b)from iodoisatins

To a solution of iodoisatin **3b–c** (1 equiv) in DME (50 mL) under argon was added arylboronic acid (1.2 equiv) followed by the addition of $Pd(PPh_3)_4$ (0.05 equiv) and sodium hydrogen carbonate (2 equiv) in H_2O (10 mL). The reaction mixture was refluxed for 12 h. The solvent was then evaporated under vacuum and the residue was taken up with sodium hydroxide (10 mL, 5%). Impurities were then extracted with CH_2Cl_2 and hydrogen peroxide (10 mL, 30%) were then added to the aqueous layer. The mixture was stirred at 50 °C for 30 min and then allowed to reach room temperature. The filtered solution is acidified to pH 4 with 1 N hydrochloric acid and the solid product is collected by filtration.

3.4.1. 5-Phenylanthranilic acid (7a). From **3b**: (62%).

3.4.2. 5-(4-Methoxyphenyl)anthranilic acid (7b). From **3b**: (67%).

3.4.3. 4-Phenylanthranilic acid (9a). From **3c**: (42%).

3.4.4. 4-(4-Methoxyphenyl)anthranilic acid (9b). From **3c**: (13%).

Acknowledgements

We thank Mr. Y. Dat for high resolution mass spectrometry measurements and Eloisa Pardo for kindness during this work.

References and notes

1. Quan, M. L.; Wityak, J.; Dominguez, C.; Duncia, J. V.; Kettner, C. A.; Ellis, C. D.; Liauw, A. Y.; Park, J. M.; Santella, J. B.; Knabb, R. M.; Thoolen, M. J.; Weber, P. C.; Wexler, R. R. *Biorg. Med. Chem. Lett.* **1997**, *7*, 1595.
2. Smet, M.; Schacht, E.; Dehaen, W. *Angew. Chem., Int. Ed.* **2002**, *41*, 4547.
3. Martinez, F.; Naarman, H. *Synth. Met.* **1990**, *39*, 195.
4. Lisowski, V.; Robba, M.; Rault, S. *J. Org. Chem.* **2000**, *65*, 4193.
5. Lisowski, V.; Léonce, S.; Kraus-Berthier, L.; Sapkova-de Oliveira Santos, J.; Atassi, G.; Calgnard, D.-H.; Renard, P.; Rault, S. *J. Med. Chem.* **2004**, *47*, 1448.
6. Le Foulon, F. X.; Braud, E.; Fabis, F.; Lancelot, J. C.; Rault, S. *Tetrahedron* **2003**, *59*, 10051.
7. Le Foulon, F. X.; Braud, E.; Fabis, F.; Lancelot, J. C.; Rault, S. *J. Comb. Chem.* **2005**, *7*, 253.
8. (a) Marvel, C. S.; Hiers, G. S. *Organic syntheses*; Collect. Vol. I; Wiley: New York, 1932; p 327. (b) Newman, M. S.; Logue, M. W. *J. Org. Chem.* **1971**, *36*, 1398. (c) O'Sullivan, D. G.; Sadler, P. W. *J. Chem. Soc.* **1956**, 2202–2207. (d) Carmellino,

M. L.; Pagani, G.; Pregnolato, M.; Terreni, M.; Pastoni, F. *Eur. J. Med. Chem.* **1994**, *29*, 143.
9. Sadler, P. W. *J. Org. Chem.* **1956**, *21*, 169.
10. (a) Miyaura, N.; Suzuki, A. *Chem. Commun.* **1979**, 866. (b) Suzuki, A. *Pure Appl. Chem.* **1991**, *63*, 419. (c) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263.
11. Baker, B. R.; Shaub, R. E.; Joseph, J. P.; Mc Evoy, F. J.; Williams, J. H. *J. Org. Chem.* **1952**, *17*, 141.
12. Valentine, D.; Tilley, J. W.; LeMahieu, R. A. *J. Org. Chem.* **1981**, *46*, 4614.
13. Hewawasam, P.; Meanwell, N. A.; Gribkoff, V. K. U.S. Patent 5, 565, 483, 1996.
14. Barnett, M. D.; Daub, G. H.; Hayes, F. N.; Ott, D. G. *J. Am. Chem. Soc.* **1959**, *81*, 4583.
15. Kranzlein, G.; Ochwat, P.; Moldaenke, K. U.S. Patent 2, 012, 569, 1935.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 61 (2005) 6088–6096
Tetrahedron

One-pot three-component reaction of fluoroalkanesulfonyl azide, vinyl ether and aldehyde: the formation of polysubstituted fluorinated oxazolidines

Ping He[a] and Shizheng Zhu[a,b,*]

[a]*Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China*
[b]*College of Chemical Environment, South China Normal University, Guangzhou 510631, China*

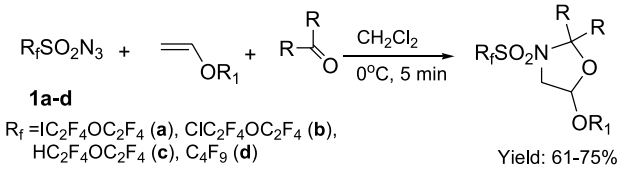
Received 28 January 2005; revised 6 April 2005; accepted 8 April 2005

Available online 13 May 2005

Abstract—Efficient and diastereoselective synthesis of highly substituted fluorinated oxazolidines was achieved via a one-pot three-component reaction of fluoroalkanesulfonyl azides **1**, vinyl ether **2** and various aldehydes at 0 °C within 10 min in moderate to good diastereoselectivities (*syn*/*anti*). A competing process could be involved in the initial step and an unstable fluorinated aziridine was postulated as the intermediate for these reactions. Additionally, rational transition states were also proposed to elucidate the diastereoselectivities. This synthetic method provides a convenient and expeditious access to *N*-per(poly)fluoroalkanesulfonyl oxazolidines.

1. Introduction

In recent years, fluoro-compounds have received a great deal of interest. Introduction of the fluorine atom can confer unusual chemical reactivity to organic molecules and often exert profound effects on the physical properties of biologically active compounds.[1] The importance of organofluorine compounds is reflected in the ever-increasing research activity in the field, for example, their stereoselective synthesis.[2] So the development of practical methods for the preparation of organofluorine compounds continues to challenge and attract synthetic chemists. Meanwhile, the increasing environmental consciousness of the chemical community has led to the search for more efficient and environmentally friendly methods for chemical syntheses.[3] Among them, the multi-component reactions (MCRs), by virtue of their converge, productivity, facile execution and generally high yields of products, have attracted much attention from the vantage point of combinatorial chemistry.[4] Oxazolidines, usually obtained from amino acids, have been extensive used as chiral nonracemic ligands in asymmetric catalysis.[5] Thus, diastereoselective synthesis of fluorine-containing oxazolidines is of particular importance. Semenov et al.[6] once reported their studies on the reactions of arylsulfonyl azides, vinyl ethers and carbonyl compounds for the synthesis of oxazolidines but in low yield. Due to the strong electron-withdrawing property of the R_fSO_2 group, per(poly)fluoroalkanesulfonyl azides $R_fSO_2N_3$ **1** are more reactive than other nonfluorinated organic azides. However, their reactions are studied rarely. Recently, we reported a facile one-step method for the synthesis of trisubstituted oxazolidines in moderate yields by three-component reaction of ketones, vinyl ethers and fluoroalkanesulfonyl azides (Scheme 1).[7] Thus, as a continuation of our investigation on fluoroalkanesulfonyl azides **1**,[8] we report here a convenient and versatile method for the diastereoselective synthesis of highly substituted fluorinated oxazolidines by a one-pot three-component reaction of fluoroalkanesulfonyl azides, vinyl ethers and aldehydes.



Scheme 1.

Keywords: Multi-component reactions (MCRs); Fluoroalkanesulfonyl azide; Aldehyde; Diastereoselective; Oxazolidine.
* Corresponding author. Tel.: +86 21 54925184; fax: +86 21 64166128; e-mail: zhusz@mail.sioc.ac.cn

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.04.020

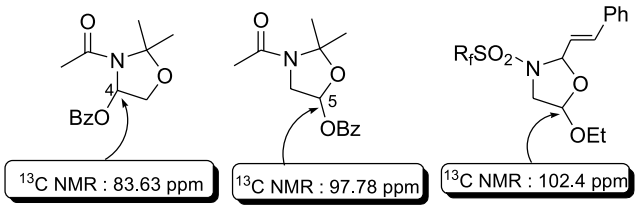


Figure 1. Determination of the ethoxyl position in the ring of oxazolidine **4ad**.

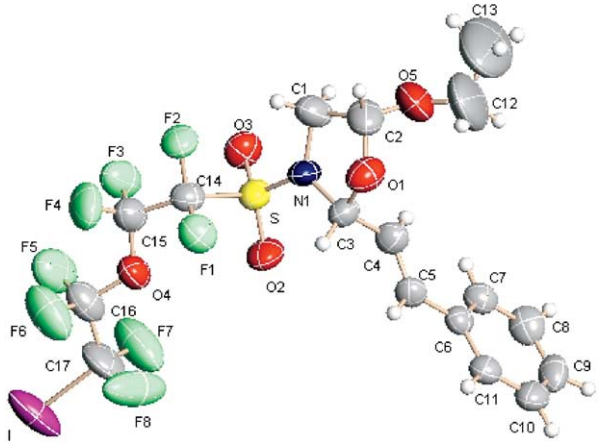
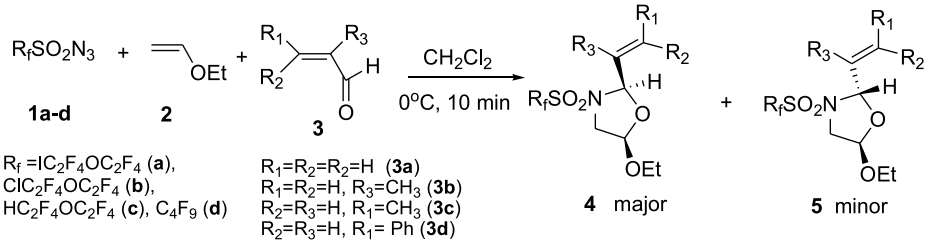


Figure 2. The molecular structure of compound **4ad**.

2. Results and discussion

The reaction of fluoroalkanesulfonyl azide **1a** with equimolar of vinyl ether **2a** and acrolein **3a** in anhydrous CH_2Cl_2 at 0 °C was first investigated. An immediate nitrogen gas release was observed. TLC analysis showed the consumption of azide **1a** within 5 min and the formation of three products. They were separated and purified by column chromatography using petroleum ether/diethyl ether (100:1) as eluent. According to their ^{1}H NMR spectra, one product obtained in 25% yield with the lowest R_f value was identified as 1-fluoroalkanesulfonyl 1,2,3-triazolines, same product from the reaction of **1a** and **2a**.[8d] The other two products, obtained in 47 and 15% yields, respectively, as colorless oil, were identified as trisubstituted oxazolidines. According to the spectra data, we found **4** and **5** were isomeric compounds and the relative correlation between the alkoxyl and vinyl groups was difficult to assign. To solve this problem, this reaction protocol was applied on *trans*-cinnamaldehyde **3d** and two expected solid products **4ad** and **5ad** were obtained. Under the similar reaction conditions, the total yields of the expected oxazolidine was increased to 80%. According to our previous results,[9] we noticed that azides **1** added to electron-rich alkenes in such a fashion which the heteroatom (O, N) in electron-rich alkenes and azide nitrogen were bonded to the same carbon atom in the product. So firstly we deduced that the oxazolidine was 2,3,4-trisubstituted. Later, by comparing with similar oxazolidine, we found that this was incorrect. It was well documented that when substitute group was in 5-position of the oxazolidine ring, the signal observed in ^{13}C NMR spectrum generally appears at lower field than that in the 4-position analogue.[9] To determine the concrete position of the ethoxyl group, ^{13}C NMR spectrum of **4ad** was further investigated according to the literature. The chemical shift observed at δ 102.4 in ^{13}C NMR spectrum of **4ad** indicated that the ethoxyl group should be attached to the 5-C of the oxazolidine ring (Fig. 1).

A comparison with the reaction results of arylsulfonyl azides[6] indicated that the product should be characterized as 5-ethoxy-2-styryl-3-fluoroalkanesulfonyl-oxazolidine **4ad**, rather than the postulated 4-position substituted isomers.

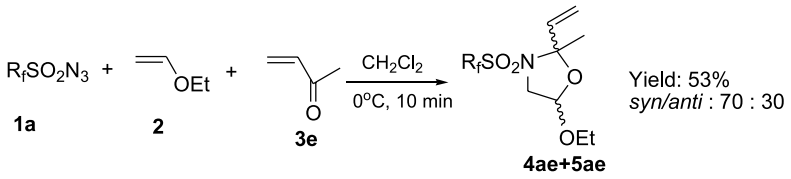


Scheme 2.

Table 1. Reaction results of fluoroalkanesulfonyl azides, vinyl ethers and α,β-unsaturated aldehydes[a]

Entry	Azides	Unsaturated aldehydes	Products and yields (%)[b]		*syn*:*anti*[c]
1	**1a**	**3a**	**4aa** (47)	**5aa** (15)	76:24
2	**1a**	**3b**	**4ab** (43)	**5ab** (11)	80:20
3	**1a**	**3c**	**4ac** (27)	**5ac** (13)	68:32
4	**1a**	**3d**	**4ad** (54)	**5ad** (25)	68:32
5	**1b**	**3a**	**4ba** (42)	**5ba** (9)	82:18
6	**1b**	**3b**	**4bb** (43)	**5bb** (18)	70:30
7	**1b**	**3c**	**4bc** (23)	**5bc** (9)	72:28
8	**1c**	**3a**	**4ca** (26)	**5ca** (9)	74:26
9	**1c**	**3d**	**4cd** (31)	**5cd** (19)	62:38
10	**1d**	**3d**	**4dd** (61)	**5dd** (20)	75:25

[a] **1**:**2**:**3**=1:1:1.
[b] Isolated yields based on **1**.
[c] Due to the difficult differentiation of their corresponding spectra of ^{1}H NMR (overlapped) and ^{19}F NMR (broad peaks), the crude *syn*: *anti* was determined by isolated yields of **4** and **5**.



Scheme 3.

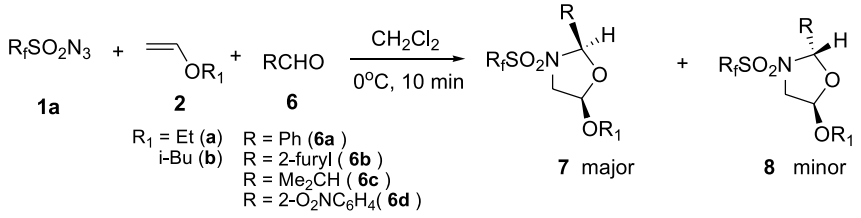
Additionally, to assign the relative configuration of the two oxazolidines, the major product **4ad** was further studied by a single crystal X-ray diffraction analysis. The molecular structure was shown in Figure 2. A *syn* correlation between ethoxyl (EtO) and styryl (*trans*-PhCH═CH–) at the C-2 and the C-3 was observed. The bulky fluoroalkanesulfonyl group R_fSO_2 was not in the same plane with the ethoxyl and styryl groups.

The reactions of other azides with vinyl ether and various α,β-unsaturated aldehydes also could proceed smoothly, the expected *syn* and *anti* oxazolidines were obtained. All the results were summarized in Table 1 (Scheme 2).

The MCRs were found to be general and efficient. During the reaction process, the corresponding 1,2,3-triazolines were obtained inevitably. Due to the difficult differentiation from the corresponding spectra of ^{1}H NMR (overlapped) and ^{19}F NMR (broad peaks), the diastereoselectivities were determined crudely by the isolated yields of the corresponding oxazolidines **4** and **5**. Moderate to good diastereoselectivities (*syn*: *anti*) were obtained. It was found that the substituent (R_1) in **3** had a dramatic impact on the yields. In the cases of crotonaldehyde **3c** decreased to 23% (Table 1, entries 3, 7). In addition, the use of methyl vinyl ketone **3e** as the substrate to the MCRs was also found efficiently and corresponding trisubstituted fluorinated oxazolidine was obtained in moderate yield (Scheme 3). However, different from the α,β-unsaturated aldehydes, the two oxazolidines **4ae** and **5ae** could not be separated by flash chromatography and their diastereoselectivity was determined by ^{1}H NMR spectrum.

To elaborate the utility of this method and introduce more useful functional groups into the oxazolidine ring, we further investigated the reaction of other aldehydes, including aromatic aldehydes, aliphatic aldehydes and hetero-aromatic aldehydes. Under the same reaction conditions, the MCRs of fluoroalkanesulfonyl azides **1**, vinyl ether and aldehydes also proceeded smoothly. Comparing the similar peak shape observed in ^{1}H NMR with the above-identified products **4** and **5**, the relative molecular configurations of **7** and **8** were attributed to *syn* and *anti*, respectively. Some typical results were shown in Table 2 (Scheme 4).

As can be seen from Table 2, the substituents of the aldehydes affected the yields of the products. 2-nitrobenzaldehyde gave the lowest yield (Table 2, entry 5). In most cases, the minor stereoisomers **8** could not be isolated due to the small amount except the 2-furylaldehydes (Table 2, entry 3). The diastereoselectivity (*syn*: *anti*), crudely determined by the isolated yields of **7ab** and **8ab**, was 76:24. To the aromatic aldehydes, due to the small amount (<5%) of the *anti*-**8**, the good disastereoselectivities (*syn*: *anti*) were always obtained at least 85:15. However, when treated equimolar amount of the three reactants, TLC showed the aromatic aldehydes could not be converted completely upon the consumption of azides **1**, which added more difficulties in the purification

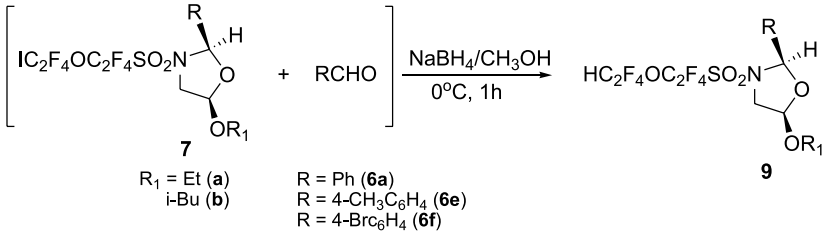


Scheme 4.

Table 2. Yields of oxazolidines from the reaction of **1a**, **2** and aldehydes[a]

Entry	2	R in 6[b]	Products and yields (%) [c]	
1	**2a**	R=Ph (**6a**)	**7aa** (60)	**8aa** (−)[d]
2	**2b**	R=Ph (**6a**)	**7ba** (58)	**8ba** (−)[d]
3	**2a**	R=2-furyl (**6b**)	**7ab** (56)	**8ab** (18)
4	**2a**	R=Me_2CH (**6c**)	**7ac** (54)	**8ac** (−)[d]
5	**2a**	R=2-$O_2NC_6H_4$ (**6d**)	**7ad** (26)	**8ad** (−)[d]

[a] **1**:**2**:**6**=1:1:1.
[b] Aromtic aldehydes **6a**, **6d** were not consumed completely.
[c] Isolated yields based on **1**.
[d] The *anti*-**8** could not be isolated successfully due to its small amount (<5%).



Scheme 5.

Table 3. Reaction results of the formation of **9** from the mixture system of **6** and **7**

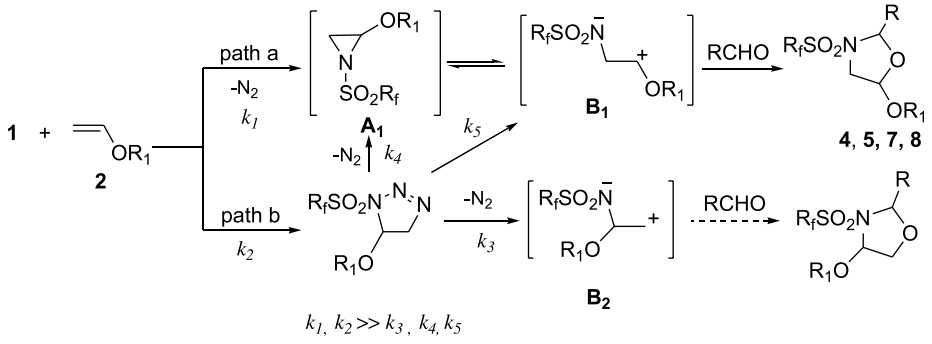
Entry	**6**+**7**	Product	Yields[a]
1	**6a**+**7ba**	**9ba**	50
2	**6e**+**7ae**	**9ae**	37
3	**6f**+**7af**	**9af**	47

[a] The yields are calculated based on azides **1**.

due to the similar polarities of aldehyde and **7** (Table 2, entry 1, 2, 5). To remove the unreacted aromatic aldehydes, further chemical transformation was tried. To an anhydrous methanol solution was added the mixture of unseparated **7** and the remained aromatic aldehyde, sodium borohydride (~5.0 equiv) in turn at 0 °C. A total consumption of aldehydes and the formation of product **9** were observed. According to the spectra data and elemental analysis, the product **9** was determined as *syn* 2-aryl-5-ethoxy-3-fluoroalkanesulfonyl]-oxazolidine (Scheme 5). By this way, a selective approach to product **9**, which also could be obtained by the MCRs of the corresponding fluoroalkanesulfonyl azide **1c**, was achieved. The reaction results of the formation of **9** from the mixture system of **6** and inseparated **7** were shown in Table 3. It was noteworthy that in the case of 4-nitrobenzene the corresponding **9** could not be separated successfully by chromatography method due to the too closer polarities of the former **7** and 1,2,3-triazoline resulted from the reaction of **1** and **2**.

MCRs comparing with the competing reaction of **1** and **2**. We proposed that products (**4**, **5**, **7**, **8**) should be formed via the intermediate $\mathbf{A_1}$ or zwitter ionic $\mathbf{B_1}$ (path a), though a reversible equilibrium process might exist. Due to the relative stability of the competing products triazolines, which could not release N_2 gas immediately under the same conditions, so the correlation of the reaction equilibrium constants during the process is k_1, $k_2 \gg k_3$, k_4, k_5. In addition, due to the p–π conjugated action in the structure of $\mathbf{B_1}$,[10] meanwhile $\mathbf{B_1}$ is one of the secondary carbonium, so $\mathbf{B_1}$ is more stable than $\mathbf{B_2}$, that is, the formation of $\mathbf{B_1}$ is easier than the other zwitterionic $\mathbf{B_2}$. Thus the isomers in 4-position could not be obtained (path b). To rationalize this proposal, the further transformation of triazolines was studied. We found that no reaction occurred when mixing equimolar of triazoline and acrolein under the same reaction condition, which indicated the competing products triazolines were not the reaction intermediate for the formation of oxazolidine (**4**, **5**, **7**, **8**).

Due to the steric effect between fluoroalkanesulfonyl groups and the substituents of aldehyde (Fig. 3), the following reaction transition state **II** has lower energy level than the transition state **I**. Thus, the reaction followed the reaction pathway through the predominant transition state **II** to disastereoselectively give the corresponding *syn*-oxazolidine **4** or **7** as major products. Due to the differences among the alkyl, aryl, heteroaryl and vinyl groups, various



Scheme 6.

Based on the above results and similar mechanism reported by Semenov et al.,[6] a possible reaction pathway for the formation of the oxazolidine (**4**, **5**, **7**, **8**) was proposed (Scheme 6). A competing reaction between fluoroalkanesulfonyl azides **1** and vinyl ethers **2** should be involved during the initial process. For example, in the case of aromatic aldehydes, the aldehydes could not be consumed completely which might be attributed to the slow process of

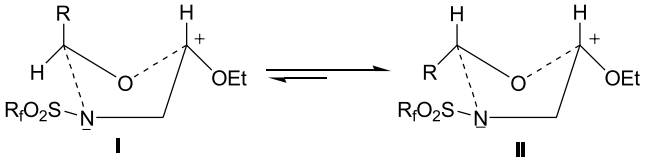


Figure 3.

disatereoselectivities (*syn*/*anti*) were attributed to the equilibrium between the transition states **I** and **II**. Therefore, to the relatively bulkier aryl groups, the higher disastereoselectivies were always obtained than that of alkyl, heteroaryl and vinyl groups, which may result in the rotation of the group and quick equilibrium establishment between **I** and **II**.

3. Conclusion

In summary, we have demonstrated a concise and efficient synthetic protocol for the synthesis of fluorinated 2,3,5-trisubstituted oxazolidines by a one-pot three-component reaction of fluoroalkanesulfonyl azides, vinyl ethers and aldehydes under mild conditions with moderate to good disastereoselectivities. In all cases, the *syn* 2,5-disubstitutued fluorinated oxazolidines were obtained as major products. Possible mechanism for the formation of oxazolidine and transition state to rationalize the diastereoselectivities were proposed. Further chemical transformations are under investigation in our group.

4. Experimental

Melting points were measured in Temp-Melt apparatus and were uncorrected. ^{1}H, and ^{19}F NMR spectra were recorded in $CDCl_3$ on Bruker AM-300 instruments with Me_4Si and $CFCl_3$ (with upfield negative) as the internal and external standards, respectively. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Lower resolution mass spectra were obtained on a Finnigan MAT-8430 instrument using the electron impact ionization technique (70 eV). Elemental analyses were performed in Elementar Vario EL III by this Institute. X-ray diffraction crystal structure analysis was obtained on Bruker P4 instrument. All reactions as well as column chromatography were monitored routinely with the aid of TLC or ^{19}F NMR spectroscopy. All aldehydes were redistilled or recrystallized prior to use. All solvents were purified before use. Fluoroalkanesulfonyl azides **1** were prepared according to literature.[11]

4.1. General procedure for the synthesis of 2,3,5-trisubstituted fluorinated oxazolidines from α,β-unsaturated aldehydes

To a 10 mL round-bottom flask containing vinyl ether **2** (2.0 equiv) and acrolein **3a** (2.0 equiv) in 2 mL CH_2Cl_2 was added slowly fluoroalkanesulfonyl azides **1a** (2.0 equiv) at 0 °C within 2 min. The reaction was finished within 5 min., according to TLC analysis. Then the solvent was evaporated under reduced pressure and the residue was chromatographed on a silica column using petroleum ether/diethyl ether (100:1) as eluant to give two colorless products **4aa** (47%) and **5aa** (15%), respectively.

4.1.1. *syn*-5-Ethoxy-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-2-iodo-ethoxy)-ethanesulfonyl]-2-vinyl-oxazolidine (4aa). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.04–5.93 (1H, m), 5.79 (1H, d, J=7.2 Hz), 5.43 (1H, d, J=17.7 Hz), 5.38 (1H, d, J=3.0 Hz), 5.32 (1H, d, J=10.5 Hz), 4.03 (1H, dd, J=5.4, 11.1 Hz), 3.82 (1H, dq, J=7.2, 9.3 Hz), 3.60–3.47 (2H, m), 1.21 (1H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.6 (CF_2, t, J=6.0 Hz), −82.4 (CF_2, s), −86.1 (CF_2, m), −115.7 (CF_2, br). IR (KBr) cm^{-1}: 2982, 2934, 1399, 1294, 1205, 1148, 1094, 915. MS (70 eV, EI) *m*/*z* (%): 522 ($M^+-C_2H_3$, 8), 504 (M^+−EtO, 7), 227 ($IC_2F_4^+$, 5), 177 (ICF_2^+, 3), 68 ($M^+-R_fSO_2NH-C_2H_5OCH_2$, 100), 41 ($C_3H_5^+$, 45). Anal. Calcd for $C_{11}H_{12}F_8INO_5S$: C, 24.06; H, 2.20; N, 2.55%. Found: C, 24.33; H, 2.08; N, 2.95%.

4.1.2. *anti*-5-Ethoxy-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-2-iodo-ethoxy)-ethanesulfonyl]-2-vinyl-oxazolidine (5aa). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.87–5.76 (1H, m), 5.73 (1H, d, J=6.6 Hz), 5.55 (1H, d, J=17.1 Hz), 5.45 (1H, d, J=10.2 Hz), 5.35 (1H, d, J=3.9 Hz), 3.90–3.76 (2H, m), 3.61–3.51 (2H, m), 1.23 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.4 (CF_2, t, J=6.0 Hz), −82.2 (CF_2, m), −86.0 (CF_2, m), −116.4 (CF_2, br). IR (KBr) cm^{-1}: 2982, 1396, 1294, 1201, 1151, 1038, 915. MS (70 eV, EI) *m*/*z* (%): 522 ($M^+-C_2H_3$, 3), 504 (M^+−EtO, 8), 227 ($IC_2F_4^+$, 4), 177 (ICF_2^+, 3), 68 ($M^+-R_fSO_2NH-C_2H_5OCH_2$, 100), 41 ($C_3H_5^+$, 39). Anal. Calcd for $C_{11}H_{12}F_8INO_5S$: C, 24.06; H, 2.20; N, 2.55%. Found: C, 24.36; H, 2.25; N, 2.78%.

4.1.3. *syn*-5-Ethoxy-2-isopropenyl-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-2-iodo-ethoxy)-ethanesulfonyl]-oxazolidine (4ab). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.78 (1H, s), 5.37 (1H, t, J=5.3 Hz), 5.26 (1H, s), 5.09 (1H, s), 4.15 (1H, dd, J=5.4, 12 Hz), 3.87 (1H, dq, J=7.2, 9.6 Hz), 3.60 (1H, dq, J=7.2, 9.6 Hz), 3.42 (1H, dd, J=4.8, 12 Hz), 1.82 (3H, s), 1.23 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ−65.2 (CF_2, t, J=7.3 Hz), −82.1 (CF_2, s), −85.8 (CF_2, m), −115.2 (CF_2, br). IR (KBr) cm^{-1}: 2982, 2931, 1402, 1293, 1204, 1147, 1093, 915. MS (70 eV, EI) *m*/*z* (%): 522 ($M^+-C_3H_5$, 80), 494 ($M^+-C_3H_5$−Et, 7), 227 (11), 156 ($M^+-R_fSO_2$, 29), 82 ($M^+-R_fSO_2NH-C_2H_5OCH_2$, 100), 41 ($C_3H_5^+$, 42). Anal. Calcd for $C_{12}H_{14}F_8INO_5S$: C, 25.59; H, 2.51; N, 2.49%. Found: C, 25.87; H, 2.68; N, 2.80%.

4.1.4. *anti*-5-Ethoxy-2-isopropenyl-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-2-iodo-ethoxy)-ethanesulfonyl]-oxazolidine (5ab). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.75 (1H, s), 5.37 (1H, d, J=3.6 Hz), 5.28 (1H, s), 5.18 (1H, s), 3.95 (1H, d, J=10.5 Hz), 3.81 (1H, dq, J=7.2, 9.6 Hz), 3.62–3.52 (2H, m), 1.73 (3H, s), 1.24 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.1 (CF_2, t, J=6.0 Hz), −82.0 (CF_2, m), −85.7 (CF_2, m), −116.6 (CF_2, br). IR (KBr) cm^{-1}: 2982, 2926, 1402, 1293, 1204, 1147, 1093, 915. MS (70 eV, EI) *m*/*z* (%): 522 ($M^+-C_3H_5$, 40), 494 ($M^+-C_3H_5$–Et, 7), 227 ($IC_2F_4^+$, 5), 156 ($M^+-R_fSO_2$, 2), 82 ($M^+-R_fSO_2NH-C_2H_5OCH_2$, 100), 41 ($C_3H_5^+$, 27). Anal. Calcd for $C_{12}H_{14}F_8INO_5S$: C, 25.59; H, 2.51; N, 2.49%. Found: C, 25.82; H, 2.54; N, 2.46%.

4.1.5. *syn*-5-Ethoxy-2-propenyl-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-2-iodo-ethoxy)-ethanesulfonyl]-oxazolidine (4ac). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.89 (1H, dq, J=6.9, 15 Hz), 5.78 (1H, d, J=7.8 Hz), 5.66 (1H, dd, J=7.5, 15 Hz), 5.38 (1H, dd, J=3.3, 5.1 Hz), 4.02

(1H, dd, J=5.4, 10.8 Hz), 3.84 (1H, dq, J=7.2, 9.9 Hz), 3.61–3.49 (2H, m), 1.75 (3H, dd, J=6.9, 1.5 Hz), 1.24 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.1 (CF_2, t, J=6.0 Hz), −82.1 (CF_2, s), −85.7 (CF_2, m), −115.3 (CF_2, br). IR (KBr) cm^{-1}: 2980, 2925, 1397, 1294, 1203, 1148, 1094, 915. MS (70 eV, EI) m/z (%): 518 (M^+−OEt, 20), 227 (3), 156 (M^+−R_fSO_2, 20), 82 (M^+−R_fSO_2NH–$C_2H_5OCH_2$, 100). Anal. Calcd for $C_{12}H_{14}F_8INO_5S$: C, 25.59; H, 2.51; N, 2.49%. Found: C, 25.89; H, 2.51; N, 2.51%.

4.1.6. *anti*-5-Ethoxy-2-propenyl-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-2-iodo-ethoxy)-ethanesulfonyl]-oxazolidine (5ac). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.01 (1H, dq, J=6.9, 15 Hz), 5.69 (1H, d, J=7.8 Hz), 5.45 (1H, dd, J=7.5, 15 Hz), 5.32 (1H, d, J=3.9 Hz), 3.88–3.75 (2H, m), 3.60–3.50 (2H, m), 1.78 (3H, dd, J=6.9, 1.5 Hz), 1.23 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.1 (CF_2, t, J=6.3 Hz), −82.0 (CF_2, s), −85.7 (CF_2, m), −115.8 (CF_2, br). IR (KBr) cm^{-1}: 2982, 2927, 1396, 1294, 1200, 1152, 1037, 915. MS (70 eV, EI) m/z (%): 518 (M^+−OEt, 25), 227 ($IC_2F_4^+$, 3), 156 (M^+−R_fSO_2, 16), 82 (M^+−R_fSO_2NH–$C_2H_5OCH_2$, 100). Anal. Calcd for $C_{12}H_{14}F_8INO_5S$: C, 25.59; H, 2.51; N, 2.49%. Found: C, 25.86; H, 2.48; N, 2.79%.

4.1.7. *syn*-5-Ethoxy-2-styryl-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-2-iodo-ethoxy)-ethanesulfonyl]-oxazolidine (4ad). White solid. Mp 54–56 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41–7.26 (5H, m), 6.71 ($1H_1$, d, J=16 Hz), 6.31 ($1H_2$, dd, J=16, 7.5 Hz) 6.00 ($1H_3$, d, J=6.9 Hz), 5.45 ($1H_4$, t, J=2.4 Hz), 4.11–4.05 ($1H_5$, m), 3.92–3.82 ($1H_6$, m), 3.64–3.57 (2H, m), 1.25 (3H, t, J=7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 135.5, 134.9, 129.0, 128.8, 127.1, 126.6, 102.4, 93.2, 64.2, 52.7, 15.0. ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.3 (CF_2, t, J=6.0 Hz), −82.2 (CF_2, s), −85.9 (CF_2, d, J=15 Hz), −115.8 (CF_2, br). IR (KBr) cm^{-1}: 2983, 2955, 1399, 1294, 1206, 1127, 1080, 915. MS (70 eV, EI) m/z (%): 625 (M^+, 6), 580 (M^+−EtO, 1), 522 (M^+−C_6H_5CH=CH, 1), 493 (M^+−Et–C_6H_5CH=CH, 8), 227 ($IC_2F_4^+$, 11), 218 (M^+−R_fSO_2, 53), 115 (C_6H_5CH=CHC^+, 100). Anal. Calcd for $C_{17}H_{16}F_8INO_5S$: C, 32.66; H, 2.58; N, 2.24%. Found: C, 32.96; H, 2.60; N, 2.02%.

Crystal data for compound **4ad** (CCDC 262795): $C_{17}H_{16}F_8INO_5S$, MW=625.27, monoclinic, $C2/C$, Mo Kα, final R indices [$I>2\sigma(I)$], R_1=0.0591, wR_2=0.1355, a=27.364(4) Å, b=5.370(7) Å, c=32.357(4) Å, α=90°, β=102.54°, γ=90°, V=4640.9(10) Å^3, T=293(2) K, Z=8, reflections collected/unique: 12,934/5300 (R_{int}=0.0790), no observation [$I>2\sigma(I)$] 2200, parameters 343.

4.1.8. *anti*-5-Ethoxy-2-styryl-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-2-iodo-ethoxy)-ethanesulfonyl]-oxazolidine (5ad). White solid. Mp 44–46 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.44–7.26 (5H, m), 6.83 ($1H_1$, d, J=16 Hz), 6.10 ($1H_2$, dd, J=16, 7.2 Hz), 5.91 ($1H_3$, d, J=7.2 Hz), 5.40 ($1H_4$, d, J=3.9 Hz), 3.97–3.85 (2H, m), 3.65–3.59 (2H, m), 1.23 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.5 (CF_2, t, J=5.6 Hz), −82.1 (CF_2, t, J=13.8 Hz), −86.0 (CF_2, m), −116.3 (CF_2, br). IR (KBr) cm^{-1}: 2983, 2930, 1396, 1294, 1206, 1150, 1037, 915. MS (70 eV, EI) m/z (%): 625 (M^+, 15), 580 (M^+−EtO, 12), 522 (M^+−C_6H_5CH=CH, 11), 493 (M^+−Et–C_6H_5CH=CH, 13), 227 ($IC_2F_4^+$, 7), 218 (M^+−R_fSO_2, 79), 115 (C_6H_5CH=CHC^+, 100). Anal. Calcd for $C_{17}H_{16}F_8INO_5S$: C, 32.66; H, 2.58; N, 2.24%. Found: C, 33.00; H, 2.64; N, 2.22%.

4.1.9. *syn*-3-[2-(2-Chloro-1,1,2,2-tetrafluoro-ethoxy)-1,1,2,2-tetrafluoroethane sulfonyl]-5-ethoxy-2-vinyl-oxazolidine (4ba). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.06–5.95 (1H, m), 5.81 (1H, d, J=6.9 Hz), 5.45 (1H, d, J=18.0 Hz), 5.41 (1H, d, J=3.3 Hz), 5.34 (1H, d, J=10.2 Hz), 4.05 (1H, dd, J=5.4, 11.1 Hz), 3.84 (1H, dq, J=7.2, 9.6 Hz), 3.62–3.49 (2H, m), 1.23 (1H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −74.1 (CF_2, s), −82.1 (CF_2, s), −87.0 (CF_2, t, J=13 Hz), −115.2 (CF_2, br). IR (KBr) cm^{-1}: 2983, 2935, 1398, 1306, 1176, 970. MS (70 eV, EI) m/z (%): 432/430 (M^+-C_2H_3, 7/19), 414/412 (M^+−OEt, 17/44), 142 (M^+−R_fSO_2, 7), 135 ($ClC_2F_4^+$, 3), 68 (M^+−R_fSO_2NH–$C_2H_5OCH_2$, 100). Anal. Calcd for $C_{11}H_{12}ClF_8NO_5S$: C, 28.87; H, 2.64; N, 3.06%. Found: C, 29.14; H, 2.86; N, 3.15%.

4.1.10. *anti*-3-[2-(2-Chloro-1,1,2,2-tetrafluoro-ethoxy)-1,1,2,2-tetrafluoroethane sulfonyl] -5-ethoxy-2-vinyl-oxazolidine (5ba). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.88–5.76 (1H, m), 5.73 (1H, d, J=6.6 Hz), 5.56 (1H, d, J=15.9 Hz), 5.45 (1H, d, J=9.6 Hz), 5.36 (1H, d, J=3.6 Hz), 3.90–3.77 (2H, m), 3.62–3.52 (2H, m), 1.24 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −74.0 (CF_2, s), −82.0 (CF_2, t, J=11.6 Hz), −87.0 (CF_2, t, J=11.1 Hz), −116.2 (CF_2, br). IR (KBr) cm^{-1}: 2983, 2936, 1398, 1306, 1176, 971. MS (70 eV, EI) m/z (%): 414/412 (M^+-OEt, 4/10), 135 ($ClC_2F_4^+$, 11), 68 (M^+−R_fSO_2NH–$C_2H_5OCH_2$, 100). Anal. Calcd for $C_{11}H_{12}ClF_8NO_5S$: C, 28.87; H, 2.64; N, 3.06%. Found: C, 28.97; H, 2.68; N, 3.16%.

4.1.11. *syn*-3-[2-(2-Chloro-1,1,2,2-tetrafluoro-ethoxy)-1,1,2,2-tetrafluoro-ethane sulfonyl]-5-ethoxy-2-isopropenyl-oxazolidine (4bb). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.78 (1H, s), 5.37 (1H, t, J=5.4 Hz), 5.26 (1H, s), 5.09 (1H, s), 4.15 (1H, dd, J=5.4, 12 Hz), 3.87 (1H, dq, J=7.2, 9.6 Hz), 3.60 (1H, dq, J=7.2, 9.6 Hz), 3.42 (1H, dd, J=4.8, 12 Hz), 1.83 (3H, s), 1.23 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −74.1 (CF_2, s), −82.1 (CF_2, s), −87.1 (CF_2, t, J=13 Hz), −115.4 (CF_2, br). IR (KBr) cm^{-1}: 2983, 2926, 1403, 1304, 1207, 1143, 1019, 971. MS (70 eV, EI) m/z (%): 432/430 (M^+−C_3H_5, 37/100), 404/402 (M^+−C_3H_5-Et, 8/21), 156 (M^+−R_fSO_2, 3), 135 ($ClC_2F_4^+$, 5), 82 (M^+−R_fSO_2NH–$C_2H_5OCH_2$, 8). Anal. Calcd for $C_{12}H_{14}ClF_8NO_5S$: C, 30.55; H, 2.99; N, 2.97%. Found: C, 30.50; H, 2.94; N, 2.92%.

4.1.12. *anti*-3-[2-(2-Chloro-1,1,2,2-tetrafluoro-ethoxy)-1,1,2,2-tetrafluoroethane-sulfonyl]-5-ethoxy-2-isopropenyl-oxazolidine (5bb). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.75 (1H, s), 5.38 (1H, d, J=3.6 Hz), 5.28 (1H, s), 5.18 (1H, s), 3.94 (1H, d, J=11.1 Hz), 3.81 (1H, dq, J=6.6, 9.1 Hz), 3.62–3.52 (2H, m), 1.73 (3H, s), 1.24 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −74.0 (CF_2, s), −82.0 (CF_2, m), −87.1 (CF_2, m), −116.6 (CF_2, br). IR (KBr) cm^{-1}: 2927, 2855, 1399, 1204, 1144, 1038, 971. MS

(70 eV, EI) *m/z* (%):MS (70 eV, EI) *m/z* (%): 432/430 (M^+-C_3H_5, 20/56), 404/402 ($M^+-C_3H_5$-Et, 6/16), 156 ($M^+-R_fSO_2$, 19), 82 ($M^+-R_fSO_2NH–C_2H_5OCH_2$, 100). Anal. Calcd for $C_{12}H_{14}ClF_8NO_5S$: C, 30.55; H, 2.99; N, 2.97%. Found: C, 30.33; H, 2.95; N, 3.17%.

4.1.13. *syn*-3-[2-(2-Chloro-1,1,2,2-tetrafluoro-ethoxy)-1,1,2,2-tetrafluoroethane-sulfonyl]-5-ethoxy-2-propenyl-oxazolidine (4bc). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.89 (1H, dq, J=6.6, 15 Hz), 5.77 (1H, d, J=8.1 Hz), 5.66 (1H, dd, J=8.0, 15 Hz), 5.38 (1H, dd, J=3.0, 5.4 Hz), 4.02 (1H, dd, J=5.4, 10.8 Hz), 3.84 (1H, dq, J=7.2, 9.3 Hz), 3.61–3.49 (2H, m), 1.75 (3H, dd, J=6.3, 1.5 Hz), 1.24 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −74.1 (CF_2, s), −82.1 (CF_2, s), −87.0 (CF_2, t, J=13 Hz), −115.6 (CF_2, br). IR (KBr) cm^{-1}: 2981, 2926, 1398, 1306, 1175, 967. MS (70 eV, EI) *m/z* (%): 473/471 (M^+, 1/4), 428/426 (M^+-OEt, 5/13), 156 ($M^+-R_fSO_2$, 13), 135 ($ClC_2F_4^+$, 5), 82 ($M^+-R_fSO_2NH–C_2H_5OCH_2$, 100). Anal. Calcd for $C_{12}H_{14}ClF_8NO_5S$: C, 30.55; H, 2.99; N, 2.97%. Found: C, 30.82; H, 3.17; N, 3.26%.

4.1.14. *anti*-3-[2-(2-Chloro-1,1,2,2-tetrafluoro-ethoxy)-1,1,2,2-tetrafluoro-ethane sulfonyl] -5-ethoxy-2-propenyl-oxazolidine (5bc). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.02 (1H, dq, J=6.6, 15 Hz), 5.69 (1H, d, J=7.8 Hz), 5.45 (1H, dd, J=7.5, 15 Hz), 5.32 (1H, d, J=3.9 Hz), 3.88–3.75 (2H, m), 3.58–3.50 (2H, m), 1.78 (3H, dd, J=7.8, 1.5 Hz), 1.23 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −74.0 (CF_2, s), −82.0 (CF_2, m), −87.0 (CF_2, m), −116.3 (CF_2, br). IR (KBr) cm^{-1}: 2979, 2926, 1399, 1306, 1175, 967. MS (70 eV, EI) *m/z* (%): 473/471 (M^+, 1/3), 428/426 (M^+-OEt, 6/16), 156 ($M^+-R_fSO_2$, 13), 135 (5), 82 ($M^+-R_fSO_2NH–C_2H_5OCH_2$, 100). Anal. Calcd for $C_{12}H_{14}ClF_8NO_5S$: C, 30.55; H, 2.99; N, 2.97%. Found: C, 30.75; H, 2.97; N, 2.97%.

4.1.15. *syn*-5-Ethoxy-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-ethoxy)-ethane sulfonyl]-2-vinyl-oxazolidine (4ca). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.05–5.94 (1H, m), 5.87 (1H, t-t, J=3.0, 52.2 Hz), 5.80 (1H, d, J=7.2 Hz), 5.45 (1H, d, J=17.1 Hz), 5.41 (1H, d, J=5.4 Hz), 5.34 (1H, d, J=10.2 Hz), 4.04 (1H, dd, J=5.4, 10.8 Hz), 3.83 (1H, dq, J=9.6, 7.2 Hz), 3.62–3.48 (2H, m), 1.23 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −81.8 (CF_2, s), −88.8 (CF_2, m), −115.7 (CF_2, br), −137.8 (CF_2, d, J=53.0 Hz). IR (KBr) cm^{-1}: 2984, 2936, 1398, 1285, 1143, 949. MS (70 eV, EI) *m/z* (%): 423 (M^+, 1), 396 ($M^+-C_2H_3$, 17), 378 (M^+-OEt, 42), 142 ($M^+-R_fSO_2$, 7), 68 ($M^+-R_fSO_2NH–C_2H_5OCH_2$, 100). Anal. Calcd for $C_{11}H_{13}F_8NO_5S$: C, 31.21; H, 3.10; N, 3.31%. Found: C, 31.34; H, 3.12; N, 3.35%.

4.1.16. *anti*-5-Ethoxy-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-ethoxy)-ethane sulfonyl]-2-vinyl-oxazolidine (5ca). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.86 (1H, t-t, J=3.0, 53.0 Hz), 5.84–5.76 (1H, m), 5.73 (1H, d, J=6.9 Hz), 5.56 (1H, d, J=16.8 Hz), 5.45 (1H, d, J=10.2 Hz), 5.36 (1H, d, J=3.3 Hz), 3.89–3.77 (2H, m), 3.62–3.52 (2H, m), 1.24 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −81.6 (CF_2, s), −88.7 (CF_2, s), −116.2 (CF_2, br), −137.7 (CF_2, d, J=53.3 Hz). IR (KBr) cm^{-1}: 2984, 2936, 1395, 1324, 1285, 1140, 1038. MS (70 eV, EI) *m/z* (%): 396 ($M^+-C_2H_3$, 7), 378 (M^+-OEt, 15), 142 ($M^+-R_fSO_2$, 4), 68 ($M^+-R_fSO_2NH–C_2H_5OCH_2$, 100). Anal. Calcd for $C_{11}H_{13}F_8NO_5S$: C, 31.21; H, 3.10; N, 3.31%. Found: C, 31.38; H, 3.04; N, 3.39%.

4.1.17. *syn*-5-Ethoxy-2-styryl-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-ethoxy)-ethanesulfonyl]-oxazolidine (4cd). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.45–7.27 (5H, m), 6.73 ($1H_1$, d, J=15.3 Hz), 6.34 ($1H_2$, dd, J=16.2, 7.8 Hz), 6.02 ($1H_3$, d, J=7.2 Hz), 5.86 (1H, t-t, J=52.8, 3.0 Hz), 5.47 ($1H_4$, d, J=5.4 Hz), 4.09 ($1H_5$, dd, J=5.4, 11.1 Hz), 3.89 ($1H_6$, dq, J=9.6, 7.2 Hz), 3.67–3.56 (2H, m), 1.27 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −81.7 (CF_2, s), −88.7 (CF_2, t, J=5.6 Hz), −115.5 (CF_2, br), −137.7 (CF_2, d, J=53.3 Hz). IR (KBr) cm^{-1}: 2981, 2935, 1398, 1284, 1206, 1141. MS (70 eV, EI) *m/z* (%): 499 (M^+, 8), 454 (M^+-EtO, 2), 367 (M^+-Et–C_6H_5CH=CH, 6), 218 ($M^+-R_fSO_2$, 26), 115 (C_6H_5CH=CHC^+, 100). Anal. Calcd for $C_{17}H_{17}F_8NO_5S$: C, 40.89; H, 3.43; N, 2.80%. Found: C, 41.03; H, 3.42; N, 2.87%.

4.1.18. *anti*-5-Ethoxy-2-styryl-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-ethoxy)-ethanesulfonyl]-oxazolidine (5cd). White solid. Mp 68–70 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.44–7.27 (5H, m), 6.83 ($1H_1$, d, J=15.6 Hz), 6.10 ($1H_2$, dd, J=16.2, 7.2 Hz), 5.92 ($1H_3$, d, J=6.6 Hz), 5.83 (1H, t-t, J=52.5, 3.0 Hz), 5.40 ($1H_4$, d, J=3.3 Hz), 3.93–3.82 (2H, m), 3.67–3.54 (2H, m), 1.26 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −81.6 (CF_2, t, J=12.5 Hz), −88.7 (CF_2, m), −116.1 (CF_2, br), −137.6 (CF_2, d, J=54.4 Hz). IR (KBr) cm^{-1}: 2981, 2931, 1395, 1284, 1146, 1035, 966. MS: *m/z* (%) 499 (M^+, 5), 454 (M^+-EtO, 2), 394 (33), 367 (4), 218 ($M^+-R_fSO_2$, 19), 115(61), 86(100). Anal. Calcd for $C_{17}H_{17}F_8NO_5S$: C, 40.89; H, 3.43; N, 2.80%. Found: C, 40.88; H, 3.44; N, 2.72%.

4.1.19. *syn*-5-Ethoxy-3-(nonafluorobutane-1-sulfonyl)-2-styryl-oxazolidine (4dd). White solid. Mp 56–58 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43–7.27 (5H, m), 6.73 ($1H_1$, d, J=16.2 Hz), 6.32 ($1H_2$, dd, J=15.3, 7.2 Hz), 6.02 ($1H_3$, d, J=7.8 Hz), 5.47 ($1H_4$, d, J=5.4 Hz), 4.11 ($1H_5$, dd, J=5.4, 11.1 Hz), 3.89 ($1H_6$, dq, J=9.6, 7.2 Hz), 3.66–3.56 (2H, m), 1.27 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −81.0 (CF_2, t, J=8.9 Hz), −111.9 (CF_2, br), −121.4 (CF_2, m), −126.1 (CF_2, s). IR (KBr) cm^{-1}: 2978, 2931, 1398, 1240, 1200, 1133. MS (70 eV, EI) *m/z* (%): 501 (M^+, 10), 456 (M^+-EtO, 2), 369 (M^+-Et–C_6H_5CH=CH, 5), 218 ($M^+-R_fSO_2$, 41), 115 (C_6H_5-CH=CHC^+, 100). Anal. Calcd for $C_{17}H_{16}F_9NO_4S$: C, 40.73; H, 3.22; N, 2.79%. Found: C, 40.88; H, 3.21; N, 2.76%.

4.1.20. *anti*-5-Ethoxy-3-(nonafluorobutane-1-sulfonyl)-2-styryl-oxazolidine (5dd). White solid. Mp 68–70 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.44–7.29 (5H, m), 6.84 ($1H_1$, d, J=15.6 Hz), 6.10 ($1H_2$, dd, J=15.6, 7.5 Hz), 5.93 ($1H_3$, d, J=6.9 Hz), 5.41 ($1H_4$, d, J=3.6 Hz), 3.95–3.80 (2H, m), 3.69–3.55 (2H, m), 1.27 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −81.0 (CF_2, m), −112.3 (CF_2, br), −121.4 (CF_2, s), −126.1 (CF_2, m). IR (KBr) cm^{-1}: 2982, 2940, 1398, 1259, 1183, 1133, 1102, 956. MS (70 eV, EI)

m/z (%): 501 (M^+, 8), 456 (M^+-EtO, 3), 369 ($M^+-Et-C_6H_5CH{=}CH$, 5), 218 ($M^+-R_fSO_2$, 34), 115 ($C_6H_5CH{=}CHC^+$, 100). Anal. Calcd for $C_{17}H_{16}F_9NO_4S$: C, 40.73; H, 3.22; N, 2.79%. Found: C, 40.74; H, 3.17; N, 2.71%.

4.1.21. *syn/anti*-5-Ethoxy-2-methyl-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-2-iodo-ethoxy)-ethanesulfonyl]-2-vinyl-oxazolidine (4ae+5ae). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.16–5.94 (1H, m), 5.48–5.21 (3H, m), 3.87–3.68 (3H, m), 3.54–3.44 (1H, m), 1.72 (3H, s), 1.61 (3H, s), 1.19 (3H, t, J=6.9 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.6 (CF_2, s), −82.4 (CF_2, s), −86.2 (CF_2, m), −114.8 (CF_2, br). IR (KBr) cm^{-1}: 2982, 2935, 1396, 1202, 1153, 915. MS (70 eV, EI) *m/z* (%): 548 (M^+-CH_3, 41), 536 ($M^+-C_2H_3$, 29), 518 (M^+-OEt, 9), 227 ($IC_2F_4^+$, 16), 177 (ICF_2^+, 11), 55 ($C_4H_7^+$, 100). Anal. Calcd for $C_{12}H_{14}F_8INO_5S$: C, 25.59; H, 2.51; N, 2.49%. Found: C, 25.89; H, 2.51; N, 2.66%.

4.2. General procedure for the synthesis of fluorinated oxazolidines from other kinds of aldehydes

To a 10 mL round-bottom flask containing vinyl ether **2a** (2.0 equiv) and benzaldehyde **6a** (2.0 equiv) in 2 mL CH_2Cl_2 was added slowly fluoroalkanesulfonyl azides **1a** (2.0 equiv) at 0 °C within 2 min. The reaction was finished within 10 min, according to TLC analysis. Then the solvent was evaporated under reduced pressure and the residue was chromatographed on a silica column using petroleum ether/diethyl ether (100:1) as eluant to give a colorless *syn*-oxazolidine **7aa** (60%). In the case of 2-furylaldehyde **6b**, the *syn*- and *anti*-oxazolidines **7ab** and **8ab** were isolated successfully.

4.2.1. *syn*-5-Ethoxy-2-phenyl-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-2-iodo-ethoxy)-ethanesulfonyl]-oxazolidine (7aa). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.53–7.32 (5H, m), 6.50 (1H, s), 5.47 (1H, t, J=5.1 Hz), 4.19 (1H, dd, J=5.4, 12.0 Hz), 3.77 (1H, dq, J=9.6, 7.2 Hz), 3.58–3.43 (2H, m), 1.07 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.4 (CF_2, s), −82.2 (CF_2, s), −85.9 (CF_2, m), −115.0 (CF_2, br). IR (KBr) cm^{-1}: 2982, 2932, 1402, 1333, 1293, 1203, 1143, 1093, 915. MS (70 eV, EI) *m/z* (%): 554 (M^+-EtO, 4), 118(100). Anal. Calcd for $C_{15}H_{14}F_8INO_5S$: C, 30.03; H, 2.35; N, 2.34%. Found: C, 29.64; H, 2.59; N, 2.35%.

4.2.2. *syn*-5-Isobutoxy-2-phenyl-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-2-iodo-ethoxy)-ethanesulfonyl]-oxazolidine (7ba). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.58–7.38 (5H, m), 6.54 (1H, s), 5.51 (1H, t, J=5.1 Hz), 4.25 (1H, dd, J=5.7, 11.7 Hz), 3.56–3.50 (2H, m), 3.28 (1H, dd, J=6.3, 9.0 Hz), 1.81–1.73 (1H, m), 0.85 (3H, d, J=6.6 Hz), 0.81 (3H, d, J=6.9 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.1 (CF_2, m), −82.1 (CF_2, s), −85.8 (CF_2, m), −115.0 (CF_2, br). IR (KBr) cm^{-1}: 2961, 2876, 1403, 1333, 1292, 1203, 1142, 1021, 915. MS (70 eV, EI) *m/z* (%): 554 (M^+-EtO, 4), 118(100). Anal. Calcd for $C_{17}H_{18}F_8INO_5S$: C, 32.55; H, 2.89; N, 2.23%. Found: C, 32.64; H, 3.00; N, 2.46%.

4.2.3. *syn*-5-Ethoxy-2-furan-2-yl-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-2-iodo-ethoxy)-ethanesulfonyl]-oxazolidine (7ab). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.45 (1H, s), 6.50 (1H, d, J=3.6 Hz), 6.45 (1H, s), 6.38 (1H, dd, J=3.0, 1.8 Hz), 5.50 (1H, dd, J=5.4, 3.9 Hz), 4.22 (1H, dd, J=5.4, 11.4 Hz), 3.79 (1H, dq, J=9.6, 7.2 Hz), 3.60–3.52 (2H, m), 1.15 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.3 (CF_2, t, J=6.0 Hz), −82.0 (CF_2, s), −85.8 (CF_2, m), −114.9 (CF_2, br). IR (KBr) cm^{-1}: 2982, 2934, 1402, 1334, 1293, 1153, 1009, 915. MS (70 eV, EI) *m/z* (%): 589 (M^+, 1), 544 (3), 493 ($M^+-C_5H_4O_2$, 1), 227(4), 177(3), 108(100). Anal. Calcd for $C_{13}H_{12}F_8INO_6S$: C, 26.49; H, 2.04; N, 2.38%. Found: C, 26.59; H, 2.10; N, 2.48%.

4.2.4. *anti*-5-Ethoxy-2-furan-2-yl-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-2-iodo-ethoxy)-ethanesulfonyl]-oxazolidine (8ab). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.47 (1H, s), 6.56 (1H, d, J=3.6 Hz), 6.40 ($1H_2$, dd, J=1.8, 3.3 Hz), 6.36 (1H, s), 5.52 (1H, d, J=3.3 Hz), 4.01 (1H, d, J=10.5 Hz), 3.88–3.79 (2H, m), 3.62 (1H, dq, J=9.6, 7.2 Hz), 1.27 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.2 (CF_2, t, J=6.0 Hz), −82.0 (CF_2, m), −85.7 (CF_2, s), −117.5 (CF_2, br). IR (KBr) cm^{-1}: 2982, 2919, 1397, 1332, 1294, 1154, 1036, 915. MS (70 eV, EI) *m/z* (%): 589 (M^+, 1), 544 (M^+-EtO, 5), 493 ($M^+-C_5H_4O_2$, 7), 227(8), 177(5), 108 (100). Anal. Calcd for $C_{13}H_{12}F_8INO_6S$: C, 26.49; H, 2.04; N, 2.38%. Found: C, 26.65; H, 2.09; N, 2.37%.

4.2.5. *syn*-5-Ethoxy-2-isopropyl-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-2-iodo-ethoxy)-ethanesulfonyl]-oxazolidine (7ac). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.38–5.33 (1H, m), 5.07 (1H, d, J=7.8 Hz), 4.19 (1H, dd, J=6.0, 12.6 Hz), 3.94–3.83 (1H, m), 3.65–3.54 (1H, m), 3.40 (1H, dd, J=4.2, 12.9 Hz), 2.14–2.02 (1H, m), 1.25 (3H, t, J=7.2 Hz), 1.02 (6H, d, J=8.1 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.2 (CF_2, m), −82.2 (CF_2, s), −85.8 (CF_2, t, J=6.3 Hz), −115.0 (CF_2, br). IR (KBr) cm^{-1}: 2979, 2934, 1403, 1328, 1292, 1203, 1148, 1020, 915. MS (70 eV, EI) *m/z* (%): 522 (M^+-C_3H_7, 100), 494 (11), 227 (16), 177 (10). Anal. Calcd for $C_{12}H_{16}F_8INO_5S$: C, 25.50; H, 2.85; N, 2.48%. Found: C, 25.79; H, 2.81; N, 2.53%.

4.2.6. *syn*-5-Ethoxy-2-(2-nitro-phenyl)-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-2-iodo-ethoxy)-ethanesulfonyl]-oxazolidine (7ad). White solid. Mp 48–50 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.95 (1H, d, J=8.1 Hz), 7.75–7.56 (3H, m), 7.25 (1H, s), 5.44 (1H, dd, J=2.7, 5.7 Hz), 4.27 (1H, dd, J=5.7, 11.7 Hz), 3.57 (1H, dd, J=2.7, 11.7 Hz), 3.38–3.32 (2H, m), 0.77 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −65.3 (CF_2, t, J=5.6 Hz), −82.0 (CF_2, s), −85.7 (CF_2, m), −113.8 (CF_2, br). IR (KBr) cm^{-1}: 2984, 1532, 1404, 1294, 1205, 1152, 1096, 1007, 915. MS (70 eV, EI) *m/z* (%): 599 (M^+-EtO, 6), 136(100). Anal. Calcd for $C_{15}H_{13}F_8IN_2O_7S$: C, 27.97; H, 2.03; N, 4.35%. Found: C, 28.17; H, 2.21; N, 4.15%.

4.3. Further chemical transformation of the mixture system of aromatic aldehyde and 7 by $NaBH_4$

During the first step, the *syn*-oxazolidines **7** were not separated but were collected with the remained **6** to the further chemical transformation. To 10 mL round-bottom

flask containing 4 mL anhydrous methanol was added the mixture of the remained benzaldehyde **6a** and unseparated **7ba**, sodium borohydride (~5.0 equiv) in turn at 0 °C to afford a colorless oil **9ba** in 50% yield by conventional disposal.

4.3.1. *syn*-5-Isobutoxy-2-phenyl-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-ethoxy)-ethanesulfonyl]-oxazolidine (9ba). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.55–7.33 (5H, m), 6.50 (1H, s), 5.85 (1H, t-t, J=3.0, 52.8 Hz), 5.47 (1H, t, J=4.8 Hz), 4.22 (1H, dd, J=5.7, 12.0 Hz), 3.53–3.47 (2H, m), 3.25 (1H, dd, J=6.3, 9.1 Hz), 1.78–1.67 (1H, m), 0.82 (3H, d, J=6.6 Hz), 0.78 (3H, d, J=6.3 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −81.7 (CF_2, s), −88.7 (CF_2, t, J=10.3 Hz), −115.2 (CF_2, br), −137.6 (CF_2, d, J=53.3 Hz). IR (KBr) cm^{-1}: 2963, 2877, 1402, 1325, 1284, 1202, 1141, 1021. MS (70 eV, EI) *m/z* (%): 428 (M^+ − ^{i}BuO, 4), 118 (100). Anal. Calcd for $C_{17}H_{19}F_8NO_5S$: C, 40.72; H, 3.82; N, 2.79%. Found: C, 40.76; H, 3.85; N, 2.75%.

4.3.2. *syn*-5-Ethoxy-3-[1,1,2,2-tetrafluoro-2-(1,1,2,2-tetrafluoro-ethoxy)-ethane sulfonyl]-2-*p*-tolyl-oxazolidine (9ae). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39 (2H, d, J=8.1 Hz), 7.19 (2H, d, J=8.1 Hz), 6.45 (1H, s), 5.84 (1H, t-t, J=3.0, 52.8 Hz), 5.47 (1H, t, J=4.5 Hz), 4.17 (1H, dd, J=5.7, 12.0 Hz), 3.78 (1H, dq, J=12.0, 7.2 Hz), 3.55 (1H, dq, J=9.9, 6.9 Hz), 3.46 (1H, dd, J=4.5, 12.0 Hz), 2.36 (3H, s), 1.10 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −81.9 (CF_2, s), −88.9 (CF_2, s), −115.3 (CF_2, br), −137.8 (CF_2, d, J=54.1 Hz). IR (KBr) cm^{-1}: 2982, 2930, 1402, 1325, 1284, 1198, 1141, 1017. MS (70 eV, EI) *m/z* (%): 487 (M^+, 1), 442 (M^+ − EtO, 4), 132 ($M^+ - R_fSO_2NH–C_2H_5OCH_2$, 100). Anal. Calcd for $C_{16}H_{17}F_8NO_5S$: C, 39.43; H, 3.52; N, 2.87%. Found: C, 39.51; H, 3.51; N, 2.78%.

4.3.3. *syn*-2-(4-Bromo-phenyl)-5-ethoxy-3-[1,1,2,2-tetra-fluoro-2-(1,1,2,2-tetra-fluoro-ethoxy)-ethanesulfonyl]-oxazolidine (9af). Colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.53 (2H, d, J=8.4 Hz), 7.40 (2H, d, J=8.7 Hz), 6.43 (1H, s), 5.86 (1H, t-t, J=3.0, 52.5 Hz), 5.48 (1H, t, J=4.5 Hz), 4.18 (1H, dd, J=5.7, 12.0 Hz), 3.76 (1H, dq, J=9.3, 7.2 Hz), 3.56 (1H, dq, J=9.3, 6.9 Hz), 3.44 (1H, dd, J=4.5, 12.0 Hz), 1.11 (3H, t, J=7.2 Hz). ^{19}F NMR ($CDCl_3$, 282 MHz): δ −81.8 (CF_2, s), −88.8 (CF_2, s), −115.2 (CF_2, br), −137.8 (CF_2, d, J=52.7 Hz). IR (KBr) cm^{-1}: 2982, 2933, 1594, 1487, 1403, 1326, 1284, 1140, 1010. MS (70 eV, EI) *m/z* (%): 508/506 (M^+ − EtO, 3/3), 198/196 ($M^+ - R_fSO_2NH–C_2H_5OCH_2$, 98/100). Anal. Calcd for $C_{15}H_{14}BrF_8NO_5S$: C, 32.62; H, 2.56; N, 2.54%. Found: C, 32.61; H, 2.58; N, 2.51%.

Acknowledgements

This work is supported by the National Science Foundation of China (Nos. 20372077 and 20472106).

References and notes

1. (a) Ramachandran, P. V. *Asymmetric Fluoroorganic Chemistry: Synthesis, Applications, and Future Directions*; American Chemical Society: Washington, DC, 2000. (b) Ojima, I.; McCarthy, J. R.; Welch, J. T. *Biomedical Frontiers of Fluorine Chemistry*; American Chemical Society: Washington, DC, 1996. (c) Kukhar', V. P.; Soloshonok, V. A. Fluorine-Containing Amino Acids: Synthesis and Properties; Wiley: New York, 1995. (d) Welch, J. T. *Selective Fluorination in Organic and Bioorganic Chemistry*; American Chemical Society: Washington, DC, 1991. (e) Welth, J. T.; Eswarakrishnan, S. Fluorine in Bioorganic Chemistry; Wiley: United States, 1991.
2. Bravo, P.; Resnati, G. *Tetrahedron: Asymmetry* **1990**, *1*, 661–692.
3. Anastasm, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, 1998.
4. Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210.
5. (a) Okuyama, Y.; Nakano, H.; Hongo, H. *Tetrahedron: Asymmetry* **2000**, *11*, 1193–1198. (b) Falorni, M.; Collu, C.; Conti, S.; Giacomelli, G. *Tetrahedron: Asymmetry* **1996**, *7*, 293–299. (c) Joshi, N. N.; Prasad, P. R. K. *J. Org. Chem.* **1997**, *62*, 3770–3771.
6. (a) Semenov, V. P. *Khim. Geterotsikl. Soedin.* **1976**, *12*, 1613–1618. (b) Semenov, V. P.; Stroiman, I. M.; Ogloblin, K. A. *Khim. Geterotsikl. Soedin.* **1977**, *1*, 27–29. (c) Semenov, V. P.; Stroiman, I. M.; Ozemaya, S. V.; Ogloblin, K. A. *Khim. Geterotsikl. Soedin.* **1977**, *3*, 332–336.
7. He, P.; Zhu, S. Z. *Synthesis* **2005**, in press.
8. (a) Xu, Y.; Wang, Y. L.; Zhu, S. Z. *J. Fluorine Chem.* **2000**, *104*, 195–200. (b) Xu, Y.; Zhu, S. Z. *Tetrahedron* **2001**, *57*, 669–674. (c) Zhu, S. Z.; Jin, G. F.; Zhao, J. W. *J. Fluorine Chem.* **2003**, *120*, 65–69. (d) Zhu, S. Z.; He, P.; Zhao, J. W.; Cai, X. *J. Fluorine Chem.* **2004**, *125*, 445–449.
9. Weuthen, M.; Scharf, H. D.; Runsink, J. *Chem. Ber.* **1987**, *120*, 1023–1026.
10. Wang, L. J.; Seiders, J. R., II; Floreancig, P. E. *J. Am. Chem. Soc.* **2004**, *126*, 12596–12603.
11. Zhu, S. Z. *Tetrahedron. Lett.* **1992**, *33*, 6503–6504.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 6097–6107

Synthesis of regioselectively ^{18}O-labelled chlorophyll derivatives at the 3^1- and/or 13^1-positions through one-pot exchange of carbonyl oxygen atoms

Hidetada Morishita and Hitoshi Tamiaki*

Department of Bioscience and Biotechnology, Faculty of Science and Engineering, Ritsumeikan University, Noji-higashi 1-1-1, Kusatsu, Shiga 525-8577, Japan

Received 14 February 2005; revised 7 April 2005; accepted 7 April 2005

Available online 13 May 2005

Abstract—3^1- and/or 13^1-^{18}O-oxo-labelled methyl pyropheophorbides (84–90% ^{18}O atoms at each position) were prepared by exchanging carbonyl oxygen atoms under biphasic conditions of acidic $H_2^{18}O$ (ca. 95% ^{18}O) and dichloromethane. The (un)labelling occurred more rapidly at less sterically hindered (13-C=O possessing 13^2-$COOCH_3$ > 13-C=O lacking it) or more reactive carbonyl groups (formyl > keto group), and not at any hydroxy groups. Reduction of a carbonyl to carbinol group was useful for preparation of regioselectively ^{18}O-labelled chlorophyll derivatives. Following the labelling procedure, 13^1-^{18}O-pheophytin-*a* and 3^1-^{18}O-pheophytin-*d* were obtained. All the synthetic ^{18}O-labelled compounds were characterized by their FAB-mass, ^{13}C NMR and IR spectra. Especially, ^{18}O-labelling induced 0.02 (^{13}C–O) and 0.04–0.05 ppm high field shifts (^{13}C=O) in ^{18}O-attached carbon resonances and about 30 cm^{-1} down-shifts in ^{18}O-labelled carbonyl stretching vibrational bands.

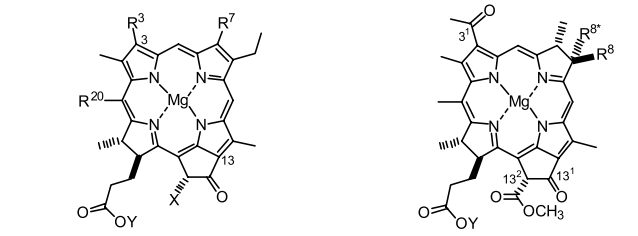
1. Introduction

Chlorophylls are naturally occurring magnesium complexes of cyclic tetrapyrroles and are characterized by an *exo*-five-membered ring possessing a keto carbonyl group. Naturally photoactive chlorophylls possess a C=O group at the 13-position (Fig. 1). Some of them have a C–OH or C=O group at the 3-position (R^3) such as chlorophyll-*d* and bacteriochlorophylls-*a*, *b*, *c*, *d*, *e*.[1] These oxygen functional groups play various important roles to organize and modify photochemical function in photosynthetic apparatus by specific non-covalently bonding interactions.[2–4] Our attention has thus been focused on such 3^1- and 13^1-oxygen atoms and facile, efficient and regioselective ^{18}O-labelling of chlorophyll derivatives by organic synthesis, not by biosynthesis.[5] ^{18}O-Labelling techniques induce specific isotope effects in vibrational and ^{13}C NMR spectroscopies,[6,7] which would give unique information for elucidation of supramolecular structures of any chlorophyll-containing systems. We have already described 13^1-singly and 3^1,13^1-doubly ^{18}O-labelling procedures of pyrochlorophyll derivatives by using acidic hydrolysis of the ethylene ketal and acetal (two-step reaction).[8] However, these ^{18}O-labelling procedures were difficult to apply to some chlorophyll derivatives, because (I) ethylene ketal of the 3-acetyl group could not be transformed to C=^{18}O by hydrolysis using $H_2^{18}O$, and (II) the 13^2-methoxycarbonyl group inhibited ketalization at the 13-C=O. To solve the above two problems, we developed simpler and milder preparation of regioselectively ^{18}O-labelled chlorophyll derivatives than those previously used.

Under acidic conditions, carbonyl oxygen atoms are attacked by protons, and then exchangeable to the oxygen atom of additional H_2O.[6] For example, in acidic $H_2^{18}O$ and tetrahydrofuran, aldehyde and ketone carbonyl oxygens were exchanged to ^{18}O under homogeneous conditions.[9,10] In this work, carbonyl oxygen atoms of various chlorophyll derivatives including pheophytins reacted with $H_2^{18}O$ under acidic biphasic conditions to give the corresponding ^{18}O-labelled compounds at the 3^1- and/or 13^1-position by simple one-step procedures. Here we report on synthesis of such regioselectively labelled chlorophyll derivatives with high ^{18}O-contents and their characterization by FAB-mass, FT-IR and ^{13}C NMR spectroscopies.

Keywords: Oxygen-18; Isotope; IR spectroscopy; ^{13}C NMR spectroscopy; (Pyro)pheophorbide; Pheophytin.
* Corresponding author. Tel.: +81 77 566 1111; fax: +81 77 561 2659; e-mail: tamiaki@se.ritsumei.ac.jp

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.04.012



Chl-*a*: R^3 = CH=CH_2, R^7 = CH_3, X = $COOCH_3$, R^{20} = H
Chl-*b*: R^3 = CH=CH_2, R^7 = CHO, X = $COOCH_3$, R^{20} = H
Chl-*d*: R^3 = CHO, R^7 = CH_3, X = $COOCH_3$, R^{20} = H
BChl-*c*: R^3 = CH(OH)CH_3, R^7 = CH_3, X = H, R^{20} = CH_3
BChl-*d*: R^3 = CH(OH)CH_3, R^7 = CH_3, X = H, R^{20} = H
BChl-*e*: R^3 = CH(OH)CH_3, R^7 = CHO, X = H, R^{20} = CH_3

BChl-*a*: R^8 = C_2H_5, R^{8*} = H
BChl-*b*: R^8, R^{8*} = CH_3, H

Figure 1. Molecular structures of chlorophyll(Chl)s-*a*/*b*/*d* and bacteriochlorophyll(BChl)s-*a*/*b*/*c*/*d*/*e* (Y = phytyl, farnesyl, stearyl, etc.).

2. Results and discussion

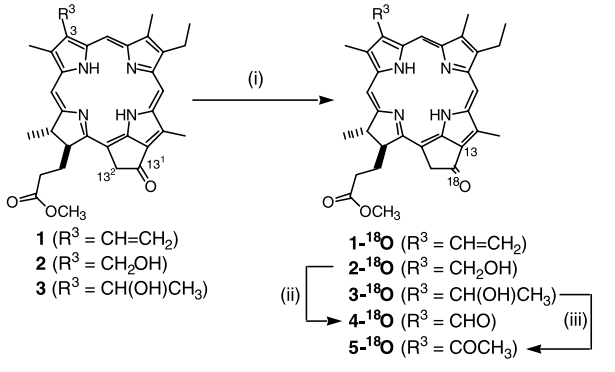
2.1. Synthesis of 13^1-^{18}O-labelled pyropheophorbides (lacking 13^2-$COOCH_3$)

First, we examined preparation of 13^1-^{18}O-oxo-labelled methyl pyropheophorbide-*a* (**1**-^{18}**O**) possessing a vinyl group at the 3-position (Scheme 1). The synthetic procedure was easy and simple: $H_2^{18}O$ (95% ^{18}O atom, 0.1 ml) and trifluoroacetic acid (TFA, 8 μl) was added to a CH_2Cl_2 solution (2 ml) of unlabelled methyl pyropheophorbide-*a* (**1**, 26 μmol) and the biphasic solution was stirred in a closed vial at room temperature for one day. ^{1}H NMR and visible spectra of the product were the same as those of starting material **1**, indicating that the product was methyl pyropheophorbide-*a*. On the other hand, the product gave different MS, ^{13}C NMR and IR spectra as follows.

The FAB-MS spectra (Fig. 2) showed that one of the chlorophyllous oxygen atoms in the product was ^{18}O-labelled: the major peak was at m/z = 550 and the value was 2 mass larger than that of M^+ for **1**. IR spectrum of the product in CH_2Cl_2 exhibited a new band at 1663 cm^{-1} as the 13-C=^{18}O stretching vibrational peak, compared with that of **1** (1692 cm^{-1}, see Table 1). The ^{18}O-labelling degree of the product was determined from its IR and FAB-MS spectral analyses.[8] The FAB-MS spectral data led to 86±1% for the ^{18}O-degree by simulation of the observed pattern of molecular ion peaks based on the observed ion peaks of **1** and the expected ones of fully labelled **1**-^{18}**O** (plus 2 mass to **1**). IR spectra of the product in CH_2Cl_2 gave 86±3% for the ^{18}O-labelling degree by comparison of the deconvolution peak heights in the 13-C=^{16}O stretching bands of unlabelled **1** and the ^{18}O-labelled product (normalized at the unchanged 17^2-C=O peak at 1734 cm^{-1}). The value estimated from IR spectra was consistent with that from MS spectra. A labelling degree of about 86% is high, considering there is at most 91% of ^{18}O-atom content in the starting reaction mixture (5.33 mmol $H_2^{18}O$, 0.28 mmol $H_2^{16}O$, 0.11 mmol TFA and 0.03 mmol **1** possessing 13-C=^{16}O). The present labelling degree (86%) is slightly lower than 92% given by the reported two-step procedures (ketal protection of 13-C=^{16}O and acidic cleavage in $H_2^{18}O$)[8] but the former has a simpler procedure than the latter. The chemical yield of the present ^{18}O-exchange reaction (one-step procedure) was 93% and higher than the previous (68%).

The ^{13}C NMR spectrum showed that the product gave the main 13-^{13}C resonance at 196.167 ppm which was about 0.04 ppm smaller than that of **1** (196.211 ppm) (see Fig. 3). The main resonance was ascribed to the ^{13}C of 13-C=^{18}O. The high field shift by C=^{16}O (**1**)→C=^{18}O (**1**-^{18}**O**) was the same as the reported value (0.04 ppm) of the 17^2-^{13}C of 17^2-C=^{16}O→C=^{18}O in bacteriochlorophyll-*a*.[7] By the side of the major peak, a minor 196.211 ppm peak of 13-C=^{16}O was observed and the 13^1-^{18}O-degree was also estimated by these peak heights. The ^{13}C signal heights of 13-C=^{16}O and C=^{18}O were 15:85, which was consistent with the above value (86%).

Next, we applied the above procedure for methyl 3-devinyl-3-hydroxymethyl-pyropheophorbide-*a* (**2**) and methyl 3-devinyl-3-(1-hydroxyethyl)-pyropheophorbide-*a* (methyl bacteriopheophorbide-*d*, **3**), both of which possessed the 3^1-hydroxy group (Scheme 1). FAB-MS spectra of both the products indicated only mono-^{18}O-labelling of **2** and **3**. Their IR spectra showed about 30 cm^{-1} down-shifts of the 13-C=O stretching bands. From their ^{13}C NMR measurements, two 13-C=O and one 3-C–O peaks were observed



Scheme 1. Synthesis of mono-^{18}O-labelled methyl pyropheophorbides at the 13^1-position; (i) $H_2^{18}O$-TFA/CH_2Cl_2; (ii) PDC/CH_2Cl_2–C_6H_6; (iii) $CH_3(O)N(CH_2CH_2)_2O$–Pr_4NRuO_4/CH_2Cl_2.

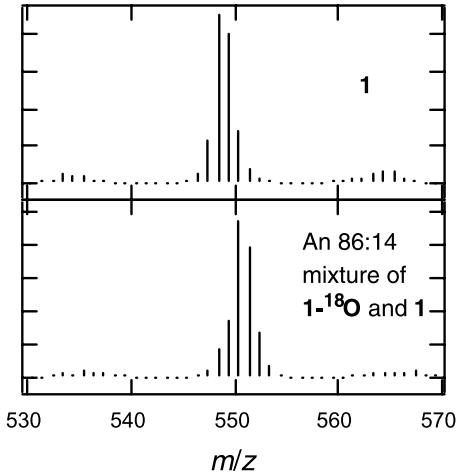


Figure 2. FABMS spectra of **1** (upper) and its ^{18}O-labelled product (lower).

Table 1. Keto and formyl carbonyl stretching vibrational peaks νs (cm^{-1}) of ^{18}O-labelled and non-labelled (pyro)chlorophyll derivatives, 3-substituted 13^1-oxo-chlorins in CH_2Cl_2

Non-/^{18}O-labelled compounds	3-position			13-position		
	ν(C=^{16}O)	ν(C=^{18}O)	$\Delta\nu$[a]	ν(C=^{16}O)	ν(C=^{18}O)	$\Delta\nu$[a]
1/1-^{18}O	—	—	—	1692	1663	29
2/2-^{18}O[b]	—	—	—	1700	1670	30
2/^{18}O-2-^{18}O[b]	—	—	—	1700	1670	30
2/^{18}O-2[b]	—	—	—	1700	—	—
3/3-^{18}O (*R*/*S* =1:1)[b]	—	—	—	1699	1670	29
3/^{18}O-3-^{18}O (*R*/*S*=1:1)[b]	—	—	—	1699	1670	29
3/^{18}O-3 (*R*/*S* =1:1)[b]	—	—	—	1699	—	—
4/4-^{18}O	1678	—	—	1697	1670	27
4/^{18}O-4-^{18}O	1678	1649	29	1697	1669	28
4/^{18}O-4	1678	1648	30	1697	—	—
5/5-^{18}O	1672	—	—	1695	1667	28
5/^{18}O-5-^{18}O	1672	1642	30	1695	1666	29
5/^{18}O-5	1672	1640	32	1695	—	—
6/6-^{18}O (*a*/*a*′ =7/1)	1737[c]	1699[c]	38[c]	1699	1669	30
7/^{18}O-7 (*d*/*d*′ =7/1)	1678	1650	28	1703	—	—
9/9-^{18}O (*a*/*a*′ =6/1)	1736[c]	1699[c]	37[c]	1699	1669	30
10/^{18}O-10 (*d*/*d*′ =11/2)	1677	1649	28	1703	—	—

[a] $\Delta\nu=\nu$(C=^{16}O)−ν(C=^{18}O).
[b] In THF.
[c] ν values in 17^2-C=O stretching vibration.

(see Table 2). These spectral data clearly indicated that mono-^{18}O-labelling occurred exclusively at the 13^1-oxo-position but not at the 3^1-hydroxy-oxygen atom. Both 13^1-^{18}O-labelled products were afforded in moderate isolated yields of 59% for a 87:13 mixture of **2-^{18}O** and **2** and of 72% for a 86:14 mixture of **3-^{18}O** and **3** with high ^{18}O-degrees which were the same as the exchange value in **1**→**1-^{18}O** (86:14). It is noteworthy that no ^{18}O-labelling at the hydroxy group could be obtained in the present acidic reaction.

The 3-CHOH of **2-^{18}O** (87%-^{18}O) and **3-^{18}O** (86%-^{18}O) were oxidized with pyridinium dichlochromate (PDC)[11] and with *N*-methylmorphorine oxide and a tetra-*n*-propyl-ammonium perruthenate,[18] respectively, to give 13^1-^{18}O-labelled **4-^{18}O** (86%-^{18}O) and **5-^{18}O** (84%-^{18}O). Little loss of the ^{18}O-atoms was detected during the oxidation.

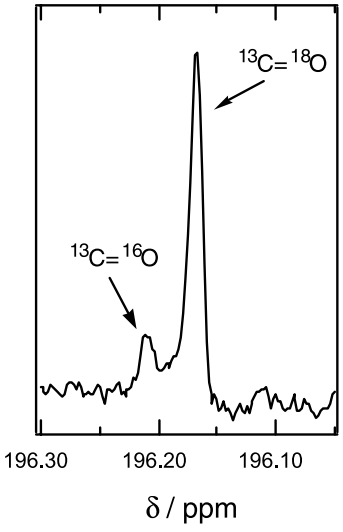


Figure 3. ^{13}C NMR resonances of the 13^1C in an ^{18}O-labelled product of **1** in $CDCl_3$.

2.2. Synthesis of 3^1,13^1-doubly-^{18}O-labelled pyropheophorbides

Using the above procedures for mono-labelling, preparation of 3^1,13^1-dioxo-labelled chlorophyll derivatives was examined ((i) in Scheme 2). Methyl pyropheophorbide-*d* (**4**) possessing the 3-formyl group and lacking the 13^2-methoxycarbonyl group in CH_2Cl_2 was treated with $H_2^{18}O$ in the presence of TFA to give a mixture of ^{18}O-(un)labelled **4** (79%). In the double labelling, a double amount of TFA was added, compared with the mono-labelling. In general, the 3-formyl group of chlorophyll derivatives has more reactivity than the 13-keto-carbonyl group.[13,14] Therefore, when the ^{18}O-exchanging reaction of **4** was quenched, a solid basic reagent (K_2CO_3) was used instead of an aq. basic solution (aq. 4% $NaHCO_3$) to avoid undesired rapid $CH^{18}O\rightarrow CH^{16}O$ by acidic $H_2^{16}O$ during the neutralization. The product in CH_2Cl_2 has two 13-carbonyl stretching vibrational bands at 1670 cm^{-1} (major) arising from both **4-^{18}O** and **^{18}O-4-^{18}O** and 1700 cm^{-1} (minor) of **^{18}O-4** and **4**. The present abbreviation for ^{18}O-labelled compounds is as follows; '**^{18}O-**' before a compound number means ^{18}O-labelling at the 3^1-position and '**-^{18}O**' after a number means ^{18}O-labelling at the 13^1-position. ^{18}O-Labelling degrees at the 3^1- and 13^1-positions of the product containing mainly **^{18}O-4-^{18}O** were estimated by combination of FAB-MS and IR studies according to the reported literature.[8] The FAB-MS analysis indicated the ratio of 65(±2):31(±2):4 for di-^{18}O-, mono-^{18}O- and unlabelled compounds, and the IR analysis indicated 86±1% for the 13^1-^{18}O-labelling degree in the product. The resulting product was thus a 65:10:21:4 mixture of **^{18}O-4-^{18}O**, **^{18}O-4**, **4-^{18}O** and **4** and the ^{18}O-labelling degrees of the 3-formyl and 13-keto carbonyl groups in **4** were estimated to be about 76 and 86%, respectively. Well-resolved ^{13}C signals of 13-C=^{16}O and C=^{18}O in $CDCl_3$ also gave ca. 84% of the 13^1-^{18}O-labelling: a ca. 0.04 ppm high-field shift of 13-^{13}C resonance by the C=$^{16}O\rightarrow$ C=^{18}O. On the other hand, the 3-^{13}CHO signals were

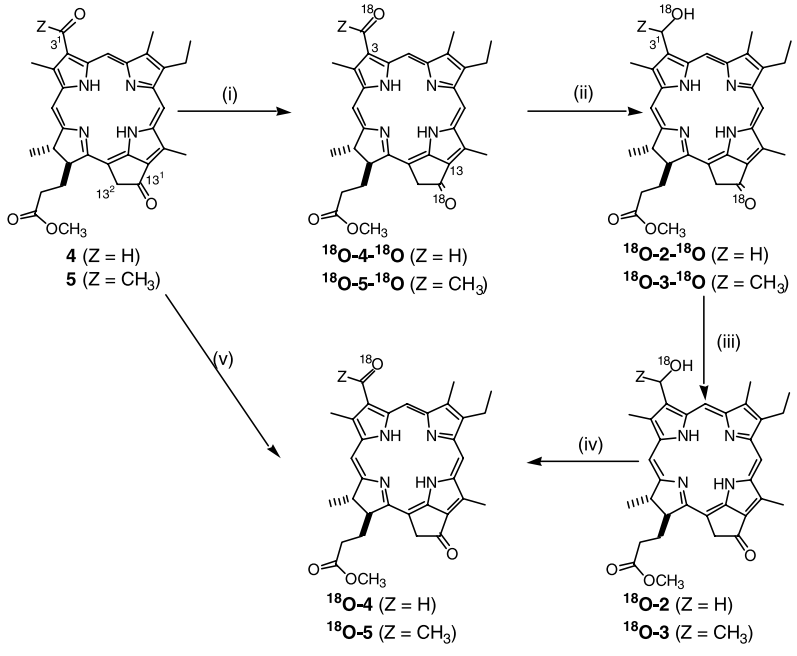
Table 2. ^{13}C chemical shifts δs (ppm) of the 3^1- and/or 13^1-carbon(s) in ^{18}O-labelled (pyro)chlorophyll derivatives, 3-substituted 13^1-oxo-chlorins in $CDCl_3$

Non-/^{18}O-labelled compounds	3^1-position				13^1-position		
	δ ($^{13}C{=}/{-}^{16}O$)	δ ($^{13}C{=}/{-}^{18}O$)	$\Delta\delta$[a]		δ ($^{13}C{=}^{16}O$)	δ ($^{13}C{=}^{18}O$)	$\Delta\delta$[a]
1-^{18}**O**	—	—	—		196.211	196.167	0.042
2-^{18}**O**	56.111	—	—		196.235	196.195	0.040
^{18}**O-2**-^{18}**O**	56.202	56.186	0.014		196.226	196.186	0.040
^{18}**O-2**	56.234	56.219	0.015		196.214	—	—
3-^{18}**O**	65.585	—	—		196.271	196.231	0.040
($3^1R/S$ =1:1)	65.516	—	—		196.261	196.219	0.042
^{18}**O-3**-^{18}**O**	65.560	65.539	0.021		196.259	196.219	0.040
($3^1R/S$ =1:1)	65.486	65.467	0.019		196.247	196.207	0.040
^{18}**O-3**	65.587	65.568	0.019		196.246	—	—
($3^1R/S$ =1:1)	65.514	65.495	0.019		196.235	—	—
4-^{18}**O**	≈188.265	—	—		195.938	195.898	0.040
^{18}**O-4**-^{18}**O**	n.d.	≈188.165	—		195.951	195.909	0.042
^{18}**O-4**	n.d.	≈188.325	—		196.004	—	—
5-^{18}**O**	199.438	—	—		196.122	196.080	0.042
^{18}**O-5**-^{18}**O**	199.357	199.311	0.046		196.066	196.024	0.040
^{18}**O-5**	199.400	199.352	0.048		196.099	—	—
6-^{18}**O**	173.340[b]	173.304[b]	0.036[b]		189.620	189.580	0.040
^{18}**O-7**	n.d.	≈188.090	—		189.470	—	—
^{18}**O-8**	56.226	56.213	0.013		189.604	—	—
9-^{18}**O**	172.930[b]	172.892[b]	0.038[b]		189.634	189.594	0.040
^{18}**O-10**	n.d.	≈188.110	—	—	189.514	—	—

[a] $\Delta\delta = \delta(C{=}/{-}^{16}O) - \delta(C{=}/{-}^{18}O)$.
[b] δ values in $17^3C{=}O$.

broader than the keto 13-^{13}CO and the ^{18}O-exchanging degree could not be estimated from the poorly-resolved ^{13}C of 3-C=^{16}O and C=^{18}O.

Regioselective reduction of the 3-formyl group of the above ^{18}O-label-mixed compounds containing **^{18}O-4-^{18}O** by t-Bu$NH_2\cdot BH_3$ gave a mixture of the corresponding 3-hydroxymethyl products possessing a molecular structure of **2** ((ii) in Scheme 2). The IR spectra of the mixed product of ^{18}O-(un)labelled **2** in THF indicated that the 13-C=^{18}O peaks of **2**-^{18}**O** and ^{18}**O-2**-^{18}**O** appeared at the same position (1670 cm^{-1}) and were shifted 30 cm^{-1} lower than the corresponding unlabelled 13-C=^{16}O (1700 cm^{-1}). The 3^1-O–H bands were so broad at around 3420 cm^{-1} that no apparent shift could be detected in the present mixture.[8] We estimated ^{18}O-labelling degrees at the 3^1- and 13^1-positions of the product by combination of FAB-MS and IR (vide supra), and confirmed them as 79 and 84%, respectively



Scheme 2. Synthesis of ^{18}O-labelled methyl pyropheophorbides at the 3^1- and/or 13^1-positions; (i) $H_2^{18}O$-TFA/CH_2Cl_2; (ii) t-BuNH_2BH_3/CH_2Cl_2 (for R^1=H); $NaBH_4$/MeOH–CH_2Cl_2 (for R^1=CH_3); (iii) H_2O–HCl/CH_3COCH_3; (iv) PDC/CH_2Cl_2–C_6H_6 (for R^1=H); $CH_3(O)N(CH_2CH_2)_2O$–Pr_4NRuO_4/CH_2Cl_2 (for R^1=CH_3); (v) $H_2^{18}O$-TFA (1/20 of (i))/CH_2Cl_2 (R^1=H).

(**^{18}O-2-^{18}O**:**^{18}O-2**:**2-^{18}O**:**2**=66:13:18:3).[†] The ^{13}C NMR measurements of the product in $CDCl_3$ showed that the 3^1C and 13^1C carbon resonances moved to high-fields about 0.02 ppm (56.202→56.186 ppm) and 0.04 ppm (196.250→196.210 ppm), respectively, by their ^{18}O-labelling. These peak heights (2:8) roughly afforded 80% ^{18}O-labelling at both the 3^1- and 13^1-positions.

Reaction of methyl 3-devinyl-3-acetyl-pyropheophorbide-*a* (**5**) with $H_2^{18}O$ in catalytic TFA afforded mainly **^{18}O-5-^{18}O** (see Scheme 2), identified by FAB-MS and IR spectra ((i) in Scheme 2). IR spectra of starting **5** and the product indicate that both 3- and 13-keto carbonyl stretching vibrational bands of **5** were down-shifted to about 30 cm^{-1} by exchanging the carbonyl oxygen atoms from ^{16}O to ^{18}O; 1672→1643 cm^{-1} for 3-C=O and 1695→1667 for 13-C=O. Their ^{13}C NMR spectra show that both the 3- and 13-C=O carbonyl carbon chemical shifts were high-field shifted about 0.04–0.05 ppm by the exchange from ^{16}O to ^{18}O; 199.357→199.311 and 196.066→196.024 ppm (Table 2). ^{18}O-Labelling degrees at the 3^1- and 13^1-positions of the product mixture containing mainly **^{18}O-5-^{18}O** were determined from FAB-MS and IR studies, similar to the case of **^{18}O-4-^{18}O**. Both ^{18}O-labelling degrees of **5** at the 3^1- and 13^1-positions were 85% and the product was a 72:13:13:2 mixture of **^{18}O-5-^{18}O**, **^{18}O-5**, **5-^{18}O** and **5**. Alternatively, the ^{13}C NMR spectrum was used for estimation of roughly ^{18}O-labelling degrees of **5** at the 3^1- and 13^1-positions, which were given as 85 and 84%, respectively, from the ratio of each ^{13}C=^{18}O and ^{13}C=^{16}O resonance peak height.

Regioselective reduction of the 3-acetyl group of the resulting mixture of ^{18}O-(un)labelled **^{18}O-5-^{18}O**, **^{18}O-5**, **5-^{18}O** and **5** by $NaBH_4$ gave a mixture of 3-(1-^{18}O-hydroxyethyl)-13^1-^{18}O-oxo-chlorin **^{18}O-3-^{18}O** (74%), **^{18}O-3** (12%), **3-^{18}O** (12%) and **3** (2%) [estimation from the FAB-MS and IR data] ((ii) in Scheme 2). The ^{18}O-content of **^{18}O-3-^{18}O**, **^{18}O-3**, **3-^{18}O** and **3** at the 3^1-position (86%) was nearly equal to that of **^{18}O-5-^{18}O**, **^{18}O-5**, **5-^{18}O** and **5** (85%), and the ^{18}O-content of the former at the 13^1-position was the same as that of the latter (85%). These results showed the ^{18}O-atoms at the 3^1- and 13^1-positions did not change during the reduction.

2.3. Synthesis of 3^1-singly-^{18}O-labelled pyropheophorbides

As described above, hydroxy-oxygen atoms cannot be exchanged by the present ^{18}O-labelling methods. We attempted the synthesis of 3^1-singly-^{18}O-labelled pyropheophorbides through ^{18}O-delabelling of the 13-keto-oxygen atoms. Doubly ^{18}O-labelled 3^1-hydoxy-13^1-oxo-chlorins **^{18}O-2-^{18}O** (79% for 3^1-^{18}O) and **^{18}O-3-^{18}O** (86% for 3^1-^{18}O) in acetone were treated with an aq. 2 M HCl solution (containing only unlabelled water) to give **^{18}O-2** and **^{18}O-3**, respectively ((iii) in Scheme 2). These products were identified as mono-^{18}O-labelled, 13^1-^{18}O-unlabelled and 3^1-^{18}O-labelled compounds by FAB-MS, IR and ^{13}C NMR spectra, respectively. From their FAB-MS analyses, 3^1-^{18}O-degrees of the products **^{18}O-2** and **^{18}O-3** were estimated to be 80±1 and 86±1%, respectively, indicating no ^{18}O-loss of the 3^1-hydroxy group during the delabelling at the 13^1-position.

Oxidation of the 3^1-^{18}O-hydroxy group of **^{18}O-2** (80%-^{18}O) and **^{18}O-3** (86%-^{18}O) afforded singly-3^1-^{18}O-oxo-compounds **^{18}O-4** and **^{18}O-5**, respectively ((iv) in Scheme 2). From their FAB-MS spectra, the 3-^{18}O-degrees of the products **^{18}O-4** and **^{18}O-5** were 69±1 and 85±1%, respectively, which were smaller than the ^{18}O-contents of the starting alcohols. The decrease would be ascribable to undesired delabelling of the relatively exchangeable (unstable) 3-carbonyl group (vide supra) and/or of the oxidation procedures.

Based on the difference in the reactivity between 3-CHO and 13-C=O (vide supra), we attempted regioselective ^{18}O-labelling at the 3-position of **4** by the present procedure ((v) in Scheme 2). Unlabelled **4** was treated with $H_2^{18}O$ and a one-tenth amount of TFA for **1**→**1-^{18}O**. The IR spectrum of the product gave 3-C=^{18}O stretching vibrational band at 1648 cm^{-1} and no more apparent shifted C=O (see Fig. 4). Its ^{13}C NMR spectra showed a small ^{13}C-resonance for the 13-C=^{18}O, indicating that a small amount of 13^1-oxo-oxygen atoms were exchanged to ^{18}O from ^{16}O. Predominant ^{18}O-labelling at the 3-CHO of **4** occurred as expected. From FAB-MS and IR spectral analyses, the regioselective ^{18}O-exchanging gave a mixture of **^{18}O-4-^{18}O**:**^{18}O-4**:**4-^{18}O**:**4**=2:88:0:10.

We attempted similar regioselective ^{18}O-labelling of 3-acetyl-**5** because the 3-C=O was more reactive in its reduction than the 13-C=O.[15] Under various acidic conditions, both the positions were labelled not to give selectively 3^1-^{18}O-labelled **^{18}O-5** by the above procedure.

2.4. Synthesis of ^{18}O-labelled pheophorbides (possessing 13^2-$COOCH_3$)

We tried preparation of 13^1-^{18}O-labelled methyl pheophorbide-*a* (**6-^{18}O**) possessing a methoxycarbonyl group at

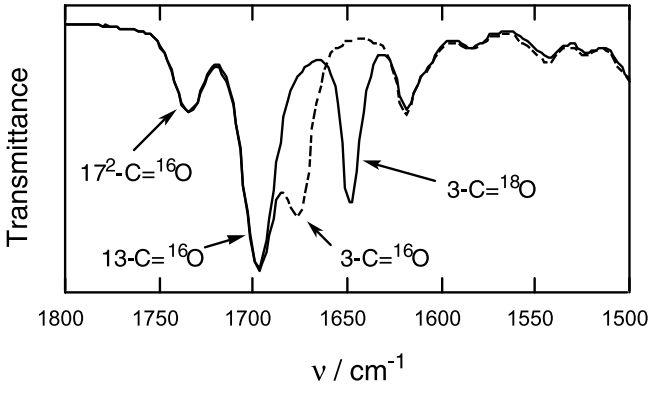


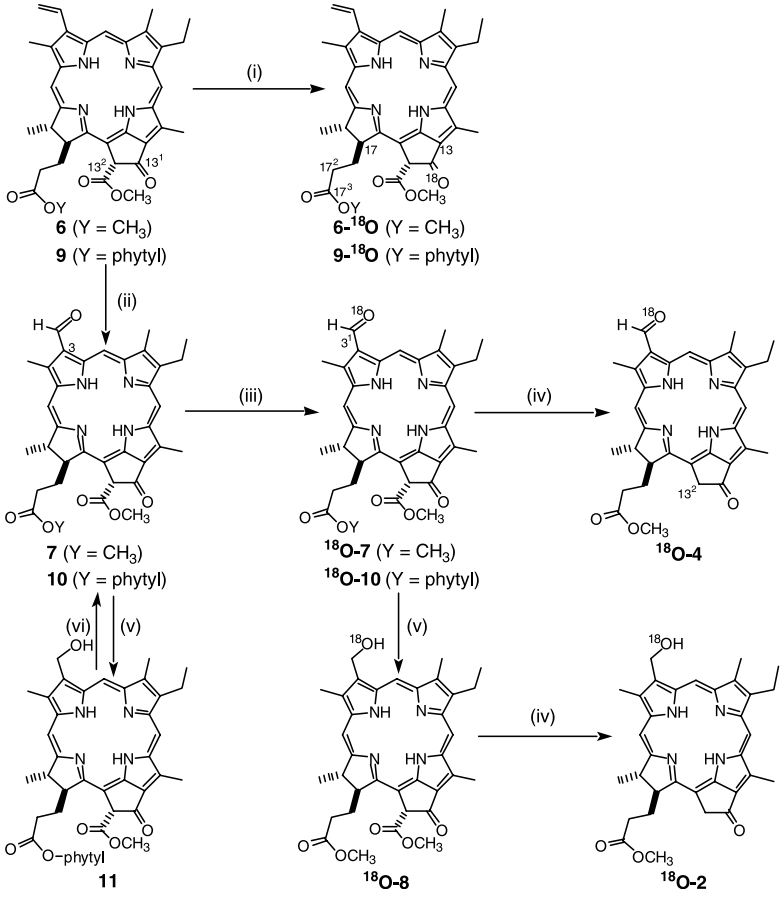
Figure 4. IR spectrum of **4** (broken) and its regioselectively ^{18}O-labelled product (solid) in CH_2Cl_2.

[†] Although **^{18}O-2-^{18}O** was yielded from reduction of **^{18}O-4-^{18}O**, the 3^1-^{18}O-degree of **^{18}O-2-^{18}O** and **^{18}O-2** (79±2%) was a little higher than that of **^{18}O-4-^{18}O** and **^{18}O-4** (76±2%), indicating the ^{18}O-atom of the reactive 3-formyl group would be slightly exchanged by ^{16}O coming from used matrix or environmental moisture in the of FAB-MS sample. In other words, the above ^{18}O-degree (76%) at the 3-CHO in **^{18}O-4-^{18}O** and **^{18}O-4** was underestimated.

the 13^2-position (see (i) in Scheme 3). In this paper, a mixture of 13^2-stereoisomers (pheophorbides possessing 13^2-$COOCH_3$) derived from chlorophyll-*a*/*a*′ was used as the starting materials of ^{18}O-labelling, and not separated. The 13^2-*S*/13^2-*R* (*a*/*a*′ or *d*/*d*′) ratio of each pheophorbide is shown in the Section 4. Under the same conditions described for **1**→**1**-^{18}**O**, methyl pheophorbide-*a* (**6**) could be partially ^{18}O-labelled (<15%), which would be ascribable to less reactivity and more steric hindrance of the keto carbonyl group. The labelling conditions were then changed severely to a higher reaction temperature and a higher acid concentration. After heating in $CHCl_3$ (50 °C) at five-fold concentrated TFA for 2-days, the ^{18}O-labelling of **6** was moderately achieved (ca. 25% of the chemical yield). Prolonged reaction led to decomposition of the desired product **6**-^{18}**O**. The FAB-MS spectra of the product indicated that they were constituted of doubly-, singly- and non-^{18}O-labelled **6** (9:60:31). ^{18}O-Labelling degrees of the products at the 13- and 13^2- or 17^2-C=O could not be estimated by IR analysis because of some overlapping bands in the three (un)labelled carbonyl groups; *ν*s of 13^2-C=^{16}O and 17^2-C=^{16}O were at around 1737 and *ν*s of 13-C=^{16}O, 13^2-C=^{18}O and 17^2-C=^{18}O were at around 1699 cm^{-1}. The ^{13}C NMR spectral analysis of the product was useful for determination of the ^{18}O-labelled positions and rough estimation of their ^{18}O-labelling ratios. In the ^{13}C NMR spectrum (Fig. 5), two new peaks appeared at about 0.04 ppm high-field sides of ^{16}O-attached 13- and 17^2-^{13}C peaks, which were assigned to ^{18}O-labelled 13- and 17^2-^{13}C, and no additional peak around ^{18}O-labelled 13^2-^{13}C was observed. Their peak intensities indicated that ^{18}O-labellings of 13- and 17^2-C=O were ca. 70 and 15%, respectively, and **6**-^{18}**O** was thus a major product.

Similarly to the ^{18}O-labelling of **4** to ^{18}**O**-**4**, methyl pheophorbide-*d* (**7**) possessing 3-CHO and 13^2-$COOCH_3$ in CH_2Cl_2 gave 3^1-singly-^{18}O-oxo-labelled compound ^{18}**O**-**7** in 86% yield ((iii) in Scheme 3). The obtained product was confirmed by ^1H-, ^{13}C NMR, IR and FAB-MS spectra, and was ^{18}O-labelled in an about 90% degree at the 3^1-position. The 13-keto group of **7** was restrained from conversion of ^{16}O to ^{18}O under the weakly acidic conditions. In this case, the 13^2-methoxycarbonyl group suppressed the reactivity of neighboring 13-keto-carbonyl group by its steric effect. Regioselective reduction of the 3-CHO of ^{18}**O**-**7** gave 3^1-^{18}O-hydroxy-chlorin ^{18}**O**-**8** (86%-^{18}O).

The resulting ^{18}**O**-**7** (90%-^{18}O) was further refluxed in collidine for 30 min to give 3^1-^{18}O-labelled pyrochlorin ^{18}**O**-**4** (60%-^{18}O) lacking 13^2-$COOCH_3$ ((iv) in Scheme 3). One-third amount of the ^{18}O-content in fairly reactive 3-C$H^{18}O$ (vide supra) was delabelled during the pyrolysis. On the other hand, pyrolysis of ^{18}**O**-**8** (86%-^{18}O) gave



Scheme 3. Synthesis of ^{18}O-labelled methyl pheophorbides and pheophytins; (i) $H_2^{18}O$-TFA/$CHCl_3$ (50 °C); (ii) OsO_4–$NaIO_4$–CH_3COOH/H_2O-THF; (iii) $H_2^{18}O$-TFA (1/50 of (i))/CH_2Cl_2; (iv) collidine (reflux); (v) *t*-$BuNH_2BH_3$/CH_2Cl_2; (vi) PDC/CH_2Cl_2–C_6H_6.

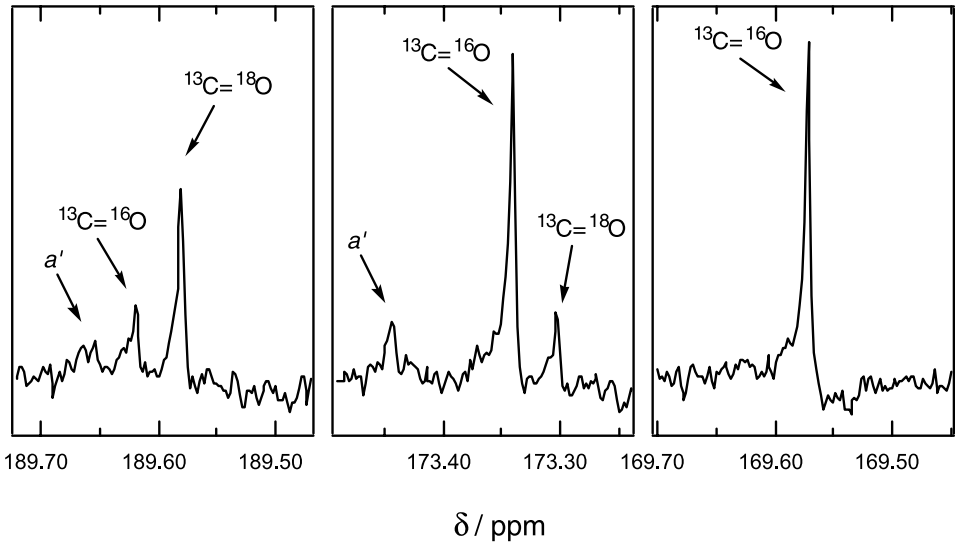


Figure 5. ^{13}C NMR resonances of the 13^1C (left), 17^3C (middle) and 13^2C (right) in an ^{18}O-labelling product of **6** in $CDCl_3$. The ^{13}C-resonances marked with a′ originated from 13^2-(*R*)stereoisomer of **6**.

3^1-^{18}O-hydroxy-pyrochlorin **^{18}O-2** (87%-^{18}O) without ^{18}O-delabelling of the 3^1-^{18}O-hydroxy oxygen.

2.5. Synthesis of ^{18}O-labelled pheophytins

Pheophytin-*a* (**9**, top-left drawing in Scheme 3) is one of the cofactors of the reaction center in PS2 of oxygenic photosynthetic organisms. Naturally occurring **9** possessing phytyl ester was a demetallation from the central Mg in chlorophyll-*a*. Using similar procedures to **6**→**6**-**^{18}O**, a doubly-, singly- and non-^{18}O-labelled mixture of **9** was obtained (13:67:20) in 10% chemical yield ((i) in Scheme 3). The yield was lower than that in **6**→**6**-**^{18}O** (20%), and was ascribable to the chemically labile 17^3-phytyl ester. The FAB-MS and ^{13}C NMR spectra indicated that the major product was **9**-**^{18}O** and the 17^2-C═O was partially ^{18}O-labelled.

Pheophytin-*d* (**10**) is a demetallated pigment of chlorophyll-*d* (3-devinyl-3-formyl-chlorophyll-*a*), and recently found as a cofactor in PS2 of *Acaryochloris marina*.[16] In this study, **10** possessing the 3-formyl group was derived from chlorophyll-*a* by organic synthetic modifications, not from chlorophyll-*d*. The oxidation of the 3-vinyl to formyl group ((ii) in Scheme 3) was stopped before disappearance of **9** to avoid prolonged reaction (undesired oxidation of the allyl positions in phytyl group). Separation of desired **10** from unchanged **9** using FCC was difficult due to their similar polarities. Therefore, the 3-CHO of **10** was reduced selectively in the mixture ((v) in Scheme 3), followed by separation of **11** (3-CH_2OH) and **9** (3-vinyl) using FCC. Oxidation of the separated **11** with PDC led to **10** ((iv) in Scheme 3). Under similar conditions as **7**→**^{18}O-7**, **^{18}O-10** (90%-^{18}O) were given from **10** in 75% yield ((iii) in Scheme 3). The phytyl ester remained during the acidic ^{18}O-labelling.

3. Conclusion

The keto and formyl carbonyl oxygen atoms of (pyro)pheophorbides and pheophytins reacted with $H_2^{18}O$ under acidic conditions to give efficiently the corresponding ^{18}O-labelled compounds at the 3^1- and/or 13^1-positions in the one-pot procedure. Regioselective ^{18}O-(un)labelling was achieved by use of the difference in the reactivities: 3-CHO > 3-C═O, 13-C═O (with 13^2-H_2) > 13-C═O (with 13^2-$COOCH_3$) ≫ 3-CHOH. The above ^{18}O-labelling procedures solved the two problems as shown in Introduction section; (I) the 3-acetyl group of **5** was readily ^{18}O-labelled and (II) the 13-carbonyl groups of pheophorbides possessing 13^2-COOMe were moderately ^{18}O-labelled. The spectral results of the all above prepared ^{18}O-compounds imply that the ^{18}O-labelling methods will be available for assignments of several chlorophyll structures and also for elucidation of environments around the chlorophyll pigments in a photosynthetic apparatus by means of FT-IR and NMR spectroscopies (see Tables 1 and 2). The present ^{18}O-labelling procedures would be useful for other natural chlorophylls including chlorophyll-*b*, *d* and bacteriochlorophyll-*e* possessing the formyl group and bacteriopheophytin-*a* possessing 3^1-keto group.

4. Experimental

4.1. General

Fourier-transfer IR measurements were carried out by CH_2Cl_2 or THF solutions at room temperature in a 0.1 mm KBr cell. Proton- and ^{13}C NMR measurements were performed on a 600 MHz NMR instrument. Further ^{13}C NMR information was gained by Distortionless Enhancement by Polarization Transfer (DEPT) techniques. MS spectra were recorded on a FAB mode. FAB-mass samples were dissolved in CH_2Cl_2 and *m*-nitrobenzyl alcohol was used as a matrix. In HRMS samples, glycerol and PEG-600 were further added as a matrix and an internal reference, respectively. CH_2Cl_2, $CHCl_3$ and THF for IR measurements and/or ^{18}O-labelling reaction were freshly distilled over CaH_2 before use. Flash column chromatography (FCC) was carried out on silica gel (particle size of 0.045–0.075 mm). Neutral alumina (particle size of

0.063–0.200 mm, 6.8–7.8 of pH) deactivated with water (6%) was used for gravity column chromatography.

4.2. Determination of ^{18}O-labelling degrees

The ^{18}O-labelling degrees of 3^1- and/or 13^1-^{18}O-labelled compounds were determined by using combination of the following two different methods: (1) simulation of the pattern of molecular ion peaks from FAB-MS spectra and (2) deconvolution peak height of the 13-C=^{16}O stretching bands from IR spectra in CH_2Cl_2 or THF.[8] Additionally, the ^{18}O-labelling degrees of 3^1- and/or 13^1-^{18}O-labelled compounds were estimated by using the peak height ratios of carbon-13 resonance of C=^{16}O and C=^{18}O in $CDCl_3$.

4.3. Compounds and synthetic procedures

All the synthetic ^{18}O-labelled compounds showed the same ^{1}H NMR, UV–visible and melting point data as the corresponding non-labelled compounds and their data are not described in this paper: please see their data of unlabelled compounds in cited references. ^{13}C NMR chemical shift of **10** and **11** were assigned from observed DEPT signals and reported data of pheophytin-*a*.[17] All the present ^{18}O-labelled products were abbreviated as the following rule; 3^1-^{18}O-, 13^1-^{18}O- and 3^1, 13^1-doubly-^{18}O-labelled compounds were **^{18}O-X**, **X-^{18}O** and **^{18}O-X-^{18}O** (**X** = compound number), respectively.

Non-^{18}O-labelled chlorophyll derivatives, methyl pyropheophorbide-*a* (**1**),[18] methyl 3-devinyl-3-hydroxymethyl-pyropheophorbide-*a* (**2**),[13] methyl bacteriopheophorbide-*d* (**3**),[18] methyl pyropheophorbide-*d* (**4**),[13] methyl 3-devinyl-3-acetyl-pyropheophorbide-*a* (**5**),[12] methyl pheophorbide-*a* (**6**),[19] methyl pheophorbide-*d* (**7**),[19] methyl 3-devinyl-3-hydroxymethyl-pheophorbide-*a* (**8**)[19] and pheophytin-*a* (**9**)[20] were prepared according to reported procedures by modifying chlorophyll-*a* extracted from *Spirulina geitleri*. Pheophytin-*d* (**10**) was derived from **9** (vide infra).

An unlabelled and its labelled chlorins were purified with the same conditions (FCC and recrystallization): please see the details at the first mentioned part in this section.

4.3.1. Synthesis of pheophytin-*d* (10). To an ice-chilled and stirred THF (20 ml) solution of pheophytin-*a* (**9**, 196.7 mg)[20] was added OsO_4 (ca. 5 mg) and an aq. solution (2 ml) of $NaIO_4$ (266 mg) and acetic acid (0.12 ml) was slowly dropped. After stirred overnight at room temperature under N_2, the reaction mixture was poured into ice water and CH_2Cl_2. The aq. phase was extracted with CH_2Cl_2 several times of and the combined organic phases were washed with aq. 4% $NaHCO_3$ and water (twice), dried over Na_2SO_4 and evaporated to dryness. Purification of the residue by FCC (2% Et_2O-CH_2Cl_2, the first brown fraction) gave a mixture of desired 3-formyl-**10** and unreacted 3-vinyl-**9**. Prolonged oxidation mainly led to an undetermined degradation compound. Separation of **10** from **9** was difficult due to their similar polarities. The resulting mixture in CH_2Cl_2 (30 ml) was reduced with *t*-BuNH_2·BH_3 (58.2 mg)[19] to give 3-hydroxymethyl-**11** and unchanged **9**. The mixture was easily separated by FCC to afford **9** as the first black fraction (2% Et_2O-CH_2Cl_2) and **11** as the second black fraction (7% Et_2O-CH_2Cl_2, $a/a' = 7/2$). The separated **11** in distilled CH_2Cl_2 (2 ml) and dry benzene (8 ml) was oxidized with PDC (106.7 mg)[11] to afford **10** (38.6 mg, 20% yield, $d/d' = 11/2$) as a black solid.

Compound **10**. ($d/d' = 11/2$): mp 150–153 °C; Vis (CH_2Cl_2) λ_{max} 659 (relative intensity, 81), 633 (9.6), 552 (17), 520 (15), 426 (100), 357 (88), 333 (28), 311 nm (30); IR (CH_2Cl_2) 1738 (13^2-, 17^2-C=O), 1704 (13-C=O), 1678 (3-C=O), 1614 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ (d/d') 11.49 (1H, s, 3-CHO), 10.15/14, 9.54/52, 8.81/76 (each 1H, s, 5-, 10-, 20-H), 6.34/23 (1H, s, 13^1-CH), 5.13/19 (1H, br-t, $J = 7$ Hz, phytyl-vinyl-H), 4.56–4.41 (3H, m, 17^2-CO_2CH_2, 18-H), 4.30/37 (1H, td, $J = 12$, 18 Hz, 17-H), 3.92/83 (3H, s, 13^2-CO_2CH_3), 3.62 (2H, q, $J = 8$ Hz, 8-CH_2), 3.72, 3.71, 3.20 (each 3H, s, 2-, 7-, 12-CH_3), 2.69–2.15 (4H, m, 17-CH_2CH_2), 1.92–1.83, 1.52–1.46 (each 1H, m, phytyl-allyl-H), 1.85 (3H, d, $J = 7$ Hz, 18-CH_3), 1.67 (3H, t, $J = 8$ Hz, 8^1- CH_3), 1.60 (3H, s, phytyl-allyl-CH_3), 1.37–0.94 (19H, phytyl-tertiary-H×3, phytyl-secondary-H×8), 0.84, 0.79/78, 0.78/76 (6H, 3H, 3H, each d, $J = 6$, 7, 7 Hz, phytyl-CH_3×4), −0.16/00, −2.12/1.91 (each 1H, s, NH); ^{13}C NMR ($CDCl_3$) δ (d) 189.490 (13^{1}C), 188.228–188.155 (3^{1}CH), 172.787 (17^{3}C), 170.498 (19C), 169.363 (13^{3}C), 162.429 (16C), 155.370 (6C), 152.327 (9C), 149.332 (14C), 145.021 (8C), 142.932, 141.119 (1C, phytyl-3C), 139.793, 137.771, 134.290, 131.008 (2C, 3C, 4C, 7C), 130.302 (13C), 129.568 (12C), 117.616 (phytyl-2CH), 106.141 (15C), 103.775 (10CH), 100.294 (5CH), 94.866 (20CH), 64.839 (13^{2}CH), 61.510 (phytyl-1CH_2), 52.953 (13^5CH_3), 51.666 (17CH), 49.606 (18CH), 39.771 (phytyl-4CH_2), 39.313 (phytyl-14CH_2), 37.348, 37.282, 37.224 (phytyl-8CH_2, -10CH_2, -12CH_2), 36.595 (phytyl-6CH_2), 32.722 (phytyl-11CH), 32.589 (phytyl-7CH), 31.148 (17^1CH_2), 29.775 (17^2CH_2), 27.934 (phytyl-15CH), 24.958, 24.768, 24.385 (phytyl-5CH_2, -9CH_2, -13CH_2), 23.346 (18^1CH_3), 22.687, 22.592 (phytyl-15^1CH_3, -16CH_3), 19.692, 19.626 (phytyl-7^1CH_3, -11^1CH_3), 19.330 (8^1CH_2), 17.308 (8^2CH_3), 16.258 (phytyl-3^1CH_3), 12.224 (2^1CH_3), 11.241 (12^1CH_3), 11.117 (7^1CH_3); HRMS (FAB) m/z 873.5521, calcd for $C_{54}H_{73}N_4O_6$ (MH^+) 873.5530.

4.3.2. 3-Hydroxtmethyl-3-devinyl-pheophytin-*a* (11). ($a/a' = 7/2$): mp 166–169 °C; Vis (CH_2Cl_2) λ_{max} 662 (rel., 50), 605 (10), 535 (11), 504 (12), 410 (100), 322 nm (23); IR (THF) ca. 3420 (br, 3^1-OH), 1741 (13^2-COO and 17^2-COO), 1705 (13-C=^{16}O), 1620 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) δ (a/a') 9.38/39, 9.33/27, 8.53/48 (each 1H, s, 5-,10-,20-H), 6.21/16 (1H, s, 13^1-CH), 5.79/77 (2H, s, 3-CH_2), 5.21–5.14 (1H, m, phytyl-vinyl-H), 4.56–4.42 (3H, m, 17^2-CO_2CH_2, 18-H), 4.18/28 (1H, dt, $J = 8$, 2 Hz, 17-H), 3.88/82 (3H, s, 13^2-CO_2CH_3), 3.58 (2H, q, $J = 8$ Hz, 8-CH_2), 3.61, 3.35/34, 3.16/13 (each 3H, s, 2-, 7-, 12-CH_3), 2.63–2.12 (5H, m, 3^1-OH, 17-CH_2CH_2), 1.92–1.83, 1.52–1.46 (each 1H, m, phytyl-allyl-H_2), 1.78 (3H, d, $J = 8$ Hz, 18-CH_3), 1.64 (3H, t, $J = 8$ Hz, 8^1-CH_3), 1.60 (3H, s, phytyl-allyl-CH_3), 1.37–0.94 (19H, phytyl-tertiary-H×3, phytyl-secondary-2H×8), 0.85, 0.80/79, 0.79/76 (6H, 3H, 3H, d, $J = 7$, 6, 6 Hz, phytyl-CH_3×4), 0.26/48, −1.82/1.58 (each 1H, s, NH); ^{13}C NMR ($CDCl_3$) δ (a) 189.632 (13^{1}C), 172.949 (17^{3}C), 172.129 (19C), 169.544 (13^{3}C), 161.169 (16C), 155.484 (6C), 150.991 (9C), 149.456 (14C), 145.182 (8C), 142.912, 141.586 (1C, phytyl-3C), 137.866 (11C), 136.703, 136.278,

136.259, 133.879 (2C, 3C, 4C, 7C), 129.091 (13C), 128.919 (12C), 117.692 (phytyl-2CH), 105.282 (15C), 104.281 (10CH), 97.079 (5CH), 93.235 (20CH), 64.638 (13^2CH), 61.510 (phytyl-1CH_2), 56.235 (3^1CH_2), 52.858 (13^5CH_3), 51.131 (17CH), 50.063 (18CH), 39.800 (phytyl-4CH_2), 39.332 (phytyl-14CH_2), 37.367, 37.300, 37.234 (phytyl-8CH_2, -10CH_2, -12CH_2), 36.633 (phytyl-6CH_2), 32.741 (phytyl-11CH), 32.607 (phytyl-7CH), 31.224 (17^1CH_2), 29.794 (17^2CH_2), 27.943 (phytyl-15CH), 24.986, 24.757, 24.404 (phytyl-5CH_2, -9CH_2, -13CH_2), 23.040 (18^1CH_3), 22.697, 22.601 (phytyl-15$^1CH_3$, -16CH_3), 19.702, 19.644 (phytyl-7$^1CH_3$, -11$^1CH_3$), 19.368 (8^1CH_2), 17.365 (8^2CH_3), 16.287 (phytyl-3$^1CH_3$), 12.052 (2^1CH_3), 11.193 (12^1CH_3), 11.098 (7^1CH_3); HRMS (FAB) *m/z* 875.5658, calcd for $C_{54}H_{75}N_4O_6$ (MH^+) 875.5687.

4.4. General procedures for modification and ^{18}O-labelling of chlorophyll derivatives

^{18}O-Labelling procedure at the 3^1- and/or 13^1-oxo-oxygen of chlorophyll derivatives under biphasic conditions. TFA (0.8–16 μl) and $H_2^{18}O$ (ca. 95% ^{18}O atom, 0.1 ml) were added to a distilled CH_2Cl_2 solution (2 ml) of a chlorin (ca. 14–40 μmol) and the mixture in a sealed vial was stirred at room temperature for one day. After opening the vial, the reaction mixture was neutralized by an aq. 4% $NaHCO_3$ solution and extracted by CH_2Cl_2. The organic phase was washed with distilled water (twice), dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness to give the ^{18}O-labelled compound after FCC and recrystallization.

^{18}O-delabelling procedure at 13^1-oxo-oxygen of 3^1-^{18}OH-13^1-^{18}O-labelled 3^1-hydroxy-chlorins. A 3^1,13^1-^{18}O-labelled 3^1-hydroxy-13^1-oxo-chlorin (ca. 16–20 μmol) was treated with an aq. 2 M HCl solution (2 ml) in acetone (5 ml) by stirring at room temperature for 3.5 h to give the 13^1-oxo-unlabelled compound after the same work-up as in the above labelling.

Oxidation of the 3-hydroxymethyl to 3-formyl group of chlorins. A 3-hydroxymethyl-chlorin (14.1–15.7 μmol) was dissolved in distilled CH_2Cl_2 (1 ml) and dry benzene (5 ml). After addition of PDC (ca. 3–5 equiv), the solution was stirred overnight at room temperature under N_2.[11] The reaction mixture was poured into Et_2O and the same work-up as in the above labelling afforded the 3-formyl-chlorin.

Oxidation of the 3-(1-hydroxyethyl) to 3-acetyl group of chlorins. *N*-Methylmorpholine-*N*-oxide (ca. 4–6 equiv) and tetra-*n*-propylammonium perruthenate (a catalytic amount) were added to a distilled CH_2Cl_2 solution (5 ml) of a 3-hydroxymethyl-chlorin (12.3–15.1 μmol) with stirring at room temperature under N_2.[12] When the starting material disappeared on thin layer chromatography (TLC), water was added to the mixture. The same work-up as in the above labelling gave the 3-acetyl-chlorin.

Reduction of the 3-formyl to 3-hydroxymethyl group of chlorins. The 3-formyl group of a chlorin (26.0–39.5 μmol) was dissolved in CH_2Cl_2 (5 ml) and treated with *t*-$BuNH_2 \cdot BH_3$ (ca. 5 equiv) for 1 h at room temperature under N_2, followed by addition of a 2% aq. HCl solution.[13] The same work-up as in the above labelling yielded the 3-hydroxymethyl-chlorin.

Reduction of the 3-acetyl to 3-(1-hydroxyethyl) group of chlorins. A methanol solution (ca. 0.05–0.1 ml) saturated with $NaBH_4$ was added in small aliquots to stirring dry CH_2Cl_2 solution (3 ml) of a 3-acetyl-chlorin (ca. 22 μmol) with stirring at room temperature under N_2.[15] When the starting acetyl-chlorin disappeared as soon from monitoring of the visible absorption spectra (682→660 nm), the same quenching and work-up as in the above reduction gave the 3-(1-hydroxyethyl)-chlorin.

Removal of the 13^2-methoxycarbonyl group of pheophorbides to pyropheophorbides. A pheophorbide (ca. 20–32 μmol) possessing 13^2-$COOCH_3$ was refluxed in collidine (20–25 ml) for 30–45 min under N_2.[17] The cooled mixture was distilled in vacuo at ca. 50 °C and the residues were purified by FCC and recrystallization to afford the corresponding pyropheophorbides lacking 13^2-$COOCH_3$.

4.5. Synthesis of ^{18}O-labelled chlorophyll derivatives

4.5.1. 13^1-^{18}O-Labelled methyl pyropheophorbide-*a* (1-^{18}O). 3-Vinyl-chlorin **1** (14.0 mg) was ^{18}O-labelled with catalytic TFA (8 μl) to give an 86:14 mixture of **1**-^{18}**O** and **1** (13 mg, 93% yield)[8] as a black solid after FCC (5% Et_2O-CH_2Cl_2) and recrystallization (CH_2Cl_2–MeOH); ^{13}C NMR ($CDCl_3$) δ 196.211 ($13^1C{=}{}^{16}O$), 196.167 ($13^1C{=}{}^{18}O$); MS (FAB) *m/z* 550 (M^+ for **1**-^{18}**O**).

4.5.2. 13^1-^{18}O-Labelled methyl 3-devinyl-3-hydroxymethyl-pyropheophorbide-*a* (2-^{18}O). Unlabelled **2** (17.2 mg) was ^{18}O-labelled with catalytic TFA (16 μl) and gave an 87:13 mixture of **2**-^{18}**O** and **2** (10.1 mg, 59% yield)[8] as a black solid after FCC (15% Et_2O-CH_2Cl_2) and recrystallization (CH_2Cl_2–hexane); ^{13}C NMR ($CDCl_3$) δ 196.235 ($13^1C{=}{}^{16}O$), 196.195 ($13^1C{=}{}^{18}O$); MS (FAB) *m/z* 554 (M^+ for **2**-^{18}**O**).

4.5.3. 3^1,13^1-^{18}O-Labelled methyl 3-devinyl-3-hydroxymethyl-pyropheophorbide-*a* (^{18}O-2-^{18}O). A 65:10:21:4 mixture of ^{18}**O**-4-^{18}**O**, ^{18}**O**-**4**, **4**-^{18}**O** and **4** (see below, 14.4 mg) was reduced with *t*-$BuNH_2 \cdot BH_3$ (12.5 mg) to give a 66:12.5:17.5:4 mixture of ^{18}**O**-2-^{18}**O**, ^{18}**O**-**2**, **2**-^{18}**O** and **2** (13.4 mg, 93% yield)[8]; ^{13}C NMR ($CDCl_3$) δ 196.226 ($13^1C{=}{}^{16}O$), 196.186 ($13^1C{=}{}^{18}O$), 56.202 ($3^1C{-}{}^{16}O$), 56.186 ($3^1C{-}{}^{18}O$); MS (FAB) *m/z* 556 (M^+ for ^{18}**O**-2-^{18}**O**).

4.5.4. 3^1-^{18}O-Labelled methyl 3-devinyl-3-hydroxymethyl-pyropheophorbide-*a* (^{18}O-2). The above mixture of ^{18}**O**-2-^{18}**O**, ^{18}**O**-**2**, **2**-^{18}**O** and **2** (11.1 mg) was ^{18}O-delabelled to give an 8:2 mixture of ^{18}**O**-**2** and **2** (8.3 mg, 75% yield); IR (THF) 3400 (br, 3^1-^{16,18}O–H,), 1741 (17^2-$C{=}{}^{16}O$), 1700 (13-$C{=}{}^{16}O$), 1622 cm^{-1} (C=C); ^{13}C NMR ($CDCl_3$) δ 56.234 ($3^1C{-}{}^{16}O$), 56.219 ($3^1C{-}{}^{18}O$); MS (FAB) *m/z* 554 (M^+ for ^{18}**O**-**2**).

Alternatively, an 86:14 mixture of ^{18}**O**-**8** and **8** (see below, 19.3 mg) was pyrolyzed to give an 87:13 mixture of ^{18}**O**-**2** and **2** (9.3 mg, 53% yield).

4.5.5. 13^1-^{18}O-Labelled methyl bacteriopheophorbide-*d*

(3-^{18}O). Unlabelled **3** (13.4 mg) was ^{18}O-labelled with catalytic TFA (16 μl) to give an 86:14 mixture of **3**-^{18}**O** and **3** (9.7 mg, 72% yield)[8] as a black solid after FCC (7–12% Et_2O-CH_2Cl_2) and recrystallization (CH_2Cl_2–hexane); ^{13}C NMR ($CDCl_3$) δ (3^1-*R*:*S*=1:1) 196.271/261 ($13^1C{=}{}^{16}O$), 196.231/219 ($13^1C{=}{}^{18}O$); MS (FAB) *m*/*z* 568 (M^+ for **3**-^{18}**O**).

4.5.6. 3^1,13^1-^{18}O-Labelled methyl bacteriopheophorbide-*d* (^{18}O-3-^{18}O). A 72:13:13:2 mixture of ^{18}O-5-^{18}O, ^{18}O-5, 5-^{18}O and **5** (12.5 mg) was reduced with $NaBH_4$ to give a 74:12:12:2 mixture of ^{18}O-3-^{18}O, ^{18}O-3, 3-^{18}O and **3** (8.5 mg, 68% yield); IR (THF) 3410 (br, 3^1-^{16,18}O–H), 1740 (17^2-C=^{16}O), 1699 (13-C=^{16}O), 1670 (13-C=^{18}O), 1621 cm^{-1} (C=C); ^{13}C NMR ($CDCl_3$) δ (3^1-*R*:*S*=1:1) 196.259/247 ($13^1C{=}{}^{16}O$), 196.219/207 ($13^1C{=}{}^{18}O$), 65.560/486 (3^1C–^{16}O), 65.539/467 (3^1C–^{18}O); MS (FAB) *m*/*z* 570 (M^+ for ^{18}O-3-^{18}O).

4.5.7. 3^1-^{18}O-Labelled methyl bacteriopheophorbide-*d* (^{18}O-3). A 72:13:13:2 mixture of ^{18}O-3-^{18}O, ^{18}O-3, 3-^{18}O and **3** (9.2 mg) was ^{18}O-delabelled to give an 86:14 mixture of ^{18}O-3 and **3** (6.9 mg, 75% yield) as a black solid; IR (THF) 3410 (3^1-^{16,18}O–H, br), 1741 (17^2-C=^{16}O), 1700 (13-C=^{16}O), 1622 cm^{-1} (C=C); ^{13}C NMR ($CDCl_3$) δ (3^1-*R*:*S* =1:1) 65.587/65.514 (3^1C–^{16}O), 65.568/65.495 (3^1C–^{18}O); MS (FAB) *m*/*z* 568 (M^+ for ^{18}O-3).

4.5.8. 13^1-^{18}O-Labelled methyl pyropheophorbide-*d* (4-^{18}O). An 87:13 mixture of 2-^{18}O and **2** (8.7 mg) was oxidized with PDC (14.3 mg) to give a mixture of 4-^{18}O and **4** (5.1 mg, 59% yield)[8] as a dark brown solid after purification by FCC (4–5% Et_2O-CH_2Cl_2, the first brown fraction) and recrystallization (CH_2Cl_2–hexane); ^{13}C NMR ($CDCl_3$) δ 195.938 ($13^1C{=}{}^{16}O$), 195.898 ($13^1C{=}{}^{18}O$); MS (FAB) *m*/*z* 552 (M^+ for 4-^{18}O).

4.5.9. 3^1,13^1-^{18}O-Labelled methyl pyropheophorbide-*d* (^{18}O-4-^{18}O). Compound **4** (7.5 mg) was ^{18}O-labelled with catalytic TFA (16 μl) [neutralization by addition of solid K_2CO_3] to give a 65:10:21:4 mixture of ^{18}O-4-^{18}O, ^{18}O-4, 4-^{18}O and **4** (6.0 mg, 79% yield)[8]; ^{13}C NMR ($CDCl_3$) δ 195.951 ($13^1C{=}{}^{16}O$), 195.909 ($13^1C{=}{}^{18}O$), 188.222–188.136 (br, $3^1C{=}{}^{16,18}O$); MS (FAB) *m*/*z* 554 (M^+ for ^{18}O-4-^{18}O).

4.5.10. 3^1-^{18}O-Labelled methyl pyropheophorbide-*d* (^{18}O-4). An 8:2 mixture of ^{18}O-2 and **2** (7.8 mg) was oxidized by PDC (26.7 mg) to afford a 69:31 mixture of ^{18}O-4 and **4** (4.1 mg, 53% yield); IR (CH_2Cl_2) 1734 (17^2-C=^{16}O), 1698 (13-C=^{16}O), 1676 (sh, 3-C=^{16}O), 1648 (3-C=^{18}O), 1618 cm^{-1} (C=C); ^{13}C NMR ($CDCl_3$) δ 188.283–188.189 (br, $3^1C{=}{}^{16,18}O$); MS (FAB) *m*/*z* 552 (M^+ for ^{18}O-4).

Alternatively, **4** (9.9 mg) was ^{18}O-labelled with catalytic TFA (0.8 μl) to give a 2:88:10 mixture of ^{18}O-4-^{18}O, ^{18}O-4 and **4** (8.0 mg, 81% yield) or a 9:1 mixture of ^{18}O-7 and **7** (see below, 12.0 mg) in collidine (20 ml) was pyrolyzed for 45 min to give a 6:4 mixture of ^{18}O-4 and **4** (5.7 mg, 72% yield).

4.5.11. 13^1-^{18}O-Labelled methyl 3-devinyl-3-acetyl pyropheophorbide-*a* (5-^{18}O). An 87:13 mixture of 3-^{18}O and **3** (7.0 mg) was oxidized with *N*-oxide (6.1 mg) and perruthenate (0.8 mg) to give a 84:16 mixture of 5-^{18}O and **5** (4.0 mg, 57% yield)[8] as a black solid after FCC (5–6% Et_2O-CH_2Cl_2, the first brown fraction) and recrystallization (CH_2Cl_2–hexane); ^{13}C NMR ($CDCl_3$) δ 196.122 ($13^1C{=}{}^{16}O$), 196.080 ($13^1C{=}{}^{18}O$); MS (FAB) *m*/*z* 566 (M^+, for 5-^{18}O).

4.5.12. 3^1,13^1-^{18}O-Labelled methyl 3-devinyl-3-acetyl-pyropheophorbide-*a* (^{18}O-5-^{18}O). Compound **5** (9.8 mg) was ^{18}O-labelled with catalytic TFA (16 μl) to give a 72:13:13:2 mixture of ^{18}O-5-^{18}O, ^{18}O-5, 5-^{18}O and **5** (8.1 mg, 82% yield); IR (CH_2Cl_2) 1734 (17^2-C=^{16}O), 1695 (13-C=^{16}O), 1667 (13-C=^{18}O), 1643 (3-C=^{18}O), 1618 cm^{-1} (C=C); ^{13}C NMR ($CDCl_3$) δ 199.357 ($3^1C{=}{}^{16}O$), 199.311 ($3^1C{=}{}^{18}O$), 196.066 ($13^1C{=}{}^{16}O$), 196.024 ($13^1C{=}{}^{18}O$); MS (FAB) *m*/*z* 568 (M^+, for ^{18}O-5-^{18}O).

4.5.13. 3^1-^{18}O-Labelled methyl 3-devinyl-3-acetyl pyropheophorbide-*a* (^{18}O-5). An 86:14 mixture of ^{18}O-3 and **3** (8.6 mg) was oxidized with *N*-oxide (10.9 mg) and perruthenate (2.0 mg) to give an 85:15 mixture of ^{18}O-5 and **5** (6.9 mg, 80% yield); IR (CH_2Cl_2) 1734 (17^2-C=^{16}O), 1695 (13-C=^{16}O), 1640 (3-C=^{18}O), 1619 cm^{-1} (C=C); ^{13}C NMR ($CDCl_3$) δ 199.400 ($3^1C{=}{}^{16}O$), 199.352 ($3^1C{=}{}^{18}O$); MS (FAB) *m*/*z* =566 (M^+ for ^{18}O-5).

4.5.14. 13^1-^{18}O-Labelled methyl pheophorbide-*a* (6-^{18}O). Compound **6** (12.1 mg, *a*/*a*′ =6/1) was ^{18}O-labelled with TFA (40 μl) and $H_2^{18}O$ (0.1 ml) in distilled $CHCl_3$ (2 ml) at 50 °C for 2 d, and gave a mixture containing 6-^{18}O (3.1 mg, 26% yield, doubly-:singly-:non-^{18}O-labelled **6**=9:60:31, *a*/*a*′ ratio of 6-^{18}O was approx. 7/1) as a black solid after FCC (5% Et_2O/CH_2Cl_2), successive alumina column (CH_2Cl_2) and recrystallization (CH_2Cl_2–hexane); IR (CH_2Cl_2) 1737 (13^2-, 17^2-C=^{16}O), 1699 (13-C=^{16}O and 17^2-C=^{18}O), 1669 (13-C=^{18}O), 1619 cm^{-1} (C=C); ^{13}C NMR ($CDCl_3$) δ (*a*/*a*′) 189.620 ($13^1C{=}{}^{16}O$, *a*), 189.580/653 ($13^1C{=}{}^{18}O$), 173.340/443 ($17^3C{=}{}^{16}O$), 173.304 ($17^3C{=}{}^{18}O$, *a*); MS (FAB) *m*/*z* 608 (M^+ for 6-^{18}O).

4.5.15. 3^1-^{18}O-Labelled methyl pheophorbide-d (^{18}O-7). Compound **7** (10.2 mg, *d*/*d*′=9/1) was ^{18}O-labelled with catalytic TFA (0.8 μl) to give a 9:1 mixture of ^{18}O-7 and **7** (8.8 mg, 86% yield, *d*/*d*′=ca.7/1) as a black solid after FCC (3–5% Et_2O-CH_2Cl_2, a main brown fraction) and recrystallization (CH_2Cl_2–hexane); IR (CH_2Cl_2) 1739 (13^2-, 17^2-C=^{16}O), 1703 (13-C=^{16}O), 1678 (sh, 3-C=^{16}O), 1650 (3-C=^{18}O), 1619 cm^{-1} (C=C); ^{13}C NMR ($CDCl_3$) δ 188.19–188.045 ($3^1C{=}{}^{16,18}O$); MS (FAB) *m*/*z* 610 (M+ for ^{18}O-7).

4.5.16. 3^1-^{18}O-Labelled methyl 3-devinyl-3-hydroxymethyl-pheophorbide-*a* (^{18}O-8). A 9:1 mixture of ^{18}O-7 and **7** (24.1 mg, *d*/*d*′=7/1) was reduced with *t*-$BuNH_2 \cdot BH_3$ (22.0 mg) to give an 86:14 mixture of ^{18}O-8 and **8** (19.3 mg, 80% yield, *a*/*a*′=ca. 8/1) after FCC (8–10% Et_2O-CH_2Cl_2, a main black fraction) and recrystallization (CH_2Cl_2–hexane); IR (THF) ca. 3415 (br, 3^1-^{16,18}O–H), 1742 (13^2-, 17^2-C=^{16}O), 1705 (13-C=^{16}O), 1620 cm^{-1} (C=C); ^{13}C

NMR ($CDCl_3$) δ (a/a') 56.226 (3^1C–^{16}O, a), 56.213/56.190 (3^1C–^{18}O); MS (FAB) m/z 612 (M^+ for **^{18}O-8**).

4.5.17. 13^1-^{18}O-Labelled pheophytin-*a* (9-^{18}O). Pheophytin-*a* (**9**, $a/a'=3/1$, 22.2 mg) was ^{18}O-labelled with TFA (40 μl) and $H_2^{18}O$ (0.1 ml) in $CHCl_3$ (2 ml) at 50 °C for 2 d to give a mixture containing **9-^{18}O** (2.2 mg, 10% yield, doubly-/singly-/non-^{18}O-labelled **9**=13:67:20, a/a'=ca. 6/1) as a black solid after FCC (2% Et_2O-CH_2Cl_2), alumina column (CH_2Cl_2) and recrystallization (CH_2Cl_2–MeOH); IR (CH_2Cl_2) 1736 (13^2-, 17^2-C=^{16}O), 1699 (13-C=^{16}O and 17^2-C=^{18}O), 1669 (13-C=^{18}O), 1619 cm^{-1} (C=C); ^{13}C NMR ($CDCl_3$) δ (a/a') 189.634 (13^1C=^{16}O, a), 189.594/691 (13^1C=^{18}O), 172.930/173.005 (17^3C=^{16}O), 172.892 (17^3C=^{18}O, a); MS (FAB) m/z 872 (M^+ for **9-^{18}O**).

4.5.18. 3^1-^{18}O-Labelled pheophytin-*d* (^{18}O-10). Pheophytin-*d* (**10**, 13.9 mg, d/d' =11/2) was ^{18}O-labelled with catalytic TFA (0.8 μl) to give a 9:1 mixture of **^{18}O-10** and **10** (10.5 mg, 75%, d/d' =11/2) as a black solid after FCC (1–2% Et_2O-CH_2Cl_2 as a main brown fraction) and recrystallization (CH_2Cl_2–MeOH); IR (CH_2Cl_2) 1739 (13^2-, 17^2-C=^{16}O), 1703 (13-C=^{16}O), 1677 (sh, 3-C=^{16}O), 1649 (3-C=^{18}O), 1617 cm^{-1} (C=C); ^{13}C NMR ($CDCl_3$) δ 188.190–188.045 (3^1-C=^{16,18}O); MS (FAB) m/z 876 (MH^+ for **^{18}O-10**).

Acknowledgements

We thank Dr. Tomohiro Miyatake, Ryukoku University, and Dr. Tadashi Mizoguchi, Ritsumeikan University, for measurements of FAB-MS and NMR spectra, respectively, as well as for their helpful discussion. This work was partially supported by Grants-in-Aid for Science Research (No. 15033271/17029065) on Priority Areas (417) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of the Japanese Government and for Scientific Research (B) (No. 15350107) from the Japan Society for the Promotion of Science (JSPS).

References and notes

1. Scheer, H. In Green, B. R., Parson, W. W., Eds.; Light-harvesting antennas in photosynthesis; Kluwer: Dordrecht, The Netherlands, 2003; pp 29–81.
2. Roszak, A. W.; Howard, T. D.; Southall, J.; Gardiner, A. T.; Low, C. J.; Isaacs, N. W.; Cogdell, R. J. *Science* **2003**, *302*, 1969–1972.
3. McDermott, G.; Prince, S. M.; Freer, A. A.; -Lawless, A. M. H.; Papiz, M. Z.; Cogdell, R. J. *Nature* **1995**, *374*, 517–521.
4. Tamiaki, H. *Coord. Chem. Rev.* **1996**, *148*, 183–197.
5. Porra, R. J.; Scheer, H. *Photosynth. Res.* **2001**, *66*, 159–175. Hynninen, P. H.; Hyvärinen, K. *J. Org. Chem.* **2002**, *67*, 4055–4061.
6. Pinchus, S.; Laulicht, I. In *Infrared spectra of labelled compounds*; Academic: London, 1971; pp 258–311.
7. Emery, V. C.; Akhtar, M. *Biochemistry* **1987**, *26*, 1200–1208.
8. Morishita, H.; Tamiaki, H. *Bioorg. Med. Chem.* **2003**, *11*, 4049–4057.
9. Morishita, H.; Tamiaki, H. *J. Photosci.* **2002**, *9*, 356–358.
10. Byrn, M.; Calvin, M. *J. Am. Chem. Soc.* **1966**, *88*, 1916–1922.
11. Tamiaki, H.; Omoda, M.; Kubo, M. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1631–1632. Tamiaki, H.; Omoda, M.; Saga, Y.; Morishita, H. *Tetrahedron* **2003**, *59*, 4337–4350.
12. Tamiaki, H.; Yagai, S.; Miyatake, T. *Bioorg. Med. Chem.* **1998**, *6*, 2171–2178.
13. Tamiaki, H.; Amakawa, M.; Shimono, Y.; Tanikaga, R.; Holzwarth, A. R.; Schaffner, K. *Photochem. Photobiol.* **1996**, *63*, 92–99.
14. Tamiaki, H.; Shimono, Y.; Rattray, A. G. M.; Tanikaga, R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2085–2086.
15. Tamiaki, H.; Miyatake, T.; Tanikaga, R. *Tetrahedron Lett.* **1997**, *38*, 267–270.
16. Miyashita, H.; Adachi, K.; Kurano, N.; Ikemoto, H.; Chihara, M.; Miyachi, S. *Plant Cell Physiol.* **1997**, *38*, 274–281.
17. Lötjönen, S.; Hynninen, P. H. *Org. Magn. Reson.* **1983**, *21*, 757–765.
18. Tamiaki, H.; Takeuchi, S.; Tsudzuki, S.; Miyatake, T.; Tanikaga, R. *Tetrahedron* **1998**, *54*, 6699–6718.
19. Oba, T.; Tamiaki, H. *Photosynth. Res.* **1999**, *61*, 23–31. Kosaka, N.; Tamiaki, H. *Eur. J. Org. Chem.* **2004**, 2325–2330.
20. Oba, T.; Masada, Y.; Tamiaki, H. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1905–1909.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 61 (2005) 6108–6114
Tetrahedron

Smectic A liquid crystals from dihydrazide derivatives with lateral intermolecular hydrogen bonding☆

Dongmei Pang, Haitao Wang and Min Li*

Key Laboratory of Automobile Materials (Jilin University), Ministry of Education, Institute of Materials Science and Engineering, Jilin University, Changchun 130012, People's Republic of China

Received 24 December 2004; revised 29 March 2005; accepted 4 April 2005

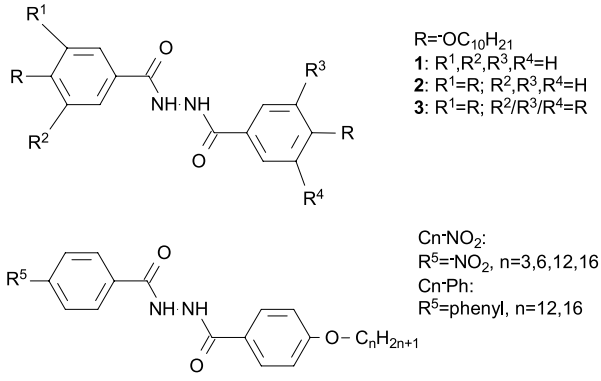
Available online 17 May 2005

Abstract—Six dissymmetrical dihydrazide derivatives, *N*-(4-alkoxybenzoyl)-*N*′-(4′-nitrobenzoyl) hydrazine (C*n*–NO_2) and *N*-(4-alkoxybenzoyl)-*N*′-(4′-biphenyl carbonyl) hydrazine (C*n*–Ph), were synthesized and investigated by means of differential scanning calorimetry, polarized optical microscopy and wide angle X-ray diffraction. The compounds exhibit smectic A_1 phase. Based on the results of ^{1}H NMR and variable temperature FT-IR spectroscopy, lateral intermolecular hydrogen bonding between –C═O and –N–H groups was proposed and the effect of hydrogen bonding on the phase transitions was discussed. It was concluded that the combination of lateral intermolecular hydrogen bonding and microphase segregation stabilized the smectic A phase.

1. Introduction

Hydrogen bonding is crucial to mesophase formation and stabilization.[1–4,7] In the past decade, various types of rod-like,[2] discotic[3] and network[4] supramolecular liquid crystals based on hydrogen bonding have been reported. However, many efforts have been restricted in the generation of calamitic mesophases with molecules bearing a donor or an acceptor site at their terminals, in which hydrogen bonding along the molecular long axis was utilized to form a new and elongated mesogen to stabilize the mesophase, such as a dimer of aromatic carboxyl acid[5] or dimerization between the carboxyl acid and pyridyl moieties.[6] However, lateral intermolecular hydrogen bonding has not been extensively investigated, except a few reports which claimed that it can stabilize the smectic layer structure.[7]

The linear *N*,*N*′-bis (4′-decyloxybenzoyl) hydrazide[8] **1** (Scheme 1) exhibits the unusual phase sequence Cr→ Cubic→Sm C →Isotropic. Elongating the terminal alkoxy chains, such as bisubstituted by the cetyloxy chains results in exclusively cubic phase.[9] The introduction of another



Scheme 1. The molecular structures of **1**-**3**, C*n*–NO_2, and C*n*–Ph.

decyloxy chain, for instance in compound **2**, will decrease the linearity of the calamatic molecule, preventing the formation of cubic phase and driving the smectic phase metastable.[10] Continuing to add terminal chains **3** will further enlarge the volume fraction of flexible chains, which gives rise to a more curvature of the aromatic–aliphatic interface, leading to columnar phases.[10] Beginn has investigated the effect of the number of the terminal chains and the structure of the hydrogen bonded rigid core on the mesophases. He concluded that both the molecular shape determined by the substituted chains and the intermolecular hydrogen bonding dramatically affected the type and the stability of the mesophases.[10]

Dissymmetric dihydrazide derivatives, with one alkoxy

☆ CCDC 258072 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Keywords: Lateral intermolecular hydrogen bonding; Liquid crystals; Smectic A phase; Dihydrazide derivatives.
* Corresponding author; e-mail: minli@mail.jlu.edu.cn

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.04.004

chain as terminal group, exhibit smectic and/or nematic phases. Karamysheva and co-workers have reported the phase transitional properties of the derivatives with different substituents.[11] In fact, the introduction of a hydarzide group as linkage or part of the rigid unit to calamitic molecules, for example the dissymmetric dihydrazide derivatives C*n*–NO_2 and C*n*–Ph synthesized in our laboratory (Scheme 1), can simplify the molecular model, providing an opportunity to investigate the influence of lateral intermolecular hydrogen bonding on the mesophase without the worry of steric effect, as in the system of calamitic molecules with laterally attached hydrophilic groups.[7d] Herein, we focused on the hydrogen bonding motifs and the thermotropic liquid crystalline properties of C*n*–NO_2 and C*n*–Ph, to reveal the role of the lateral intermolecular interactions in the formation of the mesophases.

2. Results and discussion

2.1. Crystal structure

The powder X-ray diffraction pattern of C3–NO_2 was recorded at ambient temperature on a Rigaku D/max 2500 PC X-ray diffractometer (reflection, Cu K-alpha1). The 2θ range was 2–35°, measured in steps of 0.02°. The crystal structure determination from the powder diffraction data was carried out using Materials Studio.[†] All the diffraction peaks can be indexed as the monoclinic structure, and the unit cell contains two molecules. It belongs to *P*121 space group and the lattice parameters are $a=17.179(5)$ Å, $b=3.319(2)$ Å, $c=16.692(8)$ Å and $\beta=92.533(8)°$. The density calculated was 1.20 g cm^{-3}. The final Rietveld refinement gave $R_{wp}=7.38\%$ and $R_p=5.45\%$ (110 reflections, 1627 data points). Figure 1 illustrated the molecules stacking of C3–NO_2 in the crystal. What can be observed directly was that the intermolecular hydrogen bonding was more easily accessible due to the higher linearity of the intermolecular N–H···O bond.[12] The angle of intermolecular hydrogen bond of N–H···O (141.37 and 117.52°) was larger than that of intramolecular one (103.98 and 103.43°).

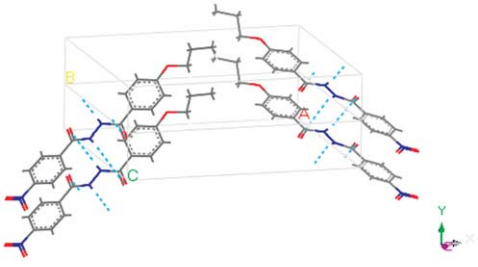


Figure 1. The crystal structure of C3–NO_2. The dashed line illustrated the hydrogen bonding.

2.2. Hydrogen-bonding motif

In order to explore the hydrogen-bonding motif, temperature dependent FT-IR and ^{1}H NMR spectroscopic experiments were performed. In ^{1}H NMR dilution studies, the amide protons of C*n*–NO_2 and C*n*–Ph showed strong concentration dependence, for example, reducing the concentration of C6–NO_2 in $CDCl_3$ from 15.6 to 0.2 mM causes both NH-1 (near to nitro phenyl, $\Delta\delta=0.57$ ppm) and NH-2 (near to alkoxy phenyl, $\Delta\delta=0.19$ ppm) to shift upfield remarkably, as shown in Table 1. These results strongly indicated that N–H groups were involved in intermolecular hydrogen bonding.[13] The variable-temperature measurements of amide protons further supported above conclusion. Generally, internally hydrogen bonded amides are expected to show a much smaller shift with temperature ($<3.0\times10^{-3}$ ppm K^{-1}) compared to those directed externally and accessible for hydrogen bonding to a polar solvent ($>4.0\times10^{-3}$ ppm K^{-1}).[14] However, both NH-1 and NH-2 of C6–NO_2 showed large shifts (5.85×10^{-3} and 7.74×10^{-3} ppm K^{-1} respectively, as shown in Fig. 2) with temperature in 20% DMSO-d_6/$CDCl_3$, suggesting the primary involvement of N–H protons in intermolecular hydrogen bonding. This may be due to a more favorable geometry for the formation of the intermolecular hydrogen bonding than the intramolecular one, as have been discussed in the crystal structure section.

Table 1. The chemical shifts of amide protons for C6–NO_2 at different concentrations in $CDCl_3$ (NH-1: near to nitro phenyl, NH-2: near to alkoxy phenyl)

Concentration/mM	NH-1 chemical shifts /ppm	NH-2 chemical shifts /ppm
15.6	9.85	9.19
7.8	9.64	9.09
3.9	9.44	9.02
2.6	9.40	9.01
0.2	9.28	9.00

(*continued on next page*)

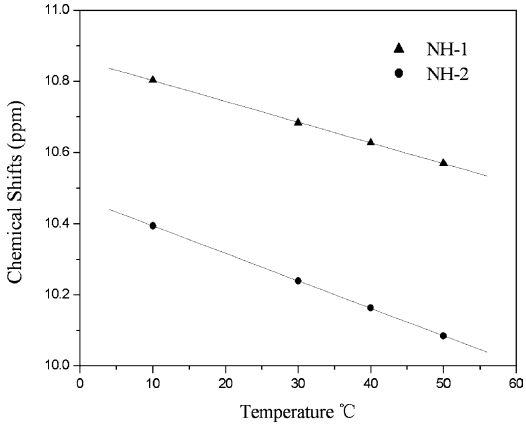


Figure 2. The chemical shifts of NH-1 and NH-2 of C6–NO_2 in 20% DMSO-d_6/$CDCl_3$ versus temperature. NH-1: near to nitro phenyl, NH-2: near to alkoxy phenyl.

Position, intensity and shape of IR absorption bands are known to be sensitive to conformations and intermolecular interactions. So, in order to evaluate the effect of hydrogen bonding on the phase transitional properties of the compounds, temperature dependent FT-IR spectra of C16–NO_2 and C16–Ph were measured. Table 2 presented the assignments of infrared frequencies for C16–NO_2 and

[†] The solution of the crystal structure from powder diffraction data was performed on Materials Studio, and the modeling details will be published elsewhere.

Table 2. Assignments of infrared frequencies for C16–Ph and C16–NO_2 at room temperature

Assignments	IR frequencies (cm^{-1})	
	C16–Ph	C16–NO_2
ν (N–H)	3247	3203
ν (Ar-H)	3013	3017
ν_{as} (CH_3), ν_{as} (CH_2)	2954, 2916	2953, 2918
ν_s (CH_3), ν_s (CH_2)	2849	2871, 2850
amide I, ν C=O	1684, 1650	1590, 1567
$\nu_{C=C}$ of phenyl ring	1609, 1580 1506, 1485 1472, 1449	1608, 1578
Amide II, III, $\nu_{C-N}+\delta_{N-H}$	1529, 1297	1493
ν_{as}, ν_s (NO_2)	—	1522, 1345
δ (CH_2)	1464	1466
ν (Ar-O)	1255	1254
ν (C–O)	1025	1026
δ (Ar-H)$_{o.o.p}$, *para*-	845	844
δ (Ar-H)$_{o.o.p}$, mono-	741, 692	—
$(CH_2)_n$ rocking, $n\geq 4$	720	720

C16–Ph.[15] At room temperature, apart from characteristic bands of aromatic ring at 1609, 1580, 1506, 1485, 1472, 845, 741, and 692 cm^{-1}, C16–Ph exhibits absorptions at 3247 cm^{-1} (ν (N–H)), 1684, 1650 cm^{-1} (amide I, $\nu_{C=O}$), and 1529, 1297 cm^{-1} (amide II, III, $\nu_{C-N}+\delta_{N-H}$). The absorption bands at 2954, 2916 cm^{-1} (ν_{as} (CH_3, CH_2)), 2872, 2849 cm^{-1} (ν_s (CH_3, CH_2)), 1465 cm^{-1} (δ (CH_2)), and 720 cm^{-1} ($(CH_2)_n$ rocking, $n\geq 4$) were attributed to the vibrations of alkoxy chains. The presence of N–H stretching vibrations at 3247 cm^{-1} (the absence of free N–H, a relatively sharp peak with the frequency higher than 3400 cm^{-1}), intense absorption of amide I at 1650 cm^{-1}, and relatively weak absorption at 1684 cm^{-1} clearly indicated that almost all the N–H groups are associated with C=O groups via N–H···O=C hydrogen bonding.[16] For C16–NO_2, the N–H stretching vibration located at 3202 cm^{-1}, amide I at 1590, 1567 cm^{-1}, and characteristic absorption of nitro group at 1522 cm^{-1} (ν_{as} (NO_2)) and 1345 cm^{-1} (ν_s (NO_2)). The same conclusion can be drawn for C16–NO_2, in spite of the stronger hydrogen bonding confirmed by the red-shift of the N–H and C=O stretching vibrations in C16–NO_2 with respect to C16–Ph. Thus, along with the results of crystal structure, FT-IR, and ^1H NMR dilution experiments, we can get a clear hydrogen-bonding motif, in which N–H and C=O group were involved in intermolecular hydrogen bonding. The direction of the interaction is perpendicular to the molecular long axis, as depicted in Figure 3a, in contrast to the intramolecular hydrogen bonding pattern speculated by Karamysheva, etc.[11] as shown in Figure 3b.

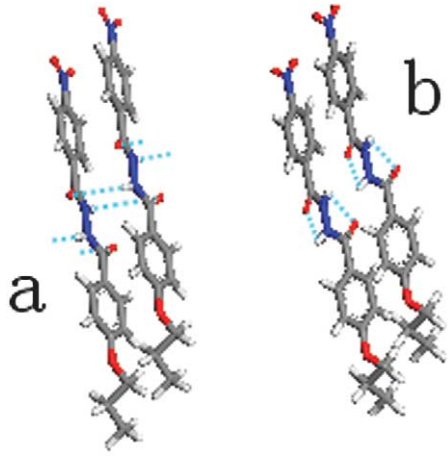


Figure 3. Schematic hydrogen bonding motifs. The dashed line illustrated the hydrogen bonding.

Moreover, these conclusions were further supported by the fact that the ν_{N-H} and amide I band became weaker and shifted to higher frequencies upon heating. Figure 4 showed the temperature dependence of ν_{N-H} of C16–Ph. We found a sharp increase of ν_{N-H} wavenumbers on going from crystalline to smectic A and from smectic A to isotropic liquid. The typical wavenumbers of N–H vibration of C16–Ph are at around 3250, 3295 and 3310 cm^{-1} in the crystalline state, smectic A phase and isotropic phase, respectively. The observed N–H stretching vibration frequency at 3295 cm^{-1} in the smectic A phase and the increase of N–H stretching vibration by ca. 15 cm^{-1} at the isotropic transition strongly indicated that the presence of the hydrogen bonding in the smectic A phase of C16–Ph. Furthermore, this conclusion was also supported by the fact that the blue-shift of C=O stretching vibration was companied by an increase in intensity at around 1655 cm^{-1}, while the absorption at 1690 cm^{-1} diffused and decreased, as shown in Figure 5a. For C16–NO_2, the N–H vibrations shift from 3210 to 3295 cm^{-1} and the amide I band from 1590, 1567 to 1654, 1688 cm^{-1}, as shown in Figure 5b and c, during the transition from crystalline to smectic A phase. Due to the limitation of infrared spectrometer range, FT-IR spectra of C16–NO_2 in its isotropic phase were not measured. However, based on these observation, we have already been able to draw the same conclusion that the intermolecular hydrogen bonding exists in the smectic A phase, as that of the C16–Ph.

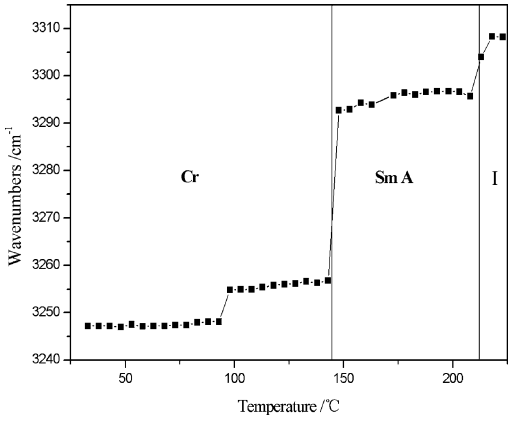


Figure 4. The temperature dependent N–H stretching vibrations of C16–Ph: Cr, Sm A and I indicates crystalline state, smectic A phase and isotropic liquid, respectively.

2.3. Phase behaviors

The phase behaviors of C*n*–NO_2 and C*n*–Ph were studied by polarized optical microscopy, differential scanning calorimetry and wide angle X-ray diffraction. Their transitional temperatures and associated enthalpies were summarized in Table 3. The molecules of C*n*–NO_2 and C*n*–Ph exhibited enantiotropic smectic A behavior with a fan-shaped texture

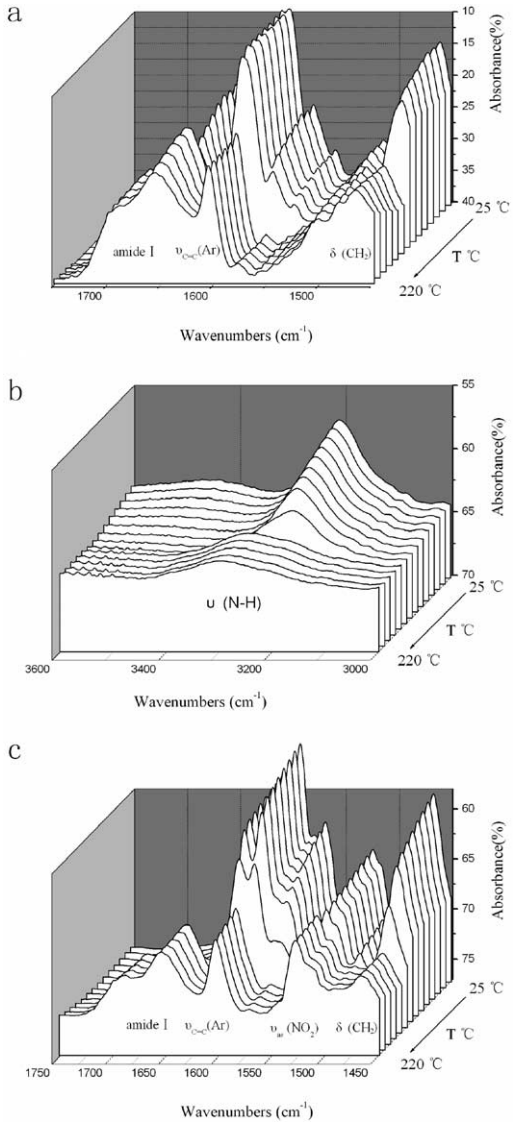


Figure 5. The temperature dependent FT-IR spectra at the interval of 15 °C. (a) C16–Ph at the range of 1450–1750 cm^{-1}, (b) C16–NO_2 at the range of 3000–3600 cm^{-1}, (c) C16–NO_2 at the range of 1450–1750 cm^{-1}.

(as shown in Figure 6). In the thermodynamic studies, it should be noticed that remarkably stable smectic A phase was obtained, which was characterized by wide mesophase ranges (even broader than 110 °C), high clearing points (as

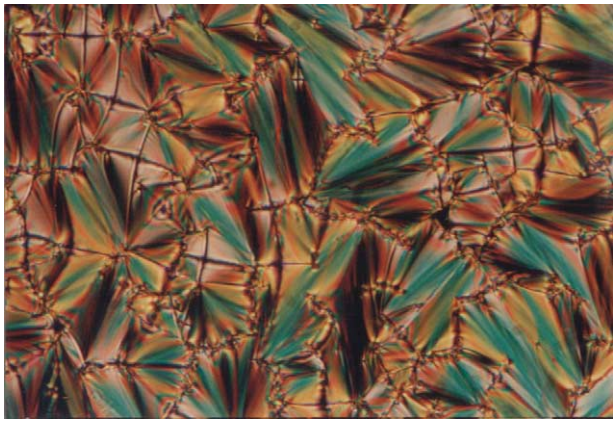


Figure 6. The fan-shaped texture (×400) of C3–NO_2 at 193 °C in the cooling run.

high as 268 °C) and large isotropic transition enthalpy (>6 kJ/mol). The high stability of the smectic A phase may be ascribed to the combination of lateral intermolecular hydrogen bonding and microphase segregation. Firstly, the large transitional enthalpies implied that strong attractive force still existed in the smectic A phase. This might be due to the lateral hydrogen bonding, as have been confirmed by the temperature dependent FT-IR spectroscopic study. The presence of intermolecular cohesive forces within the layer may have stabilized the parallel alignment of the smetogen in the layer structures.[7] Secondly, the clearing points rise, the transition enthalpies increase, and the mesophase ranges broaden with the elongating terminal chain. This may be explained as the elongation of the terminal chains increased the microphase segregation effect by enhancing the incompatibility between the hydrogen bonded rigid aromatic rings and flexible alkoxy chains. Such micro-segregation effect was considered to be the driving force for the formation of smectic phase.[17] Moreover, the hydrogen bonding and the strong dipole substitute were considered to enhance the incompatibility. Therefore C*n*–NO_2 has higher thermal stability than C*n*–Ph. Additionally, the clearing point increased while the melting temperature decreased with the elongation of alkoxy chain (see Table 3), which suggested that the terminal chains have bigger impact on the melting process than that on the isotropic transition. The elongating alkoxyl chain may be favorable to the formation of the mesophase by decreasing the melting point, whereas the stability of the mesophase must be ascribed to the

Table 3. Transition temperatures and enthalpies of C*n*–NO_2 and C*n*–Ph

Compound	Transition[a]	*T*/°C heating (Δ*H*/kJ mol^{-1})	*T*/°C cooling (Δ*H*/kJ mol^{-1})
C3–NO_2	Cr–Sm A	208.2(19.86)	184.0(21.12)
	Sm A–I	232.8(6.54)	230.3(6.32)
C6–NO_2	Cr–Sm A	172.2(19.17)	158.2(18.84)
	Sm A–I	259.5(9.07)	257.82(8.16)
C12–NO_2	Cr–Sm A	144.2(14.90)	139.3(11.04)
	Sm A–I	262.5(13.90)	263.1(8.21)
C16–NO_2	Cr–Sm A	146.3(8.86)	141.2(11.30)
	Sm A–I	260.6(12.14)	258.8(8.87)
C12–Ph	Cr–Sm A	147.7(36.53)	117.2(9.90)[b]
	Sm A–I	208.6(4.76)	204.0(4.39)
C16–Ph	Cr–Sm A	145.2(57.37)	113.3(66.09)
	Sm A–I	210.9(7.48)	208.6(7.22)

[a] Cr, Sm A and I indicate crystalline state, Smectic A phase and isotropic liquid, respectively.
[b] The small enthalpy was due to another phase transition observed below the melting process.

presence of attractive force or the combination of the two. Thus, based on these analyses, we can conclude that combination of the lateral intermolecular hydrogen bonding and microphase segregation played an important role in generating the stable smectic phase.

2.4. Mesophase structure

X-ray diffraction measurements have been performed on the mesophases of C*n*–NO_2 and C*n*–Ph. Characteristic patterns of smectic A phase with sharp peaks at lower angle region and a broad halo at higher angle region (about 20°) were observed, as shown in Fig. 7. The layer spacing values (*d*) collected in the Table 4, were almost independent to the temperature. The *d*-spacings of C*n*–NO_2 in their mesophases were 2–5 Å longer than the calculated molecular lengths (*l*). These *d*/*l* ratios were from 1.10 to 1.14, while the layer spacings of C*n*–Ph were almost equal to the molecular lengths. These results indicated that the molecules of C*n*–NO_2 and C*n*–Ph kept a Semectic A_1 arrangement in their liquid crystalline phases.[18]

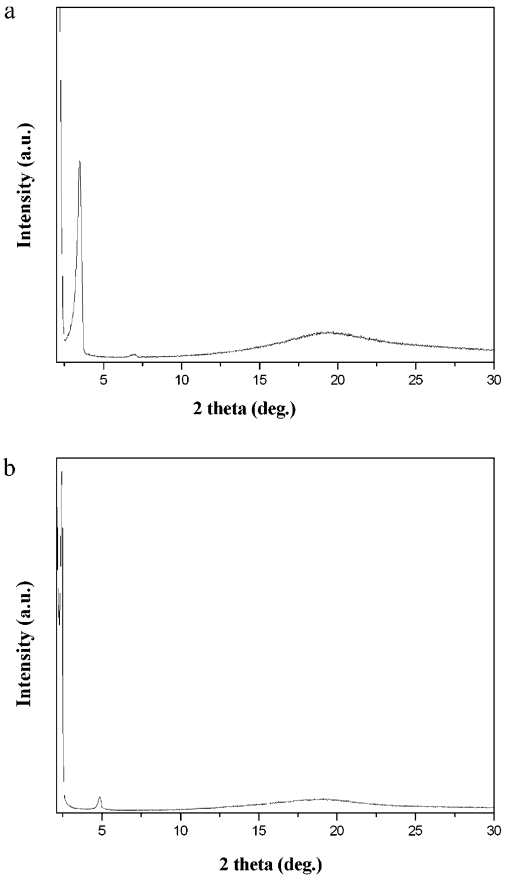


Figure 7. X-ray diffraction patterns of dissymmetric dihydrazide derivatives: (a) C6–NO_2 at 190 °C, (b) C16–Ph at 170 °C.

Table 4. Summary of X-ray diffraction results of C*n*–NO_2 and C*n*–Ph

Compound	Molecular length[a] (*l*)/Å	*T*/°C	Layer spacing (*d*)/Å	*d*/*l*
C3–NO_2	19.5	225	21.4, 10.9	1.10
C6–NO_2	22.5	190	25.4	1.13
C12–NO_2	30.0	160	33.5	1.12
C16–NO_2	34.6	200	39.4, 19.7	1.14
C12–Ph	32.6	190	32.7	1.00
C16–Ph	37.4	170	36.2, 18.1	0.97

[a] Molecular length was calculated by MM2.

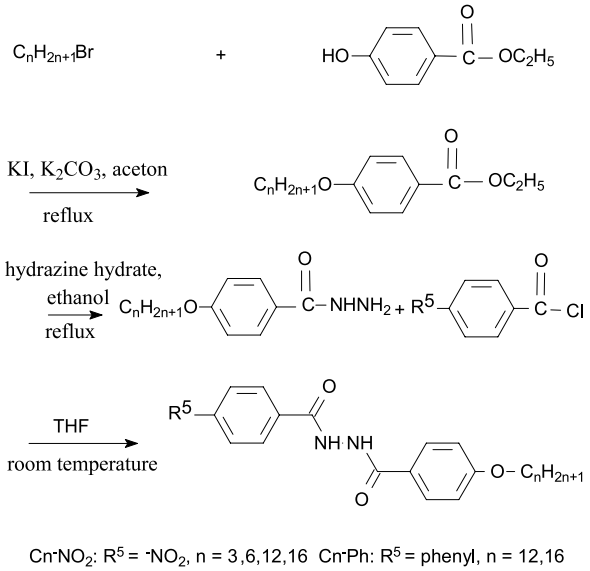
3. Conclusion

Lateral intermolecular hydrogen bonding was considered undesirable for the calamitic mesogenic materials, because it could lead to a high melting temperature. However, high stable smectic A phase was generated from these dissymmetric dihydrazide derivatives. Based on our investigations, the presence of intermolecular attractive force in the semectic A phase may enhance the parallel alignment and the combination of lateral intermolecular interaction and microphase segregation effect may be the leading contribution to the stable smectic phase. In fact, lateral hydrogen bonding has been applied to main chain liquid crystal polymers to obtain high mechanical strength, and to LB films to stabilize the layer structure. In conclusion we hope that more attention will be paid to exploit the potential use of the lateral hydrogen bonding in materials science. Now the investigations using C*n*–Ph and C*n*–NO_2 as organogelators are in progress.

4. Experimental

4.1. Synthesis

C*n*–NO_2 and C*n*–Ph were synthesized according to the route shown in Scheme 2. 4-Nitrobenzoyl chloride or 4-biphenyl carbonyl chloride was reacted with 4-alkoxyl-benzoyl-hydrazine in THF at room temperature for 8 h, yielding the products of C*n*–NO_2 and C*n*–Ph. All the compounds were purified by a recrystallization from methanol or alcohol for further NMR, FT-IR, measurements and elemental analysis.



Scheme 2. The synthesis of C*n*–NO_2 and C*n*–Ph.

4.1.1. *N*-(4-Propyloxybenzoyl)-*N′*-(4′-nitrobenzoyl) hydrazine (C3–NO_2). ^{1}H NMR (500 MHz, DMSO), (ppm, from TMS): 10.83 (s, 1H); 10.50 (s, 1H); 8.39 (d, 2H, J=7.9 Hz); 8.15 (d, 2H, J=7.7 Hz); 7.90 (d, 2H, J=8.1 Hz); 7.06 (d, 2H, J=7.9 Hz); 4.02 (t, 2H, J=5.7 Hz); 1.78–1.74 (m, 2H); 0.99 (t, 3H, J=6.9 Hz). FT-IR (KBr disc, cm^{-1}): 3205, 2964, 2937, 2879, 2855, 1609, 1593, 1566, 1527, 1495, 1465, 1416, 1393, 1345, 1317, 1255, 1175, 1111, 1066, 1011, 977, 866, 842, 819, 758, 724, 714, 702, 684, 657, 639, 622. Anal. calcd for $C_{17}H_{17}N_3O_5$: C, 59.47; H, 4.99; N, 12.24. Found C, 59.57; H, 4.78; N, 12.18.

4.1.2. *N*-(4-Hexyloxybenzoyl)-*N′*-(4′-nitrobenzoyl) hydrazine (C6–NO_2). ^{1}H NMR: (500 MHz, DMSO), (ppm, from TMS): 10.79 (s, 1H); 10.47 (s, 1H); 8.38 (d, 2H, J=8.6 Hz); 8.14 (d, 2H, J=8.4 Hz); 7.90 (d, 2H, J=8.5 Hz); 7.05 (d, 2H, J=8.6 Hz); 4.05 (t, 2H, J=6.2 Hz); 1.75–1.71 (m, 2H); 1.43–1.40 (m, 2H), 1.34–1.32 (m, 4H), 0.86 (t, 3H, J=6.4 Hz). FT-IR (KBr disc, cm^{-1}): 3196, 2932, 2857, 1609, 1592, 1568, 1525, 1495, 1467, 1396, 1344, 1317, 1253, 1175, 1110, 1030, 866, 846, 759, 723, 702, 661, 623. Anal. calcd for $C_{20}H_{23}N_3O_5$: C, 62.33; H, 6.02; N, 10.90. Found C, 62.56; H, 5.71; N, 10.68.

4.1.3. *N*-(4-Dodecyloxybenzoyl)-*N′*-(4′-nitrobenzoyl) hydrazine (C12–NO_2). ^{1}H NMR (500 MHz, DMSO), (ppm, from TMS): 10.79 (s, 1H); 10.47 (s, 1H); 8.38 (d, 2H, J=8.4 Hz); 8.15 (d, 2H, J=8.5 Hz); 7.90 (d, 2H, J=8.5 Hz); 7.04 (d, 2H, J=8.4 Hz); 4.04 (t, 2H, J=6.2 Hz); 1.74–1.70 (m, 2H); 1.42–1.40 (m, 2H); 1.33–1.25 (m, 16H); 0.86 (t, 3H, J=6.4 Hz). FT-IR (KBr disc, cm^{-1}): 3202, 2920, 2851, 1609, 1591, 1567, 1523, 1494, 1466, 1395, 1345, 1318, 1254, 1172, 1109, 1028, 1010, 871, 844, 810, 759, 721, 699, 682, 658, 638, 623. Anal. calcd for $C_{26}H_{35}N_3O_5$: C, 66.50; H, 7.51; N, 8.95. Found C, 66.70; H, 7.71; N, 9.07.

4.1.4. *N*-(4-Cetyloxybenzoyl)-*N′*-(4′-nitrobenzoyl) hydrazine (C16–NO_2). ^{1}H NMR (500 MHz, DMSO), (ppm, from TMS): 10.81 (s, 1H); 10.49 (s, 1H); 8.38 (d, 2H, J=8.6 Hz); 8.15 (d, 2H, J=8.6 Hz); 7.90 (d, 2H, J=8.6 Hz); 7.04 (d, 2H, J=8.7 Hz); 4.04 (t, 2H, J=6.4 Hz); 1.74–1.71 (m, 2H); 1.41–1.40 (m, 2H); 1.32–1.24 (m, 24H); 0.85 (t, 3H, J=6.7 Hz). FT-IR (KBr disc, cm^{-1}): 3203, 2919, 2850, 1608, 1591, 1567, 1523, 1493, 1466, 1394, 1346, 1318, 1254, 1172, 1109, 1027, 872, 844, 810, 758, 720, 698, 658, 637, 622. Anal. calcd for $C_{30}H_{43}N_3O_5$: C, 68.54; H, 8.24; N, 7.99. Found C, 68.76; H, 8.41; N, 8.05.

4.1.5. *N*-(4-Dodecyloxybenzoyl)-*N′*-(4′-biphenyl carbonyl) hydrazine (C12–Ph). ^{1}H NMR: (500 MHz, DMSO) (ppm, from TMS): 10.53 (s, 1H); 10.40 (s, 1H); 8.02 (d, 2H, J=8.1 Hz); 7.91 (d, 2H, J=8.6 Hz); 7.84 (d, 2H, J=8.1 Hz); 7.77 (d, 2H, J=7.5 Hz); 7.52 (t, 2H, J=7.5 Hz); 7.43 (t, 1H, J=7.3 Hz); 7.05 (d, 2H, J=8.6 Hz); 4.04 (t, 2H, J=6.3 Hz); 1.75–1.72 (m, 2H); 1.42–1.41 (m, 2H); 1.32–1.25 (m, 16H); 0.86 (t, 3H, J=6.5 Hz). FT-IR (KBr disc, cm^{-1}): 3233, 3053, 2954, 2936, 2858, 1678, 1643, 1609, 1579, 1535, 1507, 1485, 1448, 1393, 1296, 1253, 1181, 1111, 1076, 1038, 1013, 898, 846, 742, 696. Anal. calcd for $C_{32}H_{40}N_2O_3$: C, 76.77; H, 8.05; N, 5.60. Found C, 76.73; H, 8.30; N, 5.65.

4.1.6. *N*-(4-Cetyloxybenzoyl)-*N′*-(4′-biphenyl carbonyl) hydrazine (C16–Ph). ^{1}H NMR: (500 MHz, DMSO) (ppm, from TMS): 10.46 (s, 1H); 10.33 (s, 1H); 8.01 (d, 2H, J=8.4 Hz); 7.89 (d, 2H, J=8.8 Hz); 7.82 (d, 2H, J=8.4 Hz); 7.75 (d, 2H, J=7.4 Hz); 7.50 (t, 2H, J=7.6 Hz); 7.41 (t, 1H, J=7.3 Hz); 7.02 (d, 2H, J=8.8 Hz); 4.03 (t, 2H, J=6.5 Hz); 1.73–1.70 (m, 2H); 1.42–1.39 (m, 2H); 1.31–1.23 (m, 24H); 0.84 (t, 3H, J=6.9 Hz). FT-IR (KBr disc, cm^{-1}): 3247, 3013, 2964, 2916, 2849, 1684, 1650, 1609, 1580, 1529, 1506, 1485, 1472, 1464, 1449, 1396, 1297, 1255, 1181, 1109, 1025, 1006, 924, 895, 845, 741, 720, 685. Anal. calcd for $C_{36}H_{48}N_2O_3$: C, 77.66; H, 8.69; N, 5.03. Found C, 77.63; H, 8.81; N, 5.02.

4.2. Characterization

^{1}H NMR spectra were recorded with a Bruker Avance 500 MHz spectrometer, using chloroform-*d* or DMSO-*d*6 as solvent and tetramethylsilane (TMS) as an internal standard. FT-IR spectra were recorded with a Perkin–Elmer spectrometer (Spectrum One B). The sample was pressed tablet with KBr. Phase transitional properties were investigated by a Mettler Star DSC 821^e. Texture observation was conducted on a Leica DMLP polarized optical microscope equipped with a Leitz 350 microscope heating stage. X-ray diffraction was carried out with a Rigaku D/max 2500 PC X-ray diffractometer.

Acknowledgements

The authors are grateful to the National Science Foundation Committee of China (Project No. 29974013, 50373016) and the Excellent Young Teachers Program of MOE, China for their financial support of this work.

References and notes

1. (a) Kato, T. *Struct. Bond.* **2000**, *96*, 95–146. (b) Paleos, C. M.; Tsiourvas, D. *Liq. Cryst.* **2001**, *28*, 1127–1161. (c) Beginn, U. *Prog. Polym. Sci.* **2003**, *28*, 1049–1105.
2. (a) Kato, T.; Frechet, J. M. J. *J. Am. Chem. Soc.* **1989**, *111*, 8533–8534. (b) Price, D. J.; Willis, K.; Richardson, T.; Ungar, G.; Bruce, D. W. *J. Mater. Chem.* **1997**, *7*, 883–891. (c) Price, D. J.; Adams, H.; Bruce, D. W. *Mol. Cryst. Liq. Cryst.* **1999**, *289*, 127. (d) Sideratou, Z.; Tsiourvas, D.; Paleos, C. M.; Skoulios, A. *Liq. Cryst.* **1997**, *22*, 51–64. (e) Wallage, M. J.; Imrie, C. T. *J. Mater. Chem.* **1997**, *7*, 1163–1167. (f) Kato, T.; Frechet, J. M. J.; Wilson, P. G.; Saito, T.; Uryu, T.; Fujishima, A.; Jin, C.; Kaneuchi, F. *Chem. Mater.* **1993**, *5*, 1094–1100.
3. (a) Brienne, M. J.; Gabard, J.; Lehn, J. M.; Stibor, J. *J. Chem. Soc., Chem. Comm.* **1989**, 1868–1870. (b) Kleppinger, R.; Lillya, C. P.; Yang, C. *Angew. Chem., Int., Ed. Engl.* **1995**, *34*, 1637–1638. (c) Kleppinger, R.; Lillya, C. P.; Yang, C. *J. Am. Chem. Soc.* **1997**, *119*, 4097–4102. (d) Suarez, M.; Lehn, J. M.; Zimmermann, S. C.; Skoulios, A.; Heinrich, B. *J. Am. Chem. Soc.* **1998**, *120*, 9526–9532. (e) Goldmann, D.; Janietz, R. D.; Festag, R. H.; Schmidt, C.; Wendorff, J. H. *Liq. Cryst.* **1996**, *21*, 619. (f) Kraft, A.; Reichert, A.; Kleppinger, R. *Chem. Comm.* **2000**, 1015–1016. (g) Lee, C. J.; Lee, S. J.; Chang, J. Y.

Tetrahedron Lett. **2002**, *43*, 3863–3866. (h) Lee, H. K.; Lee, H.; Ko, Y. H.; Chang, Y. J.; Oh, N. K.; Zin, W. C.; Kim, K. *Angew. Chem.* **2001**, *113*, 2741–2743.

4. (a) Kihara, H.; Kato, T.; Uryu, T.; Frechet, J. M. *J. Chem. Mater.* **1996**, *8*, 961–968. (b) Kihara, H.; Kato, T.; Uryu, T.; Frechet, J. M. J. *Liq. Cryst.* **1998**, *24*, 413–418. (c) Wilson, L. M. *Liq. Cryst.* **1995**, *18*, 381. (d) Malthete, J.; Levelut, A. M.; Liebert, L. *Adv. Mater.* **1992**, *4*, 37.
5. Gray, G. W. *Molecular Structure and the Properties of Liquid Crystals*; Academic: New York, NY, 1962; p 163.
6. Kato, T.; Frechet, J. M. J. *J. Am. Chem. Soc.* **1989**, *111*, 8533–8534.
7. (a) Mori, A.; Katahira, K.; Kida, K.; Takeshita, H. *Chem. Lett.* **1992**, 1767–1770. (b) Mori, A.; Nimura, R.; Isobe, M.; Takeshita, H. *Chem. Lett.* **1992**, 859–862. (c) Mori, A.; Nimura, R.; Takeshita, H. *Chem. Lett.* **1991**, 77–80. (d) Plehnert, R.; Schroter, J. A.; Tschierske, C. *J. Mater. Chem.* **1998**, *8*, 2611–2626. (e) Kajitani, T.; Kohmoto, S.; Yamamoto, M.; Kishikawa, K. *Chem. Mater.* **2004**, *16*, 2329–2331.
8. (a) Demus, D.; Gloza, A.; Hauser, H.; Rapthel, I.; Wiegeleben, A. *Cryst. Res. Technol.* **1981**, *16*, 1445. (b) Kutsumizu, S. *Curr. Opin. Solid State* **2002**, *6*, 537.
9. Tang, B. C. Dissertation Thesis, Jilin University, China, 2003.
10. (a) Beginn, U. Dissertation Thesis, Bayreuth, Germany, 1994.(b) Beginn, U. *Prog. Polym. Sci.* **2003**, *28*, 1049–1105.
11. Karamysheva, L. A.; Agafonova, I. F. *Mol. Cryst. Liq. Cryst.* **1999**, 2527–2536.
12. Steiner, T. *Angew. Chem., Int., Ed.* **2002**, *41*, 48–76.
13. Zhao, X.; Wang, X.; Jiang, X.; Chen, Y.; Li, Z.; Chen, G. *J. Am. Chem. Soc.* **2003**, *125*, 15128–15139.
14. Hamuro, Y.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1996**, *118*, 7529–7541.
15. The assignments of IR absorption bands were based on Refs., (a) Gunzler, H.; Gremlich, H. IR Spectroscopy; Wiley-VCH: New York, 2002. (b) Bellamy, L. J., 3rd ed. In *The Infra-Red Spectra of Complex Molecules*, *Vol. 1*; Chapman and Hall: London, 1975.
16. Xue, C.; Jin, S.; Weng, X.; Ge, J. J.; Shen, Z.; et al. *Chem. Mater.* **2004**, *16*, 1014–1025 and references cited therein.
17. (a) Tschierske, C. *J. Mater. Chem.* **1998**, *8*, 1485–1508. (b) Tschierske, C. *J. Mater. Chem.* **2001**, *11*, 2647–2671 and references cited there in.
18. Tasaka, T.; Okamoto, H.; Morita, Y.; Kasatani, K.; Takenaka, S. *Liq. Cryst.* **2003**, 961–977.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 6115–6130

Synthesis of porphyrazine-octaamine, hexamine and diamine derivatives

Matthew J. Fuchter,[a] L. Scott Beall,[a] Sven M. Baum,[a] Antonio Garrido Montalban,[a] Efstathia G. Sakellariou,[a] Neelakandha S. Mani,[b] Todd Miller,[b] Benjamin J. Vesper,[c] Andrew J. P. White,[a] David J. Williams,[a] Anthony G. M. Barrett[a,*] and Brian M. Hoffman[c,*]

[a]*Department of Chemistry, Imperial College London, London SW7 2AZ, UK*
[b]*Department of Chemistry, Colorado State University, Fort Collins, CO 80523, USA*
[c]*Department of Chemistry, Northwestern University, Evanston, IL 60208, USA*

Received 11 February 2005; revised 14 March 2005; accepted 23 March 2005

Abstract—The syntheses of a variety of substituted diaminomaleonitriles, with variable nitrogen substituents, were undertaken. Linstead macrocyclization of the resulting diaminomaleonitriles gave access to a wide range of functionalized porphyrazine-octaamines and hexamines and norphthalocyaninediamines. Conversion of these macrocycles into metallic derivatives and studies of their electronic absorption, solubility and electrochemistry are described. These flexible tetraazaporphyrins show potential in a range of applications including biomedical agents, novel charge–transfer complexes, chemical sensors, novel electronic materials and non-linear optics.

1. Introduction

Tetraazaporphyrins (porphyrazines, pz) can be viewed as porphyrin analogues, with *meso* nitrogen atoms replacing the *meso* carbon atoms. This alteration results in significant structural and electronic changes within the macrocycle.[1] Porphyrazines, however, have received considerably less synthetic interest than the related porphyrins and phthalocyanines.[2,3] Peripheral heteroatom functionalization of the macrocycle results in significant modulation of their physical and electronic properties.[1] Barrett, Hoffman and co-workers have published extensively on the synthesis of porphyrazines bearing thiols, amines or alcohols as ring substituents, with the conversion of these polydentate ligands to a variety of coordination complexes.[1,4] Porphyrazines containing peripheral amino substituents constitute an important class of these flexible molecules. Since our original report on these electron-rich octaaminomacrocycles,[5] several structural analogues have been prepared, including *trans*-A_2B_2[6] and A_3B type porphyrazines[7–9] and porphyrazine–phthalocyanine hybrids.[10] We have explored the coordination chemistry of these novel ligands, preparing palladium(II) star-porphyrazines,[11] as well as a variety of solitaire-macrocycles.[8,12,13] The platinum(II) solitaire porphyrazines are potent photosensitizers and have the potential as dual-warhead anti-cancer agents.[14] In addition, we have prepared several charge-transfer complexes with C_{60}[15,16] and utilized amino-porphyrazine nitrogen donor pockets in metal sensing applications.[17] An important discovery was the oxidative scission of one of the pyrrole units to yield the *seco*-porphyrazines.[18] Detailed photophysical studies into these curious macrocycles unveiled their potent photosensitizing ability for the production of singlet oxygen.[19] We have utilized this feature in the dye catalyzed photooxygenation of dienes[20] and have prepared several novel *seco*-porphyrazines with variable solubility and photophysical profiles.[21,22] Ercolani and co-workers have prepared a variety of amino-porphyrazines with annulated heterocyclic rings.[23–27] We have exploited this 'protection' of the free amino functionality with selenium in the synthesis of Schiff Base porphyrazines, for application as molecular scaffolds.[28,29] Recently we have also disclosed a ROM-polymerization-capture-release strategy for the chromatographically-free synthesis of amino-porphyrazines.[30]

This report describes the syntheses of diverse amino-porphyrazines prepared in our laboratories with the aim to provide information on how the substituents bonded to the peripheral nitrogens intimately influence the physical,

Keywords: Porphyrazine; Aminoporphyrazine; Nickel porphyrazines; Linstead macrocyclization; UV–vis spectroscopy; Electrochemistry.
* Corresponding authors. Tel.: +44 207 594 5766; fax: +44 207 594 5805 (A.G.M.); Tel.: +1 847 491 3104; fax: +1 847 491 7713 (B.M.H.); e-mail addresses: agmb@imperial.ac.uk; bmh@northwestern.edu

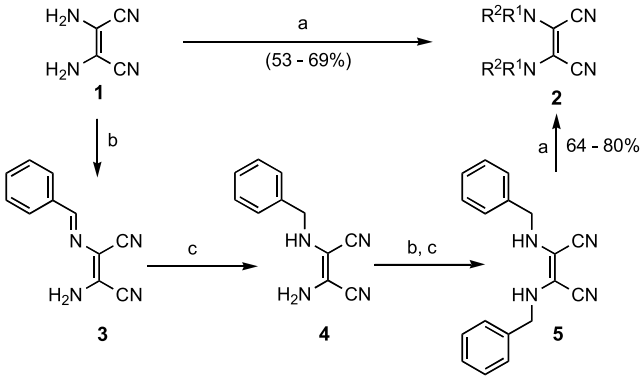
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.03.090

chemical and electronic properties of the porphyrazinic macrocycle.

2. Results and discussion

2.1. Dialkylamino functionalized porphyrazines

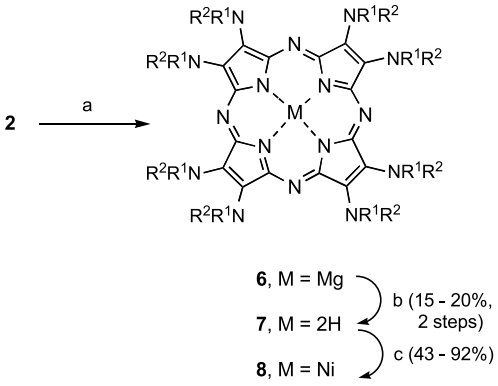
The peripheral nitrogen substituents of octaamino-porphyrazines have a profound influence on the physical and chemical properties of the macrocycle. This readily adaptable effect can be exploited for the synthesis of porphyrazines which display flexible solubility, variable electronic absorption spectra and tuneable redox properties. Following the method of Sheppard and co-workers,[31] tetra-functionalized maleonitriles were prepared in a controlled manner and subsequently cyclized to the desired porphyrazine products. Thus, commercially inexpensive diaminomaleonitrile (DAMN) was alkylated under strongly basic conditions to yield tetraalkylated maleonitriles **2a**–**2c** (53–69%) (Scheme 1). Alternatively, successive reductive alkylations with benzaldehyde yielded the dibenzyl derivative **5**,[31] which was subsequently converted into the fully substituted maleonitriles **2d**–**2e** (64–80%). Notably, derivative **5** has proved a robust derivative for the synthesis of various functionalized maleonitriles (vide infra).



In structure **2; a** $R^1 = R^2 =$ Me, **b** $R^1 = R^2 =$ Bn, **c** $R^1 = R^2 =$ allyl, **d** R^1 = Me, R^2 = Bn, **e** R^1 = allyl, R^2 = Bn

Scheme 1. Reagents and conditions: (a) Me_2SO_4 or BnBr or $CH_2{=}CHCH_2Br$, NaH, DME or THF, −30 to 20 °C. (b) C_6H_5CHO, MeOH, Δ. (c) $NaBH_4$, MeOH, THF.

Linstead macrocyclization[32] of dinitriles **2** gave access to the octaamino-porphyrazines **6** in reasonable yields (15–48%) (Scheme 2). The porphyrazines were isolated as blue-black solids with purple reflections. Acidic demetallation by short exposure to trifluoroacetic acid or prolonged contact with acetic acid gave access to the free base porphyrazines **7**. Remetallation with a variety of metal salts was then possible using the metal (II) acetate in DMF.[4] In particular, porphyrazines **7** were converted to the nickel(II) derivatives **8** in good yield (43–92%). All the octaamino-porphyrazines prepared were readily soluble in organic solvents, a feature of the heteroatom-substituted porphyrazines, which is more favorable than the structurally analogous phthalocyanines. Many of the derivatives were also crystalline. As a result, X-ray crystal structures have been solved for **6b** and **8e**.[5]



In structures **2, 6 - 8; a** $R^1 = R^2 =$ Me, **b** $R^1 = R^2 =$ Bn, **c** $R^1 = R^2 =$ allyl, **d** R^1 = Me, R^2 = Bn, **e** R^1 = allyl, R^2 = Bn

Scheme 2. Reagents and conditions: (a) $Mg(O^nBu)_2$, ^{n}BuOH, Δ, 24 h. (b) TFA or AcOH. (c) $Ni(OAc)_2$, PhCl, DMF, Δ.

The electronic absorption spectra for the amino-porphyrazines were consistent with previous observations[4] and can be rationalized using Gouterman's four orbital model.[33] Octaamino-porphyrazines have D_{4h} symmetry, with a doubly degenerate lowest unoccupied molecular orbital (LUMO) (e_g) and two highest occupied molecular orbitals (HOMOs) that complete the four Gouterman orbitals with a_{1u} and a_{2u} symmetry. The compounds therefore displayed two visible transitions, a long-wavelength Q band (~650 nm), corresponding to $a_{2u} \rightarrow e_g$ and a short wavelength B band (Soret) (~350 nm) corresponding to $a_{1u} \rightarrow e_g$. In addition, heteroatom-substituted porphyrazines display intense coupling between the non-bonding, lone pair electrons and the macrocyclic π-system. The resultant n–π* transitions were visible in the electronic absorption spectra (~550 nm). The strong coupling of the non-bonding electrons with the π-system also resulted in significant broadening due to vibrational fine structure. A representative UV–vis spectrum for porphyrazine **6a** is shown in Figure 1.

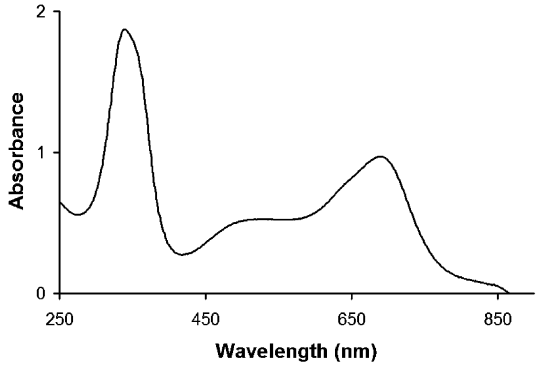


Figure 1. Electronic absorption spectra of **6a**.

The electronic absorption data for representative porphyrazines **6**–**8** are listed in Table 1.

As can be seen in Table 1, all the macrocycles prepared displayed qualitatively similar spectra with visible Soret and Q bands as well as an n–π* transition. However, it is difficult to glean any structure–absorption trends with

Table 1. Electronic absorption data for porphyrazines **6–8**

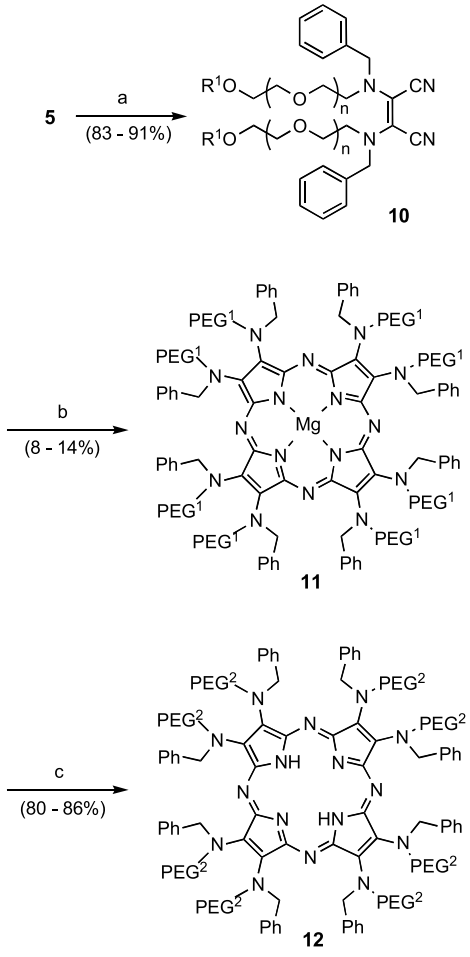
pz	R^1, R^2	Metal	λ_{max} (log ε)
6a[7]	Me, Me	Mg	335 (4.81), 599 (4.27), 752 (4.33)
6b	Bn, Bn	Mg	368 (4.75), 574 (4.45), 707 (4.51)
6d	Me, Bn	Mg	350 (4.56), 544 (4.10), 714 (4.38)
7a[7]	Me, Me	2H	334 (4.57), 531 (4.29), 709 (4.16)
7c	allyl, allyl	2H	333 (4.67), 526 (4.47), 730 (4.36)
7e	allyl, Bn	2H	330 (4.75), 536 (4.59), 734 (4.44)
8a	Me, Me	Ni	325 (4.92), 360 (4.50), 561 (4.42), 704 (4.52)
8b	Bn, Bn	Ni	322 (4.71), 536 (3.95), 654 (4.04), 674 (4.00)
8e	allyl, Bn	Ni	324 (4.72), 511 (4.53), 688 (4.49)

respect to either the amino substituents or the metal occupying the porphyrazine cavity. For example, on going from **6a** to **7a** to **8a** (M=Mg to 2H to Ni), the Soret band remained approximately stationary, whereas the Q band underwent a blue shift (~43 nm) on conversion to the free base, with no real change on remetallation with nickel. In addition, the n–π* transition also underwent a hypsochromic effect on demetallation (~68 nm), with a red shift on insertion of nickel (~30 nm). On changing the substituents from methyl ($R^1=R^2=$Me) to benzyl ($R^1=R^2=$Bn) for the magnesium derivatives (**6a** vs **6b**), the Soret underwent a red shift (~13 nm), whereas the Q band and n–π* transitions underwent a blue shift (~45 and ~25 nm, respectively). For the nickel macrocycles (**8a** vs **8b**), the Soret underwent no such shift and the Q band and n–π* transitions underwent a similar shift as observed for the magnesium derivative. Furthermore, the Soret was split for **8a**, whereas the Q band was split for **8b**. In general, the electronic absorptions of the macrocycles were sensitive to both the amino-substituents as well as the cavity metal, although it is hard to predict the differences these changes will produce.

2.2. Polyethyleneglycol-amino-functionalized porphyrazines

Polyetherol-appended thioporphyrazines have already shown promise as both chemical sensors[34] and biomedical imaging and therapeutic agents.[35,36] In particular, the polyethyleneglycol (PEG) chains confer enhanced aqueous solubility, which makes them ideal candidates for binding metal ions in water or for medical applications. Recently we have disclosed the synthesis of one such PEG-functionalized maleonitrile and its application to the synthesis of a novel *seco*-porphyrazine.[21] Alkylation of benzyl derivative **5**, with iodo-derivatives **9a**[37] or **9b** (formed on treatment of the mono-protected PEG[38] with iodine and triphenylphosphine), under the basic conditions gave the maleonitriles **10a** and **10b** with varying PEG chain lengths. In addition, reaction with iodide **9c**[39] yielded the methyl-capped derivative **9c** (Scheme 3). Macrocyclization furnished the PEG substituted amino porphyrazines **11** in low yield. In the case of THP-protected derivatives **11a** and **11b**, demetallation and concomitant deprotection using acidic conditions[21] gave access to the free base macrocycles **12a** and **12b**. For the methyl-capped product **11c**, simple acidic demetallation occurred on exposure to acetic acid (Scheme 3). Remetallation within the macrocyclic cavity was possible for the PEG-appended porphyrazines; for example **12c** was readily converted to its nickel(II) derivative (not shown).

As expected, the tuning of the amino substituent altered the solubility profile of the macrocycles. Although porphyrazines **12a** and **12c** showed a greatly enhanced solubility in polar, protic solvents such as methanol, unfortunately, they were not water soluble. However, to our delight porphyrazine **12b** was freely soluble in water, producing a homogeneous purple solution. Thus, one possibility for the synthesis of water soluble, neutral amino-porphyrazine analogues is the substitution of PEG chains of sufficient length, with free hydroxyl-functionality at the termini. We



In structures **9**, **10**; **a** n = 0, R^1 = THP, **b** n = 2, R^1 = THP, **c** n = 2, R^1 = Me; **11**; **a** $PEG^1 = CH_2CH_2OTHP$, **b** $PEG^1 = (CH_2CH_2O)_3THP$, **c** $PEG^1 = (CH_2CH_2O)_3Me$; **12**; **a** $PEG^2 = CH_2CH_2OH$, **b** $PEG^2 = (CH_2CH_2O)_3H$, **c** $PEG^2 = (CH_2CH_2O)_3Me$

Scheme 3. (a) $I(CH_2CH_2O)_{(n+1)}R^1$ (**9**), Cs_2CO_3, DMF, 50 °C. (b) $Mg(O^nBu)_2$, ^{n}BuOH, Δ, 24 h. (c) AcOH or AcOHHCl, $CHCl_3$, MeOH, 20 °C.

are currently looking to exploit this result in the context of porphyrazine biomedical agents.

In addition to the physical properties, PEG-appended aminoporphyrazines display intriguing electronic absorption spectra. We have previously noted this for the thioporphyrazine PEG derivatives.[4] For example, **12b** displays a complex spectrum with a split Soret band (327 and 356 nm) as well as a split Q band, which was further complicated by shoulders (667 and 741 nm). Furthermore, an intensive n–π* transition was visible at 556 nm.

2.3. Carboxymethylamino-functionalized porphyrazines

In order to extend the coordination chemistry of the aminoporphyrazines and moreover, provide new and varied macrocycles for application to chemical sensing of metal ions in solution, the synthesis of an acetic acid functionalized porphyrazine **6** ($R^1=R^2=CH_2CO_2H$) was examined. The linking of two acetic acid chains to each peripheral amino group would produce an analogue, which should mimic ethylenediaminetetracetic acid (EDTA). Previously reported macrocyclic analogues of EDTA have been reported to display much higher binding constants with metal ions.[40,41] Unfortunately, this challenging target has thus far eluded preparation. However, these failed attempts have led to several important observations, highlighting the limitations of both maleonitrile **5** as a difunctional starting material and the Linstead macrocyclization reaction.

Early in these synthetic studies, the direct tetra-functionalization of DAMN **1**, proved to be untenable. Attempted alkylation with methyl chloroacetate, the orthoester **13** (X=Cl, Br), the *ortho* ester precursor **14** or protected derivatives of chloroacetaldehyde (e.g., **15**) under basic conditions (NaH or Cs_2CO_3) all failed, resulting either in decomposition or no reaction (Fig. 2).

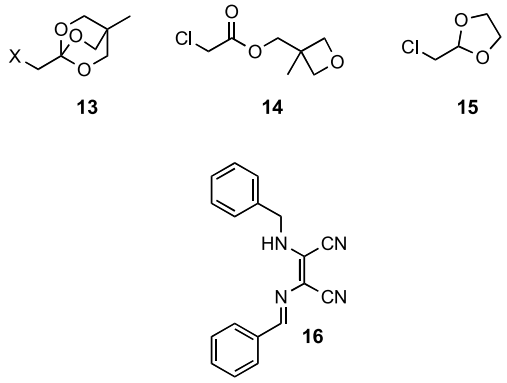
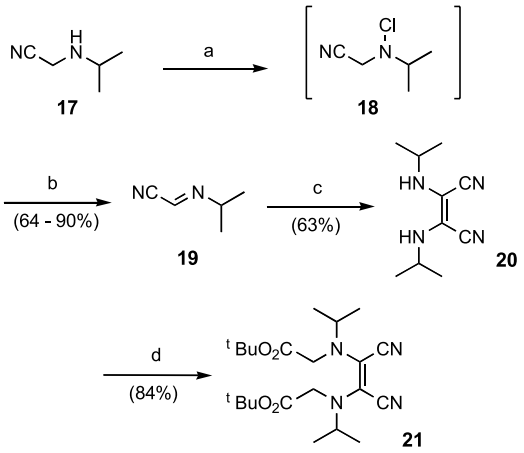


Figure 2.

The use of benzyl derivative **5** was therefore employed for the synthesis of acetic acid functionalized analogues. However, curiously, attempts to alkylate maleonitrile **5** with methyl chloroacetate in the presence of sodium hydride resulted in the formation of the imine **16** (Fig. 2) in 64% yield. Attempted alkylation with a range of functionally equivalent electrophiles provided the same result. Palladium catalyzed amination of **5** using methyl chloroacetate also provided imine **16** in 77% yield. Therefore, in the presence of certain electrophiles, benzyl maleonitrile **5** acts more like a hydride donor than a nucleophile. This is most probably due to the high acidity of the benzyl protons coupled with the low solubility of imine **16**, driving the reaction in an undesired direction.

It was anticipated that the introduction of aliphatic substituents would avoid this predominant side reaction and would serve as a better model for further investigations. Selective dialkylation of DAMN **1** with limited quantities of alkyl halides (for example methyl iodide) gave mixtures of substituted products. Likewise, aliphatic aldehydes proved troublesome in the reductive alkylation pathway (vide supra). An alternative strategy, which would allow the introduction of alkyl substituents prior to the formation of the maleonitrile, was therefore examined. The dimerization of imines has been previously demonstrated for this application.[42,43] *N*-(Isopropylamino)acetonitrile **17** was readily prepared following the procedure of Boyer et al.[43] The preparation of imine **19** was carried out by treatment with *tert*-butyl hypochlorite followed by dehydrochlorination with triethylamine[42,44] or using calcium hypochlorite as the chlorination agent followed by elimination with calcium hydroxide[43] (49%) (Scheme 4). Alternatively, the use of *N*-chlorosuccinimide (NCS) in carbon tetrachloride resulted in a quantitative conversion to the corresponding *N*-chloro derivative **18**, as judged by NMR, after 5 min. Subsequent elimination of intermediate **18** with calcium hydroxide provided imine **19** in an improved 90% yield. Dimerization of imine **19** was carried out by reaction with stannic chloride in dry benzene[43] and gave *N*,*N*′-diisopropyldiaminomaleonitrile **20** in 56% yield, along with 7% of the corresponding *trans*-isomer (as judged by ^{1}H NMR) (Scheme 4). Changing the solvent from benzene to carbon tetrachloride did not suppress dimerization and gave imine **19**, which was used directly without isolation to provide **20**. This provided multigram quantities of an alternative disubstituted aminomaleonitrile derivative **20**, a useful intermediate in our quest for other functionalized aminoporphyrazines.

Initially attempted alkylation of **20** with alkyl chlorides and



Scheme 4. Reagents and conditions: (a) $Ca(OCl)_2$, $CaCl_2$, CH_2Cl_2, 20 °C or NCS, CCl_4, 55 °C. (b) $Ca(OH)_2$, $CaCl_2$, CH_2Cl_2, Δ. (c) $SnCl_4$, PhH, 20 °C. (d) $BrCH_2CO_2$ ^{t}Bu, NaH, DMF, −10 to 20 °C.

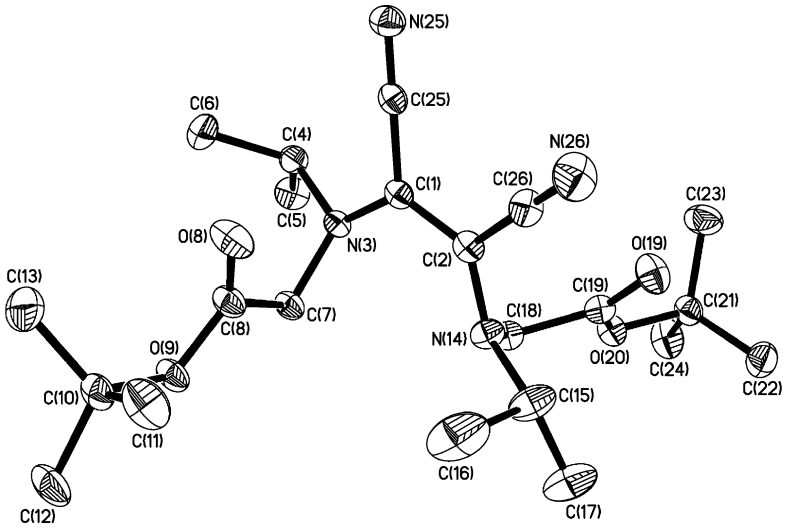
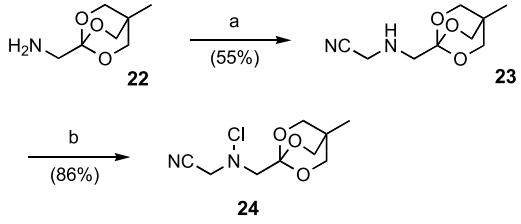


Figure 3. X-ray crystal structure of dinitrile **21**.

sodium hydride in THF was unsuccessful, with quantitative recovery of starting material. However, when DMF was used as the solvent, dinitrile **21** was obtained in an excellent 84% yield (Scheme 4). A single crystal X-ray analysis confirmed the structure of dinitrile **21** with the requisite *cis*-geometry of the double bond in place (Fig. 3).

Unfortunately, attempted macrocyclization of dinitrile **21** under Linstead conditions using either magnesium butoxide or propoxide failed to provide any of the corresponding porphyrazine and resulted in the decomposition of the starting material. It seems reasonable to assume that the failure of the reaction could be due to (a) the acidic protons adjacent to the carbonyl group or (b) steric hindrance of the *tert*-butyl ester. It was therefore considered that conversion of dinitrile **21** to its carboxylic acid counterpart would not only reduce the acidity of the α-protons, but also the steric hindrance. Thus, hydrolysis of the *tert*-butyl ester using neat TFA, produced a dark brown oil, the identity of which was established by spectroscopic analysis (NMR, IR, MS). Exposure of the crude material to magnesium butoxide resulted only in decomposition and none of the desired porphyrazine could be isolated.

In a final effort to utilize this methodology in the synthesis of an acetic acid functionalized porphyrazine, ortho-ester derivative **22** was converted into the *N*-alkylaminoacetonitrile derivative **23** (Scheme 5). Although *N*-chlorination was straightforward, dehydrohalogenation of the resultant derivative **24** gave only polymeric intractable products under a variety of conditions.



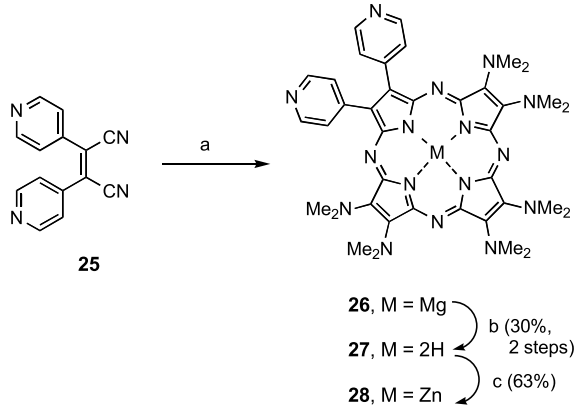
Scheme 5. Reagents and conditions: (a) $ClCH_2CN$, Et_3N, Et_2O, −10 to 20 °C. (b) $Ca(OCl)_2$, $CaCl_2$, CCl_4, 20 °C.

Despite these disappointing results, EDTA appended porphyrazines are still a valuable target in our studies on the aminoporphyrazines and alternate strategies for their production are currently being explored in our laboratories. The current synthetic efforts, however, highlight the problems associated with maleonitrile **5** as a functional intermediate and the incompatibility of certain substrates with Linstead macrocyclization.

2.4. Pyridyl functionalized porphyrazines

Following previous reports of cationic porphyrins as potential DNA-binding and cleavage agents,[45] as well as sensitizers for photodynamic therapy,[46] we first reported the synthesis of an octacationic pyridyl porphyrazine in 1999.[47] These novel systems were both freely soluble in water as the chloride salt and showed strong binding to calf thymus DNA.[48] Thus, in continuation of these studies, the synthesis of unsymmetrical pyridyl-substituted aminoporphyrazines was carried out. The resultant macrocycles should display rich and varied redox chemistry and could be of use in the application of non-linear optics due to the presence of both donor and acceptor functionality.

A statistical, mixed Linstead macrocyclization of pyridyl



Scheme 6. Reagents and conditions: (a) **2a**, $Mg(O^nBu)_2$, ^{n}BuOH, Δ, 24 h. (b) TFA. (c) $Zn(OAc)_2$, DMF, Δ.

maleonitrile **25**,[47] with aminomaleontrile **2a** furnished porphyrazine **26**, the desired (A_3B) hexamine, along with octaaminoporphyrazine **6a** (A_4) (Scheme 6). Traces of *cis* and *trans* A_2B_2 porphyrazines were also observable by mass spectrometry and were isolated as an inseparable mixture. Exposure of porphyrazine **26** to TFA gave the free base derivative **27** (30% overall) and subsequent remetallation under standard conditions gave the zinc(II) macrocycle **28** (63%).

A comparison of the electrochemical data of the novel pyridyl-appended porphyrazine **27** and the related octa-amino-porphyrazine **6a** is presented in Table 2.

Table 2. Electrochemical data for porphyrazines **27** and **6a**

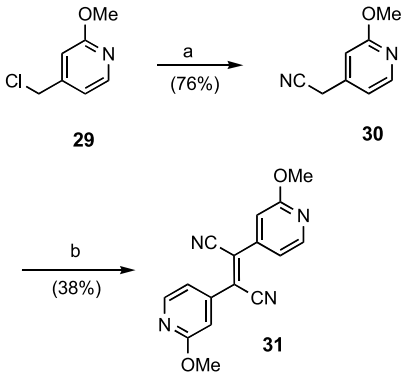
	pz^{2+}/pz^{+}	pz^{+}/pz	pz/pz^{1-}	pz^{1-}/pz^{2-}
27	+1.08	+0.95	−0.29	−0.49
6a	−0.06	−0.27	−1.61	—

Measured in dichloromethane, with 0.1 M Bu_4NPF_6 as electrolyte, Pt disk working electrode, at a scan rate of 110 mV s^{-1}.

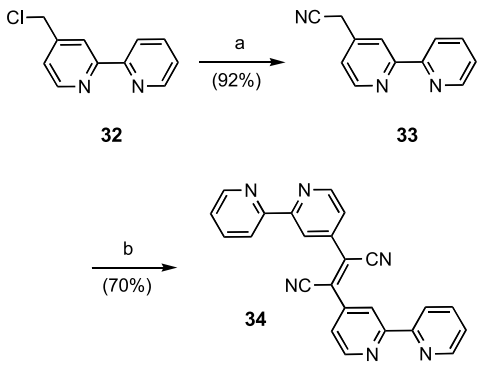
The presence of eight electron donating dimethylamino groups in ligand **6a** results in a system that is extremely easy to oxidize with a first reversible oxidation centered at $E_{1/2} = -0.27$ V with respect to Fc^{+}/Fc. Upon replacement of two NMe_2 units by the electron withdrawing pyridyl groups, the first oxidation potential is shifted to $E_{1/2} = +0.95$ V, thus, indicating that oxidation of the new system is, as expected, more difficult. Also as a consequence of the electron withdrawing pyridyl groups, the first reduction potential of compound **27** is found at −0.29. In contrast, the electron rich ligand **2a** is more difficult to reduce with the first reduction potential centered at −1.61 V. This result demonstrates how simple modification of the porphyrazine substituents can lead to profound differences in the redox potentials of the macrocycles.

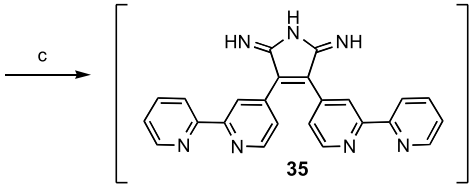
In addition to the potential biomedical applications of pyridyl-appended porphyrazines, we have demonstrated the synthesis of amino porphyrazines bearing pyridyl-based metal donor pockets **6** (R^1=Bn, R^2=2-pyridylmethyl).[17] Such systems show efficient binding of 4 equiv of a variety of metal cations including heavy metals such as cadmium(II) and therefore have potential in sensor applications. In a continuation of this work, the preparation of a bipyridyl porphyrazine **36** was initiated. Two strategies were envisaged, whereby the bipyridyl linkage could be constructed pre- or post-macrocyclization. Towards the latter goal, nitrile **30** was prepared by nucleophilic displacement of the corresponding chloride **29** (prepared from 2-methoxy-4-methylpyridine,[49] by chlorination of a transient silyl derivative synthesized following the method of Katrizky et al.[50]). Dimerization of **30** with sodium methoxide and iodine gave the requisite dinitrile **31** (Scheme 7). However, macrocyclization of dinitrile **31** was problematic, with low yields of a high polarity material, which could not be fully purified. Therefore, introduction of the bipyridyl residue before the Linstead macrocyclization reaction was investigated.

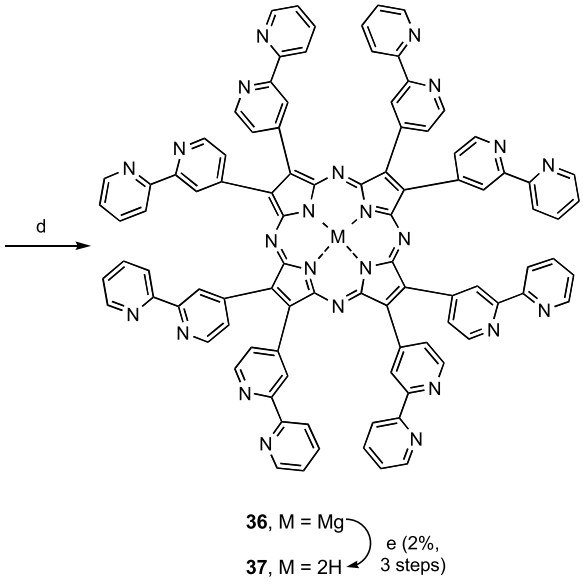
Similar cyanide displacement of acid sensitive chloride



Scheme 7. Reagents and conditions: (a) NaCN, DMSO. (b) I_2, NaOMe, MeOH, Δ.







Scheme 8. Reagents and conditions: (a) KCN, 18-crown-6, MeCN. (b) I_2, NaOMe, MeOH, Δ. (c) NH_3, cat Na, $HOCH_2CH_2OH$, Δ. (d) $Mg(O^nBu)_2$, ^{n}BuOH, Δ, 24 h. (e) TFA.

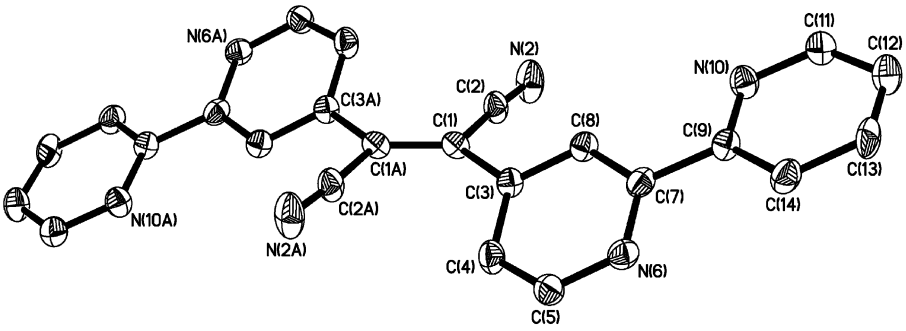


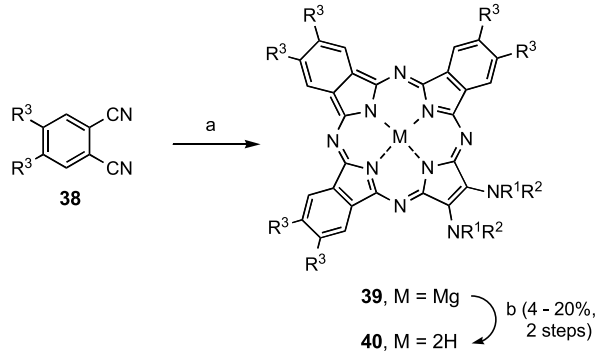
Figure 4. X-ray crystal structure of dinitrile **34**.

32,[51] yielded nitrile **33**, which was subsequently oxidatively dimerized in excellent yield (64% over 2 steps) (Scheme 8). The *trans* geometry of dinitrile **34** was elucidated by X-ray crystallography (Fig. 4). Unfortunately, attempted Linstead macrocyclization of dinitrile led to decomposition of the substrate. This was attributed to the slow thermal isomerization of dinitrile **34** and the general sensitive nature of the substrate. Instead, dinitrile **34** was first converted to the diiminopyrroline **35**, upon treatment with ammonia gas in ethylene glycol at reflux catalyzed by sodium 2-hydroxyethoxide.[52] The crude product **35** was immediately macrocyclized to yield the porphyrazine **36**, which was subsequently demetallated with trifluoroacetic acid, giving macrocycle **37**, albeit in low yield (ca. 2% from **34**) (Scheme 8).

The UV–vis spectra of the octabipyridyl porphyrazines **36** and **37** exhibited qualitatively similar spectra to the corresponding octapyridyl porphyrazines.[47] The magnesium derivative **36** displayed a Soret band at 337 nm and a Q band at 537 nm. In addition, there were also strong absorption bands at higher energy, 241 and 283 nm, which were assigned to the peripherally attached bipyridyl groups. The UV–vis spectrum of the demetallated ligand **37** displayed a Soret band at 362 nm and a split Q-band at 593 and 660 nm. Again, higher energy bands at 240 and 283 nm were assigned to the bipyridyl groups. The applications of these novel bipyridyl porphyrazines is currently being investigated with particular attention to their metal binding properties.

2.5. Amino functionalized norphthalocyanines

Norphthalocyanines are phthalocyanine–porphyrazine hybrids, consisting of three phthalonitrile units and one maleonitrile unit. Previously we reported the synthesis of norphthalocyanine dithiolates and coordination of these ligands to a variety of metals, yielding solitaire porphyrazines.[53,54] In addition, we have reported the preparation of pyridyl-appended systems as novel metal sensors[17] and a bis(dimethylamino)norphthalocyanine, which was characterized by X-ray crystallography.[10] We initiated the synthesis of several additional amino-appended norphthalocyanines to investigate how the benzo-substitution of these novel hybrids affects their physical properties and electronic absorption spectra. Commercially available phthalonitrile **38a** was utilized in a mixed Linstead macrocyclization with amino-maleonitriles **2b** and **2c**. This furnished magnesium norphthalocyanine derivatives **39a** and **39b** (Scheme 9). Chromatographic purification of these highly insoluble pigments proved impossible and therefore the macrocycles were demetallated to give free-bases **40a** and **40b**, which were sufficiently soluble to purify. However, the solubility of **40a** and **40b** precluded further manipulation and conversion to the nickel (II) derivatives lead to macrocycles with an even lower solubility profile. The poor solubility of the norphthalocyanines has been previously noted.[10]



In structures **38; a** R^3 = H, **b** R^3 = ^{n}Bu; **39**, **40**; **a** R^1 = R^2 = allyl, R^3 = H, **b** R^1 = R^2 = $PhCH_2$, R^3 = H, **c** R^1 = R^2 = allyl, R^3 = ^{n}Bu, **d** R^1 = R^2 = $PhCH_2$, R^3 = ^{n}Bu, **e** R^1 = $PhCH_2$, R^2 = allyl, R^3 = ^{n}Bu; **39f** R^1 = $PhCH_2$, R^2 = CH_2CH_2OTHP, R^3 = ^{n}Bu; **40f** R^1 = $PhCH_2$, R^2 = CH_2CH_2OH, R^3 = ^{n}Bu,

Scheme 9. Reagents and conditions: (a) **2**, $Mg(O^nBu)_2$, ^{n}BuOH, Δ, 24 h. (b) TFA.

The synthesis of more soluble derivatives was achieved by the modification of the norphthalocyanine cyclization partner. In particular, 4-*n*-butylphthalonitrile **38b**[55] was utilized in the Linstead macrocyclization to yield norphthalocyanines **39c–f**, with benzyl, allyl and tetrahydropyranoxylethyl substituents (Scheme 9). Demetallation was achieved to yield the free base macrocycles **40c** and **40d**, whereas demetallation and concomitant deprotection of norphthalocyanine **39f** was achieved, furnishing the di-(hydroxyethylamino)-porphyrazine **40f**. All the butyl-substituted norphthalocyanines were more soluble in organic solvents than their unsubstituted counterparts.

The electronic absorption data for porphyrazines **40a–d** are shown in Table 3.

As can be seen in Table 3, all the macrocycles prepared displayed qualitatively similar spectra containing Soret

Table 3. Electronic absorption data for porphyrazines **40a–d**

pz	R^1, R^2	R^3	λ_{max} (log ε)
40a	allyl, allyl	H	293 (4.46), 338 (4.83), 528sh, 577 (4.42), 649 (4.69), 688 (4.60), 723 (4.60)
40b	Bn, Bn	H	292 (4.45), 341 (4.83), 527sh, 583 (4.46), 644 (4.57), 691 (4.56), 727 (4.61)
40c	allyl, allyl	^{n}Bu	299 (4.56), 345 (4.89), 524 (4.25), 577sh, 656 (4.62), 691 (4.61), 733 (4.69)
40d	Bn, Bn	^{n}Bu	298 (4.58), 347 (4.90), 517 (4.24), 590sh, 655 (4.64), 691 (4.62), 734 (4.74)

transitions (~340 nm), as well as split Q bands (centered around 690 nm). In addition, n–π* transitions are observable (~570 nm) as well as high-energy bands at 290 nm. The splitting of the Q band is due to both the reduced symmetry of the norphthalocyanine (C_{2v}), combined with the reduced symmetry of the free base macrocycles. This reduction in symmetry destroys the degeneracy of the LUMO, resulting in two separate orbitals b_{2g} and b_{3g}.[33] In general, the substituents of norphthalocyanines **40a–d** have little effect on the position of the bands. Interestingly, the Q bands of the norphthalocyanines are only slightly blue shifted in comparison to the corresponding octaaminoporphyrazines **7** (see Table 1). Parent phthalocyanines display Q bands around 690 nm, whereas the Q band for unsubstituted porphyrazines is around 600 nm.[4] Benzo-substitution therefore results in approximately a 100 nm red shift. Heteroatom substitution of the porphyrazine macrocycle also results in approximately a 100 nm red shift. Therefore, norphthalocyanines containing three sites of benzo-substitution and one of amino-substitution result in a similar Q band shift than parent phthalocyanines or octaaminoporphyrazines, when compared to unsubstituted porphyrazines. This indicates that the benzo-substitution, present in the norphthalocyanines has approximately the same effect on the energetics of electronic transitions as amino-substitution does.

3. Conclusions

The synthesis of a wide range of amino-functionalized porphyrazines has been described in this report. It shows how the amino-groups, attached to the periphery of the macrocycle, can be tailored to alter the physical properties of the porphyrazine as well as its electronic absorption and reactivity. Some of the macrocycles prepared in this report are expected to find applications as diverse as biomedical agents, novel charge-transfer complexes, chemical sensors, novel electronic materials and non-linear optics. We are currently pursuing this direction and such work will be reported in due course.

4. Experimental

4.1. General procedures

All reactions were conducted in oven or flame dried glassware under N_2. Reaction temperatures reported refer to external bath temperatures. Solvents used in chromatography were BDH AnalR or GPR grade and were used without further purification. Hexanes refers to the alkane fraction boiling between 40 and 60 °C. Solvents used for reactions were distilled prior to use: THF, DME, and Et_2O (from K-Ph_2CO ketal); Et_3N, pyridine, CH_2Cl_2, and MeCN (from CaH_2); DMF (predried over BaO, distilled from neutral Al_2O_3 (activity I)); MeOH, *n*-PrOH, and *n*-BuOH (from Mg). All other reagents were purchased from commercial sources and were used without further purification. Thin layer chromatography (TLC) was performed on Merck Kieselgel 60 F-254 glass plates. Visualization was accomplished using the quenching of UV fluorescence (λ_{max} 254 nm), and by $KMnO_4$ (basic), ceric molybdate, anisaldehyde, and vanillin solutions, followed by heat. Flash chromatography utilized Merck Kieselgel 60 (230–400 mesh) or Aluminum oxide 90 active (activity I). Size exclusion chromatography was performed on Sephadex LH-20 or Bio-Beads S-X3 supports. All solvents were rotary evaporated at or below 50 °C under reduced pressure. Cyclic voltammetry data were recorded with a Cypress Systems 2000 computer-controlled potentiostat. A three electrode configuration was employed: a platinum disk working electrode, a silver wire counter electrode, and a silver–silver chloride reference electrode. Measurements were made in CH_2Cl_2, freshly distilled from CaH_2, with Bu_4NPF_6 as the supporting electrolyte. All measurements were calibrated by addition of ferrocene as an internal reference and $E_{1/2}$ values were calculated from $(E_{pa}+E_{pc})/2$ at a scan rate of 110 mV s^{-1}.

4.1.1. 2,3-*Bis*(dibenzylamino)-2(*Z*)-butene-1,4-dinitrile (2b). Diamine **1** (10.0 g, 92.6 mmol) in DME (60 mL) was added with rapid stirring to NaH (60% dispersion in mineral oil, 17.0 g, 425 mmol) in DME (100 mL) at −22 °C. After the addition was complete (0.5 h), the brown suspension was stirred at −22 °C for 0.5 h. $PhCH_2Br$ (69.1 g, 400 mmol) in DME (30 mL) was slowly added and stirring continued at −22 °C for 1 h, when the mixture was allowed to warm slowly up to room temperature. The suspension was filtered through Celite, rotary evaporated and crystallized from EtOAc–hexanes to give dinitrile **2b** (23 g, 53%) as a light brown solid: mp 129–130.5 °C (Et_2O/hexanes); TLC 0.71 (EtOAc/hexanes 1:1); IR ($CHCl_3$) 2400, 2186, 1591, 1579, 1454, 1215, 1152, 1028 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.2 (s, 8H), 7.05 (m, 8H), 7.28 (m, 12H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 55.9, 115.3, 118.0, 128.1, 128.6, 129.1, 136.4; MS (EI) *m/z* 468 ($M^{+\cdot}$), 377, 260, 181, 91, 65; HRMS (EI) *m/z* Calcd for $C_{32}H_{28}N_4$: ($M^{+\cdot}$), 468.2316; found: ($M^{+\cdot}$), 468.2324. Anal. Calcd for $C_{32}H_{28}N_4$: C, 82.01; H, 6.03; N, 11.96. Found: C, 82.15; H, 6.05; N, 11.96%.

4.1.2. 2,3-Bis(diallylamino)-2(*Z*)-butene-1,4-dinitrile (2c). Following the same procedure as for the preparation of dinitrile **2b**, diamine **1** and allyl bromide gave dinitrile **2c** (8.5 g, 69%) as an orange-yellow oil: TLC R_f 0.40 (EtOAc/hexanes 1:9); IR (film) ν_{max} 2186, 1643, 1585, 1443, 1403, 1244, 1178, 991, 928 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 3.71 (8H, d, J=6.3 Hz), 5.19–5.26 (8H, m), 5.66–5.81 (4H, m); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 54.7, 115.1, 117.1,

119.7, 132.9; MS (CI, NH_3) *m/z* 286 $(M+NH_4)^+$, 269 $(M+H)^+$, 227; HRMS (CI, NH_3) Calcd for $C_{16}H_{24}N_5$ $(M+NH_4)^+$, 286.2032; found: $(M+NH_4)^+$, 286.2035. Anal. Calcd for $C_{16}H_{20}N_4$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.51; H, 7.74; N, 20.84.

4.1.3. 2,3-Di(benzyl(methyl)amino)-2(*Z*)-butene-1,4-dinitrile (2d). Following the same procedure as for the preparation of dinitrile **2b**, diamine **5**[31] and dimethyl sulfate gave dinitrile **2d** (7.0 g, 64%) as a colorless solid: mp 86 °C (EtOAc/hexane); TLC 0.55 (EtOAc/hexanes 2:3); IR (film) 2184, 1593, 1450, 1429, 1284, 1233, 947, 881, 710, 675, 654 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.74 (s, 6H), 4.20 (s, 4H), 7.15 (m, 4H), 7.34 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.5, 58.7, 115.0, 117.5, 128.0, 128.4, 128.8, 136.1. Anal. Calcd for $C_{20}H_{20}N_4$: C, 75.91; H, 6.37; N, 17.71. Found: C, 75.99; H, 6.54; N, 17.89%.

4.1.4. 2,3-Di(allyl(benzyl)amino)-2(*Z*)-butene-1,4-dinitrile (2e).[5] Dinitrile **5** (10.0 g, 34.7 mmol) was added with rapid stirring to NaH (60% in mineral oil; 3.1 g, 76.4 mmol) in dry THF (350 mL) at −22 °C. After 30 min, allyl bromide (16.8 g, 139.0 mmol) was added and stirring continued at −22 °C for 2 h. The mixture was allowed to warm up to room temperature. After stirring for 2 h, distilled H_2O (40 mL) was added, the aqueous layer was extracted with Et_2O (3×200 mL), and the solvent evaporated. Chromatography (SiO_2, Et_2O/hexanes 9:1 to 1:1) gave dinitrile **2e** (10.3 g, 80%) as a viscous yellow oil: TLC R_f 0.16 (Et_2O/hexanes 9:1); IR (film) ν_{max} 2185, 1642, 1590, 1581, 1495, 1454, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 3.65 (4H, d, J=6.3 Hz), 4.25 (4H, s), 5.11–5.24 (4H, m), 5.56–5.68 (2H, m), 7.11–7.34 (10H, m); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 54.7, 55.4, 114.8, 117.1, 119.5, 127.9, 128.4, 128.8, 132.3, 136.1; MS (EI) *m/z* 368 $(M)^+$, 277; HRMS (EI) *m/z* Calcd for $C_{24}H_{24}N_4$: $(M^{+\cdot})$, 368.2001; found: $(M^{+\cdot})$, 368.2011. Anal. Calcd for $C_{24}H_{24}N_4$: C, 78.22; H, 6.57; N, 15.22. Found: C, 78.11; H, 6.76; N, 15.15.

4.1.5. (2,3,7,8,12,13,17,18-Octa(benzyl(methyl)amino)-porphyrazinato)-magnesium(II) (6d). PrOH (100 mL) and Mg turnings (550 mg, 22.6 mmol) were heated to reflux for 10 h and cooled to room temperature. Dinitrile **2d** (2.0 g, 6.3 mmol) was added and the mixture was heated to reflux for 48 h. The blue suspension was filtered off through celite and the solids leached with CH_2Cl_2 (150 mL). Rotary evaporation and chromatography (Al_2O_3 EtOAc/hexanes) gave **6d** (500 mg, 25%) as a dark blue amorphous solid: TLC 0.60 (EtOAc/hexanes 2:3); IR (nujol) 1567, 1450, 1394, 1065, 730, 696 cm^{-1}; UV–vis (PhCl) λ max (log ε) 350 (4.56), 544 (4.10), 714 (4.38) nm; ^1H NMR (300 MHz, $CDCl_3$) δ 3.44 (s, 24H), 5.32 (s, 16H), 7.16 (m, 24H), 7.32 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.7, 60.8, 126.9, 128.4, 128.9, 139.5, 140.5, 152.8; HRMS (FAB) *m/z* Calcd for $C_{80}H_{80}MgN_{16}$: $(M^{+\cdot})$, 1288.6602; found: $(M^{+\cdot})$, 1288.6912.

4.1.6. 2,3,7,8,12,13,17,18-Octa(diallylamino)porphyrazine (7c). Dry *n*-PrOH (22 mL), Mg turnings (68 mg, 2.8 mmol) and I_2 (1 crystal) were heated to reflux for 24 h. After cooling to room temperature, dinitrile **2c** (2 g, 7.5 mmol) in dry *n*-PrOH (5 mL) was added and reflux continued for 24 h. After cooling, the deep purple mixture was diluted with $CHCl_3$, filtered through Celite and the filtrate evaporated. AcOH (15 mL) was added and, after 0.5 h in the dark, the mixture was added to ice and H_2O (100 mL) and the pH adjusted to 7.5 with 1 M NaOH. The dark precipitate was collected by filtration and washed with H_2O. Chromatography (SiO_2, EtOAc/hexanes 1:19) gave porphyrazine **7c** (300 mg, 15%) as a dark purple pasty solid: TLC R_f 0.73 (EtOAc/hexanes 1:9); IR ($CHCl_3$) ν_{max} 3301, 1848, 1639, 1573, 1551, 1415, 1190, 1121, 993, 921, 860, 562 cm^{-1}; UV–vis ($CHCl_3$) λ_{max} (log ε) 333 (4.67), 526 (4.47), 730 (4.36) nm; ^1H NMR ($CDCl_3$, 300 MHz) δ −1.01 (2H, s), 4.90 (24H, d, J=6.0 Hz), 5.17 (16H, d, J=10.0 Hz), 5.37 (16H, d, J=17.0 Hz), 6.10–6.23 (16H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.0, 116.7, 136.3, 148.5; FABMS *m/z* 1075 $(M^{+\cdot})$, 1034.

4.1.7. 2,3,7,8,12,13,17,18-Octakis(allyl(benzyl)amino)-porphyrazine (7e). Dry *n*-PrOH (375 mL), Mg turnings (2.6 g, 109 mmol) and I_2 (1 crystal) were heated at reflux for 24 h. After cooling to room temperature, dinitrile **2e** (10 g, 27.2 mmol) in *n*-PrOH (20 mL) was added and the mixture heated at reflux for 36 h. After cooling to room temperature, the deep purple mixture was diluted with CH_2Cl_2 (300 mL), filtered through Celite and the filtrate evaporated. Chromatography (Al_2O_3 EtOAc/hexanes 5:95) gave porphyrazine **7e** (M=Mg) (2.0 g, 20%) as a purple solid, which was used without further purification. AcOH (20 mL) was added to porphyrazine **7c** (M=Mg) (570 mg, 0.38 mmol) and the mixture stirred at room temperature for 3 h. The blue-purple solution was slowly added to ice and H_2O (300 mL) and the pH adjusted to 7.5 using aqueous 2.0 M NaOH. The dark precipitate was filtered off and washed repeatedly with H_2O. Chromatography (SiO_2, EtOAc/hexanes 1:19) gave porphyrazine **7e** (M=2H) (460 mg, 82%) as a purple solid: TLC R_f 0.6 (Et_2O/hexanes 1:4); IR (CH_2Cl_2) ν_{max} 3304, 1644, 1572, 1548, 1494, 1452, 1414, 1297, 924, 873 cm^{-1}; UV–vis (CH_2Cl_2) λ_{max} (log ε) 330 (4.75), 536 (4.59), and 734 (4.44) nm; ^1H NMR ($CDCl_3$, 270 MHz) δ −0.93 (2H, s, N*H*), 4.70 (16H, d, J=6.4 Hz), 5.09 (8H, dd, J=2.0, 10.0 Hz) 5.23 (8H, dd, J=2.0, 17.0 Hz), 5.34 (16H, s), 5.97–6.07 (8H, m), 7.10–7.18 (24H, m), 7.30–7.34 (16H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 54.9, 55.2, 117.1, 126.7, 128.2, 128.7, 136.0, 136.5, 139.7, 148.5; FABMS *m/z* 1475 $(M^{+\cdot})$, 1435, 1385. Anal. Calcd for $C_{96}H_{98}N_{16}$: C, 78.11; H, 6.70; N, 15.19. Found: C, 78.12; H, 6.71; N, 14.96.

4.1.8. (2,3,7,8,12,13,17,18-Octakis(dimethylamino)porphyrazinato)nickel(II) (8a). Porphyrazine **7a**[7] (60 mg, 0.09 mmol), anhydrous $Ni(OAc)_2$ (160 mg, 0.9 mmol), PhCl (15 mL) and DMF (5 mL) were heated to reflux with stirring overnight. After cooling to room temperature, the mixture was filtered through celite and the solids leached with Et_2O and $CHCl_3$. The filtrate was evaporated, dissolved in heptanes, re-evaporated and chromatographed (SiO_2 Et_2O). The colored band remaining on the silica was eluted with MeOH and evaporated. Size exclusion chromatography (Sephadex LH20 $CHCl_3$) gave **8a** (28 mg, 43%) as a black amorphous solid: TLC 0.84 (EtOAc/hexanes 3:2); IR (nujol) 1599, 1385, 1092 cm^{-1}; UV–vis (CH_2Cl_2) λ max (log ε) 325 (4.92) 360 (4.90), 561 (4.42), 704 (4.52) nm; ^1H NMR (300 MHz, $CDCl_3$) δ 3.63 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 45.3, 138.5, 144.1; HRMS (FAB) *m/z* Calcd for

$C_{32}H_{48}N_{16}Ni$: $(M+H^+)$, 715.3680, $(M^{+\cdot})$, 714.3601; found: $(M+H^+)$, 715.3726, $(M^{+\cdot})$, 714.3708.

4.1.9. (2,3,7,8,12,13,17,18-Octakis(dibenzylamino)porphyrazinato)nickel(II) (8b). CF_3CO_2H (10 mL) was added to porphyrazine **6b**[5] (200 mg, 0.29 mmol), the mixture stirred at room temperature for 12 h and added to ice and the pH adjusted to 7.5 using aqueous NaOH (1.0 M). The dark precipitate was filtered off and chromatographed (SiO_2 EtOAc/hexane) to provide **7b** (170 mg, 86%) as a black amorphous solid: TLC 0.85 (EtOAc/hexanes 3:2); HRMS (FAB) *m/z* Calcd for $C_{128}H_{114}N_{16}$: $(M+H^+)$, 1875.9490, found: $(M+H^+)$, 1875.9456. The crude porphyrazine **7b** was used directly without further purification. The crude porphyrazine **7b** (160 mg, 0.085 mmol), anhydrous $Ni(OAc)_2$ (300 mg, 1.7 mmol), PhCl (10 mL) and DMF (10 mL) were heated to reflux with stirring for 12 h. After evaporation, the residue was dissolved in CH_2Cl_2 and filtered through celite. The filtrate was evaporated and chromatographed (SiO_2 EtOAc/hexanes) to give porphyrazine **8b** (98 mg, 59%) as a purple-black amorphous solid: TLC 0.63 (EtOAc/hexanes 2:3); IR (nujol) 1576, 1493, 1448, 765, 689 cm^{-1}; UV–vis (PhCl) λ max (log ε) 322 (4.71), 536 (3.95), 654 (4.04), 674 (4.00) nm; ^1H NMR (300 MHz, $CDCl_3$) δ 4.1 (s, 32H), 7.10 (m, 32H), 7.25 (m, 48H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 57.5, 114.3, 120.5, 128.2, 129.1, 136.2; MS (FAB) *m/z* 1932 $(M^{+\cdot})$, 1841, 1749, 1737.

4.1.10. (2,3,7,8,12,13,17,18-Octakis(allyl(benzyl)amino)-porphyrazinato)nickel(II) (8e). Porphyrazine **7e** (100 mg, 0.034 mmol), anhydrous $Ni(OAc)_2$ (84.0 mg, 0.34 mmol), PhCl (7 mL) and DMF (2.3 mL) were heated at reflux with stirring for 18 h. After cooling to room temperature, the mixture was filtered through Celite, the solids leached with $CHCl_3$ and the filtrate evaporated. Chromatography (SiO_2, Et_2O/hexanes 1:25) gave porphyrazine **8e** (96 mg, 92%) as a purple solid: mp 112–114 °C; TLC R_f 0.50 (Et_2O/hexanes 1:9); IR ($CHCl_3$) ν_{max} 1576, 1511, 1493, 1438, 1320, 1186, 1123, 918, 698 cm^{-1}; UV–vis (CH_2Cl_2) λ_{max} (log ε) 324 (4.72), 511 (4.53), and 688 (4.49) nm; ^1H NMR ($CDCl_3$, 270 MHz) δ 4.62 (16H, d, $J=6.0$ Hz), 5.07 (8H, dd, $J=2.0$, 10.0 Hz) 5.20 (8H, dd, $J=2.0$, 17.0 Hz), 5.31 (16H, s), 5.94–6.04 (8H, m), 7.11–7.34 (40H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.3, 55.6, 117.2, 126.8, 128.3, 128.7, 136.1, 138.0, 140.0, 143.7; FABMS *m/z* 1532 $(M+H)^+$, 1491, 1441; HRFABMS *m/z* Calcd for $C_{96}H_{96}N_{16}Ni$: $(M^{+\cdot})$, 1530.7357; found: $(M^{+\cdot})$, 1530.7359. Anal. Calcd for $C_{96}H_{96}N_{16}Ni$: C, 75.23; H, 6.31; N, 14.62. Found: C, 75.13; H, 6.45; N, 14.43.

4.1.11. 1-Iodo-8-tetrahydropyranyloxy-3,6-dioxaoctane (9b). I_2 (15.5 g, 61 mmol) was slowly added rapidly with stirring to $THPO(CH_2CH_2O)_2CH_2CH_2OH$[38] (10 g, 43 mmol), Ph_3P (14.6 g, 55.5 mmol), and imidazole (4.0 g, 58.5 mmol) in MeCN (50 mL) and Et_2O (75 mL) at 0 °C. The brown-black slurry was stirred at 0 °C for 1.5 h, the mixture was diluted with Et_2O (900 mL), filtered, and washed with saturated aqueous $Na_2S_2O_3$ (3×250 mL), saturated aqueous $CuSO_4$ (3×250 mL), H_2O (3×250 mL), dried ($MgSO_4$: K_2CO_3 1:1), filtered, and rotary evaporated to give a white oily solid. Et_2O was added (100 mL), the suspension was filtered and the filtrate was rotary evaporated to give another white oily solid. This procedure was repeated with Et_2O (50 mL) to give a clear slightly yellow oil. Chromatography (SiO_2, EtOAc/hexanes 1:3) gave iodide **9b** (11.8 g, 80%) as a clear yellow oil: TLC R_f 0.35 (EtOAc/hexanes 1:3); IR (film) ν_{max} 1453, 1440, 1352, 1261, 1200, 1124, 1077, 1034, 988, 872, 814, 618 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.49–1.74 (6H, m), 3.24 (2H, t, $J=7$ Hz), 3.48–3.88 (14H, m), and 4.60–4.63 (1H, m); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 2.9, 19.4, 25.4, 30.5, 62.1, 66.6, 70.2, 71.9, 98.9; MS (CI, NH_3) *m/z* 362 $(M+NH_4)^+$, 345 $(M+H)^+$, 278, 261; HRMS (CI, NH_3) *m/z* Calcd for $C_{11}H_{22}O_4I$: $(M+H)^+$, 345.0563; found: $(M+H)^+$, 345.0559.

4.1.12. 2,3-Di(benzyl(2-tetrahydropyranyloxyethyl)-amino)-2-butene-1,4-dinitrile (10a). Dinitrile **5** (250 mg, 0.87 mmol) and $THPOCH_2CH_2I$ **9a**[37] (890 mg, 3.5 mmol) in dry DMF (2.5 mL) was added over 1 h to a rapidly stirring suspension of Cs_2CO_3 (620 mg, 1.9 mmol) in dry DMF (2.5 mL). After the addition was complete, the mixture was heated at 40 °C for 5 h and allowed to cool to room temperature. After 12 h, the mixture was poured into ice and H_2O (50 mL) and extracted with EtOAc (2× 20 mL). The combined organic layers were washed with H_2O (2×30 mL), brine (1×20 mL), dried ($MgSO_4$: K_2CO_3 1:1), and the solvent evaporated. Chromatography (SiO_2, EtOAc/hexanes 1:3) gave dinitrile **10a** (390 mg, 83%) as a mixture of E and Z isomers as a clear amber oil: TLC R_f 0.29, 0.42 (EtOAc/hexanes 1:3); IR (film) ν_{max} 2200, 1563, 1495, 1453, 1390, 1348, 1202, 1128, 1075, 1035, 976, 751, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.46–1.85 (12H, m), 3.25–3.53 (4H, m), 3.75–3.85 (4H, m), 4.30–4.66 (4H, m), 7.17–7.35 (10H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.4, 25.4, 30.6, 50.6, 55.9, 62.3, 65.0, 99.0, 115.2, 116.9, 127.8, 128.5, 128.8, 136.9; MS (CI, NH_3) *m/z* 545 $(M+H)^+$, 461 $(M\text{-}THP+H)^+$; HRMS (CI, NH_3) *m/z* Calcd for $C_{32}H_{41}N_4O_4$: $(M+H)^+$, 545.3128; found: $(M+H)^+$, 545.3102. Anal. Calcd for $C_{32}H_{40}N_4O_4$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.65; H, 7.26; N, 10.04.

4.1.13. 2,3-Di(benzyl(8-tetrahydropyranyloxy-3,6-dioxa-octyl)amino)-2-butene-1,4-dinitrile (10b). Following the same procedure as for the preparation of dinitrile **10a**, dinitrile **5** and $THPO(CH_2CH_2O)_2CH_2CH_2I$ **9b** gave dinitrile **10b** (6.98 g, 91%) as a mixture of E and Z isomers as a clear amber oil: TLC R_f 0.68 (EtOAc); IR (film) ν_{max} 2185, 1587, 1494, 1453, 1125, 1076, 1035, 988, 873, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.46–1.84 (12H, m), 3.19–3.27 (4H, m), 3.45–3.68 (16H, m), 3.81–3.90 (4H, m), 4.27, 4.38 (4H, 2 s), 4.59–4.62 (2H, m), 7.15–7.35 (10H, m); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 19.5, 25.4, 30.6, 50.6, 52.8, 55.9, 58.7, 62.20, 62.25, 66.6, 68.9, 69.3, 70.51, 70.55, 98.9, 114.1, 115.0, 116.7, 119.3, 127.8, 128.4, 128.6, 128.65, 128.72, 136.3, 136.9; MS (CI, NH_3) *m/z* 721 $(M+H)^+$, 634, 553; HRMS (CI, NH_3) *m/z* Calcd for $C_{40}H_{60}N_5O_8$: $(M+NH_4)^+$, 738.4442; found: $(M+NH_4)^+$, 738.4495. Anal. Calcd for $C_{40}H_{60}N_5O_8$: C, 66.64; H, 7.83; N, 7.77. Found: C, 66.57; H, 7.53; N, 7.66.

4.1.14. 2,3-Di(benzyl(3,6,9-trioxadecyl)amino)-2-butene-1,4-dinitrile (10c). Following the same procedure as for the preparation of dinitrile **10a**, dinitrile **5** and $Me(OCH_2CH_2)_3I$ **9c**[37] gave dinitrile **10c** (5.0 g, 83%) as a clear amber oil:

TLC R_f 0.11 (EtOAc/hexanes 1:1); IR (film) ν_{max} 2197, 1584, 1493, 1453, 1111, 747, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.27 (4H, t, $J=5.2$ Hz), 3.37 (6H, s), 3.49 (4H, t, $J=5.2$ Hz), 3.50–3.60 (16H, m), 4.40 (4H, s), 7.19 (6H, m), 7.29 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 50.6, 56.0, 59.0, 69.0, 70.5, 70.58, 70.61, 72.0, 115.1, 116.8, 127.8, 128.4, 128.8, 137.0; MS (CI, NH_3) *m/z* 581 $(M+H)^+$, 491; HRMS (CI, NH_3) *m/z* Calcd for $C_{32}H_{45}N_4O_6$: $(M+H)^+$, 581.3339, found: $(M+H)^+$, 581.3366. Anal. Calcd for $C_{32}H_{44}N_4O_6$: C, 66.18; H, 7.64; N, 9.65. Found: C, 65.94; H, 7.34; N, 9.64.

4.1.15. 2,3,7,8,12,13,17,18-Octakis(benzyl(2-tetrahydropyranyloxyethyl)amino)-porphyrazinato)magnesium(II) (11a). Dry *n*-BuOH (2.5 mL), I_2 (1 crystal) and Mg turnings (0.11 g, 4.6 mmol) were heated at reflux for 24 h. After cooling to room temperature, dinitrile **10a** (250 mg, 0.46 mmol) in dry *n*-BuOH (2.5 mL) was added and the suspension heated at reflux for 24 h. After cooling to room temperature, the purple-black suspension was diluted with $CHCl_3$ (10 mL), filtered through Celite, and rotary evaporated. Chromatography (SiO_2, EtOAc/hexanes 1:3 to 2:3) gave porphyrazine **11a** (36 mg, 14%) as a purple oil: TLC R_f 0.30 (EtOAc/hexanes 1:2); IR ($CHCl_3$) ν_{max} 1601, 1556, 1493, 1452, 1285, 1122, 1070, 1032, 975, 733, 698 cm^{-1}; UV–vis ($CHCl_3$) λ_{max} (log ε) 347sh, 359 (4.77), 516sh, 569 (4.38), 713 (4.58) nm; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.88–1.56 (48H, m), 3.20–4.70 (56H, m), 5.45 (16H, m), 7.08–7.92 (40H, m); FABMS *m/z* 2201 $(M+H)^+$, 2110. Anal. Calcd for $C_{128}H_{158}MgN_{16}O_{16}$: C, 69.85; H, 7.24; N, 10.18. Found: C, 69.57; H, 7.00; N, 10.08.

4.1.16. (2,3,7,8,12,13,17,18-Octakis(benzyl(8-tetrahydropyranyloxy-3,6-dioxa-octyl)amino)porphyrazinato)magnesium(II) (11b). Mg turnings (1.35 g, 35.6 mmol) were heated to 300 °C under vacuum, allowed to cool to room temperature under dry N_2. Dry *n*-PrOH (250 mL) and I_2 (1 crystal) were added and the suspension heated at reflux for 24 h. After cooling to room temperature, dinitrile **10b** (4.0 g, 5.6 mmol) in dry *n*-PrOH (10 mL) was added and the suspension heated at reflux for 60 h. After cooling to room temperature, the purple-black suspension was diluted with $CHCl_3$ (200 mL), filtered through Celite, and rotary evaporated. The dark residue was dissolved in $CHCl_3$ (50 mL), filtered through Celite to remove the remaining particulates, and rotary evaporated. Chromatography (SiO_2, EtOAc/hexanes 1:2 to EtOAc/MeOH 9:1) gave porphyrazine **11b** (320 mg, 8%) as a purple oil: TLC R_f 0.32 (EtOAc/MeOH 95:5); IR (film) ν_{max} 1561, 1555, 1452, 1351, 1285, 1200, 1122, 1076, 1034, 987, 703 cm^{-1}; UV–vis (CH_2Cl_2) λ_{max} (log ε) 333 (4.69), 365 (4.75), 574 (4.47), and 711 (4.57) nm; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.08–1.62 (48H, m), 2.77–2.85 (8H, m), 3.12–3.19 (8H, m), 3.21–3.50 (64H, m), 3.67–3.70 (16H, m), 3.89–3.91 (8H, m), 4.51–4.60 (16H, m), 5.38 (16H, br s,), 7.05–7.09 (24H, m), 7.40–7.43 (16H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.9, 24.9, 30.0, 51.2, 55.5, 61.4, 66.3, 70.0, 70.17, 70.23, 70.4, 98.2, 126.4, 128.0, 128.3, 137.1, 140.9, 151.5; FABMS *m/z* 2908 $(M+H)^+$, 2818. Anal. Calcd for $C_{160}H_{224}MgN_{16}O_{32}$: C, 66.09; H, 7.76; N, 7.71. Found: C, 65.79; H, 7.46; N, 7.56.

4.1.17. (2,3,7,8,12,13,17,18-Octakis(benzyl(3,6,9trioxadecyl)amino)-porphyrazinato)magnesium(II) (11c). Mg turnings (2.09 g, 86.2 mmol) were heated to 300 °C under vacuum, allowed to cool to room temperature under dry N_2. Dry *n*-PrOH (450 mL) and I_2 (1 crystal) were added and the suspension heated at reflux for 24 h. After cooling to room temperature, dinitrile **10c** (5.0 g, 8.6 mmol) in dry *n*-PrOH (10 mL) was added and the suspension heated at reflux for 60 h. After cooling to room temperature, the purple-black suspension was diluted with $CHCl_3$ (400 mL), filtered through Celite, and rotary evaporated. $CHCl_3$ (100 mL) was added, and the suspension was filtered to remove the remaining fine solids. Rotary evaporation and chromatography (SiO_2 EtOAc/hexanes 1:1 to EtOAc/MeOH 95:5) gave porphyrazine **11c** (400 mg, 8%) as a purple oil: TLC R_f 0.5 ($CHCl_3$: Me_2CO 7:3); IR (film) ν_{max} 1559, 1452, 1290, 1195, 1110, 1029, 850, 736, 701 cm^{-1}; UV–vis ($CHCl_3$) λ_{max} (log ε) 330 (4.63), 365 (4.66), 577 (4.36), and 708 (4.51) nm; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.92 (24H, s), 3.01–3.04 (16H, m), 3.13–3.17 (16H, m), 3.19–3.23 (16H, m), 3.31–3.35 (16H, m), 3.70–3.74 (16H, m), 4.51–4.54 (16H, m), 5.40 (16H, s), 7.08–7.11 (24H, m), 7.42–7.45 (16H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.1, 56.1, 58.4, 69.9, 70.2, 70.3, 70.4, 71.4, 126.4, 128.1, 128.5, 137.2, 140.9, 151.9; FABMS *m/z* 2347 $(M+H)^+$, and 2256. Anal. Calcd for $C_{128}H_{176}MgN_{16}O_{24}$: C, 65.50; H, 7.56; N, 9.55. Found: C, 65.28; H, 7.39; N, 9.32.

4.1.18. (2,3,7,8,12,13,17,18-Octakis(benzyl(2-hydroxyethyl)amino)porphyrazine) (12a). AcOH (4 drops) was added with stirring to porphyrazine **11a** (30 mg, 14 μmol) in $CHCl_3$ (2 mL) and MeOH (0.5 mL) at room temperature. After 1 h and 2.5 h respectively, concd HCl (1 drop) and 1 M NaOH (1.5 mL) were added and the layers separated. The aqueous layer was extracted with $CHCl_3$ (1×10 mL) and the combined organic extracts rotary evaporated. Chromatography (SiO_2, $CHCl_3$/MeOH 95:5 to 90:10) gave porphyrazine **12a** (17 mg, 80%) as a purple solid: TLC R_f 0.45 ($CHCl_3$/MeOH 90:10); IR ($CHCl_3$) ν_{max} 3336, 3297, 1568, 1548, 1494, 1453, 1378, 1310, 1174, 1135, 1060, 741, 699 cm^{-1}; UV–vis ($CHCl_3$) λ_{max} (log ε) 335 (4.63), 556 (4.32), 725 (4.32) nm; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.09 (2H, s), 3.65 (16H, br s), 3.73 (16H, br s), 5.33 (16H, s), 6.13 (8H, br s), 7.12–7.28 (40H, m); FABMS *m/z* 1508 $(M+H)^+$, 1417, 1326.

4.1.19. (2,3,7,8,12,13,17,18-Octakis(benzyl(8-hydroxy-3,6-dioxaoctyl)amino)-porphyrazine) (12b). AcOH (4 drops) was added with stirring to porphyrazine **11b** (30 mg, 10.3 μmol) in $CHCl_3$ (2 mL) and MeOH (0.5 mL). After 1 h, conc HCl (1 drop) was added and stirring continued for 1.5 h. 1 M NaOH (1.5 mL) was added, the layers were separated, the aqueous layer was extracted with $CHCl_3$ (1×10 mL) and the combined organic extracts rotary evaporated. Gel permeation chromatography (Sephadex LH20 $CHCl_3$) gave porphyrazine **12b** (18 mg, 80%) as a purple oil: TLC R_f 0.75 (MeOH/MeCN 1:1; Whatman $MKC_{18}F$ Reversed Phase TLC Plates); IR (film) ν_{max} 3412, 3303, 1551, 1492, 1449, 1130, 1074, 742, 701 cm^{-1}; UV–vis ($CHCl_3$) λ_{max} (log ε) 328 (4.62), 348sh, 556 (4.53), 661sh, 740sh nm; ^1H NMR ($CDCl_3$, 300 MHz) δ −0.94 (2H, s) 3.28–3.83 (80H, m), 4.42 (16H, br s), 5.33 (16H, s), 7.08–7.35 (40H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.8, 55.9, 61.5, 70.15, 70.23, 72.4, 126.7, 128.2, 128.5, 136.0, 140.0, 148.0; FABMS *m/z* 2212 $(M^{+\cdot})$, 2122, 1106

$(M)^{2+}$. Anal. Calcd for $C_{120}H_{162}N_{16}O_{24}\cdot CHCl_3$: C, 62.32; H, 7.04; N, 9.61. Found: C, 62.50; H, 6.90; N, 9.41.

4.1.20. 2,3,7,8,12,13,17,18-Octakis(benzyl(3,6,9-trioxadecyl)amino)porphyrazine (12c). AcOH (2.5 mL) was added to porphyrazine **11c** (M=Mg) (35 mg, 15 μmol) under N_2 in the dark. After 2 h, the purple solution was slowly added to ice and H_2O (100 mL) and neutralized with 1 M NaOH, extracted with $CHCl_3$ (3×20 mL), and dried ($MgSO_4$). Rotary evaporation and chromatography (SiO_2 $CHCl_3$: Me_2CO 4:1) gave porphyrazine **12c** (30 mg, 86%) as a viscous purple oil: TLC R_f 0.5 ($CHCl_3$: Me_2CO 7:3); IR ($CHCl_3$) ν_{max} 3301, 1571, 1550, 1495, 1452, 1292, 1248, 1105, 1029, 850, 715, 700 cm^{-1}; UV–vis ($CHCl_3$) λ_{max} (log ε) 327 (4.60), 356 (4.60), 556 (4.60), 667sh, and 741sh nm; ^1H NMR ($CDCl_3$, 270 MHz) δ −1.05 (2H, s), 3.22 (24H, s), 3.24–3.34 (64H, m), 3.59–3.64 (16H, m), 4.34–4.40 (16H, m), 5.29 (16H, s), 7.04–7.11 (24H, m), 7.29–7.36 (16H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.9, 55.2, 58.8, 70.1, 70.2, 71.7, 126.6, 128.1, 128.5, 136.0, 140.2, 148.0; FABMS *m/z* 2323 $(M+H)^+$. Anal. Calcd for $C_{128}H_{178}N_{16}O_{24}$: C, 66.13; H, 7.72; N, 9.64. Found: C, 65.88; H, 7.63; N, 9.66.

4.1.21. (2,3,7,8,12,13,17,18-Octakis(benzyl(3,6,9-trioxadecyl)amino)-porphyrazinato)nickel(II). Porphyrazine **12c** (M=2H) (15 mg, 6.5 μmol) and $Ni(OAc)_2$ (15 mg, 65 μmol) in DMF (1 mL) and PhCl (2 mL) were heated at 100 °C for 4 h. After allowing to cool to room temperature, the dark purple solution was filtered through Celite, rotary evaporated and chromatographed (SiO_2 $CHCl_3$: Me_2CO 4:1) to yield the nickel(II) porphyrazine (13 mg, 84%) as a viscous purple oil: TLC R_f 0.40 ($CHCl_3$: Me_2CO 8:2); IR (film) ν_{max} 1578, 1513, 1494, 1449, 1351, 1322, 1250, 1195, 1111, 1030, 851, 745, 701 cm^{-1}; UV–vis ($CHCl_3$) λ_{max} (log ε) 312 (4.68), 379sh, 532 (4.46), and 680 (4.38) nm; ^1H NMR ($CDCl_3$, 270 MHz) δ 3.21 (24H, s), 3.26–3.28 (64H, m), 3.63 (16H, s), 7.09–7.17 (24H, m), 7.35–7.38 (16H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.0, 56.0, 58.9, 70.2, 70.26, 70.30, 70.7, 126.6, 128.2, 128.5, 137.3, 140.3, 143.3; FABMS *m/z* 2381 $(M^{+\cdot})$, 2290. Anal. Calcd for $C_{128}H_{176}N_{16}O_{24}Ni$: C, 64.55; H, 7.45; N, 9.41. Found: C, 64.73; H, 7.26; N, 9.18.

4.1.22. *N*-Isopropylformimidoyl cyanide (19).[43] Calcium hypochlorite (21.5 g, 0.09 mol, 60%) and anhydrous $CaCl_2$ (1.6 g, 0.015 mol) were added to (isopropylamino)acetonitrile **17**[43,56] (8.7 g, 0.09 mol) in CH_2Cl_2 (200 mL). The mixture was stirred for 2 days at ambient temperature, filtered, and the filtrate was heated to reflux for 2 days in the presence of powdered calcium hydroxide (13.0 g, 0.18 mol) and anhydrous $CaCl_2$ (1.6 g, 0.015 mol) until the *N*-chloro-*N*-isopropylaminoacetonitrile **18** was not detected by GC/MS. The mixture was filtered, rotary evaporated and distilled to give cyanide **19** (4.2 g, 64%) as a colorless oil (*Z*/*E* 64:36): bp 60 °C /20 mm; IR (film) ν_{max} 1620, 1465, 1384, 1366, 1143 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (s, 1H, *E*), 7.28 (s, 1H, *Z*), 4.07 (heptet, *J*=6.3 Hz, 1H, *Z*), 3.60 (heptet, *J*=6.3 Hz, 1H, *E*), 1.25 (d, *J*=6.3 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.5 (*E*), 128.9 (*Z*), 115.0 (*Z*), 108.0 (CN, *E*), 63.4 (*C*HMe$_2$, *E*), 60.5 (*C*HMe$_2$, *Z*), 23.2; MS (EI) *m/z* 96 $(M^{+\cdot})$. Alternatively, to a preheated (55 °C) suspension of *N*-chlorosuccinimide (285 mg, 2.1 mmol) in CCl_4 (5 mL), *N*- isopropylaminoacetonitrile **17** (210 mg, 2.1 mmol) in CCl_4 (1 mL) was added dropwise. After 5 min the reaction mixture was allowed to cool to ambient temperature. The suspension was filtered, and the filtrate was heated to reflux for 6 h in the presence of powdered calcium hydroxide (316 mg, 4.3 mmol) and anhydrous $CaCl_2$ (40 mg, 0.4 mmol). Filtration, evaporation and distillation of the solvent gave cyanide **19** (184 mg, 90%) as a colorless oil.

4.1.23. *N*,*N*′-Diisopropyl-*N*,*N*′-di-((*tert*-butyloxycarbonyl)methyl)diamino-maleonitrile (21). $SnCl_4$ (12 mL, 26.6 g, 0.102 mol) in dry PhH (100 mL) was added over 1 h to *N*-isopropylformimidoyl cyanide **19** (8.2 g, 0.09 mol) in dry PhH (50 mL), at 0 °C.[43] The mixture was stirred overnight at 20 °C. H_2O (200 mL) and Et_2O (300 mL) were added and the organic layer separated. The organic phase was washed with aqueous $NaHCO_3$ (200 mL) and H_2O (200 mL), dried ($MgSO_4$) and rotary evaporated. Chromatography (Al_2O_3, hexanes/EtOAc 7:3) followed by sublimation (80 °C/20 mm) gave *N*,*N*′-diisopropyldiaminomaleonitrile **20** (5.2 g, 63%) as bright yellow crystals (2 isomers, *Z*/*E* 9:1): mp 74 °C; R_f 0.39 (hexanes/EtOAc 7:3); IR (film) ν_{max} 3361, 2205, 1603, 1465, 1366, 1178, 1126 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.20 (heptet, *J*=6.3 Hz, 2H, CH, *E*), 3.54 (heptet, *J*=6.3 Hz, 2H, CH, *Z*), 3.28 (bs, 2H), 1.36 (d, *J*=6.3 Hz, 12H, *E*), 1.18 (d, *J*=6.3 Hz, 12H, *Z*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 114.7, 113.0, 48.1, 23.5; MS (EI) *m/z* 192 $(M^{+\cdot})$. The dinitrile **20** was used directly without further purification. NaH (44 mg, 1.1 mmol, 60% dispersion in mineral oil, 10% excess) was added rapidly to dinitrile **20** (96 mg, 0.5 mmol) in DMF (10 mL) at −10 °C. After 2 h, *t*-butyl bromoacetate (0.29 mL, 2 mmol) in DMF (10 mL) was added to the dark green solution, which was stirred at −10 °C for 2 h, allowed to warm up to 20 °C, poured onto ice (50 mL) and extracted with Et_2O (3×50 mL). The combined extracts were dried ($MgSO_4$), rotary evaporated and chromatographed (SiO_2 hexanes/EtOAc 9:1) to give dinitrile **21** (177 mg, 84%) as yellow crystals: mp 78 °C (EtOAc); R_f 0.6 (hexanes/EtOAc 7:3); IR (film) ν_{max} 2203, 1740, 1561, 1461, 1370, 1226, 1154 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.82–3.79 (m, 6H, CH), 1.48 (s, 18H), 1.16 (d, *J*=6.6 Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 117.4, 115.2, 82.1, 52.2, 46.7, 28.0, 20.6; MS (CI, NH_3) *m/z* 438 $(M+NH_4)^+$, 421 $(M+H)^+$, 420 $(M^{+\cdot})$. Anal. Calcd for $C_{22}H_{36}N_4O_4$: C, 62.83; H, 8.63; N, 13.32. Found: C, 63.10; H, 8.51; N 13.43.

4.1.24. 1-((*N*-Cyanomethyl)aminomethyl)-4-methyl-2,6,7-trioxabicyclo[2,2,2]octane (23). $ClCH_2CN$ (2.6 mL, 3.1 g, 0.40 mol) in Et_2O (20 mL) was added dropwise to 1-(aminomethyl)-4-methyl-2,6,7-trioxabicyclo[2,2,2]-octane **22**[57] (6.4 g, 0.40 mol) and Et_3N (6.2 mL, 4.5 g, 0.45 mol) in Et_2O (300 mL) at −10 °C. After stirring overnight at 20 °C, rotary evaporation and chromatography (Al_2O_3 hexanes/EtOAc 7:3) gave nitrile **23** (4.4 g, 55%) as a white solid: mp 31 °C; R_f 0.35 (hexanes/EtOAc 1:1); IR (film) ν_{max} 3347, 2235, 1723, 1472, 1405, 1356, 1286, 1193, 1148, 1115, 1052, 989, 935, 882, 749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, 6H), 3.68 (s, 2H), 2.89 (s, 2H), 1.71 (s, 1H), 0.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 117.9, 107.4, 72.5, 52.4, 37.1, 30.5, 14.3; MS (CI, NH_3) *m/z*

199 $(M+H)^+$. Anal. Calcd for $C_9H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13. Found: C, 54.83; H, 7.02; N, 13.92.

4.1.25. 1-(*N*-Chloro-(*N*-cyanomethyl)aminomethyl)-4-methyl-2,6,7-trioxabicyclo[2,2,2]octane (24). Amine **23** (0.6 g, 3 mmol) in CCl_4 (10 mL) was heated to reflux with calcium hypochlorite (0.72 g, 5.1 mmol, 60%) and anhydrous $CaCl_2$ (55 mg, 0.5 mmol) for 30 min. The suspension was filtered and the solvent evaporated to give chloramine **24** (0.6 g, 86%) as a white solid: mp 79 °C; IR (CCl_4) ν_{max} 1703, 1398, 1354, 1281, 1205, 1101, 1059, 1024, 993, 976, 933, 889 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.13 (s, 2H), 3.91 (s, 6H), 3.34 (s, 2H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.7, 107.0, 72.5, 65.1, 51.2, 30.6, 14.4; MS (CI, NH_3) *m/z* 233 $(M^{+\cdot})$.

4.1.26. 2,3-Dipyridyl-7,8,12,13,17,18-hexakis(dimethylamino)porphyrazine (27). Mg (19.5 mg, 0.8 mmol), *n*-BuOH (10 mL) and I_2 (3 small crystals) were heated to reflux under N_2 for 24 h. After cooling, dinitrile **2a** (180 mg, 1.09 mmol) and dipyridylmaleonitrile **25**[47] (36 mg, 0.15 mmol) were added, the mixture was heated at 110 °C for 12 h under N_2, filtered (Celite) and the solids washed with CH_2Cl_2. Rotary evaporation and chromatography (SiO_2 hexanes/EtOAc 9:1; $CHCl_3$/MeOH 9:1) gave the crude Mg-porphyrazine **26** as a blue solid: R_f 0.2 ($CHCl_3$/MeOH 9:1); MS (FAB) *m/z* 749 $(M^{+\cdot})$; HRMS (FAB) Calcd for $C_{38}H_{45}N_{16}Mg$: $(M+H)^+$, 749.3863; found: $(M+H)^+$, 749.3866. A small amount of a mixture of the *cis*- and *trans* tetrapyridyl-tetrakis(dimethylamino)porphyrazines were isolated by chromatography (SiO_2 hexanes/EtOAc 9:1; $CHCl_3$/MeOH 9:1; $CHCl_3$/MeOH 6:1) of the crude product obtained from the previous reaction, as confirmed by mass spectroscopy: MS (FAB) *m/z* 817 $(M^{+\cdot})$; HRMS (FAB) Calcd for $C_{44}H_{41}N_{16}Mg$: $(M+H)^+$, 817.3551; found: $(M+H)^+$, 817.3510. Porphyrazine **26** was demetallated without any further purification. CF_3CO_2H (7 mL) was added to the partially purified porphyrazine **26** (87 mg, 0.116 mmol), the mixture stirred at 20 °C for 30 min under N_2 and poured onto ice and H_2O (50 mL) and the suspension neutralized with 1 M NaOH. The solid was collected by filtration, redissolved in CH_2Cl_2, dried ($MgSO_4$), rotary evaporated and chromatographed (SiO_2 EtOAc/MeOH 9:1) to give porphyrazine **27** (25 mg, 30%) as a dark purple solid: mp >350 °C; R_f 0.4 (EtOAc/MeOH 9:1); IR (CH_2Cl_2) 3299, 1596, 1500, 1388, 1321, 1199, 1081, 1058, 869, 748 cm^{-1}; UV–vis (CH_2Cl_2) λ_{max} (log ε) 339 (4.49), 539 (4.38) nm; ^1H NMR (300 MHz, $CDCl_3$) δ 3.48 (s, 12H), 3.72 (s, 12H), 3.9 (s, 12H), 7.89 (d, $J=5.8$ Hz), 8.72 (d, $J=5.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.6, 45.0, 45.7, 126.6, 127.1, 135.6, 138.9, 140.2, 143.9, 145.4, 149.7, 149.9, 151.0, 163.6; MS (FAB) *m/z* 727 $(M^{+\cdot})$; HRMS (FAB) calc for $C_{38}H_{47}N_{16}$: $(M+H)^+$, 727.4169; found: $(M+H)^+$, 727.4134. Anal. Calcd for $C_{38}H_{46}N_{16}$: C, 62.79; H, 6.38; N, 30.83. Found: C, 62.87; H, 6.38; N, 30.65.

4.1.27. (2,3-Dipyridyl-7,8,12,13,17,18-hexa(dimethylamino)porphyrazinato)-zinc(II) (28). Porphyrazine **27** (6.2 mg, 0.008 mmol) and anhydrous $Zn(OAc)_2$ (1.7 mg, 0.009 mmol) in dry DMF (10 mL) were heated at 100 °C for 16 h under N_2. The mixture was allowed to cool, filtered (Celite) and the solids washed with CH_2Cl_2. Rotary evaporation and chromatography (SiO_2 EtOAc/MeOH 9:1; EtOAc/MeOH 7:1) gave the zinc porphyrazine **28** (4 mg, 63%) as a dark blue solid: R_f 0.2 (EtOAc/MeOH 9:1); IR (CH_2Cl_2) 1650, 1608, 1380, 1313, 1097, 1018, 873 cm^{-1}; UV–vis (CH_2Cl_2) λ_{max} (log ε) 357 (4.77), 593 (4.46) nm; ^1H NMR (270 MHz, pyridine-d_5) δ 3.60 (s, 12H), 3.80 (s, 12H), 3.89 (s, 12H), 8.16 (d, $J=5.9$ Hz, 4H), 9.01 (d, $J=5.9$ Hz, 4H); ^{13}C NMR (67.5 MHz, pyridine-d_5) δ 43.4, 44.5, 45.5, 127.3, 129.0, 143.8, 146.8, 152.0, 160.0, 161.7; MS (FAB) *m/z* 789 $(M^{+\cdot})$; HRMS (FAB) calc for $C_{38}H_{45}N_{16}Zn$: $(M+H)^+$, 789.3304; found: $(M+H)^+$, 789.3275.

4.1.28. 2-Methoxy-4-pyridylacetonitrile (30). Finely powdered NaCN (0.46 g, 9.4 mmol) was added to 4-(chloromethyl)-2-methoxypyridine **29** (0.98 g, 6.2 mmol) in dry DMSO (50 mL), the mixture stirred for 8 h, diluted with H_2O (300 mL) and extracted with Et_2O (8×100 mL). The combined extracts were dried ($MgSO_4$), rotary evaporated and chromatographed (deactivated SiO_2 hexanes/EtOAc 7:3) to give nitrile **30** (0.74 g, 76%), as a white solid: mp 106 °C ($CHCl_3$); R_f 0.23 (deactivated silica, hexanes/EtOAc 7:3); IR (DRIFTS) ν_{max} 2248, 1939, 1614, 1563, 1486, 1455, 1401, 1324, 1221, 1184, 1152, 1040, 928, 813, 768 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, $J=5.3$ Hz, 1H), 6.85 (dd, $J=5.3$, 1.3 Hz, 1H), 6.74 (d, $J=1.3$ Hz, 1H), 3.95 (s, 3H), 3.71 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 147.8, 141.5, 116.3, 116.0, 110.1, 53.7, 23.1; MS (CI, NH_3) *m/z* 149 $(M+H)^+$. Anal. Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.90; H, 5.57; N, 19.02.

4.1.29. 2,3-Di-(4-(2-methoxy)pyridyl)fumaronitrile (31). I_2 (1.8 g, 7.15 mmol) was added to nitrile **30** (0.58 g, 3.9 mmol) in MeOH (10 mL), the mixture heated to reflux under N_2 for 1 h, cooled to room temperature and NaOMe, from Na (0.2 g, 8.6 mmol) in MeOH (5 mL) was added dropwise. The mixture was heated to reflux for 3 h, during which time a brown precipitate formed, allowed to cool, the solid filtered off and redissolved in $CHCl_3$. The solution was filtered, rotary evaporated and the residue recrystallized from $CHCl_3$ to give dinitrile **31** (0.22 g, 38%) as a light brown solid: mp 167 °C ($CHCl_3$); R_f 0.63 (deactivated silica, hexanes/EtOAc 1:1); IR (film) ν_{max} 2222, 1602, 1550, 1483, 1451, 1397, 1325, 1198, 1111, 1041, 867, 822, 787 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, $J=5.5$ Hz, 2H), 7.27 (dd, $J=5.5$, 1.5 Hz, 2H), 7.15 (d, $J=1.5$ Hz, 2H), 4.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 148.7, 140.9, 125.8, 114.9, 114.8, 110.5, 54.1; MS (CI, NH_3) *m/z* 293 $(M+H)^+$. Anal. Calcd for $C_{16}H_{12}N_4O_2$: C, 65.75; H, 4.14; N, 19.17. Found: C, 66.08; H, 4.36; N, 19.39.

4.1.30. 2,2′-Bipyridyl-4-acetonitrile (33). Finely powdered KCN (0.26 g, 4 mmol) was added to 4-chloromethyl-2,2′-bipyridine **32**[51] (0.1 g, 0.5 mmol) and 18-crown-6 (26 mg, 0.01 mmol) in CH_3CN (10 mL), the mixture stirred for 4 h, diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (4× 75 mL). The combined extracts were dried ($MgSO_4$), rotary evaporated, and rapidly chromatographed (deactivated SiO_2 hexanes/EtOAc 7:3) to give nitrile **33** (90 mg, 92%) as a white solid: mp 105 °C (EtOAc); R_f 0.9 (deactivated silica, hexanes/EtOAc 7:3); IR (DRIFTS) ν_{max} 2246, 1604, 1586, 1561, 1462, 1401, 1253, 1067, 992, 932, 853, 788, 751 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.74–8.71 (m, 2H), 8.50–8.47

(m, 2H), 7.92 (td, J=7.8, 1.8 Hz, 1H), 7.44–7.40 (m, 2H), 3.90 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 155.1, 150.0, 149.2, 140.0, 137.1, 124.2, 122.7, 121.3, 120.3, 116.5, 23.4; MS (CI, NH_3) m/z 212 $(M+NH_4)^+$, 196 $(M+H)^+$. Anal. Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 74.17; H, 4.79; N, 21.45.

4.1.31. 2,3-Di-(4-(2,2′-bipyridyl))fumaronitrile (34). Following the same procedure as for the preparation of dinitrile **31**, nitrile **33** gave dinitrile **34** (0.41 g, 70%) as a white solid: mp 241°C ($CHCl_3$); IR (DRIFTS) ν_{max} 2222, 1583, 1547, 1461, 1391, 1253, 1211, 1111, 1072, 993, 920, 846, 791 cm^{-1}; UV/vis λ_{max} (log ε) 286 (4.68); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (d, J=5.0 Hz, 2H), 8.93 (s, 2H), 8.75 (d, J=5.1 Hz, 2H), 8.49 (d, J=7.8 Hz, 2H), 7.90 (td, J=7.8, 1.6 Hz, 2H), 7.74 (dd, J=5.1, 2.0 Hz, 2H), 7.41 (ddd, J=7.8, 5.0, 1.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 154.5, 150.5, 149.5, 139.7, 137.2, 126.5, 124.6, 121.6, 121.4, 119.9, 115.0; MS (CI, NH_3) m/z 387 $(M+H)^+$. Anal. Calcd for $C_{24}H_{14}N_6$: C, 74.60; H, 3.65; N, 21.75. Found: C, 74.61; H, 3.73; N, 21.85.

4.1.32. 2,3,7,8,12,13,17,18-Octakis((2-(2-pyridyl)-4-pyridyl)porphyrazine (37). Na (17 mg, 0.75 mmol) was added to dinitrile **34** (0.29 g, 0.75 mmol) in ethylene glycol (100 mL) and NH_3 bubbled through the suspension for 3 h, during which turned dark green. The solution was filtered hot and the filtrate was poured onto ice (200 mL) and extracted with $CHCl_3$ (4×100 mL). The combined extracts were dried ($MgSO_4$) and rotary evaporated to give crude 3,4-di-(4-(2,2′-bipyridyl))pyrroline-2,5-diimine **35** as a dark green oily residue that was used in the subsequent step without further purification. n-BuOH (100 mL), Mg (0.4 g) and I_2 (2 small crystals) were heated to reflux for 12 h under N_2. The suspension was cooled and the crude diimine **35** in n-BuOH (5 mL) added and the mixture further heated at reflux for 12 h. The dark green suspension was allowed to cool, filtered (Celite) and the solids washed with CH_2Cl_2. After rotary evaporation, the dark green residue was dissolved in TFA (10 mL). After 30 min at 20 °C under N_2, the mixture was poured onto ice and H_2O (50 mL), neutralized with 4 M NaOH, and filtered. The precipitate was filtered off and washed thoroughly with H_2O, dissolved in a minimum of CH_2Cl_2, dried (Na_2SO_4) and the solvent rotary evaporated. Double gel filtration (Sephadex LH20 $CHCl_3$; Biobeads SX3 $CHCl_3$), gave porphyrazine **37** (23 mg, 2% from **34**) as a dark green solid: mp 328 °C ($CHCl_3$); IR (film) ν_{max} 2191, 1583, 1249, 1093, 989, 793 cm^{-1}; UV–vis λ_{max} 240, 283, 362, 593, 660, CH_2Cl_2; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74–8.50 (m, 16H), 8.36–8.13 (m, 16H), 7.83–7.73 (m, 8H), 7.32–7.28 (m, 16H), –1.70 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 155.5, 150.4, 150.0, 149.1, 149.0, 148.8, 137.2, 136.9, 136.8, 125.1, 124.4, 124.3, 124.2, 123.9, 123.8, 122.6, 121.5, 121.4, 121.3, 121.1, 121.0, 120.4, 119.6, 119.2; MS (FAB) m/z 1549 $(M+H)^+$; HRMS (FAB) m/z Calcd for $C_{96}H_{59}N_{24}$ $(M+H)^+$, 1547.5355; found: $(M+H)^+$, 1547.5396.

4.1.33. 2,3-Bis(diallylamino)norphthalocyanine (40a). Dry n-BuOH (250 mL), Mg turnings (880 mg, 36 mmol) and I_2 (1 crystal) were heated at reflux for 24 h. After cooling to room temperature, phthalonitrile **38a** (12.0 g, 93.3 mmol) and dinitrile **2c** (1.0 g, 3.7 mmol) were added and heated at reflux was resumed for 24 h. After cooling, the deep purple mixture was diluted with $CHCl_3$, filtered through celite and the filtrate evaporated under reduced pressure. Chromatography (SiO_2, $CHCl_3$/MeOH 99:1 to 95:5) gave the crude norphthalocyanine **39a** as a greenish solid. CF_3CO_2H (20 mL) was added and the mixture allowed to stand in the dark for 1 h, added to ice and H_2O (200 mL) and the pH adjusted to 7.5 using aqueous 1.0 M NaOH. The dark precipitate was filtered off and washed repeatedly with H_2O. Chromatography (SiO_2, PhMe/hexanes 6:4 to 7:3) gave norphthalocyanine **40a** (175 mg, 7%) as a blue solid: mp 188–192 °C; TLC R_f 0.45 ($CHCl_3$); IR ($CHCl_3$) ν_{max} 3294, 1561, 1552, 1514, 1498, 1408, 1334, 1306, 1116, 1023, 996, 923, 706 cm^{-1}; UV–vis ($CHCl_3$) λ_{max} (log ε) 293 (4.46), 338 (4.87), 528sh, 577 (4.42), 649 (4.59), 688 (4.60), 723 (4.60) nm; ^{1}H NMR ($CDCl_3$, 500 MHz) δ −3.40 (2H, s), 4.97 (8H, d, J=6.3 Hz), 5.34 (4H, d, J=10.1 Hz), 5.51 (4H, dd, J=1.6, 17.1 Hz), 6.38–6.44 (8H, m), 7.35 (2H, d, J=5.3 Hz), 7.62 (2H, t, J=6.9 Hz), 7.66 (2H, t, J=6.9 Hz), 7.91 (2H, d, J=6.9 Hz), 8.17 (2H, d, J=6.9 Hz), 8.45 (2H, d, J=6.9 Hz); ^{13}C ($CDCl_3$, 125 MHz) δ 55.6, 117.4, 122.0, 122.2, 122.6, 128.9, 129.0, 129.7, 133.0, 134.1, 136.2, 139.1, 139.9, 140.9, 141.5, 156.0, 158.4; FABMS m/z 1309 $(2\,M+H)^+$, 654 $(M^{+\cdot})$, 572; HRFABMS m/z Calcd for $C_{40}H_{35}N_{10}$: $(M+H)^+$, 655.3046; found: $(M+H)^+$, 655.3073. Anal. Calcd for $C_{40}H_{34}N_{10}$: C, 73.37; H, 5.23; N, 21.39. Found: C, 73.26; H, 5.39; N, 21.13.

4.1.34. 2,3-Bis(dibenzylamino)norphthalocyanine (40b). Following the same procedure as for the preparation of norphthalocyanine **40a**, dinitriles **2b** and **38a** gave norphthalocyanine **40b** (20 mg, 20%) as a blue solid: mp 243–245 °C; TLC R_f 0.55 ($CHCl_3$); IR ($CHCl_3$) ν_{max} 3294, 1549, 1513, 1495, 1453, 1334, 1320, 1116, 992, 875 cm^{-1}; UV–vis ($CHCl_3$) λ_{max} (log ε) 292 (4.45), 341 (4.83), 527sh, 583 (4.46), 644 (4.57), 691 (4.56), 727 (4.61) nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ −1.87 (2H, s), 5.78 (8H, s), 7.21–7.31 (12H, m), 7.49–7.53 (8H, m), 7.72 (2H, t, J=7.0 Hz), 7.80 (2H, t, J=7.0 Hz), 8.36–8.39 (2H, m), 8.57 (2H, d, J=7.0 Hz), 8.70 (2H, d, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.1, 121.7, 121.9, 127.0, 128.5, 128.7, 128.8, 129.2, 132.2, 133.8, 138.7, 139.4, 139.6, 140.3, 141.2, 155.6, and 158.2; FABMS m/z 855 $(M+H)^+$, 763, 672, 581; HRFABMS m/z Calcd for $C_{56}H_{43}N_{10}$: $(M+H)^+$, 855.3672; found: $(M+H)^+$, 855.3689. Anal. Calcd for $C_{56}H_{42}N_{10}$: C, 78.67; H, 4.95; N, 16.38. Found: C, 78.43; H, 5.24; N, 16.02.

4.1.35. 2,3-Bis(diallylamino)-9,10,18,19,27,28-hexabutylnorphthalocyanine (40c). Following the same procedure as for the preparation of norphthalocyanine **40a**, dinitriles **2c** and **38b** gave norphthalocyanine **40c** (17 mg, 4%) as a dark blue solid: mp 183–185 °C; TLC R_f 0.46 ($CHCl_3$/hexanes 1:1); IR ($CHCl_3$) ν_{max} 3296, 1552, 1515, 1456, 1320, 1107, 996, 923, 720 cm^{-1}; UV–vis ($CHCl_3$) λ_{max} (log ε) 299 (4.56), 345 (4.89), 524 (4.25), 577sh, 656 (4.62), 691 (4.61), 733 (4.69) nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ −0.89 (2H, br s), 1.15–1.19 (18H, m), 1.70–1.74 (12H, m), 1.95–2.02 (12H, m), 3.07–3.22 (12H, m), 5.00 (8H, d, J=5.8 Hz), 5.25 (4H, d, J=10.1 Hz), 5.46 (4H, d, J=16.9 Hz), 6.37–6.46 (2H, m), 8.71 (2H, s), 8.89 (2H, s), 9.20 (2H, s); ^{13}C NMR

($CDCl_3$, 100 MHz) δ 14.2, 23.1, 23.3, 33.3, 33.5, 33.6, 33.7, 33.9, 34.0, 55.6, 117.1, 122.1, 122.6, 123.1, 132.1, 133.7, 136.5, 137.3, 138.1, 140.4, 142.3, 142.4, 142.9, 144.2, 155.7, 158.9; FABMS *m/z* 991 $(M+H)$,$^+$950, 908, 868; HRFABMS Calcd for $C_{64}H_{83}N_{10}$: $(M+H)^+$, 991.6802; found: $(M+H)^+$, 991.6872. Anal. Calcd for $C_{64}H_{82}N_{10}$: C, 77.54; H, 8.34; N, 14.13. Found: C, 77.31; H, 8.24; N, 13.89.

4.1.36. 2,3-Bis(dibenzylamino)-9,10,18,19,27,28-hexabutylnorphthalocyanine (40d). Following the same procedure as for the preparation of norphthalocyanine **40a**, dinitriles **2b** and **38b** gave norphthalocyanine **40d** (100 mg, 10%) as a dark blue solid: mp 247–249 °C; TLC R_f 0.42 ($CHCl_3$/hexanes 1:1); IR ($CHCl_3$) ν_{max} 3292, 1566, 1514, 1495, 1451, 1320, 1108, 1027, 989, 746, 698 cm^{-1}; UV–vis ($CHCl_3$) λ_{max} (log ε) 298 (4.58), 347 (4.90), 517 (4.24), 590sh, 655 (4.64), 691 (4.62), 734 (4.74) nm; ^1H NMR ($CDCl_3$, 300 MHz) δ −0.40 (2H, br s), 1.12–1.20 (18H, m), 1.60–1.78 (12H, m), 1.88–2.05 (12H, m), 3.07–3.26 (12H, m), 5.68 (8H, s), 7.19–7.23 (12H, m), 7.38–7.41 (8H, m), 8.66 (2H, s), 9.07 (2H, s), 9.36 (2H, s); ^{13}C ($CDCl_3$, 125 MHz) δ 14.18, 14.21, 23.1, 23.2, 33.4, 33.6, 33.66, 33.74, 33.8, 34.0, 56.6, 122.4, 122.8, 123.3, 126.8, 128.3, 128.7, 132.3, 133.6, 137.3, 138.1, 139.5, 140.5, 142.56, 142.61, 143.6, and 144.3; FABMS *m/z* 1192 $(M+H)^+$, 1101, 1009; HRFABMS *m/z* Calcd for $C_{80}H_{91}N_{10}$: $(M+H)^+$, 1191.7428; found: $(M+H)^+$, 1191.7353. Anal. Calcd for $C_{80}H_{90}N_{10}$: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.34; H, 7.38; N, 12.05.

4.1.37. 2,3-Bis(allyl(benzyl)amino)-9,10,18,19,27,28-hexabutylnorphthalocyanine (40e). Following the same procedure as for the preparation of norphthalocyanine **40a**, dinitriles **2e** and **38b** gave norphthalocyanine **40e** (25 mg, 6%) as a dark blue solid: mp 168–170 °C; TLC R_f 0.72 ($CHCl_3$/hexanes 1:1); IR ($CHCl_3$) ν_{max} 3297, 1549, 1514, 1496, 1452, 1321, 1106, 1033, 983, 767, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ −0.74 (2H, br s), 1.17 (18H, t, J=7.1 Hz), 1.66–1.75 (12H, m), 1.88–2.00 (12H, m), 3.05–3.16 (12H, m), 5.00 (4H, d, J=5.8 Hz), 5.22 (2H, d, J=10.3 Hz), 5.39 (2H, d, J=16.7 Hz), 5.74 (4H, s), 6.26–6.32 (2H, m), 7.20–7.28 (6H, m), 7.51 (4H, d, J=6.5 Hz), 8.62 (2H, s), 8.97 (2H, s), 9.22 (2H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2, 23.1, 23.2, 33.4, 33.6, 33.7, 33.9, 34.0, 56.0, 56.7, 117.3, 122.4, 122.8, 123.2, 126.8, 128.2, 128.8, 132.2, 133.9, 136.1, 137.4, 138.2, 139.7, 140.7, 142.5, 142.6, 143.4, 144.3, 155.8, 159.1; FABMS *m/z* 1091 $(M+H)$,$^+$1049, 999, 958; HRFABMS *m/z* Calcd for $C_{72}H_{87}N_{10}$: $(M+H)^+$, 1091.7115; found: $(M+H)^+$, 1091.7058. Anal. Calcd for $C_{72}H_{86}N_{10}$: C, 79.23; H, 7.94; N, 12.83. Found: C, 79.48; H, 7.75; N, 12.61.

4.1.38. 2,3-Bis(benzyl(2-hydroxyethyl)amino)-9,10,18,19,27,28-hexabutyl-norphthalocyanine (40f). Following the same procedure as for the preparation of norphthalocyanine **40a**, dinitriles **10a** and **38b** gave norphthalocyanine **40f** (33 mg, 7%) as a dark blue solid: mp 189–193 °C; TLC R_f 0.19 (EtOAc/hexanes 1:3); IR ($CHCl_3$) ν_{max} 3400, 3300, 1551, 1514, 1495, 1453, 1322, 1109, 1012, 970, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ −0.33 (2H, br s), 1.10–1.21 (18H, m), 1.63–1.76 (12H, m), 1.93–2.04 (12H, m), 2.68–2.72 (2H, m), 3.08–3.27 (12H, m), 3.99 (4H, br s), 4.39 (4H, br s), 5.64 (4H, s), 7.17–7.24 (6H, m), 7.51–7.59 (4H, m), 8.79 (2H, s), 9.05 (2H, s), 9.32 (2H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2, 23.1, 23.2, 33.5, 33.6, 33.7, 33.8, 33.9, 34.0, 56.0, 58.8, 61.3, 122.5, 123.0, 123.5, 127.1, 128.4, 128.6, 132.5, 135.1, 137.2, 137.6, 139.5, 140.8, 143.0, 143.2, 155.5, 159.4; FABMS *m/z* 1099 $(M+H)$,$^+$1008, 916; HRFABMS *m/z* Calcd for $C_{70}H_{87}N_{10}O_2$: $(M+H)^+$, 1099.7013; found: $(M+H)^+$, 1099.6948. Anal. Calcd for $C_{70}H_{86}N_{10}O_2$: C, 76.47; H, 7.88; N, 12.74. Found: C, 76.44; H, 7.72; N, 12.70.

Acknowledgements

We thank GlaxoSmithKline for the generous endowment (to A.G.M.B.), the Royal Society and the Wolfson Foundation for a Royal Society Wolfson Research Merit Award (to A.G.M.B.), the Wolfson Foundation for establishing the Wolfson Centre for Organic Chemistry in Medical Sciences at Imperial College London, the Engineering and Physical Sciences Research Council, the National Science Foundation and Schering AG for generous support of our studies.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.03.090

References and notes

1. Stuzhin, P. A.; Ercolani, C. In Kadish, K. M., Smith, K. M., Guilard, R., Eds.; The Porphyrin Handbook; Academic: New York, 2003; Vol. 15, p 263.
2. Dolphin, D. In *The Porphyrins*, *Vols. 1–7*; Academic: New York, 1978–1979.
3. Leznoff, C. C.; Lever, A. B. P. In *Phthalocyanines: Properties and Applications*, *Vols. 1–4*; VCH: Weinheim, 1989–1996.
4. Michel, S. L.; Baum, S.; Barrett, A. G. M.; Hoffman, B. M. In Karlin, K. D., Ed.; Progress in Inorganic Chemistry; Wiley: New York, 2001; Vol. 50, p 473.
5. Mani, N. S.; Beall, L. S.; Miller, T.; Anderson, O. P.; Hope, H.; Parkin, S. R.; Williams, D. J.; Barrett, A. G. M.; Hoffman, B. M. *Chem. Commun.* **1994**, 2095.
6. Forsyth, T. P.; Williams, D. B. G.; Montalban, A. G.; Stern, C. L.; Barrett, A. G. M.; Hoffman, B. M. *J. Org. Chem.* **1998**, *63*, 331.
7. Montalban, A. G.; Lange, S. J.; Beall, L. S.; Mani, N. S.; Williams, D. J.; White, A. J. P.; Barrett, A. G. M.; Hoffman, B. M. *J. Org. Chem.* **1997**, *62*, 9284.
8. Lange, S. J.; Nie, H.; Stern, C. L.; Barrett, A. G. M.; Hoffman, B. M. *Inorg. Chem.* **1998**, *37*, 6435.
9. Nie, H.; Barrett, A. G. M.; Hoffman, B. M. *J. Org. Chem.* **1999**, *64*, 6791.
10. Montalban, A. G.; Jarell, W.; Riguet, E.; McCubbin, Q. J.; Anderson, M. E.; White, A. J. P.; Williams, D. J.; Barrett, A. G. M.; Hoffman, B. M. *J. Org. Chem.* **2000**, *65*, 2472.

11. Goldberg, D. P.; Montalban, A. G.; White, A. J. P.; Williams, D. J.; Barrett, A. G. M.; Hoffman, B. M. *Inorg. Chem.* **1998**, *37*, 2873.
12. Sakellariou, E. G.; Montalban, A. G.; Meunier, H. G.; Rumbles, G.; Philips, D.; Ostler, R. B.; Suhling, K.; Barrett, A. G. M.; Hoffman, B. M. *Inorg. Chem.* **2002**, *41*, 2182.
13. Goldberg, D. P.; Michel, S. L.; White, A. J. P.; Williams, D. J.; Barrett, A. G. M.; Hoffman, B. M. *Inorg. Chem.* **1998**, *37*, 2100.
14. Sakellariou, E. G.; Montalban, A. G.; Meunier, H. G.; Ostler, R. B.; Rumbles, G.; Barrett, A. G. M.; Hoffman, B. M. *J. Photochem. Photobiol. A: Chem.* **2000**, *136*, 185.
15. Hochmuth, D. H.; Michel, S. L.; White, A. J. P.; Williams, D. J.; Barrett, A. G. M.; Hoffman, B. M. *Eur. J. Inorg. Chem.* **2000**, 593.
16. Eichorn, D. M.; Yang, S.; Jarell, W.; Baumann, T. F.; Beall, L. S.; White, A. J. P.; Williams, D. J.; Barrett, A. G. M.; Hoffman, B. M. *Chem. Commun.* **1995**, 1703.
17. Beall, L. S.; Mani, N. S.; White, A. J. P.; Williams, D. J.; Barrett, A. G. M.; Hoffman, B. M. *J. Org. Chem.* **1998**, *63*, 5806.
18. Montalban, A. G.; Baum, S.; Hoffman, B. M.; Barrett, A. G. M. *J. Chem. Soc., Dalton Trans.* **2003**, 2093.
19. Montalban, A. G.; Meunier, H. G.; Ostler, R. B.; Barrett, A. G. M.; Hoffman, B. M.; Rumbles, G. *J. Phys. Chem.* **1999**, *103*, 4352.
20. (a) Trabanco, A. A.; Montalban, A. G.; Rumbles, G.; Barrett, A. G. M.; Hoffman, B. M. *Synlett* **2000**, 1010. (b) Ahmed, M.; Atkinson, C. E.; Barrett, A. G. M.; Malagu, K.; Procopiou, P. A. *Org. Lett.* **2003**, *5*, 669.
21. Sakellariou, E. G.; Montalban, A. G.; Beall, L. S.; Henderson, D.; Meunier, H. G.; Philips, D.; Suhling, K.; Barrett, A. G. M.; Hoffman, B. M. *Tetrahedron* **2003**, *59*, 9083.
22. Baum, S.; Trabanco, A. A.; Montalban, A. G.; Micallef, A. S.; Zhong, C.; Meunier, H. G.; Suhling, K.; Philips, D.; White, A. J. P.; Williams, D. J.; Barrett, A. G. M.; Hoffman, B. M. *J. Org. Chem.* **2003**, *68*, 1665.
23. Stuzhin, P. A.; Bauer, E. M.; Ercolani, C. *Inorg. Chem.* **1998**, 1533.
24. Bauer, E. M.; Cardarilli, D.; Ercolani, C.; Stuzhin, P. A.; Russo, U. *Inorg. Chem.* **1999**, *38*, 6114.
25. Bauer, E. M.; Ercolani, C.; Galli, P.; Popkova, I. A.; Stuzhin, P. A. *J. Porphyrins Phthalocyanines* **1999**, *3*, 371.
26. Angeloni, S.; Bauer, E. M.; Ercolani, C.; Popkova, I. A.; Stuzhin, P. A. *J. Porphyrins Phthalocyanines* **2001**, *5*, 881.
27. Donzello, M. P.; Dini, D.; D'Arcangelo, G.; Ercolani, C.; Zhan, R.; Ou, Z.; Stuzhin, P. A.; Kadish, K. M. *J. Am. Chem. Soc.* **2003**, *125*, 14190.
28. Zhao, M.; Stern, C.; Barrett, A. G. M.; Hoffman, B. M. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 462.
29. Zhao, M.; Zhong, C.; Stern, C.; Barrett, A. G. M.; Hoffman, B. M. *Inorg. Chem.* **2004**, *43*, 3377.
30. Fuchter, M. J.; Vesper, B. J.; Murphy, K. A.; Collins, H. A.; Philips, D.; Hoffman, B. M.; Barrett, A. G. M. *J. Org. Chem.* **2005**, *70*, 2793
31. Begland, R. W.; Hartter, D. R.; Jones, F. N.; Sam, D. J.; Sheppard, W. A.; Webster, O. W.; Weigert, F. J. *J. Org. Chem.* **1974**, *39*, 2341.
32. Linstead, R. P.; Whalley, M. *J. Chem. Soc.* **1952**, 4839.
33. Gouterman, M. In Dolphin, D., Ed.; The Porphyrins; Academic: New York, 1978; Vol. 3, p 1.
34. Ehrlich, L. A.; Skrdla, P. J.; Jarell, W. K.; Sibert, J. W.; Armstrong, N. R.; Saavendra, S. S.; Barrett, A. G. M.; Hoffman, B. M. *Inorg. Chem.* **2000**, *39*, 3963.
35. Lee, S.; Stackow, R.; Foote, C. S.; Barrett, A. G. M.; Hoffman, B. M. *Photochem. Photobiol.* **2003**, *77*, 18.
36. Hammer, N. D.; Lee, S.; Vesper, B. J.; Elseth, K.; Hoffman, B. M.; Barrett, A. G. M.; Radosevich, J. Charge Dependence of Cellular Uptake and Selective Anti-Tumor Activity of Porphyrazines **2005**, submitted for publication.
37. Anantanarayan, A.; Dutton, P. J.; Fyles, T. M.; Pitre, M. J. *J. Org. Chem.* **1986**, *51*, 752.
38. Loiseau, F. A.; Hii King, K.; Hill, A. M. *J. Org. Chem.* **2004**, *69*, 639.
39. Marquis, D.; Desvergne, J.-P.; Bouas-Laurent, H. *J. Org. Chem.* **1995**, *60*, 7984.
40. Khana, N.; Arad-Yellin, R.; Warshawsky, A. *J. Org. Chem.* **1994**, *59*, 4832.
41. Moi, M. K.; Meares, C. F.; DeNardo, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 6266.
42. Ferris, J. P.; Donner, D. B.; Lotz, W. *J. Am. Chem. Soc.* **1972**, *94*, 6968.
43. Boyer, J. H.; Kooi, J. *J. Am. Chem. Soc.* **1976**, *98*, 1099.
44. Boyer, J. H.; Dabek, H. *Chem Commun.* **1970**, 1204.
45. Groves, J. T.; Farell, T. P. *J. Am. Chem. Soc.* **1989**, *111*, 4998.
46. Villanueva, A.; Caggiari, L.; Jori, G.; Milanesi, C. *J. Photochem. Photobiol. B: Biol.* **1994**, *23*, 49.
47. Anderson, M. E.; Barrett, A. G. M.; Hoffman, B. M. *Inorg. Chem.* **1999**, *38*, 6143.
48. Anderson, M. E.; Letsinger, R. L.; Barrett, A. G. M.; Hoffman, B. M. *J. Inorg. Biochem.* **2000**, *80*, 257.
49. Wiberg, K. B.; Shryne, T. M.; Kintner, R. R. *J. Am. Chem. Soc.* **1957**, *79*, 3160.
50. Katritzky, A. R.; Long, Q.-H.; Malhotra, N.; Ramanarayanan, T. A.; Vedage, H. *Synthesis* **1992**, 911.
51. Savage, S. A.; Smith, A. P.; Fraser, C. L. *J. Org. Chem.* **1998**, *63*, 10048.
52. Baumann, T. F.; Barrett, A. G. M.; Hoffman, B. M. *Inorg. Chem.* **1997**, *36*, 5661.
53. Baumann, T. F.; Sibert, J. W.; Olmstead, M. M.; Barrett, A. G. M.; Hoffman, B. M. *J. Am. Chem. Soc.* **1994**, *116*, 2639.
54. Baumann, T. F.; Nasir, M. S.; Sibert, J. W.; White, A. J. P.; Olmstead, M. M.; Williams, D. J.; Barrett, A. G. M.; Hoffman, B. M. *J. Am. Chem. Soc.* **1996**, *118*, 10479.
55. Cuellar, E. A.; Marks, T. M. *Inorg. Chem.* **1981**, *20*, 3766.
56. Cook, A. H.; Cox, S. F. *J. Chem. Soc.* **1949**, 2337.
57. Moore, W. J.; Luzzio, F. A. *Tetrahedron Lett.* **1995**, *36*, 6599.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 6131–6137

Thermal rearrangement of spiro[naphthalene(naphthopyranofurazan)]oxides to spiro[naphthalene(phenalenofurazan)oxides. A probable furazan oxide triggered tandem isomerisation process

Paraskevi Supsana,[a] Theodoros Liaskopoulos,[a] Stavroula Skoulika,[a] Antonios Kolocouris,[b] Petros G. Tsoungas[c] and George Varvounis[a,*]

[a]*Department of Chemistry, University of Ioannina, GR-451 10 Ioannina, Greece*
[b]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Athens, Panepistimioupoli-Zografou, GR-157 71 Athens, Greece*
[c]*Department of Research and Technology, Ministry of Development, Messogeion Ave. 14-18, GR-115 10 Athens, Greece*

Received 22 October 2004; revised 7 March 2005; accepted 18 March 2005

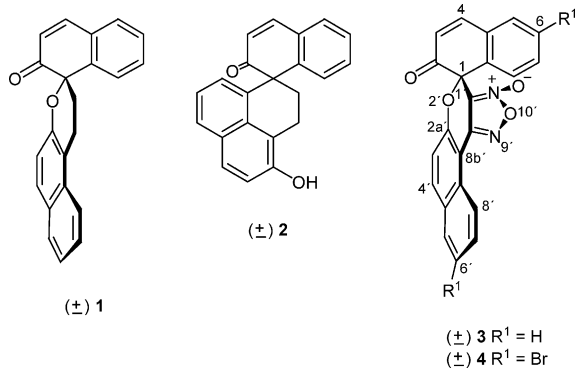
Available online 17 May 2005

Abstract—Thermal rearrangement of (±)-spiro{naphthalene-1(2*H*),4′-(naphtho-[2′,1′:2,3]pyrano[4,5-*c*]furazan)}-2-one-11′-oxides in DMF or acetic anhydride at 140 °C gave an isomeric mixture of (±)-spiro{naphthalene-1(2*H*),1′-(5′-hydroxyphenalene[1,2-*c*]furazan)}-2-one-2′-oxides and 4′-oxides. The rearranged structure was confirmed from X-ray analysis and was consistent with the through space NOE data. The rearrangement is suggested to be an overall tandem isomerization process. Using variable temperature ^{1}H NMR spectroscopy the lower limit for the isomerisation barrier for a pair of tautomers was calculated to be 22 kcal mol^{-1} at 423 K. The isomerisation equilibrium for a pair of isomers was studied by variable temperature ^{1}H NMR. The lower limit for the isomerisation barrier was calculated to be 22 kcal mol^{-1} at 423 K. This low value may be indicative of the difficulty encountered in separating the isomers by chromatography. Semi-empirical AM1 and molecular mechanics calculations suggest that the (±)-spiro{naphthalene-1(2*H*),1′-(5′-hydroxyphenalene[1,2-*c*]-furazan)}-2-one-2′-oxides are more stable than their 4′-oxide counterparts, in accordance to the X-ray structure. The lower population of the 4′-oxide isomers relative to that of the 2′-oxide isomers was explained in terms of an unfavourable intramolecular steric interaction found in the low energy structure of the former.

1. Introduction

The pyran ring attached to arenes, either in a fused or in a spiro motif, is an important structure. Naphthopyrans (benzochromenes), as core units, are found in numerous natural products with significant biological and medicinal properties.[1] They are also fundamental components in modern technology materials because of their photochromic properties.[2] Naphthalenone derivatives have recently been used to develop positive-type photosensitive polymers.[3] Furazan oxides (1,2,5-oxadiazole-2-oxides or furoxans), on the other hand, have been the subject of extensive research from the early 1960s.[4] A resurgence of interest in this heterocycle has occurred lately,[5] owing to, perhaps, its recently realised biological and pharmacological properties.[6]

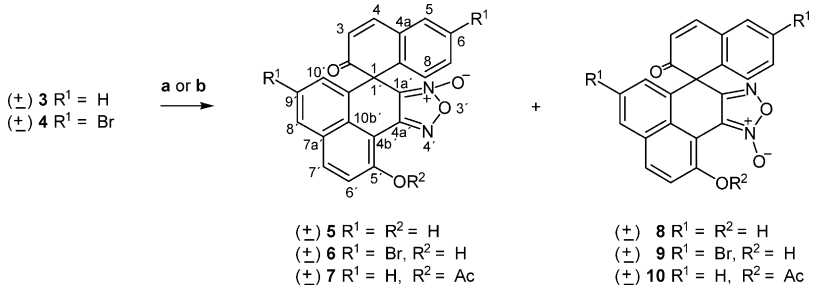
Spiro structure **1** has been known as early as 1962 (Scheme 1). It was obtained as the product of thermal decomposition[7] or oxidation[8] of suitably *o*-substituted naphthols.



Scheme 1.

Keywords: Furazan oxides; Spiro[naphthalene(phenalenofurazan)oxides; Spiro compounds; Thermal rearrangement.
* Corresponding author. Tel.: +30 26510 98382; fax: +30 26510 98799; e-mail: gvarvoun@cc.uoi.gr

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.03.068



Scheme 2. Reagents: (a) DMF, 140 °C; (b) Ac_2O, reflux.

The furazan oxide analogues of **1**, (±)-spiro{naphthalene-1(2*H*),4′-(naphtho[2′,1′:2,3]pyrano[4,5-*c*]furazan)}-2-one-11′-oxides **3** and **4**, were recently obtained by the oxidative cyclodimerisation of 2-hydroxynaphthaldehyde oxime and 6-bromo-2-hydroxynaphthaldehyde oxime, respectively, with lead(IV) acetate.[9] Because of the known thermal ring opening of the furazan oxide ring[10] and the thermally-induced rearrangement of **1** into its isomer **2** that involves initially cleavage of the pyran ring,[11] we were interested in investigating the response to thermal treatment of structures **3** and **4** that contain both these entities.

2. Results and discussion

Compounds **3** and **4** were heated in DMF at 140 °C for 12 h to afford the rearranged isomeric mixtures of **5** and **8** and **6** and **9**, respectively (Scheme 2). No reaction was observed at various lower temperatures and shorter reaction times. The separation of tautomers **5** and **8**, and **6** and **9** by flash chromatography was partially successful, the isolation of isomers **5** and **6** in a pure state was achieved up to 15% και 23% yield, respectively. In order to establish whether the transformation of compound **3** into **5** and **8** is in any way affected by a different solvent, compound **3** was heated with acetic anhydride for 6 h to afford the isomeric compounds **7** and **10** (Scheme 2). This time the separation of isomers **7** and **10** by flash chromatography was conducted with considerable ease and the isomers were obtained pure in 36 and 31% yield, respectively. At first the characterization of pure isomers **5**, **6**, **7** and **10** was not easy using 1D and 2D NMR spectroscopy and mass spectrometry alone. However, after the rearranged structure of compound **7** was resolved by single crystal X-ray crystallography (Fig. 1), compounds **5**, **6**, **7** and **10** were fully characterised by NMR spectroscopy in particular with DQF-COSY, HMQC, HMBC and NOESY spectra.

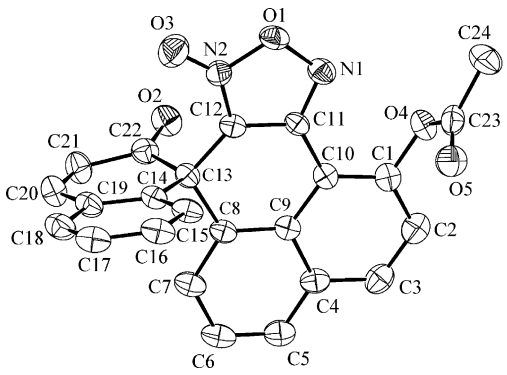


Figure 1. Schakal diagram of compound **7** (thermal ellipsoids at 40% probability).

From the crystal structure of **7** (Fig. 1) it is evident that the molecule possesses two almost planar ring systems, one two-membered and one four-membered. The angle between their mean planes is 95°. The sp^3-hybridised carbon atom (C13) deviates by 0.06 Å from the mean plane of the four-membered ring system and by 0.1 Å from that of the two-membered ring system. The bond lengths C13–C14 of 1.520 (5) Å, C13–C8 of 1.552 (5) Å, C13–C22 of 1.553 (5) Å, C13–C12 of 1.492 (5) Å, and bond angles C12–C13–C8 of 108.2°, C12–C13–C22 of 107.0°, C22–C13–C14 of 114.3°, C14–C13–C8 of 110.1° around C13 are slightly distorted from the ideal sp^3 geometry, probably due to the extended conjugated π-system in the four-membered unit. Furthermore, the respective bond lengths and angles of the furazan oxide ring of compound **7** are similar to those of compound **3**.[9] Finally, the average plane of the acetoxy group deviates from the average plane of the four-membered ring by 89° whereas the dihedral angle O_5–C_{23}–O_4–C_1 has a value of 5°.

A comparison of the ^{1}H NMR spectra of isomers **7** and **10** revealed features that were used to differentiate between isomers **5** and **8**, and **6** and **9**. Thus, in **7**, H-3, H-8 and H-10′ resonate at 6.38, 7.04 and 7.24 ppm, respectively, while in **10** these nuclei resonate at 6.21, 6.95 and 7.09 ppm. The chemical shift due to H-10′ of **10** is 0.15 ppm upfield than the chemical shift of the corresponding proton of **7**. This difference is probably due to the conjugative shielding effect exerted by the exocyclic oxygen atom of the furazan oxide ring which is well-documented.[4,13] A smaller but similar chemical shift difference is found between the H-10′ resonances of **5** and **8**, and **6** and **9**. The resonance of H-3 appears at 6.38 ppm in **7** and 6.21 ppm in **10**. A through-space deshieding effect by the *N*-oxide group of **7** could probably account for this difference, even though the mean distance 4.58 Å for O(3)–H(21) of **7** (crystal structure) is slightly larger than the normal. The resonances of H-3 at 6.35 and 6.45 ppm in **5** and **8**, and 6.18 and 6.34 ppm in **6** and **9** follow the same trend. Furthermore there are some obvious trends in chemical shift values because of ring substituents. A comparison of H-5 and H-7 resonances in the spectra of **5** and **7** with those of **6**, and in the spectra of **8** and **10** with those of **9**, reveals a downfield shift for the protons in **6** and **9**, as expected, because of the inductive effect of the bromine atom at C-6. In the spectra of **8** and **9**, H-6′ resonates at about 7.39 and 7.58, respectively. The higher value, 7.70 ppm, for H-6′ in the spectrum of **10** confirms the less effective shielding effect of the acetoxy

Table 1. AM1 relative energies and calculated, experimental populations for the exchanged tautomer pairs **5** and **8**, and **7** and **10**

Compound	AM1 relative energy (kcal mol^{-1})	% Calculated population (T=298 K)	% Observed population (T=298 K)
5	0.00	81.30	56.73
8	0.86	18.70	43.26
7	0.00	91.40	76.10
10	1.40	8.60	23.90

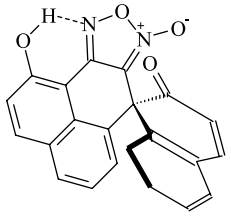
group at C-5′ compared to the more efficient shielding effect of the hydroxy group at C-5′ in **8** and **9**. The thermal rearrangement structure of isomers **5**–**7** were further substantiated using NOESY spectroscopy. The NOE correlation between H-3 and H-10′ found in all these spectra is indicative that the structures of **5** and **6** are similar to the structure of **7**, that has been unambiguously assigned by X-ray crystallography.

The involvement of 1,2-dinitrosoarenes as intermediates in the ring chain tautomerism of benzofurazan oxide has been firmly established by matrix isolation experiments[14] and supported by theoretical calculations.[15] The factors influencing both the equilibrium constants and the equilibration rates have been discussed in reviews by Ruccia et al.[16] Gasco and Boulton[17] and by Katritzky and Gordeev.[18] The kinetic and thermodynamic parameters for these furazan oxide isomerizations can often be measured by NMR spectroscopy. ^{1}H NMR spectroscopy played a major role in establishing the structure and investigating the ring-chain tautomerism of benzofurazan oxides.[18] The rate of equilibrium is strongly substituent dependent. The energy barrier for the interconversion of benzofurazan oxide tautomers is $\sim\Delta G^{\#}$ 14 kcal mol^{-1} at ambient temperature. Naphtho[1,2-*c*]furoxans isomerize more slowly and give $\sim\Delta G^{\#}$ 20 kcal mol^{-1}.

We found that ring-chain tautomerism in **5** and **7** is slow at ambient temperature and both isomer pairs **5** and **8**, and **7** and **10** are observed. Isomer populations are however different. Semi-empirical AM1 and molecular mechanics calculations all suggest that **5** and **7** are more stable than their counterparts **8** and **10**, this tautomer corresponds to the solid state structure, see Figure 1. Semi-empirical AM1 calculations predict the trends for the relative abundance of the two tautomers. The population of each conformer can be calculated from equation $\Delta G^{\circ} = -RT \ln K_{eq}$. The results are summarised in Table 1.

The lower population of **8** and **10** relative to those of their counterparts **5** and **7** may be explained in terms of the unfavourable steric interaction between the exocyclic furazan oxide oxygen atom and the naphthalene ring substituent (OH or OAc) as shown for the equilibrium calculated structures **7** and **10** (Fig. 2). Thus, the OAc group is oriented towards the side opposite to the ring C=O and the conformation resulting from rotation around the O=C–O bond is *anti*.

A comparison of the populations of **8** and **10** revealed that the former is larger (Table 1). This population increase can be rationalised in terms of the smaller size of OH relative to OAc group and possibly through a hydrogen bond between OH and furazan oxide could impart additional stabilisation to that conformation (Fig. 3).



8

Figure 3. Low energy structure of isomer **8** obtained using AM1 calculations. The hydrogen bond between OH and furazan oxide is denoted by a dotted line.

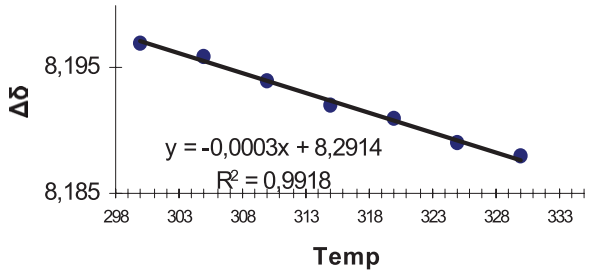
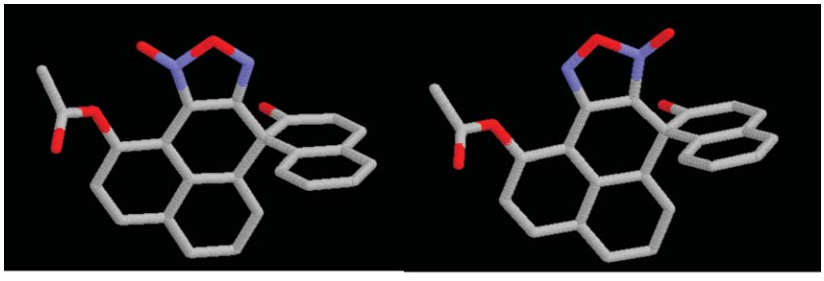


Figure 4.



7 10

Figure 2. Low energy structures for equilibrating isomers **7** and **10** obtained using AM1 geometry optimization. **10** is destabilised by the unfavourable steric interaction between N–O and acetyl groups.

Evidence of the proposed intramolecular hydrogen bond in **8** was obtained from variable temperature ^{1}H NMR spectra in acetone. Consistently a small thermal coefficient of $\Delta\delta/\Delta T = 310^{-4}$ was estimated (Fig. 4).

The isomerisation equilibrium for the tautomeric mixture **7** and **10** was also studied by variable temperature ^{1}H NMR. At 403 K a significant broadening of the signals was observed indicating a dynamic effect (Fig. 5). Since, above 403 K, the sample starts to decompose we will give a lower limit for the free energy of activation, assuming a coalescence point of at least 20 K higher and using the values $\delta\nu = 66.04$ Hz (400 MHz) at 298 K and $\Delta P = 0.52$, and the Shanan–Atidi and Bar–Eli equation for unequally populated isomers exchange,[19] the lower limit for the isomerisation barrier was calculated to be 22 kcal mol^{-1} at 423 K.

Structure **3**, unequivocally determined by X-ray crystallography[9] and by extrapolation **4**,[9] are the only exclusively formed isomers to undergo the thermal rearrangement leading to **5** and **8** or **6** and **9** or **7** and **10**. According to Dean and co-workers an ionic [3,3]-sigmatropic mechanism was proposed for the thermal transformation of **1** to **2** that worked equally well in both acidic and polar solvents.[12] It is well documented that the isomerisation of furoxans, through the postulated dinitrosoalkene intermediate, is initiated by the exocyclic oxygen atom of the *N*-oxide.[4] Based on these facts we propose an ionic mechanism (Scheme 3) where the exocyclic oxygen atom of the furoxan ring is probably the incipient trigger of the process. The much lower temperature required to effect these rearrangements compared to that needed for **1**, lends support to this concept. Thus, ring-opening of the pyran ring of **3** or **4** gives intermediate **11**, reversibly. The drive to aromatisation of the furoxan ring could encourage intramolecular cylisation to intermediate **12**. Aromatisation of the naphthalene ring of **12** would then lead to spiro isomers **5** and **6** in the case where DMF was the solvent, and to acetylated isomer **7** in the case where **3** was heated in acetic anhydride. Isomers **5**, **6** and **7** could then ring-open to the dinitrosoalkene intermediate **13** which could ring-close to the corresponding isomers **8**, **9** and **10**.

Thermal ring-opening of **3** or **4** could, via the appropriate dinitrosoalkene intermediates,[4c] lead to the corresponding isomeric (±)-spiro{naphthalene-1(2*H*),4′(naphtho[2′,1′:-2,3]pyrano[4,5-*c*]furazan)}-2-one-9′-oxides. Ring-opening of the latter could occur but calculations of the resulting intermediate revealed that it cannot give the observed products. It is therefore very probable that isomeric (±)-spiro{naphthalene-1-(2*H*),4′(naphtho-[2′,1′:2,3]pyrano-[4,5-*c*]furazan)}-2-one-9′-oxides may be forming but reverting back to **3** or **4**.

Attempts to deoxygenate **3** or **4** and, thus, remove the alleged trigger of the rearrangement, were all unsuccessful,

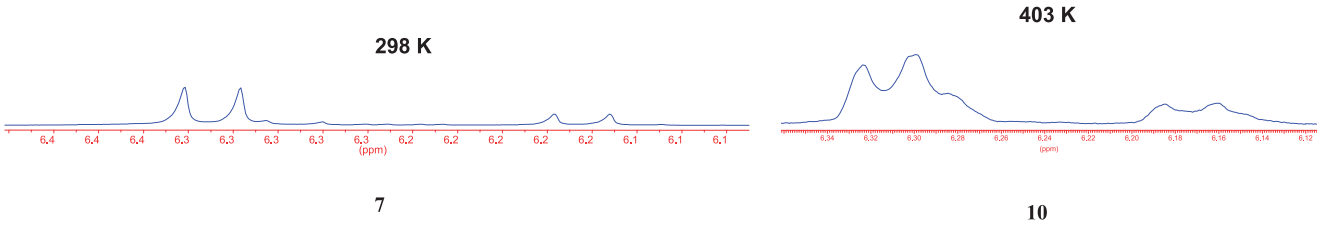
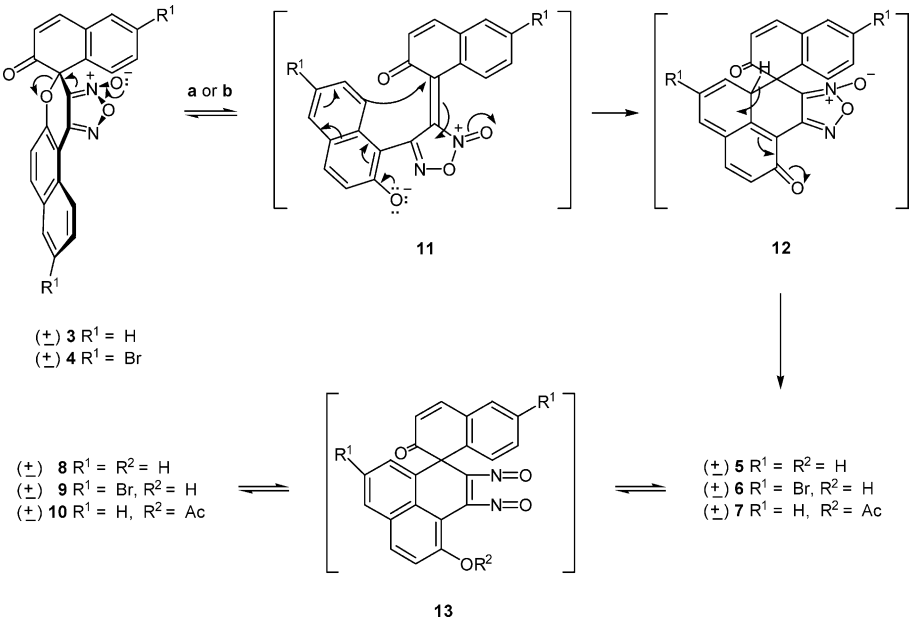


Figure 5. Part of the ^{1}H NMR spectrum of mixture of the slow interchanged tautomers **7** and **10** in DMSO-d$_6$ solution (400 MHz) at 298 K (left hand part) and 403 K (right hand part) when a dynamic broadening effect is observed.



Scheme 3. Reagents: (a) DMF, 140 °C; (b) Ac_2O, reflux.

while using a variety of standard [PCl_3, $POCl_3$, $P(OEt)_3$][13] and more recent [$Al(H_2O)_6Cl_3$/KI][19,20] reaction conditions. The result is consistent with the proposed rationale and reflects the partial double bond character of the *N*-oxide bond as evidenced by the N2—O3 bond distance of 1.188 (4) Å.

In conclusion, there is substantial evidence from NOESY and X-ray crystallographic studies that thermal rearrangement of spiro[naphthalene(naphthopyrano-furazan)]one *N*-oxides in *N*,*N*-dimethylformamide leads to isomeric mixtures of spiro[naphthalene(hydroxyphenalene-furazan)one *N*-oxides. Similar thermal rearrangement of the parent spiro[naphthalene(naphthopyranofurazan)]one *N*-oxide with acetic anhydride afforded spiro[naphthalene-(acetoxyphenalenefurazan)one *N*-oxide. An ionic mechanism for the rearrangement is tentatively proposed.

3. Experimental

3.1. General methods

Melting points were taken on a Büchi 510 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 257 spectrometer, as Nujol mulls between sodium chloride discs. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser. Nuclear magnetic resonance spectra were measured at 400 MHz on Brüker AMX 400 and DRX 400 spectrometers, using tetramethylsilane as internal standard. Mass spectra were obtained by use of Finnigan 4500 (low resolution) or JEOL JMS-AX 505W (high resolution) instruments using EI. Analytical TLC was carried out on Fluka silica gel 60 F254. Preparative flash chromatography was carried out using Merck 9385 silica gel. Solvents and reagents were used as received from the manufacturers except for dichloromethane, ethanol, ethyl acetate, hexane and methanol that were purified and dried according to recommended procedures.[21]

The assignment of ^1H and ^{13}C signals were achieved by the combined use of DEPT, 2D COSY, NOESY, HMQC and HMBC experiments. A relaxation delay of 2 s was used for all experiments. For the NOESY experiment a mixing time of 600 ms was used. Calculations were performed using the Hyperchem program[22] in Pentium IV platform. For each molecule an initial structure was constructed and minimized using conjugate gradient and Newton–Raphson algorithms and an energy gradient tolerance of 0.01 kcal mol^{-1} $Å^{-1}$.

3.2. Thermal rearrangement of (±)-spiro{naphthalene-1-(2*H*),4′(naphtho[2′,1′:2,3]pyrano[4,5-*c*]furazan)}-2-one-11′-oxide in DMF

A solution of **3**[9] (0.2 g, 0.54 mmol) in DMF (5 mL) was heated at 140 °C for 12 h. The reaction mixture was allowed to reach room temperature, water (20 mL) was added and the mixture extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated in vacuo to give an oily residue. The residue was purified by column chromatography (20% ethyl acetate/hexane) to give in the first fraction a mixture of isomers (±)-spiro{naphthalene-1(2*H*),1′-(5′-hydroxyphenalene[1,2-*c*]furazan)}-2-one-4′-oxide **8** and (±)-spiro-{naphthalene-1(2*H*),1′-(5′-hydroxy-phenalene[1,2-*c*]furazan)}-2-one-2′-oxide **5** (120 mg) and in the second fraction (±)-**5**.

3.2.1. (±)-Spiro{naphthalene-1(2*H*),1′-(5′-hydroxyphenalene[1,2-*c*]furazan)}-2-one-2′-oxide (5). 30 mg, 15% as a colourless powder (ethyl acetate/hexane); mp 245–247 °C; [found: C, 71.79; H, 3.21; N, 7.54. $C_{22}H_{12}N_2O_4$ requires C, 71.74; H, 3.28; N, 7.61%]; ν_{max} (Nujol) 3380, 1670, 1200 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 6.35 (1H, d, J=10 Hz, H-3), 6.97 (1H, d, J=7.7 Hz, H-8), 7.07 (1H, d, J=7.4 Hz, H-10′), 7.24–7.33 (2H, m, H-7, H-9′), 7.43 (1H, t, J=7.6 Hz, H-6), 7.48 (1H, d, J=9.1 Hz, H-6′)7.72 (1H, d, J=7.5 Hz, H-5), 7.86 (1H, d, J=8.0 Hz, H-8′), 8.05–8.10 (2H, m, H-4, H-7′), 11.59 (1H, br s, OH); δ_H (400 MHz; $CDCl_3$) δ: 6.31 (1H, d, J=10.0 Hz, H-3), 6.87 (1H, d, J=7.5 Hz, H-8), 7.09 (1H, d, J=7.6 Hz, H-10′), 7.22–7.31 (2H, m, H-7, H-9′), 7.35–7.42 (2H, m, H-6, H-6′), 7.51 (1H, d, J=7.5 Hz, H-5), 7.72–7.76 (2H, m, H-8′, H-4), 7.95 (1H, d, J=9.1 Hz, H-7′), 8.02 (1H, br s, OH); δ_C (400 MHz; DMSO-d_6) 53.51 (C-1), 100.46 (C-4b′), 115.07 (C-4a′), 119.34 (C-6′), 122.99 (C-3), 124.02 (C-9′), 124.45 (C-10b′), 126.48 (C-10′), 128.27 (C-4a), 128.63 (C-8, C-6), 128.88 (C-8′), 129.13 (C-7a′), 129.94 (C-10a′), 130.43 (C-5), 131.44 (C-7), 134.19 (C-7′), 141.88 (C-8a), 148.31 (C-4), 151.63 (C-1a′), 156.03 (C-5′), 194.62 (C-2); *m*/*z* (EI) 368 (39, M^+), 352 (100), 324 (96), 307 (25), 250 (20), 239 (11), 201 (13), 162 (21), 151 (18), 113 (21), 101 (7), 70 (5), 50 (2%).

3.2.2. (±)-Spiro{naphthalene-1(2*H*),1′-(5′-hydroxyphenalene[1,2-*c*]furazan)}-2-one-4′-oxide (8). δ_H (400 MHz; $CDCl_3$) 6.18 (1H, d, J=10.0 Hz, H-3), 6.82 (1H, d, J=7.7 Hz, H-8), 7.03 (1H, d, J=7.4 Hz, H-10′), 7.23–7.28 (2H, m, H-7, H-9′), 7.36–7.41 (2H, m, H-6, H-6′), 7.52 (1H, d, J=7.6 Hz, H-5), 7.73–7.77 (2H, m, H-8′, H-4), 7.97 (1H, d, J=9.1 Hz, H-7′), 8.14 (1H, br s, OH). This ^1H NMR was extracted from a mixture containing compound **5**.

3.3. Thermal rearrangement of (±)-6,6′-dibromospiro-{naphthalene-1-(2*H*),4′-(naphtho[2′,1′:2,3]pyrano[4,5-*c*]-furazan)}-2-one-11′-oxide in DMF

A solution of **4** (0.3 g, 0.57 mmol) in DMF (5 mL) was heated at 120 °C for 12 h. The reaction mixture was allowed to reach room temperature, water (20 mL) was added and the mixture extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated in vacuo to give an oily residue. The residue was purified by column chromatography (20, 25, 33, 50% ethyl acetate/hexane) to give in the first fraction a mixture of isomers (±)-6,9′-dibromospiro{naphthalene-1(2*H*),1′-(5′-hydroxyphenalene[1,2-*c*]furazan)}-2-one-4′-oxide **9** and (±)-6,9′-dibromospiro{naphthalene-1(2*H*),1′-(5′-hydroxy-nalene[1,2-*c*]furazan)}-2-one-2′-oxide **6** (183 mg) and in the second fraction (±)-**6**.

3.3.1. (±)-6,9′-Dibromospiro{naphthalene-1(2*H*),1′-(5′-hydroxyphenalene[1,2-*c*]furazan)}-2-one-2′-oxide (6). 70 mg, 23% as yellow needles (acetonitrile); mp 207–210 °C; [found: C, 50.29; H, 1.86; N, 5.25. $C_{22}H_{10}Br_2N_2O_4$

requires C, 50.22; H, 1.92; N, 5.32%]; ν_{max} (Nujol) 3310, 1680, 1210 cm^{-1}; δ_H (400 MHz; DMSO-d_6) δ: 6.45 (1H, d, $J=10.0$ Hz, H-3), 7.02–7.07 (2H, m, H-8, H-10′), 7.51–7.53 (2H, m, H-7, H-6′), 8.03–8.09 (3H, m, H-4, H-5, H-7′), 8.17 (1H, s, H-8′) 11.72 (1H, br s, OH); δ_C (100 MHz; DMSO-d_6) δ: 53.03 (C-1), 100.79 (C-4b′), 114.50 (C-4a′), 116.09 (C-9′), 120.88 (C-6′), 122.10 (C-6), 123.96 (C-3), 126.55 (C-10b′), 128.52 (C-10′), 129.55 (C-7a′), 131.09 (C-8), 131.17 (C-8′), 131.35 (C-10a′), 131.80 (C-4a), 132.94 (C-5), 133.48 (C-7′), 134.13 (C-7), 139.88 (C-8a), 147.21 (C-4), 151.27 (C-1a′), 156.63 (C-5′), 193.72 (C-2); *m/z* (EI) 524 (3, M^+), 512 (18), 510 (30), 508 (12), 482 (16) 438 (16), 418 (7), 373 (6), 295 (12), 264 (7), 249 (7), 238 (13), 234 (48), 169 (100), 140 (16), 77 (12%); HRMS (EI): $M^+ -$ O, found 509.9065. $C_{22}H_{10}^{81}Br_2N_2O_3$ requires 509.9038.

3.3.2. (±)-6,9′-Dibromospiro{naphthalene-1(2*H*),1′-(5′-hydroxyphenalene[1,2-*c*]furazan)}-2-one-4′-oxide (9). δ_H (400 MHz; DMSO-d_6) δ: 6.34 (1H, d, $J=9.9$ Hz, H-3), 6.97–7.01 (2H, m, H-8, H-10′), 7.55–7.59 (2H, m, H-7, H-6′), 8.11–8.15 (2H, m, H-5, H-7′), 8.25 (1H, s, H-8′), 11.77 (1H, br s, OH). This ^{1}NMR was extracted from a mixture containing compound **6**.

3.4. Thermal rearrangement of (±)-spiro{naphthalene-1-(2*H*),4′-(naphtho[2′,1′:2,3]pyrano[4,5-*c*]furazan)}-2-one-11′-oxide in acetic anhydride

A solution of **3** (0.16 g, 0.43 mmol) in acetic anhydride (10 mL) was heated under reflux for 6 days. The reaction mixture was allowed to reach room temperature and then poured into ice-water (15 mL) and extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was evaporated in vacuo to give an oily residue. The residue was purified by column chromatography (20% ethyl acetate/hexane) to give in the first fraction (±)-spiro{naphthalene-1(2*H*),1′-(5′-acetyl-oxy-phenalene[1,2-*c*]-furazan)}-2-one-4′-oxide **10** and in the second fraction (±)-spiro{naphthalene-1(2*H*),1′-(5′-acetyl-oxyphenalene[1,2-*c*]furazan)}-2-one-2′-oxide **7**.

3.4.1. (±)-Spiro{naphthalene-1(2*H*),1′-(5′-acetyloxyphenalene[1,2-*c*]furazan)}-2-one-2′-oxide (7). 64 mg, 36% as pale yellow powder (ethyl acetate/hexane); mp 139–142 °C; [found: C, 70.27; H, 3.39; N, 6.79. $C_{24}H_{14}N_2O_5$ requires C, 70.24; H, 3.44; N, 6.83%]; ν_{max} (Nujol) 1723, 1685, 1200 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 2.47 (3H, s, Me), 6.38 (1H, d, $J=9.9$ Hz, H-3), 7.04 (1H, d, $J=7.6$ Hz, H-8), 7.24 (1H, d, $J=7.2$ Hz, H-10′), 7.34 (1H, t, $J=7.6$ Hz, H-7), 7.44–7.60 (2H, m, H-6, H-9′), 7.69–7.79 (2H, m, H-6′, H-5), 8.07–8.15 (2H, m, H-4, H-8′), 8.36 (1H, d, $J=9.0$ Hz, H-7′); δ_C (400 MHz; DMSO-d_6) 20.97, 53.51, 110.01, 114.59, 122.71, 123.65, 127.11, 127.17, 128.87, 128.99, 129.16, 129.27, 130.69, 131.15, 131.63, 131.87, 134.25, 140.85, 143.96, 147.19, 148.80, 150.74, 168.93, 193.98; *m/z* (EI) 410 (39, M^+), 394 (17), 368 (32), 366 (34), 326 (55), 324 (91), 321 (90), 308 (88), 293 (93), 282 (100), 267 (78), 240 (28), 92 (11), 74 (52), 45 (27%).

Crystal data of **7**. $[C_{24}H_{14}N_2O_5]0.5C_2H_5OH$. $M=433.41$, triclinic, space group *P-1*, $a=8.900$ (2) Å, $b=10.668$ (2) Å, $c=13.193$ (2) Å, $\alpha=108.64$ (1)°, $\beta=109.57$ (1)°, $\gamma=92.99(2)$°, $V=1100.4(4)$ Å^3, $Z=2$, $Dc=1.308$ g cm^{-3}, $\mu=0.094$ mm^{-1} (Mo Kα, $\lambda=0.71073$ Å), $T=293$ K. Of 3297 reflections measured on a Bruker P4 diffractometer, 3032 were unique ($R_{int}=0.019$). The structure was solved by direct methods and refined on F^2. A solvent (ethanol) molecule, possessing a great disorder was located by difference Fourier maps in the vicinity of a centre of symmetry. This molecule was refined only isotropically with an atomic occupancy factor of 0.5. Hydrogen atoms were located by difference Fourier maps and refined isotropically. $R=0.0801$, $wR2=0.2547$ [F^2 values, 2413 reflections with $I>2\sigma(I)$], goodness-of-fit=1.143, final difference map extremes +0.609 and −0.448 e Å^{-3}. Software: SHELXS-97, SHELXL-97. Crystallographic data (excluding structural factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 264135.

3.4.2. (±)-Spiro{naphthalene-1(2*H*),1′-(5′-acetyloxyphenalene[1,2-*c*]furazan)}-2-one-4′-oxide (10). 54 mg, 31% as pale yellow powder (ethyl acetate/hexane); mp 149–152 °C; [found: C, 70.28; H, 3.41; N, 6.80. $C_{24}H_{14}N_2O_5$ requires C, 70.24; H, 3.44; N, 6.83%]; ν_{max} (Nujol) 1720, 1680, 1200 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 2.50 (3H, s, Me), 6.21 (1H, d, $J=9.9$ Hz, H-3), 6.95 (1H, d, $J=7.7$ Hz, H-8), 7.09 (1H, d, $J=7.3$ Hz, H-10′), 7.36 (1H, t, $J=7.4$ Hz, H-7), 7.50 (1H, t, $J=7.4$ Hz, H-6), 7.56 (1H, t, $J=7.7$ Hz, H-9′), 7.70 (1H, d, $J=9.0$ Hz, H-6′), 7.77 (1H, d, $J=7.3$ Hz, H-5), 8.05–8.12 (2H, m, H-4, H-8′), 8.35 (1H, d, $J=9.0$ Hz, H-7′); δ_C (400 MHz; DMSO-d_6) 20.98 (Me), 54.51 (C-1), 104.33 (C-1a′), 110.30 (C-4b′), 121.09 (C-3), 123.41 (C-6′), 127.04 (C-9′), 127.19 (C-10b′), 127.54 (C-10′), 128.68 (C-4a), 128.82 (C-8′, C-6), 130.28 (C-8), 130.40 (C-5), 131.47 (C-7), 131.81 (C-7a′), 132.85 (C-10a′), 133.82 (C-7′), 143.73 (C-8a), 147.28 (C-5′), 148.43 (C-4), 155.69 (C-4a′), 168.88 (O*C*OCH$_3$), 194.97 (C-2); *m/z* (EI) 408 (2, M^+-2), 394 (30), 353 (24), 352 (95), 325 (24), 324 (100), 310 (27), 308 (24), 294 (13), 281 (17), 264 (16), 239 (13), 91 (2%).

Acknowledgements

This work was supported by a grant from Program Interreg II, Greece Italy, Action 5-2 (coordinator Prof. M. Karayiannis, University of Ioannina) (to P. S.). We thank Dr. A. Troganis for NMR spectra measured on a Brüker AMX 400 spectrometer and Professor N. Hadjiliadis for elemental analyses on machines financed by the University of Ioannina. We are particularly grateful to A. Cakebread and R. Tye for mass spectra obtained on machines funded by the University of London Intercollegiate Research Services Scheme.

References and notes

1. (a) Ohashi, K.; Bohgaki, T.; Matsubara, T.; Shibuya, H. *Chem. Pharm. Bull.* **2000**, *48*, 433. (b) Ohashi, K.; Bohgaki, T.; Shibuya, H. *Yakugaku Zasshi (J. Pharm. Soc. Jpn.)* **2000**, *120*, 474. (c) Hollick, J. J.; Golding, B. T.; Hardcastle, I. R.; Martin, N.; Richardson, C.; Rigoreau, L. J. M.; Smith, G. C. M.;

Griffin, R. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3083. (d) Hussein, A. A.; Barberena, I.; Capson, T. L.; Kursar, T. A.; Coley, P. D.; Solis, P. N.; Gupta, M. P. *J. Nat. Prod.* **2004**, *67*, 451.

2. (a) Zayat, M.; Levy, D. *J. Mater. Chem.* **2003**, *13*, 727. (b) Ushakov, E. N.; Nazarov, V. B.; Fedorova, O. A.; Gromov, S. P.; Chebun'kova, A. V.; Alfimov, M. V.; Barigelletti, F. *J. Phys. Org. Chem.* **2003**, *16*, 306. (c) Nakatsuji, S. *Chem. Soc. Rev.* **2004**, *33*, 348. (d) Gabbutt, C. D.; Hepworth, J. D.; Heron, B. M.; Thomas, D. A.; Kilner, C.; Partington, S. A. *Heterocycles* **2004**, *63*, 567.
3. (a) Morita, K.; Ebara, K.; Shibasaki, Y.; Ueda, M.; Goto, K.; Tamai, S. *Polymer* **2003**, *44*, 6235. (b) Fukukawa, K.; Shibasaki, Y.; Ueda, M. *Polym. J.* **2004**, *36*, 489. (c) Morita, K.; Shibasaki, Y.; Ueda, M. *J. Photopolym. Sci. Tech.* **2004**, *17*, 263.
4. (a) Gasco, A.; Boulton, A. *J. Adv. Heterocycl. Chem.* **1981**, *29*, 251. (b) Sliva, W.; Thomas, A. *Heterocycles* **1985**, *23*, 339. (c) Khmelnitskii, L. J.; Novikov, S. S.; Godovikova, T. I. *Chemistry of Furoxans: Reactions and Applications*, 2nd ed.; Nauka: Moscow, 1996. (d) Stevens, J.; Schweizer, M.; Rauhut, G. *J. Am. Chem. Soc.* **2001**, *123*, 7326.
5. (a) Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O.; Ballini, R.; Bosica, G. *Tetrahedron Lett.* **2000**, *41*, 8817. (b) Boschi, D.; Sobra, G.; Bertinaria, M.; Fruttero, R.; Calvino, R.; Gasco, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1751.
6. (a) Cerecetto, H.; Di Maio, R.; Gonzáles, M.; Risso, M.; Saenz, P.; Seoane, G.; Denicola, A.; Peluffo, G.; Quijano, C.; Olea-Azar, C. *J. Med. Chem.* **1999**, *42*, 1941. (b) Rolando, B.; Cena, C.; Caron, G.; Marini, E.; Grosa, G.; Fruttero, R.; Gasco, A. *J. Med. Chem. Res.* **2002**, *11*, 322. (c) Sorba, G.; Galli, U.; Cena, C.; Fruttero, R.; Gasco, A.; Morini, G.; Adami, M.; Coruzzi, G.; Brenciaglia, M. I.; Dubini, F. *ChemBioChem* **2003**, *4*, 899. (d) Bertinaria, M.; Galli, U.; Sorba, G.; Fruttero, R.; Gasco, A.; Brenciaglia, M. I.; Scaltrito, M. M.; Dubini, F. *Drug Dev. Res.* **2003**, *60*, 225. (e) Boschi, D.; Tron, G. C.; Di Stilo, A.; Fruttero, R.; Gasco, A.; Poggesi, E.; Motta, G.; Leonardi, A. *J. Med. Chem.* **2003**, *46*, 3762. (f) Moharram, S.; Zhou, A.; Wiebe, L. I.; Knaus, E. E. *J. Med. Chem.* **2004**, *47*, 1840. (g) Visentin, S.; Rolando, B.; Di Stilo, A.; Fruttero, R.; Novara, M.; Carbone, E.; Roussel, C.; Vanthuyne, N.; Gasco, A. *J. Med. Chem.* **2004**, *47*, 2688.
7. Cavitt, S. B.; Sarrafizadeh, R.; Gardner, P. D. *J. Am. Chem. Soc.* **1962**, *84*, 1211.
8. Kasturi, T. R.; Reddy, P. A.; Mandal, A. B.; SivaraMakrishnan, R.; Rajasekhar, B.; Prasad, K. B.; Radhakrishnan, R.; Viswamitra, M. A. *Tetrahedron* **1990**, *46*, 7047.
9. Supsana, P.; Tsoungas, P. G.; Aubry, A.; Skoulika, S.; Varvounis, G. *Tetrahedron* **2001**, *57*, 3445.
10. Molotov, S. I.; Kulikov, A. S.; Makhova, N. N.; Lyssenko, K. A. *Mendeleev Commun.* **2003**, *4*, 188.
11. Catterall, G. *J. Chem. Soc., Chem. Commun.* **1974**, 41.
12. Dick, A. W. S.; Dean, F. M.; Matkin, D.; Robinson, M. L. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2204.
13. Albini, A.; Pietra, S. *Heterocyclic N-Oxides*; CRC: Boca Raton, 1991.
14. Hacker, N. P. *J. Org. Chem.* **1991**, *56*, 5216.
15. Ponder, M.; Fowler, J. E.; Schaefer, H. F. *J. Org. Chem.* **1994**, *59*, 6431.
16. Ruccia, M.; Vivona, N. *Adv. Heterocycl. Chem.* **1981**, *29*, 141.
17. (a) Gasco, A.; Boulton, A. J. *Adv. Heterocycl. Chem.* **1981**, *29*, 251. (b) Khmelnitskii, L. J.; Novikov, S. S.; Godovikova, T. I. *Chemistry of Furoxans: Reactions and Applications*; Nauka: Moscow, 1996.
18. Katritzky, A. R.; Gordeev, M. F. *Heterocycles* **1993**, *35*, 483.
19. Shanan-Atidi, H.; Bar-Eli, K. H. *J. Phys. Chem.* **1970**, *74*, 961.
20. Boruar, M.; Konwar, D. *Synlett* **2001**, 795.
21. Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*; Butterworth-Heinemann: Oxford, 1996.
22. *HyperChem 5.1, Professional version, Molecular Visualization and Simulation Program Package*; Hypercube Inc.: Gainesville Florida, 1998.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 61 (2005) 6138–6142
Tetrahedron

A novel phosphoramidite for the synthesis of α-oxo aldehyde-modified oligodeoxynucleotides

Samia Far,[a] Catherine Gouyette[b] and Oleg Melnyk[a,*]

[a]*UMR 8525, CNRS-Université de Lille 2, Biological Institute of Lille, 1 rue du Pr Calmette, 59021 Lille, France*
[b]*Pasteur Institute, 25-28 rue du Dr Roux, 75724 Paris Cedex 15, France*

Received 3 February 2005; revised 10 March 2005; accepted 17 March 2005

Available online 13 May 2005

Abstract—The synthesis and use of a novel phosphoramidite derivatized by a bis[2-(*tert*-butyldisulfanyl)ethoxycarbonylamino]acetyl moiety for the synthesis of oligodeoxynucleotides modified at the 5′-end by an α-oxo aldehyde functionality is presented. Incorporation of the phosphoramidite reagent was performed after the automated solid-phase oligonucleotide synthesis. Simultaneous cleavage/deprotection of the oligodeoxynucleotides and unmasking of the α-oxo aldehyde group could be achieved using NaOH in aqueous methanol in the presence of dithiothreitol.

1. Introduction

Synthetic tools allowing the site-specific modification of oligodeoxynucleotides (ODN) have many applications such as the synthesis of conjugates,[1] of biomaterials or of miniaturized devices.[2] In this context, the unique reactivity of aldehyde functionality has been exploited for the modification of ODNs using thiazolidine, oxime, hydrazone or semicarbazone ligation chemistries.[1–5] Not surprisingly, the efficiency of aldehyde Schiff-base chemistry has stimulated the last few years many synthetic efforts toward the synthesis of aldehyde–ODNs. Most of the time, the aldehyde functionality was obtained by oxidative cleavage of a vicinal diol with periodate.[6–11] The direct introduction of a protected aldehyde moiety during solid phase elongation is less common.[1] Usually, ODNs were modified by aliphatic,[9] aromatic[12] or glycol aldehyde groups.[10] Little attention was given to α-oxo aldehydes despite the numerous applications of glyoxylyl group in the peptide field.[13–17] Recent results demonstrating the good stability of the α-oxo semicarbazone bond toward hydrolysis and the utility of the glyoxylyl group in either the synthesis of peptide–ODN conjugates,[11] or the preparation of ODN microarrays[18] should stimulate the use of this ligation chemistry.

To date, α-oxo aldehyde–ODNs were prepared in solution by oxidative cleavage of tartaramide[11] or seryl[19] deprotected precursors with periodate. However, these valuable two-step procedures are not ideally suited for the parallel synthesis of α-oxo aldehyde–ODNs as is usually required for ODN microarray projects. In addition, the use of periodate in the final step may be harmful to moieties sensitive to oxidants such as thiol or biotin as already documented in the peptide field.[20] Thus, the preparation of a phosphoramidite that could generate the α-oxo aldehyde group during the final basic treatment used for the deprotection of the ODN should simplify the synthesis of COCHO–ODNs and stimulate their use for the preparation of bioconjugates.

2. Results and discussion

We report in this article the synthesis of a novel phosphoramidite derivative[21,22] incorporating a bis[2-(*tert*-butyldisulfanyl)ethoxycarbonylamino]acetyl group as a masked α-oxo aldehyde functionality. This phosphoramidite was coupled to the 5′-terminus of CPG supported oligodeoxynucleotides using standard protocols. Unmasking of the COCHO group and cleavage/deprotection of the ODN could be realized in one step using mild and non-oxidative experimental conditions.

Recently, bis-(9*H*-fluoren-9-ylmethoxycarbonylamino)-acetic acid had been prepared in one step from glyoxylic acid and introduced into the peptide chain after solid-phase peptide elongation. Deprotection and cleavage of the

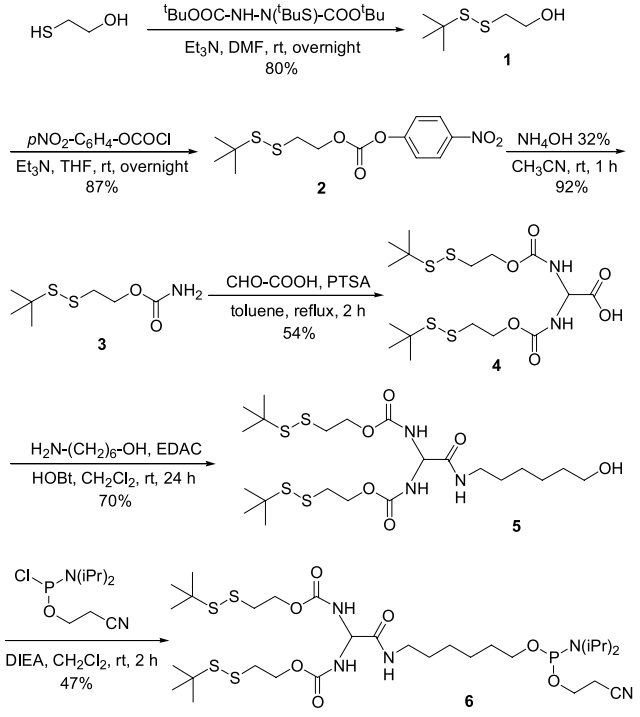
Keywords: Alpha-oxo aldehyde; Oligodeoxynucleotide; Phosphoramidite; DTT.
* Corresponding author. Tel.: +33 320871214; fax: +33 320871235; e-mail: oleg.melnyk@ibl.fr

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.03.144

peptide from the solid support using trifluoroacetic acid was followed by unmasking of the glyoxylyl group in the presence of a base.[23,24] Replacement of Fmoc groups by 2-(*tert*-butyldisulfanyl)ethoxycarbonyl groups led to a novel derivative that could be cleanly deprotected in the presence of a phosphine.[25] The *tert*-butyldisulfanyl moiety was already used in the context of solid phase phosphoramidite chemistry,[26,27] thus the utility of the bis[2-(*tert*-butyldisulfanyl)ethoxycarbonylamino]acetyl group as a way to introduce a masked glyoxylyl group during solid phase ODN synthesis on CPG support was examined.

The synthesis of phosphoramidite **6** is depicted in Scheme 1. In a first step, *tert*-butylsulfenyl group was introduced on 2-mercaptoethanol using di-*tert*-butyl 1-(*tert*-butylthio)-1,2-hydrazine dicarboxylate[28] to afford disulfide **1** in 80% yield. This latter was converted to carbamate **3** by reaction with *p*-nitrophenyl chloroformate and ammonia successively. Reaction of solid glyoxylic acid hydrate with 2 equiv of carbamate **3** in refluxing toluene and in the presence of a catalytic amount of *p*-toluenesulfonic acid afforded bis-[2-(*tert*-butyldisulfanyl)ethoxycarbonylamino] acetic acid **4** in 54% yield following purification by silica gel chromatography. Acid **4** was then coupled to 6-aminohexan-1-ol using *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride/HOBt activation. Phosphitylation of the resulting alcohol **5** using 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite afforded the desired phosphoramidite **6** in 47% yield. ^{1}H, ^{13}C, ^{31}P NMR and high-resolution mass spectrometry confirmed the identity of phosphoramidite **6**.

Next, the coupling of phosphoramidite **6** to the 5′-end of the 5′-dT$_7$-3′-CPG solid support[29] was examined (Fig. 1). This supported ODN was obtained by coupling 6 times β-cyanoethyl phosphoramidite DMT-dT to DMT-dT-CPG



Scheme 1. Synthesis of phosphoramidite **6**.

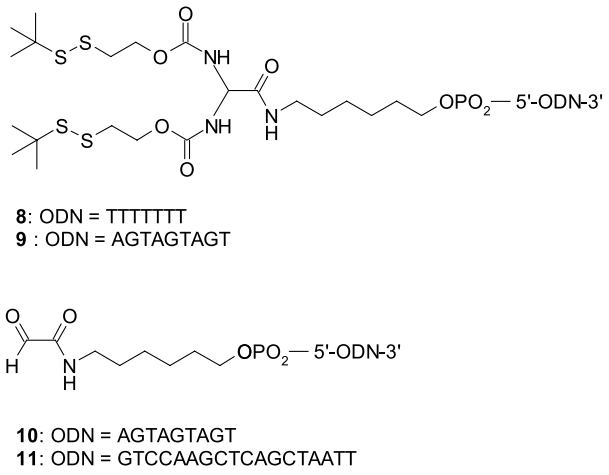


Figure 1. 5′-Modified ODNs synthesized in this study.

support. The coupling of **6** was performed using a 0.5 M solution in acetonitrile (10 min, twice). After the coupling, the formed phosphite group was oxidized into phosphate diester moiety using iodine in acetonitrile as for standard ODN synthesis. The product was separated from the CPG support with 32% aqueous NH_4OH at rt during 1 h and analyzed by RP-HPLC. The retention time of ODN **8** (Fig. 2, 16.35 min) was significantly higher than those of unmodified ODN **7** (9.10 min) as the result of the presence of two *tert*-butylsulfanyl moieties on the molecule. The structure of ODN **8** was confirmed by MALDI-TOF mass spectrometry (ODN **8**: *m*/*z* $[M-H]^-$ Calcd 2700.52, found 2700.91).

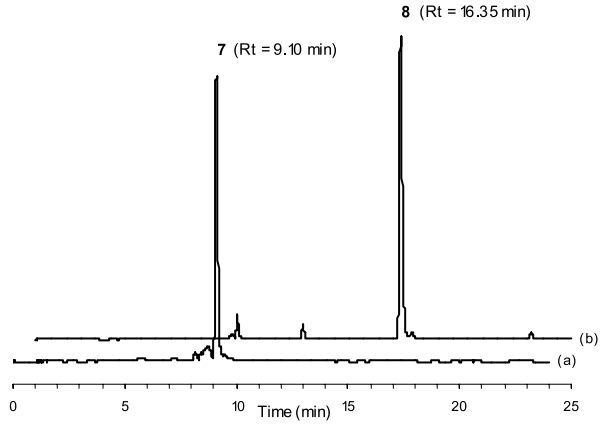


Figure 2. RP-HPLC traces of (a) crude trityl off ODN **7** (retention time: 9.10 min) and (b) crude ODN **8** (retention time: 16.35 min). C18 nucleosil column (4.6×250 mm), eluent A: 10 mM TEAA, eluent B: CH_3CN; linear gradient 5–50% B in 20 min, 1 mL/min, detection at 260 nm.

These results show the stability of the bis[2-(*tert*-butyldisulfanyl)ethoxycarbonylamino]acetyl group in the presence of iodine (oxidation step), the efficiency of the coupling reaction and the stability of the masked aldehyde moiety toward concentrated ammonia at room temperature.

Next, synthesis of glyoxylyl ODN **10** was examined using mild deprotection conditions (0.4 M NaOH in MeOH/H_2O

4/1 by vol at rt for 17 h).[30,31] RP-HPLC analysis of the crude desalted product revealed a single peak. However, the MALDI-TOF spectrum of the product displayed a peak at *m/z* 3262.45 (negative ion mode) which did not correspond to the calculated *m/z* ratio for ODN **10** nor **9**. The loss of 148.22 mass units relative to **9** ($[M-H]^-$: *m/z* Calcd 3410.67) was suspected to be due to an instability of the *tert*-butylsulfanyl groups in the presence of NaOH/MeOH. Model ODN **8** obtained by coupling phosphoramidite **6** to 5′-dT$_7$-3′-CPG led to similar results. Thus, simultaneous reduction of the disulfide bonds and deprotection of the ODN was attempted. Addition of an excess of DTT to the mild deprotection mixture led successfully to the desired ODN **10** (MALDI-TOF $[M-H]^-$: *m/z* Calcd 3010.57, found 3010.65). The usefulness of this procedure was confirmed with compound **11** using acetyl-protected dC for solid phase ODN synthesis (Fig. 3).

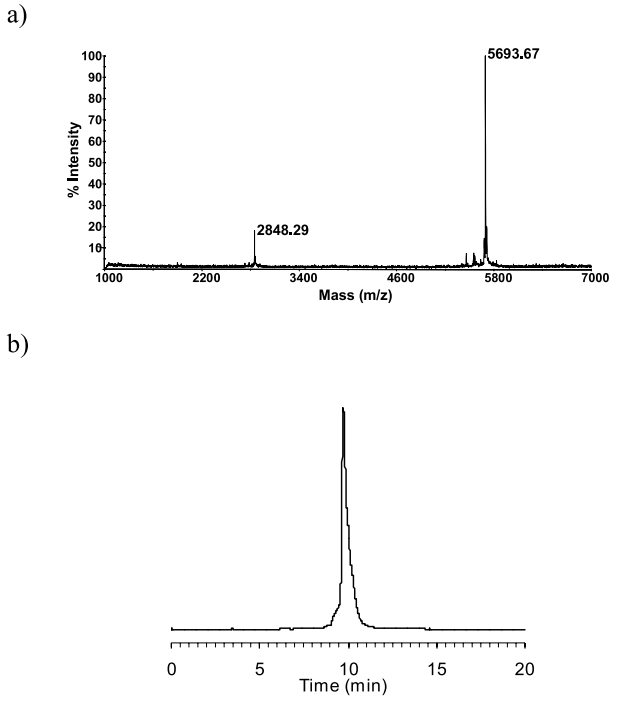


Figure 3. (a) MALDI-TOF spectrum of ODN **11**. Positive ion mode, 3-hydroxypicolinic acid was used as matrix; $[M+H]^+$: *m/z* Calcd 5693.02, found 5693.67; (b) RP-HPLC trace of ODN **12** purified on a C18 Sep-Pak cartridge. C18 nucleosil column (4.6×250 mm), eluent A: 10 mM TEAA, eluent B: CH_3CN; linear gradient 5–50% B in 20 min, 1 mL/min, detection at 260 nm.

In conclusion, we describe in this article that a phosphoramidite derivatized by a bis[2-(*tert*-butyldisulfanyl)ethoxycarbonylamino]acetyl moiety allows the introduction of a glyoxylyl group at the 5′-end of ODNs. The phosphoramidite was coupled using standard protocols. The bis[2-(*tert*-butyldisulfanyl)ethoxycarbonylamino]acetyl moiety was found to be stable in the presence of iodine. Clean unmasking of the α-oxo aldehyde group and deprotection of the ODN chain (acetyl protection for dC) was performed simultaneously using NaOH/MeOH in the presence of an excess of DTT.

3. Experimental

3.1. General

All commercially available chemical reagents were used without purification. Reactions were monitored by thin layer chromatography (TLC) on silica gel sheets containing UV fluorescent indicator (Macherey Nagel).

3.2. Experimental procedures

NMR spectra were recorded on a Bruker DRX 300 spectrometer at 300 MHz for ^{1}H NMR, 75 MHz for ^{13}C NMR and 121 MHz for ^{31}P NMR. Chemical shifts were reported in ppm and tetramethylsilane (TMS) was used as an internal reference. MALDI-TOF spectra were recorded on a PerSeptive Biosystems Voyager-DE STR spectrometer, using either 3-hydroxypicolinic acid (3-HPA) or 6-aza-2-thiothymine (ATT) matrices, in positive or negative ion mode, respectively. IR spectra were recorded on a Perkin–Elmer Spectrum 1000 FT-IR spectrometer. Melting points were taken on a Büchi 530 apparatus in open capillary tubes and are uncorrected. RP-HPLC analyses were performed on a Shimadzu LC10-A, using a C18 Nucleosil column (4.6×250 mm) and the following conditions: eluent A: 10 mM TEAA, eluent B: acetonitrile; linear gradient 5–50% B in 20 min, 1 mL/min, detection at 260 nm. Automated oligonucleotide syntheses were performed on an Applied Biosystems 392 synthesizer. CPG columns were purchased from Applied Biosystems (France). β-Cyanoethyl-protected phosphoramidites Bz-dC, Bz-dA, iBu-dG and dT were purchased from Proligo (Germany) and Ac-dC from Eurogentec (France). All automated oligonucleotide synthesis reagents were purchased from Proligo (Germany), except anhydrous acetonitrile, from VWR (France).

3.2.1. 2-(*tert*-Butyldisulfanyl)ethanol 1. To a stirred solution of di-*tert*-butyl 1-(*tert*-butylthio)-1,2-hydrazinedicarboxylate (12.5 g, 39 mmol) and triethylamine (4.53 mL, 32.5 mmol) in DMF (150 mL) was added dropwise 2.28 mL (32.5 mmol) of 2-mercaptoethanol under argon. After stirring overnight at room temperature, the reaction mixture was evaporated to dryness. Petroleum ether was added to the resulting oily residue under vigorous stirring. The white solid that precipitates was eliminated by filtration and the filtrate was evaporated in vacuo. The residue was purified by chromatography on silica gel (CH_2Cl_2/AcOEt: 9/1). The pure compound **1** was obtained as a pale yellow oil (4.32 g, 26 mmol) in 80% yield. IR (NaCl) ν (cm^{-1}) 3350 (OH), 2960 (CH), 1046 (C–O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 9H, $3CH_3$), 2.09 (t, 1H, OH), 2.86 (t, 2H, J=6.0 Hz, CH_2–S), 3.87 (t, 2H, J=6.0 Hz, CH_2–O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.9 (CH_3), 42.7 (CH_2–S), 48.0 (C–$(CH_3)_3$), 60.7 (CH_2–O); MS (CI, NH_3) *m/z* 184 $[M+NH_4]^+$; HRMS (CI, NH_3) *m/z* Calcd for $[M+NH_4]^+$ $C_6H_{18}NOS_2$ 184.0830, found 184.0826.

3.2.2. 2-(*tert*-Butyldisulfanyl)ethyl 4-nitrophenyl carbonate 2. Compound **1** (4.0 g, 24 mmol) and 4-nitrophenyl chloroformate (7.26 g, 36 mmol) were dissolved in anhydrous THF (50 mL) under argon and the mixture was cooled to 0 °C. Triethylamine (5.02 mL, 36 mmol) was added

dropwise to the stirred solution. The reaction mixture was stirred at 0 °C for 10 min then at rt overnight. The solution was filtered and the filtrate was evaporated in vacuo to give a yellow oil which was purified by chromatography on silica gel (cyclohexane/AcOEt: 9/1). The pure compound **2** was obtained as a clear oil (6.96 g, 21 mmol) in 87% yield. IR (NaCl) ν (cm^{-1}) 3085 (CH Ar), 2962 (CH), 1769 (C=O), 1617 (C=C Ar), 1526 (NO_2), 1347 (NO_2), 1215 (C–N), 1165 (C–O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 9H, $3CH_3$), 3.01 (t, 2H, J=6.8 Hz, CH_2–S), 4.52 (t, 2H, J=6.8 Hz, CH_2–O), 7.39 (d, 2H,, J=9.2 Hz, 2CH Ph), 8.27 (d, 2H, J=9.2 Hz, 2CH Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.8 (CH_3), 37.9 (CH_2–S), 48.2 (*C*–$(CH_3)_3$), 67.3 (CH_2–O), 121.8 (CH Ar), 125.3 (CH Ar), 145.5 (C Ar), 152.7 (CO), 155.9 (C Ar); MS (CI, NH_3) *m/z* 349 $[M+NH_4]^+$; HRMS (CI, NH_3) *m/z* Calcd for $[M+NH_4]^+$ $C_{13}H_{21}N_2O_5S_2$ 349.0892, found 349.0888. Anal. Calcd for $C_{13}H_{17}NO_5S_2$: C, 47.11; H, 5.17; N, 4.23; S, 19.35. Found: C, 47.01; H, 5.37; N, 4.33; S, 19.07.

3.2.3. 2-(*tert*-Butyldisulfanyl)ethyl carbamate 3. To a suspension of compound **2** (6.5 g, 19.6 mmol) in acetonitrile (80 mL) was added dropwise 32% aqueous ammonia solution (16 mL) under stirring. The reaction mixture was stirred at room temperature for 1 h. Ethyl acetate (800 mL) was added to the reaction mixture and the resulting solution was washed with water (5×400 mL) and saturated NaCl (200 mL). The organic layer was dried on $MgSO_4$ and evaporated in vacuo. After drying on P_2O_5 under reduced pressure, carbamate **3** (3.77 g, 18 mmol) was obtained as a white solid in 92% yield. Mp 80–82 °C; IR (KBr) ν (cm^{-1}) 3402 (NH_2), 2957 (CH), 1682 (C=O), 1168 (C–O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 9H, $3CH_3$), 2.91 (t, 2H, J=6.6 Hz, CH_2–S), 4.30 (t, 2H, J=6.6 Hz, CH_2–O), 4.73 (br, 2H, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.8 (CH_3), 38.9 (CH_2–S), 47.9 (*C*–$(CH_3)_3$), 63.3 (CH_2–O), 156.5 (CO); MS (CI, NH_3) *m/z* 227 $[M+NH_4]^+$; HRMS (CI, NH_3) *m/z* Calcd for $[M+NH_4]^+$ $C_7H_{19}N_2O_2S_2$ 227.0888, found 227.0890. Anal. Calcd for $C_7H_{15}NO_2S_2$: C, 40.17; H, 7.22; N, 6.69; S, 30.63. Found: C, 39.89; H, 7.36; N, 6.71; S, 31.18.

3.2.4. Bis[2-(*tert*-butyldisulfanyl)ethoxycarbonylamino]acetic acid 4. Carbamate **3** (3.5 g, 16.7 mmol), glyoxylic acid monohydrate (0.77 g, 8.35 mmol) and PTSA (15.8 mg, 83 μmol) were dissolved in toluene (500 mL) and refluxed for 2 h (Dean-Stark trap). The reaction mixture was cooled to rt and allowed to precipitate overnight. The resulting precipitate was filtered and washed with toluene. The crude product was purified by silica gel chromatography ($CHCl_3$/MeOH/AcOH: 36/1/0.5). The product was concentrated, co-evaporated three time with toluene and dried in vacuo on P_2O_5. Compound **4** (2.14 g, 4.51 mmol) was obtained as a white solid in 54% yield. Mp 112–114 °C; IR (KBr) ν (cm^{-1}) 3313 (OH), 2961 (CH), 1731 (C=O), 1690 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 18H, $6CH_3$), 2.90 (t, 4H, J=6.7 Hz, $2CH_2$–S), 4.07 (br, 2H, 2NH), 4.32 (t, 4H, J=6.7 Hz, $2CH_2$–O), 5.42 (t, 1H, J=7.0 Hz, C*H*–COOH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.2 (CH_3), 39.0 (CH_2–S), 48.4 (*C*–$(CH_3)_3$), 60.2 (*C*H–COOH), 64.4 (CH_2–O), 156.2 (OCO–NH), 170.3 (COOH); MS (FAB) *m/z* 497.1 $[M+Na]^+$; HRMS (FAB) *m/z* Calcd for $[M+Na]^+$ $C_{16}H_{30}N_2O_6S_4Na$ 497.0884, found 497.0881. Anal. Calcd for $C_{16}H_{30}N_2O_6S_4$: C, 40.49; H, 6.37; N, 5.90; S, 27.02. Found: C, 40.41; H, 6.48; N, 6.00; S, 26.79.

3.2.5. Compound 5. A mixture of compound **4** (2.0 g, 4.21 mmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (1.21 g, 6.31 mmol) and HOBt (0.852 g, 6.31 mmol) was dissolved in CH_2Cl_2 (100 mL) under argon. 6-Aminohexan-1-ol (0.739 g, 6.31 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was evaporated to dryness and the crude residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH: 95/5). The pure compound **5** was obtained as a white solid (1.69 g, 2.95 mmol) in 70% yield. Mp 93–95 °C; IR (KBr) ν (cm^{-1}) 3294 (OH), 2938 (CH), 1714 (C=O), 1651 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.20–1.40 (m, 22H, $6CH_3$+$2CH_2$ alkyl chain), 1.47 (m, 4H, $2CH_2$ alkyl chain), 1.60 (br, 1H, OH), 2.83 (t, 4H, J=6.6 Hz, $2CH_2$–S), 3.21 (m, 2H, CH_2 alkyl chain), 3.57 (m, 2H, CH_2 alkyl chain), 4.26 (t, 4H, J=6.6 Hz, $2CH_2$–OCO), 5.43 (t, 1H, J=7.0 Hz, C*H*–CONH), 5.96 (br, 2H, 2NH), 6.70 (br, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.6 (CH_2), 26.7 (CH_2), 29.5 (CH_2), 30.2 (CH_3), 32.8 (CH_2), 39.1 (CH_2–S), 40.1 (CH_2), 48.4 (*C*–$(CH_3)_3$), 60.7 (*C*H–CONH), 63.0 (CH_2), 64.1 (CH_2–OCO), 156.0 (OCONH), 167.8 (CONH); MS (FAB) *m/z* 596.2 $[M+Na]^+$; HRMS (FAB) *m/z* Calcd for $[M+Na]^+$ $C_{22}H_{43}N_3O_6S_4Na$ 596.1932, found 596.1935. Anal. Calcd for $C_{22}H_{43}N_3O_6S_4$: C, 46.05; H, 7.55; N, 7.32; S, 22.35. Found: C, 45.97; H, 7.45; N, 7.34; S, 22.40.

3.2.6. Phosphoramidite 6. DIEA (1.82 mL, 10.44 mmol) and 2-cyanoethyl *N,N*-diisopropylchlorophosphoramidite (872 μL, 3.91 mmol) were added to a solution of compound **5** (1.50 g, 2.61 mmol) in freshly distilled CH_2Cl_2 (20 mL) at room temperature under argon. After stirring the mixture for 2 h, methanol (105 μL, 2.61 mmol) was added and the mixture was stirred for an additional 30 min. The reaction mixture was evaporated to dryness and cyclohexane/AcOEt/Et_3N (60/40/2) was added. The resulting precipitate was eliminated by filtration and the filtrate was evaporated in vacuo. The crude product was purified by silica gel chromatography (cyclohexane/AcOEt/Et_3N 60/40/2). The product was concentrated, coevaporated three time with toluene and dried in vacuo. Compound **6** was obtained as a clear viscous oil (0.952 g, 1.23 mmol) in 47% yield. IR (KBr) ν (cm^{-1}) 3293 (NH), 2966 (CH), 2252 (C≡N), 1713 (C=O), 1652 (C=O), 975 (P–O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.05–1.15 (m, $6CH_3$ *i*Pr), 1.20–1.35 (m, 22H, $6CH_3$ ^{t}Bu+$2CH_2$ alkyl chain), 1.51 (m, 4H, $2CH_2$ alkyl chain), 2.57 (t, J=6.4 Hz, C*H*$_2$–CN), 2.83 (t, 4H, J=6.6 Hz, $2CH_2$–S), 3.19 (m, 2H, CH_2 alkyl chain), 3.45–3.65 (m, 4H, 2CH *i*Pr+CH_2 alkyl chain), 3.70–3.85 (m, 2H, C*H*$_2$–CH_2CN), 4.26 (t, 4H, J=6.6 Hz, $2CH_2$–OCO), 5.41 (t, 1H, J=7.0 Hz, C*H*–CONH), 5.86 (br, 2H, 2NH), 6.55 (br, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 20.7–20.8 (*C*H_2–CN), 25.0–25.1 (CH_3 *i*Pr), 26.0 (CH_2), 26.9 (CH_2), 29.6 (CH_2), 30.2 (CH_3 ^{t}Bu), 31.4–31.5 (CH_2), 39.1 (CH_2–S), 40.3 (CH_2), 43.3–43.4 (CH *i*Pr), 48.4 (*C*–$(CH_3)_3$), 58.5–58.8 (*C*H_2–CH_2CN), 60.7 (*C*H–CONH), 63.8–64.0 (CH_2), 64.1 (CH_2–OCO), 117.9 (CN), 156.0 (CO), 167.6 (CO); ^{31}P NMR (121 MHz, $CDCl_3$) δ 147.4; MS (FAB) *m/z* 796.3 $[M+Na]^+$; HRMS (FAB) *m/z* Calcd for $[M+Na]^+$ $C_{31}H_{60}N_5O_7PS_4Na$ 796.3011, found 796.3019.

3.3. Typical experimental procedure, synthesis of ODN 11

The 5′-modified oligonucleotides were assembled on an Applied Biosystems 392 synthesizer in 1.0 μmol scales, using the standard phosphoramidite protocol. Bz-dA, iBu-dG and Ac-dC β-cyanoethyl-5′-DMT protected phosphoramidites were used. Phosphoramidite **6** was introduced at the last cycle using an extended coupling time with a double delivery (2×10 min) and a phosphoramidite concentration of 0.5 M. Simultaneous cleavage/deprotection of the 5′-modified oligonucleotide and unmasking of the α-oxo aldehyde function was performed by treating the solid support with 0.4 M NaOH in MeOH/H_2O (4/1 by vol, 1 mL) containing DTT (100 equiv) at room temperature for 17 h, using the double syringe method. The mixture was then transferred on a flask and 1.5 mL of 2 M TEAA was added. The methanol was eliminated from the mixture by evaporation on a rotary evaporator and the product was desalted on a NAP-5 column (Sephadex G25, Amersham Biosciences), and then purified on a C18 Sep-Pak cartridge (Waters). Overall yield 29% (determined by UV at 260 nm).

Acknowledgements

We gratefully acknowledge le Ministère de l'Economie, des Finances et de l'Industrie (GenHomme, Coquepuce Project), CNRS, Université de Lille 2 and Institut Pasteur de Lille for financial support. We thank Gérard Montagne for NMR experiments and Anthony Romieu, David Hot, Ludovic Huot and Yves Lemoine for useful discussions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at 10.1016/j.tet.2005.03.144

References and notes

1. Tung, C. H. *Bioconjugate Chem.* **2000**, *11*, 605–618.
2. (a) Schena, M.; Shalon, D.; Davis, R. W.; Brown, P. O. *Science* **1995**, *270*, 467–470. (b) Zammatteo, N.; Jeanmart, L.; Hamels, S.; Courtois, S.; Louette, P.; Hevesi, L.; Remacle, J. *Anal. Biochem.* **2000**, *280*, 143–150. (c) Debouck, C.; Goodfellow, P. N. *Nat. Genet.* **1999**, *21*, 48–50.
3. (a) Zatsepin, T. S.; Romanova, E. A.; Stetsenko, D. A.; Gait, M. J.; Oretskaya, T. S. *Nucleosides, Nucleotides Nucleic Acids* **2003**, *22*, 1383–1385. (b) Zatsepin, T. S.; Stetsenko, D. A.; Arzumanov, A. A.; Romanova, E. A.; Gait, M. J.; Oretskaya, T. S. *Bioconjugate Chem.* **2002**, *13*, 822–830.
4. Kozlov, I. A.; Melnyk, P. C.; Stromsborg, K. E.; Chee, M. S.; Barker, D. L.; Zhao, C. *Biopolymers* **2004**, *73*, 621–630.
5. (a) Edupuganti, O. P.; Defrancq, E.; Dumy, P. *J. Org. Chem.* **2003**, *68*, 8708–8710. (b) Forget, D.; Boturyn, D.; Defrancq, E.; Lhomme, J.; Dumy, P. *Chem. Eur. J.* **2001**, *7*, 3970–3984.
6. Edupuganti, O. P.; Renaudet, O.; Defrancq, E.; Dumy, P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2839–2842.
7. Zubin, E. M.; Stetsenko, D. A.; Oretskaya, T. S.; Gait, M. J. *Nucleosides, Nucleotides Nucleic Acids* **2003**, *22*, 1375–1378.
8. Kachalova, A. V.; Stetsenko, D. A.; Gait, M. J.; Oretskaya, T. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 801–804.
9. Skrzypczynski, Z.; Wayland, S. *Bioconjugate Chem.* **2003**, *14*, 642–652.
10. Urata, H.; Akagi, M. *Tetrahedron Lett.* **1993**, *34*, 4015–4018.
11. Ollivier, N.; Olivier, C.; Gouyette, C.; Huynh-Dinh, T.; Gras-Masse, H.; Melnyk, O. *Tetrahedron Lett.* **2002**, *43*, 997–999.
12. Podyminogin, M. A.; Lukhtanov, E. A.; Reed, M. *Nucleic Acids Res.* **2001**, *29*, 5090–5098.
13. (a) Dixon, H. B. F.; Fields, R.; Methods in Enzymology; Academic: New York, 1972; Vol. 25. (b) Dixon, H. B. F.; Weitkamp, L. R. *Biochem. J.* **1962**, *84*, 462–468.
14. (a) Shao, J.; Tam, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 3893–3899. (b) Rao, C.; Tam, J. P. *J. Am. Chem. Soc.* **1994**, *116*, 6975–6976. (c) Tam, J. P.; Spetzler, J. C. *Current Protocols in Protein Science*; Wiley: New York, 1999; pp 18.5.1–18.5.35.
15. (a) Qasmi, D.; de Rosny, E.; René, L.; Badet, B.; Vergely, I.; Boggetto, N.; Reboud-Ravaux, M. *Bioorg. Med. Chem.* **1997**, *5*, 707–714. (b) Qasmi, D.; René, L.; Badet, B. *Tetrahedron Lett.* **1994**, *35*, 4343–4344.
16. For a review see: Melnyk, O.; Fehrentz, J. A.; Martinez, J.; Gras-Masse, H. *Biopolymers* **2000**, *55*, 165–186.
17. (a) Fruchart, J. S.; Gras-Masse, H.; Melnyk, O. *Tetrahedron Lett.* **1999**, *40*, 6225–6228. (b) Melnyk, O.; Fruchart, J.-S.; Grandjean, C.; Gras-Masse, H. *J. Org. Chem.* **2001**, *66*, 4153–4160.
18. (a) Olivier, C.; Hot, D.; Huot, L.; Ollivier, N.; El-Mahdi, O.; Gouyette, C.; Huynh-Dinh, T.; Gras-Masse, H.; Lemoine, Y.; Melnyk, O. *Bioconjugate Chem.* **2003**, *14*, 430–439. In this article, the stability of α-oxo and benzaldehyde semicarbazones toward hydrolysis was compared. The α-oxo semicarbazone was found to be stable 24 h in HEPES buffer at 65 °C and at different pHs (7.1–8.0), whereas 40% of hydrolysis was observed for the benzaldehyde semicarbazone using the same experimental conditions (see Ref. 12). (b) Hot, D.; Olivier, C.; Ollivier, N.; Huot, L.; Gouyette, C.; Lemoine, Y.; Melnyk, O. *Curr. Protoc. Nucleic Acid Chem.* **2004**, 12.6.1–12.6.19.
19. Singh, Y.; Defrancq, E.; Dumy, P. *J. Org. Chem.* **2004**, *69*, 8544–8546.
20. Geoghegan, K. F.; Stroh, J. G. *Bioconjugate Chem.* **1992**, *3*, 138–146.
21. Beaucage, S. L.; Iyer, R. P. *Tetrahedron* **1992**, *48*, 2223–2311.
22. Beaucage, S. L.; Iyer, R. P. *Tetrahedron* **1993**, *49*, 1925–1963.
23. Far, S.; Melnyk, O. *Tetrahedron Lett.* **2004**, *45*, 1271–1273.
24. Far, S.; Melnyk, O. *J. Pept. Sci.* **2004**, published on line 10 January 2005.
25. Far, S.; Melnyk, O. *Tetrahedron Lett.* **2004**, *45*, 7163–7165.
26. Goodwin, J. T.; Glick, G. D. *Tetrahedron Lett.* **1993**, *34*, 5549–5552.
27. Gundlach, C. W.; Ryder, T. R.; Glick, G. D. *Tetrahedron Lett.* **1997**, *38*, 4039–4042.
28. Wünsch, E.; Moroder, L.; Romani, S.; Hoppe-Seyler's, Z. *Physiol. Chem.* **1982**, *363*, 1461–1464.
29. Gait, M. J. In *Oligonucleotide Synthesis: a Practical Approach*; Gait, M. J., Ed.; IRL: Oxford, 1984; pp 1–22.
30. Köster, H.; Kulikowski, K.; Liese, T.; Heikens, W. *Tetrahedron* **1981**, *37*, 363–369.
31. The bis[2-(*tert*2-butyldisulfanyl)ethoxycarbonylamino] acetyl moiety was found to be unstable in AMA mixture at rt (40% aqueous methylamine/32% aqueous ammonia, 1/1 by vol, see Reddy, M. P.; Hanna, N. B.; Farooqui, F. *Tetrahedron Lett.* **1994**, *35*, 4311–4314) and in 32% NH_4OH at 55 °C.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 61 (2005) 6143–6153

2,2,6,6-Tetramethylcyclohexanethione *S*-methylide, a highly hindered thiocarbonyl ylide: two-step cycloadditions☆

Rolf Huisgen,* Henry Giera† and Kurt Polborn

Department Chemie und Biochemie der Ludwig-Maximilians-Universität München, Butenandtstr. 5-13, D-81377 München, Germany

Received 13 January 2005; revised 15 February 2005; accepted 22 February 2005

Available online 17 May 2005

Dedicated to Johann Mulzer, University of Vienna, on the occasion of his 60th birthday

Abstract—The switching from the concerted 1,3-dipolar cycloaddition to a two-step pathway via zwitterionic intermediates requires a major energy difference between HOMO–LUMO energies of 1,3-dipole and dipolarophile, as well as sterically demanding reactants. In contrast to previously studied models, the title compound **1C**, a thiocarbonyl ylide prepared by N_2 extrusion from dihydrothiadiazole **7C** at 80 °C, combined with 2,3-bis(trifluoromethyl)fumaronitrile (**11**) to give a zwitterion (*gauche*-**10**); the latter failed to close the thiolane ring by 1,5-cyclization, but formed the seven-membered ketene imine **9C** by 1,7-cyclization. X-ray analysis of **9C** revealed an angle-deformed cumulated bond system and a *transoid* relation of the CF_3 groups. The relatively stable **9C** allowed ^{19}F NMR recordings from −90 to +90 °C; temperature-dependent line broadening resulted from equilibration with ≤1% of an unknown isomer. Among various possible angle-strained rate processes, an inversion *transoid* **19** ⇌ *cisoid* **20** is preferred which involves a topomerization at the C=N bond; lateral inversion and rotation are discussed. At 80 °C in solution, ketene imine **9C** slowly suffered fragmentation to give *trans*- and *cis*-1,2-bis(trifluoromethyl)cyclopropane-1,2-dicarbonitrile (**13**) + thioketone **6C** by intramolecular substitution. The reaction of **1C** with ethenetetracarbonitrile furnished a tetracyanothiolane **3C**, whereas **1C** and dimethyl 2,3-dicyanofumarate ((*E*)-**26**) afforded thiolanes of the same *trans*,*cis*-ratio as **1C** with dimethyl 2,3-dicyanomaleate ((*Z*)-**26**); a preceding (*E*,*Z*)-equilibration of **26** thwarts mechanistic conclusions. When the solvent contained water or methanol, short-lived ketene imines **4C** and **31** were intercepted.

1. Introduction

Like the related Diels–Alder reactions,[3] 1,3-dipolar cycloadditions can be achieved by several mechanistic pathways.[4] The wide-spread 'normal' type fulfils the expectations for the concerted course.[5] When highly nucleophilic thiocarbonyl ylides **1** were reacted with ethenetetracarbonitrile (TCNE)[6] or benzylidenemalononitrile,[7] competing 1,5- and 1,7-cyclizations—the latter involving a nitrile group—revealed a mechanism via 1,5-zwitterionic intermediates. Due to rotation in the zwitterion, (*E*,*Z*)-isomeric dipolarophiles, like dimethyl 2,3-dicyanofumarate and dimethyl 2,3-dicyanomaleate, did not retain their configuration during the cycloaddition.[8,9] A second structural requirement must be fulfilled for the two-step pathway to occur: steric hindrance at least at one terminus of the thiocarbonyl ylide **1**. Voluminous substituents are likely to raise the activation barrier of the concerted cycloaddition; to a far lesser degree they impede formation of a zwitterionic intermediate.

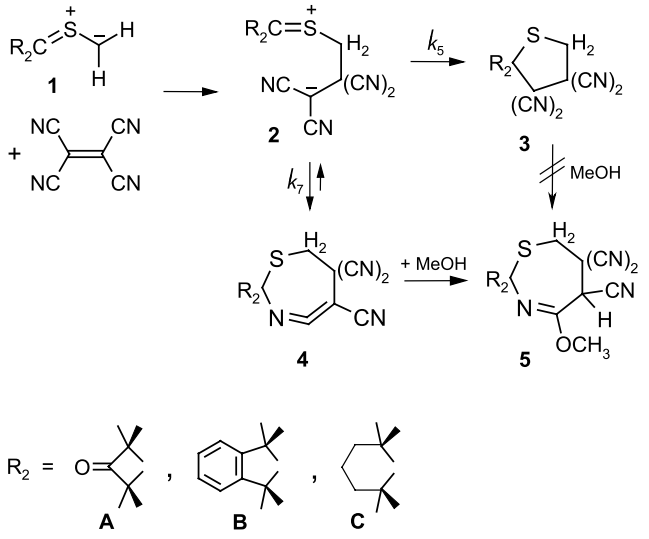
In the reaction of 2,2,4,4-tetramethyl-3-thioxocyclobutanone *S*-methylide (**1A**) with TCNE, the zwitterion **2A** provided thiolane **3A** and the seven-membered cyclic ketene imine **4A** in the ratio 35:65. The strained **4A** was neither isolable nor detectable by IR or ^1H NMR spectroscopy, but was in situ intercepted by methanol to give **5A** when the solvent THF contained 1.2 equiv of methanol. If not captured, **4A** returns to the zwitterion and is again distributed by k_5 and k_7, until all the material arrives at the favored thiolane **3A** (Scheme 1).[6] A recent quantum-chemical calculation (B3LYP/6-31G*) of TSs and intermediates by Domingo and Picher[10] fully confirmed the experimentally established reaction course.

When TCNE was replaced by 2,3-bis(trifluoromethyl)-fumaronitrile (**11**), the reactions with thiocarbonyl ylides **1A** and **1B** furnished the crystalline spirocyclic imines **9A** and **9B**. They were isolable here despite substantial angle strain (Scheme 2).[11–14]

☆ See Ref. 1.

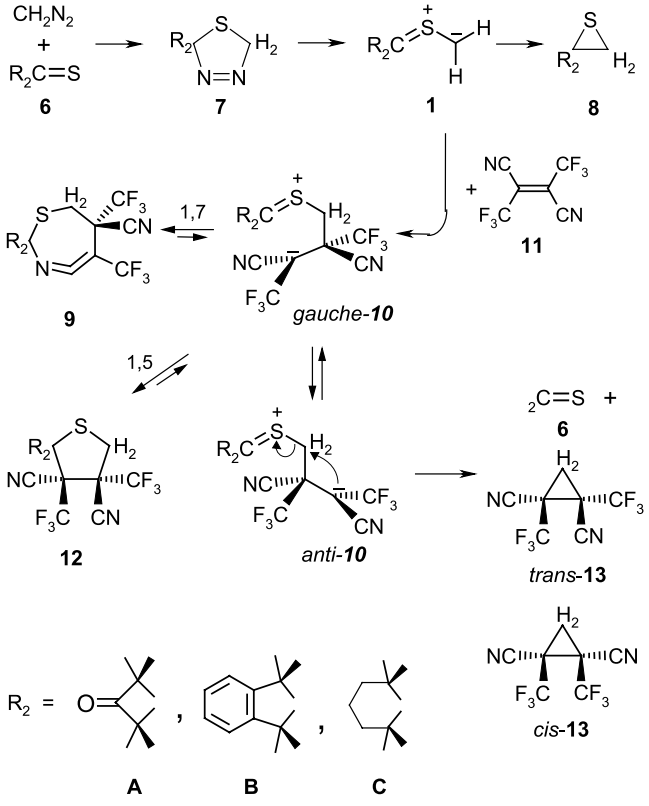
Keywords: 1,3-Dipolar cycloadditions; Thiocarbonyl ylides; Cyclic ketene imines; Dynamic ^{19}F NMR.
* Corresponding author. Tel.: +49 89 2180 77712; fax: +49 89 2180 77717; e-mail: rolf.huisgen@cup.uni-muenchen.de
† Present address: Fachhochschule München, Fachbereich 05, Lothstr. 34, D-80334 München, Germany.

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.02.062



Scheme 1.

In the four-membered cyclobutanone ring of **1A**, the pairs of *gem*-dimethyl groups are bent back as a result of bond angles. This phenomenon reduces the hindrance at the *tertiary* terminal of the 1,3-dipole, an effect that disappears in the five- and six-membered ring of thiocarbonyl ylides **1B** and **1C**. Our expectation of increasing steric hindrance in the sequence **1A**<**1B**<**1C** found support in the experiments described in this paper. In particular, the top member, 2,2,6,6-tetramethylcyclohexanethione *S*-methylide (**1C**), revealed noteworthy changes in reactivity, and the relatively stable spiroketene imine **9C** allowed to study NMR phenomena over a range of 180 °C.



Scheme 2.

2. Results and discussion

2.1. Preparation and properties of the cyclic ketene imine 9C

Thiocarbonyl ylide **1C** was conveniently accessible by the cycloaddition of diazomethane to thioketone **6C** and thermolysis of the isolated 2,5-dihydrospiro-1,3,4-thiadiazole **7C** (Scheme 2).[2] The N_2 extrusion from **7C** proceeded with a half-life of 15.6 min in xylene at 100 °C, that is, substantially slower than that of the tetramethylindan derivative **7B**.[15] This is probably a consequence of further weakening of the allylanionic resonance in **1C**. Recent calculations ((U)B3LYP/6-31G*) of related examples by Sustmann et al. showed that the local C_s of the thiocarbonyl ylide is preserved with a widened angle C–S–C reflecting the strain.[16] The elusive **1C** underwent complete electrocyclization to thiirane **8C** if not intercepted in situ by an electron-deficient dipolarophile.

When **7C** was refluxed in benzene for 15 h in the presence of 1.1 equiv of 2,3-bis(trifluoromethyl)fumaronitrile (**11**), the crystalline spirocyclic ketene imine **9C**, a pale-yellow substance, was isolated. The N_2 elimination from **7C** and the subsequent fragmentation of **9C**, affording 1,2-bis(trifluoromethyl)cyclopropane-1,2-dicarbonitrile (**13**, *trans*/*cis*=95:5) and thioketone **6C**, were monitored by ^{19}F NMR analysis in the presence of a weight standard. The first-order thermolysis of **7C** is the slow step ($t_{1/2}$=5.1 h, C_6D_6, 80 °C) which was measured via the formation of (**9C**+**13**). The concentration of **9C** rose, went through a shallow maximum (73% after ~15–16 h), and then fell off, as is typical of the intermediate in a kinetic system of two consecutive first-order reactions. An induction period was observed for the formation of the final product **13** (+**6C**). In a separate experiment, the first-order conversion of **9C** to **13** took place with $t_{1/2}$=38.5 h, that is, slower by a factor of 7.5, than its formation from **7C**. By-the-way, the true rate of cycloaddition, **1C**+**11**→**9C**, is rather high, but is kinetically hidden behind the preceding slow N_2 expulsion from **7C**.

In consecutive first order reactions, both time of occurrence and percentage of the maximal concentration of the intermediate are functions of the two rate constants.[17] Applied to our example,

$$\%(\mathbf{9C})_{\max} = 100(k_1/k_2)^{k_2/(k_2-k_1)} = 74 \quad (1)$$

$$t_{\max} = \frac{1}{k_2 - k_1}\ln(k_2/k_1) = 17.1\ \text{h} \quad (2)$$

the agreement with observation is fair when the modest precision of the rate measurements is taken into consideration.

The role of thiolane **12** in Scheme 2 highly depends on the cycloaliphatic residue R_2. Ketene imine **9A** was quantitatively converted to **12A** at 60 °C in a first-order reaction; its rate constant was increased by 10^3 with rising solvent polarity.[12] As for ketene imine **9B**, the reversible formation of **12B** and the irreversible generation of cyclopropane **13**+thione **6B** took place in the ratio of about 4:1 ($CDCl_3$,

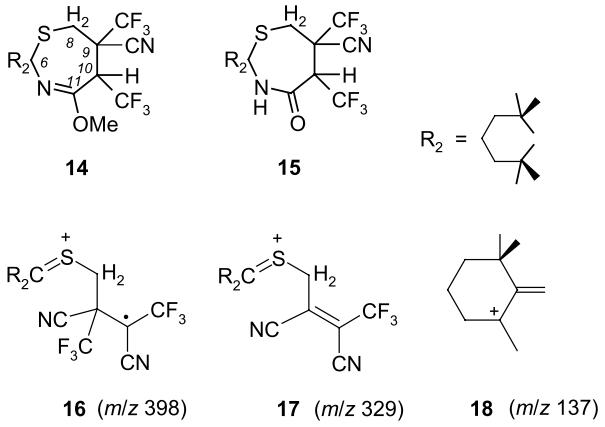
40 °C).[14] Thiolane **12C**, however, was not observed in the thermolysis of **9C** (C_6D_6, 80 °C).

When we invoke the 1,5-zwitterion **10** as short-lived mediator for the reactions of Scheme 2, the increasing steric requirements of R_2 in the sequence **A**<**B**<**C** explain the change in product composition. The *gauche* conformation of **10** is favored by its Coulomb potential over *anti*-**10** in which the distance of charge centers is nearly doubled. The *tert*-carbanion and the N-atom of the nitrile group compete in *gauche*-**10** for reaction with the thiocarbonylium function. The 1,5-cyclization (→**12**) will be more severely hampered than the 1,7-ring closure (→**9**) with growing size of R_2. As a consequence, the tetramethylcyclohexylidenesulfonium ion in *gauche*-**10C** refuses to combine with the *tert*-carbanion, while still allowing for combination with the linear nitrile group.

On the other hand, the high steric demand of R_2 increases the van der Waals strain in *gauche*-**10C**, and diminishes the energetic disadvantage of *anti*-**10C**. The latter offers the structural prerequisites for an intramolecular nucleophilic substitution with thione **6C** as leaving group. Without and with rotation about the former double bond of **11**, *gauche*-**10C** furnishes *trans*-**13** and *cis*-**13** (95:5); the 'forbidden' front-side attack, *gauche*-**10**→**13**+**6**, is avoided, as previously stated.[14]

On addition of methanol or water, ketene imine **9C** followed the pattern of **9A**[11,12] and **9B**.[15] The structures of the lactim ether **14** and the lactam **15** were confirmed by the spectra; the H,F and C,F couplings helped in assigning the NMR signals.

The mass spectra of **9C**, **14**, and **15** show common features, as briefly discussed for **9C** (Scheme 3). The formulation of $\mathbf{9C}^+$ as distonic radical cation **16** (*m*/*z* 398, 5%) suggests that the strain loss now shifts the balance in favor of the open-chain structure. Elimination of CF_3 leads to sulfonium ion **17** (*m*/*z* 329, 17%) which, in turn, could be the precursor of thioketone radical cation $\mathbf{6C}^+$ ($C_{10}H_{18}S^+$, *m*/*z* 170, 31%). It has been reported that the MS of thioketones—those with blocked α-positions included—generally show strong peaks for $[M^+ - SH]$.[18,19] In our example, the base peak $C_{10}H_{17}^+$ (*m*/*z* 137, 100%) results. It can be formulated cyclically (e.g., **18**) or as open-chain dienyl cation. A cascade of $C_nH_{2n-3}^+$ fragments, down to $C_5H_7^+$ (*m*/*z* 67, 18%), was observed, then replaced by the sequence $C_nH_{2n-1}^+$: $C_5H_9^+$ (52%), $C_4H_7^+$ (39%), $C_3H_5^+$ (61%). High resolution secured the molecular formulae; however, the structures are tentative.



Scheme 3.

2.2. Structure and dynamics of cyclic ketene imine 9C

The X-ray structure of ketene imine **9B** was described in 1990; **9B** was the first isolated cumulated bond system ever observed in a seven-membered ring.[13] The stereochemical aspects appeared somewhat improbable, and thus made a second example all the more desirable. The monocrystal diffraction of ketene imine **9C** furnished a structure which is shown in Figure 1 from two perspectives. Bond lengths and angles of the seven-membered ring are rather similar to those of **9B** (Table 1). The bending of the cumulated system to 163.2° (163.8° for **9B**) and the dihedral angle C6–N12⋯C10–C9 (90° in allene) of 57.8° for both **9B** and **9C** demonstrate the ring strain. The conformation of the seven-membered ring resembles a deformed twist-chair (Fig. 1a). The spiro-annellated cyclohexane chair shows local C_s symmetry (Fig. 1b), and the average intracyclic torsion angle (53.9°) exhibits nearly the same flattening as observed for cyclohexane itself (54.9°, gas).[20]

Our cyclic ketene imines share the short C═N bond

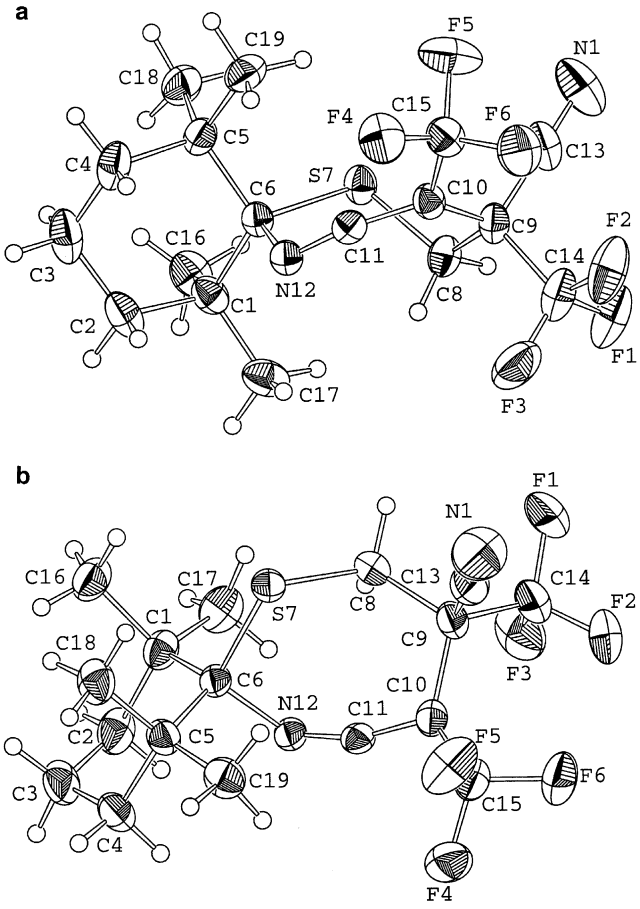


Figure 1. X-ray structure of 1,1,5,5-tetramethyl-9,10-bis(trifluoromethyl)-10,11-didehydro-7-thia-12-azaspiro [5.6]dodecane-9-carbonitrile (**9C**); ZORTEP plot from two perspectives (thermal ellipsoids represent 30% probability).

Table 1. X-ray structure of ketene imine **9C**: selected bond lengths and angles

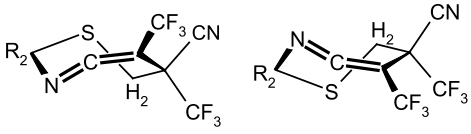
Bond lengths (Å)			
S7–C8	1.812(3)	N12–C6	1.504(3)
C8–C9	1.557(4)	C6–S7	1.877(2)
C9–C10	1.526(4)	C9–CF_3	1.540(5)
C10–C11	1.318(4)	C10–CF_3	1.475(4)
C11–N12	1.201(3)	C1–C6	1.568(4)
Bond angles (°)			
C6–S7–C8	105.1(1)	C10–C11–N2	163.2(3)
S7–C8–C9	115.7(2)	C11–N12–C6	118.5(2)
C8–C9–C10	110.4(2)	N12–C6–S7	105.9(1)
C9–C10–C1	112.5(2)	C11–C10–C15	120.8(2)
Intracyclic torsion angles (°)			
C6–S7	27.2(2)	C10–C11	−0.91(1.0)
S7–C8	−90.3(2)	C11–N12	−61.6(1.0)
C8–C9	54.4(3)	N12–C6	34.4(3)
C9–C10	9.7(3)	(C10–N12)	57.8

(1.195 Å for **9B** and 1.201 Å for **9C**) with open-chain ketene *N*-arylimines,[21–23] which suggests partial nitrilium salt character. If C10 holds a partial anionic charge, a certain pyramidalization would be expected. Indeed, C10 is located by 0.13 Å above the plane defined by C9, C11, C15, and the three angles at C10 add up to 357.8° in **9C**. The ^{13}C chemical shift at the terminus C10 (61.7 ppm in **9B**, 60.6 ppm in **9C**) is also in accordance with a partial ylide character.[24]

An even shorter C═N bond (1.172 Å) was reported for the nine-membered cyclic ketene imine **21** which likewise bears electron-attracting substituents;[25] as expected, the bending of C═C═N (172.2°) is smaller than in **9B** and **9C**.

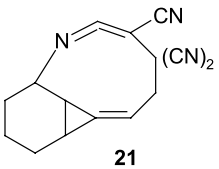
Pivotal in our context is the *transoid* configuration **19** with respect to the CF_3 groups in the crystals of both **9B** and **9C** (Scheme 4). The cumulated bond system is a stereogenic element which—together with the adjacent center of tetrahedral asymmetry—should give rise to a pair of diastereomers, **19** and **20**. At first glance, one set of NMR parameters (^1H, ^{13}C, ^{19}F) is in conformity with one frozen structure in solution. However, the varying sharpness of the two quadruplets in the ^{19}F NMR spectra of **9A**–**9C** rather points to a dynamic phenomenon.

The superior thermal stability of **9C** ($t_{½}$ = 38.5 h in C_6D_6 at 80 °C), compared with **9A**[12] and **9B**,[14] allowed ^{19}F NMR recording (376 MHz) from +90 to −90 °C in [D_8] toluene (Fig. 2). The two CF_3 groups of **9C** couple with $^5J(F,F)$ = 5.8 Hz. The quadruplet at δ −55.3 ° (30 °C), tentatively assigned to the CF_3 group in 10-position, gains in sharpness and height on stepwise raising of the temperature to 90 °C. On cooling, line broadening occurs, and a maximum half-width is passed at about −30 °C; below that temperature, distinct resharpening takes place. The 9-CF_3 signal at −73.2, on the other hand, shows maximal broadening at +30 °C and sharpens on both rise and fall of the temperature. The quadruplet shape of the signal is just discernible at +90 °C, but fully developed at −20 °C.

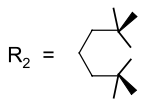


transoid **19**

cisoid **20**



21



Scheme 4.

For the case of equal exchange partners A and B, the Gutowsky–Holm equation relates the rate constant at coalescence temperature (T_c) with the chemical shift difference $|\nu_A-\nu_B|$.[26] Anet and Basus calculated the exchange broadening for very unequal populations (mole fraction $p \ll 1$ for the minor component).[27] The maximal half-width of a Lorentzian line is approximated by (Eq. 3), and the corresponding rate constant by (Eq. 4).

$$\Delta_{1/2}^{\max} = p|\nu_A - \nu_B| \tag{3}$$

$$k = 2\pi|\nu_A - \nu_B| \tag{4}$$

Inserting the latter into the Eyring equation leads to (Eq. 5) for the free energy of activation.

$$\Delta G^{\#} = RT_c\left(23.76 + \ln\frac{T_c}{2\pi|\nu_A - \nu_B|}\right) \tag{5}$$

Since we are dealing with a pair of quadruplets instead of a single line, both line broadenings in Figure 2 refer to the same rate process with $\Delta G^{\#}$. A larger value of $2\pi|\nu_A-\nu_B|$ must be compensated for by a higher T_c (see Eq. 5). At −70 °C (and lower) small signals without fine structure are visible in Figure 2: one on the right side of the left quadruplet, at a distance of 154 Hz, and another 87 Hz left of the right quadruplet. The T_c of the 10-CF_3 signal is lower than that of the 9-CF_3, and a smaller $|\nu_A-\nu_B|$ is expected. The tiny companions show the opposite relation and hence cannot be the signals of the minor equilibrium partners. Plotting the δ values of the two CF_3 resonances against temperature yields curvilinear functions which do not reveal a discontinuity in the region of coalescence. No asymmetry of the signals is discernible (Fig. 2). Both phenomena support a small population ($\leq$1%) of the minor partner.

Several possibilities for the exchange process—none of them completely satisfactory—will be briefly discussed. The first is an equilibrium of ketene imine **9C** with a tiny concentration of the open-chain zwitterion **10C**. It was shown for the isomerization of **9A** to thiolane **12A** (see above) that the ring-opening is the rate-determining step. Given that the conversion **9C**→**13C**+**6C** has a half-reaction time of 38.5 h in C_6D_6 at 80 °C, it is, however, barely imaginable that the rate of ring-opening equilibration, **9C**⇌**10C**, should reach the NMR time scale in the nonpolar medium toluene at a temperature as low as −30 °C (Fig. 2).

Less readily assailable is a variant which assumes an ionization equilibrium of ketene imines **9** with an intramolecular contact ion pair via a modest barrier. The subsequent dissociation to afford the zwitterions *gauche*-**10**

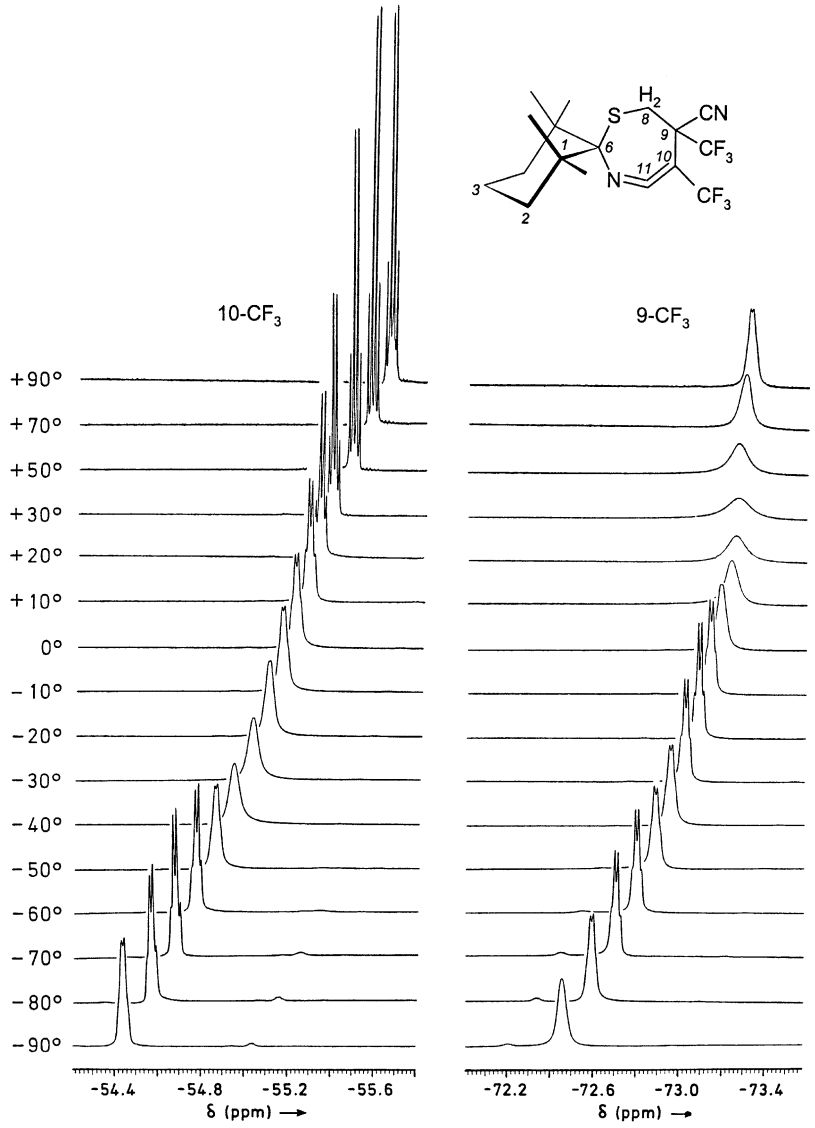


Figure 2. Temperature-dependent ^{19}F NMR spectra of cyclic ketene imine **9C** in [D_8]toluene.

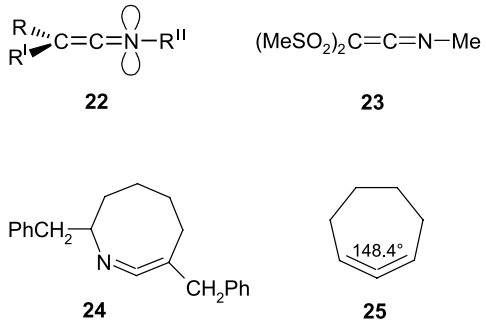
and *anti*-**10** would have to overcome a larger barrier, that is, the ionization equilibrium is established at a temperature which still does not allow dissociation. Yet, this time, it is difficult to explain why our scenario leading from **9** to **10** (namely, structural changes in the course of delocalization of ionic charges, relief of ring strain, build-up of the Coulombic term) should necessitate a two-barrier process.

Among processes without ring opening, an inversion of the tetramethylcyclohexane chair of **9C** has to be considered. The spiro-C-atom (6-position) constitutes a further stereoelement. The size of the inversion barrier of such a hexasubstituted cyclohexane is hard to predict. We need to consider that, in the ^{19}F NMR spectrum of **9A**, line broadening was observed as well.[12] At any rate, for the 'soft' inversion of the tetramethylcyclobutanone ring (spiro partner in **9A**), a substantial barrier is not probable.

Thus, we are left with the equilibration of *transoid* **19** with a small population of *cisoid* **20** by ring inversion as reason for the line broadening observed in **9C**. This process involves a *E*,*Z* isomerization at the C=N double bond. Kinetic studies with open-chain ketene imines are in harmony with a lateral inversion through a linear TS **22**.[21–23,28] Trialkylketene imines show barriers of about 15 kcal mol^{-1}. The topomerization of ketene *N*-phenylimine was calculated (SCF/STO-3G) by Jochims et al., and barriers of 12.5 kcal mol^{-1} for the lateral inversion (linear TS) and 34.9 kcal mol^{-1} for the rotation about the C=N bond (planar bent TS) resulted.[23] Interestingly, like TS **22**, bis(sulfonyl)ketene imine **23** is linear in the ground state, reflecting the stabilization of the nitrilium ylide resonance contributor (Scheme 5).[29]

Firl et al. prepared the cyclic eight-membered ketene imine **24** (not obtained pure) and observed two diastereomers; a barrier of 19 kcal mol^{-1} was evaluated from a slight broadening of ^{13}C NMR signals and ascribed to an inversion at the C=N bond.[30]

The step from the eight-membered ring **24** to the seven-membered ketene imine **9C** is accompanied by a drastic



Scheme 5.

increase in strain. Only three ring members of **9C** are disposable to span the termini of a quasi-linear TS of type **22**. The S-atom in the bridge offers some alleviation, but it is doubtful whether such a high-energy TS can reasonably be assigned to a rate process with $T_c = -30\,^{\circ}C$. On the other hand, the shrinking of the allene-type torsion angle from 90 to 57.8° in **9C** presents a ketene imine on the way to the quasi-planar TS of C=N rotation.

Cyclohepta-1,2-diene (**25**) and cyclohexa-1,2-diene make fleeting appearances, but can be intercepted by Diels–Alder reactions with diphenylisobenzofuran.[31] According to calculations (B3LYP/TZP//B3LYP/DZP),[32] the allene subunit is still chiral (C_2), but the bending of C=C=C to 148.4° in the seven-membered ring and to 132.8° in the six-membered ring signals increasing strain. The topomerization of allene itself by rotation via a planar biradical (angle C–C–C 143°) requires 44.6 kcal mol^{-1} (B3LYP/TZP).[33] For cyclohexa-1,2-diene, the calculated barrier shrinks to 14.1 kcal mol^{-1} (MR-CI+Q/ANO-1//DFT).[34]

In view of these data, a diastereomerization of **9C** (*transoid* **19** ⇆ *cisoid* **20**) by rotation about the C=N bond, rather than inversion, ought to be considered as an alternate possibility.

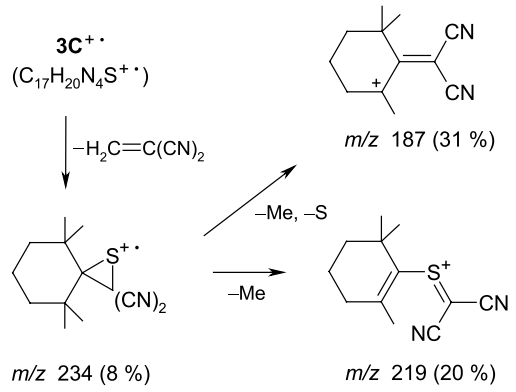
2.3. Reactions of 1C with further tetra-acceptor-substituted ethylenes

The reaction of dihydrothiadiazole **7C** with TCNE in benzene (80 °C, 20 h) exclusively furnished the tetracyanothiolane **3C** (Scheme 1). When the medium contained some methanol, the ^{1}H NMR analysis indicated the presence of the seven-membered lactim ether **5C** and thiolane **3C** in a ratio of about 84:16. Thus, the 1,7-cyclization of zwitterion **2C** prevailed over the 1,5-cyclization, as it did for **2A** (**5A**/**3A** = 68:32)[6] and **2B** (**5B**/**3B** = 97:3).[15] The short-lived ketene imine **4C**, lacking the stabilization by the 'perfluoroalkyl effect',[35] quickly isomerizes via **2C** to the thiolane **3C**, but can be intercepted by methanol.

As reported above, the reaction of **1C** with 2,3-bis(trifluoromethyl)fumaronitrile (**11**) gave rise to ketene imine **9C** and fragmentation products **13**+**6C**, but no thiolane **12C** was detected (Scheme 2). Probably, steric hindrance thwarts the 1,5-cyclization of the zwitterion *gauche*-**10C**.

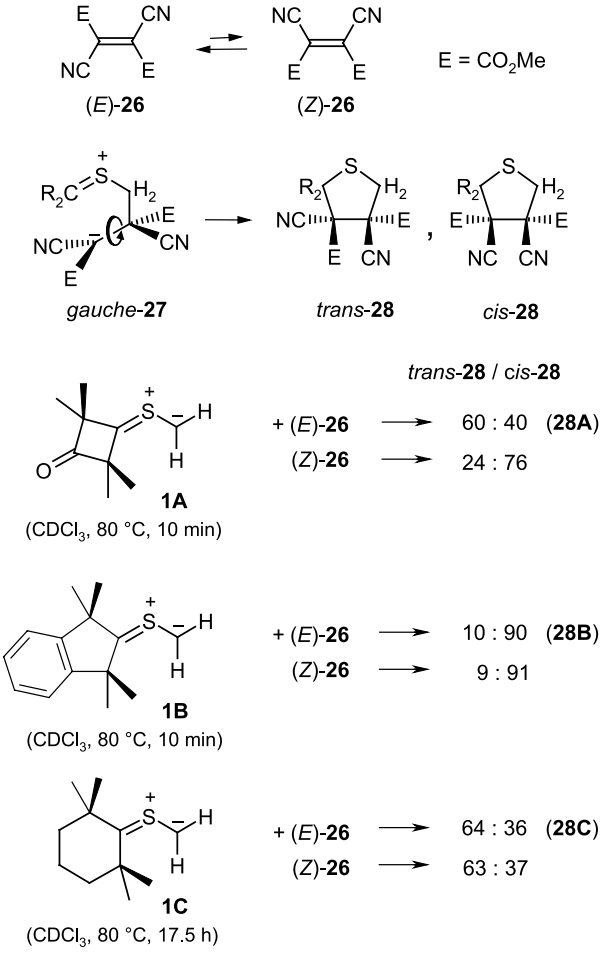
As radical cations, many cycloadducts break up into their original building blocks. Not so **3C**$^+$ which eliminates methylenemalononitrile with subsequent loss of Me and S, as suggested by Scheme 6. The molecular formulae were confirmed by high resolution and isotope peaks, but the proposed structures are speculative.

The isomer pair of dimethyl 2,3-dicyanofumarate ((*E*)-**26**)



Scheme 6.

and dimethyl 2,3-dicyanomaleate ((*Z*)-**26**) had provided first evidence for non-retentive cycloadditions of thiocarbonyl ylides (Scheme 7).[8] The different *trans*,*cis* ratios of thiolanes **28A**, which were observed in reactions of **1A** with (*E*)-**26** and (*Z*)-**26**, indicated a keen competition of rotation and 1,5-cyclization governing the zwitterion



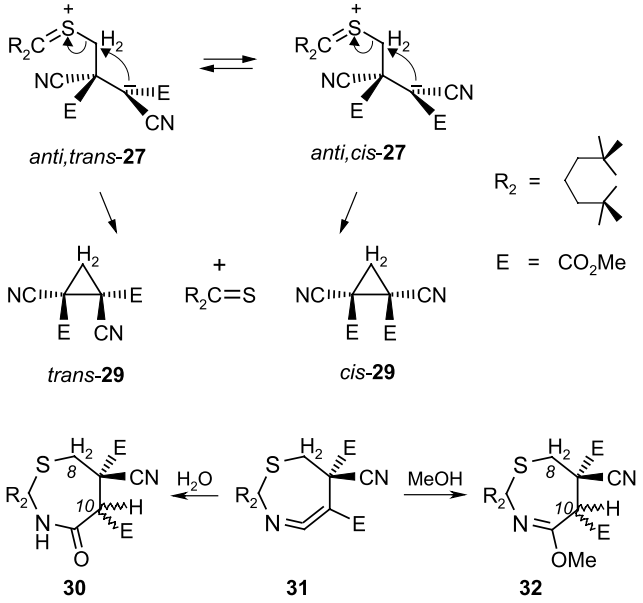
Scheme 7.

gauche-**27A**.[9] Growing steric screening in **27B** reduces the rate of 1,5-cyclization and allows the rotational equilibrium to be established before cyclization takes place: the same ratio of thiolanes **28B** was obtained from reactions with (*E*)-**26** and (*Z*)-**26**.[15]

The cycloadditions of **1C** likewise produced virtually identical ratios of thiolanes **28C** with (*E*)-**26** and (*Z*)-**26** (Scheme 7), but, regrettably, the results are mechanistically insignificant for several reasons: (a) after the reactions with (*E*)-**26** or (*Z*)-**26** ($CDCl_3$, 80 °C, 17.5 h), 16% of the dihydrothiadiazole **7C** were still unconsumed. That suggests $t_{½} \approx 6.7$ h for the first-order N_2 expulsion from **7C** versus $t_{½} = 3.0$ min for **7B**.[15] Thus, the liberation of thiocarbonyl ylide **1C** is slower by a factor of about 135 than that of **1B**, and the long time gives subsequent reactions an increased chance. (b) Among the dihydrothiadiazoles **7**, spiro-compound **7C** belongs to the most active catalysts for the *E*,*Z* isomerization of **26**. The precautions we took to curb it in the reactions of **7A** and **7B**[8] were ineffective here. After the reaction with **7C**, the excess of **26** revealed an established equilibrium at (*E*)/(*Z*)= 87:13. This did not permit us to draw any conclusion concerning the steric course of cycloaddition.

The *trans*,*cis*-isomeric thiolanes **28C** were separated and obtained in crystalline form. The stereochemical assignment was based on the value of $\Delta\delta_H$ of the diastereotopic protons 2-H_2: 0.19 ppm for *trans*-**28C** and 0.39 ppm for *cis*-**28C**. This empirical criterion, $\Delta\delta_H$ *trans*<*cis*,[9] was found to be valid for all tested thiolane pairs **28**,[15] and the structures were confirmed by several X-ray analyses.[15]

The reactions of **7C** with (*E*)-**26** under the above conditions furnished 41% of the thiolanes **28** (*trans*/*cis*=64:36) and 47% of dimethyl 1,2-dicyanocyclopropane-1,2-dicarboxylate (**29**, *trans*/*cis*=57:43). The zwitterions *gauche*-**27** undergo cyclization, and the conformers *anti*-**27** are responsible for the intramolecular substitution (Scheme 8), a process described above for zwitterions **10**. The fragmentation products, **29**+**6C**, are thermodynamically favored. When the pure thiolanes, *trans*-**28** and *cis*-**28**, were heated to 100 °C for 3 h in $CDCl_3$, complete conversion to **29** (*trans*/*cis*=50:50) was observed.



Scheme 8.

The intervention of ketene imine **31** was demonstrated by reactions of **1C** with (*E*)-**26** in the presence of water or methanol. The resulting pairs of diastereomeric lactams **30** and lactim methyl ethers **32** differ in their configurations at C-10; one of the lactams was isolated in pure state. The value of ^2J(H,H) of the ring—CH_2 group offers a diagnostic tool for five-membered versus seven-membered rings, for example, 12.6 Hz (*trans*-**28C**), 12.8 Hz (*cis*-**28C**), and 12.7 Hz (*trans*-**28B**) versus 15.4 Hz (**9C** and **14**), 16.5 Hz (**15**), and 15.2 Hz (**30**).

3. Experimental

3.1. Instruments and procedures[2]

The NMR solvent was $CDCl_3$, if not stated otherwise. As weight standards in the quantitative ^{1}H NMR analysis (±5% relative) were used: *sym*-tetrachloroethane (δ 5.92), the *as*-isomer (4.28), trichloroethene (6.70), or dibenzyl (2.92); standard in ^{19}F NMR analysis: (1,1-dichloro-2,2,2-trifluoroethyl)benzene (δ −78.2), abbrev. DICHLO. Multiplicities of ^{13}C NMR (20.2 MHz) signals were determined by comparison of ^{1}H decoupled and off-resonance spectra. The MS are EI spectra with 70 eV; intensities of isotope peaks are reported as, for example, ^{13}C% calcd/% found. Several MS made use of the program CMass and were recorded on a MAT 90 or MAT 95Q instrument. PLC is preparative layer chromatography on 20×20 cm glass plates, usually with 2 mm of Merck Silica gel 60 PF_{254}.

3.2. Materials

6,6,10,10-tetramethyl-4-thia-1,2-diazaspiro[4.5]dec-1-ene (**7C**).[2] The rate of the first-order N_2 extrusion was volumetrically measured and evaluated by $k_1t = \ln[V_\infty/(V_\infty - V_t)]$. Linear regression afforded 10^4k_1 [s^{-1}]: 1.48, 1.39 in DMSO at 95 °C; 2.53, 2.80 in mesitylene at 95 °C; 6.88, 7.92 in xylene at 100 °C. 4,4,8,8-Tetramethyl-1-thiaspiro[5.2]octane (**8C**);[2] 2,3-bis(trifluoromethyl)fumaronitrile (**11**);[12,36] dimethyl 2,3-dicyanofumarate (*E*)-**26**;[37] dimethyl 2,3-dicyanomaleate (*Z*)-**26**.[38]

3.3. Reactions of thiocarbonyl ylide 1C with bis(trifluoromethyl)fumaronitrile (11)

3.3.1. 1,1,5,5-Tetramethyl-9,10-bis(trifluoromethyl)-7-thia-12-azaspiro[5.6]dodeca-10,11-diene-9-carbonitrile (9C). Dihydrothiadiazole **7C** (1.91 g, 9.0 mmol) and **11** (2.14 g, 10.0 mmol) in benzene (25 mL) were refluxed for 15 h (incomplete N_2 elimination; see Section 3.3.4). After evaporation of the red solution, the pale-yellow ketene imine **9C** crystallized from pentane in 2 fractions (1.85 g, 52%), mp 93–94 °C. IR (KBr): ν 712 s cm^{-1}, 727m, 901m, 917m; 1080, 1126, 1159, 1191, 1208, 1254, 1268, 1288 (all vs, C–F); 1397m, 1476m; 2010+2030vs (C=C=N), 2245vw (C=N). ^{1}H NMR (80 MHz): δ 1.10, 1.25 (2s, 2Me), 1.33 (s, 2Me), 1.41–1.84 (m, 3CH_2), 3.14, 3.40 (AB,

J=15.4 Hz, 8-H_2). ^{13}C NMR (20.15 Hz): δ 18.3 (t, C-3), 24.6, 26.0, 29.5, 29.6 (4q, 4Me), 36.9, 38.3, 38.4 (3t, C-2, C-4, C-8), 41.9, 45.2 (2s, C-1, C-5), 43.7 (q, ^2J(C,F)=31.3 Hz, C-9), 60.6 (q, broadened, ^2J(C,F)=42.7 Hz, C-10), 95.2 (q, ^5J(C,F)=1.8 Hz, C-6), 112.9 (s, CN), 122.5 (q, ^1J(C,F)=269.8 Hz, CF_3), 122.8 (q, ^1J(C,F)=285.3 Hz, CF_3), 182.6 (q, ^3J(C,F)=4.3 Hz, C-11). ^{19}F NMR (376 MHz, 25 °C): −55.94 (q, ^5J(F,F)=5.8 Hz, 10-CF_3), −73.38 (br, 9-CF_3); (−30 °C): −55.74 (br, 10-CF_3), −73.16 (q, ^5J(F,F)=5.6 Hz, 9-CF_3); s.a. Figure 2. MS (MAT 90, CMass, 25 °C, calcd/found), *m/z* (%): 398.125/398.136 (5) [M^+, **16**, ^{13}C 0.92/0.90], 329.129/329.123 (17) [$C_{16}H_{20}F_3N_2S^+$, M^+-CF_3, **17**], 329.055/329.046 (22) [$C_{12}H_{11}F_6N_2S^+$, $M^+-C_5H_9$], 275.008/275.011 (7) [$C_8H_5F_6N_2S^+$, $M^+-C_9H_{15}$], 247.052/247.047 (15) [$C_{10}H_{10}F_3N_2S^+$, $M^+-CF_3-C_6H_{10}$], 170.113/170.110 (31) [$C_{10}H_{18}S^+$, **6C**$^+$, ^{13}C 3.4/3.9], 169.105/169.104 (21) [$C_{10}H_{17}S^+$], 137.133/137.132 (100) [$C_{10}H_{17}^+$, possibly **18**], 123.117/123.116 (28) [$C_9H_{15}^+$, probably trimethylcyclohexenyl$^+$], 114.050/114.046 (13) [$C_6H_{10}S^+$], 113.042/113.041 (30) [$C_6H_9S^+$], 100.035/100.033 (11) [$C_5H_8S^+$], 99.027/99.026 (16) [$C_5H_7S^+$], 95.086/95.085 (28) [$C_7H_{11}^+$], 88.035/88.032 (11) [$C_4H_8S^+$], 85.011/85.010 (12) [$C_4H_5S^+$], 81.070/81.075 (27) [$C_6H_9^+$], 79.055/79.053 (10) [$C_6H_7^+$], 69.070/69.069 (52) [$C_5H_9^+$], 68.995/68.994 (19) [CF_3^+], 67.055/67.054 (18) [$C_5H_7^+$], 57.070/57.069 (12) [$C_4H_9^+$], 55.055/55.054 (39) [$C_4H_7^+$], 53.039/53.038 (14) [$C_4H_5^+$], 41.039/41.041 (61) [$C_3H_5^+$]. Anal. Calcd for $C_{17}H_{20}F_6N_2S$ (398.41): C, 51.25; H, 5.06; N, 7.03. Found: C, 51.30; H, 5.17; N, 7.09.

3.3.2. Variable temperature NMR of 9C. *(a) ^{19}F NMR (376 MHz, [D$_8$]toluene).* After the spectrum was taken at 90 °C (Fig. 2, see above), a new recording at 30 °C indicated no irreversible changes. The standard signal (Cl_3CF) remained sharp over the whole temperature range. The half-width of the 9-CF_3 signal increases from 21 Hz at 0 °C to 55 Hz at 25 °C and decreases to 20 Hz at 90 °C; the half-width is ill-defined for structured quadruplets. The small unidentified peaks at −70 °C (Fig. 2), δ −55.26 on the low-frequency side of q (−54.67) and δ −72.69 which accompanies the q at δ −72.69 are not ^{13}C-satellites. The latter were recognized and showed ^1J(C,F)=271 Hz, high-field shifted by 54 Hz (isotope effect). Figure 2 reveals a greater height of the sharp q (δ −72.69) at 90 °C than at lower temperatures. At −70 °C quadruplets, both signals lose fine structure at −90 °C. Besides the increasing viscosity of the solvent toluene at low temp., beginning hindrance of CF_3 rotations may be responsible, as recently studied for an adamantyl-spiro-thiolane.[14]

(b) ^{1}H NMR (400 MHz, [D$_8$]toluene). The 8-H_2 appears at −90 °C as AM spectrum at δ 1.98 and 2.45 with ^2J=15.6 Hz and at 20 °C as AB at δ 2.70 and 2.75; the $\Delta\delta$ diminishes with increasing temperature: 12 Hz at 50 °C, ~2 Hz at 60 °C, and an A_2 spectrum with δ 2.92 at 90 °C. The half-width of the signals were not measured.

3.3.3. X-ray diffraction analysis of 9C. The monocyclic crystal (0.17×0.33×0.53 mm^3) of space group $P2_1/c$ No. 14 was sealed in a glass capillary and mounted on the goniometer head of CAD4 diffractometer operating with Mo K_α radiation (λ=0.71069 Å) and graphite monochromator. Unit cell dimensions: a=1187.9(3) Å, b=1059.3(2) Å, c=1472.1(5) Å, β=100.89(2)°, V=1.8191 nm^3, Z=4, D_{calc}=1.455 g/cm^3, $F(000)$=824, T=294(1) K, μ=2.39 cm^{-1}. The unit cell dimensions resulted from a least-square fit of the setting angles of 25 centered reflections; ω–2θ scan, width 1.00° +0.35 tan θ, maximum measuring time 120 s, 2θ range 4–46° for all $\pm h/\pm k/+l$ reflections; 2638 reflections collected, 2521 unique, and 2074 with $I>2\sigma(I)$. The structure was solved by the SHELXTL program package,[39] non-hydrogen atoms refined anisotropically, hydrogen atoms fixed isotropically with U_i=1.2×U_{eq} of the adjacent carbon atom, full matrix refinement; final R_1=0.0365 and R_w=0.0315. The final difference map was featureless with 239 refined variables; ZORTEP plot.[40] The deposition No. CCDC-160826 contains supplementary data, which can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 IEZ, UK (fax: +44 (1233) 336-003; e-mail: deposit@ccdc.cam.ac.uk

3.3.4. Kinetics of formation and conversion of ketene imine 9C. (a) The solution of **7C** (298 µmol), **11** (325 µmol), and DICHLO (190 µmol) as weight standard in C_6D_6 (0.6 mL) in a closed NMR tube was immersed in a 80 °C bath. Periodically, within 242 h, ^{19}F NMR spectra were recorded, and the concentrations of **9C**, **13** and **11** were determined by machine integrals. The comparison with the integral of the standard compensates field inconstancies over the reaction time. The (*E*),(*Z*) isomerization of **11** was catalyzed by the dihydrothiadiazole **7C**; (*E*)-**11**/(*Z*)-**11** amounted to 94:6 after 3.3 h, and the 90:10 equilibrium was established after 14.5 h. This catalysis has been studied with dihydrothiadiazole **7A**, and (*E*)-**11**/(*Z*)-**11**=93:7 was reported for C_6D_6 at 40 °C.[12] The concentration of **9C** passed a shallow maximum of 73% after ~16 h. The formation of 1,2-bis(trifluoromethyl)cyclopropane-1,2-dicarbonitrile (**13**, *trans*/*cis*=95: 5)[14] displayed an induction period: % *trans*-**13**+ *cis*-**13** (after h at 80 °C)=2 (3.25), 4 (7), 11 (14.5), 13 (18.5), 18 (26.5), 43 (70), 57 (114), 73 (177). The increase of the product concentrations, (**9C**)+(**13**), corresponds to the decrease of (**7C**), invisible in ^{19}F NMR spectrum, and follows the first-order law. Linear regression of the time function of ln (**7C**)$_o$/[(**7C**)$_o$−(**9C**+**13**)$_t$] furnished $k_1=3.8\times10^{-5}$ [s^{-1}] (five values up to 82% reaction and 14.5 h, r=0.998). After 50 h, new ^{19}F NMR signals suggested secondary reactions, and after 242 h, the sum (**9C**+**13**) amounted only to 67% of (**7C**)$_o$. Thus, the given rate constant is only an approximative value.

(b) Pure ketene imine **9C** (240 µmol) and DICHLO in C_6D_6 (0.6 mL) in a sealed NMR tube were heated to 80 °C and ^{19}F NMR-analyzed as above. A first-order reaction described the decrease of (**9C**) up to 91% after 137 h with $k_2=5.0\times10^{-6}$ [s^{-1}] (six points, r=0.999). The cyclopropanes, *trans*-**13** and *cis*-**13**, were the only visible products for 30 h at 80 °C. On longer heating, small signals showed up; after 294 h, **9C** had disappeared, but (**13**)$_\infty$ reached only 182 µmol, that is, 76% of (**7C**)$_o$. Whether or not thiolane **12C** is one of the minor side-products, is not clear.

(c) Ketene imine **9C** stores astonishingly well. A specimen which was kept in a stoppered glass for more than 10 years,

contained, according to the IR spectrum, mainly **9C** and lactams **15** (hydration product of **9C**).

3.3.5. 11-Methoxy-1,1,5,5-tetramethyl-9,10-bis(trifluoromethyl)-7-thia-12-azaspiro[5.6]dodec-11-ene-9-carbonitrile (14). Ketene imine **9C** (1.0 mmol) was dissolved in $CHCl_3$ (5 mL) and MeOH (0.1 mL). After one hour at rt, the solvent was removed and ^{1}H NMR analysis indicated 67% of **14**. The colorless lactim ether (46%) crystallized from MeOH. Mp 106–108 °C. IR (KBr): ν 983m cm^{-1}; 1167s, 1207s, 1249s, 1279s (C–F), 1690s (C=N). ^{1}H NMR (80 MHz): δ 1.04, 1.10, 1.21, 1.30 (4s, 4Me), 1.0 – 2.1 (m, 3CH_2), 3.22, 3.55 (AB, ^2J=15.4 Hz, 8-H_2), 3.83 (s, OMe), 5.24 (q, ^3J(F,H)=8.2 Hz, 10-H). ^{13}C NMR (20.2 MHz): δ 18.9(t, C-3), 24.7, 26.0, 29.6, 29.8 (4q, 4Me), 37.0 (tq, ^3J(C,F)=2.4 Hz, C-8), 37.2, 37.9 (2t, C-2, C-4), 43.1, 46.6 (2s, C-1, C-5), 45.4 (q, ^2J(C,F)=31.7 Hz, C-9), 48.5 (dq, ^2J(C,F)=30.5 Hz, C-10), 54.3 (s, OMe), 81.9 (s, C-6), 113.7 (q, ^3J(C,F)=2.0 Hz, CN), 122.7 (q, ^1J(C,F)=285.6 Hz, CF_3), 123.2 (q, ^1J(C,F)=280.8 Hz, CF_3), 148.2 (s, C-11). ^{19}F NMR (376 MHz): δ −61.9 (dq, ^3J(F,H)∼8 Hz, ^5J(F,F)=9.1 Hz, 10-CF_3), −69.0 (q, ^5J(F,F)=9.2 Hz, 9-CF_3). MS (MAT 90, CMass), *m/z* (%): 430.151/430.151 (10) [M^+], 415.127/415.124 (8) [M^+−Me], 372.176/372.176 (32) [$C_{17}H_{24}F_6NO^+$], M^+−S−CN, ^{13}C 6.1/7.0], 348.073/348.071 (10) [$C_{12}H_{14}F_6N_2OS^+$, M^+−C_6H_{10}], 346.057/346.058 (10) [348−2H], 305.018/305.018 (12) [$C_9H_7F_6N_2OS^+$, M^+−C_9H_{17}], 278.007/278.008 (100) [$C_8H_6F_6NOS^+$, M^+−HCN−C_9H_{17}, ^{13}C 8.9/9.0], 152.144/152.143 (31) [$C_{10}H_{18}N^+$], 141 (23), 137.133/137.134 (15) [$C_{10}H_{17}^+$, **18**], 136.037/136.039 (18) [$C_5H_5NF_3^+$], 107 (23), 105 (10), 95.086/95.086 (9) [$C_7H_{11}^+$], 89.039/89.042 (26) [$C_4H_9S^+$], 79.053/79.053 (9) [$C_6H_7^+$], 77.039/77.040 (45) [$C_6H_5^+$], 69.070/69.070 (37) [$C_5H_9^+$], 68.995/68.995 (5) [CF_3^+], 68.050/68.057 (11) [$C_4H_6N^+$], 55.055/55.054 (37) [$C_4H_7^+$]. Anal. Calcd for $C_{18}H_{24}F_6N_2OS$ (430.45): C, 50.22; H, 5.62; N, 6.51. Found: C, 50.29; H, 5.59; N, 6.58.

3.3.6. 1,1,5,5-Tetramethyl-11-oxo-9,10-bis(trifluoromethyl)-7-thia-12-azaspiro[5.6] dodecane-9-carbonitrile (15). Ketene imine **9C** (1.0 mmol) was reacted with H_2O (0.25 mL) in THF (20 mL) 1 h at rt and gave **15** (48%) from MeOH. Mp 192–193 °C (green, gas evol.). IR (KBr): ν 1126 s cm^{-1}, 1169s, 1213s, 1268s (C–F), 1636vs (C=O), 3260m br (N–H). ^{1}H NMR (80 MHz): δ 1.11, 1.35 (2s, 2Me), 1.25 (s, 2Me), 1.3–1.8 (br s, 3CH_2), 3.27, 3.66 (AB, ^2J=16.5 Hz, right branch broadened, 8-H_2), 5.20 (q, ^3J(C,F)=6.8 Hz, 10-H), 6.70 (s, br, NH). ^{13}C NMR (100.6 MHz, DEPT): δ 17.9 (C-3), 24.8, 26.6, 28.4, 30.1 (slightly broadened, 4Me), 36.35, 36.83 (C-2, C-4), 36.45 (^3J(C,F)=1.9 Hz, C-8), 43.8, 44.8 (C-1, C-5), 44.6 (^2J(C,F)=29.4 Hz, C-9), 49.4 (^2J(C,F)=29.4 Hz, C-10), 77.2 (C-6), 112.7 (^3J(C,F)=1.9 Hz, CN), 122.51 (^1J(C,F)=286.1 Hz, CF_3), 122.76 (^1J(C,F)=280.6 Hz, CF_3), 163.8 (C=O). ^{19}F NMR (376 MHz): δ −61.9 (dq, 6 lines visible, ^5J(F,F)=9.2 Hz, ^3J(H,F)≈9 Hz, 10-CF_3), −69.0 (q, ^5J(F,F)=9.2 Hz, 9-CF_3). MS (MAT 95Q, CMass), *m/z* (%): 416.135/416.134 (0.8) [M^+], 358.160/358.161 (6) [$C_{16}H_{22}F_6NO^+$, M^+−S−CN; ^{13}C 2.8/2.4], 334.057/334.058 (29) [$C_{11}H_{12}F_6N_2OS^+$, M^+−C_6H_{10}; $^{13}C_2$+^{34}S 4.3/4.4], 247.031/247.033 (13) [$C_7H_5F_6N_2O^+$, M^+−**6C**+H], 224 (12), 211.028/211.029 (6) [$C_7H_8F_3NOS^+$], 152.144/152.144 (35) [$C_{10}H_{18}N^+$], 137.133/137.133 (100) [$C_{10}H_{17}^+$, **18**], 136.125/136.124 (8) [$C_{10}H_{16}^+$], 121.101/121.101 (12) [$C_9H_{13}^+$], 96.081/96.083 (12) [$C_6H_{10}N^+$], 95.086/95.085 (14) [$C_7H_{11}^+$; methylcyclohexenyl$^+$ or dimethylcyclopentyl$^+$], 82.078/82.076 (42) [$C_6H_{10}^+$], 71.073/71.074 (34) [$C_4H_9N^+$], 69.070/69.070 (47) [$C_5H_9^+$, dimethylallyl$^+$], 69.058/69.057 (33) [$C_4H_7N^+$], 68.995/68.995 (8) [CF_3^+], 55.055/55.055 (22) [$C_4H_7^+$, methallyl$^+$]. Anal. Calcd for $C_{17}H_{22}F_6N_2OS$ (416.43): C, 49.03; H, 5.33; N, 6.73. Found: C, 49.24; H, 5.30; N, 6.50.

3.4. Reactions of thiocarbonyl ylide 1C with ethenetetracarbonitrile (TCNE)

3.4.1. 6,6,10,10-Tetramethyl-1-thiaspiro[4,5]decane-3,3,4,4-tetracarbonitrile (3C). Dihydrothiadiazole **7C** (425 mg, 2.00 mmol) and TCNE (282 mg, 2.20 mmol) in C_6H_6 (10 mL) were refluxed for 20 h. After removal of the solvent, the ^{1}H NMR analysis in $CDCl_3$ with trichloroethene indicated quantitative formation of **3C**. From MeOH, **3C** (330 mg, 54%) was isolated as yellow plates, mp 181 °C (dec.). IR (KBr): ν 980m cm^{-1}, 1398m, 1404m, 1433m, 1465m, 2250vw (C≡N). ^{1}H NMR (80 MHz): δ 1.60 (s, 4Me), 1.28 – 1.75 (m, 6 ring-H), 3.58 (s, 2-H_2). ^{13}C NMR (20.2 MHz): δ 17.5 (t, C-8), 25.9, 32.3 (2s, 2×2 Me), 41.3 (t, C-2), 42.1 (t, C-7+C-9), 42.6 (s, C-6+C-10), 51.6, 55.0 (2s, C-3, C-4), 84.2 (s, C-5), 111.1, 112.7 (2s, 2×2 CN). MS (80 °C), *m/z* (%): 297 (3) [M^+−Me], 285 (3) [M^+−HCN], 259 (8) [M^+−HCN−CN; $^{13}C_2$+^{34}S 0.44/0.49], 234 (8) [$C_{13}H_{18}N_2S^+$, M^+−H_2C=C(CN)$_2$; ^{13}C 1.1/1.1; $^{13}C_2$+^{34}S 0.42/0.48], 228 (32) [$C_{11}H_8N_4S^+$, M^+−C_6H_{12}; HR 228.0469/228.0474], 219 (20) [$C_{12}H_{15}N_2S^+$, 234−Me; ^{13}C 2.6/2.3], 201 (28) [$C_{10}H_7N_3S^+$, 228−HCN; HR 201.036/201.019], 187 (31) [$C_{12}H_{15}N_2^+$, possibly dicyanomethylene-trimethylcyclohexyl$^+$; ^{13}C 4.1/4.3], 174 (11), 152 (13), 150 (33), 149 (13), 147 (16), 146 (13), 145 (15), 134 (33) [$C_{10}H_{14}^+$; ^{13}C 3.5/3.8; HR 134.109/134.096], 133 (78) [$C_{10}H_{13}^+$], 119 (17), 106 (18), 91 (11) [tropylium$^+$], 83 (57) [$C_6H_{11}^+$, trimethylallyl$^+$], 78 (54) [$C_4H_2N_2^+$, methylenemalononitrile$^+$; HR 78.022/78.023], 77 (35) [$C_6H_5^+$], 70 (100) [$C_5H_{10}^+$, ^{13}C 5.6/5.9], 69 (65) [dimethylallyl$^+$], 55 (77) [methylallyl$^+$]. Anal. Calcd for $C_{17}H_{20}N_4S$ (312.43): C, 65.35; H, 6.45; N, 17.93. Found: C, 64.94; H, 6.60; N, 17.84.

3.4.2. Interception of ketene imine 4C. In a cursory experiment, **7C** (198 μmol) and TCNE (258 μmol) in C_6H_6 (5 mL)+MeOH (100 μL, 2.5 mmol) were heated to 80 °C for 20 h. After evaporation of the solvent, the ^{1}H NMR signals ($CDCl_3$) of MeO (s, δ 3.83) and 8-H_2 (δ 3.32, 3.56, AB, ^2J=16.2 Hz) are indicative of the lactim methyl ether **5C**. Quantitative analysis with *sym*-$C_2H_2Cl_4$ pointed to 68% of **5C** and 13% of thiolane **3C**. During 20 h at 80 °C, part of the TCNE probably reacted with the MeOH, before **1C** was completely set free.

3.5. Reactions of 1C with dimethyl 2,3-dicyanofumarate ((*E*)-26) and dimethyl 2,3-dicyanomaleate ((*Z*)-26)

3.5.1. Isolation of spirothiolanes. Dihydrothiadiazole **7C** (1.06 g, 5.0 mmol) and (*Z*)-**26** (1.07 g, 5.5 mmol) in abs. octane (10 mL) were reacted in the 130 °C bath for 10 min. PLC (Et_2O/pentane 30:70, 2×) furnished *trans*-**28C**

(475 mg, 25%) as first fraction and *cis*-**28C** (340 mg, 18%) as second fraction.

3.5.2. Dimethyl *trans*-3,4-dicyano-6,6,10,10-tetramethyl-1-thiaspiro[4.5]decane-3,4-dicarboxylate (*trans*-28C). Recrystallised from MeOH, mp 141–143 °C (dec.). IR (KBr): ν 918m cm^{-1}; 1244s+1254s br (C–O), 1754vs (C=O), 2235, 2250vw (C≡N). ^{1}H NMR (80 MHz): δ 1.15, 1.59, 1.68, 1.76 (4s, 4Me), 1.3–1.5 (nonresolv. m, 3CH_2), 3.41, 3.60 (AB, ^2J=12.6 Hz, 2-H_2), 3.89, 3.95 (2s, 2MeO). ^{13}C NMR (20.2 MHz): δ 17.9 (t, C-8), 24.5, 25.5, 32.7, 33.0 (4q, 4Me), 39.0 (t, C-2), 41.3, 44.6 (2s, C-6, C-10), 43.9, 44.7 (2t, C-7, C-9), 54.5, 54.9 (2q, 2MeO), 63.9, 64.7 (2s, C-3, C-4), 83.5 (s, C-5), 116.7, 119.0 (2s, 2CN), 164.2, 164.5 (2s, 2C=O). MS (60 °C), *m/z* (%): 378 (3) [M^+], 364 (3) [M^+-CH_2; ^{13}C 0.7/0.9], 319 (58) [M^+-CO_2Me; ^{13}C 11.0/11.2; $^{13}C_2+^{34}S$ 3.6/3.1], 294 (28 [$C_{13}H_{14}N_2O_4S^+$, $M^+-C_6H_{12}$; $^{13}C_2+^{34}S$ 1.52/1.53; HR 294.067/294.074), 292 (30) [$C_{16}H_{22}NO_2S^+$, 319−HCN; HR 292.137/292.131], 267 (52) [$C_{14}H_{21}NO_2S^+$, M^+-H_2C=C(CN)−CO_2Me], ^{13}C 8.1/8.5; HR 267.129/267.124], 252 (14) [267−Me; ^{13}C 2.0/2.2], 237 (13), 235 (17) [267−S, $C_{14}H_{21}NO_2^+$], 211 (11), 191 (16), 185 (11), 177 (38), 176 (78) [$C_9H_8N_2S^+$, possibly dicyano-isopropyl-thiophene$^+$], 170 (54) [$C_{10}H_{18}S^+$, **6C**$^+$], 155 (10), 148 (33), 137 (37) [$C_{10}H_{17}^+$, **18**; ^{13}C 4.1/4.6], 127 (17), 125 (11), 121 (17) [$C_9H_{13}^+$], 114 (11), 101 (30), 95 (20) [$C_7H_{11}^+$], 93 (12), 88 (19), 83 (24) [$C_6H_{11}^+$], 82 (31) [$C_6H_{10}^+$], 81 (25), 69 (100) [$C_5H_9^+$, dimethylallyl$^+$], 67 (24), 59 (38) [MeO−C≡O$^+$], 55 (29) [methylallyl$^+$]. Anal. Calcd for $C_{19}H_{26}N_2O_4S$ (378.48): C, 60.29; H, 6.92; N, 7.40; S, 8.47. Found: C, 60.07; H, 6.87; N, 7.34; S, 8.47.

3.5.3. Dimethyl *cis*-3,4-dicyano-6,6,10,10-tetramethyl-1-thiaspiro[4.5]decane-3,4-dicarboxylate (*cis*-28C). Mp 101–103 °C (MeOH). IR (KBr): ν 1030w cm^{-1}, 1235+1245vs, br (C–O), 1437m; 1745vs, sh 1760 (C=O), 2250vw (C≡N). ^{1}H NMR (80 MHz): δ 1.21, 1.26, 1.70, 1.81 (4s, 4Me), 1.4–2.0 (m, 7-H_2, 8-H_2, 9-H_2), 3.44, 3.83 (AB, ^2J=12.8 Hz, 2-H_2), 3.83, 3.85 (2s, 2MeO). ^{13}C NMR (20.2 MHz): δ 17.9 (t, C-8), 24.6, 26.0, 31.0, 34.3 (4q, 4Me), 39.9 (t, C-2), 41.8, 44.1 (2s, C-6, C-10), 42.6, 45.4 (2t, C-7, C-9), 54.31, 54.43 (2q, 2MeO), 63.0, 66.6 (2s, C-3, C-4), 87.1 (s, C-5), 117.1, 118.0 (2s, 2CN), 164.6, 167.6 (2s, 2C=O). Anal. Calcd for $C_{19}H_{26}N_2O_4S$ (378.48): C, 60.29; H, 6.92; N, 7.40; S, 8.47. Found: C, 60.08; H, 6.90; N, 7.57; S, 8.62.

3.5.4. ^{1}H NMR product analysis of the reaction at 80 °C. (a) Dihydrothiadiazole **7C** (22.0 mg, 104 μmol) and (*E*)-**26** (22.0 mg, 113 μmol) in 7.6 mM H_2SO_4 in $CDCl_3$ (1.0 mL),[9] sealed in a NMR tube, were reacted at 80 °C for 17.5 h. After cooling of the pink solution with liquid N_2, the tube was opened, and 100 μL of a standard solution of dibenzyl in $CDCl_3$ was added. The ^{1}H NMR analysis (270 MHz) showed that still 17 μmol (16%) of **7C** (δ 0.53) remained unconsumed; product yields refer to consumed **7C**. The excess of dipolarophile (δ 4.04 for (*E*)-**26** and 3.98 for (*Z*)-**26**, OMe) turned out to be equilibrated: (*E*)-**26**/(*Z*)-**26**= 87:13. Thiolanes *trans*-**28C** (δ 3.60, 3.90, 3.96) and *cis*-**28C** (δ 3.85, 3.87, MeO) were present in yields of 26 and 15%, respectively. Furthermore, 27% of dimethyl *trans*-1,2-dicyanocyclopropane-1,2-dicarboxylate (*trans*-**29**, δ 2.60, 3.98) and 20% of the isomer *cis*-**29** (δ 2.34, 2.60, 3.88) were analyzed; both *trans*-**29** and *cis*-**29** were characterized previously.[41] Finally, ~10% of the lactam **30** (δ 3.82, 3.91) resulted from reaction with a trace of humidity.

(b) An analogous experiment with **7C** (102 μmol) and (*Z*)-**26** (114 μmol) showed likewise 17 μmol of unconsumed **7C** and afforded *trans*-**28C** (24%), *cis*-**28C** (14%), *trans*-**29** (26%), *cis*-**29** (21%), and **30** (~9%).

(c) Preceding studies dealt with the catalysis of equilibration, (*E*)-**26**⇌(*Z*)-**26** by dihydrothiadiazoles **7**.[8,9] The activity of **7C** could not be suppressed by a trace of acid, for example, (*Z*)-**26** in 7.6 mM H_2SO_4 in $CDCl_3$ at rt after 12 h showed 12% isomerization to (*E*)-**26**.

3.5.5. Thermolysis of *trans*-28C and *cis*-28C at 100 °C. The reactions were carried out in $CDCl_3$ in sealed NMR tubes and revealed after 3 h at 100 °C a complete fragmentation into 2,2,6,6-tetramethylcyclohexanethione (**6C**) and *trans*-**29**/*cis*-**29**=1:1 (^{1}H NMR analysis).

3.5.6. Interception of ketene imine 31. (a) Dihydrothiadiazole **7C** (3.3 mmol) and (*E*)-**26** (3.0 mmol) in dioxane +1 vol% H_2O (6 mL) were heated to 80 °C for 20 h. Treatment of the yellow residue (after evaporation) with Et_2O afforded lactam **30** (39%) in two diastereoisomers, one of which was obtained pure by fractional crystallization from Et_2O.

(b) In a separate experiment, **7C** was reacted with 1.1 equiv of (*E*)-**26** in THF+1 vol% H_2O 5 h at 100 °C. After evaporation and dissolving in $CDCl_3$, the diastereoisomer ratio of **30** (66:34) was determined by the ^{1}H NMR integrals of 10-H at δ 5.11 and 5.38, and comparison with Cl_2C=CHCl as weight standard showed 55% yield.

(c) Compound **7C** (0.69 mmol) was reacted with (*Z*)-**26** (1.1 mmol) in C_6H_6+2 vol% MeOH (5 mL) at 80 °C for 20 h. In the NMR analysis ($CDCl_3$), 2s at δ 5.14 and 5.39 (70:30) were assigned to the 10-H of diastereoisomeric lactim methyl ethers **32** (not isolated). The missing of the signals of *trans*- and *cis*-**28** suggested a complete trapping of **31** by MeOH.

3.5.7. Dimethyl 9-cyano-1,1,5,5-tetramethyl-11-oxo-7-thia-12-azaspiro[5.6]dodecane-9,10-dicarboxylate (30). Mp 148–149 °C. IR (KBr): ν 1182 cm^{-1}, 1214m, 1251m, 1290m, 1327m, 1388s (C–O), 1436m, 1659vs (C=O, amide I), 1752vs (C=O, ester), 2247vw (C≡N), 3260m (N–H, also in nujol). ^{1}H NMR (80 MHz): δ 1.10, 1.24, 1.28, 1.33 (4s, 4Me), 1.40–1.57 (m, 2-H_2, 3-H_2, 4-H_2), 3.31, 3.43 (AB, ^2J=15.2 Hz, 8-H_2), 3.78, 3.85 (2s, 2MeO), 5.11 (s, 10-H), 5.96 (s br, NH). MS (205 °C), *m/z* (%): 396 (10) [M^+], 365 (10) [M^+−OMe, ^{13}C 1.9/1.8], 338 (100) [$C_{18}H_{28}NO_5^+$, M^+-S-CN, S-free], 314 (45) [$C_{13}H_{18}N_2O_5S^+$, $M^+-C_6H_{10}$, ^{13}C 6.6/6.8, $^{13}C_2+^{34}S$ 2.5/2.7], 253 (11), 244 (20), 220 (10), 212 (53), 202 (17), 198 (33) [$C_8H_5NO_5^+$, ^{13}C 2.9/3.2], 185 (14), 184 (13) [perhaps **1C**$^+$], 170 (35) [$C_{10}H_{18}S^+$, **6C**$^+$], 154 (13), 153 (13), 152 (19), 138 (22), 137 (59) [$C_{10}H_{17}^+$], 117 (11), 71 (22), 69 (20). Anal. Calcd for $C_{19}H_{28}N_2O_5S$ (396.50): C, 57.55; H, 7.12; N, 7.07; S, 8.09. Found: C, 57.33; H, 7.29; N, 7.09; S, 8.09.

Acknowledgements

We are grateful to the Fonds der Chemischen Industrie, Frankfurt, for the continued support of our research program. We thank Dr. Elke Langhals and cand. chem. Christoph Schön for carrying out one series of experiments. R. H. expresses thanks to Prof. Rudolf Knorr, München, for a discussion. Our thanks are going to Dr. David S. Stephenson and Helmut Huber for their help in the recording of NMR spectra, and to Dr. Werner Spahl, Helmut Seidl, and Brigitte Tschuck for the mass spectra. Helmut Schulz and Magdalena Schwarz carried out the elemental analyses.

References and notes

1. 1,3-Dipolar Cycloadditions, Part 131. For part 130, see Ref. 2.
2. Huisgen, R.; Mloston, G.; Giera, H.; Langhals, E.; Polborn, K.; Sustmann, R. *Eur. J. Org. Chem.* **2005**, 1519.
3. Review: Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779.
4. Brief survey: Huisgen, R. In *Chemistry and Biological Applications of Oxygen- and Sulfur Containing Heterocycles*; Kartsev, V. E., Ed.; IBS: Moscow, 2003; pp 83–101.
5. Review: Huisgen, R. In Padwa, A., Ed.; 1,3-Dipolar Cycloaddition Chemistry; Wiley: New York, 1984; Vol. 1, pp 1–176.
6. (a) Huisgen, R.; Mloston, G.; Langhals, E. *J. Org. Chem.* **1986**, *51*, 4085. (b) Huisgen, R.; Mloston, G.; Langhals, E. *Helv. Chim. Acta* **2000**, *84*, 1805.
7. Huisgen, R.; Penelle, J.; Mloston, G.; Buyle-Padias, A.; Hall, H. K. *J. Am. Chem. Soc.* **1992**, *114*, 266.
8. Mloston, G.; Langhals, E.; Huisgen, R. *Tetrahedron Lett.* **1989**, *30*, 5373.
9. Huisgen, R.; Mloston, G.; Giera, H.; Langhals, E. *Tetrahedron* **2002**, *58*, 507.
10. Domingo, L. R.; Picher, M. T. *Tetrahedron* **2004**, *60*, 5053.
11. Huisgen, R.; Langhals, E.; Mloston, G.; Oshima, T. *Heterocycles* **1989**, *29*, 2069.
12. Huisgen, R.; Mloston, G.; Langhals, E.; Oshima, T. *Helv. Chim. Acta* **2002**, *85*, 2668.
13. Huisgen, R.; Langhals, E.; Nöth, H. *J. Org. Chem.* **1990**, *55*, 1412.
14. Huisgen, R.; Langhals, E.; Polborn, K.; Kharagiosoff, K. *Helv. Chim. Acta* **2004**, *87*, 1426.
15. Giera, H.; Huisgen, R.; Langhals, E.; Polborn, K. *Helv. Chim. Acta* **2002**, *85*, 1523.
16. Sustmann, R.; Sicking, W.; Huisgen, R. *Eur. J. Org. Chem.* **2005**, in press.
17. Swinbourne, E. S. *Analysis of Kinetic Data*; Th. Nelson & Sons Ltd: London, 1971.
18. (a) Campbell, M. M.; Anthony, G. H.; Brooks, C. J. S. *Org. Mass. Spectrom.* **1971**, *5*, 297. (b) Paquer, D.; Morin, L.; Vazeux, M.; Andrieu, C. G. *Rec. Trav. Chim. Pays-Bas* **1981**, *100*, 36.
19. Mloston, G.; Huisgen, R.; Polborn, K. *Tetrahedron* **1999**, *55*, 11475.
20. Review: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 686–690.
21. Naqvi, R. R.; Wheatley, P. J. *J. Chem. Soc. A* **1970**, 2053.
22. Lambrecht, J.; Gambke, B.; v. Seyerl, J.; Huttner, G.; Kollmannsberger-von-Nell, G.; Herzberger, S.; Jochims, J. C. *Chem. Ber.* **1981**, *114*, 3751.
23. Jochims, J. C.; Lambrecht, J.; Burkert, U.; Zsolnai, L.; Huttner, G. *Tetrahedron* **1984**, *40*, 893.
24. Runge, W. *Org. Magn. Reson.* **1980**, *14*, 25.
25. Kreuzholz, R.; Schmidt-Vogt, W.; Maierhofer, M.; Polborn, K.; Stephenson, D. S.; Szeimies, G. *Eur. J. Org. Chem.* **1998**, 29.
26. Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys.* **1956**, *25*, 1228.
27. Anet, F. S. L.; Basus, V. J. *J. Magn. Reson.* **1978**, *32*, 339.
28. (a) Jochims, J. C.; Anet, F. A. L. *J. Am. Chem. Soc.* **1970**, *92*, 5524. (b) Jochims, J. C.; Herzberger, S.; Gambke, B.; Anet, F. A. L. *Tetrahedron Lett.* **1977**, 2255.
29. Wheatley, P. W. *Acta Crystallogr.* **1954**, *7*, 68.
30. Firl, J.; Schink, K.; Kosbahn, W. *Tetrahedron Lett.* **1981**, 527.
31. (a) Wittig, G.; Meske-Schüler, J. *Liebigs Ann. Chem.* **1968**, *711*, 76. (b) Wittig, G.; Fritze, P. *Liebigs Ann. Chem.* **1968**, *711*, 82. (c) Balci, M.; Jones, W. M. *J. Am. Chem. Soc.* **1980**, *102*, 7608.
32. Bettinger, H. G.; Schleyer, P. v. R.; Schreiner, P. R.; Schaefer, H. F., III. *J. Org. Chem.* **1997**, *62*, 9267.
33. Bettinger, H. F.; Schreiner, P. R.; Schleyer, P. v. R.; Schaefer, H. F., III. *J. Phys. Chem.* **1996**, *100*, 16147.
34. Engels, B.; Schöneboom, J. C.; Münster, A. F.; Groetsch, S.; Christl, M. *J. Am. Chem. Soc.* **2002**, *124*, 287.
35. Lemal, D. M.; Dunlap, L. H. *J. Am. Chem. Soc.* **1972**, *94*, 6562.
36. Proskow, S.; Simmons, H. E.; Cairns, T. L. *J. Am. Chem. Soc.* **1966**, *88*, 5254.
37. (a) Kudo, K. *Bull. Soc. Chim. Jpn* **1962**, *35*, 1490. (b) Ireland, C. J.; Jones, K.; Pizey, J. S.; Johnson, S. *Synth. Commun.* **1976**, *6*, 185.
38. Huisgen, R.; Li, X.; Giera, H.; Langhals, H. *Helv. Chim. Acta* **2001**, *84*, 981.
39. Sheldrick, G. M. *Programs for Crystal Structure Solution*; University of Göttingen, 1986, 1993.
40. Zsolnai, L.; Huttner, G. *Program ZORTEP*; University of Heidelberg.
41. Huisgen, R.; Mitra, A.; Moran, J. R. *Chem. Ber.* **1987**, *120*, 159.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 6154

Corrigendum

Corrigendum to "In situ 1,3-dipolar azide cycloaddition reaction: synthesis of functionalized D-glucose based chiral piperidine and oxazepine analogues"

[Tetrahedron 60 (2004) 4959]

Subhankar Tripathi, Kaushik Singha, Basudeb Achari and Sukhendu B. Mandal*

Division of Medicinal Chemistry, Indian Institute of Chemical Biology, Jadavpur, 4, Raja S. C. Mullick Road, Kolkata 700 032, India

Available online 17 May 2005

1. On page 4960 of the above paper the penultimate sentence should read as follows:

"In the ^{1}H NMR spectrum, the coupling constants $J_{2,3}$ are found to be somewhat different for **10** (8.5 Hz) and **11** (6.1 Hz). This may be due to difference in dihedral angle of the H–C_2–C_3–H unit (18° in **10** and 40° in **11**) in the energy-minimized structures obtained using Chem. Office 6.0."

2. In the References and notes section on page 4965 the sentence should read as follows:

"**13**: ^{1}H NMR ($CDCl_3+D_2O$, 300 MHz): δ 1.36 (s, 3H), 1.58 (s, 3H), 3.73 (dd, 1H, $J=3.5$, 5.8 Hz), 3.75 (dd, 1H, $J=2.8$, 5.8 Hz), 3.92 (dd, 1H, $J=4.0$, 6.0 Hz), 4.01–4.24 (m, 2H), 4.63 (t-like, 1H, $J=3.9$ Hz), 5.24–5.36 (m, 2H), 5.78 (d, 1H, $J=$ 3.6 Hz), 5.85–6.01 (m, 1H). **14**: ^{1}H NMR ($CDCl_3+D_2O$, 300 MHz): δ 1.32 (s, 3H), 1.47 (s, 3H), 3.75 (dd, 1H, $J=3.6$, 6.0 Hz), 3.82 (dd, 1H, $J=2.7$, 6.0 Hz), 3.87 (m, 1H), 4.03 (dd, 1H, $J=3.6$, 7.5 Hz), 4.08–4.15 (m, 2H), 4.55 (d, 1H, $J=3.6$ Hz), 5.19–5.35 (m, 2H), 5.85–5.98 (m, 2H)."

DOI of original article: 10.1016/j.tet.2004.04.036
* Corresponding author. Tel.: +91 33 2473 3491; fax: +91 33 2473 5197; e-mail: sbmandal@iicb.res.in

doi:10.1016/j.tet.2005.04.033