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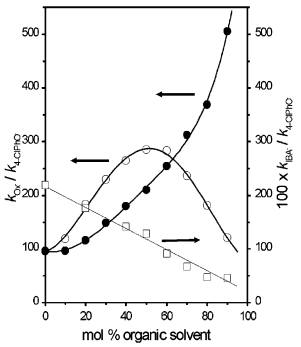
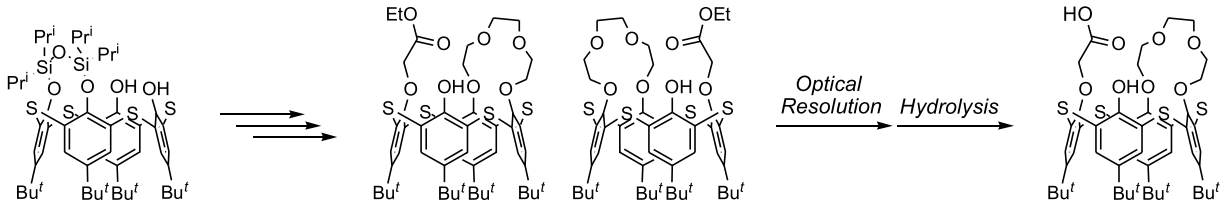
Contents

REPORT

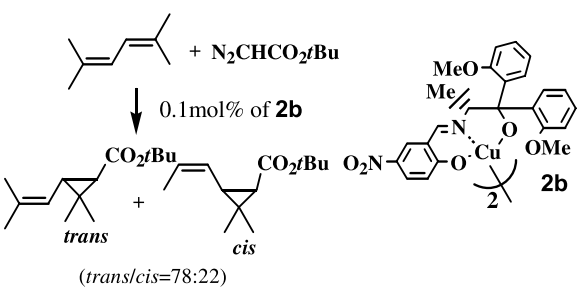
Plots showing the effect of solvent on the α-effect for the reactions of PNPA at 25.0±0.1 °C: $k_{Ox}^{-}/k_{4\text{-ClPhO}}^{-}$ in MeCN–H_2O (●); [*Chem. Commun*. **2000**, *19*, 1917] $k_{Ox}^{-}/k_{4\text{-ClPhO}}^{-}$ in DMSO–H_2O (○); [*J. Org. Chem*. **2000**, *65*, 577] $k_{IBA}^{-}/k_{4\text{-ClPhO}}^{-}$ in DMSO–H_2O (□) [*J. Chem. Soc., Chem. Commun*. **1987**, *11*, 860].



ARTICLES



A combination of chiral copper Schiff-base **2b** with $AI(OE)_3$ showed an increasing yield (up to 90%) and in enantioselectivity (91% ee for the *trans* isomer for the asymmetric cyclopropanation of the diene with *t*-butyl diazoacetate at 20 °C.



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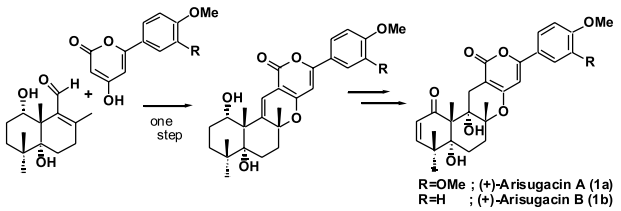
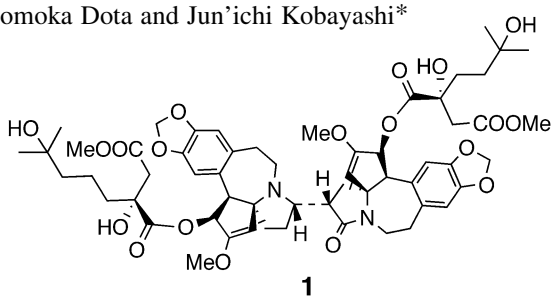
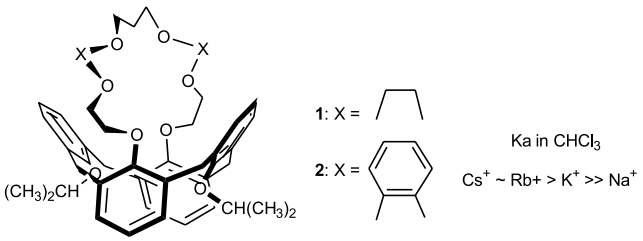


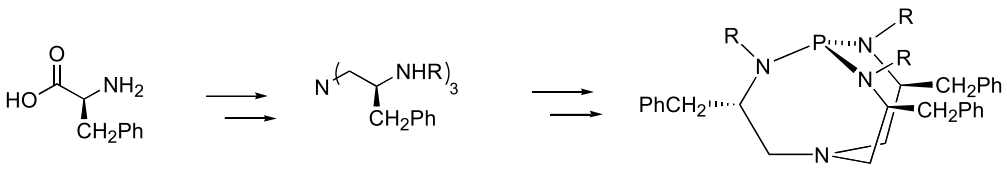


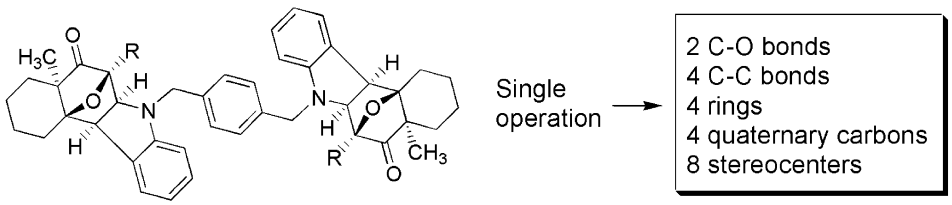
1

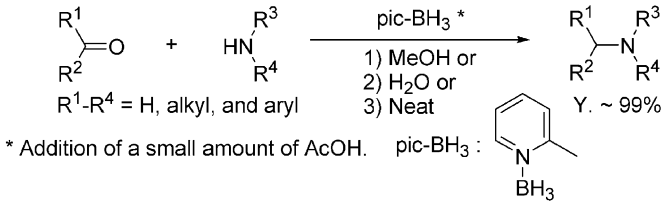
Five new dimeric *Cephalotaxus* alkaloids, bis-cephalezomines A–E (**1**–**5**), have been isolated from the leaves of *Cephalotaxus harringtonia* var. *nana*, and the structures and stereochemistry were elucidated on the basis of spectroscopic data including 2D NMR and FABMS/MS spectra, and chemical means.

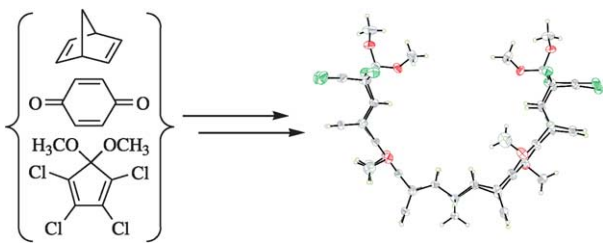


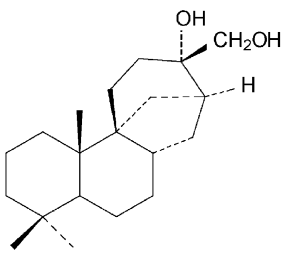
Following molecular modeling suggestion, calix[4]arene-propylene-crown-6 **1** and **2** were synthesised and their binding properties toward alkali metal picrates assessed in $CHCl_3$.







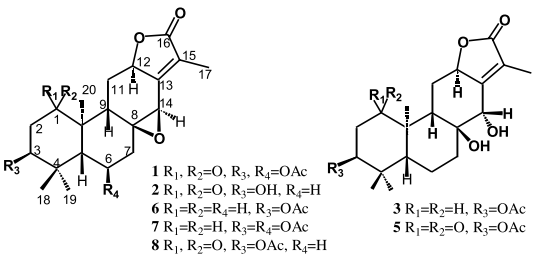




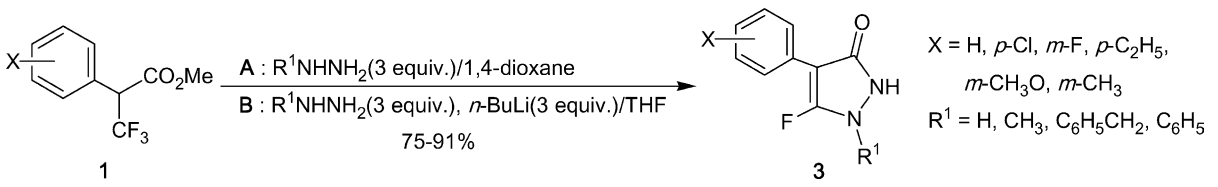
The microbiological transformation of 13α,17-dihydroxy-stemodane and 13α,14α-dihydroxy stemodane diterpenes by *Mucor plumbeus* preferently lead to metabolites hydroxylated at C-2 (α), C-3(β) and C-19. An interesting rearrangement of the second group of diterpenes to compounds with a prestemodane skeleton has been observed under acetylation conditions.

Revisiting diterpene lactones of *Suregada multiflora* **pp 7933–7941**
M. Iqbal Choudhary,* Humaira Y. Gondal, Ahmed Abbaskhan, Ismat A. Jahan, Masood Parvez, Nilufar Nahar and Atta-ur-Rahman

A study of the cytotoxic extracts of the leaves of *Suregada multiflora* has led to the isolation of ten tetracyclic diterpene lactone members of a rare group of diterpenes. Strucutre revision of some earlier reported diterpene lactones on the basis of 2D NMR and X-ray diffraction analyses is discussed.

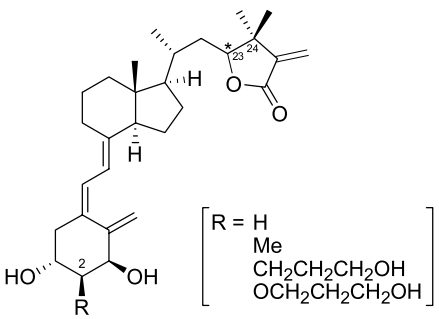


An efficient preparation of novel 5-fluoropyrazolin-3-one derivatives from α-trifluoromethylated α-arylacetates **pp 7943–7949**
No Kyun Park, Bum Tae Kim,* Surk Sik Moon, Sung Lan Jeon and In Howa Jeong*

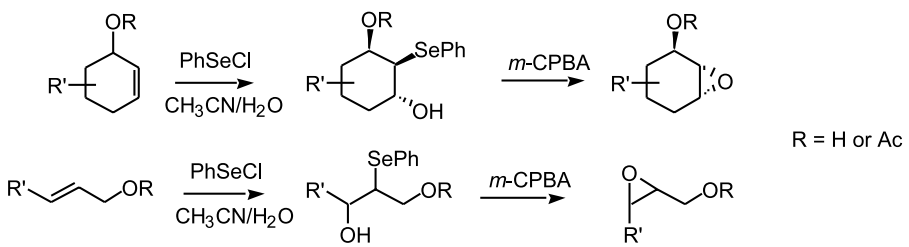


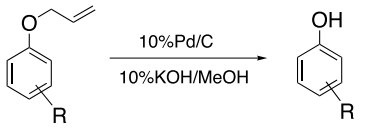
24,24-Dimethylvitamin D_3-26,23-lactones and their 2α-functionalized analogues as highly potent VDR antagonists **pp 7951–7961**
Nozomi Saito, Manami Masuda, Toshihiro Matsunaga, Hiroshi Saito, Miyuki Anzai, Kazuya Takenouchi, Daishiro Miura, Seiichi Ishizuka, Midori Takimoto-Kamimura and Atsushi Kittaka*

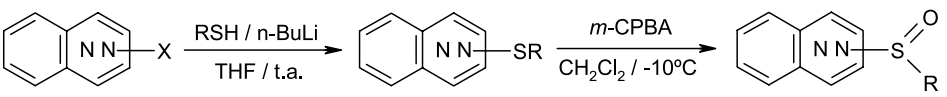
Novel 24,24-dimethyl-1α-hydroxyvitamin D_3-26,23-lactones and their 2α-substituted analogues with highly potent VDR antagonistic activity were efficiently synthesized.



Formation of dihydroxyselenides from allylic alcohols and their conversion to β-hydroxy epoxides via substitution of a phenylselenonyl group **pp 7963–7972**
Matthew A. Cooper and A. David Ward*







X = Cl, I

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The α-effect and its modulation by solvent

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Contents

1. Introduction

The α-effect was at first defined by the authoritative Glossary of Terms used in Physical Organic Chemistry as "the enhancement of nucleophilicity that is found when the atom adjacent to a nucleophilic site bears a lone pair of electrons".[1] Since this definition does not specify the reference nucleophile, it is somewhat ambiguous. Thus, an alternative definition of the α-effect was proposed, and adopted subsequently, that is, a positive deviation exhibited by an α-nucleophile from a Brønsted type nucleophilicity plot.[2] According to this definition, the reference (or normal) nucleophile of the first definition[1] is one which possesses the same basicity as the α-nucleophile but does not deviate from the Brønsted-type plot. However, structurally similar nucleophiles have often been used as the α- and normal nucleophiles, for example, HOO^- versus HO^-, $^tBuOO^-$ versus $^tBuO^-$, etc. although their basicity is very different.[3–5]

Keywords: Solvent; α-Effect; Nucleophilic site.
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Although several reviews of the α-effect have been published previously,[2,6–8] the effect of solvent on the α-effect has been neglected, probably due to a lack of relevant data on solvent effects at that time. Furthermore, finding of an α-effect in three such diverse solvents as MeCN, toluene and H_2O casts doubt on a connection between a particular solvent and the α-effect.[5,9] Moreover, a 'two point' analysis can be misleading. In fact, solvent effects on the α-effect have indeed been shown to be significant for various reactions performed in DMSO–H_2O and MeCN–H_2O mixtures whose compositions are varied systematically and incrementally.[10–21]

A change in solvent composition, or going from a protic to an aprotic solvent, can influence reactivity remarkably by affecting the transition state (TS) and/or the ground state (GS) energy.[22,23] We believe that properly balanced information of the solvent effect on the α-effect would be useful not only to physical organic but also to synthetic organic chemists. Therefore, the present review will mainly deal with the effect of solvent on the α-effect for various types of reactions, though factors influencing the magnitude of the α-effect will also be discussed.

As expounded upon by Reichardt,[25] solvent effects refer to all different types of interaction between solvent and solute molecules, that is, reactants, transition states and products—hydrogen bonding, ion–dipole, dipole–dipole, etc.—and their effect on homogeneous chemical equilibria, rates of chemical reactions, absorption spectra, etc.

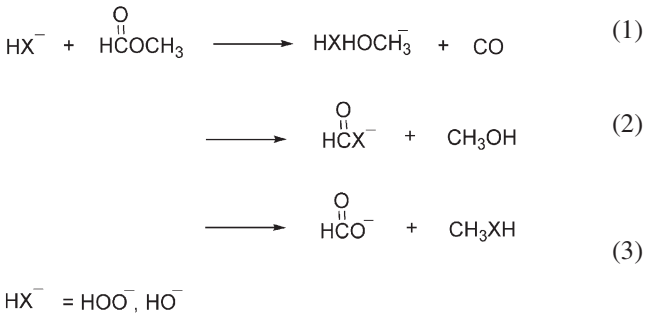
2. Magnitude of the α-effect in diverse media

2.1. In H_2O, MeCN, toluene

The α-effect has been investigated not only in H_2O but also in pure organic solvents such as toluene and MeCN. Curci et al. have found that ^{t}BuOO$^-$ exhibits an α-effect in its reactions with *p*-nitrophenyl benzoate (PNPB) and *p*-nitrophenyl diphenylphosphinate (PNPDPP) in toluene as well as H_2O (Table 1).[5] Similarly, Bruice et al. have reported that hydrazine is more reactive than similarly basic benzylamine toward *p*-nitrophenyl acetate (PNPA) in pure MeCN.[9] The finding of an α-effect in such diverse solvents could bring into question as to the role of solvent on the phenomenon of the α-effect.

2.2. Gas phase experimental studies

Hydroperoxide anion has often been found to exhibit higher reactivity than HO$^-$ or $CF_3CH_2O^-$ toward a variety of substrates in aqueous solution. However, in the gas phase HOO$^-$ has been reported to show no enhanced reactivity compared with HO$^-$.[24] Using the flowing afterglow technique, DePuy et al. showed that the gas phase reaction of methyl formate with HOO$^-$ and HO$^-$ (HX$^-$) occurred by three competitive pathways: proton abstraction (Eq. 1), $B_{AC}2$ addition to the carbonyl center (Eq. 2), and S_N2 displacement on the methyl group (Eq. 3).



The rate-determining step (RDS) in these processes is collision between the ion and the substrate. The relative rates of the three processes—proton abstraction, nucleophilic addition to the carbonyl group and S_N2 displacement on the methyl group—were found to be the same for the two anions.[24] In view of the finding that HOO$^-$ shows no enhanced nucleophilic reactivity compared to HO$^-$ in the gas phase, it seems plausible to propose that solvent effects are indeed responsible for the α-effect in the solution phase.

2.3. Gas phase calculations

The absence of an α-effect in the above gas phase reaction is consistent with gas phase calculations. At the 4-31G level, calculation for a set of oxyanions revealed that the heteroatom adjacent to the reaction O$^-$ center in nucleophiles such as HOO$^-$, ClO$^-$, and FO$^-$ causes a lowering of their out-of-phase HOMO's relative to HO$^-$. However, this would cause a decrease in reactivity for such nucleophiles rather than the observed enhanced reactivity corresponding to an α-effect.[26] The generally accepted HOMO–LUMO orbital interpretation of the α-effect was hence brought in question.[26] In any event, since gas phase S_N2 reactions of HOO$^-$ and FO$^-$ did not exhibit an α-effect, the important role of a hydroxylic solvent as the source of positive deviations from rate-equilibrium plots became evident.[26]

To take account of a solvent effect, Klopman et al. calculated the HOMO energies of HO$^-$ and HOO$^-$ in the gas and aqueous phase by a semi-empirical MINDO/3 method.[27] The HOMO energy of HOO$^-$ was calculated to

Table 1. Magnitudes of the α-effect ($k_{\alpha\text{-Nu}}/k_{\text{normal-Nu}}$) for various reactions performed in H_2O and organic solvents

Substrate	α-Nu	Normal-Nu	Solvent	α-effect	Reference
PNPB	^{t}BuOO$^-$	^{t}BuO$^-$	Toluene	5.2	5
	^{t}BuOO$^-$	$CF_3CH_2O^-$	H_2O	5.5	5
PNPDPP	^{t}BuOO$^-$	^{t}BuO$^-$	Toluene	2.7	5
	^{t}BuOO$^-$	$CF_3CH_2O^-$	H_2O	6.6	5
PNPA	NH_2NH_2 (16.61)[a]	$PhCH_2NH_2$ (16.76)[a]	MeCN	38	9

[a] pK_a value in MeCN.

be 0.48 kcal/mol higher than that of HO^- in the gas phase,[27] opposite to the ab initio results reported by Wolfe et al.[26] where the HOMO of HOO^- was reported to be 1.43 kcal/mol lower than that of HO^-. However, the difference was considered to be small and consistent with the aforementioned experimental finding of there being little reactivity difference between HOO^- and HO^- in the gas phase reactions with methyl formate.[24] On the other hand, the calculations showed that on transfer to the aqueous phase the HOMO of HO^- becomes more stabilized than that of HOO^-.[27] Consequently, the HOMO of HO^- drops substantially below that of HOO^- (2.86 kcal/mol). Overall, orbital-splitting was considered to play an important role in the enhanced nucleophilicity of HOO^- over HO^- in the aqueous phase.[27] However, the gas phase calculations did not take into account the effect of changing the HOMO may have on the basicity (and therefore on the conclusions).

Hoz and Buncel attributed the α-effect exhibited by HOO^- to TS stabilization rather than GS destabilization of HOO^-.[28,29] Importantly, Hoz suggested that the α-effect is large for reactions in which the TS entails significant electron transfer character.[30] Consider the α-nucleophile in its radical form (i.e., $HOO^{\cdot}$ for HOO^-), which has an odd electron α to a lone pair; the stability of radicals α to a lone pair is a well known phenomenon.[30]

Figure 1 shows a simple MO picture of the three-electron system which accounts for the stability of HOO·. According to this MO representation, there is a net energy stabilization since two electrons become lowered in energy to the bonding level and only one electron is raised to the antibonding orbital. Consequently, the α-nucleophile which possesses partial radical character at the TS will stabilize the TS in a way which is not available for normal nucleophiles.

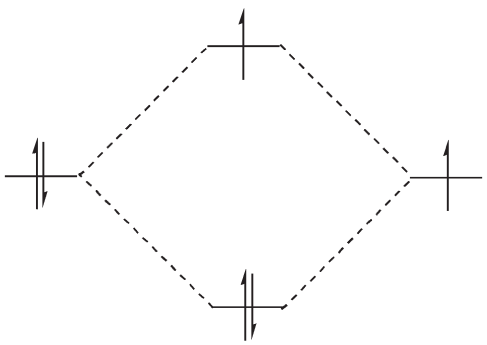


Figure 1. A simplified MO diagram of a three-electron system.[30]

According to the Hoz explanation, the magnitude of the α-effect should be dependent on the extent of single electron transfer (SET) at the TS.[30] Since the extent of SET can be correlated with the β_{nuc} value, one can expect that the α-effect should be directly related to the β_{nuc} value. That the magnitude of the α-effect does in fact increase with increasing β_{nuc} for various processes, such as the reactions of different substrates reacting with hydrazine and glycylglycine,[31] is consistent with Hoz's proposal.

3. Systematic variation of the medium

3.1. Rationale

Studies of the effect of solvent on the α-effect are subject to an ambiguity when the measurements are limited to a two-point study, that is, one determination in each pure solvent.[4,5,9] As shown in Figure 2, an imaginary linear function (dotted line) could be deduced from such a two-point determination, whereas in reality, if measurements are performed systematically over the whole range of solvent composition, a curved function, or even one with extrema, could result. An example of a bell-shaped curve is shown in Figure 3, for the variation of the α-effect with mol% DMSO/H_2O in the reaction of an oximate versus a normal nucleophile with PNPA.[11,12] Systematic studies of the

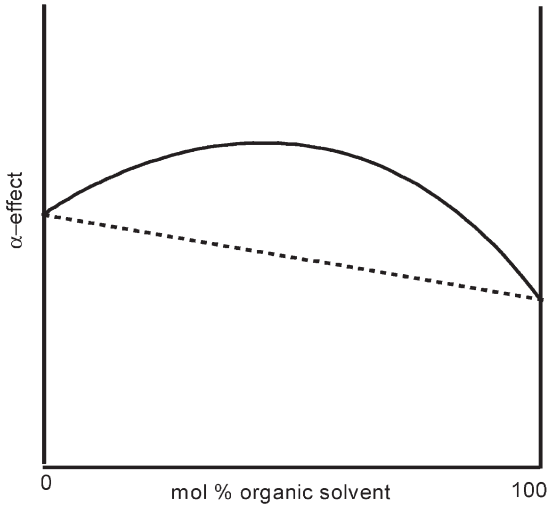


Figure 2. Hypothetical plots of the α-effect versus mol% organic solvent.

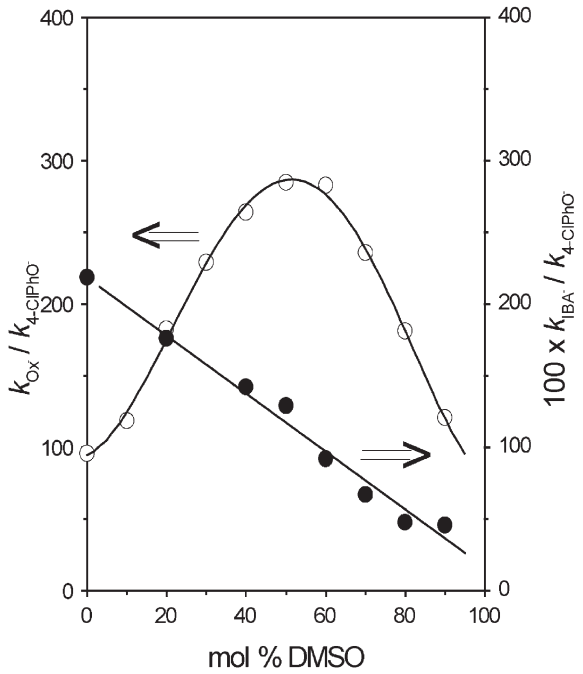


Figure 3. Plots showing the effect of solvent on the α-effect for the reactions of PNPA with Ox^- versus 4-$ClPhO^-$ (○),[11] and with IBA^- versus 4-$ClPhO^-$ (●), in DMSO–H_2O mixtures at 25.0±0.1 °C.[43]

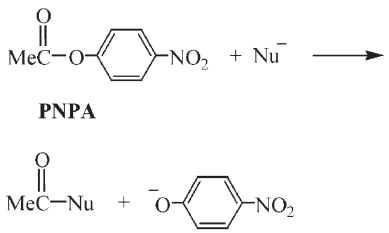
α-effect with solvent composition are considered in Section 3.2.

3.2. DMSO–H_2O and MeCN–H_2O mixtures

DMSO is known to be one of the most useful dipolar aprotic solvents in investigations of reactivity and reaction mechanism.[22,23,32–34] Since the negative end of the dipole in DMSO is exposed while the positive one is buried within the molecule, anions are effectively desolvated in the dipolar aprotic solvent. On the other hand, DMSO can stabilize a charge dispersed anionic transition state due to its high polarizability. Accordingly, the medium change from H_2O to DMSO often results in significant rate enhancements for nucleophilic reactions by anionic reagents.[22,23]

MeCN has also been widely used in such studies and can destabilize anions through dipole–anion repulsion, though its polarizability is lower than that of DMSO.[35–41] Importantly, the degree of destabilization of the GS, or stabilization of the TS, by these dipolar aprotic solvents is in general not the same. In fact, rate enhancements upon solvent change from H_2O to DMSO have often been found to be much more significant than from H_2O to MeCN.[22,36] One could well expect to gain useful information of the solvent effect on the α-effect from a medium change from DMSO–H_2O to MeCN–H_2O.

The first systematic study of the effect of solvent on the α-effect was reported by Terrier et al. in 1984 for the reaction of PNPA with α,α,α-trifluoroacetophenone oximate (TFA–Ox^-, an α-nucleophile) and 4-chlorophenoxide (4-$ClPhO^-$, as a corresponding normal nucleophile) in DMSO–H_2O mixtures of varying composition up to 70 vol% (35.6 mol%) DMSO.[10] The choice of the reagent pair in Eq. 4 was dictated by their finding that the proton basicities of these two anions are similar not only in H_2O but also throughout the whole range of the solvent composition studied.

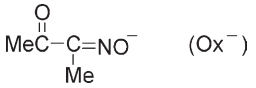


(4)

Nu^- = $PhC(CF_3)=NO^-$ (TFA-Ox^-) and 4-$ClC_6H_4O^-$ (4-$ClPhO^-$)

As shown in Table 2, the reactivity of these anionic nucleophiles toward PNPA increases with increasing DMSO content in the medium. However, the reactivity of the α-nucleophile, TFA–Ox^- is enhanced considerably relative to that of the similarly basic 4-$ClPhO^-$ on addition of DMSO to the medium; the α-effect increases from 53 in H_2O to 126 and 345 in 50 and 70% (v/v) DMSO, respectively.

Interestingly, an unexpected result was observed in a following study for the reaction of PNPA with butane-2,3-dione monoximate (Ox^-) as an α-nucleophile, in comparison with 4-$ClPhO^-$ as a corresponding normal nucleophile on extending the DMSO solvent composition range.[11] A previous study showed that the reaction in water is associated with an α-effect of considerable magnitude ($k_{Ox^-}/k_{4\text{-}ClPhO^-}=100$)[42] and it could reasonably be expected that this might show some variation in DMSO–H_2O mixtures.[22,23] Also, the pK_a values of Ox^- and 4-$ClPhO^-$ have been reported to vary in a similar manner on changing the DMSO–H_2O composition.[10]



As shown in Figure 3, the α-effect, $k_{Ox^-}/k_{4\text{-}ClPhO^-}$ for the reaction is markedly dependent on solvent composition: it increases from ca. 100 in H_2O to ca. 300 in 50 mol% DMSO, but then decreases to ca. 120 in 90 mol% DMSO. Thus, the magnitude of the α-effect exhibits a maximum at ca. 50 mol% DMSO; clearly, measurements confined to water and DMSO would have revealed only a slight solvent dependence of the α-effect, as shown in Figure 2.

Moreover, as shown in Figure 4, bell-shaped α-effect profiles have also been observed for the reactions of Ox^- and 4-$ClPhO^-$ with 4-nitrophenyl diphenylphosphinate (PNPDPP)[14] and 4-nitrophenyl benzenesulfonate (PNPBS)[15] in DMSO–H_2O mixtures.

Contrastingly, the reaction of PNPA with *o*-iodosylbenzoate (IBA^-, pK_a=7.1 in H_2O, an α-nucleophile) and 4-$ClPhO^-$ in DMSO–H_2O mixtures at 25.0 °C showed different behavior; in fact, as shown in Figure 3, the α-effect, $k_{IBA^-}/k_{4\text{-}ClPhO^-}$ decreases steadily with DMSO content.[43] However, in the absence of information on the variation of pK_a for *o*-iodosylbenzoate with mol% DMSO, it is difficult to draw definitive conclusions as to the generality of this finding (Scheme 1).

Table 2. Effect of DMSO on the rate-equilibrium behavior of TFA–Ox^- and 4-$ClPhO^-$ in the reaction with PNPA at 25.0 °C (I=0.5 M $Me_4N^+Cl^-$)[a]

DMSO (v/v, %)	p$K_a^{4\text{-}ClPhO-}$	$k_{4\text{-}ClPhO^-}/M^{-1}\,s^{-1}$	p$K_a^{TFA-Ox-}$	$k_{TFA-Ox^-}/M^{-1}\,s^{-1}$	$k_{TFA-Ox^-}/k_{4\text{-}ClPhO^-}$
0	9.35	0.57	9.05	30	53
10 (2.5 mol%)	9.45	0.52	9.21	31	60
20 (5.5 mol%)	9.65	0.50	9.42	34	68
30 (9.1 mol%)	9.90	0.54	9.85	43	80
40 (13.5 mol%)	10.15	0.66	10.15	57	86
50 (19.0 mol%)	10.55	0.84	10.65	106	126
60 (26.0 mol%)	10.95	1.38	10.95	360	260
70 (35.6 mol%)	11.60	2.90	11.60	1000	345

[a] Data taken from Ref. 10.

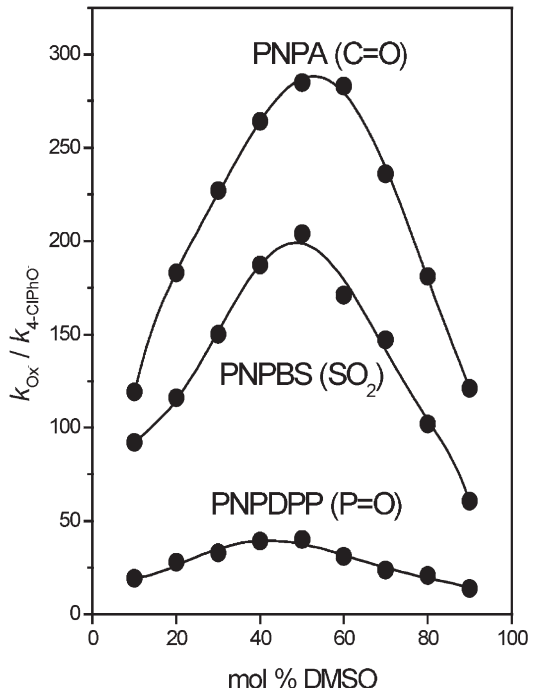
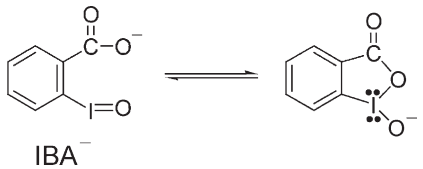


Figure 4. Plots showing the effect of solvent on the α-effect for the reactions of PNPA, PNPDPP and PNPBS with Ox^- versus 4-$ClPhO^-$ in DMSO–H_2O mixtures at 25.0±0.1 °C.[15]



Scheme 1.

As suggested earlier, a medium change from DMSO–H_2O to MeCN–H_2O mixtures may lead to a different solvent dependence of the α-effect.[16–19] Thus, as shown in Figure 5 for the reaction of PNPA with Ox^- and 4-$ClPhO^-$, the magnitude of the α-effect, $k_{Ox^-}/k_{4\text{-}ClPhO^-}$, increases continuously as the mol% MeCN in the medium increases, from 100 in H_2O to 500 in 90 mol% MeCN. Such an increasing α-effect trend has also been found for the corresponding reactions of 4-acetylphenyl acetate (PAPA) and 2,4-dinitrophenyl acetate (DNPA), indicating that this type of solvent dependence of the α-effect is general to this series (Fig. 13).[19]

Unexpectedly, in view of the above behaviors, the magnitude of the α-effect for the reaction of PNPA with benzohydroxamate (BHA^-, pK_a=8.88, an α-nucleophile) and 3-chlorophenoxide (3-$ClPhO^-$, pK_a=9.02, a normal-nucleophile) was found to decrease with increasing MeCN content in the medium.[20,21] As shown in Figure 6, the α-effect, $k_{BHA^-}/k_{3\text{-}ClPhO^-}$, decreases from 160 in H_2O to 110 and 30 in 50 and 90 mol% MeCN, respectively. Clearly, the α-effect profile found for the reactions of PNPA with BHA^- versus 3-$ClPhO^-$ is opposite to that found for the corresponding reactions with Ox^- versus 4-$ClPhO^-$ in the same solvent system.

The systematic studies described above have revealed

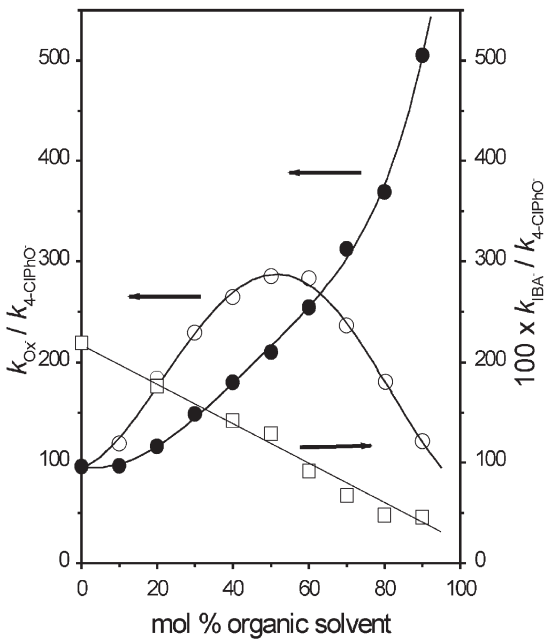


Figure 5. Plots showing the effect of solvent on the α-effect for the reactions of PNPA at 25.0±0.1 °C: $k_{Ox^-}/k_{4\text{-}ClPhO^-}$ in MeCN–H_2O (●);[18] $k_{Ox^-}/k_{4\text{-}ClPhO^-}$ in DMSO–H_2O (○);[12] $k_{IBA^-}/k_{4\text{-}ClPhO^-}$ in DMSO–H_2O (□).[43]

different kinds of solvent dependent α-effects: bell-shaped,[11,12,14,15] increasing,[16–19] or even a decreasing α-effect plot[20,21,43] depending on the nature of the solvent (DMSO vs. MeCN) and the type of α-nucleophiles (Ox^-, BHA^- and IBA^-). Such medium dependent α-effect profiles amply demonstrate that medium can have a significant influence and that two-point solvent plots can

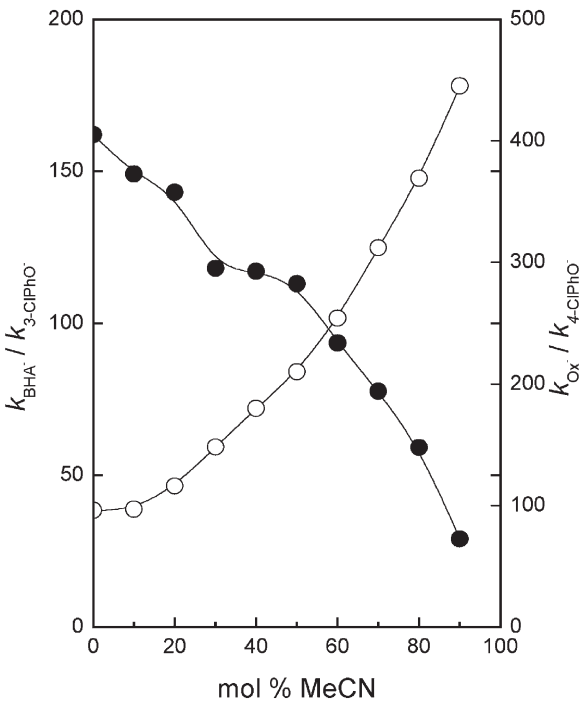


Figure 6. Plots showing dependence of the α-effect on the solvent composition for the reactions of PNPA with BHA^- versus 3-$ClPhO^-$ (●) and with Ox^- versus 4-$ClPhO^-$ (○) at 25.0 °C.[20]

be misleading. However, for more complete interpretation of the role of solvent, a dissection into GS and TS contributions through kinetic and thermodynamic studies is required[44–46] and is discussed in Section 3.3.

3.3. Dissection of kinetics and thermodynamics

In principle, a reaction pathway in a given solvent may be represented by a qualitative two-dimensional energy profile.[12,23] Figure 7 shows such a profile for a reaction carried out in two different media, H_2O and a DMSO–H_2O mixture, for example. The standard free energy of the reactant, R, in H_2O is designated as G_0^R and in a given DMSO–H_2O mixture as G_s^R. The difference in free energies of the reactant between the two solvents ($G_s^R - G_0^R$) is termed the transfer free energy δG_{tr}^R.

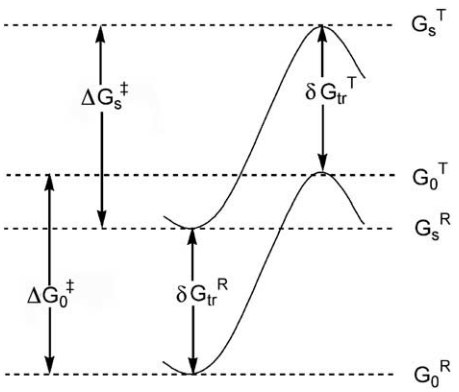


Figure 7. Illustration of relationship between the transfer free energies of reactant and the transition state and the free energies of activation for a reaction occurring in two solvent systems, the reference solvent (H_2O in this case) denoted by zero suffix, and the solvent under investigation (such as DMSO–H_2O mixture) denoted by suffix s.

$$\delta G_{tr}^R = G_s^R - G_0^R \tag{5}$$

Similarly, for the transition state T one obtains

$$\delta G_{tr}^T = G_s^T - G_0^T \tag{6}$$

The difference in free energies of activation for the two solvents is designated as $\delta\Delta G_{tr}^{\neq}$, and from Figure 7 it is apparent that

$$\delta\Delta G_{tr}^{\neq} = \Delta G_s^{\neq} - \Delta G_0^{\neq} = (G_s^T - G_s^R) - (G_0^T - G_0^R) \tag{7}$$

which simplifies to

$$\delta\Delta G_{tr}^{\neq} = \delta G_{tr}^T - \delta G_{tr}^R \tag{8}$$

δG_{tr}^T can be evaluated from the measurable transfer free energies of reactants (δG_{tr}^R) and the kinetic activation parameters ($\delta\Delta G_{tr}^{\neq}$). The foregoing derivations apply equally to the derived thermodynamic functions, that is, equations corresponding to δG_{tr}^R or δG_{tr}^T can readily be written for $\delta\Delta H_{tr}^R$ or $\delta\Delta H_{tr}^T$.

The purpose of this methodology is to dissect the relative contribution of the overall solvent effect on the GS and on the TS as the solvent composition is systematically changed from H_2O to 90 mol% DMSO. This in turn can lead to better understanding of the origin of the different types of response of the α-effect to solvent composition, as displayed above.[12]

Calorimetric measurements afford evaluation of enthalpies of solution. Using this technique, enthalpies of solution (ΔH_s) were determined for the sodium salts of Ox^- and 4-$ClPhO^-$ in the various DMSO–H_2O mixtures used in the corresponding kinetic studies.[12] As shown in Figure 8, ΔH_s for OxNa increases from ca. −5.0 kcal/mol in H_2O to ca. +1.0 kcal/mol in 30 mol% DMSO and then remains nearly unchanged beyond that point. A similar result is obtained for 4-ClPhONa, that is, ΔH_s increases from ca. −9.0 kcal/mol in H_2O to ca. −6.0 kcal/mol in 30 mol% DMSO and then remains almost constant beyond that point. These results indicate that OxNa is less strongly solvated than 4-ClPhONa in H_2O and becomes more desolvated upon addition of DMSO to the medium. This argument can be seen more clearly from the enthalpy of solution difference between Ox^- and 4-$ClPhO^-$ ($\Delta\Delta H_s$), which can be calculated from the following relationship since the enthalpy of solution of Na^+ cancels.

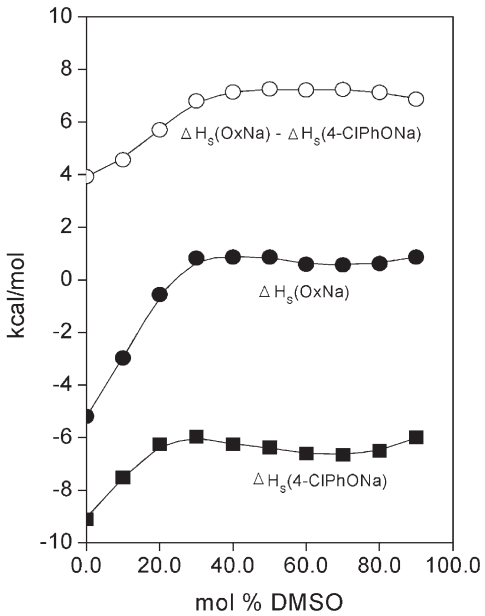


Figure 8. Plots of enthalpies of solution (ΔH_s) as a function of mol% DMSO for the sodium salts of 4-$ClPhO^-$ and Ox^- in DMSO–H_2O mixtures at 25.0 °C.[12]

$$\Delta\Delta H_s = \Delta H_s(\text{OxNa}) - \Delta H_s(\text{4-ClPhONa}) \tag{9}$$

It is seen in Figure 8 that $\Delta\Delta H_s$ increases by over 3 kcal/mol upon addition of DMSO up to ca. 50 mol% DMSO and remains almost constant beyond that point, indicating that Ox^- experiences much greater desolvation than 4-$ClPhO^-$ upon addition of DMSO to the medium.

It follows from Figure 8 that the increasing $\Delta\Delta H_s$ up to 50 mol% DMSO parallels the increasing α-effect trend observed over that medium range. Thus, the greatly increasing desolvation of Ox^- over 4-$ClPhO^-$ appears to be the dominant factor in the increasing α-effect up to 50 mol% DMSO. If the difference in the GS desolvation were mainly responsible for the α-effect throughout the whole range of DMSO–H_2O mixtures studied, one would have expected the α-effect to remain constant, at the maximum value, extending to the DMSO-rich region. In

fact, the magnitude of the α-effect decreases beyond 50 mol% DMSO in this and related systems (Figs. 3 and 4). Since the pK_a values of Ox^- and 4-$ClPhO^-$ change in parallel manner upon addition of DMSO to the medium,[10,11,14] the bell-shaped α-effect cannot be due to differential change in pK_a values of the two nucleophiles, and an additional factor must be operating in the DMSO-rich region.

To aid in the investigation of the effect of solvent on the TS, activation parameters were determined from rate constants measured at 25.0, 35.0 and 45.0 °C for the reaction of PNPA with Ox^- and 4-$ClPhO^-$ in DMSO–H_2O mixtures.[12] As shown in Figure 9, $\Delta G^{\neq}$ decreases by ca. 4 kcal/mol for both Ox^- and 4-$ClPhO^-$ systems as the DMSO content increases from 0 to 90 mol% DMSO, which is in accord with the rate enhancement upon addition of DMSO. The $T\Delta S^{\neq}$ value increases initially by 1–1.5 kcal/mol but remains almost constant beyond 20 mol% DMSO for both the Ox^- and 4-$ClPhO^-$ systems. The $\Delta H^{\neq}$ value also shows an initial increase upon solvent change from 0 to 20 mol% DMSO for both systems. However, unlike the entropy term, $\Delta H^{\neq}$ decreases for both systems upon further addition of DMSO, suggesting that the reaction is mainly governed by the enthalpy term beyond 20 mol% DMSO. As well, the decrease in $\Delta H^{\neq}$ for the 4-$ClPhO^-$ system was shown to be steeper than for the Ox^- system in the medium range 50–90 mol% DMSO. The differential trend in $\Delta H^{\neq}$ between the Ox^- and 4-$ClPhO^-$ systems in the DMSO-rich region is thus responsible for the decreasing α-effect in that medium range.[12]

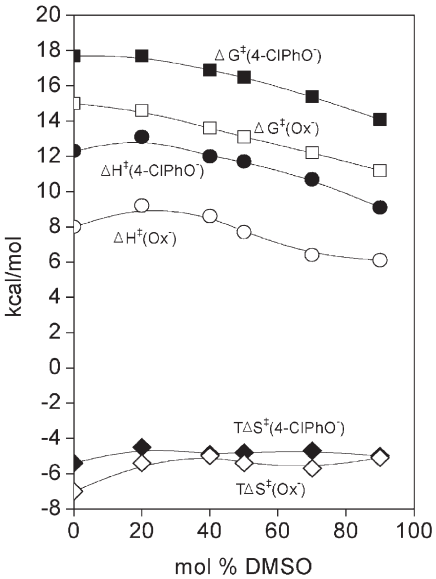
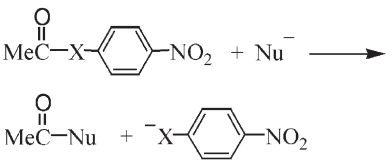


Figure 9. Comparative plots of activation parameters ($\Delta G^{\neq}$, $\Delta H^{\neq}$, and $T\Delta S^{\neq}$) as a function of mol% DMSO for the reaction of PNPA with 4-$ClPhO^-$ and Ox^- at 25.0 °C.[12]

The dissection of GS and TS contributions reveals that a single factor such as GS destabilization or TS stabilization is not by itself sufficient to explain the origin of the α-effect and its variation with solvent composition over the entire DMSO–H_2O system. The GS effect is more important than the TS effect in the H_2O-rich region, while the TS effect is dominant as the cause of the α-effect in the DMSO-rich region.[12] Solute–solvent interactions could well account for this variation since the H_2O-rich region will tend to stabilize the ionic GS while the polarizable TS will be stabilized in the DMSO-rich region.



(10)

X = O (PNPA), S (PNPTA)

$Nu^- = Ox^-$, 4-$ClPhO^-$

A novel type of solvent dependent α-effect has been reported recently for the reaction of *S*-4-nitrophenyl thioacetate (PNPTA), an analogue of PNPA, with Ox^- and 4-$ClPhO^-$ in DMSO–H_2O mixtures (Eq. 10).[13] As shown in Figure 10, the α-effect for the PNPTA system increases up to ca. 30 mol% DMSO and then levels off. Now, the α-effect trend in the PNPTA system corresponds to the ΔH_s difference between Ox^- and 4-$ClPhO^-$ ($\Delta\Delta H_s$) as shown previously in Figure 8. Therefore, in this system, the differential GS desolvation between Ox^- and 4-$ClPhO^-$ appears to be largely responsible for the α-effect over the whole medium range studied. This is consistent with the linear dependence of the α-effect on $\Delta\Delta H_s$ as shown in Figure 11.

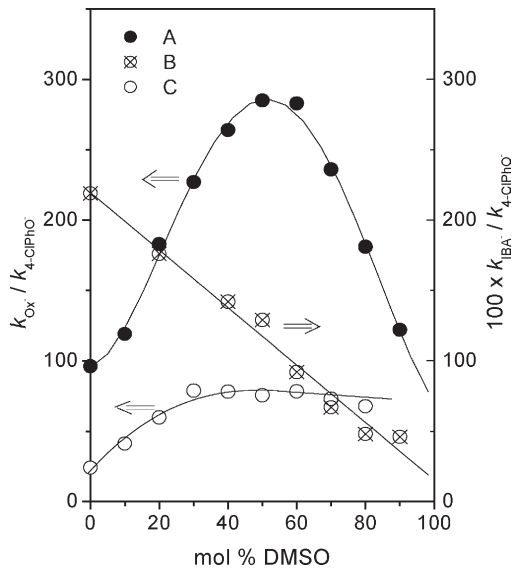


Figure 10. Illustration of the contrasting α-effect as a function of mol% DMSO at 25 °C. (A): Reaction of PNPA with Ox^- versus 4-$ClPhO^-$; (B): Reaction of PNPA with *o*-iodosylbenzoate (IBA^-) versus 4-$ClPhO^-$; (C): Reaction of *S*-4-nitrophenyl thioacetate (PNPTA) with Ox^- versus 4-$ClPhO^-$.[13]

The corresponding plot for the PNPA system reveals a bilinear relationship: up to ca. 50 mol% DMSO the α-effect displays linear dependence on $\Delta\Delta H_s$, but thereafter it becomes almost independent of $\Delta\Delta H_s$, implying that in that region the α-effect does not originate from differential GS desolvation. This is consistent with the notion expounded above that for PNPA reacting with Ox^- and 4-$ClPhO^-$, $\Delta\Delta H_s$ is responsible for the increasing α-effect up to ca.

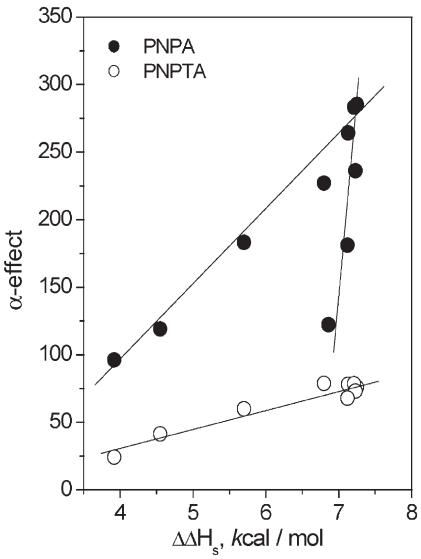


Figure 11. Illustration of the bilinear plot for the α-effect behavior of PNPA, contrasting with the linear plot for PNPTA, as a function of the differential heat of solution of Ox^- versus 4-$ClPhO^-$ in DMSO–H_2O mixtures. The break in the plot for PNPA occurs at ca. 50 mol% DMSO.[13]

50 mol% DMSO, as a GS effect, while differential TS stabilization is responsible for the decreasing α-effect beyond 50 mol% DMSO.[12]

It may be seen from this dissection of kinetic and thermodynamic effects, that the role of solvent on the α-effect is indeed remarkable, and that both the GS and TS can be influenced by solvent. To highlight but one example, elaborated on above, the study with PNPTA has shown that the GS contribution to the α-effect is dominant in this system.

3.4. pK_a Variation with solvent: DMSO–H_2O versus MeCN–H_2O

It is important to emphasize that in α-effect studies, the pK_a values of the α- and normal nucleophiles must be the same, or very nearly so.[2] Moreover, this applies equally when the solvent is varied.[10–15,18,19]

The pK_a values of the conjugate acids of Ox^- and 4-$ClPhO^-$ vary in a parallel manner in DMSO–H_2O mixtures, that is, the basicity of the two nucleophiles (Ox^- and 4-$ClPhO^-$) increases with increasing DMSO content in the medium but the difference in the basicity between the two is constant over the whole range of DMSO–H_2O mixtures studied.[10–15] Therefore, the bell-shaped α-effect profile found for the reactions of PNPA,[11,12] PNPDPP[14] and PNPBS[15] with Ox^- and 4-$ClPhO^-$ in DMSO–H_2O mixtures cannot be attributed to a possible difference in basicity of the two nucleophiles as the solvent is varied.

Though actual pK_a values in MeCN–H_2O have not been determined, however, the relative basicity of Ox^- and 4-$ClPhO^-$ determined in MeCN–H_2O mixtures reveals a different behavior compared with DMSO–H_2O mixtures.[18,19] The relative basicity (ΔpK_a) of Ox^- and 4-$ClPhO^-$ in MeCN–H_2O can be defined as the pK_a difference between the conjugate acids of the nucleophiles (Ox^- or 4-$ClPhO^-$) and a reference base (piperazine), that is, $\Delta pK_a = pK_a$ of the conjugate acid of Ox^- or 4-$ClPhO^-$ $- pK_a$ of the conjugate acid of piperazine. The magnitude of ΔpK_a thus represents the relative basicity of these nucleophiles.

Table 3. Summary of the relative basicity of the nucleophile ($\Delta pK_a = pK_a$ of the conjugate acid of the nucleophile $- pK_a$ of the conjugate acid of the reference base, piperazine) in MeCN–H_2O mixtures of varying compositions at 25.0±0.1 °C[a]

MeCN (mol%)	ΔpK_a (Ox^-)	ΔpK_a (4-$ClPhO^-$)	$\Delta\Delta pK_a$[b]
0	−0.38	−0.44	0.06
10	0.58	0.43	0.15
20	1.17	0.90	0.27
30	1.80	1.44	0.36
40	2.32	1.89	0.43
50	2.69	2.19	0.50
60	3.43	2.84	0.59
70	3.90	3.20	0.70
80	4.96	4.18	0.78
90	5.85	4.90	0.95

[a] Data taken from Ref. 19. The uncertainty in ΔpK_a values is estimated to be less than ±0.03 pK_a units.
[b] $\Delta\Delta pK_a = \Delta pK_a(Ox^-) - \Delta pK_a$(4-$ClPhO^-$).

As shown in Table 3, the ΔpK_a value of Ox^- and 4-$ClPhO^-$ increases with increasing mol% MeCN in the medium. However, the increase in ΔpK_a is greater for Ox^- than 4-$ClPhO^-$ and, as a result, the difference in the relative basicity between Ox^- and 4-$ClPhO^-$, defined as $\Delta\Delta pK_a$, that is, $\Delta\Delta pK_a = \Delta pK_a(Ox^-) - \Delta pK_a$(4-$ClPhO^-$), becomes larger with increasing mol% MeCN in the medium. It is apparent that the increasing $\Delta\Delta pK_a$ with increasing MeCN content is responsible for the increasing α-effect profile found for the reactions of PNPA with Ox^- and 4-$ClPhO^-$ in MeCN–H_2O mixtures. This argument can be supported from the linear plot of log $k_{Ox^-}/k_{4\text{-}ClPhO^-}$ versus $\Delta\Delta pK_a$ shown in Figures 12 and 14. Furthermore, the fact that the

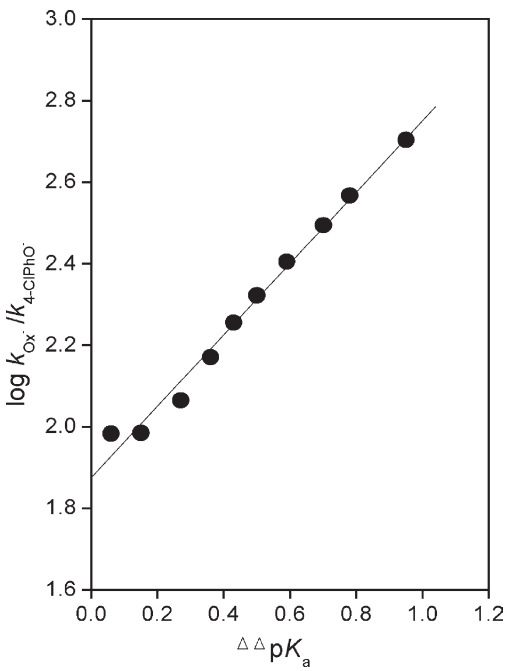


Figure 12. Plot of log $k_{Ox^-}/k_{4\text{-}ClPhO^-}$ versus $\Delta\Delta pK_a$ for the reaction of PNPA with Ox^- and 4-$ClPhO^-$ in MeCN–H_2O mixtures at 25.0±0.1 °C.[18]

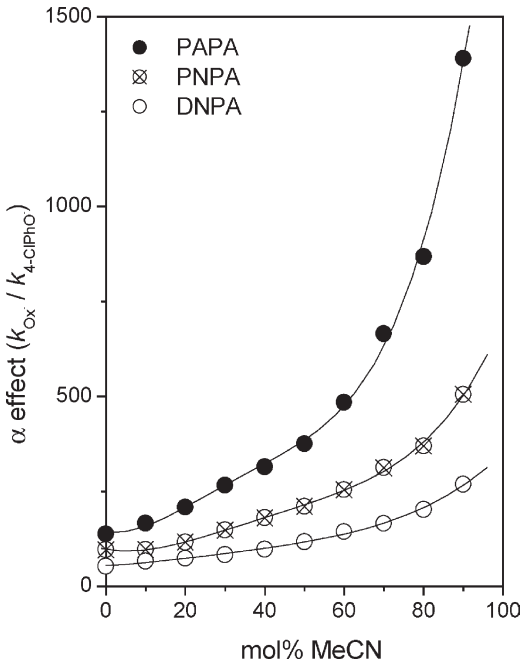


Figure 13. Plots of α-effect versus mol% MeCN for reactions of aryl acetates with Ox^- and 4-ClPhO^- in MeCN–H_2O mixtures at 25.0±0.1 °C.[19]

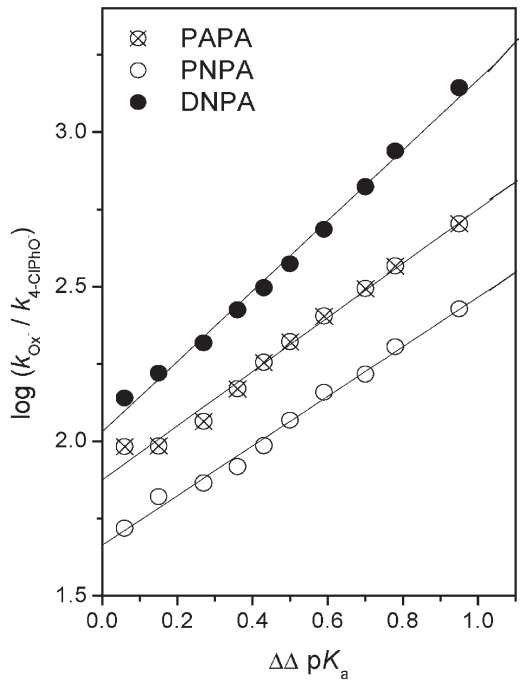
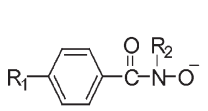


Figure 14. Plots of log $k_{Ox^-}/k_{4\text{-ClPhO}^-}$ versus $\Delta\Delta pK_a$ for the reactions of aryl acetates with Ox^- and 4-ClPhO^- in MeCN–H_2O mixtures at 25.0±0.1 °C.[19]

slope of the linear plot is ca. 1 indicates that the increase in the $\Delta\Delta pK_a$ is almost fully reflected in the increase in the α-effect for the reaction of 4-acetylphenyl acetate (PAPA), PNPA and 2,4-dinitrophenyl acetate (DNPA) with Ox^- and 4-ClPhO^- upon addition of MeCN to the medium.

Depending on the solvent, hydroxamic acids behave either as NH or OH acids, according to the tautomeric equilibrium:[47–54] (Scheme 2).

Thus, one might attribute the origin of the decreasing α-effect shown in Figure 6 in MeCN–H_2O mixtures for the reactions of PNPA with BHA^- and 3-ClPhO^- to this tautomerization.[21]



BHA^-; $R_1 = R_2 = H$

$MBHA^-$; $R_1 = Me$, $R_2 = H$

M_2BHA^-; $R_1 = R_2 = Me$

To ascertain the validity of this argument, the reactions of PNPA with 4-methylbenzohydroxamate ($MBHA^-$) and 4-methyl-*N*-methylbenzohydroxamate (M_2BHA^-) were examined.[21] BHA^- and $MBHA^-$ can react via their tautomeric structures II and III, while M_2BHA^- cannot tautomerize. The α-effect for the reactions with BHA^- and $MBHA^-$ decreases as the mol% MeCN in the medium increases as shown in Figure 15. On the contrary, the α-effect for the corresponding reactions with M_2BHA^- increases for such a solvent composition change. This

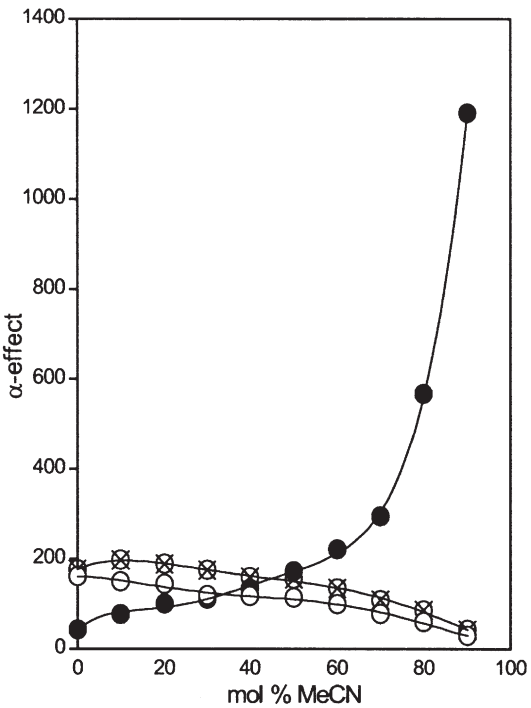
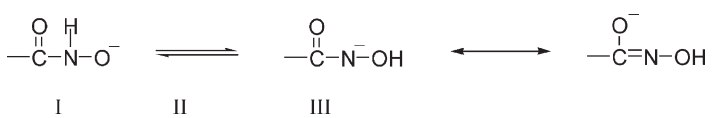


Figure 15. Plots showing dependence of the α-effect for reactions of PNPA with 3-ClPhO^-, BHA^-, $MBHA^-$, and M_2BHA^- in MeCN–H_2O mixtures of varying compositions at 25.0±0.1 °C. $k_{BHA^-}/k_{3\text{-ClPhO}^-}$ (○), $k_{MBHA^-}/k_{3\text{-ClPhO}^-}$ (⊗), $k_{M2BHA^-}/k_{3\text{-ClPhO}^-}$ (●).[21]



I II III

Scheme 2.

contrasting α-effect profile clearly supports the proposal that tautomerization of hydroxamic acids is responsible for the decreasing α-effect profile for the reactions of PNPA with BHA^- and $MBHA^-$ in $MeCN–H_2O$ mixtures.

However, product analysis revealed that only the *O*-acylated product is produced quantitatively from the reaction of PNPA with BHA^- under kinetic conditions for all the solvent mixtures studied.[21] This is in accord with tautomer II or III being less reactive than I; thus the equilibrium shift from I to the less reactive II or III is responsible for the decreasing α-effect upon addition of MeCN to the medium.

The above argument can be further supported from the relative basicities of these nucleophiles, ΔpK_a (i.e., $\Delta pK_a = pK_a$ of the conjugate acid of the nucleophile $- pK_a$ of the conjugate acid of the reference base, 3-nitrophenoxide) in $MeCN–H_2O$ mixtures. The ΔpK_a values for BHA^- and $MBHA^-$ decrease by ca. 0.96 and 0.34 pK_a units, respectively, upon solvent change from H_2O to 90 mol% MeCN (Fig. 16). However, the ΔpK_a values for M_2BHA^- and 3-ClPhO^- increase by ca. 1.1 and 0.6 pK_a units, respectively, on going from H_2O to 90 mol% MeCN. Thus, the contrasting solvent effect on the ΔpK_a is consistent with BHA^- and $MBHA^-$ undergoing tautomerization upon addition of MeCN to the medium, while M_2BHA^- does not.

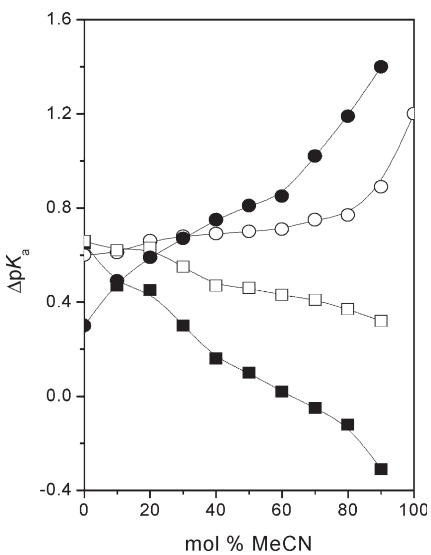


Figure 16. Plots showing solvent effect on the relative basicity (ΔpK_a) of the nucleophiles: (○) 3-ClPhO^-, (■) BHA^-, (□) $MBHA^-$, and (●) M_2BHA^-.[21]

The fact that the increase in the ΔpK_a value upon the solvent change is more significant for M_2BHA^- than for 3-ClPhO^- accounts for the increasing α-effect profile found for the reactions of PNPA with M_2BHA^- and 3-ClPhO^-. It can therefore be concluded that the decreasing, or increasing, α-effects found for the reactions of PNPA with the benzohydroxamates and 3-ClPhO^- in $MeCN–H_2O$ mixtures have as origin the differential ΔpK_a between the hydroxamate and 3-ClPhO^-.[21]

3.5. Principle of non-perfect synchronization, the importance of nucleophile desolvation: oximates versus aryloxides

The requirement of the shedding of one or more molecules of solvent of an anionic reagent before bond formation to the electrophilic center can take place, has been one of the principles governing nucleophilic reactivity over several decades.[55] Discussions of this idea date back to Moelwyn–Hughes,[56a] Ingold,[56b] Bell,[57] Marcus,[58a] Robertson,[58b] Hammond,[59] Polany,[60] Thornton,[61] Leffler,[62] Ritchie,[63] Jencks[55] and more recently Bernasconi[64] and Terrier.[65–69] The degree of correspondence or lack thereof, that is, imbalance, between nucleophile desolvation and bond formation forms the basis of the principle of non-perfect synchronization (PNS) put forward by Bernasconi.[64] It will be seen in the following that understanding of the α-effect in terms of the Bema Hopothle[55] is intimately tied to the idea of the PNS.[65–69]

The first study in the realm of the α-effect where satisfactory explanation invokes the idea of the PNS was reported by Terrier et al.[65] The reaction of PNPA with a series of α-ketoaldoximate anions of moderate basicity (pK_a=6.54–8.30) in H_2O generated a Brønsted-type plot that was linear at low pK_a with a β_{nuc} value of ca. 0.7 but displayed marked levelling-off at $pK_a > 7.8$.[65] More recently, similar results were found for the reactions of PNPA and diisopropyl phosphorotrifluoridate with a series of pyridinium carbaldoximates (pK_a=7.13–9.02),[66,67] and for the S_NAr reaction of 2,4-dinitrofluorobenzene with a series of oximate anions in H_2O.[68] The Brønsted-type plots for the reactions with oximate anions exhibited a plateau at pK_a of ca. 8 in all cases, while the corresponding reactions with aryloxides resulted in linear Brønsted-type plots (Fig. 17).[67]

Although downward curvature in Brønsted-type plots has

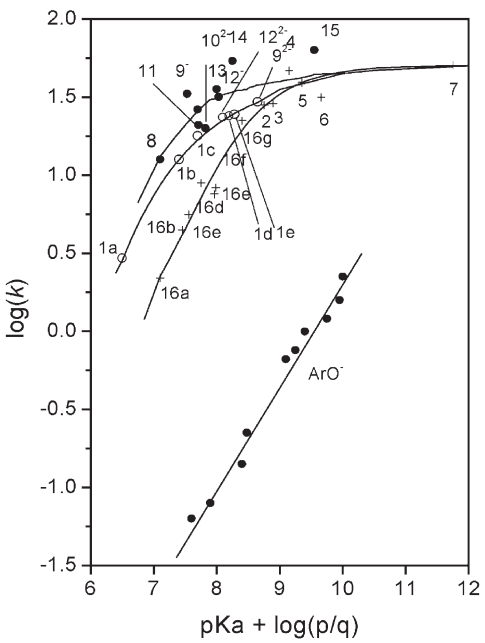


Figure 17. Brønsted-type nucleophilicity plots for reactions of oximates and phenoxides (ArO^-) with PNPA at 25 °C in aqueous solution.[67] See Ref. 67 for identification of the oximate families.

been frequently observed in reactions of normal oxyanions with esters, the curvature appeared for strongly basic oxyanions such as hydroxide and alkoxide with pK_a's 12–16.[70,71] Thus, the Brønsted-type plot showing a levelling at low pK_a (ca. 8) differentiates curvature in the α-effect plots with oximate nucleophiles from the Jencks-type curvature of hydroxide or alkoxide ions.

A different approach toward investigating the bell-shaped profile characterizing oximate reactivity was reported by Tarkka and Buncel which invoked discussion of the PNS.[14] The reactions of 4-nitrophenyl diphenylphosphinate (PNPDPP) with Ox^- and 4-$ClPhO^-$ in DMSO–H_2O mixtures exhibit a marked though non-uniform dependence of rate on solvent composition (Fig. 18). For both nucleophiles, there is an initial decrease in rate, with a shallow minimum occurring at 10 mol% DMSO; however, from 20 to 90 mol% DMSO the rate increases. The overall solvent rate-enhancing effect is about 10^3 for both nucleophiles. Importantly, the α-nucleophile, Ox^-, is more reactive than the normal-nucleophile, 4-$ClPhO^-$, by a factor of ca. 15–40 depending on solvent composition, with the rate enhancement being maximum at ca. 50 mol% DMSO.[14]

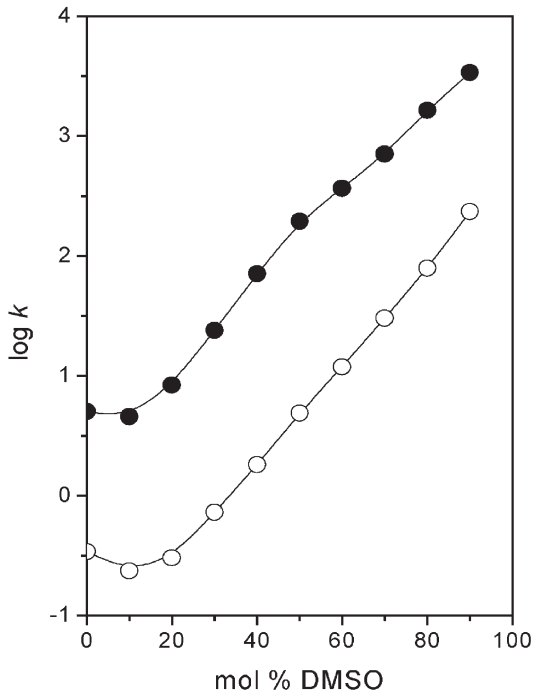


Figure 18. Plot of log k versus mol% DMSO for the reaction of butane-2,3-dione monoximate (Ox^-, ●) and 4-chlorophenoxide (4-$ClPhO^-$, ○) with 4-nitrophenyl diphenylphosphinate (PNPDPP) at 25.0 °C.[14]

The initial rate decrease in the region of high H_2O content seen in Figure 18 for both α- and normal nucleophilic reactions, is in line with trends seen in a number of physical properties including adiabatic compressibility and excess free energy.[72–77] Hydrophobic interactions induced by the addition of small quantities of DMSO to water induce 'rigidification' of hydrogen bonds between H_2O molecules.[77] The 'irregular' behavior of these solvent mixtures appears to vanish at higher DMSO concentrations. In view of this, our ensuing discussion will focus on the kinetic data obtained in media containing ≥20 mol% DMSO.

Examination of the plots of log k versus mol% DMSO (Fig. 18) shows that the plot for 4-$ClPhO^-$ is linear in media containing ≥20 mol% DMSO, while the one for Ox^- is best described as being either curved or consisting of two intersecting linear portions. Between 20 and 50 mol% DMSO, the slope of the Ox^- plot is steeper than that of the 4-$ClPhO^-$ plot, and the plots diverge as the DMSO content increases. This leads to a net increase in the magnitude of the α-effect, the $k_{Ox^-}/k_{4\text{-}ClPhO^-}$ ratio; at 50 mol% DMSO the gap between the Ox^- plot and 4-$ClPhO^-$ plot is at a maximum as is the magnitude of the α-effect. Between 60 and 90 mol% DMSO, the slope of the Ox^- plot is smaller than that of the 4-$ClPhO^-$ plot and the plots head toward convergence. The magnitude of the α-effect thus decreases.

It is apparent that if each plot in Figure 18 were linear with identical slope, the magnitude of the α-effect would be independent of solvent composition. The non-linearity of the Ox^- plot in ≥20 mol% DMSO thus leads to the bell-shaped α-effect plot shown in Figure 4. This phenomenological account of the bell-shaped α-effect plot, however, cannot explain what molecular-level phenomena are responsible for the individual trends (linearity of the 4-$ClPhO^-$ plot vs. non-linearity of the Ox^- plot), and a more in-depth analysis is required to explain the results.

A new methodology for constructing Brønsted-type plots was employed to investigate the possible reasons why the Ox^- plot is non-linear while the 4-$ClPhO^-$ plot is linear. The pK_a values of Brønsted acids, specifically phenols, increase in a regular manner as DMSO is added to DMSO–H_2O mixtures.[10,64,78,79] In fact, the pK_a values are essentially a linear function of mol% DMSO.[80] This suggested that it would be possible to plot log k versus pK_a (Nu) for the reaction of single base with a given substrate, with variation in the pK_a and log k terms being brought about through changes in the solvent composition, as contrasted to traditional Brønsted-type plots in which basicity and nucleophilicity are varied through changes in remote substituent while solvent identity is maintained.[80]

The novel Brønsted-type plots are shown in Figure 19. The 4-$ClPhO^-$ plot is linear with slope β_{nuc}=0.53 (r^2=0.999), while the Ox^- plot is non-linear. In a manner similar to the plot of log k versus mol% DMSO (Fig. 18), the gap between the two novel Brønsted-type plots (at a given pK_a value) increases with increasing pK_a up to ca. pK_a=12.8. The slope of the Ox^- plot is larger than that of the 4-$ClPhO^-$ plot as the plots diverge, and the magnitude of the α-effect increases until a maximum is reached at ca. pK_a=12.8. As the pK_a of the nucleophile is increased further, the slope of the Ox^- plot becomes smaller than that of the 4-$ClPhO^-$ plot, the gap between the two plots decreases, and the magnitude of the α-effect decreases.

In the context of the definition of the α-effect being a positive deviation from the Brønsted-type plot (from reference nucleophiles), the bell-shaped α-effect plot thus

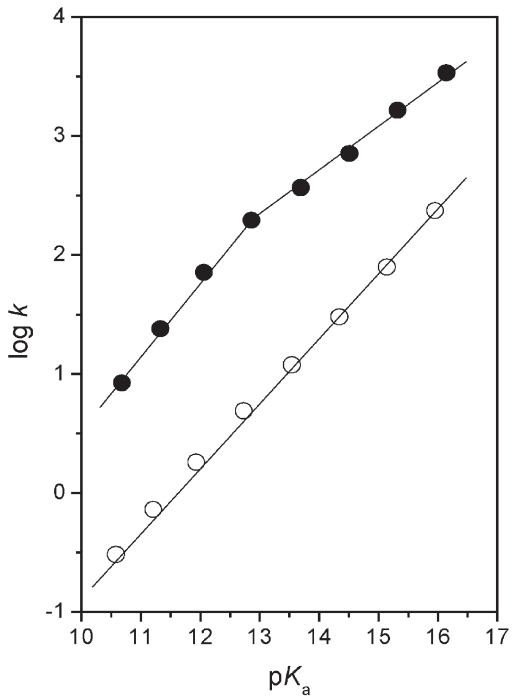


Figure 19. Novel Brønsted-type plots: log k versus pK_a for the reaction of butane-2,3-dione monoximate (Ox^-, ●) and 4-chlorophenoxide (4-$ClPhO^-$, ○) with *p*-nitrophenyl diphenylphosphinate (PNPDPP) at 25.0 °C.[14]

results from the bell-shaped gap between the two novel Brønsted-type plots. This is analogous to the result obtained by Terrier et al. for the reaction of PNPA in aqueous media with a series of substituted oximates relative to a series of substituted phenoxides.[65–69] Brønsted-type plots constructed from the data set revealed two types of behavior (e.g., Fig. 17). For the oximate set an initial linear portion was followed by a plateau for oximate nucleophiles with pK_a values >ca. 8. For the phenoxide series the plot was linear over the entire pK_a region studied (7.7–10.2). The α-effect increased as the pK_a of the oximates increases up to pK_a of ca. 7.5 and then decreased steadily with further increase in pK_a.

The result obtained through the use of the novel Brønsted-type plots is similar to the results obtained by Terrier et al. who used traditional Brønsted-type plots. In both cases, a bell-shaped α-effect is obtained due to the differential nature of the Brønsted-type plots: the reference series of aryloxides give rise to plots that are linear in both studies, whereas the oximates yield non-linear plots in both studies.

The requirement for desolvation of anions in nucleophilic bond formation with an electrophilic center has been a long-accepted dogma.[8,70,71,81] Jencks ascribed curvature in Brønsted-type plots observed for carbonyl centers to the progressively more difficult desolvation of anions as their basicity increases.[70,71] Furthermore, he considered that this desolvation would occur ahead of bond formation, leading to TS imbalance. More recently, the idea of imbalance has been quantified by Bernasconi as the principle of non-perfect synchronization (PNS), which can be applied to the present system.[64]

Considering the effect of increasing the basicity of a nucleophile on reaction rate, an empirical quantification of the PNS is given by Eq. 11, where δ log k_0 is the

$$\delta \log k_0 = (\alpha_{DES} - \beta_{nuc})\delta \log K_{DES} \quad (11)$$

decrease in reaction rate from the reference reaction induced by enhanced desolvation. The δ log K_{DES} term represents the change in the equilibrium constant for desolvation of the nucleophile, while nucleophilic bond formation to the substrate is measured by β_{nuc} and the extent of anion desolvation by α_{DES}. If a perturbation is made to the nucleophile and the extent of synchronicity between bond formation and nucleophile desolvation ($\alpha_{DES}-\beta_{nuc}$) remains constant, and if the δ log K_{DES} term also remains constant, then the rate does not differ from that of the reference reaction. On the other hand, if the ($\alpha_{DES}-\beta_{nuc}$) term increases in magnitude, the reaction rate will decrease.

The non-linearity of the novel Brønsted-type plot for the reaction of Ox^- with PNPDPP finds explanation in terms of the PNS model as follows. The deviation in reaction rate from the reference reaction, the δ log k_0 term, is non-linear, which would arise if the ($\alpha_{DES}-\beta_{nuc}$) term or the δ log K_{DES} term, or both terms, were non-linear functions of pK_a. In the case of non-linear Brønsted-type plots it is concluded that the ($\alpha_{DES}-\beta_{nuc}$) term is the source of the non-linearity, specifically that the α_{DES} term varies while the β_{nuc} term remains constant.[65–69] This would indicate that non-synchronicity between bond formation and desolvation exists for reaction of the oximate, and the extent of non-synchronicity varies as the solvent composition changes. In other words, the ($\alpha_{DES}-\beta_{nuc}$) term varies with changes in the solvent composition. In the case of the phenoxide, the ($\alpha_{DES}-\beta_{nuc}$) term is constant (but not necessarily zero) for changes in solvent composition.

On this basis, the non-linearity of the Brønsted-type plot for the reaction of Ox^- with PNPDPP in DMSO–H_2O mixtures could arise from variation in the desolvation term for Ox^-. However, for the reference nucleophile the TS structure remains constant, leading to a linear Brønsted-type plot. The bell-shaped dependence on solvent composition of the α-effect magnitude hence originates from changes in the extent of desolvation at the TS for reaction of Ox^-.

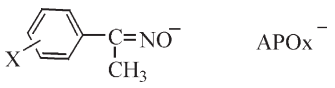
Terrier et al. likewise accounted for their results by considering PNS effects.[65–69] In their case, though, the extent of desolvation of the nucleophile increases as the basicity of the substituted oximates increases. It appears, then, that not only the results but also the significance of PNS effects are common to the Tarkka–Buncel and Terrier's study. The contrast between these studies is that, while Terrier's study, based on the traditional Brønsted-type plot analysis, requires use of a family of oximates and aryloxides, the novel Brønsted-type plots in conjunction with solvent pK_a variation enable analogous conclusions to be reached with a single oximate and phenoxide.[14]

3.6. A remarkable inversal in oximate reactivity brought about by solvent DMSO–H_2O composition

The question can be posed henceforth: how could one change the solvational imbalance pertaining to the oximates

and thereby reverse their levelling-off in reactivity? It appeared that one approach would be to change from aqueous medium to DMSO-rich media using highly basic oximates in view of previous findings of the modulation of basicities and nucleophilicities through the use of DMSO–H_2O mixtures.[82]

The effect of solvent on the reactivity of highly basic oximate ions was systematically investigated for the reactions of 4-nitrophenyl benzoate (PNPB) with a series of aryloxides and acetophenone oximates ($APOx^-$) in 20 and 90 mol% DMSO.[82] The Hammett plots are linear for the reactions performed in 20 mol% DMSO with ρ values of -1.86 and 0.20 for the reactions of PNPB with aryloxides and the oximates, respectively (Fig. 20A). The smaller ρ value for the reactions with the oximates is not surprising since the substituent in the acetophenone oximate is further away from the reaction site than the one in the aryloxides. However, the ρ value of $+0.20$ is striking since it corresponds to a decrease in reactivity of the oximates with increasing base-strengthening ability of the substituent. As noted above, a rapid levelling-off in a Brønsted-type plot has often been reported for reactions of oximates with high basicity (pK_a>ca. 8), however, the positive ρ value found for the reactions with the oximates appears without precedent.



As mentioned above, basic oximates (pK_a>ca. 8) have been observed to exhibit a plateauing in Brønsted-type plots, and strong solvation of such highly basic oximates has been suggested to be responsible for the levelling.[65–69] Since acetophenone oximate (pK_a=11.4) is more basic than the oximates which exhibit levelling in the Brønsted-type plot, solvation of these highly basic oximates in the water-rich medium would be important. Furthermore, solvation would become greater as the substituent in the acetophenone oximate becomes stronger electron-donating, suggesting that solvation is responsible for the positive ρ value obtained for the reactions with the acetophenone oximates in 20 mol% DMSO.

To scrutinize the above argument further, the reactions were performed in 90 mol% DMSO. H-bonding interactions between H_2O and DMSO are stronger than between H_2O molecules, and DMSO forms a strong complex with two H_2O molecules.[22,23] In 90 mol% DMSO, there would be no free H_2O molecules available for H-bonding with the anionic nucleophiles. On the other hand, repulsion between the anionic nucleophiles and the negative dipole end of DMSO would become stronger with increasing negative charge density on the oxygen atom of the nucleophiles. Therefore, the rate enhancement would be more significant for the oximate substituted with a stronger electron-releasing group on changing the solvent from 20 to 90 mol% DMSO.

Comparison of Figure 20A and B reveals an appreciable overall rate enhancement on changing the medium from 20 to 90 mol% DMSO. Importantly, while the Hammett plots are linear with ρ values of -2.97 and -0.15 for the reactions with the aryloxides and the oximates, respectively, the ρ value for the reactions with the oximates in 90 mol% DMSO is negative, albeit small. The change in sign of ρ from positive to negative upon the medium change from 20 to 90 mol% DMSO points to a significant solvent effect for the reaction with highly basic oximates. The positive ρ

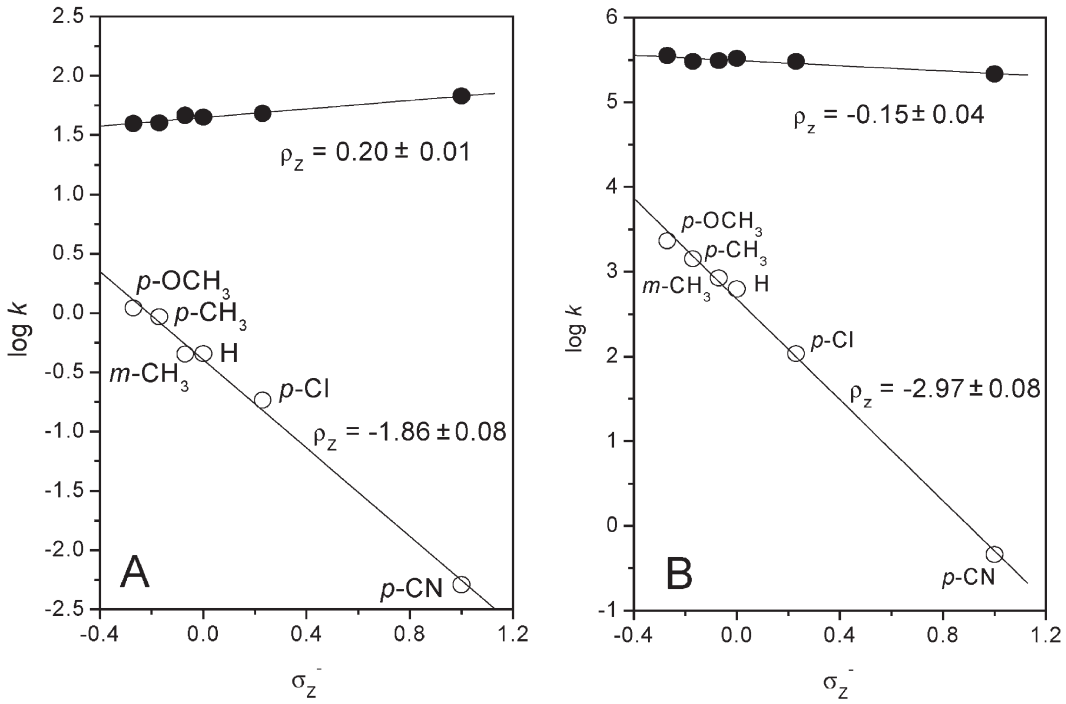


Figure 20. Hammett plots for reactions of PNPB with substituted acetophenone oximates (●) and with aryloxides (○) in 20 mol% DMSO (A) and 90 mol% DMSO (B) at 25.0±0.1 °C.[82]

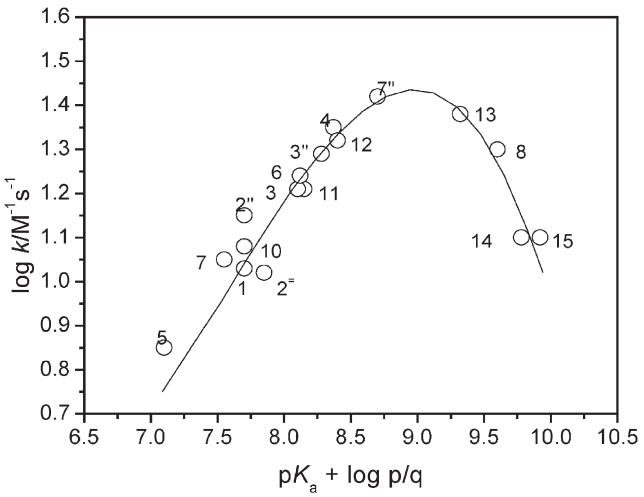


Figure 21. Brønsted-type nucleophilicity plot for the reaction of the oximates with bis(4-nitrophenyl) phenylphosphonate at 25 °C in aqueous solution.[69] See Ref. 69 for identification of the oximate species.

value for the reactions of PNPB with acetophenone oximates in 20 mol% DMSO can then be attributed to stronger solvation of the more basic oximate.[82]

Recently, a similar result has been found by Terrier et al. for the reaction of bis(4-nitrophenyl)phenylphosphonate with a series of oximates in H_2O.[69] As shown in Figure 21, the reactivity of the oximates is characterized by a bell-shaped profile where the attainment of maximum reactivity is followed by a decrease in rate at pK_a>9–9.5. Surprisingly, in the region of pK_a>ca. 9, the more basic oximates become less reactive, resulting in a negative β_{nuc} value. Since a normal positive β_{nuc} value was obtained for the corresponding reactions performed in 70 and 80% DMSO, the negative β_{nuc} value can be accounted for through stronger solvation of the more basic oximate.

3.7. Reactions in micellar solutions

Reactions of anionic nucleophiles in aqueous media often show enhanced nucleophilicity on addition of cationic surfactants.[83–96] It is generally understood that the rate enhancements in the presence of surfactants are due to an increase in the concentration of reactants in the small volume of the surfactant aggregates in which the reaction occurs.[85–87] Accordingly, the anionic nucleophiles having stronger interactions with the cationic micellar aggregates would exhibit higher rate enhancements.

The effect of surfactants on the α-effect has been investigated for reactions of PNPA and PNPDPP with Ox^- and 4-$ClPhO^-$ as an α-effect nucleophile and a reference normal nucleophile, respectively, in various concentrations of cethyltrimethylammonium bromide (CTAB).[93,94] As shown in Figures 22 and 23, the reactivity of these anionic nucleophiles increases on addition of CTAB, although the rate maximum occurs at different surfactant concentrations, that is, near 1×10^{-3} and 8×10^{-3} M CTAB in H_2O for the reaction of PNPDPP and PNPA, respectively. The rate enhancement is greater for

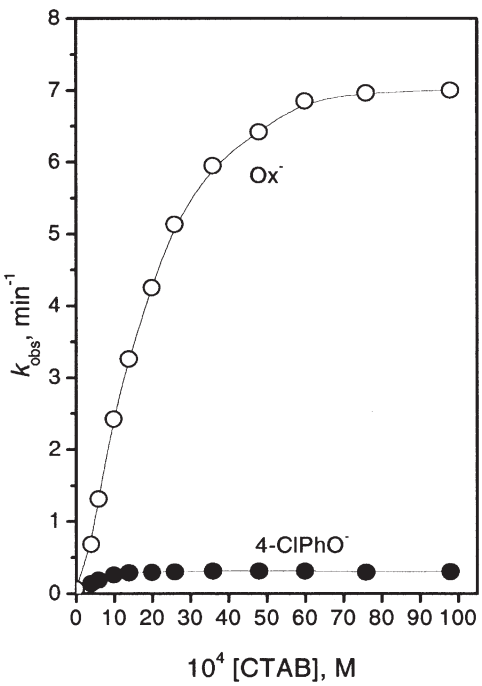


Figure 22. Plots of observed rate constants (k_{obs}) versus the concentration of CTAB for the reaction of PNPA with 4-$ClPhO^-$ and Ox^- in 0.1 M borate buffer (pH 9.2) at 25.0 °C.[93]

reaction of the former than the latter. This is consistent with the greater hydrophobic character of PNPDPP compared with PNPA; the micellar effect would be larger for the more hydrophobic substrate. Interestingly, the rate enhancement is greater for the reactions with Ox^- than with 4-$ClPhO^-$ for both PNPA and PNPDPP systems.

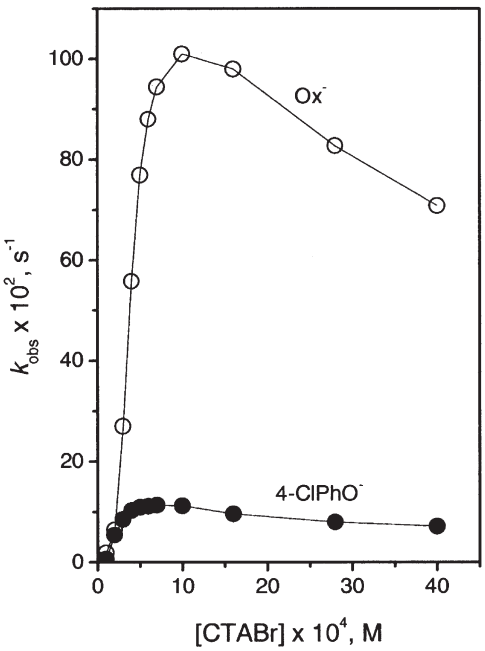


Figure 23. Plots of observed rate constants (k_{obs}) versus concentration of CTAB for the reaction of PNPDPP with 4-$ClPhO^-$ and Ox^- in 0.1 M borate buffer (pH 10.0) at 25.0 °C.[94]

4. Factors affecting α-nucleophilicity

Different factors, apart from the solvent, are known to influence the magnitude of the α-effect. For example, large α-effects have been reported for reactions at sp and sp^2 hybridized carbon centers[3,4] but small for reactions at a saturated carbon atom,[97–108] and even absent for proton-transfer reactions.[109,110] Notably, a small α-effect has generally been observed for reactions with a small β_{nuc} value[15,31,97,98,111–118] or with highly basic α-nucleophiles.[65–69,105,119] In this section, we will discuss how factors such as the magnitude of β_{nuc}, hybridization of substrate, the type of reaction, etc. affect the magnitude of the α-effect.

4.1. β_{nuc} value

As shown in Figure 4, bell-shaped α-effect behavior appears to be typical for various nucleophilic reactions with Ox^- and 4-$ClPhO^-$ in DMSO–H_2O mixtures. However, the magnitude of the α-effect is markedly dependent on the electrophilic center; for the carbonyl, sulfonyl and phosphinyl systems, the α-effect in 50 mol% DMSO is ca. 300, 200 and 40, respectively. Noteworthy is the small α-effect for the phosphinyl system compared to carbonyl and sulfonyl systems.

As described earlier (Fig. 8), the GS of Ox^- and 4-$ClPhO^-$ becomes destabilized upon addition of DMSO to aqueous mixtures. However, the GS energy difference between the two nucleophiles is constant irrespective of the substrates as long as the nucleophiles are limited to Ox^- and 4-$ClPhO^-$. Hence, if the GS energy difference between Ox^- and 4-$ClPhO^-$ were mainly responsible for the α-effect, then the magnitude of the α-effect should be about the same, regardless of the nature of the electrophilic center. In fact, the magnitude of the α-effect is markedly dependent on the nature of the electrophilic centers. Thus, the results show that the difference in the GS energy cannot solely determine the α-effect.

A number of studies have shown that the α-effect decreases with decreasing β_{nuc}.[15,31,97,98,111–118] β_{nuc} values for the reactions of PNPA, PNPBS and PNPDPP with a series of substituted phenoxides in 50 mol% DMSO in which the maximum α-effect observed are 0.64, 0.54 and 0.21, respectively.[15] Thus, β_{nuc} follows the same order as the α-effect in magnitude and, evidently, the small α-effect exhibited by the phosphinyl system derives from the small β_{nuc} value in that system.

The magnitude of the β_{nuc} value has been understood as a measure of the extent of bond formation between the nucleophile and the substrate in the TS of the rate-determining step.[8,80,120,121] It follows that the TS structures for the carbonyl, sulfonyl and phosphinyl systems would vary according to the different β_{nuc} values; one can expect that the TS stabilizing effect would be smaller for the reaction system in which the degree of bond formation between nucleophile and substrate in the TS is less advanced (reactant-like TS), and vice versa. Accordingly, the TS stabilizing effect would be developed to a lesser extent for the phosphinyl system compared with the carbonyl and sulfonyl systems, based on the smaller β_{nuc} value obtained for the former system, so accounting for the small α-effect observed for the phosphinyl system.

The α-effect for the reactions of 4-acetylphenyl and 2,4-dinitrophenyl acetates with Ox^- and 4-$ClPhO^-$ increases upon addition of MeCN to the medium, similar to the α-effect trend for PNPA (Fig. 13). The magnitude of the α-effect is dependent on the nature of the substrate leaving group: the α-effect is largest for the least reactive 4-acetylphenyl acetate system and smallest for the most reactive 2,4-dinitrophenyl acetate system.

The increasing α-effect for the reaction of PNPA correlates linearly with the difference in the relative basicity of Ox^- and 4-$ClPhO^-$ in MeCN–H_2O mixtures ($\Delta\Delta pK_a$), Figure 12. Similarly, one finds linear correlations between the magnitude of the α-effect and $\Delta\Delta pK_a$ for all the reactions of the aryl acetates with Ox^- and 4-$ClPhO^-$, indicating that the difference in the relative basicity between Ox^- and 4-$ClPhO^-$ is responsible for the increasing α-effect profile on increasing the MeCN content in the medium (Fig. 14).

The enhanced reactivity of Ox^- compared to 4-$ClPhO^-$ can be achieved by destabilizing the GS and/or by stabilizing the TS of the Ox^- system. The GS of Ox^- and 4-$ClPhO^-$ would be destabilized upon addition of MeCN to the medium due to the repulsion between the negative dipole end of MeCN and the anionic species, as noted earlier.[35–41] As long as the nucleophiles are limited to Ox^- and 4-$ClPhO^-$, the difference in the GS desolvation between the two nucleophiles will be constant, irrespective of the substrate. Thus, the fact that the magnitude of the α-effect is strongly dependent on the nature of the substrates indicates that the GS effect cannot solely be responsible for the increasing α-effect. This is consistent with the finding that Ox^- is less solvated than 4-$ClPhO^-$ in H_2O by ca. 3.92 kcal/mol,[12] equivalent to an α-effect of 750. The α-effect in H_2O for the reaction of 4-acetylphenyl, 4-nitrophenyl and 2,4-dinitrophenyl acetate is only 138, 96 and 52, respectively,[19] indicating that the α-effect is not fully reflected in differential GS energy.

The β_{nuc} values for nucleophilic substitution reactions of a series of aryloxides with 4-acetylphenyl, 4-nitrophenyl and 2,4-dinitrophenyl acetates are 0.89, 0.79 and 0.38, respectively.[19,70,122] These β_{nuc} values follow the same order in magnitude as the α-effect. This is consistent with the result obtained for the reactions in DMSO–H_2O mixtures of three different electrophilic centers (PNPA, PNPBS and PNPDPP) with Ox^- and 4-$ClPhO^-$: the α-effects are ca. 300, 200 and 40 while the β_{nuc} values for the carbonyl, sulfonyl and phosphinyl ester are 0.64, 0.54 and 0.21, respectively.[15]

As already noted, the β_{nuc} value can be taken as a measure of the extent of bond formation between the nucleophile and the substrate in the TS of the rate-determining step;[8,80,120,121] then the TS structure of the reactions of the aryl acetates would vary according to the different β_{nuc} values. Based on β_{nuc} values, the TS stabilizing effect would be most significant for the reaction of 4-acetylphenyl acetate

and least for 2,4-dinitrophenyl acetate. This accords with the direct relationship between the magnitude of the α-effect and β_{nuc} in this and other systems as mentioned above.

4.2. Substitution at sp^3 carbon atoms; single electron transfer character

A particularly interesting aspect of the α-effect phenomenon is that in nucleophilic attack at carbon centers there appears to be a strong dependence on hybridization type.[3,4,9,71,97–108] The largest α-effect has been observed[3,4] for reaction by HOO^- at the sp carbon of benzonitriles, $k_{HOO^-}/k_{HO^-}=10^3-10^4$. Nucleophilic attack at sp^2 carbon centers is typically associated with α-effects of the order of 50–100.[71] On the other hand, nucleophilic attack at an sp^3 carbon is associated with only a very small α-effect or even none at all.[97–108] Intramolecular general acid–base catalysis[123] or stabilization of TS by means of an aromatic-type structure[124] cannot operate for the saturated carbon centers. The following elaborates on these observations.

A Hammett-type investigation of the α-effect for reactions at sp^3 carbon centers was performed on a series of methyl substituted phenyl sulfates; an S_N2 mechanism with the aryl sulfate moiety as leaving group was followed (Eq. 12).[97] For the reaction of 4-nitrophenyl methyl sulfate the α-nucleophiles NH_2NH_2, $HONH_2$ and $MeONH_2$ exhibited positive deviations from the Brønsted-type plot (Fig. 24). The slope of the Brønsted-type plot, $\beta_{nuc}=0.12$, is consistent with the generally small β_{nuc} values reported for reactions at sp^3 carbon centers and is also in accord with the aforementioned observation that the magnitude of the α-effect decreases steadily with decreasing β_{nuc}.[31]

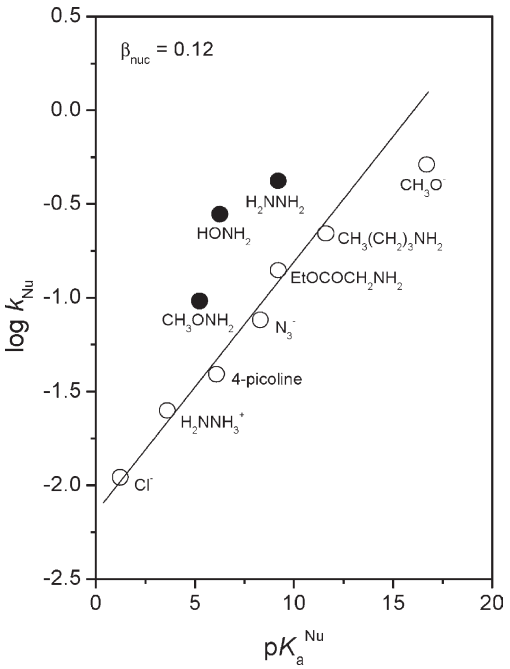
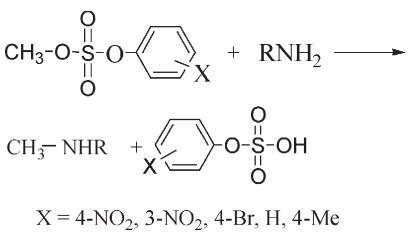


Figure 24. Brønsted-type plot of log k_{Nu} versus pK_a for the reaction of nucleophiles with methyl *p*-nitrophenyl sulfate. The α-nucleophiles are shown as solid circles.[97]



(12)

X = 4-NO_2, 3-NO_2, 4-Br, H, 4-Me

Linear Hammett plots for the leaving group effect on the α-effect were obtained for both the α- and normal-nucleophile systems (Fig. 25). However, the ρ value is larger for reactions with the less reactive glycine ethyl ester (ρ=1.00) than for the more reactive NH_2NH_2 (ρ=0.70), in accord with the reactivity–selectivity principle.[125–127] As a result, the α-effect in this series increases as the leaving group ability decreases (Table 4). This leaving group dependence of the α-effect tends to confirm the hypothesis that α-effect at saturated carbon atom, albeit small in magnitude, has valid significance.

Brønsted β_{nuc} values for the α-effect nucleophiles (HOO^- and NH_2NH_2) and the normal nucleophiles (MeO^- and glycine ethyl ester) are 0.16 and 0.07, respectively.[98] The

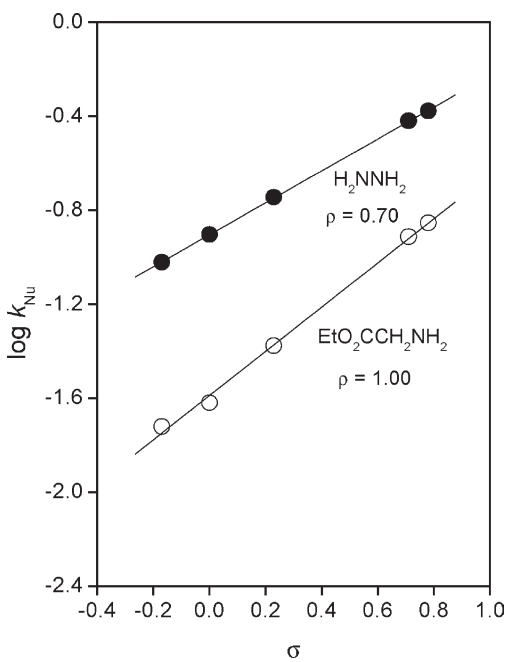


Figure 25. Hammett log k_{Nu} versus σ plots for reactions of nucleophiles with substituted phenyl methyl sulfates: glycine ethyl ester versus hydrazine.[97]

Table 4. Second-order rate constants and magnitudes of the α-effect for nucleophilic substitution reactions of methyl X-substituted phenyl sulfates in MeOH at 25 °C

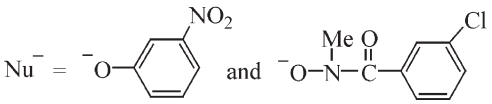
$MeOSO_3C_6H_4-X$ (X)	$k_{NH_2NH_2}$[a] (M^{-1} s^{-1})	$k_{glyester}$[a] (M^{-1} s^{-1})	$k_{NH_2NH_2}/k_{glyester}$[a]
4-NO_2	0.419	0.140	3.00
3-NO_2	0.380	0.122	3.11
4-Br	0.180	0.042	4.29
H	0.125	0.024	5.21
4-Me	0.095	0.019	5.01

[a] Data taken from Ref. 97.

larger β_{nuc} value for the α-nucleophiles would represent greater extent of bond formation at the TS compared to the normal nucleophiles. To account for the smaller ρ and larger β_{nuc} values measured for the α-nucleophiles, the TS has to move to a direction corresponding to decreased leaving group departure and increased bond order between the α-nucleophile and the sp^3 carbon atom. Such a TS movement is possible by stabilizing the α-nucleophile or by making a tighter TS. Since stabilization of the α-nucleophile would not result in an α-effect, a tighter TS, (or stabilization of TS) was proposed to be the origin of the α-effect in this system.[98]

As discussed earlier, the possible advent of SET mechanism, as an alternative to the S_N2 type mechanism, has been advanced by Hoz in order to explain the reactivity of α-ncleophiles.[30] Recent studies by Fountain have produced pertinent evidence toward connection of SET character to the α-effect.[128,129] The methylation of aryldimethylsulfonium ions with *N*-methyl-3-chlorobenzohydroxamate and 3-nitrophenoxide in MeOH (Eq. 13) was found to increase from 13.3 to 32.5 and 68.4 as the aromatic moiety of the sulfonium ion changes from phenyl to 1-naphthyl and 9-anthracenyl, respectively.[128]

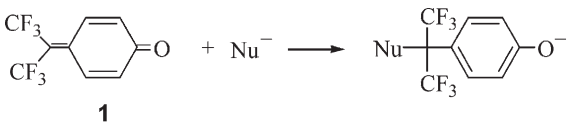
Ar = phenyl, 1-naphtyl, 9-anthracenyl (13)



The magnitude of the α-effect exhibited a linear correlation with the calculated methyl radical affinity, that is, the α-effect increases with increasing ease of SET. The methyl radical affinity value varies from −18.12 to −20.77 and −31.84 kcal/mol as the substrate is changed from methyl phenyl sulfide to methyl 1-naphthyl and 9-anthracenyl sulfides, respectively, in accord with involvement of SET behavior.[128,129]

4.3. Nucleophilic addition at sp^2 carbon centers

The addition of a wide range of nucleophiles in aqueous medium to quinone methide 4-[bis(trifluoromethyl)-methylene]cyclohexa-2,5-dienone, **1**, (Eq. 14) gives a linear



1 (14)

correlation of log k_{Nu} with the Ritchie's nucleophilicity parameter N_+,[130] slope s=0.92±0.10 (Fig. 26A).[131] The α-effect nucleophiles (HOO^-, SO_3^{2-} and $HONH_2$) do not deviate from the linear correlation. These α-effect nucleophiles and N_3^- ion exhibit positive deviations from the linear correlation of N_+ for nucleophilic addition to the trivalent carbon electrophile with Swain–Scott n values,[132] slope 2.0 (Fig. 26B).[131] The positive deviations for the α-effect nucleophiles reflect the well-known larger α-effect for reaction at sp^2 carbon than at sp^3 carbon.

Additions of amines to the vinyl group of 1-methyl-4-vinylpyridinium cation (**2**) were investigated in aqueous solution at 25 °C (Eq. 15).[114] Nucleophilic attack was shown

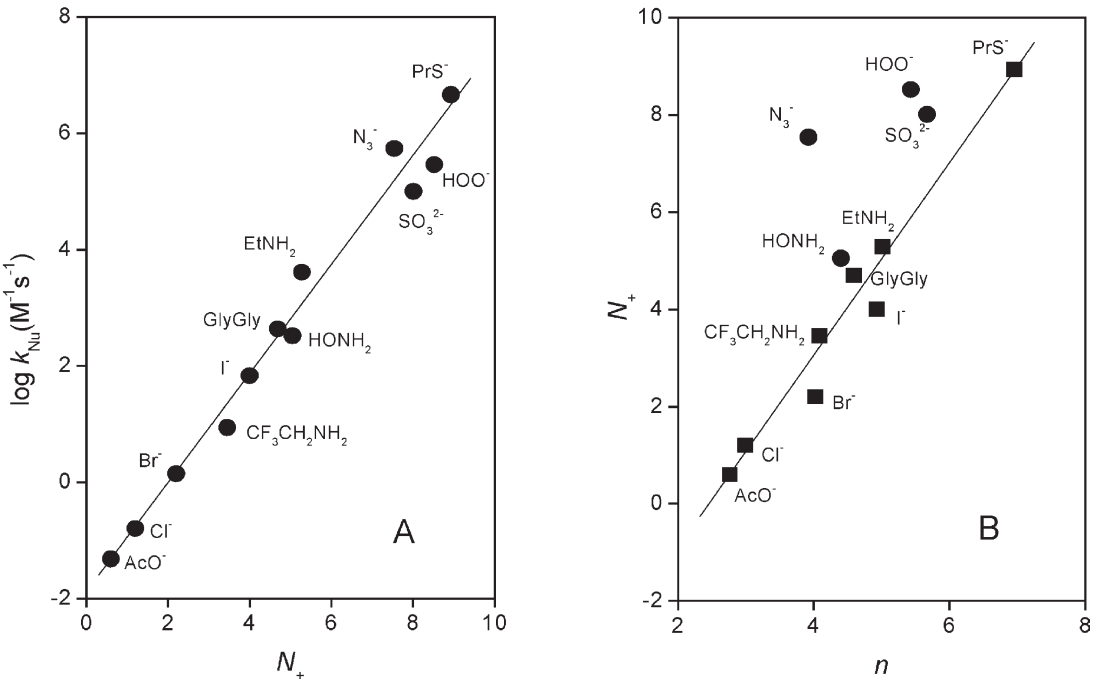
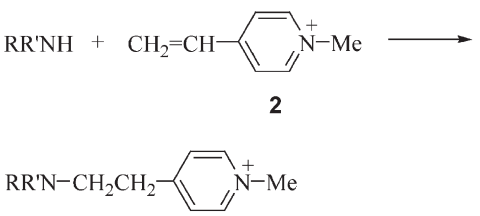
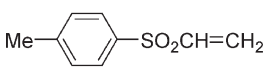


Figure 26. (A) Correlation of the second-order rate constants k_{Nu} (M^{-1} s^{-1}) for the addition of nucleophiles to 4-[bis(trifluoromethyl)methylene]cylohexa-2,5-dienone in water at 25 °C and I=1.0 ($NaClO_4$) with Ritchie N_+ values; (B) Correlation of the values of N_+ for nucleophile addition to trivalent carbon electrophiles with the Swain–Scott n values for bimolecular nucleophilic substitution at aliphatic carbon.[131]



(15)

to be rate-determining for primary and secondary amines. Secondary amines are more reactive than primary amines of the same basicity, while tertiary amines are in general less reactive than other amines of the same basicity. After classification of these species in terms of structure, a number of Brønsted-type correlations were obtained with β_{nuc} values in the range 0.23–0.54.[114] Derivatives of hydrazine and hydroxylamine show ca. 12 times enhanced reactivity than reference primary amines of the same basicity.[114] In a related study by Oae et al. but with solvent change to EtOH and MeCN, the Michael-type addition of amines to 4-methylphenyl vinyl sulfone (**3**) gave α-effect values, $k_{NH_2NH_2}/k_{NH_3}$ and $k_{NH_2NH_2}/k_{morpholine}$, below 10 in both solvents.[115]



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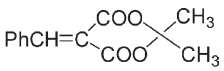

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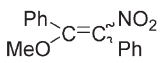

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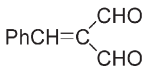


6

In contrast, Bernasconi et al. did not observe an α-effect for addition of amines to the activated C=C bonds of benzylidene Meldrum's acid (**4**), β-methoxy-α-nitrostilbene (**5**) and benzylidenemalonodialdehyde (**6**). The

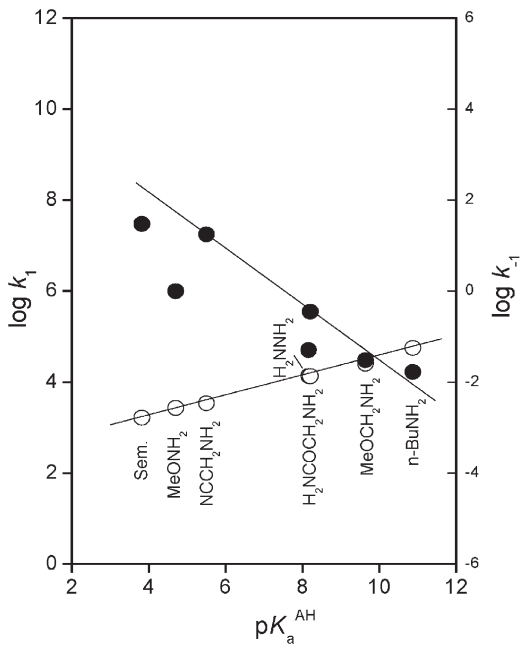
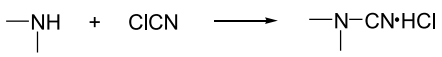


Figure 27. Correlation of rate constants for adduct formation (k_1, ○) and decomposition (k_{-1}, ●) with pK_a of RNH_3^+ in water at 25 °C.[111]

k_1 values for nucleophilic attack by α-nucleophiles (hydrazine, methoxylamine and semicarbazide) correlate well with those for the other amines with a β_{nuc} value of ca. 0.2 in all cases.[111–113] On the other hand, the rate constants for the reverse process (k_{-1}) are markedly depressed for reactions with hydrazine, methoxylamine and semicarbazide (Fig. 27). As a result, these α-nucleophiles exhibit positive deviations from the log k_1/k_{-1} versus amine basicity plot. Bernasconi et al. suggested that the small β_{nuc} is responsible for the absence of the α-effect for the k_{-1} process and attributed the enhanced k_1/k_{-1} ratio for the α-nucleophiles to a thermodynamic phenomenon.[111–113]

4.4. Nucleophilic substitution at sp carbon centers

Nucleophilic substitution reactions in ClCN by nitrogen and oxygen nucleophiles in H_2O proceed by C–Cl bond scission (Eqs. 16 and 17),[118] with nitrogen nucleophiles more reactive than oxygen nucleophiles of comparable basicity. Brønsted-type plots for both nitrogen and oxygen nucleophiles are linear with β_{nuc} values of 0.36 and 0.52, respectively, and yield α-effects $k_{NH_2NH_2}/k_{glycine\ amide}$=18 and k_{HOO^-}/k_{HO^-}=730.[118]

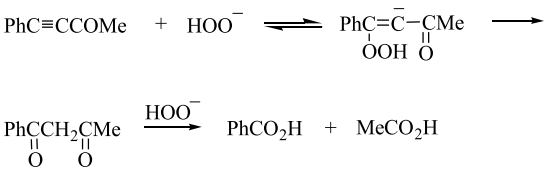


(16)

$$RO^- + ClCN \rightarrow ROCN + Cl^- \quad (17)$$

4.5. Nucleophilic addition at sp carbon centers

The reaction of 4-phenyl-3-butyn-2-one with alkaline hydrogen peroxide affords benzoic and acetic acids (Eq. 18), via benzoylacetone as the major pathway for the cleavage. The reactivity ratio (k_{HOO^-}/k_{HO^-}) is 1400.[133]



(18)

A similar reactivity ratio is found for the addition of HOO^- and HO^- to benzylideneacetone (PhCH=CHCOMe), k_{HOO^-}/k_{HO^-}=1900. Thus, there appears to be no significant difference in the magnitude of the α-effect for reaction with an acetylene (sp carbon) and the structurally related olefin (sp^2 carbon).[133]

An unexpectedly small α-effect was found for the addition of primary amines to 3-butyn-2-one in H_2O (Eq. 19).[116]

$$RNH_2 + HC{\equiv}CC(O)Me \rightarrow RNHCH{=}CHC(O)Me \quad (19)$$

The Brønsted-type plot is linear with a β_{nuc} value of 0.32 for reactions with normal-nucleophiles (Fig. 28) while the α-nucleophiles NH_2NH_2 and $MeONH_2$ exhibit small positive deviations from linearity. The α-effect is about 10, comparable to an sp^3 system.[97–103] This result is quite unusual noting that the α-effect has been reported to be about 10, 10^2 and 10^3~10^4 for reactions at sp^3, sp^2 and sp hybridized carbon.[6,7]

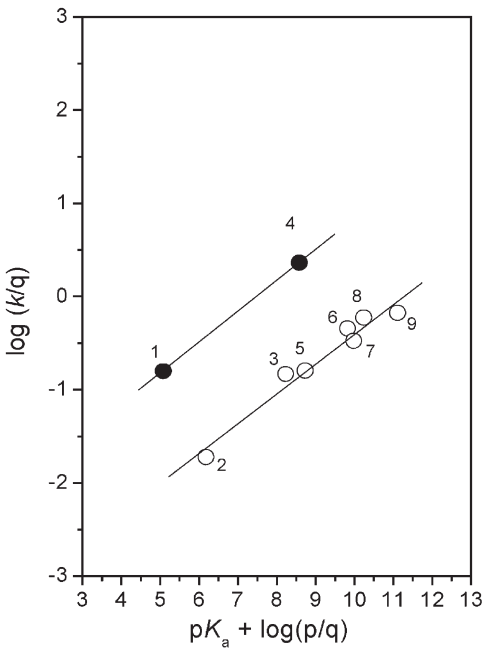


Figure 28. Brønsted-type plots for the addition reactions of primary amines to 3-butyn-2-one in H_2O at 25.0 °C. 1, Methoxylamine; 2, trifluoroethylamine; 3, glycine ethyl ester; 4, hydrazine; 5, glycylglycine; 6, benzylamine; 7, ethanolamine; 8, glycine; 9, ethylamine.[116]

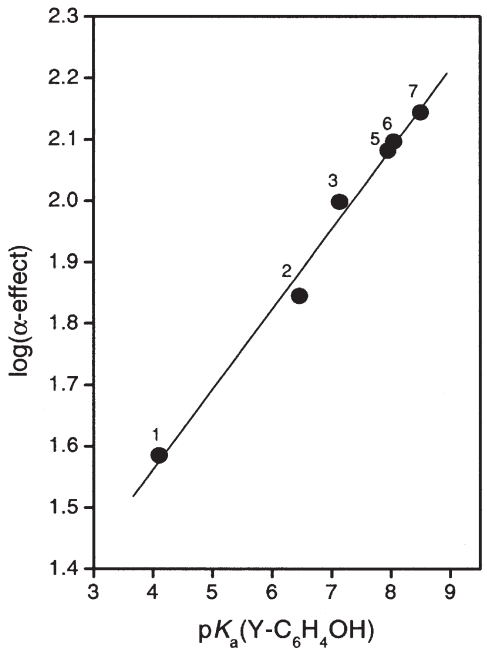
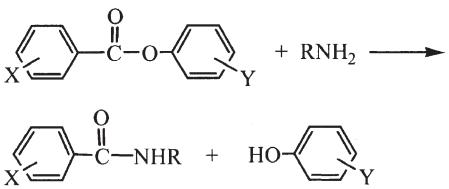


Figure 29. Plot showing dependence of α-effect ($k_{NH_2NH_2}/k_{glygly}$) on the basicity of the leaving group for the reactions of Y-substituted phenyl benzoates ($C_6H_5COOC_6H_4$–Y) with hydrazine and glycylglycine in 20 mol% DMSO at 25.0±0.1 °C. 1, Y=2,4-$(NO_2)_2$; 2, Y=4-Cl–2-NO_2; 3, Y=4-NO_2; 4, Y=4-CHO; 5, Y=4-CN; 6, Y=4-MeCO; 7, Y=4-CO_2Et.[135]

4.6. Neutral amine versus anionic nucleophile

To quantify the effect of substituents X and Y on the α-effect at C=O centers, systematic studies were performed for reactions of Y-substituted phenyl X-substituted benzoates with a series of primary amines in 20 mol% DMSO (Eq. 20).[134,135]



(20)

Linear Brønsted-type plots were obtained for the aminolyses of 4-nitrophenyl X-substituted benzoates (X=4-MeO, H, 4-NO_2) with the exception of the α-nucleophiles NH_2NH_2 and $HONH_2$ which exhibit positive deviations. The β_{nuc} value for the normal amines was determined to be 0.77±0.01,[135] independent of the electronic nature of the substituent X.

The kinetic study was extended to the reactions of hydrazine and glycylglycine with seven different Y-substituted benzoates and 10 different 4-nitrophenyl X-substituted benzoates in 20 mol% DMSO.[135] The Brønsted-type plots for the reaction of Y-substituted phenyl benzoates were linear for both the hydrazine and glycylglycine systems. However, the β_{lg} value was larger for the reactions with glycylglycine ($\beta_{lg}=-1.25$) than hydrazine ($\beta_{lg}=-1.08$).[135] The difference in the β_{lg} value resulted in a leaving group dependent α-effect. As shown in Figure 29, the plot of log $k_{NH_2NH_2}/k_{glygly}$ versus pK_a (Y-C_6H_4OH) exhibits good linearity, signifying direct proportionality between the α-effect, log $k_{NH_2NH_2}/k_{glygly}$, and leaving group basicity. This result is consistent with that obtained by Buncel et al. for the methyl transfer reactions of methyl aryl sulfates in MeOH.[97]

Linear Hammett plots were obtained for the reactions of 10

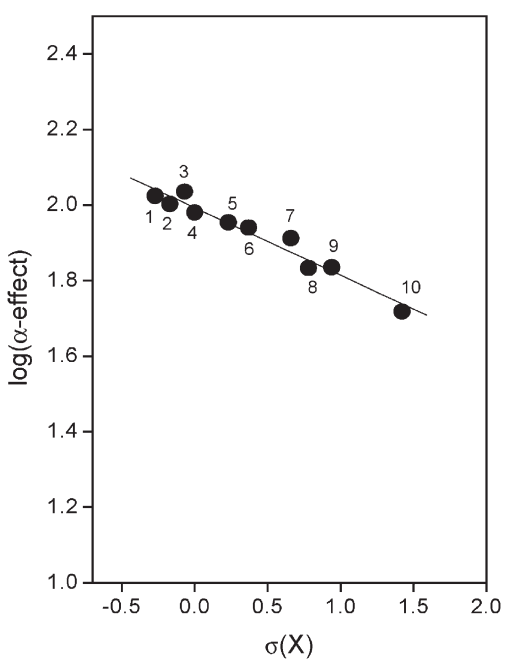
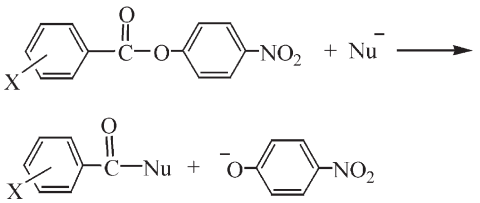


Figure 30. Plot showing dependence of α-effect ($k_{NH_2NH_2}/k_{glygly}$) on the electronic nature of the substituent X for the reactions of 4-nitrophenyl X-substituted benzoates (X–$C_6H_5COOC_6H_4$–4-NO_2) with hydrazine and glyglycine in 20 mol% DMSO at 25.0±0.1 °C. 1, X=4-MeO; 2, X=4-Me; 3, 3-Me; 4, X=H; 5, X=4-Cl; 6, X=3-Cl; 7, X=4-CN; 8, X=4-NO_2; 9, X=4-Cl–3-NO_2; 10, X=3.5–$(NO_2)_2$.[135]

different 4-nitrophenyl X-substituted benzoates with hydrazine and glycylglycine with a ρ value of 0.76 and 0.90, respectively.[135] There is a linear correlation between log $k_{NH_2NH_2}/k_{glygly}$ and σ_x (Fig. 30); the α-effect increases as the substituent X in the benzoyl moiety changes from an electron withdrawing group to an electron donating group.

The effect of substituent X on the α-effect in this series was extended to the reaction of *p*-nitrophenyl X-substituent benzoates with Ox^- and 4-$ClPhO^-$ in 20 mol% DMSO (Eq. 21).[136]



(21)

$Nu^- = Ox^-$ and 4-$ClPhO^-$

The effect of substituent X on the α-effect for reactions with Ox^- and 4-$ClPhO^-$ is diplayed in Figure 31 with NH_2NH_2 and glygly results for comparison. It is seen that the α-effect for reactions with the anionic nucleophiles is much larger than that for neutral amine nucleophiles. More surprisingly, the α-effect profile obtained from reactions with Ox^- and 4-$ClPhO^-$ contrasts with that obtained with NH_2NH_2 and glygly: log $k_{Ox^-}/k_{4\text{-}ClPhO^-}$ remains independent of the electronic nature of the substituent X, while log $k_{NH_2NH_2}/k_{glygly}$ increases as the substituent X changes from a strong EWS to a strong EDS.

The GS and TS contributions to the origin of the α-effect appear to be dependent on the reaction mechanism as well as the nature of the α-nucleophiles (e.g., anionic vs. neutral

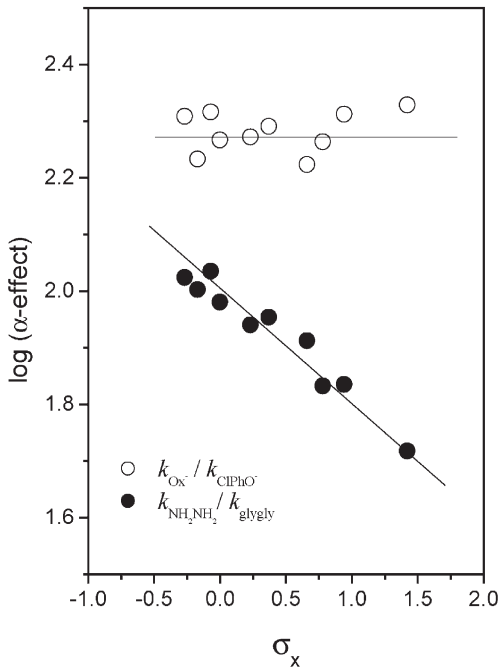


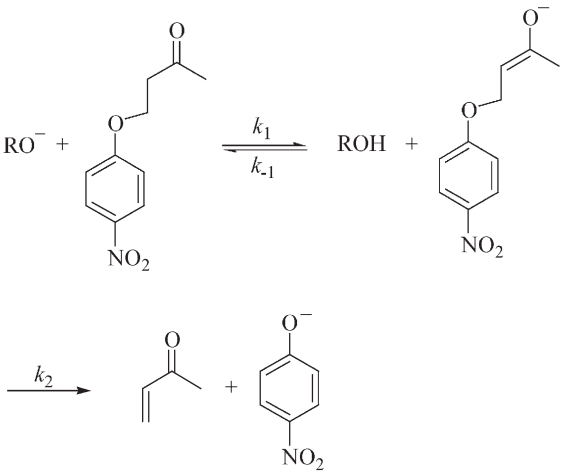
Figure 31. The effect of substituent X on the α-effect for reactions of 4-nitrophenyl X-substituted benzoates with Ox^- and $ClPhO^-$, and with NH_2NH_2 and glygly in 20 mol% DMSO at 25.0±0.1 °C.[136]

nucleophiles).[137–141] This argument is consistent with the previous reports that NH_2NH_2 exhibits the α-effect for the reaction which proceeds through rate-limiting breakdown of the addition intermediate with a large β_{nuc}, while it does not exhibit the α-effect for the reaction which proceeds through a rate-limiting nucleophilic attack with a small β_{nuc}.[143]

4.7. Proton transfer reactions

As discussed above (Sections 3.2–3.7), oximates have often been found to exhibit enhanced reactivity compared with aryloxides of similar basicity in nucleophilic substitution reactions of various substrates, although the enhanced reactivity decreases on increasing the oximate basicity (pK_a>ca. 8).[65–69] However, up to recently oximates and phenoxides have been found to exhibit essentially identical behavior in proton transfer reactions.

Proton transfer from 4-(4-nitrophenoxy)butan-2-one with various oxygen bases (alkoxides, phenoxides, oximates, hydroxamates) in H_2O at 25 °C (Eq. 22) shows no α-effect.[110]



(22)

The Brønsted plot for the rate-determining enolization was found to be curved, with β_{nuc}=0.75 for bases of pK_a=3–10 and β_{nuc}=0.3 for bases of pK_a>10. HO^- ion was not anomalous but behaved like other highly basic oxyanions and, similarly, HOO^- and oximate anions behaved like other oxyanions of the same basicity and showed no α-effect.[110]

Terrier et al. investigated the deprotonation of bis(2,4-dinitrophenyl)methane by a series of oximates and aryloxides, and reprotonation of the corresponding carbanion by the conjugate acids of the oximates and aryloxides in 50:50 (v/v) DMSO–H_2O mixture (Eq. 23).[109a] The Brønsted plots for the reactions of bis(2,4-dinitrophenyl)methane with

$Ar_2CH_2 + Ox^- \rightleftharpoons Ar_2CH^- + OxH$

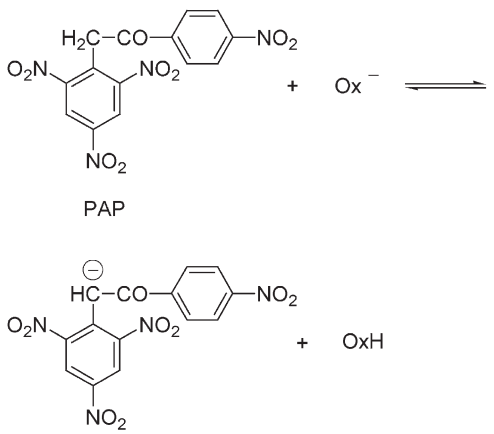
(23)

Ar = 2,4-dinitrophenyl
OxH : oximes

oximates and phenoxides were found to be nearly identical, with similar reactivities and β_{nuc} (0.45); no tendency to level off at high pK_a was detected.[109a]

In contrast, deprotonation at the trinitrobenzylic carbon of

picrylacetophenone (PAP) by oximate bases in 50:50 (v/v) DMSO–H_2O does in fact exhibit levelling off at pK_a greater than 10 (Eq. 24).[109b]



(24)

This first observation of levelling in reactivity by oximate bases in a deprotonation process occurs under highly thermodynamically favorable conditions and was shown to have as origin the desolvation of the oximate ion prior to actual proton transfer. In the Marcus formulation this would be in accord with the large predominance of the work term (w_r) far exceeding the intrinsic barrier term.

5. Summary and prognosis

A partial summary of the α-effect for different processes which have been discussed herein is presented in Table 5.

The α-effect has been demonstrated to be remarkably dependent on the nature of the solvent and composition: often bell-shaped, increasing or even decreasing α-effect profiles have been observed, amply demonstrating that a "two point analysis" can be misleading. Dissection into GS and TS contributions through kinetic and thermodynamic studies has shown that the effect of solvent on the GS energy difference between α- and normal nucleophiles is not solely responsible for the α-effect but the TS contribution is also an important factor.

While β_{nuc} is clearly an important factor, the magnitude of β_{nuc} appears to be more important than the type of hybridization and reaction, or the nature of the electrophilic center.

Substrates studied have been mostly C═O or P═O bond containing compounds, while corresponding substrates containing C═S or P═S bonds have rarely been investigated.

Solvent effects on the α-effect have been intensively investigated using anionic nucleophiles (e.g., oximates, hydroxamates and peroxides). However, studies with neutral amine nucleophiles (NH_2NH_2, $HONH_2$, $MeONH_2$, etc.) have not been systematically performed. Studies of substrates containing C═S or P═S bonds, particularly with neutral α-nucleophiles, would be informative on the α-effect.

Table 5. Magnitude of the α-effect for nucleophilic substitution reactions of various substrates

Substrate	α-Nucleophile	*n*-Nucleophile	α-Effect	β_{nuc}	Reference
PNPA	NH_2NH_2	Glycylglycine	38	0.82	142
PNPA	$HONH_2$	$CF_3CH_2NH_2$	1200	0.82	142
PNPA	$MeONH_2$	Aniline	14	0.82	142
PNPA	TFM–Ox^-	4-$ClPhO^-$	60	—	143
PNPA	IBA^-	—	64	—	139
PNPA	HOO^-	—	128	—	139
PNPTA	NH_2NH_2	Glycylglycine	38	0.67	142
PNPTA	$HONH_2$	$CF_3CH_2NH_2$	430	0.67	142
PNPTA	$MeONH_2$	Aniline	12	0.67	142
PNPB	NH_2NH_2	Glycylglycine	96	0.75	134
PNPB	Ox^-	4-$ClPhO^-$	130	0.97	144
PNPB	BHA^-	4-$ClPhO^-$	56	0.97	144
PNPB	SO_3^{2-}	4-$CHOPhO^-$	140	0.97	144
PNPB	IBA^-	Imidazole	78	—	145
7	BHA^-	4-$ClPhO^-$	67	0.85	146
7	Ox^-	4-$ClPhO^-$	41	0.85	146
8	HOO^-	$CF_3CH_2O^-$	1300	0.49	147
8	Ox^-	4-$ClPhO^-$	37	0.49	147
9	HOO^-	HO^-	50	0.47	148
9	IBA^-	PhO^-	13	0.47	148
10	NH_2NH_2	NH_3	85	0.89	149
11	Ox^-	4-$ClPhO^-$	130	—	150
12	NH_2NH_2	Glycine	410	—	151
13	NH_2NH_2	Glycylglycine	14	—	152

7, *O*-4-nitrophenyl thionobenzoate; **8**, *O*,*O*-dimethyl *O*-(3-methyl-4-nitrophenyl) phosphorothioate; **9**, 2,4-dinitrophenyl ethyl methylphosphonate; **10**, 4-toluenesulfonyl chloride; **11**, 4-nitrophenyl benzenesulfonate; **12**, *N*-methyl-*N*-nitrosotoluene-4-sulfonamide; **13**, 2,4-dinitrochlorobenzene.

Gas phase studies, both calculational and experimental, will be vital to glean fundamental insight into the effect of solvent on the α-effect. Another area requiring further insight is to further delineate the SET process and the role of solvent on the α-effect in these processes.

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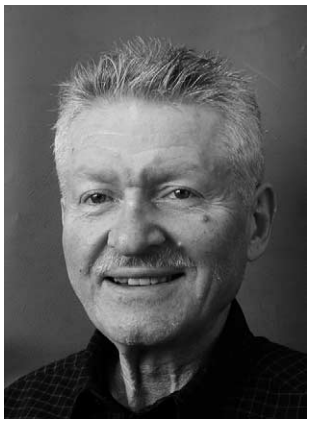
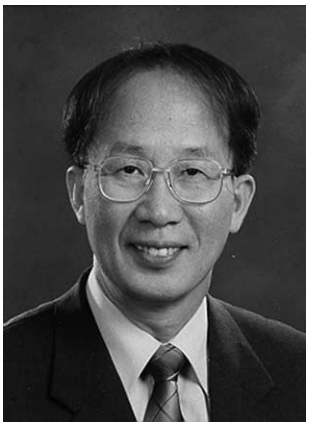
Biographical sketch



Erwin Buncel, Professor Emeritus at Queen's University, is a physical organic chemist with strong interests in the cognate disciplines of bioorganic, environmental and materials science. His studies have illuminated the alpha-effect and solvent effects including introduction of a new solvent polarity scale. Other major interests include photochromic materials, the pathways of degradation of biocides, the reactivity of heteroaromatic superelectrophiles and carbanion chemistry, the last highlighted in the recent book "Carbanion Chemistry. Structures and Mechanisms." (2003). Buncel is the author/coauthor of over 300 research papers in these areas, as well as a number of chapters, review articles and monographs, notably including "The Role of Solvent in Chemical Reactions" (2003). He is the recipient of the Syntex award in Physical Organic Chemistry and R.U, Lemieux Award in Organic Chemistry, both from the Canadian Society for Chemistry and he has been an editor of the Canadian Journal of Chemistry and the Journal of Labelled Compounds and Radiopharmaceuticals. As an Emeritus Professor, Erwin leads a robust research program involving graduate students, postdoctoral fellows and colleagues in countries throughout the world and he looks forward to the exciting challenges that the world of chemistry holds.



Professor Ik-Hwan Um obtained his BSc from Yonsei University in Seoul, Korea in 1977 and worked as a research chemist at Technical Institute of the Pacific Chemical Industrial Co., Ltd Seoul, Korea from 1977 to 1982. He then moved to Canada and received his PhD degree under the supervision of Professor Erwin Buncel at Queen's University in 1987. While at Queen's University, he was awarded an R. S. McLaughlin Fellowship (1982–1985). After working as a postdoctoral researcher with Professor A. J. Kresge at the University of Toronto for a year, he was appointed as a faculty member in the Chemistry Department at Ewha Womans University, Seoul, Korea (Assistant Professor 1988–1992; Associative Professor 1992–1997; Full Professor of Chemistry 1999–present). His research interests include nucleophilic substitution reactions of carbonyl, sulfonyl and phosphinyl derivatives with various nucleophiles and medium effects on the alpha-effect.

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Synthesis of an inherently chiral *O*,*O*′-bridged thiacalix[4]crowncarboxylic acid and its application to a chiral solvating agent

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Abstract—Treatment of readily available *O*,*O*′-1,1,3,3-tetraisopropyldisiloxane-1,3-diyl-bridged *p-tert*-butylthiacalix[4]arene (**1**) with tri(ethylene glycol) di-*p*-tosylate and subsequent desilylation gave *O*,*O*′-bridged thiacalix[4]crown **3** in an excellent yield. Mono-*O*-alkylation of **3** with ethyl bromoacetate, followed by optical resolution by chiral HPLC, and subsequent hydrolysis of the ester moiety gave inherently chiral *O*,*O*′-bridged thiacalix[4]crowncarboxylic acid (+)-**6**, which clearly discriminated enantiomeric primary amines, as well as amino esters, by ^{1}H NMR spectroscopy.

1. Introduction

Calix[*n*]crowns which are composed of two kinds of receptor elements, a calix[*n*]arene[1] and a crown ether,[2] have attracted much interest as host compounds in the hope for improving the binding ability as well as selectivity to a particular guest species such as an organic molecule[3] or alkali metal ion[4] by the synergic effects of the two receptor elements arranged in a defined three-dimensional alignment. In these endeavors, *O*,*O*″-bridged calix[4]crowns, in which a calix[4]arene is linked at the distal phenolic oxygens with a poly(oxyethylene) chain, have been employed as a molecular scaffold, while only little attention has been paid toward the proximally *O*,*O*′-bridged analogs.[5] This is partly due to the difficulty in preparing the latter type of compounds in substantial quantities. In previous papers, we reported an efficient method for a net proximal dialkylation of calix[4]arenes at the lower rim via the dialkylation of readily available *O*,*O*′-disiloxane-diyl-bridged calix[4]arenes (e.g., **1**) and subsequent desilylation,[6] which could be advantageously utilized for the synthesis of *O*,*O*′-bridged thiacalix[4]crowns.[7] It is readily conceivable that *O*,*O*′-bridged calix[4]crowns having only one symmetry plane are desymmetrized to inherently chiral derivatives by introducing an achiral substituent at one of the two remaining hydroxy groups.[8] In this respect, it should be noted that in spite of the considerable efforts which had been paid to the preparation of inherently chiral calixarenes,[8,9] their chiral recognition abilities have yet to be improved except a recent report by Matt et al. dealing with an application to chiral ligands for asymmetric catalysis.[10] This is in sharp contrast to the fact that another type of chiral calixarenes prepared by introducing chiral substituents at the lower rim through the phenolic oxygens have enjoyed many successful applications to chromogenic receptors,[11] additives in capillary electrophoresis,[12] chiral stationary phases for GC and HPLC,[13] chiral solvating agents for NMR,[14] and so on.[15] Herein, we report facile synthesis of inherently chiral *O*,*O*′-bridged thiacalix[4]-crowncarboxylic acid **6** and its chiral recognition ability as a chiral solvating agent in discriminating enantiomeric amines, as well as amino esters, by ^{1}H NMR spectroscopy. Also reported is the absolute stereochemistry of acid **6** determined by an X-ray crystallographic analysis.

2. Results and discussion

2.1. Synthesis of inherently chiral *O*,*O*′-bridged thiacalix[4]crowncarboxylic acid (+)-6

O,*O*′-Bridged thiacalix[4]crown **3** was prepared according

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to our previously reported procedure (Scheme 1). Thus, treatment of *O*,*O*′-disiloxane-1,3-diyl-bridged thiacalix[4]-arene **1**[6] with tri(ethylene glycol) di-*p*-tosylate in the presence of Cs_2CO_3 in THF gave *O*″,*O*‴-bridged thiacalix[4]crown **2** in high yield, which was desilylated with tetrabutylammonium fluoride to liberate diol **3**. Subsequent monoalkylation of **3** with ethyl bromoacetate in the presence of Na_2CO_3 in THF gave two stereoisomers **4** and **5**, originated from the *syn* and *anti* conformations of the ethoxycarbonylmethyl and crown moieties with respect to the mean plane defined by the calix ring. The ^{1}H NMR spectrum of the major isomer **4** showed two doublets (each 1H) for the methylene protons of the $OCH_2C{=}O$ moiety at 4.71 and 4.87 ppm, while one of the corresponding signals (4.05 and 4.87 ppm) of the minor isomer **5** resonated at a higher field owing to the shielding effects by the facing benzene rings. This indicates that compound **5** adopts a partial cone or 1,2-alternate conformation with the *anti* arrangement of the ethoxycarbonylmethyl and crown moieties and that the relative configuration of the two substituents in compound **4** can consequently be assigned to *syn*. This assignment was unambiguously confirmed by an X-ray crystallographic analysis of acid **6** prepared from compound **4** (vide infra). Although the unsymmetrical ^{1}H NMR resonance pattern of compound **4** gave no information about the conformation of the free *p*-*tert*-butylphenol residue, it is conceivable that this compound adopted a cone conformation in the solution by virtue of possible intramolecular hydrogen bond of the hydroxyl proton to the nearby oxygen atoms at the lower rim. Compound **4** could be optically resolved by chiral HPLC on a preparative scale to give several 100-mg yields of both the enantiomers (>99% ee) (Fig. 1). Subsequent alkaline hydrolysis of one enantiomer (+)-**4** gave enantiomerically pure acid (+)-**6** (Scheme 2).

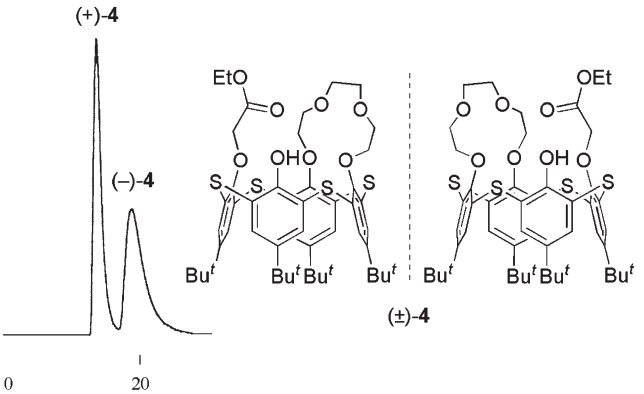
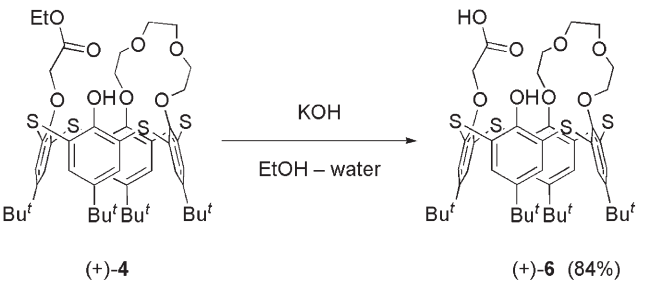
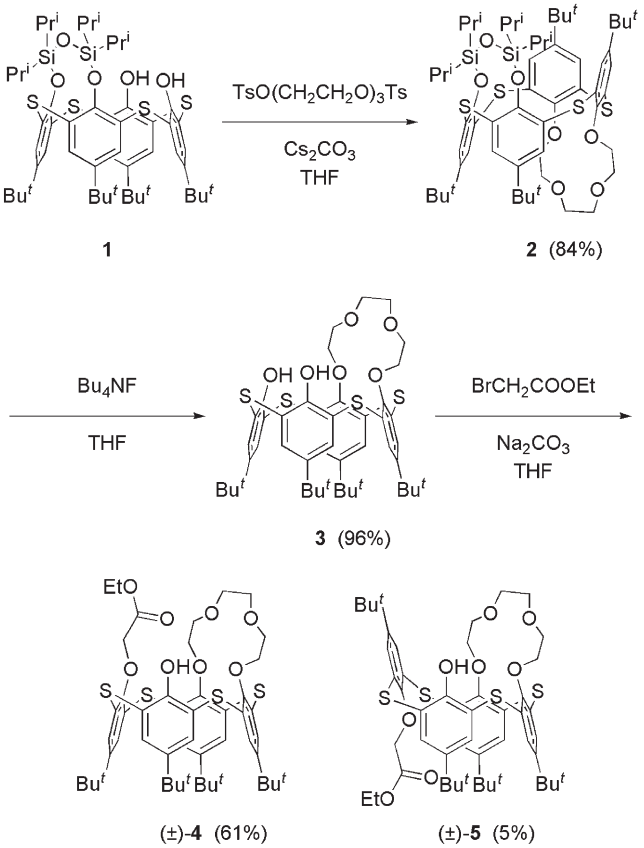


Figure 1. HPLC chromatogram of compound (±)-**4**. Column: Daicel Chiralpak AD (4.6 mm i.d.×250 mm); mobile phase: hexane–2-propanol (98:2); flow rate: 0.5 ml min^{-1}.



Scheme 2.



Scheme 1.

2.2. Chiral recognition ability of acid (+)-6

Measurement of the enantiomeric composition of a chiral compound with the aid of a chiral solvating agent in NMR spectroscopy is a classical but convenient and reliable way based on the transient diastereomeric interactions between the chiral compound and the agent.[16,17] With the desired acid in hand, we next examined its chiral recognition ability as a chiral solvating agent in discriminating enantiomeric amines as well as amino esters. Figure 2 shows the ^{1}H NMR spectra of 1-phenylethylamine in the presence or absence of acid (+)-**6**. The methyl signal of the racemic amine resonating at 1.39 ppm as a doublet (a) shifted to downfield with splitting into two doublets (b) upon addition of 1.0 mol equiv. of acid (+)-**6**, while the broad NH_2 signal centered at 1.52 ppm (a) shifted to 8.0–9.0 ppm (not shown), indicating the formation of diastereomeric ammonium salts. One diastereomer, which showed the methyl signal at the lower field, was assigned to the (*S*)-ammonium salt by comparison of the chemical shift value with that of the sample prepared from the (*S*)-amine and acid (+)-**6** (c). The results of enantiodiscrimination of amines, as well as amino esters are listed in Table 1. The

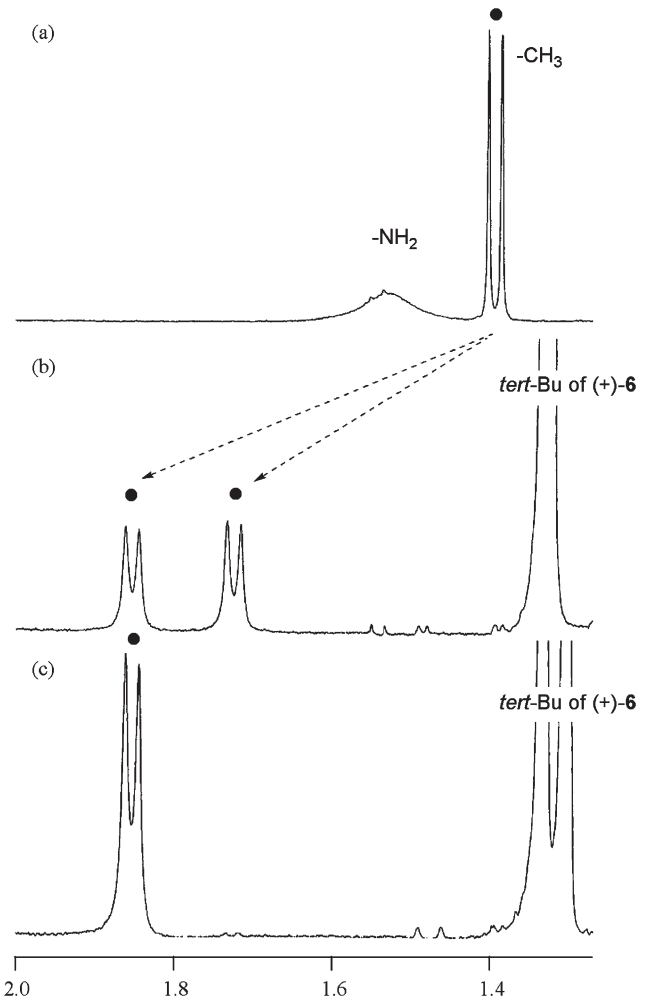
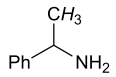
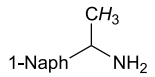
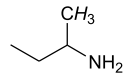
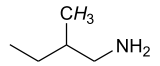
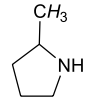
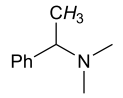
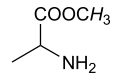
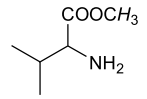
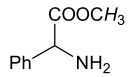
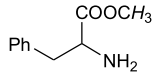
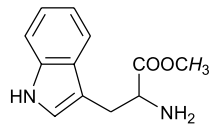


Figure 2. 500 MHz ^{1}H NMR spectra of 10 mM 1-phenylethylamine in $CDCl_3$ in the presence or absence of 1.0 mol equiv. of acid (+)-**6**. (a) (±)-1-Phenylethylamine; (b) (±)-1-phenylethylamine in the presence of acid (+)-**6**; (c) (*S*)-1-phenylethylamine in the presence of acid (+)-**6**.

methyl signals of an enantiomeric pair of primary amines were clearly differentiated from each other (entries 1–4), including the cases of *sec*-butylamine and 2-methylbutylamine (entries 3 and 4) where the difference in the steric bulk of the two alkyl substituents attached to the asymmetric carbon center is rather subtle; in both cases it required differentiation between methyl and ethyl group and furthermore, in the latter case the chiral carbon was separated from the amino nitrogen by a methylene group. It is noteworthy that the methyl signal of an (*S*)-ammonium salt shifted to a lower field than that of the (*R*)-counterpart in every case (entries 1–3). Although secondary and tertiary amines could also be discriminated by acid (+)-**6** (entries 5 and 6), the chemical shift difference between the diastereomeric salts $\Delta\delta_H(S-R)$ was insufficient for quantitative analysis. In the case of amino acid methyl esters, chiral discrimination could be advantageously carried out by using the intense singlet signal of the ester methyl moiety (entries 7–11). Consequently, baseline separation of the methyl signals were achieved for each amino ester except the case of the phenylalanine derivative (entry 10) although the $\Delta\delta_H(S-R)$ values are relatively small as compared to those for primary amines.

Table 1. Chiral recognition ability of acid (+)-**6** in discriminating enantiomeric amines and amino esters by ^{1}H NMR spectroscopy in $CDCl_3$ at 22 °C

Entry	Analyte	δ_H(Free)[a]	$\delta_H(S)$[a]	$\delta_H(R)$[a]	$\Delta\delta_H(S-R)$[b]
1		1.393	1.856	1.733	0.123
2		1.560	2.006	1.863	0.143
3		1.052	1.493	1.415	0.078
4		0.886	1.070, 1.031[c]		(0.039)
5		1.154	1.403, 1.401[c]		(0.002)
6		1.373	1.606	1.619	−0.013
7		3.727	3.676	3.752	−0.076
8		3.724	3.700	3.673	0.027
9		3.706	3.721	3.697	0.024
10		3.722	3.686	3.682	0.004
11		3.717	3.645	3.665	−0.020

[a] Chemical shift values of the methyl protons specified in italics in the presence [$\delta_H(S)$ and $\delta_H(R)$] or absence [δ_H(Free)] of 1.0 mol equiv. of acid (+)-**6**.
[b] $\Delta\delta_H(S-R)=\delta_H(S)-\delta_H(R)$.
[c] The signals are not assigned to the (*S*)- and (*R*)-isomers.

2.3. Determination of the absolute stereochemistry of acid (+)-6 by X-ray crystallographic analysis and consideration of the chiral discrimination mechanism

The ammonium salt prepared from acid (+)-**6** and (*S*)-1-phenylethylamine was crystallized from methanol–water to give colorless plates, one of which was subjected to X-ray crystallographic analysis (Fig. 3). The absolute stereochemistry of acid (+)-**6** could be determined to be *S* by using the (*S*)-1-phenylethyl moiety as an internal reference.[18] It can be seen that the 1-phenylethylammonium cation is associated with the deprotonated (+)-**6** by three

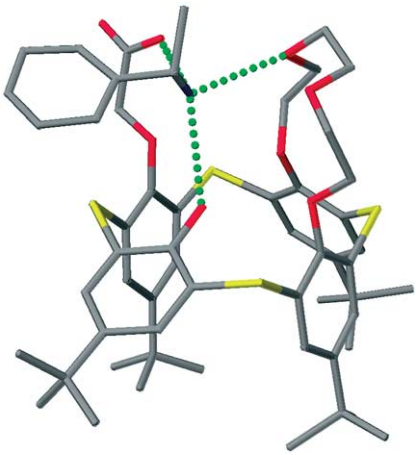


Figure 3. X-ray structure of the ammonium salt between acid (+)-**6** and (*S*)-1-phenylethylamine. Dotted lines indicate hydrogen bonds.

hydrogen bonds between the ammonio group and three oxygen atoms, that is, the carboxylato oxygen, the phenolic hydroxy oxygen and one of the four oxygens of the crown moiety, the distance from the nitrogen to these oxygens being 2.703, 2.901, and 2.886 Å, respectively. It should be noted that the phenyl group of the ammonium ion is arranged to turn away from the crown and carboxylato moieties to avoid steric repulsion.

A Job plot between (*S*)-1-phenylethylamine and acid (+)-**6** revealed that the stoichiometry of the ammonium salt in $CDCl_3$ was the same as that in the crystals (amine:acid=1:1) (Fig. 4).[20] In the ^{13}C NMR spectrum of a diastereomeric mixture of 1-phenylethylammonium salts, the asymmetric carbon centers of the (*S*)- and (*R*)-1-phenylethyl moieties resonated in the close vicinity [$\Delta\delta_C(S-R)$=0.098 ppm], while the methyl signals appeared considerably apart from each other [$\Delta\delta_C(S-R)$=0.441 ppm]. This suggests that the asymmetric carbons are located at a nearly same position in both the diastereomeric salts, because the electrostatic interaction between the carboxylate anion and ammonium cation assisted with three intramolecular hydrogen bonds as were found in the X-ray structure (Fig. 3) should play a

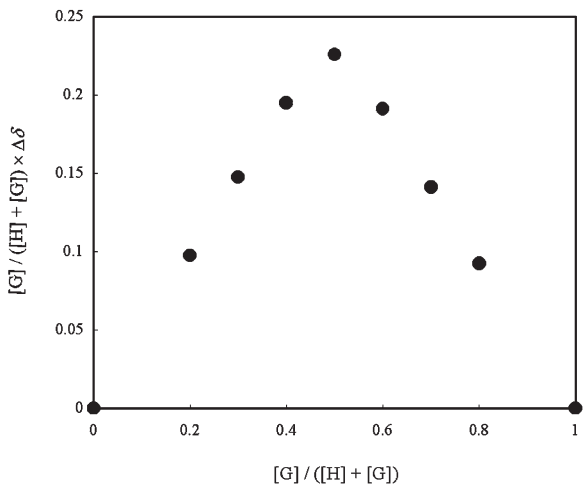


Figure 4. Job plot for the titration of (*S*)-1-phenylethylamine with acid (+)-**6** in $CDCl_3$.

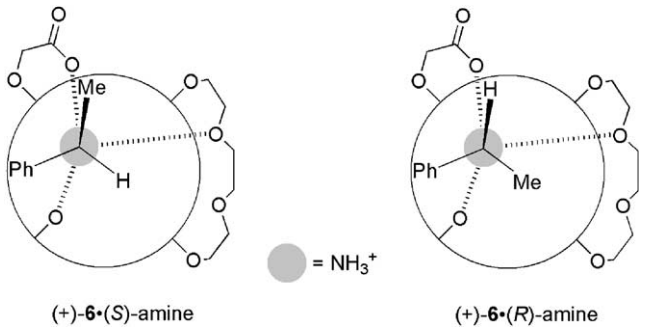


Figure 5. A steric model for the chiral discrimination of (*S*)- and (*R*)-1-phenylethylamine by acid (+)-**6**.

critical role for the salt formation. On the other hand, the difference in the chemical shifts of the methyl protons between the diastereomeric salts is ascribed to the dispositions of three substituents bonded to the asymmetric carbon center (Fig. 5). Molecular model inspections suggest that the bulkiest substituent should orient as far apart as possible from the crown and carboxylato moieties to minimize steric repulsion. This forces the methyl group of the (*R*)-ammonium salt to face against the crown ring to be the more strongly affected by its electronic effects, showing the ^1H NMR signal at a higher field than that of the (*S*)-counterpart.[21] In the case of the secondary and tertiary amines, the bulkiness of the ammonium center seemingly makes it difficult to form such a well-arranged ammonium salt, resulting in the insufficient separation of the methyl signals. If the chiral discrimination model depicted in Figure 5 were applicable to amino esters where the bulkiest substituent directs apart from the crown and carboxylato moieties, an (*S*)-amino ester having a substituent bulkier than the ester moiety at the asymmetric carbon center should show the methyl signal at a higher field than the (*R*)-counterpart because the relevant methoxycarbonyl group will locate near to the polyoxyethylene chain. However, inspection of the results shown in Table 1 indicates that the simple steric model based on apparent bulk of the substituents cannot be applied to the methyl esters (entries 7–11), indicating participation of stereoelectronic effect of the polar ester function.

3. Conclusion

We have shown here an efficient method for the synthesis of optically active *O*,*O*′-bridged thiacalix[4]crowncarboxylic acid (+)-**6**. The absolute stereochemistry was determined by an X-ray crystallographic analysis. The compound could discriminate enantiomeric amines as well as amino acid methyl esters by ^1H NMR spectroscopy.

4. Experimental

4.1. General

Melting points (mps) were taken using a Mitamura Riken MP-P apparatus. Samples for the mp measurement were routinely recrystallized from chloroform–methanol, unless

otherwise noted. Optical rotations were measured on a JASCO DIP-1000 polarimeter and $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. Microanalyses were carried out in the Microanalytical Laboratory of the Institute of Multidisciplinary Research for Advanced Materials, Tohoku University. IR spectra were recorded on a JEOL JIR-3510 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 or DRX-500 spectrometer using tetramethylsilane (^{1}H NMR) or chloroform (^{13}C NMR) as an internal standard and $CDCl_3$ as a solvent. Mass spectra were measured on a JEOL JMS-DX602 spectrometer. Silica gel columns were prepared by use of Merck silica gel 60 (63–200 μm). THF was distilled from sodium diphenylketyl just before use. Compound **1** was prepared as reported previously.[6] Other materials were used as purchased.

4.2. Synthesis of acid (+)-6

4.2.1. 5,11,17,23-Tetra-*tert*-butyl-25,26-(2,2,4,4-tetraisopropyl-1,3,5-trioxa-2,4-disilapentane-1,5-diyl)-27,28-(1,4,7,10-tetraoxadecane-1,10-diyl)thiacalix[4]arene (2). To a solution of *O*,*O*′-disiloxane-bridged thiacalix[4]arene **1** (482 mg, 500 μmol) in THF (50 ml) were added Cs_2CO_3 (489 mg, 1.50 mmol) and tri(ethylene glycol) di-*p*-tosylate (275 mg, 600 μmol). After heating at reflux with stirring for 30 h, the mixture was cooled to 0 °C and quenched with 2 M HCl. The mixture was extracted with chloroform and the extract was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel with hexane–ethyl acetate (10:1) as an eluent to give disiloxane-bridged thiacalix[4]crown **2** (451 mg, 84%) as a colorless powder, mp 319–321 °C (Found: C, 64.5; H, 7.85; S, 11.6. Calcd for $C_{58}H_{84}O_7S_4Si_2$: C, 64.6; H, 7.9; S, 11.9%); δ_H (400 MHz) 0.43 (6H, d, *J*=7.4 Hz, CHC*H*$_3$×2), 0.76 (6H, d, *J*=7.5 Hz, CHC*H*$_3$×2), 0.80–0.92 [2H, m, C*H*(CH$_3$)$_2$×2], 1.02 (6H, d, *J*=7.5 Hz, CHC*H*$_3$×2), 1.06 (6H, d, *J*=7.4 Hz, CHC*H*$_3$×2), 1.15–1.24 [2H, m, C*H*(CH$_3$)$_2$×2], 1.28 [18H, s, C(CH$_3$)$_3$×2], 1.35 [18H, s, C(CH$_3$)$_3$×2], 2.64–2.73 (2H, m, OCH$_2$), 3.28–3.60 (6H, m, OCH$_2$×3), 3.73–3.82 (4H, m, OCH$_2$×2), 7.32 (2H, d, *J*=2.4 Hz, ArH×2), 7.55 (2H, d, *J*=2.4 Hz, ArH×2), 7.57 (2H, d, *J*=2.5 Hz, ArH×2) and 7.78 (2H, d, *J*=2.5 Hz, ArH×2); FAB-MS *m*/*z* 1076 (M^+).

4.2.2. 5,11,17,23-Tetra-*tert*-butyl-25,26-dihydroxy-27,28-(1,4,7,10-tetraoxadecane-1,10-diyl)thiacalix[4]arene (3). To a solution of disiloxane-bridged thiacalix[4]crown **2** (323 mg, 300 μmol) in THF (15 ml) was added a 1.0 M solution of tetrabutylammonium fluoride in THF (300 μl, 300 μmol). The mixture was stirred at room temperature for 1 h and quenched with 2 M HCl. The mixture was extracted with chloroform and the extract was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel with hexane–ethyl acetate (3:1) as an eluent to give calix[4]crown **3** (240 mg, 96%) as a colorless powder, mp 132–134 °C (Found: C, 65.9; H, 7.05; S, 15.6. Calcd for $C_{46}H_{58}O_6S_4$: C, 66.15; H, 7.00; S, 15.4%); δ_H (400 MHz) 1.04 [18H, s, C(CH$_3$)$_3$×2], 1.23 [18H, s, C(CH$_3$)$_3$×2], 3.28–4.65 (12H, m, OCH$_2$CH$_2$O×3), 7.36 (4H, br, ArH×4), 7.55 (2H, d, *J*=2.5 Hz, ArH×2), 7.58 (2H, d, *J*=2.5 Hz, ArH×2) and 8.87 (2H, s, OH×2); FAB-MS *m*/*z* 835 [(M+1)$^+$].

4.2.3. *syn*- and *anti*-5,11,17,23-Tetra-*tert*-butyl-25-ethoxycarbonylmethoxy-26-hydroxy-27,28-(1,4,7,10-tetraoxadecane-1,10-diyl)thiacalix[4]arene (4 and 5). To a solution of calix[4]crown **3** (835 mg, 1.00 mmol) in THF (20 ml) were added Na_2CO_3 (106 mg, 1.10 mmol) and ethyl bromoacetate (1.67 g, 9.96 mmol) and the mixture was heated at reflux with stirring for 48 h. After cooling, the mixture was quenched with 2 M HCl and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica gel with hexane–ethyl acetate (4:1) as an eluent to give ester **4** (562 mg, 61%) and **5** (42.3 mg, 5%) as colorless powders. Ester **4**: mp 104–106 °C (Found: C, 65.2; H, 7.0; S, 14.0. Calcd for $C_{50}H_{64}O_8S_4$: C, 65.2; H, 7.0; S, 13.9%); ν_{max} (KBr)/cm^{-1} 1765 (CO); δ_H (400 MHz) 0.62 [9H, s, C(CH$_3$)$_3$], 1.04 [9H, s, C(CH$_3$)$_3$], 1.31 (3H, t, *J*=7.1 Hz, OCH$_2$C*H*$_3$), 1.32 [18H, s, C(CH$_3$)$_3$×2], 3.80–4.51 (12H, m, OCH$_2$CH$_2$O×3), 4.26 (2H, q, *J*=7.1 Hz, OC*H*$_2$CH$_3$), 4.71 (1H, d, *J*=16.3 Hz, OCH$_2$CO), 4.87 (1H, d, *J*=16.3 Hz, OCH$_2$CO), 6.57 (1H, d, *J*=2.4 Hz, ArH), 6.63 (1H, d, *J*=2.4 Hz, ArH), 7.29 (1H, d, *J*=1.9 Hz, ArH), 7.31 (1H, d, *J*=2.5 Hz, ArH), 7.59 (1H, d, *J*=2.5 Hz, ArH), 7.65 (1H, d, *J*=2.5 Hz, ArH), 7.68 (1H, d, *J*=2.5 Hz, ArH), 7.71 (1H, d, *J*=2.5 Hz, ArH) and 8.02 (1H, s, OH); FAB-MS *m*/*z* 921 [(M+1)$^+$]. Ester **5**: δ_H (400 MHz) 1.00 (3H, t, *J*=7.2 Hz, OCH$_2$C*H*$_3$), 1.23 [9H, s, C(CH$_3$)$_3$], 1.31 [9H, s, C(CH$_3$)$_3$], 1.32 [9H, s, C(CH$_3$)$_3$], 1.36 [9H, s, C(CH$_3$)$_3$], 2.67–4.09 (12H, m, OCH$_2$CH$_2$O), 3.98 (2H, q, *J*=6.8 Hz, OC*H*$_2$CH$_3$), 4.05 (1H, d, *J*=15.1 Hz, OCH$_2$CO), 4.87 (1H, d, *J*=15.1 Hz, OCH$_2$CO), 7.42 (1H, d, *J*=2.4 Hz, ArH), 7.43 (1H, d, *J*=2.4 Hz, ArH), 7.46 (1H, d, *J*=2.4 Hz, ArH), 7.54 (1H, d, *J*=2.5 Hz, ArH), 7.59 (1H, d, *J*=2.5 Hz, ArH), 7.64 (1H, d, *J*=2.5 Hz, ArH), 7.65 (1H, d, *J*=2.5 Hz, ArH), 7.77 (1H, d, *J*=2.5 Hz, ArH) and 7.91 (1H, s, OH).

4.2.4. Optical resolution of compound 4. Racemic ester **4** was subjected to optical resolution by chiral HPLC [column: Daicel CHIRALPAK AD, 20 mm i.d.×25 cm; mobile phase:hexane-2-propanol (98:2); flow rate: 6.0 ml min^{-1}]. A solution of racemic **4** (20 mg) in hexane (500 μl) was injected into the column per one operation and three fractions were collected. Enantiomerically pure (+)- and (−)-**4** (>99% ee) were recovered in 37 and 24% yields from the first and third fractions, respectively. Ester (+)-**4**: $[\alpha]_D^{26}$=+9.0 (*c* 0.50, ethanol). Ester (−)-**4**: $[\alpha]_D^{26}$=−9.0 (*c* 0.50, ethanol).

4.2.5. *syn*-5,11,17,23-Tetra-*tert*-butyl-25-hydroxy-26-hydroxycarbonylmethoxy-27,28-(1,4,7,10-tetraoxadecane-1,10-diyl)thiacalix[4]arene (+)-6. A mixture of ester (+)-**4** (340 mg, 369 μmol), 5.5 M KOH (2.0 ml) and ethanol (15 ml) was heated at reflux with stirring for 48 h. After cooling, the mixture was quenched with 2 M HCl and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by recrystallization from methanol to give acid (+)-**6** as a colorless powder (326 mg, 99%); mp 145–147 °C (Found: C, 64.3; H, 6.8; S, 14.5. Calcd for $C_{48}H_{60}O_8S_4$: C, 64.5; H, 6.8; S, 14.4%); $[\alpha]_D^{27}$=+14.5 (*c* 1.05, chloroform); ν_{max} (KBr)/cm^{-1} 1722 (CO); δ_H (400 MHz) 1.03 [9H, s, C(CH$_3$)$_3$], 1.04 [9H, s, C(CH$_3$)$_3$], 1.18 [9H, s, C(CH$_3$)$_3$], 1.22 [9H, s, C(CH$_3$)$_3$], 3.81–4.59 (12H, m, OCH$_2$CH$_2$O×3), 4.55 (1H, d, *J*=16.2 Hz, OCH$_2$CO), 5.53 (1H, d, *J*=16.2 Hz,

OCH_2CO), 7.30 (1H, d, J=2.5 Hz, ArH), 7.31 (2H, br, ArH), 7.34 (1H, d, J=2.5 Hz, ArH), 7.50 (1H, d, J=3.3 Hz, ArH), 7.51 (1H, d, J=2.5 Hz, ArH), 7.57 (1H, d, J=2.5 Hz, ArH), 7.60 (1H, d, J=2.5 Hz, ArH) and 8.35 (1H, s, OH); FAB-MS m/z 893 [$(M+1)^+$].

4.3. General procedure for the ^{1}H NMR shift experiments

The sample containing an amine was prepared by mixing a 20.0 mM solution of acid (+)-**6** (0.25 ml) in $CDCl_3$ with a 20.0 mM solution of an appropriate amine (0.25 ml) in $CDCl_3$. The sample containing an amino ester was similarly prepared from two 40.0 mM solutions of acid (+)-**6** and an amino ester (0.25 ml each). These samples, together with the solutions of the amine (10.0 mM) and amino ester (20.0 mM) in $CDCl_3$, were analyzed by ^{1}H NMR spectroscopy (500 MHz) at 22 °C.

4.4. Determination of the stoichiometry of the salt between acid (+)-6 and (*S*)-1-phenylethylamine

Two 10.0 mM solutions of acid (+)-**6** and (*S*)-1-phenylethylamine in $CDCl_3$ were mixed in the following volume ratios; 10:0, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8 and 0:10. These samples were analyzed by ^{1}H NMR spectroscopy (500 MHz) at 22 °C. The chemical shift value of the methyl protons of the amine (δ_{obs}) was converted to the chemical shift change ($\Delta\delta$) as follows: $\Delta\delta=\delta_{obs}-\delta_{amine}$, where δ_{amine} is the chemical shift value in the absence of acid (+)-**6**. Finally $[G]/([H]+[G])\times\Delta\delta$ was plotted against $[G]/([H]+[G])$, where [G] is the total concentration of the amine and [H] is that of acid (+)-**6**.

4.5. X-ray analysis of the salt between acid (+)-6 and (*S*)-1-phenylethylamine

Data were collected on a Rigaku/MSC Mercury CCD diffractometer using Mo K_α radiation (λ=0.71069 Å). The calculation was performed using the software package TeXsan (v. 1.11).[22] The structure was solved by the direct methods with SIR92[23] and refined by full-matrix least squares methods with SHELXL-97.[24] All non-hydrogen atoms were refined anisotropically. Crystal data and refinement statistics are as follows: $C_{57}H_{81}NO_{14}S_4$, M=1132.51, monoclinic, a=15.459(4), b=14.821(3), c=15.978(4) Å, β=113.416(3)°, V=3359(1) Å^3, T=223(2) K, space group $P2_1$, Z=2, μ (Mo K_α)=0.197 mm^{-1}, 42641 reflections measured, 12887 unique (R_{int}=0.058). Final R_1=0.077 for 9856 data [$I>2\sigma(I)$] and wR_2=0.214 for all data, GOF=1.047. The absolute stereochemistry of acid (+)-**6** was assigned to be *S* by using the (*S*)-1-phenylethyl moiety as an internal reference. The details of the crystal data have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 238754.

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Highly efficient chiral copper Schiff-base catalyst for asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene

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Abstract—A remarkable increase in catalytic activity is found for the asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene with diazoacetate by use of the chiral copper Schiff-base complexes, which are derived from substituted salicylaldehydes, chiral aminoalcohols, and copper acetate monohydrate. Furthermore, a combination of a chiral copper Schiff-base with a Lewis acid showed an increase in yield (up to 90%) and in enantioselectivity (up to 90% ee) for the asymmetric cyclopropanation of the diene with *t*-butyl diazoacetate at 20 °C.

1. Introduction

Catalytic asymmetric cyclopropanation of alkenes with diazoacetate has been a powerful tool in the synthesis of chiral cyclopropyl esters, which are very important intermediates for biologically active compounds.[1–4] 3-(1-Isobutenyl)-2,2-dimethyl cyclopropanecarboxylate (chrysanthemate) is of particular importance as an intermediate of pyrethroid insecticides, and the (1*R*,3*R*) isomer ((+)-*trans* isomer) shows the most insecticidal activity among the four isomers of the chrysanthemate.[5] Among the efficient catalysts which have been developed, copper Schiff-base complexes derived from chiral aminoalcohols are very attractive catalysts. Using this kind of catalysts, Aratani first achieved a high ee (94%) and *trans*/*cis* ratio (93/7) for the cyclopropanation of 2,5-dimethyl-2,4-hexadiene with *l*-menthyl diazoacetate to give the chrysanthemate, and Aratani's asymmetric process leads to successful industrial application in the synthesis of chiral 2,2-dimethylcyclopropane carboxylic acid, by asymmetric cyclopropanation of isobutene with ethyl diazoacetate.[5–7]

To the best of our knowledge, only a few successful reports, in which high *trans* selectivity and high enatioselectivity were achieved, have been presented in the asymmetric cyclopropanation of the diene as a substrate, although many asymmetric cyclopropanations of styrene with diazoacetate have been reported over the last 20 years (Scheme 1).[1–4,8–10]

In Aratani's catalyst, the structure of the chiral aminoalcohol part played an important role on the enantioselectivity,[6,7] so that the modification of the aminoalcohol has been tried to achieve higher enantioselectivity up to 1999. In 2000, Li et al. reported an investigation on the framework of the benzene ring of salicylaldehyde in the copper Schiff-base complex for the asymmetric cyclopropanation of styrene, and more than 98% ee of the *cis* product was obtained with *i*-butyl diazoacetate using the copper Schiff-base catalyst **3b** derived from 5-nitrosalicylaldehyde.[11] They also applied the copper Schiff-base catalyst **3b** to the cyclopropanation of 2,5-dimethyl-2,4-hexadiene with *l*-menthyl diazoacetate with 1 mol% catalyst loading. However the enantioselectivity of the *trans* product and the *trans*/*cis* ratio were moderate (74% ee, *t*/*c*=72/28), and the catalytic amount used in their report (1 mol%) should increase the cost of the cyclopropane products (Scheme 2).[12]

Therefore, we have developed new highly efficient catalysts for the cyclopropanation of the dienes with a simple alkyl diazoacetate such as ethyl or *t*-butyl diazoacetate, which means that the formed chrysanthemate would be easy to convert to the chiral chrysanthemic acid as the intermediate for pyrethroid insecticides. Here, we report that the copper Schiff-base catalysts derived from 5-substituted salicylaldehyde with an electron-withdrawing group remarkably

Keywords: Asymmetric cyclopropanation; Copper Schiff-base; Lewis acid; Diazoacetate; 2,5-Dimethyl-2,4-hexadiene.
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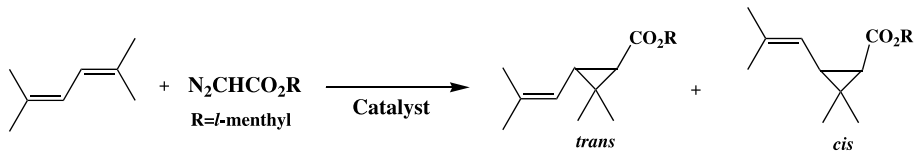
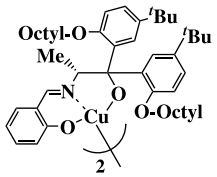
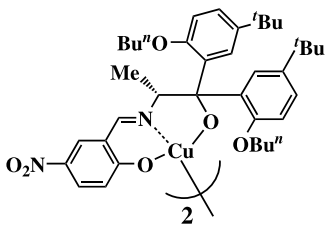




Aratani's catalyst (R-1648)

Yield 75%
t/c = 93/7
94%ee (*trans*)

Scheme 1. The structures of Aratani's catalysts R-1648, and the results of the cyclopropanation of 2,5-dimethyl-2,4-hexadiene with *l*-menthyl diazoacetate with 1 mol% catalyst loading.



Li 's catalyst (3b)

t/c = 72/28
74% ee (*trans*)

Scheme 2. Structures of Li's catalyst **3b**, and the results of the cyclopropanation of 2,5-dimethyl-2,4-hexadine with *l*-menthyl diazoacetate with 1 mol% catalyst loading.

enhanced the catalytic efficiency for the asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene. Furthermore, we found that a combination of a copper Schiff-base complex with a Lewis acid achieved 90% yield and more than 90% ee with *t*-butyl diazoacetate at 20 °C with 0.1 mol% catalyst loading.

2. Results and discussion

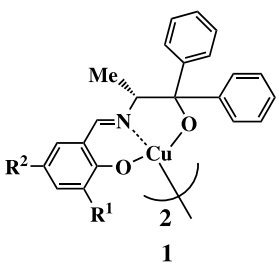
2.1. Effect of substituents of aminoalcohol framework and salicylaldehyde framework on the stereoselectivity and the catalytic efficiency

The results of the asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene (DMHD) with ethyl diazoacetate (EDA) are shown in Table 1, using the copper Schiff-base complexes as catalysts as shown in Scheme 3. They were synthesized from chiral aminoalcohols, salicylaldehyde derivatives, and copper(II) acetate hydrate (Scheme 4). In the order of **1a**, **2a**, and **3a**, the enantioselectivety of the *trans* product was enhanced, while the *trans*/*cis* ratio of the product was lowered in the presence of 0.5 mol% catalyst loading (entries 1, 5, 9).[7] The results are consistent with those of Aratani,[7] although the presence of a nitrogen group on the salicylaldehyde framework did not show a remarkable difference with 0.5 mol% catalyst (entries 3, 7, 11). All cases with 0.1 mol% catalysts **1a**, **2a**, and **3a** decreased not only in the yield but also in enantioselectivity, compared to those with 0.5 mol% (entries 1 vs. 2, 5 vs. 6, 9 vs. 10). However, almost the same yield and ee were retained in each case with 0.1 mol% catalysts **1b**, **2b**, and **3b** as those with 0.5 mol% catalyst (entries 3 vs. 4, 7 vs. 8, 11 vs. 12). These results clearly indicated that the copper Schiff-base catalysts derived from salicylaldehyde lose catalytic activity faster than those derived with 5-nitrosalicylaldehyde. Actually, we analyzed the reaction mixture based on the structure of the used catalyst **2a** after the cyclopropanation by HPLC. We found that not only the original copper complex **2a** but also the corresponding Schiff-base ligand

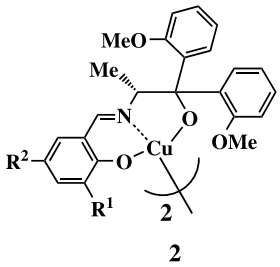
Table 1. Asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene (DMHD) with EDA[a]

Entry	Catalyst	mol%[b]	Yield (%)[c]	*trans*/*cis*[d]	ee (%)[e]	
					trans[f]	*cis*[g]
1	**1a**	0.5	95	61/39	60	59
2	**1a**	0.1	80	63/37	32	30
3	**1b**	0.5	97	61/39	59	50
4	**1b**	0.1	96	61/39	58	48
5	**2a**	0.5	96	58/42	65	69
6	**2a**	0.1	83	60/40	40	39
7	**2b**	0.5	97	58/42	67	65
8	**2b**	0.1	96	58/42	65	60
9	**3a**	0.5	96	55/45	80	61
10	**3a**	0.1	82	58/42	44	39
11	**3b**	0.5	96	54/46	80	60
12	**3b**	0.1	95	54/46	78	56

[a] Reaction conditions: 10 mmol of EDA, 70 mmol of DMHD, 5 mL of ethyl acetate, 80 °C, 0.01 mmol of the monomerized copper complex with 0.5 mol of phenylhydrazine to the binuclear complex as shown in Scheme 4.
[b] Mol% of the mononuclear complex based on EDA.
[c] Based on EDA and determined by GC analysis with *n*-decane as internal standard.
[d] Determined by GC analysis (DB-1, 30 m×0.25 mm ID, 0.25 mm film, column temp. 100 °C).
[e] Determined by LC analysis (Sumichiral OA-2500 (25 cm×4 mm ID, 5 μm film)×2, UV 220 nm, *n*-hexane 0.7 mL/min).
[f] 1*R*,3*R* as a major enantiomer.
[g] 1*R*,3*S* as a major enantiomer.



1



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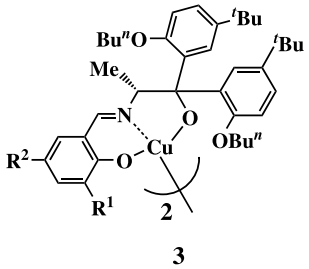
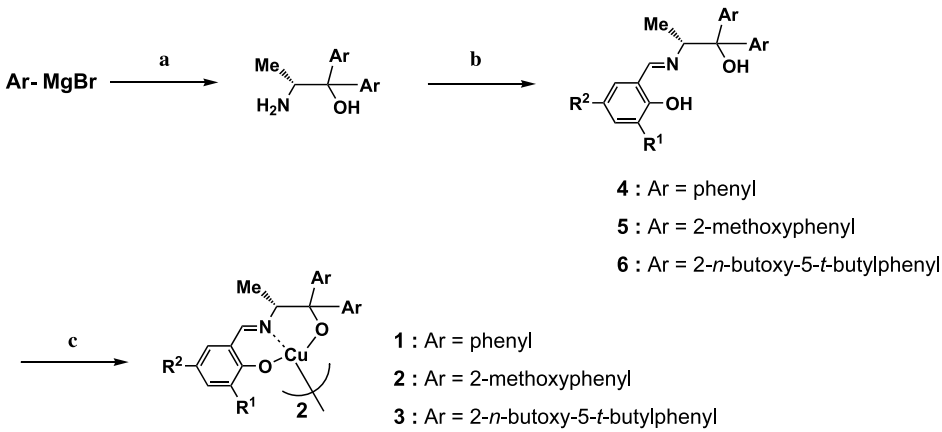


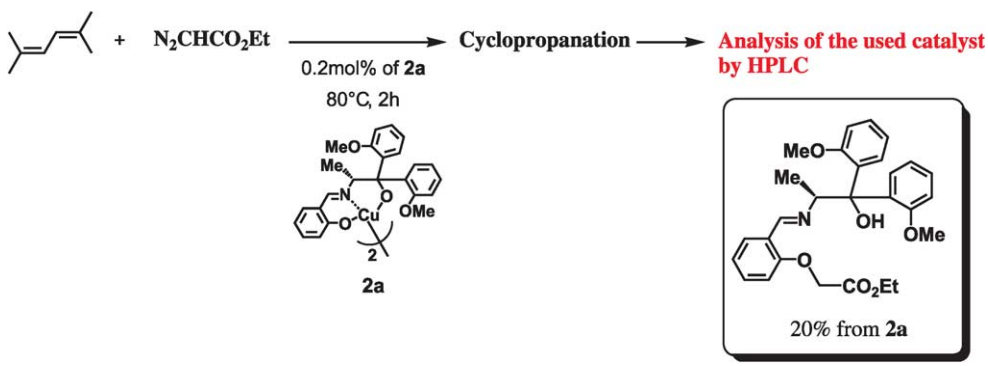
3

	R^1	R^2
1a	H	H
1b	H	NO_2
2a	H	H
2b	H	NO_2
3a	H	H
3b	H	NO_2

Scheme 3. Structures of the copper Schiff-base catalysts **1a**-**1b**, **2a**-**2b**, **3a**-**3b**.



Scheme 4. Synthesis of copper Schiff-base complexes **1**-**3**. (a) *D*-alanine methyl ester hydrochloride; (b) substituted salicylaldehyde; (c) copper acetate monohydrate, NaOH.

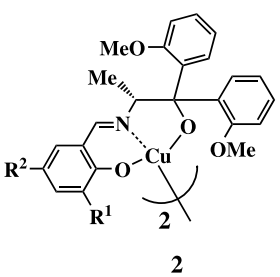


Scheme 5. The structure of the used catalyst **2a** after the cyclopropanation.

did not exist in the reaction mixture any more, and an adduct of ethyl diazoacetate with the phenol oxygen of the Schiff-base ligand was detected as shown in Scheme 5.

Li et al. described that reducing the electron density on the salicylaldehyde framework by the introduction of a nitro group favors the enantioselectivity for the cyclopropanation of styrene. Although our results above suggest that the introduction of a nitro group does not affect the enantioselectivity, the catalytic robustness can be enhanced more strongly with the Cu–O bond from the phenol.

Therefore, several Schiff-bases with various electron-withdrawing substituents on the salicylaldehyde framework in copper complex **2** were examined (Scheme 6). We found that 5-substituted copper complexes with an



2

	R^1	R^2
2a	H	H
2b	H	NO_2
2c	NO_2	H
2d	NO_2	NO_2
2e	H	CO_2Me
2f	CO_2Me	H
2g	H	CN
2h	H	CF_3
2i	H	F
2j	F	H

Scheme 6. Structures of the copper catalysts **2a**-**2k**.

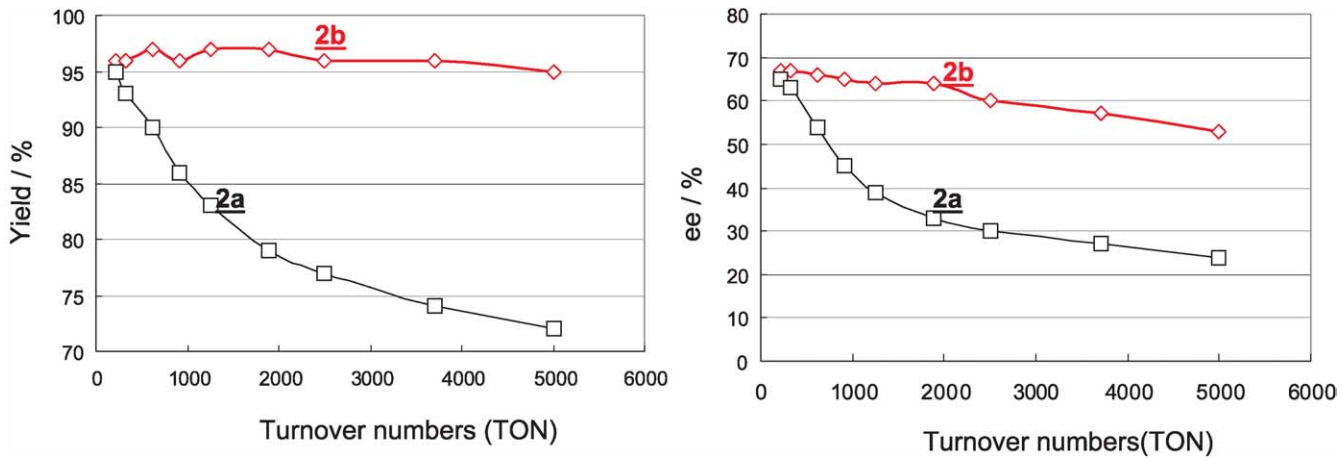


Figure 1. Comparison of catalytic efficiency between **2a** and **2b** at 80 °C.

electron-withdrawing group were more effective for the enantioselectivity than 3-substituted ones, except for the fluorine substituted complex.

Comparison of turnover numbers between **2a** and **2b** is shown in Figure 1. A remarkable decrease in both the yield and ee was observed with higher turnover numbers in the case of **2a**, while in the case of catalyst **2b**, the ratio of the decrease in the yield and the ee is much smaller than that by **2a**.

These results suggested that the copper Schiff-base catalyst derived from the 5-substituted salicylaldehyde with an electron-withdrawing group becomes more efficient for the asymmetric cyclopropanation of the diene, although the same performance is essentially exhibited in enantioselectivity as the unsubstituted copper complex on the salicylaldehyde moiety. This point is also different from the introduction of a nitro group in salicylaldehyde at the 5-position in the copper complex which enhanced the enantioselectivity for the cyclopropanation of styrene by Li et al. (Table 2).

Table 2. Asymmetric cyclopropanation of DMHD with EDA using **2** as the catalyst[a]

Entry	Catalyst	mol%[b]	Yield (%)	*trans*/*cis*	ee (%)	
					trans[c]	*cis*[d]
1	**2a**	0.1	83	60/40	40	39
2	**2b**	0.1	96	58/42	65	60
3	**2c**	0.1	97	59/41	55	48
4	**2d**	0.1	98	60/40	42	33
5	**2e**	0.1	97	58/42	65	58
6	**2f**	0.1	94	60/40	46	40
7	**2g**	0.1	97	58/42	63	57
8	**2h**	0.1	97	58/42	62	58
9	**2i**	0.1	96	60/40	43	41
10	**2j**	0.1	97	59/41	62	57

[a] Reaction conditions: 10 mmol of EDA, 70 mmol of DMHD, 5 mL of ethyl acetate, 80 °C, 0.01 mmol of the monomerized copper complex with 0.5 mol phenylhydrazine to the binuclear complex as shown in Scheme 6.
[b] Mol% of the mononuclear complex based on EDA.
[c] 1*R*,3*R* as a major enantiomer.
[d] 1*R*,3*S* as a major enantiomer.

2.2. Effect of temperatures on the selectivity

Under lower temperatures for the reaction, higher enantiomeric excesses of the product were obtained, but the yield of the product was lowered with the catalyst **2b** or **3b**, as shown in Table 3.

Table 3. The influence of reaction temperature and alkyls in diazoacetate (RDA) in the presence of 0.1mol%[a] of the catalysts[b]

Entry	Catalyst	R in RDA	Temp (°C)	Yield (%)	*trans*/*cis*	ee (%)[c]	
						trans[d]	*cis*[e]
1	**2b**	Et	80	96	58/42	65	60
2	**2b**	Et	20	58	58/42	75	70
3	**2b**	Et	0	35	57/43	83	78
4	**2b**	*t*-Bu	80	88	72/28	83	55
5	**2b**	*t*-Bu	20	27	78/22	91	63
6	**2b**	*t*-Bu	0	6	79/21	93	64
7	**3b**	Et	80	95	54/46	78	56
8	**3b**	Et	0	56	50/50	82	67
9	**3b**	*t*-Bu	80	87	72/28	84	20
10	**3b**	*t*-Bu	20	11	77/23	93	23

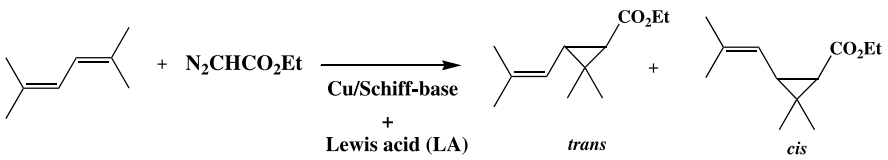
[a] Mol% of mononuclear complex based on RDA.
[b] Reaction conditions: 0.01 mmol of catalyst as the monomeric copper complex, 10 mmol of RDA, 70 mmol of DMHD, 5 mL of ethyl acetate.
[c] Determined by LC analysis (Chiral AGP (25 cm×4 mm ID, 5 μm film) ×2, UV 210 nm, 20 mM KH_2PO_4/CH_3CN=87/13 (v/v), 0.5 mL/min) in the case where $N_2CHCO_2^tBu$ was used.
[d] 1*R*,3*R* as a major enantiomer.
[e] 1*R*,3*S* as a major enantiomer.

A bulky group in the diazoacetate was reported to increase the enantioselectivity and *trans*/*cis* ratio.[5] When *t*-butyl diazoacetate was used, the enantiomeric excesses for the *trans* product reached 93% in the case of both catalysts **2b** and **3b** at 0 °C, although the yield was low. The *trans*/*cis* ratio was slightly better with **2b** than **3b**. The slow rate of the process and the low yield of the product could be dramatically improved by addition of a Lewis acid.

2.3. Effect of a Lewis acid on the selectivity

In order to achieve high yields and high enantioselectivities, addition of an equimolar amount of a Lewis acid was examined with 0.1 mol% catalyst **2b** at 0 or 20 °C. The results are shown in Table 4. It is noteworthy that addition of

Table 4. Asymmetric cyclopropanation of DMHD with EDA using the new catalyst system, consistent for the copper Schiff-base complex and various Lewis acids (LA)[a]



Entry	Cu-complex	LA	Temp (°C)	Yield (%)	*trans*/*cis*	ee (%) *trans*[b]	ee (%) *cis*[c]
1	**2b**	None	20	58	58/42	75	70
2	**2b**	None	0	35	57/43	83	78
3	**2b**	$HfCl_4$	20	84	58/42	76	71
4	**2b**	$B(C_6F_5)_4$	20	91	58/42	76	71
5	**2b**	$Al(OC_6F_5)_3$	20	91	58/42	72	68
6	**2b**	$Ti(O-^iPr)_4$	20	85	58/42	76	70
7	**2b**	$Al(OEt)_3$	20	95	58/42	77	71
8	**2b**	$Al(OEt)_3$	0	86	57/43	84	79
9	**3b**	None	0	56	50/50	82	67
10	**3b**	$Al(OEt)_3$	0	83	49/51	83	68

[a] Reaction conditions: 0.01 mmol of the copper Schiff-base complex as the monomeric copper complex, 0.01 mmol of Lewis acid, 10 mmol of EDA, 70 mmol of DMHD, 5 mL of ethyl acetate.
[b] 1*R*,3*R* as a major enantiomer.
[c] 1*R*,3*S* as a major enantiomer.

Table 5. The effect of adding $Al(OEt)_3$ to the copper Schiff-base catalyst on the asymmetric cyclopropanation of DMHD with RDA[a]

Entry	Cu-complex	LA	R in RDA	Temp (°C)	Yield (%)	*trans*/*cis*	ee (%) *trans*[b]	ee (%) *cis*[c]
1	**2b**	None	*t*-Bu	20	27	78/22	91	63
2	**2b**	$Al(OEt)_3$	*t*-Bu	20	90	78/22	91	62
3	**3b**	None	*t*-Bu	20	11	77/23	93	23
4	**3b**	$Al(OEt)_3$	*t*-Bu	20	86	77/23	93	24

[a] Reaction conditions: 0.01 mmol of copper Schiff-base as the monomeric copper complex, 0.01 mmol of Lewis acid, 10 mmol of RDA, 70 mmol of DMHD, 5 mL of ethyl acetate.
[b] 1*R*,3*R* as a major enantiomer.
[c] 1*R*,3*S* as a major enantiomer.

a Lewis acid increased the reaction rate, and even at 20 °C a 95% yield was obtained in the presence of $Al(OEt)_3$ (77% ee, entries 7 vs. 1); the reaction proceeded smoothly at 0 °C to give 86% yield and 84% ee (entries 8 vs. 2). The combination of the copper complex **3b** with $Al(OEt)_3$ was also examined with EDA, and enhancement of the yield was observed (entries 9 vs. 10).

Furthermore, when *t*-butyl diazoacetate was used instead of ethyl diazoacetate, 91% yield and 91%ee for the *trans* product were obtained at 20 °C in the presence of 0.1 mol% of **2b** combined with $Al(OEt)_3$ (entries 1 vs. 2, in Table 5). The use of the catalyst composed of **3b** and $Al(OEt)_3$ also achieved 86% yield and 93% ee.

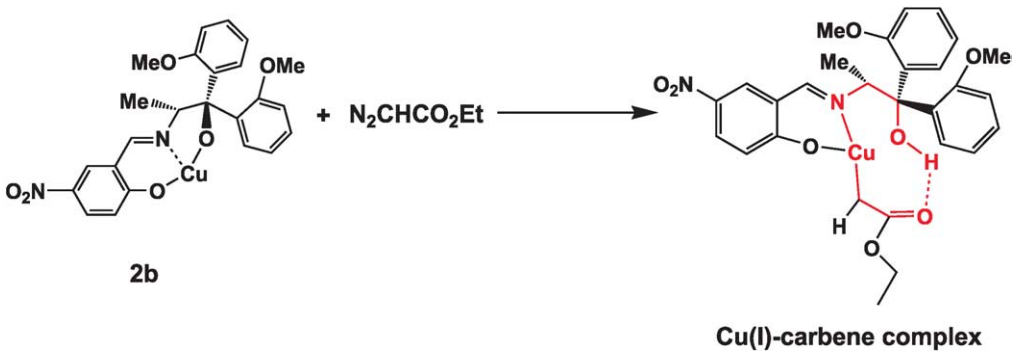
Aratani achieved more than 90% ee for the *trans* product with 1 mol% of a chiral [(*R*)-*N*-salicylidene-2-amino-1,1-di(2-*n*-octyloxy-5-*t*-butylphenyl)-1-propanol] copper complex as a catalyst in the asymmetric cyclopropanation of DMHD with *l*-menthyl diazoacetate, while more than 90% ee for the *trans* product was achieved using 2,6-*t*-butyl-4-methylphenyl diazocetate catalyzed by a copper-chiral-bisoxazoline complex.

To the best of our knowledge, the achievement of more than 90% ee is the first case of the asymmetric cyclopropanation of DMHD with *t*-butyl diazoacetate. It should be noted the *t*-butyl chrysanthemate formed is easy to hydrolyze to convert to chrysanthemic acid by an acid catalyst, which is a key intermediate for synthetic pyrethroids.

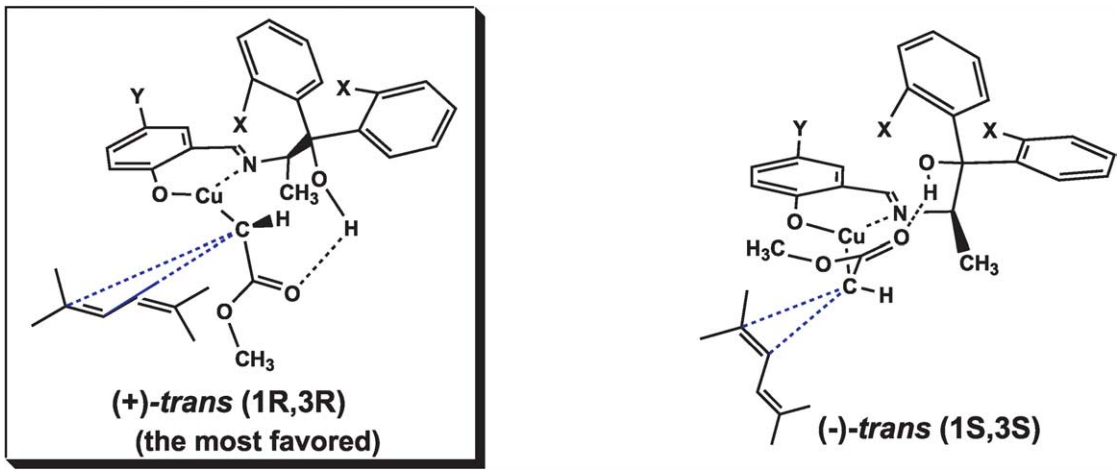
2.4. Study of the possible mechanism based on the calculations

In order to probe the possible mechanism of the asymmetric induction, hybrid density functional calculations were carried out. As the details of the calculation were reported elsewhere,[13] these calculations suggested that the catalytic key intermediate can be the copper(I) carbene complex bearing the intramolecular hydrogen bond between the hydrogen of the hydroxyl group and the carbonyl oxygen of the ester group in the case of catalyst **2b** as shown in Scheme 7.

The reaction proceeds by the [2+1] addition from DMHD to the carbene carbon of the Cu(I)–carbene complex. The enantioselectivity of the chrysanthemate calculated from the Boltzmann distribution of the nine transition states was qualitatively consistent with the experimental result that the (+)-*trans*(1*R*,3*R*) isomer is predominantly



Scheme 7. Structures of the copper(I) carbene complex from catalyst **2b**.



Scheme 8. Schematic representation of the possible orientation of DMHD, which approaches the carbene carbon of the Cu(I)–carbenoid complex for methyl chrysanthemate.

produced. Scheme 8 shows the most favorable transition state for the (+)-*trans*(1*R*,3*R*) isomer and the (−)-*trans*(1*S*,3*S*) isomer, respectively. The conformations of the 9-ring-members bearing the intramolecular hydrogen bond in the copper(I) carbene complex are different from each other, leading the formation of the enantio-isomer of the *trans* chrysanthemate. The *trans*/*cis* ratio should depend on the steric repulsion among the isobutenyl group of DMHD, the ester group on the Cu(I)–carbene complex, and a substituent X on the phenyl group.

The introduction of the electron-withdrawing substituents on the benzene ring of the salicylaldehyde moiety in the copper complex enhances the electrophilicity of the carbene carbon through the copper atom. This enhancement should bring about the high reactivity of the Cu(I)–carbene complex toward the diene.

2.5. Possible mechanism for effect of addition of Lewis acids

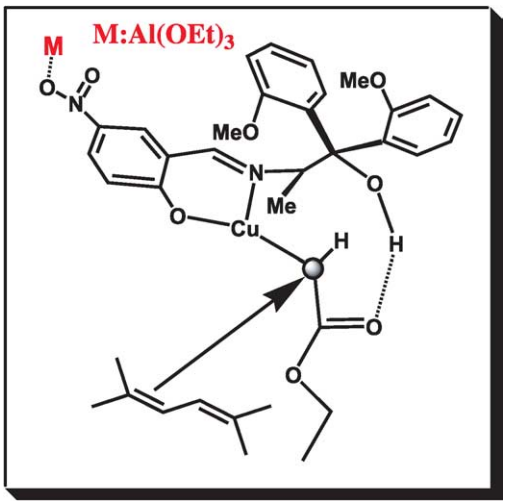
The effect of Lewis acids can also be explained based on the following experimental results in Table 6. Although the effect of $Al(OEt)_3$ is not observed in **2a** and **2h** (entries 1 vs 2, 9 vs. 10), remarkable enhancement of the yield of the product was observed at 0 °C in **2e** as well as **2b** (entries 3 vs. 4, 5 vs. 6). In the case of **2g**, a slight enhancement of the yield was observed (entries 7 vs. 8).

These results suggested that $Al(OEt)_3$ coordinates with the oxygen atom of the nitro group on the salicylaldehyde moiety in the copper carbene complex in the use of the complex **2b** and $Al(OEt)_3$, and that lowered the electron density on the carbene carbon of the carbene complex to enhance the reactivity toward DMHD as shown in Scheme 9.

Table 6. The effect of substituents at the 5-position on the salicylaldehyde group in copper Schiff-base **2** with $Al(OEt)_3$ as the catalyst on the asymmetric cyclopropanation of DMHD with EDA[a]

Entry	Cu-complex	Lewis acid	Yield (%)	*trans*/*cis*	ee (%) *trans*[b]	ee (%) *cis*[c]
1	**2a**	None	5	60/40	38	36
2	**2a**	$Al(OEt)_3$	6	60/40	36	35
3	**2b**	None	35	57/43	83	78
4	**2b**	$Al(OEt)_3$	86	57/43	84	79
5	**2e**	None	35	57/43	84	81
6	**2e**	$Al(OEt)_3$	72	57/43	83	76
7	**2g**	None	29	58/42	84	79
8	**2g**	$Al(OEt)_3$	37	57/43	85	80
9	**2h**	None	32	58/42	84	78
10	**2h**	$Al(OEt)_3$	33	58/42	85	80

[a] Reaction conditions: 0.01 mmol of copper Schiff-base as the monomeric copper complex, 0.01 mmol of $Al(OEt)_3$, 10 mmol of EDA, 70 mmol of DMHD, 5 mL of ethyl acetate, 0 °C, 3h.
[b] 1*R*,3*R* as a major enantiomer.
[c] 1*R*,3*S* as a major enantiomer.



Scheme 9. Tentative scheme for the addition to the copper complex **2b**.

3. Conclusions

New copper Schiff-base complexes derived from substituted salicylaldehydes bearing an electron-withdrawing group at the 5-position were found to be highly efficient for asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene with diazoacetate. These compounds demonstrated much more remarkable enhancement of the turnover number than the copper catalyst derived from the salicylaldehyde. In addition, we found that high yield and high enantioselectivity with highly catalytic efficiency using *t*-butyl diazoacetate was achieved by addition of a Lewis acid such as $Al(OEt)_3$. The products were easily converted to chrysanthemic acid.

4. Experimental

Unless otherwise noted, all reactions were carried out under a nitrogen atmosphere. Optical rotations were measured on a JASCO DIP-370. Melting points were measured with a METTLER TOLEDO TYPE FP62. NMR spectra were recorded by a Bruker DPX-300NMR spectrometer with trimethyl silane as an internal standard (δ value in $CDCl_3$). The yields and ee values were determined by GC analyses with a capillary column and LC analyses with a chiral column in the cyclopropanation, respectively.

4.1. Aminoalcohol

4.1.1. (*R*)-2-Amino-1,1-diphenyl-1-propanol. The methyl ester hydrochloride of *D*-alanine (7.0 g, 50.1 mmol) was added to a cooled Grignard solution derived from bromobenzene (41.6 g, 265 mmol) and magnesium (6.7 g, 276 mmol) in THF at 0 °C. The mixture was stirred for 3 h at room temperature and then added to cooled 2% hydrochloric acid (200 mL) at 0 °C. 150 mL of toluene was added to the mixture, and the aqueous phase was separated. The aqueous solution was neutralized with ammonium hydroxide, and 150 mL of toluene was added to the mixture. The organic phase was separated, washed with saturated brine, dried, and concentrated. The pale yellow solid was obtained, recrystallized from CH_2Cl_2-*n*-hexane and gave the product as a white solid (8.1 g, 71%). $[\alpha]_D$=87.2 (*c*=1, $CHCl_3$); mp 102–103 °C; ^1H NMR ($CDCl_3$) δ 7.63 (d, *J*=1.7 Hz, 2H), 7.60 (d, *J*=1.3 Hz, 2H), 7.50–7.12 (m, 6H), 4.14 (q, *J*=6.4 Hz, 1H), 0.94 (d, *J*=6.6 Hz, 3H).

4.1.2. (*R*)-2-Amino-1,1-di(2-methoxyphenyl)-1-propanol. Yield 75%, white solid; $[\alpha]_D$=35.5 (*c*=1, $CHCl_3$); mp 89–90 °C; ^1H NMR ($CDCl_3$) δ 7,66 (d, *J*=1.3 Hz, 2H), 7.19–6.73 (m, 6H), 5.31 (s, 1H), 4.33 (q, *J*=6.5 Hz, 1H), 3.58 (s, 3H), 3.52 (s, 3H), 1.01 (d, *J*=6.6 Hz, 3H).

4.1.3. (*R*)-Amino-1,1-di(2-*n*-butoxy-5-*t*-butylphenyl)-1-propanol. Purified by column chromatography (SiO_2, *n*-hexane/AcOEt=10/1→MeOH). Yield 55%, pale yellow viscous oil; $[\alpha]_D$=35.3 (*c*=1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.70 (s, 2H), 7.24–7.12 (m, 2H), 6.73–6.64 (m, 2H), 5.24 (s, 1H), 4.27 (q, *J*=6.5 Hz, 1H), 3.81–3.67 (m, 4H), 1.59–1.43 (m, 6H), 1.38–1.23 (m, 2H), 1.34 (s, 9H), 1.33 (s, 9H), 1.03 (d, *J*=6.3 Hz, 3H), 0.89 (t, *J*=7.3 Hz, 6H).

4.2. The Schiff bases. General procedure for 4a, 5a, and 6a

4.2.1. (*R*)-(*N*-Salicylidene)-2-amino-1,1-diphenyl-1-propanol 4a. (*R*)-2-Amino-1,1-diphenyl-1-propanol (5.00 g, 22.0 mmol) and salicylaldehyde (2.69 g, 22.0 mmol) were dissolved in toluene (30 mL), and the mixture was refluxed for 1 h. Methanol was removed under vacuum and the residue was purified by column chromatography (SiO_2, *n*-hexane:ethyl acetate=1:1) to afford the pure Schiff base **4a** (7.09 g, 97%) as yellow solid. $[\alpha]_D$=−36.8 (*c*=1, $CHCl_3$); mp 112–113 °C; ^1H NMR ($CDCl_3$) δ 12.63 (s, 1H), 8.37 (s, 1H), 7.56–7.48 (m, 4H), 7.35–7.15 (m, 8H), 6.89–6.81 (m, 2H), 4.57 (q, *J*=6.5 Hz, 1H), 2.67 (s, 1H), 1.25 (d, *J*=6.6 Hz, 3H).

Compound **5a**. Yield 96%, yellow solid; $[\alpha]_D$=−166 (*c*=1, $CHCl_3$); mp 141–142 °C; ^1H NMR ($CDCl_3$) δ 13.91 (s, 1H), 8.29 (s, 1H), 7.72–7.61 (m, 2H), 7.26–6.72 (m, 10H), 5.37 (s, 1H), 5.06 (q, *J*=6.4 Hz, 1H), 3.56 (s, 3H), 3.53 (s, 3H), 1.33 (d, *J*=6.6 Hz, 3H).

Compound **6a**. Yield 95%, yellow viscous oil; $[\alpha]_D$=−135 (*c*=1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.17 (s, 1H), 7.69–7.66 (m, 2H), 7.21–6.61 (m, 7H), 5.21 (s, 1H), 4.84(q, *J*=6.4 Hz, 1H), 3.78–3.61 (m, 4H), 1.51–1.18 (m, 8H), 1.41 (d, *J*=6.5 Hz, 3H), 1.34 (s, 9H), 1.20 (s, 9H), 0.86 (t, *J*=7.3 Hz, 6H).

4.3. General procedure for 4b, 5b, 5c, 5d, 5e, 5f, 5g, 5h, 5i, 5j, and 6b

4.3.1. (*R*)-(*N*-5-Nitrosalicylidene)-2-amino-1,1-diphenyl-1-propanol 4b. (*R*)-2-Amino-1,1-diphenyl-1-propanol (2.00 g, 8.80 mmol) and 5-nitrosalicylaldehyde (1.47 g, 8.80 mmol) were dissolved in toluene (20 mL) and the mixture was refluxed for 1 h. The reaction mixture was then cooled to room temperature, and the precipitated Schiff-base was filtered and washed with heptane/toluene (=2/1 (v/v)) to yield the pure Schiff base **4b** (3.22 g, 97%) as a yellow solid. [Anal. Found: C, 70.1%; H, 5.4%; N, 7.4%. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.21%; H, 5.32%; N, 7.45%];

$[\alpha]_D$=−85.0 (c=1, $CHCl_3$); mp 208–209 °C; ^{1}H NMR ($CDCl_3$) δ 8.26 (s, 1H), 8.15–8.12 (m, 2H), 7.54–7.20 (m, 10H), 6.89–6.82 (m, 1H), 4.65 (q, J=6.6 Hz, 1H), 2.61 (s, 1H), 1.29 (d, J=6.6 Hz, 3H).

Compound **5b**. Yield 95%, yellow solid; [Anal. Found: C, 68.1%; H, 5.8%; N, 5.6%. Calcd for $C_{22}H_{20}N_2O_4{\cdot}0.5C_7H_8$: C, 68.45%; H, 5.85%; N, 5.85%]; $[\alpha]_D$=−131 (c=1, $CHCl_3$); mp 128–130 °C; ^{1}H NMR ($CDCl_3$) δ 8.10–8.03 (m, 3H), 7.67–7.52 (m, 2H), 7.27–6.65 (m, 8H), 5.66 (s, 1H), 5.26 (q, J=6.5 Hz, 1H), 3.62 (s, 6H), 1.41 (d, J=6.6 Hz, 3H).

Compound **5c**. Yield 91%, yellow solid; [Anal. Found: C, 68.2%; H, 5.8%; N, 5.6%. Calcd for $C_{22}H_{20}N_2O_4{\cdot}0.5C_7H_8$: C, 68.45%; H, 5.85%; N, 5.85%]; $[\alpha]_D$=−389 (c=1, $CHCl_3$); mp 132–135 °C; ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1H), 7.72–7.61 (m, 2H), 7.23–6.69 (m, 9H), 5.33 (s, 1H), 5.03 (q, J=6.5 Hz, 1H), 3.55 (s, 3H), 3.51 (s, 3H), 2.23 (s, 3H), 1.31 (d, J=6.5 Hz, 3H).

Compound **5d**. Yield 96%, yellow solid; [Anal. Found: C, 62.3%; H, 5.1%; N, 7.8%. Calcd for $C_{24}H_{23}N_3O_8{\cdot}0.5C_7H_8$: C, 62.61%; H, 5.16%; N, 7.97%]; $[\alpha]_D$=−242 (c=1, $CHCl_3$); mp 144–147 °C; ^{1}H NMR ($CDCl_3$) δ 8.92 (d, J=3.0 Hz, 1H), 8.30 (d, J=3.1 Hz, 1H), 8.25–8.21 (m, 1H), 7.63 (d, J=7.8 Hz, 1H), 7.50 (d, J=7.9 Hz, 1H), 7.29–6.78 (m, 6H), 5.81 (s, 1H), 5.41(bs, 1H), 3.65 (s, 3H), 3.64 (s, 3H), 1.41 (t, J=6.6 Hz, 3H).

Compound **5e**. Yield 94%, yellow solid; [Anal. Found: C, 71.2%; H, 6.2%; N, 2.6%. Calcd for $C_{26}H_{27}NO_6{\cdot}0.5C_7H_8$: C, 71.50%; H, 6.31%; N, 2.83%]; $[\alpha]_D$=−122 (c=1, $CHCl_3$); mp 115–117 °C; ^{1}H NMR ($CDCl_3$) δ 8.18 (d, J=4.5 Hz, 1H), 7.86 (s, 1H), 7.68 (d, J=7.8 Hz, 1H), 7.59 (d, J=7.8 Hz, 1H), 7.28–6.72 (m, 7H), 5.53 (s, 1H), 5.35 (bs, 1H), 3.84 (s, 3H), 3.59 (s, 3H), 3.56 (s, 3H), 1.36 (t, J=6.6 Hz, 3H).

Compound **5f**. Yield 93%, yellow solid; [Anal. Found: C, 69.1%; H, 6.0%; N, 2.9%. Calcd for $C_{26}H_{27}NO_6$: C, 69.47%; H, 6.06%; N, 3.12%]; $[\alpha]_D$=−235 (c=1, $CHCl_3$); mp 135–138 °C; ^{1}H NMR ($CDCl_3$) δ 8.18 (s, 1H), 7.89 (d, J=7.8 Hz, 1H), 7.70 (d, J=7.8 Hz, 1H), 7.52 (d, J=7.8 Hz, 1H), 7.26–6.62 (m, 7H), 5.44 (s, 1H), 5.10 (bs, 1H), 3.89 (s, 3H), 3.55 (s, 3H), 3.54 (s, 3H), 1.33 (t, J=6.6 Hz, 3H).

Compound **5g**. Yield 62%, yellow solid; [Anal. Found: C, 73.4%; H, 6.1%; N, 5.9%. Calcd for $C_{25}H_{24}N_2O_4{\cdot}0.5C_7H_8$: C, 74.00%; H, 6.11%; N, 6.06%]; $[\alpha]_D$=−142 (c=1, $CHCl_3$); mp 120–122 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (s, 1H), 7.67 (d, J=7.8 Hz, 1H), 7.55 (d, J=7.8 Hz, 1H), 7.38–6.74 (m, 8H), 5.57 (s, 1H), 5.21 (q, J=6.6 Hz, 1H), 3.60 (s, 3H), 3.58 (s, 3H), 1.37 (t, J=6.6 Hz, 3H).

Compound **5h**. Yield 94%, yellow solid; [Anal. Found: C, 67.3%; H, 5.6%; N, 2.6%. Calcd for $C_{25}F_3H_{24}NO_4{\cdot}0.5C_7H_8$: C, 67.71%; H, 5.59%; N, 2.77%]; $[\alpha]_D$=−103 (c=1, $CHCl_3$); mp 108–110 °C, ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1H), 7.69 (d, J=7.8 Hz, 1H), 7.60 (d, J=7.8 Hz, 1H), 7.42–6.72 (m, 8H), 5.47 (s, 1H), 5.16 (q, J=6.3 Hz, 1H), 3.60 (s, 3H), 3.58 (s, 3H), 1.34 (t, J=6.6 Hz, 3H).

Compound **5i**. Yield 97%, yellow solid; [Anal. Found: C, 72.0%; H, 6.2%; N, 2.9%. Calcd for $C_{24}FH_{24}NO_4{\cdot}0.5C_7H_8$: C, 72.51%; H, 6.20%; N, 3.08%]; $[\alpha]_D$=−105 (c=1, $CHCl_3$); mp 102–104 °C; ^{1}H NMR ($CDCl_3$) δ 8.23 (s, 1H), 7.68 (d, J=7.8 Hz, 1H), 7.61 (d, J=7.8 Hz, 1H), 7.25–6.70 (m, 8H), 5.42 (s, 1H), 5.09 (q, J=6.5 Hz, 1H), 3.60 (s, 3H), 3.56 (s, 3H), 1.29 (t, J=6.5 Hz, 3H).

Compound **5j**. Yield 78%, yellow solid; [Anal. Found: C, 70.1%; H, 6.0%; N, 3.4%. Calcd for $C_{24}FH_{24}NO_4$: C, 70.40%; H, 5.91%; N, 3.42%]; $[\alpha]_D$=−168 (c=1, $CHCl_3$); mp 116–118 °C; ^{1}H NMR ($CDCl_3$) δ 8.16 (s, 1H), 7.69 (d, J=7.8 Hz, 1H), 7.58 (d, J=7.8 Hz, 1H), 7.25–6.71 (m, 7H), 6.51–6.45 (m, 1H), 5.49 (s, 1H), 5.13 (q, J=6.5 Hz, 1H), 3.57 (s, 3H), 3.55 (s, 3H), 1.34 (t, J=6.6 Hz, 3H).

Compound **6b**. Yield 95%, yellow solid; [Anal. Found: C, 72.2%; H, 8.1%; N, 4.6%. Calcd for $C_{38}H_{52}N_2O_6$: C, 72.15%; H, 8.23%; N, 4.43%]; $[\alpha]_D$=−153 (c=1, $CHCl_3$); m.p. 67–69 °C; ^{1}H NMR ($CDCl_3$) δ 8.05–7.98 (m, 2H), 7.84 (s, 1H), 7.61 (s, 1H), 7.55 (m, 1H), 7.25–7.21 (m, 1H), 7.25–7.21 (m, 1H), 7.12–7.08 (m, 1H), 6.76–6.64 (m, 3H), 5.49 (s, 1H), 5.08 (m, 1H), 3.84–3.72 (m, 4H), 1.53–1.46 (m, 7H), 1.35 (s, 9H), 1.33–1.26 (m, 4H), 1.16 (s, 9H), 0.93–0.87 (m, 6H).

4.4. The copper complex

General procedure. 4.90 g (11.2 mmol) of the Schiff-base **2b** was dissolved in 250 g of ethyl acetate, and 2.24 g (11.2 mmol) of copper acetate monohydrate was added to the above solution. The mixture was refluxed for 1 h, and aqueous sodium hydroxide was then added and further stirred for 30 min at room temperature. The organic layer was separated, washed with water, dried, concentrated in vacuo, and 5.47 g of the copper Schiff-base complex was obtained as a deep green solid. Yield 98%. The copper complex was used without further purification. [LC-MS (positive mode); m/z=997]; $[\alpha]_D$=546 (c=0.1%, $CHCl_3$); mp 160–163 °C (dec.).

4.5. Cyclopropanation

Under a nitrogen atmosphere, 4.96 mg (0.010 mmol) of the copper complex **2b** was dissolved in 5 mL of ethyl acetate, and 7.71 g (70.0 mmol) of 2,5-dimethyl-2,4-hexadiene was added to the solution. 1 μL (0.01 mmol) of phenylhydrazine was added by a microsyringe and the temperature of the reaction mixture was then raised to 80 °C. 8 mL of a solution of ethyl diazoacetate (1.14 g, 10 mmol) in ethyl acetate was added dropwise over 2 h using a syringe pump at 80 °C. After further stirring for 30 min at 80 °C, the reaction mixture was analyzed by GC (DB-1, 30 m×0.25 mm ID, 0.25 mm film, column temp. 100 °C–10 min to 250 °C) using the internal method with *n*-decane as a standard for determining the yield and *trans*/*cis* ratio, and LC Sumichiral OA-2500 (25 cm×4 mm ID, 5 μm film)×2, UV 220 nm hexane 0.7 mL/min) for determining the enantioselectivity. Products were determined by comparison of the LC elution order of the enantiomers with authentic samples.

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Absolute stereochemistries and total synthesis of (+)-arisugacins A and B, potent, orally bioactive and selective inhibitors of acetylcholinesterase

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Abstract—In the current studies, we used the Kakisawa–Kashman modification of the Mosher NMR method to determine the complete absolute stereochemistry of arisugacins. We also report the convergent total synthesis of (+)-arisugacins A and B by a sequence including (i) ruthenium complex-catalyzed asymmetric reduction of the cyclohexenone derivative; (ii) stereoselective construction of the arisugacin skeleton by a Knoevenagel-type reaction of an α,β-unsaturated aldehyde derivative with production of a 4-hydroxy-2-pyrone derivative as a key reaction; and (iii) stereoselective dihydroxylation to give the diol derivative, followed by deoxygenation. Accordingly, we defined the absolute structures of arisugacins A and B as 4a-(*R*),6a-(*R*),12a-(*R*), and 12b-(*S*). Finally, we characterized the bioactivities of the synthetic intermediates to understand the structure–activity relationships of the arisugacins.

1. Introduction

Because of increased life expectancy associated with improved healthcare, the aged population is increasing. Thus, without countermeasures, the number of senile dementia patients is expected to increase. Alzheimer's disease is a senile dementia associated with anomalies in neurotransmitter systems, including cholinergic, catecholaminergic, and serotonergic neurons, as well as in the amino acid and neuropeptide systems. Because cholinergic neurons play a key role in higher order brain functions such as memory, learning, and cognition, a number of groups have searched for potential substances that can normalize cholinergic neuron dysfunction as a potential treatment for Alzheimer's disease.[1] Recently, a synthetic inhibitor of acetylcholinesterase (AChE), 1-benzyl-4-[(5,6-dimethoxy-1-oxoindan-2-yl)methyl]piperidine (E2020), was approved by the United States Food and Drug Administration for treatment of Alzheimer's disease. As a result, synthetic AChE inhibitors have recently attracted particular attention.[2]

We have reported the screening of 10,000 soil isolates, containing predominantly actinomycetes and fungi, for new classes of AChE inhibitors. We isolated the (+)-arisugacins A and B (**1a** and **1b**), as architecturally interesting inhibitors of AChE derived from a culture broth of *Penicillium* sp. FO-4259,[3–5] together with a structurally related known compound, territrem B (**2**) (Fig. 1). We found that a mutant of *Penicillium* sp. FO-4259 produced a series of metabolites, arisugacins C (**1c**), D (**1d**), E (**1e**), F (**1f**), G (**1g**), and H (**1h**).[6] The structures of **1a** and **1b** are comprised of a highly oxygenated *trans*-decalin system and an α-pyrone moiety. We elucidated the structure by extensive spectroscopic studies, including a combination of 1-D and 2-D NMR techniques. The absolute configurations, however, remained undetermined.

Biogenetically, the arisugacins belong to the mixed polyketide–terpenoid group (meroterpenoids).[7,8] We previously proposed that they were generated by biosynthetic pathways via arisugacin F (**1f**) as the key intermediate (Scheme 1), including (1) condensation of an acetoacetate with a benzoic acid derived from shikimate to produce a

Keywords: α-Pyrone; Meroterpenoid; AChE inhibitor; 6π-Electron electrocyclic ring closure; Inversion of stereochemistry; Stereoselective dihydroxylation.
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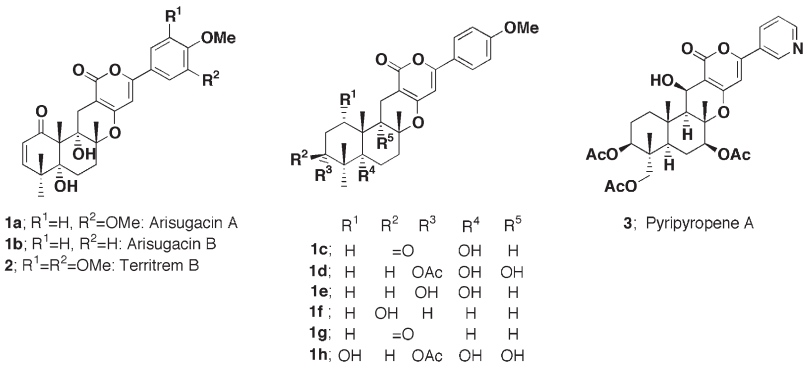


Figure 1. Structures of arisugacins A, B, and F (**1a**, **1b**, **1f**), territrem B (**2**), and pyripyropene A (**3**).

phenyl-α-pyrone moiety; (2) substitution of an all-trans farnesyl group to the α-pyrone moiety; (3) epoxidation of the terminal of the farnesyl group followed by cyclization to give the core skeleton, arisugacin F; and (4) oxidation leading to arisugacins A, B, and territrem B.[9,10]

During our screening program of acyl-CoA:cholesterol acyltransferase (ACAT) inhibitors, we also obtained the potent inhibitor pyripyropene A (**3**) from a culture broth of *Asperigillus fumigatus* FO-1289.[11–14] We reported the absolute configuration and the first total synthesis of **3** via a convergent and efficient strategy.[15] Interestingly, the structures of **1a** and **1b** are similar to **3**. However, **3** does not inhibit AChE, and **1a** and **1b** do not inhibit ACAT.

Based on initial biological studies in human erythrocytes, we found that **1a** and **1b** inhibit AChE in vitro with IC_{50} values of 1 and 26 nM, respectively.[3] These compounds were more than 20,000-fold more potent against AChE than against horse serum butyrylcholinesterase, an enzyme thought to be important for liver function. In addition, **1a** protects against scopolamine-induced amnesia in mice but has weak effects on salivation and hypothermia, which are peripheral and central cholinergic responses, respectively.[16]

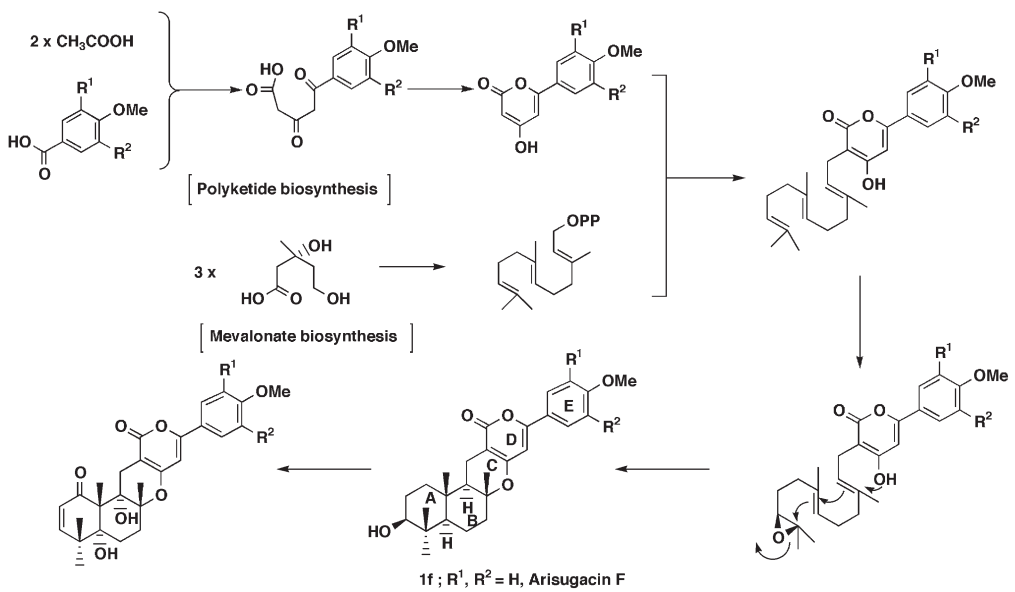
R. P. Hsung et al. reported the total synthesis of this interesting natural product[17–22] using a similar strategy that we had reported.[23–26]

In conjunction with our continuing investigations on the structure and synthesis of important bioregulatory products, we report the absolute configuration of **1f** and **2**, analogs of arisugacins A and B.[9] We also describe the first total synthesis of (+)-**1a** and (+)-**1b**, the most active members of this family,[26] via a flexible, concise, and highly efficient route that can provide the natural arisugacins as well as a variety of analogs. Finally, based on the activities of synthetic intermediates, we discuss the structure–activity relationship for AChE inhibition by the arisugacins.

2. Results and discussion

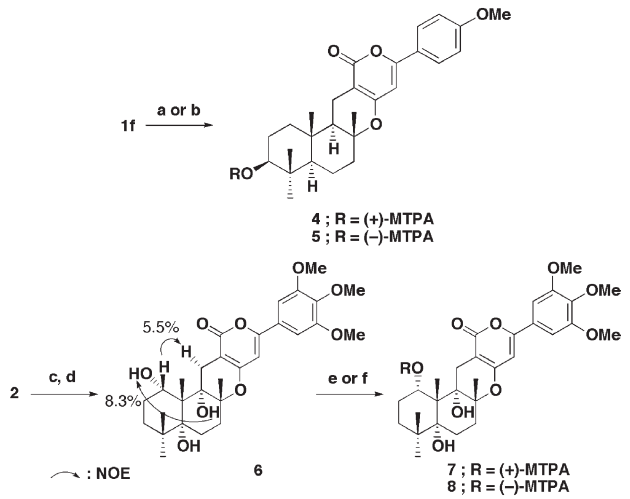
2.1. Determination of the absolute stereochemistries of arisugacins

A modified Mosher method[27,28] was used to elucidate the absolute configuration of arisugacin F (**1f**) at C-3. **1f** was



Scheme 1. Proposed biosynthetic pathway for arisugacins.

treated with (*R*)-(+)- and (*S*)-(−)-2-methoxy-2-trifluoromethyl-2-phenylacetic acid (MTPA) in the presence of DCC and DMAP to afford the (*R*)-(+)- and (*S*)-(−)-MTPA esters (**4** and **5**) (Scheme 2). The $\Delta\delta$ values ($\delta_S-\delta_R$) obtained from the ^{1}H NMR data of **4** and **5** are shown in Figure 2. The $\Delta\delta$ values for H_2-1, H_2-2, H-3, H_2-12, and H_3-12b-Me were negative, while positive $\Delta\delta$ values were observed for H_6-4α, β-Me, and H-5 thus indicating a 3*S* configuration. Therefore, the absolute configurations at C-3, C-4a, C-6a, C-12a, and C-12b of **1f** were assigned as *S*,*R*,*R*,*R*, and *S*, respectively, based on the previously elucidated relative stereochemistry.[6]



Scheme 2. (a) (+)-MTPA, DCC, DMAP, CH_2Cl_2, rt, 88%. (b) (−)-MTPA, DCC, DMAP, CH_2Cl_2, rt, 99%. (c) H_2, Pd/C, MeOH, rt, 88%. (d) $NaBH_4$, THF, 0 °C, 85%. (e) (+)-MTPA, DCC, DMAP, CH_2Cl_2, rt, 50%. (f) (−)-MTPA, DCC, DMAP, CH_2Cl_2, rt, 100%.

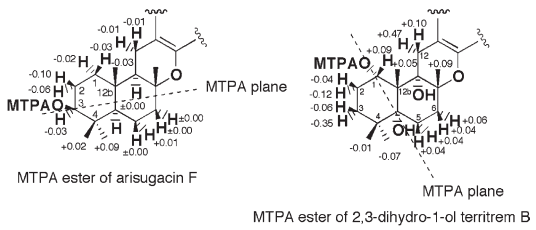


Figure 2. $\Delta\delta$ Values of MTPA esters derived from arisugacin F (**1f**) and 2,3-dihydro-1α-ol territrem B (**6**).

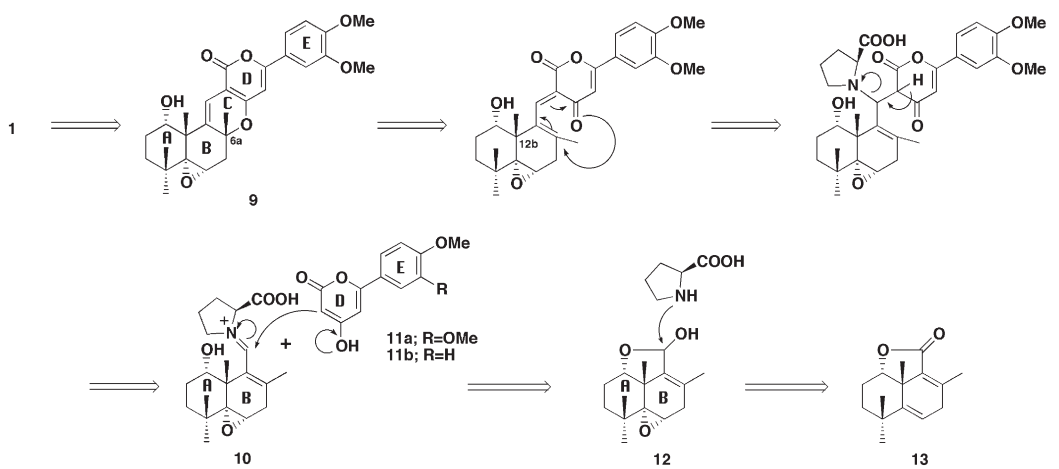
To determine the absolute configuration of territrem B (**2**), we prepared its MTPA esters by subjecting **2** to enone hydrogenation followed by reduction with $NaBH_4$ to give **6**. NOE correlations from H-12a-OH to H-1-OH and from H-1 to H-12 in **6** indicated that the 1-hydroxy group was oriented toward the α-side (Scheme 2). The calculated $\Delta\delta$ values ($\delta_S-\delta_R$) of (*R*)-(+)- and (*S*)-(−)-MTPA esters (**7** and **8**) are indicated in Figure 2, and the absolute stereochemistry of **2** was determined as 1-(*S*),4a-(*R*),6a-(*R*),12a-(*R*), and 12b-(*S*). The absolute stereochemistry of **2** was the same as for **1f**. Given that the arisugacins and territrems have a commom biosynthetic pathway, we anticipated that the relative and absolute stereochemistries of **1a** and **1b** should be the same as for **1f** and **2**.[9]

2.2. Synthetic plan to arisugacins

According to retrosynthetic analyses (Scheme 3), arisugacin A should be accessible by several steps of oxidation from pentacycle **9**, which would be derived from the α,β-unsaturated lactol **12** and the known 4-hydroxy 2-pyrone **11a**[17,18] via a Knoevenagel-type reaction in the presence of L-proline. In this process, condensation of the α-pyrone with a Shiff-base formed by a lactol and an amino acid, and subsequent amine elimination followed by 6π-electron electrocyclic ring closure are performed. The cyclization step should proceed with the requisite geometry at the BC ring fusion, which is controlled by the steric effect of the C-12b angular methyl group. The known lactone **13**, an intermediate for the synthesis of forskolin,[29] would then lead to lactol **12**.

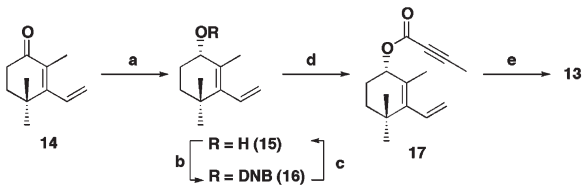
2.3. Construction of the arisugacin skeleton

To synthesize (+)-arisugacin A, the chiral building block **15** was prepared from **14**, which, in turn, was synthesized from the commercially available α-ionone as previously described.[30] The known CBS reduction procedure was not feasible in our case because of poor reproducibility and the need for a large amount of expensive catalyst.[31,32] On the other hand, asymmetric hydrogenation using a ruthenium catalyst can be conducted easily on a preparative scale with a S/C ratio up to 500 and a substrate concentration as high as 2.5 M in 2-propanol.[33] When the achiral cyclic enone **14** was hydrogenated with a catalyst system containing



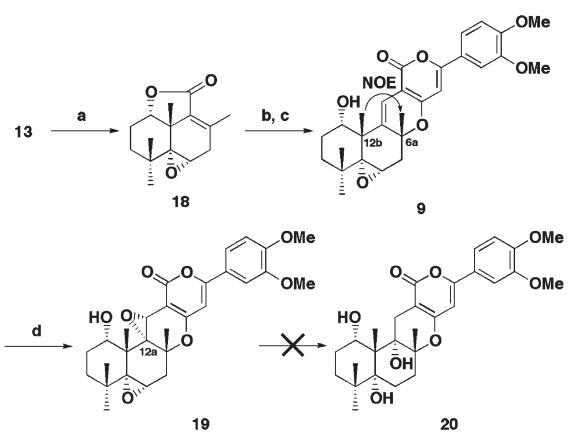
Scheme 3. Retrosynthetic analysis of arisugacin A.

$RuCl_2$[(*R*)-binap, (*S*,*S*)-DPEN] in 2-propanol containing KOH (**14**:Ru:KOH=500:1:40, 8 atm, rt, 24 h), the allylic alcohol **15** was obtained in 90% ee and 97% yield. The enantiomeric mixture of **15** was converted to the 3,5-dinitrobenzoate **16**, which was purified by recrystallization. The pure **16** was reconverted into **15** (98% ee) upon treatment with potassium carbonate in methanol. Their enantiomeric purities were determined by NMR analysis of the corresponding MTPA esters. Finally, by optical rotation, we determined that the absolute configuration of (−)-**15** is *S* (Scheme 4).[31]



Scheme 4. (a) $RuCl_2$[(*R*)-binap, (*S*,*S*)-DPEN], KOH, 2-propanol, H_2, 8 atm, rt, 97%, 90% ee (b) 3,5-dinitrobenzoyl chloride, DMAP, pyridine, rt; recrystallization. (c) K_2CO_3, CH_2Cl_2–MeOH, rt, 58% from **15**. (d) 2-butynoic acid, DCC, DMAP, CH_2Cl_2, rt, 85%. (e) *n*-decane, 180 °C, 72%.

The lactol **12**, a coupling unit, was prepared in four steps starting from the chiral building block **15**. Esterification of **15** with 2-butynoic acid to produce **17** followed by an intramolecular Diels–Alder reaction generated **13**, which was treated with *m*-CPBA to stereoselectively produce the epoxide **18**. The resulting epoxide **18** was converted into a lactol with DIBAL. Subsequently, we tested condensation with α-pyrone **11a** using L-proline as a catalyst for construction of the pentacycle **9**. By treatment of lactol with α-pyrone **11a** in the presence of a catalytic amount of L-proline in EtOAc at 80 °C, the coupling reaction proceeded smoothly to provide the desired pentacyclic skeleton **9** in 50% yield for the two steps. Subsequently, we studied the introduction of a hydroxy group at the 12a position via epoxidation. Epoxidation of **9** to yield **19** with *m*-CPBA or DMDO was inefficient, and oxidation with *t*-BuOOH in the presence of $Mo(CO)_6$[34] gave the best results, although this was only a 29% yield. For the following epoxide opening reaction to obtain **20**, we examined various conditions, including $LiAlH_4$, Super-H®, and Birch reduction, but none of them was successful (Scheme 5). Therefore, we abandoned this strategy for the induction of the two hydroxy groups.



Scheme 5. (a) *m*-CPBA, CH_2Cl_2, rt, 77%. (b) DIBAL, CH_2Cl_2, −78 °C. (c) **11a**, L-proline, AcOEt, 80 °C, 50% from **18**. (d) *t*-BuOOH, $Mo(CO)_6$, benzene, 80 °C, 29%.

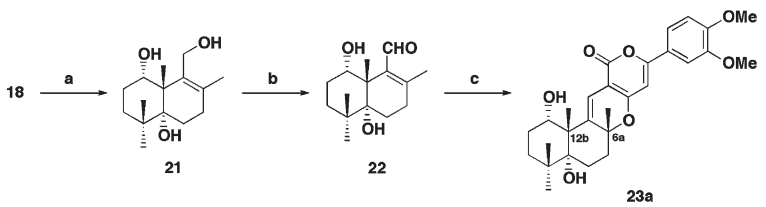
We therefore, planned opening of the epoxide on the B ring of **18** prior to the coupling. Reduction with $LiAlH_4$ produced a diol together and the unreacted epoxide. Attempts to reduce **18** with DIBAL or Super-H® also failed. Fortunately, we found that $LiAlH_4$ together with $AlCl_3$ generated the desired triol **21** in nearly quantitative yield (Scheme 6). Selective oxidation of the primary alcohol **21** with TPAP (0.02 equiv.) and NMO (1.5 equiv.) produced **22** in 73% yield. We initially attempted coupling of aldehyde **22** with α-pyrone **11a** using the previous conditions for the formation of **9**, but this gave the corresponding pentacycle **23a** in only 17% yield. We therefore, examined the reaction conditions in detail to try to improve this step. Table 1 summarizes the results obtained by varying the catalyst loading, concentration, or solvent. The data indicated that high loading of L-proline and the use of THF as solvent are essential for efficient formation of **23a**. The reaction using 2.0 equiv. L-proline in THF at 65 °C gave the best result, producing the desired pentacycle **23a** in 61% yield (Entry 7).

2.4. Completion of arisugacin A synthesis

We planned the introduction of a hydroxy group at the 12a position in **23a** via epoxidation and epoxy opening as was performed for **9**. Unexpectedly, oxidation of **23a** with *t*-BuOOH did not produce the desired epoxide **24**. We therefore, tried a series of epoxidation conditions (i.e., *m*-CPBA, DMDO, AcOOH, or CF_3COOOH), but these were all unsuccessful and gave complex mixtures. Dihydroxylation of 12-ene with OsO_4 also failed.[21] This is surprising because **9** and **23a** only differ in the terms of the presence of either an epoxy or a hydroxy group at the 4a position. Therefore, we suspected that the difference in the ability to produce the desired epoxide may be due to hydrogen bonding between 1-OH and 4a-OH, which prevents hydrogen bond formation between 1α-OH and peracids. We thus attempted inversion of 1α-OH to form 1β-OH (Fig. 3). Treatment of **23a** with TPAP and NMO followed by the stereoselective reduction mediated by 4a-OH produced the β-alcohol **25a** in 71% yield for the two steps.

Epoxidation of **25a** with *m*-CPBA generated only the β-epoxide **27a**. NMR analysis of **27a** and its acetate **28** proved that the hexacycle reported by R. P. Hsung et al.[21,22] must be revised to **27a**. Treatment of **25a** with AcOOH gave a mixture of triol **26a** and β-epoxide **27a**, while treatment with performic acid or trifluoroperacetic acid produced **27a** and the α-epoxide. Because we could not obtain the desired α-epoxide as the major product under the conditions examined, we attempted to increase the yield of the triol. The optimal condition for this reaction was AcOOH in a CH_2Cl_2–phosphate buffer system to maintain low acidity at room temperature (Scheme 7). The stereochemistry of the introduced hydroxy groups in **26a** was confirmed by NOE experiments as shown in Figure 4 (Scheme 8).

As shown in Scheme 9, we speculated that the dihydroxylation reaction occurs via an acyl migration. The endocyclic olefin in 2*H*-pyran fused to 2-pyrone has unique reactivity due to activation by the pyranyl oxygen. The electron-rich C12a would selectively attack AcOOH, producing the



Scheme 6. (a) $LiAlH_4$, $AlCl_3$, THF, 0 °C, 98%. (b) TPAP, NMO, CH_2Cl_2, rt, 73%. (c) **11a**, L-proline, THF, 65 °C, 61%.

Table 1. Conditions for coupling of aldehyde **22** with α-pyrone **11a**

Entry	L-proline (equiv.)	MS-3 Å	Solvent	Temp. (°C)	Yield[a] (%)
1	0.5	+	Benzene	70	26
2	3.0	+	Benzene	80	31
3	3.0	−	Benzene	80	29
4	2.0	−	Benzene	80	32
5	2.0	−	1,2-Dichloroethane	80	16
6	2.0	−	2-Propanol	80	20
7	2.0	−	THF	65	61
8	2.0	−	DMF	80	14

[a] Isolated product.

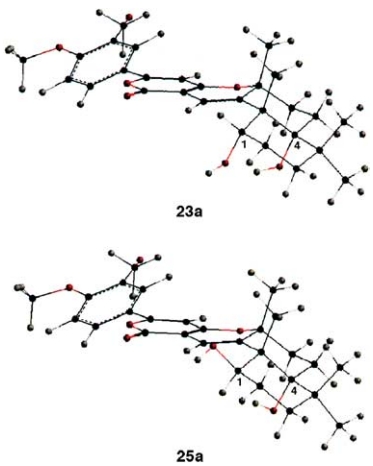


Figure 3. Conformations of **23a** and **25a**.

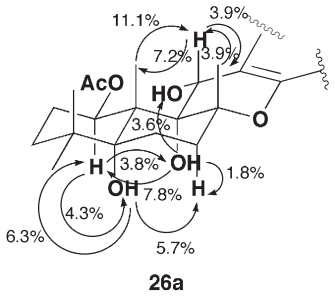
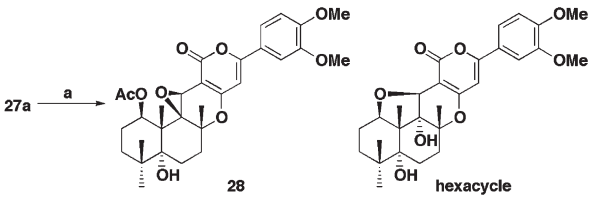


Figure 4. Summary of NOE data for **26a**.

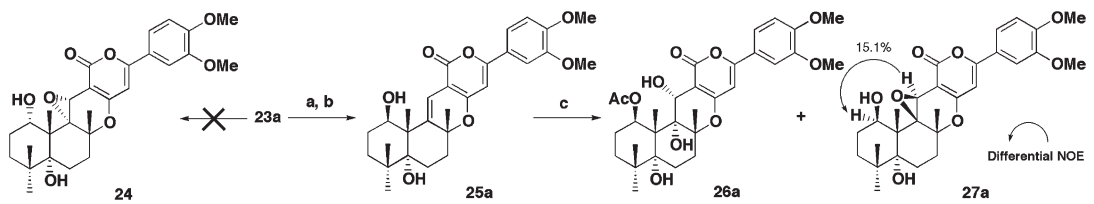


Scheme 8. (a) Ac_2O, DMAP, pyridine, rt, 89%.

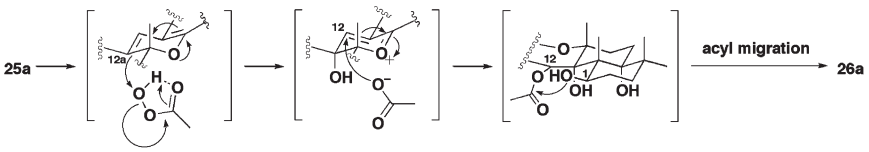
oxocarbenium intermediate. Stereoselective addition of the AcO^- anion to the initially formed oxocarbenium intermediate would occur exclusively from the bottom face because the two angular methyl groups shield the top face of the olefin. The acetyl group would then migrate from the C12 hydroxy to the C1 hydroxy located at a conformationally close position (Scheme 9).

The next step is the reductive elimination of 12-OH in **26a**. Because the formation of xantate and mesylate failed, probably due to the steric hindrance around this functionality, we attempted the direct reduction of the hydroxy group. Reaction with BH_3–THF/BF_3–OEt_2, Et_3SiH/BF_3–OEt_2, or $NaBH_3CN$/TFA did not give the desired product but produced the unidentifiable product. While the adaptation of $NaBH_3CN/ZnI_2$ furnished **29a** in low yield, this procedure was not satisfactory because the starting material remained at the end of the reaction. Finally, treatment of **26a** with Et_3SiH and TFA[35] successfully generated the desired product in good yield. Subsequent methanolysis of the C-1 acetate produced the triol **29a** in 82% yield for the two steps.

In the last step, **29a** was readily quantitatively oxidized to the ketone **30a** by treatment with TPAP and NMO. We used 2, 3-dihydroterritrem B as a model compound to examine the conversion of the ketone to an enone. The procedure via bromination[36] failed due to attack of the 4a-hydroxy group to α-bromoketone to form an ether ring. IBX[37] and the Saegusa method[38] were also unsuccessful. Fortunately, the phenylselenenylation–oxidation method, enolization by Schlosser's base followed by phenylselenenylation, was effective. The phenylselenide was treated with H_2O_2 to give territrem B, although in low yield. Therefore, we examined several reaction conditions with compound **30a** to optimize



Scheme 7. (a) TPAP, NMO, CH_2Cl_2, rt, 100%. (b) $NaBH_4$, AcOH, THF, 0 °C–rt, 71%. (c) AcOOH, CH_2Cl_2–phosphate buffer, rt, 41% (**26a**) and 38% (**27a**).



Scheme 9. Proposed mechanism for oxidation of **25a** with peracetic acid.

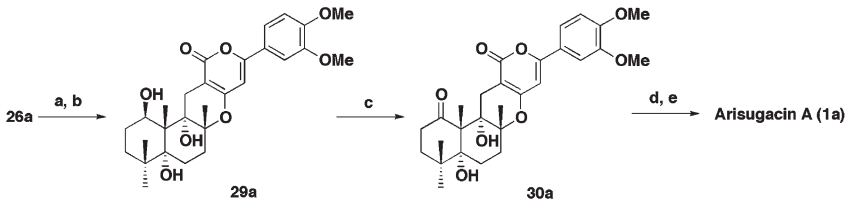
the yield. The best conditions were enolization at −20 °C and phenylselenenylation at room temperature. Without a retro-aldol–aldol reaction, this protocol furnished arisugacin A in 47% yield. The IR, HRMS, and $^{1}H/^{13}C$ NMR spectra of this synthetic **1a** agreed with the data reported for natural **1a**. Furthermore, we determined an $[\alpha]_D^{25}$ value of+144.0° (*c* 0.10, $CHCl_3$) for the synthetic sample. Although the reported value for the natural product was $[\alpha]_D^{23}$ +72° (*c* 0.10, $CHCl_3$), upon reexamination, the optical rotation for the natural compound was found to be $[\alpha]_D^{25}$ +150.0° (*c* 0.10, $CHCl_3$). Therefore, the absolute configurations at C-4a, C-6a, C-12a, and C-12b were assigned as *R*,*R*,*R*, and *S*, respectively (Scheme 10).

2.5. Total synthesis of arisugacin B

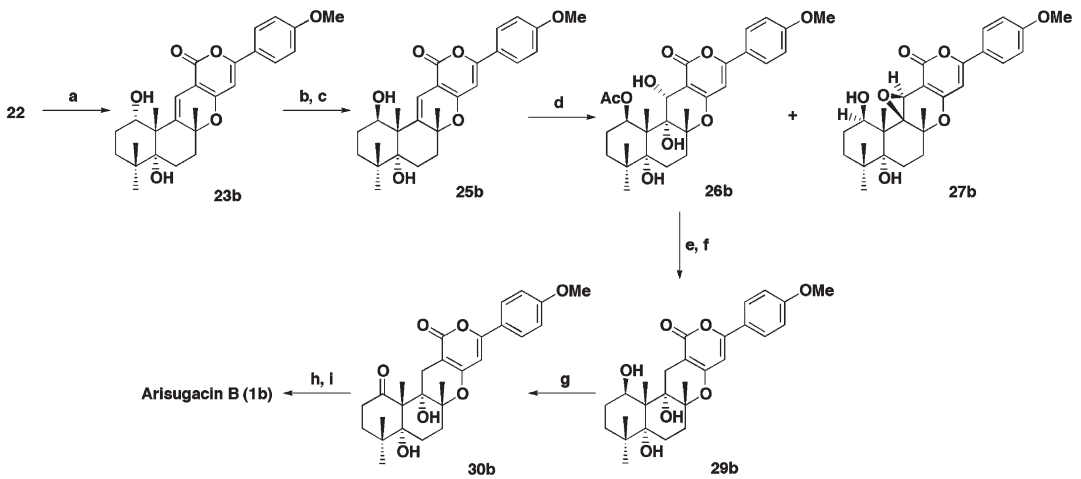
To demonstrate the applicability of our strategy, we prepared the analogue (+)-arisugacin B. The intermediate in the analogous skeleton was obtained in 62% yield by the method described in Scheme 11 and using the 4-methoxy-α-pyrone **11b** instead of 3,4-dimethoxy-α-pyrone **11a**. We performed the synthetic procedures from **22** to **1b** as was carried out for (+)-arisugacin A. The spectroscopic data of the obtained (+)-arisugacin B agreed with those published for the natural product, except for the optical rotation. Specifically, we determined $[\alpha]_D^{24}$ +168.5° (*c* 0.10, $CHCl_3$/MeOH 10/1) for our isolate. The reported rotation for the natural substance was $[\alpha]_D^{23}$ +26° (*c* 0.10, $CHCl_3$). Reexamination of the natural sample, however, gave an $[\alpha]_D^{25}$ value of+139.8° (*c* 0.10, $CHCl_3$/MeOH 10/1). Therefore, the absolute configurations at C-4a, C-6a, C-12a, and C-12b were assigned as *R*,*R*,*R*, and *S*, respectively.

2.6. Bioactivity

Because we were interested in bioactivities of the synthetic intermediates, we tested the activities of 1-keto-**23a/b**, **25a/b**, **26a/b**, **27a/b**, **29a/b**, and **30a/b** against AChE using our previously published method.[4] We found that only **30a** showed activity, and this was 80-fold lower than for **1a**. We found that 1-keto-**23a** lacking both an enone moiety on the A ring and a 12aα-hydroxy group and that **29a** and **30b** lacking the enone moiety no longer inhibited AChE. This suggests that these functionalities are essential for the inhibition of AChE by arisugacins. In addition, Peng reported that 1β-hydroxy-territrem B was 300-fold less potent than territrem B at inhibiting AChE.[39] Furthermore, we found that **1a** was 25-fold more potent than **1b**.[4]



Scheme 10. (a) Et_3SiH, TFA, $ClCH_2CH_2Cl$, 50 °C. (b) K_2CO_3, MeOH, rt, 82% from **26a**. (c) TPAP, NMO, CH_2Cl_2, rt, 100%. (d) KDA, PhSeBr, THF:HMPA=10:1, −78 °C–rt. (e) H_2O_2, AcOH, THF, 0 °C–rt, 47% from **30a**.



Scheme 11. (a) **11b**, L-proline, THF, 65 °C, 62%. (b) TPAP, NMO, CH_2Cl_2, rt, 100%. (c) $NaBH_4$, AcOH, THF, 0 °C–rt, 98%. (d) AcOOH, CH_2Cl_2–phosphate buffer, rt, 38% (**26b**) and 33% (**27b**). (e) Et_3SiH, TFA, $ClCH_2CH_2Cl$, 50 °C. (f) K_2CO_3, MeOH, rt, 82% from **26b**. (g) TPAP, NMO, CH_2Cl_2, rt, 100%. (h) KDA, PhSeBr, THF:HMPA=10:1, −78 °C–rt. (i) H_2O_2, AcOH, THF, 0 °C–rt, 46% from **30b**.

Consequently, we suggest that the enone moiety in ring A, the hydroxy group at position 12a, and the E ring substituents play important roles in the inhibition of AChE by arisugacins.

3. Conclusion

In conclusion, we achieved the first total syntheses of (+)-**1a** and (+)-**1b** via an efficient and convergent 22-step strategy starting from α-ionone (total yield 0.9 and 1.1% for (+)-**1a** and (+)-**1b**, respectively). From this, we determined the absolute stereochemistry of (+)-**1a** and (+)-**1b**. This successful synthetic approach can provide further synthetic analogues of arisugacin as potent inhibitors of AChE.

4. Experimental

4.1. General

Melting points were determined on a hot stage apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 270, 300 and 400 MHz and ^{13}C NMR at 67.5, 75 and 100.6 MHz. Assignments were obtained using J-mod experiments and, when necessary, COSY, HMBC, HMQC and NOE experiments. Thin-layer chromatography (TLC) was performed on a percolated plate of silica gel 60F 254. Analytical visualization was accomplished with ultraviolet light and/or 5% phosphoromolybdic acid in ethanol stain with heating. Flash chromatography was performed on silica gel 60. Assay for AChE inhibitory activity was performed according to the reported procedure[4] with slight modification. AChE from bovine erythrocytes was used instead of that from human erythrocytes used in reported protocol, because of the commercial availability.

4.1.1. (3*S*,4a*R*,6a*R*,12a*R*,12b*S*)-1,3,4,4a,5,6,6a,12,12a,12b-Decahydro-3-[(+)-α-methoxy-α-trifluoromethylphenyl]acetoxy-4,4,6a,12b-tetramethyl-9-(4′-methoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one (4). To a solution of **1f** (5.1 mg, 11.6 μmol) in CH_2Cl_2 (240 μL) at room temperature was added (+)-MTPA (8.3 mg, 34.9 μmol), DCC (14.4 mg, 69.8 μmol) and DMAP (1.4 mg, 11.6 μmol), and the mixture was stirred for 10 min, and then quenched with H_2O (5 mL). The resultant mixture was extracted with $CHCl_3$ (3x10 mL) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Preparative TLC (hexane/EtOAc 1/1) furnished **4** (6.7 mg, 10.2 μmol, 88% yield) as a colorless crystal: $[\alpha]_D^{22}$ +68.1° (*c* 0.34, $CHCl_3$); TLC R_f 0.57 (hexane/EtOAc 1/1); mp 93–94 °C; IR (KBr) 1745, 1707, 1639, 837, 810 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (3H, s), 0.86 (3H, s), 0.95 (3H, s), 1.11 (1H, dd, *J*=12.0, 2.0 Hz), 1.22 (1H, m), 1.26 (3H, s), 1.44 (1H, m), 1.52 (1H, dd, *J*=12.9, 4.9 Hz), 1.69 (1H, m), 1.79 (2H, m), 1.87 (1H, m), 1.90 (1H, m), 2.13 (1H, ddd, *J*=12.3, 3.0, 3.0 Hz), 2.24 (1H, dd, *J*=17.0, 12.9 Hz), 2.51 (1H, dd, *J*=17.0, 4.9 Hz), 3.85 (3H, s), 4.75 (1H, dd, *J*=12.0, 4.4 Hz), 6.25 (1H, s), 6.93 (2H, d, *J*=8.9 Hz), 7.73 (2H, d, *J*=8.9 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.1, 16.3, 17.3, 19.2, 20.7, 23.4, 27.8, 36.7, 37.1, 37.9, 40.2, 51.5, 55.0, 55.4, 80.3, 83.3, 96.7, 98.3, 114.2 (2C), 124.0, 127.0 (2C), 158.5, 161.5, 163.5, 164.6; HRMS (FAB, NBA, PEG+600 matrix) Calcd for $C_{37}H_{41}O_7F_3$ $[M]^+$ 654.2804, found 654.2793.

4.1.2. (3*S*,4a*R*,6a*R*,12a*R*,12b*S*)-1,3,4,4a,5,6,6a,12,12a,12b-Decahydro-3-[(−)-α-methoxy-α-trifluoromethylphenyl]acetoxy-4,4,6a,12b-tetramethyl-9-(4′-methoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one (5). To a solution of **1f** (5.5 mg, 12.5 μmol) in CH_2Cl_2 (260 μL) at room temperature was added (−)-MTPA (8.9 mg, 37.6 μmol), DCC (15.5 mg, 75.3 μmol) and DMAP (1.5 mg, 12.5 μmol), and the mixture was stirred for 3 h, and then quenched with H_2O (5 mL). The resultant mixture was extracted with $CHCl_3$ (3×10 mL) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Preparative TLC (hexane/EtOAc 1/1) furnished **5** (8.1 mg, 12.4 μmol, 99% yield) as a colorless crystal: $[\alpha]_D^{22}$ +59.3° (*c* 0.41, $CHCl_3$); TLC R_f 0.50 (hexane/EtOAc 1/1); mp 98–99 °C; IR (KBr) 1743, 1709, 1639, 839, 814 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (3H, s), 0.92 (3H, s), 0.95 (3H, s), 1.11 (1H, dd, *J*=12.0, 2.0 Hz), 1.20 (1H, m), 1.25 (3H, s), 1.44 (1H, m), 1.52 (1H, dd, *J*=12.9, 4.9 Hz), 1.69 (2H, m), 1.80 (1H, m), 1.84 (2H, m), 2.13 (1H, ddd, *J*=12.5, 3.0, 3.0 Hz), 2.23 (1H, dd, *J*=17.0, 12.9 Hz), 2.50 (1H, dd, *J*=17.0, 4.9 Hz), 3.85 (3H, s), 4.72 (1H, dd, *J*=11.8, 4.2 Hz), 6.25 (1H, s), 6.93 (2H, d, *J*=8.8 Hz), 7.73 (2H, d, *J*=8.8 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.1, 16.5, 17.2, 19.2, 20.7, 23.1, 28.2, 36.7, 37.0, 37.8, 40.2, 51.5, 55.0, 55.4, 80.3, 83.5, 96.7, 98.3, 114.2 (2C), 124.0, 127.0 (2C), 158.5, 161.5, 163.5, 164.6; HRMS (FAB, NBA, PEG+600 matrix) Calcd for $C_{37}H_{41}O_7F_3$ $[M]^+$ 654.2804, found 654.2807.

4.1.3. (4a*R*,6a*R*,12a*R*,12b*S*)-3,4,4a,5,6,6a,12,12a,12b-Nonahydro-4a,12a-dihydroxy-4,4,6a,12b-tetramethyl-9-(3′,4′,5′-trimethoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-1,11(3*H*)-dione (ketone). To a mixture solution of **2** (35.0 mg, 66.5 μmol) in MeOH (29 mL) at room temperature was added 10% Pd/C (21.7 mg), and under an atmosphere of hydrogen the resultant mixture was stirred at room temperature for 14 h. The catalyst was removed by filtration through Celite, washing with $CHCl_3$ (3×10 mL). The filtrate was evaporated to dryness. Preparative TLC (benzene/EtOAc 1/1) provided ketone (31.0 mg, 58.7 μmol, 88% yield) as a colorless solid: $[\alpha]_D^{27}$ +98.4° (*c* 0.22, $CHCl_3$); TLC R_f 0.53 (benzene/EtOAc 1/1); mp 209–211 °C; IR (KBr) 3452, 1690, 1583, 1504, 1458, 1407, 1126 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.06 (3H, s), 1.23 (3H, s), 1.42 (3H, s), 1.49 (3H, s), 1.67–2.04 (4H, m), 2.16 (1H, m), 2.47 (2H, m), 2.84 (1H, m), 2.84 (1H, d, *J*=17.8 Hz), 3.28 (1H, d, *J*=17.8 Hz), 3.89 (9H, s), 4.28 (1H, s), 6.10 (1H, s), 6.33 (1H, s), 6.95 (2H, s); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.5, 24.0, 25.9, 26.4, 27.1, 27.9, 28.7, 35.4, 37.3, 38.6, 56.3 (2C), 57.9, 61.0, 76.9, 80.0, 81.8, 97.3, 97.6, 102.8 (2C), 126.8, 140.3, 153.5 (2C), 158.5, 162.9, 164.4, 215.9; HRMS (FAB, NBA, PEG600+NaI matrix) Calcd for $C_{29}H_{37}O_9$ $[M+H]^+$ 529.2438, found 529.2414.

4.1.4. (1*S*,4a*R*,6a*R*,12a*R*,12b*S*)-1,3,4,4a,5,6,6a,12,12a,12b-Decahydro-1,4a,12a-trihydroxy-4,4,6a,12b-tetramethyl-9-(3′,4′,5′-trimethoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one (6). To a solution of ketone (12.2 mg, 23.1 μmol) in THF (0.77 mL) at 0 °C was

added $NaBH_4$ (1.3 mg, 34.6 μmol), and the reaction mixture was stirred for 1 h, and then quenched with 5% NaOH. The resultant mixture was extracted with EtOAc (3×5 mL) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography ($CHCl_3$) furnished **6** (10.4 mg, 19.6 μmol, 85% yield) as a colorless solid: $[\alpha]_D^{27}$ +57.5° (*c* 0.46, $CHCl_3$); TLC R_f 0.39 (benzene/EtOAc 1/1); mp 286 °C; IR (KBr) 3420, 1686, 1582, 1504, 1458, 1408, 1128 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, s), 1.09 (3H, s), 1.10 (3H, s), 1.19 (1H, m), 1.44 (3H, s), 1.74 (1H, m), 1.82 (3H, m), 2.01 (1H, m), 2.19 (1H, m), 2.40 (1H, m), 2.68 (1H, d, *J*=17.0 Hz), 2.85 (1H, d, *J*=17.0 Hz), 3.90 (9H, s), 4.18 (1H, d, *J*=3.6 Hz), 4.69 (1H, d, *J*=3.6 Hz), 5.08 (1H, s), 6.26 (1H, s), 6.38 (1H, s), 6.99 (2H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.5, 24.6, 24.9, 25.0, 25.4, 26.2, 27.4, 29.4, 29.9, 39.1, 44.4, 56.3 (2C), 61.0, 74.1, 79.5, 80.8, 81.1, 97.6, 97.8, 102.8 (2C), 126.9, 140.2, 153.5 (2C), 158.4, 163.0, 164.7; HRMS (FAB, NBA, PEG600+NaI matrix) Calcd for $C_{29}H_{39}O_9$ $[M+H]^+$ 531.2594, found 531.2582.

4.1.5. (1*S*,4a*R*,6a*R*,12a*R*,12b*S*)-1,3,4,4a,5,6,6a,12,12a,12b-Decahydro-1-[(+)-α-methoxy-α-trifluoromethylphenyl]acetoxy-4a,12a-dihydroxy-4,4,6a,12b-tetramethyl-9-(3′,4′,5′-trimethoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one (7). To a solution of **6** (7.4 mg, 14.0 μmol) in CH_2Cl_2 (700 μL) at room temperature was added (+)-MTPA (45.9 mg, 19.6 μmol), DCC (77.7 mg, 0.40 mmol) and DMAP (1 crystal), and the mixture was stirred for 4.5 h, and then quenched with saturated aqueous $NaHCO_3$ (0.1 mL) and H_2O (5 mL). The resultant mixture was extracted with $CHCl_3$ (3×10 mL) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Preparative TLC (benzene/EtOAc 1/1) furnished **7** (5.2 mg, 7.00 μmol, 50% yield) as a colorless crystal: $[\alpha]_D^{27}$ +193.3° (*c* 0.26, $CHCl_3$); TLC R_f 0.68 (benzene/EtOAc 1/1); mp 108–109 °C; IR (KBr) 3431, 1744, 1703, 1583, 1504, 1457, 1407, 1168, 1127 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (3H, s), 1.07 (3H, s), 1.10 (1H, m), 1.13 (3H, s), 1.33 (3H, s), 1.70 (1H, m), 1.80 (2H, m), 1.85 (1H, d, *J*=18.0 Hz), 1.99 (1H, m), 2.20 (1H, m), 2.26 (1H, m), 2.38 (1H, m), 2.72 (1H, d, *J*=18.0 Hz), 2.80 (1H, s), 3.91 (3H, s), 3.94 (6H, s), 5.11 (1H, d, *J*=3.0 Hz), 5.71 (1H, s), 6.30 (1H, s), 7.02 (2H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.6, 23.3, 24.4, 24.6, 25.8, 26.2, 27.5, 29.2, 30.7, 39.0, 44.4, 56.4 (2C), 61.0, 77.9, 78.0, 78.3, 81.3, 96.4, 97.6, 102.8 (2C), 126.7, 140.4, 153.6 (2C), 158.2, 162.6, 164.1; HRMS (FAB, NBA, PEG600+NaI matrix) Calcd for $C_{39}H_{46}O_{11}F_3$ $[M+H]^+$ 747.2992, found 747.3005.

4.1.6. (1*S*,4a*R*,6a*R*,12a*R*,12b*S*)-1,3,4,4a,5,6,6a,12,12a,12b-Decahydro-1-[(−)-α-methoxy-α-trifluoromethylphenyl]acetoxy-4a,12a-dihydroxy-4,4,6a,12b-tetramethyl-9-(3′,4′,5′-trimethoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one (8). To a solution of **6** (4.2 mg, 7.9 μmol) in CH_2Cl_2 (500 μL) at room temperature was added (−)-MTPA (26.0 mg, 11.0 μmol), DCC (44.0 mg, 0.21 mmol) and DMAP (1 crystal), and the mixture was stirred for 2.5 h, and then quenched with saturated aqueous $NaHCO_3$ (0.1 mL) and H_2O (5 mL). The resultant mixture was extracted with $CHCl_3$ (3×10 mL) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Preparative TLC (benzene/EtOAc 1/1) furnished **8** (5.9 mg, 7.9 μmol, 100% yield) as a colorless crystal: $[\alpha]_D^{27}$ +106.0° (*c* 0.25, $CHCl_3$); TLC R_f 0.71 (benzene/EtOAc 1/1); mp 100–101 °C; IR (KBr) 3419, 1740, 1701, 1583, 1503, 1457, 1408, 1170, 1127 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, s), 1.04 (1H, m), 1.06 (3H, s), 1.18 (3H, s), 1.42 (3H, s), 1.74 (1H, m), 1.84 (2H, m), 1.85 (1H, m), 1.87 (1H, m), 2.22 (1H, m), 2.32 (1H, d, *J*=17.5 Hz), 2.44 (1H, m), 2.82 (1H, d, *J*=17.5 Hz), 3.90 (3H, s), 3.92 (6H, s), 4.20 (1H, s), 5.11 (1H, s), 5.20 (1H, d, *J*=3.0 Hz), 6.37 (1H, s), 7.02 (2H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 22.6, 23.1, 24.5, 24.8, 25.6, 26.1, 27.4, 29.3, 30.3, 38.8, 45.6, 56.3 (2C), 61.0, 77.6, 78.1, 78.6, 81.4, 96.8, 97.8, 102.8 (2C), 126.8, 140.3, 153.5 (2C), 158.2, 162.9, 165.1; HRMS (FAB, NBA, PEG600+NaI matrix) Calcd for $C_{39}H_{46}O_{11}F_3$ $[M+H]^+$ 747.2992, found 747.3024.

4.1.7. (1*S*)-3-Ethenyl-2,4,4-trimethyl-2-cyclohexen-1-ol (15). To $RuCl_2$[(*R*)-binap,(*S*,*S*)-DPEN] (104 mg, 103 μmol) in a glass autoclave was added **14** (8.44 g, 51.4 mmol) in 2-propanol (11.4 mL) and 0.45 M KOH in 2-propanol (9.15 mL, 4.12 mmol), and then, hydrogen was pressured to 8 atm. The solution was vigorously stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and flash chromatography (hexane/EtOAc 15/1) provided **15** (8.27 g, 49.8 mmol, 97% yield, 90% ee) as a colorless solid: $[\alpha]_D^{23}$ −47.0° (*c* 1.0, $CHCl_3$); TLC R_f 0.53 (hexane/EtOAc 5/2); mp 47–48 °C; IR (KBr) 3367, 1621 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.01 (3H, s), 1.04 (3H, s), 1.40–1.76 (2H, m), 1.84 (3H, s), 1.88–1.96 (2H, m), 4.00 (1H, t, *J*=4.5 Hz), 5.04 (1H, dd, *J*=18.0, 2.0 Hz), 5.32 (1H, dd, *J*=11.5, 2.0 Hz), 6.21 (1H, dd, *J*=18.0, 11.5 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 18.2, 27.0, 28.4, 28.7, 34.2, 34.3, 70.2, 118.9, 129.1, 134.8, 142.3; HRMS (EI) Calcd for $C_{11}H_{18}O$ $[M]^+$ 166.1358, found 166.1326. Anal. Calcd for $C_{11}H_{18}O{\cdot}1/7H_2O$: C, 78.25; H, 10.91, Found: C, 78.18; H, 11.08.

4.1.8. (1*S*)-3′-Ethenyl-2′,4′,4′-trimethyl-2′-cyclohexenyl 3,5-dinitrobenzoate (16). To a solution of **15** (9.20 g, 55.4 mmol) in pyridine (110 mL) at room temperature was added DMAP (541 mg, 4.43 mmol) and 3,5-dinitrobenzoyl chloride (15.3 g, 66.5 mmol), and the mixture was stirred for 1.5 h, and then quenched with H_2O (200 mL). The resultant mixture was extracted with $CHCl_3$ (3×200 mL) and the combined organic layers were washed with saturated aqueous NaCl and dried over Na_2SO_4, filtered and concentrated. The crude mixture was recrystallized from hexane/EtOAc 4/1 to yield pure (*S*)-**16** (11.6 g, 32.2 mmol, 58% yield) as colorless needle-like crystals: $[\alpha]_D^{24}$ −69.2° (*c* 1.0, $CHCl_3$); TLC R_f 0.56 (hexane/EtOAc 5/2); mp 130–131 °C; IR (KBr) 1714, 1547, 1344, 1286, 1173 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (3H, s), 1.12 (3H, s), 1.52 (1H, ddd, *J*=13.0, 7.0, 3.0 Hz), 1.71 (1H, ddd, *J*=13.0, 11.0, 3.0 Hz), 1.74 (3H, s), 1.90 (1H, m), 2.08 (1H, m), 5.10 (1H, dd, *J*=17.5, 2.0 Hz), 5.38 (1H, dd, *J*=11.0, 2.0 Hz), 5.58 (1H, t, *J*=5.0 Hz), 6.24 (1H, ddt, *J*=17.5, 11.0, 1.0 Hz), 9.15 (2H, d, *J*=2.0 Hz), 9.20 (1H, t, *J*=2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2, 25.4, 27.0, 28.6, 34.4, 34.6, 75.9, 119.7, 122.1, 124.2, 129.3 (2C), 134.1, 134.4, 146.1, 148.5 (2C), 162.3; HRMS (FAB, NBA, PEG200+400+NaI matrix) Calcd for $C_{18}H_{20}O_6N_2$ $[M]^+$

360.1321, found 360.1329. Anal. Calcd for $C_{18}H_{20}O_6N_2$: C, 59.98; H, 5.60; N, 7.78, Found: C, 59.83; H, 5.64; N, 7.61.

4.1.9. Regeneration of (1*S*)-3-ethenyl-2,4,4-trimethyl-2-cyclohexen-1-ol (15). To a solution of **16** (11.5 g, 31.9 mmol) in CH_2Cl_2/MeOH 1/1 (160 mL) at room temperature was added K_2CO_3 (8.83 g, 63.8 mmol), and the mixture was stirred for 2.5 h, and then quenched with saturated aqueous NH_4Cl (200 mL). The resultant mixture was extracted with $CHCl_3$ (3×200 mL) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography ($CHCl_3$, 1% Et_3N) provided **15** (5.23 g, 31.5 mmol, 99% yield, 98% ee) as a colorless solid: $[\alpha]_D^{24}$ −50.6° (*c* 1.0, $CHCl_3$); mp 52–53 °C.

4.1.10. (1*S*)-3′-Ethenyl-2′,4′,4′-trimethyl-2′-cyclohexen-1-yl-2-butynoate (17). To a solution of **15** (11.5 g, 69.5 mmol) in CH_2Cl_2 (189 mL) at 0 °C was added 2-butynoic acid (7.0 g, 83.4 mmol), DMAP (2.1 g, 17.4 mmol) and then was added a solution of DCC (21.5 g, 105 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 5 h at room temperature, and then the resultant mixture was filtered through a celite pad and concentrated. Flash chromatography (hexane/Et_3N 100/3) provided **17** (13.7 g, 59.1 mmol, 85% yield) as a colorless oil: $[\alpha]_D^{24}$ −93.4° (*c* 1.0, $CHCl_3$); TLC R_f 0.73 (hexane/EtOAc 5/1); IR (KBr) 2241, 1707, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (3H, s), 1.02 (3H, s), 1.41 (1H, ddd, *J*=13.5, 7.0, 3.0 Hz), 1.64 (1H, ddd, *J*=13.5, 11.5, 3.0 Hz), 1.69 (3H, s), 1.78 (1H, dddd, *J*=14.5, 7.0, 4.5, 3.0 Hz), 1.92 (1H, dddd, *J*=14.5, 11.5, 4.5, 3.0 Hz), 1.98 (3H, s), 5.02 (1H, dd, *J*=18.0, 2.5 Hz), 5.28 (1H, t, *J*=4.5 Hz), 5.31 (1H, dd, *J*=12.0, 2.5 Hz), 6.17 (1H, dd, *J*=18.0, 12.0 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 3.8, 18.0, 25.1, 26.7, 28.5, 34.0, 34.2, 72.7, 74.2, 85.2, 119.4, 124.7, 134.3, 145.4, 153.8; HRMS (EI) Calcd for $C_{15}H_{20}O_2$ $[M]^+$ 232.1463, found 232.1452. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68, Found: C, 76.27; H, 8.68.

4.1.11. (8a*S*,8b*S*)-4,6,7,8,8a,8b-Hexahydro-3,6,6,8b-tetramethyl-2*H*-naphtho[1,8-*bc*]furan-2-one (13). A solution of **17** (6.5 g, 28.0 mmol) in *n*-decane (22 mL) was stirred for 14 h at 180 °C. After cooling, the solvent was removed under high vacuum, and then flash chromatography (hexane/EtOAc 5/1) provided **13** (2.3 g, 9.91 mmol, 35% yield, 72% based on recovered starting material) and starting material (3.3 g, 14.2 mmol, 51%) as a colorless oil: $[\alpha]_D^{24}$ −70.2° (*c* 1.0, $CHCl_3$); TLC R_f 0.55 (hexane/EtOAc 5/1); IR (KBr) 1747, 1687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (3H, s), 1.17 (1H, dddd, *J*=14.0, 8.5, 4.5, 3.5 Hz), 1.19 (6H, s), 1.40 (1H, dt, *J*=14.0, 3.5 Hz), 1.58 (1H, ddd, *J*=14.0, 4.5, 3.5 Hz), 1.89 (1H, dddd, *J*=14.0, 8.5, 5.0, 3.5 Hz), 2.24 (3H, s), 2.77 (1H, dd, *J*=21.0, 6.0 Hz), 2.90 (1H, dd, *J*=21.0, 2.0 Hz), 4.28 (1H, dd, *J*=12.0, 5.0 Hz), 5.65 (1H, dd, *J*=6.0, 2.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.0, 26.1, 27.4, 30.9, 33.6, 34.6, 35.4, 35.9, 44.6, 84.5, 119.4, 127.9, 150.0, 150.3, 168.5; HRMS (EI) Calcd for $C_{15}H_{20}O_2$ $[M]^+$ 232.1463, found 232.1491. Anal. Calcd for $C_{15}H_{20}O_2 \cdot 1/5H_2O$: C, 76.36; H, 8.65, Found: C, 76.19; H, 8.65.

4.1.12. (1a*S*,5a*S*,8a*R*,8b*R*)-1a,2,5a,7,8,8b-Hexahydro-3,8,8,8b-tetramethyl-4*H*,6*H*-oxireno[4a,5]naphtho[1,8-*bc*]furan-4-one (18). To a solution of **13** (1.3 g, 5.5 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added *m*-CPBA (1.4 g, 8.3 mmol), and the mixture was stirred for 24 h at room temperature, and then quenched with $NaHSO_3$ and saturated aqueous $NaHCO_3$. The resultant mixture was extracted with $CHCl_3$ (3×20 mL) and the combined organic layers were washed with saturated aqueous NaCl and dried over Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc 5/1) provided **18** (1.1 g, 4.2 mmol, 77% yield) as a colorless crystal: $[\alpha]_D^{24}$ −161.2° (*c* 1.0, $CHCl_3$); TLC R_f 0.32 (hexane/EtOAc 5/2); mp 127–128 °C; IR (KBr) 1743, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (3H, s), 1.25 (3H, s), 1.35 (3H, s), 1.40 (1H, dt, *J*=14.0, 2.0 Hz), 1.58 (1H, ddt, *J*=14.0, 11.5, 2.5 Hz), 1.71 (1H, ddd, *J*=14.0, 5.0, 2.5 Hz), 2.01 (1H, dddd, *J*=14.0, 6.0, 5.0, 2.0 Hz), 2.19 (3H, s), 2.62 (1H, dd, *J*=18.0, 3.0 Hz), 2.76 (1H, d, *J*=18.0 Hz), 3.13 (1H, d, *J*=3.0 Hz), 4.19 (1H, dd, *J*=11.5, 6.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 19.2, 25.3, 25.7, 29.8, 30.9, 33.4, 34.4, 34.7, 44.7, 48.3, 65.3, 84.6, 126.8, 145.8, 168.2; HRMS (EI) Calcd for $C_{15}H_{20}O_3$ $[M]^+$ 248.1412, found 248.1423. Anal. Calcd for $C_{15}H_{20}O_3 \cdot 1/4H_2O$: C, 71.26; H, 8.17, Found: C, 71.22; H, 8.16.

4.1.13. 1,3,4,4a,5,6,6a,12b-Octahydro-4aα,5α-epoxy-1α-hydroxy-4,4,6aβ,12bβ-tetramethyl-9-(3′,4′-dimethoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one (9). To a solution of **18** (201 mg, 0.81 mmol) in CH_2Cl_2 (9.1 mL) at −78 °C was added a hexane solution of DIBAL (1.3 mL, 1.21 mmol) slowly over a period of 30 min. After complete addition the stirring was continued for 1.5 h and quenched with H_2O. The resultant mixture was diluted with $CHCl_3$ and extracted with $CHCl_3$. The combined extracts were washed with saturated aqueous NaCl and dried over Na_2SO_4, filtered and concentrated. The crude mixture was used for the next step without purification.

To a solution of crude mixture and **11a** (217 mg, 0.97 mmol) in EtOAc (3.7 mL) at room temperature was added L-proline (42.0 mg, 0.41 mmol), and the resultant mixture was warmed to 80 °C for 21 h. The solution was cooled to room temperature. The solution was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried over Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc 1/2) provided **9** (194 mg, 405 μmol, 50% yield) as a yellow crystal: TLC R_f 0.29 (hexane/EtOAc 1/2); mp 95–97 °C; IR (KBr) 3442, 1709, 1545, 1513, 1460, 1271 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (3H, s), 1.18 (3H, s), 1.25 (1H, m), 1.42 (3H, s), 1.61 (3H, s), 1.97 (1H, m), 2.05 (2H, m), 2.44 (1H, d, *J*=14.0 Hz), 2.57 (1H, d, *J*=5.0 Hz), 3.19 (1H, dd, *J*=14.0, 5.0 Hz), 3.93 (3H, s), 3.94 (3H, s), 4.28 (1H, brs), 6.42 (1H, s), 6.50 (1H, s), 6.90 (1H, d, *J*=9.0 Hz), 7.30 (1H, d, *J*=2.0 Hz), 7.41 (1H, dd, *J*=9.0, 2.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.1, 26.5, 26.6, 26.9, 30.3, 31.0, 33.6, 34.1, 48.8, 49.0, 56.0, 56.1, 64.2, 71.0, 80.1, 96.1, 102.6, 108.3, 111.1, 114.1, 119.1, 124.0, 138.3, 149.2, 151.6, 160.5, 161.6, 162.5; HREIMS Calcd for $C_{28}H_{32}O_7$ $[M]^+$ 480.2148, found 480.2145.

4.1.14. 1,3,4,4a,5,6,6a,12b-Octahydro-4aα,5α,12α,12aα-diepoxy-1α-hydroxy-4,4,6aβ,12bβ-tetramethyl-9-(3′,4′-dimethoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one (19). To a solution of **9** (46.6 mg, 97.0 μmol)

in benzene (1.9 mL) at room temperature was added $Mo(CO)_6$ (25.6 mg, 97.0 μmol), 5.0 M *t*-BuOOH (58 μL, 291 μmol), and the reaction mixture was stirred for 1 h at 80 °C. The solution was cooled to room temperature, and then added saturated aqueous $NaHSO_3$. The resultant mixture was extracted with $CHCl_3$ (5x5 mL) and the combined extracts were washed with saturated aqueous NaCl, and dried over Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc 1/2) provided **19** (14.0 mg, 28.1 μmol, 29% yield) as a yellow crystal: TLC R_f 0.23 (hexane/EtOAc 1/2); mp 97–105 °C; IR (KBr) 3439, 1703, 1550, 1516, 1462, 1269 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (3H, s), 1.02 (1H, m), 1.08 (3H, s), 1.14 (3H, s), 1.52 (3H, s), 1.84 (1H, m), 2.00 (1H, m), 2.07 (1H, m), 2.17 (1H, d, *J*=16.5 Hz), 3.11 (1H, dd, *J*=16.5, 7.5 Hz), 3.92 (3H, s), 3.93 (3H, s), 4.07 (1H, dd, *J*=5.0, 3.5 Hz), 4.32 (1H, br), 4.87 (1H, s), 6.22 (1H, s), 6.90 (1H, d, *J*=8.5 Hz), 7.28 (1H, d, *J*=2.0 Hz), 7.39 (1H, dd, *J*=8.5, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 22.1, 22.9, 23.6, 25.0, 33.5, 34.1, 46.7, 48.5, 56.0, 56.2, 71.1, 71.2, 78.4, 84.4, 91.4, 92.4, 95.8, 97.9, 108.4, 111.1, 119.2, 123.6, 149.2, 151.7, 160.8, 162.0, 164.5; HREIMS Calcd for $C_{28}H_{32}O_7$ $[M]^+$ 496.2097, found 496.2115.

4.1.15. (4a*R*,8*S*,8a*S*)-3,4,4a,5,6,7,8,8a-Octahydro-4a,8-dihydroxy-1-hydromethyl-2,5,5,8a-tetramethylnaphthalene (21). To a solution of **18** (203 mg, 0.82 mmol) in THF (820 μL) at 0 °C was added $AlCl_3$ (120 mg, 0.92 mmol), and the reaction mixture was stirred for 10 min, and then added $LiAlH_4$ (135 mg, 4.1 mmol) in four portions. The mixture was stirred for 1 h and quenched with H_2O. The resultant mixture was diluted with $CHCl_3$ and extracted with $CHCl_3$. The combined extracts were washed with saturated aqueous NaCl and dried over Na_2SO_4, filtered and concentrated. The crude mixture of **21** (204 mg, 803 μmol, 98% yield) was used for the next step without purification: $[\alpha]_D^{24}$ +116.6° (*c* 1.0, $CHCl_3$); TLC R_f 0.36 (hexane/EtOAc 5/2); mp 141–142 °C; IR (KBr) 3482, 1631 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ 1.05 (3H, s), 1.08 (3H, s), 1.11 (1H, m), 1.22 (3H, s), 1.73 (3H, s), 1.76–1.83 (2H, m), 1.89 (1H, m), 1.95 (1H, m), 2.06 (1H, ddt, *J*=14.0, 4.5, 3.0 Hz), 2.38 (1H, m), 2.55 (1H, m), 4.32 (1H, d, *J*=12.0 Hz), 4.34 (1H, m), 4.65 (1H, d, *J*=12.0 Hz), 5.86 (1H, brs), 7.13 (1H, brs); ^{13}C NMR (100.6 MHz, pyridine-d_5) δ 19.8, 24.2, 24.9, 25.6, 25.7, 28.7, 30.4, 31.3, 39.0, 46.6, 57.4, 73.8, 77.1, 134.4, 135.5; HRMS (FAB, NBA, NaI matrix) Calcd for $C_{15}H_{26}O_3Na$ $[M+Na]^+$ 277.1780, found 277.1783. Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30, Found: C, 70.62; H, 10.42.

4.1.16. (4a*R*,8*S*,8a*S*)-1-Formyl-3,4,4a,5,6,7,8,8a-octahydro-4a,8-dihydroxy-2,5,5,8a-tetramethylnaphthalene (22). To a solution of **21** (45.6 mg, 180 μmol) in CH_2Cl_2 (900 μL) at room temperature was added 4-methylmorpholine *N*-oxide (31.5 mg, 269 μmol) and tetrapropylammonium perruthenate (1.9 mg, 5.39 μmol), and the mixture was stirred for 1.5 h. The resultant mixture was concentrated, and preparative TLC (benzene/acetone 5/2) furnished unstable aldehyde (**22**) (33.1 mg, 131 μmol, 73% yield) as a colorless solid: TLC R_f 0.55 (benzene/acetone 5/2); ^1H NMR (270 MHz, $CDCl_3$) δ 1.01 (6H, s), 1.16 (3H, s), 1.59–1.73 (2H, m), 1.77 (2H, m), 2.02 (2H, m), 2.12 (3H, s), 2.26 (2H, m), 2.28 (1H, brs), 4.40 (1H, brs), 4.78 (1H, brs), 10.18 (1H, s).

4.1.17. (1*S*,4a*R*,6a*R*,12b*S*)-1,3,4,4a,5,6,6a,12b-Octahydro-1,4a-dihydroxy-4,4,6a,12b-tetramethyl-9-(3′,4′-dimethoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one (23a). To a mixture solution of **22** (40.9 mg, 162 μmol) and **11a** (60.4 mg, 244 μmol) in THF (1.6 mL) at room temperature was added L-proline (37.4 mg, 325 μmol), and the resultant mixture was warmed to 65 °C for 14 h. The solution was cooled to room temperature, and then filtered through celite, washing with $CHCl_3$ (3×10 mL). The filtrate was washed with H_2O (30 ml), and dried over Na_2SO_4, filtered and concentrated. Flash chromatography ($CHCl_3$) provided **23a** (47.7 mg, 99.0 μmol, 61% yield) as a yellow crystal: $[\alpha]_D^{25}$ +127.9° (*c* 0.83, $CHCl_3$); TLC R_f 0.35 (hexane/EtOAc 1/2); mp 116–117 °C; IR (KBr) 3482, 1685, 1550, 1515, 1460, 1269 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (3H, s), 1.03 (3H, s), 1.15 (1H, m), 1.30 (3H, s), 1.53 (3H, s), 1.75 (1H, m), 1.83 (2H, m), 1.92 (1H, m), 2.07 (1H, m), 2.17 (1H, m), 2.55 (1H, m), 3.13 (1H, brs), 3.92 (3H, s), 3.94 (3H, s), 4.35 (1H, brs), 4.61 (1H, brs), 6.40 (1H, s), 6.44 (1H, s), 6.90 (1H, d, *J*=8.5 Hz), 7.27 (1H, d, *J*=2.0 Hz), 7.39 (1H, dd, *J*=8.5, 2.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 23.9, 24.1, 24.9, 27.6, 27.7, 27.9, 30.4, 34.3, 38.3, 47.4, 56.0, 56.1, 72.0, 76.6, 80.5, 96.5, 100.5, 108.2, 111.1 (2C), 119.0, 124.1, 142.2, 149.2, 151.4, 159.9, 162.1, 162.6; HRMS (FAB, NBA matrix) Calcd for $C_{28}H_{34}O_7$ $[M]^+$ 482.2305, found 482.2319.

4.1.18. (4a*R*,6a*R*,12b*R*)-3,4,4a,5,6,6a,12b-Heptahydro-4a-hydroxy-4,4,6a,12b-tetramethyl-9-(3′,4′-dimethoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-1,11(3*H*)-dione (1-keto-23a). To a solution of **23a** (33.2 mg, 68.8 μmol) in CH_2Cl_2 (350 μL) at room temperature was added 4-methylmorpholine *N*-oxide (16.1 mg, 138 μmol) and tetrapropylammonium perruthenate (0.5 mg, 1.37 μmol), and the mixture was stirred for 1.5 h. The resultant mixture was concentrated, and flash chromatography ($CHCl_3$/MeOH 10/1) furnished 1-keto-**23a** (33.0 mg, 68.8 μmol, 100% yield) as a yellow crystal: $[\alpha]_D^{25}$ +157.6° (*c* 0.90, $CHCl_3$); TLC R_f 0.58 ($CHCl_3$/MeOH 10/1); mp 101–102 °C; IR (KBr) 3427, 1711, 1551, 1516, 1464, 1269 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$) δ 1.04 (3H, s), 1.15 (3H, s), 1.50 (3H, s), 1.60 (3H, s), 1.63 (1H, ddd, *J*=13.5, 7.5, 5.5 Hz), 1.80 (1H, ddd, *J*=14.0, 5.5, 3.5 Hz), 1.93 (1H, dt, *J*=14.0, 4.5 Hz), 2.00 (1H, ddd, *J*=14.0, 4.5, 3.5 Hz), 2.01 (1H, ddd, *J*=13.5, 9.5, 5.5 Hz), 2.39 (1H, dt, *J*=14.0, 5.5 Hz), 2.59 (1H, ddd, *J*=14.5, 7.5, 5.5 Hz), 2.76 (1H, ddd, *J*=14.5, 9.5, 5.5 Hz), 3.89 (3H, s), 3.90 (3H, s), 6.35 (1H, s), 6.87 (1H, d, *J*=8.0 Hz), 7.28 (1H, d, *J*=2.0 Hz), 7.36 (1H, dd, *J*=8.0, 2.0 Hz), 7.38 (1H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.3, 25.7, 26.6, 27.3, 27.9, 33.5, 36.3, 36.9, 37.6, 55.9, 56.0, 56.9, 78.8, 79.6, 96.1, 100.7, 108.2, 111.1, 118.5, 119.0, 124.6, 134.5, 149.2, 151.5, 160.2, 162.0, 162.7, 211.5; HRMS (FAB, NBA matrix) Calcd for $C_{28}H_{33}O_7$ $[M+H]^+$ 481.2194, found 481.2226.

4.1.19. (1*R*,4a*R*,6a*R*,12b*S*)-1,3,4,4a,5,6,6a,12b-Octahydro-1,4a-dihydroxy-4,4,6a,12b-tetramethyl-9-(3′,4′-dimethoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one (25a). A solution of $NaBH(OAc)_3$ was prepared by adding $NaBH_4$ (72.0 mg, 1.90 mmol) to glacial acetic acid (1.9 mL) while keeping the temperature below 20 °C (ice bath). After the H_2 evolution ceased, a solution of

1-keto-**23a** (91.3 mg, 190 μmol) in THF (3.8 mL) was added in one portion and the reaction mixture was stirred for 15 h at room temperature, and then quenched with 0.2 N HCl (20 mL). The resultant mixture was extracted with $CHCl_3$ (3×10 mL) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Preparative TLC ($CHCl_3$/MeOH 15/1) furnished **25a** (65.4 mg, 136 μmol, 71% yield) as a yellow crystal: $[\alpha]_D^{25}$ +6.67° (*c* 0.69, $CHCl_3$); TLC R_f 0.54 ($CHCl_3$/MeOH 10/1); mp 181–182 °C; IR (KBr) 3427, 1684, 1614, 1554, 1515, 1271 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, s), 1.01 (3H, s), 1.18 (1H, m), 1.33 (3H, s), 1.57 (3H, s), 1.74 (1H, m), 1.77 (1H, m), 1.78 (1H, m), 1.96 (1H, m), 1.98 (1H, m), 2.07 (1H, ddd, *J*=13.5, 5.0, 2.0 Hz), 2.33 (1H, dt, *J*=13.5, 6.0 Hz), 3.93 (3H, s), 3.94 (3H, s), 4.36 (1H, dd, *J*=9.5, 6.2 Hz), 6.33 (1H, s), 6.89 (1H, d, *J*=8.5 Hz), 7.00 (1H, s), 7.29 (1H, d, *J*=2.0 Hz), 7.39 (1H, dd, *J*=8.5, 2.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.2, 23.6, 24.6, 27.0, 28.2, 28.9, 34.6, 35.6, 37.9, 49.9, 56.0, 56.1, 71.7, 77.4, 81.2, 96.1, 99.7, 108.3, 111.0, 114.8, 119.0, 124.2, 140.5, 149.2, 151.4, 160.0, 161.9, 162.5; HRMS (FAB, NBA, PEG+400 matrix) Calcd for $C_{28}H_{35}O_7$ $[M+H]^+$ 483.2383, found 483.2392. Anal. Calcd for $C_{28}H_{34}O_7 \cdot 7/8H_2O$: C, 67.49; H, 7.23, Found: C, 67.30; H, 7.05.

4.1.20. (1*R*,4a*R*,6a*R*,12*R*,12a*R*,12b*S*)-1-Acetoxy-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4a,12,12a-trihydroxy-4,4,6a,12b-tetramethyl-9-(3′,4′-dimethoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one (26a) and (1*R*,4a*R*,6a*R*,12*S*,12a*S*,12b*S*)-12,12a-epoxy-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-1,4a-dihydroxy-4,4,6a,12b-tetramethyl-9-(3′,4′-dimethoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one (27a). A solution of **25a** (6.6 mg, 13.7 μmol) in CH_2Cl_2:KH_2PO_4–Na_2HPO_4 buffer (prepared by dissolving 340 mg of KH_2PO_4 and 355 mg of Na_2HPO_4 in 100 mL of total aqueous solution)=5:1 (680 μL) at room temperature was treated with 32% peracetic acid in AcOH (72.0 μL, 342 μmol), and the reaction mixture was stirred for 5 days, quenched with $NaHSO_3$ (10 mg). The mixture was then extracted with $CHCl_3$ (3x8 mL) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Preparative TLC ($CHCl_3$/MeOH 20/1) furnished **26a** (3.1 mg, 5.56 μmol, 41% yield) and **27a** (2.6 mg, 5.22 μmol, 38% yield) as colorless crystals. **26a**: $[\alpha]_D^{25}$ +107.4° (*c* 0.86, $CHCl_3$); TLC R_f 0.54 (benzene/acetone 2/1); mp 198–199 °C; IR (KBr) 3415, 1722, 1684, 1572, 1516, 1269 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, s), 1.04 (3H, s), 1.09 (1H, m), 1.25 (3H, s), 1.46 (3H, s), 1.64 (1H, m), 1.73 (1H, dt, *J*=13.5, 3.5 Hz), 1.80 (1H, s), 1.90 (1H, m), 2.05 (3H, s), 2.07 (1H, m), 2.11 (1H, m), 2.56 (1H, dt, *J*=13.5, 4.5 Hz), 3.93 (3H, s), 3.94 (3H, s), 4.63 (1H, s), 5.00 (1H, s), 5.03 (1H, s), 5.39 (1H, dd, *J*=10.0, 5.5 Hz), 6.37 (1H, s), 6.50 (1H, s), 6.92 (1H, d, *J*=8.0 Hz), 7.26 (1H, d, *J*=2.0 Hz), 7.39 (1H, dd, *J*=8.0, 2.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.6, 21.9, 22.7, 24.3, 24.9, 25.7, 27.1, 29.9, 33.7, 38.9, 48.1, 56.0, 56.1, 61.8, 71.9, 78.2, 79.8, 83.5, 96.9, 100.0, 108.3, 111.2, 119.3, 123.4, 149.3, 151.9, 160.4, 164.2, 165.2, 170.7; HRMS (FAB, NBA, NaI matrix) Calcd for $C_{30}H_{38}O_{10}Na$ $[M+Na]^+$ 581.2363, found 581.2377, and **27a**: $[\alpha]_D^{25}$ −35.7° (*c* 0.89, $CHCl_3$); TLC R_f 0.38 (benzene/acetone 2/1); mp 91–93 °C; IR (KBr) 3450, 1697, 1572, 1516, 1269 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, s), 0.94 (3H, s), 1.23 (1H, m), 1.27 (3H, s), 1.64 (3H, s), 1.65 (1H, m), 1.75 (1H, m), 1.77 (1H, m), 1.78 (1H, m), 1.82 (1H, m), 2.00 (1H, m), 2.02 (1H, m), 3.92 (3H, s), 3.93 (3H, s), 4.57 (1H, dd, *J*=11.1, 4.9 Hz), 4.89 (1H, s), 6.28 (1H, s), 6.87 (1H, d, *J*=8.5 Hz), 7.25 (1H, d, *J*=2.0 Hz), 7.35 (1H, dd, *J*=8.5, 2.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.8, 23.8, 24.4, 26.1, 26.4, 26.6, 30.8, 35.7, 36.5, 50.3, 56.2, 56.4, 71.2, 73.6, 80.0, 84.2, 88.7, 96.4, 98.4, 108.6, 111.2, 119.4, 124.2, 149.3, 151.7, 160.8, 164.0, 164.4; HRMS (FAB, NBA matrix) Calcd for $C_{28}H_{35}O_8$ $[M+H]^+$ 499.2332, found 499.2329.

4.1.21. 1β-Acetoxy-12β,12aβ-epoxy-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4aα-hydroxy-4,4,6aβ,12bβ-tetramethyl-9-(3′,4′-dimethoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one (28). A solution of (±)-**27a** (38.5 mg, 71.8 μmol) in pyridine (1.4 mL) was treated with DMAP (0.9 mg, 7.18 μmol) and Ac_2O (13.6 μL, 143 μmol) and the reaction mixture was stirred for 4 h at room temperature, quenched with H_2O (5 mL). The resultant mixture was extracted with $CHCl_3$ (3×10 mL), and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Preparative TLC ($CHCl_3$/MeOH 20/1) furnished (±)-**28** (34.4 mg, 63.7 μmol, 89% yield) as a yellow crystal: TLC R_f 0.50 ($CHCl_3$/MeOH 15/1); mp 119–120 °C; IR (KBr) 3433, 1713, 1635, 1574, 1516, 1458, 1377, 1269, 1144, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, s), 0.96 (3H, s), 1.22 (1H, dt, *J*=13.5, 3.5 Hz), 1.30 (3H, s), 1.61 (3H, s), 1.68 (1H, m), 1.72–1.86 (3H, m), 1.85 (1H, m), 2.01 (1H, m), 2.05 (3H, s), 2.09 (1H, m), 2.56 (1H, brs), 3.92 (3H, s), 3.93 (3H, s), 4.91 (1H, s), 5.61 (1H, dd, *J*=11.5, 5.0 Hz), 6.29 (1H, s), 6.89 (1H, d, *J*=8.5 Hz), 7.28 (1H, d, *J*=2.0 Hz), 7.39 (1H, dd, *J*=8.5, 2.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.6, 21.5, 23.2, 24.1, 24.6, 25.9, 26.0, 30.3, 34.6, 36.1, 50.4, 56.0, 56.1, 70.7, 74.4, 78.6, 83.5, 88.5, 96.1, 97.8, 108.4, 111.0, 119.2, 124.1, 149.1, 151.4, 160.7, 163.5, 163.8, 171.8; HRMS (FAB, NBA matrix) Calcd for $C_{30}H_{37}O_9$ $[M+H]^+$ 541.2438, found 541.2431.

4.1.22. (1*R*,4a*R*,6a*R*,12a*R*,12b*S*)-1,3,4,4a,5,6,6a,12,12a,12b-Decahydro-1,4a,12a-trihydroxy-4,4,6a,12b-tetramethyl-9-(3′,4′-dimethoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one (29a). At room temperature a solution of **26a** (6.7 mg, 12.0 μmol) in $ClCH_2CH_2Cl$ (1.2 mL) was treated with Et_3SiH (17.3 μL, 108 μmol) and TFA (6.1 μL, 79.3 μmol) and the reaction mixture was stirred for 18 h at 50 °C, quenched with saturated aqueous $NaHCO_3$ (3 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 mixture of **12-deoxydiol** and **29a** was used for the next step without purification.

To a solution of the crude mixture in MeOH (1.2 mL) at room temperature was added K_2CO_3 (3.3 mg, 24.0 μmol). The solution was stirred for 4 h at room temperature, quenched with saturated aqueous NH_4Cl (3 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 (benzene/acetone 2/1) furnished **29a** (4.9 mg, 9.80 μmol, 82% yield) as a colorless crystal; $[\alpha]_D^{25}$ +88.0° (*c* 0.12, $CHCl_3$); TLC R_f 0.54 ($CHCl_3$/

MeOH 15/1); mp >300 °C; IR (KBr) 3433, 1682, 1637, 1572, 1516, 1269 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (3H, s), 1.04 (3H, s), 1.15 (1H, m), 1.16 (3H, s), 1.43 (3H, s), 1.70 (1H, m), 1.72 (1H, m), 1.74 (1H, m), 1.75 (1H, m), 1.86 (1H, dt, J=14.0, 4.0 Hz), 2.04 (1H, dt, J=13.0, 4.5 Hz), 2.43 (1H, dt, J=13.0, 4.0 Hz), 2.87 (1H, d, J=18.0 Hz), 3.22 (1H, d, J=18.0 Hz), 3.92 (6H, s), 4.63 (1H, dd, J=10.5, 5.0 Hz), 6.24 (1H, s), 6.85 (1H, d, J=8.5 Hz), 7.19 (1H, d, J=2.0 Hz), 7.28 (1H, dd, J=8.5, 2.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 16.1, 24.4, 24.6, 25.7, 27.2, 29.1 (2C), 29.7, 34.9, 38.9, 48.6, 56.0, 56.1, 68.8, 77.9, 81.0, 82.0, 97.0, 98.0, 108.1, 111.0, 118.7, 124.0, 149.1, 151.1, 158.3, 163.3, 165.2; HRMS (FAB, NBA, PEG600 matrix) Calcd for $C_{28}H_{37}O_8$ $[M+H]^+$ 501.2488, found 501.2483.

4.1.23. (4a*R*,6a*R*,12a*R*,12b*S*)-3,4,4a,5,6,6a,12,12a,12b-Nonahydro-4a,12a-dihydroxy-4,4,6a,12b-tetramethyl-9-(3′,4′-dimethoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-1,11(3*H*)-dione (30a). To a solution of **29a** (5.0 mg, 10.0 μmol) in CH_2Cl_2 (1.0 mL) at room temperature was added 4-methylmorpholine *N*-oxide (2.3 mg, 20.0 μmol) and tetrapropylammonium perruthenate (0.4 mg, 1.00 μmol), and the mixture was stirred for 20 min. The resultant mixture was concentrated, and preparative TLC ($CHCl_3$/MeOH 20/1) furnished **30a** (5.0 mg, 10.0 μmol, 100% yield) as a colorless powder: $[\alpha]_D^{25}$ +85.5° (*c* 0.11, $CHCl_3$); TLC R_f 0.58 ($CHCl_3$/MeOH 15/1); mp 234–235 °C; IR (KBr) 3477, 1711, 1639, 1578, 1516, 1267 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ added C_5D_5N 20 drops) δ 0.94 (3H, s), 1.04 (3H, s), 1.26 (3H, s), 1.28 (3H, s), 1.59 (1H, m), 1.60 (1H, m), 1.70 (1H, m), 1.74 (1H, m), 1.93 (1H, ddd, J=13.5, 7.8, 6.5 Hz), 2.37 (1H, dt, J=13.0, 5.2 Hz), 2.47 (1H, m), 2.55 (1H, m), 2.70 (1H, d, J=17.5 Hz), 3.44 (1H, d, J=17.5 Hz), 3.74 (3H, s), 3.75 (3H, s), 6.21 (1H, s), 6.74 (1H, d, J=8.5 Hz), 7.11 (1H, d, J=2.0 Hz), 7.21 (1H, dd, J=8.5, 2.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$ added C_5D_5N 20 drops) δ 19.0, 23.4, 25.7, 26.5, 26.8, 27.0, 28.5, 35.6, 36.3, 37.9, 55.6, 55.7, 57.3, 76.1, 80.2, 80.5, 96.4, 96.8, 107.8, 110.8, 118.4, 123.9, 150.8 (2C), 158.0, 162.6, 163.9, 213.5; HRMS (FAB, S-GTG, PEG400 matrix) Calcd for $C_{28}H_{35}O_8$ $[M+H]^+$ 499.2332, found 499.2335.

4.1.24. (4a*R*,6a*R*,12a*R*,12b*S*)-4a,6,6a,12,12a,12b-Hexahydro-4a,12α-dihydroxy-4,4,6a,12b-tetramethyl-9-(3′,4′-dimethoxyphenyl)-4*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-1,11(5*H*)-dione ((+)-arisugacin A, 1a). A solution of 100 μmol of KDA was prepared by adding *n*-butyllithiun (64 μL, 1.57 M in *n*-hexane, 100 μmol) to a solution of potassium *t*-butoxide (11.8 mg, 100 μmol) and diisopropylamine (15 μL, 103 μmol) in THF (200 μL) at −78 °C and stirring for 15 min. To this was added a solution of **30a** (15.1 mg, 30.3 μmol) in THF (360 μL) containing HMPA (56 μL). The mixture was stirred for 10 min at −78 °C and for 30 min at −20 °C and then treated with a solution of phenylselenenyl bromide (21.9 mg, 30.3 μmol) in THF (200 μL) containing HMPA (20 μL). The resultant mixture was stirred for 15 min at −78 °C, for 15 min at 0 °C and then for 40 min at room temperature, quenched with saturated aqueous NH_4Cl (5 mL) and extracted with Et_2O (3×10 mL), and the combined organic layers were washed with saturated aqueous NaCl (20 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated. Preparative TLC ($CHCl_3$/MeOH 30/1) furnished phenyl selenide (10.2 mg, 15.6 μmol, 51% yield) as a colorless solid.

A solution of phenyl selenide (7.2 mg, 11.0 μmol) in THF (550 μL) containing acetic acid (55 μL) at 0 °C was treated with 30% H_2O_2 (7 μL, 66.1 μmol) and the mixture was stirred for 15 min at 0 °C, and then warmed to room temperature, where stirring was continued for an additional 75 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), and extracted with $CHCl_3$ (3×10 mL) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Preparative TLC ($CHCl_3$/MeOH 30/1) furnished (+)-arisugacin A (**1a**) (5.1 mg, 10.3 μmol, 93% yield) as a colorless solid: $[\alpha]_D^{25}$ +144.0° (*c* 0.10, $CHCl_3$); TLC R_f 0.38 ($CHCl_3$/MeOH 20/1); mp 292 °C; IR (KBr) 3437, 1686, 1637, 1574, 1518, 1267 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ 1.18, (3H, s), 1.29 (3H, s), 1.45 (3H, s), 1.49 (3H, s), 1.89 (1H, m), 1.91 (1H, m), 1.96 (1H, m), 2.89 (1H, m), 3.16 (1H, d, J=17.9 Hz), 3.76 (3H, s), 3.77 (3H, s), 4.34 (1H, d, J=17.9 Hz), 5.94 (1H, d, J=10.2 Hz), 6.27 (1H, d, J=10.2 Hz), 6.78 (1H, s), 6.99 (1H, d, J=8.5 Hz), 7.48 (1H, d, J=2.0 Hz), 7.58 (1H, m), 7.68 (1H, s), 8.94 (1H, s); ^{13}C NMR (100.6 MHz, pyridine-d_5) δ 22.1, 23.6, 23.9, 25.9, 26.2, 27.6, 29.5, 42.8, 56.0 (2C), 56.6, 76.3, 79.5, 81.5, 97.4, 98.0, 109.2, 112.3, 119.2, 124.1, 125.0, 149.7, 152.1, 153.1, 158.7, 163.3, 164.1, 202.2; HRMS (FAB, NBA, PEG400 matrix) Calcd for $C_{28}H_{33}O_8$ $[M+H]^+$ 497.2175, found 497.2194.

4.1.25. (1*S*,4a*R*,6a*R*,12b*S*)-1,3,4,4a,5,6,6a,12b-Octahydro-1,4a-dihydroxy-4,4,6a,12b-tetramethyl-9-(4′-methoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one (23b). To a mixture solution of **22** (210 mg, 835 μmol) and **11b** (273 mg, 1.25 mmol) in THF (8.35 mL) at room temperature was added L-proline (192 mg, 1.67 mmol), and the resultant mixture was warmed to 65 °C for 16 h. The solution was cooled to room temperature, and then filtered through celite, washing with $CHCl_3$ (3×30 mL). The filtrate was washed with H_2O (100 mL), and dried over Na_2SO_4, filtered and concentrated. Flash chromatography (hexane/EtOAc 1/1) provided **23b** (235 mg, 519 μmol, 62% yield) as a yellow crystal: $[\alpha]_D^{23}$ +140.0° (*c* 0.62, $CHCl_3$); TLC R_f 0.53 ($CHCl_3$/MeOH 10/1); mp 108 °C; IR (KBr) 3440, 3380, 1699, 1684, 1552, 1514, 1454, 1259 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (3H, s), 0.91 (3H, s), 0.98 (1H, m), 1.17 (3H, s), 1.46 (3H, s), 1.60 (3H, m), 1.83 (1H, m), 2.02 (2H, m), 2.40 (1H, m), 3.74 (3H, s), 4.16 (1H, brs), 6.29 (1H, s), 6.33 (1H, s), 6.85 (2H, d, J=9.0 Hz), 7.64 (2H, d, J=9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6, 23.9, 25.3, 27.3, 27.6, 27.7, 30.2, 34.2, 38.1, 46.8, 55.2, 71.1, 76.9, 80.7, 96.4, 100.2, 110.8, 114.2 (2C), 123.5, 127.0 (2C), 141.6, 159.7, 161.7, 163.0, 163.1; HRMS Calcd for $C_{27}H_{33}O_6$ $[M+H]^+$ 453.2277, found 453.2271.

4.1.26. (4a*R*,6a*R*,12b*R*)-3,4,4a,5,6,6a,12b-Heptahydro-4a-hydroxy-4,4,6a,12b-tetramethyl-9-(4′-methoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-1,11(3*H*)-dione (1-keto-23b). To a solution of **23b** (21.8 mg, 48.2 μmol) in CH_2Cl_2 (200 μL) at room temperature was added 4-methylmorpholine *N*-oxide (11.3 mg, 96.4 μmol) and tetrapropylammonium perruthenate (7.6 mg, 21.7 μmol),

and the mixture was stirred for 15 min. The resultant mixture was concentrated, and flash chromatography (CH_2Cl_2/MeOH 20/1) furnished 1-keto-**23b** (21.7 mg, 48.2 μmol, 100% yield) as a yellow crystal: $[\alpha]_D^{22}$ +162.9° (*c* 0.41, $CHCl_3$); TLC R_f 0.32 (CH_2Cl_2/MeOH 20/1); mp 220 °C; IR (KBr) 3440, 1713, 1551, 1516, 1259 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (3H, s), 1.19 (3H, s), 1.53 (3H, s), 1.64 (3H, s), 1.69 (1H, ddd, *J*=14.0, 7.0, 5.5 Hz), 1.83 (1H, ddd, *J*=14.5, 5.0, 2.5 Hz), 1.94 (1H, dd, *J*=14.0, 4.0 Hz), 2.02 (1H, m), 2.06 (1H, ddd, *J*=14.0, 10.0, 5.0 Hz), 2.31 (1H, dt, *J*=14.0, 5.0 Hz), 2.61 (1H, ddd, *J*=14.5, 7.0, 5.0 Hz), 2.81 (1H, ddd, *J*=14.5, 10.0, 5.5 Hz), 3.86 (3H, s), 6.34 (1H, s), 6.94 (2H, d, *J*=9.0 Hz), 7.76 (2H, d, *J*=9.0 Hz), 7.45 (1H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.4, 25.7, 26.7, 27.3, 28.0, 33.7, 36.4, 37.1, 37.7, 55.5, 57.1, 79.1, 79.5, 95.7, 100.7, 114.3 (2C), 119.4, 123.9, 127.3 (2C), 133.7, 160.4, 161.7, 161.8, 162.6, 211.0; HRMS Calcd for $C_{27}H_{31}O_6$ $[M+H]^+$ 451.2121, found 451.2078.

4.1.27. (1*R*,4a*R*,6a*R*,12b*S*)-1,3,4,4a,5,6,6a,12b-Octahydro-1,4a-dihydroxy-4,4,6a,12b-tetramethyl-9-(4′-methoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one (25b). A solution of $NaBH(OAc)_3$ was prepared by adding $NaBH_4$ (15.9 mg, 420 μmol) to glacial acetic acid (420 μL) while keeping the temperature below 20 °C (ice bath). After the H_2 evolution ceased, a solution of 1-keto-**23b** (18.9 mg, 42.0 μmol) in THF (840 μL) was added in one portion and the reaction mixture was stirred for 1.5 h at room temperature, and then quenched with 0.2 N HCl (5 mL). 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 (hexane/EtOAc 1/2) furnished **25b** (18.6 mg, 41.2 μmol, 98% yield) as a yellow crystal: $[\alpha]_D^{23}$ +2.4° (*c* 0.34, $CHCl_3$); TLC R_f 0.24 ($CHCl_3$/MeOH 20/1); mp 90–95 °C; IR (KBr) 3430, 1691, 1558, 1512, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, s), 1.00 (3H, s), 1.17 (1H, dt, *J*=13.0, 3.5 Hz), 1.33 (3H, s), 1.56 (3H, s), 1.69 (1H, s), 1.73 (1H, ddt, *J*=13.0, 6.5, 3.5 Hz), 1.74 (1H, ddd, *J*=13.0, 6.0, 2.0 Hz), 1.80 (1H, dddd, *J*=13.0, 10.0, 3.5, 2.0 Hz), 1.94 (1H, ddd, *J*=13.0, 3.5, 2.0 Hz), 1.95 (1H, ddd, *J*=14.0, 13.0, 5.0 Hz), 2.07 (1H, ddd, *J*=14.0, 5.0, 2.0 Hz), 2.33 (1H, dt, *J*=14.0, 6.0 Hz), 3.85 (3H, s), 4.36 (1H, dd, *J*=10.0, 6.5 Hz), 6.30 (1H, s), 6.92 (2H, d, *J*=9.0 Hz), 6.99 (1H, s), 7.73 (2H, d, *J*=9.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.2, 23.6, 24.6, 27.1, 28.2, 28.9, 34.6, 35.6, 37.9, 49.9, 55.4, 71.6, 77.3, 81.1, 95.8, 99.6, 114.2, 114.7 (2C), 123.9, 127.2 (2C), 140.4, 160.0, 161.7, 161.9, 162.6; HRMS Calcd for $C_{27}H_{33}O_6$ $[M+H]^+$ 453.2277, found 453.2280.

4.1.28. (1*R*,4a*R*,6a*R*,12*R*,12a*R*,12b*S*)-1-Acetoxy-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-4a,12,12a-trihydroxy-4,4,6a,12b-tetramethyl-9-(4′-methoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one (26b) and (1*R*,4a*R*,6a*R*,12*S*,12a*S*,12b*S*)-12,12a-epoxy-1,3,4,4a,5,6,6a,12,12a,12b-decahydro-1,4a-dihydroxy-4,4,6a,12b-tetramethyl-9-(4′-methoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one (27b). A solution of **25b** (160 mg, 354 μmol) in CH_2Cl_2:KH_2PO_4–Na_2HPO_4 buffer (prepared by dissolving 340 mg of KH_2PO_4 and 355 mg of Na_2HPO_4 in 100 mL of total aqueous solution)=5:1 (17.7 mL) at room temperature was treated with 32% peracetic acid in AcOH (750 μL, 3.54 mmol), and the reaction mixture was stirred for 2 days, quenched with $NaHSO_3$ (400 mg). The mixture was then extracted with $CHCl_3$ (3×30 mL) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Flash chromatography ($CHCl_3$) furnished **26b** (70.6 mg, 134 μmol, 38% yield) and **27b** (55.3 mg, 118 μmol, 33% yield) as colorless crystals. **26b**: $[\alpha]_D^{23}$ +112.9° (*c* 0.56, $CHCl_3$); TLC R_f 0.47 (benzene/acetone 2/1); mp 206–207 °C; IR (KBr) 3440, 1728, 1674, 1633, 1574, 1514, 1257 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.96 (3H, s), 1.05 (3H, s), 1.09 (1H, m), 1.25 (3H, s), 1.45 (3H, s), 1.61–1.97 (4H, m), 2.05–2.17 (2H, m), 2.05 (3H, s), 2.56 (1H, dt, *J*=13.0, 4.6 Hz), 3.86 (3H, s), 4.64 (1H, brs), 5.00 (1H, s), 5.39 (1H, dd, *J*=9.9, 5.6 Hz), 6.35 (1H, s), 6.96 (2H, d, *J*=8.9 Hz), 7.73 (2H, d, *J*=8.9 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 18.6, 21.9, 22.6, 24.3, 24.9, 25.6, 27.1, 29.9, 33.7, 38.8, 48.0, 55.4, 61.7, 71.8, 78.2, 79.8, 83.5, 96.5, 99.9, 114.4 (2C), 123.0, 127.4 (2C), 160.4, 162.1, 164.3, 165.2, 170.7; HRMS Calcd for $C_{29}H_{36}O_9Na$ $[M+Na]^+$ 551.2257, found 551.2276, and **27b**: $[\alpha]_D^{23}$ −36.9° (*c* 0.51, $CHCl_3$); TLC R_f 0.37 (benzene/acetone 2/1); mp 113–114 °C; IR (KBr) 3460, 1695, 1633, 1574, 1514, 1261, 1178 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.88 (3H, s), 0.95 (3H, s), 1.23 (1H, m), 1.27 (3H, s), 1.65 (3H, s), 1.65–1.90 (5H, m), 1.97–2.07 (2H, m), 3.85 (3H, s), 4.60 (1H, dd, *J*=11.0, 5.0 Hz), 4.90 (1H, s), 6.30 (1H, s), 6.93 (2H, d, *J*=8.6 Hz), 7.74 (2H, d, *J*=8.6 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.5, 23.6, 24.1, 25.8, 26.0, 26.3, 30.5, 35.5, 36.2, 49.9, 55.4, 70.9, 73.2, 79.7, 84.0, 88.4, 96.0, 98.1, 114.2 (2C), 123.6, 127.3 (2C), 160.5, 161.8, 164.0, 164.4; HRMS Calcd for $C_{27}H_{32}O_7Na$ $[M+Na]^+$ 491.2046, found 491.2060.

4.1.29. (1*R*,4a*R*,6a*R*,12a*R*,12b*S*)-1,3,4,4a,5,6,6a,12,12a,12b-Decahydro-1,4a,12a-trihydroxy-4,4,6a,12b-tetramethyl-9-(4′-methoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-11-one (29b). At room temperature a solution of **26b** (6.3 mg, 11.9 μmol) in $ClCH_2CH_2Cl$ (600 μL) was treated with Et_3SiH (22.9 μL, 143 μmol) and TFA (9.2 μL, 119 μmol) and the reaction mixture was stirred for 3 h at 50 °C, quenched with saturated aqueous $NaHCO_3$ (3 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 mixture of 12-deoxydiol and **29b** was used for the next step without purification.

To a solution of the crude mixture in MeOH (600 μL) at room temperature was added K_2CO_3 (3.3 mg, 24.0 μmol). The solution was stirred for 6 h at room temperature, quenched with saturated aqueous NH_4Cl (3 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 ($CHCl_3$/MeOH 20/1) furnished **29b** (4.6 mg, 9.79 μmol, 82% yield) as a colorless crystal; $[\alpha]_D^{24}$ +65.5° (*c* 0.11, $CHCl_3$/MeOH 10/1); TLC R_f 0.31 ($CHCl_3$/MeOH 10/1); mp 257–258 °C; IR (KBr) 3392, 1699, 1643, 1583, 1514, 1255, 1215, 1176 cm^{-1}; ^1H NMR (400 MHz, pyridine-d_5) δ 1.13 (3H, s), 1.14 (3H, s), 1.21 (1H, ddd, *J*=13.5, 4.0, 2.5 Hz), 1.42 (3H, s), 1.53 (3H, s), 1.87 (2H, m), 2.00 (1H, m), 2.06 (1H, m), 2.15 (1H, m), 2.41 (1H, dt, *J*=13.5, 5.0 Hz), 2.93 (1H, m), 3.39 (1H, d, *J*=18.0 Hz), 3.66 (3H, s), 4.22 (1H, d, *J*=18.0 Hz), 5.27 (1H, dd, *J*=11.0, 5.0 Hz), 6.65 (1H, s), 6.99 (2H, d,

J=9.0 Hz), 7.49 (1H, s), 7.83 (2H, d, J=9.0 Hz), 8.54 (1H, s); ^{13}C NMR (100.6 MHz, pyridine-d_5) δ 17.0, 24.6, 24.7, 26.4, 27.9, 30.0, 30.1, 30.7, 35.9, 39.4, 49.2, 55.4, 69.2, 78.3, 81.0, 82.5, 97.4, 99.2, 114.8 (2C), 124.9, 127.3 (2C), 158.2, 161.9, 163.4, 164.6; HRMS Calcd for $C_{27}H_{35}O_7$ $[M+H]^+$ 471.2383, found 471.2396.

4.1.30. (4a*R*,6a*R*,12a*R*,12b*S*)-3,4,4a,5,6,6a,12,12a,12b-Nonahydro-4a,12a-dihydroxy-4,4,6a,12b-tetramethyl-9-(4′-methoxyphenyl)-2*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-1,11(3*H*)-dione (30b). To a solution of **29b** (37.6 mg, 80.0 μmol) in CH_2Cl_2 (4.0 mL) at room temperature was added 4-methylmorpholine *N*-oxide (18.7 mg, 160 μmol) and tetrapropylammonium perruthenate (2.8 mg, 8.00 μmol), and the mixture was stirred for 40 min. The resultant mixture was concentrated, and preparative TLC ($CHCl_3$/MeOH 20/1) furnished **30b** (37.4 mg, 80.0 μmol, 100% yield) as a colorless powder: $[\alpha]_D^{22}$ +126.7° (*c* 0.15, $CHCl_3$/MeOH 10/1); TLC R_f 0.50 ($CHCl_3$/MeOH 15/1); mp 256–257 °C; IR (KBr) 3443, 1709, 1641, 1583, 1516, 1254 cm^{-1}; ^{1}H NMR (400 MHz, pyridine-d_5) δ 1.14 (3H, s), 1.19 (3H, s), 1.40 (3H, s), 1.45 (3H, s), 1.70 (1H, ddd, J=14.0, 8.5, 5.5 Hz), 1.82 (1H, m), 1.84 (1H, m), 1.93 (1H, dt, J=14.0, 4.0 Hz), 2.04 (1H, ddd, J=14.0, 7.5, 6.0 Hz), 2.71 (1H, ddd, J=16.0, 7.5, 5.5 Hz), 2.82 (1H, ddd, J=16.0, 8.5, 6.0 Hz), 2.85 (1H, m), 3.17 (1H, d, J=17.5 Hz), 3.68 (3H, s), 4.25 (1H, d, J=17.5 Hz), 6.71 (1H, s), 7.02 (2H, d, J=9.0 Hz), 7.58 (1H, s), 7.87 (2H, d, J=9.0 Hz), 8.70 (1H, s); ^{13}C NMR (100.6 MHz, pyridine-d_5) δ 19.5, 23.6, 26.4, 27.0, 27.5, 27.6, 29.5, 36.5, 36.6, 38.2, 55.4, 58.0, 76.8, 80.7, 81.4, 97.0, 97.9, 114.8 (2C), 124.7, 127.3 (2C), 158.4, 161.9, 163.1, 163.9, 212.6; HRMS Calcd for $C_{27}H_{32}O_7Na$ $[M+Na]^+$ 491.2046, found 491.2043.

4.1.31. (4a*R*,6a*R*,12a*R*,12b*S*)-4a,6,6a,12,12a,12b-Hexahydro-4a,12a-dihydroxy-4,4,6a,12b-tetramethyl-9-(4′-methoxyphenyl)-4*H*,11*H*-naphtho[2,1-*b*]pyrano[3,4-*e*]pyran-1,11(5*H*)-dione ((+)-arisugacin B, 1b). A solution of 226 μmol of KDA was prepared by adding *n*-butyllithiun (142 μL, 1.59 M in *n*-hexane, 100 μmol) to a solution of potassium *t*-butoxide (26.7 mg, 226 μmol) and diisopropylamine (32.7 μL, 233 μmol) in THF (450 μL) at −78 °C and stirring for 15 min. To this was added a solution of ketone **30b** (32.1 mg, 68.5 μmol) in THF (1.64 mL) containing HMPA (254 μL). The mixture was stirred for 10 min at −78 °C and for 30 min at −20 °C and then treated with a solution of phenylselenenyl bromide (49.5 mg, 205 μmol) in THF (440 μL) containing HMPA (44 μL). The resultant mixture was stirred for 15 min at −20 °C, and then for 30 min at room temperature, quenched with saturated aqueous NH_4Cl (5 mL) and extracted with Et_2O (3×10 mL), and the combined organic layers were washed with saturated aqueous NaCl (20 mL). The organic solution was dried over Na_2SO_4, filtered and concentrated. The crude mixture was used for the next step without purification.

A solution of the crude mixture (68.5 μmol) in THF (3.4 mL) containing acetic acid (340 μL) at 0 °C was treated with 30% H_2O_2 (40 μL, 411 μmol) and the mixture was stirred for 15 min at 0 °C, and then warmed to room temperature, where stirring was continued for an additional 75 min. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), and extracted with $CHCl_3$ (3×10 mL) and the combined extracts were dried over Na_2SO_4, filtered and concentrated. Preparative TLC ($CHCl_3$/MeOH 30/1) furnished (+)-arisugacin B (**1b**) (14.6 mg, 31.3 μmol, 46% yield) as a colorless solid: $[\alpha]_D^{24}$ +168.5° (*c* 0.10, $CHCl_3$/MeOH 10/1); TLC R_f 0.41 ($CHCl_3$/MeOH 20/1); mp >300 °C; IR (KBr) 3508, 3371, 1705, 1674, 1635, 1516, 1402, 1254, 1209, 1174, 1119, 1024 cm^{-1}; ^{1}H NMR (400 MHz, pyridine-d_5) δ 1.17, (3H, s), 1.28 (3H, s), 1.43 (3H, s), 1.47 (3H, s), 1.87 (1H, ddd, J=12.5, 6.5, 3.5 Hz), 1.89 (1H, m), 1.95 (1H, m), 2.88 (1H, ddd, J=13.0, 12.5, 4.5 Hz), 3.14 (1H, d, J=17.5 Hz), 3.68 (3H, s), 4.32 (1H, d, J=17.5 Hz), 5.94 (1H, d, J=10.0 Hz), 6.26 (1H, d, J=10.0 Hz), 6.74 (1H, s), 7.03 (2H, d, J=9.5 Hz), 7.66 (1H, s), 7.88 (2H, d, J=9.5 Hz), 8.92 (1H, s); ^{13}C NMR (100.6 MHz, pyridine-d_5) δ 22.1, 23.6, 23.9, 25.9, 26.2, 27.6, 29.5, 42.8, 55.5, 56.6, 76.3, 79.5, 81.5, 97.1, 98.0, 114.9 (2C), 124.2, 124.8, 127.4 (2C), 153.1, 158.6, 162.0, 163.3, 164.0, 202.2; HRMS Calcd for $C_{27}H_{31}O_7$ $[M+H]^+$ 467.2070, found 467.2078.

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Bis-cephalezomines A–E from *Cephalotaxus harringtonia* var. *nana*

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Abstract—Five new dimeric *Cephalotaxus* alkaloids, bis-cephalezomines A–E (**1**–**5**), have been isolated from the leaves of *Cephalotaxus harringtonia* var. *nana*, and the structures and stereochemistry were elucidated on the basis of spectroscopic data including 2D NMR and FABMS/MS spectra, and chemical means.

Cephalotaxus alkaloids are a family of cytotoxic heterocyclic natural products with unique ring systems and elaborated by trees of the genus *Cephalotaxus* (Cephalotaxaceae), some of which showed antileukemic activity.[1] Recently, we have isolated 12 new cytotoxic alkaloids, cephalezomines A~M,[2] from the leaves of *Cephalotaxus harringtonia* var. *nana* and a novel pentacyclic alkaloid, cephalocyclidin A,[3] from the fruits of the same plant. Our continuing search for structurally unique and biogenetically interesting *Cephalotaxus* alkaloids resulted in the isolation of five new dimeric alkaloids, bis-cephalezomines A–E (**1**–**5**), consisting of two cephalotaxine skeletons from the leaves of *C. harringtonia* var. *nana*. In this paper we describe the isolation and structure elucidation of **1**–**5**.

The leaves of *C. harringtonia* var. *nana* were extracted with MeOH, and the MeOH extract was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials adjusted at pH 10 with sat. Na_2CO_3 aq. were partitioned with $CHCl_3$. $CHCl_3$-soluble materials were subjected to LH-20 column chromatography ($CHCl_3$/MeOH, 1:1) followed by silica gel column chromatography ($CHCl_3$/MeOH, 30:1→MeOH), and then C_{18} HPLC (35–45% CH_3CN/0.1% TFA) to afford bis-cephalezomines A (**1**, 0.0001%), B (**2**, 0.0001%), C (**3**, 0.0001%), D (**4**, 0.00004%), and E (**5**, 0.00004%) together with cephalotaxidine[4] (**6**, 0.0005%).

Bis-cephalezomine A (**1**) showed the pseudomolecular ion peak at *m/z* 1089 $(M+H)^+$ in the FABMS, and the molecular formula, $C_{57}H_{72}N_2O_{19}$, was established by HRFABMS [*m/z* 1089.4780, $(M+H)^+$, Δ −2.7 mmu]. IR absorptions implied the presence of hydroxyl, ester carbonyl, and amide carbonyl (3580, 1740, and 1650 cm^{-1}, respectively) functionalities. ^1H and ^{13}C NMR data (Table 1) revealed 57 carbon signals due to 15 sp^2 and six sp^3 quaternary carbons, six sp^2 methines, six sp^3 methines, 16 sp^3 methylenes, and eight methyl groups. Among them, two sp^3 methylene (δ_C 45.6; δ_H 2.60 and 2.68; δ_C 39.1; δ_H 3.04 and 3.83), two sp^3 quaternary carbons (δ_C 71.5 and 70.0), one sp^3 methine (δ_C 62.4; δ_H 3.29), and one sp^2 quaternary carbon (δ_C 176.1) were ascribed to those bearing a nitrogen. Since 13 out of 23 elements of unsaturation were accounted for, **1** was inferred to possess 10 rings. The gross structure of **1** was elucidated by analyses of 2D NMR data including ^1H–^1H COSY, HOHAHA, HMQC, and HMBC spectra in CD_3OD (Fig. 1). Each pair of the observed ^1H and ^{13}C NMR signals seemed to be due to each half moiety (parts A and B) of a dimeric compound.

In part A, connectivities of C-3 to C-4, C-6–C-8, C-10 to C-11, and C-1″–C-3″ were deduced from ^1H–^1H COSY and HOHAHA correlations. In the HMBC spectrum, long-range ^1H–^{13}C correlations (Fig. 1) indicated that **1** possessed a cephalotaxine-type framework. HMBC cross-peaks of H-3″ to C-1′ and C-1″, H_3-OMe (5′) to C-4′, and H-5″ and H-6″ to C-3″ revealed the presence of the methyl ester of 2-hydroxy-2-(4-hydroxyisohexyl)-butanedioic acid. The connectivity between C-3 and C-1′ was indicated by HMBC correlations of H-3 and H-3′ to C-1′. On the other hand, the corresponding ^1H–^1H COSY, HOHAHA, and HMBC correlations were also observed for part B (Fig. 1). HMBC correlations of H-3‴ to C-1‴ and C-1⁗, H_3-OMe (5‴) to C-4‴, and H-4⁗ and H-5⁗ to C-2⁗ revealed the presence of

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Table 1. ^{1}H NMR data (δ_H) of bis-cephalezomines A–E (**1**–**5**) in $CDCl_3$ at 300 K

	1		**2**		**3**		**4**		**5**	
	Part A[a]	Part B[a]	Part A	Part B	Part A	Part B	Part A	Part B	Part A	Part B
1(20)	4.96 s	4.69 s	4.97 s	4.68 s	4.95 s	4.70 s	4.97 s	4.71 s	4.95 s	4.68 s
3(22)	5.95 d (10.0)	5.89 d (9.2)	5.94 d (10.1)	5.90 d (9.4)	5.96 d (10.0)	5.91 d (10.6)	5.96 d (9.8)	5.93 d (9.3)	5.95 d (9.8)	5.92 d (9.5)
4(23)	3.68 m	3.52 m	3.71 d (10.1)	3.51 m	3.71 d (10.0)	3.51 d (10.6)	3.69 d (10.0)	3.53 m	3.69 m	3.52 m
6(25)a	1.70 m	1.46 m	1.70 m	1.46 m	1.72 m	1.56 m	1.70 m	1.50 m	1.71 m	1.49 m
6(25)b	1.70 m	1.60 m	1.70 m	1.60 m	1.72 m	1.62 m	1.70 m	1.57 m	1.71 m	1.60 m
7(26)a	0.79 m		0.79 m		0.88 m		0.82 m		0.81 m	
7(26)b	1.54 m	2.68 m	1.53 m	2.68 m	1.60 m	2.61 m	1.55 m	2.70 m	1.56 m	2.69 m
8(27)b	3.29 m		3.29 m		3.31 m		3.32 m		3.30 m	
10(29)a	2.68 m	3.83 m	2.68 m	3.83 m	2.70 m	3.84 ddd (12.7, 12.7, 6.6)	2.70 m	3.86 m	2.69 m	3.84 ddd (12.6, 12.6, 6.6)
10(29)b	2.60 m	3.04 m	2.59 m	3.05 m	2.61 m	3.10 m	2.60 m	3.07 m	2.60 m	3.06 m
11(30)a	2.31 m	2.54 m	2.33 m	2.54 m	2.34 m	2.56 ddd (12.2, 6.6, 2.5)	2.33 m	2.63 m	2.32 m	2.55 m
11(30)b	3.06 m	3.17 m	3.05 m	3.17 m	3.07 m	3.18 ddd (12.7, 12.2, 6.6)	3.07 m	3.19 m	3.09 m	3.18 m
14(33)	6.54 s	6.51 s	6.54 s	6.51 s	6.56 s	6.53 s	6.55 s	6.52 s	6.54 s	6.52 s
17(36)	6.56 s	6.56 s	6.56 s	6.56 s	6.57 s	6.57 s	6.60 s	6.58 s	6.57 s	6.57 s
18(37)a	5.86 d (1.3)	5.86 d (1.4)	5.86 d (1.3)	5.86 d (1.4)	5.88 d (1.1)	5.88 d (1.1)	5.88 s	5.83 s	5.88 d (1.2)	5.86 s
18(37)b	5.97 d (1.3)	5.89 d (1.4)	5.97 d (1.3)	5.88 d (1.4)	6.00 d (1.2)	5.90 d (1.3)	5.99 s	5.90 s	5.99 d (1.2)	5.90 d (1.1)
19(38)Me	3.66 s	3.62 s	3.65 s	3.63 s	3.71 s	3.67 s	3.67 s	3.64 s	3.66 s	3.63 s
3′ (3‴)a	1.90 d (16.4)	2.05 d (16.4)	1.89 d (16.4)	2.04 d (16.5)	1.91 d (16.5)	2.07 d (16.5)	1.92 d (16.4)	3.48 d (8.2)	1.89 d (16.4)	2.06 d (16.4)
3′ (3‴)b	2.24 d (16.4)	2.34 d (16.4)	2.26 d (16.4)	2.31 d (16.5)	2.28 d (16.5)	2.35 d (16.5)	2.26 d (16.4)		2.26 d (16.4)	2.30 d (16.4)
3′ (3‴)Me	3.55 s	3.56 s	3.53 s	3.57 s	3.56 s	3.59 s	3.58 s	3.57 s	3.54 s	3.57 s
1″(1⁗)a	1.38 m	1.57 m	1.56 m	1.38 m	1.58 m	1.58 m	1.42 m	1.49 m	1.41 m	1.41 m
1″(1⁗)b	1.38 m	1.57 m	1.56 m	1.38 m	1.58 m	1.58 m	1.42 m	1.85 ddd (13.4, 13.4, 4.0)	1.41 m	1.41 m
2″ (2⁗)a	1.17 m	1.52 m	1.56 m	1.11 m	1.60 m	1.60 m	1.14 m	0.88 m	0.95 m	1.13m
2″ (2⁗)b	1.37 m	1.52 m	1.56 m	1.35 m	1.60 m	1.60 m	1.37 m	1.21 m	0.95m	1.41 m
3″ (3⁗)	1.38 m			1.32 m			1.37 m	1.37 m	1.27 m	1.35 m
4″ (4⁗)		1.13 s	1.14 s		1.15 s	1.16 s		0.84 d (6.6)	0.73 d (6.6)	
5″ (5⁗)	1.16 s	1.12 s	1.12 s	1.15 s	1.14 s	1.14 s	1.18 s	0.82 d (6.6)	0.75 d (6.6)	1.16 s
6″ (6⁗)	1.16 s			1.15 s			1.18 s			1.17 s

[a] Parts A and B indicate the partial structures as shown in Figure 1.

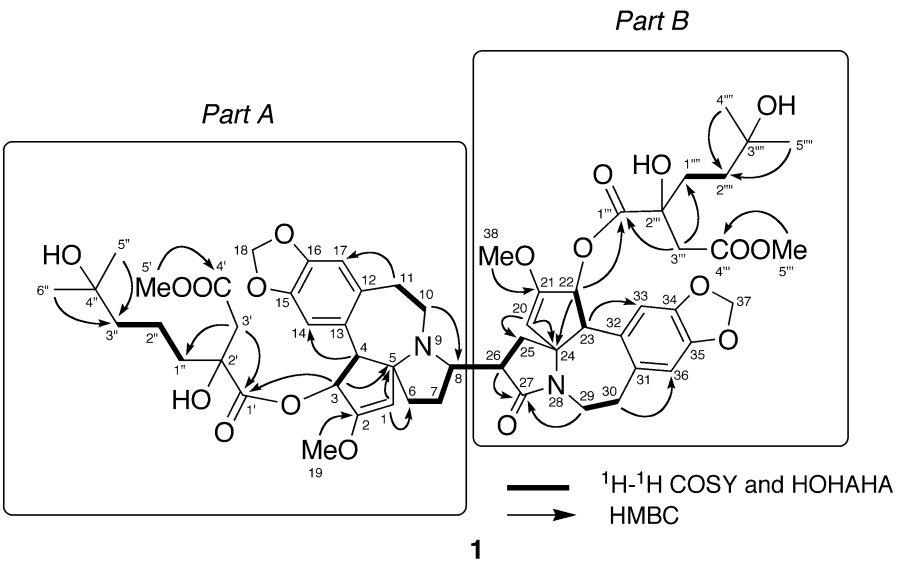
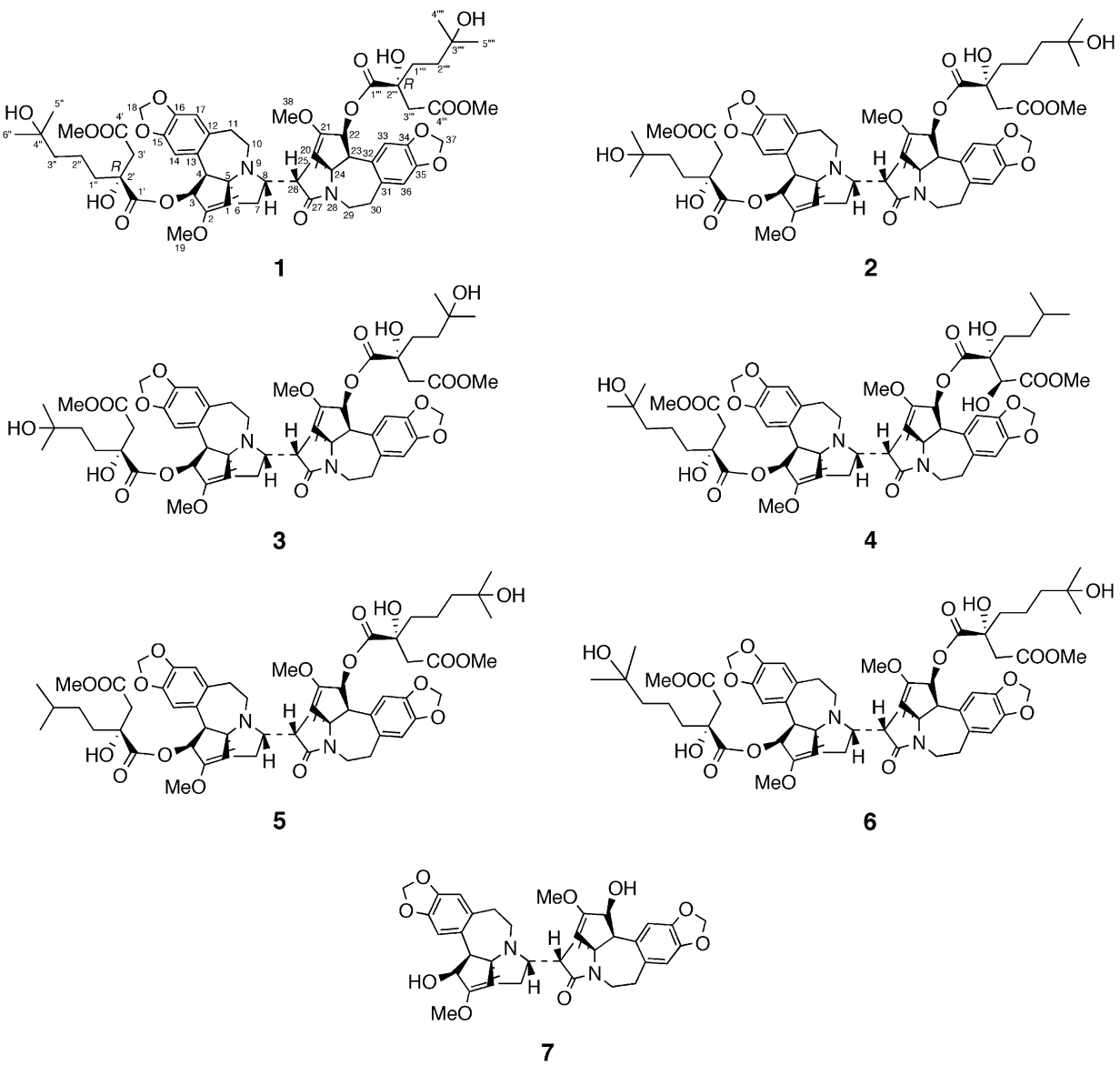


Figure 1. Selected 2D NMR correlations for bis-cephalezomine A (**1**).



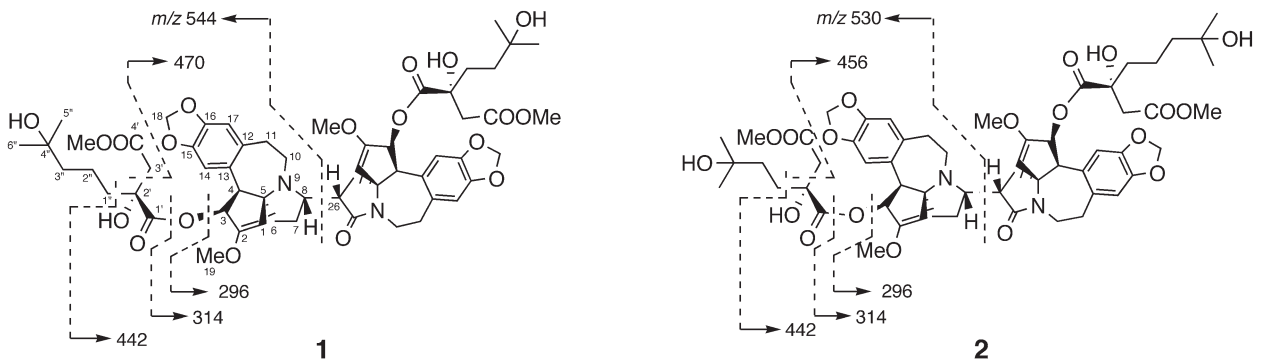


Figure 2. Fragmentation patterns observed in positive ion FABMS/MS spectrum of bis-cephalezomine A (**1**) (precursor ion *m/z* 544.6) and bis-cephalezomine B (**2**) (precursor ion *m/z* 530.6).

the methyl ester of 2-hydroxy-2-(3-hydroxyisopentyl)-butanedioic acid. In addition, HMBC correlations for H_2-29 and H-26 to C-27 (δ_C 176.1) suggested the presence of an amide carbonyl at C-27 such as cephalotaxinamide[5] in the part B. The connection of C-8 to C-26 between parts A and B was provided by $^1H-^1H$ COSY and HOHAHA correlations as shown in Figure 1. Thus, the gross structure of bis-cephalezomine A (**1**) was assigned as **1**.

Further evidence supporting the proposed structure of **1** was provided by tandem mass spectrometry through examination of the collision-induced dissociation (CID) mass spectrum of the $(M+H)^+$ ions. The positive ion FABMS spectra of **1** showed the product ion peak (*m/z* 544) generated by fission at C-8–C-26 bond between the two partial units A and B. In addition, the FABMS/MS fragmentation patterns corresponding to the part A indicated that the side chain at C-3 was the ester of 2-hydroxy-2-(4-hydroxyisohexyl)-butanedioic acid (Fig. 2).

The relative stereochemistry of **1** was deduced from ROESY correlations as shown in computer-generated 3D drawing (Fig. 3). The decacyclic core in **1** was elucidated to have the same relative stereochemistry as that of cephalotaxidine (**6**).[4] The absolute configurations of the cyclic core of **1** were derived from chemical correlations as follows. Spectroscopic data including optical rotation of a hydrolysate (**7**) prepared from **1** through hydrolysis with LiOH were identical with that derived from cephalotaxidine (**6**).[4] The CD spectrum for the molybdate complex of each dicarboxy acid moiety (C-1′–C-4′ and C-1‴–C-4‴) derived from the acid hydrolysates of **1** showed a negative Cotton effect at 270 nm ($\Delta\varepsilon_{270}$ −1.1),[6] indicating that the absolute configurations at C-2′ and C-2‴ of **1** were both *R*.

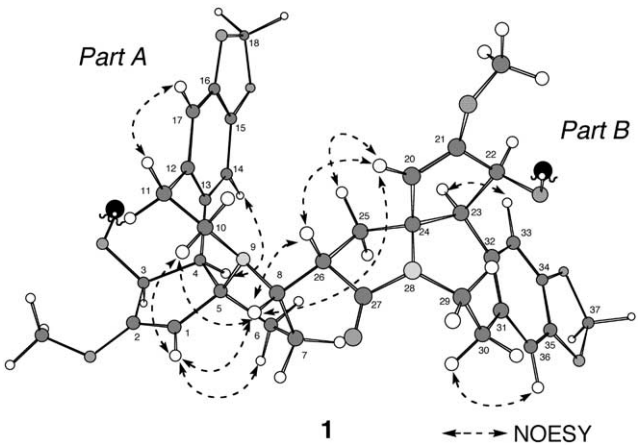


Figure 3. Selected ROESY correlations for bis-cephalezomine A (**1**). Two ester side chains are omitted for clarify.

The molecular formula of bis-cephalezomine B (**2**) was determined to be $C_{57}H_{72}N_2O_{19}$ by HRFABMS [*m/z* 1089.4812, $(M+H)^+$, Δ +0.5 mmu], which was the same as that of **1**. The IR spectrum implied the presence of hydroxyl (3580 cm^{-1}) and carbonyl (1740 and 1650 cm^{-1}) functionalities. ^1H and ^{13}C NMR data (Tables 1 and 2) suggested that **2** had the same cephalotaxine-type framework as **1**. The ^1H and ^{13}C NMR signals observed for **2** were also close to those of **1**. The positive ion FABMS spectra of **2** showed the product ion peak (*m/z* 530) generated by fission at C-8–C-26 bond between two partial units A and B. In addition, FABMS/MS fragmentation patterns corresponding to the part A indicated that the side chain at C-3 was the ester of 2-hydroxy-2-(3-hydroxyisopentyl)-butanedioic acid (Fig. 2). Therefore, the side chains of parts A and B in **1** and **2** were reversed for each other. The CD spectrum ($\Delta\varepsilon_{212}$ −19.5, $\Delta\varepsilon_{230}$ +2.5, $\Delta\varepsilon_{247}$ +2.7, and $\Delta\varepsilon_{291}$ −3.3) of **2** showed Cotton effects similar to that ($\Delta\varepsilon_{211}$ −22.7, $\Delta\varepsilon_{229}$ +2.9, $\Delta\varepsilon_{249}$ +3.3, and $\Delta\varepsilon_{292}$ −3.8) of bis-cephalezomine A (**1**), and the hydrolysate of **2** was identical with that prepared from **1**. Furthermore, the CD spectrum for the molybdate complex of the dicarboxy acid moiety (C-1′–C-4′ and C-1″–C-6″), which was derived from the acid hydrolysates of **2**, showed a negative Cotton effect at 270 nm ($\Delta\varepsilon_{270}$ −1.0),[6] indicating that the absolute configurations at C-2′ and C-2‴ of **2** were both *R*.

Bis-cephalezomine C {**3**, $[\alpha]_D$ −118° (*c* 0.5, MeOH)} showed the pseudomolecular ion at *m/z* 1075 $(M+H)^+$, and the molecular formula, $C_{56}H_{70}N_2O_{19}$, was established by HRFABMS [*m/z* 1075.4738, $(M+H)^+$, Δ +8.7 mmu]. IR absorptions were attributed to hydroxyl (3585 cm^{-1}) and carbonyl (1745 and 1665 cm^{-1}) groups, respectively. The FABMS spectrum of **3** showed a common fragment ion peak at *m/z* 530, characteristic for bis-cephalezomine B (**2**). ^1H and ^{13}C NMR data (Tables 1 and 2) in one of the two partial units A and B corresponded well to those of isoharringtonine.[7] The hydrolysate of **3** was identical with that prepared from bis-cephalezomine A (**1**), and the CD

Table 2. ^{13}C NMR data (δ_C) of bis-cephalezomines A–E (**1**–**5**) in $CDCl_3$ at 300 K

	1		**2**		**3**		**4**		**5**	
	Part A[a]	Part B[a]	Part A	Part B	Part A	Part B	Part A	Part B	Part A	Part B
1(20)	101.4	103.4	101.9	103.0	102.0	103.5	101.5	103.4	101.1	103.1
2(21)	157.5	158.4	157.2	158.6	157.3	158.4	157.6	158.7	157.7	158.6
3(22)	74.4	74.4	74.4	74.4	74.5	74.5	74.5	74.5	74.7	74.7
4(23)	56.6	59.2	56.6	59.1	56.8	59.2	56.7	59.0	56.7	59.2
5(24)	71.5	70.0	71.4	69.7	71.5	69.7	71.5	69.9	71.5	69.7
6(25)	42.4	36.7	42.3	36.5	42.4	36.5	42.5	34.7	42.5	36.6
7(26)	22.9	41.8	22.9	41.8	23.0	41.9	23.0	41.9	23.0	42.0
8(27)	62.4	176.1	62.3	176.2	62.4	176.2	62.4	176.0	62.5	176.3
10(29)	45.6	39.1	45.6	39.1	45.6	39.1	45.6	39.1	45.7	39.1
11(30)	31.3	30.1	31.2	30.3	31.3	30.2	31.4	30.3	31.3	30.2
12(31)	133.6	132.6	133.5	132.7	133.6	132.7	133.8	132.8	133.6	132.7
13(32)	129.0	126.1	128.8	126.1	129.0	126.2	129.1	125.8	129.1	126.2
14(33)	112.5	112.5	112.5	112.5	112.6	112.6	112.5	112.5	112.5	112.5
15(34)	145.4	146.1	145.4	146.1	145.5	146.2	145.4	146.2	145.4	146.2
16(35)	146.1	147.2	146.1	147.2	146.2	147.3	146.2	147.3	146.2	147.3
17(36)	109.3	110.0	109.3	110.0	109.4	110.1	109.4	110.4	109.3	110.1
18(37)	100.8	101.0	101.0	100.7	100.8	101.1	100.8	101.1	101.3	100.8
19(38)	57.6	57.4	57.7	57.3	57.6	57.3	57.6	57.4	57.7	57.4
1′ (1‴)	173.8	173.6	173.7	173.7	173.9	173.7	174.0	174.0	174.0	173.8
2′ (2‴)	74.6	74.7	74.7	74.7	74.7	74.8	74.6	74.6	74.4	74.5
3′ (3‴)	42.5	42.8	42.7	42.5	42.8	42.8	42.6	74.7	42.6	42.8
4′ (4‴)	170.2	170.3	170.2	170.3	170.3	170.3	170.4	170.4	170.4	170.5
3′ (3‴)-Me	51.5	51.5	51.5	51.5	51.6	51.6	51.5	51.5	51.5	51.6
1″ (1⁗)	39.1	33.2	33.3	39.1	33.1	33.2	38.8	33.0	36.7	39.1
2″ (2⁗)	17.9	36.7	36.8	17.8	36.8	36.9	17.9	31.5	31.6	17.9
3″ (3⁗)	43.7	70.0	70.7	43.6	70.1	70.1	43.8	28.5	28.0	43.7
4″ (4⁗)	70.8	28.8	29.0	70.0	28.6	28.8	70.6	22.7	22.3	70.8
5″ (5⁗)	29.0	29.2	29.5	28.7	29.6	29.6	29.3	22.7	22.6	29.1
6″ (6⁗)	29.5			29.3			29.7			29.3

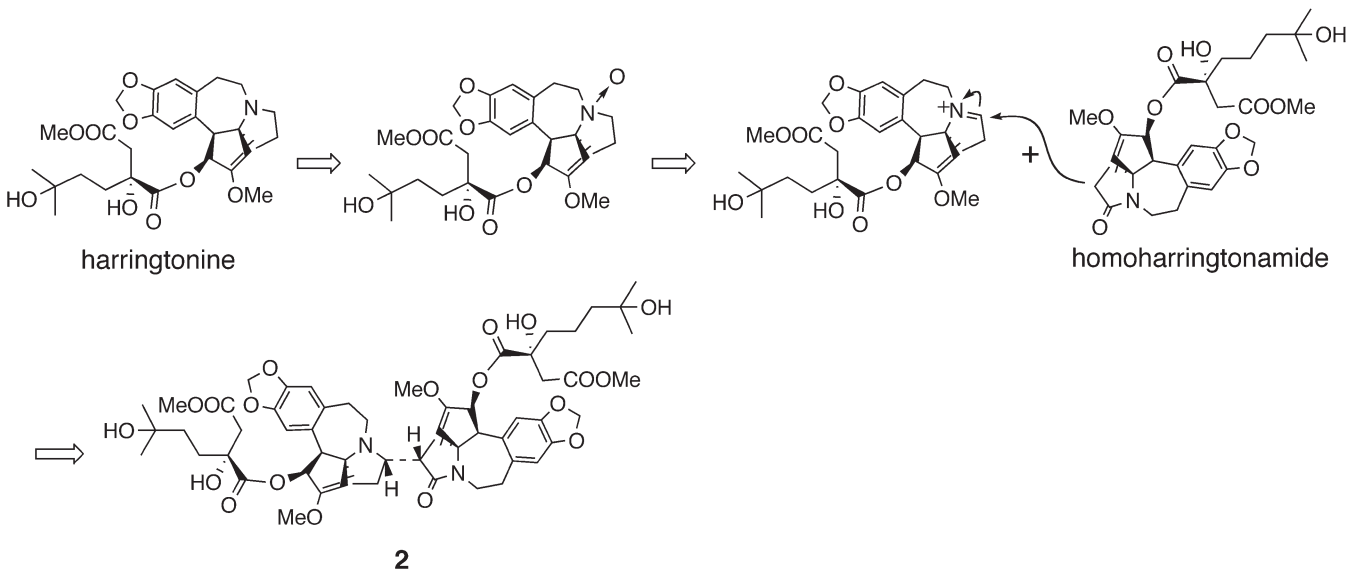
[a] Parts A and B indicate the partial structures as shown in Figure 1.

spectrum for the molybdate complex of each dicarboxy acid moiety (C-1′–C-4′ and C-1″–C-5″, and C-1‴–C-4‴ and C-1⁗–C-5⁗) derived from the acid hydrolysate showed a negative Cotton effect at 270 nm ($\Delta\varepsilon_{270}$ −1.1),[6] indicating that the absolute configurations at C-2′ and C-2‴ of **3** were both *R*.

Bis-cephalezomine D {**4**, $[\alpha]_D$ −86° (*c* 0.3, MeOH)} showed the pseudomolecular ion at *m/z* 1089 $(M+H)^+$, and the molecular formula, $C_{57}H_{72}N_2O_{19}$, was established by HRFABMS [*m/z* 1089.4830, $(M+H)^+$, Δ +2.3 mmu]. IR absorptions were attributed to hydroxyl (3585 cm^{-1}) and carbonyl (1745 and 1645 cm^{-1}) groups, respectively. The FABMS spectrum of **4** showed a common fragment ion peak at *m/z* 544, characteristic for biscephalezomine A (**1**). ^1H and ^{13}C NMR data (Tables 1 and 2) in one of the two parts corresponded well to those of isoharringtonine.[7] Since the FABMS spectrum of acetate of **4** showed the same fragment ion peak at *m/z* 544 as **1**, the side chains of parts A and B were elucidated to be 2-hydroxy-2-(4-hydroxy-isohexyl)-butanedioic acid and 2,3-hydroxy-2-isopentyl-butanedioic acid, respectively. To determine the absolute configuration at C-3‴, **4** was converted into its (*S*)- and (*R*)-2-methoxy-2-trifluoromethylphenylacetic acid (MTPA) esters. The values of Δδ [δ(*S*-MTPA ester) − δ(*R*-MTPA ester)] obtained from the ^1H NMR spectra of the MTPA esters suggested that the absolute configuration at C-3‴ of **4** was *S*.[8] Furthermore, the hydrolysate of **4** was identical with that prepared from bis-cephalezomine A (**1**) and the CD spectrum for the molybdate complex of each dicarboxy acid moiety (C-1′–C-4′ and C-1″–C-5″) derived from the acid hydrolysates of **4** showed a negative Cotton effect at 270 nm ($\Delta\varepsilon_{270}$ −1.1), indicating that the absolute configurations at C-2′ and C-2‴ of **4** were *R*.[6,9] Therefore the absolute stereochemistry of **4** was elucidated to be 3*S*, 4*S*, 5*R*, 8*S*, 2′*R*, 22*S*, 23*S*, 24*R*, 26*S*, and 2‴*R*.

Bis-cephalezomine E {**5**, $[\alpha]_D$ −146° (*c* 0.4, MeOH)} showed the pseudomolecular ion peak at *m/z* 1073 $(M+H)^+$ and the molecular formula, $C_{57}H_{72}N_2O_{18}$, was established by HRFABMS [*m/z* 1073.4820, $(M+H)^+$, Δ −3.8 mmu], which was smaller than those of **1**, **2**, and **4** by one oxygen atom. IR absorptions implied the presence of hydroxyl (3585 cm^{-1}) and carbonyl (1745 and 1655 cm^{-1}) functionalities. In the FABMS spectra, **5** gave the fragment ion at *m/z* 514, which was smaller than that (*m/z* 530) of **2** by one oxygen atom. In the ^1H NMR spectrum, two doublet methyl signals at δ 0.73 and 0.75 (*J*=6.6 Hz) were observed. Therefore, the side chain in the part A was elucidated to be 2-hydroxy-2-isopentylbutanedioic acid. Detailed analyses of the ^1H–^1H COSY, HOHAHA, HMQC, and HMBC spectra of **5** led to the presence of a dimer with cephalotaxine-type backbone like **1**–**4**, and of the side chains at C-3 and C-22. The CD spectrum ($\Delta\varepsilon_{216}$ −19.3, $\Delta\varepsilon_{229}$ +6.2, $\Delta\varepsilon_{248}$ +6.9, and $\Delta\varepsilon_{291}$ −7.1) of **5** was similar to those of **1**–**4**. Furthermore, the hydrolysate of **4** was identical with that prepared from bis-cephalezomine A (**1**) and the molybdate complex of the dicarboxy acid moiety (C-1′–C-4′ and C-1″–C-5″, and C-1‴–C-4‴ and C-1⁗–C-6⁗) derived from the acid hydrolysates of **5** showed a negative Cotton effect at 270 nm ($\Delta\varepsilon_{270}$ −1.3),[6] indicating that the absolute configurations at C-2′ and C-2‴ were both *R*.

A plausible biogenetic path for bis-cephalezomines A–E



Scheme 1. A plausible biogenetic path of bis-cephalezomine B (**2**).

(**1**–**5**) is proposed as shown in Scheme 1. A series of dimers might be derived by coupling of imine intermediate generated from the corresponding alkaloid such as homoharringtonine through Polonovski-type fragmentation,[10] with the corresponding amide derivatives such as homoharringtonamide[11] as shown in Scheme 1.

Bis-cephalezomines A–E (**1**–**5**) are new dimeric *Cephalotaxus* alkaloids consisting of two cephalotaxine-type skeletons with different side chains at C-3. Bis-cephalezomines A–E (**1**–**5**) exhibited cytotoxicity against murine lymphoma L1210 cells in vitro with IC_{50} values of 1.9, 1.9, 2.6, 3.1, and 3.7 μg/ml, respectively. These dimeric alkaloids exhibited relatively weak cytotoxicity, although each monomeric alkaloid corresponding to the parts A and B showed potent cytotoxicity.[1]

1. Experimental

1.1. General methods

^1H and 2D NMR spectra were recorded on a 600 MHz spectrometer at 300 K, while ^{13}C NMR spectra were measured on a 150 MHz spectrometer. The NMR samples of bis-cephalezomines A–E (**1**–**5**) were prepared by dissolving 1.0 mg each in 30 μl of $CDCl_3$ in 2.5 mm micro cells (Shigemi Co. Ltd) and chemical shifts were recorded using residual $CDCl_3$ (δ_H 7.26 and δ_C 77.0) as internal standards. Standard pulse sequences were employed for the 2D NMR experiments. COSY, HOHAHA, and NOESY spectra were measured with spectral widths of both dimensions of 4800 Hz, and 32 scans with two dummy scans were accumulated into 1 K data points for each of 256 t_1 increments. NOESY and HOHAHA spectra in the phase sensitive mode were measured with a mixing time of 800 and 30 ms, respectively. For HMQC spectra in the phase sensitive mode and HMBC spectra, a total of 256 increments of 1 K data points were collected. For HMBC spectra with *Z*-axis PFG, a 50 ms delay time was used for long-range C–H coupling. Zero-filling to 1 K for F_1 and multiplication with squared cosine-bell windows shifted in both dimensions were performed prior to 2D Fourier transformation. FABMS was measured by using glycerol as a matrix.

1.2. Material

The leaves of *Cephalotaxus harringtonia* var. *nana* were collected in Sapporo (Hokkaido, Japan) in 2001. The botanical identification was made by Mr N. Yoshida, Health Sciences University of Hokkaido. A voucher specimen has been deposited in the herbarium of Hokkaido University.

1.3. Extraction and isolation

The leaves of *C. harringtonia* var. *nana*(13 kg) were crashed and extracted with MeOH (20 L) three times and the extract (1016 g) was treated with 3% tartaric acid to adjust pH 2 and then partitioned with EtOAc. The aqueous layer was treated with sat. Na_2CO_3 aq. to adjust pH 10 and extracted with $CHCl_3$ to give a crude alkaloidal fraction (18.3 g), in which a portion (3.1 g) was subjected to LH-20 column chromatography ($CHCl_3$/MeOH, 1:1) followed by silica gel column chromatography ($CHCl_3$/MeOH, 30:1→MeOH), and then C_{18} HPLC (35–45% CH_3CN/0.1% TFA) to afford bis-cephalezomines A (**1**, 0.0001%), B (**2**, 0.0001%), C (**3**, 0.0001%), D (**4**, 0.00004%), and E (**5**, 0.00004%) together with cephalotaxidine (**6**, 0.0005%).

1.3.1. Bis-cephalezomine A (1). A colorless solid; $[\alpha]_D$ −151° (*c* 1.0, MeOH); IR (KBr) ν_{max} 3585, 2960, 1740, 1650, 1490. 1370, 1225, and 1035 cm^{-1}; UV (MeOH) λ_{max} 291 (ε 6400) and 209 (34700); ^1H and ^{13}C NMR data (Tables 1 and 2, respectively); CD (MeOH) $\Delta\varepsilon_{211}$ −22.7, $\Delta\varepsilon_{229}$ +2.9, $\Delta\varepsilon_{249}$ +3.3, and $\Delta\varepsilon_{292}$ −3.8; FABMS *m*/*z* 1089 $(M+H)^+$; HRFABMS *m*/*z* 1089.4780 (M+H; calcd for $C_{57}H_{73}N_2O_{19}$, 1089.4807).

1.3.2. Bis-cephalezomine B (2). A colorless solid; $[\alpha]_D$ −126° (*c* 1.0, MeOH); IR (KBr) ν_{max} 3580, 2960, 1740, 1650, 1490, 1370, 1225, and 1035 cm^{-1}; UV (MeOH) λ_{max}

291 (ε 5300) and 208 (28200); CD (MeOH) $\Delta\varepsilon_{212}$ −19.5, $\Delta\varepsilon_{230}$ +2.5, $\Delta\varepsilon_{247}$ +2.7, and $\Delta\varepsilon_{291}$ −3.3; ^{1}H and ^{13}C NMR data (Tables 1 and 2, respectively); FABMS *m/z* 1089 $(M+H)^+$; HRFABMS *m/z* 1089.4812 (M+H; calcd for $C_{57}H_{73}N_2O_{19}$, 1089.4807).

1.3.3. Bis-cephalezomine C (3). A colorless solid; $[\alpha]_D$ −118° (*c* 0.5, MeOH); IR (KBr) ν_{max} 3585, 2925, 1745, 1665, 1220, and 1030 cm^{-1}; UV (MeOH) λ_{max} 290 (ε 4000) and 207 (27000); CD (MeOH) $\Delta\varepsilon_{210}$ −22.3, $\Delta\varepsilon_{230}$ +1.7, $\Delta\varepsilon_{248}$ +2.1, and $\Delta\varepsilon_{290}$ −2.8; ^{1}H and ^{13}C NMR data (Tables 1 and 2, respectively); FABMS *m/z* 1075 $(M+H)^+$; HRFABMS *m/z* 1075.4738 (M+H; calcd for $C_{56}H_{71}N_2O_{19}$, 1075.4651).

1.3.4. Bis-cephalezomine D (4). A colorless solid; $[\alpha]_D$ −86° (*c* 0.3, MeOH); IR (KBr) ν_{max} 3585, 2920, 1745, 1645, 1035, and 720 cm^{-1}; UV (MeOH) λ_{max} 290 (ε 4800) and 207 (41000); CD (MeOH) $\Delta\varepsilon_{210}$ −8.2, $\Delta\varepsilon_{231}$ +0.2, $\Delta\varepsilon_{248}$ +0.3, and $\Delta\varepsilon_{292}$ −1.3; ^{1}H and ^{13}C NMR data (Tables 1 and 2, respectively); FABMS *m/z* 1089 $(M+H)^+$; HRFABMS *m/z* 1089.4830 (M+H; calcd for $C_{57}H_{73}N_2O_{19}$, 1089.4807).

1.3.5. Bis-cephalezomine E (5). A colorless solid; $[\alpha]_D$ −146° (*c* 0.4, MeOH); IR (KBr) ν_{max} 3585, 2925, 1745, 1655, 1440, 1200, and 890 cm^{-1}; UV (MeOH) λ_{max} 290 (ε 4300) and 208 (33600); CD (MeOH) $\Delta\varepsilon_{216}$ −19.3, $\Delta\varepsilon_{229}$ +6.2, $\Delta\varepsilon_{248}$ +6.9, and $\Delta\varepsilon_{291}$ −7.1; ^{1}H and ^{13}C NMR data (Tables 1 and 2, respectively); FABMS *m/z* 1073 $(M+H)^+$; HRFABMS *m/z* 1073.4820 (M+H; calcd for $C_{57}H_{73}N_2O_{18}$, 1073.4858).

1.3.6. Molybdate complexes of hydrolysates of bis-cephalezomines A–E (1–5) and cephalotaxidine (6). Each of bis-cephalezomines **1**–**5** and cephalotaxidine (**6**) (0.5 mg) was hydrolyzed with 3 N HCl (1 ml) under reflux for 4 days. After cooling, 3 M NH_4OH was added and the alkaline phase was extracted with $CHCl_3$. Excess NH_4OH was neutralized and the solvent was evaporated under reduced pressure. The residue was used directly in the preparation of solution for CD measurement, which contained 3 mM each hydrolysates and 2.7 mM Na molybdate. HCl and NaOH solution were added until pH 2.9–3.1 was reached. Measurements of CD spectra were carried out in a 1 mm cell 5 days after the solution had been prepared. CD data: bis-cephaloezomines A (**1**, $\Delta\varepsilon_{270}$ −1.1), B (**2**, $\Delta\varepsilon_{270}$ −1.0), C (**3**, $\Delta\varepsilon_{270}$ −1.1), D (**4**, $\Delta\varepsilon_{270}$ −1.1), E (**5**, $\Delta\varepsilon_{270}$ −1.3), and cephalotaxidine (**6**, $\Delta\varepsilon_{270}$ −1.2).

1.3.7. Hydrolysis of bis-cephalezomines A–E. To each solution of bis-cephalezomines A–E (**1**–**5**) (0.5 mg) in dioxane (0.2 ml) and H_2O (0.2 ml) was added lithium hydroxide (1.1 mg). After the reaction mixture was stirred at 40 °C for 1 h, it was poured into water and was extracted with $CHCl_3$ three times. The combined organic phase was washed with brine, dried over $MgSO_4$ and evaporated to give hydrolysate (**7**) of **1**–**5** (0.4 mg) as an amorphous powder, whose spectral data and $[\alpha]_D$ value were identical with those of that derived from cephalotaxidine by the same procedure. Compound **7**: a colorless solid; $[\alpha]_D$ −84° (*c* 0.1, MeOH); IR (KBr) ν_{max} 3585, 2920, 1655, 1560, and 1025 cm^{-1}; UV (MeOH) λ_{max} 290 (ε 3000) and 208 (17,000); ^{1}H NMR ($CDCl_3$) δ 4.85 (1H, s, H-1), 4.71 (1H, m, H-3), 3.59 (1H, d, 9.5, H-4), 1.76 (2H, m, H_2-6), 0.88 (1H, m, Ha-7), 1.56 (1H, m, Hb-7), 3.34 (1H, m, H-8), 2.70 (1H, m, Ha-10), 2.60 (1H, m, Hb-10), 2.31 (1H, m, Ha-11), 3.22 (1H, m, Hb-11), 6.59 (1H, s, H-14), 6.63 (1H, s, H-17), 4.56 (1H, s, H-20), 4.62 (1H, d, 8.3, H-22), 3.31 (1H, d, 8.3, H-23), 1.48 (1H, m, Ha-25), 1.47 (1H, m, Hb-25), 2.60 (1H, m, H-26), 3.84 (1H, m, Ha-29), 3.22 (1H, m, Hb-29), 2.60 (1H, m, Ha-30), 3.22 (1H, m, Hb-30); FABMS *m/z* 643 $(M+H)^+$; HRFABMS *m/z* 643.2651 (M+H; calcd for $C_{36}H_{39}N_2O_9$, 643.2646).

1.3.8. (*R*)- and (*S*)-MTPA esters of bis-cephalezomine D (4). To a solution of **4** (0.5 mg) in CH_2Cl_2 (50 μl) was added (−)- or (+)-MTPACl (1.1 μl), triethylamine (1.3 μl) and *N*,*N*-dimethylamino pyridine (0.2 mg). The mixture was allowed to stand at room temperature for 2 h. *N*,*N*-Dimethylamino-1,3-propandiamine (1.0 μl) was added, and after evaporation of solvent, the residue was applied to a silica gel column ($CHCl_3$–MeOH, 50:1→10:1) to give the (*S*)- or (*R*)-MTPA esters of **4** (0.6 mg, 87%).

(*R*)-MTPA ester of **4**. ^{1}H NMR ($CDCl_3$) δ 4.97 (1H, s, H-1), 5.97 (1H, d, 9.5, H-3), 3.70 (1H, d, 9.5, H-4), 1.71 (2H, m, H-6), 0.85 (1H, m, Ha-7), 3.32 (1H, m, H-8), 2.71 (1H, m, Ha-10), 2.60 (1H, m, Hb-10), 2.35 (1H, m, Ha-11), 3.09 (1H, m, Hb-11), 6.56 (1H, s, H-14), 6.59 (1H, s, H-17), 5.89 (1H, s, Ha-18), 5.99 (1H, s, Hb-18), 3.67 (1H, s, H-19), 1.92 (1H, d, 16.7, Ha-3′), 2.26 (1H, d, 16.3, Hb-3′), 3.58 (3H, s, H-3′COOMe), 1.35–1.45 (2H, m, H-1″), 1.14 (1H, m, Ha-2″), 1.35–1.45 (1H, m, Hb-2″), 1.35–1.45 (2H, m, H-3″), 1.19 (3H, s, H-5″), 1.18 (3H, s, H-6″), 4.73 (1H, s, H-20), 5.96 (1H, m, H-22), 3.56 (1H, d, 10.3, H-23), 1.52 (2H, m, H-25), 2.71 (1H, m, H-26), 3.85 (1H, m, Ha-29), 3.09 (1H, m, Hb-29), 2.61 (1H, m, Ha-30), 3.18 (1H, m, Hb-30), 6.54 (1H, s, H-33), 6.59 (1H, s, H-36), 5.88 (1H, s, Ha-37), 5.91 (1H, s, Hb-33), 3.64 (3H, s, H-38), 3.52 (1H, m, Ha-3‴), 1.34 (1H, m, H-1⁗), 0.91 (1H, m, Ha-2⁗), 1.18 (1H, m, Hb-2⁗), 1.38 (1H, m, H-3⁗), 0.80 (3H, d, 6.6, H-4⁗), 0.81 (3H, d, 6.6, H-5⁗), 7.42–7.60 (5H, m, H-MTPA); FABMS *m/z* 1306, $(M+H)^+$; HRFABMS *m/z* 1305.5160 (M+H; calcd for $C_{67}H_{80}N_2O_{21}F_3$, 1305.5207).

(*S*)-MTPA ester of **4**. ^{1}H NMR ($CDCl_3$) δ 4.98 (1H, s, H-1), 5.83–6.02 (1H, m, H-3), 3.68 (1H, m, H-4), 1.73 (2H, m, H-6), 0.76–0.92 (1H, m, Ha-7), 3.35 (1H, m, H-8), 2.52–2.75 (2H, m, H-10), 2.35 (1H, m, Ha-11), 3.11 (1H, m, Hb-11), 6.56–6.69 (1H, m, H-14), 6.56–6.69 (1H, m, H-17), 5.83–6.02 (2H, m, H-18), 3.66 (1H, s, H-19), 1.93 (1H, d, 16.5, Ha-3′), 2.27 (1H, m, Hb-3′), 3.59 (3H, s, H-3′COOMe), 1.35–1.45 (2H, m, H-1″), 1.14 (1H, m, Ha-2″), 1.28–1.42 (1H, m, Hb-2″), 1.28–1.42 (2H, m, H-3″), 1.19 (3H, s, H-5″), 1.18 (3H, s, H-6″), 4.72 (1H, s, H-20), 5.83–6.02 (1H, m, H-22), 3.56 (1H, m, H-23), 1.53 (2H, m, H-25), 2.52–2.75 (1H, m, H-26), 3.83 (1H, m, Ha-29), 3.11 (1H, m, Hb-29), 2.61 (1H, m, Ha-30), 3.21 (1H, m, Hb-30), 6.56–6.69 (1H, m, H-33), 6.56–6.69 (1H, m, H-36), 5.83–6.02 (2H, m, H-37), 3.66 (3H, s, H-38), 3.49 (1H, m, Ha-3‴), 1.30 (1H, m, H-1⁗), 0.88 (1H, m, Ha-2⁗), 1.10 (1H, m, Hb-2⁗), 1.25 (1H, m, H-3⁗), 0.69 (3H, d, 6.6, H-4⁗), 0.70 (3H, d, 6.6, H-5⁗), 7.40–7.64 (5H, m, H-MTPA); FABMS *m/z* 1306 $(M+H)^+$; HRFABMS *m/z* 1305.5160 (M+H; calcd for $C_{67}H_{80}N_2O_{21}F_3$, 1305.5207).

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Enlarging the size of calix[4]arene-crowns-6 to improve Cs^+/K^+ selectivity: a theoretical and experimental study☆

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Abstract—Ab initio calculations in the gas-phase indicate that the substitution of an ethylene with a propylene moiety in the polyether bridge of 1,3-di-*iso*-propoxycalix[4]arene-crowns-6 could result in an enhanced Cs^+/K^+ selectivity which is of particular interest in nuclear waste treatment. We therefore synthesised two novel calix[4]arene-crown-6 compounds (**1** and **2**) having a propylene moiety in their structure and for this named calix[4]arene-propylene-crown-6. The structures of compounds **1** and **2** were elucidated by NMR in solution and for **1** also by X-ray diffraction studies in the solid state. Association constants (K_a) in $CHCl_3$ of the two novel calix-crowns were measured and pointed out a plateau selectivity towards alkali metal ions which was not predicted by molecular modelling calculations. These results indicate the important role played by the solvent molecules and counter-anions in binding for this class of ionophores.

1. Introduction

Calix[4]arene-crown ethers or calix[4]crowns are among the most widely studied class of synthetic ionophores.[1,2] They show binding properties for alkali metal ions strongly dependent on the number of oxygen atoms in the ether bridge and on the conformation of the calixarene skeleton. In the last 20 years, we synthesised a large number of these macrobicyclic ionophores and showed that cation binding involves not only ether oxygen atoms but also the calixarene aromatic nuclei providing experimental evidence for the operation of cation/π interactions.[3] As expected from the size complementarity, 1,3-calix[4]crowns-4 are selective for sodium ion,[4] 1,3-calix[4]crowns-5[5,6] for potassium and the 1,3-calix[4]crowns-6 for cesium.[7] Usually, the conformationally mobile derivatives are much less efficient and selective than the more preorganized receptors fixed in the 1,3-alternate conformation. The high Cs^+/Na^+ selectivity exhibited by the 1,3-dialkoxy-calix[4]crowns-6 in the 1,3-alternate conformation (**I**) prompted us[8,9] to use this class of compound for the selective extraction of cesium from acidic radioactive waste where sodium is present at high concentration (5–7 M) while cesium is only present in trace amounts (10^{-4}–10^{-6} M). Other authors[10–12] have slightly modified the calix-crown-6 structure in order to enhance the cesium selectivity. Compound **Ia** is still one of the ionophores having the highest Cs^+/Na^+ selectivity ($\alpha_{Cs/Na}$=28,500) in extraction and its application in the removal of cesium from radioactive fuel reprocessing waste is currently under study.[9] The substitution of ethylene moieties Y or X with benzo units allowed us also to develop the calix[4]-monobenzo- (**Ib**) and dibenzo- (**Ic**) crown-6[13–15] compounds where the Cs^+/Na^+ selectivity is even slightly increased ($\alpha_{Cs/Na}$=34,000 and 31,000, respectively). However, all these compounds suffer from an $\alpha_{Cs/K}$ at least two orders of magnitude lower than the $\alpha_{Cs/Na}$ selectivity, which might be a drawback in the case of some basic radioactive waste where K^+ concentration can reach values around 1 M. Ring-enlarged crown-ethers, (3*m*+*n*)-crown-*m*, also known as crown ethers of low symmetry,[16] usually show decreased cation binding ability in comparison to the corresponding symmetric crown ethers, but sometimes enhanced selectivity.[17] For example, the potassium selectivity of 18-crown-6 is shifted to rubidium and cesium for less symmetric 20-crown-6 and 22-crown-6, respectively. Therefore, in the present work, we modified the structure of calix[4]crown-6 (**Ia**) and calix[4]dibenzocrown-6 (**Ic**) enlarging the crown ether

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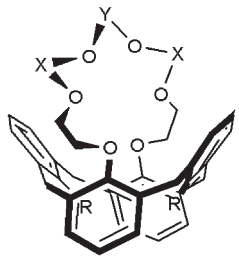
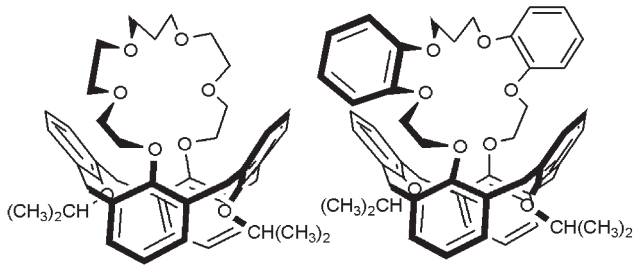
bridge by the introduction of a propylene unit in the Y position and thus obtaining compounds **1** and **2**.



Ia: X = Y = CH_2CH_2; R = O-*i*Pr
Ib: X = CH_2CH_2; Y = 4-*t*-Oct-1,2-C_6H_4; R = O-*n*Oct
Ic: X = 1,2-C_6H_4; Y = CH_2CH_2; R = O-*n*Oct



1 2

2. Results and discussion

2.1. Modeling studies

We first investigated the structural and electronic factors which influence the binding properties of ligand **1** by using ab initio calculations in the gas-phase. In order to find the equilibrium geometries of the **1**·K^+ and **1**·Cs^+ cationic complexes we also preliminarily modelled the structure of the ligand **1** in the gas-phase which was obtained in two steps: (i) the structure of the minimum energy conformer was calculated with semiempirical methods at the PM3 level; (ii) the geometry of the minimum energy conformer was further minimized at the HF/3-21G level. The final equilibrium geometry of the isolated molecule **1** is shown in Figure 1. In the gas-phase the calix[4]arene moiety shows a pseudo C_{2v} symmetry where all the aromatic rings are almost orthogonal to the reference plane R (the weighted

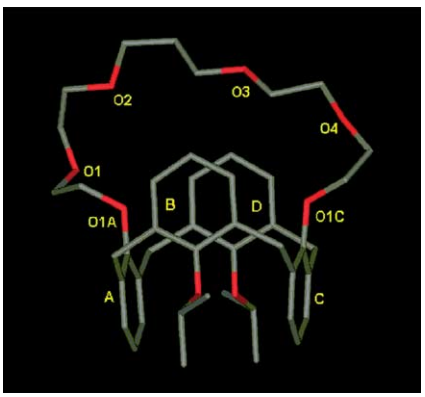


Figure 1. Optimised geometry of the ligand **1** at the HF/3-21G level in the gas-phase.

Table 1. Dihedral angles τ (°) between the reference plane (R) and the planes through the phenolic rings in the calculated structures of **1**, **1**·K^+ and **1**·Cs^+ in the gas-phase and in the solid state structure of **Ia**·Cs^+[7]

	τ			
	1(gas)	**1**·K^+	**1**·Cs^+	**Ia**·Cs^+
R–A	86.99	99.99	101.26	103.3(3)
R–B	257.07	262.3	258.74	257.5(2)
R–C	87.27	101.83	103.02	105.9(2)
R–D	271.44	255.65	248.87	246.3(2)

Table 2. Dihedral angles θ (°) between opposite phenolic rings

	θ			
	1(gas)	**1**·K^+	**1**·Cs^+	**Ia**·Cs^+
A–C	5.81	22.06	24.28	29.2(3)
B–D	3.71	21.82	38.81	36.2(2)

least-squares plane between the four CH_2 bridging groups according to standard rules for calixarenes)[18] and the opposite rings are almost parallel (Tables 1 and 2). This conformation of the calix forces the crown to adopt an elliptical shape with the major axis orthogonal to the pseudo C_2 axis (see Fig. 1). In a second step of calculations, the geometries of **1**·K^+ and **1**·Cs^+ (Fig. 2(a) and (b), respectively) have been obtained by geometry optimisation at the HF/3-21G level. As an initial guess for geometry optimisation the structure of each complex was built-up from that of **1** (optimised in the gas-phase) by placing the metal cation in the barycentre of the six oxygen atoms of the crown. The final structures of **1**·K^+ and **1**·Cs^+, optimised without geometrical constraints, are shown in Figure 2.

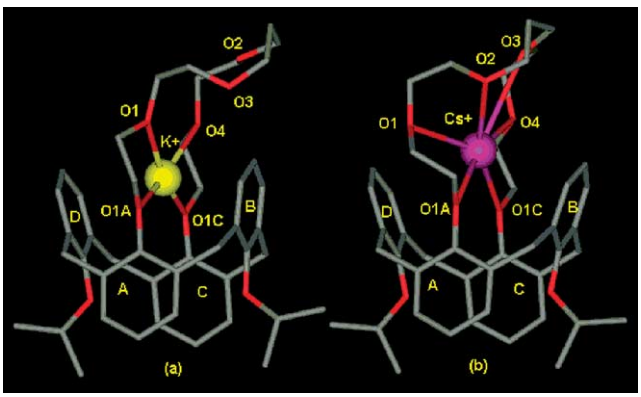


Figure 2. Optimised geometries of the cationic complexes in the gas-phase. (a) **1**·K^+, (b) **1**·Cs^+.

The calix[4]arene basket undergoes a significant conformational reorganization upon complexation. The strong variations of the dihedral angles τ and θ reported in Tables 1 and 2 indicate that the opposite phenolic units are forced to rotate towards the exterior of the macrocycle to favour the binding of the metal ion and that the rotations increase as the size of the cation increases.

The analysis of the interatomic M^+-O distances, summarized in Table 3, shows that the K^+ ion is tetracoordinated to

Table 3. $M^+\cdots O$ interatomic distances (Å) in the **1**·K^+ and **1**·Cs^+ complexes calculated in the gas-phase and in the solid state structure of **Ia**·Cs^+

	1·K^+	**1**·Cs^+	**Ia**·Cs^+
$M^+\cdots$O1A	2.64	3.15	3.189(5)
$M^+\cdots$O1C	2.65	3.00	3.188(5)
$M^+\cdots$O1	2.89	3.09	3.245(6)
$M^+\cdots$O2	4.44	3.43	3.475(7)
$M^+\cdots$O3	4.55	3.13	3.276(9)
$M^+\cdots$O4	2.71	3.23	3.100(5)

O1A, O1C, O1 and O4, whereas the two oxygen atoms O2 and O3 with $K^+-O>4.4$ Å are excluded from the cooordination sphere of the potassium ion.

The K^+-O bond distances range from 2.64 to 2.89 Å (av. 2.72 Å) and are shorter than those found in the X-ray structure of the partial cone di-*iso*propoxy-*p*-*tert*-butylcalix[4]arene-crown-5·KPic (Pic=picrate),[19] (from 2.748(8) to 3.015(10) Å av. 2.872 (9) Å) and in the cone di-ethoxy-*p*-*tert*-butylcalix[4]arene-crown-5·KPic[19] (from 2.76(1) to 2.87(1) Å av. 2.81(1) Å). On the contrary in **1**·Cs^+ the cesium ion is hexacoordinated: the Cs^+-O bond distances range from 3.0 to 3.43 Å (av. 3.172 Å) and are slightly shorter than those in the X-ray structure of the 1,3-alternate di-*iso*-propoxycalix[4]arene-crown-6·CsPic **Ia**·Cs^+ previously reported by us[7] (from 3.100(5) to 3.475(7) Å av. 3.245(7) Å). It is also of some interest to compare the optimised molecular geometry of **1**·Cs^+ with the X-ray structure[6] of the **Ia**·Cs^+ to highlight how the substitution of the ethylene moiety with a propylene unit influences the binding ability of the ligand. In the two structures, shown in Figure 3, the calix[4]arene conformation is quite similar with small differences in the dihedral angles τ (see Table 1). The crown conformation is almost identical at least from O1A to O1 and from O1C to O4. Then, along the chain from O1 to O4 the conformational differences are more relevant, as expected. It is however surprising that the increase in size of the crown length in **1**·Cs^+ does not increase the Cs^+-O bond distances but, on the contrary, a small but not negligible shortening of them (av. 3.172 vs. 3.245(8) Å) is observed.

Therefore these data, which show a relevant difference in the coordination numbers of the two metal ions suggesting a high Cs^+/K^+ selectivity, which prompted us to synthesise

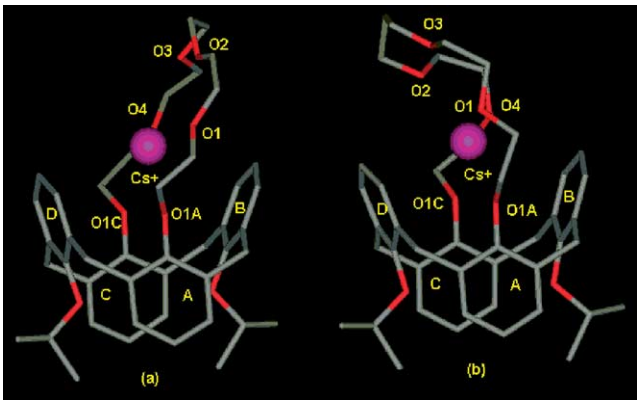
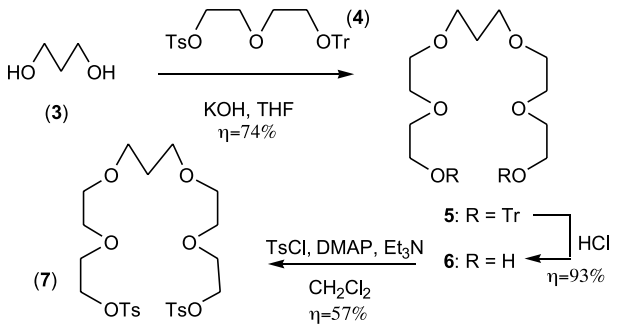


Figure 3. Molecular structure of the cationic complexes (a) **Ia**·Cs^+ (solid state), (b) **1**·Cs^+ (gas-phase).

the two calix[4]arene-propylene-crown-6 compounds **1** and **2** in order to experimentally determine their binding properties.

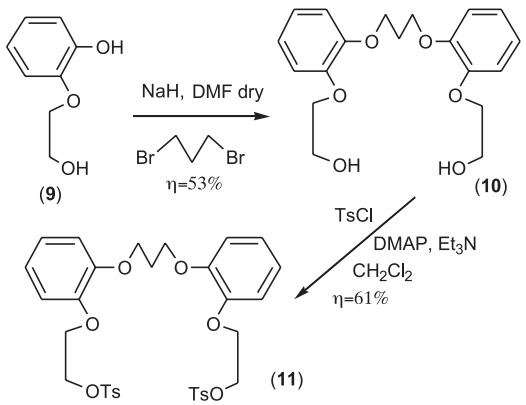
2.2. Synthesis and structure of the ligands

Ditosylate **7** was prepared starting from propylene glycol **3** and diethylene glycol monotrityloxy monotosylate **4**,[20] in 40% overall yield through a protection–deprotection strategy (Scheme 1).



Scheme 1.

After coupling of the glycol **3** with 2.2 equiv. of the diethylene glycol monotosylate **4**, the resulting trityloxy derivative **5** was deprotected with HCl to give the diol **6**. The latter was reacted with tosyl chloride (TsCl) and triethylamine in dichloromethane using a catalytic amount of dimethylamino pyridine (DMAP). Ditosylate **11** was obtained by reaction (Scheme 2) of 1,3-dibromopropane with 2 equiv. of 2-(2-hydroxyethoxy)phenol (**9**)[15] with NaH in DMF. Under these conditions alkylation of the catechol free hydroxy group was mainly obtained and compound **10** could be isolated in 53% yield. Subsequent reaction of **10** with tosyl chloride (TsCl) and triethylamine in dichloromethane gave **11** in 61% yield.



Scheme 2.

For the final cyclization reaction we followed the classical conditions reported for calix[4]crown-6 and reacted 1,3-di-*i*-propoxycalix[4]arene (**8**) with a slight excess (1.2 equiv.) of the appropriate ditosylate **7** or **11** and an excess of Cs_2CO_3 in dry acetonitrile. After quenching, extraction and purification by column chromatography, calix[4]arene-propylene-crown-6 compounds **1** and **2** were obtained in 54 and 59% yield, respectively. The identity of the two calix[4]crowns were characterised using NMR and mass

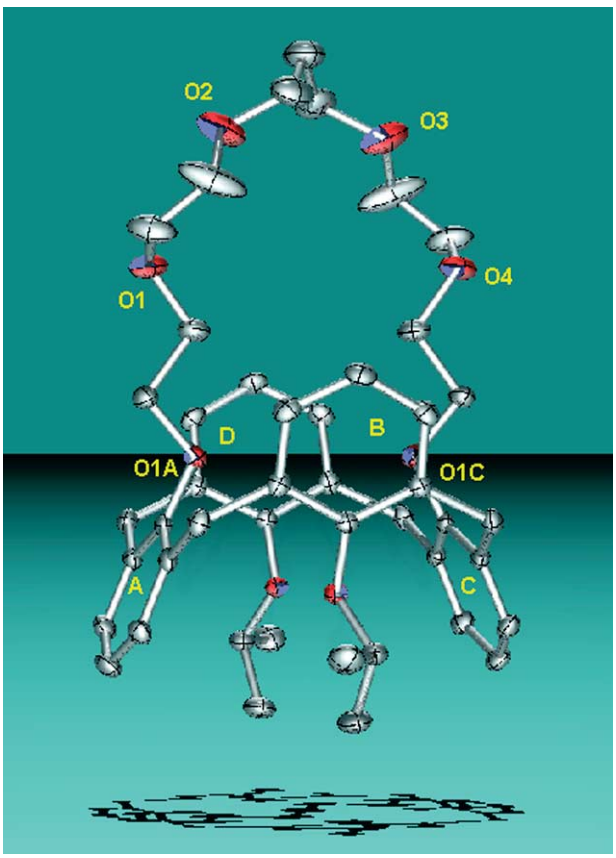


Figure 4. ORTEP view of the molecular structure of the ligand **1**. Thermal ellipsoids at 20% probability. Hydrogen atoms have been omitted for clarity.

spectrometry. In particular the 1,3-alternate structure was confirmed by the presence of an AB system for the methylene bridge at δ_H=3.75–3.82 and a triplet at δ_C=38.5 in the NMR spectra. Isolation of a single crystal of compound **1** allowed us to solve its X-ray diffraction structure. The molecular geometry of **1** in the solid state is shown in Figure 4.

Table 4. Conformational parameters ϕ, χ (°) and dihedral angles τ (°) between the least-squares reference plane (R) and the least-squares planes through the phenolic rings in the solid state structure of **1**

Conformational parameters (°)			Dihedral angles (°)	
	ϕ	χ		τ
A–B	128.5(3)	130.6(3)	R–A	111.18(6)
B–C	−129.5(3)	−130.7(3)	R–B	252.24(6)
C–D	130.4(3)	127.6(3)	R–C	110.87(6)
D–A	−129.2(3)	−131.4(3)	R–D	252.71(7)

The calix[4]arene is blocked in the 1,3-alternate conformation in a pseudo C_{2v} symmetry. The polyether crown moiety shows an elliptical shape with its minor axis orthogonal to the pseudo C_2 axis. The dihedral angles τ between opposite phenolic rings are: A–C 42.06(8)° and B–D 35.05(8)°. The whole conformation of the calix[4]-arene basket is unequivocally described by the dihedral angles τ and by the conformational parameters[21] reported in Table 4 leading to the symbolic representation C_1 ++,−−,++,−−.

The values of the pairs ϕ and χ, together with the τ values clearly indicate that the distortion of the 1,3-alternate structure from an ideal C_{2v} symmetry is very small. Probably due to packing forces, this solid state structure slightly differs from the calculated one (Fig. 1) both in the shape of the calixarene basket and in the conformation of the crown. In the gas-phase, in fact, the calix[4]arene moiety shows also a pseudo C_{2v} symmetry but the phenolic rings are almost orthogonal to the reference plane R and the opposite rings are almost parallel in pairs (Tables 1 and 2). This conformation of the calix forces the crown to adopt an elliptical shape with the major axis orthogonal to the pseudo C_2 axis (see Fig. 1).

2.3. Complexation studies

In order to evaluate the binding properties of ligands **1**-**2** in comparison with calix[4]arene-crown-6 **Ia** and -dibenzo-crown-6 **Ic** we determined the association constants (log K_a) with alkali picrates in chloroform, using Cram's method[22,23] (Table 5 and Fig. 5).

The data show, in general, a strong decrease in cation binding properties of propylene-crown-6 (**1** and **2**) in comparison with calix[4]crown-6 (**Ia** and **Ic**). This effect is more significant for larger cations ($Cs^+ > Rb^+ > K^+$) and

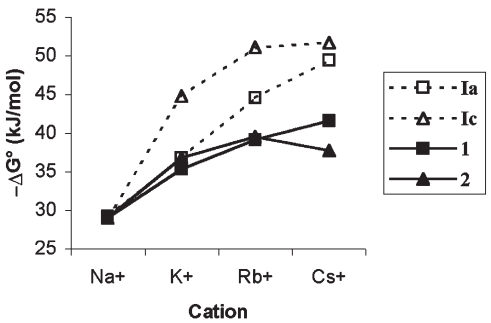


Figure 5. Binding free energies (−ΔG°, kJ/mol) of complexes of calixcrowns-6 with alkali metal picrates in $CHCl_3$ saturated with water at 22 °C.

Table 5. Association constants (K_a)[a] and binding free energies (−ΔG°, kJ/mol) of complexes of calixcrowns-6 with alkali metal picrates in $CHCl_3$ saturated with water at 22 °C

Ligand	log K_a				−ΔG° (kJ/mol)				$\alpha_{Cs/K}$
	Na^+	K^+	Rb^+	Cs^+	Na^+	K^+	Rb^+	Cs^+	(ΔΔG°)
Ia[7]	5.2	6.4	7.9	8.8	29.2	36.8	44.6	49.4	12.6
Ic[15]	<5	7.8	8.9	9.0	<29.0	44.8	51.1	51.7	6.9
1	<5	6.1	6.8	7.2	<29.0	35.3	39.1	41.6	6.3
2	<5	6.4	6.9	6.6	<29.0	36.8	39.5	37.7	1.2

[a] Errors <10%.

in the dibenzo-crown-6 derivative **2**. The stability of the cesium complex drops by 14.0 kJ/mol with the introduction of the propylene moiety in the dibenzo-crown-6 series, while it decreases only by 7.8 kJ/mol when no benzo units are present in the crown bridge. This causes a plateau selectivity of calix-dibenzo-propylene-crown-6 (**2**) which indeed shows only a very weak preference for Rb^+. Moreover, while in calixcrowns-6 (**I**) the stabilities of the complexes remarkably rise with the introduction of two benzo units, in propylene-crown-6 there are only minor differences between propylene-dibenzo-crown-6 (**2**) and -propylene-crown-6 (**1**). In conclusion, the substitution of an ethylene with a propylene moiety in the bridge of calix-crown-6 compounds decreases both the efficiency and selectivity of cesium complexation in contrast to what was predicted by ab initio calculations. The origin of such a discrepancy should be ascribed to the fact that, in the modeling, effects due to solvation and interaction with the counter-anion are not taken into account.

3. Experimental

3.1. Synthesis

Materials and methods. Most of the solvents and all reagents were obtained from commercial supplies and used without further purification. DMF was freshly distilled and stored over 4 Å molecular sieves while acetonitrile for synthesis was dried over 3 Å molecular sieves. Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker AC300 and Bruker 300 Avance spectrometers of the Centro Interdipartimentale of the Parma University. Chemical shifts are reported as δ values in ppm from TMS (δ 0.0) as internal standard. Analytical thin-layer chromatography was carried out on silica gel plates (SiO_2, Merk 60 F_{254}). Mass spectra were performed with FINNIGAN MAT SSQ 710 (CI, CH_4). Melting points were obtained in a nitrogen-sealed capillary on an Electrothermal Apparatus. Diethylene glycol monotrityloxy monotosylate (**4**),[20] 2-(2-hydroxyethoxy)phenol (**9**)[15] and 25,27-di-*iso*-propoxycalix[4]arene (**8**)[7] were synthesised according to the literature.

3.1.1. 2-(2-{3-[2-(2-Trityloxy-ethoxy)-ethoxy]-propoxy}-ethoxy)-ethanol (5). A sample of propylene glycol **3** (0.46 g, 6.0 mmol) in dry THF (20 mL) was added to a suspension of KOH (1.30 g, 23 mmol) in dry THF (30 mL) at reflux under nitrogen atmosphere; the mixture was stirred for 1 h. Then compound **4** (6.7 g, 13.3 mmol) in dry THF (20 mL) was added and the reaction mixture stirred for 2 days. After cooling, the solvent was distilled off and the residue extracted with 50 mL of CH_2Cl_2 and 50 mL of water; the organic solvent was removed under reduced pressure. The pure product **5** was obtained by column chromatography (SiO_2 CH_2Cl_2/hexane/ethyl acetate 3:8:1) as an oil (3.30 g, 74%); ^{1}H NMR ($CDCl_3$): δ 7.44–7.41 (m, 12H, ArH *meta*), 7.32–7.22 (m, 18H, ArH *ortho* and *para*), 3.69–3.55 (m, 16H, OCH_2CH_2O), 3.16 (t, J=6.2 Hz, 4H, $OCH_2CH_2CH_2O$), 1.90 (quin, J=6.2 Hz, 2H, $OCH_2CH_2CH_2O$); ^{13}C NMR ($CDCl_3$): δ 144.1 (Ar), 128.7, 127.6, 126.8 (ArH), 86.5 ($C(C_6H_5)_3$), 70.7, 70.6, 70.2, 68.3, 63.3 (OCH_2), 30.0 ($CH_2CH_2CH_2$); MS *m/z*: 660 ($M-C_6H_5$), 493 ($M-C_{19}H_{15}$). Anal Calcd for $C_{49}H_{52}O_6$: C, 79.86; H, 7.11. Found: C, 80.02; H, 7.19.

3.1.2. 2-(2-{3-[2-(2-Hydroxy-ethoxy)-ethoxy]-propoxy}-ethoxy)-ethanol (6). A sample of compound **5** (3.3 g, 4.5 mmol) was dissolved at room temperature in 100 mL of a 1:1 mixture of CH_2Cl_2 and CH_3OH and then 0.5 mL of a 12 M HCl solution were added. After 3 h the reaction was cooled to 0 °C, 50 mL of a 5% $NaHCO_3$ solution were slowly added (CAUTION!) and the solution was stirred for 30 min. Then the solvent was distilled off under reduced pressure and the residue extracted with 100 mL of CH_2Cl_2 and 100 mL of 1 M HCl. Water was removed under vacuum from the aqueous layer and the solid residue extracted twice with MeOH (2×30 mL). After removal of methanol pure product **6** was isolated as an oil (1.05 g, 93%). ^{1}H NMR (CD_3OD): δ 3.70–3.50 (m, 20H, OCH_2), 1.85 (quin, J=6.3 Hz, 2H, $CH_2CH_2CH_2$); ^{13}C NMR (CD_3OD): δ 72.5, 70.24, 70.16, 68.2 ($CH_2CH_2CH_2$), 61.1 (CH_2OH), 29.8 ($CH_2CH_2CH_2$); MS *m/z*: 253.0 (M+1). Anal Calcd for $C_{11}H_{24}O_6$: C, 52.36; H, 9.59. Found: C, 52.41; H, 9.63.

3.1.3. 2-(2-{3-[2-(2-Tosyloxy-ethoxy)-ethoxy]-propoxy}-ethoxy)-ethanol (7). Compound **6** (1.0 g, 4.0 mmol) was dissolved in dry CH_2Cl_2 (50 mL) at room temperature and under nitrogen atmosphere. The stirred solution was cooled at 0 °C and tosyl chloride (1.86 g, 9.8 mmol), dry triethylamine (1.8 mL), and a catalytic amount of dimethylaminopyridine (DMAP) were slowly added. After 20 h the solvent was removed under reduced pressure and the residue was extracted with 100 mL of CH_2Cl_2 and 100 mL of 1 M HCl. The organic layer was washed twice with water (2×100 mL) and the solvent distilled off to give compound **7** (57%) as oil; ^{1}H NMR ($CDCl_3$): δ 7.79 (d, J=8.4 Hz, 4H, TsH), 7.34 (d, J=8.4 Hz, 4H, TsH), 4.15 (t, J=4.8 Hz, 4H, CH_2OTs), 3.68 (t, J=4.8 Hz, 4H, OCH_2CH_2OTs), 3.59–3.55 (m, 4H, $OCH_2CH_2OCH_2CH_2OTs$), 3.52–3.48 (m, 8H, $CH_2OCH_2CH_2CH_2OCH_2$), 2.44 (s, 6H, $TsCH_3$), 1.82 (quin, J=6.5 Hz, 2H, $CH_2CH_2CH_2$; ^{13}C NMR ($CDCl_3$): δ 144.7, 133.0 (Ar), 129.7, 127.9 (ArH), 70.6, 70.0, 69.1, 68.6, 68.1 (OCH_2), 29.8 ($CH_2CH_2CH_2$), 21.5 (CH_3); MS *m/z*: 561 (M+1). Anal Calcd for $C_{25}H_{36}O_{10}S_2$: C, 53.55; H, 6.47. Found: C, 53.60; H, 6.45.

3.1.4. Glycol 10. A mixture of compound **9** (5.3 g, 34.4 mmol) and NaH (0.83 g, 34.4 mmol) in dry DMF (100 mL) was stirred at room temperature for 30 min. Then a solution of 1,3-dibromopropane (**9**) (3.5 g, 17.2 mmol) dissolved in dry DMF (50 mL) was added dropwise and the mixture stirred at room temperature for 24 h. After removal of DMF under vaccum, the residue was dissolved in dichloromethane and washed with water (CAUTION!). The organic layer was dried over sodium sulfate and the solvent evaporated under reduced pressure. The pure product **10** (3.2 g, 53%) was obtained by crystallization from ethanol/water (1:1); mp 87–88 °C; ^{1}H NMR ($CDCl_3$): δ 7.00–6.89 (m, 8H, ArH), 4.30 (t, J=5.7 Hz, 4H, $OCH_2CH_2CH_2O$), 4.08 (t, J=4.2 Hz, 4H, $ArOCH_2CH_2OH$), 3.90 (t, J=4.2 Hz, 4H, $ArOCH_2CH_2OH$), 2.23 (quin, J=5.7 Hz, 2H, $OCH_2CH_2CH_2O$); ^{13}C NMR ($CDCl_3$): δ 149.3, 148.4 (Ar), 122.2, 121.6, 115.7, 114.4 (ArH), 71.1, 66.5 ($ArOCH_2$), 61.2 (CH_2OH), 29.0 ($CH_2CH_2CH_2$); MS *m/z*:

348.15 (M^+). Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.45; H, 6.85.

3.1.5. Ditosylate 11. A mixture of compound **10** (2.5 g, 7.2 mmol) and triethylammine (3 mL, 21 mmol) in dichloromethane (50 mL) was stirred at room temperature. To this solution were added tosyl chloride (3.2 g, 16.8 mmol) and a catalytic amount of 4-dimethylaminopyridine DMAP. After heating at reflux for 24 h the mixture was cooled at room temperature and extracted with 60 mL of 1 M HCl. The organic layer was dried over sodium sulfate and the solvent evaporated under vacuum. The residue was purified by column chromatography (SiO_2 Et_2O/hexane 7:3) to afford compound **11** as white solid (2.9 g, 61%); mp 79–83 °C; ^{1}H NMR ($CDCl_3$): δ 7.78 (d, J=8.3 Hz, 4H, TsH), 7.29 (d, J=8.3 Hz, 4H, TsH), 6.94–6.91 (m, 4H, ArH), 6.87–6.79 (m, 4H, ArH), 4.31 (t, J=4.2 Hz, 4H, TsOCH_2CH$_2$O), 4.19–4.15 (m, 8H, CH_2OArOCH_2), 2.41 (s, 6H, TsCH_3), 2.25 (quin, J=6.2 Hz, 2H, CH$_2$CH_2CH$_2$); ^{13}C NMR ($CDCl_3$): δ 149.4, 147.9, 144.8, 132.9 (Ar), 129.8, 127.9, 122.7, 121.2, 116.1, 114.4 (ArH), 68.2, 67.3, 65.7 (OCH_2), 29.3 (CH$_2$$CH_2CH_2$), 21.5 (CH$_3$). MS m/z: 656.6 (M^+). Anal. Calcd for $C_{33}H_{36}O_{10}S_2$: C, 60.35; H, 5.52. Found: C, 60.44; H, 5.46.

3.2. General procedure for the synthesis of calix-crown-6 (1 and 2)

25,27-Di-*iso*-propoxycalix[4]arene **8** (2 mmol) was dissolved in CH_3CN (300 mL) and an excess of Cs_2CO_3 (2.60 g, 8 mmol) and of the appropriate glycol di-*p*-toluenesulfonate (2.5 mmol) added under a nitrogen atmosphere. The reaction mixture was refluxed for 24 h. Then CH_3CN was removed under reduced pressure and the residue extracted with 70 mL of CH_2Cl_2 and 70 mL of 10% HCl. The organic phase was separated, washed twice with water (2×100 mL) and the solvent distilled off. The pure compounds were isolated as described below.

3.2.1. Calix[4]arene-propylene-crown-6 (1). Calix-crown-6 **1** was obtained after purification on a silica gel column using ethyl acetate/hexane (2:3) as eluent; yield=54%; mp 216–218 °C; ^{1}H NMR ($CDCl_3$): δ 7.07 (d, J=7.4 Hz, 4H, ArH *meta*), 7.01 (d, J=7.4 Hz, 4H, ArH *meta*), 6.79 (t, J=7.4 Hz, 2H, ArH *para*), 6.78 (t, J=7.4 Hz, 2H, ArH *para*), 4.22 (ept, J=6.1 Hz, 2H, CH(CH$_3$)$_2$), 3.81 (d, J=15.6 Hz, 4H, ArCH_2Ar), 3.74 (d, J=15.6 Hz, 4H, ArCH_2Ar), 3.67 (t, J=5.8 Hz, 4H, OCH_2CH$_2$CH_2O), 3.63 (t, J=4.8 Hz, 4H, ArOCH$_2$CH$_2$OCH$_2$CH_2O), 3.54–3.49 (m, 8H, ArOCH$_2$CH_2 and ArOCH$_2$CH$_2$OCH_2CH$_2$O), 3.31 (t, J=5.8 Hz, 4H, ArOCH_2CH$_2$), 1.86 (quin, J=5.8 Hz, 2H, OCH$_2$CH_2CH$_2$O), 0.92 (d, J=6.1 Hz, 12H, CH(CH_3)$_2$); ^{13}C NMR ($CDCl_3$): δ 156.6, 154.7 (Ar *ipso*), 134.4, 133.4 (Ar *ortho*), 130.0, 129.6 (ArH *meta*), 121.8, 121.4 (ArH *para*), 70.7 (*C*H(CH$_3$)$_2$), 70.4, 70.2, 69.8, 69.2, 66.9 (OCH$_2$), 38.5 (Ar*C*H$_2$Ar), 30.1 (CH$_2$*C*H$_2$CH$_2$), 21.8 (CH(*C*H$_3$)$_2$). MS m/z: 724.5 (M^+). Anal Calcd for $C_{45}H_{56}O_8$: C, 74.56; H, 7.79. Found: C, 74.63; H, 7.71.

3.2.2. Calix[4]arene-propylene-dibenzocrown-6 (2). Calix-benzocrown-6 **2** was obtained after column chromatography on silica gel using first CH_2Cl_2/hexane (1:1) and then ethyl acetate/methanol (95:5) as eluent and crystallisation from methanol; yield=59%; mp 83–85 °C; ^{1}H NMR ($CDCl_3$): δ 7.04–6.93 (m, 12H, ArH), 6.86 (d, J=7.4 Hz, 4H, ArH *meta*), 6.81 (t, J=7.4 Hz, 2H, ArH *para*), 6.65 (t, J=7.4 Hz, 2H, ArH *para*), 4.28 (t, J=6.2 Hz, 4H, CH_2CH$_2$CH_2), 4.20 (ept, J=6.0 Hz, 2H, CH(CH$_3$)$_2$), 3.82 (d, J=15.9 Hz, 4H, ArCH_2Ar), 3.74 (d, J=15.9 Hz, 4H, ArCH_2Ar), 3.67 (t, J=6.4 Hz, 4H, ArOCH_2CH$_2$OArOCH$_2$), 3.44 (t, J=6.4 Hz, 4H, ArOCH$_2$CH_2OArOCH$_2$), 2.32 (quin, J=6.2 Hz, 2H, CH$_2$CH_2CH$_2$), 0.88 (d, J=6.0 Hz, 12H, CH(CH_3)$_2$). ^{13}C NMR ($CDCl_3$): δ 156.2, 154.8 (Ar *ipso*), 150.5, 149.7 (Bn), 134.5, 133.7 (Ar *ortho*), 130.2, 129.5 (Ar *meta*), 123.0, 121.98, 121.97, 121.92 (ArH *para* and BnH), 119.9, 117.0 (BnH), 70.5, 69.9, 68.0, 67.1 (OCH_2), 38.9 (Ar*C*H$_2$Ar), 30.1 (CH$_2$*C*H$_2$CH$_2$), 21.7 (*C*H$_3$); MS m/z: 820.1 (M^+). Anal. Calcd for $C_{53}H_{56}O_8$: C, 77.53; H, 6.87. Found: C, 77.58; H, 6.93.

3.3. X-ray crystallographic studies of 1

Crystal data and the most significant parameters for the structure refinement of **1** are reported in Table 6. A single transparent crystal was mounted on a glass fibre and protected from air by a thin film of perfluoric oil.

Table 6. Crystallographic data and experimental details for **1**[a]

Crystal data	
Empirical formula	$C_{45}H_{56}O_8$
Formula weight	724.933
Crystal size [mm]	0.4×0.3×0.4
Crystal system	Triclinic
Space group	*P*-1
a (Å)	10.962(5)
b (Å)	17.945(5)
c (Å)	11.009(5)
α (°)	104.06(2)
β (°)	91.34(2)
γ (°)	76.09(2)
V (Å^3)	2038(2)
Z	2
ρ (Calcd) (g/cm^3)	1.182
F(000)	780
Data collection	
T (K)	295
Index range	$-12\le h\le 12, -20\le k\le 19, 0\le l\le 19$
Reflections collected	6757
Independent reflections	6374(R_{int}=0.016)
Observed reflections	4262 [$F_0\ge 4\sigma(F_0)$]
Structure refinement	
Data/restraints/parameters	6374/0/488
Goodness-of-fit on F^2[a]	1.161
Final R indices (obs. data)[a]	R_1=0.056, wR_2=0.178
R indices (all data)	R_1=0.0832, wR_2=0.164
Largest diff. peak and hole (e/Å^3)	0.53, −0.43

[a] $R_1=\sum||F_0|-|F_c||/\sum|F_0|$, $wR_2=[\sum w(F_0^2-F_c^2)^2/\sum wF_0^4]^{1/2}$. Goodness-of-fit=$[\sum w(F_0^2-F_c^2)^2/(n-p)]^{1/2}$, where n is the number of reflections and p the number of parameters.

The X-ray measurements were performed at room temperature on a Philips PW1100 diffractometer using graphite monochromated Mo K_α radiation (λ=0.71073 Å). The cell parameters were obtained from a least-squares fitting on 25 $I_{\theta,\chi,\phi}$ reflections found in a random search on the reciprocal lattice in the range $16\le\theta\le20°$. One standard reflection, collected every 100 to monitor crystal decay and instrumental linearity, showed a linear decay of almost 10%. The intensities were corrected for Lorentz and polarization but not for absorption. The structure was solved by Direct

Methods using SIR92[24] and refined by full-matrix least-squares methods on F^2 using SHELXL-97.[25] All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. The hydrogen atoms were placed at their calculated positions with the geometrical constraint C–H 0.96 Å and refined 'riding' on their parent carbon atoms. The structure has also been tested in the monoclinic system (a=15.716, b=15.353, c=17.945 Å, β=109.03°), space group $C2/c$, however the refinement was unsuccesful. Geometrical calculations were obtained by PARST97.[26] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre: CCDC deposition number 232991.

3.4. Computational methods

All the calculations were executed on a Pentium IV PC (2.5 MHz). The semiempirical calculations at the PM3 level were performed with SPARTAN 02.[27] The ab initio calculations at the HF level were carried out using GAUSSIAN03 in the G03W suite.[28] Molecular symmetry was disabled in all calculations. The basis set for cesium was taken from literature.[29]

4. Supplementary data available

Cartesian coordinates of HF/3-21G** optimized structures of all compounds reported in this work and the .cif file of the X-ray crystal structure of ligand **1** are available on-line as Supplementary Data.

Acknowledgements

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P[(*S*,*S*,*S*)-$CH_3NCH(CH_2Ph)CH_2]_3N$: a new C_3-symmetric enantiomerically pure proazaphosphatrane

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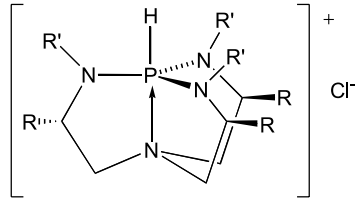
Abstract—A new approach for the synthesis of C_3-symmetric proazaphosphatranes with chirality at the bridging methylene positions is reported.

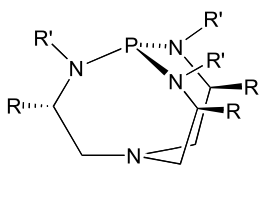
During the last ten years bicyclic proazaphosphatranes **2a**–**g**, first synthesized in our laboratories, have proven to be versatile very strong non-ionic bases and potent catalysts for a variety of useful base-catalyzed reactions.[1] These transformations appear to be quite dependent upon the occurrence of transannulation of the bridgehead nitrogen lone pair to phosphorus that enhances the basicity of these phosphines and the stability of reaction intermediates. Moreover, the frameworks of these phosphines are fairly rigid but strain-free in a bicyclic (approximately C_{3v}) structure, thus augmenting the lone pair electron density at phosphorus. Additionally, the electronic and steric properties of these molecules can be easily tuned by introducing suitable organic substituents at each N–P nitrogen. We have used them successfully for the synthesis of β-nitroalkanols,[2] β-hydroxy nitriles,[3] silylated alcohols,[4] glutaronitriles,[5] oxazolines,[6] a novel ylide,[7] α, β-unsaturated nitriles[8] and homoallylic alcohols.[9] These non-ionic bases have also been successfully employed in the promotion of oxa-Michael addition reactions,[6] Knoevenagel condensations,[10] Wittig olefination reactions[11] and 1,2-addition reactions of activated allylic synthons.[12] Very recently, we reported that bicyclic P(*i*-$BuNCH_2CH_2)_3N$ **2d** serves as an effective ligand for palladium-catalyzed Suzuki cross-coupling,[13] aminations[14,15] and α-arylations of nitriles[16] with a wide array of aryl chlorides, bromides and iodides. These achievements stimulated our interest in exploring the possibility of realizing asymmetric versions of some these reactions.

Recently, we synthesized the C_3-symmetric proazaphosphatrane **3** possessing non-racemic substituents at the PN_3 nitrogen atoms.[17] Enantiomerically pure **3**, derived from (*S*)-α-phenylethylamine, was found to be an efficient derivatizing agent for the direct determination of enantiomeric ratios of chiral azides by means of ^{31}P and ^{1}H NMR spectroscopy.[17] Derivatives of azaphosphatranes with non-racemic substituents at the PN_3 nitrogen atoms may not exert good stereocontrol in catalytic reactions, because of the flexibility of the C_3 conformations of the cage moieties.



1

	R'	R	
1a	H	H	**2a**
1b	Me	H	**2b**
1c	Et	H	**2c**
1d	$CH_2CH(CH_3)_2$	H	**2d**
1e	$CH(CH_3)_2$	H	**2e**
1f	CH_2Ph	H	**2f**
1g	Me_3Si	H	**2g**
1h	Me	Me	**2h**
1i	Me	*i*-Pr	**2i**
1j	Me	CH_2Ph	**2j**



2

Keywords: Chiral; Proazaphosphatrane; Synthesis; Non-ionic base.
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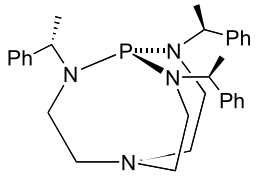
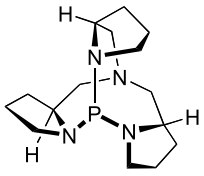
On the other hand, azaphosphatrane derivatives substituted at either methylene position of the three CH_2CH_2 moieties could be expected to be more rigid owing to intramolecular steric hindrance on the three bridges of a C_3-symmetric cage and hence, may possibly be advantageous for efficient chirality transfer in catalytic applications. Yamamoto's group successfully accomplished the synthesis of proazaphosphatrane **4** from (*S*)-proline.[18] However, this compound showed no asymmetric induction in the incomplete silylation of racemic 1-phenylethanol and when **4** was applied as a catalyst in the addition of diethylzinc to benzaldehyde, 1-phenyl-1-propanol was obtained with a low ee value (15%). Additionally, the synthesis of **4** is difficult and it precludes the introduction of organic substituents on the PN_3 nitrogens aimed at fine tuning the electronic and steric properties of **4**. Moberg et al. have recently synthesized C_3-symmetric proazaphosphatranes[19] from non-racemic C_3-symmetric TREN analogs, which were prepared from enantiomerically pure aminoalcohols via aziridines.[20] However, they were unable to purify the hydrochlorides **1h** and **1i** (ca. 90%), or the respective proazaphosphatranes **2h** and **2i** (ca. 70% purity) and, surprisingly, observed incomplete deprotonation of the former even in the presence of potassium *tert*-butoxide in acetonitrile.



3



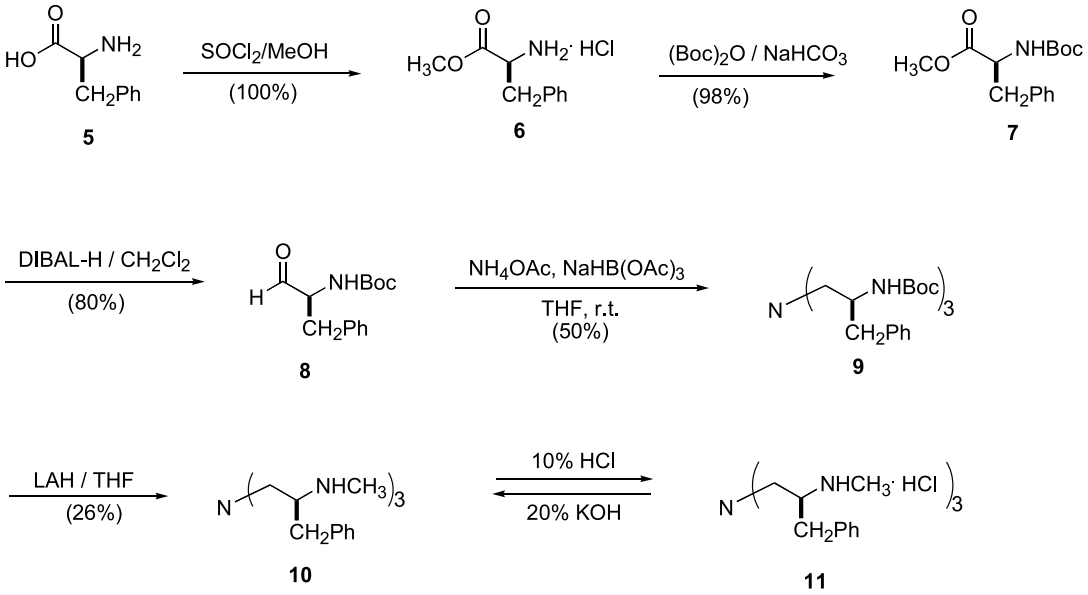
4

Known methods for the synthesis of tripodal tris(aminoalkyl)amines possessing chiral centers at the carbon beta to the tertiary nitrogen rely on the use of aminoacids as starting materials. The first such method involved nucleophilic opening of aziridines derived from β-aminoalcohols with ammonia,[20] while in the second route (*S*)-proline was used in a multistep synthesis which included three $LiAlH_4$ reductions, two condensations, and also protection and deprotection steps.[18] The most promising approach is the third reported method, which depends on the reductive amination of *N*-Boc-protected non-racemic α-aminoaldehydes in the presence of ammonium acetate.[21] Herein, an extension of this methodology to the synthesis of proazaphosphatrane **1j** is presented.

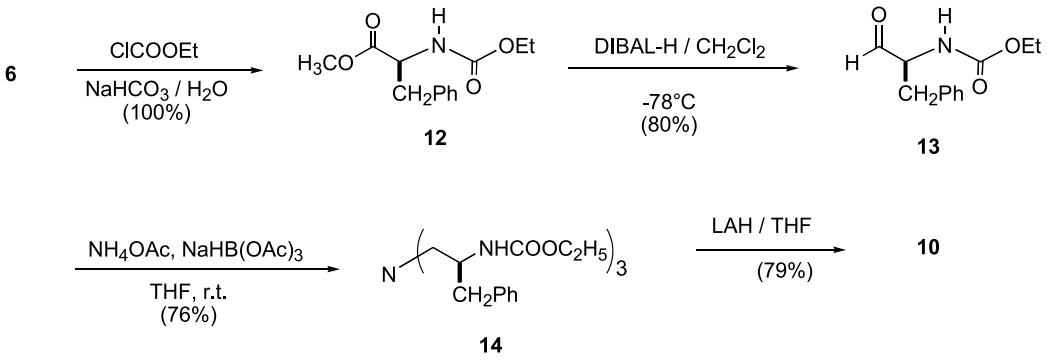
1. Results and discussion

Our initial exploration of the synthesis of C(β)-substituted enantiomerically pure TREN **10** is shown in Scheme 1. In the first step, L-phenylalanine was readily converted to *N*-Boc-L-phenylalanine methyl ester **7** in nearly quantitative yield. The transformation of the ester **7** into aldehyde **8** was carried out in 90% yield in the presence of DIBAL-H at −78 °C for 2 h. The ^1H NMR spectrum of aldehyde **8** was consistent with that previously reported for this compound.[22] Due to concern over the configurational stability of aldehyde **8**, the product was used immediately without further purification in the subsequent reductive amination reaction with $NaHB(OAc)_3$,[23] affording (*S*,*S*,*S*)-tris(*N*-*tert*-butoxycarbonyl-2-amino-3-phenylpropyl)amine **9** as a white solid in 50% yield. Vigorous stirring was critical for achieving the highest possible yield. Unfortunately, the subsequent reduction of **9** with $LiAlH_4$ gave (*S*,*S*,*S*)-tris-[2-(*N*-methylamino)-3-phenylpropyl]amine **10** in only 26% yield.

It was very difficult to purify tetraamine **10** by chromatography on a silica gel column. However, when the crude amine **10** was treated with 10% hydrochloric acid, the corresponding hydrochloride (that separated immediately) was easily purified by recrystallization from methanol/ether to give pure (*S*,*S*,*S*)-tris[2-(*N*-methylamino)-3-phenylpropyl]amine trihydrochloride **11** as white needles. Compound **11** was then neutralized with 20% aqueous KOH to produce pure amine **10** quantitatively.



Scheme 1.



Scheme 2.

Although the use of the *N*-Boc group as a precursor to the MeNH substituent afforded **10** in low yield, the use of inexpensive ethyl chloroformate[24] led to a significant improvement of the overall yield (Scheme 2). Reductive amination of **13**[25] gave (*S*,*S*,*S*)-tris[2-(*N*-ethoxycarbonylamino)-3-phenylpropyl]amine **14** in 76% yield. Although *N*-ethoxycarbonyl-(*S*)-phenylalaninol[26,27] formed in variable amounts as a by-product in the reductive amination step, it was easily removed on a silica gel column. $LiAlH_4$ reduction of **14** gave the desired compound **10** in 79% yield.

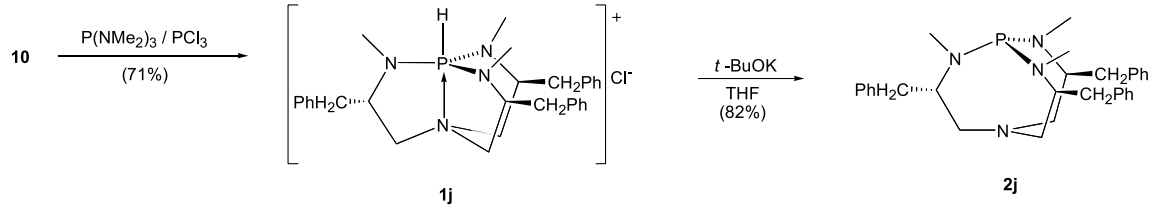
The intermediate *N*-protected α-aminoaldehydes **8** and **13** appeared to be configurationally stable under the conditions of the reductive amination, since detailed analyses of the ^1H NMR spectra of the crude products **9** and especially **14** showed no presence of additional resonances that could be assigned to diastereoisomeric (*R*,*S*,*S*)-**9** or (*R*,*S*,*S*)-**14**.

Azaphosphatrane **1j** was synthesized according to our established procedure for analogues of this compound as shown in Scheme 3.[24,28] The crude product was purified on a silica gel column followed by crystallization from benzene to give enantiomerically pure **1j** in 71% yield. In the presence of potassium *tert*-butoxide in THF, **1j** was converted in 2 h to proazaphosphatrane **2j** in 82% yield.

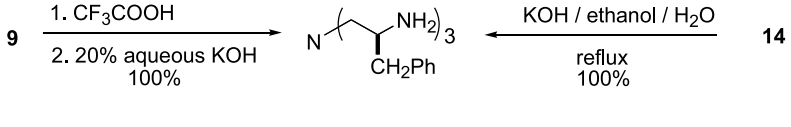
Additionally, the synthesis of the *N*-unsubstituted tetraamine **15** was also developed as outlined in Scheme 4. Treatment of **9** with trifluoroacetic acid for several hours removed the Boc protecting groups. Subsequent neutralization with base afforded tetraamine **15** in excellent yield. In the case of the *N*-ethoxycarbonyl-protected TREN derivative **14**, we found that all three carboxyethyl groups could be removed quantitatively by refluxing in ethanol/aqueous KOH for 20 h (Scheme 4). The successful preparation of **15** provides a route to the synthesis of a variety of enantiomerically pure proazaphosphatranes by allowing facile introduction of suitable organic substituents at each PN_3 nitrogen as described previously.[28] Because the parent proazaphophatrane $P(HNCH_2CH_2)_3N$ is very unstable with respect to polymerization,[1] we did not attempt to convert **15** to its corresponding proazaphosphatrane.

When proazaphosphatrane **2j** (0.1 equiv.) was used to catalyze the addition of trimethylsilyl cyanide to benzaldehyde,[29] mandelonitrile was obtained in 47% yield. The product appeared to be a racemic mixture as shown by derivatization with (4*R*,5*R*)-diisopropoxycarbonyl-2-chloro-1,3,2-dioxaphospholane.[30] Although quinine was found useful as an enantiodifferentiating medium[31] for mandelonitrile, the estimation of the ee was not possible, because in the presence of excess quinine, a retro-cyanohydrin reaction occurred leading to the formation of ca. 20% benzaldehyde within 2 h.

The rearrangement of *meso*-epoxides to allylic alcohols is an important transformation in organic chemistry since chiral products are formed. Enantioselective versions of this reaction using a variety of non-racemic ionic bases have been extensively investigated in recent years[32–35] and the enantioselective deprotonation of cyclohexene oxide appeared to be a good model reaction to try.[32,36–39]



Scheme 3.



Scheme 4.

However, when cyclohexene oxide was treated with **2j** (0.2 equiv.) at room temperature for 27 h, only a negligible amount of 2-cyclohexenol was detected.

Proazaphosphatrane **2j** was also unsuccessful in catalyzing the addition of allyl cyanide to benzaldehyde, leading instead to a complex mixture of products. However, it was pointed out that **2b** also gave low conversions in this transformation.[12]

In summary, a general route to C_3-symmetric enantiomerically pure TRENs from L-phenylalanine is reported, thus facilitating access to a wide variety of enantiomerically pure proazaphosphatranes. Proazaphosphatrane **2j** was found ineffective in inducing asymmetry in the formation of mandelonitrile, not sufficiently basic to execute the rearrangement of cyclohexene oxide to 2-cyclohexenol, and (not unexpectedly) inefficient in catalyzing the addition of allyl cyanide to benzaldehyde. The lack of observable ee in the reaction products reported here may be attributable to an excessive distance of the chiral centers on **2j** to a substrate in an intermediate that might be formed. It is also possible that the strong basicity of a proazaphosphatrane racemizes the chiral center in the product via a deprotonation equilibrium. Results of further experiments with other PN_3 nitrogen-substituted analogues of **2j** will be reported in due course.

2. Experimental

2.1. General methods

^1H and ^{13}C NMR spectra were recorded at 400 or 300 MHz, and at 100.6 or 75.5 MHz, respectively. Elemental analyses were performed by Desert Analytics (Tucson, Arizona). Mass spectra were recorded on a Kratos MS 50 instrument. Melting points were determined in unsealed capillary tubes and are uncorrected. All reactions were performed under an argon atmosphere. Solvents were dried over P_4O_{10} (dichloromethane), CaH_2 (acetonitrile) or sodium/benzophenone (diethyl ether, THF, dioxane and toluene) and were freshly distilled prior to use. Chemicals employed were purchased from Aldrich Chemical Co. and were used without further purification.

2.1.1. *N*-Boc-L-phenylalaninal 8. To a suspension of L-phenylalanine **5** (10.0 g, 60.5 mmol) in ice-cooled dry methanol (100 mL) was added dropwise thionyl chloride (10.0 g, 6.15 mL, 84.2 mmol) and the solution was stirred at room temperature overnight. Removal of the volatiles under reduced pressure gave L-phenylalanine methyl ester hydrochloride **6** as a colorless crystalline solid quantitatively. To the mixture of the methyl ester hydrochloride **6** (15.77 g, 73.10 mmol) in 150 mL of aqueous $NaHCO_3$ (13.51 g, 160.8 mmol) was added dropwise a solution of $(Boc)_2O$ (17.55 g, 80.41 mmol) in dioxane (150 mL). The mixture was stirred at room temperature for 12 h, then concentrated to half of its original volume and extracted with ether (3× 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to leave a colorless oil, which was purified by chromatography on silica gel using ether/hexane (1:1, v/v) as eluent to give *N*-Boc-L-phenylalanine methyl ester **7** as a colorless oil (20.0 g, 98%). To a cold (−78 °C) solution of **7** (5.10 g, 18.3 mmol) in CH_2Cl_2 (60 mL) was added dropwise a 1.0 M solution of DIBAL-H in hexane (40 mL, 40 mmol) over 1 h. After 2 h, the reaction mixture was quenched with AcOH (34 mL, 5 M in benzene) at −78 °C and then warmed to room temperature. The mixture was poured into 10% aqueous tartaric acid (100 mL) and extracted with hexane/AcOEt (1:1) (3×60 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed to leave crude *N*-Boc-L-phenylalaninal **8** as a white solid (4.5 g), which usually was immediately used in the next step without further purification. This material was once purified by chromatography on silica gel using AcOEt/hexane (1:3, v/v) as eluent to give a white solid (3.64 g, 80%). ^1H NMR (300 MHz, $CDCl_3$): $\delta=1.43$ (s, 9H, $C(CH_3)_3$), 3.11 (d, $J=$ 6.5 Hz, 2H, $PhCH_2$), 4.40 (m, 1H, $NHCHCH_2Ph$), 5.04 (br s, 1H, NH), 7.16–7.31 (m, 5H, Ph), 9.63 (s, 1H, CHO).

2.1.2. (*S*,*S*,*S*)-Tris(*N*-*tert*-butoxycarbonyl-2-amino-3-phenylpropyl)amine 9. *N*-Boc-L-phenylalaninal **8** (4.88 g, 19.6 mmol, 4.0 equiv.), ammonium acetate (0.38 g, 4.9 mmol, 1.0 equiv.) and $NaHB(OAc)_3$ (6.23 g, 29.4 mmol, 6.0 equiv.) were placed in a flask under an argon atmosphere and THF (200 mL) was added via canula. The reaction mixture was stirred overnight and then was quenched with 10% AcOH/MeOH (50 mL). The solvent was removed in vacuo, and the residue was dissolved in methylene chloride (120 mL) and washed with KOH (4%, 2×50 mL). The organic phase was washed with brine, dried over Na_2SO_4 and evaporated to dryness leaving a yellow solid. The residue was first purified by chromatography on silica gel with ether/hexanes (1:1, v/v) as eluent and then recrystallized from ether/hexanes to give the tetraamine **9** as a white foamy solid (1.76 g, 50%). Mp 108–110 °C. ^1H NMR (300 MHz, $CDCl_3$): $\delta=1.39$ (s, 27H, 3 $C(CH_3)_3$), 2.20 (dd, $J=13.0$, 4.1 Hz, 3H, 3 NCH_aH_b), 2.52 (dd, $J=$ 13.0, 9.5 Hz, 3H, 3 NCH_aH_b), 2.68 (dd, $J=13.7$, 6.6 Hz, 3H, 3 $PhCH_aH_b$), 2.79 (dd, $J=13.7$, 6.7 Hz, 3H, 3 $PhCH_aH_b$), 3.87 (m, 3H, 3 CHNH), 4.83 (brs, 3H, 3 NH), 7.14–7.28 (m, 15H, 3 Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=28.8$, 40.4, 49.8, 57.8, 79.5, 126.5, 128.6, 129.4, 138.44, 156.1.

2.1.3. *N*-Ethoxycarbonyl-L-phenylalaninal 13. L-Phenylalanine methyl ester hydrochloride **6** (20.2 g, 93.6 mmol) was dissolved in water (300 mL) and $NaHCO_3$ (38.3 g, 456 mmol) was added portion-wise. Ethyl chloroformate (25.86 mL, 270.6 mmol) was then added drop wise with vigorous stirring at 0 °C. After 5 h the mixture was allowed to warm to room temperature and was allowed to stir overnight. The mixture was extracted with AcOEt (3× 100 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure to leave *N*-ethoxycarbonyl-L-phenylalanine methyl ester **12** as a colorless oil in a quantitative yield. To a cold (−78 °C) solution of **12** (16.22 g, 64.61 mmol) in CH_2Cl_2 (150 mL) was added drop wise a 1.0 M solution of DIBAL-H in hexane (100 mL, 100 mmol) over 1 h. After 2 h, the reaction mixture was quenched with AcOH (64 mL, 5 M in benzene) at −78 °C and then warmed to room temperature. The mixture was poured into 10% aqueous tartaric acid (200 mL) and extracted with hexane/AcOEt

(1:1, v/v) (3×60 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed to give crude *N*-ethoxycarbonyl-L-phenylalaninal **13** as a white solid (14.12 g, 99%), which was immediately used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.21 (t, J=7.0 Hz, 3H, OCH_2CH_3), 3.12 (d, J=6.6 Hz, 2H, $PhCH_2$), 4.09 (q, J=7.0 Hz, 2H, OCH_2CH_3), 4.48 (q, J=6.6 Hz, 1H, $NHCHCH_2Ph$), 5.18 (br s, 1H, NH), 7.18–7.32 (m, 5H, Ph), 9.64 (s, 1H, CHO).

2.1.4. (*S*,*S*,*S*)-Tris(*N*-ethoxycarbonyl-2-amino-3-phenylpropyl)amine 14. *N*-Ethoxycarbonyl-L-phenylalaninal (5.40 g, 24.4 mmol, 4.0 equiv.), ammonium acetate (0.47 g, 6.1 mmol, 1.0 equiv.) and $NaHB(OAc)_3$ (6.46 g, 30.5 mmol, 5.0 equiv.) were placed in a flask under an argon atmosphere and THF (150 mL) was added via canula. The reaction mixture was stirred overnight at room temperature and was quenched with 10% AcOH/MeOH (50 mL). The solvent was removed in vacuo, the residue was dissolved in methylene chloride (120 mL) and washed with KOH (4%, 2×50 mL). The organic phase was washed with brine, dried over Na_2SO_4 and evaporated to dryness leaving a yellow solid. The residue was first purified by chromatography on silica gel using ether/hexanes (1:1, v/v) as eluent, and then recrystallized from ether/hexanes to give the amine **14** as a white amorphous solid (2.93 g, 76%). Mp 108–110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (s, J=7.2 Hz, 9H, 3 OCH_2CH_3), 2.06 (br d, J=11.7 Hz, 3H, 3 NCH_aH_b), 2.49 (br t, J=12.0 Hz, 3H, 3 NCH_aH_b), 2.59 (dd, J=13.8, 7.2 Hz, 3H, 3 $PhCH_aH_b$), 2.83 (dd, J=13.8, 6.3 Hz, 3H, 3 $PhCH_aCH_b$), 3.90–4.08 (m, 6H, 3 OCH_2CH_3), 4.08–4.25 (m, 3H, 3 CHNH), 5.16 (br d, J=7.5 Hz, 3H, 3 NH), 7.10–7.25 (m, 15H, 3 Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ= 14.8, 40.5, 49.4, 57.4, 60.9, 126.6, 128.6, 129.3, 138.3, 157.5. Anal. calcd for $C_{36}H_{48}N_4O_6$: C, 68.33; H, 7.65; N, 8.85. Found: C, 68.58; H, 7.61; N, 8.73.

From more polar fractions, variable amounts of *N*-ethoxycarbonyl-L-phenylalaninol[26,27] were obtained. Mp 66–67 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.21 (t, J= 7.2 Hz, 3H, CH_3CH_2), 2.1–2.4 (br s, 1H, OH), 2.85 (d, J=7.2 Hz, 2H, $PhCH_2$), 3.56 (dAB, J=11.1, 8.1 Hz, 1H, CH_aH_bOH), 3.67 (dAB, J=11.1, 3.9 Hz, 1H, CH_aH_bOH), 3.85–3.98 (m, 1H, HCN), 4.08 (q, J=7.2 Hz, 2H, CH_2CH_3), 4.85–4.95 (br s, 1H, HN), 7.18–7.34 (m, 5H, Ph).

2.1.5. (*S*,*S*,*S*)-Tris[2-(*N*-methylamino)-3-phenylpropyl]amine 10. *Method A*. To a suspension of $LiAlH_4$ (4.14 g, 109 mmol) in dry THF (130 mL) was added drop wise a solution of the *N*-Boc protected amine **9** (3.00 g, 4.19 mmol) in THF (30 mL) at 0 °C and the reaction mixture was refluxed overnight. Aqueous KOH [KOH (5.0 g) dissolved in H_2O (10 mL)] was carefully added at 0 °C. After addition, the mixture was refluxed for 2 h, and the solution was decanted from the inorganic gel. The gel was refluxed with THF (100 mL) for 1 h, and the solution was decanted. Evaporation of the combined extracts gave a pale yellow oil. The crude **10** was placed in a 10% aqueous HCl (50 mL) solution, the mixture was stirred at room temperature for 4 h, and the solid was filtered off. This pale yellow solid was recrystallized from hot methanol/ether to give **11** as white needles. The solid was dissolved in CH_2Cl_2 (80 mL) and H_2O (30 mL) was added. The biphasic mixture was adjusted to pH 10 by slow addition of 20% aqueous KOH. The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure to give **10** as a pale yellow oil (0.5 g, 26%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.8–2.1 (br s, 3H, 3 NH), 2.13–2.24 (m, 6H, 3 NCH_2), 2.42 (s, 9H, 3 CH_3), 2.44 (dd, J=13.2, 7.2 Hz, 3H, 3 $PhCH_aH_b$), 2.68 (m, 3H, 3 CHNH), 2.81 (dd, J=13.2, 8.4 Hz, 3H, 3 $PhCH_aCH_b$), 7.1–7.3 (m, 15H, 3 Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=34.2, 39.0, 59.5, 59.5, 126.3, 128.6, 129.5, 139.4. HRMS (EI) calcd for $C_{30}H_{42}N_4$: 458.34095. Found: 458.34180.

(S,S,S)-Tris[2-(N-methylamino)-3-phenylpropyl]amine trihydrochloride **11**. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.95 (d, J=13.8 Hz, 3H, 3 $PhCH_aH_b$), 2.73 (dd, J=12.9, 11.4 Hz, 3H, 3 NCH_aH_b), 2.98 (s, 9H, 3 CH_3), 3.05 (t, J= 12.9 Hz, 3H, 3 NCH_aH_b), 3.33 (d, J=13.8 Hz, 3H, 3 $PhCH_aH_b$), 4.27 (m, 3H, CHNH), 7.2–7.4 (m, 15H, 3 Ph), 9.21 (s, 3H, $NH_aH_b^+$), 9.95 (s, 3H, $NH_aH_b^+$).

Method B. To a suspension of $LiAlH_4$ (4.50 g, 118 mmol) in dry THF (150 mL) was added drop wise a solution of *N*-ethoxycarbonyl protected amine **14** (9.80 g, 15.5 mmol) in THF (50 mL) at 0 °C and the reaction mixture was refluxed overnight. Aqueous KOH [from KOH (7.5 g) and water (15 mL)] was carefully added at 0 °C. The mixture was refluxed for 2 h and the solution was decanted from the inorganic gel. The gel was refluxed with THF (100 mL) for 1 h. Evaporation of solvents from the combined extracts gave a pale yellow oil, which was treated with a 10% aqueous HCl (100 mL). The mixture was stirred at room temperature for 4 h, the solid was filtered and recrystallized from hot methanol/ether to give the trihydrochloride **11** as white needles. The solid was dissolved in CH_2Cl_2 (150 mL) and H_2O (50 mL) was added. The biphasic mixture was adjusted to pH 10 by slow addition of 20% aqueous KOH. The organic phase was dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford **10** as a pale yellow oil (5.6 g, 79%) identical in all respects with the material described in Method A.

2.1.6. (3*S*,7*S*,10*S*)-3,7,10-Tribenzyl-2,8,9-trimethyl-2,8,9-triaza-5-azonia-1λ^5-phosphatricyclo[3.3.3.0^{1,5}]undecane chloride 1j. To a solution of $P(NMe_2)_3$ (1.51 g, 9.25 mmol) in CH_3CN (15 mL), PCl_3 (405 μL, 4.67 mmol) was syringed at 0 °C. The resulting solution was stirred at 0 °C for 30 min and then a solution of (*S*,*S*,*S*)-tris[2-(*N*-methylamino)-3-phenylpropyl)amine **10** (5.73 g, 12.5 mmol) in CH_3CN (10 mL) was added via canula at 5 °C. The mixture was stirred at room temperature overnight and the volatiles were removed under vacuum to leave a white foam, which was purified by chromatography on silica gel using $CHCl_3/CH_3OH$ (20:1, v/v) as eluent. The appropriate fractions were collected and recrystallized from benzene to give **1j** (4.63 g, 71%) as colorless plates. Mp 84–86 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.17 (d, J= 18.0 Hz, 9H, 3 CH_3), 2.53 (t, J=12.4 Hz, 3H, 3 NCH_aH_b), 2.55 (br d, J=14.4 Hz, 3H, 3 $PhCH_aH_b$), 2.70–2.77 (m, 3H, 3 NCH_aH_b), 2.85 (dd, J=14.4, 5.6 Hz, 3H, 3 $PhCH_aCH_b$), 3.85 (dt, J=12.4, 5.6 Hz, 3H, 3 NCH), 4.92 (d, J= 515.2 Hz, 1H, PH), 6.99–7.02 (m, 6H, Ph), 7.20–7.30 (m, 9H, Ph). ^{13}C NMR (100 MHz, $CDCl_3$): δ=32.1 (d, J= 14.2 Hz), 35.6 (d, J=6.7 Hz), 49.8 (d, J=7.4 Hz), 51.2

(d, $J=2.1$ Hz), 127.2, 128.6, 130.4, 134.9. ^{31}P NMR (162 MHz, $CDCl_3$): $\delta=-6.76$.

2.1.7. (3*S*,7*S*,10*S*)-3,7,10-Tribenzyl-2,8,9-trimethyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane 2j. A suspension of the hydrochloride **1j** (5.20 g, 9.97 mmol) and potassium *tert*-butoxide (2.24 g, 19.9 mmol) in THF (40 mL) was stirred at room temperature for 2 h. The volatiles were removed in vacuo, and toluene (150 mL) was added to the residue. The mixture was left without stirring overnight, inorganic salts were filtered off, and the solvent was removed in vacuo (0.1 mm Hg) to give proazaphosphatrane **2j** as a white solid (4.0 g, 82%). ^{1}H NMR (400 MHz, C_6D_6): $\delta=2.25$ (dd, $J=14.0$, 11.6 Hz, 3H, 3 NCH_aH_b), 2.30 (dd, $J=14.4$, 6.8 Hz, 3H, 3 PhCH_aH_b), 2.54 (d, $J=10.0$ Hz, 9H, 3 NCH_3), 2.57 (dd, $J=14.0$, 2.4 Hz, 3H, 3 NCH_aH_b), 2.69 (dd, $J=14.4$, 7.8 Hz, 3H, 3 $PhCH_aCH_b$), 3.25 (dddd, $J=11.6$, 7.8, 6.8, 2.4 Hz, 3H, 3 NCH), 7.04–7.20 (m, 15H, 3 Ph). ^{13}C NMR (75.5 MHz, C_6D_6): $\delta=28.7$ (d, $J=34.0$ Hz), 36.1 (d, $J=2.3$ Hz), 54.4 (d, $J=8.4$ Hz), 54.9 (d, $J=3.0$ Hz), 126.1, 128.5, 128.7, 141.0. ^{31}P NMR (162 MHz, C_6D_6): $\delta=124.66$. MS (EI): m/z (M^+, 486). Anal. calcd for $C_{30}H_{39}N_4P$: C, 74.04; H, 8.08; N, 11.51. Found: C, 74.65; H, 7.82; N, 10.99.

2.1.8. (*S*,*S*,*S*)-Tris(2-amino-3-phenylpropyl)amine 15. *Method A*. The *N*-Boc protected amine **9** (2.0 g, 2.8 mmol) was dissolved in trifluoroacetic acid (15 mL) and stirred at room temperature for 2 h. All volatiles were evaporated, the residue was dissolved in methylene chloride (30 mL) and evaporated several times with fresh portions of this solvent in order to remove excess acid leaving finally a pale yellow foamy solid. The salt was dissolved in methylene chloride (50 mL) and water (50 mL) was added. While stirring, the biphasic solution was adjusted to pH 10 by slow addition of 20% KOH. The layers were separated and the aqueous phase was extracted with additional methylene chloride (50 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give the tetraamine **15** as a pale yellow solid (1.15 g) quantitatively. Mp 47–49 °C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.30$–1.70 (br s, 6H, 3 NH_2), 2.29 (dd, $J=12.5$, 2.8 Hz, 3H, 3 NCH_aH_b), 2.39 (dd, $J=12.5$, 10.3 Hz, 6H, 3 NCH_aH_b), 2.44 (dd, $J=13.3$, 8.9 Hz, 3H 3 PhCH_aH_b), 2.66 (dd, $J=13.3$, 4.5 Hz, 3H, 3 $PhCH_aH_b$), 3.15–3.30 (m, 3H, 3 C*H*NH), 7.19–7.29 (m, 15H, 3 Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta=42.6$, 49.9, 61.9, 126.5, 128.7, 129.4, 139.3. HRMS (EI) calcd for $C_{27}H_{36}N_4$: 416.29400, found 416.29495. Anal. calcd for $C_{27}H_{36}N_4$: C, 77.84; H, 8.71; N, 13.45. Found: C, 77.29; H, 8.70; N, 13.19.

Method B. The mixture of the *N*-ethoxycarbonyl protected amine **14** (6.0 g, 9.5 mmol), KOH (17.0 g), ethanol (48 mL) and H_2O (12 mL) was refluxed under an argon atmosphere for 20 h. The volatiles were removed and chloroform (100 mL) was added. The organic phase was washed with water (2×50 mL), brine (50 mL) and was dried over Na_2SO_4. After evaporation of solvents the tetraamine **15** was obtained (4.0 g, 100%) as a pale yellow solid identical in all respects with the material obtained by Method A.

2.2. ee Estimation of mandelonitrile

Method A. To a solution of (4*R*,5*R*)-diisopropoxycarbonyl-2-chloro-1,3,2-dioxaphospholane (33.0 mg, 110 μmol) in chloroform-*d* (0.7 mL) containing triethylamine (17 μL, 120 μmol), mandelonitrile (12.8 mg, 96.1 μmol) was added and the reaction mixture was analyzed by ^{31}P NMR (162 MHz). Two resonances at $\delta=144.38$ and 142.28 ppm in a 1:1 ratio were observed.

Method B. The ^{1}H NMR spectrum of a solution of the racemic mandelonitrile (8.1 mg, 61 μmol) in chloroform-*d* (0.7 mL) was recorded and quinine (39.5 mg, 122 μmol) was added. A clear solution was obtained which was immediately analyzed by ^{1}H NMR spectroscopy (400 MHz). Two resonances for the methine proton in mandelonitrile at $\delta=5{,}512$ and 5.501 ppm were observed in a 1:1 ratio.

Acknowledgements

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Regioselective synthesis of mono- and bis-decahydrobenzocarbazoles via tandem reactions of α-diazo ketones☆

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Abstract—Regioselective intermolecular 1,3-dipolar cycloaddition reactions of rhodium generated carbonyl ylides with indoles are reported in this paper. Intermolecular 1,3-dipolar cycloaddition reactions of five-membered-ring cyclic carbonyl ylides with indole and substituted indoles afforded hexahydro-2*H*-carbazol-2-ones in a regioselective manner. Similarly, reactions of cyclic carbonyl ylides were carried out to afford decahydrobenzo[*c*]carbazoles or decahydrocyclopenta[*c*]carbazoles with high regioselectivity. Interestingly, the other possible regioisomer decahydrobenzo[*a*]carbazoles were also obtained by the reaction of cyclic carbonyl ylides and indoles having electron withdrawing substituents. The structure and stereochemistry of regioisomers 6,11c-epoxy-1,2,3,4,4a,5,6,6a,11b,11c-decahydro-4a-methyl-5-oxo-7*H*-benzo[*c*]carbazole and 11-benzenesulfonyl-6,11b-epoxy-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-4a-methyl-5-oxo-1*H*-benzo[*a*]-carbazole were unequivocally corroborated by single-crystal X-ray analyses. To advance this study, regioselective double 1,3-dipolar cycloaddition reaction of five-membered-ring cyclic carbonyl ylides has been demonstrated for the first time with biindoles having various aryl and alkyl spacers. This process constructed up to eight stereocenters, four carbon–carbon and two carbon–oxygen bonds in a single step with an excellent molecular complexity and stereoselectivity.

1. Introduction

Achieving the maximum pertinent complexity increase while minimizing step count is an ideal synthesis in organic chemistry.[1] Reaction leading to many carbon–carbon bond formations through tandem processes, which can rapidly generate the molecular complexity in a controlled and predictable manner, is a contemporary theme in modern organic synthesis and finds application in accessing newer entities. Complexity and brevity mostly rely on the coupling of individual transformations into one synthetic process. Tandem processes of diverse nature, promoted through thermal or photochemical activation or catalysis, have already proven their utility in organic synthesis and found many applications in the acquisition of complexity in the form of functionalized carbo- and heterocyclic systems. 1,3-Dipolar cycloaddition reaction offers a versatile route[2] for the construction of several synthetically useful complex five-membered heterocycles. Intermolecular 1,3-dipolar cycloadditions have found wide application in the synthesis of a variety of heterocyclic systems. Reactions based on carbenoid transformations are among the synthetically most useful to increase the molecular complexity.[3] Carbenoid reactions provide transient carbonyl ylides, which can readily be trapped inter- or intramolecularly with π-bonds via a range of 1,3-dipolar cycloaddition reactions to afford oxygen-containing polycyclic systems that are amenable to further diverse transformations. Pioneering studies by Padwa and co-workers have established Rh(II)-catalyzed tandem carbonyl ylide formation-1,3-dipolar cycloaddition of diazo carbonyl compounds as an excellent method for the synthesis of oxapolycycles. The carbonyl ylide 1,3-dipolar cycloaddition methodology has been applied to the synthesis of various natural products such as illudin[4] (sesquiterpene), phorbol esters[5] (diterpene), brevicomin[6] (pheromone) and further utilized to approach zaragozic acid[7] and *cis*-nemorensic acids.[8] In addition, complex oxapolycyclics can be readily manouvered to furnish carbocyclic compounds and the reactions of carbonyl ylides have therefore found applications in the synthesis of both heterocyclic as well as carbocyclic systems. The reactions of diazo carbonyl compounds mediated by rhodium(II) acetate catalyst offer in the synthesis of complex oxapolycyclic systems, which are mainly useful for alkaloid and terpenoid synthesis. Indole could prove to be an appropriate starting material for further alkaloid synthesis if suitable chemistry can be developed from this parent skeleton. Successful endeavor has been made to use the

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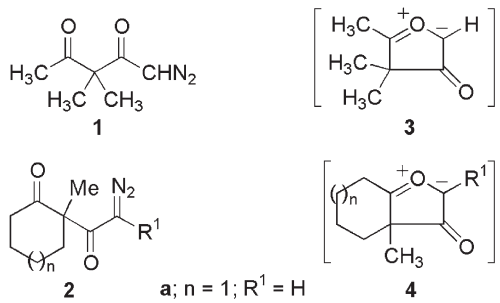


Figure 1.

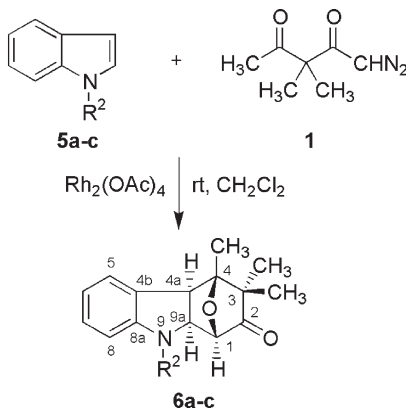
2,3-double bond of indole in 1,3-dipolar cycloaddition reaction of carbonyl ylides,[9] which lead to the synthesis of benzocarbazole derivatives; well known antitumor agents[10] and also used as photoreceptors in electrophotography.[11] Our persisting interest in the chemistry of diazo ketones[12] and 3-diazooxindole systems[13] encouraged us to investigate the detailed reactions of carbonyl ylides with indoles. The synchronizing effects of coupling more than one 1,3-dipolar cycloaddition reaction in a single step can lead to desirable increase in molecular complexity as well as brevity. However, no such attempt has so far been made to couple the 1,3-dipolar carbonyl ylide cycloaddition reactions.[3] Herein, we report highly effective, regioselective rhodium-(II) acetate catalyzed 1,3-dipolar cycloaddition reactions of carbonyl ylides with indoles and biindole systems.

2. Results and discussion

α-Diazo ketones **1** and **2** are used to generate the transient cyclic five-membered-ring carbonyl ylides **3**, **4** (Fig. 1) in the presence of rhodium(II) acetate catalyst. Intramolecular formation and intermolecular 1,3-dipolar cycloaddition reactions of diazo ketones **1** and **2** with heteroaromatic π bonds are investigated in this account. α-Diazo ketone **1** was obtained from ethyl 2,2-dimethyl-3-oxobutyrate and compounds **2a-c** were prepared according to our earlier work[14] from the corresponding carboethoxy cycloalkanones. The required substituted indoles were obtained according to literature[15] methods.

We explored the rhodium(II)-catalyzed behavior of the above α-diazo ketones **1**, **2** with indoles **5** in an intermolecular fashion. The reaction of α-diazo ketone **1** and indole (**5a**) with 0.3 mol% rhodium(II) acetate dimer catalyst in dry dichloromethane was stirred at room temperature under an argon atmosphere for 1.45 h. The chromatographic purification of the above reaction mixture using neutral alumina column furnished the product **6a** in 86% yield (Scheme 1, Table 1) as a single regioisomer.

The presence of a singlet at δ 4.30 for the bridgehead H-1 proton, two doublets at δ 3.85 and 4.24 for the H-4a and H-9a protons, respectively, in the ^{1}H NMR spectrum; an oxygen attached tertiary bridgehead CH-signal (C-1) at δ 85.1 and a quaternary carbon (C-4) at δ 91.9 in the ^{13}C NMR and DEPT experiments confirmed the formation of the oxa-



Scheme 1.

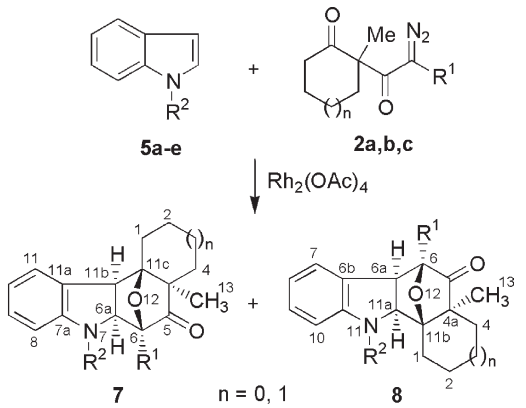
Table 1. Hexahydro-2*H*-carbazol-2-ones produced via Scheme 1

Entry	R^2	Time	Product	Yield[a]
1	H	1.45 h	**6a**	86
2	CH_3	30 min	**6b**	89
3	CH_2Ph	30 min	**6c**	87

[a] Yields refer to isolated and chromatographically pure compounds **6**.

bridged hexahydro-2*H*-carbazol-2-one system **6a**. All these spectral data clearly revealed that the carbonyl ylide underwent 1,3-dipolar cycloaddition to the 2,3-π-bond of the indole systems. Exclusive *exo*-cycloaddition was observed and the assignment of *exo*-addition was made upon inspection of the ^{1}H NMR spectra; the bridgehead H-1 proton of compound **6a** showed a singlet without any coupling. This *exo*-diastereoselection is unique to the intermolecular 1,3-dipolar cycloaddition of carbonyl ylides with indoles. In contrast, the intramolecular cycloaddition reactions with indoles proceeded by *endo*-cycloaddition directed to the α-face of the isomünchnone 1,3-dipoles as observed by Padwa[16] and recently in carbonyl ylides by Boger.[17] The reaction of the α-diazo ketone **1** was further carried out with indoles having an electron donating substituent on the nitrogen atom **5b**,**c** for generality.

Further studies of the Rh(II)-catalyzed behavior of the α-diazo ketone **2a** with unsubstituted indole **5a** and substituted indoles **5b-c** furnished the cycloadducts **7a-c**, respectively, in very good yields (Scheme 2, Table 2) in a regioselective manner. We were further interested to study



Scheme 2.

Table 2. Synthesis of decahydrobenzocarbazoles

Entry	*n*	R^1	R^2	Method[a]	Products
1	1	H	H	A	**7a**
2	1	H	CH_3	A	**7b**
3	1	H	CH_2Ph	A	**7c**
4	1	COOEt	H	B	**7d**
5	1	COOEt	CH_3	B	**7e**
6	1	COOEt	CH_2Ph	B	**7f**
7	0	H	H	A	**7g**
8	0	H	CH_3	A	**7h**
9	1	H	COPh	A	**7i/8i**
10	1	H	SO_2Ph	A	**7j/8j**

[a] Method A, reactions were carried out in CH_2Cl_2 at rt. Method B, reactions were performed in dry benzene at reflux conditions.

the rhodium(II)-catalyzed reactions with a different ring size (*n*) and substituent (R^1) on the diazo substrate **2**. The reaction of α-diazo ketone **2b** with indole, *N*-methylindole or *N*-benzylindole afforded only decahydrobenzo[*c*]carbazole derivatives **7d**-**f** in good yields with regioselectivity. Although the reaction of 1-diazo-2-(1-methyl-2-oxocyclopentyl)-ethan-2-one (**2c**) with indoles **5a**-**b** delivered the decahydrocyclopentacarbazoles **7g**,**h** as the only products, the observed yields are low when compared to the diazo ketones **2a**,**b**. This may be the result of steric hindrance present in decahydrocyclopentacarbazoles **7g**,**h**. The yield of products **7a**-**h** indicated at the maximum of 86% for indoles having electron donating groups (see Section 4). The presence of an electron withdrawing substituent on the indole nitrogen atom (**5d**-**e**) afforded a mixture of regioisomers **7i**, **8i** and **7j**, **8j** with the yields of 36 and 32%, respectively. This indicates that the introduction of electron withdrawing substituents on N-atom of indole ring not only affected the regioselectivity but also reduced the reactivity of the indole heteroaromatic π-bond towards the 1,3-dipolar cycloaddition reactions.

To characterize the regioisomers **7** and **8**, NOE experiments were performed at 25 °C in $CDCl_3$ on the products **7a**-**j** to explicitly indicate that the protons at C-13 on the methyl function underwent an NOE interaction with the proton located at C-11b. On the other hand, the regioisomers **8i** and **8j** showed characteristic NOE interaction of the proton of the C-13 methyl group with the proton at C-11a. Additionally, the proton at C-11b of the cycloadducts **7a**-**j** and C-6a of the cycloadducts **8i**-**j** showed the NOE interaction with a proton present in the aromatic part of the carbazole ring. The protons at 6a of products **7i**-**j** and C-11a of products **8i**-**j** experienced the NOE interactions with the aromatic protons of the benzoyl or benzenesulfonyl groups. A few selected results of NOE interactions are depicted in Figure 2 for the regioisomers **7a**, **7i**, **7j**, **8i**.

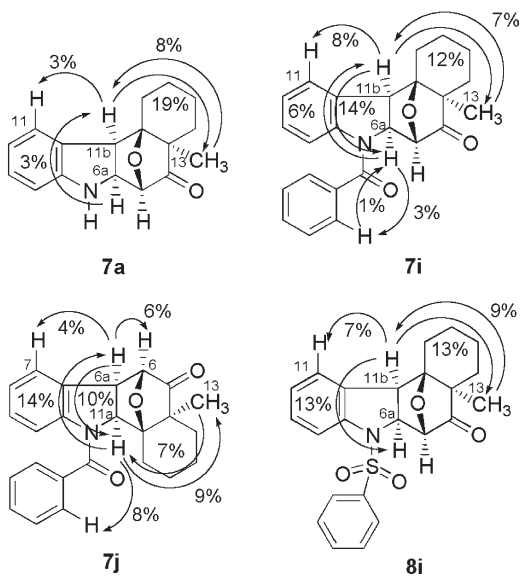


Figure 2.

Alternatively, to characterize the stereo- and regiochemical assignments of the products precisely, we planned to study the single-crystal X-ray analysis.[18] The compound **7a** was recrystallized in chloroform–hexane to provide plate-shaped colorless crystals and subjected to X-ray crystallographic analysis. The X-ray structure of the compound **7a** is shown in Figure 3 and confirms the exact stereochemistry of 6,11c-epoxy-1,2,3,4,4a,5,6,6a,11b,11c-decahydro-4a-methyl-5-oxo-7*H*-benzo[*c*]carbazole (**7a**). The single-crystal X-ray structure revealed that the methyl group at the ring junction is *endo* with respect to the oxa-bridge and the observed angle of oxa-bridge (C6–O12–C11c) is 97.70° in the compound **7a**.

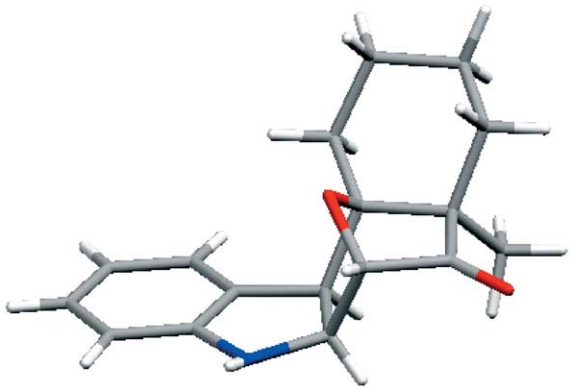


Figure 3. X-ray crystal structure of the cycloadduct **7a**.

The stereochemistry of the product **8j** was unequivocally corroborated by the single crystal analysis. Slow evaporation of a ethyl acetate–hexane solution containing the compound **8j** provided plate-shaped colorless crystals that belongs to the space group $P2_1/n,a$. The X-ray structure of the compound **8j** is shown in Figure 4. The angle of an

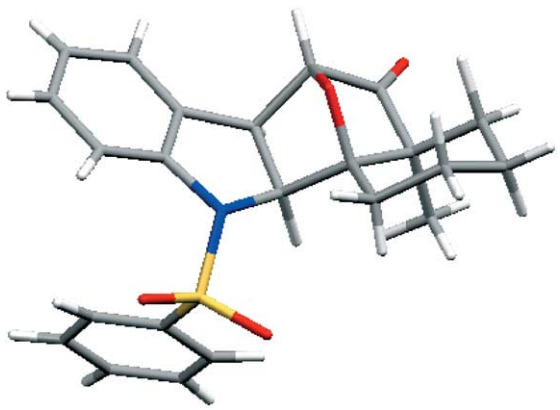
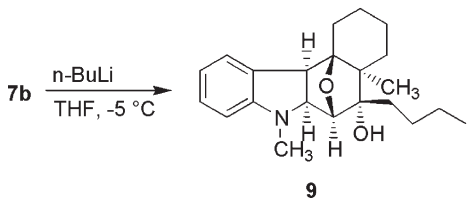


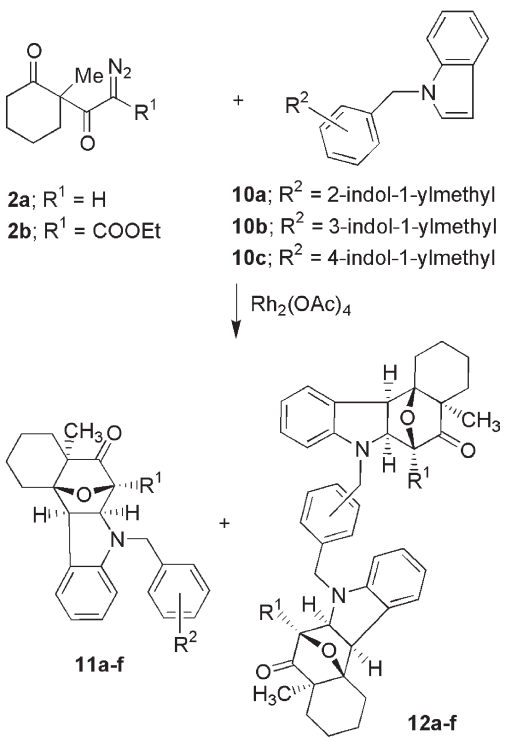
Figure 4. X-ray crystal structure of the cycloadduct **8j**.

oxa-bridge (C6–O12–C11b) is observed as 98.30° in the product **8j**. Moreover, the crystal structure confirms the complete diastereoselectivity and is the result of *exo*-cycloaddition.

The presence of a methyl group at the ring junction in the cycloadducts **7a** and **8j** *endo* with respect to the oxa-bridge is tentatively assigned for other products based on their similarity in spectral data. In all reactions, the exclusive products in the presence of indoles as dipolarophiles were the *exo*-isomers of oxa-bridged hexahydrocarbazoles/decahydrobenzocarbazoles/decahydrocyclopentacarbazoles. In order to further functionalize the decahydrobenzocarbazoles, an attempt was performed in the presence of *n*-butyllithium to afford the nucleophilic addition product **9** in a stereoselective manner. Decahydrobenzo[*c*]carbazole **7b** was reacted with *n*-butyllithium in THF at −5 °C, which gave the nucleophilic addition product **9** (Scheme 3). The product **9** was characterized by the spectral data and the stereochemistry of the butyl group was tentatively assigned based on the favourable *exo*-addition.



Scheme 3.



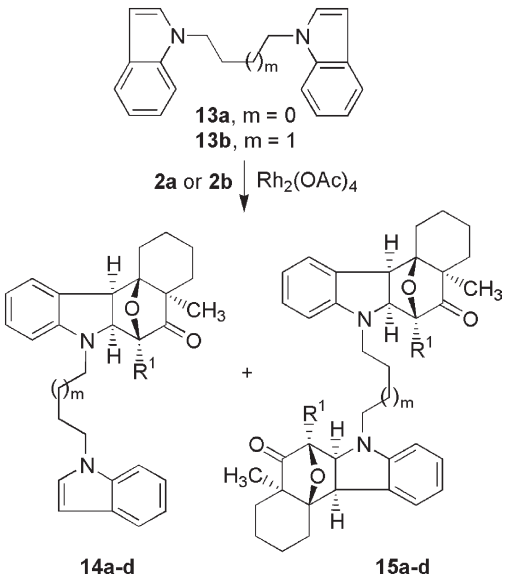
Scheme 4.

After studying the successful intermolecular 1,3-dipolar cycloaddition of the carbonyl ylides, we embarked on the investigation of multiple intermolecular 1,3-dipolar cycloaddition reactions. To perform the rhodium(II)-catalyzed tandem ylide generation and multiple cycloaddition reactions, biindoles[19] **10a-c** were selected as prototypical substrates. Initially, the reaction of biindole **10a** and diazo ketone **2a** in the presence of rhodium(II) acetate catalyst (0.5 mol%) at room temperature (Method A) was performed. An excess amount of diazo ketone was used and the reaction monitored by TLC. The column chromatographic purification of the reaction mixture afforded the products **11a**, **12a** in 40 and 52% yield, respectively (Scheme 4). Spectroscopic analyses revealed that the compound **11a** was a mono-cycloaddition product and that the compound **12a** resulted from an interesting bis-cycloaddition of the carbonyl ylide. Next, the diazo ketone **2b** was reacted with the biindole **10a** in the presence of rhodium(II) acetate dimer catalyst (Method B) to deliver the bis-cycloadduct **12b** in good yield. In an attempt to increase the yield of bis-cycloaddition products, reactions were carried out using various solvents such as 1,2-dichloroethane, hexane and toluene. The reaction in toluene furnished the expected cycloadduct with comparable yield but the yield was reduced in hexane. To our delight, the reactions of diazo ketone **2b** with biindoles **10** in 1,2-dichloroethane (Method C) furnished only the respective bis-cycloadducts **12** in higher yields with almost none or negligible quantities of mono-cycloadducts **11** (Table 3). Unfortunately, at room temperature the reaction of mono-substituted diazo ketone **2a** in 1,2-dichloroethane (Method C) did not produce any significant improvement. Thus in a single step, four carbon–carbon bonds, two carbon–oxygen bonds and eight stereocenters are formed to furnish the highly functionalized polycyclic products in a stereoselective manner.

Table 3. Regioselective synthesis of bis-decahydrobenzocarbazoles having aryl spacer

Entry	R^1	R^2	Method[a]	Product	Yield of **11** (%)	Yield of **12** (%)
1	H	2-Indol-1-methyl	A	**a**	40	52
2	CO_2Et	2-Indol-1-methyl	B	**b**	27	68
3	H	3-Indol-1-methyl	A	**c**	36	63
4	CO_2Et	3-Indol-1-methyl	B	**d**	24	70
5	H	4-Indol-1-methyl	A	**e**	45	50
6	CO_2Et	4-Indol-1-methyl	B	**f**	9	80
7	H	2-Indol-1-methyl	C	**a**	39	48
8	CO_2Et	2-Indol-1-methyl	C[b]	**b**	—	85
9	CO_2Et	3-Indol-1-methyl	C[b]	**d**	—	89
10	CO_2Et	4-Indol-1-methyl	C[b]	**f**	—	84

[a] Method A, reactions were carried out in CH_2Cl_2 at rt. Method B, reactions were performed in dry benzene at reflux conditions. Method C, reactions were performed in 1,2-dichloroethane at rt.
[b] Reactions were refluxed.



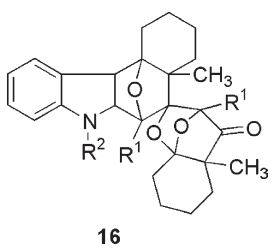
Scheme 5.

After the successful attainment of bis-cycloaddition of carbonyl ylide dipoles with biindoles having aromatic spacers, we were interested to elaborate the utility of the bis 1,3-dipolar cycloaddition processes with the biindoles having aliphatic spacers (Table 4). The biindolyl derivatives **13a**-**b** were synthesized and reacted with diazo ketone **2a** using Method A. The reaction proceeds smoothly and the chromatographic purification afforded the products **14a**, **15a** in 23 and 65% yield (Scheme 5). Gratifyingly, this multiple bond forming reaction delivered the product **15a** in a stereospecific manner. The treatment of α-diazo ketone **2b** with **13a**-**b** in the presence of rhodium(II) acetate following Method C resulted in the selective formation of products **15b** and **15d** (entries 2 and 4, Table 4) respectively, with added functionality. In the presence of excess diazo ketones, it is known[20] that the intermediate carbonyl ylide cycloadd to the carbonyl group of the formed cycloadduct. Interestingly, no 2:1 (**16**, Fig. 5) or 3:1 cycloadducts were observed in these reactions even in the presence of excess α-diazo ketone.

Table 4. Regioselective synthesis of bis-decahydrobenzocarbazoles having aliphatic spacer

Entry	R^1	*m*	Method	Product	Yield of **14** (%)[a]	Yield of **15** (%)[a]
1	H	0	A	**a**	23	65
2	COOEt	0	C	**b**	—	85
3	H	1	A	**c**	29	57
4	COOEt	1	C	**d**	—	80

[a] Yields refer to (with respect to indoles **13**) isolated and chromatographically pure compounds of **14** and **15**.



16

Figure 5. Possible 2:1 cycloadduct.

The above results show that the mechanism by which **1** and **2a**-**c** were converted into cycloadducts involves rapid cyclization of the rhodium carbenoid onto the carbonyl group present at γ-position to give the five-membered cyclic carbonyl ylides **3**, **4a**-**c**, respectively, as intermediates, followed by [3+2]-cycloaddition with the indole derivatives **5**, **10**, **13** as dipolarophiles. The cycloaddition of carbonyl ylides to indoles was highly regio- and stereoselective. The presence of a fused cyclohexane ring and a methyl group in dipole **4a** makes it facially dissymmetric for the approach of a dipolarophile. The reactive center ($C{=}O^{+}{-}C^{-}$) of dipole **4a** is completely planar and the fused cyclohexane ring adopts a chair-like conformation. Indoles as dipolarophile preferably approach the *syn* face to the methyl group of 1,3-dipole **4a** to yield the exclusive *exo*-cycloadducts, which is similar to our earlier experimental and theoretical studies.[12b,14] Thus, we observe only one stereoisomer in the mono-cycloaddition with very good yield. We did not observe any other stereoisomers. In the case of bisindoles, the second indole unit also underwent *exo*-addition to the carbonyl ylide intermediate in a similar manner. The assignment of *exo*-addition in bis-cycloadducts was confirmed based on a characteristic singlet resonance signal for the bridgehead OCH proton in the ^{1}H NMR spectrum. Further, no products resulting from the potential competitive intramolecular C–H insertion[21] and intermolecular N–H insertion[22] reactions (when $R^2{=}H$) of the rhodium carbenoid could be detected.

3. Conclusion

We have demonstrated that the five-membered-ring cyclic carbonyl ylides **3** and **4**, generated from the rhodium(II)-catalyzed reaction of α-diazo ketones **1** and **2**, undergo successful 1,3-dipolar cycloaddition reaction across indole π-bonds to provide novel oxa-bridged mono- and bis-decahydrobenzocarbazoles/decahydrocyclopentacarbazoles in a facile manner. The presence of an electron withdrawing substituent on the indole nitrogen atom provided lower reactivity towards the carbonyl ylide cycloaddition and loss of regioselectivity was observed. This tandem intramolecular cyclization–intermolecular cycloaddition sequence is particularly attractive as eight stereocenters, four carbon–carbon bonds and two carbon–oxygen bonds are formed concomitantly in a single step with a high degree of stereo- and regiocontrol under mild experimental conditions. The stereo- and regiochemistry of the products were unequivocally confirmed by the NOE and X-ray crystallographic studies. Polycyclic compounds with specific stereochemistry are quickly and efficiently generated from simple starting materials. These highly functionalized polycyclic products could serve as flexible building blocks for complex target synthesis.

4. Experimental

4.1. General

Melting points were determined on a capillary melting point

apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer Spectrum GX FT-IR spectrophotometer using KBr pellets or in CH_2Cl_2. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker DPX 200 at 200 MHz using $CDCl_3$ in ppm (δ) related to tetramethylsilane (δ=0.00) as an internal standard and are reported as follows; chemical shift (ppm), multiplicity (br=broad, s=singlet, t=triplet, quat=quartet, m=multiplet), coupling constant (Hz) and integration. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 50.3 MHz in $CDCl_3$. Chemical shifts are reported in delta (δ) units, parts per million (ppm) relative to the center of the triplet at 77.7 ppm for $CDCl_3$. Carbon types were determined from ^{13}C NMR and DEPT experiments. Mass analyses were performed on Jeol DX-303 (with an ionizing voltage of 70 eV), Jeol M Station 700 (FD^+ method in absolute dichloromethane) mass spectrometers or by FAB technique and reported as *m/z* (relative intensity). Elemental analyses were performed on a Perkin Elmer Model 2400 analyzer. X-ray crystallographic analyses were carried out in a Endraf Nonius CAD-4 difractometer with Mo K_α radiation. All solvents were purified by distillation following standard procedures. Thin layer chromatography was performed on silica or alumina plates and components visualized by observation under iodine/UV light at 254 nm. Column chromatography was performed on neutral alumina. All air sensitive reactions were conducted in oven-dried glassware under a positive pressure of argon with magnetic stirring. Reagents were added via syringes through septa. Care has been taken to avoid light during the course of reaction in the synthesis of α-diazo ketones and its further conversion. Biindoles **13a**-**b** were prepared by the literature[19] procedure.

CAUTION! Even though we have noted no explosive tendencies of these α-diazo ketones, it is strongly recommended that they be handled with great care and proper precaution.

4.1.1. Synthesis of 1-diazo-3,3-dimethyl-pentane-2,4-dione (1). Hydrolysis of ethyl 2,2-dimethyl-3-oxobutyrate (3.0 g, 19.0 mmol) was carried out using 5% aqueous KOH solution (20 mL) for 5 h to afford 2,2-dimethyl-3-oxobutyric acid (2.3 g, 91%). To a reaction mixture containing a solution of crude 2,2-dimethyl-3-oxobutyric acid (1.9 g, 14.6 mmol) in dry ether (25 mL) was added oxalyl chloride (1.9 mL, 21.9 mmol) at room temperature for 3 h under an argon atmosphere, concentration at reduced pressure afforded the crude acid chloride which was treated with a solution containing triethylamine (2.6 mL, 19.0 mmol) and ethereal diazomethane solution (300 mL, 30 mmol) under an argon atmosphere at 0 °C for 3 h. After the appropriate period the reaction mixture was stirred at room temperature for 3 h. Concentration under vacuum and purification through a short alumina column afforded 1-diazo-3,3-dimethylpentane-2,4-dione (**1**) (1.5 g, 67%) as a yellow liquid; IR (neat) 3101, 2982, 2106, 1713, 1643, 1468, 1150 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34 (s, 6H, C*H*$_3$), 2.17 (s, 3H, C*H*$_3$), 5.54 (s, 1H, C*H*N$_2$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 22.0 (*C*H$_3$), 26.3 (*C*H$_3$), 54.3 (*C*H), 60.5 (*quat*-C), 194.9 (*C*=O), 207.5 (*C*=O). Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.19. Found: C, 54.65; H, 6.60; N, 18.21.

4.2. General procedure for the synthesis of epoxy-bridged hexahydro-2*H*-carbazol-2-ones (6a-c)

To a dry CH_2Cl_2 solution (10 mL) of an appropriate indole (**5**, 1.5 mmol) and a catalytic amount (0.3 mol%) of $Rh_2(OAc)_4$ taken in a dried round-bottom flask, the CH_2Cl_2 solution (10 mL) of diazo ketone **1** (1.0 mmol) was added slowly under an argon atmosphere using syringe at room temperature. The reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated in vacuo and the residue purified by neutral alumina column chromatography using hexane/ethyl acetate as eluant.

4.2.1. 1,4-Epoxy-3,3,4-trimethyl-1,3,4,4a,9,9a-hexahydro-2*H*-carbazol-2-one (6a). Light brownish solid (86%). Mp 120–122 °C. IR (KBr) 3416 (NH), 2978, 2875, 1758, 1607, 1486, 1468, 1385, 1092, 909, 734 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.08 (s, 3H, C*H*$_3$), 1.15 (s, 3H, C*H*$_3$), 1.38 (s, 3H, C*H*$_3$), 1.91 (s, 1H, N*H*), 3.85 (d, 1H, *J*=8.2 Hz, *H*-4a), 4.24 (d, 1H, *J*=8.2 Hz, *H*-9a), 4.30 (s, 1H, OC*H*, *H*-1), 6.58 (d, 1H, *J*=8.0 Hz, Ar*H*), 6.71 (t, 1H, *J*=7.1 Hz, Ar*H*), 7.01–7.08 (m, 2H, Ar*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 13.7 (*C*H$_3$), 19.7 (*C*H$_3$), 21.5 (*C*H$_3$), 52.1 (*quat-C*), 52.3 (*C*H), 64.9 (N*C*H), 88.5 (O*C*H), 91.9 (*quat-C*), 110.0 (*arom-C*H), 119.0 (*arom-C*H), 126.9 (*quat-C*), 127.2 (*arom-C*H), 129.0 (*arom-C*H), 153.1 (*quat-C*), 218.3 (*quat-C*, *C*=*O*); MS (EI) *m/z* 244 (M+1, 33), 243 (M$^+$, 55), 223 (11), 200 (12), 186 (6), 158 (14), 157 (20), 144 (8), 131 (8), 130 (71). Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.26; H, 7.16; N, 5.85.

4.2.2. 1,4-Epoxy-3,3,4,9-tetramethyl-1,3,4,4a,9,9a-hexahydro-2*H*-carbazol-2-one (6b). Colorless solid (89%). Mp 106–107 °C. IR (KBr) 2976, 1755, 1603, 1491, 1376, 1321, 908 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (s, 3H, C*H*$_3$), 1.16 (s, 3H, C*H*$_3$), 1.37 (s, 3H, C*H*$_3$), 2.83 (s, 3H, NC*H*$_3$), 3.78 (d, 1H, *J*=8.3 Hz, *H*-4a), 3.94 (d, 1H, *J*=8.3 Hz, *H*-9a), 4.42 (s, 1H, OC*H*, *H*-1), 6.36 (d, 1H, *J*=7.9 Hz, Ar*H*), 6.60 (t, 1H, *J*=6.9 Hz, Ar*H*), 6.97 (d, 1H, *J*=7.2 Hz, Ar*H*), 7.12 (d, 1H, *J*=7.8 Hz, Ar*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 13.4 (*C*H$_3$), 19.9 (*C*H$_3$), 21.4 (*C*H$_3$), 33.9 (N*C*H$_3$), 50.4 (*C*H), 52.4 (*quat-C*), 72.2 (*C*H), 85.1 (O*C*H), 92.2 (*quat-C*), 106.5 (*arom-C*H), 116.1 (*arom-C*H), 126.7 (*quat-C*), 126.8 (*arom-C*H), 129.1 (*arom-C*H), 154.3 (*quat-C*), 218.6 (*quat-C*, *C*=*O*); MS (FD^+) *m/z* 257 (M$^+$). Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.79; H, 7.56; N, 5.53.

4.2.3. 1,4-Epoxy-9-benzyl-3,3,4,-trimethyl-1,3,4,4a,9,9a-hexahydro-2*H*-carbazol-2-one (6c). Yellow solid (87%). Mp 109–110 °C. IR (KBr) 2977, 1757, 1604, 1493, 1455, 1384, 1325, 1006, 909, 734 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.05 (s, 3H, C*H*$_3$), 1.13 (s, 3H, C*H*$_3$), 1.41 (s, 3H, C*H*$_3$), 3.84 (d, 1H, *J*=8.3 Hz, *H*-4a), 4.09 (d, 1H, *J*=8.3 Hz, *H*-9a), 4.24 (s, 1H, OC*H*, *H*-1), 4.41 (s, 2H, NC*H*$_2$), 6.34 (d, 1H, *J*=7.9 Hz, Ar*H*), 6.66 (t, 1H, *J*=6.9 Hz, Ar*H*), 7.00–7.07 (m, 2H, Ar*H*), 7.21–7.29 (m, 5H, Ar*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 13.6 (*C*H$_3$), 19.2 (*C*H$_3$), 21.4 (*C*H$_3$), 50.6 (*C*H), 51.7 (NC*H*$_2$), 50.4 (*C*H), 52.5 (*quat*-C), 71.1 (*C*H), 85.6 (O*C*H), 92.3 (*quat*-C), 106.5 (*arom-CH*), 117.3 (*arom-C*H), 126.5 (*quat*-C), 127.0 (*arom-C*H), 127.7 (*arom-C*H), 129.2 (*arom-C*H), 129.4 (*arom-C*H), 138.5 (*quat*-C),

153.9 (*quat*-C), 218.3 (*quat*-C, *C*=*O*); MS (EI) *m*/*z* 335 (M+2, 5), 334 (M+1, 24), 333 (M^+, 78), 290 (7), 276 (9), 247 (8), 223 (10), 220 (10), 207 (7), 91 (100). Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.42; H, 7.12; N, 4.29.

4.3. General procedure for the synthesis of decahydrobenzocarbazole/decahydrocyclopentacarbazole

Method A. In an oven-dried flask, a solution containing appropriate diazo ketone (**2**, 1.0 mmol) and appropriate indole (**5**, 1.5 mmol) in 15 mL of dry CH_2Cl_2 was degassed under an argon atmosphere. To this reaction mixture, 0.3 mol% of rhodium(II) acetate dimer was added at room temperature. The reaction mixture was allowed to stir and followed by TLC until the disappearance of the starting material. The solvent was removed under reduced pressure and the residue purified by neutral alumina column chromatography (EtOAc/hexane) to afford the decahydrobenzocarbazole/decahydrocyclopentacarbazoles.

Method B. By following Method A, dry benzene is used as solvent and the reaction mixture was refluxed.

4.3.1. 6,11c-Epoxy-1,2,3,4,4a,5,6,6a,11b,11c-decahydro-4a-methyl-5-oxo-7*H*-benzo[*c*]carbazole (7a). Colorless solid (71%). Mp 173–175 °C. IR (KBr) 3401 (NH), 2923, 2858, 1752 (C=O), 1603, 1483, 1325, 994, 744 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.13 (s, 3H, CH_3), 1.32–1.97 (m, 8H), 3.72 (d, 1H, *J*=8.2 Hz, *H*-11b), 4.04 (br s, 1H, *H*-7), 4.16 (d, 1H, *J*=8.2 Hz, *H*-6a), 4.34 (s, 1H, *H*-6), 6.54 (d, 1H, *J*=7.8 Hz), 6.66 (t, 1H, *J*=7.8 Hz, Ar*H*), 6.97–7.02 (m, 2H, Ar*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 16.8 (*C*H_3), 20.9 (*C*H_2), 22.6 (*C*H_2), 25.9 (*C*H_2), 30.9 (*C*H_2), 52.1 (*C*-4a), 52.2 (*C*-11b), 64.7 (*C*-6a), 88.4 (*C*-6), 91.0 (*C*-11c), 109.9 (*arom*-*C*H), 118.6 (*arom*-*C*H), 126.3 (*quat*-*C*), 126.8 (*arom*-*C*H), 128.9 (*arom*-*C*H), 157.9 (*quat*-*C*), 217.8 (*C*-5); MS (FD^+) *m*/*z* 269 (M^+). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.67; H, 7.24; N, 5.39.

X-ray crystal data for the compound **7a**. $C_{17}H_{19}NO_2$, *M*=269.33, 0.20×0.16×0.12 mm^3, triclinic, *P*-1, *a*=7.104(2) Å, *b*=8.469(3) Å, *c*=11.607(2) Å, α=82.91(2)°, β=75.74(2)°, γ=89.48(2)°, *V*=671.5(3) $Å^3$, *T*=293(2) K, R_1 =0.0564, wR_2=0.1562 on observed data, *z*=2, D_{calcd}=1.332 mg/m^3, *F*(000)=288, absorption coefficient=0.087 mm^{-1}, λ=0.7107 Å, 1745 reflections were collected on a CAD-4 diffractometer, 1392 observed reflections ($I \geq 2\sigma(I)$). The largest difference peak and hole=0.195 and −0.313 $eÅ^{-3}$, respectively. Crystallographic data for this compound have been deposited[23] with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 232210.

4.3.2. 4a,7-Dimethyl-6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-5-oxo-1*H*-benzo[*c*]carbazole (7b). Colorless solid (84%). Mp 115–117 °C. IR (KBr) 2940, 1750 (C=O), 1603, 1495, 1382, 1302, 993, 746 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.13 (s, 3H, 4a-CH_3), 1.27–1.94 (m, 8H), 2.82 (s, 3H, 7-CH_3), 3.68 (d, 1H, *J*=8.2 Hz, *H*-11b), 3.92 (d, 1H, *J*=8.2 Hz, *H*-6a), 4.50 (s, 1H, *H*-6), 6.35 (d, 1H, *J*=7.8 Hz, Ar*H*), 6.58 (t, 1H, *J*=7.8 Hz, Ar*H*), 6.94 (d, 1H, *J*=7.8 Hz, Ar*H*), 7.07 (t, 1H, *J*=7.8 Hz, Ar*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 16.7 (4a-*C*H_3), 21.0 (*C*H_2), 22.6 (*C*H_2), 25.7 (*C*H_2), 30.9 (*C*H_2), 33.7 (7-*C*H_3), 50.6 (*C*-11b), 51.4 (*C*-4a), 72.0 (*C*-6a), 85.2 (*C*-6), 91.2 (*C*-11c), 106.4 (*arom*-*C*H), 116.9 (*arom*-*C*H), 125.8 (*quat*-*C*), 126.5 (*arom*-*C*H), 129.1 (*arom*-*C*H), 154.6 (*quat*-*C*), 218.4 (*C*-5); MS (FD^+) *m*/*z* 283 (M^+). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.09; H, 7.32; N, 5.13.

4.3.3. 7-Benzyl-6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole (7c). Colorless solid (85%). Mp 204–206 °C. IR (KBr) 2938, 1748, 1600, 1492, 1356, 1299, 1005, 737 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.12 (s, 3H, CH_3), 1.24–1.77 (m, 7H), 2.03–2.06 (m, 1H), 3.75 (d, 1H, *J*=8.2 Hz, *H*-11b), 4.07 (d, 1H, *J*=8.2 Hz, *H*-6a), 4.33 (s, 1H, *H*-6), 4.41 (s, 2H, NCH_2), 6.35 (d, 1H, *J*=7.8 Hz, Ar*H*), 6.60 (t, 1H, *J*=7.6 Hz, Ar*H*), 6.97–7.07 (m, 2H, Ar*H*), 7.21–7.31 (m, 5H, Ar*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 16.8 (*C*H_3), 21.0 (*C*H_2), 22.7 (*C*H_2), 25.9 (*C*H_2), 30.9 (*C*H_2), 50.9 (*C*-11b), 51.0 (*C*-4a), 51.7 (N*C*H_2), 70.9 (*C*-6a), 85.9 (*C*-6), 91.3 (*C*-11c), 106.6 (*arom*-*C*H), 117.1 (*arom*-*C*H), 125.8 (*quat*-*C*), 126.8 (*arom*-*C*H), 127.8 (*arom*-*C*H), 127.9 (*arom*-*C*H), 129.3 (*arom*-*C*H), 129.3 (*arom*-*C*H), 138.5 (*quat*-*C*), 153.9 (*quat*-*C*), 217.9 (*C*-5); MS (FD^+) *m*/*z* 359 (M^+). Anal. Calcd for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.02; H, 7.16; N, 3.76.

4.3.4. [6,11c-Epoxy-1,2,3,4,4a,5,6,6a,11b,11c-decahydro-4a-methyl-5-oxo-7*H*-benzo[*c*]carbazole]-6-carboxylic acid ethyl ester (7d). Brown solid (69%). Mp 155–157 °C. IR (KBr) 3433 (NH), 2939, 1748, 1606, 1489, 1320, 1234, 1083 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.21 (s, 3H, CH_3), 1.35 (t, 3H, *J*=7.1 Hz, OCH$_2$CH_3), 1.38–2.07 (m, 8H), 3.85 (d, 1H, *J*=8.2 Hz, *H*-11b), 4.15 (br s, 1H, *H*-7), 4.29–4.42 (m, 2H, OCH_2CH$_3$), 4.51 (d, 1H, *J*=8.2 Hz, *H*-6a), 6.56 (d, 1H, *J*=7.8 Hz, Ar*H*), 6.66 (t, 1H, *J*=7.7 Hz, Ar*H*), 6.98–7.06 (m, 2H, Ar*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.9 (OCH$_2$*C*H$_3$), 17.1 (4a-*C*H_3), 20.9 (*C*H_2), 22.5 (*C*H_2), 25.7 (*C*H_2), 31.3 (*C*H_2), 51.7 (*C*-4a), 52.9 (*C*-11b), 62.8 (O*C*H_2), 67.1 (*C*-6a), 90.3 (*C*-11c), 95.2 (*C*-6), 110.2 (*arom*-*C*H), 118.8 (*arom*-*C*H), 125.2 (*quat*-*C*), 126.9 (*arom*-*C*H), 129.4 (*arom*-*C*H), 152.8 (*quat*-*C*), 165.7 (*C*OOEt), 211.6 (*C*-5); MS (FD^+) *m*/*z* 341 (M^+). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.59; H, 6.87; N, 4.32.

4.3.5. [4a,7-Dimethyl-6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-5-oxo-1*H*-benzo[*c*]carbazole]-6-carboxylic acid ethyl ester (7e). Brown solid (82%). Mp 150–152 °C. IR (KBr) 2935, 1747, 1602, 1494, 1315, 1141, 1084, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.21 (s, 3H, 4a-CH_3), 1.37 (t, 3H, *J*=7.2 Hz, OCH$_2$CH_3), 1.40–2.09 (m, 8H), 2.86 (s, 3H, 7-CH_3), 3.85 (d, 1H, *J*=8.2 Hz, *H*-11b), 4.17 (d, 1H, *J*=8.2 Hz, *H*-6a), 4.37 (q, 2H, *J*=7.2 Hz, OCH_2CH$_3$), 6.45 (d, 1H, *J*=7.7 Hz, Ar*H*), 6.65 (t, 1H, *J*=7.6 Hz, Ar*H*), 6.96 (d, 1H, *J*=7.7 Hz, Ar*H*), 7.10 (t, 1H, *J*=7.7 Hz, Ar*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.9 (OCH$_2$*C*H$_3$), 17.1 (4a-*C*H_3), 20.9 (*C*H_2), 22.4 (*C*H_2), 25.9 (*C*H_2), 31.4 (*C*H_2), 31.1 (N*C*H_3), 51.4 (*C*-4a), 52.2 (*C*-11b), 62.5 (O*C*H_2), 75.6 (*C*-6a), 89.6 (*C*-11c), 94.5 (*C*-6), 109.1 (*arom*-*C*H), 118.3 (*arom*-*C*H), 125.8 (*quat*-*C*), 126.4 (*arom*-*C*H), 129.3 (*arom*-*C*H), 155.6 (*quat*-*C*), 165.0 (*C*OOEt), 211.1 (*C*-5); MS (FD^+) *m*/*z* 355. Anal. Calcd for

$C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.69; H, 7.21; N, 4.15.

4.3.6. [7-Benzyl-6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole]-6-carboxylic acid ethyl ester (7f). Colorless solid (86%). Mp 178–180 °C. IR (KBr) 2933, 1770, 1719, 1598, 1487, 1325, 1242, 1127, 1016, 762 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.16 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.19 (s, 3H, 4a-CH_3), 1.29–1.39 (m, 2H), 1.66–1.86 (m, 5H), 2.06–2.15 (m, 1H), 3.73–3.98 (m, 3H), 4.29 (d, 1H, J=16.6 Hz), 4.37 (d, 1H, J=8.2 Hz, *H*-6a), 4.61 (d, 1H, J=16.6 Hz), 6.28 (d, 1H, J=8.0 Hz), 6.66 (t, 1H, J=7.8 Hz, Ar*H*), 6.95–7.02 (m, 2H, Ar*H*), 7.14–7.31 (m, 5H, Ar*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.5 (OCH_2CH_3), 17.0 (4a-CH_3), 20.8 (CH_2), 22.4 (CH_2), 25.8 (CH_2), 31.2 (CH_2), 51.3 (*C*-4a), 52.5 (*C*-11b), 55.9 (NCH_2), 62.3 (OCH_2), 74.3 (*C*-6a), 89.4 (*C*-11c), 95.0 (*C*-6), 109.4 (*arom*-CH), 118.5 (*arom*-CH), 126.0 (*quat*-C), 126.4 (*arom*-CH), 127.3 (*arom*-CH), 127.3 (*arom*-CH), 129.0 (*arom*-CH), 129.2 (*arom*-CH), 139.2 (*quat*-C), 155.2 (*quat*-C), 164.8 (*C*OOEt), 211.2 (*C*-5); MS (FD^+) *m*/*z* 431 (M^+). Anal. Calcd for $C_{27}H_{29}NO_4$: C, 75.15; H, 6.77; N, 3.25. Found: C, 75.31; H, 6.82; N, 3.39.

4.3.7. 5,10c-Epoxy-1,2,3,3a,4,5,5a,6,10b,10c-decahydro-3a-methyl-4-oxo-cyclopenta[*c*]carbazole (7g). Brown solid (34%). Mp 148–150 °C. IR (KBr) 3392 (NH), 2963, 2931, 1753, 1653, 1606, 1485, 1461, 1334, 751 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.11 (s, 3H, CH_3), 1.92–2.35 (m, 6H), 3.88 (d, 1H, J=7.8 Hz, *H*-10b), 3.97 (br s, 1H, *H*-6), 4.29 (s, 1H, *H*-5), 4.33 (d, 1H, J=7.8 Hz, *H*-5a), 6.59 (d, 1H, J=7.8 Hz, Ar*H*), 6.70 (t, 1H, J=7.6 Hz, Ar*H*), 7.01–7.33 (m, 2H, Ar*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 19.4 (CH_3), 23.9 (CH_2), 28.4 (CH_2), 34.9 (CH_2), 47.5 (*C*-10b), 60.4 (*C*-3a), 72.8 (*C*-5a), 85.9 (*C*-5), 104.6 (*C*-10c), 106.3 (*arom*-CH), 117.8 (*arom*-CH), 125.8 (*arom*-CH), 127.9 (*quat*-*C*), 127.3 (*arom*-CH), 155.8 (*quat*-*C*), 218.3 (*C*-4); MS (FD^+) *m*/*z* 255 (M^+). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.44; H, 6.65; N, 5.63.

4.3.8. 3a,6-Dimethyl-5,10c-epoxy-1,2,3,3a,4,5,5a,6,10b,10c-decahydro-5-oxo-cyclopenta[*c*]carbazole (7h). Brown solid (44%). Mp 134–136 °C. IR (KBr) 2938, 1754, 1605, 1498, 1460, 1301, 1096, 990, 740 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.09 (s, 3H, 3a-CH_3), 1.90–2.19 (m, 6H), 2.85 (s, 3H, 6-CH_3), 3.79 (d, 1H, J=8.1 Hz, *H*-10b), 4.07 (d, 1H, J=8.1 Hz, *H*-5a), 4.43 (s, 1H, *H*-5), 6.33 (d, 1H, J=7.8 Hz, Ar*H*), 6.58 (t, 1H, J=7.6 Hz, Ar*H*), 6.98–7.11 (m, 2H, Ar*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 19.2 (3a-CH_3), 23.6 (CH_2), 28.0 (CH_2), 33.4 (NCH_3), 34.6 (CH_2), 47.4 (*C*-10b), 59.9 (*C*-3a), 72.5 (*C*-5a), 85.5 (*C*-5), 103.5 (*C*-10c), 105.9 (*arom*-CH), 117.1 (*arom*-CH), 124.8 (*arom*-CH), 127.3 (*quat*-*C*), 129.1 (*arom*-CH), 153.9 (*quat*-*C*), 216.0 (*C*-4); MS (FD^+) *m*/*z* 269 (M^+). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.59; H, 6.97; N, 5.09.

4.3.9. Reaction of 2a with *N*-benzoylindole (5d). Data for 7-benzoyl-6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole (**7i**). Colorless solid (22%). Mp 164–166 °C. IR (KBr) 2939, 1760, 1646 (NCO), 1483, 1382, 1273, 1160, 999, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.19 (s, 3H, CH_3), 1.22–2.24 (m, 8H), 3.73 (d, 1H, J=8.0 Hz, *H*-11b), 4.70 (s, 1H, *H*-6), 4.88 (d, 1H, J=8.0 Hz, *H*-6a), 6.97–7.00 (m, 2H, Ar*H*), 7.11–7.15 (m, 2H, Ar*H*), 7.46–7.56 (m, 5H, Ar*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 16.7 (CH_3), 20.7 (CH_2), 22.8 (CH_2), 26.0 (CH_2), 30.9 (CH_2), 49.0 (*C*-11b), 50.9 (*C*-4a), 66.7 (*C*-6a), 85.9 (*C*-6), 91.4 (*C*-11c), 115.8 (*arom*-CH), 123.4 (*arom*-CH), 127.2 (*arom*-CH), 127.5 (*arom*-CH), 128.6 (*arom*-CH), 129.1 (*quat*-*C*), 129.5 (*arom*-CH), 131.2 (*arom*-CH), 137.1 (*quat*-*C*), 144.9 (*quat*-*C*), 169.3 (NCO), 215.6 (*C*-5); MS (FD^+) *m*/*z* 373 (M^+). Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.03; H, 6.34; N, 3.87.

Data for 11-benzoyl-6,11b-epoxy-2,3,4,4a,5,6,6a,11,11a,11b-decahydro-4a-methyl-5-oxo-1*H*-benzo[*a*]carbazole (**8i**). Colorless solid (14%). Mp 161–163 °C. IR (KBr) 2941, 1758, 1646, 1482, 1378, 1216, 1003, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.19 (s, 3H, CH_3), 1.22–2.18 (m, 8H), 3.83 (d, 1H, J=7.9 Hz, *H*-6a), 4.44 (s, 1H, *H*-6), 5.31 (d, 1H, J=7.9 Hz, *H*-11a), 6.89–7.02 (m, 2H, Ar*H*), 7.22–7.26 (m, 2H, Ar*H*), 7.47–7.54 (m, 5H, Ar*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 16.4 (CH_3), 21.2 (CH_2), 22.6 (CH_2), 24.8 (CH_2), 31.3 (CH_2), 48.3 (*C*-6a), 50.2 (*C*-4a), 65.2 (*C*-6a), 85.5 (*C*-6), 92.9 (*C*-11b), 115.8 (*arom*-CH), 124.9 (*arom*-CH), 125.6 (*arom*-CH), 127.9 (*arom*-CH), 128.1 (*quat*-*C*), 128.8 (*arom*-CH), 129.6 (*arom*-CH), 131.3 (*arom*-CH), 137.2 (*quat*-*C*), 144.3 (*quat*-*C*), 170.9 (NCO), 216.7 (*C*-5); MS (FD^+) *m*/*z* 373 (M^+). Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.43; H, 6.05; N, 3.63.

4.3.10. Crystal data for the compound 8j. $C_{23}H_{23}NO_4S$, M=409.48, 0.18×0.14×0.10 mm^3, monoclinic, $P2_1/n$,a=15.018(4) Å, b=8.054(5) Å, c=16.571(6) Å, β=94.8(2)°, V=1997.3(15) $Å^3$, T=293(2) K, R_1=0.0778, wR_2=0.2328 on observed data, z=4, D_{calcd}=1.362 mg/m^3, $F(000)$=864, absorption coefficient=0.192 mm^{-1}, λ=0.7107 Å, 2602 reflections were collected on a CAD-4 diffractometer, 1576 observed reflections ($I \geq 2\sigma(I)$). The largest difference peak and hole=0.406 and −0.655 $eÅ^{-3}$, respectively. Crystallographic data for this compound have been deposited[23] with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 232211.

4.3.11. Compound 9. Addition of *n*-butyllithium in hexane (1.6 M, 0.46 mL, 7.4 mmol, 7.0 equiv.) to a solution of 4a,7-dimethyl-6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-5-oxo-1*H*-benzo[*c*]carbazole (**7b**, 30 mg, 0.11 mmol) in dry THF (5 mL), was performed under an argon atmosphere at −5 °C provided stirring. The reaction was followed by TLC, the complete disappearance of the starting material **7b** took place after 10 min. The reaction mixture was quenched by dilute hydrochloric acid. The acidic aqueous layer was washed with EtOAc (3×5 mL). The organic layer was washed with water, brine dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (6:94 hexane–EtOAc) to yield **9** as a greenish solid (23 mg, 64%). Mp 162–164 °C. IR (KBr) 3466 (OH), 2931, 1604, 1491, 1381, 1298, 1144, 1028, 909, 735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88–0.99 (m, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.22–1.82 (m, 15H), 2.79 (s, 3H, NCH_3),

3.63 (d, 1H, *J*=8.1 Hz, *H*-11b), 4.23 (s, 1H, *H*-6), 4.34 (d, 1H, *J*=8.1 Hz, *H*-6a), 6.35 (d, 1H, *J*=7.8 Hz, Ar*H*), 6.58 (t, 1H, *J*=7.3 Hz, Ar*H*), 6.91 (d, 1H, *J*=7.2 Hz, Ar*H*), 7.03 (t, 1H, *J*=7.8 Hz, Ar*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.7 (*C*H_3), 16.7 (4a-*C*H_3), 23.1 (*C*H_2), 23.4 (*C*H_2), 24.0 (*C*H_2), 27.6 (*C*H_2), 27.9 (*C*H_2), 34.0 (*C*H_2), 35.1 (N*C*H_3), 37.0 (*C*H_2), 49.3 (*quat-C*), 50.0 (*C*H), 72.0 (*C*H), 82.1 (*quat-C*), 85.8 (*C*H), 91.1 (*quat-C*), 107.1 (*arom-C*H), 116.7 (*arom-C*H), 126.9 (*arom-C*H), 128.2 (*quat*-C), 128.6 (*arom-C*H), 155.3 (*quat-C*); MS (FD$^+$) *m*/*z* 341 (M$^+$). Anal. Calcd for $C_{22}H_{31}NO_2$: C, 76.30; H, 7.47; N, 4.94. Found: C, 76.17; H, 7.59; N, 4.81.

4.4. General procedure for the double 1,3-dipolar cycloaddition of carbonyl ylides with biindoles

Method A. An appropriate biindole (1.0 mmol) was taken in a freshly distilled dry CH_2Cl_2 with a catalytic amount (0.5 mol%) of $Rh_2(OAc)_4$. To the above stirred reaction mixture the CH_2Cl_2 solution of diazo ketones **2a** (4.0 mmol) was added slowly using syringe at rt under an argon atmosphere. The reaction was followed by TLC. After completion of the reaction, the solvent was evaporated in vacuo and the residue purified by neutral alumina column chromatography.

Method B. An appropriate biindole (1.0 mmol), diazo carbonyl compound (4.0 mmol) and the catalyst (0.5 mol%) was taken together in dry benzene at the outset, the reaction mixture was refluxed and proceeded further as in Method A.

Method C. An appropriate biindole (1.0 mmol), diazo carbonyl compound (3.0 mmol) and the catalyst (0.5 mol%) was taken together in dry 1,2-dichloroethane and the reaction mixture stirred or refluxed and proceeded further as in Method A.

4.4.1. Reaction of diazo ketone 2a with 1,2-di[(indol-1-yl)methyl]benzene (10a). *Method A*. Data for compound 6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-7-yl-[2-indol-1-ylmethylbenzyl]-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole (**11a**). Brown solid (40%). Mp 168–170 °C. IR (CH_2Cl_2) 2931, 1751, 1603, 1265 cm^{-1}; ^{1}H NMR (200 MHz, C_6D_6) δ 0.73 (s, 3H, C*H*$_3$), 0.76–0.85 (m, 2H), 0.92–1.36 (m, 5H), 1.05–1.55 (m, 1H), 3.25 (d, *J*=8.2 Hz, 1H, C*H*Ar), 3.47–3.55 (m, 2H), 3.88–3.99 (m, 2H), 4.79 (q, *J*=9.2 Hz, 2H, NC*H*$_2$), 6.00 (d, *J*=7.9 Hz, 1H, Ar*H*), 6.01–6.53 (m, 2H, Ar*H*), 6.56–6.63 (m, 2H, Ar*H*), 6.65–6.73 (m, 2H, Ar*H*), 6.80–6.90 (m, 2H, Ar*H*), 7.03–7.20 (m, 4H, Ar*H*), 7.55–7.64 (m, 1H, Ar*H*); ^{13}C NMR (50.3 MHz, C_6D_6) δ 16.6 (*C*H$_3$), 21.0 (*C*H$_2$), 22.8 (*C*H$_2$), 25.9 (*C*H$_2$), 31.0 (*C*H$_2$), 47.7 (N*C*H$_2$), 49.9 (N*C*H$_2$), 50.9 (*C*HAr), 51.1 (*quat-C*, *C*qCH$_3$), 71.9 (N*C*H), 85.9 (O*C*H), 91.1 (*quat-C*, *C*-11c), 102.8 (*arom-C*H), 106.8 (*arom-C*H), 110.5 (*arom-C*H), 117.6 (*arom-C*H), 120.6 (*arom-C*H), 122.0 (*arom-C*H), 122.6 (*arom-C*H), 126.9 (*arom-C*H), 127.9 (*quat-C*), 128.2 (*arom-C*H), 128.6 (*arom-C*H), 128.7 (*arom-C*H), 128.8 (*arom-C*H), 128.9 (*arom-C*H), 129.2 (*arom-C*H), 135.8 (*quat-C*), 136.1 (*quat-C*), 137.5 (*quat-C*), 153.8 (*quat-C*), 216.0 (*quat-C*, *C*=*O*); MS (FD$^+$) *m*/*z* 488 (M$^+$). Anal. Calcd for $C_{33}H_{32}N_2O_2$: C, 81.12; H, 6.60; N, 5.73. Found: C, 80.89; H, 6.72; N, 5.86.

Data for compound 1,2-di[6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole-7-ylmethyl]benzene (**12a**). Yellow solid (52%). Mp 215–217 °C. IR (CH_2Cl_2) 2933, 1755, 1603, 1491, 1268 cm^{-1}; ^{1}H NMR (200 MHz, C_6D_6) δ 0.94 (s, 6H, C*H*$_3$), 0.99–1.05 (m, 2H), 1.17–2.12 (m, 12H), 1.99–2.07 (m, 2H), 3.45–3.53 (m, 2H, C*H*Ar), 3.77–3.93 (m, 2H, NC*H*), 4.10 (s, 2H, OC*H*), 4.15–4.26 (m, 2H, NC*H*$_2$Ar), 4.37–4.52 (m, 2H, NC*H*$_2$Ar), 6.37 (d, *J*=7.4 Hz, 2*H*, ArH), 6.77 (t, *J*=7.1 Hz, 2H, Ar*H*), 6.92 (d, *J*=6.9 Hz, 2H, Ar*H*), 7.10–7.23 (m, 4H, Ar*H*), 7.42–7.25 (m, 2H, Ar*H*); ^{13}C NMR (50.3 MHz, C_6D_6) δ 16.5 (*C*H$_3$), 21.0 (*C*H$_2$), 22.7 (*C*H$_2$), 25.9 (*C*H$_2$), 31.0 (*C*H$_2$), 49.4 (N*C*H$_2$), 49.7 (N*C*H$_2$), 50.9 (*C*HAr), 51.1 (*quat*-C, *C*qCH$_3$), 71.6 (N*C*H), 71.7 (N*C*H), 85.7 (O*C*H), 85.9 (O*C*H), 91.1 (*quat*-C), 106.5 (*arom-C*H), 106.8 (*arom-C*H), 117.2 (*arom-C*H), 117.4 (*arom-C*H), 126.9 (*arom-C*H), 128.6 (*arom-C*H), 129.0 (*arom-C*H), 129.2 (*arom-C*H), 136.2 (*quat*-C), 136.4 (*quat*-C), 153.9 (*quat*-C), 215.9 (*quat*-C, *C*=*O*); MS (FAB) *m*/*z* 640 (M$^+$). Anal. Calcd for $C_{42}H_{44}N_2O_4$: C, 78.72; H, 6.92; N, 4.37. Found: C, 78.95; H, 6.76; N, 4.48.

4.4.2. Reaction of diazo ketone 2b with 1,2-di[(indol-1-yl)methyl]benzene (10a). *Method B*. Data for compound [6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-7-yl-[2-indol-1-ylmethylbenzyl]-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole]-6-carboxylic acid ethyl ester (**11b**). Brown solid (27%). Mp 187–189 °C. IR (CH_2Cl_2) 3055, 2938, 1769, 1747, 1604, 1489, 1266 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.03 (t, *J*=7.2 Hz, 3H, CH_2CH_3), 1.22 (s, 3H, C*H*$_3$), 1.26–1.40 (m, 2H), 1.59–1.85 (m, 5H), 2.06–2.21 (m, 1H), 3.53–3.63 (m, 2H), 3.93 (d, *J*=8.2 Hz, 1H, C*H*Ar), 4.18 (d, *J*=17.2 Hz, 1H), 4.41 (d, *J*=8.2 Hz, 1H, NC*H*$_2$), 4.50 (d, *J*=17.2 Hz, 1H), 5.30 (s, 2H, NC*H*$_2$), 6.14 (d, *J*=7.8 Hz, 1H, Ar*H*), 6.55 (d, *J*=3.0 Hz, 1H), 6.65–6.78 (m, 2H, Ar*H*), 6.96–7.35 (m, 9H, Ar*H*), 7.64 (d, *J*=8.2 Hz, 1H, Ar*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.4 (*C*H$_3$), 17.1 (*C*H$_3$), 20.8 (*C*H$_2$), 22.5 (*C*H$_2$), 25.9 (*C*H$_2$), 31.3 (*C*H$_2$), 48.1 (*C*H$_2$), 51.3 (*quat-C*, *Cq*CH$_3$), 52.5 (Ar*C*H), 53.6 (*C*H$_2$), 62.3 (*C*H$_2$), 75.4 (N*C*H), 89.7 (*quat-C*), 95.1 (*quat-C*), 102.6 (*arom-C*H), 108.7 (*arom-C*H), 110.3 (*arom-C*H), 118.7 (*arom-C*H), 120.3 (*arom-C*H), 121.7 (*arom-C*H), 122.4 (*arom-C*H), 126.0 (*quat-C*), 126.4 (*arom-C*H), 127.3 (*arom-C*H), 127.6 (*arom-C*H), 128.1 (*arom-C*H), 128.4 (*arom-C*H), 128.7 (*arom-C*H), 129.4 (*arom-C*H), 134.2 (*quat-C*), 137.0 (*quat-C*), 137.2 (*quat-C*), 155.1 (*quat-C*), 165.0 (*quat-C*), 211.3 (*quat-C*, *C*=O); MS (FD$^+$) *m*/*z* 560 (M$^+$). Anal. Calcd for $C_{36}H_{36}N_2O_4$: C, 77.12; H, 6.47; N, 5.00. Found: C, 77.41; H, 6.35; N, 4.86.

Data for compound 1,2-di[((6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole)-6-carboxylic acid ethyl ester)-7-ylmethyl]benzene (**12b**). Colorless solid (68%). Mp 213–215 °C. IR (CH_2Cl_2) 2940, 1769, 1746, 1602, 1489, 1267 cm^{-1}; ^{1}H NMR (200 MHz, C_6D_6) δ 0.67–0.95 (m, 12H, C*H*$_3$), 1.07–1.51 (m, 12H), 1.79–1.92 (m, 4H), 3.26–3.61 (m, 6H), 4.13–4.28 (m, 4H), 4.41–4.55 (m, 2H), 6.15–6.33 (m, 1H), 6.31 (d, *J*=7.8 Hz, 1H, Ar*H*), 6.62–7.05 (m, 8H, Ar*H*), 7.41 (m, 2H, Ar*H*); ^{13}C NMR (50.3 MHz, C_6D_6) δ 14.2 (*C*H$_3$), 14.4 (*C*H$_3$), 16.7 (*C*H$_3$), 20.9 (*C*H$_2$), 22.4 (*C*H$_2$), 25.9 (*C*H$_2$), 31.3 (*C*H$_2$), 51.0 (*quat-C*, *Cq*CH$_3$), 52.5 (*C*H), 52.7 (*C*H), 53.5 (N*C*H$_2$), 53.7 (N*C*H$_2$), 61.9 (O*C*H$_2$), 74.6 (N*C*H), 75.3

(NCH), 89.4 (*quat-C*), 89.6 (*quat-C*), 95.4 (*quat-C*), 108.7 (*arom-C*H), 109.0 (*arom-C*H), 118.3 (*arom-C*H), 118.4 (*arom-C*H), 126.4 (*arom-C*H), 126.7 (*arom-C*H), 127.1 (*arom-C*H), 129.5 (*arom-C*H), 135.9 (*quat-C*), 136.2 (*quat-C*), 155.4 (*quat-C*), 164.9 (*quat-C*), 210.8 (*quat-C*, *C*=*O*); MS (FAB) *m*/*z* 807.3 $(M+Na)^+$, (784.3, M^+). Anal. Calcd for $C_{48}H_{52}N_2O_8$: C, 73.45; H, 6.68; N, 3.57. Found: C, 73.25; H, 6.56; N, 3.68.

4.4.3. Reaction of diazo ketone 2a with 1,3-di[(indol-1-yl)methyl]benzene (10b). *Method A*. Data for compound 6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-7-yl-[3-indol-1-ylmethylbenzyl]-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole (**11c**). Yellow solid (36%). Mp 208–210 °C. IR (CH_2Cl_2) 3055, 2937, 1756, 1604, 1490, 1265 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 0.73 (s, 3H, C*H*$_3$), 0.79–0.89 (m, 2H), 0.94–1.71 (m, 5H), 1.80–1.87 (m, 1H), 3.20 (d, *J*=8.2 Hz, 1H, C*H*Ar), 3.49–3.77 (m, 3H), 4.10 (s, 1H, OC*H*), 4.52 (s, 2H, NCH_2), 5.97 (d, *J*=7.9 Hz, 1H, Ar*H*), 6.43 (d, *J*=3.0 Hz, 1H, Ar*H*), 6.54 (t, *J*=7.1 Hz, 2H, ArH), 6.63–6.92 (m, 6H, Ar*H*), 6.98–7.09 (m, 3H, Ar*H*), 7.56–7.61 (m, 1H, Ar*H*); ^{13}C NMR (50.3 MHz, C_6D_6) δ 16.6 (*C*H$_3$), 21.1 (*C*H$_2$), 22.8 (*C*H$_2$), 25.9 (*C*H$_2$), 31.1 (*C*H$_2$), 50.1 (N*C*H$_2$), 50.9 (N*C*H$_2$), 51.2 (*quat-C*, *Cq*CH$_3$), 71.2 (N*C*H), 85.9 (O*C*H), 91.1 (*quat-C*, *C*-11c), 102.5 (*arom-C*H), 106.4 (*arom-C*H), 110.5 (*arom-C*H), 117.1 (*arom-C*H), 120.4 (*arom-C*H), 121.9 (*arom-C*H), 122.5 (*arom-C*H), 125.8 (*arom-C*H), 126.1 (*arom-C*H), 126.8 (*arom-C*H), 126.9 (*arom-C*H), 128.7 (*arom-C*H), 129.1 (*arom-C*H), 129.6 (*arom-C*H), 137.2 (*quat-C*), 139.0 (*quat-C*), 139.6 (*quat-C*), 153.9 (*quat-C*), 216.1 (*quat-C*, *C*=*O*); MS (FD^+) *m*/*z* 488 (M^+). Anal. Calcd for $C_{33}H_{32}N_2O_2$: C, 81.12; H, 6.60; N, 5.73. Found: C, 81.36; H, 6.78; N, 5.61.

Data for compound 1,3-di[6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole-7-ylmethyl]benzene (**12c**). Colorless solid (63%). Mp 209–211 °C. IR (CH_2Cl_2) 2938, 1756, 1604, 1266 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 0.75 (s, 3H, C*H*$_3$), 0.78 (s, 3H, C*H*$_3$), 0.83–0.96 (m, 2H), 1.04–1.44 (m, 9H), 1.53–1.65 (m, 3H), 1.81–1.87 (m, 2H), 3.20–3.31 (m, 2H, C*H*Ar), 3.65–3.83 (m, 6H, NCH_2Ar, NC*H*), 4.20 (s, 2H, OC*H*), 6.01–6.11 (m, 2H, Ar*H*), 6.52–6.59 (m, 2H, Ar*H*), 6.68–6.74 (m, 2H, Ar*H*), 6.88–6.97 (m, 4H, Ar*H*), 7.04 (m, 2H, Ar*H*); ^{13}C NMR (50.3 MHz, C_6D_6) δ 16.6 (*C*H$_3$), 16.7 (*C*H$_3$), 21.1 (*C*H$_2$), 22.8 (*C*H$_2$), 25.9 (*C*H$_2$), 31.1 (*quat-C*, *Cq*CH$_3$), 31.2 (*C*H$_2$), 50.6 (N*C*H$_2$), 50.9 (*C*HAr), 51.0 (*C*HAr), 51.2 (N*C*H$_2$), 70.8 (N*C*H), 71.1 (N*C*H), 85.8 (O*C*H), 85.9 (O*C*H), 91.0 (*quat-C*, O*Cq*), 91.1 (*quat-C*, O*Cq*), 106.5 (*arom-C*H), 106.6 (*arom-C*H), 116.9 (*arom-C*H), 117.0 (*arom-C*H), 126.1 (*arom-C*H), 126.9 (*arom-C*H), 129.1 (*arom-C*H), 129.2 (*arom-C*H), 129.7 (*arom-C*H), 139.3 (*quat-C*), 139.5 (*quat-C*), 154.0 (*quat-C*), 216.2 (*quat-C*, *C*=*O*); MS (FAB) *m*/*z* 663.3 $(M+Na)^+$, 640.3 (M^+). Anal. Calcd for $C_{42}H_{44}N_2O_4$: C, 78.72; H, 6.92; N, 4.37. Found: C, 78.93; H, 6.85; N, 4.46.

4.4.4. Reaction of diazo ketone 2b with 1,3-di[(indol-1-yl)methyl]benzene (10b). *Method B*. Data for compound [6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-7-yl-(3-indol-1-ylmethylbenzyl)-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole]-6-carboxylic acid ethyl ester (**11d**). Yellow oil (24%). IR (CH_2Cl_2) 2939, 1770, 1748, 1608, 1488, 1329 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 0.71–0.86 (m, 6H), 0.93–1.08 (m, 2H), 1.15–1.65 (m, 5H), 1.86–1.98 (m, 1H), 3.41–3.52 (m, 2H), 3.63–3.79 (m, 1H), 4.07–4.16 (m, 2H), 4.32–4.47 (m, 1H), 4.56–4.75 (m, 2H), 6.35 (d, *J*=7.2 Hz, 1H), 6.52–6.89 (m, 6H, Ar*H*), 6.94–7.16 (m, 6H, Ar*H*), 7.67–7.70 (m, 1H, Ar*H*); ^{13}C NMR (50.3 MHz, C_6D_6) δ 13.9 (*C*H$_3$), 16.3 (*C*H$_3$), 20.5 (*C*H$_2$), 22.0 (*C*H$_2$), 25.5 (*C*H$_2$), 30.9 (*C*H$_2$), 49.9 (N*C*H$_2$), 50.7 (*quat-C*, *Cq*CH$_3$), 52.2 (*C*H), 55.3 (N*C*H$_2$), 61.5 (*C*H$_2$), 73.9 (N*C*H), 88.9 (*quat-C*), 95.1 (*quat-C*), 102.1 (*arom-C*H), 108.8 (*arom-C*H), 110.2 (*arom-C*H), 118.1 (*arom-C*H), 119.9 (*arom-C*H), 121.4 (*arom-C*H), 122.0 (*arom-C*H), 125.1 (*arom-C*H), 125.3 (*arom-C*H), 125.9 (*arom-C*H), 126.1 (*quat-C*), 126.3 (*arom-C*H), 128.4 (*arom-C*H), 128.9 (*arom-C*H), 129.1 (*quat-C*), 136.9 (*quat-C*), 138.7 (*quat-C*), 139.9 (*quat-C*), 155.0 (*quat-C*), 164.5 (*quat-C*), 210.4 (*quat-C*, *C*=*O*); MS (FD^+) *m*/*z* 560 (M^+). Anal. Calcd for $C_{36}H_{36}N_2O_4$: C, 77.12; H, 6.47; N, 5.00. Found: C, 76.85; H, 6.39; N, 5.13.

Data for compound 1,3-di[((6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole)-6-carboxylic acid ethyl ester)-7-ylmethyl]benzene (**12d**). Colorless solid (70%). Mp 108–110 °C. IR (CH_2Cl_2) 2939, 1770, 1749, 1604, 1267 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 1.09 (s, 6H, C*H*$_3$), 1.10–1.14 (m, 6H), 1.38–1.86 (m, 12H), 2.06–2.18 (m, 4H), 3.72–4.06 (m, 6H), 4.34–4.49 (m, 4H), 4.62–4.79 (m, 2H), 6.37 (d, *J*=8.1 Hz, 1H, Ar*H*), 6.46–6.50 (m, 2H, Ar*H*), 6.84–7.00 (m, 4H, Ar*H*), 7.09–7.39 (m, 5H, Ar*H*); ^{13}C NMR (50.3 MHz, C_6D_6) δ 14.4 (*C*H$_3$), 16.6 (*C*H$_3$), 20.9 (*C*H$_2$), 22.4 (*C*H$_2$), 25.9 (*C*H$_2$), 31.4 (*C*H$_2$), 51.0 (*quat-C*, *Cq*CH$_3$), 52.5 (*C*H), 52.6 (*C*H), 55.3 (N*C*H$_2$), 55.8 (N*C*H$_2$), 62.0 (O*C*H$_2$), 73.9 (N*C*H), 74.3 (N*C*H), 89.3 (*quat-C*), 95.4 (*quat-C*), 109.2 (*arom-C*H), 118.2 (*arom-C*H), 118.3 (*arom-C*H), 125.0 (*arom-C*H), 125.1 (*arom-C*H), 125.7 (*arom-C*H), 126.4 (*arom-C*H), 126.5 (*arom-C*H), 140.0 (*quat*-C), 140.1 (*quat-C*), 155.3 (*quat-C*), 155.6 (*quat-C*), 164.9 (*quat-C*), 211.0 (*quat-C*, *C*=*O*); MS (FAB) *m*/*z* 785 (M+1), 784 (M^+). Anal. Calcd for $C_{48}H_{52}N_2O_8$: C, 73.45; H, 6.68; N, 3.57. Found: C, 73.27; H, 6.57; N, 3.82.

4.4.5. Reaction of diazo ketone 2a with 1,4-di[(indol-1-yl)methyl]benzene (10c). *Method A*. Data for compound 6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-7-yl-[4-indol-1-ylmethylbenzyl]-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole (**11e**). Orange solid (45%). Mp 152–154 °C. IR (CH_2Cl_2) 2934, 1758, 1727, 1604, 1285 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 1.10 (s, 3H, C*H*$_3$), 1.18–1.99 (m, 7H), 2.17–2.24 (m, 1H), 3.64 (d, *J*=8.2 Hz, 1H, C*H*Ar), 4.02–4.25 (m, 3H), 4.52 (s, 1H, OC*H*), 4.92 (s, 2H, NCH_2), 6.37 (d, *J*=7.8 Hz, 1H, Ar*H*), 6.80 (d, *J*=3.0 Hz, 1H, Ar*H*), 6.88–7.04 (m, 4H, Ar*H*), 7.10 (d, *J*=7.1 Hz, 1*H*), 6.19–7.46 (m, 6H, Ar*H*), 7.95–7.99 (m, 1H, Ar*H*); ^{13}C NMR (50.3 MHz, C_6D_6) δ 16.5 (*C*H$_3$), 21.0 (*C*H$_2$), 22.7 (*C*H$_2$), 25.8 (*C*H$_2$), 31.0 (*C*H$_2$), 49.9 (N*C*H$_2$), 50.7 (N*C*H$_2$), 50.9 (Ar*C*H), 51.1 (*quat-C*, *Cq*CH$_3$), 71.1 (N*C*H), 85.8 (O*C*H), 91.0 (*quat-C*, *C*-11c), 102.5 (*arom-C*H), 106.4 (*arom-C*H), 110.4 (*arom-C*H), 117.0 (*arom-C*H), 120.4 (*arom-C*H), 121.8 (*arom-C*H), 122.4 (*arom-C*H), 126.8 (*arom-C*H), 127.5 (*arom-C*H), 127.9 (*arom-C*H), 128.6 (*arom-C*H), 129.1 (*arom-C*H), 137.3 (*quat-C*), 138.2 (*quat-C*), 153.8 (*quat-C*), 216.2 (*quat-C*, *C*=*O*); MS (EI) *m*/*z* 489 (M+1, 5),

489 (M^+, 15), 376 (9), 336 (32), 298 (22), 269 (17), 255 (27), 241 (14), 236 (14), 227 (11), 220 (36), 181 (38), 153 (37), 123 (50), 111 (28), 91 (42). Anal. Calcd for $C_{33}H_{32}N_2O_2$: C, 81.12; H, 6.60; N, 5.73. Found: C, 81.34; H, 6.74 N, 5.62.

Data for compound 1,4-di[6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole-7-ylmethyl]benzene (**12e**). Yellow solid (50%). Mp 208–210 °C. IR (CH_2Cl_2) 2935, 1756, 1604, 1491, 1286 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 1.07 (s, 6H, C*H*$_3$), 1.22–1.83 (m, 12H), 1.92–2.04 (m, 2H), 2.16–2.27 (m, 2H), 3.65 (d, *J*=8.1 Hz, 2H, C*H*Ar), 4.08 (d, *J*=8.1 Hz, 2H, NC*H*), 4.13–4.29 (m, 4H, NCH_2Ar), 4.55 (s, 2H, OC*H*), 6.42–6.52 (m, 2H, Ar*H*), 6.92 (t, *J*=7.3 Hz, 2H, Ar*H*), 7.10 (d, *J*=7.1 Hz, 2H, Ar*H*), 7.18–7.43 (m, 6H, Ar*H*); ^{13}C NMR (50.3 MHz, C_6D_6) δ 22.1 (*C*H$_3$), 26.6 (*C*H$_2$), 28.3 (*C*H$_2$), 31.4 (*C*H$_2$), 36.6 (*C*H$_2$), 56.5 (Ar*C*H), 56.7 (*quat-C*, *CqC*H$_3$), 76.5 (N*C*H), 76.6 (N*C*H), 91.4 (O*C*H), 96.6 (*quat-C*, O*Cq*), 105.0 (*arom-C*H), 112.1 (*arom-C*H), 122.4 (*arom-C*H), 131.7 (*quat-C*), 132.3 (*arom-C*H), 133.7 (*arom-C*H), 134.7 (*arom-C*H), 136.7 (*quat-C*), 143.4 (*quat-C*), 159.5 (*quat-C*), 221.7 (*quat-C*, *C*=*O*); MS (EI) *m*/*z* 641 (M+1, 3), 640 (M^+, 7), 488 (33), 387 (22), 376 (17), 349 (11), 336 (81), 235 (15), 124 (11), 123 (100), 104 (58). Anal. Calcd for $C_{42}H_{44}N_2O_4$: C, 78.72; H, 6.92; N, 4.37. Found: C, 78.93; H, 6.83; N, 4.45.

4.4.6. Reaction of diazo ketone 2b with 1,4-di[(indol-1-yl)methyl]benzene (10c). *Method B*. Data for compound [6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-7-yl-(4-indol-1-ylmethylbenzyl)-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole]-6-carboxylic acid ethyl ester (**11f**). Brown solid (9%). Mp 152–154 °C. IR (CH_2Cl_2) 2942, 1769, 1746, 1488, 1265 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 0.73–0.83 (m, 6H), 0.92–1.00 (m, 1H), 1.14–1.65 (m, 5H), 1.85–1.97 (m, 2H), 3.42–3.66 (m, 3H), 4.08–4.22 (m, 2H), 4.50 (d, *J*=7.4 Hz, 1H), 4.63 (s, 2H, NCH_2), 6.15–6.19 (m, 1H, Ar*H*), 6.51 (d, *J*=2.1 Hz, 1H, Ar*H*), 6.68–6.80 (m, 4H, Ar*H*), 6.98 (t, *J*=7.4 Hz, 1H), 7.06–7.15 (m, 6H, Ar*H*), 7.67–7.69 (m, 1H, Ar*H*); ^{13}C NMR (50.3 MHz, C_6D_6) δ 14.2 (*C*H$_3$), 16.6 (*C*H$_3$), 20.8 (*C*H$_2$), 22.4 (*C*H$_2$), 25.9 (*C*H$_2$), 31.3 (*C*H$_2$), 50.0 (N*C*H$_2$), 51.0 (*quat-C*, *CqC*H$_3$), 52.5 (N*C*H), 55.4 (*C*H$_2$), 61.9 (*C*H$_2$), 74.1 (N*C*H), 85.8 (O*C*H), 89.3 (*quat-C*, *C*-11c), 102.4 (*arom-C*H), 109.1 (*arom-C*H), 110.5 (*arom-C*H), 118.4 (*arom-C*H), 120.3 (*arom-C*H), 121.8 (*arom-C*H), 122.3 (*arom-C*H), 126.5 (*arom-C*H), 127.5 (*arom-C*H), 128.3 (*arom-C*H), 128.7 (*arom-C*H), 129.3 (*arom-C*H), 136.9 (*quat-C*), 139.1 (*quat-C*), 155.3 (*quat-C*), 164.8 (*quat-C*), 210.8 (*quat-C*, *C*=*O*); MS (FD^+) *m*/*z* 560 (M^+). Anal. Calcd for $C_{36}H_{36}N_2O_4$: C, 77.12; H, 6.47; N, 5.00. Found: C, 77.37; H, 6.63; N, 5.16.

Data for compound 1,4-di[((6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole)-6-carboxylic acid ethyl ester)-7-ylmethyl]benzene (**12f**). Colorless solid (80%). Mp 122–124 °C. IR (CH_2Cl_2) 2941, 1770, 1748, 1605, 1267 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 0.77 (s, 6H, C*H*$_3$), 0.84–1.01 (m, 6H), 1.07–1.55 (m, 12H), 1.76–1.89 (m, 4H), 3.36–3.41 (m, 2H, C*H*Ar), 3.54–3.86 (m, 4H), 4.04–4.16 (m, 4H), 4.43 (d, *J*=16.5 Hz, 2H), 6.12–6.20 (m, 3H, Ar*H*), 6.56–6.67 (m, 4H, Ar*H*), 6.81–6.86 (m, 2H, Ar*H*), 7.02–7.17 (m, 3H, Ar*H*); ^{13}C NMR (50.3 MHz, C_6D_6) δ 14.4 (*C*H$_3$), 16.6 (*C*H$_3$), 20.8 (*C*H$_2$), 22.4 (*C*H$_2$), 25.9 (*C*H$_2$), 31.3 (*C*H$_2$), 51.0 (*quat-C*, *CqC*H$_3$), 52.4 (*C*H), 52.5 (*C*H), 55.3 (NCH_2), 62.0 (OCH_2), 62.1 (OCH_2), 73.8 (N*C*H), 74.0 (N*C*H), 89.3 (*quat-C*), 95.4 (*quat-C*), 109.2 (*arom-C*H), 109.4 (*arom-C*H), 118.3 (*arom-C*H), 126.5 (*quat-C*), 127.4 (*arom-C*H), 127.6 (*arom-C*H), 129.2 (*arom-C*H), 138.2 (*quat-C*), 155.4 (*quat-C*), 164.9 (*quat-C*), 210.9 (*quat-C*, *C*=*O*); MS (FD^+) *m*/*z* (784, M^+). Anal. Calcd for $C_{48}H_{52}N_2O_8$: C, 73.45; H, 6.68; N, 3.57. Found: C, 73.32; H, 6.79; N, 3.66.

4.4.7. Preparation of 1,3-di(indol-1-yl)propane (13a). Indole (2.00 g, 17.07 mmol) was added to a suspension of potassium hydroxide (3.83 g, 68.29 mmol) in dry DMSO (30 mL) under nitrogen. After 0.75 h, 1,3-dibromopropane (1.73 g, 8.54 mmol) was added at 0 °C and stirred at the same temperature for an hour and allowed to warm to room temperature. After 16 h, water (10 mL) was added and the mixture extracted with dichloromethane (3×40 mL). The combined organics were washed with water (3×40 mL), brine (3×40 mL) and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. Purification by neutral alumina column chromatography (EtOAc–hexane, 10:90) yielded the title compound **13a** (2.89 g, 65%) as yellow oil. IR (CH_2Cl_2) 1512, 1461, 1400, 1315, 1242, 1174, 908, 735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.31 (p, *J*=7.5 Hz, 2H, CH_2), 3.99 (t, *J*=6.7 Hz, 4H, NCH_2), 6.49 (d, *J*=3.0 Hz, 2H, Ar*H*), 6.97 (d, *J*=3.0 Hz, 2H, Ar*H*), 7.05–7.35 (m, 6H, Ar*H*), 7.63 (d, *J*=7.1 Hz, 2H, Ar*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 30.9 (*C*H$_2$), 44.1 (N*C*H$_2$), 102.5 (*arom-C*H), 110.3 (*arom-C*H), 120.5 (*arom-C*H), 122.1 (*arom-C*H), 122.6 (*arom-C*H), 128.5 (*arom-C*H), 129.7 (*quat-C*), 136.8 *quat-C*).

4.4.8. Reaction of diazo ketone 2a with 1,3-di(indol-1-yl)propane (13a). *Method A*. Data for compound 6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-[-7-yl-(indol-1-ylpropyl)]-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole (**14a**). Brown solid (23%). Mp 128–130 °C. IR (CH_2Cl_2) 2939, 1755, 1604, 1489, 1462, 1159 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.17 (s, 3H, C*H*$_3$), 1.36–1.69 (m, 7H), 1.81–2.20 (m, 3H), 3.21 (t, *J*=7.2 Hz, 2H, NCH_2), 3.73 (d, *J*=8.2 Hz, 1H, C*H*Ar), 4.07 (d, *J*=8.2 Hz, 1H, NC*H*), 4.22 (t, *J*=6.8 Hz, 2H, NCH_2), 4.47 (s, 1H, OC*H*), 6.22 (d, *J*=7.9 Hz, 1H, Ar*H*), 6.54 (d, *J*=2.3 Hz, 1H, Ar*H*), 6.62 (t, *J*=7.3 Hz, 1H, C*H*Ar), 6.95–7.34 (m, 6H, Ar*H*), 7.66 (d, *J*=7.8 Hz, 1H, Ar*H*); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 16.9 (*C*H$_3$), 21.1 (*C*H$_2$), 22.8 (*C*H$_2$), 26.0 (*C*H$_2$), 28.6 (*C*H$_2$), 31.1 (*C*H$_2$), 44.5 (N*C*H$_2$), 45.7 (N*C*H$_2$), 51.0 (Ar*C*H), 51.5 (*quat*-C, *Cq*CH$_3$), 70.6 (N*C*H), 86.2 (O*C*H), 91.4 (*quat*-C, *C*-11c), 102.3 (*arom-C*H), 107.3 (*arom-C*H), 110.0 (*arom-C*H), 117.6 (*arom-C*H), 120.1 (*arom-C*H), 121.8 (*arom-C*H), 122.3 (*arom-C*H), 126.1 (*quat-C*), 126.9 (*arom-C*H), 128.3 (*arom-C*H), 129.2 (*arom-C*H), 136.7 (*quat-C*), 138.2 (*quat-C*), 153.6 (*quat-C*), 218.0 (*quat-C*, *C*=*O*); MS (FAB) *m*/*z* 427 (M+1). Anal. Calcd for $C_{28}H_{30}N_2O_2$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.72; H, 7.16; N, 6.59.

Data for compound 1,3-di[6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole-7-yl]propane (**15a**). Brown solid (65%). Mp 91–93 °C. IR (CH_2Cl_2) 3020, 2939, 1755, 1604, 1490, 1216 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.15 (s, 6H,

CH_3), 1.31–2.13 (m, 18H), 3.27 (dt, J=19.9, 7.4 Hz, 4H, NCH_2), 3.27 (dd, J=8.2, 3.3 Hz, 2H, CHAr), 3.72 (dd, J=8.2, 3.8 Hz, 2H, NCH), 4.46 (s, 1H, OCH), 4.47 (s, 1H, OCH), 6.35 (dd, J=7.8, 3.7 Hz, 2H, ArH), 6.59 (t, J=7.3 Hz, 2H, ArH), 6.97 (d, J=7.2 Hz, 2H, ArH), 7.05 (t, J=7.8 Hz, 2H, ArH); ^{13}C NMR (50.3 MHz, C_6D_6) δ 16.9 (*C*H_3), 21.1 (*C*H_2), 22.7 (*C*H_2), 25.5 (*C*H_2), 25.9 (*C*H_2), 31.0 (*C*H_2), 45.6 (N*C*H_2), 45.7 (N*C*H_2), 50.9 (*C*H), 51.5 (*quat*-C, *Cq*CH_3), 70.5 (N*C*H), 70.6 (N*C*H), 86.1 (O*C*H), 91.4 (*quat-C*, O*C*q), 107.0 (*arom-C*H), 107.2 (*arom-C*H), 117.3 (*arom-C*H), 126.1 (*quat-C*), 126.8 (*arom-C*H), 129.2 (*arom-C*H), 153.5 (*quat*-C), 218.1 (*quat-C*, *C*=*O*); MS (FAB) *m*/*z* 578 (M^+). Anal. Calcd for $C_{37}H_{42}N_2O_4$: C, 76.79; H, 7.31; N, 4.84. Found: C, 76.92; H, 7.43; N, 4.89.

4.4.9. Reaction of diazo ketone 2b with 1,3-di(indol-1-yl)propane (13a) in 1,2-dichloroethane. *Method C*. Data for compound 1,3-di[((6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole)-6-carboxylic acid ethyl ester)-7-yl]propane (**15b**). Colorless solid (85%). Mp 126–128 °C. IR (CH_2Cl_2) 2941, 1769, 1746, 1603, 1488, 1374, 1325, 1017, cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.19 (s, 6H, CH_3), 1.27–1.51 (m, 12H), 1.58–1.80 (m, 10H), 2.00–2.04 (m, 2H), 3.09–3.26 (m, 4H, NCH_2), 3.81 (m, 2H, NCH), 4.21–4.36 (m, 4H), 6.36 (dd, J=7.6, 5.7 Hz, 2H, ArH), 6.61–6.66 (m, 2H, ArH), 6.92 (d, J=7.2 Hz, 4H, ArH), 6.99–7.09 (m, 2H, ArH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.9 (*C*H_3), 17.0 (*C*H_3), 20.8 (*C*H_2), 22.4 (*C*H_2), 25.9 (*C*H_2), 31.2 (*C*H_2), 47.5 (N*C*H_2), 47.9 (N*C*H_2), 51.2 (*quat-C*, *Cq*CH_3), 51.3 (*quat-C*, *Cq*CH_3), 52.2 (Ar*C*H) 62.2 (O*C*H_2), 72.7 (N*C*H), 72.9 (N*C*H), 89.5 (*quat*-C, O*Cq*), 94.7 (*quat-C*, O*Cq*), 94.8 (*quat-C*, O*Cq*), 109.4 (*arom-C*H), 118.2 (*arom-C*H), 126.1 (*quat-C*), 126.2 (*quat-C*), 126.5 (*arom-C*H), 126.6 (*arom-C*H), 129.1 (*arom-C*H), 129.3 (*arom-C*H), 153.8 (*quat-C*), 154.0 (*quat-C*), 165.0 (*quat-C*), 211.0 (*quat-C*, *C*=*O*); MS (FAB) *m*/*z* 723 (M^+). Anal. Calcd for $C_{43}H_{50}N_2O_8$: C, 71.45; H, 6.97; N, 3.88. Found: C, 71.67; H, 6.84; N, 3.76.

4.4.10. Preparation of 1,4-di(indol-1-yl)butane (13b). The procedure was followed as described for compound **13a** to yield the title compound **13b** as a yellow solid (78%). Mp 90 °C (lit.,[24] mp 88 °C). IR (CH_2Cl_2) 1512, 1461, 1315, 1242, 1174, 908, 735 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.09 (m, 4H, CH_2), 3.19 (m, 4H, NCH_2), 6.49 (m, 4H, ArH), 6.99 (d, J=7.3 Hz, 2H, ArH), 7.12–7.26 (m, 4H, ArH), 7.70 (d, J=6.5 Hz, 2H, ArH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 27.6 (*C*H_2), 45.5 (N*C*H_2), 101.6 (*arom-C*H), 109.7 (*arom-C*H), 119.9 (*arom-C*H), 121.6 (*arom-C*H), 121.9 (*arom-C*H), 127.7 (*arom-C*H), 128.2 (*quat-C*), 128.6 (*quat-C*).

4.4.11. Reaction of diazo ketone 2a with 1,4-di(indol-1-yl)-butane (13b). *Method A*. Data for compound 6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-[-7-yl-(indol-1-ylbutyl)]-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole (**14c**). Brown solid (29%). Mp 132–134. IR (CH_2Cl_2) 3020, 2936, 1754, 1604, 1490, 1216 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88–1.01 (m, 2H), 1.13 (s, 3H, CH_3), 1.27–1.92 (m, 9H), 2.61–2.76 (m, 1H), 3.10–3.20 (m, 2H, NCH_2), 3.67 (d, J=8.2 Hz, 1H, CHAr), 3.93 (d, J=8.2 Hz, 1H, NCH), 4.14 (t, J=6.9 Hz, 2H, NCH_2), 4.39 (s, 1H, OCH), 6.29 (d, J=7.9 Hz, 1H, ArH), 6.49 (d, J=3.1 Hz, 1H, ArH), 6.58 (t, J=7.4 Hz, 1H, CHAr), 6.95–7.34 (m, 6H, ArH), 7.62 (d, J=7.3 Hz, 1H, ArH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 16.9 (*C*H_3), 21.1 (*C*H_2), 22.7 (*C*H_2), 25.6 (*C*H_2), 25.9 (*C*H_2), 28.5 (*C*H_2), 31.0 (*C*H_2), 46.8 (*C*H_2), 47.6 (*C*H_2), 50.9 (Ar*C*H), 51.5 (*quat-C*, *Cq*CH_3), 70.4 (N*C*H), 86.1 (O*C*H), 91.4 (*quat-C*, *C*-11c), 102.0 (*arom-C*H), 106.8 (*arom-C*H), 110.0 (*arom-C*H), 117.1 (*arom-C*H), 120.0 (*arom-C*H), 121.7 (*arom-C*H), 122.2 (*arom-C*H), 125.9 (*quat-C*), 126.8 (*arom-C*H), 128.3 (*arom-C*H), 129.1 (*arom-C*H), 136.6 (*quat-C*), 153.7 (*quat-C*), 218.1 (*quat-C*, *C*=*O*); MS (FAB) *m*/*z* 440 (M^+). Anal. Calcd for $C_{29}H_{32}N_2O_2$: C, 79.06; H, 7.32; N, 6.36. Found: C, 79.33; H, 7.46; N, 6.27.

Data for compound 1,4-di[6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole-7-yl]butane (**15c**). Brown solid (57%). Mp 183–185 °C. IR (CH_2Cl_2) 2938, 1754, 1604, 1491, 1286 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.82–1.09 (m, 2H), 1.15 (s, 6H, CH_3), 1.31–2.00 (m, 16H), 2.19–2.24 (m, 2H), 3.17–3.27 (m, 4H, NCH_2), 3.71 (d, J=8.2 Hz, 2H, ArCH), 4.01 (d, J=8.2 Hz, 2H, NCH), 4.45 (s, 2H, OCH), 6.35 (d, J=7.9 Hz, 2H, ArH), 6.58 (t, J=7.3 Hz, 2H, ArH), 6.94 (d, J=7.2 Hz, 2H, ArH), 7.06 (t, J=7.6 Hz, 2H, ArH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 16.9 (*C*H_3), 21.0 (*C*H_2), 22.7 (*C*H_2), 25.5 (*C*H_2), 25.8 (*C*H_2), 25.9 (*C*H_2), 30.4 (*C*H_2), 31.0 (*C*H_2), 47.4 (N*C*H_2), 47.8 (N*C*H_2), 50.9 (Ar*C*H), 51.6 (*quat-C*, *Cq*CH_3), 70.3 (N*C*H), 70.6 (N*C*H), 86.1 (O*C*H), 86.2 (O*C*H), 96.6 (*quat*-C, O*Cq*), 106.9 (*arom-C*H), 117.0 (*arom-C*H), 126.0 (*quat-C*), 126.8 (*arom-C*H), 129.2 (*arom-C*H), 153.7 (*quat-C*), 218.2 (*quat-C*, *C*=*O*); MS (FAB) *m*/*z* 592 (M^+). Anal. Calcd for $C_{38}H_{44}N_2O_4$: C, 77.00; H, 7.48; N, 4.73. Found: C, 77.24; H, 7.59; N, 4.66.

4.4.12. Reaction of diazo ketone 2b with 1,4-di(indol-1-yl)butane (13b) in 1,2-dichloroethane. *Method C*. 1,4-Di[((6,11c-epoxy-2,3,4,4a,5,6,6a,7,11b,11c-decahydro-4a-methyl-5-oxo-1*H*-benzo[*c*]carbazole)-6-carboxylic acid ethyl ester)-7-yl]butane (**15d**). Colorless solid (90%). Mp 149–151 °C. IR (CH_2Cl_2) 2935, 1768, 1748, 1604, 1489, 1462, 1372, 1323, 1281, 1131, 750 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.21 (s, 6H, CH_3), 1.26–1.38 (m, 14H), 1.51–1.95 (m, 10H), 2.05 (d, J=8.3 Hz, 2H), 3.04–3.31 (m, 4H), 3.80 (d, J=8.2 Hz, 2H, CH), 4.23–4.39 (m, 6H), 6.35–6.41 (m, 2H, ArH), 6.63 (t, 2H, J=7.3 Hz, ArH), 6.94 (d, J=7.2 Hz, 2H, ArH), 7.06 (t, J=7.6 Hz, 2H, ArH); ^{13}C NMR (50.3 MHz, C_6D_6) δ 14.8 (*C*H_3), 16.9 (*C*H_3), 20.7 (*C*H_2), 22.3 (*C*H_2), 23.9 (*C*H_2), 24.3 (*C*H_2), 25.7 (*C*H_2), 31.1 (*C*H_2), 49.6 (*C*H_2), 50.0 (*C*H_2), 51.2 (*quat*-C, *Cq*CH_3), 52.1 (*C*H), 62.3 (O*C*H_2), 72.7 (O*C*H), 73.0 (O*C*H), 89.4 (*quat-C*), 94.6 (*quat-C*), 109.2 (*arom-C*H), 118.0 (*arom-C*H), 126.0 (*quat-C*), 126.5 (*arom-C*H), 129.1 (*arom-C*H), 153.8 (*quat-C*), 154.0 (*quat-C*), 164.9 (*quat-C*), 211.0 (*quat-C*, *C*=*O*); MS (FAB) *m*/*z* 759.3 (M+Na)$^+$ 722.3 (M^+). Anal. Calcd for $C_{43}H_{52}N_2O_8$: C, 71.25; H, 7.23; N, 3.86. Found: C, 71.42; H, 7.41; N, 3.72.

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One-pot reductive amination of aldehydes and ketones with α-picoline-borane in methanol, in water, and in neat conditions☆

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Abstract—A one-pot reductive amination of aldehydes and ketones with amines using α-picoline-borane as a reducing agent is described. The reaction has been carried out in MeOH, in H_2O, and in neat conditions in the presence of small amounts of AcOH. This is a highly efficient and mild procedure that is applicable for a wide variety of substrates. In particular, this is the first successful demonstration that this type of reaction can be carried out in water and in neat conditions.

1. Introduction

In biological and chemical systems, one-pot reductive amination of aldehydes and ketones is an important transformation, which allows the direct conversion of carbonyl compounds into amines using simple operations.[1] A variety of reducing agents, such as sodium cyanoborohydride ($NaBH_3CN$),[1a,2] sodium triacetoxyborohydride [$NaBH(OAc)_3$],[3] pyridine-borane (pyr-BH_3),[4] Ti(O*i*-Pr)$_4$/$NaBH_4$,[5] borohydride exchange resin,[6] $Zn(BH_4)_2/SiO_2$,[7] Bu_3SnH/SiO_2,[8] and $PhSiH_4/Bu_2SnCl_2$[9] have been developed for this conversion.

The choice of the reducing agent is very critical to the success of the reaction, since the reducing agent must reduce imines selectively over aldehydes or ketones. The reductive aminations with $NaBH_3CN$ are successfully carried out using a five-fold excess of amine at pH 6–8.[2b] However, the use of expensive and highly toxic $NaBH_3CN$ that carries the risk of having residual cyanide in the product as well as in the work-up stream, makes this procedure less attractive. Clearly the use of $NaBH_3CN$ is not acceptable in the context of green synthesis, especially in industry.

In a search for alternatives to the cyanohydroborates as reductants for reductive amination, the use of $NaBH(OAc)_3$ has been reported.[3e] Although this reagent reduces imines selectively over carbonyl compounds in 1,2-dichloroethane, solvents such as methanol or water are not suitable because of rapid reduction of the carbonyl compound or because of decomposition of the reducing agent in water. In addition, this reagent has only one available hydrogen in a molecule and 1.3–1.6 mol equiv of the reagent are necessary for the reaction. Reductive aminations with pyr-BH_3[4a] and methanolic pyr-BH_3[4b] in the presence of 4 Å molecular sieves were also reported. Very recently, it has been reported that amine-boranes possess interesting properties that could overcome the disadvantages of using $NaBH_4$ and $NaBH_3CN$.[10] It was previously reported that pyr-BH_3 was found to be superior to $NaBH_3CN$ for the reductive amination of aldehydes with piperidines.[4c] Usually pyr-BH_3 from commercial sources was utilized without further purification,[11] because this reagent is quite unstable to heat and attempted distillation of the liquid residue at reduced pressures sometimes resulted in violent decompositions.[12] Thus, extreme care must be used if this reagent is handled in large quantities. Industrial applications seem problematic, despite the availability of a patented method for purification, because of this instability that also leads to difficulty of storage for extended periods.[13] Therefore, introduction of new reagents that alleviate or eliminate the above-mentioned problems would be a useful contribution to synthetic organic chemistry. We have approached this challenge to discover a new reagent and methodology from the view point of both process chemistry and green chemistry.

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.06.045

Keywords: Reductive amination; Picoline-borane; Water solvent; Neat condition.

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Table 1. Reductive amination of carbonyl compounds with pic-BH_3 in MeOH–AcOH (10:1)[a]

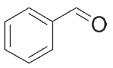
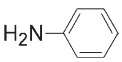
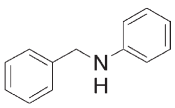
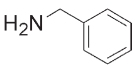
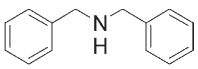
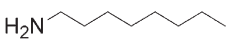
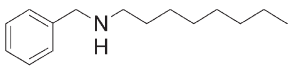
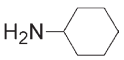
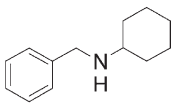
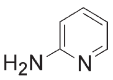
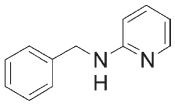
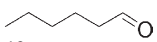
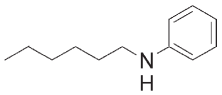
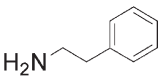
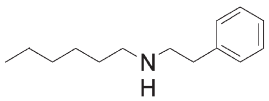
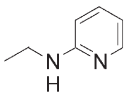
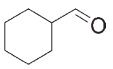
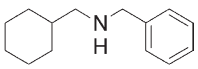
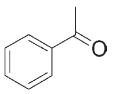
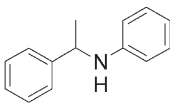
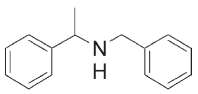
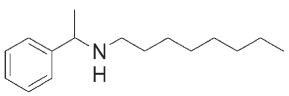
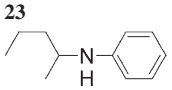
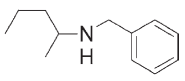
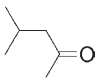
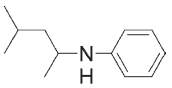
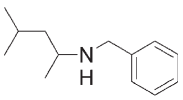
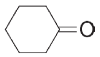
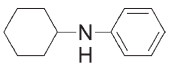
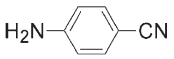
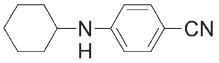
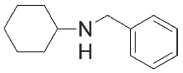
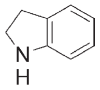
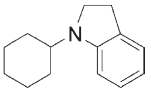
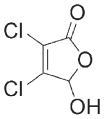
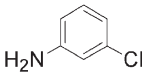
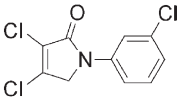
Entry	Carbonyl compound	Amine	Time (h)	Product	Yield (%)
1	 **1**	 **2**	2	 **3**	95
2	**1**	 **4**	2	 **5**	76
3	**1**	 **6**	1	 **7**	72
4	**1**	 **8**	18	 **9**	60
5	**1**	 **10**	1	 **11**	73
6	 **12**	**2**	1[b]	 **13**	82[c]
7	**12**	 **14**	1	 **15**	62[d]
8	 **16**	**10**	1	 **17**	80[e]
9	 **18**	**4**	1	 **19**	77
10	 **20**	**2**	24	 **21**	73
11	**20**	**4**	72	 **22**	72
12	**20**	**4**	24	**22**	52
13	**20**	**6**	30	 **23**	45
14	 **24**	**2**	6	 **25**	89
15	**24**	**4**	6	 **26**	79

Table 1 (*continued*)

Entry	Carbonyl compound	Amine	Time (h)	Product	Yield (%)
16	 **27**	**2**	17	 **28**	95
17	**27**	**4**	6	 **29**	80
18	 **30**	**2**	1	 **31**	95
19	**30**	 **32**	3	 **33**	73
20	**30**	**4**	1	 **9**	73
21	**30**	 **34**	1	 **35**	98
22	 **36**	 **37**	40	 **38**	76

[a] Equimolar equiv of carbonyl compounds, amines, and pic-BH_3 was used.
[b] Minute.
[c] Without addition of AcOH.
[d] Two equiv of 2-phenethylamine were used.
[e] Three equiv of acetaldehyde were used.

2. Results and discussion

2.1. Reductive amination in MeOH with α-picoline-borane

In the course of our investigations of the chemistry of amine-boranes, we have found that α-picoline-borane (pic-BH_3) is a cheap and commercially available alternative to $NaBH_3CN$ or pyr-BH_3 for the purpose of reductive amination reaction. Pic-BH_3 is superior to pyr-BH_3 in the following respects. (1) Pic-BH_3 is a commercially available crystalline solid (mp 44–45 °C) that is more stable to heat than pyr-BH_3 (melting point of pic-BH_3 was not changed after it was heated to above 150 °C). (2) Pic-BH_3 can be purified by recrystallization from hexane and be stored for long periods without noticeable decomposition. It was reported in the recently published Callery bulletin[14] that above a temperature 54 °C, pyr-BH_3 undergo a self-sustaining exothermic decomposition that may cause fire or explosions. The shelf-life of pyr-BH_3 is 6 months.

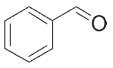
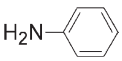
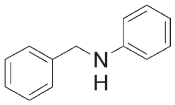
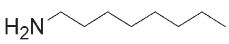
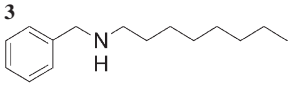
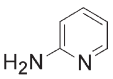
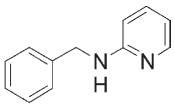
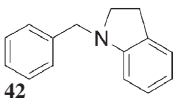
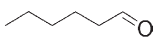
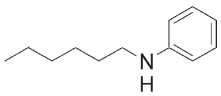
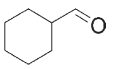
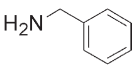
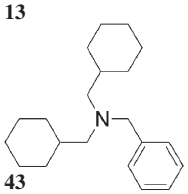
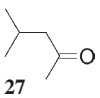
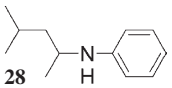
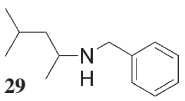
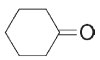
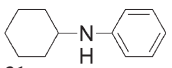
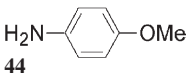
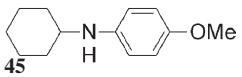
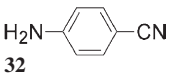
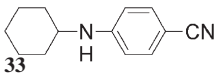
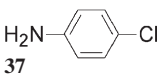
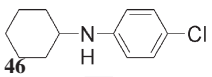
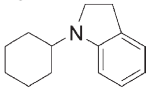
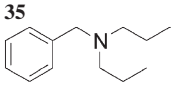
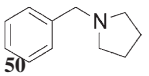
The direct reductive amination reactions were carried out in MeOH–AcOH (10:1) using pic-BH_3 as a reducing agent. The reductive amination of a wide variety of aldehydes and ketones with primary and secondary amines was successful and gave the desired products in good to excellent yields as shown in Table 1.

Equimolar amounts of amine, carbonyl compounds, and pic-BH_3 were generally used for the reaction. For most ketones, reactions were improved by the addition of AcOH. However, for hexanal (**12**), a better result was obtained without addition of AcOH (Table 1, entry 6). Recently 2-ethylaminopyridine (**17**) was synthesized from 2-aminopyridine (**10**) in three steps.[15] According to the present method **17** was obtained from **10** and acetaldehyde in a one-pot operation in 80% yield (Table 1, entry 8). More recently, the direct reductive amination of mucochloric acid has been reported and compound **38** was obtained in 65% yield using 3 equiv of $NaBH(OAc)_3$ in CH_2Cl_2–AcOH for 24 h at room temperature.[16] According to the present method **38** was obtained from the same starting compounds in 76% yield for 40 h (Table 1, entry 22).

2.2. Reductive amination in water

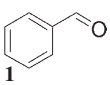
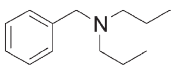
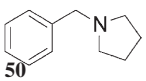
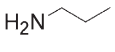
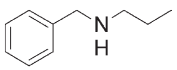
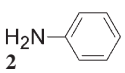
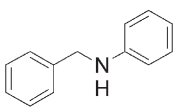
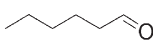
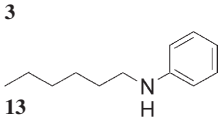
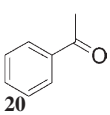
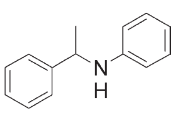
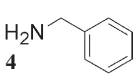
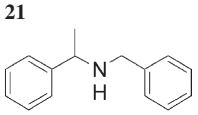
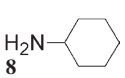
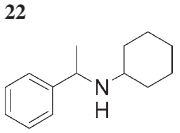
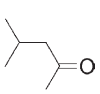
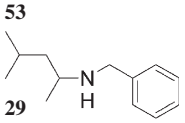
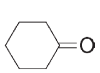
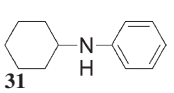
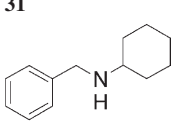
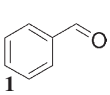
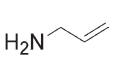
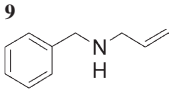
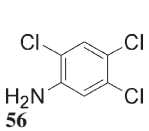
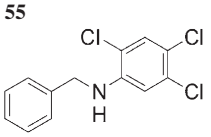
It is generally accepted that strict anhydrous conditions are favorable to generate imines or imminium ions, which are subsequently reduced by the reducing agents. Therefore, combinations of a reducing agent and dry molecular

Table 2. Reductive amination of carbonyl compounds with pic-BH_3 in H_2O–AcOH (10:1)

Entry	Carbonyl compound	Amine	Time (h)	Product	Yield (%)
1	 **1**	 **2**	2	 **3**	91
2	**1**	 **6**	1	 **7**	71
3	**1**	 **10**	3	 **11**	59
4	**1**	 **34**	1	 **42**	88
5	 **12**	**2**	5[a]	 **13**	73[b]
6	 **18**	 **4**	1	 **43**	91[c]
7	 **27**	**2**	17	 **28**	90
8	**27**	**4**	6	 **29**	51
9	 **30**	**2**	1	 **31**	94
10	**30**	 **44**	1	 **45**	97
11	**30**	 **32**	4.5	 **33**	74
12	**30**	 **37**	9	 **46**	91
13	**30**	**34**	1	 **35**	90
14	**1**	 **47**	3	 **48**	3[d]
15	**1**	 **49**	3	 **50**	30

[a] Minute.
[b] Without addition of AcOH.
[c] Four equiv of cyclohexanecarboxaldehyde were used.
[d] Plus benzyl alcohol (77%).

Table 3. Solvent-free reductive amination of carbonyl compounds with pic-BH_3

Entry	Carbonyl compound	Amine	Time (h)	Product	Yield (%)
1	 **1**	 **47**	24	 **48**	48[a]
2	**1**	 **49**	10	 **50**	76[a]
3	**1**	 **51**	72	 **52**	66[a]
4	**1**	 **2**	2	 **3**	99
5	 **12**	**2**	1	 **13**	77[b]
6	 **20**	**2**	63.5	 **21**	91
7	**20**	 **4**	72	 **22**	87
8	**20**	 **8**	120	 **53**	27
9	 **27**	**4**	3.5	 **29**	63
10	 **30**	**2**	3.5	 **31**	94
11	**30**	**4**	15.5	 **9**	78
12	 **1**	 **54**	48	 **55**	65[c]
13	**1**	 **56**	24	 **57**	65[c]

[a] Three equiv of amine were used.
[b] Without addition of AcOH.
[c] Minimum amounts of MeOH were added to dissolve the solid **56**.

sieves[2,3a,d,4b,17,18] or anhydrous $MgSO_4$[19] or Na_2SO_4[20] or titanium(IV) isopropoxide[21] were employed for imine or imminium ion formation and subsequent reduction. However, it is operationally troublesome to keep anhydrous conditions during a reaction and we, therefore, have tried a solvent system containing a small amount of water (MeOH–AcOH–H_2O (10:1:1)). We have tried several examples of reductive amination reactions using the above

solvent system and found that yields of products are slightly lowered, but practically the same, compared with those in the methanol solvent system.

Encouraged by the above results, we have conducted the same reductive amination reaction in water. Water is a cheap, nontoxic, nonflammable, and environmentally benign solvent. As a consequence of serious pollution problems, the use of organic transformations in water is presently undergoing a very rapid growth.[22] On the other hand, it is generally accepted that dehydration is one of the reactions that is difficult to carry out in water.[23] Reductive amination in solvents containing water has not been reported except for some aldehydes which are only available commercially as aqueous solution.[24] This is because the equilibrium formation of imines or imminium ions from carbonyl compounds and amines by elimination of water molecules is favored in anhydrous conditions and would be expected to be highly disfavored in water.

First, we carried out the reductive amination of cyclohexanone (**30**) (200 mg, 2.04 mmol) with aniline (**2**) (190 mg, 2.04 mmol) using pic-BH_3 (218 mg, 2.04 mmol) in H_2O (5 mL) and AcOH (0.5 mL) at room temperature for 2 h. Although the reaction should occur in the heterogeneous phase, the reaction mixture seemed to be homogeneous and after usual work up cyclohexylphenylamine (**31**) (334 mg, 94%) was obtained in high yield (Table 2, entry 9). The same reaction was conducted in larger scale (**30**, 3.0 g; **2**, 2.85 g; pic-BH_3, 3.27 g; H_2O, 50 mL; AcOH, 5 mL; room temperature; 3.5 h) and **31** (5.09 g, 95%) was obtained in a similar yield. This reaction is successful in water although it involves the elimination of a molecule of water. Several carbonyl compounds and amines reacted in this way and the results are presented in Table 2.

Reductive amination reactions with highly water soluble amines do not proceed satisfactorily (Table 2, entries 14 and 15). On the other hand, reactions with poorly water-soluble carbonyl compounds and amines proceed smoothly to give high yields of the products. Although, the exact role of water in these reactions is still not well understood, this might be ascribed to promotion of hydrophobic association of carbonyl compounds, amines, and pic-BH_3 in water, when respective substrates are poorly soluble in water. This could facilitate smooth formation of imines or imminium ions and subsequent reduction by pic-BH_3. In addition, a good selectivity of pic-BH_3 for reduction of imines over carbonyls is assumed.

2.3. Solvent-free reductive amination

Finally, we have undertaken the reductive amination in neat conditions. Many organic solvents are ecologically harmful, and the best solvent formulation from an ecological point of view is no solvent.[25]

Initially, we carried out the solvent-free reductive amination of cyclohexanone (3.00 g, 30.57 mmol) with aniline (2.85 g, 30.57 mmol) using pic-BH_3 (3.27 g, 30.57 mmol) at room temperature for 6 h. After the usual workup cyclohexylphenylamine (4.36 g, 81%) was obtained. The same reaction was conducted by the addition of AcOH (0.5 mL) and the product (5.05 g, 94%) was obtained in high yield. Several carbonyl compounds and amines reacted in this way and the results are presented in Table 3.

The reaction proceeded smoothly even in the case of water soluble amines to afford the corresponding products in good yields (Table 3, entries 2 and 3).

Generally, aromatic ketones are poor substrates for reductive amination protocols. In the reductive amination of acetophenone with benzylamine, the desired product was obtained with $NaBH(OAc)_3$ in 10 days in 55% yield[3e] and with a combination of pyr-BH_3 and dry molecular sieves in 10% yield.[4b] Furthermore, 1-phenylethanol, the reduction product of acetophenone, is the only isolable product from the reactions of aliphatic amines with acetophenone using pyr-BH_3 and acetic acid.[4a] On the other hand, in this neat condition using pic-BH_3 as a reducing agent, reductive amination of acetophenone proceeded smoothly to afford the corresponding amines in good yields for 72 h (Table 3, entries 6 and 7).

Solvent-free reductive amination seems to hold promise to be a highly useful technique, especially for industry. Nevertheless, workup processes, except for a few examples, invariably involve the use of solvent. Therefore, since the use of solvent should be minimized as far as possible, or even avoided altogether, devising workup conditions on a case by case basis would be necessary. However, this solvent-free process using pic-BH_3 throws a challenge to the existing reductive amination procedures, which use ecologically harmful solvents and toxic reagents.

3. Conclusion

Pic-BH_3 is a thermally stable transparent solid and can be stored on a shelf for months without appreciable loss of reducing ability. The use of pic-BH_3 eliminates the problems encountered with the use of other reducing agents such as $NaBH_3CN$, $NaBH(OAc)_3$ and pyr-BH_3. Especially, the use of water as solvent and/or solvent-free conditions can offer a great opportunity for green chemistry. In summary, we have developed an expeditious, easy-to-handle and environmentally friendly approach to the synthesis of a variety of amines through a three-component one-pot reaction of carbonyl compounds, amines, and pic-BH_3.

4. Experimental

4.1. General

All melting points were determined with a Yanagimoto hot-stage melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured at 270 MHz on a JEOL JNM-EX270 spectrometer with tetramethylsilane (Me_4Si) as an internal reference and $CDCl_3$ as the solvent, unless otherwise noted. ^{1}H NMR spectral data are reported in parts per million (δ) relative to Me_4Si. IR spectra were recorded on a JASCO IR 810 spectrophotometer. Mass spectra were obtained with a JEOL JMS-700 spectrometer with a direct inlet system at

70 eV. Elemental analyses were performed in the Microanalytical Laboratory of this University.

All starting carbonyl compounds and amines were purchased from Tokyo Kasei Kogyo Co., Ltd and α-picoline-borane was obtained from Shiroi Yakuhin Co., Ltd and used without further purification.

4.2. Typical procedure for the preparation of 3 in MeOH–AcOH

To benzaldehyde (**1**) (200 mg, 1.88 mmol) and aniline (**2**) (176 mg, 1.88 mmol) in MeOH–AcOH (10:1, 5.5 mL) was added pic-BH_3 (201 mg, 1.88 mmol) and the reaction mixture was stirred for 2 h at room temperature. After the reaction, MeOH was evaporated in vacuo and 10% HCl (10 mL) was added to the residue. The aqueous solution was stirred for 0.5 h at room temperature, and Na_2CO_3 (ca. 2.5 g) and H_2O (10 mL) were added under cooling to make the solution alkaline. The aqueous layer was extracted with AcOEt (30 mL×2), and the combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, and concentrated. The crude product was chromatographed on a column of silica gel with AcOEt–*n*-hexane (1:6) to afford benzylphenylamine (**4**) (329 mg, 95%).

4.2.1. Hexylphenethylamine (15). Oil. IR (neat): 3300, 3030, 2930, 2860, 2820, 1610, 1500, 700 cm^{-1}; ^1H NMR (270 MHz) δ 0.87 (t, J=6.6 Hz, 3H), 1.15–1.60 (m, 9H), 2.60 (t, J=7.3 Hz, 2H), 2.76–2.92 (m, 4H), 7.15–7.35 (m, 5H); ^{13}C NMR (68 MHz) δ 14.1, 22.7, 27.1, 30.1, 31.8, 36.5, 49.9, 51.3, 125.9, 128.3, 128.5, 140.0; FAB-MS (3-nitrobenzyl alcohol) m/z 206 (M^++H); HR-MS (FAB) for $C_{14}H_{23}N$ Calcd 206.1909 (M^++H), found 206.1912.

4.2.2. 4-Cyclohexylaminobenzonitril (33). White crystals. Mp 114–116 °C (AcOEt–*n*-hexane); IR (KBr): 3330, 2940, 2850, 2210, 1610, 1530 cm^{-1}; ^1H NMR (270 MHz) δ 1.10–1.48 (m, 5H), 1.60–1.84 (m, 3H), 1.96–2.10 (m, 2H), 3.20–3.38 (m, 1H), 4.11 (br s, 1H), 6.52 (dt, J=8.7, 2.1 Hz, 2H), 7.39 (dt, J=8.4, 2.0 Hz, 2H); ^{13}C NMR (68 MHz) δ 24.8, 25.7, 33.0, 51.2, 97.7, 112.2, 120.5, 133.5, 150.3; EI-MS m/z 200 (M^+, 32.83), 157 (100). Anal. Calcd for $C_{13}H_{16}N_2$: C, 77.96; H, 8.05; N, 13.99, found: C, 77.71; H, 8.20; N, 13.82.

4.2.3. *N*-Cyclohexylindoline (35). Oil. IR (neat): 2930, 2850, 1610, 1490 cm^{-1}; ^1H NMR (270 MHz) δ 1.02–1.95 (m, 10H), 2.93 (t, J=8.4 Hz, 2H), 3.28–3.42 (m, 3H), 6.40 (d, J=8.1 Hz, 1H), 6.57 (td, J=7.3, 0.9 Hz, 1H), 6.98–7.09 (m, 2H); ^{13}C NMR (68 MHz) δ 26.1, 26.2, 28.4, 28.8, 46.7, 54.6, 106.7, 116.4, 124.2, 127.0, 129.9, 151.0; EI-MS m/z 201 (M^+, 46.36), 158 (100); HR-MS (EI) for $C_{14}H_{19}N$ Calcd 201.1517, found 201.1525.

4.3. Typical procedure for the preparation of 31 in H_2O–AcOH

A mixture of cyclohexanone (**30**) (200 mg, 2.04 mmol), aniline (**2**) (190 mg, 2.04 mmol), and pic-BH_3 (218 mg, 2.04 mmol) was stirred for 1 h at room temperature in H_2O–AcOH (10:1, 5.5 mL). After the reaction, 10% Na_2CO_3 (20 mL) was added and the aqueous solution was extracted with AcOEt (30 mL×2), and the combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, and concentrated. The crude product was chromatographed on a column of silica gel with AcOEt–*n*-hexane (1:3) to afford cyclohexylphenylamine (**31**) (334 mg, 94%).

4.3.1. *N*-Benzylindoline (42). Oil. IR (neat): 3030, 2920, 2830, 1610, 1490 cm^{-1}; ^1H NMR (270 MHz) δ 2.96 (t, J=8.3 Hz, 2H), 3.30 (t, J=8.3 Hz, 2H), 4.24 (s, 2H), 6.50 (d, J=7.8 Hz, 1H), 6.66 (t, J=7.2 Hz, 1H), 7.00–7.12 (m, 2H), 7.20–7.40 (m, 5H); ^{13}C NMR (68 MHz) δ 28.6, 53.6, 53.7, 106.9, 117.6, 124.4, 127.0, 127.2, 127.8, 128.3, 129.9, 138.3, 152.4; EI-MS m/z 209 (M^+, 100), 132 (35.54), 118 (29.45), 91 (96.68); HR-MS (EI) m/z for $C_{15}H_{15}N$ Calcd 209.1204, found 209.1214.

4.3.2. Benzyl-bis-cyclohexylmethylamine (43). Oil. IR (neat): 3030, 2930, 2850, 2800, 1610, 1500, 740, 700 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6) δ 0.62–0.82 (m, 4H), 0.98–1.86 (m, 18H), 2.08 (d, J=7.1 Hz, 4H), 3.42 (s, 2H), 7.16–7.36 (m, 5H); ^{13}C NMR (68 MHz) δ 26.3, 27.0, 31.9, 36.1, 59.9, 62.0, 126.3, 127.8, 128.7, 140.6; EI-MS m/z 299 (M^+, 1.89), 216 (100), 91 (39.61); HR-MS (EI) for $C_{21}H_{33}N$ Calcd 299.2613, found 299.2610.

4.3.3. *N*-Cyclohexyl-*p*-anisidine (45). Oil. IR (neat): 3380, 2930, 2850, 1620, 1510 cm^{-1}; ^1H NMR (270 MHz, DMSO-d_6) δ 1.00–1.39 (m, 5H), 1.52–1.76 (m, 3H), 1.83–1.96 (m, 2H), 2.99–3.15 (m, 1H), 3.62 (s, 3H), 4.85 (d, J=7.9 Hz, 1H), 6.50 (d, J=8.7 Hz, 2H), 6.68 (d, J=8.9 Hz, 2H); ^{13}C NMR (68 MHz) δ 25.1, 26.0, 33.6, 52.8, 55.8, 114.7, 114.8, 141.4, 151.6; EI-MS m/z 205 (M^+, 68.28), 162 (100); HR-MS (EI) for $C_{13}H_{19}NO$ Calcd 205.1467, found 205.1464.

4.3.4. (4-Chlorophenyl)cyclohexylamine (46). Oil. IR (neat): 3420, 2930, 2860, 1600, 1500 cm^{-1}; ^1H NMR (270 MHz) δ 1.05–1.46 (m, 5H), 1.50–1.83 (m, 3H), 1.95–2.10 (m, 2H), 3.14–3.26 (m, 1H), 3.52 (br s, 1H), 6.49 (dt, J=8.7, 2.7 Hz, 2H), 7.08 (dt, J=8.7, 2.6 Hz, 2H); ^{13}C NMR (68 MHz) δ 25.0, 25.9, 33.3, 51.8, 114.0, 121.1, 128.9, 145.8; EI-MS m/z 211 (M^++2, 16.84), 209 (M^+, 51.68), 166 (100); HR-MS (EI) for $C_{12}H_{16}ClN$ Calcd 209.0971, found 209.0990.

4.3.5. *N*,*N*-Dipropylbenzylamine (48). Oil. IR (neat): 2960, 2880, 2800, 1610, 1500, 740, 700 cm^{-1}; ^1H NMR (270 MHz) δ 0.86 (t, J=7.4 Hz, 6H), 1.40–1.55 (m, 4H), 2.37 (t, J=7.3 Hz, 4H), 3.55 (s, 2H), 7.18–7.36 (m, 5H); ^{13}C NMR (68 MHz) δ 12.0, 20.3, 55.9, 58.7, 126.4, 127.9, 128.6, 140.3; EI-MS m/z 191 (M^+, 2.33), 162 (38.96), 91 (100); HR-MS (EI) for $C_{13}H_{21}N$ Calcd 191.1674, found 191.1672.

4.3.6. *N*-Benzylpyrrolidine (50). Oil. IR (neat): 3040, 2970, 2800, 1610, 1500 740, 700 cm^{-1}; ^1H NMR (270 MHz) δ 1.70–1.87 (m, 4H), 2.43–2.58 (m, 4H), 3.61 (s, 2H), 7.19–7.36 (m, 5H); ^{13}C NMR (68 MHz) δ 23.4, 54.1, 60.7, 126.8, 128.1, 128.9, 139.3; EI-MS m/z 161 (M^+, 34.21), 91 (100), 84 (49.07), 70 (32.29); HR-MS (EI) for $C_{11}H_{15}N$ Calcd 161.1204, found 161.1205.

4.4. Typical procedure for the preparation of 22 in neat condition

To acetophenone (**20**) (1.00 g, 8.32 mmol), benzylamine (**4**)

(0.89 g, 8.32 mmol), and AcOH (0.3 mL) was added pic-BH_3 (0.89 g, 8.32 mmol) over 5 min and the reaction mixture was stirred for 72 h. After the reaction, 10% HCl (10 mL) was added and the aqueous solution was stirred for 0.5 h at room temperature. Na_2CO_3 (ca. 2.5 g) and H_2O (10 mL) were added to the solution under cooling to make the solution alkaline. The aqueous layer was extracted with AcOEt (30 mL×2), and the combined organic layer was washed with brine (15 mL), dried over Na_2SO_4, and concentrated. The crude product was chromatographed on a column of silica gel with AcOEt–*n*-hexane (1:3) to afford *N*-benzyl-1-phenylethylamine (**22**) (1.53 g, 87%).

4.4.1. Benzylpropylamine (52). Oil. IR (neat): 3320, 3070, 3030, 2960, 2930, 2880, 2820, 1610, 1500, 740, 700 cm^{-1}; ^1H NMR (270 MHz) δ 0.92 (t, J=7.4 Hz, 3H), 1.45–1.61 (m, 3H), 2.60 (t, J=7.3 Hz, 2H), 3.79 (s, 2H), 7.19–7.36 (m, 5H); ^{13}C NMR (68 MHz) δ 11.8, 23.2, 51.3, 53.9, 126.6, 127.9, 128.1, 140.3; EI-MS *m/z* 149 (M^+, 3.56), 120 (28.15), 91 (100); HR-MS (EI) for $C_{10}H_{15}N$ Calcd 149.1204, found 149.1226.

4.4.2. Allylbenzylamine (55). Oil. IR (neat): 3300, 3060, 3020, 2910, 2800, 1640, 1600, 1495, 695 cm^{-1}; ^1H NMR (270 MHz) δ 1.44 (s, 1H), 3.28 (dt, J=5.9, 1.2 Hz, 2H), 3.79 (s, 2H), 5.11 (dd, J=10.2, 1.3 Hz, 1H), 5.20 (dq, J=17.1, 1.5 Hz, 1H), 5.85–6.04 (m, 1H), 7.20–7.38 (m, 5H); ^{13}C NMR (68 MHz) δ 51.8, 53.3, 115.9, 126.8, 128.0, 128.3, 136.6, 140.1; EI-MS *m/z* 147 (M^+, 22.95), 120 (7.78), 91 (100); HR-MS (EI) for $C_{10}H_{13}N$ Calcd 147.1048, found 147.1049.

4.4.3. *N*-Benzyl-2,4,5-trichloroaniline (57). White crystals. Mp 46–49 °C (*n*-hexane); IR (KBr): 3420, 1600, 1500, 700 cm^{-1}; ^1H NMR (270 MHz) δ 4.36 (d, J=5.4 Hz, 2H), 4.73 (bs, 1H), 6.68 (s, 1H), 7.23–7.43 (m, 6H); ^{13}C NMR (68 MHz) δ 47.9, 112.1, 117.6, 119.3, 127.2, 127.6, 128.8, 129.7, 131.5, 137.4, 143.1; EI-MS *m/z* 291 (M^++6, 0.76), 289 (M^++4, 6.57), 287 (M^++2, 20.37), 285 (M^+, 21.49), 208 (3.48), 91 (100). Anal. Calcd for $C_{13}H_{10}Cl_3N$: C, 54.48; H, 3.52; N, 4.89, found: C, 54.49; H, 3.31; N, 4.77.

5. Supplementary material

^1H NMR spectra of all products reported in Table 1–3.

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Bicyclo[2.2.2]octene-based molecular spacers. Construction of U-shaped *syn*-facial etheno-bridged polyhydrononacenyl frameworks

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Abstract—Based on the methodology of repetitive Diels–Alder reactions, the rack- and U-shaped polycyclic compounds **15b**, **17b**, **19**, **20**, and **21** were constructed utilizing 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene (TDCp), *p*-benzoquinone, and norbornadiene as starting materials. These spacer molecules are composed of nine linearly *syn*-fused polyhydrobenzene rings (i.e., polyhydrononacene), in which all the etheno-bridge double bonds are arranged on the same side of the carbon skeletons. Upon irradiation with an ordinary tungsten lamp, **17b** and **21** underwent [2+2]photocyclization to form quadruple- and double-caged compounds **18** and **22**, respectively. The structure of **20** was analyzed by X-ray crystallography and found to have U-shaped framework.

1. Introduction

The synthetic endeavor toward rigid polycyclic molecules of specially designed architecture has been actively demonstrated in the search for new structure systems that may possess specific functions of various interests. Rigid and often symmetric polycyclic molecules are able to function as 'spacer' for use as probes to delineate the intramolecular nonconjugated orbital interactions in terms of the through-space and through-bond mechanisms,[1] to investigate the biologically and possibly the practically important long-range electron and energy transfer phenomena with regard to dependence of the intervening medium, distance, and orientation between electronically coupled donor and acceptor groups.[2] They are also able to act as 'template' for use as a synthetic tactic to direct specific bond formation or to convey selectivity into chemical transformation.[3] Recently, intensive research activity on supramolecular chemistry has also attracted much interest in the synthesis of rigid polycyclic molecules with convex–concave topology for use as host molecules for the formation of host–guest complexes,[4] and with specially designed functionality to act as complementary components for achieving molecular self-assembly to construct new materials of biological and practical importance.[5] A variety of smaller molecules have been utilized to serve as basic building blocks and connectors to construct polycyclic spacer molecules. Among them, bicyclo[2.2.1]heptane[2,6] and 7-oxabicyclo[2.2.1]heptane[7] are most notable examples. Toward the synthesis of these types of polycyclic molecules, the most commonly employed strategy is based on the concept of repetitive Diels–Alder (DA) reactions using appropriate bis-dienes and bis-dienophiles.

For years, we have been also working on a research project aiming at the synthesis of polycarbocycles that possess rigid rack-shaped frameworks for serving as spacer molecules.[8] Different from those systems that contain bicyclo[2.2.1]-heptane and 7-oxabicyclo[2.2.1]heptane units, our polycyclic systems are constructed based on bicyclo[2.2.2]octene ring as the major building blocks and have all the etheno-bridge double bonds positioned on the same face of the carbon skeleton as illustrated by the generic structures **A** and **B** in Chart 1. In rack-shaped polyenes of system **A**, which we have successfully demonstrated in several reports,[8] all the proximate bridge double bonds are *syn*-facially arranged

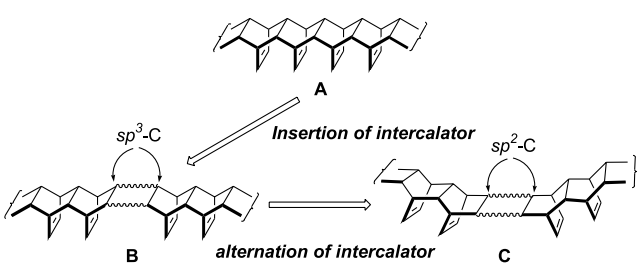

Chart 1.

Keywords: Polycyclic compounds; U-shaped molecules; Diels–Alder reaction; [2+2]Photocyclization.
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and separated by an internuclear distance of ca. 2.9 Å for effective laticyclic conjugation,[9] and is taken to account for the sizable splittings of π-orbitals in the photoelectron spectra[1] and the facile transannular ring formation via [2+2]photocyclization[8,10] and electrophilic addition reactions.[8,11] Formal insertion of a ring, referred to as an intercalator, between the bicyclo[2.2.2]octene rings forms the polycyclic polyenes of system **B**. An intercalator is originally equipped with dienophilic moieties at terminals for synthetic maneuver and can be tailored to take any form to serve as the determinant of molecular length, shape, and configuration of polycyclic polyenes. For instance, using *p*-benzoquinone as a bis-dienophile to construct framework **B** via the DA reaction with appropriate dienes, and then through the alteration of intercalator by 'sp^2-hybridizing' all of the carbon atoms at the ring junction, the rack-shaped spacer molecules can be bent to become U-Shaped, as illustrated by **B** → **C**, Chart 1. By changing intercalator as such, a concave space between two terminals is created, and the dimension of which varies with the number of alteration of intercalators along the molecular framework, besides of the number of bicyclo[2.2.2]octene rings.

Synthetic approaches toward these systems require excellent stereoselective control on the configuration at each ring junction (*cis*-fused) and the orientation of all etheno-bridges of the bicyclo[2.2.2]octene rings (*syn*-facial). To construct the bicyclo[2.2.2]octene ring with good stereoselective control, the DA reaction of 1,3-cyclohexadiene and a dienophile is definitely the most reliable and convenient method. This thought led us to adopt the DA reaction as the key reaction and prepared 1,8,9,10-tetrachloro-11,11-dimethoxytricyclo[6.2.1.0^{2,7}]undeca-3,5,9-triene (**1**) from easily available 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene (TDCp)[12] and *p*-benzoquinone for serving as a masked bis-1,3-cyclohexadiene; a synthetic equivalent of *cis*-9,10-dihydronaphthalene (*cis*-DHN, **2**).[13,14] Because of its curved-in configuration, the masked *cis*-DHN **1** reacts exclusively with the less hindered *exo* face of the diene unit being attacked by the dienophile, resulting in the formation of an adduct, in which the newly formed double bond of the bicyclo[2.2.2]octene substructure is disposed in parallel with and in close proximity to the chlorine-substituted double bond (Scheme 1).[13,15]

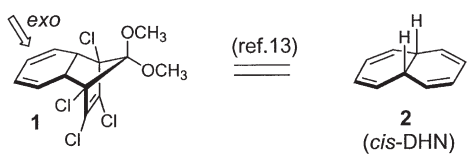
Norbornadiene is known to react with TDCp to give a DA bis-adduct, in which the chlorine-substituted double bonds are on the same side relative to the methano-bridge.[16] Upon reductive dechlorination followed by deketalization, this bis-adduct could be converted to the corresponding thermally labile bis-norbornenone **3**, which could serve as a synthon for the *syn*,*syn*-isomer of 4a,8a,9,9a,10,10a-hexahydro-9,10-methanoanthracene (*syn*,*syn*-HMA, **4**) via thermal decarbonylation.[16] Resembling *cis*-DHN **2** to have the curved-in structure, *syn*,*syn*-HMA **4** undergoes the DA reaction stereoselectively with the attack of dienophile upon the *exo*-face, resulting in the formation of bis-adduct that retains relative stereochemistry of etheno-bridges as the precursor dione **3**.[16] Thus, *syn*,*syn*-HMA **4** is viewed as an expanded version of *cis*-DHN **2**, and can be utilized to synthesize polycyclic polyenes of system **B** (Scheme 2).

As our synthetic endeavor on the construction of bicyclo[2.2.2]octene-based polycyclic polyenes continues, we have converted *syn*,*syn*-HMA **4** and the masked *cis*-DHN **1** to the corresponding bis-*p*-benzoquinone **7** and *p*-benzoquinone **11**, respectively, for use as dienophiles in the DA reactions. In this paper, we describe the synthetic results that led to the implementation of B-type molecules and via aromatization of the intercalators the U-shaped molecular spacers (type **C**), in which all the etheno-bridge double bonds are arranged on the same face of the carbon skeletons that are composed of nine linearly *syn*-fused polyhydrobenzene rings (i.e., polyhydrononacene). The [2+2]photocyclization of some synthetic intermediates to form poly-caged compounds were also reported to demonstrate the close proximity of *syn*-facially arranged double bonds in bicyclo[2.2.2]octene-based polycyclic polyenes. The structure of **20** was analyzed by X-ray crystallography and is also reported herein.

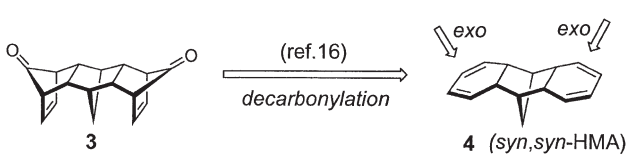
2. Results and discussion

2.1. Synthesis

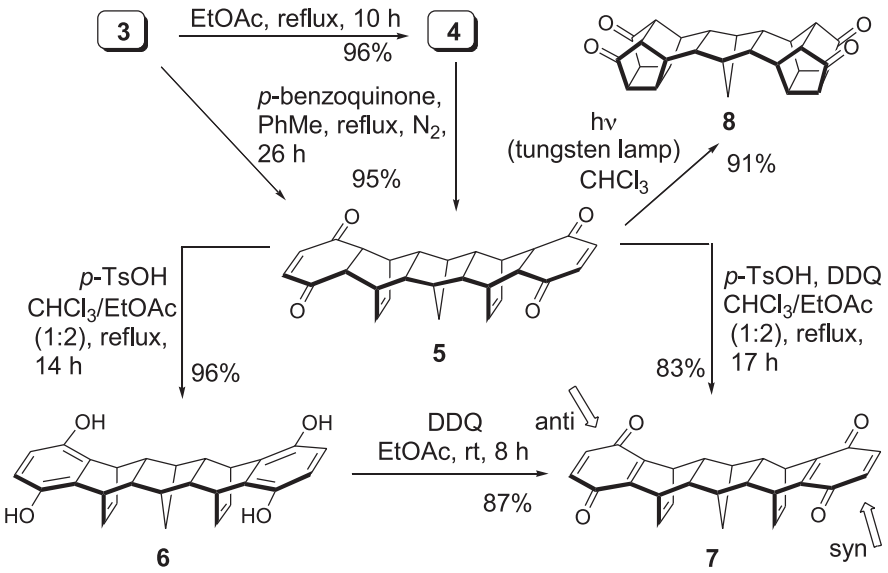
As illustrated in Scheme 3, the DA reaction of *syn*,*syn*-HMA **4** with *p*-benzoquinone in refluxing toluene proceeded with the dienophile approaching **4** exclusively from the less hindered *exo* face, as expected by the curved-in structure of **4** and known facts,[16] to give the bis-adduct **5**. The bis-adduct **5** could also be obtained in 96% yield under the same reaction conditions, in which *syn*,*syn*-HMA **4** was generated in situ from its precursor dione **3** via thermal decarbonylation. The fact that the DA reaction followed the Alder rule to yield **5** was evident by the feasibility of [2+2]photocyclization displayed by **5**, thereby affording the double-caged compound **8**. The infrared spectrum of **8** displayed characteristic carbonyl absorptions at 1748 and 1728 cm^{-1} due to the closely disposed cyclopentanone rings, confirmed by the signal at δ 210.3 in the ^{13}C NMR spectrum of **8**. For obvious reason of steric constraint, bis-enedione **5** would likely undergo the DA reactions with *syn*,*syn*-HMA **4** or other dienes via the course in which the diene approaches **5** from the face opposite to the existing etheno-bridges, thereby yielding the second bis-adduct of unwanted stereochemistry. Thus, recourse was taken to converting bis-enedione **5** into the ring-fused bis-*p*-benzoquinone **7** by the *p*-toluenesolfonic acid-catalyzed enolization of **5**, followed by oxidation of the resulting



Scheme 1.



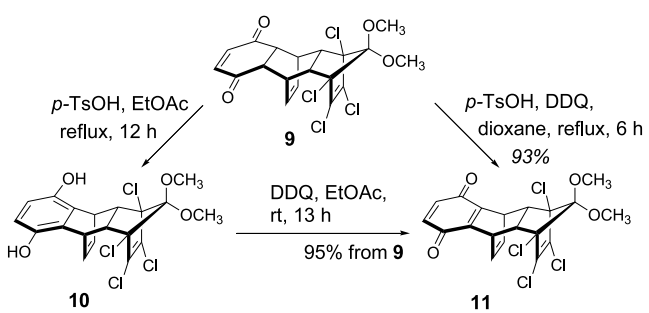
Scheme 2.



Scheme 3.

hydroquinone **6** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), or more conveniently by an one-pot operation in which the acid-catalyzed enolization was carried out in the presence of the oxidant (Scheme 3). Through this transformation, the folded cyclohexendione ring in **5** is unfolded to become *p*-benzoquinone unit in **7**, resulting in creating a sterically less inhibited space between the etheno-bridge and *p*-benzoquinone unit. Consequently, in the subsequent DA reaction of bis-*p*-benzoquinone **7**, dienes such as the masked *cis*-DHN **1** would have a chance to add onto the *p*-benzoquinone unit from the π-face same to the etheno-bridge of **7** (defined as *syn*-face). Similarly, the DA adduct **9**[13] obtained from the reaction of the masked *cis*-DHN **1** with *p*-benzoquinone was converted to *p*-benzoquinone **11** via the corresponding hydroquinone **10**, as shown in Scheme 4.[17] The structures of bis-*p*-benzoquinone **7** and *p*-benzoquinone **11** were secured by spectral and elemental analyses.

Dienophiles, *p*-benzoquinone **7** and **11**, are π-facially dissymmetic, so are the dienes **1** and **4**. In principle, sixteen modes of DA reaction of **7** and **1** (**11** and **4**) leading to sixteen stereoisomeric adducts are possible, taking into account the π-facial selectivity (π-face on which bond formation is taking place), the *endo*/*exo* selectivity (the alignment of the two reacting components in the transition state interpreted by the Alder rule), and site multiplicity (there are two dienophilic sites in bis-*p*-benzoquinone **7** and



Scheme 4.

diene sites in **4**). However, it seems reasonable to expect that the DA reaction of **7** and **1** (**11** and **4**) via the *anti*-Alder modes of cycloaddition would lead to transition states of higher energy because of the disfavored steric interactions between two reacting components that are aligned in parallel with each other (Fig. 1). Together with the fact that the masked *cis*-DHN **1** and *syn*,*syn*-HMA **4**, though π-facially dissymmetic, can offer only one π-face (*exo*-face) for cycloaddition,[13,15,16] the modes of DA reaction of **1** and **7** (**4** and **11**) would therefore be reduced to only four. These are the cycloadditions that occur in accordance with the Alder's *endo*-rule (Fig. 1a and b). Taking symmetry element present in **7** (and **4**) into consideration, only three bis-adducts thereby are possible, namely, *anti*,*anti*-, *syn*,*syn*- and *syn*,*anti*-=*anti*,*syn*-bis-adducts.

Experimentally, when a solution of the masked *cis*-DHN **1** and bis-*p*-benzoquinone **7** in benzene was refluxed for 38 h, the DA reaction produced single bis-adduct isolated in 82%

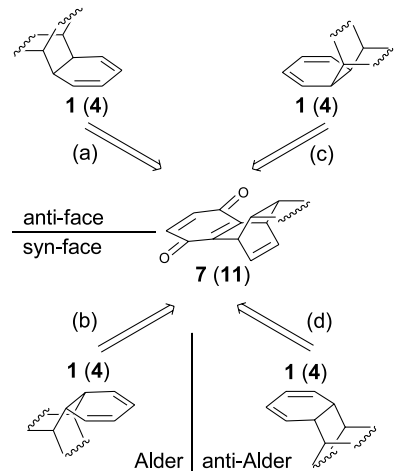
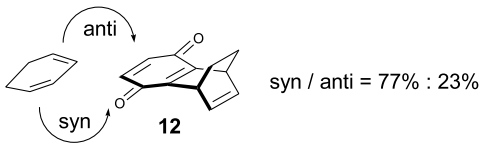
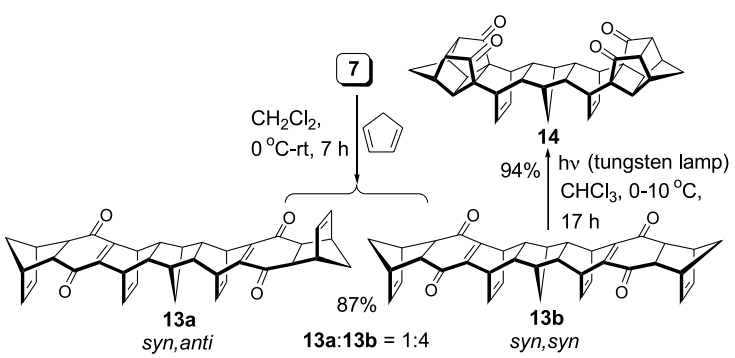


Figure 1. The Diels–Alder reactions of the masked *cis*-DHN **1** and *syn*,*syn*-HMA **4** with dienophiles **7** and **11**. The π-faces with respect to the etheno-bridge in **7** and **11** are denoted by *syn* and *anti*. Sterically favored additions leading to two possible adducts in accordance with the Alder rule: (a) and (b). Sterically disfavored *anti*-Alder additions: (c) and (d).

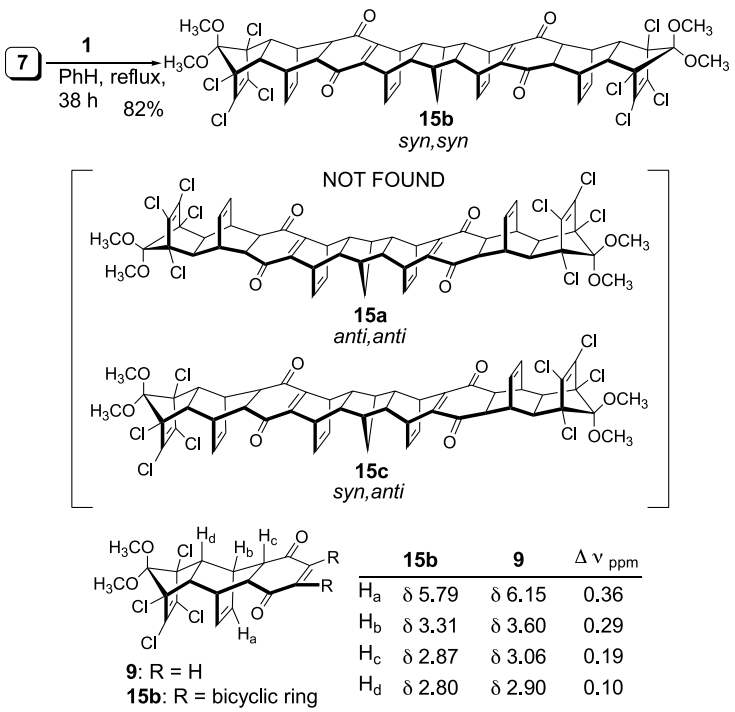
yield after recrystallization from CH_2Cl_2/EtOAc. This result was rather surprising in respect of the DA reaction of 1,3-cyclohexadiene with tricyclo[6.2.2.0^{2,7}]dodeca-2(7),4,9-triene-3,6-dione (**12**), the bicyclo[2.2.2]octadiene-fused *p*-benzoquinone of simplest form, which produced *anti*- and *syn*-adducts in a ratio of 1:3.3 (23% vs 77%).[18] Presumably, the curved framework of bis-*p*-benzoquinone **7**, as a consequence of the in-between norbornane linker, results in creating greater steric difference between the *syn*-face (convex side) and *anti*-face (concave side) of *p*-benzoquinone ring, and thus the higher π-facial selectivity in the DA reaction with the masked *cis*-DHN **1**. As shown in Scheme 5, the DA reaction of bis-*p*-benzoquinone **7** with less sterically demanding cyclopentadiene, however, did show less π-facial selectivity and afforded bis-adducts *syn*,*anti*-**13a** and *syn*,*syn*-**13b** in a ratio of 1:4. Bis-adduct **13b** was converted via [2+2]photocyclization to the double-caged compound **14**, indicating the DA reaction followed the Alder rule.



The fact that the *syn*-face of bicyclo[2.2.2]octadiene-fused *p*-benzoquinone **12** is more likely to undergo cycloaddition with dienes led us to suggest *syn*,*syn*-bis-adduct **15b** be given the highest preference of being the product over the other two stereoisomers, *anti*,*anti*-bis-adduct **15a** and *syn*,*anti*-bis-adduct **15c** in the DA reaction of bis-*p*-benzoquinone **7** with the masked *cis*-DHN **1** (Scheme 6). The bis-adduct **15c** was expelled from consideration on the basis of ^{1}H and ^{13}C NMR spectral data, which were not in accordance with the symmetry element (C_s) present in **15c**. The ^{1}H and the proton-decoupled ^{13}C NMR spectra of the



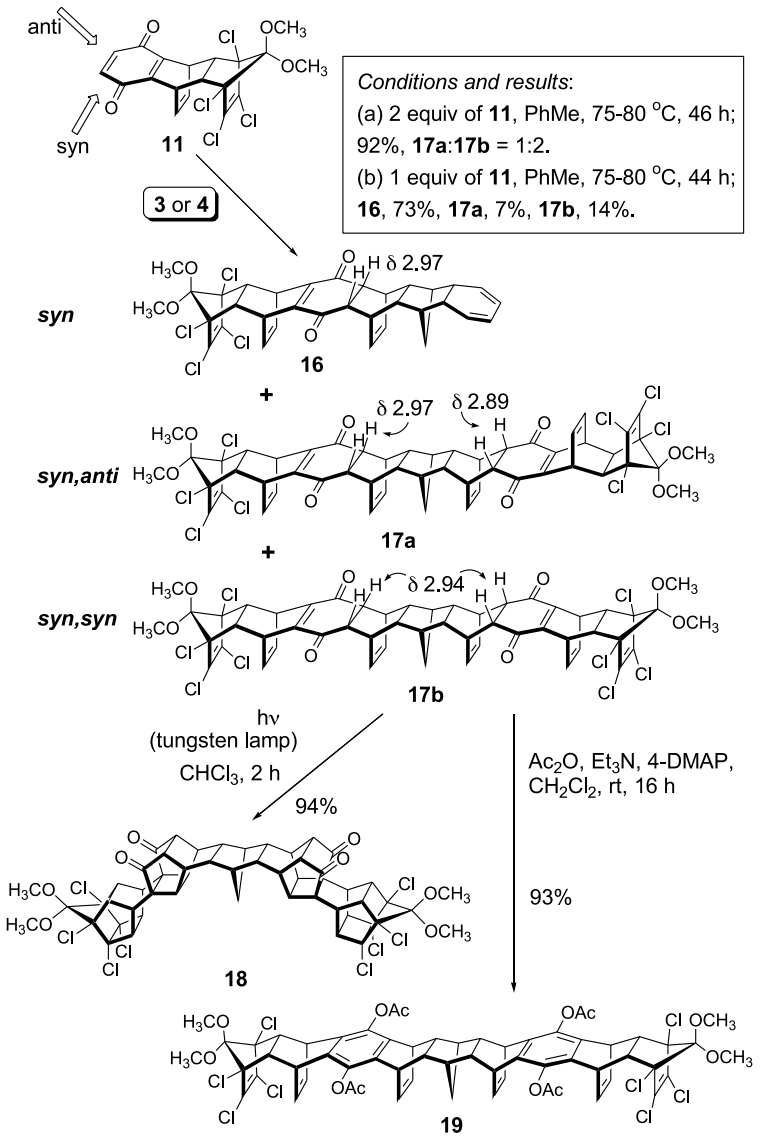
Scheme 5.



Scheme 6.

product, showing respectively 11 groups of absorption signals for 44 hydrogens and 16 lines of carbon signals for 53 carbons, evidently argued for the presence of C_{2v} symmetry in the molecule and could not rule out the formation of **15a** or **15b** as the possible product. Comparison of ^{1}H chemical shifts of the relevant hydrogens in **15b** with structurally similar compound **9**[13b] revealed upfield shifts for all absorption signals, particularly those for vinyl hydrogens (Scheme 6). These upfield shifts of ^{1}H chemical shifts may be attributed to the consequence of anisotropic shielding effect caused by the face-to-face juxtaposed double bond in the fused bicyclo[2.2.2]octadiene ring, and are well demonstrated in other similar compounds.[8,19] This observation supported the fact, which would become manifest in the later stage of synthesis, that the product obtained from the DA reaction of **1** and **7** was *syn*,*syn*-bis-adduct **15b**, but not **15a**.

The bicyclo[2.2.2]octadiene-annulated *p*-benzoquinone **11** is more similar to the simpler analogous *p*-benzoquinone **12** in shape and thus expected to exhibit comparable π-facial selectivity in the DA reactions with dienes, in which the *syn*-facial attack of diene upon **11** is expected to be predominant but not exclusive. As shown in Scheme 7, when 2 molar equiv. of **11** were allowed to react with *syn*,*syn*-HMA **4** or its precursor **3** in toluene at 75–80 °C for 46 h, two isomeric bis-adducts were obtained in a total yield of 92% with a ratio of 1:2. *syn*,*syn*-Isomer **17b** is assigned to the major adduct as suggested by the simpler ^{1}H and ^{13}C NMR spectral data, which are in accordance with the C_{2v}-symmetric molecular framework, and by the favorable reaction course via which the enedione moiety of **11** (and **12**) participates in DA reaction preferentially with its *syn*-face (Fig. 2).[17b,18] The preference of the *syn*-facial attack of diene upon **11** was further denoted by the isolation of sole mono-adduct **16** in 73% yield, when the DA reaction was performed using dienophile **11** and bis-diene **4** in a molar ratio of 1:1 (Scheme 7). The assignment of the stereostructure of **16** is suggested by the configuration of newly formed ring junction, which is similar to those in *syn*,*syn*-isomer **17b** as indicated by the similarity in ^{1}H chemical shifts (ca. δ 2.97) of the methine hydrogens at these ring junctions. However, the two pairs of methine hydrogens at the relevant ring junctions in *syn*,*anti*-isomer **17a** display absorption



Scheme 7.

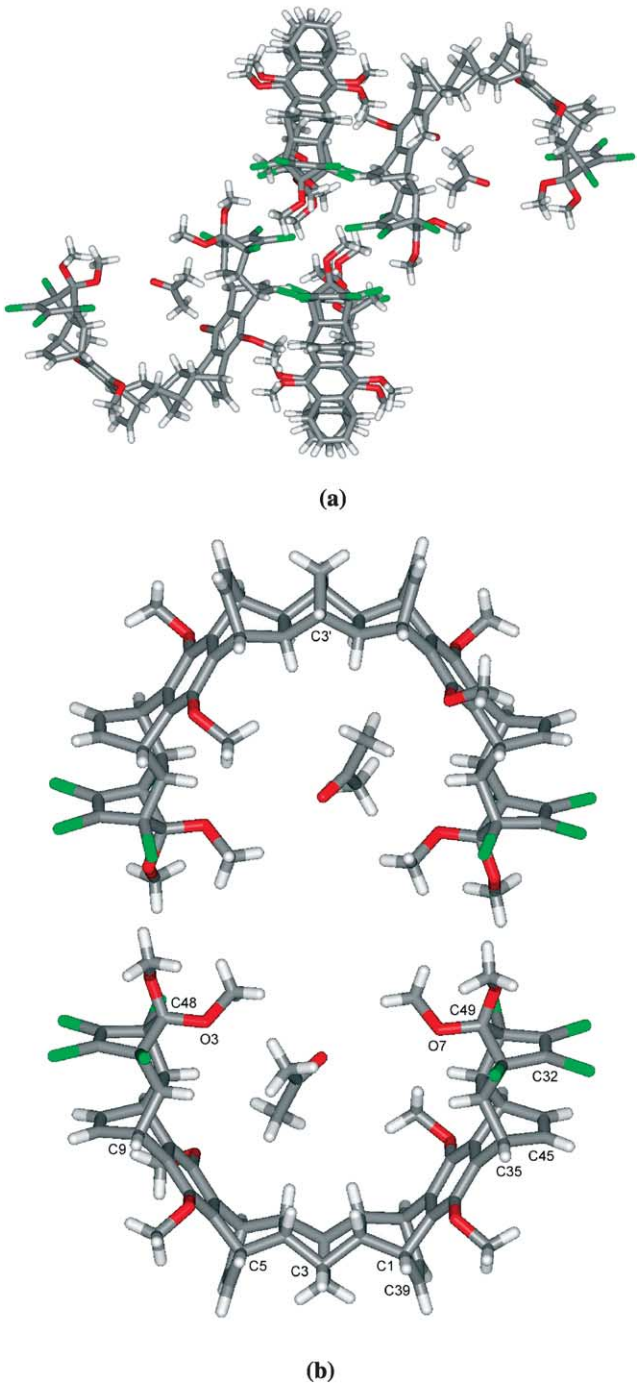
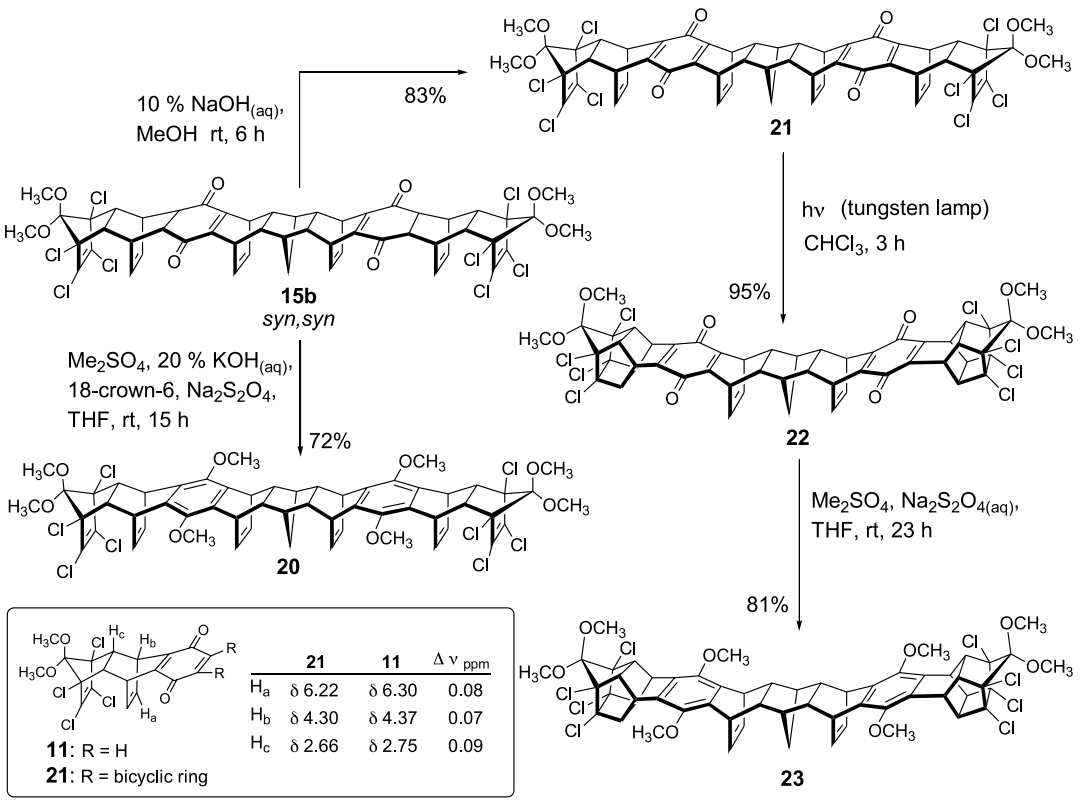


Figure 2. X-ray crystal structure of **20@acetone**. (a) Crystal packing in a unit cell that contains four molecules of **20** with four acetone solvent molecules included. (b) Two molecules of **20@acetone** in unit cell form an elliptical belt-like dimer. Representative interatomic distances: 22.17 Å (C3–C3′), 11.86 Å (C9–C35), 10.39 Å (C48–C49), 5.31 Å (C1–C5), 2.93 Å (C32–C45), 6.70 Å (C45–C39), 7.69 Å (O3–O7).

signals at δ 2.89 and 2.97. This difference in chemical shift implies that the second DA reaction occurs via the *anti*-facial attack of **16** upon **11** and results in the formation of **17a**, in which the methine hydrogens at newly formed ring junction are shielded by the neighboring etheno-bridge double bond to exhibit absorption signal at relatively higher field. Upon irradiation with an ordinary tungsten lamp (500-W) for 2 h, polyene **17b** could be induced to undergo four [2+2]photocyclizations to furnish a C_{2v}-symmetric quadruple-caged compound **18**, mp 386–388 °C (decomp.). The photochemical reaction is believed to proceed first with the ring-closure of the closely aligned chloro-substituted and unsubstituted double bonds, which is induced by the nearby cyclohexenedione moiety, followed by the photocyclization of the central etheno-bridge and endione C=C double bonds.[20] Treatment of a solution of **17b** in CH_2Cl_2 with a mixture of acetic anhydride and triethylamine in the presence of 4-dimethylaminopyridine (4-DMAP) for 16 h afforded diacetate **19** in 93% yield.

An attempt at transforming cyclohexendione rings in bis-adduct **15b** to *p*-dimethoxybenzene rings by base-promoted enolization followed by *O*-alkylation in the presence of alkylating agent (Me_2SO_4), however, experienced difficulty. The corresponding di-hydroquinone or its *O*-methylated derivative **20** could not be obtained even when the reaction was performed under N_2 atmosphere. The diquinone **21** was attained instead. Attainment of **20** was finally realized by performing enolization and *O*-alkylation in one pot with 20% aqueous KOH in the presence of 18-crown-6 to enhance the reactivity of enolate toward alkylation and sodium dithionite ($Na_2S_2O_4$) to suppress oxidation or reduce the resulting diquinone **21** back to the di-hydroquinone enolate. In this manner, the reaction furnished di-(1,4-dimethoxybenzene)-intercalated polyene **20** directly in 72% yield (Scheme 8). The infrared spectrum of **21** displays an absorption at 1650 cm^{-1} assignable to benzoquinone-type carbonyl groups. The intrinsic molecular symmetry (C_{2v}) of **21** is clearly shown by 16 lines of carbon signal for 53 carbons in the proton-decoupled ^{13}C NMR spectrum, which include absorption lines at δ 179.5, 150.8, and 149.9 attributed to the *p*-benzoquinone unit. In the ^1H NMR spectrum of diquinone **21**, eight absorption signals by the relative intensity of 8:8:6:6:4:2:2:4 were observed for ten groups of chemically different hydrogens, in which the signals due to the vinyl hydrogens (8H) at the etheno-bridges and methine hydrogens (8H) at bridgehead carbons of all bicyclo[2.2.2]octadiene rings appeared at δ 6.22 and 4.30, respectively, as overlapping multiplets. Taking structurally similar compound **11**[17] for comparison, the chemical shifts of the relevant hydrogens and carbon of carbonyl groups in **21** were shifted upfield, in line with those between **15b** and **9** albeit in much lesser magnitude for ^1H chemical shifts. Presumably, the anisotropic shielding effect displayed by the double bond of the fused bicyclo[2.2.2]octadiene ring in **21** is much less effective because of the enlargement of distance between *syn*-facially juxtaposed double bonds caused by rehybridization of the ring junction carbons from tetrahedral sp^3- to planar sp^2-carbon (insert, Scheme 8). Compound **21** contains benzoquinone moieties and thus is very light-sensitive. In fact, upon irradiation with a 500 W tungsten lamp for 3 h or prolonged exposure to laboratory light, the etheno-bridge double bonds in **21** underwent [2+2]photocyclization resulting in the formation of double cage-annulated *p*-benzoquinone **22** in 95% yield. When a solution of **22** in THF was exposed to the reduction with $Na_2S_2O_4$ in the presence of Me_2SO_4, the reaction gave di-(1,4-dimethoxybenzene)-intercalated double caged compound **23** in 81% yield (Scheme 8). Attempt of attainment of compound **23** directly from di-(1,4-dimethoxybenzene)-intercalated polyene **20** by irradiation with UV light



Scheme 8.

(medium-pressure Hg lamp) was not fruitful; an intractable complex mixture of products resulted.

Compound **20** is also C_{2v}-symmetric as indicated by the ^{13}C NMR spectrum, which contains 17 absorption lines for 57 carbons including those at δ 144.9, 137.0, and 135.2 ascribed to three nonequivalent sp^2-carbons of 1,4-dimethoxybenzene rings and δ 131.3 and 135.2 due to the etheno-bridge carbons of two differently located bicyclo[2.2.2]octadiene rings. The ^1H NMR spectrum of **20** exhibits a 12-hydrogen singlet at δ 3.72 for four $-OCH_3$ groups at two aromatic rings and two distinct 4-hydrogen doublet-of-doublets at δ 6.35 and 6.31 for vinyl hydrogens of etheno-bridges. Since the stereochemistry of *syn*,*syn*-**15b** was suggested by the preferred course of DA reaction and the ^1H NMR spectrum, it could not be unequivocally established, as with those of compounds **20** and **21** derived from it. Thus the solid-state structure of **20** was elucidated by X-ray crystallographical analysis (vide infra). The structural establishment of **20** thereby validated our prediction that, in the DA reaction of bis-*p*-benzoquinone **7** with the masked *cis*-DHN **1** (Scheme 6), the diene **1** approached the *p*-benzoquinone rings of dienophile **7** exclusively from the *syn*-faces (convex side), resulting in producing *syn*,*syn*-bis-adduct **15b** (Fig. 1b).

2.2. X-ray structure analysis of 20[21]

Suitable monoclinic single crystal of **20** for analysis was obtained by recrystallization from a mixture of dichloromethane and acetone (2:1 by vol.). There are four molecules of **20@acetone** in a unit cell (Fig. 2a), two of which form an elliptical 'belt-like' framework as shown in Figure 2b. As for the other two molecules of **20**, each arranges itself perpendicularly and in *anti*-manner on the face of belt framework with its terminal dichloro-substituted double bond locked-in to fill the in-between space of the elliptical assembly for achieving maximum tightness of packing. As shown in Figure 2b, each molecule of **20** is U-shaped (horseshoe-like) with all the etheno-bridges located *syn*-facially on the convex side of carbon scaffold and contains one molecule of acetone in the cavity. The dimension of U-shaped scaffold of **20** is defined by the transannular distances between carbon atoms at upper (C48–C49), middle (C9–C35), and bottom parts (C1–C5) of rim, which are 10.39, 11.86, and 5.31 Å, respectively. The longest top-to-bottom distance across elliptical framework is 22.17 Å (C3–C3′). The passage flanked by the cavities is seemingly 'guarded' by the inward bound methoxyl groups at the methano-bridges with transannular atomic distance of 7.69 Å between two oxygen atoms (O3–O7) and 5.99 Å between two methyl carbon atoms. The distance between dichloro-substituted etheno-bridge and nearby double bond of bicyclo[2.2.2]octadiene ring is 2.93 Å and that between two etheno-bridges flanking the benzene ring is 6.70 Å.

3. Conclusion

We have demonstrated the application of repetitive Diels–Alder reaction for the stereoselective synthesis of bicyclo[2.2.2]octene-based polycyclic compounds **15b**, **17b**, **19**, **20**, and **21**, that are composed of nine linearly *syn*-fused polyhydrobenzene rings, using only three very simple and easily available starting materials. These polycyclic compounds possess rack- or U-shaped framework, in which all

the etheno-bridge double bonds are arranged on the same side of the carbon skeletons and in close proximity. Upon irradiation with an ordinary tungsten lamp, compounds **17b** and **21** underwent [2+2]photocyclization to form quadruple- and double-caged compounds **18** and **22**, respectively, demonstrating that nearby conjugated enedione moiety can effectively induce the etheno-bridge double bonds to participate in photochemical ring-closure. The structure of **20** was analyzed by X-ray crystallography to have U-shaped framework with outward oriented etheno-bridge double bonds. The synthetic practicability now enables the investigation of accessibility to additional polycyclic compounds and their application as spacer molecules.

4. Experimental

4.1. General

Melting points were determined in capillaries on a Thomas–Hoover apparatus and are uncorrected. Infrared (IR) spectra were recorded as KBr pellets on an FT-IR spectrophotometer. The ^{1}H NMR spectra were obtained at 400 MHz (^{13}C NMR at 100 MHz) using $CDCl_3$ as solvent (unless otherwise specified). All chemical shifts were expressed in δ (ppm) with reference to $CHCl_3$ (δ 7.26 for ^{1}H and δ 77.0 for ^{13}C). Coupling constants are reported in hertz (Hz). The number of attached hydrogens on the carbon atom was determined by the DEPT analysis. The assignment of proton and carbon NMR peaks was supported by ^{1}H–^{1}H COSY and HMQC spectra and for some compounds in addition by NOESY spectra. Mass (MS) spectra were done in EI (70 eV) unless otherwise indicated. All solvents used were either reagent grade or were distilled prior to use. Analytical thin-layer chromatography (TLC) was performed on E. Merck silica gel 60 F_{254} plate (0.20 mm). Flash chromatography was performed on E. Merck silica gel (230–400 mesh). Microanalyses were performed by the NSC Analytical Centers operated by the Cheng Kung University, Tainan, or the Chung Hsing University, Taichung, Taiwan.

4.1.1. (4aβ,5β,5aβ,6β,6aβ,7β,7aβ,11aβ,12β,12aβ,13-β,13aβ,14β,14aβ)-4a,5,5a,6,6a,7,7a,11a,12,12a,13,13a,14,14a-Tetradecahydro-5,14:7,12-dietheno-6,13-methanopentacene-1,4,8,11-tetraone (5). A solution of bis-norbornenone **3**[16] (2.00 g, 7.9 mmol) and *p*-benzoquinone (1.78 g, 16.5 mmol) in toluene (60 mL) was stirred under N_2 atmosphere and heated at refluxing temperature for 26 h. After the reaction mixture was cooled to room temperature, half volume of the solvent was removed under reduced pressure and the solid residue was collected by suction filtration. The same process was repeated three times and the combined solid products were washed with a small amount of ether to give bis-endione adduct **5** (3.12 g, 95%) as a pale yellow solid: mp 202–203 °C (decomp); IR (KBr) 1671 (s), 1607 (w), 1275 cm^{-1}(m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (s, 4H, $H_{2,3,9,10}$), 6.04 (dd, J=4.6, 3.2 Hz, 4H, $H_{5',7',12',14'}$), 3.31–3.28 (m, 4H, $H_{5,7,12,14}$), 2.92 (br, 4H, $H_{4a,7a,11a,14a}$), 2.06 (s, 2H, $H_{6,13}$), 1.77 (br, 4H, $H_{5a,6a,12a,13a}$), 1.61 (s, 2H, $H_{6'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7 (s, $C_{1,4,8,11}$), 142.2 (d, $C_{2,3,9,10}$), 133.1 (d, $C_{5',7',12',14'}$), 50.3 (d, $C_{4a,7a,11a,14a}$), 49.9 (d, $C_{5a,6a,12a,13a}$), 46.8 (d, $C_{6,13}$), 39.9 (d, $C_{5,7,12,14}$), 30.3 (t, C_6); MS (EI, 50eV) *m*/*z* (relative intensity) 413 (M^++1, 0.4), 412 (M^+, 2), 384 (1), 305 (1), 304 (4), 253 (1), 252 (2), 161 (11), 160 (100), 158 (8), 131 (11), 82 (33), 66 (32). Anal. Calcd for $C_{27}H_{24}O_4$: C, 78.62; H, 5.86. Found: C, 78.56; H, 5.86.

4.1.2. (5β,5aβ,6β,6aβ,7β,12β,12aβ,13β,13aβ,14β)-5,5a,6,6a,7,12,12a,13,13a,14-Decahydro-5,14:7,12-dietheno-6,13-methanopentacene-1,4,8,11-tetraol (6). A stirring solution of bis-endione **5** (0.50 g, 1.2 mmol) in $CHCl_3$/EtOAc (vol. 1:2; 50 mL) was heated under reflux in the presence of *p*-toluenesulfonic acid monohydrate (0.025 g, 0.1 mmol) for 14 h. After the reaction mixture was cooled to room temperature, the solvent was removed under reduced pressure to leave a solid residue which was recrystallized from acetone to afford tetraol **6** as colorless crystallines (0.48 g, 96%): mp 243–244 °C; IR (KBr) 3404 (m), 2944 (s), 2915 (s), 2886 (s), 1232 cm^{-1} (s); ^{1}H NMR (400 MHz, CH_3CN-d_3/acetone-d_6) δ 6.33–6.28 (m, 8H, $H_{5',7',12',14',2,3,9,10}$), 4.24–4.20 (m, 4H, $H_{5,7,12,14}$), 2.62 (br, 4H, $H_{1',4',8',11'}$), 2.17 (s, 2H, $H_{6,13}$), 1.98 (s, 2H, $H_{6'}$), 1.38 (s, 4H, $H_{5a,6a,12a,13a}$); ^{13}C NMR (100 MHz, CH_3CN-d_3/acetone-d_6) δ 144.5 (s, $C_{1,4,8,11}$), 136.2 (d, $C_{2,3,9,10}$), 134.5 (s, $C_{4a,7a,11a,14a}$), 113.2 (d, $C_{5',7',12',14'}$), 52.0 (d, $C_{5a,6a,12a,13a}$), 46.1 (d, $C_{6,13}$), 39.0 (d, $C_{5,7,12,14}$), 31.1 (t, $C_{6'}$); MS (EI, 70eV) *m*/*z* (relative intensity) 413 (0.2), 412 (M^+, 0.6), 394 (M^+-H_2O, 0.3), 253 (15), 230 (8), 161 (100), 160 (86), 158 (33), 131 (42), 91 (40). Anal. Calcd for $C_{27}H_{24}O_4$: C, 78.62; H, 5.86. Found: C, 78.70; H, 5.61.

4.1.3. (5β,5aβ,6β,6aβ,7β,12β,12aβ,13β,13aβ,14β)-5,5a,6,6a,7,12,12a,13,13a,14-Decahydro-5,14:7,12-dietheno-6,13-methanopentacene-1,4,8,11-tetraone (7). *Method A*. A solution of tetraol **6** (0.52 g, 1.3 mmol) and DDQ (0.69 g, 3.0 mmol) in EtOAc (40 mL) was stirred at room temperature for 8 h. The solvent was removed under reduced pressure to leave a solid residue, from which the crude product was extracted by stirring with CH_2Cl_2 (30 mL) for 10 min. After removal of solvent, the crude product was purified by flash chromatography on a silica gel column (EtOAc/*n*Hex: 1:10; R_f=0.46) and recrystallized from EtOAc/*n*Hex to furnish bis-benzoquinone **7** as bright yellow flakes (0.45 g, 87%).

Method B. Into a stirring solution of bis-endione **5** (3.47 g, 8.40 mmol) in $CHCl_3$/EtOAc (1:2 by vol.; 100 mL) were added *p*-toluenesulfonic acid monohydrate (0.16 g, 0.84 mmol) and DDQ (3.79 g, 16.7 mmol). The reaction mixture was heated under gentle reflux for 17 h, and was then cooled to room temperature and concentrated under reduced pressure. The resulting solid residue was stirred with dichloromethane (50 mL) for 10 min. and filtered. After removal of solvent from the filtrate, the crude product was subjected to flash column chromatography (silica gel, EtOAc/*n*Hex: 1:10; R_f=0.46) followed by recrystallization from EtOAc/*n*Hex to furnish bis-benzoquinone **7** (2.85 g, 83%) as bright yellow flakes: mp 128–129 °C; IR (KBr) 1740 (m), 1648 (s), 1578 cm^{-1} (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.55 (s, 4H, $H_{2,3,9,10}$), 6.25 (dd, J=4.3, 3.4 Hz, 4H, $H_{5',7',12',14'}$), 4.30–4.27 (m, 4H, $H_{5,7,12,14}$), 2.23 (s, 2H, $H_{6,13}$), 1.87 (s, 2H, $H_{6'}$), 1.42 (br, 4H, $H_{5a,6a,12a,13a}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.5 (s, $C_{1,4,8,11}$), 150.6 (s,

$C_{4a,7a,11a,14a}$), 135.5 (d, $C_{2,3,9,10}$), 133.9 (d, $C_{5',7',12',14'}$), 50.8 (d, $C_{5a,6a,12a,13a}$), 44.3 (d, $C_{6,13}$), 38.5 (d, $C_{5,7,12,14}$), 30.3 (t, $C_{6'}$); MS (EI, 70eV) *m/z* (relative intensity) 409 (M^++1, weak), 408(M^+, 0.1), 250 (2), 184 (23), 158 (41), 130 (14), 102 (31), 92 (100). Anal. Calcd for $C_{27}H_{20}O_4$: C, 79.40; H, 4.94. Found: C, 79.32; H, 4.68.

4.1.4. (1β,2α,3β,4β,5β,7α,8α,10β,11β,12α,13α,14β,15α,16β,17β,18β,20α,21α,23β,24β,25β,26α)-Dodecacyclo[12.12.1.$0^{2,13}$.$0^{3,7}$.$0^{4,11}$.$0^{5,10}$.$0^{8,12}$.$0^{15,26}$.$0^{16,20}$.$0^{17,24}$.$0^{18,23}$.$0^{21,25}$]heptacosan-6,9,19,22-tetraone (8). A solution of bis-endione adduct **5** (132 mg, 0.32 mmol) in $CHCl_3$ (10 mL) was irradiated with a 500-W tungsten lamp for 3 h. Solvent was removed and the resulting solid residue was recrystallized from acetone to give the corresponding cage compound **8** (120 mg, 91%) as white powder: mp 369–371 °C (decomp.); IR (KBr) 1748 (s), 1728 cm^{-1} (s); ^1H NMR (400 MHz, $CDCl_3$) δ 3.18–3.14 (m, 4H, $H_{4,11,17,24}$), 2.92–2.87 (m, 4H, $H_{5,10,18,23}$), 2.44 (br, 4H, $H_{7,8,20,21}$), 2.30 (s, 2H, $H_{1,14}$), 2.25 (br, 4H $H_{3,12,16,25}$), 1.99 (br, 4H, $H_{2,13,15,26}$), 1.49 (s, 2H, H_{27}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.3 (s, $C_{6,9,19,22}$), 48.7 (d, $C_{7,8,20,21}$), 46.1 (d, $C_{5,10,18,23}$), 44.7 (d, $C_{1,14}$), 39.4 (d, $C_{2,13,15,26}$), 35.2 (d, $C_{3,12,16,25}$), 33.5 (d, $C_{4,11,17,24}$), 31.6 (t, C_{27}); MS (EI, 70eV) *m/z* (relative intensity) 413 (M^++1, 24), 412 (M^+, 100), 411 (M^+−1, 26), 384 (8), 356 (7), 303 (10), 160 (59), 128 (72), 115 (73), 104 (59), 91 (83), 82 (87), 78 (67). Anal. Calcd for $C_{27}H_{24}O_4$: C, 78.62; H, 5.86. Found: C, 78.66; H, 6.17.

4.1.5. (5α,8α,8aβ,9β,10β,10aβ)-5,6,7,8-Tetrachloro-5,8,8a,9,10,10a-hexahydro-9,10-etheno-5,8-dimethoxymethanoanthracene-1,4-dione (11). Into a stirring solution of endione **9**[13] (18.4 g, 40.9 mmol) in dioxane (300 mL) were added DDQ (10.2 g, 45.1 mmol) and *p*-tolunesulfonic acid (8.6 g, 45.1 mmol). The reaction mixture was heated under gentle reflux for 6 h, and then concentrated under reduced pressure. The resulting slurry was diluted with water (100 mL) and extracted with CH_2Cl_2 (3×200 mL). The organic layers were combined and successively washed with water (2×200 mL), saturated sodium bicarbonate solution (250 mL), and brine (250 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to leave a brownish viscous residue, which was triturated with small amount of Et_2O. The resulting precipitates were collected and washed with Et_2O. The filtrate was concentrated and the residue was subjected to flash column chromatography (silica gel) using EtOAc/*n*Hex (2:5) as eluent to afford additional light yellowish solids. Recrystallization of combined solids from CH_2Cl_2/Et_2O furnished yellow flakes of diendione **11** (17.1 g, 93%): mp 189–190 °C; IR ($CHCl_3$) 1655 (s), 1609 (m), 1581 cm^{-1} (m); ^1H NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 2H, $H_{2,3}$), 6.30 (dd, *J*=4.8, 3.7 Hz, 2H, $H_{9',10'}$), 4.35–4.39 (m, 2H, $H_{9,10}$), 3.52 (s, 3H, $-OCH_3$), 3.49 (s, 3H, $-OCH_3$), 2.75 (br, 2H, $H_{8a,10a}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.9 (s, $C_{1,4}$), 151.7 (s, $C_{4a,9a}$), 135.6 (d, $C_{2,3}$), 130.0 (d, $C_{11,12}$), 127.7 (s, $C_{6,7}$), 115.6 (s, C_{13}), 76.4 (s, $C_{5,8}$), 52.8 (q, $-OCH_3$), 51.6 (q, $-OCH_3$), 51.5 (d, $C_{8a,10a}$), 33.5 (d, $C_{9,10}$); MS (EI) *m/z* (relative intensity) 450 (0.6), 448 (0.5), 446 (M^+, weak), 415 (3), 413 (6), 411 (M^+−Cl, 6), 257 (76), 255 (99), 254 (25), 253 (100), 216 (10), 211 (17), 209 (52), 207 (54), 181 (12), 179 (12), 160 (13), 104 (13), 102 (14), 76 (17), 59 (42). Anal. Calcd for $C_{19}H_{14}Cl_4O_4$: C, 50.92; H, 3.15; O, 14.28. Found: C, 50.88; H, 3.22; O, 14.38.

Diendione **11** was also prepared in 95% yield by heating a stirring solution of bis-endione **9** in EtOAc under reflux for 12 h in the presence of *p*-toluenesulfonic acid monohydrate, followed by oxidation of hydroquinone **10** thereby obtained in EtOAc with DDQ.

4.1.6. (1β,4β,4aβ,6β,6aα,7β,7aα,8β,9aα,10β,13β,13aα,15β,15aα,16β,16aα,17β,18aβ)- and (1β,4β,4aα,6β,6aα,7β,7aα,8β,9aα,10β,13β,13aα,15β,15aα,16-β,16aα,17β, 18aα)-1,4,4a,6,6a,7,7a,8,9a,10,13,13a,15,15a,16,16a,17,18a-Octadecahydro-6,17:8,15-dietheno-1,4:7,16:10,13-trimethanoheptacene-5,9,14,18-tetraone (13a/13b). A solution of **7** (100 mg, 0.25 mmol) and cyclopentadiene (0.2 mL, 2.5 mmol) in CH_2Cl_2 (10 mL) was stirred under nitrogen atmosphere for 7 h. The solvent was removed to leave a solid residue, which was determined by ^1H NMR spectral analysis to contain two adducts in a ratio of 4:1. The product mixture was rinsed with a small amount of Et_2O and the pale yellow solid (116 mg, 87%) thereby obtained was subjected to separation by column chromatography (silica gel) using EtOAc/*n*Hex (1:1) as eluent, followed by recrystallization from EtOAc/*n*Hex to give **13a** (23 mg, 17%) and **13b** (90 mg, 68%) as pale yellow crystals.

Compound **13a**. R_f=0.44; mp 143–144 °C (decomp.); IR (KBr) 1653 (s), 1620 (m), 1586 cm^{-1} (m); ^1H NMR (400 MHz, $CDCl_3$) δ 6.18–6.13 (m, 4H, $H_{6',8',15',17'}$), 5.90 (dd, *J*=1.8, 1.8 Hz, 2H, $H_{2,3}$), 5.76 (dd, *J*=1.6, 1.6 Hz, 2H, $H_{11,12}$), 4.24–4.16 (m, 4H, $H_{6,8,15,17}$), 3.48 (s, 2H, $H_{1,4}$), 3.40 (s, 2H, $H_{10,13}$), 3.16 (dd, *J*=2.2, 1.4 Hz, 2H, $H_{9a,13a}$), 3.11 (dd, *J*=2.2, 1.2 Hz, 2H, $H_{4a,18a}$), 2.13 (s, 2H, $H_{7,16}$), 1.76 (s, 2H, $H_{7'}$), 1.50–1.44 (m, 2H, $H_{1'\alpha,10'\beta}$), 1.37 (d, *J*=8.7 Hz, 2H, $H_{1'\beta,10'\alpha}$), 1.27 (s, 2H, $H_{7a,15a}$), 1.22 (s, 2H, $H_{6a,16a}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2 (s, $C_{9,14}$), 194.8 (s, $C_{5,18}$), 157.0 (s, $C_{8a,14a}$), 156.5 (s, $C_{5a,17a}$), 134.9 (d, $C_{2,3}$), 134.4 (d, $C_{11,12}$), 134.1 (d, $C_{8',15'}$), 133.8 (d, $C_{6',17'}$), 50.8 (d, $C_{6a,16a}$), 50.5 (d, $C_{7a,15a}$), 49.6 (d, $C_{4a,18a}$), 49.5 (d, $C_{9a,13a}$), 49.5 (t, $C_{10'}$), 49.4 (d, $C_{10,13}$), 48.6 (t, $C_{1'}$), 48.4 (d, $C_{1,4}$), 44.5 (d, $C_{7,16}$), 39.0 (d, $C_{8,15}$), 38.9 (d, $C_{6,17}$), 30.2 (t, $C_{7'}$); MS (EI, 70 eV) *m/z* (relative intensity) 541 (M^++1, 4), 540 (M^+, 18), 539 (M^+−1, 5), 474 (9), 316 (15), 250 (18), 224 (35), 160 (94), 91 (100), 66 (69). Anal. Calcd for $C_{37}H_{22}O_4$: C, 82.19; H, 5.96. Found: C, 82.26; H, 6.06.

Compound **13b**: R_f=0.72; mp 151–152 °C (decomp.); IR (KBr) 1656 (s), 1622 (m), 1587 cm^{-1} (m); ^1H NMR (400 MHz, $CDCl_3$) δ 6.15 (dd, *J*=4.3, 3.3 Hz, 4H, $H_{6',8',15',17'}$), 5.77 (dd, *J*=1.5, 1.5 Hz, 4H, $H_{2,3,11,12}$), 4.19 (dd, *J*=3.7, 3.7 Hz, 4H, $H_{6,8,15,17}$), 3.40 (s, 4H, $H_{1,4,10,13}$), 3.13 (dd, *J*=2.2, 1.4 Hz, 4H, $H_{4a,9a,13a,18a}$), 2.16 (s, 2H, $H_{7,16}$), 1.76 (s, 2H, $H_{7'}$), 1.46 (ddd, *J*=8.6, 1.6, 1.6 Hz, 2H, $H_{1'\beta,10'\beta}$), 1.36 (d, *J*=8.6 Hz, 2H, $H_{1'\alpha,10'\alpha}$), 1.31 (s, 4H, $H_{6a,7a,15a,16a}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ195.0 (s, $C_{5,9,14,18}$), 156.9 (s, $C_{5a,8a,14a,17a}$), 134.5 (d, $C_{2,3,11,12}$), 134.1 (d, $C_{6',8',15',17'}$), 50.5 (d, $C_{6a,7a,15a,16a}$), 49.5 (d, $C_{4a,9a,13a,18a}$), 49.4 (t, $C_{1',10'}$), 49.3 (d, $C_{1,4,10,13}$), 44.6 (d, $C_{7,16}$), 38.9 (d, $C_{6,8,15,17}$), 30.3 (t, $C_{7'}$); MS (EI, 70 eV) *m/z* (relative intensity) 541 (M^++1, 1), 540 (M^+, 2), 539 (M^+−1, 1), 474 (4), 224 (29), 184 (42), 158 (35), 91 (100), 66 (84). Anal.

Calcd for $C_{37}H_{22}O_4$: C, 82.19; H, 5.96. Found: C, 82.32; H, 6.10.

4.1.7. (1β,2α,3β,6β,7β,8β,9β,10β,11β,14β,15α,16β,17α,18β,21β,22β,23β,24β,25β,26β,29β,30α)-Hexacyclo[14.14.1.2^{3,14}.2^{18,29}.1^{7,10}.1^{22,25}.0^{2,15}.0^{4,8}.0^{4,13}.0^{6,11}.0^{9,13}.0^{17,30}.0^{19,23}.0^{19,28}.0^{21,26}.0^{24,28}]heptatriacontan-32,33-dien-5,12,20,27-tetraone (14). A solution of bis-endione adduct **13b** (200 mg, 0.37 mmol) in $CHCl_3$ (20 mL) was irradiated with a 500-W tungsten lamp for 17 h. Solvent was removed and the resulting solid residue was recrystallized from CH_2Cl_2/acetone to give the cage compound **14** (188 mg, 94%) as white powder: mp 353–355 °C (decomp.); IR (KBr) 2961 (s), 1741 (s), 1725 cm^{-1} (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (dd, J=4.7, 3.3 Hz, 4H, $H_{32,33,34,35}$), 2.73–2.69 (m, 8H, $H_{3,7,10,14,18,22,25,29}$), 2.63–2.61 (m, 4H, $H_{6,11,21,26}$), 2.45–2.42 (m, 4H, $H_{8,9,23,24}$), 2.03 (s, 4H, $H_{2,15,17,30}$), 1.88 (s, 2H, $H_{1,16}$), 1.85 (d, J=11.2 Hz, 2H, $H_{36\alpha,37\alpha}$), 1.75 (s, 2H, H_{31}), 1.66 (d, J=11.2 Hz, 2H, $H_{36\beta,37\beta}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.8 (s, $C_{5,12,20,27}$), 133.2 (d, $C_{32,33,34,35}$), 55.6 (d, $C_{6,11,21,26}$), 54.5 (s, $C_{4,13,19,28}$), 46.7 (d, $C_{1,16}$), 43.3 (d, $C_{2,15,17,30}$), 43.2 (d, $C_{7,10,22,25}$), 41.7 (d, $C_{8,9,23,24}$), 40.6 (t, $C_{36,37}$), 35.2 (d, $C_{3,14,18,29}$), 32.4 (t, C_{31}); MS (EI, 70eV) m/z (relative intensity) 541 (M^++1, 3), 540 (M^+, 10), 539 (M^+−1, 7), 474 (25), 316 (7), 289 (4), 250 (9), 224 (336), 196 (13), 167 (15), 91 (14), 66 (47), 32 (100). Anal. Calcd for $C_{37}H_{22}O_4$: C, 82.19; H, 5.96. Found: C, 82.15; H, 5.72.

4.1.8. (1β,4β,4aα,5β,5aα,7β,7aα,8β,8aα,9β,10aα,11β,11aα,12β,15β,15aα,16β,16aα,18β,18aα,19β,19aα,20β,21aα,22β,22aα)-1,2,3,4,12,13,14,15-Octachloro-1,4,4a,5,5a,7,7a,8,8a,9,10a,11,11a,12,15,15a,16,16a,18,18a,19,19a,20,21a,22,22a-hexacosahydro-1,4:12,15-di(dimethoxymethano)-5,22:7,20:9,18:11,16-tetraetheno-8,19-methanononacene-6,10,17,21-tetraone (15b). A solution of bis-benzoquinone **7** (0.621 g, 1.52 mmol) and the masked *cis*-DHN **1** (1.052 g, 3.08 mmol) in benzene (70 mL) was stirred under N_2 atmosphere and heated at refluxing temperature for 38 h. After the reaction mixture was cooled to room temperature, solvent was removed under reduced pressure and the solid residue was washed with a small amount of ether and collected by suction filtration. Recrystallization of solids from $CHCl_3$/EtOAc afforded bis-adduct **15b** (1.36 g, 82%) as a pale yellow powder: mp 152–153 °C (decomp.); IR (KBr) 1661 (s), 1625 (m), 1605 (m), 1590 (m), 1190 cm^{-1} (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (dd, J=4.3, 3.4 Hz, 4H, $H_{7',9',18',20'}$), 5.79 (dd, J=4.4, 3.3 Hz, 4H, $H_{5',11',16',22'}$), 4.24–4.19 (m, 4H, $H_{7,9,18,20}$), 3.57 (s, 6H, $H_{1'\alpha,12'\alpha}$), 3.47 (s, 6H, $H_{1'\beta,12'\beta}$), 3.33–3.29 (m, 4H, $H_{5,11,16,22}$), 2.87 (s, 4H, $H_{5a,10a,16a,21a}$), 2.80 (s, 4H, $H_{4a,11a,15a,22a}$), 2.17 (s, 2H, $H_{8,19}$), 1.75 (s, 2H, $H_{8'}$), 1.29 (s, 4H, $H_{7a,8a,18a,19a}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2 (s, $C_{6',10',17',21'}$), 157.3 (s, $C_{6a,9a,17a,20a}$), 133.8 (d, $C_{7',9',18',20'}$), 128.0 (d, $C_{5',11',16',22'}$), 127.7 (s, $C_{2,3,13,14}$), 113.6 (s, $C_{1',12'}$), 77.0 (s, $C_{1,4,12,15}$), 52.7 (q, $C_{1'\beta,12'\beta}$), 51.6 (q, $C_{1'\alpha,12'\alpha}$), 50.8 (d, $C_{5a,10a,16a,21a}$), 50.5 (d, $C_{7a,8a,18a,19a}$), 50.2 (d, $C_{4a,11a,15a,22a}$), 44.5 (d, $C_{8,19}$), 39.1 (d, $C_{7,9,18,20}$), 35.8 (d, $C_{5,11,16,22}$), 30.3 (t, $C_{8'}$); MS (FAB, 3-NBA) m/z (relative intensity) 1096 (M^++8, 12), 1094 (M^++6, 15), 1092 (M^++4, 21), 1090 (M^++2, 15), 1088 (M^+, 11), 1057 (M^++4-Cl, 44), 1055 (M^++2-Cl, 41), 1053 (M^+−Cl, 27), 591 (18), 556 (30), 499 (52), 468 (57), 301 (100). Anal. Calcd for $C_{53}H_{44}Cl_8O_8$: C, 58.26; H, 4.05; O, 11.71. Found: C, 58.28; H, 4.09; O, 11.57.

4.2. Diels–Alder reaction of *p*-benzoquinone 11 and *syn*,*syn*-HMA 4 (1:1 molar ratio)

A solution of **11** (661 mg, 1.50 mmol) and **4** (372 mg, 1.47 mmol) in toluene (50 mL) was stirred under N_2 atmosphere and heated at 75–80 °C for 44 h. After the reaction mixture was cooled to room temperature, solvent was removed under reduced pressure to leave a solid residue, which was rinsed with Et_2O and collected by suction filtration. The pale yellow solid (261 mg, 96%) thereby obtained was subjected to separation by column chromatography (silica gel) using EtOAc/*n*Hex (1:1) as eluent to give **16** (694 mg, 73%), **17a** (113 mg, 7%), and **17b** (226 mg, 14%).

4.2.1. (1β,4β,4aα,5β,6aα,7β,7aα,8β,8aα,12aα,13β,13aα,14β,14aα,16β,16aα)-1,2,3,4-Tetrachloro-1,4,4a,5,6a,7,7a,8,8a,12a,13,13a,14,14a,16,16a-hexadecahydro-1,4-(dimethoxymethano)-5,16:7,14-dietheno-8,13-methano-hexacene-6,15-dione (16). R_f=0.61; mp 210–212 °C (decomp.); IR (KBr) 1656 (s), 1629 (m), 1610 (m), 1593 (m), 1185 cm^{-1} (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (dd, J=4.2, 3.4 Hz, 2H, $H_{5',16'}$), 5.93 (dd, J=4.5, 3.2 Hz, 2H, $H_{7',14'}$), 5.53 (dd, J=7.7, 2.9 Hz, 2H, $H_{10,11}$), 5.33 (ddd, J=7.7, 2.3, 2.3 Hz, 2H, $H_{9,12}$), 4.29–4.26 (m, 2H, $H_{5,16}$), 3.50 (s, 3H, $H_{1'\alpha}$), 3.47 (s, 3H, $H_{1'\beta}$), 3.20 (br s, 2H, $H_{7,14}$), 2.97 (s, 2H, $H_{6a,14a}$), 2.61 (s, 2H, $H_{4a,16a}$), 2.43 (br s, 2H, $H_{8a,12a}$), 2.05 (s, 2H, $H_{7a,13a}$), 1.89 (s, 2H, $H_{8,13}$), 1.31 (d, J=10.4 Hz, 2H, $H_{8'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3 (s, $C_{6,15}$), 158.0 (s, $C_{5a,15a}$), 132.5 (d, $C_{7',14'}$), 130.1 (d, $C_{5',16'}$), 127.7 (s, $C_{2,3}$), 127.5 (d, $C_{9,12}$), 121.8 (d, $C_{10,11}$), 115.5 (s, $C_{1'}$), 76.5 (s, $C_{1,4}$), 52.8 (q, $C_{1'\beta}$), 51.6 (q, $C_{1'\alpha}$), 51.3 (d, $C_{4a,16a}$), 51.3 (d, $C_{6a,14a}$), 50.7 (d, $C_{8,13}$), 49.3 (d, $C_{7a,13a}$), 44.9 (d, $C_{8a,12a}$), 41.0 (d, $C_{7,14}$), 34.0 (d, $C_{5,16}$), 31.0 (t, $C_{8'}$); MS (EI, 70 eV) m/z (relative intensity) 646 (M^++4, 0.1), 644 (M^++2, 0.2), 642 (M^+, 0.2), 611 (M^+−Cl+4, 0.2), 609 (M^+−Cl+2, 0.3), 607 (M^+−Cl, 0.3), 500 (2), 253 (100), 209 (48), 104 (54), 91 (17). Anal. Calcd for $C_{34}H_{30}Cl_4O_4$: C, 63.37; H, 4.69; O, 9.93. Found: C, 63.45; H, 4.29; O, 10.12.

4.2.2. (1β,4β,4aα,5β,6aα,7β,7aα,8β,8aα,9β,9aα,11β,11aβ,12β,15β,15aβ,16β,17aα,18β,18aα,19β,19aα,20β,20aα,22β,22aα)-1,2,3,4,12,13,14,15-Octachloro-1,4,4a,5,6a,7,7a,8,8a,9,9a,11,11a,12,15,15a,16,17a,18,18a,19,19a,20,20a,22,22a-hexacosahydro-1,4:12,15-di(dimethoxymethano)-5,22:7,20:9,18:11,16-tetraetheno-8,19-methanononacene-6,10,17,21-tetraone (17a). Mp 214–216 °C (decomp.); IR (KBr) 1661 (s), 1627 (m), 1606 (m), 1592 (m), 1225 (s), 1187 cm^{-1} (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.21 (dd, J=3.8, 3.8 Hz, 2H, $H_{11',16'}$), 6.18 (dd, J=4.0, 3.6 Hz, 2H, $H_{5',22'}$), 6.03 (dd, J=4.3, 3.4 Hz, 2H, $H_{9',18'}$), 5.86 (dd, J=4.3, 3.4 Hz, 2H, $H_{7',20'}$), 4.30–4.25 (m, 4H, $H_{5,11,16,22}$), 3.50 (s, 3H, $H_{12'\alpha}$), 3.49 (s, 3H, $H_{1'\alpha}$), 3.46 (s, 3H, $H_{12'\beta}$), 3.46 (s, 3H, $H_{1'\beta}$), 3.34 (br s, 2H, $H_{9,18}$), 3.21 (br s, 2H, $H_{7,20}$), 2.94 (s, 2H, $H_{6a,20a}$), 2.89 (s, 2H, $H_{9a,17a}$), 2.60 (s, 2H, $H_{4a,22a}$), 2.49 (s, 2H, $H_{11a,15a}$), 2.05 (s, 2H, $H_{8,19}$), 1.77 (s, 2H, $H_{7a,19a}$), 1.77 (s, 2H, $H_{8a,18a}$), 1.53 (s, 2H, $H_{8'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1 (s, $C_{6,21}$), 193.8 (s, $C_{10,17}$), 158.1 (s, $C_{5a,21a}$), 157.5 (s, $C_{10a,16a}$),

133.0 (d, $C_{9',18'}$), 132.6 (d, $C_{7',20'}$), 130.1 (d, $C_{5',22'}$), 129.9 (d, $C_{11',16'}$), 127.71/127.67 (s, $C_{2,3,13,14}$), 115.53/115.47 (s, $C_{1',12'}$), 76.5 (s, $C_{12,15}$), 76.4 (s, $C_{1,4}$), 52.8 (2C, q, $C_{1'\beta,12'\alpha}$), 51.6 (2C, q, $C_{1'\alpha,12'\beta}$), 51.6 (d, $C_{6a,20a}$), 51.5 (d, $C_{11a,15a}$), 51.4 (d, $C_{9a,17a}$), 51.3 (d, $C_{4a,22a}$), 50.3 (d, $C_{7a,19a}$), 50.0 (d, $C_{8a,18a}$), 46.8 (d, $C_{8,19}$), 40.8 (d, $C_{7,20}$), 40.1 (d, $C_{9,18}$), 34.05/34.01 (d, $C_{5,11,16,22}$), 30.4 (t, $C_{8'}$); MS (FAB, 3-NBA) *m/z* (relative intensity) 1094 (M^++6, 13), 1092 (M^++4, 13), 1061 (3), 1060 (3), 1058 (3), 646 (32), 644 (34), 450 (47), 448 (49). Anal. Calcd for $C_{53}H_{44}Cl_8O_8$: C, 58.26; H, 4.05; O, 11.71. Found: C, 58.40; H, 4.23; O, 11.61.

4.2.3. (1β,4β,4aα,5β,6aα,7β,7aα,8β,8aα,9β,9aα,11β,11aα,12β,15β,15aα,16β,17aα,18β,18aα,19β,19aα,20β,20aα,22β,22aα)-1,2,3,4,12,13,14,15-Octachloro-1,4,4a,5,6a,7,7a,8,8a,9,9a,11,11a,12,15,15a,16,17a,18,18a,19,19a,20,20a,22,22a-hexacosahydro-1,4:12,15-di(dimethoxymethano)-5,22:7,20:9,18:11,16-tetraetheno-8,19-methanononacene-6,10,17,21-tetraone (17b). Mp 223–224 °C (decomp.); IR (KBr) 1662 (s), 1628 (m), 1606 (m), 1594 (m), 1226 (s), 1212 (s), 1186 (s), 1154 (s), 1126 cm^{-1} (s); ^1H NMR (400 MHz, $CDCl_3$) δ 6.17 (dd, *J*=4.2, 3.4 Hz, 4H, $H_{5',11',16',22'}$), 5.84 (dd, *J*=4.6, 3.4 Hz, 4H, $H_{7',9',18',20'}$), 4.28–4.24 (m, 4H, $H_{5,11,16,22}$), 3.50 (s, 6H, $H_{1'\alpha,12'\alpha}$), 3.46 (s, 6H, $H_{1'\beta,12'\beta}$), 3.20 (br s, 4H, $H_{7,9,18,20}$), 2.94 (s, 4H, $H_{6a,9a,17a,20a}$), 2.59 (s, 4H, $H_{4a,11a,15a,22a}$), 2.02 (s, 2H, $H_{8,19}$), 1.77 (s, 4H, $H_{7a,8a,18a,19a}$), 1.53 (s, 2H, $H_{8'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1 (s, $C_{6,10,17,21}$), 158.1 (s, $C_{5a,10a,16a,21a}$), 132.6 (d, $C_{7',9',18',20'}$), 130.0 (d, $C_{5',11',16',22'}$), 127.7 (s, $C_{2,3,13,14}$), 115.5 (s, $C_{1',12'}$), 76.4 (s, $C_{1,4,12,15}$), 52.8 (q, $C_{1'\beta,12'\beta}$), 51.6 (d, $C_{6a,9a,17a,20a}$), 51.6 (d, $C_{4a,11a,15a,22a}$), 51.3 (q, $C_{1'\alpha,12'\alpha}$), 50.2 (d, $C_{7a,8a,18a,19a}$), 46.7 (d, $C_{8,19}$), 40.8 (d, $C_{7,9,18,20}$), 34.0 (d, $C_{5,11,16,22}$), 30.4 (t, $C_{8'}$); MS (FAB, 3-NBA) *m/z* (relative intensity) 1098 (M^++10, 5), 1096 (M^++8, 12), 1094 (M^++6, 18), 1092 (M^++4, 16), 1090 (M^++2, 6), 1065 (4), 1063 (6), 1061 (8), 1059 (5), 1057 (weak), 646 (54), 644 (45), 450 (100), 448 (82). Anal. Calcd for $C_{53}H_{44}Cl_8O_8$: C, 58.26; H, 4.05; O, 11.71. Found: C, 58.60; H, 4.34; O, 11.49.

4.3. Diels–Alder reaction of *p*-benzoquinone 11 and *syn,syn*-HMA 4 (2:1 molar ratio)

A solution of **11** (484 mg, 1.08 mmol) and **4** (106 mg, 0.54 mmol) in toluene (50 mL) was stirred under N_2 atmosphere and heated at 75–80 °C for 46 h. The reaction mixture was worked up following previous process to afford a product mixture (550 mg, 93%), which was shown by ^1H NMR spectrum to contain **17a** and **17b** in a ratio of 1:2. The two bis-adducts were separated by repetitive recrystallization form $CHCl_3$/EtOAc, thereby affording **17a** (183 mg, 31%) and **17b** (342 mg, 58%) as pale yellow powder.

4.3.1. (1β,2α,3β,4β,5β,7β,8β,9β,10β,11α,12α,13β,14β,15β,16β,19α,20α,21β,22α,23β,24α,25β,26β,27β,29β,30β,31β,32β,33α,34α,35β,36β,37β,38β,41α,42α,43β,44α)-9,10,13,14,31,32,35,36-Octachloro-48,48,49,49-tetramethoxytricosacyclo[21.21.1.$1^{6,20}$.$1^{10,13}$.$1^{28,42}$.$1^{32,35}$.$0^{2,11}$.$0^{3,19}$.$0^{4,17}$.$0^{5,21}$.$0^{6,17}$.$0^{7,11}$.$0^{8,15}$.$0^{9,14}$.$0^{12,16}$.$0^{24,44}$.$0^{25,41}$.$0^{26,39}$.$0^{28,39}$.$0^{29,33}$.$0^{30,37}$.$0^{31,36}$.$0^{34,38}$]nonatetracontane-18,40,46,47-tetraone (18). A solution of bis-endione adduct **17b** (195 mg, 0.18 mmol) in $CHCl_3$ (30 mL) was irradiated with a 500-W tungsten lamp for 2 h. Solvent was removed and the resulting solid residue was recrystallized from acetone to give the cage compound **18** (183 mg, 94%) as white powder: mp 386–388 °C (decomp.); IR (KBr) 1753 (s), 1731 (s), 1233 cm^{-1} (s); ^1H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 6H, $H_{51,53}$), 3.60 (s, 6H, $H_{50,52}$), 3.11 (br s, 4H, $H_{11,12,33,34}$), 3.06 (br s, 4H, $H_{8,15,30,37}$), 2.87 (br s, 4H, $H_{4,5,26,27}$), 2.59 (br s, 4H, $H_{7,16,29,38}$), 2.49 (br s, 4H, $H_{19,20,41,42}$), 2.27 (br s, 4H, $H_{3,21,25,43}$), 2.26 (s, 2H, $H_{1,23}$), 1.96 (br s, 4H, $H_{2,22,24,44}$), 1.39 (s, 2H, H_{45}); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4 (s, $C_{40,41,46,48}$), 103.8 (s, $C_{48,49}$), 78.7 (s, $C_{9,14,31,36}$), 77.7 (s, $C_{10,13,32,35}$), 51.9 (q, $C_{50,52}$), 51.3 (q, $C_{51,53}$), 49.7 (s, $C_{6,17,28,39}$), 49.1 (d, $C_{19,20,41,42}$), 46.6 (d, $C_{11,12,33,34}$), 46.2 (d, $C_{8,15,30,37}$), 44.5 (d, $C_{1,23}$), 39.2 (d, $C_{2,22,24,44}$), 36.3 (d, $C_{4,5,26,27}$), 34.4 (d, $C_{3,21,25,43}$), 31.9 (t, C_{45}), 31.5 (d, $C_{7,16,29,38}$); MS (FAB, 3-NBA) *m/z* (relative intensity) 1063 (M^+−Cl+10, 6), 1061 (M^+−Cl+8, 6), 1059 (M^+−Cl+6, 6), 672 (8), 597 (29), 444 (100), 425 (74). Anal. Calcd for $C_{53}H_{44}Cl_8O_8$: C, 58.26; H, 4.05; O, 11.71. Found: C, 58.46; H, 4.29; O, 11.60.

4.3.2. (1β,4β,4aα,5β,7β,7aα,8β,8aα,9β,11β,11aα,12β,15β,15aα,16β,18β,18aα,19β,19aα,20β,22β,22aα)-1,2,3,4,12,13,14,15-Octachloro-6,10,17,21-tetraacetyl-1,4,4a,5,7,7a,8,8a,9,11,11a,12,15,15a,16,18,18a,19,19a,20,22,22a-dodecosahydro-1,4:12,15-di(dimethoxymethano)-5,22:7,20:9,18:11,16-tetraetheno-8,19-methanononacene (19). Into a solution of **17b** (109 mg, 0.10 mmol) in CH_2Cl_2 (10 mL) were added triethylamine (0.7 mL, 5.2 mmol), acetic anhydride (0.81 mL, 8.1 mmol) and catalytic amount of 4-DMAP (1 mg). The reaction mixture was stirred at room temperature under N_2 atmosphere for 16 h, cooled to 0 °C with an ice-water bath, added ice-water (20 mL), and the resulting mixture was then extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were washed subsequently with saturated sodium carbonate solution (20 mL), water (10 mL), and brine (20 mL). The solution was dried ($MgSO_4$), filtered, and concentrated to leave a yellow residue, which was recrystallized from CH_2Cl_2 to afford **19** (117 mg, 93%) as white crystals: mp 225–226 °C; IR (KBr) 3050 (w), 2940 (m), 1764 (s), 1604 (w), 1542 (w), 1473 (s), 1458 (m), 1311 (w), 1277 (m), 1193 (s), 1117 (w), 1054 (w), 986 (m), 749 (w), 719 cm^{-1} (m); ^1H NMR (400 MHz, $CDCl_3$) δ 6.28–6.25 (m, 8H, $H_{5',7',9',11',16',18',20',22'}$), 3.91 (dd, *J*=3.36, 3.36 Hz, 4H, $H_{7,9,18,20}$), 3.84 (dd, *J*=3.72, 3.72 Hz, 4H, $H_{5,11,16,22}$), 3.49 (s, 6H, $H_{1'\alpha,12'\alpha}$), 3.46 (s, 6H, $H_{1'\beta,12'\beta}$), 2.76 (s, 4H, $H_{4a,11a,15a,22a}$), 2.43 (s, 12H, $H_{6',10',17',21'}$), 2.17 (s, 2H, $H_{8,19}$), 1.90 (s, 2H, $H_{8'}$), 1.53 (s, 4H, $H_{7a,8a,18a,19a}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1 (s, $C_{6'',10'',17'',21''}$), 136.6 (s, $C_{5a,10a,16a,21a}$), 136.5 (s, $C_{6a,9a,17a,20a}$), 134.9 (s, $C_{6,1017,21}$; d, $C_{7',9',18',20'}$), 130.9 (d, $C_{5',11',16',22'}$), 127.8 (s, $C_{2,3,13,14}$), 115.0 (s, $C_{1',12'}$), 77.2 (s, $C_{1,4,12,15}$), 52.5 (q, $C_{1'\beta,12'\beta}$), 51.6 (q, $C_{1'\alpha,12'\alpha}$), 51.4 (d, $C_{4a,11a,15a,22a}$), 50.5 (d, $C_{7a,8a,18a,19a}$), 45.0 (d, $C_{8,19}$), 39.3 (d, $C_{7,9,18,20}$), 34.2 (d, $C_{5,11,16,22}$), 31.0 (t, $C_{8'}$), 20.7 (q, $C_{6',10',17',21'}$); MS (FAB, 3-NBA) *m/z* (relative intensity) 1262 (M^++6, 5), 1260 (M^++4, 6), 1258 (M^++2, 5), 1227 (M^++6-Cl, 11), 1225 (M^++4-Cl, 6), 1185 (5), 985 (9), 543 (15), 511 (44), 500 (100), 469 (33), 432 (64), 396 (70), 381 (63), 365 (67). Anal. Calcd for $C_{61}H_{52}Cl_8O_{12}$: C, 58.11; H, 4.15; O, 15.22. Found: C, 58.49; H, 4.27; O, 15.35.

4.3.3. (1β,4β,4aα,5β,7β,7aα,8β,8aα,9β,11β, 11aα,12β,15β,15aα,16β,18β,18aα,19β,19aα,20β,22β, 22aα)-1,2,3,4,12,13,14,15-Octachloro-1,4,4a,5,7, 7a,8,8a,9,11,11a,12,15,15a,16,18,18a,19,19a,20,22,22a-doeicosahydro-6,10,17,21-tetramethoxy-1,4:12,15-di(dimethoxymethano)-5,22:7,20:9,18:11,16-tetraetheno-8,19-methanononacene (20). Into a solution of bis-adduct **15b** (100 mg, 0.09 mmol), dimethyl sulfate (0.17 mL, 1.8 mmol), and 18-crown-6 (24 mg, 0.09 mmol) in THF (5 mL) was added $Na_2S_2O_4$ (32 mg, 0.18 mmol). The mixture was sonicated under the nitrogen atmosphere for 20 min and then was added dropwise 20% aqueous NaOH solution (0.38 mL, 1.4 mmol). After stirring at room temperature under the nitrogen atmosphere for 15 h, the reaction mixture was added water (20 mL) and extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were washed successively with saturated $NaHCO_3$ soulution (20 mL), water (20 mL), and brine. Dried over anhydrous Mg_2SO_4, filtered, and the filtrate was concentrated to give a pale yellow residue which was recrystallized from CH_2Cl_2/acetone to afford pure **20** (75 mg, 72%) as colorless prisms: mp 170–171 °C; IR (KBr) 1604 (w), 1473 (s), 1277 (m), 1193 cm^{-1} (s); ^1H NMR (400 MHz, $CDCl_3$) δ 6.35 (dd, J=4.4, 3.4 Hz, 4H, $H_{7',9',18',20'}$), 6.31 (dd, J=4.2, 3.4 Hz, 4H, $H_{5',11',16',22'}$), 4.25–4.21 (m, 8H, $H_{5,7,9,11,16,18,20,22}$), 3.72 (s, 12H, $H_{6',10',17',21'}$), 3.48 (s, 6H, $H_{1'\alpha,12'\alpha}$), 3.47 (s, 6H, $H_{1'\beta,12'\beta}$), 2.72 (s, 4H, $H_{4a,11a,15a,22a}$), 2.29 (s, 2H, $H_{8,19}$), 1.99 (s, 2H, $H_{8'}$), 1.53 (br s, 4H, $H_{7a,8a,18a,19a}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9 (s, $C_{6,10,17,21}$), 137.0 (s, $C_{5a,10a,16a,21a}$), 135.2 (d, $C_{7',9',18',20'}$), 135.2 (s, $C_{6a,9a,17a,20a}$), 131.3 (d, $C_{5',11',16',22'}$), 127.7 (s, $C_{2,3,13,14}$), 114.9 (s, $C_{1',12'}$), 77.1 (s, $C_{1,4,12,15}$), 62.8 (q, $C_{6',10',17',21'}$), 52.6 (q, $C_{1'\beta,12'\beta}$), 52.5 (d, $C_{4a,11a,15a,22a}$), 52.0 (d, $C_{7a,8a,18a,19a}$), 51.4 (q, $C_{1'\alpha,12'\alpha}$), 45.1 (d, $C_{8,19}$), 38.8 (d, $C_{7,9,18,20}$), 33.4 (d, $C_{5,11,16,22}$), 30.9 (t, $C_{8'}$); MS (FAB, 3-NBA) m/z (relative intensity) 1152 (M^++8, 3), 1150 (M^++6, 5), 1148 (M^++4, 4), 1135 (M^++6-Me, 3), 1117 (M^++4-OMe, 3), 845 (5), 620 (11), 529 (100), 514 (76), 498 (64). Anal. Calcd for $C_{57}H_{52}Cl_8O_8$: C, 59.60; H, 4.56; O, 11.14. Found: C, 59.80; H, 4.56; O, 11.11.

4.3.4. (1β,4β,4aα,5β,7β,7aα,8β,8aα,9β,11β, 11aα,12β,15β,15aα,16β,18β,18aα,19β,19aα,20β,22β, 22aα)-1,2,3,4,12,13,14,15-Octachloro-1,4,4a,5,7, 7a,8,8a,9,11,11a,12,15,15a,16,18,18a,19,19a,20,22,22a-doeicosahydro-1,4:12,15-di(dimethoxymethano)-5,22:7,20:9,18:11,16-tetraetheno- 8,19-methanononacen-6,10,17,21-tetraone (21). Into a solution of bis-adduct **15b** (151 mg, 0.14 mmol) in THF (20 mL) cooled with an ice-water bath was added dropwise 10% aqueous NaOH solution (2 mL). After the addition was complete (ca. 0.5 h), the reaction mixture was allowed to warm up to room temperature, stirred for 6 h, and then cooled back to 0 °C. The reaction mixture was neutralized by addition of 10% HCl solution, extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were washed subsequently with saturated sodium carbonate solution (20 mL), water (10 mL), and brine (20 mL). The solution was dried ($MgSO_4$), filtered, and concentrated to leave a yellow residue, which was recrystallized from $CHCl_3$ to afford pure **21** (125 mg, 83%) as yellow powder: mp 162–163 °C; IR (KBr) 1650 (s), 1610 (m), 1580 cm^{-1} (m); ^1H NMR (400 MHz, $CDCl_3$) δ 6.22 (dd, J=7.6, 4.0 Hz, 8H, $H_{5',7',9',11',16',18',20',22'}$), 4.33–4.27 (m, 8H, $H_{5,7,9,11,16,18,20,22}$), 3.48 (s, 6H, $H_{1'\alpha,12'\alpha}$), 3.46 (s, 6H, $H_{1'\beta,12'\beta}$), 2.66 (s, 4H, $H_{4a,11a,15a,22a}$), 2.24 (s, 2H, $H_{8,19}$), 1.85 (s, 2H, $H_{8'}$), 1.47 (s, 4H, $H_{7a,8a,18a,19a}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.5 (s, $C_{6',10',17',21'}$), 150.8 (s, $C_{5a,10a,16a,21a}$), 149.9 (s, $C_{6a,9a,17a,20a}$), 133.9 (d, $C_{7',9',18',20'}$), 130.2 (d, $C_{5',11',16',22'}$), 127.7 (s, $C_{2,3,13,14}$), 115.5 (s, $C_{1',12'}$), 76.5 (s, $C_{1,4,12,15}$), 52.8 (q, $C_{1'\beta,12'\beta}$), 51.8 (d, $C_{4a,11a,15a,22a}$), 51.5 (q, $C_{1'\alpha,12'\alpha}$), 51.1 (d, $C_{7a,8a,18a,19a}$), 44.3 (d, $C_{8,19}$), 38.6 (d, $C_{7,9,18,20}$), 33.5 (d, $C_{5,11,16,22}$), 30.4 (t, $C_{8'}$); MS (FAB, 3-NBA) m/z (relative intensity) 1092 (M^++8, 7), 1090 (M^++6, 6), 1088 (M^++4, 3), 500 (100), 443 (36), 425 (32), 414 (21). Anal. Calcd for $C_{53}H_{40}Cl_8O_8$: C, 58.48; H, 3.70; O, 11.75. Found: C, 58.65; H, 3.69; O, 11.68.

4.3.5. (1β,2α,3β,7β,8α,9β,10β,11β,12β,13β,14β, 15α,16β,20β,21α,22β,23α,24β,28β,29α,30β,31β, 32β,33β,34β,35β,36α,37β,41β,42α)-9,10,13,14, 30,31,34,35-Octachloro-48,48,49,49-tetramethoxyeicosacyclo[20.20.1.2^{3,20}.2^{24,41}.1^{9,14}.1^{30,35}.0^{2,21}.0^{4,19}.0^{6,17}.0^{7,11}. 0^{8,15}.0^{10,13}.0^{12,16}.0^{23,42}.0^{25,40}.0^{27,38}.0^{28,32}.0^{29,36}.0^{31,34}.0^{33,37}] nonatetracontane-4(19),6(17),25(40),27(38),44,46-hexaen-5,18,26,39-tetraone (22). A solution of diquinone **21** (1.30 g, 1.20 mmol) in $CHCl_3$ (100 mL) was irradiated with a 500-W tungsten lamp for 72 h. Solvent was removed and the resulting solid residue was recrystallized from $CHCl_3$ to give the double caged compound **22** (1.24 g, 95%) as yellow transparent prisms: mp 164–165 °C; IR (KBr) 1650 (s), 1611 (w), 1584 (m), 1223 cm^{-1} (s); ^1H NMR (400 MHz, $CDCl_3$) δ 6.26 (dd, J=4.2, 3.5 Hz, 4H, $H_{44,45,46,47}$), 4.36–4.33 (m, 4H, $H_{3,20,24,41}$), 4.14–4.11 (m, 4H, $H_{7,16,28,37}$), 3.62 (s, 6H, $H_{51,53}$), 3.60 (s, 6H, $H_{50,52}$), 2.64–2.61 (m, 4H, $H_{8,15,29,36}$), 2.61–2.58 (m, 4H, $H_{11,12,32,33}$), 2.25 (s, 2H, $H_{1,22}$), 1.87 (br, 2H, H_{43}), 1.42 (s, 4H, $H_{2,21,23,42}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.5 (s, $C_{5,18,26,39}$), 150.7 (s, $C_{4,19,25,40}$), 141.8 (s, $C_{6,17,27,38}$), 133.9 (d, $C_{44,45,46,47}$), 106.6 (s, $C_{48,49}$), 77.7 (s, $C_{9,14,30,35}$), 76.8 (s, $C_{10,13,31,34}$), 53.0 (d, $C_{11,12,32,33}$), 51.8 (q, $C_{50,52}$), 51.3 (q, $C_{51,53}$), 50.9 (d, $C_{2,21,23,42}$), 49.9 (d, $C_{8,15,29,36}$), 44.3 (d, $C_{1,22}$), 38.7 (d, $C_{3,20,24,41}$), 33.6 (d, $C_{7,16,28,37}$), 30.4 (t, C_{43}); MS (FAB, 3-NBA) m/z (relative intensity) 1091 (M^++1+6, 2), 1089 (M^++1+4, 2), 1087 (M^++1+2, 2), 1085 (M^++1, 1), 504 (11), 502 (42), 500 (81), 498 (63). Anal. Calcd for $C_{53}H_{40}Cl_8O_8$: C, 58.48; H, 3.70; O, 11.75. Found: C, 58.32; H, 4.27; O, 12.00.

4.3.6. (1β,2α,3β,7β,8α,9β,10β,11β,12β,13β,14β, 15α,16β,20β,21α,22β,23α,24β,28β,29α,30β,31β,32β, 33β,34β,35β,36α,37β,41β,42α)-9,10,13,14,30,31,34,35-Octachloro-5,18,26,39,48,48,49,49-octamethoxyeicosacyclo[20.20.1.2^{3,20}.2^{24,41}.1^{9,14}.1^{30,35}.0^{2,21}.0^{4,19}.0^{6,17}.0^{7,11}. 0^{8,15}.0^{10,13}.0^{12,16}.0^{23,42}.0^{25,40}.0^{27,38}.0^{28,32}.0^{29,36}.0^{31,34}.0^{33,37}] nonatetracontane-4(19),5,17,25(40),26,38,44,46-octaene (23). A mixture of cage compound **22** (320 mg, 0.29 mmol) and Me_2SO_4 (0.28 mL, 2.9 mmol) in THF (30 mL) was sonicated under N_2 atmosphere for 20 min. Into the resulting solution was added dropwise an aqueous solution of $Na_2S_2O_4$ (258 mg, 1.45 mmol; 3 mL) in ca. 30 min, and stirring was continued at room temperature for additional 23 h. Water (20 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were washed subsequently with saturated sodium bicarbonate solution (20 mL), water (10 mL), and

brine (20 mL). The solution was dried ($MgSO_4$), filtered, and concentrated to leave a yellow residue, which was recrystallized from EtOAc/*n*-hexane to give pure **23** (273 mg, 81%) as white powder: mp 240–241 °C; IR (KBr) 1629 (w), 1476 (s), 1226 (s), 1119 (s), 1070 cm^{-1} (s); ^1H NMR (400 MHz, $CDCl_3$) δ 6.40 (dd, J=3.8, 3.8 Hz, 4H, $H_{44,45,46,47}$), 4.29 (br, 4H, $H_{3,20,24,41}$), 4.07 (br, 4H, $H_{7,16,28,37}$), 3.70 (s, 12H, $H_{54,55,56,57}$), 3.63 (s, 6H, $H_{51,53}$), 3.62 (s, 6H, $H_{50,52}$), 2.64–2.61 (m, 4H, $H_{11,12,32,33}$), 2.56 (br, 4H, $H_{8,15,29,36}$), 2.30 (s, 2H, $H_{1,22}$), 1.99 (br, 2H, H_{43}), 1.45 (s, 4H, $H_{2,21,23,42}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.7 (s, $C_{5,18,26,39}$), 137.9 (s, $C_{6,17,27,38}$), 135.2 (d, $C_{44,45,46,47}$), 125.7 (s, $C_{4,19,25,40}$), 106.0 (s, $C_{48,49}$), 78.0 (s, $C_{10,13,31,34}$), 76.6 (s, $C_{9,14,30,35}$), 63.1 (q, $C_{54,55,56,56}$), 52.8 (d, $C_{8,15,29,36}$), 51.8 (q, $C_{50,52}$), 51.7 (d, $C_{2,21,23,42}$), 51.3 (q, $C_{51,53}$), 49.7 (d, $C_{11,12,32,33}$), 45.1 (d, $C_{1,22}$), 38.7 (d, $C_{3,20,24,41}$), 33.9 (d, $C_{7,16,28,37}$), 30.9 (t, C_{43}); MS (FAB, 3-NBA) *m*/*z* (relative intensity) 1151 (M^++1+6, 0.6), 1149 (M^++1+4, 1), 1147 (M^++1+2, 1), 1145 (M^++1, 1), 1116 (M^++1-Cl+6, 1), 1115 (M^++1-Cl+5, 1), 1112 (M^++1-Cl+2, 0.6). Anal. Calcd for $C_{57}H_{52}Cl_8O_8$: C, 59.60; H, 4.56; O, 11.14. Found: C, 59.76; H, 4.96; O, 11.03.

4.4. Crystal structure of 20@acetone[21]

$C_{57}H_{52}Cl_8O_8+C_3H_6O$, crystal dimensions 0.20×0.20×0.20 mm^3, measured on a Bruker Smart APEX CCD X-ray diffractometer with Mo Kα radiation. T=300(2) K. Cell dimensions a=23.4623(12), b=15.7897(8), c=15.7747(8) Å, β=99.1340(10)°, V=5769.8(5) $Å^3$, monoclinic crystal system, Z=4, d_{calcd}=1.332 g/cm^3, μ=0.442 mm^{-1}, space group $P2_1/c$, data collection of 24852 intensities, 8322 independent (R_{int}=0.0469, 1.56°<Θ<23.31°). Structure solution with direct methods (SHELXS) and refinement on $F2$ (SHELXTL rel. 5.01) (705 parameters), the hydrogen atom positions were calculated and refined as riding groups with the 1.2 fold of the corresponding C atoms. $R1$=0.0468, $wR2$ (all data)= 0.1429. The residual peak and hole of electron density were 0.974 and −0.269 $eÅ^{-3}$.

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Biotransformation of two stemodane diterpenes by *Mucor plumbeus*

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Abstract—The microbiological transformation of 13α,17-dihydroxy-stemodane (**2**) by the fungus *Mucor plumbeus* afforded 13α,17,19-trihydroxy-stemodane (**3**), 3β,13α,17-trihydroxy-stemodane (**5**), 3-oxo-13α,17-dihydroxy-stemodane (**7**), 7α,13α,17,19-tetrahydroxy-stemodane (**8**), 3β,11α,13α,17-tetrahydroxy-stemodane (**10**), 3β,7α,13α,17-tetrahydroxy-stemodane (**12**), 3β,8β,13α,17-tetrahydroxy-stemodane (**14**), 2α,13α,17-trihydroxy-stemodane (**16**), 2α,13α,17,19-tetrahydroxy-stemodane (**17**), 2α,3β,13α,17-tetrahydroxy-stemodane (**20**) and 3β,11β,13α,17-tetrahydroxy-stemodane (**22**), whilst the incubation of 13α,14-dihydroxy-stemodane (**25**) gave 3β,13α,14-trihydroxy-stemodane (**28**), 2α,13α,14-trihydroxy-stemodane (**29**) and 13α,14,19-trihydroxy-stemodane (**30**). Preference for hydroxylations of ring A at C-2(α), C-3(β) and C-19 were observed in both incubations. An interesting rearrangement of 13α,14α-dihydroxy-stemodanes to 14-oxo derivatives with an unusual carbon framework has been observed under acetylation conditions. We have named this skeleton prestemodane, which, as a hydrocarbon ion, had been postulated as a biogenetic precursor of stemodane.

1. Introduction

Selective functionalization at unactivated carbon atoms has been a difficult challenge in organic synthesis using chemical methods, and thus, microbiological methods have frequently been used for this purpose.[1] In recent years, we have used *Mucor plumbeus*, a fungus with low specificity in the substrate, in the functionalization of sesquiterpenes and diterpenes. In this way the biotransformation of cedrol,[1] manoyl oxide,[2] *ent*-13-*epi*-manoyl oxide,[3] dehydroabietane[4] and *ent*-kaur-16-ene[5] derivatives has been studied. The aim of these works was also to develop models to explain the microbiological hydroxylation of these natural products.

Stemodane diterpenoids are attractive because of their structural similarity with aphidicolin (**1**), an antiviral agent and a specific inhibitor of DNA polymerase, which has been isolated from *Cephalosporium aphidicola*.[6] Several of these diterpenoids have been isolated from Chilean plants,[7] and it will be interesting to continue our studies of microbiological transformations by *M. plumbeus* using substrates with this carbon skeleton. In this work, we describe the results obtained in the incubation of two stemodane derivatives, 13α,17-dihydroxy-stemodane (**2**) and 13α,14-dihydroxy-stemodane (**25**), by this fungus.

2. Results and discussion

The substrates **2** and **25** were isolated from the aerial parts of *Stemodia chilensis*, a plant that grows in central Chile.[7] Compound **25** had also been obtained in the incubation of stemodin (**4**) with *Cunninghamella echinulata*.[8] The substrate was added to 36 hours-old shake cultures of *M. plumbeus* and the metabolites were extracted after a further 6 days. The whole extract from the medium was chromatographed eluting with mixtures of petroleum ether–EtOAc of increasing polarity. In some cases mixtures of products were obtained, which were separated after acetylation.

The incubation of 13α,17-dihydroxy-stemodane (**2**) led to the isolation of 11 metabolites **3**, **5**, **7**, **8**, **10**, **12**, **14**, **16**, **17**, **20** and **22**. The lowest polarity compound (**3**) showed in its mass spectrum the highest peak at *m/z* 304.2411, which is formed from the molecular ion by loss of water. Therefore, the molecular formula was $C_{20}H_{34}O_3$, which indicated that a new oxygen was introduced into the molecule during the

Keywords: *Mucor plumbeus*; Microbiological transformations; Diterpenes; Stemodane; Prestemodane; 13,14-Dihydroxy-stemodane rearrangement.
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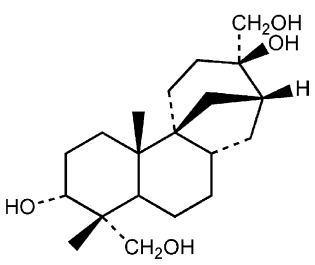

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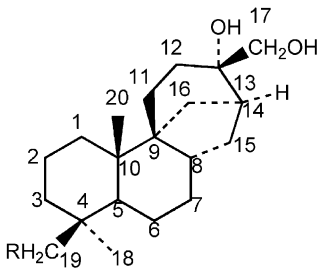

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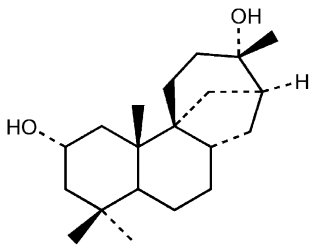

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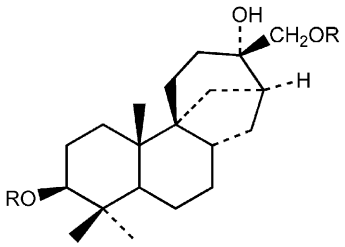

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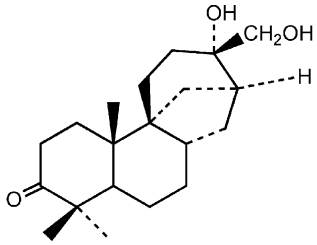

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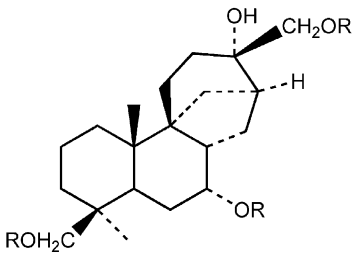

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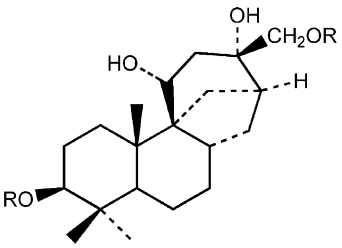

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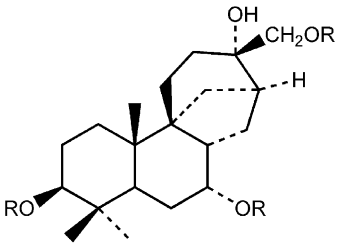

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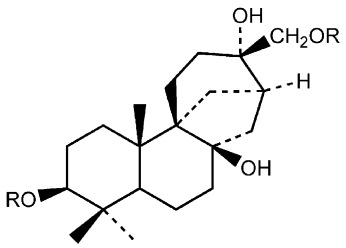
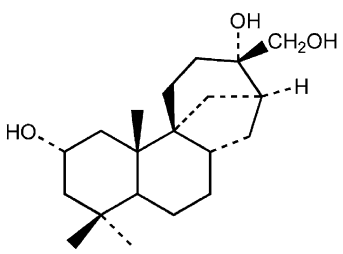


14 R = H
15 R = Ac

feeding. Its ^{1}H NMR showed, in comparison with that of the substrate (**2**), the disappearance of a methyl and the presence of a new hydroxymethylene group at δ 3.45 and 3.85 (J=10.7 Hz). These chemical shifts are characteristic of a hydroxyl group at C-19,[9] which was confirmed by assignment of its ^{13}C NMR spectrum (Table 1). Thus, the axial hydroxymethylene carbon resonates at δ 65.7 and the geminal equatorial methyl at δ 27.4, both being characteristic resonances of these substituents at C-4.[10] An equatorial CH_2OH group appears at δ 71.7 and the geminal axial methyl at δ 18.3.[11] Therefore, the structure of 13α,17,19-trihydroxy-stemodane (**3**) was assigned to this metabolite.

Another compound obtained from this fermentation was **5**, which is isomeric with **3**. Its high resolution mass spectrum showed that a new oxygen had been introduced into the molecule during the fermentation. The ^{1}H NMR spectrum, compared with that of the substrate **2**, showed a new signal at δ 3.19 resonating as a double doublet (J=11.5, 4.4 Hz), characteristic of an axial proton geminal to a hydroxyl group at C-1, C-3, C-11 or C-12. A 2D NMR study (COSY, HSQC and HMBC) permitted it to be assigned to C-3(β). Thus, in the HMBC spectrum correlations were observed between H-3 and the C-18 (δ 29.4) and C-19 (δ 16.4) methyls, and of H-18 (δ 1.00) and H-19 (δ 0.83) with C-3 (δ 79.2). Therefore, the structure of this metabolite was determined as 3β,13α,17-trihydroxy-stemodane (**5**).

The next product to be identified was **7**, which showed a peak in the mass spectrum at m/z 320.2359. The corresponding formula, $C_{20}H_{32}O_3$, indicated the presence of a new oxygen and the removal of two hydrogens, in comparison with the molecule of the substrate (**2**). These facts point to the existence of an oxo group in this metabolite, which was confirmed in the ^{13}C NMR spectrum by a signal at δ 216.9. The high chemical shift of this resonance and the presence of two coupled one-proton signals at δ 2.27 and 2.56 in the ^{1}H NMR spectrum indicated that the oxo group was located



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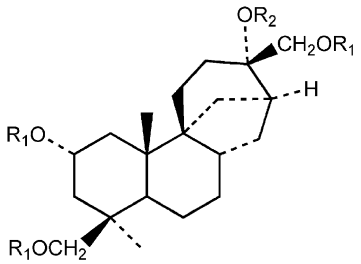
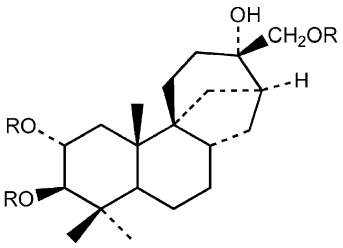


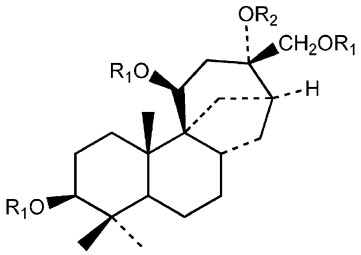
17 $R_1 = R_2 = H$

18 $R_1 = Ac$ $R_2 = H$

19 $R_1 = R_2 = Ac$



21 R = Ac



22 $R_1 = R_2 = H$

23 $R_1 = R_2 = Ac$

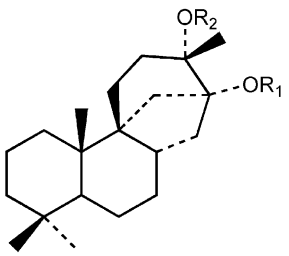
24 $R_1 = Ac$ $R_2 = H$

between a methylene and a tetrasubstituted carbon. 2D NMR studies led to the assignment of their ^1H and ^{13}C NMR spectra and to the location of the oxo group at C-3. The H-18 and H-19 methyls showed correlations with the C-3 oxo group in the HMBC spectrum. Thus, the structure of this compound was determined as 3-oxo-13α,17-dihydroxy-stemodane (**7**). This metabolite must be formed from **5** by further oxidation at C-3.

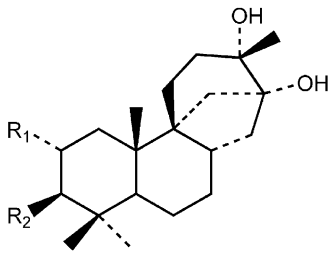
The mass spectrum of the fourth component to be isolated (**8**) showed that two oxygens had been introduced into the molecule, probably in the form of two hydroxyl groups. This compound showed in its ^1H NMR spectrum only two methyl groups and a new hydroxymethylene group, which was assigned to C-19 by comparison with the corresponding spectrum of **3**. A doublet of this AB system was overlapped with a doublet from H-17, and the other doublet with a new hydrogen signal geminal to an alcohol group. This was assigned at C-7 according to the ^{13}C and 2D NMR spectra. The α-stereochemistry of the hydroxyl at C-7 was determined in accordance with the resonance of the geminal hydrogen to the acetoxy group in its triacetate **9**, which resonates as a broad singlet at δ 5.01. In this spectrum a clean AB system of H-19 can now be observed at δ 3.89 and 4.29 (J=11 Hz). Also the HSQC and the HMBC spectra were in accordance with the structure **9** for this triacetate. Therefore, the structure of the alcohol **8** was determined as 7α,13α,17,19-tetrahydroxy-stemodane.

The fifth metabolite in polarity (**10**) was obtained as its diacetate **11** by acetylation of the fractions containing it. Its mass spectrum did not show the molecular ion, but a peak at 404.2570 corresponding to the loss of H_2O. Therefore, this compound has a molecular formula of $C_{24}H_{38}O_6$, indicating that two new oxygens, as parts of hydroxy groups, have been added to the molecule, and that only two of the four alcohol groups were acetylated. The ^1H NMR spectra showed three angular methyls and two acetoxy groups. A singlet at δ 3.95 (2H), was assigned to H-17, which was deshielded, compared with the incubated substrate **2**, because it now bears one of the acetoxy groups. A double doublet at δ 4.50 (J=10.0, 6.2 Hz), corresponding to an axial proton, geminal to the second acetate group, was assigned to C-3(α), considering that the chemical shift and coupling constants were similar to those observed in the diacetate **6**. Two hydroxyl groups were not acetylated, and located at C-11 and C-13, in accordance with the ^{13}C NMR spectrum (Table 1), which was unambiguously assigned by 2D NMR studies. The α-stereochemistry of the hydroxyl group at C-11 was given considering the form of resonance of its geminal proton, a broad doublet at δ 3.93, which is coupled with the hydrogen of the 11-OH (δ 3.00, d, J=10 Hz). One peak of the H-11 doublet is overlapped with the two-protons singlet of H-17, but using deuterated benzene as NMR solvent a clear doublet could be observed. The 11α-alcohol forms a hydrogen bond with the hydroxyl group at C-13(α), which also explains the difficulty of its acetylation. Thus, the structure of the original metabolite formed in the feeding must be 3β,11α,13α,17-tetrahydroxy-stemodane (**10**).

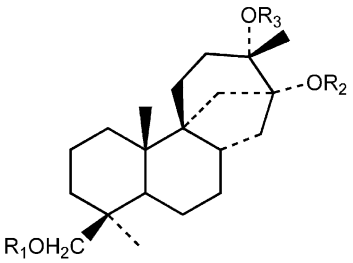
Another compound isolated was **12**, which was obtained as the triacetate **13** by acetylation and chromatography of the fractions containing it. The mass spectrum of **13** showed a peak at 391.2473 formed from the molecular ion by loss of $-CH_2OAc$. Thus its molecular formula must be $C_{26}H_{40}O_7$.



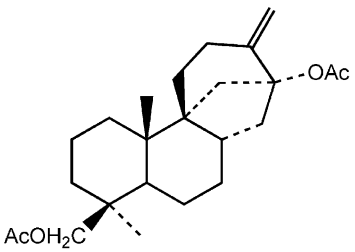
25 $R_1 = R_2 = H$
26 $R_1 = Ac$ $R_2 = H$
27 $R_1 = H$ $R_2 = Ac$



28 $R_1 = H$ $R_2 = OH$
29 $R_1 = OH$ $R_2 = H$



30 $R_1 = R_2 = R_3 = H$
31 $R_1 = R_3 = Ac$ $R_2 = H$
32 $R_1 = R_2 = Ac$ $R_3 = H$
33 $R_1 = R_2 = R_3 = Ac$



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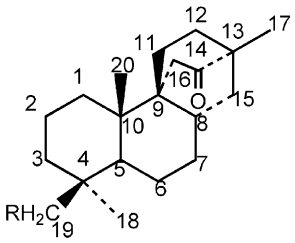
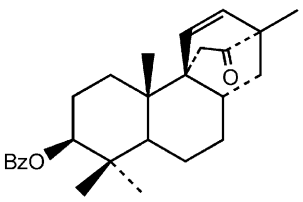


35 R = OAc
36 R = H



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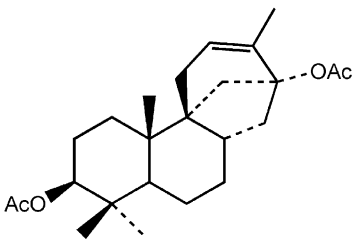

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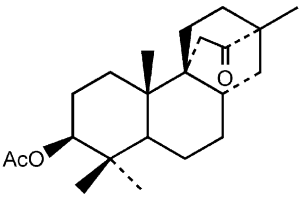


39

The ^{1}H NMR spectrum showed three angular methyls, three acetate groups, an acetoxymethylene resonating at δ 3.92 and 3.99 (J=11.3 Hz) corresponding to H-17, a double doublet at δ 4.55 (J=11.0, 4.3 Hz) and a broad singlet at δ 5.02. The form of resonance of the double doublet was very similar to that appearing in **6** and was assigned to H-3(α), geminal to a β-hydroxyl group. The broad singlet may correspond to an equatorial hydrogen at C-7 or C-11. The study of the ^{13}C and bidimensional NMR spectra allowed it to be located at the first position. Thus, in the HMBC spectrum correlations of H-7 with C-5 and C-9, of H-5 with C-3, C-4, C-7, C-10 and C-20, and of H-20 with C-5 and C-9 were observed. Therefore, the structure of the original alcohol was determined as 3β,7α,13α,17-tetrahydroxy-stemodane (**12**).

Acetylation and chromatography of the fractions containing **14** led to the diacetate **15**. Its ^{1}H NMR spectrum was very

Table 1. ^{13}C NMR data of compounds **2**, **3**, **5**–**9**, **11**, **13**, **15**, **16**, **18** and **21**

C	2	3	5	6	7	8	9	11	13	15	16	18	21
1	36.2	36.1	34.2	33.9	34.6	36.2	36.2	36.1	33.9	34.1	45.7	41.5	40.0
2	18.8	18.4	27.4[a]	23.9	22.9	18.4	18.3	24.0	23.8	23.6	65.2	68.4	69.9
3	41.8	35.3	79.2	81.0	216.9	35.5	36.0	81.0	80.7	80.8	50.4	40.8	80.5
4	33.2	38.4[a]	38.4	37.7	47.3	38.3	36.4	38.1	37.2	37.8	39.7	38.5	39.2[a]
5	47.2	48.6	46.9	47.1	48.7	41.9	41.3	49.6	40.0	47.6	46.6	48.0	46.8
6	22.2	22.1	22.1	21.9	22.9	28.4	26.7	21.4	26.4	19.1	22.1	21.8	21.8
7	36.6	36.7	36.6	36.4	36.1	68.5	72.6	35.5	72.8	38.3	36.4	36.4	36.3
8	37.3	37.1	37.1	37.1	37.0	37.9	40.7	36.9	40.7	79.5	36.9	36.7	36.8
9	50.7	50.7	50.8	50.8	50.4	51.3	51.1	54.6	51.2	52.0	50.8	50.7	50.7
10	38.5	38.3[a]	38.8	38.3	37.9	38.2	38.1	39.5	38.0	38.7	40.2	39.9	39.3[a]
11	27.2	27.2	27.1[a]	27.0	27.3	27.6	27.2	73.0	27.2	22.8	27.3	27.2	27.1
12	28.1	28.1	28.1	28.0	27.9	28.2	28.3	37.6	28.2	28.7	27.9	28.1	28.0
13	74.3	74.0	74.1	72.9	73.8	74.2	73.0	74.7	72.9	73.2	74.6	72.9	72.9
14	40.4	40.4	40.4	40.9	40.2	40.4	40.8	41.0	40.7	38.7	40.3	41.0	40.9
15	37.4	37.2	37.1	37.2	36.9	32.1	31.4	38.1	31.3	43.7	37.4	37.2	37.1
16	29.7	29.7	29.6	29.3	29.4	30.2	29.0	25.2	28.8	31.5	29.9	29.5	29.4
17	68.0	68.0	68.0	69.8	69.9	68.3	69.9	69.2	69.8	69.5	68.0	69.9	69.7
18	34.5	27.4	29.4	29.3	26.9	27.0	27.6	29.6	28.7	29.4	34.7	28.3	29.7
19	22.8	65.7	16.4	17.5	22.8	66.0	67.5	17.6	17.4	17.6	23.4	67.4	18.5
20	18.8	20.2	18.7	18.7	18.1	27.1	20.1	17.8	18.7	16.7	19.6	20.7	19.2

[a] These values can be interchanged.

similar to that of the diacetate **6**, indicating the presence of an acetoxy group at C-3(β). The mass spectrum did not show the molecular ion, but a peak was observed at 404.2600 corresponding to the loss of a molecule of water therefrom. Thus, its molecular formula was determined as $C_{24}H_{38}O_6$ indicating that another alcohol group had been introduced into the molecule, in comparison with **6**, which was not easily accessible for acetylation. Its ^{13}C NMR spectrum also showed some differences with that of **6**, such as a new singlet at 79.5 ppm, that was assigned to a tertiary carbon at C-5, C-8 or C-14 bearing the new hydroxy group. The second position was chosen by assignment of the ^{13}C NMR spectrum (Table 1) using 2D NMR data. The β-stereochemistry assigned to this 8-alcohol was determined considering the resonance of H-20 (δ 1.12) in comparison with δ 0.98 in **6**. Therefore, the structure of 3β,8β,13α,17-tetrahydroxy-stemodane (**14**) was assigned to the original tetraol.

Compound **16** was isomeric with **3** and **5**. Its high resolution MS showed the highest peak at *m/z* 320.2343 ($C_{20}H_{32}O_3$), which is formed by loss of water from the molecular ion. In its ^1H NMR spectrum appeared a triple triplet at δ 3.73 with coupling constants of 11.4 and 3.6 Hz. This broad form of resonance is typical of an axial hydrogen geminal to a hydroxyl group, surrounded by two methylene groups, in a cyclohexane ring with chair conformation. Thus, this alcohol was assigned to C-2(α). The study of the ^{13}C NMR spectrum confirmed this assert, the structure being determined as 2α,13α,17-trihydroxy-stemodane (**16**).

Two minor metabolites **17** and **20** were also obtained from this incubation and isolated as their triacetates **18** and **21**, respectively. In the mass spectra of both a peak at *m/z* 446 was observed, corresponding to the loss of a molecule of water from the molecular ion. This fact indicated that these metabolites were isomers ($C_{26}H_{40}O_7$). The first of them (**18**) showed in its ^1H NMR spectrum two angular methyls, three acetoxy groups, two acetoxymethylenes and a geminal hydrogen to an acetoxy group. The last signal resonates as a broad triple triplet at 4.88 (J=11.8, 3.8 Hz), which permitted this alcohol to be assigned to C-2(α), in accordance with the arguments given for **16**. Therefore, the structure of 2α,13α,17,19-tetrahydroxy-stemodane (**17**) was assigned to the corresponding alcohol. The second of these minor metabolites (**20**) was obtained as its triacetate **21**, which showed in its ^1H NMR spectrum signals of three angular methyls and three acetoxy groups. Other resonances observed in this spectrum were the expected AB system of H-17 and another two signals, which were coupled between them: a doublet at δ 4.75 (J=10.4 Hz) and a double doublet of doublets at δ 5.00 (J=11.0, 10.4, 4.0 Hz). The shape of the signals indicated that they correspond to two axial protons geminal to acetoxy groups situated at C-1, C-2 or C-2, C-3. A bidimensional NMR study permitted us to locate both acetate groups at C-2 and C-3. Therefore, the structure of the original alcohol formed in the incubation was determined as 2α,3β,13α,17-tetrahydroxy-stemodane (**20**).

The structure of 3β,11β,13α,17-tetraacetoxy-stemodane (**23**) was assigned to a tetraacetate obtained by acetylation of the fractions containing the alcohol **22**. The molecular formula of **23**, $C_{28}H_{48}O_8$, was determined by HRMS, in which the higher ion at *m/z* 446.2667 is formed from the molecular ion by loss of AcOH. Their ^1H NMR spectrum showed the characteristc signals of the H-3 and H-17 observed in other metabolites obtained in this work, such as **5** and **13**, respectively, indicating the presence of 3β, 13α and 17 alcohols in the molecule. The fourth hydroxyl was assigned to C-11(β) considering 2D NMR data, whilst the β-stereochemistry was given considering the coupling observed for the 11-H(α) in the ^1H NMR spectrum (δ 5.29, t, J=7.5 Hz). Therefore, the structure 3β,11β,13α,17-tetrahydroxy-stemodane (**22**) was determined for the corresponding alcohol isolated from the feeding, which is the 11-epimer of compound **10**.

As a continuation of this work, we carried out a further incubation with *M. plumbeus* using 13α,14-dihydroxy-stemodane (**25**) as substrate giving metabolites **28**–**30**. Compounds **28** and **29** were isolated from the main

Table 2. ^{13}C NMR data of compounds **23**, **25**–**29**, **32**–**35**, **38** and **39**

C	23	25	26	27	28	29	32	33	34	35	38	39
1	34.1	36.3	36.1	36.1	34.1	45.7	35.9	35.5[a]	32.6[a]	33.4	32.8	31.1
2	23.4	18.8	18.7	18.7	27.5	65.2	18.3	18.3	18.1	18.7	23.7	23.7
3	80.8	41.9	41.8	41.8	79.1	50.7	35.9	35.7[a]	33.1[a]	42.1	80.9	80.8
4	37.6	33.3	33.2	33.2	38.8	34.8	36.9	37.0	37.0	33.3	37.8	37.8
5	47.0	47.5	47.3	47.1	47.1	46.7	48.7	48.7	48.3	47.1	47.5	46.8
6	21.6	22.3	22.1	22.2	21.8	21.9	22.0	21.9	22.1	22.2	21.6	21.7
7	34.6	37.2	36.4	36.5	37.3	37.4	36.5	35.9[a]	36.1	32.6	36.1[a]	32.3
8	33.7	37.9	36.2	37.2	37.5	37.3	36.1	37.6	33.1	33.0	40.5	32.9
9	54.8	51.7	53.0	52.6	51.6	51.6	53.0	50.1	43.4	43.3	50.8	43.3
10	38.8	38.6	38.6	38.4	38.3	40.2	38.5	38.4	38.8	39.0	38.6	38.6
11	71.1	27.7	27.2	27.5	27.2	27.6	27.3	27.5	25.4	25.3	36.8[a]	25.4
12	35.0	34.1	34.8	34.3	33.8	33.4	34.6	28.0	30.1	30.2	119.4	30.0
13	84.9	75.1	74.1	82.1	75.0	75.0	74.1	85.7	42.1	41.5	143.5	42.0
14	37.7	83.4	96.1	91.2	83.2	83.3	95.9	92.2	218.0	218.9	87.0	217.3
15	35.5	44.9	45.0	45.8	44.5	44.7	44.7	38.7	40.1	40.5	49.6	40.0
16	28.5	37.5	33.6	38.1	37.2	36.9	33.6	32.3	40.5	40.3	37.4[a]	40.4
17	64.4	23.0	23.2	18.2	22.9	22.9	23.5	19.0	19.6	19.7	16.3	19.6
18	29.5	34.5	34.5	34.5	29.4	34.5	28.0	28.0	27.9	34.2	29.2	29.0
19	17.5	22.8	22.8	22.7	16.3	23.6	67.2	67.3	67.0	22.2	17.5	17.0
20	19.4	18.2	18.2	18.2	18.1	19.0	19.8	19.8	16.6	15.5	16.6	15.5

[a] These values can be interchanged.

chromatography of the extract of this biotransformation, while the acetates **32**–**34** were obtained by acetylation and chromatography of other fractions thereof.

Compound **28** showed the molecular formula $C_{20}H_{34}O_3$, determined by high resolution MS, indicating that a new oxygen was introduced into the molecule during the incubation. The ^1H NMR spectrum showed the four methyls of the incubated substrate and a new signal as a double doublet at δ 3.20 (J=11.6, 4.2 Hz), typical of a hydrogen geminal to an equatorial hydroxy group at C-1, C-3, C-11 or C-12. A study of the ^{13}C NMR spectrum and comparison with that of **5** indicated that this substance was 3β,13α,14α-trihydroxy-stemodane (**28**). Further 2D NMR studies confirmed this assignment.

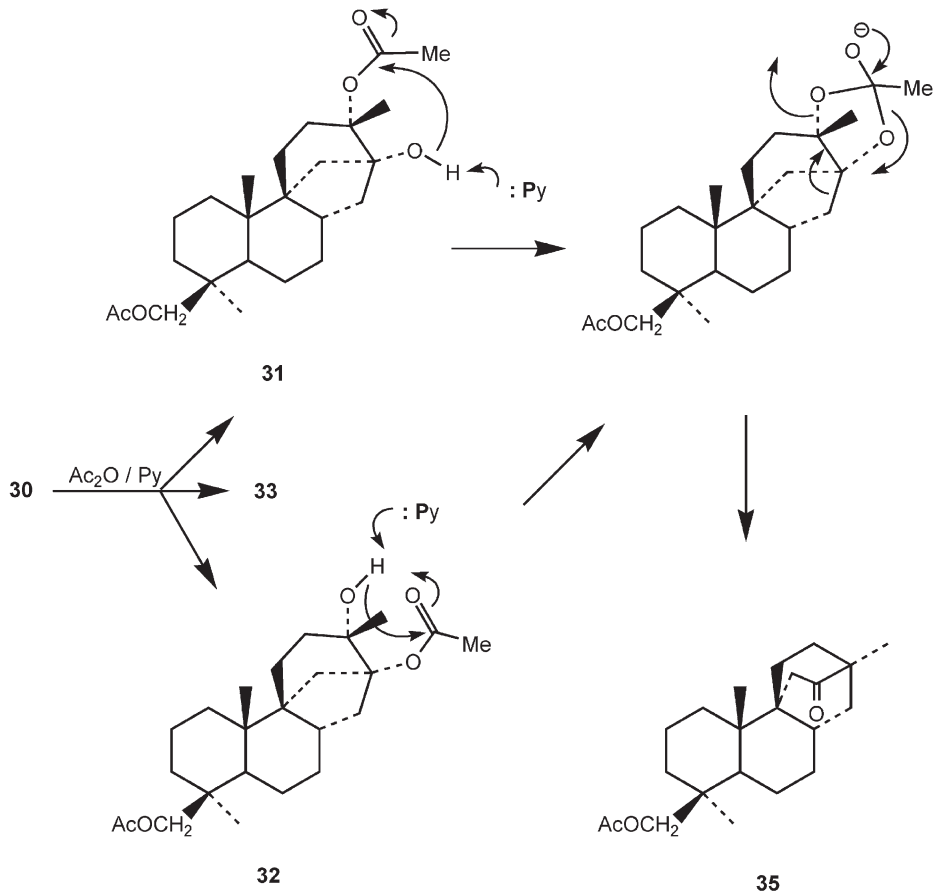
Another metabolite isolated from this fermentation was **29** ($C_{20}H_{34}O_3$). Its ^1H NMR spectrum showed four quaternary methyls and a new signal of a hydrogen geminal to a hydroxyl group, which appears as a triplet of triplets at δ 3.75 (J=12.0, 3.8 Hz). This resonance was similar to that observed in the corresponding spectrum of **16** and in consequence the alcohol group was assigned to C-2(α). Analysis of the ^{13}C NMR spectrum (Table 2) confirmed this assert. Thus, the new metabolite was identified as 2α,13α,14α-trihydroxy-stemodane (**29**).

The HRMS of **32** was in accordance with the formula $C_{24}H_{34}O_5$ indicating that an oxygen was introduced during the biotransformation. Its ^1H NMR spectrum showed three angular methyls and a CH_2OAc group as two doublets at δ 3.92 and 4.30 (J=10.8 Hz). These values indicated that the acetoxy group was at C-19. Unambiguous assignment of the ^{13}C NMR spectrum based on 2D NMR spectra showed that this compound must have the structure **32**. Thus the original metabolite formed in the biotransformation was 13α,14,19-trihydroxy-stemodane (**30**). In this chromatography the triacetate **33** was also isolated and characterized.

Compound **34** was obtained in a very low yield. In consequence, its structure was determined as 14α,19-diacetoxy-stemod-13,17-ene only considering its ^1H NMR and mass spectra. The latter was in accordance with the molecular formula $C_{24}H_{36}O_4$, whilst the first showed signals of two methyls, two acetoxy groups, an acetoxymethylene group, as two doublets at δ 3.70 and 4.10 (J=13 Hz), and the hydrogens of an exocyclic double bond, as two singlets at δ 4.45 and 4.59.

The structure of the oxo derivative **35** was given on the basis of the following considerations: Its HRMS indicated that the molecule had lost one oxygen and a new insaturation had now appeared. In the ^{13}C NMR spectrum a signal appears at δ 218.0, typical of an oxo group, whilst the disappearance of the two tertiary alcohols of the substrate was noted. These facts indicated that a rearrangement involving the 13,14-diol had occurred. Its ^1H NMR spectrum showed resonances of three angular methyls, a $-CH_2OAc$ group, which resonates as two doublets at δ 3.88 and 4.29 (J=11.0 Hz), and the hydrogens of a methylene group in α-position to the oxo group (δ 2.16, d, J=18.7 Hz and δ 2.62, dd, J=18.7, 3.0 Hz). The acetoxy group was allocated at C-19, by comparison of its ^1H and ^{13}C chemical shifts with those of other compounds obtained in this work. The oxo group was assigned to C-14 considering that **34** should be originated by the formation of a carbocation at C-13 in **30**, migration of the 14,15-bond to C-13, creating a new carbon-carbon bond between C-15 and C-13, and neutralization of the charge at C-14 by formation of the oxo group with loss of the hydroxyl proton. Finally, 2D NMR data were also in accordance with the structure **35**. We have named this skeleton prestemodane, because a hydrocarbon ion at C-14, with this carbon framework, has been postulated as a biogenetic precursor of the stemodane skeleton.[6,12] Moreover, a product **37**, also of this type, has been prepared as an intermediate in the synthesis of the stemodane diterpene (±)-maritimol.[13]

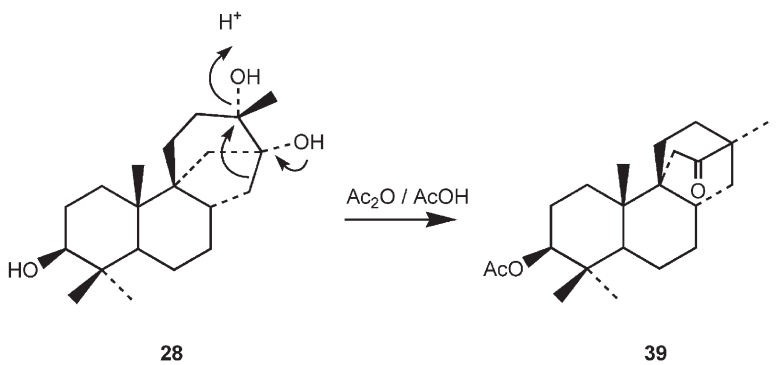
We think that **34** and **35** are not produced in the incubation and must be formed from **30**, during the acetylation of the fraction containing it, considering two main reasons: (a) the non-isolation of compounds of this type in alcohol form,



Scheme 1.

such as **36**, from the incubation. (b) If a compound such as **34** were formed in the biotransformation, the corresponding 13,17-epoxide must also be obtained, because one of the characteristic bioreactions of *M. plumbeus* is the epoxidation of double bonds, especially exocyclic.[2,3,5] On the other hand, if the formation of **35** occurs during the acetylation, since the hydroxyl group is a poor leaving group, the rearrangement probably occurs, as indicated in Scheme 1, from the diacetates **31** and **32**, which form the same intermediate in the pyridine medium. With reference to the formation of the dehydro-derivative **34**, the dehydration of tertiary alcohols with acetic anhydride in pyridine and 4-dimethylaminopyridine has been reported.[14]

Confirmation that rearrangement of **30** occurs during acetylation was obtained by treatment of the substrate **25** with acetic anhydride in pyridine, which led to the monoacetates **26** and **27** and to the rearranged oxo derivative **36**. The positions of the acetoxy groups in **26** and **27** were determined considering the ^{13}C NMR spectra (Table 2), which were assigned by 2D NMR studies. When **26**, in $CDCl_3$, was left in a NMR tube for four weeks transacetylation occurred giving 27 (30%). The mixture of **26** and **27** in pyridine was heated at reflux for 8 h giving the oxo derivative **36** (16%), whilst the triacetate 33 remained unchanged when treated under the same conditions. These facts support the mechanism described in Scheme 1. On the



Scheme 2.

other hand, the structure of the oxo derivative **36** was determined in an analogous way to that of **35**, including a study of its 2D NMR spectra.

An alternative procedure for the rearrangement of 13,14-dihydroxy stemodane derivatives was acid treatment. Thus, the triol **28**, also obtained in this incubation, by reaction with Ac_2O/AcOH was transformed into the dehydrated stemodane **38** and the prestemodane derivative **39**. The mechanism of formation of the oxo derivative **39** as a pinacolinic rearrangement of **28** is indicated in Scheme 2. Now, the endocyclic double bond in **38** is formed, whilst in the rearrangement of **30** with Ac_2O/pyridine the exocyclic double bond of **34** was obtained (see above). Thus, although the formation of the exocyclic double bond is probably sterically favoured in both cases, in the acid medium an isomerization to the more stable endocyclic double bond has occurred.

Several consequences can be deduced from these biotransformations with *M. plumbeus*:

1. The main hydroxylations occur in ring A, especially at C-2(α) and C-3(β). Thus, metabolites **5**, **16**, **28** and **29** are the main products obtained in these fermentations. These results are in concordance with our previous results and indicate a low specificity in the substrate, but an acceptable regioselectivity for the functionalization of these carbons.
2. We can now affirm that position C-3 (equatorial) is the most frequently hydroxylated by this microorganism in diterpenoids, and does not depend on the absolute configuration of the substrate. A competitive hydroxylation at the near axial methyl at C-4, probably produced by the same enzyme, was also now obtained in the incubations carried out with this fungus. With other diterpenes the hydroxylation of the axial or equatorial methyl at C-4 had also been observed.[2,15,16]
3. Positions C-2 or C-3 are also frequently oxidised by this fungus to an oxo group, as occurs with dehydroabietane diterpenes for C-2,[4] and with manoyl and manoyl oxyde derivatives,[16] and now with compounds such as 7, for C-3.
4. The formation during acetylation with Ac_2O/pyridine of the rearranged compounds **35** and **36** from the stemodane derivatives **30** and **25**, respectively, is very interesting. Thus, the treatment with Ac_2O/pyridine is an easy procedure to transform 13,14-dihydroxy-stemodanes into compounds with the prestemodane skeleton of **35** and **36**.
5. An alternative procedure for the rearrangement of 13,14-dihydroxy-stemodanes into compounds with the prestemodane skeleton is acid treatment with Ac_2O/AcOH.

3. Experimental

3.1. General experimental procedures

Mps were determined with a Reichert Thermovar apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 500.1 and 125.8 MHz, respectively, with a Bruker AMX-500 spectrometer with pulsed field gradient, using the solvent as internal standard. Mass spectra were taken in a Micromass Autospect instrument at 70 eV (probe). Dry column chromatographies were made on silica gel Merck 0.02–0.063 mm. When further purification was required, semipreparative HPLC in a Beckman System Gold with a Beckman ultrasphere Si 1×25 cm column was used.

3.2. Organism

The fungal strain was *M. plumbeus* CMI 116688 and was a gift from Prof. J. R. Hanson, School of Chemistry, Physics and Environmental Science (University of Sussex, UK).

3.3. Incubation of 13α,17-dihydroxy-stemodane (2)

M. plumbeus was grown in shake cultures at 25 °C, in 12–20 conical flasks (250 ml), each containing 100 ml of a sterile medium comprising (per dm^3) glucose (80 g), NH_4NO_3 (0.48 g), KH_2PO_4 (5 g), $MgSO_4$ (1 g), and trace elements solution (2 ml). The trace elements solution contained (per 100 ml) $Co(NO_3)_2$ (0.01 g), $CuSO_4$ (0.015 g), $ZnSO_4$ (0.16 g), $MnSO_4$ (0.01 g), $(NH_4)_6Mo_7O_{24}$ (0.01 g). 13α,17-Dihydroxy-stemodane (**2**) (250 mg) dissolved in ethanol (4.5 ml) was evenly distributed in 20 flasks after one day of growth. After a further six days, the fermentation was harvested. The mycelium was filtered and the culture filtrate was extracted with EtOAc. The extract was dried over Na_2SO_4 and the solvent evaporated to yield a residue (500 mg), that was chromatographed on a silica gel column with a petroleum ether–ethyl acetate gradient, to afford 13α,17,19-trihydroxy-stemodane (**3**) (2 mg), 3-oxo,13α,17-dihydroxy-stemodane (**7**) (2 mg), 3β,13α,17-trihydroxy-stemodane (**5**) (10 mg), 7α,13α,17,19-tetrahydroxy-stemodane (**8**) (8 mg), 3β,11α,13α,17-tetrahydroxy-stemodane (**10**) (3 mg), 3β,7α,13α,17-tetrahydroxy-stemodane (**12**) (1 mg), 3β,8β,13α,17-tetrahydroxy-stemodane (**14**) (0.8 mg), 2α,13α,17-trihydroxy-stemodane (**16**) (21 mg), 3β,11β,13α,17-tetrahydroxy-stemodane (**22**) (2 mg), 2α,13α,17,19-tetrahydroxy-stemodane (**17**) (1 mg) and 2α,3β,13α,17-tetrahydroxy-stemodane (**20**) (1 mg).

3.3.1. 13α,17,19-Trihydroxy-stemodane (3). Colourless crystals (petroleum ether–ethyl acetate), mp 196–198 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (3H, s, H-20), 0.99 (3H, s, H-18), 1.21 (1H, m, 6β-H), 1.47 (1H, br d, J=16 Hz, 6α-H), 1.86 (1H, m, H-7), 2.14 (1H, br t, J=7 Hz, H-14), 3.36 and 3.45 (each 1H, d, J=11.0 Hz, H-17), 3.47 and 3.87 (each 1H, d, J=10.7 Hz, H-19). EIMS m/z (rel. int.) 304 $[M-H_2O]^+$ (1), 291 (100), 273 (66), 255 (29), 232 (7), 215 (7), 203 (14), 185 (9), 173 (13), 159 (12), 123 (63). Found $[M-H_2O]^+$ at m/z 304.2409. $C_{20}H_{32}O_2$ requires 304.2402.

3.3.2. 3β,13α,17-Trihydroxy-stemodane (5). Colourless crystals (petroleum ether–ethyl acetate), mp 199–201 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 0.83 (3H, s, H-19), 0.94 (3H, s, H-20) 1.00 (3H, s, H-18), 1.76 (1H, d, J=11.6 Hz, H-16), 1.90 (1H, m, H-7), 2.13 (1H, br triplet, $W_{1/2}$=15 Hz, H-14), 3.19 (1H, dd, J=11.5, 4.4 Hz, H-3), 3.33 and 3.43 (each 1H, d, J=11.0 Hz, H-17). EIMS m/z (rel. int.) 307 $[M-CH_3]^+$ (0.7), 304 (0.6), 291 (100), 273 (4), 255 (3), 232 (3), 215 (4),

173 (3), 159 (3), 145 (3), 133 (5), 121 (9). Found $[M-CH_3]^+$ at *m/z* 307.2253. $C_{19}H_{31}O_3$ requires 307.2273.

3.3.3. 3β,17-Diacetate 6. Colourless crystals (petroleum ether–ethyl acetate), mp 128–130 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, s, H-18), 0.92 (3H, s, H-19), 0.98 (3H, s, H-20), 1.11 (1H, m, H-7α), 1.86 (1H, d, *J*=11.6 Hz, H-16), 1.93 (1H, m, H-7β), 2.05 and 2.10 (each 3H, s), 2.11 (1H, H-14, signal overlap. with –OAc), 3.90 and 3.98 (each 1H, d, *J*=11.3 Hz, H-17), 4.49 (1H, dd, *J*=11.1, 4.3 Hz, H-3). EIMS *m/z* (rel. int) 406 $[M]^+$ (0.4), 388 (5), 346 (28), 333 (100), 328 (14), 316 (6), 286 (15), 271 (14), 268 (22), 253 (16), 215 (11), 199 (11), 188 (57). Found $[M]^+$ at *m/z* 406.2731. $C_{24}H_{38}O_5$ requires 406.2719.

3.3.4. 3-Oxo-13α,17-dihydroxy-stemodane (7). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07 (3H, s, H-19), 1.08 (3H, s, H-18) 1.11 (3H, s, H-20), 1.74 (1H, t, *J*=6.0 Hz; –OH), 1.97 (2H, m, H-1 and H-7), 2.15 (1H, br t, *J*=6.8 Hz, H-14), 2.27 (1H, dt, *J*=15.0, 4.0 Hz, H-2β), 2.56 (1H, td, *J*=15, 5.7 Hz, H-2α), 3.35 and 3.44 (each 1H, dd, *J*=10.9, 6.0 Hz, H-17), 3.44 (1H, d, *J*=10.9 Hz, H-17). EIMS *m/z* (rel. int.) 320 $[M]^+$ (1), 302 (22), 289 (100), 271 (4), 216 (9), 204 (6), 199 (5), 173 (4). Found $[M]^+$ at *m/z* 320.2359. $C_{20}H_{32}O_3$ requires 320.2351.

3.3.5. 7α,13α,17,19-Tetrahydroxy-stemodane (8). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, s, H-20), 0.98 (3H, s, H-18), 1.38 and 1.68 (each 1H, m, H-1), 1.60 (1H, m, H-16), 1.73 (2H, br s, H-15), 1.84 (1H, dd, *J*=12, 2.4 Hz, H-5), 3.38 (1H, dd, *J*=11.0, 5.1 Hz, H-17), 3.48 (2H, br d, $W_{1/2}$=18 Hz, H-17 and H-19), 3.86 (2H, br d, $W_{1/2}$=20 Hz, H-19 and H-7). EIMS *m/z* (rel. int.) 320 $[M-H_2O]^+$ (1), 307 (93), 289 (37), 271 (100), 259 (15), 253 (19), 231 (14), 213 (11), 201 (15), 189 (10). Found $[M-H_2O]^+$ at *m/z* 320.2346. $C_{20}H_{32}O_3$ requires 320.2351.

3.3.6. 7α,17,19-Triacetate 9. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91(3H, s, H-18), 0.96 (3H, s, H-20), 1.73 (2H, m, H-5 and H-15), 1.85 (1H, m, H-8), 2.04, 2.06 and 2.10 (each 3H, s), 2.12 (1H, br t, *J*=6 Hz, H-14), 3.89 and 4.29 (each 1H, d, *J*=11.0 Hz, H-19), 3.95 and 3.98 (each 1H, d, *J*=11.6 Hz, H-17), 5.01 (1H, br s, H-7). EIMS *m/z* (rel. int.) 446 $[M]^+$ (0.4), 421 (2), 404 (3), 391 (100), 344 (27), 331 (20), 313 (12), 284 (13), 271 (74), 253 (31), 225 (13), 213 (17). Found $[M-H_2O]^+$ at *m/z* 446.2708. $C_{26}H_{38}O_6$ requires 446.2668.

3.4. 3β,11α,13α,17-Tetrahydroxy-stemodane (10)

Fractions containing compound **10** were acetylated (Ac_2O/py, 40 °C) and purified by chromatography affording **11**.

3.4.1. 3β,17-Diacetate 11. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (3H, s, H-18), 0.93 (3H, s, H-19), 1.12 (3H, s, H-20), 2.05 and 2.11 (each 3H, s), 2.16 (1H, br t, *J*=5.5 Hz, H-14), 2.50 (1H, dt, *J*=14.0, 3.3 Hz, H-1β), 2.57 (1H, s, HO-13), 3.00 (1H, d, *J*=9.6 Hz, HO-11), 3.93 (1H, br d, H-11), 3.95 (2H, s, H-17), 4.50 (1H, dd, *J*=10.0, 6.2 Hz, H-3). ^{1}H NMR (500 MHz, C_6D_6) δ 0.92, 0.96 and 1.06 (each 3H, s), 1.57 and 1.69 (each 3H, s), 2.69 (1H, dt, *J*=13.5, 3.5 Hz, H-1β), 2.88 (1H, d, *J*=9.5 Hz, HO-11), 3.68 (1H, br d, *J*=9.5 Hz, H-11), 3.73 (2H, s, H-17), 4.74 (1H, dd, *J*=11.8, 4.4 Hz). EIMS *m/z* (rel. int.) 404 $[M-H_2O]^+$ (8), 391 (16), 362 (6), 344 (13), 331 (7), 289 (15), 274 (54), 215 (63), 199 (27), 175 (43), 159 (21), 147 (53), 133 (49). Found $[M-H_2O]^+$ at *m/z* 404.2570. $C_{24}H_{36}O_5$ requires 404.2563.

3.5. 3β,7α,13α,17-Tetrahydroxy-stemodane (12)

Fractions containing **12** were purified by acetylation (Ac_2O/py, 40 °C) and chromatography giving **13**.

3.5.1. 3β,7α,17-Triacetate 13. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (3H, s, H-18), 0.91 (3H, s, H-19), 1.00 (3H, s, H-20), 1.55 (1H, m, H-1), 1.64 (1H, br d, *J*=12 Hz), 1.68–1.74 (2H, m, H-15 and H-1), 1.88 (1H, d, *J*=11 Hz, H-15), 1.96 (1H, m, H-8), 2.04, 2.06 and 2.11 (each 3H, s), 2.12 (1H, br t, *J*=5.5 Hz, H-14), 3.92 and 3.99 (each 1H, d, *J*=11.3 Hz, H-17), 4.55 (1H, dd, J=11.0, 4.3 Hz, H-3), 5.02 (1H, br s, H-7). EIMS *m/z* (rel. int.) 391 $[M-C_3H_5O_2]^+$ (11), 344 (3), 326 (29), 311 (18), 284 (17), 269 (30), 266 (70), 251 (68), 223 (38), 186 (65), 171 (48), 157 (39). Found $[M-CH_2OAc]^+$ at *m/z* 391.2473. $C_{23}H_{35}O_5$ requires 391.2484.

3.6. 3β,8β,13α,17-Tetrahydroxy-stemodane (14)

Compound **14** was obtained as the diacetate **15** by acetylation (Ac_2O/py, 40 °C) and chromatography of the fractions containing it.

3.6.1. 3β,17-Diacetate 15. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, s, H-18), 0.94 (3H, s, H-19), 1.12 (3H, s, H-20), 1.33 (1H, br d, *J*=12 Hz, H-5), 1.98 (1H, br signal, H-14), 2.05 and 2.10 (each 3H, s), 3.92 and 4.01 (each 1H, d, *J*=11.4 Hz, H-17), 4.48 (1H, dd, *J*=11.0, 4.9 Hz, H-3); EIMS *m/z* (rel. int.) 404 $[M-H_2O]^+$ (18), 391 (14), 386 (13), 349 (17), 344 (51), 326 (45), 311 (14), 289 (28), 284 (45), 271 (44), 266 (41), 251 (55), 223 (24), 213 (21), 197 (29), 186 (53). Found $[M-H_2O]^+$ at *m/z* 404.2599. $C_{24}H_{36}O_5$ requires 404.2563.

3.6.2. 2α,13α,17-Trihydroxy-stemodane (16). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, s, H-19), 0.92 (3H, s, H-18), 0.96 (3H, s, H-20), 1.05 (1H, t, *J*=11 Hz, H-3α), 1.82 (1H, d, *J*=11.5 Hz, H-16), 2.00 (1H, dt, *J*=11.5, 2 Hz, H-1β), 2.16 (1H, br t, *J*=6.8 Hz, H-14), 3.32 and 3.40 (each 1H, d, *J*=11.2 Hz, H-17), 3.73 (1H, tt, *J*=11.4, 3.6 Hz, H-2); EIMS *m/z* (rel. int.) 338 $[M-H_2O]^+$ (2), 307 (26), 305 (11), 291 (100), 273 (6), 271 (9), 255 (4), 215 (5), 175 (5), 173 (7). Found $[M-H_2O]^+$ at *m/z* 320.2343. $C_{20}H_{32}O_3$ requires 320.2351.

3.7. 2α,13α,17,19-Tetrahydroxy-stemodane (17)

This compound was purified by acetylation at 80 °C and chromatography giving **18** and **19**.

3.7.1. 2α,17,19-Triacetate 18. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (6H, s, H-18 and H-20), 1.08 (1H, t, *J*=11.8 Hz, H-3α), 1.32 (1H, t, *J*=11.8 Hz, H-1α), 1.43 (1H, d, *J*=10 Hz, H-5), 1.88 (1H, d, *J*=11.5 Hz, H-16), 1.95 (1H, m, H-7), 2.02, 2.06 and 2.10 (each 3H, s), 2.12 (1H, br t, *J*=6 Hz, H-14), 3.93 and 3.98 (each 1H, d, *J*=11.4 Hz, H-17), 3.99 and 4.20 (each 1H, d, *J*=11.4 Hz, H-19), 4.88 (1H, tt, *J*=11.8, 3.8 Hz, H-2); EIMS *m/z* (rel. int.) 446

$[M-H_2O]^+$ (1), 404 (5), 391 (66), 344 (13), 331 (10), 326 (12), 311 (6), 284 (72), 271 (100), 246 (46), 213 (23), 186 (78), 173 (37). Found $[M-H_2O]^+$ at *m/z* 446.2652. $C_{26}H_{36}O_6$ requires 446.2668.

3.7.2. Tetraacetate 19. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 and 1.04 (each 3H, s, H-18 and H-20), 2.04, 2.05, 2.06 and 2.06 (each 3H, s), 2.84 (1H, t, *J*=6.6 Hz, H-14), 3.98 and 4.20 (each 1H, d, *J*=11.1 Hz, H-19), 4.33 and 4.53 (each 1H, d, *J*=12.2 Hz, H-17), 4.88 (1H, tt, *J*=11.8, 3.7 Hz, H-2); EIMS *m/z* (rel. int.) 446 $[M-AcOH]^+$ (7), 404 (15), 391 (11), 386 (18), 373 (10), 344 (10), 326 (27), 311 (9), 284 (24), 266 (37), 246 (68), 186 (100), 173 (50), 157 (38). Found $[M-AcOH]^+$ at *m/z* 446.2662. $C_{26}H_{38}O_6$ requires 446.2668.

3.8. 2α,3β,13α,17-Tetrahydroxy-stemodane (20)

Compound **20** was obtained as its triacetate **21** by acetylation (Ac_2O/py at 40 °C) and chromatography of the fractions containing it.

3.8.1. 2α,3β,17-Triacetate 21. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (3H, s, H-18), 0.96 (3H, s, H-19), 1.10 (3H, s, H-20), 1.86 (1H, d, *J*=11.6 Hz, H-16), 1.95 (1H, m, H-7), 1.99, 2.06 and 2.10 (each 3H, s), 2.03 (1H, m, H-1), 2.13 (1H, br t, *J*=6.5 Hz, H-14), 3.90 and 3.99 (each 1H, d, *J*=11.4 Hz, H-17), 4.75 (1H, d, *J*=10.4 Hz, H-3), 5.00 (1H, ddd, *J*=11.0, 10.4, 4.0 Hz, H-2); EIMS *m/z* (rel. int.) 446 $[M-H_2O]^+$ (2), 404 (14), 391 (100), 386 (5), 344 (13), 326 (7), 302 (36), 284 (67), 271 (39), 266 (29), 246 (34), 213 (24), 204 (14), 186 (37), 171 (53). Found $[M-H_2O]^+$ at *m/z* 446.2670. $C_{26}H_{38}O_6$ requires 446.2668.

3.9. 3β,11β,13α,17-Tetrahydroxy-stemodane (22)

This compound was obtained as the tetraacetate **23** and the triacetate **24** (traces) by acetylation (Ac_2O/py at 80 °C) and chromatography of the fractions containing it.

3.9.1. 3β,11β,13α,17-Tetraacetate 23. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, s, H-18), 0.91 (3H, s, H-19), 0.98 (3H, s, H-20), 1.52 (1H, m, H-12), 1.72 (1H, dt, *J*=12.6, 1.5 Hz, H-1β, 1.78 (1H, dd, *J*=14.6, 7.9 Hz, H-7α), 1.93 (1H, m, H-7β), 1.97 (1H, dd, *J*=13.0, 6.3 Hz, H-15), 2.01 and 2.04 (each 3H, s), 2.06 (6H, s), 2.25 (1H, dd, *J*=15.0, 7.1 Hz, H-12), 2.32 (1H, m, H-8), 2.85 (1H, t, *J*= 7.3 Hz, H-14), 4.39 and 4.53 (each 1H, d, *J*=12.2 Hz, H-17), 4.42 (1H, dd, *J*=10.7, 4.2 Hz, H-3), 5.29 (1H, t, *J*= 7.5 Hz, H-11). EIMS *m/z* (rel. int): 446 $[M-AcOH]^+$ (2), 386 (30), 344 (21), 326 (63), 311 (40), 284 (77), 269 (38), 266 (39), 251 (52), 241 (19), 223 (28), 188 (96). Found $[M-AcOH]^+$ at *m/z* 446.2667. $C_{26}H_{38}O_6$ requires 446.2668.

3.9.2. 3β,11β,17-Triacetate 24. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, s, H-18), 0.91 (3H, s, H-19), 0.99 (3H, s, H-20), 1.99, 2.04 and 2.08 (each 3H, s), 2.29 (1H, m, H-8), 3.96 (2H, s, H-17), 4.47 (1H, dd, *J*=11.0, 4.2 Hz, H-3), 5.33 (1H, t, *J*=7.6 Hz, H-11).

3.10. Incubation of 13α,14-dihydroxy-stemodane (25)

The substrate **25** (140 mg) dissolved in ethanol (3 ml) was fed to *M. plumbeus* (12 flasks), as described above. The extraction gave a crude extract (385 mg) that was purified by column chromatography on silica gel. Elution with petroleum ether–EtOAc mixtures of increasing polarity afforded starting material (**25**) (8 mg), fractions containing **30**, 3β,13α,14-trihydroxy-stemodane (**28**) (22 mg) and 2α,13α,14-trihydroxy-stemodane (**29**) (14 mg).

3.10.1. 13α,14,19-Trihydroxy-stemodane (30). The fractions containing this metabolite were acetylated (Ac_2O/py; 80 °C) and purified by chromatography affording the unsaturated compound **34** (0.6 mg), the 14-oxo derivative **35** (2 mg), the triacetate **33** (1 mg) and the diacetate **32** (1.3 mg).

3.10.2. 14,19-Diacetate 32. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, s, H-20), 0.98 (3H, s, H-18), 1.11 (3H, s, H-17), 1.20 and 1.53 (each 1H, m, H-6), 1.38 (3H, m, H-15, H-5 and H-2), 1.96 (2H, m, H-3 and H-16), 2.04 and 2.09 (each 3H, s), 2.19 (1H, dd, *J*=14.1, 8.1 Hz, H-15), 2.58 (1H, d, *J*=10.9 Hz, H-16), 3.92 and 4.30 (each 1H, d, *J*=10.8 Hz, H-19), 4.58 (1H, d, *J*=2.2 Hz, –OH); EIMS *m/z* (rel. int) 406 $[M]^+$ (3), 388 (6), 364 (20), 346 (57), 318 (21), 303 (10), 291 (13), 275 (70), 273 (54), 255 (10), 215 (100). Found $[M]^+$ at *m/z* 406.2705. $C_{24}H_{38}O_5$ requires 406.2719.

3.10.3. 13α,14,19-Triacetate 33. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, s, H-20), 1.00 (3H, s, H-18), 1.48 (3H, s, H-17), 2.01 (1H, d, *J*=11.1 Hz, H-16β), 2.02 (3H, s), 2.03 (6H, s), 2.66 (1H, m, H-12), 2.87 (1H, dd, *J*=11.1, 2.1 Hz, H-16α), 3.90 and 4.32 (each 1H, d, *J*=10.9 Hz, H-18). EIMS *m/z* (rel. int): 406 $[M-C_2H_2O]^+$ (13), 388 (14), 346 (100), 328 (21), 318 (16), 291 (14), 273 (25), 255 (14), 215 (36), 173 (15). Found $[M-C_2H_2O]^+$ at *m/z* 406.2711. $C_{24}H_{38}O_5$ requires 406.2719.

3.10.4. 14,19-Diacetoxy-stemod-13,17-ene (34). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 and 0.99 (each 3H, s, H-18 and H-20), 2.04 and 2.09 (each 3H, s), 3.91 and 4.31 (each 1H, d, *J*=13 Hz, H-19), 4.41 and 4.59 (each 1H, s, H-17); EIMS *m/z* (rel. int) 388 $[M]^+$ (100), 360 (11), 345 (22), 328 (15), 315 (19), 300 (7), 285 (47), 273 (21), 255 (37), 225 (10), 213 (27), 185 (23), 173 (32), 159 (30). Found $[M]^+$ at *m/z* 388.2622. $C_{24}H_{36}O_4$ requires 388.2614.

3.10.5. 14-Oxo-19-acetoxy derivative 35. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, s, H-17), 0.94 (3H, s, H-18), 0.99 (3H, s, H-20), 1.89 (1H, dd, *J*=13.5, 10.9 Hz, H-15α), 1.99 (1H, m, H-8), 2.04 (3H, s), 2.16 (1H, d, *J*= 18.7 Hz, H-15α), 2.62 (1H, dd, *J*=18.7, 3.0 Hz, H-15β), 3.88 and 4.29 (each 1H, d, *J*=11.0 Hz, H 19); EIMS *m/z* (rel. int) 346 $[M]^+$ (32), 302 (19), 286 (15), 273 (92), 255 (12), 244 (12), 229 (8), 203 (11), 175 (12), 163 (15), 149 (18), 123 (100). Found $[M]^+$ at *m/z* 346.2521. $C_{22}H_{34}O_3$ requires 346.2508.

3.10.6. 3β,13α,14-Trihydroxy-stemodane (28). Colourless crystals ($CHCl_3$), mp 193–195 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (3H, s, H-19), 0.91 (3H, s, H-20), 1.02 (3H, s, H-18), 1.14 (1H, dd, *J*=14.0, 3.0 Hz, H-15), 1.19 (3H, s, H-17), 1.65 (1H, dt, *J*=13, 3.4 Hz, H-1β), 1.84 (1H, dd, *J*=10.9, 2.8 Hz, H-16), 1.94 (1H, d, *J*=10.9 Hz, H-16), 2.07 (1H, dd, *J*=8.0, 14.0 Hz, H-15), 3.20 (1H, dd, *J*=11.6,

4.2 Hz, H-3); EIMS *m/z* (rel. int) 322 $[M]^+$ (74), 304 (39), 289 (8), 286 (11), 271 (22), 260 (24), 249 (56), 233 (81), 215 (65), 189 (11), 173 (19), 167 (100), 149 (35), 135 (30). Found $[M]^+$ at *m/z* 322.2527. $C_{20}H_{34}O_3$ requires 322.2508.

3.10.7. 2α,13α,14-Trihydroxy-stemodane (29). Colourless crystals (petroleum ether–EtOAc), mp 189–192 °C (lit.[8] 190–191 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, s, H-19), 0.94 (3H, s, H-20), 0.96 (3H, s, H-18), 1.10 (1H, t, *J*=12.0 Hz, H-3α), 1.20 (3H, s, H-17), 1.28 (1H, dd, *J*=12, 1.5 Hz, H-5), 1.75 (1H, dt, *J*=12, 3.8 Hz, H-3β), 1.89 (1H, dd, *J*=11.0, 2.8 Hz, H-16), 1.95 (1H, d, *J*=11.0 Hz, H-16), 2.08 (1H, dd, *J*=13.9, 8.2 Hz, H-15), 3.75 (1H, tt, *J*=12.0, 3.8 Hz, H-2); EIMS *m/z* (rel. int) 322 $[M]^+$ (66), 304 (5), 289 (7), 271 (5), 264 (6), 259 (12), 249 (49), 233 (21), 231 (22), 215 (100), 173 (14), 167 (77). Found $[M]^+$ at *m/z* 322.2511. $C_{20}H_{34}O_3$ requires 322.2508.

3.10.8. Acetylation of 25. The substrate **25** (4 mg) dissolved in pyridine (five drops) was treated with Ac_2O (10 drops) and heated to 80 °C for 8 h. The solvent was eliminated in vacuo and the residue chromatographed using HPLC giving in order of elution **36** (0.6 mg), **26** (1 mg), **27** (0.8 mg) and starting material **25** (1 mg).

3.10.9. 14-Oxo derivative 36. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (6H, s, H-18 and H-19), 0.90 (3H, s, H-17), 0.96 (1H, ddd, *J*=13.5, 4.4, 2.8 Hz, H-15α), 0.98 (3H,s, H-20), 1.88 (3H, *J*=13.5, 10.9 Hz, H-15β), 2.02 (1H, m, H-8), 2.09 (3H, s), 2.15 (1H, dd, *J*=18.8, 1.6 Hz, H-16), 2.64 (1H, dd, *J*=18.8, 3.0 Hz, H-16); EIMS *m/z* (rel. int): 288 $[M]^+$ (100), 273 (36), 270 (10), 244 (47), 229 (8), 203 (12), 189 (7), 175 (9), 161 (10), 149 (28). Found $[M]^+$ at *m/z* 288.2444. $C_{20}H_{32}O$ requires 288.2453.

3.10.10. 13α-Hydroxy-14α-acetoxy-stemodane (26). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, s, H-19), 0.89 (3H, s, H-18), 0.92 (3H, s, H-20), 1.10 (3H, s, H-17), 1.75 (1H, dt, *J*=12.0, 6.0 Hz, H-11), 1.98 (1H, dd, *J*=11.1, 2.6 Hz, H-16), 2.21 (1H, ddd, *J*=14.3, 8.2, 1.6 Hz, H-15), 2.56 (1H, d, *J*=11.1 Hz, H-16), 4.65 (1H, br s, –OH); EIMS *m/z* (rel. int): 348 $[M]^+$ (1), 330 (2), 306 (1), 288 (100), 273 (35), 270 (12), 260 (42), 245 (44), 217 (20), 203 (12), 175 (20). Found $[M]^+$ at *m/z* 348.2637. $C_{22}H_{36}O_3$ requires 348.2664.

3.10.11. 13α-Acetoxy-14α-hydroxy-stemodane (27). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, s, H-19), 0.88 (3H, s, H-18), 0.91 (3H, s, H-20), 1.25 (1H, dd, *J*=14.1, 3.4 Hz, H-15), 1.31 (1H, d, *J*=12 Hz, H-5), 1.42 (3H, s, H-17), 1.68 (1H, m, H-8), 2.00 (1H, dd, *J*=11.3, 2.9 Hz, H-16), 2.03 (1H, ddd, *J*=14.1, 7.9, 1.6 Hz, H-15), 2.09 (3H, s), 5.04 (1H, s, –OH); EIMS *m/z* (rel. int): 348 $[M]^+$ (1), 288 (100), 273 (32), 270 (10), 260 (10), 255 (10), 244 (43), 229 (8), 203 (12), 175 (11). Found $[M]^+$ at *m/z* 348.2655. $C_{22}H_{36}O_3$ requires 348.2664.

3.11. Treatment of 3β,13α,14-trihydroxystemodane (28) with Ac_2O/AcOH

Acetic anhydride (6 drops) was added to a solution of 3β, 13α,14-trihydroxystemodane (4 mg) in acetic acid (6 drops), and heated up at 80 °C for 25 h. Solvent was removed under vacuum, and the crude chromatographed by HPLC to yield 3β-acetoxy-stemod-12,13-ene (**38**) (1.4 mg) and the 3β,15-oxo-derivative (**39**) (2.2 mg).

3.11.1. 3β-Acetoxy-stemod-12,13-ene (38). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (3H, s, H-18), 0.92 (3H, s, H-19), 0.94 (3H, s, H-20), 1.60 (3H, br s, H-17), 1.80 (1H, m, H-8), 1.93 (1H, m, H-7), 2.04 and 2.06 (each 3H, s), 2.13 and 2.30 (each 1H, d, *J*=10.6 Hz, H-16), 2.34 (2H, m, H-11 and H-15), 4.47 (1H, dd, *J*=11.6, 4.3 Hz, H-3), 5.11 (1H, br s, H-12). EIMS *m/z* (rel. int.): 388 $[M]^+$ (10), 346 (100), 328 (40), 313 (52), 286 (91), 285 (32), 268 (48), 253 (30), 243 (20), 225 (17), 148 (63). Found $[M]^+$ at *m/z* 388.2581. $C_{24}H_{36}O_4$ requires 388.2614.

3.11.2. 14-Oxo derivative 39. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (3H, s, H-18), 0.89 (3H, s, H-19), 0.90 (3H, s, H-17), 0.97 (1H, ddd, *J*=13.5, 4.2, 2.4 Hz, H-15), 1.01 (3H, s, H-20), 1.11 (1H, m, H-7), 1.38 (1H, td, *J*=13.0, 4.0 Hz, H-1α), 1.43 (1H, dt, *J*=13, 3.8 Hz, H-1β), 1.89 (1H, dd, *J*=13.5, 10.9 Hz, H-15), 2.00 (1H, m, H-8), 2.04 (3H, s), 2.13 (1H, dd, *J*=18.5, 1.6 Hz, H-16), 2.59 (1H, dd, *J*=18.5, 3.2 Hz, H-16), 4.41 (1H, dd, *J*=11.7, 4.5 Hz, H-3). EIMS *m/z* (rel. int.): 346 $[M]^+$ (5), 286 (79), 271 (99), 243 (100), 230 (16), 218 (30), 204 (6), 189 (9), 175 (11), 147 (10). Found $[M]^+$ at *m/z* 346.2481. $C_{22}H_{34}O_3$ requires 346.2508.

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Revisiting diterpene lactones of *Suregada multiflora*

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Abstract—Phytochemical investigations on the organic extracts of the leaves of *Suregada multiflora* have led to the isolation of ten tetracyclic diterpene lactones **1**–**10**, members of a rare class of abiatene diterpene lactones. Compounds **1**–**5** were found to be new. The structures of gelomulides **F** (**11**), **D** (**12**) and **E** (**13**) were revised on the basis of 2D NMR and X-ray diffraction evidences. Compounds **1** and **2** contain an epoxy linkage between C-8 and C-14, whereas compounds **3**–**5** were identified as 8,14-dihydroxy analogues of diterpene lactones. The stereochemical assignments in new compound **1** are based on X-ray diffraction analysis. Compounds **6** and **7** were identified as the known gelomulides **A**, **G**. The structures of compounds **7**–**9** were unambiguously confirmed by X-ray diffraction analyses.

1. Introduction

Suregada multiflora (syn. *Gelonium multiflorum* A. Juss., family Euphorbiaceae) grows in the tropical and the subtropical areas of Asia and Africa. The plant is used for the treatment of hepatic and gum diseases in folk medicines.[1] Phytochemical investigation on the genus *Suregada* resulted in the isolation of various flavonoids,[2,3] triterpenoids,[4,5] and diterpenoids.[6–11] In our study, the crude extract MeOH–CH_2Cl_2 (1:1) of *S. multiflora* was found to exhibit selective cytotoxicity against different human cancer cell lines.[10] Several diterpenes from the bark of this plant have been previously reported by our research group.[10,11] In continuation of this investigation, we now report the isolation of five new diterpene lactones **1**–**5**, and the revised structures of the known metabolites **8**–**10** (Fig. 1).

2. Results and discussion

The MeOH–CH_2Cl_2 (1:1) extract of the leaves of *S. multiflora* was partitioned in hexane, dichloromethane and methanol. The MeOH soluble part was subjected to VLC (silica gel) and eluted with mixtures of CH_2Cl_2–MeOH. Three fractions obtained at 5, 10 and 15% MeOH–CH_2Cl_2 were further subjected to column chromatography (Silica gel, Sephadex LH-20 and ODS), and ten different diterpene lactones **1**–**10** were finally purified by recrystallization and preparative recycling HPLC.

The basic skeleton of compounds **1**–**10** was identified to be a diterpene lactone on the basis of their IR (1765–1730 cm^{-1}) and UV (λ_{max} 206–227 nm) spectroscopic studies. Their absorptions were characteristic of an α,β-unsaturated γ-lactone moiety. The ^1H NMR spectra of these compounds showed characteristic doublets for vinylic methyl protons which resonated between δ 1.95 and 1.97 (δ_C 8.7–8.8) with the coupling constant between 1.5 and 2.1 Hz.

Compound **1** was obtained as colorless needles. It showed the M^+ at *m/z* 446.1918 ($C_{24}H_{30}O_8$) in the HREI-MS spectrum. The observed molecular ion in EI-MS had an increment of 60 mass units to the known compound gelomulide **F** (**11**),[6] accounted for by one additional acetoxy group. Apart from the above-discussed general features of a diterpene mono-epoxy lactone skeleton, the ^1H NMR spectrum of **1** also showed two acetyl methyl singlets resonating at δ 2.08 and 2.04, and the corresponding methine signals appeared at δ 4.99 (t, *J*=3.0 Hz) and 5.27 (ddd, *J*=11.0, 5.4, 3.4 Hz). The ^{13}C NMR spectrum also suggested the presence of these two acetyl groups (δ 21.5, 22.4). Acetoxy methine proton (δ_H 5.27) showed correlations with C-4 (δ 52.3), C-8 (δ 58.8) and C-10 (δ 37.3) in the HMBC spectrum, suggestive of its substitution at C-6; keto group is located at C-1 since Me-20 (δ_H 1.45) exhibited ^3J interaction with carbonyl carbon δ 208.4. Acetoxy substitution at C-3 was evident from the correlations of

Keywords: *Suregada multiflora*; Epoxy-lactone-diterpene; X-ray diffraction analysis; Cancer cell lines.
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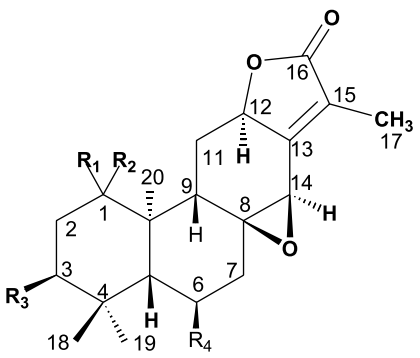
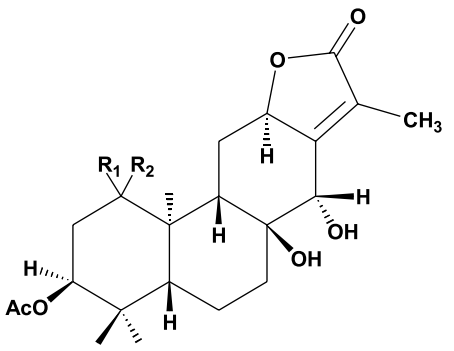
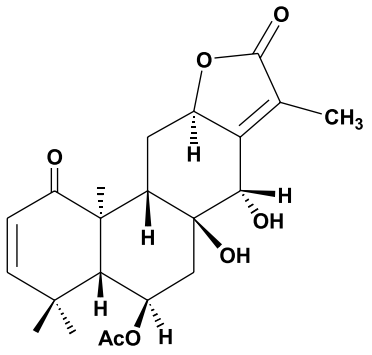


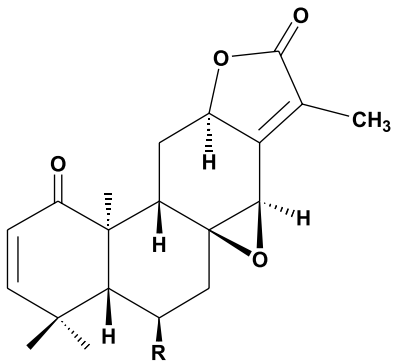
1 R_1, R_2=O, R_3, R_4=OAc
2 R_1, R_2=O, R_3=OH, R_4=H
6 R_1=R_2=R_4=H, R_3=OAc
7 R_1=R_2=H, R_3=R_4=OAc
8 R_1=R_2=O, R_3=OAc, R_4=H



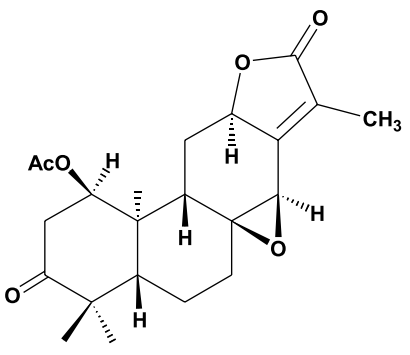
3 R_1=R_2=H
5 R_1=R_2=O



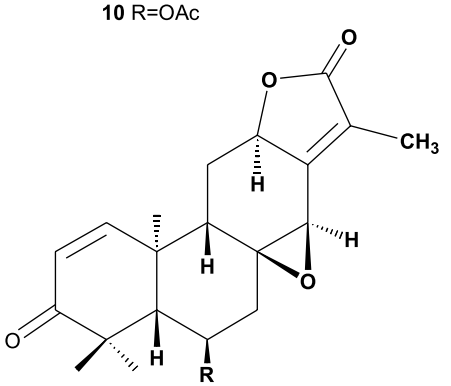
4



9 R=H
10 R=OAc



11 Gelomulide F



12 R=H Gelomulide D
13 R=OAc Gelomulide E

Figure 1. Structures of compounds **1**–**13**.

geminal dimethyl protons (δ 1.13 and 1.24) at C-4 with C-3 methine (δ 81.2). The stereochemistry of the C-6 acetoxy group was determined to be equatorial by the multiplicity of H-6 signal resonating at δ 5.27 (ddd, J=11.0, 5.4, 3.4 Hz) involving J_{ae} and J_{aa} couplings. From these data, the new compound **1** was deduced to be 3β,6β-diacetoxy-1-one-8β,14β-epoxy-13,15-abiatene-16,12-olide and its structure was finally confirmed by X-ray diffraction analysis (Fig. 2).

Compound **2** was deduced to be 3β-hydroxy-1-one-8β,14β-epoxy-13,15-abiatene-16,12-olide, a C-3 deacetyl analogue of **8** with the molecular ion at m/z 346.1805 ($C_{20}H_{26}O_5$) in HREI-MS. ^{1}H and ^{13}C NMR spectra of **2** exhibited a methine resonated at δ_H 3.91 (t, J=3.2 Hz); δ_C 79.7 indicating a hydroxyl substitution. In the COSY 45° spectrum, the aforementioned methine proton showed correlation with the C-2 methylene protons resonating at δ_H 2.31 (dd, J=13.9, 3.9 Hz) and 3.24 (dd, J=13.0, 2.7 Hz). Hence, the position of the hydroxyl group was assigned at C-3 with an axial orientation. This was further supported by the HMBC spectrum, which exhibited correlations of geminal methyls at C-4 (δ_H 1.06 and 1.14) with C-3 (δ_C 79.7). The IR spectrum also displayed absorption (3436 cm^{-1}) for hydroxyl functionality. These spectral data indicated that compound **2** has a –OH group at C-3 instead of –OAc as in compound **8**.

Compounds **3**, **4** and **5** were isolated from the polar eluate of

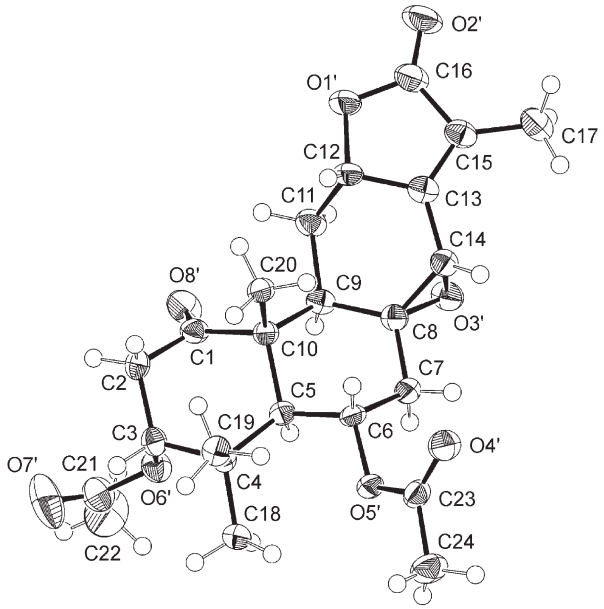


Figure 2. ORTEP drawing of compound **1**.

the plant extract at 15% MeOH–CH_2Cl_2. Apart from the basic spectral features of diterpene lactones, discussed earlier, a downfield signal of H-14 appeared at δ 4.47–4.53 (1H, s) in the ^{1}H NMR spectra of **3**–**5** instead of a typical singlet for the epoxy proton at δ 3.7–3.8, whereas in ^{13}C NMR spectra, the chemical shift of C-14 was shifted from δ 55–56 to 70–73 and for C-8 from δ 58–60 to 74–76, suggestive of the 8,14-dioxygenated structures. Similar dioxygenated analogues have also been reported earlier by the Talapatra et al.[7]

Compound **3** showed the molecular ion at *m/z* 392.2219 in HREI-MS spectrum in agreement with the formula $C_{22}H_{32}O_6$. The peak at *m/z* 332 resulted from the loss of AcOH, indicated the presence of an acetoxy group, as also inferred from ^{1}H and ^{13}C NMR signals δ_H 2.03; δ_C 21.2 and 170.5. The acetate group was deduced to be substituted at C-3 on the basis of ^3J interactions between geminal dimethyl protons (δ 0.83 and 0.92) at C-4 with C-3 methine (δ 77.5) in the HMBC spectrum, as discussed earlier. The singlet for H-14 appeared at δ 4.47 and the corresponding methine carbon resonated at δ 73.2 in the DEPT-90° spectrum. A quaternary carbon signal at δ 74.8 in the broad-band decoupled ^{13}C NMR spectrum was due to C-8. H-14 exhibited ^3J correlations with C-12 (δ 76.7) and C-15 (δ 124.0) in the HMBC spectrum. This led us to conclude that compound **3** was the 8,14-dihydroxy derivative of gelomulide **A**,[6] with the structure, 3β-acetoxy-8β, 14α-dihydroxy-13,15-abiatene-16,12-olide.

The HREI-MS of compound **4** showed the M^+ at *m/z* 404.1808 ($C_{22}H_{28}O_7$). The IR spectrum showed absorptions for α,β unsaturated carbonyl (1681 cm^{-1}) and α,β-unsaturated γ-lactone (1737 cm^{-1}) moieties. The former was also evident from the appearance of *cis* coupled olefinic protons resonating at δ 5.74 and 6.29 as doublets (J=10.0 Hz) in the ^{1}H NMR spectrum, with their carbons appearing at δ 122.6 and 156.1, respectively, in the ^{13}C NMR spectrum. Two oxymethine carbons at δ 72.4 and 70.1 and a tertiary carbon at δ 76.7 along with a carbonyl carbon at δ 203.9 also appeared in the ^{13}C NMR spectrum. The ^{1}H NMR spectrum also showed signals for an acetoxy methine proton at δ 5.49 (dt, J=11.9, 3.8 Hz), acetoxy methyl protons at δ 2.10 (3H, s) and a singlet for a hydroxyl-methine proton at δ 4.53. The position of the keto group at C-1 was inferred on the basis of HMBC cross-peaks between Me-20 protons (δ_H 1.53) and C-1 (carbonyl carbon δ 203.9). Consequently the structure 6β-acetoxy-2-ene-8β,14α-dihydroxy-1-one-13,15-abiatene-16,12-olide was proposed for this new compound (**4**).

Compound **5** was deduced to be a 8,14-dihydroxy derivative of compound **8**. The M^+ *m/z* 406.2004 in HREI-MS was in agreement with the molecular formula $C_{22}H_{30}O_7$. The ^{13}C NMR spectrum of **5** revealed the presence of two oxygen-bearing carbons resonated at δ 73.1 and 80.8 and one oxygen-bearing tertiary carbon at δ 75.0 assigned to C-14, C-3 and C-8, respectively. In the ^{1}H NMR spectrum, the acetoxy-methine proton at C-3 appeared at δ 5.03 (t, J=3.4 Hz) and the methyl protons of acetoxy group resonated at δ 2.03, whereas H-14 appeared as a singlet at δ 4.49. According to the HMBC spectrum, the carbonyl carbon resonated at δ 211.8 which showed ^3J correlations with Me-20 δ_H 1.58, whereas acetoxy substituted carbon at δ 80.8 correlated with the protons of Me-18 and Me-19 (δ 0.92 and 1.17, respectively). These observations indicated a 1-keto-3-acetoxy moiety, whereas the H-14 (δ 4.49) showed correlations with C-12 (δ 76.8), C-13 (δ 160.6) and C-15 (δ 123.7) indicating a 8,14-dihydroxy function. The structure of this new compound was thus deduced to be 3β-acetoxy-8β,14α-dihydroxy-1-one-13,15-abiatene-16,12-olide.

Compound **6** showed the M^+ at *m/z* 374.2082 ($C_{22}H_{30}O_5$) in HREI-MS. The ^{1}H NMR spectrum of compound **6** showed a singlet of acetoxy methyl protons at δ 2.06. The orientation of the acetoxy group was inferred to be axial as its geminal methine proton appeared at δ 4.70 as a triplet (J=2.7 Hz). This was assigned to be at C-3 based on HMBC correlations of H-3 with quaternary C-4 (δ 38.9), Me-18 and Me-19 (δ_C 28.4 and 22.2, respectively). The structure was proposed as 3β-acetoxy-8β,14β-epoxy-13,15-abiatene-16,12-olide and found to be identical in physical and NMR features to the gelomulide **A** reported earlier by Talapatra et al.[6] The spectral comparison is given in Tables 3 and 4.

Compound **7** was obtained as needles (mp 207–211 °C) and showed the M^+ at *m/z* 432.2150 ($C_{24}H_{32}O_7$). It was inferred to be 3β,6β-diacetoxy-8β,14β-epoxy-13,15-abiatene-16,12-olide i.e. a 6β-acetoxy derivative of compound gelumolide **A**.[7] As the ^{1}H and ^{13}C NMR spectra of compound **7** showed signals for two acetoxy methyls which resonated at δ_H 2.05 and 2.02 (δ_C 21.1 and 21.6), while carbonyl carbons of the acetoxy group were resonated at δ 170.0 and 170.3. Loss of two acetic acid units resulted in fragment ions *m/z* 372 (M^+-AcOH) and 312 (372-AcOH) in EI-MS. A corresponding geminal methine protons of these acetates appeared at δ 4.61 (m, $W_{1/2}$~5 Hz) and 5.14 (m, $W_{1/2}$~26 Hz). A comparison of spectral and physical data of compound **7** with the literature values indicated it to be a known compound, gelomulide **G**[7] (Tables 3 and 4). The structure of compound **7** was further corroborated by the single-crystal X-ray diffraction analysis (Fig. 3).

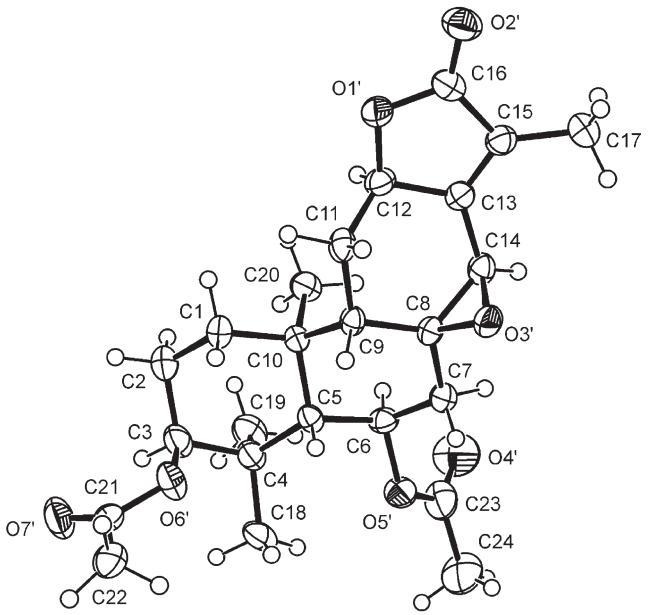


Figure 3. ORTEP drawing of compound **7**.

Compound **8** exhibited the M^+ at *m/z* 388.1914 ($C_{22}H_{28}O_6$) in HREI-MS. It was deduced to be 3β-acetoxy-1-one-8β,14β-epoxy-13,15-abiatene-16,12-olide, i.e. a keto derivative of compound **6**. The IR spectrum showed strong absorption at 1712 cm^{-1} indicating a carbonyl group, the carbon of which appeared at δ 210.2 in the ^{13}C NMR spectrum. The spectral data identified it as the gelomulide **F**, isolated earlier from the same plant by Talapatra et al.[6] Compound **8** possessed a substitution of axially displaced acetate group at C-3, as its methine proton appeared as a triplet at δ 5.02 (J=3.4 Hz). The HMBC spectrum showed some important correlations, for example, the acetoxy methine proton at δ 5.02 exhibited ^2J interaction with C-4 (δ 53.2) and ^3J interactions with geminal dimethyl carbons of Me-18 and Me-19 (δ_C 27.7 and 22.1). These geminal dimethyl protons (δ 0.96 and 1.20) showed HMBC correlations with C-3 (δ 80.6), which led to the assignment of the position of an acetoxy group at C-3. Interestingly among the HMBC interactions of H-3 (δ 5.02) a cross peak with a carbonyl carbon (δ 210.2) was also observed which indicated the position of ketonic function at C-1. The cross peaks between Me-20 (δ_H 1.35) and carbonyl carbon (δ 210.2) further substantiated the position of ketonic function at C-1. Based on 2D NMR evidence the structure of gelomulide **F** (**11**) has been revised. The final proof of the structure and its confirmation was achieved by single-crystal X-ray diffraction analysis and the ORTEP diagram of compound **8** is shown in Figure 4.

Compounds **9** and **10** were found to be monoepoxy diterpene lactone analogues with an α,β unsaturated carbonyl moiety as inferred from the IR absorptions at 1665 and 1668 cm^{-1}. This was further supported by a set of *Z*- olefinic protons resonating at δ 5.8 and 6.3–6.4 as doublets (J=10.3 Hz) in the ^1H NMR spectra, with their respective carbons at δ 124.0, 122.6, and δ 155.2, 156.2, respectively, while carbonyl carbons appeared at δ 204.3 and 202.5 in ^{13}C NMR spectra. The positions of the carbonyl group at C-1 and the double bond between C-2 and C-3 were inferred from HMBC cross peaks of H-3, Me-20, Me-18 and Me-19.

Compound **9** has the molecular formula $C_{20}H_{24}O_4$ (*m/z* 328.1648), as inferred from HREI-MS analysis. Its structure was deduced as 2-ene-1-one-8β,14β-epoxy-13,15-abiatene-16,12-olide (**9**) and ultimately confirmed by single-crystal X-ray diffraction analysis (Fig. 5).

Compound **10** $C_{25}H_{22}O_4$ (*m/z* 386.1542) was found to be 6β-acetoxy-2-ene-1-one-8β,14β-epoxy-13,15-abiatene-16,12-olide, a 6*β*-acetoxy derivative of compound **9**.

The ^1H and ^{13}C NMR and other physical data (Tables 3 and 4, experimental) of compounds **8**, **9** and **10** were consistent

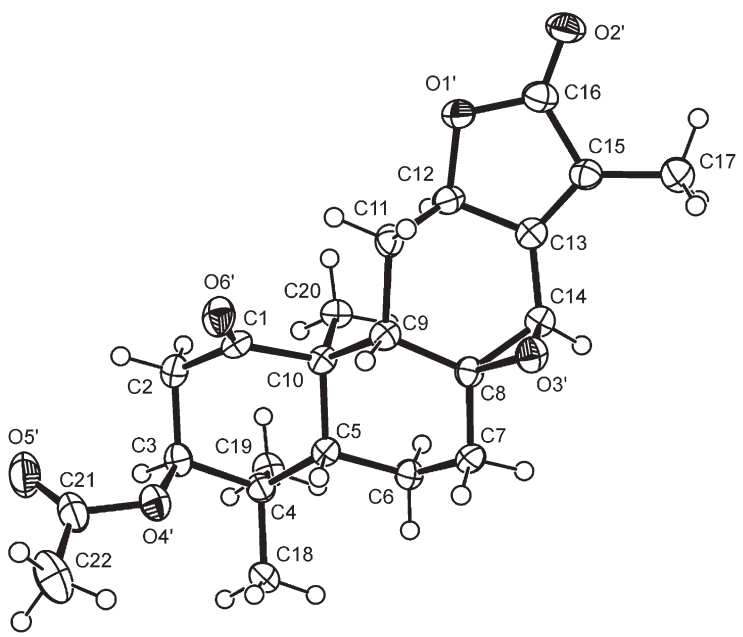


Figure 4. ORTEP drawing of compound **8**.

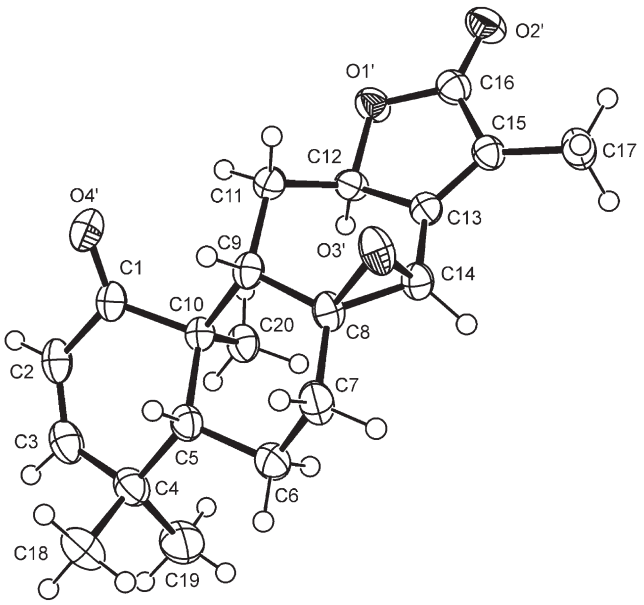


Figure 5. ORTEP drawing of compound **9**.

with the known gelomulides **F** (**11**), **D** (**12**) and **E** (**13**) reported earlier by Talapatra et al.[6,7] They reported the carbonyl substitution at C-3, which we believe must have been misinterpreted, as their report lacked 2D NMR evidences. The presence of $^{3}J_{C-H}$ interactions between Me-20 protons and carbonyl carbon in the HMBC spectra convincingly supported the presence of a keto group at C-1 in these compounds. This structural revision was finally confirmed by single-crystal X-ray diffraction analyses of compounds **8** and **9**.

Compounds **6**–**10** were evaluated in the primary anticancer assay of 3-cell lines at the National Cancer Institute (NCI), Bethesda, USA. Among them compound **10** showed promising activity against the NCI-H460 (Lung) cell line, with a growth inhibition of over 85% at concentration of 5×10^{-5} M. Compound **10** was then screened in the full panel of 60 tumors cell lines, at the aforementioned concentration, and found to be active against the CCRF-CEM (Leukemia), K-562 (Leukemia), SR (Leukemia), HCT-15 (Colon), and MD-MB-435 (Breast), with over 95% growth inhibition.

In summary, this phytochemical study has led to the isolation of ten tetracyclic diterpene lactones, belonging to a rare class of abiatene diterpene lactones. Extensive use of two-dimensional NMR spectroscopic techniques and X-ray diffraction analysis for crystalline compounds, has helped in understanding and classifying a number of structural and stereochemical details of this rare class of plant metabolites.

3. Experimental

3.1. General procedures

Melting points were determined on a Yanaco MP-S3 apparatus. UV spectra were measured on a Shimadzu UV 240 spectrophotometer. IR spectra were recorded on a JASCO A-302 spectrophotometer in $CHCl_3$. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance AM-400 spectrometer with tetramethylsilane (TMS) as an internal standard. 2D NMR spectra were recorded on a Bruker Avance AMX 500 NMR spectrometer. Optical rotations were measured on JASCO DIP-360 digital polarimeter by using 10 cm cell tube. Mass spectra (EI and HREI-MS) were measured in an electron impact mode on Varian MAT 112 or MAT 312 spectrometers and ions are given in *m/z* (%). Fast atom bombardments (FAB) MS were measured on Jeol HX110 mass spectrometer. TLC was performed on pre-coated silica gel cards (E. Merck), spots were viewed under ultraviolet light at 254 nm for fluorescence quenching spots and at 366 nm for fluorescent spots and stained by spraying with a solution of ceric sulphate in 10% H_2SO_4. For column chromatography, silica gel (E. Merck, 230–400 mesh), Sephadex LH-20, and a prepacked ODS column (Waters Sep-Pak, Vac 20 cc, C_{18}−5 g) were used. Final purification of some compounds was achieved by preparative recycling HPLC, LC-908 (JAI) and the column used was L-80 (YMC, Co. Ltd). All reagents used were of analytical grades.

3.2. Plant material

Plant material was collected from near to Cox's Bazar, Chunati Game Reserve, Harbang Beat, Bangladesh in April 1999. The plant was identified by (Late) Prof. M. Salar Khan of the Bangladesh National Herbarium (BNH), Dhaka, Bangladesh. A herbarium specimen of this plant was deposited at BNH (Voucher No. DACB, Accession No. 28004).

3.3. Extraction and isolation

Air-dried and ground leaves of *S. multiflora* (3.5 kg) were extracted three times (each 27 h) with CH_2Cl_2:MeOH (1:1, 10 L) at room temperatures. The resulting CH_2Cl_2–MeOH extract was concentrated under vacuum to obtain a crude extract (ca. 400.0 g), which was partitioned between dichloromethane and water. The concentrated dichloromethane extract (260.0 gm) was defatted by suspension in 90% MeOH and partition with hexane. The MeOH soluble part (180.0 g) was chromatographed over 400.0 g of silica gel (VLC) and eluted with the mixtures of hexane–dichloromethane (80–100%, ca. 2×750 mL each of the two fractions) and then with CH_2Cl_2–MeOH with gradient polarity (0–100%, ca. 2×1 L each of the 20 fractions). The fraction obtained with 5% MeOH–CH_2Cl_2 elution (1.2 g) was subjected to silica gel chromatography using 10% acetone–hexane, yielding a total of ten fractions. Fractions obtained at 5 and 8% acetone–hexane were separately recrystallized from acetone–hexane to obtain compounds **6** (28.0 mg) and **9** (18.0 mg), respectively. Whereas the fraction obtained at 10% MeOH–CH_2Cl_2 (4.75 g) was chromatographed on silica gel using acetone–hexane with increasing ratio of acetone (10–25%, 2×100 mL each) to obtain thirty fractions. The less polar fractions 6–10 were combined and rechromatographed over a flash silica gel column using toluene–chloroform (1:6) stepwise elution (12×50 mL) to obtain compounds **7** (610.0 mg) and **9** (9.0 mg). Fractions 12–14 were combined and compound **10** (22.0 mg) was purified by silica gel column chromatography using toluene–chloroform (1:9) as solvent. Whereas, from the polar fractions 15–22, compound **8**

(1.1 g) was purified by recrystallization with acetone–hexane. Fractions 24–25 were also combined and rechromatographed over a flash silica gel column using toluene–chloroform (1:9) to obtain compound **1** (9.0 mg). From fractions 27–28, compound **2** (5.0 mg) was purified by the combination of ODS column chromatography using H_2O–MeOH (1:2) and preparative recycling HPLC using H_2O–MeOH (1:4).

The fraction obtained using 15% MeOH–CH_2Cl_2 elution (1.4 g) was re-chromatographed on a silica gel column using acetone–hexane (40–100% acetone) to obtain ten sub-fractions. Fraction 8 (138.0 mg), obtained at 60% acetone–hexane, was subjected to ODS column chromatography using H_2O–MeOH (1:2) followed by column chromatography on flash silica using acetone–chloroform gradient. The fraction obtained at 10% acetone–chloroform as a result of column chromatography was then subjected to preparative recycling HPLC using H_2O–MeOH (1:4) to obtain compound **3** (3.0 mg). Whereas, the most polar tenth fraction, eluted from second chromatography of 15% MeOH–CH_2CL_2 on silica gel column using hexane–acetone, obtained at 100% acetone (176.0 mg), was subjected to Sephadex LH-20 column using H_2O–MeOH (1:1) and ODS column chromatography using H_2O–MeOH (1:2) as solvent system was fractionated. Finally from which, compounds **4** (4.0 mg) and **5** (4.0 mg) were purified on preparative recycling HPLC using an isocratic mixture of H_2O–MeOH (1:4).

3.3.1. Compound 1. Colorless needles (9.0 mg), mp 220–223 °C, $[\alpha]_D^{28}$=46.6 ($CHCl_3$; *c* 0.003), UV (MeOH) λ_{max} (log ε) 208 nm (2.3); IR ($CHCl_3$) ν_{max}: 2925, 1730, 1687, 1458, 1377, 1261, 1029 cm^{-1}. EI-MS: *m*/*z* (rel. int. %): 446 (M^+, 4), 386 (71), 326 (82), 311 (37), 308 (39), 293 (25), 265 (34), 230 (35), 173 (37), 105 (52), 69 (100), 55 (84). HREI-MS: *m*/*z*=446.1918 (for $C_{24}H_{30}O_8$, 446.1940). ^1H and ^{13}C NMR: see Tables 1 and 2.

3.3.2. Compound 2. White amorphous (5.0 mg), mp 206–209 °C, $[\alpha]_D^{28}$=106 ($CHCl_3$; *c* 0.003), UV (MeOH) λ_{max} (log ε) 223 nm (3.4); IR ($CHCl_3$) ν_{max}: 3463, 2958, 1747, 1706, 1452, 1028, 752 cm^{-1}. EI-MS: *m*/*z* (rel. int. %): 346 (M^+, 10), 310 (4), 285 (6), 267 (11), 213 (11), 187 (7), 160 (11), 107 (28), 95 (23), 81 (37). HREI-MS: M^+ *m*/*z*=346.1805 (for $C_{20}H_{26}O_5$, 346.1780) ^1H and ^{13}C NMR: see Tables 1 and 2.

3.3.3. Compound 3. White amorphous (3.0 mg), mp 201–204 °C, $[\alpha]_D^{28}$=−66.6 ($CHCl_3$; *c* 0.003), UV (MeOH) λ_{max} (log ε) 218 nm (4.7); IR ($CHCl_3$) ν_{max}: 3435, 2933, 1733, 1448, 1375, 1253, 1026, 755 cm^{-1}. EI-MS: *m*/*z* (rel. int. %): 392 (M^+, 0.1), 388 (2), 332 (100), 316 (59), 299 (18), 273 (14), 192 (43), 149 (26), 136 (70), 107 (21). HREI-MS: M^+ *m*/*z*=392.2219 (for $C_{22}H_{32}O_6$, 392.2198) ^1H and ^{13}C NMR: see Tables 1 and 2.

3.3.4. Compound 4. White amorphous (4.0 mg), mp 212–216 °C, $[\alpha]_D^{28}$=133 ($CHCl_3$; *c* 0.003), UV (MeOH) λ_{max} (log ε) 218 nm (4.7); IR ($CHCl_3$) ν_{max}: 3674, 3400, 2929, 1737, 1681, 1377, 1244, 1028, 756 cm^{-1}. EI-MS: *m*/*z* (rel. int. %): 404 (M^+, 43), 346 (36), 326 (75), 293 (15), 265 (21), 231 (16), 203 (22), 189 (37), 161 (22), 150 (35), 137

Table 1. ^1H NMR and HMDC data of compounds **1–5** in $CDCl_3$ (δ in ppm, *J* in Hz)

Protons	1	HMBC to C	2	HMBC to C	3	HMBC to C	4	HMBC to C	5	HMBC to C
2α	2.40 dd (13.5, 3.5)	1, 3	2.31 dd (13.9, 3.9)	1	1.32–1.67 m		5.74 d (10)	4, 10	2.30 dd (13.7, 3.4)	1, 3
2β	3.15 dd (13.4, 2.9)	1, 3	3.24 dd (13.0, 2.7)	1					3.23 dd (13.9, 3.3)	1
3	4.99 t (3.0)	1, 4	3.91 t (3.2)	1, 4	4.67 m ($W_{1/2}$~3.5)	1, 2, 4, 5	6.29 d (10)	1, 5	5.03 t (3.4)	1
3-OAc	2.08 s				2.03 s				2.03 s	
6	5.27 ddd (11.0, 5.4, 3.4)	4, 8, 10	1.56–1.62 m		1.57–1.69 m		5.49 dt (11.9, 3.8)	4, 8	1.9–2.0 m (ovlp)	
6-OAc	2.04 s						2.10 s			
9	2.64 d (7.0)	8, 12	2.67 d (7.3)	8, 12, 20	1.85 ovlp.	8, 11, 14	2.29 d (6.7)	1, 20, 11, 12	2.34 m ($W_{1/2}$~6.2)	8, 12
11β	2.51 ddd (14.3, 7.3, 1.2)	13	2.50 dd (14.0, 5.8)	9, 13	2.51 dd (14.1, 5)	9, 12, 13	2.71 dd (14.4, 6.7)	9, 12	2.6 dd (14.2, 6.7)	12
12	4.78 ddd (13.0, 5.8, 2.1)	13, 15	4.84 m ($W_{1/2}$~23)	9, 13, 15	5.20 m ($W_{1/2}$~22)	13, 14, 15	5.03 m ($W_{1/2}$~21)	13, 15	5.07 m ($W_{1/2}$~22)	9, 13, 15
14	3.80 s	9, 12, 13, 15	3.70 s	12, 13	4.47 s	12, 15	4.53 s	12, 15	4.49 s	12, 13, 15
17	1.95 d (2.1)	13, 16	1.94 d (2.1)	13, 16	1.86 d (1.6)	13, 16	1.86 d (1.6)	13, 15, 16	1.84 d (1.5)	13, 15, 16
18	1.13 s	3, 5	1.06 s	3, 5	0.83 s	3, 5	1.15 s	3, 5	0.92 s	3, 5
19	1.24 s	3, 5	1.14 s	3, 5	0.92 s	3, 5	1.27 s	3, 5	1.17 s	3, 5
20	1.45 s	1, 5, 9	1.38 s	1, 5, 9	1.20 s		1.53 s	1, 5, 9	1.58 s	1, 5, 9

Table 2. ^{13}C NMR data of compounds **1**–**5** in $CDCl_3$ (δ in ppm)

Carbons	1	2	3	4	5
1	208.4	211.7	35.1	203.9	211.8
2	39.1	43.0	23.1	122.6	39.5
3	81.2	79.7	77.5	156.1	80.8
4	52.3	53.2	36.6	49.8	53.4
5	54.2	50.4	49.3	52.1	51.2
6	75.5	20.2	20.3	72.4	20.3
7	25.9	34.8	42.0	46.3	41.4
8	58.8	60.5	74.8	76.7	75.0
9	40.6	40.8	57.0	46.0	48.0
10	37.3	38.2	38.8	39.5	37.11
11	40.3	26.0	28.9	31.6	31.6
12	67.7	75.9	76.7	76.4	76.8
13	153.8	154.8	160.0	156.1	160.6
14	55.5	56.0	73.2	70.1	73.1
15	120.0	128.8	124.0	128.0	123.7
16	174.1	173.9	174.4	174.0	174.7
17	8.8	8.7	8.4	8.5	8.4
18	20.9	22.4	21.9	21.9	21.9
19	30.3	28.0	28.3	33.9	27.7
20	17.9	16.9	17.2	18.7	16.2
OCO*Me*	22.4, 21.5	—	21.2	21.6	21.0
O*C*OMe	170.0, 169.9	—	170.5	170.4	170.1

(91), 96 (47), 55 (100). HREI-MS: *m/z*=404.1808 (for $C_{22}H_{28}O_7$, 404.1835). ^1H and ^{13}C NMR: see Tables 1 and 2.

3.3.5. Compound 5. White amorphous (4.0 mg), mp 201–208 °C, $[\alpha]_D^{28}=-33.3$ ($CHCl_3$; *c* 0.003), UV (MeOH) λ_{max} (log ε) 218 nm (4.9); IR ($CHCl_3$) ν_{max}: 3436, 2927, 1737, 1375, 1241, 1027, 755 cm^{-1}. EI-MS: *m/z* (rel. int. %): 406 (M^+, 21), 346 (26), 328 (36), 310 (8), 267 (14), 232 (20), 219 (17), 163 (37), 150 (57), 137 (56), 105 (31). HREI-MS: *m/z*=406.2004 (for $C_{22}H_{30}O_7$, 406.1991). ^1H and ^{13}C NMR: see Tables 1 and 2.

3.3.6. Compound 6. Colorless needles (28.0 mg), mp 239–248 °C, $[\alpha]_D^{28}=105$ ($CHCl_3$; *c* 0.003), UV (MeOH) λ_{max} (log ε) 223 nm (5.3); IR ν_{max} cm^{-1}: 2950, 1757, 1724, 1251, 1452, 1375, 1178, 1093, 1026, 979. EI-MS: *m/z* (rel. int. %): 374 (M^+, 14), 314 (12), 294 (4), 281 (3), 253 (18), 189 (13), 180 (29), 161 (21), 135 (56), 133 (32), 120 (16), 95 (37), 81 (52), 69 (85), 55 (100). HREI-MS: *m/z*=374.2082 (for $C_{22}H_{30}O_5$, 374.2093). ^1H and ^{13}C NMR: see Table 3.

3.3.7. Compound 7. Colorless needles (610.0 mg), mp 207–211 °C, $[\alpha]_D^{28}=96.6$ ($CHCl_3$; *c* 0.003), UV (MeOH) λ_{max} (log ε) 223 nm (5.4); IR ν_{max} cm^{-1}: 2947, 1757–28 b.sh, 1242, 1452, 1375, 1178, 1029, 754. EI-MS: *m/z* (rel. int. %): 432 (2), 372 (75), 330 (10), 312 (100), 297 (40), 279 (11), 269 (14), 251 (5), 244 (11), 218 (9), 201 (13), 187 (34), 159 (41), 81 (47). HREI-MS: *m/z*=432.2150 (for $C_{24}H_{32}O_7$, 432.2148). ^1H and ^{13}C NMR: see Table 3.

3.3.8. Compound 8. Colorless prisms (1.1 g), mp 226–232 °C, $[\alpha]_D^{28}=60$ ($CHCl_3$; *c* 0.003), UV (MeOH) λ_{max} (log ε) 223 nm (5.1); IR ν_{max} cm^{-1}: 2950, 1755, 1712, 1238, 1433, 1373, 1026, 754. EI-MS: *m/z* (rel. int. %): 388 (M^+, 6), 328 (20), 309 (19), 299 (32), 230 (29), 212 (30), 202 (18), 188 (31), 150 (52), 135 (25), 106 (35), 68 (100), 55 (81). HREI-MS: *m/z*=388.1914 (for $C_{22}H_{28}O_6$, 388.1885), ^1H and ^{13}C NMR: see Table 4.

3.3.9. Compound 9. Colorless prisms (9.0 mg), mp

Table 3. Comparison of ^1H NMR data of compounds **6**–**10** with gelomulides **A** (**6**), **G** (**7**), **F** (**11**), **D** (**12**), **E** (**13**)[6,7] in $CDCl_3$ (δ in ppm, *J* in Hz)

Protons	6	A	7	G	8	F	9	D	10	E
1						5.03 m ($W_{1/2}$~8.4)		6.44 d (10.3)		6.33 d (10.3)
2					α; 2.38 dd (13.5, 3) β; 3.15 dd (13.5, 3.8)	2.39 dd (13.5, 3.8) 3.17 dd (13.5, 2.9)	5.81 d (10.4)	5.82 d (10.7)	5.83 d (10.3)	5.84 d (10.3)
3	4.70 t (2.7)	4.70 m ($W_{1/2}$~8.0)	4.61 m ($W_{1/2}$~5.3)	4.63 m ($W_{1/2}$~8.1)	5.02 t (3.4)		6.44 d (10.3)		6.31 d (10.4)	
6			5.14 m ($W_{1/2}$~26.6)	5.16 m ($W_{1/2}$~27)					5.13 dt (11, 4.9)	5.14 m ($W_{1/2}$~28)
9	2.04 d (6.8)	2.05 d (6.7)	2.10 d (7.0)	2.10 d (6.9)	2.68 d (7.3)	2.69 d (7.2)	2.69 d (7.2)	2.66 d (7.3)	2.66 d (7.1)	2.69 d (7.3)
11β	2.28 dd (13.5, 5.6)	2.29 dd (13.4, 5.6)	2.28 dd (13.5, 5.6)	2.32 dd (13.8, 5.5)	2.50 dd (14.0, 5.8)	2.50 dd (14.0, 5.8)	2.70 dd (14.0, 5.6)	2.73 dd (14.0, 5.5)	2.59 dd (14.2, 5.7)	2.62 dd (14.3, 5.8)
12	4.98 ddd (10.1, 5.5, 2.2)	4.99 ddd (12.9, 5.3,2.1)	4.88 ddd (10.2, 5.2, 2.2)	4.90 ddd (13.1, 5.1, 2.1)	4.84 ddd (13, 5.4, 2)	4.84 ddd (13, 5.4, 2.1)	4.83 ddd (7.7, 5.4, 2.1)	4.86 ddd (13, 5.5, 2.1)	4.79 m ($W_{1/2}$~21)	4.81 ddd (13, 5.8, 1.8)
14	3.72 s	3.72 s	3.83 s	3.85 s	3.80 s	3.73 s	3.71 s	3.73 s	3.85 s	3.86 s
17	1.95 d (2.0)	1.97 d (2.0)	1.93 d (2.1)	1.95 d (2.0)	1.94 d (1.8)	1.95 d (1.9)	1.95 d (2.0)	1.98 d (1.8)	1.96 d (1.7)	1.98 d (1.8)
18	0.90 s	0.92 s	0.98 s	1.0 s	0.96 s	0.98 s	1.10 s	1.14 s	1.16 s	1.19 s
19	0.97 s	0.98 s	1.03 s	1.16 s	1.21 s	1.22 s	1.11 s	1.16 s	1.30 s	1.32 s
20	1.08 s	1.10 s	1.14 s	1.23 s	1.35 s	1.41 s	1.31 s	1.36 s	1.37 s	1.39 s
OCO*Me*	2.06 s	2.07 s	2.05 s	2.07 s	2.03 s	2.04 s			2.09 s	2.12 s
			2.02 s	2.04 s						

Table 4. Comparison of ^{13}C NMR data of compounds **6**–**10** with gelomulides **A** (**6**), **G** (**7**), **F** (**11**), **D** (**12**), **E** (**13**)[6,7] in $CDCl_3$ (δ in ppm)

Carbons	6	A	7	G	8	F	9	D	10	E
1	33.8	33.8	33.8	33.8	210.2	80.4	204.3	155.3	202.5	156.2
2	22.6	22.6	22.1	22.1	39.5	39.5	124.0	124.0	122.6	122.6
3	77.0	76.9	78.5	78.5	80.6	210.1	155.2	204.2	156.2	202.5
4	38.9	38.9	36.6	36.6	53.2	53.1	48.1	49.4	48.9	49.0
5	48.9	48.9	52.2	52.3	51.4	51.3	49.5	49.5	51.7	51.7
6	20.4	20.4	69.3	69.3	20.1	20.0	20.8	20.8	69.1	69.1
7	34.6	34.6	39.9	39.9	34.6	34.6	34.7	34.7	40.1	40.1
8	60.8	60.9	59.5	59.4	60.3	60.2	60.6	60.6	58.7	58.7
9	48.6	48.6	48.1	48.2	40.8	40.9	39.5	39.6	38.7	38.7
10	36.6	36.6	38.9	38.9	37.2	37.1	34.7	36.6	36.5	36.5
11	23.7	23.7	24.0	24.0	25.9	25.9	26.2	26.2	26.1	26.2
12	75.4	75.5	75.0	74.9	75.7	75.6	75.0	76.1	75.8	75.8
13	155.4	155.4	154.5	155.4	154.6	154.6	154.8	154.8	153.9	153.9
14	56.1	56.1	55.6	55.2	56.0	55.9	55.6	55.8	55.6	55.6
15	128.8	128.8	129.5	129.4	128.8	128.7	129.5	128.4	129.0	129.0
16	173.8	174.2	173.6	173.3	173.8	173.6	170.3	173.9	173.7	173.7
17	8.7	8.7	8.8	8.6	8.7	8.5	8.7	8.7	8.8	8.8
18	28.4	28.3	31.3	31.1	27.7	27.6	31.5	31.5	34.0	34.0
19	22.2	22.2	22.3	22.2	22.1	22.0	22.3	22.3	22.1	22.2
20	19.1	19.1	20.4	20.3	16.8	16.7	17.8	17.8	19.1	19.1
OCO*Me*	21.2	21.2	21.1, 21.6	20.9, 21.5	20.9	20.7	—	—	21.5	21.5
O*C*OMe	170.4	170.5	170.0	169.8	170.0	169.8	—	—	169.8	169.8
			170.3	170.0						

222–230 °C, $[\alpha]_D^{28}$=85 ($CHCl_3$; *c* 0.003), UV (MeOH) λ_{max} (log ε) 223 nm (5.6); IR ν_{max} cm^{-1}: 2954, 1746, 1665, 1438, 1363, 1249, 1090. EI-MS: *m*/*z* (rel. int %): 328 (M^+, 52), 310 (16), 295 (12), 267 (32), 232 (27), 214 (27), 186 (33), 160 (20), 150 (89), 137 (70), 96 (49), 53 (100). HREI-MS: *m*/*z*=328.1648 (for $C_{20}H_{24}O_4$, 328.1674). ^1H and ^{13}C NMR: see Table 4.

3.3.10. Compound 10. Colorless needles (22.0 mg), mp 245–251 °C, $[\alpha]_D^{28}$=−13.3 ($CHCl_3$; *c* 0.003), UV (MeOH) λ_{max} (log ε) 227 nm (6.3); IR ν_{max} cm^{-1}: 2960, 1758, 1730, 1240, 1668, 1460, 1378, 1025. EI-MS: *m*/*z* (rel. int. %): 386 (M^+, 17), 326 (54), 308 (43), 293 (18), 283 (9), 265 (37), 230 (8), 212 (10), 163 (17), 137 (100), 105 (37). HREI-MS: *m*/*z*=386.1542 (for $C_{25}H_{22}O_4$, 386.1518). ^1H and ^{13}C NMR: see Table 4.

3.4. X-ray diffraction analyses of compounds 1 and 7–9

X-ray diffraction data for compounds **1** and **7**–**9** were collected on a Nonius Kappa CCD diffractometer (now Bruker) with graphite monochromated Mo-Kα radiations at a temperature of 173(2) °K using the ω and φ scans at variable speeds $3.0°<\theta<27.5°$, $3.8°<\theta<27.5°$, $2.1°<\theta<27.5°$ and $2.7°<\theta<27.5°$, respectively, for **1**, **7**, **8** and **9**. A total of 5296 reflections for compound **1**, whereas 5098, 8951 and 3897 reflections for compounds **7**, **8** and **9**, respectively, were collected. The structures were solved by direct methods[12] (SIR92) and expanded using Fourier techniques.[13] The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement using F^2 was done with the aid of SHELXL97.[14]

The ORTEP drawing of the X-ray model of compound **1** is given in Figure 2. Crystal data: approximate crystal size, 0.35×0.16×0.12 mm^3. $C_{24}H_{30}O_8$, [M_r=446.48], orthorhombic, *a*=7.977(2) Å, *b*=11.808(2) Å, *c*=24.821(6) Å, *V*=2337.9(9) $Å^3$, D_c=1.268 Mg/m^3, *Z*=4, space group, $P2_12_12_1$, *R*=0.064, *wR*=0.100.

The ORTEP drawing of the final X-ray model of **7** is given in Figure 3. Crystal data: approximate crystal size, 0.14×0.05×0.03 mm^3. $C_{24}H_{32}O_7$, [M_r=432.50], monoclinic, *a*=10.503(4) Å, *b*=9.574(4) Å, *c*=11.580(6) Å, *V*=1153.8(9) $Å^3$, D_c=1.245 Mg/m^3, *Z*=2, space group, $P2_1$, *R*=0.046, *wR*=0.093.

The ORTEP drawing of compound **8** is presented in Figure 4. Crystal data: approximate crystal size, 0.20×0.18×0.16 mm^3. $C_{22}H_{28}O_6$, [M_r=388.44], orthorhombic, *a*=12.623(2) Å, *b*=14.162(2) Å, *c*=22.123(5) Å, *V*=3954.9(12) $Å^3$, D_c=1.305 Mg/m^3, *Z*=8, space group, $P2_12_12_1$, *R*=0.046, *wR*=0.122.

The ORTEP drawing of compound **9** is presented in Figure 5. Crystal data: approximate crystal size, 0.28×0.24×0.20 mm^3. $C_{24}H_{24}O_4$, [M_r=328.39], orthorhombic, *a*=9.571(3) Å, *b*=11.545(3) Å, *c*=15.666(6) Å, *V*=1731.0(10) $Å^3$, D_c=1.260 Mg/m^3, *Z*=4, space group, $P2_12_12_1$, *R*=0.039, *wR*=0.097.

The X-ray diffraction data of compounds **1** and **7**–**9** are deposited in Cambridge Crystallographic Data Centre (12 Union Road, Cambridge, CB2 1EZ, UK) and their data deposition numbers are CCDC 227056, CCDC 227055, CCDC 227057, and CCDC 227058, respectively.

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An efficient preparation of novel 5-fluoropyrazolin-3-one derivatives from α-trifluoromethylated α-arylacetates

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Abstract—The reactions of α-trifluoromethylated α-arylacetates **1** with 3 equiv of hydrazine, methylhydrazine or benzylhydrazine in 1,4-dioxane at reflux for 24 h afforded the corresponding 5-fluoropyrazolin-3-one derivatives **3a**–**m** in high yields. Similarly, treatment of **1** with 3 equiv of $PhNLiNH_2$ in THF at −78 °C, followed by warming to room temperature, resulted in the formation of **3n**–**s** in high yields.

1. Introduction

In recent years, the fluorinated pyrazole derivatives have attracted much attention because of their application to pharmaceuticals and agrochemicals.[1] In spite of their importance in these areas, methodology for the preparation of fluorinated pyrazole derivatives has been quite limited. Most of these methods are focused on the synthesis of 4-fluoropyrazoles,[2] whereas only several methods for the preparation of 5-fluoropyrazoles[3] have been reported in a previous literature. In particular, there have been no reports on the synthesis of 5-fluoropyrazolin-3-ones, which are the tautomers of 5-fluoro-3-hydroxypyrazoles and are useful synthetic intermediates to introduce another functionality at the 3-position. 5-Fluoropyrazoles are prepared in very low yields by the Balz-Schiemann type fluorination of the corresponding 5-aminopyrazoles.[3a] The electrofluorination of 1-methylpyrazole-4-carboxylate derivatives with poly-(hydrogen fluoride)-pyridine-triethylamine complex also affords the corresponding 1-methyl-5-fluoropyrazole-4-carboxylate derivatives in low yields.[3b] Recently, Ichikawa et al., accomplished the facile and high-yield preparation of 5-fluoropyrazoles from the reaction of 2,2-difluorovinyl ketones[4] with monosubstituted hydrazines as a kind of bifunctional nucleophiles.[3c] An efficient synthetic development of 2,2-difluorovinyl ketones plays a crucial role in the synthesis of 5-fluoropyrazoles. It can be supposed that 2,2-difluorovinyl esters will react with bifunctional nucleophiles in a similar manner to 2,2-difluorovinyl ketones, to give 5-fluoropyrazolin-3-ones. Although several methods for the preparation of 2,2-difluorovinyl esters have been reported previously,[5] most methods suffer from low-yield preparation, tedious procedure and lack of generalization. These synthetic limitations may originate from the hydrolytic instability of 2,2-difluorovinyl esters.[5d] Therefore, the use of precursors to 2,2-difluorovinyl esters, in which 2,2-difluorovinyl esters will be generated in solution, may overcome the limitations caused from the use of 2,2-difluorovinyl esters. In this paper, we wish to describe an efficient method for the preparation of novel 5-fluoropyrazolin-3-ones from the reaction of α-trifluoromethylated α-arylacetates **1** with bifunctional nucleophiles such as monosubstituted hydrazines.

2. Results and discussion

Although the starting materials **1** were previously prepared via several methods,[6] we developed an efficient approach to **1** through the reaction of β,β-difluoro-α-trifluoromethylstyrene with 3 equiv. of sodium methoxide.[7] Initially, we tried to synthesize 2,2-difluorovinyl esters **2** from **1** and then we were going to utilize these compounds for preparing 5-fluoropyrazolin-3-ones **3** via the reaction with hydrazine derivatives. However, **2** was obtained from **1** in only 40–50% yield even under the optimized conditions using the base such as sodium hydride. The use of other bases did not improve the yield at all. We presumed that the starting material **1** might be in equilibrium with **2** in the presence of amine base such as hydrazine derivatives and thus **2** could further react with excess hydrazine derivatives. Therefore, we performed the reaction of **1a** with 3 equiv of

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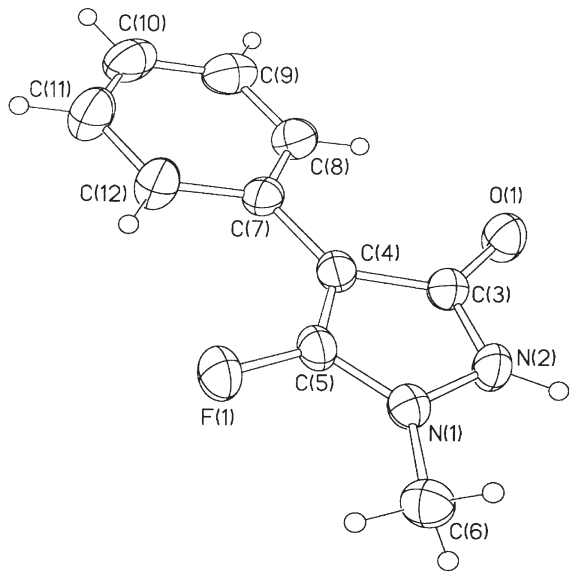
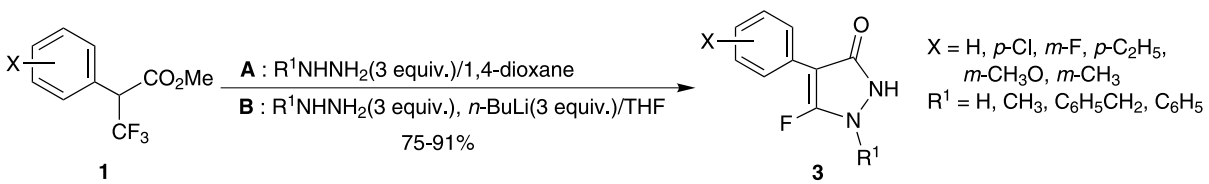


Figure 1. ORTEP representation of **3c** at the 50% probability level. Selected bond lengths (Å) and angles (°): F1–C5 1.329(3), O1–C3 1.341(3), N1–C5 1.320(3), N1–N2 1.366(3), N1–C6 1.445(3), N2–C3 1.317(3), N2–H2A 0.8600, C3–C4 1.417(3), C4–C5 1.371(4), C4–C7 1.466(3); C5–N1–N2 108.7(2), C5–N1–C6 130.0(2), N2–N1–C6 121.34(19), C3–N2–N1 105.7(2), C3–N2–H2A 127.2, N1–N2–H2A 127.2, N2–C3–O1 121.1(2), N2–C3–C4 112.8(2), O1–C3–C4 126.0(2), C5–C4–C3 100.5(2), N1–C5–F1 118.0(2), N1–C5–C4 129.7(2), F1–C5–C4 129.7(2).

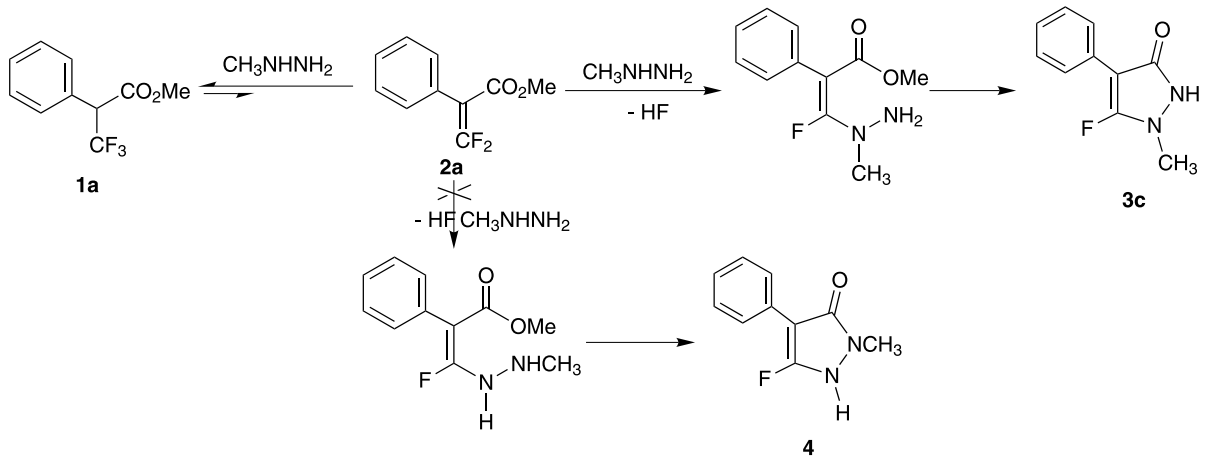
methylhydrazine to give 5-fluoro-1-methylpyrazolin-3-one **3c** under several reaction conditions. The choice of solvent and reaction temperature was found to be quite important to obtain **3c** in good yields. The reactions in solvents, such as CH_3CN, THF, DMSO and MeOH, at reflux temperatures for 24 h resulted in the formation of **3c** in low yields (50–60%), while the reaction refluxing in 1,4-dioxane for 24 h afforded **3c** in 87% yield. The other regioisomer **4**, 5-fluoro-2-methylpyrazoline-3-one was not detected. The complete regioselectivity in this reaction can be rationalized by the nucleophilic addition–elimination of more nucleophilic nitrogen bearing methyl group toward fluorinated vinyl carbon. When **1a** was treated with 1 equiv of methylhydrazine in this reaction, **3c** was obtained in 83% yield based on the 37% conversion of **1a**. The intermediate **2a** was not detected at all and the starting material **1a** was recovered in 63% yield. The structure of **3c** was confirmed by X-ray diffraction. The X-ray data[8] (Fig. 1) showed that the methyl group is attached to N-1 on the ring and one proton is attached to N-2, indicating that **3c** exists as pyrazolin-3-one instead of 3-hydroxypyrazole in a solid state. Other hydrazine derivatives such as hydrazine and benzylhydrazine were also reacted with **1a** to give **3a** and **3i** in 88 and 75% yields, respectively, but phenylhydrazine did not participate in the reaction with **1a** under the same reaction conditions. When **1a** was treated with lithium phenylhydrazine generated by using *n*-butyllithium, fluoropyrazoline derivative **3n** was formed in 76% yield. Substituents such as fluoro, chloro, ethyl, methyl and methoxy on the benzene ring of **1** did not affect the yield of **3**. The experimental results of these reactions are summarized in Table 1. The reaction mechanism involves the in situ formation of 2,2-difluorovinyl ester **2a** from **1a** in the presence of methylhydrazine and the fast addition–elimination reaction of **2a** with methylhydrazine, followed by cyclization to yield **3c** (Scheme 1). However, the reaction of α-trifluoromethylated α-alkylacetates **1f** with 3 equiv of methylhydrazine did not provide the corresponding alkyl-substituted fluoropyrazolinone **3t** under the same reaction

Table 1. Preparation of 5-fluoropyrazolin-3-one derivatives **3**

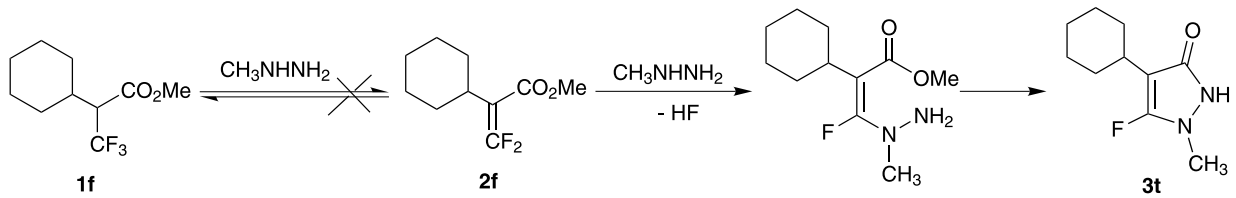


Compound **3**	X	R^1	Method	Conditions	Yield (%)[a]
3a	H	H	A	Reflux, 24 h	88
3b	*p*-C_2H_5	H	A	Reflux, 24 h	88
3c	H	CH_3	A	Reflux, 24 h	87
3d	*m*-F	CH_3	A	Reflux, 24 h	87
3e	*p*-Cl	CH_3	A	Reflux, 24 h	89
3f	*m*-CH_3	CH_3	A	Reflux, 24 h	84
3g	*p*-C_2H_5	CH_3	A	Reflux, 24 h	86
3h	*m*-CH_3O	CH_3	A	Reflux, 24 h	86
3i	H	$C_6H_5CH_2$	A	Reflux, 24 h	75
3j	*m*-F	$C_6H_5CH_2$	A	Reflux, 24 h	89
3k	*p*-Cl	$C_6H_5CH_2$	A	Reflux, 24 h	91
3l	*p*-C_2H_5	$C_6H_5CH_2$	A	Reflux, 24 h	90
3m	*m*-CH_3O	$C_6H_5CH_2$	A	Reflux, 24 h	90
3n	H	C_6H_5	B	−78 °C, 1 h→rt	76
3o	*m*-F	C_6H_5	B	−78 °C, 1 h→rt	87
3p	*p*-Cl	C_6H_5	B	−78 °C, 1 h→rt	90
3q	*m*-CH_3	C_6H_5	B	−78 °C, 1 h→rt	82
3r	*p*-C_2H_5	C_6H_5	B	−78 °C, 1 h→rt	86
3s	*m*-CH_3O	C_6H_5	B	−78 °C, 1 h→rt	86

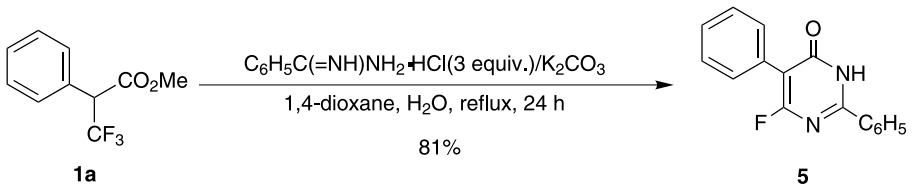
[a] Isolated yield.



Scheme 1.



Scheme 2.



Scheme 3.

conditions (Scheme 2). It is postulated that the formation of 2,2-difluorovinyl ester **2f** in situ from **1f** in the presence of methylhydrazine did not occur at all, since **2f**,[9] prepared from the reaction of methyl 2-oxo-2-cyclohexylethanoate[10] with dibromodifluoromethane, triphenylphosphine and zinc,[11] was easily reacted with 2 equiv of methylhydrazine to give **3t** in 75% yield. The treatment of **1a** with 3 equiv of benzamidine under the similar reaction conditions resulted in the formation of 6-fluoro-2,5-diphenylpyrimidin-4-one (**5**) in 81% yield (Scheme 3).

3. Conclusions

In summary, we have developed a facile and efficient procedure for the direct preparation of novel 5-fluoropyrazolin-3-one derivatives from α-trifluoromethylated α-arylacetates, which are in equilibrium with 2,2-difluorovinyl esters in the presence of amine base such as hydrazine derivatives. However, α-trifluoromethylated α-alkylacetates did not undergo the similar reaction to give 3-fluoropyrazolin-5-one derivatives. The reaction of α-trifluoromethylated α-arylacetates with benzamidine afforded the corresponding 6-fluoropyrimidin-4-one.

4. Experimental

4.1. General

^{1}H NMR was recorded on a 300 MHz Bruker AUANCE 300 NMR spectrometer with tetramethylsilane (TMS) as an internal standard and ^{19}F NMR was recorded on a 100 MHz Bruker AC-100F NMR spectrometer with $CFCl_3$ as an internal standard. All chemical shifts (δ) are expressed in parts per million and coupling constants (J) are given in Hertz. Mass spectra were obtained by using Shimadzu QP 5050 GC/MS (EI, 70 eV). Infrared spectra were determined on a Mattson Genesis II series FT high resolution spectrophotometer. Melting points were determined in open capillary tubes and are uncorrected.

Commercially available reagents were purchased from Aldrich, Lancaster, Tokyo Kasei and Fluorochem. All solvents were dried by general purification methods.

4.2. General procedure for the preparation of 5-fluoropyrazolin-3-one derivatives (Method A)

A 25 mL two-necked round-bottom flask equipped with a magnetic stirrer bar, a septum and reflux condenser

connected to an argon source was charged with **1** (1.0 mmol) and 1,4-dioxane (10 mL), and then hydrazine derivative (3.0 mmol) was added into the mixture. After being heated to reflux for 24 h, the reaction mixture was extracted twice with ethyl acetate. The ethyl acetate extracts were dried over anhydrous $MgSO_4$ and chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate (1:1) provided 5-fluoropyrazolin-3-one derivative.

4.2.1. 5-Fluoro-4-phenylpyrazolin-3-one (3a). The reaction of methyl 3,3,3-trifluoro-2-phenylpropanonate (0.218 g, 1.0 mmol) with hydrazine (0.096 g, 3.0 mmol) according to the general procedure provided **3a** (0.157 g, 88%). **3a**: mp 206–207 °C; ^{1}H NMR ($CDCl_3$) δ 11.95 (bs, 1H), 7.67 (m, 3H), 7.30 (m, 2H), 7.12 (m, 1H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −125.86 (s, 1F); MS, *m*/*z* (relative intensity) 178 (M^+, 2), 160 (86), 104 (42), 89 (36), 77 (66), 63 (52), 51 (100); IR (KBr) 3270, 3055, 2973, 1609, 1550, 1443, 1368, 1274, 1162, 762, 699 cm^{-1}. Anal. Calcd for $C_9H_7FN_2O$: C, 60.67; H, 3.96; N, 15.72. Found: C, 60.49; H, 3.94; N, 15.68.

4.2.2. 4-(*p*-Ethylphenyl)-5-fluoropyrazolin-3-one (3b). The reaction of methyl 2-(*p*-ethylphenyl)-3,3,3-trifluoropropanoate (0.246 g, 1.0 mmol) with hydrazine (0.096 g, 3.0 mmol) according to the general procedure provided **3b** (0.181 g, 88%). **3b**: mp 184–185 °C; ^{1}H NMR ($CDCl_3$) δ 11.97 (bs, 1H), 7.61 (s, 1H), 7.58 (m, 2H), 7.14 (m, 2H), 2.61 (q, J=7.6 Hz, 2H), 1.22 (t, J=7.6 Hz, 3H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −125.61 (s, 1F); MS, *m*/*z* (relative intensity) 206 (M^+, 1), 188 (38), 173 (100), 115 (14), 77 (23), 62 (18), 51 (32); IR (KBr) 3282, 3060, 2963, 1589, 1518, 1415, 1274, 1160, 1010, 830, 696 cm^{-1}. Anal. Calcd for $C_{11}H_{11}FN_2O$: C, 64.07; H, 5.38; N, 13.58. Found: C, 63.91; H, 5.33; N, 13.50.

4.2.3. 5-Fluoro-1-methyl-4-phenylpyrazolin-3-one (3c). The reaction of methyl 3,3,3-trifluoro-2-phenylpropanoate (0.218 g, 1.0 mmol) with methylhydrazine (0.138 g, 3.0 mmol) according to the general procedure provided **3c** (0.157 g, 87%). **3c**: mp 182–183 °C; ^{1}H NMR ($CDCl_3$) δ 12.03 (bs, 1H), 7.67 (m, 2H), 7.34 (m, 2H), 7.14(m, 1H), 3.60 (s, 3H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −129.96 (s, 1F); MS, *m*/*z* (relative intensity) 192 (M^+, 92), 134 (17), 120 (21), 104 (100), 96 (36), 77 (31), 61 (31), 51 (64), 43 (70); IR (KBr) 3054, 2947, 1624, 1512, 1440, 1371, 1291, 1036, 919, 768, 695 cm^{-1}. Anal. Calcd for $C_{10}H_9FN_2O$: C, 62.50; H, 4.72; N, 14.58. Found: C, 62.35; H, 4.67; N, 14.51.

4.2.4. 5-Fluoro-4-(*m*-fluorophenyl)-1-methylpyrazolin-3-one (3d). The reaction of methyl 3,3,3-trifluoro-2-(*m*-fluorophenyl)propanoate (0.236 g, 1.0 mmol) with methylhydrazine (0.138 g, 3.0 mmol) according to the general procedure provided **3d** (0.183 g, 87%). **3d**: mp 194–195 °C; ^{1}H NMR ($CDCl_3$) δ 11.99 (bs, 1H), 7.45 (m, 2H), 7.29 (m, 1H), 6.83 (m, 1H), 3.59 (s, 3H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −113.85 (s, 1F), −128.82 (s, 1F); MS, *m*/*z* (relative intensity) 210 (M^+, 100), 153 (13), 138 (17), 122 (65), 105 (34), 95 (20), 81 (21), 75 (25), 61 (53), 57 (29), 43 (96); IR (KBr) 3040, 2969, 1622, 1582, 1517, 1430, 1367, 1311, 1268, 1201, 929, 866, 792, 687 cm^{-1}. Anal. Calcd for $C_{10}H_8F_2N_2O$: C, 57.15; H, 3.84; N, 13.33. Found: C, 56.98; H, 3.82; N, 13.38.

4.2.5. 4-(*p*-Chlorophenyl)-5-fluoro-1-methylpyrazolin-3-one (3e). The reaction of methyl 2-(*p*-chlorophenyl)-3,3,3-trifluoropropanoate (0.253 g, 1.0 mmol) with methylhydrazine (0.138 g, 3.0 mmol) according to the general procedure provided **3e** (0.201 g, 89%). **3e**: mp 193–194 °C; ^{1}H NMR ($CDCl_3$) δ 12.01 (bs, 1H), 7.62 (m, 2H), 7.28 (m, 2H), 3.59 (s, 3H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −129.35 (s, 1F); MS, *m*/*z* (relative intensity) 228 (M^++2, 24), 226 (M^+, 70), 140 (13), 138 (41), 113 (26), 99 (21), 81 (22), 74 (44), 61 (70), 43 (100); IR (KBr) 3040, 2949, 1632, 1515, 1369, 1290, 1204, 1088, 1010, 921, 839, 674 cm^{-1}. Anal. Calcd for $C_{10}H_8ClFN_2O$: C, 53.00; H, 3.56; N, 12.36. Found: C, 53.21; H, 3.59; N, 12.31.

4.2.6. 5-Fluoro-1-methyl-4-(*m*-methylphenyl)pyrazolin-3-one (3f). The reaction of methyl 3,3,3-trifluoro-2-(*m*-methylphenyl)propanoate (0.232 g, 1.0 mmol) with methylhydrazine (0.138 g, 3.0 mmol) according to the general procedure provided **3f** (0.173 g, 84%). **3f**: mp 161–162 °C; ^{1}H NMR ($CDCl_3$) δ 11.90 (bs, 1H), 7.51 (m, 2H), 7.28 (m, 1H), 7.04 (m, 1H), 3.65 (s, 3H), 2.39 (s, 3H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −130.01 (s, 1F); MS, *m*/*z* (relative intensity) 206 (M^+, 72), 148 (16), 133 (36), 118 (69), 103 (23), 91 (17), 81 (16), 77 (17), 63 (24), 43 (100); IR (KBr) 3045, 2969, 1626, 1518, 1365, 1293, 1076, 845, 787, 694 cm^{-1}. Anal. Calcd for $C_{11}H_{11}FN_2O$: C, 64.07; H, 5.38; N, 13.58. Found: C, 63.85; H, 5.31; N, 13.64.

4.2.7. 4-(*p*-Ethylphenyl)-5-fluoro-1-methylpyrazolin-3-one (3g). The reaction of methyl 2-(*p*-ethylphenyl)-3,3,3-trifluoropropanoate (0.246 g, 1.0 mmol) with methylhydrazine (0.138 g, 3.0 mmol) according to the general procedure provided **3g** (0.189 g, 86%). **3g**: mp 191–192 °C; ^{1}H NMR ($CDCl_3$) δ 12.03 (bs, 1H), 7.62 (m, 2H), 7.23 (m, 2H), 3.77 (s, 3H), 2.65 (q, J=7.6 Hz, 2H), 1.25 (t, J=7.6 Hz, 3H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −130.59 (s, 1F); MS, *m*/*z* (relative intensity) 220 (M^+, 60), 205 (100), 148 (37), 133 (39), 110 (17), 102 (24), 77 (20), 63 (21), 51 (38), 43 (99); IR (KBr) 3045, 2963, 2872, 1628, 1570, 1521, 1366, 1284, 921, 836, 698 cm^{-1}. Anal. Calcd for $C_{12}H_{13}FN_2O$: C, 65.44; H, 5.95; N, 12.72. Found: C, 65.32; H, 5.93; N, 12.67.

4.2.8. 5-Fluoro-4-(*m*-methoxyphenyl)-1-methylpyrazolin-3-one (3h). The reaction of methyl 3,3,3-trifluoro-2-(*m*-methoxyphenyl)propanoate (0.248 g, 1.0 mmol) with methylhydrazine (0.138 g, 3.0 mmol) according to the general procedure provided **3h** (0.191 g, 86%). **3h**: mp 146–147 °C; ^{1}H NMR ($CDCl_3$) δ 12.01 (bs, 1H), 7.28 (m, 3H), 6.77 (m, 1H), 3.84 (s, 3H), 3.64 (s, 3H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −129.45 (s, 1F); MS, *m*/*z* (relative intensity) 222 (M^+, 48), 134 (17), 107 (16), 77 (13), 57 (13), 51 (15), 43 (100); IR (KBr) 3030, 2943, 2843, 1624, 1579, 1536, 1433, 1365, 1292, 1223, 1033, 927, 840, 781, 689 cm^{-1}. Anal. Calcd for $C_{11}H_{11}FN_2O_2$: C, 59.46; H, 4.99; N, 12.61. Found: C, 59.69; H, 4.97; N, 12.49.

4.2.9. 1-Benzyl-5-fluoro-4-phenylpyrazolin-3-one (3i). The reaction of methyl 3,3,3-trifluoro-2-phenylpropanoate (0.218 g, 1.0 mmol) with benzylhydrazine (0.366 g,

3.0 mmol) according to the general procedure provided **3i** (0.201 g, 75%). **3i**: mp 140–141 °C; ^{1}H NMR ($CDCl_3$) δ 11.86 (bs, 1H), 7.69 (m, 2H), 7.40–7.10 (m, 8H), 5.05 (s, 2H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −129.54 (s, 1F); MS, *m/z* (relative intensity) 268 (M^+, 8), 190 (4), 91 (100), 65 (23), 51 (8); IR (KBr) 3032, 2960, 1628, 1515, 1440, 1363, 1264, 763, 696 cm^{-1}. Anal. Calcd for $C_{16}H_{13}FN_2O$: C, 71.63; H, 4.88; N, 10.44. Found: C, 71.45; H, 4.82; N, 10.51.

4.2.10. 1-Benzyl-5-fluoro-4-(*m*-fluorophenyl)pyrazolin-3-one (3j). The reaction of methyl 3,3,3-trifluoro-2-(*m*-fluorophenyl)propanoate (0.236 g, 1.0 mmol) with benzylhydrazine (0.366 g, 3.0 mmol) according to the general procedure provided **3j** (0.255 g, 89%). **3j**: mp 173–174 °C; ^{1}H NMR ($CDCl_3$) δ 11.92 (bs, 1H), 7.47–7.25 (m, 8H), 6.91 (m, 1H), 5.06 (s, 2H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −113.58 (s, 1F), −128.51 (s, 1F); MS, *m/z* (relative intensity) 286 (M^+, 6), 91 (100), 65 (22); IR (KBr) 3032, 2959, 1630, 1583, 1521, 1365, 1271, 1113, 852, 779, 717, 687 cm^{-1}. Anal. Calcd for $C_{16}H_{12}F_2N_2O$: C, 67.13; H, 4.23; N, 9.79. Found: C, 66.84; H, 4.20; N, 9.81.

4.2.11. 1-Benzyl-4-(*p*-chlorophenyl)-5-fluoropyrazolin-3-one (3k). The reaction of methyl 2-(*p*-chlorophenyl)-3,3,3-trifluoropropanoate (0.253 g, 1.0 mmol) with benzylhydrazine (0.366 g, 3.0 mmol) according to the general procedure provided **3k** (0.275 g, 91%). **3k**: mp 194–195 °C; ^{1}H NMR ($CDCl_3$) δ 11.97 (bs, 1H), 7.59 (m, 2H), 7.34 (m, 7H), 5.05 (s, 2H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −129.03 (s, 1F); MS, *m/z* (relative intensity) 304 (M^++2, 2), 302 (M^+, 6), 226 (1), 224 (3), 91 (100), 65 (24), 51 (6); IR (KBr) 3033, 2953, 1629, 1518, 1362, 1267, 1093, 1043, 832, 699 cm^{-1}. Anal. Calcd for $C_{16}H_{12}ClFN_2O$: C, 63.48; H, 4.00; N, 9.25. Found: C, 63.27; H, 3.99; N, 9.16.

4.2.12. 1-Benzyl-4-(*p*-ethylphenyl)-5-fluoropyrazolin-3-one (3l). The reaction of methyl 2-(*p*-ethylphenyl)-3,3,3-trifluoropropanoate (0.246 g, 1.0 mmol) with benzylhydrazine (0.366 g, 3.0 mmol) according to the general procedure provided **3l** (0.266 g, 90%). **3l**: mp 171–172 °C; ^{1}H NMR ($CDCl_3$) δ 11.97 (bs, 1H), 7.61 (m, 2H), 7.37–7.16 (m, 7H), 5.03 (s, 2H), 2.65 (q, J=7.6 Hz, 2H), 1.25 (t, J=7.6 Hz, 3H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −130.13 (s, 1F); MS, *m/z* (relative intensity) 296 (M^+, 9), 218 (4), 91 (100), 65 (22), 51 (5); IR (KBr) 3050, 2967, 2870, 1631, 1520, 1361, 1273, 921, 834, 696 cm^{-1}. Anal. Calcd for $C_{18}H_{17}FN_2O$: C, 72.96; H, 5.78; N, 9.45. Found: C, 72.71; H, 5.66; N, 9.51.

4.2.13. 1-Benzyl-5-fluoro-4-(*m*-methoxyphenyl)pyrazolin-3-one (3m). The reaction of methyl 3,3,3-trifluoro-2-(*m*-methoxyphenyl)propanoate (0.248 g, 1.0 mmol) with benzylhydrazine (0.366 g, 3.0 mmol) according to the general procedure provided **3m** (0.268 g, 90%). **3m**: mp 164–165 °C; ^{1}H NMR ($CDCl_3$) δ 12.02 (bs, 1H), 7.37–7.24 (m, 8H), 6.71 (m, 1H), 5.06 (s, 2H), 3.80 (s, 3H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −129.46 (s, 1F); MS, *m/z* (relative intensity) 298 (M^+, 8), 220 (3), 91 (100), 65 (24), 51 (6); IR (KBr) 3030, 2997, 2953, 2832, 1630, 1587, 1520, 1423, 1367, 1230, 1051, 836, 782, 719 cm^{-1}. Anal. Calcd for $C_{17}H_{15}FN_2O_2$: C, 68.45; H, 5.07; N, 9.39. Found: C, 68.17; H, 5.05; N, 9.30.

4.3. General procedure for the preparation of 5-fluoropyrazolin-3-one derivatives (Method B)

A 25 mL two-necked round-bottom flask equipped with a magnetic stirrer bar, a septum and reflux condenser connected to an argon source was charged with phenylhydrazine (0.324 g, 3.0 mmol) and THF (10 mL). *n*-BuLi (1.84 mL, 1.63 M in hexane, 3.0 mmol) was added into the mixture at −78 °C. After the mixture was stirred for 30 min, **1** (1.0 mmol) was added into the mixture. After the reaction mixture was stirred at −78 °C for 1 h, followed by warming to room temperature, the mixture was quenched with 2% HCl solution. Organic materials were extracted twice with ethyl acetate. The ethyl acetate extracts were dried over anhydrous $MgSO_4$ and chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate (1:1) provided 5-fluoropyrazolin-3-one derivative.

4.3.1. 5-Fluoro-1,4-diphenylpyrazolin-3-one (3n). The reaction of methyl 3,3,3-trifluoro-2-phenylpropanoate (0.218 g, 1.0 mmol) with lithium phenylhydrazine generated from the reaction of phenylhydrazine (0.324 g, 3.0 mmol) with *n*-BuLi (3.0 mmol) according to the general procedure provided **3n** (0.193 g, 76%). **3n**: mp 187–188 °C; ^{1}H NMR ($CDCl_3$) δ 11.97 (bs, 1H), 7.73 (m, 2H), 7.63 (m, 2H), 7.47–7.35 (m, 4H), 7.21 (m, 2H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −126.08 (s, 1F); MS, *m/z* (relative intensity) 254 (M^+, 51), 225 (7), 180 (6), 104 (26), 77 (100), 63 (12), 51 (56); IR (KBr) 3020, 2965, 1630, 1597, 1540, 1435, 1369, 1274, 1054, 856, 768, 687 cm^{-1}. Anal. Calcd for $C_{15}H_{11}FN_2O$: C, 70.86; H, 4.36; N, 11.02. Found: C, 70.58; H, 4.33; N, 11.11.

4.3.2. 5-Fluoro-4-(*m*-fluorophenyl)-1-phenylpyrazolin-3-one (3o). The reaction of methyl 3,3,3-trifluoro-2-(*m*-fluorophenyl)propanoate (0.236 g, 1.0 mmol) with lithium phenylhydrazine generated from the reaction of phenylhydrazine (0.324 g, 3.0 mmol) with *n*-BuLi (3.0 mmol) according to the general procedure provided **3o** (0.237 g, 87%). **3o**: mp 186–187 °C; ^{1}H NMR ($CDCl_3$) δ 11.99 (bs, 1H), 7.62–7.43 (m, 5H), 7.38–7.26 (m, 3H), 6.91 (m, 1H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −113.41 (s, 1F), −124.98 (s, 1F); MS, *m/z* (relative intensity) 272 (M^+, 48), 243 (13), 198 (18), 122 (10), 96 (12), 91 (12), 77 (100), 51 (54); IR (KBr) 3050, 2966, 1638, 1587, 1517, 1431, 1395, 1280, 1196, 842, 759, 687 cm^{-1}. Anal. Calcd for $C_{15}H_{10}F_2N_2O$: C, 66.18; H, 3.70; N, 10.29. Found: C, 66.40; H, 3.68; N, 10.35.

4.3.3. 4-(*p*-Chlorophenyl)-5-fluoro-1-phenylpyrazolin-3-one (3p). The reaction of methyl 2-(*p*-chlorophenyl)-3,3,3-trifluoropropanoate (0.253 g, 1.0 mmol) with lithium phenylhydrazine generated from the reaction of phenylhydrazine (0.324 g, 3.0 mmol) with *n*-BuLi (3.0 mmol) according to the general procedure provided **3p** (0.259 g, 90%). **3p**: mp 195–196 °C; ^{1}H NMR ($CDCl_3$) δ 12.01 (bs, 1H), 7.73 (m, 2H), 7.60 (m, 2H), 7.46 (m, 2H), 7.36–7.28 (m, 3H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −125.49 (s, 1F); MS, *m/z* (relative intensity) 290 (M^++2, 11), 288 (M^+, 34), 77 (100), 63 (11), 51 (72); IR (KBr) 3040, 2968, 1641, 1599, 1550, 1517, 1495, 1449, 1372, 1278, 1096, 822, 758, 684 cm^{-1}. Anal. Calcd for $C_{15}H_{10}ClFN_2O$: C, 62.40; H, 3.49; N, 9.70. Found: C, 62.29; H, 3.45; N, 9.78.

4.3.4. 5-Fluoro-4-(*m*-methylphenyl)-1-phenylpyrazolin-3-one (3q). The reaction of methyl 3,3,3-trifluoro-2-(*m*-methylphenyl)propanoate (0.232 g, 1.0 mmol) with lithium phenylhydrazine generated from the reaction of phenylhydrazine (0.324 g, 3.0 mmol) with *n*-BuLi (3.0 mmol) according to the general procedure provided **3q** (0.220 g, 82%). **3q**: mp 174–175 °C; ^{1}H NMR ($CDCl_3$) δ 11.94 (bs, 1H), 7.62 (m, 2H), 7.50 (m, 4H), 7.29 (m, 2H), 7.05 (m, 1H), 2.38 (s, 3H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −126.03 (s, 1F); MS, *m*/*z* (relative intensity) 268 (M^+, 66), 239 (8), 194 (7), 133 (13), 118 (19), 91 (16), 77 (100), 65 (15), 51 (75); IR (KBr) 3028, 2968, 2870, 1638, 1598, 1502, 1447, 1378, 1279, 831, 781, 692 cm^{-1}. Anal. Calcd for $C_{16}H_{13}FN_2O$: C, 71.63; H, 4.88; N, 10.44. Found: C, 71.35; H, 4.81; N, 10.54.

4.3.5. 4-(*p*-Ethylphenyl)-5-fluoro-1-phenylpyrazolin-3-one (3r). The reaction of methyl 2-(*p*-ethylphenyl)-3,3,3-trifluoropropanoate (0.246 g, 1.0 mmol) with lithium phenylhydrazine generated from the reaction of phenylhydrazine (0.324 g, 3.0 mmol) with *n*-BuLi (3.0 mmol) according to the general procedure provided **3r** (0.243 g, 86%). **3r**: mp 160–161 °C; ^{1}H NMR ($CDCl_3$) δ 11.97 (bs, 1H), 7.67 (m, 2H), 7.59–7.47 (m, 4H), 7.36 (m, 1H), 7.23 (m, 2H), 2.66 (q, J=7.6 Hz, 2H), 1.26 (t, J=7.6 Hz, 3H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −126.58 (s, 1F); MS, *m*/*z* (relative intensity) 282 (M^+, 100), 267 (63), 210 (7), 141 (11), 133 (25), 116 (11), 104 (8), 77 (55), 51 (59); IR (KBr) 3050, 2966, 2865, 1636, 1597, 1538, 1514, 1371, 1276, 1071, 836, 765, 689 cm^{-1}. Anal. Calcd for $C_{17}H_{15}FN_2O$: C, 72.33; H, 5.36; N, 9.92. Found: C, 72.59; H, 5.40; N, 9.84.

4.3.6. 5-Fluoro-4-(*m*-methoxyphenyl)-1-phenylpyrazolin-3-one (3s). The reaction of methyl 3,3,3-trifluoro-2-(*m*-methoxyphenyl)propanoate (0.248 g, 1.0 mmol) with lithium phenylhydrazine generated from the reaction of phenylhydrazine (0.324 g, 3.0 mmol) with *n*-BuLi (3.0 mmol) according to the general procedure provided **3s** (0.244 g, 86%). **3s**: mp 152–153 °C; ^{1}H NMR ($CDCl_3$) δ 12.08 (bs, 1H), 7.59–7.46 (m, 4H), 7.37–7.28 (m, 4H), 6.81 (m, 1H), 3.82 (s, 3H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −125.56 (s, 1F); MS, *m*/*z* (relative intensity) 284 (M^+, 90), 221 (5), 142 (19), 134 (25), 107 (13), 77 (82), 63 (11), 51 (100), 39 (53); IR (KBr) 3045, 2994, 2834, 1637, 1595, 1517, 1433, 1372, 1225, 1051, 830, 769, 688 cm^{-1}. Anal. Calcd for $C_{16}H_{13}FN_2O_2$: C, 67.60; H, 4.61; N, 9.85. Found: C, 67.31; H, 4.66; N, 9.78.

4.3.7. Preparation of 4-cyclohexyl-5-fluoro-1-methylpyrazolin-3-one (3t). A 25 mL two-necked round-bottom flask equipped with a magnetic stirrer bar, a septum and reflux condenser connected to an argon source was charged with **2f** (0.190 g, 1.0 mmol) and 1,4-dioxane (10 mL), and then methylhydrazine derivative (0.092 g, 2.0 mmol) was added into the mixture. After stirring at room temperature for 1 h, the reaction mixture was extracted twice with ethyl acetate. The ethyl acetate extracts were dried over anhydrous $MgSO_4$ and chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate (1:1) provided **3t** (0.149 g, 75%). **3t**: mp 190–191 °C; ^{1}H NMR ($CDCl_3$) δ 11.94 (bs, 1H), 3.50 (s, 3H), 2.39 (m, 1H), 1.85–1.75 (m, 4H), 1.58–1.24 (m, 6H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −133.07 (s, 1F); MS, *m*/*z* (relative intensity) 198 (M^+, 100), 155 (66), 142 (23), 129 (49), 111 (12), 43 (19); IR (KBr) 2927, 2854, 1641, 1549, 1516, 1463, 1347, 1230, 818 cm^{-1}. Anal. Calcd for $C_{10}H_{15}FN_2O$: C, 60.59; H, 7.63; N, 14.13. Found: C, 60.28; H, 7.69; N, 14.25.

4.3.8. Preparation of 6-fluoro-2,5-diphenylpyrimidin-4-one (5). To a mixture of methyl 3,3,3-trifluoro-2-phenylpropanoate (0.218 g, 1.0 mmol) and benzamidine hydrochloride (0.467 g, 3.0 mmol) in 75% 1,4-dioxane aqueous solution (10 mL) was slowly added K_2CO_3 (0.207 g, 1.5 mmol) and the mixture was heated to reflux for 24 h. After the solvent was evaporated, organic materials were extracted with ethyl acetate three times. The ethyl acetate solution was dried over anhydrous $MgSO_4$ and chromatographed on SiO_2 column. Elution with a mixture of hexane and ethyl acetate (1:2) provided **5** (0.215 g, 81%). **5**: mp 204–206 °C; ^{1}H NMR ($CDCl_3$) δ 13.20 (bs, 1H), 8.20 (m, 2H), 7.60–7.30 (m, 8H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −74.55 (s, 1F); MS, *m*/*z* (relative intensity) 266 (M^+, 100), 238 (8), 133 (9), 115 (10), 104 (48), 77 (20); IR (KBr) 3060, 1659, 1606, 1512, 1418, 1361, 1061, 767, 693 cm^{-1}. Anal. Calcd for $C_{16}H_{11}FN_2O$: C, 72.17; H, 4.16; N, 10.52. Found: C, 72.29; H, 4.19; N, 10.38.

Acknowledgements

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8. Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 239630.
9. **2f**: oil; ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H), 2.47–2.37 (m, 1H), 1.80–1.10 (m, 10H); ^{19}F NMR ($CDCl_3$, internal standard $CFCl_3$) δ −70.40 (d, J=5.9 Hz, 1F), −75.43 (d, J=5.1 Hz, 1F); MS, m/z (relative intensity) 204 (M^+, 4), 135 (18), 111 (14), 83 (61), 55 (98), 40 (100); IR (neat) 2930, 2855, 1742, 1438, 1340, 1295, 1160 cm^{-1}. Anal. Calcd for $C_{10}H_{14}F_2O_2$: C, 58.82; H, 6.91. Found: C, 58.69; H, 6.87.
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24,24-Dimethylvitamin D_3-26,23-lactones and their 2α-functionalized analogues as highly potent VDR antagonists☆

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Abstract—Novel vitamin D receptor (VDR) antagonists, 24,24-dimethyl-1α-hydroxyvitamin D_3-26,23-lactones (**8** and **9**) and their C2α functionalized analogues (**8a**–**c** and **9a**–**c**) were efficiently synthesized and their biological activities were evaluated. The construction of vitamin D_3 triene skeleton was achieved by palladium-catalyzed alkenylative cyclization of A-ring precursor enyne (**22** and **22a**–**c**) with CD-ring bromoolefin having a 24,24-dimethyl-α-methylene-γ-lactone unit on the side chain (**13** and **14**). The CD-ring precursors **13** and **14** were prepared by using chromium-mediated allylation of the aldehyde **10** derived from vitamin D_2. On the other hand, the A-ring enyne having 2α-(3-hydroxypropyl) group (**22b**) was newly synthesized from epoxide **15** using regio- and stereoselective alkylation methodology. The potency of the antagonistic activity of the newly designed analogues (**8** and **9**) increased up to 12 times that of TEI-9647 (**2**). Furthermore, introduction of the three motifs, that is, a methyl (**8a** and **9a**), an ω-hydroxypropyl (**8b** and **9b**) or an ω-hydroxypropoxyl group (**8c** and **9c**) into the C2α position of **8** and **9**, respectively, resulted in remarkable enhancement, up to 89 times, of the antagonistic activity on VDR.

1. Introduction

1α,25-Dihydroxyvitamin D_3 (**1**), which is a hormonally active form of vitamin D, exerts various biological profiles including calcium and phosphorous homeostasis, cell proliferation and differentiation of various types of tumor cells, and immune reaction.[1,2] Most of the biological responses of **1** are mediated by its specific receptor, vitamin D receptor (VDR), which is a member of the nuclear receptor superfamily and acts as a ligand-dependent gene transcription factor with coactivators.[3,4] Recently, we have synthesized several 1α,25-dihydroxyvitamin D_3 analogues, which systematically introduced an alkyl, ω-hydroxyalkyl, and ω-hydroxyalkoxyl group into the C2α position of **1**.[5] Some of these 2α-modified vitamin D_3 analogues exhibited unique biological activities with potent agonistic activity.[6,7] In particular, introduction of the 2α-methyl (**1a**),[5a,b] 2α-(3-hydroxypropyl) (**1b**),[5c,d] and 2α-(3-hydroxypropoxy) (**1c**)[5e] groups showed 2- to 4-fold higher binding affinity to the bovine thymus VDR relative to **1** (Fig. 1).

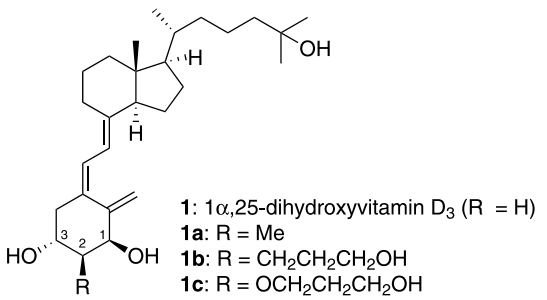

Figure 1. Structures of 1α,25-dihydroxyvitamin D_3 (**1**) and its C2α-modified analogues **1a**–**c**.

In 1999, the first VDR antagonists, 25-dehydro-1α-hydroxyvitamin D_3-26,23-lactones, TEI-9647 (**2**) and TEI-9648 (**3**) were discovered during the course of studies on the side-chain modification of the 1α,25-dihydroxyvitamin D_3-26,23-lactone metabolite[8] derived from **1** (Fig. 2).[9,10] Both vitamin D_3 analogues **2** and **3** specifically antagonize the VDR-mediated genomic action of **1**.[11] That is, **2** and **3** inhibit differentiation of human leukemia cells (HL-60 cells)[9a] as well as 25-hydroxyvitamin D_3-24-hydroxylase

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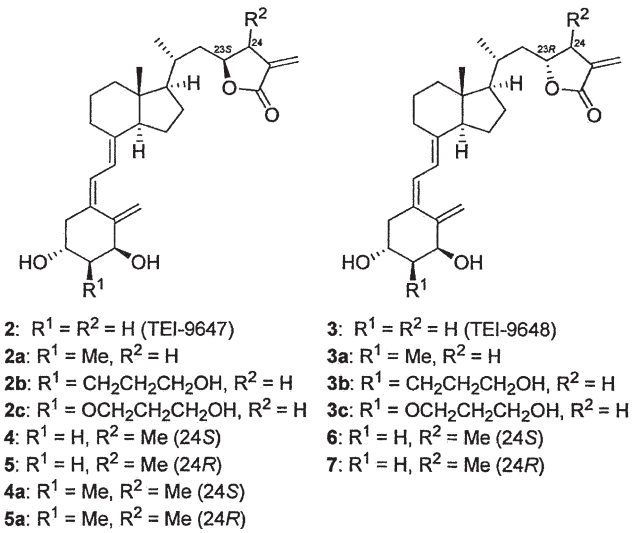


Figure 2. Structures of 1α-hydroxyvitamin D_3-26,23-lactones (TEI-9647: **2** and TEI-9648: **3**), their 2α-modified (**2a**–**c** and **3a**–**c**), 24-modified (**4**–**7**), and 2,24-double modified analogues (**4a** and **5a**).

gene expression in human osteosarcoma cells[9b] and in HL-60 cells[9d] induced by **1**. Furthermore, TEI-9647 (**2**) antagonizes the genomic-mediated calcium metabolism regulated by **1** in vivo in rat.[9e] The interesting biological profiles of the vitamin D_3 analogues **2** and **3** prompted us to investigate structure–activity relationship of the vitamin D_3 lactones from the standpoint of developing more potent anti-D molecules.

Quite recently, we found that some pertinent modifications of **2** and **3** enhanced their biological activities.[12] Namely, introduction of the above three motifs, that is, the methyl, the 3-hydroxypropyl or the 3-hydroxypropoxy group, into the C2α position of **2** and **3** (**2a**–**c** and **3a**–**c**) raised the potential of the antagonistic activity up to 30-fold.[12a] On the other hand, it was also found that the VDR binding affinity and antagonistic activity of **2** and **3** were affected by the structure including stereochemistry of the lactone part (**4**–**7**).[12b] Especially, introducing the methyl group into the C24 position on the lactone ring improved the antagonistic activity to be up to 2.5-fold more potent than that of TEI-9647 (**2**). Furthermore, we disclosed that simultaneous double functionalization of the C2α and C24 positions of **2** (**4a** and **5a**) remarkably increased the antagonistic activity of **2** to 62-fold stronger than that of the original **2**.

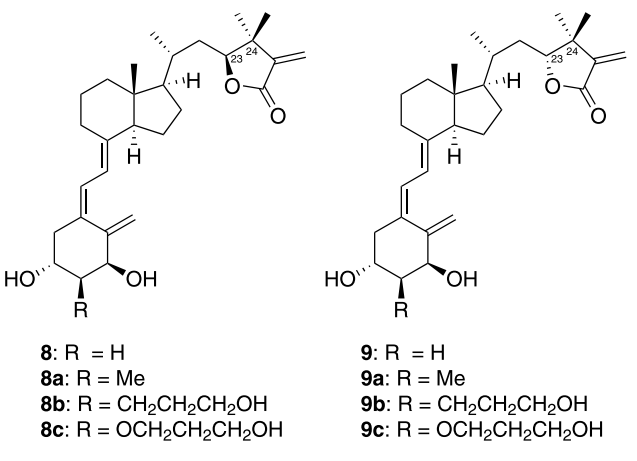


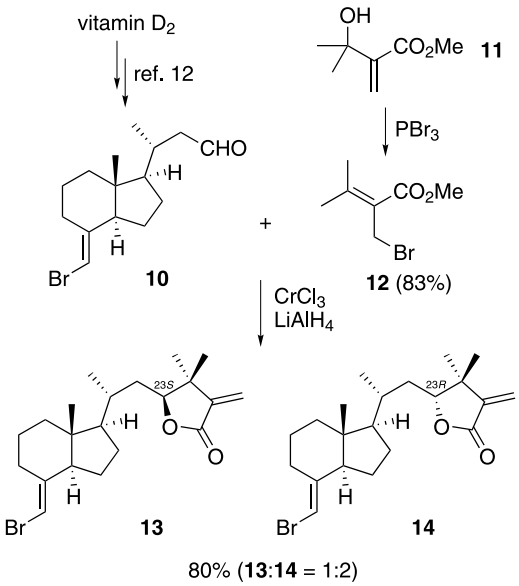
Figure 3. 24,24-Dimethylvitamin D_3 lactones (**8** and **9**) and their 2α-modified analogues (**8a**–**c** and **9a**–**c**).

On the basis of our previous results, we newly designed novel vitamin D_3 lactone analogues **8** and **9**, which have the dimethyl groups at the C24 position, to investigate further structure–activity relationships on the lactone core structure (Fig. 3). From the point of manufacturing new drug candidates, reduction of the number of chiral centers is favorable. Moreover, we expected that biological activity of the vitamin D_3 lactone analogues would be enhanced by introduction of the above three motifs, that is, the methyl (**8a** and **9a**), the 3-hydroxypropyl (**8b** and **9b**) and the 3-hydroxypropoxyl group (**8c** and **9c**) as in our previous studies.[6,7,12] Here, we report the synthesis and biological evaluation of the novel 24,24-dimethylvitamin D_3-26,23-lactones and their 2α-modified analogues.

2. Results

2.1. Synthesis and biological evaluation of 24,24-dimethylvitamin D_3-26,23-lactones

For the synthesis of the 24,24-dimethylvitamin D_3 lactone analogues, we utilized the Pd-catalyzed A-ring/CD-ring connective strategy.[13] First of all, we prepared the CD-ring precursors having the 24,24-dimethyl-α-methylene-γ-lactone side chain via the low-valent Cr-mediated allylation–lactonization process[14] (Scheme 1). The aldehyde **10** was synthesized from vitamin D_2,[12] and the alcohol **11**[15] was treated with PBr_3 to give allylic bromide **12** in 83% yield. When aldehyde **10** reacted with **12** in the presence of the Cr(II) complex generated from $CrCl_3$ and $LiAlH_4$, two hydrindan derivatives **13** and **14**, which were diastereomers with respect to the C23 position on the lactone ring (based on steroidal numbering), were obtained in 80% yield in the ratio of 1 to 2. The absolute stereochemistries at C23 position



Scheme 1. Preparation of CD-ring precursors.

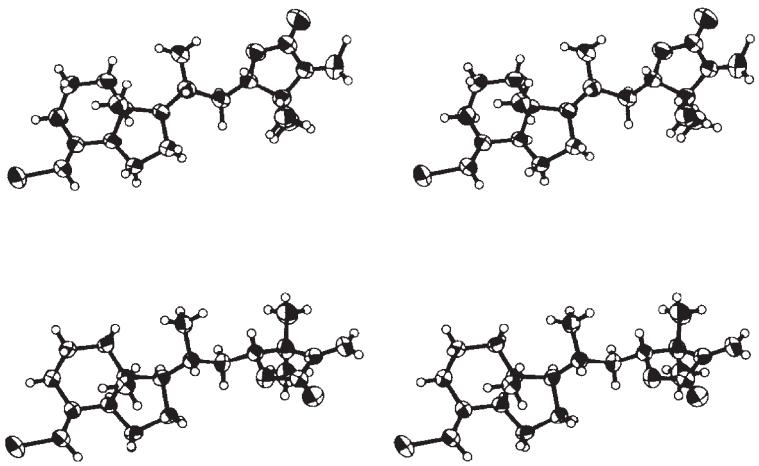
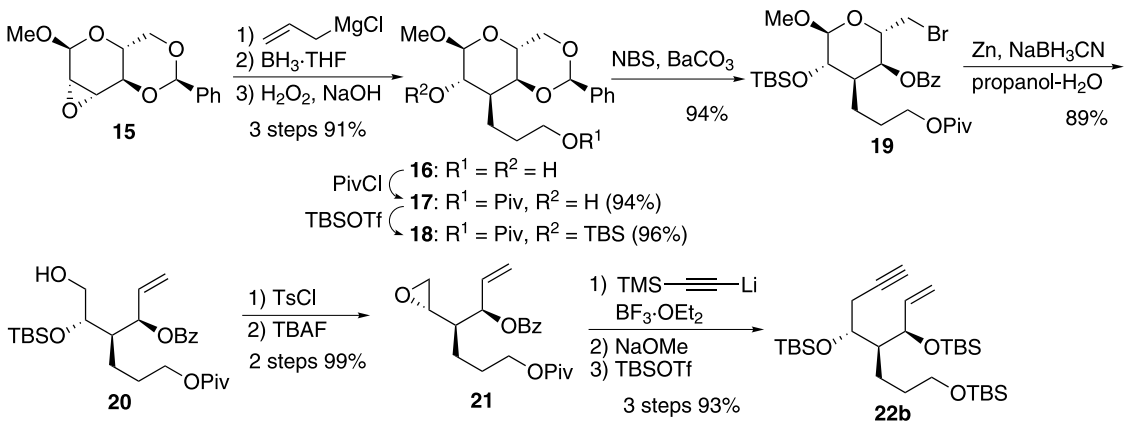


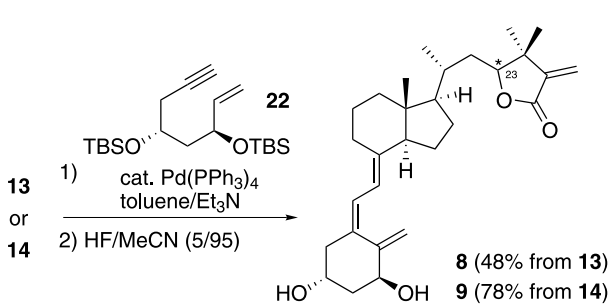
Figure 4. Stereoscopic views of the crystal structure of compounds **13** (upper) and **14** (lower). The thermal displacement parameters are drawn at both 50% probability (**13** and **14**).



Scheme 2. Improved synthesis of A-ring precursor having 3-hydroxypropyl side chain **22b**.

of **13** and **14** were confirmed by X-ray structual determination, respectively (Fig. 4).[16]

Next, the A-ring precursor having the ω-siloxypropyl side-chain **22b** was synthesized in an improved manner from known epoxide **15**[17] by using our regio- and stereoselective alkylation methodology reported previously[5e,18] (Scheme 2). The epoxide **15** was treated with allyl magnesium chloride[19] followed by hydroboration–oxidation to give diol **16** in 3 steps in 91% yield. Protection of two hydroxyl groups with Piv and TBS provided **18**, which was then converted into bromide **19** via radical benzylidene acetal cleavage by NBS. Pyranose ring-opening reaction of **19** with activated-zinc in the presence of $NaBH_3CN$ gave **20** in 89% yield. The alcohol **20** reacted with TsCl, then the resulting sulfonate derivative was treated with TBAF to afford epoxide **21**. Introduction of the TMS-ethynyl group into **21** followed by deprotection under basic conditions gave a triol. The resulting triol was protected by TBS groups to provide the desired A-ring precursor **22b** in totally 12 steps from epoxide **15**.[20]



Scheme 3. Synthesis of 24,24-dimethylvitamin D_3-26,23-lactones **8** and **9**.

Construction of the vitamin D_3 triene unit was achieved by Pd-catalyzed alkenylative cyclization of **22**[5a] with **13** or **14**;

Table 1. Biological activities of 24,24-dimethylvitamin D_3 lactones **8** and **9**

Compounds	VDR binding affinity[a]	Antagonistic activity[b] (IC_{50}, nM)
1	100	—
TEI-9647 (**2**)	12	8.3
4[c]	29	3.7
5[c]	22	3.2
8	37	0.71
TEI-9648 (**3**)	7	111.6
6[c]	12	160.0
7[c]	5	51.0
9	18	51.5

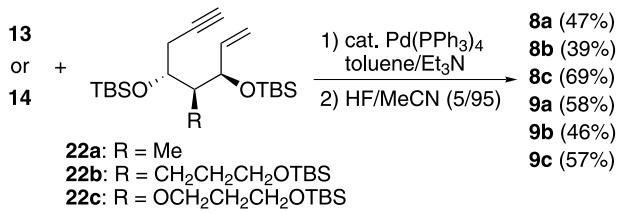
[a] The potency of **1** is normalized to 100.
[b] Antagonistic activity was assessed in terms of IC_{50} for differentiation of HL-60 cells induced by 10 nM of **1**.
[c] See: Ref. 12b.

and then deprotection of the silyl groups by HF gave the desired 24,24-dimethylvitamin D_3 lactones **8** and **9** (Scheme 3).

First, the receptor binding affinity and antagonistic activity of 24,24-dimethylvitamin D_3 lactones **8** and **9** were evaluated to see the biological effects of the 24,24-dimethyl groups (Table 1). We also show the data of 24-methylvitamin D_3 lactones (**4**–**7**) for comparison. Binding affinities of **8** and **9** to the chick intestinal VDR were examined as described previously.[21] The affinity of (23*S*)-24,24-dimethylactone derivative **8** increased to be 3.1-fold more potent than that of **2**. In the case of TEI-9648 type analogue **9**, introducing the dimethyl unit into the C24 position raised the binding affinity to 2.6 times higher compared with that of **3**. The antagonistic activities of **8** and **9** were assessed by the NBT-reduction method[22] in terms of inhibition of HL-60 cell differentiation induced by **1** (10 nM). Surprisingly, introduction of the dimethyl groups into the original antagonist **2** resulted in marked enhancement of the antagonistic activity to be ca. 12 times stronger than that of **2**. Although TEI-9648 (**3**) type analogue **9** showed weaker antagonistic activity than that of **2**, the dimethyl analogue **9** exhibited 2.2-fold higher activity compared to the original compound **3**. These results indicated that the vitamin D_3 lactone derivatives having the two-methyl groups on the C24 position (**8** and **9**) altered binding affinity for the VDR and worked on antagonism on the VDR more effectively than the mono methyl analogues (**4**–**7**).

2.2. Effect of C2α modifications of 24,24-dimethylvitamin D_3 lactones

Next, we turned our attention to C2α-functionalization of 24,24-dimethylvitamin D_3-lactone analogues **8** and **9**. According to our previous results, C2α-functionalization of 24-methylvitamin D_3 lactones effectively enhanced both binding affinity to the VDR and antagonistic activity.[12b] Therefore, we expected a high increase in VDR binding affinity and marked improvement of the VDR antagonistic activity through such functionalizations of the new 24,24-dimethylvitamin D_3 lactones. The 2α-modified vitamin D_3 analogues (**8a**–**c** and **9a**–**c**) were similarly synthesized from the corresponding CD-ring unit **13** and **14** with the A-ring precursor **22a**,[17a] **22b** and **22c**,[5e] respectively (Scheme 4).



Scheme 4. Synthesis of 2α-modified 24,24-dimethylvitamin D_3 lactones **8a**–**c** and **9a**–**c**.

The evaluation of biological activities of **8a**–**c** and **9a**–**c** disclosed that C2α modifications were also effective to enhance the biological potency of 24,24-dimethylvitamin D_3 lactones (Table 2). That is, VDR binding affinity of TEI-9647 (**2**) type analogues increased to 3.0–5.9 times stronger than that of **2** by introduction of the three motifs into the C2α position of **8** (**8a**–**c**). Such C2α modification exhibited remarkable effect on antagonistic activity. Especially, VDR antagonistic activity of 2α-methyl analogue **8a** increased to be ca. 89-fold more potent than that of the original **2** (7.6 times stronger than **8**). The other lactone derivatives **8b** and **8c** also showed 12- and 28-fold stronger antagonistic activity than that of **2**, respectively. In the case of TEI-9648 type derivatives (**9a**–**c**), receptor binding affinity was raised to be 1.7–7.6 fold more potent than TEI-9648 (**3**). Although **9a**–**c** generally showed weaker antagonistic activities than **8a**–**c**, C2α functionalization of **9** significantly increased the activities in comparison with the original compound **3** (4–19 more potent than **3**) and 24,24-dimtehylvitamin D_3 lactone derivative **9** (1.8–8.9 times stronger than **9**).

Table 2. Biological activities of 2α-modified 24,24-dimethylvitamin D_3 lactones **8a**–**c** and **9a**–**c**

Compounds	VDR binding affinity[a]	Antagonistic activity[b] (IC_{50}, nM)
TEI-9647 (**2**)	12	8.3
8a	67	0.093
8b	71	0.7
8c	36	0.3
TEI-9648 (**3**)	7	111.6
9a	48	5.8
9b	53	7.7
9c	12	28.0

[a] The potency of **1** is normalized to 100.
[b] Antagonistic activity was assessed in terms of IC_{50} for differentiation of HL-60 cells induced by 10 nM of **1**.

3. Discussion

In the generally accepted mechanism of transactivation mediated by VDR, a ligand first binds to the ligand binding-domain (LBD) of an apo form of VDR. Next, the VDR–ligand complex changes the conformation into a transcriptionally active holo form, which binds to the coactivators to activate transcription of the target gene.[23] In this conformational change process, the appropriate positioning of helix 12 of VDR, which is the most C-terminal α-helix and presents an interaction site with the other proteins such as coactivators in the active holo form, is essential, and regulates whether the function of the ligand on the VDR exhibits agonism or antagonism.[24]

The antagonist **2** binds to the LBD of a VDR, and the binding of **2** changes the conformation of the VDR into an unusual transcriptionally inactive form.[25] We at present speculate that some amino acid residues in the LBD participate in the unusual conformational change of the VDR through the interaction with the *exo*-methylene lactone moiety of **2**. Namely, there are two cysteines, that is, Cys403 on helix 11 and Cys410 on the hinge region between helix 11 and helix 12, in the LBD of the hVDR.[26] The nucleophilic thiol groups of the cysteines could attack on the α-methylene-γ-lactone of **2** via 1,4-addition to give the corresponding cysteine adduct.[27] Such interaction between the LBD and the ligand might prevent the usual positioning of helix 12. As the result, the VDR-**2** complex

could not form transcriptionally active conformation. Therefore, it is thought that the antagonist, whose *exo*-methylene unit is located on more favorable position to interact with Cys403 and/or Cys410, would show more potent antagonistic activity.

Although it is yet unclear why the newly synthesized 24,24-dimethylvitamin D_3 lactones (**8** and **9**) and their C2α modified analogues (**8a**–**c** and **9a**–**c**) exhibited more potent antagonistic activity than the original **2** and **3**, they might be situated in the above mentioned preferable position to interact with the cysteine residues after the binding to the LBD of the VDR.

4. Conclusion

We have succeeded in developing highly potent vitamin D receptor antagonists (**8**, **8a**–**c**, **9** and **9a**–**c**), 24,24-dimethyl-1α-hydroxyvitamin D_3-26,23-lactones and their C2α-functionalized analogues. Recently, the VDR antagonists are expected to be potent therapeutic agents for some diseases caused by hypersensitivity to 1α,25-dihydroxyvitamin D_3, such as Paget's bone disease.[28] We expect that these analogues with potent anti-vitamin D activity would contribute to understanding the mechanisms involved in the expression of antagonistic activity on VDR as well as to finding the seeds of new medicines for treating Paget's bone disease.

5. Experimental

5.1. General

All manipulations were performed under an argon atmosphere unless otherwise mentioned. All solvents and reagents were purified when necessary using standard procedures. Column chromatography was performed on silica gel 60 N (Kanto Chemical Co., Inc., 100–210 μm), and flash column chromatography was performed on silica gel 60 (Merck, 40–63 μm). NMR spectra were measured on a JEOL AL-400 magnetic resonance spectrometer. Infrared spectra were recorded on JASCO FTIR-8000 spectrometer. Mass spectra were measured on JEOL JMX-SX 102 mass spectrometer. Specific optical rotations were measured on JASCO DIP-370 digital polarimeter.

5.1.1. Methyl 2-(bromomethyl)-3-methylbut-2-enoate (12). To a solution of **11** (200 mg, 1.4 mmol) in Et_2O was added PBr_3 (80 μL, 0.83 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. To the mixture was added H_2O at 0 °C, and the aqueous layer was extracted with Et_2O. The organic layer was washed with saturated NaCl aq. solution, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=20/1) to give **12** (240 mg, 83%) as a colorless oil. IR (neat) 1723, 1628, 1373 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.99, (s, 3H), 2.16 (s, 3H), 3.79 (s, 3H), 4.31 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.0, 24.0, 29.4, 51.7, 124.6, 153.8, 166.9; EI-LRMS *m/z* 205 (M^+), 191, 175; EI-HRMS Calcd for $C_7H_{11}O_2^{79}Br$ 205.9942, found 205.9951.

5.1.2. (*S*)-5-{(*R*)-2-[(1*R*,4*E*,3a*R*,7a*R*)-4-Bromomethylene-7a-methylperhydroinden-1-yl]propyl}-4,4-dimethyl-3-methylenedihydrofuran-2-one (13) and (*R*)-5-{(*R*)-2-[(1*R*,4*E*,3a*R*,7a*R*)-4-bromomethylene-7a-methylperhydroinden-1-yl]propyl}-4,4-dimethyl-3-methylenedihydrofuran-2-one (14). To a suspension of $CrCl_3$ (739 mg, 4.7 mmol) in THF (23 mL) was added $LiAlH_4$ (94 mg, 2.3 mmol) at 0 °C, and the mixture was stirred at room temperature for 30 min. To the mixture were added a solution of **10** (486 mg, 2.3 mmol) in THF (8 mL) and a solution of **12** (350 mg, 1.2 mmol) at room temperature, and the resulting mixture was stirred at the same temperature for 1 h. To the mixture was added H_2O at 0 °C, and the aqueous layer was extracted with Et_2O. The organic layer was washed with saturated NaCl aq. solution, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt=10/1) to give a mixture of **13** and **14** (390 mg, 80% in the ratio of 2 to 1). Further separation was performed by recycle-HPLC (column: SHIMADZU Shim-pack PREP-SIL(H)-KIT, eluent: hexane/AcOEt=8/1, flow rate: 10 mL/min, detector: UV (235 nm)). **13**: mp. 130 °C (recrystallized from Et_2O–hexane); $[\alpha]_D^{25}$=+31.4 (*c* 0.85, $CHCl_3$); IR (film, $CHCl_3$) 1767, 1653, 1634, 1371, 1133 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.58 (s, 3H), 1.05 (s, 3H), 1.08 (d, *J*=6.6 Hz, 3H), 1.21 (s, 3H), 1.25–1.70 (m, 11H), 1.95–2.04 (m, 3H), 2.88 (dd, *J*=15.9, 3.9 Hz, 1H), 4.10 (dd, *J*=9.0, 2.9 Hz, 1H), 5.46 (s, 1H), 5.65 (s, 1H), 6.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 19.7, 22.1, 22.6, 23.0, 24.3, 27.9, 31.0, 35.3, 35.5, 39.8, 42.6, 45.6, 55.7, 55.9, 86.1, 97.5, 118.9, 114.8, 146.1, 170.5; EI-LRMS *m/z* 394 (M^+), 315, 256, 227; EI-HRMS Calcd for $C_{21}H_{31}O_2^{79}Br$ 394.1507, found 394.1508. Anal. Calcd for $C_{21}H_{31}O_2Br$: C, 63.79; H, 7.90. Found: C, 64.13; H, 8.27. **14**: mp. 117 °C (recrystallized from Et_2O–hexane); $[\alpha]_D^{25}$=+141.2 (*c* 0.38, $CHCl_3$); IR (film, $CHCl_3$) 1767, 1651, 1638, 1458, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.59 (s, 3H), 1.00 (d, *J*=6.3 Hz, 3H), 1.05 (s, 3H), 1.11 (dd, *J*=13.4, 11.2 Hz, 1H), 1.21 (s, 3H), 1.25–1.36 (m, 3H), 1.44–1.66 (m, 7H), 1.89 (m, 1H), 1.96–2.04 (m, 2H), 2.89 (dd, *J*=15.6, 6.8 Hz, 1H), 4.14 (d, *J*=10.5 Hz, 1H), 5.47 (s, 1H), 5.65 (s, 1H), 6.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 18.6, 22.1, 22.5, 22.8, 25.1, 27.6, 31.0, 32.9, 35.9, 39.9, 41.9, 45.6, 55.9, 56.2, 84.2, 97.6, 119.1, 144.7, 146.1, 170.3; EI-LRMS *m/z* 394 (M^+), 315, 256, 227; EI-HRMS Calcd for $C_{21}H_{31}O_2^{79}Br$ 394.1507, found 394.1508. Anal. Calcd for $C_{21}H_{31}O_2Br$: C, 63.79; H, 7.90. Found: C, 63.57; H, 8.20.

5.1.3. Methyl 4,6-*O*-benzylidene-3-allyl-3-deoxy-α-D-altropyranoside. To a solution of **15** (264 mg, 1.0 mmol) in THF (1.5 mL) was added a solution of allylmagnesium chloride in THF (2.0 M, 1.5 mL, 3.0 mmol) at room temperature, and the mixture was stirred at 80 °C for 1 h. To the mixture was added water at 0 °C, and the aqueous layer was extracted with Et_2O. The organic layer was washed with saturated NaCl aq. solution, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt=2/1) to give the desired allylated compound (314 mg, quant.) as an amorphous solid. IR (neat) 3422, 2930, 1642, 1456, 1381 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.90 (m, 1H), 2.26 (m, 1H), 2.53 (dd, *J*=7.1, 7.1 Hz, 2H), 3.39 (s, 3H),

3.78 (dd, J=10.2, 10.2 Hz, 1H), 3.97 (m, 1H), 4.00 (ddd, J=10.2, 10.2, 5.1 Hz, 1H), 4.12 (dd, J=10.2, 5.1 Hz, 1H), 4.29 (dd, J=10.2, 5.1 Hz, 1H), 4.60 (s, 1H), 5.06 (d, J=10.2 Hz, 1H), 5.11 (d, J=17.2 Hz, 1H), 5.60 (s, 1H), 5.83 (ddt, J=17.2, 10.2, 7.1 Hz, 1H), 7.36–7.37 (m, 3H), 7.48–7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.1, 42.8, 55.6, 59.9, 69.7, 69.9, 76.4, 102.3, 102.7, 116.9, 126.4 (2C), 128.5 (2C), 129.2, 137.3, 137.9; EI-LRMS m/z 306 (M^+); EI-HRMS Calcd for $C_{17}H_{22}O_5$ 306.1467, found 306.1469.

5.1.4. Methyl 4,6-*O*-benzylidene-3-deoxy-3-(3-hydroxypropyl)-α-D-altropyranoside (16). To a solution of the above allylated compound (1.8 g, 5.9 mmol) in THF (12 mL) was added a solution of BH_3·THF in THF (1.0 M, 14.7 mL, 14.7 mmol) at 0 °C, and the mixture was stirred at room temperature for 23 h. To the mixture was added 3N NaOH aq. solution (7.7 mL) and 30% H_2O_2 aq. solution (7.7 mL) at 0 °C, and the mixture was stirred at room temperature for 3 h. To the mixture was added saturated NH_4Cl aq. solution at 0 °C, and the aqueous layer was extracted with AcOEt. The organic layer was washed with saturated NaCl aq. solution, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt=1/2) to give alcohol (1.72 g, 91%) as a colorless oil. $[\alpha]_D^{19}$=+84.2 (c 2.31, $CHCl_3$); IR (neat) 3403, 2936, 1103, 1051 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52–1.86 (m, 4H), 2.17–2.18 (m, 3H), 3.36 (s, 3H), 3.61 (t, J=6.3 Hz, 2H), 3.76 (dd, J=10.1, 10.1 Hz, 1H), 3.92 (m, 1H), 3.97 (ddd, J=10.1, 10.1, 5.2 Hz, 1H), 4.11 (dd, J=10.1, 5.2 Hz, 1H), 4.27 (dd, J=10.1, 5.2 Hz, 1H), 4.57 (s, 1H), 5.57 (s, 1H), 7.34–7.39 (m, 3H), 7.45–7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 31.4, 42.5, 55.2, 59.5, 62.8, 69.5, 70.2, 76.4, 102.0, 102.1, 126.1 (2C), 128.2 (2C), 129.0, 137.5; EI-LRMS m/z 324 (M^+), 292, 274, 215, 162, 143, 105, 77; EI-HRMS Calcd for $C_{17}H_{24}O_6$ 324.1573, found 324.1575.

5.1.5. Methyl 4,6-*O*-benzylidene-3-deoxy-3-[(3-pivaloyloxy)propyl]-α-D-altropyranoside (17). To a solution of **16** (227 mg, 0.7 mmol) in pyridine (3.5 mL) was added pivaloyl chloride (95 μL, 0.77 mmol) at 0 °C, and the mixture was stirred at room temperature for 12 h. To the mixture was added water at 0 °C, and the aqueous layer was extracted with AcOEt. The organic layer was washed with saturated NaCl aq. solution, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt=4/1) to give **17** (270 mg, 94%) as a colorless oil. $[\alpha]_D^{19}$=+66.1 (c 2.38, $CHCl_3$); IR (neat) 3474, 2963, 1725, 1287, 1103, 1049 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 9H), 1.63–1.90 (m, 4H), 2.18 (m, 1H), 2.32 (br s, 1H), 3.36 (s, 3H), 3.77 (dd, J=10.2, 10.2 Hz, 1H), 3.91 (m, 1H), 3.97 (ddd, J=10.2, 10.2, 5.0 Hz, 1H), 4.01–4.14 (m, 3H), 4.27 (dd, J=10.2, 5.0 Hz, 1H), 4.58 (s, 1H), 5.58 (s, 1H), 7.33–7.38 (m, 3H), 7.44–7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 27.2 (3C), 27.5, 38.8, 42.5, 55.2, 59.5, 64.3, 69.5, 70.1, 76.2, 101.9, 102.1, 126.1 (2C), 128.1 (2C), 128.9, 137.6, 178.6; EI-LRMS m/z 408 (M^+), 390, 358, 241, 162, 105; EI-HRMS Calcd for $C_{22}H_{32}O_7$ 408.2140, found 408.2140.

5.1.6. Methyl 4,6-*O*-benzylidene-2-(*tert*-butyldimethylsilyloxy)-3-deoxy-3-[(3-pivaloyloxy)propyl]-α-D-altropyranoside (18). To a solution of **17** (270 mg, 0.66 mmol) in CH_2Cl_2 (6.6 mL) were added 2,6-lutidine (0.39 mL, 3.3 mmol) and TBSOTf (0.23 mL, 0.99 mmol) at 0 °C, and the mixture was stirred at room temperature for 13 h. To the mixture was added water at 0 °C, and the aqueous layer was extracted with Et_2O. The organic layer was washed with saturated NaCl aq. solution, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt=9/1) to give **18** (332 mg, 96%) as a colorless oil. $[\alpha]_D^{19}$=+35.9 (c 0.62, $CHCl_3$); IR (neat) 2955, 1728, 1258, 1107, 1051 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.086 (s, 3H), 0.092 (s, 3H), 0.92 (s, 9H), 1.19 (s, 9H), 1.60–1.89 (m, 4H), 2.05 (m, 1H), 3.34 (s, 3H), 3.77 (dd, J=10.1, 10.1 Hz, 1H), 3.87 (br s, 1H), 3.92 (ddd, J=10.1, 10.1, 5.0 Hz, 1H), 4.03–4.14 (m, 3H), 4.26 (dd, J=10.1, 5.0 Hz, 1H), 4.45 (s, 1H), 5.59 (s, 1H), 7.34–7.37 (m, 3H), 7.47–7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −4.8, 18.1, 21.1, 25.8 (3C), 27.2 (3C), 27.8, 38.8, 43.4, 55.0, 59.4, 64.4, 69.7, 70.7, 76.4, 101.9, 102.6, 126.2 (2C), 128.6 (2C), 128.9, 137.8, 178.4; EI-LRMS m/z 522 (M^+), 491, 358, 244, 159; EI-HRMS Calcd for $C_{28}H_{46}O_7$ 522.3013, found 522.3015.

5.1.7. Methyl 4-*O*-benzoyl-6-bromo-2-[(*tert*-butyldimethylsilyl)oxy]-3-deoxy-3-[(3-pivaloyloxy)propyl]-6-deoxy-α-D-altropyranoside (19). To a solution of **18** (2.28 g, 4.4 mmol) in CCl_4 (22 mL) were added $BaCO_3$ (861 mg, 4.4 mmol) and NBS (932 mg, 5.2 mmol) at room temperature, and the mixture was stirred at 80 °C for 30 min. To the mixture was added saturated $Na_2S_2O_3$ aq. solution and saturated $NaHCO_3$ aq. solution, and the aqueous layer was extracted with Et_2O. The organic layer was washed with saturated NaCl aq. solution, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt=9/1) to give **19** (2.46 g, 94%) as a colorless oil. $[\alpha]_D^{18}$=+18.4 (c 2.92, $CHCl_3$); IR (neat) 2957, 1727, 1267, 1116, 1042 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.12 (s, 3H), 0.93 (s, 9H), 1.08 (s, 9H), 1.43–1.73 (m, 3H), 1.87 (m, 1H), 2.16 (ddt, J=6.0, 5.9, 6.3 Hz, 1H), 3.43 (s, 3H), 3.58 (dd, J=10.7, 7.6 Hz, 1H), 3.66 (dd, J=10.7, 2.8 Hz, 1H), 3.82 (dd, J=6.0, 2.4 Hz, 1H), 4.00 (t, J=6.1 Hz, 2H), 4.10 (ddd, J=7.8, 7.6, 2.8 Hz, 1H), 4.55 (d, J=2.4 Hz, 1H), 5.38 (dd, J=7.8, 5.9 Hz, 1H), 7.43–7.47 (m, 2H), 7.59 (m, 1H), 7.99–8.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8, −4.6, 18.1, 21.7, 25.8 (3C), 26.9, 27.1 (3C), 33.4, 38.7, 42.1, 55.4, 64.2, 69.0, 71.0, 71.1, 103.7, 128.5 (2C), 129.5, 129.6 (2C), 133.3, 165.3, 178.3; EI-LRMS m/z 569 (M^+-OMe), 423, 339, 322, 213; EI-HRMS Calcd for $C_{27}H_{42}O_6{}^{79}Br$ 569.1934, found 569.1931.

5.1.8. (2*S*,3*R*,4*R*)-4-[(Benzoyl)oxy]-2-[(*tert*-butyldimethylsilyl)oxy]-3-[3-(pivaloyloxy)propyl]hexa-5-ene-1-ol (20). To a solution of **19** (2.40 g, 4.0 mmol) in 1-propanol/H_2O (5/1, 24 mL) were added activated Zn dust (45.5 g, 0.7 mol) and $NaBH_3CN$ (9.8 g, 0.14 mol) at 95 °C, and the mixture was stirred at the same temperature for 1.5 h. To the mixture was added saturated NH_4Cl aq. solution, and the aqueous layer was extracted with AcOEt. The organic layer was washed with saturated NaCl aq. solution, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt=6/1) to give **20** (1.76 g, 89%) as a colorless

oil. $[\alpha]_D^{19}$=+25.4 (*c* 2.62, $CHCl_3$); IR (neat) 3495, 2957, 1725, 1598, 1271, 1111, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.06 (s, 3H), 0.90 (s, 9H), 1.18 (s, 9H), 1.42–1.63 (m, 2H), 1.67–1.90 (m, 3H), 2.06 (ddt, *J*=6.3, 5.6, 6.1 Hz, 1H), 3.62 (dd, *J*=11.0, 4.9 Hz, 1H), 3.72 (dd, *J*=11.0, 5.3 Hz, 1H), 3.95 (ddd, *J*=5.6, 5.3, 4.9 Hz, 1H), 4.04 (t, *J*=6.1 Hz, 2H), 5.28 (ddd, *J*=10.5, 1.2, 1.2 Hz, 1H), 5.37 (ddd, *J*=17.1, 1.2, 1.2 Hz, 1H), 5.56 (dd, *J*=6.7, 6.3 Hz, 1H), 5.92 (ddd, *J*=17.1, 10.5, 6.7 Hz, 1H), 7.42–7.46 (m, 2H), 7.56 (m, 1H), 8.02–8.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.6, −4.2, 18.2, 22.8, 25.9 (3C), 27.2 (3C), 27.9, 38.8, 44.8, 64.4, 65.0, 73.0, 75.8, 118.4, 128.3 (2C), 129.5 (2C), 130.3, 132.9, 134.6, 165.4, 178.4; EI-LRMS *m/z* 391 (M^+-OPiv), 239, 105; EI-HRMS Calcd for $C_{22}H_{35}O_4Si$ 391.2305, found 391.2307.

5.1.9. (3*R*,4*R*)-3-Benzoyloxy-4-[(1*S*)-1-{(*tert*-butyldimethylsilyl)oxy}-2-(*p*-toluenesulfonyl)ethyl]-7-(pivaloyloxy)hept-1-ene. To a solution of **20** (1.72 g, 3.4 mmol) in pyridine (7 mL) was added TsCl (3.0 g, 16 mmol) at 0 °C, and the mixture was stirred at room temperature for 17.5 h. To the mixture was added water at 0 °C, and the aqueous layer was extracted with Et_2O. The organic layer was washed with saturated NaCl aq. solution, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt=9/1) to give the desired sulfonate (2.24 g, 99%) as a colorless oil. $[\alpha]_D^{19}$=+18.6 (*c* 0.46, $CHCl_3$); IR (neat) 2957, 1725, 1599, 1269, 1107 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ −0.06 (s, 3H), −0.04 (s, 3H), 0.83 (s, 9H), 1.17 (s, 9H), 1.33–1.79 (m, 4H), 1.95 (m, 1H), 2.43 (s, 3H), 3.92–4.05 (m, 4H), 4.14 (ddd, *J*=6.2, 5.5, 2.8 Hz, 1H), 5.26 (ddd, *J*=10.4, 1.2, 1.2 Hz, 1H), 5.35 (ddd, *J*=17.3, 1.2, 1.2 Hz, 1H), 5.43 (dd, *J*=7.3, 7.1 Hz, 1H), 5.84 (ddd, *J*=17.3, 10.4, 7.1 Hz, 1H), 7.30–7.34 (m, 2H), 7.42–7.48 (m, 2H), 7.59 (m, 1H), 7.78–7.80 (m, 2H), 8.01–8.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.0, −4.3, 18.0, 21.7, 22.3, 25.8 (3C), 27.2 (3C), 27.6, 38.8, 45.0, 64.1, 70.0, 71.3, 75.5, 118.9, 127.9 (2C), 128.4 (2C), 129.5 (2C), 129.8 (2C), 130.1, 132.7, 133.0, 134.6, 144.8, 165.2, 178.3; EI-LRMS *m/z* 475 (M^+-OTs), 329, 229; EI-HRMS Calcd for $C_{27}H_{43}O_5Si$ 475.2880, found 475.2887.

5.1.10. (3*R*,4*R*)-3-[(Benzoyl)oxy]-4-(*S*)-oxiranyl-7-(pivaloyloxy)hept-1-ene (21). To a solution of the above sulfonate (110 mg, 0.17 mmol) in THF (1.7 mL) was added a solution of TBAF in THF (1.0 M, 0.26 mL, 0.26 mmol) at 0 °C, and the mixture was stirred at room temperature for 6 h. To the mixture was added water at 0 °C, and the aqueous layer was extracted with Et_2O. The organic layer was washed with saturated NaCl aq. solution, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt=9/1) to give **21** (64 mg, quant.) as a colorless oil. $[\alpha]_D^{20}$=+28.7 (*c* 2.31, $CHCl_3$); IR (neat) 2973, 1725, 1601, 1269, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 9H), 1.50 (m, 1H), 1.59–1.78 (m, 2H), 1.79–1.92 (m, 2H), 2.59 (dd, *J*=4.9, 2.6 Hz, 1H), 2.77 (dd, *J*=4.9, 3.9 Hz, 1H), 2.93 (ddd, *J*=8.3, 3.9, 2.6 Hz, 1H), 4.06 (t, *J*=6.3 Hz, 2H), 5.28 (ddd, *J*=10.5, 1.2, 1.0 Hz, 1H), 5.37 (ddd, *J*=17.1, 1.2, 1.0 Hz, 1H), 5.62 (dddd, *J*=6.6, 6.6, 1.0, 1.0 Hz, 1H), 5.90 (ddd, *J*=17.1, 10.5, 6.6 Hz, 1H), 7.44–7.47 (m, 2H), 7.58 (m, 1H), 8.03–8.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 26.2, 27.2 (3C), 38.7, 45.9, 46.8, 53.1, 64.1, 75.5, 118, 2, 128.4 (2C), 129.5 (2C), 129.9, 133.1, 134.2, 165.3, 178.4; EI-LRMS *m/z* 360 (M^+), 259, 136, 80; EI-HRMS Calcd for $C_{21}H_{28}O_5$ 360.1937, found 360.1935.

5.1.11. (3*R*,4*R*,5*S*)-4-(3-Hydroxypropyl)oct-1-en-7-yne-3,5-diol. To a solution of ethynyltrimethylsilane (0.32 mL, 2.2 mmol) in THF (3 mL) was added a solution of *n*-BuLi in hexane (1.56 M, 1.1 mL, 1.7 mmol) at −78 °C, and the mixture was stirred at the same temperature for 30 min. To the mixture were added a solution of **21** (400 mg, 1.1 mmol) in THF (8 mL) and $BF_3{\cdot}OEt_2$ (0.15 mL, 1.2 mmol) at −78 °C, and the resulting mixture was stirred at the same temperature for 3 h. To the mixture was added saturated NH_4Cl aq. solution, and the aqueous layer was extracted with Et_2O. The organic layer was washed with saturated NaCl aq. solution, dried over Na_2SO_4, and concentrated. The residue was dissolved in MeOH (11 mL). To the mixture was added NaOMe (300 mg, 5.6 mmol) at 0 °C, and the mixture was stirred at 40 °C for 15.5 h. To the mixture was added saturated NH_4Cl aq. solution at 0 °C, and the aqueous layer was extracted with AcOEt. The organic layer was washed with saturated NaCl aq. solution, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane/AcOEt=1/4) to give the desired triol (217 mg, 99%) as a colorless oil. $[\alpha]_D^{20}$=+9.88 (*c* 0.77, $CHCl_3$); IR (neat) 3304, 2940, 2118, 1630, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45–1.77 (m, 5H), 2.02 (dd, *J*=2.7, 2.7 Hz, 1H), 2.33 (ddd, *J*=16.8, 7.1, 2.7 Hz, 1H), 2.48 (ddd, *J*=16.8, 7.1, 2.7 Hz, 1H), 3.03 (br s, 3H), 3.62–3.74 (m, 2H), 4.20 (dt, *J*=1.5, 7.1 Hz, 1H), 4.41 (m, 1H), 5.25 (ddd, *J*=10.5, 1.6, 1.6 Hz, 1H), 5.37 (ddd, *J*=17.1, 1.7, 1.7 Hz, 1H), 5.91 (ddd, *J*=17.1, 10.5, 4.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 24.3, 30.4, 44.8, 62.8, 70.3, 70.4, 73.6, 81.0, 115.5, 139.5; EI-LRMS *m/z* 180 (M^+-H_2O), 161, 105, 79; EI-HRMS Calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1149.

5.1.12. (3*R*,4*R*,5*S*)-3,5-Bis[(*tert*-butyldimethylsilyl)oxy]-4-[3-{(*tert*-butyldimethylsilyl)oxy}propyl]oct-1-en-7-yne (22b). To the solution of the above triol (14 mg, 71 μmol) in CH_2Cl_2 (0.7 mL) were added 2,6-lutidine (49 μL, 0.42 mmol) and TBSOTf (65 μL, 0.28 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. To the mixture was added water at 0 °C, and the aqueous layer was extracted with Et_2O. The organic layer was washed with saturated NaCl aq. solution, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (hexane) to give **22b** (36 mg, 94%) as a colorless oil. $[\alpha]_D^{22}$=+8.32 (*c* 0.77, $CHCl_3$); IR (neat) 3314, 2932, 1256, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 6H), 0.05 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.89 (s, 27H), 1.32 (m, 2H), 1.56 (m, 2H), 1.75 (ddt, *J*=6.4, 4.0, 6.8 Hz, 1H), 1.95 (t, *J*=2.8 Hz, 1H), 2.38 (ddd, *J*=16.8, 6.2, 2.8 Hz, 1H), 2.42 (ddd, *J*=16.8, 6.2, 2.8 Hz, 1H), 3.56 (t, *J*=6.8 Hz, 2H), 4.03 (dt, *J*=4.0, 6.2 Hz, 1H), 4.12 (dd, *J*=7.6, 6.4 Hz, 1H), 5.08 (d, *J*=10.0 Hz, 1H), 5.14 (d, *J*=17.2 Hz, 1H), 5.84 (ddd, *J*=17.2, 10.0, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1 (2C), −4.4, −4.2, −3.9, −3.4, 18.25, 18.32, 18.5, 22.2, 26.0 (3C), 26.08 (3C), 26.12 (3C), 26.2, 32.6, 49.2, 63.6, 69.9, 71.5, 75.9, 82.1, 115.5, 140.4; EI-LRMS *m/z* 483 (M^+-*t*Bu);

EI-HRMS Calcd for $C_{25}H_{51}O_3Si_3$ 483.3146, found 483.3141.

5.2. General procedure for the synthesis of vitamin D_3 lactones

To a solution of an A-ring precursor (1.5 equiv. to a CD-ring precursor), and the CD-ring precursor in toluene were added Et_3N and $Pd(PPh_3)_4$ (30 mol% to the CD-ring precursor) and the mixture was stirred at 110 °C. After the mixture was filtered through a silica gel pad, the filtrate was concentrated. The crude product was dissolved in MeCN (1 mL). To the solution was added 10% solution of conc. HF in MeCN (1 mL) at 0 °C, the mixture was stirred at room temperature. To the mixture was added saturated $NaHCO_3$ aq. solution, and the aqueous layer was extract with AcOEt. The organic layer was washed with saturated NaCl aq. solution, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel or thin-layer chromatography on silica gel to give the vitamin D_3 derivative. Further purification for biological assays was conducted by reversed-phase recycle HPLC (YMC-Pack ODS column, 20×150 mm, 9.9 mL/min, eluent: CH_3CN/H_2O=90/10).

5.2.1. (23*S*)-25-Dehydro-1α-hydroxy-24,24-dimethylvitamin D_3-26,23-lactone (8). According to the general procedure, a crude product, which was obtained from **13** (31 mg, 78 μmol), **22** (43 mg, 117 μmol), Et_3N (0.8 mL) and $Pd(PPh_3)_4$ (33 mg, 28 μmol) in toluene (0.8 mL) at 110 °C for 1 h, was treated with conc. HF in MeCN for 1 h. After usual work up, the crude product was purified by column chromatography on silica gel (hexane/AcOEt=1/1) to give **8** (17 mg, 48% in 2 steps) as an amorphous solid. UV (EtOH) λ_{max}=264.0 nm; $[\alpha]_D^{24}$=−21.8 (*c* 0.85, $CHCl_3$); IR (film, $CHCl_3$) 3382, 1765, 1663, 1057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.56 (s, 3H), 1.05 (s, 3H), 1.07 (d, *J*=6.6 Hz, 3H), 1.21 (s, 3H), 1.25–1.72 (m, 13H), 1.88–2.06 (m, 5H), 2.32 (dd, *J*=13.4, 6.3 Hz, 1H), 2.60 (dd, *J*=13.4, 3.5 Hz, 1H), 2.83 (dd, *J*=10.4, 3.8 Hz, 1H), 4.10 (dd, *J*=10.4, 3.4 Hz, 1H), 4.23 (br s, 1H), 4.43 (br s, 1H), 5.00 (dd, *J*=1.6, 1.5 Hz, 1H), 5.33 (dd, *J*=1.7, 1.6 Hz, 1H), 5.45 (s, 1H), 6.02 (d, *J*=11.2 Hz, 1H), 6.13 (s, 1H), 6.38 (d, *J*=11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 19.7, 22.3, 23.0, 23.6, 24.4, 27.9, 29.1, 35.4, 35.6, 40.4, 42.6, 42.9, 45.3, 46.0, 56.2, 56.7, 66.8, 70.8, 86.3, 111.6, 117.1, 118.8, 124.8, 133.0, 142.8, 146.2, 147.6, 170.5; EI-LRMS *m/z* 454 (M^+), 418, 403; EI-HRMS Calcd for $C_{29}H_{42}O_4$ 454.3083, found 454.3083.

5.2.2. (23*R*)-25-Dehydro-1α-hydroxy-24,24-dimethylvitamin D_3-26,23-lactone (9). According to the general procedure, a crude product, which was obtained from **14** (30 mg, 76 μmol), **22** (48 mg, 114 μmol), Et_3N (0.8 mL) and $Pd(PPh_3)_4$ (26 mg, 23 μmol) in toluene (0.8 mL) at 110 °C for 30 min, was treated with conc. HF in MeCN for 30 min. After usual work up, the crude product was purified by column chromatography on silica gel (hexane/AcOEt=1/1) to give **9** (27 mg, 78% in 2 steps) as an amorphous solid. UV (EtOH) λ_{max}=265.0 nm; $[\alpha]_D^{24}$=+56.2 (*c* 1.15, $CHCl_3$); IR (film, $CHCl_3$) 3426, 1759, 1672, 1057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.57 (s, 3H), 0.99 (d, *J*=6.6 Hz, 3H), 1.05 (s, 3H), 1.11 (dd, *J*=10.5, 1.47 Hz, 1H), 1.21 (s, 3H), 1.26 (s, 3H), 1.45–1.76 (m, 9H), 1.83–2.04 (m, 5H), 2.31 (dd, *J*=13.4, 6.5 Hz, 1H), 2.60 (dd, *J*=13.4, 3.4 Hz, 1H), 2.83 (dd, *J*=12.0, 3.9 Hz, 1H), 4.14 (dd, *J*=11.6, 1.6 Hz, 1H), 4.24 (br s, 1H), 4.43 (br s, 1H), 5.00 (s, 1H), 5.33 (s, 1H), 5.47 (s, 1H), 6.12 (d, *J*=11.4 Hz, 1H), 6.15 (s, 1H), 6.37 (d, *J*=11.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 18.6, 22.3, 22.8, 23.6, 25.1, 27.6, 29.1, 32.9, 35.9, 40.5, 42.0, 42.9, 45.3, 46.0, 56.4, 57.0, 66.8, 70.8, 84.3, 111.7, 117.2, 119.1, 124.7, 133.1, 142.6, 146.2, 147.5, 170.4; EI-LRMS *m/z* 454 (M^+), 418, 403; EI-HRMS Calcd for $C_{29}H_{42}O_4$ 454.3083, found 454.3083.

5.2.3. (23*S*)-25-Dehydro-1α-hydroxy-2α,24,24-trimethylvitamin D_3-26,23-lactone (8a). According to the general procedure, a crude product, which was obtained from **13** (25 mg, 63 μmol), **22a** (41 mg, 107 μmol), Et_3N (0.6 mL) and $Pd(PPh_3)_4$ (37 mg, 32 μmol) in toluene (0.6 mL) at 110 °C for 1.5 h, was treated with conc. HF in MeCN for 1 h. After usual work up, the crude product was purified by column chromatography on silica gel (hexane/AcOEt=1/1) to give **8a** (14 mg, 47% in 2 steps) as an amorphous solid. UV (EtOH) λ_{max}=266.0 nm; $[\alpha]_D^{26}$=+11.6 (*c* 1.08, $CHCl_3$); IR (film, $CHCl_3$) 3441, 1752, 1671, 1636, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.55 (s, 3H), 1.04 (s, 3H), 1.06 (d, *J*=6.7 Hz, 3H), 1.07 (d, *J*=6.7 Hz, 3H), 1.21 (s, 3H), 1.25–1.70 (m, 13H), 1.88–2.04 (m, 4H), 2.23 (dd, *J*=13.8, 8.1 Hz, 1H), 2.66 (dd, *J*=13.8, 4.0 Hz, 1H), 2.82 (m, 1H), 3.84 (ddd, *J*=7.6, 7.6, 4.2 Hz, 1H), 4.10 (dd, *J*=8.8, 3.4 Hz, 1H), 4.31 (d, *J*=3.2 Hz, 1H), 5.00 (d, *J*=1.7 Hz, 1H), 5.27 (dd, *J*=2.0, 1.0 Hz, 1H), 5.45 (s, 1H), 6.01 (d, *J*=11.2 Hz, 1H), 6.13 (s, 1H), 6.38 (d, *J*=11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 12.6, 19.7, 22.3, 23.0, 23.5, 24.3, 27.9, 29.1, 35.4, 35.6, 40.4, 42.6, 43.5, 44.2, 46.0, 56.2, 56.7, 71.7, 75.4, 86.2, 113.1, 117.0, 118.8, 124.7, 133.1, 142.8, 146.2, 146.5, 170.5; EI-LRMS *m/z* 468 (M^+), 451, 434, 419; EI-HRMS Calcd for $C_{30}H_{44}O_4$ 468.3240, found 468.3248.

5.2.4. (23*R*)-25-Dehydro-1α-hydroxy-2α,24,24-trimethylvitamin D_3-26,23-lactone (9a). According to the general procedure, a crude product, which was obtained from **14** (26 mg, 66 μmol), **22a** (40 mg, 105 μmol), Et_3N (1 mL) and $Pd(PPh_3)_4$ (24 mg, 21 μmol) in toluene (1 mL) at 110 °C for 2.5 h, was treated with conc. HF in MeCN for 1 h. After usual work up, the crude product was purified by column chromatography on silica gel (hexane/AcOEt=1/1) to give **9a** (18 mg, 58% in 2 steps) as an amorphous solid. UV (EtOH) λ_{max}=266.5 nm; $[\alpha]_D^{26}$=+78.5 (*c* 1.38, $CHCl_3$); IR (film, $CHCl_3$) 3476, 1750, 1649, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.56 (s, 3H), 1.00 (d, *J*=6.7 Hz, 3H), 1.06 (s, 3H), 1.08 (d, *J*=6.7 Hz, 3H), 1.12 (m, 1H), 1.21 (s, 3H), 1.26–1.34 (m, 3H), 1.46–1.72 (m, 10H), 1.90–2.04 (m, 3H), 2.23 (dd, *J*=13.4, 7.9 Hz, 1H), 2.67 (dd, *J*=13.4, 4.0 Hz, 1H), 2.83 (m, 1H), 3.85 (ddd, *J*=7.5, 7.5, 4.2 Hz, 1H), 4.15 (dd, *J*=11.6, 1.3 Hz, 1H), 4.31 (br s, 1H), 5.01 (d, *J*=2.0 Hz, 1H), 5.28 (s, 1H), 5.47 (s, 1H), 6.01 (d, *J*=11.2 Hz, 1H), 6.15 (s, 1H), 6.38 (s, *J*=11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 12.6, 18.6, 22.3, 22.9, 23.5, 25.1, 27.6, 29.1, 32.9, 35.9, 40.6, 42.0, 43.4, 44.2, 46.0, 56.4, 57.0, 71.7, 75.3, 84.3, 113.1, 117.1, 119.1, 124.6, 133.2, 142.6, 146.2, 146.5, 170.4; EI-LRMS *m/z* 468 (M^+), 451, 434, 419, 404; EI-HRMS Calcd for $C_{30}H_{44}O_4$ 468.3240, found 468.3264.

5.2.5. (23*S*)-25-Dehydro-1α-hydroxy-2α-(3-hydroxypropyl)-24,24-dimethylvitamin D_3-26,23-lactone (8b). According to the general procedure, a crude product, which was obtained from **13** (18 mg, 46 μmol), **22b** (37 mg, 68 μmol), Et_3N (0.4 mL) and $Pd(PPh_3)_4$ (30 mg, 26 μmol) in toluene (0.4 mL) at 110 °C for 4 h, was treated with conc. HF in MeCN for 4 h. After usual work up, the crude product was purified by column chromatography on silica gel (hexane/AcOEt=1/4) to give **8b** (9 mg, 39% in 2 steps) as an amorphous solid. UV (EtOH) λ_{max}=267.5 nm; $[\alpha]_D^{26}$=+13.7 (*c* 0.85, $CHCl_3$); IR (film, $CHCl_3$) 3380, 1763, 1653, 1057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.55 (s, 3H), 1.05 (s, 3H), 1.07 (d, *J*=6.6 Hz, 3H), 1.21 (s, 3H), 1.24–1.54 (m, 10H), 1.58–1.77 (m, 7H), 1.92–2.02 (m, 5H), 2.25 (dd, *J*=13.5, 8.9 Hz, 1H), 2.66 (dd, *J*=13.6, 4.3 Hz, 1H), 2.83 (m, 1H), 3.69–3.71 (m, 2H), 3.89 (ddd, *J*=8.3, 8.3, 4.4 Hz, 1H), 4.11 (dd, *J*=9.0, 3.2 Hz, 1H), 4.38 (d, *J*=2.9 Hz, 1H), 5.00 (d, *J*=1.6 Hz, 1H), 5.28 (d, *J*=1.6 Hz, 1H), 5.46 (s, 1H), 6.00 (d, *J*=11.4 Hz, 1H), 6.14 (s, 1H), 6.40 (d, *J*=11.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 12.6, 19.7, 22.3, 23.0, 23.5, 24.3, 27.9, 29.1, 35.4, 35.6, 40.4, 42.6, 43.5, 44.2, 46.0, 56.2 (2C), 56.7 (2C), 71.7, 75.4, 86.2, 113.1, 117.0, 118.8, 124.7, 133.1, 142.8, 146.2, 146.5, 170.5; EI-LRMS *m/z* 512 (M^+), 495, 478, 461; EI-HRMS Calcd for $C_{32}H_{48}O_5$ 512.3502, found 512.3490.

5.2.6. (23*R*)-25-Dehydro-1α-hydroxy-2α-(3-hydroxypropyl)-24,24-dimethylvitamin D_3-26,23-lactone (9b). According to the general procedure, a crude product, which was obtained from **14** (39 mg, 76 μmol), **22b** (68 mg, 126 μmol), Et_3N (0.8 mL) and $Pd(PPh_3)_4$ (25 mg, 22 μmol) in toluene (0.8 mL) at 110 °C for 4 h, was treated with conc. HF in MeCN for 1.5 h. After usual work up, the crude product was purified by column chromatography on silica gel (hexane/AcOEt=1/4) to give **9b** (18 mg, 46% in 2 steps) as an amorphous solid. UV (EtOH) λ_{max}=268.0 nm; $[\alpha]_D^{22}$=+69.4 (*c* 1.38, $CHCl_3$); IR (film, $CHCl_3$) 3393, 1757, 1649, 1638 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.56 (s, 3H), 0.99 (d, *J*=6.3 Hz, 3H), 1.06 (s, 3H), 1.11 (m, 1H), 1.21 (s, 3H), 1.26–1.35 (m, 5H), 1.48–1.86 (m, 11H), 1.97–2.05 (m, 3H), 2.25 (dd, *J*=13.3, 8.7 Hz, 2H), 2.28 (br s, 1H), 2.66 (dd, *J*=13.3, 4.2 Hz, 1H), 2.83 (m, 1H), 3.69–3.70 (m, 2H), 3.90 (ddd, *J*=8.2, 8.2, 4.3 Hz, 1H), 4.15 (dd, *J*=11.4, 1.1 Hz, 1H), 4.38 (d, *J*=2.9 Hz, 1H), 4.99 (d, *J*=1.7 Hz, 1H), 5.28 (d, *J*=1.7 Hz, 1H), 5.47 (s, 1H), 6.00 (d, *J*=11.2 Hz, 1H), 6.15 (s, 1H), 6.39 (d, *J*=11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 14.2, 18.6, 22.3, 22.9, 23.5, 25.1, 27.6, 29.0, 30.1, 33.0, 35.9, 40.6, 42.0, 44.3, 46.0, 49.0, 56.4, 56.9, 62.7, 70.3, 73.5, 84.3, 113.6, 117.1, 119.1, 124.5, 133.0, 142.6, 146.2, 146.4, 170.4; EI-LRMS *m/z* 512 (M^+), 495, 478, 461; EI-HRMS Calcd for $C_{32}H_{48}O_5$ 512.3502, found 512.3502.

5.2.7. (23*S*)-25-Dehydro-1α-hydroxy-2α-(3-hydroxypropoxy)-24,24-dimethylvitamin D_3-26,23-lactone (8c). According to the general procedure, a crude product, which was obtained from **13** (14 mg, 35 μmol), **22c** (35 mg, 63 μmol), Et_3N (0.4 mL) and $Pd(PPh_3)_4$ (13 mg, 11 μmol) in toluene (0.4 mL) at 110 °C for 2 h, was treated with conc. HF in MeCN for 1.5 h. After usual work up, the crude product was purified by column chromatography on silica gel (hexane/AcOEt=1/4) to give **8c** (13 mg, 69% in 2 steps) as an amorphous solid. UV (EtOH) λ_{max}=267.0 nm; $[\alpha]_D^{23}$=+13.3 (*c* 0.69, $CHCl_3$); IR (neat) 3330, 1763, 1649, 1624, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.70 (s, 3H), 1.05 (s, 3H), 1.06 (d, *J*=6.6 Hz, 3H), 1.21 (s, 3H), 1.23–1.72 (m, 11H), 1.84–2.04 (m, 5H), 2.24 (dd, *J*=13.6, 9.2 Hz, 1H), 2.53 (br s, 3H), 2.68 (dd, *J*=13.6, 4.6 Hz, 1H), 2.82 (m, 1H), 3.38 (dd, *J*=7.4, 3.3 Hz, 1H), 3.83 (m, 4H), 4.05 (m, 1H), 4.10 (dd, *J*=8.9, 3.3 Hz, 1H), 4.45 (d, *J*=2.9 Hz, 1H), 5.10 (d, *J*=1.5 Hz, 1H), 5.39 (d, *J*=1.5 Hz, 1H), 5.46 (s, 1H), 6.02 (d, *J*=11.2 Hz, 1H), 6.13 (s, 1H), 6.42 (d, *J*=11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 19.7, 22.3, 23.0, 23.5, 24.3, 27.9, 29.1, 32.0, 35.6, 40.4, 41.0, 42.6, 46.0, 52.5, 56.2, 56.7, 61.2, 68.4, 68.5, 71.9, 84.5, 86.2, 116.1, 117.2, 118.8, 125.4, 131.6, 143.1, 144.2, 146.2, 170.5; EI-LRMS *m/z* 528 (M^+), 511, 494, 477, 435; EI-HRMS Calcd for $C_{32}H_{48}O_6$ 528.3451, found 528.3451.

5.2.8. (23*R*)-25-Dehydro-1α-hydroxy-2α-(3-hydroxypropoxy)-24,24-dimethylvitamin D_3-26,23-lactone (9c). According to the general procedure, a crude product, which was obtained from **14** (30 mg, 76 μmol), **22c** (71 mg, 128 μmol), Et_3N (0.8 mL) and $Pd(PPh_3)_4$ (27 mg, 23 μmol) in toluene (0.8 mL) at 110 °C for 3 h, was treated with conc. HF in MeCN for 1 h. After usual work up, the crude product was purified by column chromatography on silica gel (hexane/AcOEt=1/4) to give **9c** (23 mg, 57% in 2 steps) as an amorphous solid. UV (EtOH) λ_{max}=267.0 nm; $[\alpha]_D^{23}$=+64.9 (*c* 1.77, $CHCl_3$); IR (film, $CHCl_3$) 3397, 1763, 1638, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.56 (s, 3H), 0.99 (d, *J*=6.6 Hz, 3H), 1.05 (s, 3H), 1.11 (m, 1H), 1.21 (s, 3H), 1.23–1.35 (m, 4H), 1.47–1.56 (m, 3H), 1.66–1.88 (m, 6H), 1.96–2.05 (m, 2H), 2.24 (dd, *J*=13.6, 8.8 Hz, 1H), 2.68 (dd, *J*=13.6, 4.4 Hz, 1H), 2.73 (br s, 3H), 2.83 (m, 1H), 3.37 (dd, *J*=7.6, 3.2 Hz, 1H), 3.74–3.91(m, 4H), 4.06 (ddd, *J*=8.2, 8.2, 4.4 Hz, 1H), 4.15 (dd, *J*=11.5, 1.2 Hz, 1H), 4.45 (d, *J*=2.9 Hz, 1H), 5.09 (d, *J*=1.7 Hz, 1H), 5.39 (s, 1H), 5.47 (s, 1H), 6.12 (d, *J*=11.2 Hz, 1H), 6.15 (s, 1H), 6.41 (d, *J*=11.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 18.6, 22.3, 22.9, 23.5, 25.1, 27.6, 29.1, 31.9, 32.9, 35.9, 40.6, 41.0, 42.0, 46.0, 56.4, 56.9, 61.1, 68.3, 68.4, 71.8, 84.3, 84.4, 116.0, 117.3, 119.1, 125.2, 131.8, 142.9, 144.2, 146.2, 170.4; EI-LRMS *m/z* 528 (M^+), 511, 494, 477, 435; EI-HRMS Calcd for $C_{32}H_{48}O_6$ 528.3451, found 528.3449.

5.3. Vitamin D receptor (VDR) binding assay

[26,27-*Methyl*-^{3}H]-1α,25-dihydroxyvitamin D_3 (specific activity 6.623 TBq/mmol, 15,000 dpm, 15.7 pg) and various amounts of 1α,25-dihydroxyvitamin D_3 and an analogue to be tested were dissolved in 50 μL of absolute ethanol in 12×75-mm polypropylene tubes. The chick intestinal VDR (0.2 mg) and 1 mg of gelatin in 1 mL of phosphate buffer solution (25 nM KH_2PO_4, 0.1 M KCl, 1 mM dithiothreitol, pH 7.4) were added to each tube in an ice bath. The assay tubes were incubated in shaking water bath for 1 h at 25 °C and then chilled in an ice bath. 1 mL of 40% polypropylene glycol 6000 in distilled water was added to each tube, which was the mixed vigorously and centrifuged at 2,260×*g* for 60 min at 4 °C. After the supernatant was decanted, the bottom of the tube containing the pellet was cut off into a scintillation vial containing 10 mL of

dioxane-based scintillation fluid and the radioactivity was counted with a Beckman liquid scintillation counter (Model LS6500). The relative potency of the analogues were calculated from their concentration needed to displace 50% of [26,27-*methyl*-^{3}H]-1α,25-dihydroxyvitamin D_3 from the receptor compared with the activity of 1α,25-dihydroxyvitamin D_3 (assigned a 100% value).

5.4. Assay for HL-60 cell differentiation

Nitro blue tetrazolium (NBT)-reducing activity was used as a cell differentiation marker. HL-60 cells were cultured in RPMI-1640 medium supplemented with 10% heat-inactivated FCS. Exponentially proliferating cells were collected, suspended in fresh medium and seeded in culture plates (Falcon, Becton Dickinson and Company, Franklin Lakes, NJ). Cell concentration at seeding was adjusted to 2×10^4 cells/mL and the seeding volume was 1 mL/well. An ethanol solution of 1α,25-dihydroxyvitamin D_3 (final concentration: 10^{-8} M) and an analogue (final concentration: 10^{-11} to 10^{-6} M) was added to the culture medium at 0.1% volume and culture was continued for 96 h at 37 °C in a humidified atmosphere of 5% CO_2/air without medium change. The same amount of vehicle was added to the control culture. NBT-reducing assay was performed according to the method of Collins.[22] Briefly, cells were collected, washed with PBS, and suspended in serum-free medium. NBT/TPA solution (dissolved in PBS) was added. Final concentrations of NBT and TPA were 0.1% and 100 ng/mL, respectively. Then, the cell suspensions were incubated at 37 °C for 25 min. After incubation, cells were collected by centrifugation and resuspended in FCS. Cytospin smears were prepared, and the counter-staining of nuclei was done with Kemechrot solution. At least 500 cells per preparation were observed.

6. Supporting Information Available

Charts of vitamin D receptor binding assay of compounds **8**, **8a–c**, **9**, and **9a–c**, and assay for HL-60 cell differentiation to test antagonistic activity of compounds **8**, **8a–c**, **9**, and **9a–c**. This material is available online with the paper in Science Direct.

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Formation of dihydroxyselenides from allylic alcohols and their conversion to β-hydroxy epoxides via substitution of a phenylselenonyl group

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Abstract—Hydroxyselenation of allylic alcohols occurs with high regio- and stereoselectivity to give β,β′-dihydroxyphenylselanyl adducts in high yields. An exception is the reaction of the terminal alcohol, 2-methylprop-2-en-1-ol, which forms only a 1,2-diol product. Generally, the addition is Markovnikov in orientation, but the fact that one *anti*-Markovnikov addition is observed and that addition to 1,2-disubstituted alkenes shows a strong preference for one regioisomer suggests that an interaction of the allylic alcohol with the selenium atom of the reaction intermediate (which weakens the C_β–Se bond in the intermediate) is also an important factor in determining the preference for addition of the phenylselanyl group to the double bond carbon nearest the allylic alcohol. The hydroxyselenated adducts of allylic alcohols can be readily converted to β-hydroxy epoxides in good yields via oxidation with *m*-chloroperbenzoic acid to a selenone and subsequent treatment with base. Hydroxyselenation of crotyl acetate and 3-acetoxycyclohexene is more regiocatholic than hydroxyselenation of the corresponding allylic alcohols. It appears that the known selectivity of additions of phenylselanyl chloride to these acetates in organic solvents is lost when water or a Lewis acid complexes to the acetate group.

1. Introduction

β-Hydroxyselenides are valuable intermediates in organic synthesis[1–4] and have been used for the formation of allylic alcohols,[5,6] C–C bonds[7] and C–N bonds.[1,4,8] They are readily formed in the presence of water from the reaction of epoxides with phenylselenide anion,[9,10] from reduction of α-keto selenides with lithium aluminium hydride,[11] and from reaction of an alkene with either phenylselanyl phthalimide[12,13] or phenylselanyl chloride[14] in the presence of water. The latter hydroxyselenation reactions have not been applied to allylic alcohols.

Liotta and co-workers have reported[15–17] that addition of phenylselanyl chloride in anhydrous organic solvents to cyclic or terminal allylic alcohols occurs in a highly regio- and stereoselective manner, whereas reaction with non-terminal allylic alcohols usually results in the formation of a mixture of regioisomers. We have noted in a preliminary report[18] that hydroxyselenation of allylic alcohols also proceeds with a high degree of regio- and stereo-selectivity. We now report that the hydroxyselenides thus obtained (Scheme 1) can be readily converted into epoxides via oxidation of the selanyl residue with *m*-chloroperbenzoic acid (*m*-CPBA) and subsequent treatment with base.[18,19] This provides a useful route to β-hydroxy epoxides from allylic alcohols (Scheme 1).

2. Results and discussion

2.1. Hydroxyselenation of allylic alcohols

Hydroxyselenation was conducted using phenylselanyl chloride in acetonitrile/water (5:1) solution at room temperature for twenty four hours. The results are summarised in Table 1. For all reactions, except that shown in entry 4, the diol product was predominantly a 1,3-diol. For entries 3, 4 and 8 the regioselectivity corresponds to Markovnikov addition whereas the addition shown in entry 2 is an *anti*-Markovnikov process. This is in contrast to the exclusive formation of Markovnikov adducts upon addition of phenylselanyl halides to similar terminal allylic alcohols in organic solvents at room temperature.[16] For the 1,2-disubstituted alkenes (entries 1, 5, 6, and 7), where the Markovnikov versus *anti*-Markovnikov preferences are less clear cut, the major product corresponds to addition of the phenylselanyl group to the double bond

Keywords: Addition; Epoxidation; Hydroxyselenation; Selenone; Regioselective.
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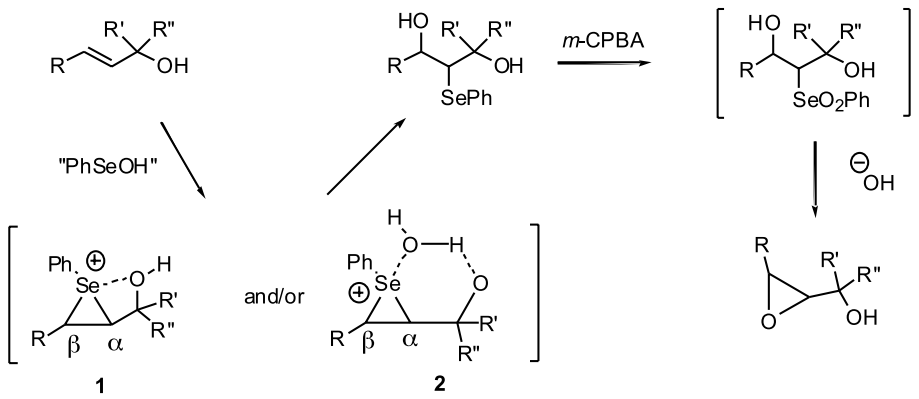
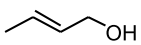
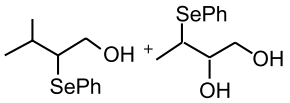
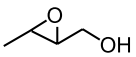
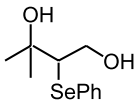
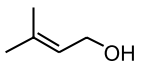
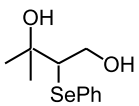
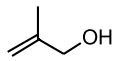
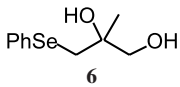
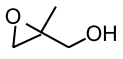
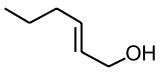
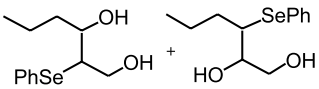
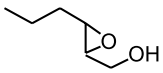
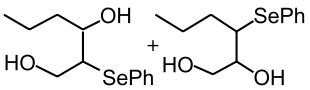
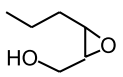
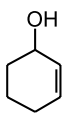
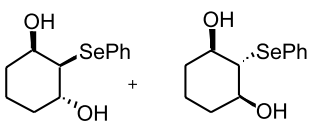
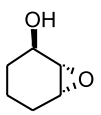
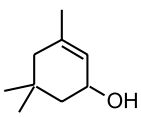
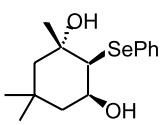
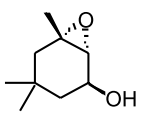


Scheme 1.

Table 1. Hydroxyselenation of allylic alcohols and conversion of the products to epoxides

Entry	Alkene	Addition product	Yield	Epoxide	Yield
1		 **3** (2 : 1) **4**	100	 **43**	66
2		 **5**	86	 **44**	74
3		 **5**	100	 **44**	74
4*		 **6**	85	 **45**	78
5		 **7** (98 : 2) **8**	91	 **46**	70
6		 **9** (9 : 1) **10**	72	 **47**	65
7		 **11** (9 : 1) **12**	91	 **48**	68
8		 **13**	60	 **49**	72

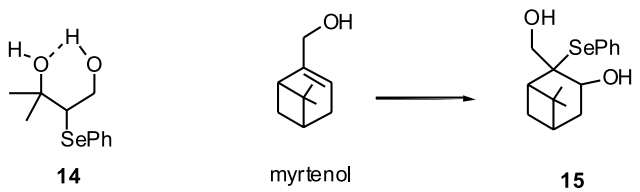
* The structure of the adduct, **6**, in this entry was incorrectly reported in our preliminary report.[18] We thank Dr. D. C. Myles for drawing this to our attention.

carbon nearest to the allylic hydroxyl. This situation is also true for the results shown in entries 2, 3 and 8 but not for that shown in entry 4. We suggest that the dominant formation of 1,3-diol containing products indicates a complexation of the selenium as shown in **1** and/or **2** (Scheme 1) which results in a weakening of the C_β–Se bond that facilitates attack by water at this carbon.

In the addition of phenylselanyl chloride to alkenes in organic solvents it has been noted that the initial *anti*-Markonikov adduct isomerises[20,21] slowly on standing to the Markovnikov adduct. This was not observed in the reaction of the terminal allylic alcohol shown in entry 2, which forms a stable *anti*-Markovnikov product. Hydroxyselenation of the disubstituted alkene, crotyl alcohol, (entry 1), gave a mixture of regioisomers. The disubstituted hex-2-ene-1-ols, (entries 5 and 6), with larger alkyl groups at the β position, exhibited a higher degree of regioselectivity with greater preference for the phenylselanyl group to be located adjacent to the hydroxyl group of the allylic alcohol. The stereochemical course of the addition was found to be *trans*-dominant as hydroxyselenation of *cis*- and *trans*-hex-2-ene-1-ols gave predominantly *threo* (7) and *erythro* (9) adducts, respectively. The possibility that the preference for the formation of 1,3-diols may be due to H-bonding stabilisation[22] (e.g. 14) of a particular adduct was rendered less likely by the observation of ^2J couplings between the hydroxyl protons in the ^{1}H NMR spectra of 5 and 7 (both 1,3-diols) and 10 (a 1,2-diol).

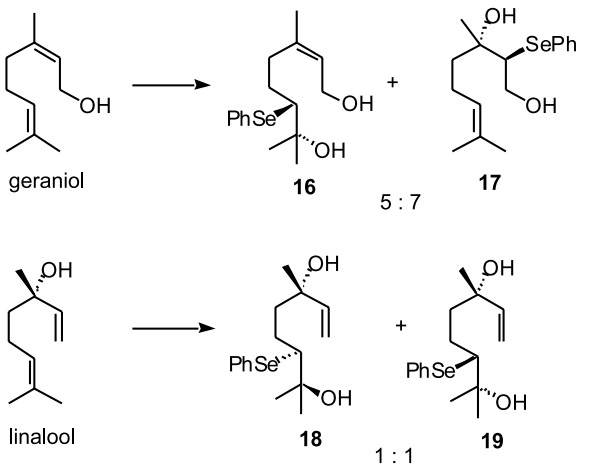
Hydroxyselenation of 2-cyclohexene-1-ol gave a 10:1 mixture of the diastereomers, 11 and 12 in high yield (Table 1). The preferential formation of the product with the *syn* orientation of the original hydroxyl group and the introduced selenium atom can be attributed to an interaction of the lone pair electrons of the oxygen atom with the electron deficient selenium atom as in 1 and/or 2 (Scheme 1).

More substituted cyclic allylic alcohols, such as myrtenol and *cis*-pulegol, gave complex product mixtures, although it was possible to isolate an *anti*-Markovnikov adduct, **15** (Scheme 2), from the reaction with myrtenol. Reaction with isophorol also gave a complex product mixture, however a major product, **13**, corresponding to a Markovnikov addition, crystallised from the mixture on standing (entry 8, Table 1).



Scheme 2.

In order to determine if coordination of the hydroxyl oxygen to the selenium atom of the reagent facilitated delivery to the allylic double bond[16,24] the alcohols geraniol and linalool were subjected to the conditions described above. In both cases no selective hydroxyselenation of the allylic double bond over the isolated double bond was observed, and two products, **16**, **17** and **18**, **19**, respectively, were



Scheme 3.

formed in each case, suggesting that prior complexation of selenium to the allylic hydroxyl group, if it occurs, does not facilitate attack on the double bond compared to attack on the isolated double bond (Scheme 3).

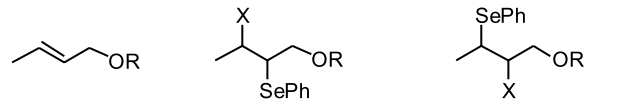
The direction of addition for the major product in the various hydroxyselenations reported above can be summarised as follows. In general the major product is a 1,3-diol, resulting from an interaction of the selenium atom in the reaction intermediate with the oxygen of the allylic alcohol (**1** and/or **2**) that preferentially favours the phenylselanyl group being attached to the double bond carbon nearest to the hydroxyl. This interaction weakens the C_β–Se bond compared to the C_α–Se bond and hence favours attack by the water at the C_β carbon. This direction of addition is only altered when, as in entry 4, electronic factors (attack by the water molecule at a tertiary carbocation or its equivalent of the intermediate episelenonium ion versus attack at a primary carbocation or its equivalent) are sufficient to outweigh this preference. This directing effect of the hydroxyl also explains the isolation of an *anti*-Markovnikov adduct from myrtenol but a Markovnikov adduct from isopulegol, (entry 8).

2.2. Hydroxyselenation of allylic acetates

The addition of phenylselanyl chloride to allylic acetates in organic, non protic, solvents proceeds with a higher degree of regio- and stereoselectivity than addition to the corresponding allylic alcohols in organic solvents.[16] For example, reaction of crotyl acetate, **20**, with phenylselanyl chloride in chloroform gives a mixture of **21** and **22** in the ratio of >20:1. In contrast, using our conditions, hydroxyselenation of **20** gave a mixture of the regioisomers, **23** and **24**, in the ratio 57:43 accompanied by the diols, **3** and **4**, in the ratio 4:1. The diols are presumably formed by in situ hydrolysis of the corresponding acetates, a process that could be enhanced by anchimeric assistance of the neighbouring phenylselanyl group.[24] When the yields are taken into account this represents an overall ratio of 7:3 in favour of selenium addition to the α position for the hydroxyselenation.

The contrasting selectivity of the addition of phenylselanyl chloride to crotyl alcohol and crotyl acetate in organic

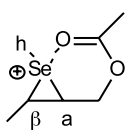
solvents has been attributed to the greater difference between the charge densities at C_α and C_β for crotyl acetate, compared to that of crotyl alcohol.[16] However the enhanced regioselectivity of additions to **20** in organic solvents may also be due to an interaction of the carbonyl group with an electron deficient episelenonium ion intermediate, as in **25**, which promotes selective attack at C_β by weakening the C_β–Se bond. If this were the case, hydroxyselenation of **20** would be more regiocatholic as interaction between the selenonium ion and the carbonyl group would be significantly blocked by a competing hydrogen bonding of the carbonyl oxygen, and, separately, of the positively charged selenium atom, with water. This hypothesis is supported by the fact that the reaction[25–27] of **20** with phenylselanyl chloride in poorer hydrogen bond donor solvents such as methanol, or acetic acid gave only the adducts, **26** and **27**, respectively. Reaction of crotyl trifluoroacetate, **28**, which possesses a more polarised double bond than **20**, with phenylselanyl chloride gave only the single adduct, **29**, in dichloromethane as solvent, and the single adduct, **30**, in methanol as solvent.



20, R = $COCH_3$
28, R = $COCF_3$

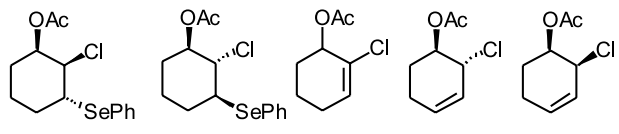
21, X = Cl, R = Ac
23, X = OH, R = Ac
26, X = OMe, R = Ac
27, X = OAc, R = Ac
29, X = Cl, R = $COCF_3$
30, X = OMe, R = $COCF_3$

22, X = Cl, R = Ac
24, X = OH, R = Ac
31, X = OMe, R = Ac

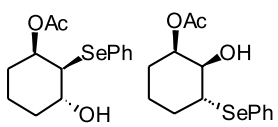


25

Reaction of the cyclic allyl acetate, **32**, with phenylselanyl chloride in deuterochloroform gave a mixture of the stereoisomers, **33** and **34**, in the ratio 9:1 (Scheme 4). The regiochemistry of this addition can be rationalised by invoking an intermediate analogous to **25** so that addition occurs predominately at the *syn* face of the double bond, which in turn suggests that complexation of the selenium with the oxygen of the acetate carbonyl is significant in directing attack to the otherwise more sterically crowded face. The regiochemistry was confirmed, at least for the major product, by an oxidative elimination of the phenylseleno group to give the vinyl chloride, **35** (Scheme 4). Reaction of **32** with phenyl-selanyl chloride in aqueous acetonitrile gave a mixture of **41** and **42** in the ratio 55:45. This result implies that under the conditions of hydroxyselenation there is no neighbouring group participation by the acetate and attack on the double bond, either *syn* or *anti* to the acetate group, is approximately equally likely. The reaction of **32** with phenylselanyl phthalimide and water also proceeds in a regiocatholic manner[23] giving **41** and **42** in a very similar ratio to that described above; surprisingly, it was noted in this paper that addition of water to the reaction of acetoxycyclohexene with phenylselanyl chloride gave only the regioisomer, **33**. However it is likely that the amount of water present in these conditions[23] is very substantially less than the amount used in our general procedure (the amount of water present was not specified in the preliminary communication[23]). If complexation of the acetate with the electron deficient selenium atom in the reaction intermediate or transition state is important in determining the regiochemistry and stereochemistry of the addition reactions to allylic acetates, then addition of a competing coordinating agent, i.e another Lewis acid, should decrease the selectivity described above.



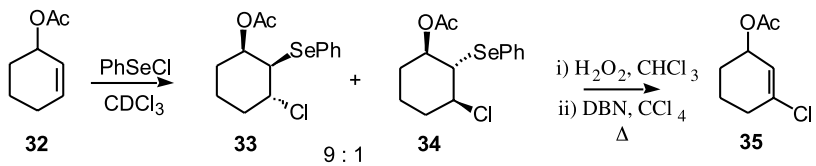
36 **37** **38** **39** **40**



41 **42**

Reaction of **20** with phenylselanyl chloride in deuterochloroform containing zinc chloride gave a mixture of **21** and **22** in the ratio 2:1; in the absence of the Lewis acid **22** was undetected. Whilst complexation of zinc to the carbonyl oxygen should further polarise the double bond, the formation of **22** suggests that the presence of the zinc ion also disrupts an electrostatic interaction between the carbonyl oxygen with the selenonium ion. Methoxyselenation of **20** in the presence of zinc chloride gave a mixture of **26** and **31** in the ratio 7:3; in the absence of the zinc chloride **31** was undetected.

Reaction of **32** with phenylselanyl chloride and zinc chloride in deuterochloroform gave a mixture of the four possible stereoisomers, **33**, **34**, **36** and **37** in the ratio 4:2:2:1. Oxidative elimination of this mixture gave a mixture of the alkenes, **35**, **38**, **39**, and **40** in the ratio 15:5:1.5:1. In the absence of the zinc chloride **36** and **37** were not detected and the ratio of **33**:**34** was 9:1. Thus, in every case, addition of a Lewis acid to the reaction mixture of an allylic acetate with phenylselanyl chloride decreases the regioselectivity, suggesting that addition of an external Lewis acid substantially decreases an intramolecular complexation of



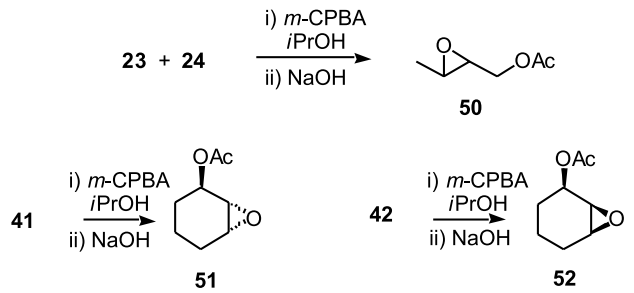
32 **33** 9 : 1 **34** **35**

Scheme 4.

the oxygen of the acetate carbonyl with the electron deficient selenium atom (which is the important factor in the predominance of the major regioisomer). Addition of titanium tetrachloride to the reaction mixture of crotyl alcohol and phenylselanyl chloride in deuterochloroform made no difference to the ratio (7:3) of the regioisomers produced in its absence,[16] showing that the effect is confined to the allylic acetate system.

2.3. Formation of epoxides

The reaction of the hydroxy selenides, obtained from the allylic alcohols shown in Table 1, with excess *m*-CPBA in isopropyl alcohol formed[4,28–31] the corresponding (non-isolated) selenones. In situ treatment of these selenones with aqueous base resulted in the formation of epoxides, **43**–**49**, in good yields (Table 1). Of particular note are the transformations of **11** and **13** to the *trans*-epoxides, **48** and **49**, respectively. Our process provides *trans*-hydroxy epoxides in two steps from the corresponding allylic alcohols, and complements established methodologies which afford *cis*-hydroxy epoxides.[32–34] The epoxide, **48** could be formed in one pot from 2-cyclohexenol by successive treatment with phenylselanyl chloride, *m*-CPBA and sodium hydroxide. The acyclic acetates, **23** and **24**, and the cyclic acetates, **41** and **42**, were also converted cleanly to the corresponding α-acetoxy epoxides by treatment with *m*-CPBA and sodium hydroxide in isopropanol (Scheme 5).



Scheme 5.

2.4. Assignment of stereochemistry

The stereochemistry of **11** was assigned on the basis of the coupling constants observed in this cyclohexyl system (Fig. 1). In **11** H_1 appeared at 4.11 ppm as a multiplet, H_2 at 3.22 ppm as a doublet of doublets (J=2.7, 9.7 Hz) and H_3 at 3.94 as a doublet of triplets (J=4.2, 9.7 Hz) in the ^{1}H NMR spectrum. In **12**, the isosteric and isoelectronic protons H_1 and H_3 were coincident at 3.28 ppm as a doublet of triplets (J=4.2, 10.1 Hz) and H_2 appeared at 2.77 ppm as a triplet (J=10.1 Hz). The COSY45 spectrum of **12** showed that H_2 was coupled only to the resonance at 3.28 ppm and H_1 and H_3 were coupled to a single OH resonance. The stereochemistry of the epoxide, **48**, was assigned as *trans* as H_2 appeared as a doublet (3.0 Hz) coupled to H_3 only. In the *cis*-epoxide, **53**,[34] H_2 appeared as a doublet of doublet of doublets (J=8.0, 5.2, 2.4 Hz), (Fig. 1).

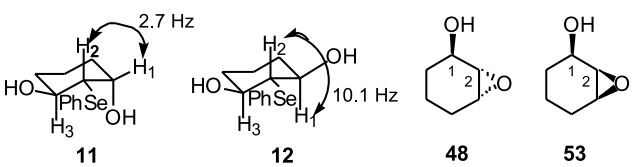


Figure 1.

The regio- and stereochemistry of **13** were assigned from examination of the ^{1}H and ^{13}C NMR, COSY90 and NOESY spectra. H_1 appeared as a triplet of triplets (J=11.3, 3.8 Hz) at 4.28 ppm, which collapsed to a doublet of triplets (J=11.3, 3.8 Hz) at 4.27 ppm upon D_2O exchange (Fig. 2). Thus H_1 was coupled to both the C_1 hydroxyl proton and H_{6a} at 11.3 Hz and to H_2 and H_{6b} at 3.8 Hz. H_2 appeared as a doublet of triplets (J=3.8, 1.8 Hz) at 3.40 ppm, the 1.8 Hz splitting arising from a ^4J coupling to H_{6a}, and the C_1 hydroxyl proton appeared as a doublet (J=11.3 Hz) at 2.49 ppm. The *trans*-epoxide, **48**, showed H_1 at 4.17 ppm as a doublet of doublets (J=7.2, 5.8 Hz) and H_2 at 2.97 ppm and the carbons C_1, C_2 and C_3 at 65.9, 62.9 and 59.4 ppm respectively. The *cis*-epoxide, **53**,[34] (Fig. 2) showed H_1 as a doublet of doublets of doublets (J=11.1, 6.1, 2.0 Hz) at 4.00 ppm, H_2 as a doublet (J=2.0 Hz) at 3.08 ppm and the carbons C_1, C_2 and C_3 at 65.4, 62.2 and 61.0 ppm respectively.

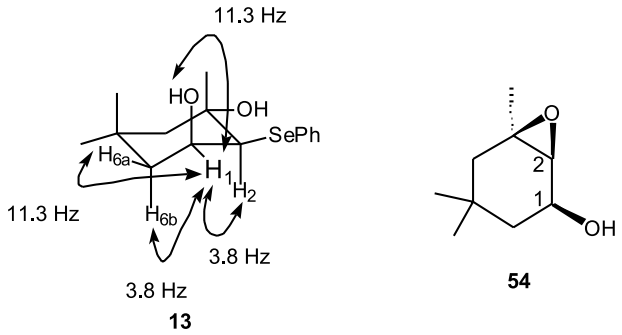


Figure 2.

3. Conclusion

Hydroxyselenation of allylic alcohols occurs readily to give products that result from an addition that is mainly controlled by an interaction of the alcohol group with the selenium atom of the reagent which favours attack by water at the carbon of the double bond remote from the alcohol group. Hydroxyselenation of allylic acetates is much more regiocatholic because the presence of water decreases the complexation of the acetate group and the selenium atom of the reagent which controls the addition of phenylselanyl halides to allylic acetates in organic solvents.

The hydroxyselenated products from allylic alcohols and allylic acetates can be smoothly converted to β-hydroxy epoxides and β-acetoxy epoxides, respectively by treatment of the adduct with *m*-CPBA followed by base. For cyclic allylic alcohols the products are *trans* β-hydroxy epoxides. Our methodology thus complements established direct epoxidation procedures for allylic alcohols that give mainly *cis* β-hydroxy epoxides.

4. Experimental

4.1. General

Infrared spectra were recorded on a Jasco A-102 spectrometer as nujol mulls or liquid films, or as solutions where indicated. ^{1}H NMR, ^{13}C NMR and all two dimensional NMR spectra were obtained at 300 MHz on a Brucker ACP-300 spectrometer using solutions in deuterochloroform with tetramethylsilane as an internal standard unless otherwise specified. Electron impact mass spectra were recorded at 70 eV on an AEI 3074 mass spectrometer. Fast atom bombardment mass spectra and CA-MIKES spectra were recorded on a VG ZAB 2HF mass spectrometer. Melting points were recorded on a Kofler hot-stage apparatus equipped with a Reichert microscope and are uncorrected. Microanalyses were performed by the Australian Microanalytical Service, Melbourne. Flash chromatography was performed using Merck Kieselgel 60 (230–400 mesh) eluting with a gradient of light petroleum/ethyl acetate. Organic extracts were dried over anhydrous sodium sulphate. Phenylselanyl phthalimide was synthesised according to the method of Nicolaou.[12] *m*-CPBA was recrystallised from dichloromethane/light petroleum and was 85% pure as determined by epoxidation of a stoichiometric amount of cyclohexene. As commercially available crotyl alcohol consists of a 70:30 mixture of *trans* and *cis* isomers, reactions using crotyl alchol or crotyl acetate gave a corresponding mixture of *erythro* and *threo* isomers. For clarity only the major *erythro* isomers are quoted.

4.2. General procedure for the hydroxyselenation of the allylic alcohols

To a stirred mixture of the allyl alcohol (5 mmol) in acetonitrile (20 ml) and water (4 ml) was added phenylselanyl chloride (960 mg, 5 mmol). The solution was stirred at room temperature for 24 h, then diluted with saturated sodium bicarbonate (10 ml) and extracted with chloroform (2×30 ml). The combined organic extracts were dried, the solvent removed under reduced pressure and the residue chromatographed to give the compounds or mixtures described below.

4.2.1. 2-Phenylselenobutane-1,3-diol (3) and 3-phenylselenobutane-1,2-diol (4). From crotyl alcohol, as a yellow oil (1.23 g, 100%), bp 135 °C, 0.03 mm, which was an inseparable mixture; [Found: C, 48.7; H, 6.0. $C_{10}H_{14}O_2Se$ requires C, 48.8; H; 5.7%]; ν_{max} (film) 3360, 1050 cm^{-1}; δ_H (**3**) 7.55 (2H, m, Ph), 7.24, (3H, m, Ph), 4.04, (1H, dq, J=7.2, 6.3 Hz, H_3), 3.97 (1H, dd, J=11.7, 4.5 Hz, H_{1a}), 3.80 (1H, dd, J=11.7, 6.5 Hz, H_{1b}), 3.57 (2H, br s, OH), 3.20 (1H, ddd, J=7.2, 6.5, 4.5 Hz, H_2), 1.34 (3H, d, J=6.3 Hz, Me). (**4**): 7.55 (2H, m, Ph), 7.24 (3H, m, Ph), 4.13 (1H, m, H_2), 4.01 (1H, dd, J=11.7, 4.5 Hz, H_{1a}), 3.85 (1H, dd, J=11.7, 6.5 Hz, H_{1b}), 3.57 (2H, s, OH), 3.22 (1H, dq, J=3.3, 6.3 Hz, H_3), 1.33 (3H, d, J=6.3 Hz, Me); *m*/*z* 246 (M), 184 (M−CH_2(OH)CH_2OH), 157 (M−SePh).

4.2.2. 3-Methyl-2-phenylselenobutane-1,3-diol (5). From 3-methyl-2-butene-1-ol, as a colourless oil (1.30 g, 100%), bp 150 °C, 0.05 mm (block); [Found: C, 50.8; H, 6.5. $C_{11}H_{16}O_2Se$ requires C, 51.0; H, 6.2%]; ν_{max} (film) 3300, 1580 cm^{-1}; δ_H 7.59 (2H, m, Ph), 7.28 (3H, m, Ph), 3.95 (2H, m, CH_2O), 3.30, (1H, t, J=5.5 Hz, CHSe), 2.88 (2H, br s, OH), 1.43 (3H, s, Me), 1.41 (3H, s, Me); *m*/*z* 260 (M), 243 (M−OH), 185.

This compound was also obtained from 2-methyl-3-butene-2-ol (1.12 g, 86%).

4.2.3. 2-Methyl-3-phenylselenopropane-1,2-diol (6). From methylallyl alcohol, as a colourless oil. (1.04 g, 85%), bp 138–140 °C, 0.05 mm (block); [Found: C, 49.3; H, 6.0. $C_{10}H_{14}O_2Se$ requires C, 49.0; H, 5.8%]; ν_{max} (film) 3350, 1570, 1470 cm^{-1}; δ_H 7.53 (2H, m, Ph), 7.23, (3H, m, Ph); 3.54 (1H, dd, J=11.1, 5.0 Hz, H_{1a}), 3.47 (1H, dd, J=11.1, 4.5 Hz, H_{1b}), 3.21 (1H, d, J=12.5 Hz, H_{3a}), 3.07 (1H, d, J=12.5 Hz, H_{3b}), 3.03 (1H, s, OH), 2.81 (1H, br dd, J=5.0, 4.5 Hz, OH), 1.22 (3H, s, Me); *m*/*z* 246 (M), 229 (M−OH).

4.2.4. *erythro*-2-Phenylselenohexane-1,3-diol (7) and erythro-3-phenylselenohexane-1,2-diol (8). From *trans*-2-hexene-1-ol, as a yellow oil (1.25 g, 91%), bp 150 °C, 0.06 mm (block) which was an inseparable mixture of (**7**) and (**8**) in the ratio 98:2; [Found: C, 52.8; H, 6.7. $C_{12}H_{18}O_2Se$ requires C, 52.8; H, 6.6%]; ν_{max} (film) 3400, 1575, 1475, 1060, 1020 cm^{-1}; δ_H (**7**) 7.58 (2H, m, Ph), 7.27 (3H, m, Ph), 4.04, (1H, ddd, 11.9, 5.7, 4.5 Hz, H_3), 3.88 (2H, m, $H_{1a}H_{1b}$), 3.29 (1H, dt, J=4.5, 5.2 Hz, H_2), 2.86 (1H, t, J=6.1 Hz, OH), 2.77 (1H, d, J=5.8 Hz, OH), 1.7–1.3, (4H, m, CH_2), 0.92 (3H, t, J=7.3 Hz, Me); *m*/*z* 274 (M), 257 (M−OH), 184 (PhSeCHCH_2), 157 (PhSe).

4.2.5. *threo*-2-Phenylselenohexane-1,3-diol (9) and threo-3-phenylselenohexane-1,2-diol (10). From *cis* 2-hexene-1-ol, as a white solid which was recrystallised (ether/light petroleum) to give the selenide (**9**) as white needles (990 mg, 72%), mp 90–91 °C; [Found: C, 52.8; H, 6.6. $C_{12}H_{18}O_2Se$ requires C, 52.8, H, 6.6%]; ν_{max} (nujol): 3360, 3300, 1580, 1475 cm^{-1}; δ_H 7.58 (2H, m, Ph), 7.25 (3H, m, Ph), 3.91 (3H, m, CHO), 3.30 (1H, dt, J=3.0, 5.3 Hz, H_2), 2.95 (2H, br s, OH), 1.7–1.3 (4H, m, CH_2), 0.90 (3H, t, J=7.2 Hz, Me); *m*/*z* 274 (M), 257 (M−OH), 184 (PhSeCHCH_2), 157 (PhSe). Further elution gave (**10**) as a colourless oil (88 mg, 6%); ν_{max} (film) 3300, 1580, 1480, 1065, 1020 cm^{-1}; δ_H 7.57 (2H, m, Ph), 7.27 (3H, m, Ph), 3.76 (1H, ddt, J=2.9, 5.3, 7.6 Hz, H_2), 3.63 (2H, m, $H_{1a}H_{1b}$), 3.21 (1H, m, H_3), 3.06 (1H, br d, J=2.9 Hz, OH), 2.25 (1H, br t, J=5.3 Hz, OH), 1.68 (2H, m, CH_2) 1.50 (2H, m, CH_2), 0.91 (3H, t, J=6.7 Hz, Me); *m*/*z* 274 (M), 257 (M−OH), 157 (PhSe).

4.2.6. *r*-2-Phenylseleno-*cis*-1,*trans*-3-cyclohexanediol (11) and *r*-2-phenylseleno-*trans*-1,*trans*-3-cyclohexanediol (12). From 2-cyclohexenol (98 mg, 1 mmol) and phenylselanyl chloride (192 mg, 1 mmol) as a yellow oil which was a mixture of the selenides (**11**) and (**12**) (248 mg, 91%), bp 165 °C, 0.03 mm (block) in the ratio 10:1; [Found: C, 53.4; H, 6.1. $C_{12}H_{16}O_2Se$ requires C, 53.14; H, 5.95%); ν_{max} (film) 3400, 1600, 1500, 1095 cm^{-1}; δ_H 7.61 (2H, m, Ph), 7.27 (3H, m, Ph), 4.11 (1H, m, H_1), 3.94 (1H, dt, J=4.2, 9.7 Hz, H), 3.22 (1H, dd, J=2.7, 9.7 Hz, H_2), 2.67 (2H, s, OH), 1.80 (2H, m, CH_2), 1.60 (2H, m, CH_2), 1.40 (2H, m,

CH_2); (**12**) 7.62 (2H, m, Ph), 7.27 (3H, m, Ph), 3.28 (2H, dt, J=4.2, 10.1 Hz, H_1H_3), 3.03 (2H, s, OH), 2.77 (1H, t, J=10.1 Hz, H_2), 1.6–1.2 (6H, m, CH_2); *m/z* 272 (M), 158 [M−(Ph+2OH)], 97 [M−(SePh+OH)].

4.2.7. *r*-2-Phenylseleno-3,5,5-trimethylcyclohexane-*cis*-1,*trans*-3-diol (13). From isophorol as a mixture (960 mg,) from which white crystals of (**13**) formed on standing (670 mg, 42%), mp 103–105 °C; [Found: C, 57.7; H, 7.1. $C_{15}H_{22}O_2Se$ requires C, 57.51; H, 7.08%]; ν_{max} (CCl_4) 3500, 3460, 1475, 1365, 1040 cm^{-1}; δ_H 7.61 (2H, m, Ph), 7.25 (3H, m, Ph), 4.28 (1H, tt, J=11.3, 3.8 Hz, H_1), 4.27 (1H, dt, J=11.3, 3.8, 11.3 Hz, one of the 11.3 couplings disappears with a D_2O shake, H_1), 3.40 (1H, dt, J=3.8, 1.8 Hz, H_2), 2.49 (1H, d, J=11.3 Hz, OH), 1.65 (1H, ddt, J=11.4, 3.8, 1.8 Hz, H_{6e}), 1.52 (1H, d, J=14.6 Hz, H_{4a}), 1.48 (3H, s, Me), 1.38 (1H, dt, J=14.6, 1.8 Hz, H_{4e}), 1.32 (1H, s, OH), 1.14 (3H, s, Me), 1.13 (1H, dd, J=11.4, 11.3 Hz, H_{6a}), 0.95 (3H, s, Me); δ_C 143.8, 134.0, 129.3, 127.6 (Ar), 76.4 (C_3), 68.1 (C_1), 65.6 (C_2), 46.8 (C_4), 45.8 (C_6), 33.6 (Me), 31.8 (Me), 28.2 (Me); *m/z* 314 (M), 297 (M−OH), 139 [M−(SePh+H_2O)], 121 [M−(SePh+$2H_2O$)].

4.2.8. 2-Hydroxymethyl-2-phenylseleno-3-hydroxy-6,6-dimethyl-bicyclo[3.3.1]-heptane (15). From (1*R*)(−) myrtenol, as a complex mixture from which it was possible to isolate the selenide (**15**) by chromatography as an oil (216 mg, 13%); ν_{max} (film) 3360, 1580, 1480, 1375, 1160, 1020, 740 cm^{-1}; δ_H 7.61 (2H, m, Ph), 7.28 (3H, m, Ph), 4.36 (1H, d, J=12.6 Hz, CH_aOH), 4.10 (1H, m, C*H*OH), 4.19 (1H, d, J=12.6 Hz, CH_bOH), 2.2–1.6 (6H, m), 2.0 (2H, br s, OH), 1.20 (3H, s, Me), 1.18 (3H, s, Me); *m/z* 326 (M), 309 (M−OH), 232 [M−(OH+Ph)], 151 (M−(OH+SePh)], 42 (CMe_2); HRMS (EI): M^+, found 326.0796. $C_{16}H_{22}O_2Se$ requires 326.0785.

4.2.9. 3(*S),7-Dimethyl-2(*S**)-phenylselenooct-6-ene-1,3-diol (17) and 3,7-dimethyl-6-phenylselenooct-2-ene-1,7-diol (16).** From geraniol (308 mg, 2 mmol) as a yellow oil which was an inseparable mixture of (**17**) and (**16**) in the ratio 7:5 (400 mg, 62%); ν_{max} (film) 3350, 1580, 1480, 1040 cm^{-1}; δ_H (**17**) 7.60 (2H, m, Ph), 7.25 (3H, m, Ph), 5.20 (1H, t, J=6.7 Hz, H_6), 4.03 (1H, m, H_{1a}), 4.02, (1H, m, H_{1b}), 3.07 (1H, m, H_2), 2.76 (2H, s, OH), 2.43 (1H, m, H_{5a}), 2.20 (1H, m, H_{5b}), 1.8–1.6 (2H, m, H_4), 1.51 (3H, s, Me), 1.35 (3H, s, Me) 1.24 (3H, s, Me); (**16**) 7. 57 (2H, m, Ph), 7.24 (3H, m, Ph), 5.09 (1H, t, J=6.8 Hz, H_2), 4.10 (2H, dd, J=15.0, 6.8 Hz, $H_{1a}H_{1b}$), 3.60 (1H, m, H_6), 2.47 (2H, br s, OH), 2.1–1.9 (4H, m, CH_2), 1.67 (3H, s, Me), 1.59 (3H, s, Me), 1.27 (3H, s, Me); *m/z* 328 (M), 154 [M−(SePh+OH)]; HRMS (EI): M^+, found 328.0938. $C_{16}H_{24}O_2Se$ requires 328.0941.

4.2.10. 2,6(*S)-Dimethyl-3(*R**)-phenylseleno-oct-7-ene-2,6-diol (18) and 2,6(*S**)-dimethyl-3(*S**)-phenylselenoct-7-ene-2,6-diol (19).** From linalool (308 mg, 2 mmol) as a yellow oil which was an inseparable mixture of **18** and **19** in the ratio 1:1 (140 mg, 42%); ν_{max} (CCl_4) 3360, 1580, 1480, 1370, 1040 cm^{-1}; δ_H (**18**) 7.57 (2H, m, Ph), 7.26 (3H, m, Ph), 6.80 (1H, dd, J=17.4, 10.7 Hz, H_x), 5.22 (1H, dd, J=17.4, 1.2 Hz, H_a), 5.03 (1H, dd, J=10.7, 1.2 Hz, H_b), 3.35, (1H, m, CHSe), 3.2 (2H, br s, OH), 2.2–1.4 (4H, m, CH_2), 1.39 (3H, s, Me), 1.31 (3H, s, Me), 1.27 (3H, s, Me); (**19**) 7.57 (2H, m, Ph), 7.26 (3H, m, Ph), 5.90 (1H, dd, J=17.4, 10.7 Hz, H_x), 5.14 (1H, dd, J=17.4, 1.2 Hz, H_a), 4.99 (1H, dd, J=10.7, 1.2 Hz, H_b), 3.2 (2H, br s, OH), 2.65 (1H, m, CHSe), 2.2–1.4 (4H, m, CH_2), 1.37, 3H, s, Me), 1.33 (3H, s, Me), 1.28 (3H, s, Me); m/s 328 (M), 171 [M−(SePh+OH)], 127 [M−(SePh+OH+CH=CH_2)]; HRMS (EI): M^+, found 328.0963. $C_{16}H_{24}SeO_2$ requires 328.0942.

4.2.11. Reactions of crotyl acetate (20). *Using the above general procedure*. 3-Hydroxy-2-phenylselenobutyl acetate (**23**) and 2-hydroxy-3-phenylselenobutyl acetate (**24**) were prepared from crotyl acetate, using the general procedure, as a yellow oil (460 mg, 32%), bp 145 °C, 0.05 mm (block) which was an inseparable mixture in the ratio 57:43 (**23**:**24**); ν_{max} (film) 3350, 1720, 1560, 1030 cm^{-1}; δ_H (**24**) 7.59 (2H, m, Ph), 7.27 (3H, m, Ph), 4.19 (2H, m, CH_2OAc), 3.87 (1H, m, CHOH), 3.44 (1H, dq, J=4.7, 7.0 Hz, CHSe), 2.60 (1H, br d, J=4.1 Hz, OH), 2.05 (3H, s, COMe), 1.43 (3H, d, J=7.0 Hz, Me); (**23**) 7.59 (2H, m, Ph), 7.27 (3H, m, Ph), 4.20 (2H, m, CH_2OAc), 3.68 (1H, m, CHO), 3.55 (1H, m, CHSe), 2.74 (1H, br s, OH), 2.06 (3H, s, COMe), 1.46 (3H, d, J=6.8 Hz, Me); *m/z* 288 (M), 245 (M−Ac), 131 (M−SePh); HRMS (EI): M^+, found 288.0253. $C_{12}H_{16}O_3Se$ requires 288.0264.

Further elution gave a mixture of (**3**) and (**4**), in the ratio 4:1, as a colourless oil (455 mg, 37%).

With phenylselanyl chloride in methanol. To crotyl acetate (114 mg, 1 mmol) in dry methanol (10 ml) under nitrogen was added phenylselanyl chloride (191 mg, 1 mmol) and the reaction was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue chromatographed to give 3-methoxy-2-phenylselenobutyl acetate (**26**) as a light yellow oil (260 mg, 86%); ν_{max} (film) 1730, 1580, 1480, 1125, 1100, 700 cm^{-1}; δ_H 7.57 (2H, m, Ph), 7.25 (3H, m, Ph), 4.43 (1H, dd, J=11.7, 4.5 Hz, H_{1a}), 4.36 (1H, dd, J=11.7, 6.4 Hz, H_{1b}), 3.62 (1H, qn, J=6.1 Hz, H_3), 3.49 (1H, dt, J=4.6, 6.1 Hz, H_2), 3.35 (3H, s, OMe), 1.97 (3H, s, COMe), 1.34 (3H, d, J=6.1 Hz, Me); *m/z* 302 (M), 242 (M−OAc), 184 (M−{OAc+[CH_3CH(OMe)]}), 157 (SePh), 85; HRMS (EI): M^+, found 302.0423. $C_{13}H_{18}O_3Se$ requires 302.0421.

With phenylselanyl chloride and zinc chloride in methanol. To a stirred mixture of crotyl acetate (114 mg, 1 mmol) and zinc chloride (136 mg, 1 mmol) in dry methanol (10 ml) under nitrogen was added phenylselanyl chloride (191 mg, 1 mmol). The mixture was stirred at room temperature for 18 h, the solvent removed under reduced pressure and the residue chromatographed to give a mixture of 3-methoxy-2-phenylselenobutyl acetate (**26**) and 2-methoxy-3-phenylselenobutyl acetate (**31**) in the ratio 7:3 as a yellow oil (83 mg, 27%); δ_H (**31**) 7.60 (2H, m, Ph), 7.26, (3H, m, Ph), 4.39 (2H, m, $H_{1a}H_{1b}$), 3.64, (1H, dt (J=6.3, 6.1 Hz), H_2), 3.47 (1H, m, H_3), 3.33 (3H, s, OMe), 1.98 (3H, s, COMe), 1.37, (3H, d J=6.1 Hz, Me).

With phenylselanyl bromide in acetic acid. A mixture of crotyl acetate (114 mg, 1 mmol), phenylselanyl bromide (236 mg, 1 mmol) and anyhdrous sodium acetate (330 mg, 4 mmol) in glacial acetic acid (10 ml) was stirred at room

temperature for 24 h. The solution was diluted with water (20 ml) then extracted with ethyl acetate (2×20 ml). The combined organic extracts were washed with water (20 ml), 10% sodium bicarbonate, dried, the solvent removed under reduced pressure and the residue chromatographed to give 3-acetoxy-2-phenylselenobutyl acetate (**27**) as a yellow oil (170 mg, 52%); ν_{max} (film) 1740, 1375, 1220, 1020, 690 cm^{-1}; δ_H 7.59 (2H, m, Ph), 7.27 (3H, m, Ph), 5.19 (1H, qn, *J*=5.9 Hz, CHOAc), 4.41 (1H, dd, *J*=11.7, 5.7 Hz, CH_aOAc), 4.29 (1H, dd, *J*=11.7, 7.1 Hz, CH_bOAc), 3.51 (1H, dt, *J*=7.1, 5.7 Hz, CHSe), 2.02 (3H, s, Me), 1.96 (3H, s, Me), 1.37 (3H, d, *J*=6.0 Hz, Me); *m/z* 330 (M), 271 (M−OAc), 173 (M−SePh); HRMS (EI): M^+, found 330.0363. $C_{14}H_{18}O_4Se$ requires 330.0369. Further elution gave the alcohol (**23**) as a yellow oil (34 mg, 12%).

With phenylselanyl chloride. To a solution of crotyl acetate (11.4 mg, 0.1 mmol) in deuterochloroform (0.5 ml) was added phenylselanyl chloride (19.1 mg, 0.1 mmol) and the reaction followed by ^1H NMR. Only the adduct 3-chloro-2-phenylselenobutyl acetate (**21**) was detected; δ_H 7.61 (2H, m, Ph), 7.30, (3H, m, Ph), 4.49 (2H, d, *J*=5.6 Hz, CH_2O), 4.37 (1H, m, CHCl), 3.47 (1H, dt, *J*=6.8, 5.5 Hz, CHSe), 2.03 (3H, s, Me), 1.67 (3H, d, *J*=6.6 Hz, Me).

With phenylselanyl chloride and zinc chloride. To a stirred mixture of crotyl acetate (114 mg, 1 mmol) and anhydrous zinc chloride (136 mg, 1 mmol) in deuterochloroform (2 ml) under nitrogen was added phenylselanyl chloride (191 mg, 1 mmol) in deuterochloroform (1 ml). ^1H NMR showed a mixture of the adducts (**21**) and (**22**) in the ratio 2:1; δ_H (**22**) 7.61 (2H, m, Ph), 7.30 (3H, m, Ph), 4.43 (2H, d, *J*=5.8 Hz, CH_2OAc), 4.31 (1H, m, CHCl), 3.23 (1H, m, CHSe), 2.10 (3H, s, COMe), 1.58 (3H, d, *J*=7.2 Hz, Me).

4.2.12. 3-Methoxy-2-phenylselenobutyl trifluoroacetate (30). To a stirred mixture of the trifluoroacetate (**28**) (169 mg, 1 mmol) in dry methanol (10 ml) under nitrogen was added phenylselanyl chloride (191 mg, 1 mmol). The mixture was stirred at room temperature overnight, the solvent removed under reduced pressure and the residue chromatographed to give the selenide (**30**) as a yellow oil (140 mg, 78%); ν_{max} (film) 1750, 1580, 1440, 1100, 695 cm^{-1}; δ_H 7.58 (2H, m, Ph), 7.28 (3H, m, Ph), 5.12 (2H, d, *J*=5.8 Hz, CH_2O), 4.30 (1H, m, CHO), 3.58 (1H, dt, *J*=7.0, 5.6 Hz, CHSe). 1.63 (3H, d, *J*=6.3 Hz, Me); *m/z* 274 (M−$COCF_3$), 184 (PhSeCH), 85 ($COCF_3$).

4.2.13. 3-Chloro-2-phenylselenobutyl trifluoroacetate (29). To crotyl trifluoroacetate (85 mg, 0.5 mmol) in deuterochloroform (2 ml) under nitrogen was added phenylselanyl chloride (96 mg, 0.5 mmol) and the reaction was followed by ^1H NMR Only the adduct (**29**) could be detected; δ_H 7.58 (2H, m, Ph), 7.28 (3H, m, Ph), 5.12 (2H, d, *J*=5.8 Hz, CH_2O), 4.30 (1H, m, CHCl), 3.58 (1H, dt, *J*=7.0, 5.6 Hz, CHSe), 1.63 (3H, d, *J*=6.7 Hz, Me).

4.2.14. Reactions of acetoxycyclohex-2-ene (32). *With phenylselanyl chloride*. To a stirred mixture of the acetate (**32**) (70 mg, 0.5 mmol) in deuterochloroform (2 ml) under nitrogen was added phenylselanyl chloride (96 mg, 0.5 mmol) and the mixture stirred at room temperature for 2 h. ^1H NMR showed a mixture of (**33**) and (**34**) in the ratio 9:1; δ_H (**33**) 7.58 (2H, m, Ph), 7.28 (3H, m, Ph), 5.33 (1H, dt, *J*=4.1, 7.8 Hz {collapses to dd, *J*=4.1, 7.8 Hz, upon irradiation at 3.8 ppm}, CHO), 4.50 (1H, m, {collapses to t, *J*=4.1 Hz, upon irradiation at 3.8 ppm}, CHCl), 3.81 (1H, m,{collapses to d, *J*=2.4 Hz, upon irradiation at 5.3 and to d, *J*=4.1 Hz, upon irradiation at 4.5 ppm}, CHSe), 2.26 (2H, m), 1.98 (3H, s, Me), 1.75 (4H, m); (**34**) 7.58 (2H, m, Ph), 7.28 (3H, m, Ph), 4.83 (1H, ddd, *J*=9.4, 9.4, 4.4 Hz, {collapses to dd, *J*=4.4, 9.4, upon irradiation at 3.2 ppm}, CHO), 3.70 (1H, m, CHCl), 3.20 (1H, t, *J*=9.4 Hz, {collapses to d, *J*=9.4 Hz, upon irradiation at 4.8 or 3.7 ppm}, CHSe), 2.26 (2H, m), 2.06 (3H, s, Me), 1.75 (4H, m).

With phenylselanyl chloride and zinc chloride. To a stirred mixture of the acetate (**32**) (70 mg, 0.5 mmol) and anyhdrous zinc chloride (68 mg, 0.5 mmol) in deutero-chloroform (2 ml) under nitrogen was added phenylselanyl chloride (96 mg, 0.5 mmol) and the mixture stirred at room temperature for 2 h. ^1H NMR showed a mixture of (**33**), (**34**), (**36**) and (**37**) in the ratio 4:2:2:1; δ_H (**36**) 7.58 (2H, m, Ph), 7.28 (3H, m, Ph), 5.51 (1H, ddd, *J*=9.4, 3.1, 3.1 Hz, CHO), 4.36 (1H, m, CHCl), 3.68 (1H, m, H_3), 2.26 (2H, m), 2.10 (3H, s, Me), 1.75 (4H, m); (**37**) 7.58 (2H, m, Ph), 7.28 (3H, m, Ph), 4.64 (1H, dt, *J*=4.1, 8.0 Hz, CHO), 4.58 (1H, m, CHCl), 3.67 (1H, m, CHSe), 2.26 (2H, m), 2.11 (3H, s, Me), 1.75 (4H, m).

4.2.15. Acetoxy-3-chlorocyclohex-2-ene (35). A mixture of the acetate, (**32**), (280 mg, 2 mmol) and phenylselanyl chloride (420 mg, 4.2 mmol) in dry chloroform (20 ml) was stirred at room temperature for 1 h. Hydrogen peroxide (34% v/v, 5 ml) was then added and the mixture stirred vigorously for a further 20 min. The solution was washed with water (10 ml), dried and the solvent removed under reduced pressure. The residue was redissolved in carbon tetrachloride (5 ml) and added to a refluxing mixture of DBN (620 mg, 5 mmol) in carbon tetrachloride (20 ml) under nitrogen. The mixture was refluxed for 15 min. then the cooled solution was washed with 10% hydrochloric acid (10 ml), water (10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the alkene[35] (**35**) as a colourless liquid (150 mg, 43%); ν_{max} (CCl_4) 1735, 1650, 1240 cm^{-1}; δ_H 5.90 (1H, dt, *J*=4.3, 1.6 Hz, H_2), 5.27 (1H, m, H_1), 2.33 (2H, m), 2.03 (3H, s, Me), 1.8–1.7 (4H, m); *m/z* 174/176 (weak, M), 139 (M−Cl), 114/116 (M−HOAc), 96 [M−(Cl+Ac)], 79 [M−(Cl+HOAc)].

4.2.16. Acetoxy-2-chlorocyclohex-2-ene (38), *trans* acetoxy-2-chlorocyclohex-3-ene (39) and *cis* acetoxy-2-chlorocyclohex-3-ene (40). The reaction was carried out as for the preparation of (**35**) above, except anhydrous zinc chloride (272 mg, 2 mmol) was added to the initial reaction mixture. Chromatography gave an inseparable mixture of (**35**), (**38**), (**39**) and (**40**) in the ratio 15:5:1.5:1; δ_H (**38**) 7.58 (2H, m, Ph), 7.24 (3H, m, Ph), 6.11 (1H, dd, *J*=3.3, 4.9 Hz, H_3), 5.35 (1H, m, H_1), 2.33 (2H, m), 2.10 (3H, s, Me), 1.8–1.7 (4H, m); (**39**) 7.58 (2H, m, Ph), 7.24 (3H, m, Ph), 5.9–5.7 (2H, m, CHX), 5.02 (1H, dt, *J*=11.6, 3.7 Hz, H_1), 4.78 (1H, m, H_2), 2.33 (2H, m), 2.12 (3H, s, Me), 1.8–1.7 (4H, m); (**40**) 7.58 (2H, m, Ph), 7.24 (3H, m, Ph), 5.9–5.7 (2H, m, CHX), 5.10 (1H, ddd, *J*=3.0, 3.5, 8.0 Hz,

H_1), 4.68 (1H, m, H_2), 2.33 (2H, m,), 2.08 (3H, s, Me), 1.8–1.7 (4H, m).

4.2.17. *r*-2-Phenylseleno-*trans*-3-hydroxycyclohexane-*cis*-1-acetate (41) and *r*-2-hydroxy-*trans*-3-phenylseleno-cyclohexane-*cis*-1-acetate (42). To a stirred mixture of the acetate (**32**) (910 mg, 6.5 mmol) in acetonitrile (20 ml) and water (5 ml) at 0 °C was added a solution of phenylselanyl chloride (1.25 g, 6.5 mmol) in acetonitrile (3 ml). The mixture was stirred at 0 °C for 1 h, then at room temperature for 24 h. The solution was then diluted with saturated sodium bicarbonate (10 ml) and extracted with chloroform (3×20 ml). The combined organic extracts were washed with saturated sodium chloride (10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the selenide (**41**) (955 mg, 47%) as a yellow oil, bp 150 °C, 0.05 mm (block); ν_{max} (film) 3350, 1720, 1580, 1480 cm^{-1}. δ_H 7.60 (2H, m, Ph), 7.28 (3H, m, Ph), 5.43 (1H, m, CHOAc), 4.12 (1H, m, CHOH), 3.47 (1H, dd, *J*=7.7, 3.3 Hz, CHSe), 2.84 (1H, br s, OH), 1.90 (3H, s, Me), 2.1–1.4 (6H, m); δ_C 170.1 (C=O), 135.0 134.7 129.8 123.7 (Ar), 73.6 (*C*OAc), 70.8 (COH), 55.6 (CSe), 33.0, 21.5, 20.8, 19.7; *m/z* 314 (M), 271 (M−Ac), 157 (M−SePh), 147, 104, 76. Further elution gave the selenide (**42**) (775 mg, 38%) as a yellow oil; δ_H 7.60 (2H, m, Ph), 7.28 (3H, m, Ph), 5.30 (1H, m, CHOAc), 3.52 (1H, dd, *J*=9.5, 2.7 Hz, CHOH), 3.39 (1H, dt, *J*=9.6, 3.7 Hz, CHSe), 2.61 (1H, br s, OH), 2.11 (3H, s, Me), 2.1–1.4 (6H, m); δ_C 170.7 (C=O), 136.2 134.2 129.0 128.3 (Ar), 72.3 (*C*OAc), 71.8 (COH), 46.3 (CSe), 31.4, 28.2, 21.2, 20.9.

4.3. General procedure for the conversion of selenides to epoxides

The selenide, or mixture of selenides (1 mmol), *m*-CPBA (1.01 g 85%, 5 mmol) and 10% potassium hydroxide (2 ml) in isopropyl alcohol (20 ml) was stirred at room temperature for 1 h. The solution was diluted with saturated sodium thiosulfate (10 ml) and extracted with chloroform (2×20 ml). The combined organic extracts were washed with 10% sodium hydroxide (10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed.

By this means the following epoxides were prepared:

4.3.1. *trans*-2,3-Epoxybutan-1-ol (43).[36] From the mixture of selenides (**3**) and (**4**), as a colourless oil (58 mg, 66%); ν_{max} (film) 3460, 1580, 1440, 1235 cm^{-1}; δ_H 4.01 (1H, br s, OH), 3.94 (1H, dd, *J*=12.7, 2.4 Hz, H_{1a}), 3.63 (1H, dd, *J*=12.7, 4.4 Hz, H_{1b}), 3.06 (1H, dq, *J*=2.4, 5.3 Hz, H_3), 2.93 (1H, dt, *J*=4.5, 2.4 Hz, H_2), 1.35 (3H, d, *J*=5.3 Hz, Me).

4.3.2. 3,4-Epoxy-2-methyl-butan-2-ol (44).[37] From the selenide (**5**), as a colourless oil (75 mg, 74%); ν_{max} (film) 3320, 1580, 1030 cm^{-1}; δ_H 3.98 (1H, br s, OH), 3.86 (1H, dd, *J*=12.2, 4.2 Hz, H_{1a}), 3.68 (1H, dd, *J*=12.2, 6.9 Hz, H_{1b}), 3.01 (1H, dd, *J*=6.9, 4.2 Hz, H_2), 1.36 (3H, s, Me), 1.32, (3H, s, Me).

4.3.3. 2,3-Epoxy-2-methylpropan-1-ol (45).[38] From the selenide (**6**), as a colourless oil (69 mg, 78%); ν_{max} (film) 3340, 1580, 1030 cm^{-1}; δ_H 3.73 (1H, d, *J*=12.3 Hz, H_{1a}), 3.62 (1H, d, *J*=12.3 Hz, H_{1b}), 2.92 (1H, d, *J*=4.8 Hz, H_{3a}), 2.66 (1H, d, *J*=4.8 Hz, H_{3b}), 1.37 (3H, s, Me).

4.3.4. *trans*-2,3-Epoxyhexan-1-ol (46).[39] From the selenide (**7**), as a colourless oil (75 mg, 65%); ν_{max} (film) 3430, 1255, 1030 cm^{-1}; δ_H 4.07 (1H, br s, OH), 3.78 (1H, dd, *J*=12.8, 3.0 Hz, H_{1a}), 3.68 (1H, dd, *J*=12.8, 6.7 Hz, H_{1b}), 2.96 (2H, m, H_2 and H_3), 1.6–1.3, (4H, m, CH_2), 0.95 (3H, t, *J*=7.5 Hz, Me).

4.3.5. *cis*-2,3-Epoxyhexan-1-ol (47).[40] From the selenide (**9**), as a colourless oil (81 mg, 70%); ν_{max} (film) 3430, 1255, 1030 cm^{-1}; δ_H 4.09 (1H, br s, OH), 3.85 (1H, dd, *J*=12.8, 2.4 Hz, H_{1a}), 3.53 (1H, dd, *J*=12.8, 4.2 Hz, H_{1b}), 2.89 (2H, m, H_2 and H_3), 1.5–1.3 (4H, m, CH_2), 0.89 (3H, t, *J*=7.3 Hz, Me).

4.3.6. *trans*-2,3-Epoxycyclohexan-1-ol (48).[41] From the selenide (**11**), as a colourless oil (79 mg, 70%); ν_{max} (CCl_4) 3620, 1230, 825 cm^{-1}; δ_H 4.02 (1H, m, H_1), 3.24 (1H, m, H_3), 3.08 (1H, d, *J*=3.0 Hz, H_2), 2.19 (1H, br d, *J*=4.3 Hz, OH), 2.0–1.7 (3H, m), 1.5–1.2 (3H, m); *m/z* 97 (M−OH), 70 (M−C_2H_4O), 57 (M−$C_2H_5O_2$).

This compound was also formed from a mixture of 2-cyclohexenol (98 mg, 1 mmol) in acetonitrile (20 ml) and water (4 ml) to which was added phenylselanyl chloride (191 mg, 1 mmol) and the mixture stirred at room temperature for 18 h. A solution of *m*-CPBA (1.01 g, 5 mmol) in isopropyl alcohol (10 ml) and 10% aqueous potassium hydroxide (2 ml) was then added and the mixture stirred at room temperature for a further hour. Work up as described in the general procedure gave the epoxide (**48**) (70 mg, 62%).

4.3.7. *trans*-2,3-Epoxy-3,5,5-trimethylcyclohexan-1-ol (49).[42] From the selenide (**13**), (31 mg, 0.1 mmol) as a colourless oil (11 mg, 72%); ν_{max} (CCl_4) 3325, 1360, 1040 cm^{-1}: δ_H 4.17 (1H, dd, *J*=7.2, 5.8 Hz, H_1), 2.97 (1H, s, H_2), 2.15 (1H, br s, OH), 1.71 (1H, d, *J*=15.1 Hz, H_{4a}), 1.64 (1H, dd, *J*=13.4, 5.8 Hz, H_{6a}), 1.52 (1H, d, *J*=15.1 Hz, H_{4b}), 1.34 (3H, s, Me), 1.17 (1H, dd, *J*=13.4, 7.2 Hz, H_{6b}), 0.97 (3H, s, Me), 0.91 (3H, s, Me); δ_C 65.9 (C_1), 62.9 (C_2), 59.4 (C_3), 42.5 (C_4), 42.4 (C_6), 31.6 (Me), 28.9 (C_5), 28.5 (Me), 24.1 (Me).

4.3.8. 2,3-Epoxy-1-butyl acetate (50).[43] From a mixture of the selenides (**23**) and (**24**), as a colourless oil (92 mg, 71%); ν_{max} (film) 3460, 1720, 1580, 1230, 1030 cm^{-1}; δ_H 4.37 (1H, dd, *J*=12.2, 3.0 Hz, H_{1a}), 3.92 (1H, dd, *J*=12.2, 6.1 Hz, H_{1b}), 2.94 (2H, m, CH_2), 2.10 (3H, s, COMe), 1.35 (3H, d, *J*=5.0 Hz, Me).

4.3.9. *trans*-2,3-Epoxycyclohexane-1-acetate (51).[44] From the selenide (**41**), as a colourless oil (52 mg, 67%); ν_{max} (film) 1725, 1370, 1245 cm^{-1}; δ_H 5.04 (1H, dt, *J*=1.2, 6.8 Hz, H_1), 3.29 (1H, m, H_3), 3.23, (1H, m, H_2), 2.11 (3H, s, Me), 1.8–1.3 (6H, m).

4.3.10. *cis*-2,3-Epoxycyclohexane-1-acetate (52).[44] From the selenide (**42**), as a colourless oil (57 mg, 73%); ν_{max} (film) 1725, 1370, 1240 cm^{-1}; δ_H 5.12 (1H, dt, *J*=1.4

5.2 Hz, H_1), 3.29 (1H, m, H_3), 3.07 (1H, d, J=3.6 Hz, H_2), 2.10 (3H, s, Me), 1.8–1.3 (6H, m).

4.3.11. *cis*-2,3-Epoxycyclohexan-1-ol (53). This compound was prepared by the method of Magnusson[34] from 2-cyclohexenol (196 mg, 2 mmol) and gave the epoxide (**54**) (155 mg, 68%) as a colourless oil; ν_{max} (CCl_4) 3590, 1230, 820 cm^{-1}. δ_H 4.01 (1H, ddd, J=8.0, 5.2, 2.4 Hz, H_1), 3.46 (1H, m, H_2), 3.45 (1H, br s, OH), 3.33 (1H, m, H_3), 1.8–1.2 (6H, m). Further elution gave the epoxide (**48**) (4 mg, 2%).

4.3.12. *cis*-2,3-Epoxy-3,5,5-trimethylcyclohexan-1-ol (54). This compound was prepared by the method of Magnusson[34] from isophorol (140 mg, 1 mmol) and gave the epoxide (**54**) (154 mg, 99%) as a colourless oil; ν_{max} (film) 3300, 1040 cm^{-1}; δ_H 4.00 (1H, ddd, J=11.1, 6.1, 2.0 Hz, H_1), 3.08 (1H, d, J=2.1 Hz, H_2), 1.57 (1H, d. J=15.0 Hz, H_{4a}), 1.37 (1H, ddd, J=12.1, 2.2, 6.1 Hz, H_{6a}), 1.38 (1H, br s, OH), 1.35 (1H, dd J=2.1, 15.0 Hz, H_{4b}),1.27 (3H, s, Me), 1.13 (1H, dd, J=12.1, 11.1 Hz, H_{6b}), 0.82 (3H, s, Me). 0.78 (3H, s, Me); δ_C 65.4 (C_1), 62.2 (C_2), 61.0 (C_3), 42.2 (C_4), 39.8 (C_6), 31.2 (C_5), 31.1 (Me), 26.3 (Me), 24.6 (Me).

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Palladium charcoal-catalyzed deprotection of *O*-allylphenols

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Abstract—Allyl aryl ethers can be easily cleaved by the use of 10% Pd/C under mild and basic conditions. The present reaction would involve a SET process rather than a π-allyl-palladium complex. The scope and limitation of this new deprotective methodology is also described.

1. Introduction

The phenolic hydroxyl group exists in various types of chemical compounds as demonstrated by the vast number of natural products in plant and animal life. The functional group plays a very important role in increasing biological activities in many cases. In developing a synthesis of any phenol-containing products, protection is often mandatory to prevent reaction with oxidizing agents and electrophiles or reaction of the nucleophilic phenoxide ion with even mild alkylating and acylating agents. Thus, many of the protective groups have been developed for phenol protection.[1] Allyl ether is known as one of the useful protective groups because of its stability in hydrolysis towards both acidic and basic conditions. Also, facile preparation of allyl ethers from a phenol with an allyl halide in the presence of a base is quite advantageous. Therefore, several one-step deprotective methods among them have appeared,[1] of which Pd-catalyzed deprotection was one of the most interesting features. In fact, combinations of $Pd(PPh_3)_4$ and reducing agents such as $NaBH_4$,[2] $LiBH_4$,[3] Bu_3SnH,[4] $PhSiH_3$,[5] morphorine,[6] $ZnCl_2$-polymethylhydrosiloxane,[7] or $TolSO_2H$[8] were reported. Also, electrochemical cleavage using $PdCl_2$[9] was investigated. As an alternative catalyst, Boss and Scheffold reported a reaction using 10% Pd/C with *p*-TsOH[10] under reflux conditions. During our synthetic studies[11] on host compounds combined with a crown ether and two orthocyclophanes, we unexpectedly found deprotection of the phenolic allyl ether of tetra(*O*-allyl-6-bromoisovanillyl)dibenzo-18-crown-6 (**1**) which gave a tetraphenol (**2a**) instead of a propyl ether (**2b**) under reductive conditions (H_2, 10% Pd/C in 10% KOH–MeOH) (Scheme 1). The structure of **2a** was determined as the corresponding acetate (**2c**), because the high polarity of **2a** prevented extraction into organic solvents. This result indicated that **1** suffered not only debromination but also deallylation. We envisaged that the present reaction could be applied to the cleavage of *O*-allylphenols. Here, we wish to describe a facile and mild reaction for deprotection of *O*-allylphenols using 10% Pd/C in 10% KOH–MeOH at ambient temperature[12] and discuss the reaction mechanism (Scheme 2).

2. Results and discussion

At first, the essential conditions for this facile reaction were investigated by the use of *O*-allylvanillin (**3**)[13] as a model compound (Scheme 3, Table 1). Without either a Pd catalyst or base, the reaction did not occur at room temperature (entries 1 and 3). The crown ether part was not necessary for the reaction (entries 2 and 5). Although the reaction proceeded in the absence of KOH under reflux, it was sluggish and isomerized enol ethers (**5a**,**b**) were formed (entry 4).[14] As a base, NaOMe was also efficient (entry 6), however, eventually, it was verified to be a simple combination of reagents (10% Pd/C and 10% KOH–MeOH) for cleavage of the allyl ether (entry 5).

Next, we applied the present reaction to various types of mono-substituted *O*-allylphenols (**6a**–**o**) for confirmation of scope and limitation (Scheme 4, Table 2). *O*-Allylphenols (**6a**–**h**), which have an electron-withdrawing or weak

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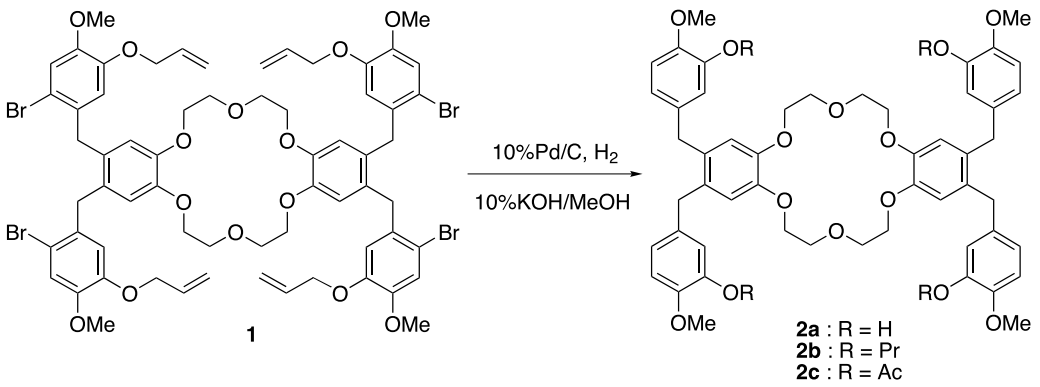
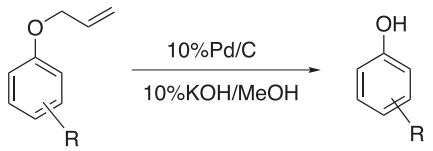
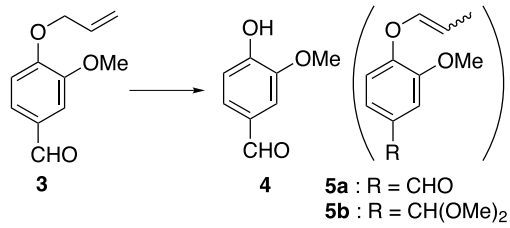


Scheme 1.



Scheme 2.



Scheme 3.

group, such as the methoxy or hydroxyl group, were lower compared with those of **6a**–**h** because of the formation of the corresponding propyl ethers (**8j**–**o**) by reduction and enol ethers (**9j**,**k**) by isomerization (entries 10–15).[14] Interestingly, although the reason was not clear, a substituted pattern on the benzene ring markedly affected the reaction. For example, deallylation of 2-methoxyallylphenol (**6l**) was faster than that of 3- and 4-methoxyallylphenols (**6j**,**k**) to yield 2-methoxyphenol (**7l**) in 76% yield (entries 10–12)

The reaction of more complex substrates (**6p**–**y**) also proceeded to afford the corresponding phenols (**7p**–**u**) in good to high yields (Table 3). Deprotection of *O*-allylphenols (**6s**,**t**), bearing an acid labile benzyl ether or acetal group, gave the corresponding phenols (**7s**,**t**) keeping another protective group (entries 4 and 5). Interestingly, in the reaction of the diether (**6u**), which has two kinds of allyl

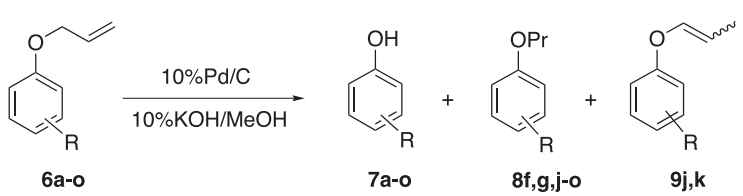
Table 1. Deallylation of *O*-allylvanillin (**3**)

Entry	Conditions	Yield (%)
1	10% KOH–MeOH, rt 24 h then reflux 24 h	0
2	10% KOH–MeOH, dibenzo-18-crown-6 (1 equiv), rt 24 h then reflux 24 h	0
3	10% Pd/C, MeOH, rt 72 h	0
4	10% Pd/C, MeOH, reflux 24 h	28[a]
5	10% Pd/C, 10% KOH–MeOH, rt 8 h	96
6	10% Pd/C, NaOMe (10 equiv), MeOH, rt 5 h	54

[a] Starting material (**3**; 49%) and enol ethers (**5a**; 9%, **5b**; 5%) were also obtained.

electron-donating group on the benzene ring, were readily deprotected to give the corresponding phenols (**7a**–**h**) in high yields (82–98%) (entries 1–8). It is noteworthy that the amido, cyano and nitro groups in the substrates remained intact during the reaction. In the case of *O*-allyl-4-bromophenol (**6i**), many by-products were observed on TLC to result in the formation of **7i** in moderate yield (entry 9). On the other hand, yields of deprotection for *O*-allylphenols (**6j**–**o**) bearing a strong electron-donating ethers, the allyl aryl ether bond was selectively cleaved to give phenol **7u** (81%) along with a small amount of benzyl propyl ether (**8u**) (10%) (entry 6). Moreover, the present reaction could apply to the substrates (**6v**–**y**), which have a variety of allyl ether moieties, to furnish *p*-nitrophenol (**7a**) in high yields (entries 7–10).

During the investigation of the present reaction, we found that the choice of the palladium catalyst was quite



Scheme 4.

Table 2. Deallylation of various *O*-allylphenols (**6a–o**)

Entry	Substrate	R	Time (h)	**7** (%)	**8** (%)	(*E*)-**9** (%)	(*Z*)-**9** (%)
1	**6a**	*p*-NO_2	9	94			
2	**6b**	*m*-NO_2	9	97			
3	**6c**	*o*-NO_2	8	96			
4	**6d**	*p*-CN	10	98			
5	**6e**	*p*-CO_2Me	10	44 (44)[a]			
6	**6f**	*p*-CO_2H	10	82	3		
7	**6g**	*p*-*t*-Bu	24	86	12		
8	**6h**	*p*-NHAc	48	86			
9	**6i**	*p*-Br	7	49			
10	**6j**	*p*-OMe	96	17	20	4[b]	20[b]
11	**6k**	*m*-OMe	48	45	23[b]	12[b]	4[b]
12	**6l**	*o*-OMe	24	76	6		
13	**6m**	*p*-OH	96	10	53		
14	**6n**	*m*-OH	96	0 (45)[b,c]	15[b]		
15	**6o**	*o*-OH	96	0 (43)[c]	21		

[a] Value in parenthesis is yield of *p*-hydroxybenzoic acid.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Value in parenthesis is recovery of starting material.

important. Although the reason was not clear, different activity in this system was observed by the use of Pd catalysts, which were purchased from four different suppliers, in the reaction of **7a** and **7h**. (Scheme 4, Table 4).[15]

Next, we turned our attention to clarify the reaction mechanism. As mentioned above, *O*-allylphenols were easily cleaved to give the corresponding phenols in good to high yields except for the substrates bearing a strong electron-donating group. To compare the reactivity of the

Table 3. Deallylation of various *O*-allylphenols (**6p–y**)

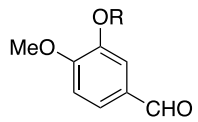
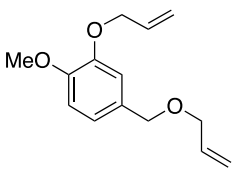
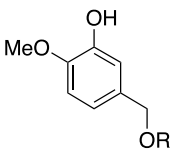
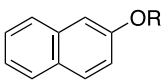
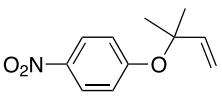
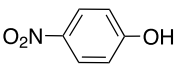
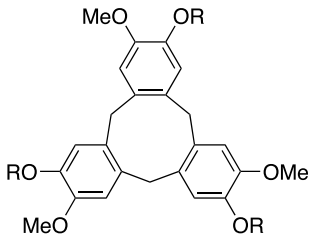
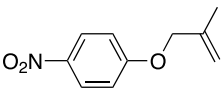
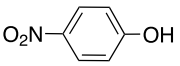
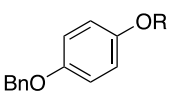
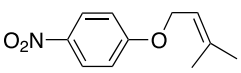
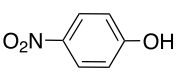
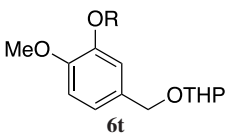
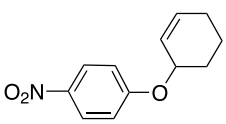
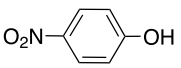
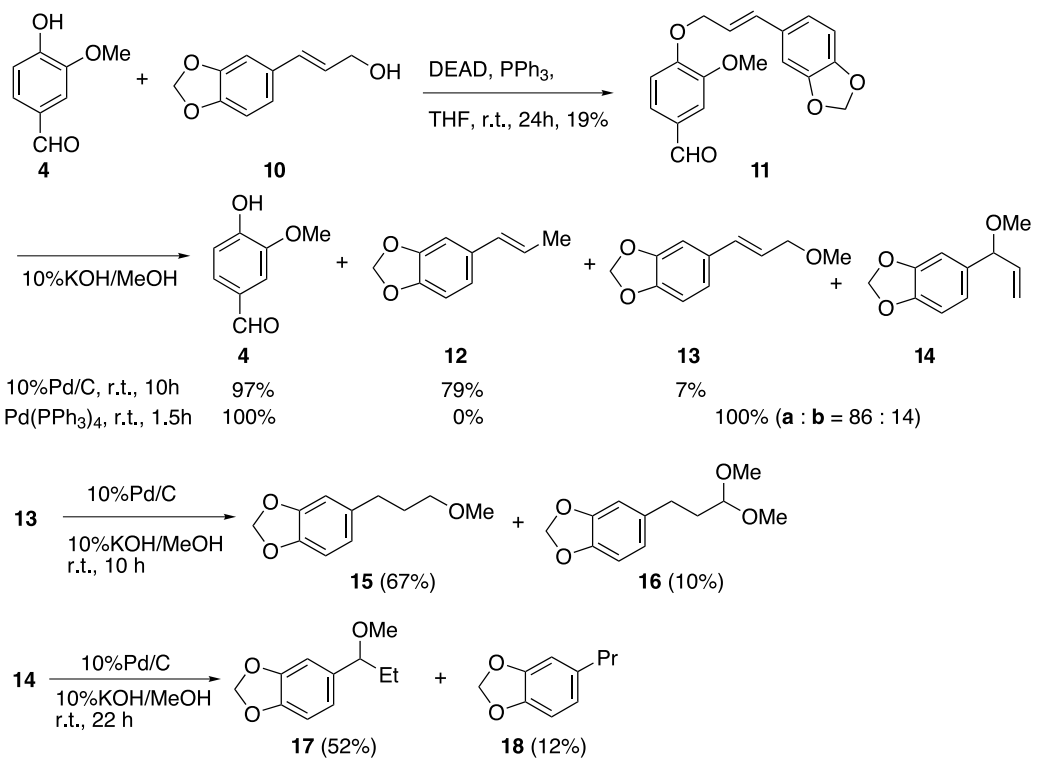
Entry	Substrate (R=allyl)	Time (h)	Product (%) (R=H)	Entry	Substrate	Time (h)	Product (%)
1	 **6p**	5	**7p** (87%)	6	 **6u**	7	 **7u**: R=Allyl (81%) **8u**: R=Pr (10%)
2	 **6q**	4	**7q** (75%)	7	 **6v**	24	 **7a** (100%)
3	 **6r**	13	**7r** (71%)	8	 **6w**	24	 **7a** (97%)
4	 **6s**	8	**7s** (95%)	9	 **6x**	30	 **7a** (96%)
5	 **6t**	7	**7t** (65%)	10	 **6y**	24	 **7a** (95%)

Table 4. Effect of Pd catalyst[a]

Entry	Substrate	Supplier of Pd	Time (h)	Product (%)	Lot. No.
1	**6a**	Kojima	9	**7a** (94)	206047
2	**6a**	Aldrich	7	**7a** (96)	07617PI
3	**6a**	Nacalai	10	**7a** (95)	V2P1618
4	**6a**	Merck	99	**7a** (68)	S37269
5	**6h**	Kojima	48	**7h** (86)	206047
6	**6h**	Aldrich	9	**7h** (87)	07617PI
7	**6h**	Nacalai	5d	**7h** (89)	V2P1618
8	**6h**	Merck	7d	**7h** (2)	S37269

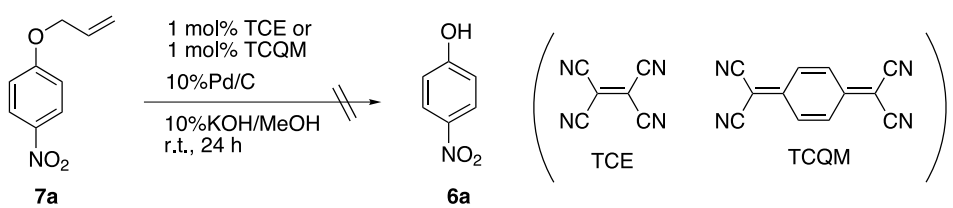
[a] The reaction was performed using substrate (100 mg) and 10% Pd/C (20 mg).

When the deallylation reaction was performed with $Pd(PPh_3)_4$, vanillin (**4**) and allyl methyl ethers (**13**, **14**) were obtained in quantitative yields via the formation of π-allyl-Pd(II) complexes. The ratio (**13**/**14**=86/14) of the ethers was determined by ^1H NMR spectroscopy. However, the reaction of **11** with 10% Pd/C under similar conditions as noted above afforded vanillin (**4**), 4-(1-propenyl)-1,2-methylenedioxybenzene (**12**), and 4-(3-methoxy-1-propenyl)-1,2-methylenedioxybenzene (**13**). With Pd/C, transformation of **13** and **14** into **12** during the reaction could not be excluded. Thus, the reaction of **13** and **14** was carried out under similar conditions in 10% KOH–MeOH. However, the reaction of both **13** and **14** did not give **12** at all and unexpected products (**15**–**18**) were produced. These results clearly indicated that the reaction involved an oxidation–reduction process by the single-electron transfer (SET) process.[15,17–19] To confirm the SET process, the reaction of **7a** with Pd/C was performed in the presence of tetracyanoethylene (TCE)[20a,b] or tetracyanoquinodimethane (TCQM),[20c,d] which are known as electron-capture reagents. As expected, the reaction of *O*-allyl-*p*-nitrophenol (**7a**) with a catalytic amount of TCE or TCQM did not form *p*-nitrophenol (**6a**) even after 24 h and the starting material (**7a**) was recovered in quantitative yield in each case (Scheme 6).

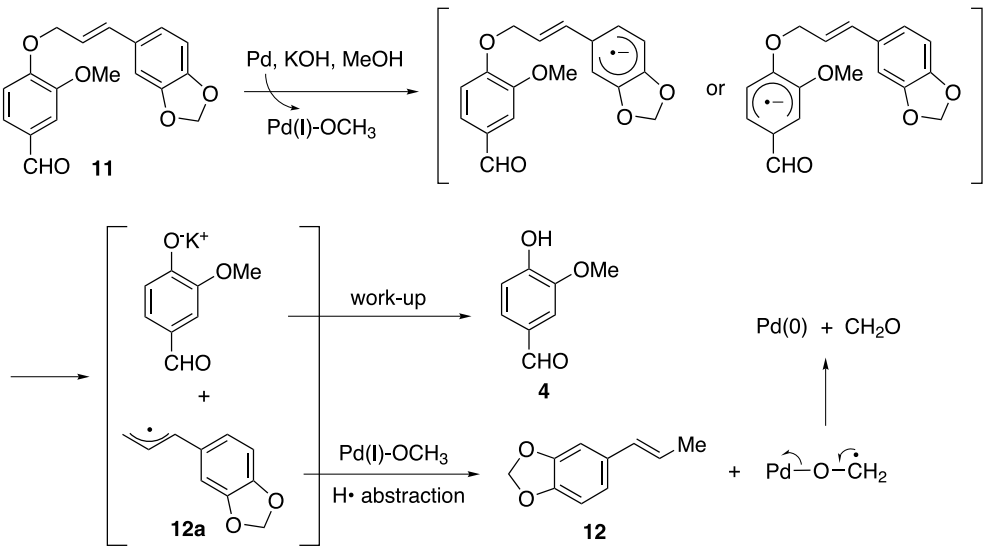


Scheme 5.

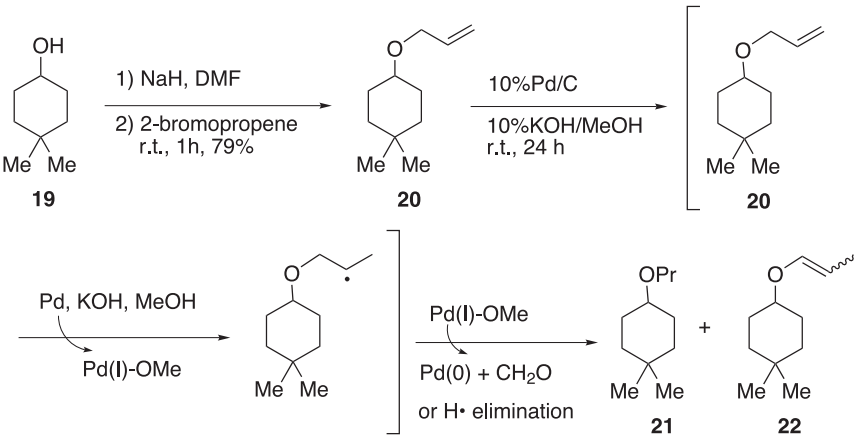
Pd catalyst in the present system, the reaction of **6m** with $Pd(PPh_3)_4$ in 10% KOH/MeOH was performed at rt for 5 h to give *p*-hydroquinone (**7m**) in 88% yield without the formation of **8** and **9**. The result suggested that the 10% Pd/C- and $Pd(PPh_3)_4$-catalyzed reaction would proceed by a different mechanism. With $Pd(PPh_3)_4$, deallylation of allyl ethers usually occurs via the formation of π-allyl-Pd(II) complexes followed by the reaction with nucleophiles.[16] To investigate the fate of an allyl moiety, the reaction of styryl ether (**11**) was carried out with Pd/C and $Pd(PPh_3)_4$ (Scheme 5).



Scheme 6.



Scheme 7.



Scheme 8.

As a result, we proposed a plausible pathway of the present deallylation as shown in Scheme 7. Namely, the coordination of the Pd atom on the aromatic ring facilitated the SET process and the resulting radical anion formed a phenoxide ion and a radical species (**12a**), which would abstract the hydrogen atom from PdOMe to give **12**.[21]

Finally, the reaction of an aliphatic allyl ether (**20**), which was obtained by allylation of **19**,[22] was investigated (Scheme 8). As expected, no deallylation product (**19**) was produced, and an inseparable mixture of a propyl ether (**21**) and an enol ether (**22**) was obtained by reduction and isomerization. The result is compatible with involving the SET process in this reaction.

3. Conclusion

In summary, we have investigated the deprotection of various *O*-allylphenols to give the corresponding phenols. The reaction of *O*-allylphenols bearing electron-withdrawing and weak electron-donating groups on the benzene ring proceeded smoothly, whereas the reaction of *O*-allylphenols having strong electron-donating groups gave phenols in nil to moderate yields. Moreover, we revealed that the present reaction proceeded via the SET process. Because 10% Pd/C was a heterogeneous catalyst, the deprotected phenol was obtained in essentially pure form by simple filtration and extraction procedure. We believe that the present reaction provides a new, convenient deprotective method for *O*-allylphenols due to its mild conditions and simple procedure.

4. Experimental

4.1. General

All melting and boiling points were measured on a Büchi or a Yanagimoto (hot plate) melting point apparatus and by a bulb-to-bulb distillation apparatus, and are uncorrected. ^{1}H NMR spectra were taken with a JEOL JNM AL-300 (300 MHz) spectrometer in a $CDCl_3$ solution with tetramethylsilane as the internal standard. Mass spectra were measured on a Hitachi M-80 or a JEOL JMS D-300 spectrometer. Column chromatography was performed over

silica gel (Merck Kiegelsel 60). Preparative TLCs were run on Merck 5744, or Merck 5715 plates. Organic extracts were dried over $MgSO_4$. Ten percent Pd/C was purchased from Kojima Co. and used as received (Lot. No. 206047).

4.1.1. 11,12,24,25-Tetra(5-allyloxy-2-bromo-4-methoxybenzyl)-2,5,8,15,18,21-hexaoxatricyclo[2-.4.0.0$^{9.4}$]heoctahydro-5,8,11,16,19,22-hexaoxa-dibenzo[*a*,*j*]cyclooctadecene 9,11,13,21,23,25-hexaene (1).[23] Mp 176–177 °C (benzene–EtOH); ^{1}H NMR δ 6.39, 6.54, 7.02 (each 4H, s), 5.86–6.00 (8H, m), J=17.8 Hz), 5.19 (4H, d, J=10.5 Hz), 4,37 (8H, d, J=5.4 Hz), 4.05 (8H, m), 3.96 (8H, m), 3,84 (12H, s), 3.82 (8H, s); MS m/z 1380 (M^+), 1382 (M^++2); HRMS m/z calcd for $C_{64}H_{68}Br_4O_{14}$ (M^+) 1380.1928, found: 1380. 1957.

4.1.2. 11,12,24,25-Tetra(5-allyloxy-2-bromo-4-methoxybenzyl)-2,5,8,15,18,21-hexaoxatricyclo[2-.4.0.0$^{9.4}$]heoctahydro-5,8,11,16,19,22-hexaoxadibenzo[*a*,*j*]cyclooctadecene 9,11,13,21,23,25-hexaene (2c). A mixture of **1** (0.050 g, 0.04 mmol) and 10% Pd/C (0.017 g) in 10% KOH–MeOH (13 mL) was stirred at rt for 30 h. The mixture was filtered by suction and the filtrate was evaporated under reduced pressure. Then, acetic anhydride was added to the residue and the mixture was stirred for 5 h. The reaction was quenched with a $NaHCO_3$ solution and the mixture was extracted with $CHCl_3$. The organic extracts were washed with brine, then dried and evaporated under reduced pressure to give a residue, which was purified by TLC ($CHCl_3$–MeOH=100:1) to afford **2c** (0.009 g, 24%) as pale yellow crystals; mp 165–166 °C ($CHCl_3$–MeOH); ^{1}H NMR δ 6.86 (8H, s), 6.64, 6.65 (each 4H, s), 4.10 (8H, brs), 3.99 (8H, brs), 3.80 (12H, s), 3.76 (8H, s), 2.29 (12H, s); MS m/z 1072 (M^+); HRMS m/z calcd for $C_{60}H_{64}O_{18}$ (M^+) 1072.4093, found: 1072.4109.

4.1.3. Deallylation of *O*-allylvanillin (3) (Table 1, entry 4). A mixture of **3** (0.100 g, 0.52 mmol) and 10% Pd/C (0.020 g) in MeOH (10 mL) was refluxed for 24 h. The mixture was filtered by suction and the filtrate was evaporated under reduced pressure. Purification of the residue on preparative TLC (hexane/AcOEt=3:1) afforded vanilline (0.022 g, 28%), **5a**[24] (0.009 g, 9%), **5b** (0.007 g, 5%) and **3** (0.049 g, 49%).

4.1.4. 4-Dimethoxymethyl-2-methoxy-1-propenyloxybenzene (5b). Oil; ^{1}H NMR δ 7.04 (1H, d, J=1.5 Hz), 6.95–6.96 (2H, m), 6.29 (1H, dq, J=12.9, 1.7 Hz), 5.34 (1H, s), 4.91 (1H, dt, J=12.9, 6.9 Hz), 3.90 (3H, s), 3.33 (6H, s), 1.74 (3H, dd, J=1.7, 6.9 Hz); MS m/z 208 (M^+); HRMS m/z calcd for $C_{13}H_{18}O_4$ (M^+) 238.1205, found: 238.1202.

4.1.5. Deallylation of *O*-allylvanillin (3) (Table 1, entry 5). A mixture of **3** (0.100 g, 0.52 mmol) and 10% Pd/C (0.020 g) in 10% KOH–MeOH (10 mL) was stirred at rt for 8 h. The mixture was filtered by suction and the filtrate was evaporated under reduced pressure. Water was added to the residue and the mixture was washed with ether. After the aqueous layer was acidified with 1 M HCl, the mixture was extracted with AcOEt. The organic extracts were washed with brine and dried. The solvent was evaporated under reduced pressure to give vanillin (**4**) (0.076 g, 96%), of which the ^{1}H NMR spectrum was identical with that of an authentic sample.

4.2. General procedure for synthesis of *O*-allylphenols (6a–r and 6v–y)

A suspension of a phenol (**6a**–**r**) (1 equiv), K_2CO_3 (1.5 equiv), and 3-bromopropene (1.15 equiv) in dry DMF (1 mL per 1 mmol of **6**) was stirred at rt for 1–18 h. The mixture was filtered by suction and water was added to the filtrate. The aqueous layer was extracted with Et_2O. The organic extracts were washed with brine, then dried and evaporated under reduced pressure to give a residue, which was purified by column chromatography to afford **6a**–**r**[25a–l] and **6v**–**y**.[25m–p]

4.2.1. 1-Allyloxy-4-benzyloxybenzene (6s). A suspension of 4-benzyloxyphenol (1.0 g, 5.0 mmol), 3-bromopopene (0.43 mL, 5.0 mmol), and K_2CO_3 (0.828 g, 6.0 mmol) in acetone (10 mL) was refluxed for 20 h. Then, a saturated aqueous NH_4Cl solution was added and the mixture was extracted with Et_2O. The organic extracts were washed with brine, dried and evaporated under reduced pressure to give a solid, which was recrystallized from Et_2O–hexane to afford **6s** (0.850 g, 71%) as colorless crystals; mp 57–58 °C (Et_2O–hexane); ^{1}H NMR δ 7.28–7.44 (5H, m), 6.83–6.92 (4H, m), 5.97–6.13 (1H, m), 5.24–5.43 (1H, m), 5.01 (2H, s), 4.48 (2H, dt, J=5.1 Hz, 1.5 Hz); MS m/z 240 (M^+); HRMS m/z calcd for $C_{16}H_{16}O_2$ (M^+) 240.1152, found: 240.1145.

4.2.2. 2-Allyloxy-4-(2-tetrahydropyranyloxy)methyl-1-methoxybenzene (6t). A solution of *O*-allylisovanillyl alcohol (3.0 g, 15.5 mmol), 3,4-dihydro-2*H*-pyrane (1.68 mL, 18.4 mmol), and *p*-TsOH (0.060 g, 3.1 mmol) in CH_2Cl_2 (40 mL) was stirred at rt for 20 h. The mixture was washed with a saturated aqueous $NaHCO_3$ solution and brine, successively, then dried and evaporated under reduced pressure to give an oily residue, which was purified by column chromatography (hexane/AcOEt=6:1) to give **6t** (1.56 g, 36%) as a colorless oil; ^{1}H NMR δ 6.83–6.94 (3H, m), 6.02–6.17 (1H, m), 5.25–5.45 (2H, m), 4.70, 4.02 (each 1H, d, J=11.8 Hz), 4.60–4.63 (3H, m), 3.89–3.96 (1H, m), 3.87 (3H, s), 3.50–3.58 (1H, m), 1.50–1.91 (6H, m); MS m/z 278 (M^+); HRMS m/z calcd for $C_{16}H_{22}O_4$ (M^+) 278.1516, found: 278.1511.

4.2.3. 2-Allyloxy-4-allyloxymethyl-1-methoxybenzene (6u). To a suspension of *O*-allylisovanillyl alcohol (1.0 g, 5.2 mmol) and 60% NaH (0.424 g, 10.6 mmol) in DMF (10 mL) at 0 °C was added 2-bromopropene (0.45 mL, 5.15 mmol) over a period of 10 min. After being stirred at rt for 18 h, the reaction was quenched with a saturated aqueous NH_4Cl solution. The mixture was extracted with a mixture of AcOEt and benzene. The organic extracts were washed with brine, then dried and evaporated in vacuo to give an oily residue, which was purified by distillation under reduced pressure (150 °C/4 mm Hg) to afford **6u** (0.950 g, 79%) as a colorless oil; ^{1}H NMR δ 6.81–6.92 (3H, m), 5.87–6.16 (2H, m), 5.16–5.44 (4H, m) 4.61 (2H, dt, J=5.4, 1.6 Hz), 4.43 (2H, s), 3.99 (2H, dt, J=5.7, 1.4 Hz), 3.85 (3H, s); MS m/z 234 (M^+); HRMS m/z calcd for $C_{14}H_{18}O_3$ (M^+) 234.1254, found: 234.1248.

4.3. General procedure for deallylation of *O*-allylphenols (6a–y)

A mixture of an *O*-allylphenol (100 mg) and 10% Pd/C (20 mg) in 10% KOH–MeOH (10 mL) was stirred at rt for an appropriate time. After the catalyst was filtered out, the filtrate was concentrated in vacuo. Water was added to the residue and the mixture was washed with ether. After the aqueous layer was acidified with 1 M HCl, the mixture was extracted with AcOEt. The organic extracts were washed with brine and dried. The solvent was evaporated under reduced pressure to give the corresponding phenol (**7a**–**q**,[26] **r**,[25l] **s**,[26] **t**, **u**). The ether layer was washed with brine, then dried and evaporated in vacuo to give a residue, which was purified by preparative TLC to afford the enol ethers (**8f**,[26]**g**,[26] **j**,[27a] **k**,[26] **l**,[27a] **m**,[26] **n**,[27b] **o**,[27c] **u**) and/or propyl ethers (**9j**,[28a] **k**[28b]).

4.3.1. 5-(Tetrahydropyran-2-yloxymethyl)-2-methoxyphenol (7t). Oil; ^{1}H NMR δ 6.92 (1H, d, J=1.3 Hz), 6.80 (1H, dd, J=1.3, 8.3 Hz), 6.76 (1H, d, J=8.3 Hz), 5.71 (1H, s), 4.65, 4.36 (each 1H, d, J=11.6 Hz), 4.63–4.68 (1H, m), 3.86–3.93 (1H, m), 3.79 (3H, s), 3.48–3.56 (1H, m), 1.48–1.86 (6H, m); MS m/z 238 (M^+); HRMS m/z calcd for $C_{13}H_{18}O_4$ (M^+) 238.1203, found: 238.1198.

4.3.2. 5-Allyloxymethyl-2-methoxyphenol (7u). Oil; ^{1}H NMR δ 6.93 (1H, s), 6.83 (2H, s), 5.59–6.01 (1H, m), 5.59 (1H, s), 5.20–5.33 (2H, m), 4.43 (2H, s), 4.00 (2H, dt, J=4.3, 1.5 Hz), 3.89 (3H, s); MS m/z 194 (M^+); HRMS m/z calcd for $C_{11}H_{14}O_3$ (M^+) 194.0942, found: 194.0940.

4.3.3. 2-Methoxy-5-propoxymethylphenol (8u). Oil; ^{1}H NMR δ 6.93 (1H, s), 6.82 (2H, s), 5.71 (1H, s), 4.40 (2H, s), 3.86 (3H, s), 3.40 (2H, t, J=6.6 Hz), 1.56–1.66 (2H, m), 0.93 (3H, t, J=7.4 Hz); m/z 196 (M^+).

4.3.4. *O*-[3-(3,4-Methylenedioxyphenyl)-2-propenyl]-vanillin (11). To a solution of vanillin (0.456 g, 3.0 mmol), **10**[29] (0.535 g, 3.0 mmol), and PPh_3 (0.790 g, 3.0 mmol) in THF (15 mL) at 0 °C was added DEAD (1.312 g, 3.0 mmol). After being stirred for 2 h, PPh_3 (0.395 g, 1.5 mmol) and DEAD (0.656 g, 1.5 mmol) were added and the mixture was stirred for an additional 24 h. Then, the solvent was evaporated under reduced pressure to give an oily residue. Ether was added to the mixture and the precipitates were filtered. Evaporation of the filtrate in vacuo gave a residue, which was purified by column chromatography (hexane/benzene/AcOEt=5:5:1) to give **11** (0.426 g, 46%) as colorless crystals; mp 130–131 °C (AcOEt–hexane); ^{1}H NMR δ 9.82 (1H, s), 7.44 (1H, dd, J=1.7, 8.0 Hz), 7.42 (1H, d, J=8.0 Hz), 7.00 (1H, d, J=8.0 Hz), 6.93 (1H, d, J=1.5 Hz), 6.82 (1H, dd, J=1.2, 8.1 Hz), 6.74 (1H, d, J=8.1 Hz), 6.64 (1H, d, J=15.8 Hz), 6.26 (1H, dt, J=6.0, 15.8 Hz), 5.93 (2H, s), 4.79 (2H, d, J=6.0 Hz), 3.93 (3H, s); MS m/z 312 (M^+); HRMS m/z calcd for $C_{18}H_{16}O_5$ (M^+) 312.0998, found: 312.0990.

4.3.5. Deallylation of 11. (a) With 10% Pd/C; a mixture of **11** (0.050 g, 0.16 mmol) and 10% Pd/C (0.010 g) in 10% KOH–MeOH (15 mL) was stirred at rt for 10 h. The usual work-up gave a residue, which was purified by preparative TLC (hexane/AcOEt=10:1) to yield vanillin (0.024 g, 97%), **12**[26] (0.021 g, 79%) and **13**[30a] (0.002 g, 7%). (b) With $Pd(PPh_3)_4$; a solution of **11** (0.050 g, 0.16 mmol) and $Pd(PPh_3)_4$ (0.001 g) in 10% KOH–MeOH (15 mL) was stirred at rt for 1.5 h. Evaporation of the solvent afforded a residue, which was partitioned into a mixture of ether and water. The organic layer was washed with brine, then dried and evaporated in vacuo to give an inseparable mixture of **13**[30a] and **14**[30b] (0.031 g, 100%, **13/14**=86/14). The aqueous layer was acidified with 3 M HCl and extracted with AcOEt. The organic extracts were washed with brine, then dried and evaporated in vacuo to give vanillin (0.024 g, 100%). The ratio of **13** to **14** was determined by integration of the peaks due to the methoxyl groups in ^{1}H NMR spectroscopy.

4.3.6. Reaction of 13 with 10% Pd/C. A mixture of **13** (0.040 g, 0.21 mmol) and 10% Pd/C (0.008 g) in 10% KOH–MeOH (5 mL) was stirred at rt for 10 h. The usual work-up gave a residue, which was purified by preparative TLC (hexane/AcOEt=5:1) to yield **15**[31a] (0.034 g, 67%) and **16**[31b] (0.006 g, 10%).

4.3.7. Reaction of 14 with 10% Pd/C. A mixture of **14** (0.100 g, 0.52 mmol) and 10% Pd/C (0.020 g) in 10% KOH–MeOH (10 mL) was stirred at rt for 22 h. The usual work-up gave a residue, which was purified by preparative TLC (benzene) to yield **17**[32] (0.052 g, 52%) and **18**[26] (0.011 g, 12%).

4.3.8. 4-Allyloxy-1,1-dimethylcyclohexane (20). To a suspension of 4,4-dimethylcyclohexanol (**19**, 0.640 g, 5.0 mmol) and 55% NaH (0.262 g, 6.0 mmol) in DMF (25 mL) at rt was added 2-bromopropene (0.52 mL, 6.0 mmol) over a period of 5 min. After being stirred for 1 h, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with Et_2O. The organic extracts were washed with brine, then dried and evaporated in vacuo to give an oily residue, which was purified by bulb-to-bulb distillation (130 °C/40 mm Hg) to afford **20** (0.662 g, 79%) as a colorless oil; ^{1}H NMR δ 5.93 (1H, ddt, J=17.1 Hz, 10.2, 5.5 Hz), 5.27(1H, ddd, J=1.5, 3.3, 17.1. Hz), 5.15 (1H, ddd, J=1.5, 3.3, 10.2 Hz), 4.00 (2H, dt, J=5.5, 1.5 Hz), 3.22–3.31 (1H, m), 1.72–1.83 (2H, m), 1.39–1.54 (4H, m), 1.12–1.22 (2H, m), 0.92, 0.90 (each 3H, s); MS m/z 168 (M^+); HRMS m/z calcd for $C_{11}H_{20}O$ (M^+) 168.1512, found: 168.1505.

4.3.9. Deallylation of 20. A mixture of **20** (0.100 g, 0.60 mmol) and 10% Pd/C (0.020 g) in 10% KOH–MeOH (10 mL) was stirred at rt for 24 h. The usual work-up gave an inseparable mixture of **21** and **22**. (0.096 g, 95%, (*E*)-**21**/(*Z*)-**21**/**22**=14/36/50). The ratio of (*E*)-**21** to (*Z*)-**21** was determined by integration of the peaks due to the olefinic protons in ^{1}H NMR spectroscopy. The ratio of **21** and **22** was determined by integration of the peaks due to C_1 protons in ^{1}H NMR spectroscopy.

Compound **21**. ^{1}H NMR δ 6.08 (0.28H, brd, J=12.3 Hz), 5.98 (0.72H, brd, J=6.5 Hz), 4.88 (0.28H, dq, J=6.4, 12.3 Hz), 4.38 (0.72H, qui, J=6.5 Hz), 3.52–3.62 (1H, m), 1.40–1.82 (9H, m), 1.14–1.28 (2H, m), 0.87–0.98 (6H, m).

Compound **22**. ^{1}H NMR δ 3.89 (2H, t, J=6.8 Hz),

3.15–3.41 (1H, m), 1.73–1.79 (2H, m), 1.38–1.64 (6H, m), 1.17 (2H, brt, J=13.3 Hz), 0.92 (3H, t, J=6.3 Hz), 0.92, 0.91 (each 3H, s).

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Syntheses of sulfoxide derivatives in the benzodiazine series. Diazines. Part 37

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Abstract—Syntheses of new sulfinylcinnolines, quinoxalines, quinazolines and phtalazines have been investigated starting from the appropriate halogenobenzodiazine derivatives. The latter were converted in one step to the corresponding sulfanyl benzodiazines which upon oxidation with *m*-CPBA led to the corresponding sulfoxide derivatives of benzodiazines in moderate to good yields. In parallel to this study, an improved method for the synthesis of 2-methylsulfinylquinoxaline starting from 2-sulfanylquinoxaline is also described and in the quinazoline series a synthetic route has been developed to prepare 2-*tert*-butyl-5-phenylsulfinylquinazoline with satisfactory yield as well as 2-*tert*-butyl-5-*tert*-butylsulfinyl-4(3*H*)-quinazolinone and 2-*tert*-butyl-8-*tert*-butylsulfinyl-4(3*H*)-quinazolinone.

1. Introduction

The benzodiazine skeleton is commonly found in compounds exhibiting a wide range of biological properties[1,2] such as inhibitor of tyrosine kinase,[3,4] antimalarial,[5] anticonvulsive,[6–9] antihypertensive,[10,11] hypolipidemic,[12] antitumoral,[13] and antiviral.[14] Usually construction of benzodiazines involves cyclization of appropriately substituted benzenes whose syntheses are not always easy. Indeed, the main synthetic route to cinnolines is the cyclization of *o*-substituted aryl hydrazones[15] or diazotation of *o*-substituted anilines.[16] Generally 2,3-substituted quinoxalines can be prepared by condensation of aryl-1,2-diamines and α-dicarbonyl compounds or their equivalents.[17–20] Frequently, quinazolines are synthesized starting from formamide and 2-aminobenzoic acid or their derivatives.[21] Alternatively, the fused phenyl ring may be assembled via a cycloaddition strategy.[22]

We had previously synthesized some diazine sulfoxides[23–25] and studied their metalation. We could highlight remarkable diastereoisomeric excesses by metalating chiral sulfoxides and using prochiral electrophiles such as aldehydes. As an extension of this topic, we have synthesized a number of sulfoxide derivatives in the benzodiazine series in order to study afterwards their metalation reactions with various substrates.

2. Results and discussion

In a previous paper,[26] we have reported the synthesis of 4-chlorocinnoline **1** by chlorination of the corresponding 4-hydroxycinnoline prepared in two steps from 2-iodoaniline.[27,28] It was converted to the sulfides **2a** and **2b** and then to the sulfoxides **3a** and **3b** by reaction with *m*-CPBA. A more vigorous oxidation of **2a** with potassium permanganate led to sulfone **4** (Scheme 1).

4-Chloro-6,7-dimethoxycinnoline[29–31] **5** (Table 1, entry 2) was synthesized from commercial 3,4-dimethoxyacetophenone. In contrast to the unstable character of 4-chlorocinnoline **1**, 4-chloro-6,7-dimethoxycinnoline **5** was completely stable at room temperature.

By analogy to the synthesis of 4-chlorocinnoline **1** described in our previous paper,[26] 4-chloro-3-*tert*-butylcinnoline **6** was obtained in good yield by an efficient Sonogashira cross-coupling reaction followed by diazotation (Scheme 2). The 4-hydroxy-3-*tert*-butylcinnoline **7**, obtained in the second step as by-product was converted smoothly by

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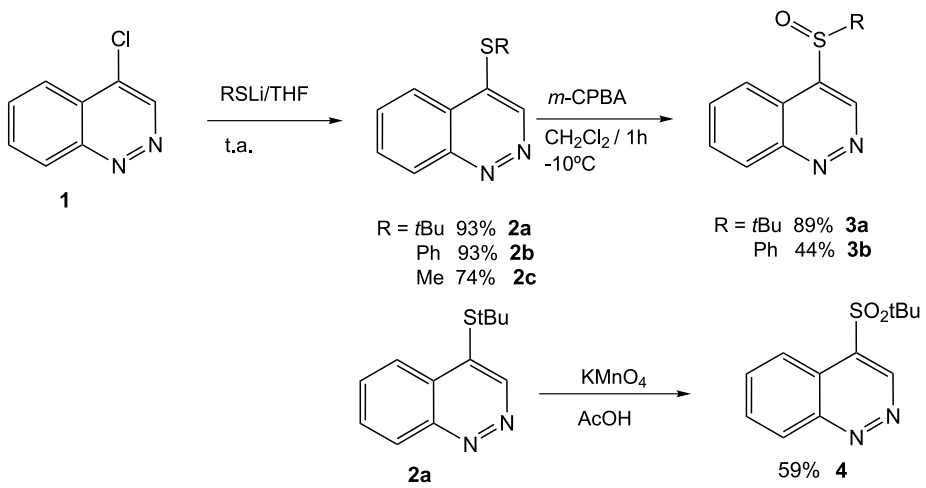
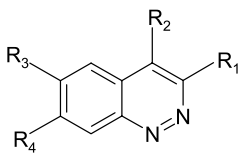
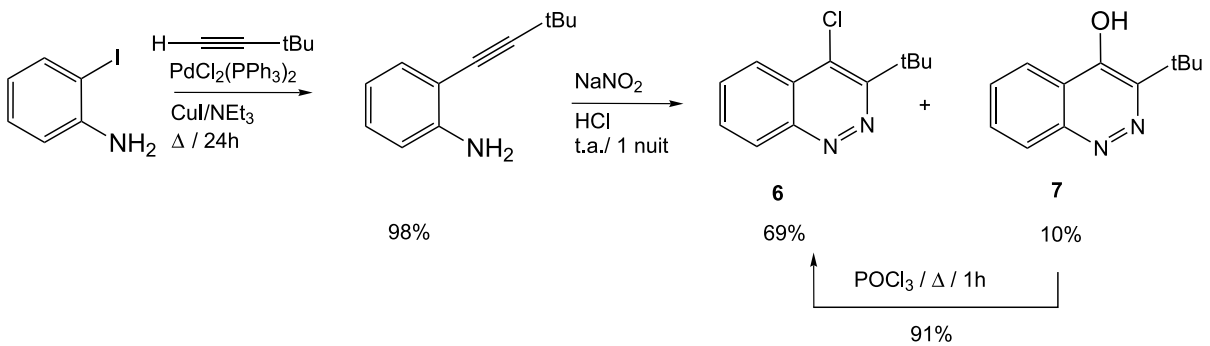


Scheme 1.

Table 1. Synthesis of sulfanyl and sulfinylcinnolines



Entry		Halocinnoline					Sulfide substrate				Yield (%)		Sulfoxide substrate				Yield (%)
		R_1	R_2	R_3	R_4		R_1	R_2	R_3	R_4			R_1	R_2	R_3	R_4	
1	**1**	H	Cl	H	H	**2a**	H	S*t*-Bu	H	H	93	**3a**	H	SO*t*-Bu	H	H	89
						2b	H	SPh	H	H	93	**3b**	H	SOPh	H	H	44
						2c	H	SCH_3	H	H	74						
2	**5**	H	Cl	OCH_3	OCH_3	**13a**	H	S*t*-Bu	OCH_3	OCH_3	86	**14a**	H	SO*t*-Bu	OCH_3	OCH_3	83
						13b	H	S*p*-Tol	OCH_3	OCH_3	92	**14b**	H	SO*p*-Tol	OCH_3	OCH_3	37
3	**6**	*t*-Bu	Cl	H	H	**15**	*t*-Bu	S*t*-Bu	H	H	95	**16**	*t*-Bu	SO*t*-Bu	H	H	49
4	**8**	OCH_3	I	H	H	**17**	OCH_3	SPh	H	H	93	**18**	OCH_3	SOPh	H	H	63
5	**9**	Cl	H	H	H	**19a**	S*t*-Bu	H	H	H	91	**20a**	SO*t*-Bu	H	H	H	66
						19b	S*p*-Tol	H	H	H	87	**20b**	SO*p*-Tol	H	H	H	76



Scheme 2.

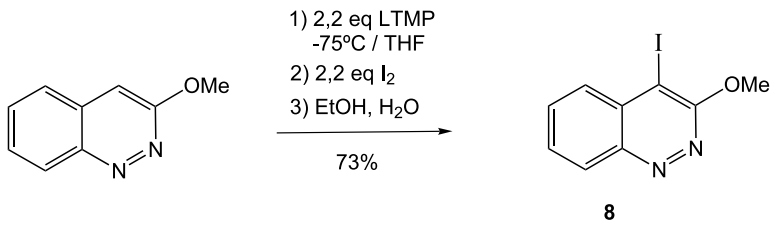
chlorination with phosphorous oxychloride into 4-chloro-3-*tert*-butylcinnoline **6** in 91% yield.

The synthesis of 4-iodo-3-methoxycinnoline **8** was performed with a 73% yield by metalation of 3-methoxycinnoline followed by reaction with iodine[27] (Scheme 3).

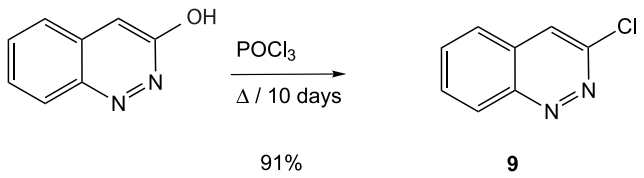
Preparation of 3-chlorocinnoline **9** was reported by Alford and Schofield[32] from 3-hydroxycinnoline in 9% yield. In our previous paper,[27] an increase of the chlorination time from 5 h to 6 days allowed us to obtain 3-chlorocinnoline **9** in better yield (72%); at present, a distinct improvement of the yield (91%) was achieved with still a longer chlorination time, from 6 days to 10 days (Scheme 4).

In the quinoxaline and quinazoline series, 2-chloroquinoxaline **10** and 4-chloro-2-phenylquinazoline **11** (Table 2, entries 1 and 2) used were both commercial compounds.

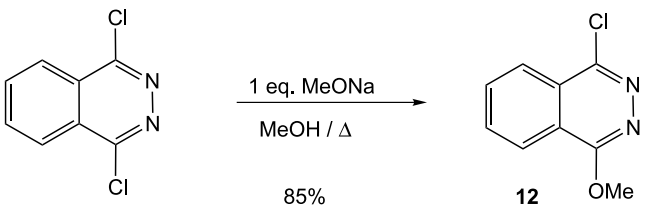
In the phtalazine series, 1-chloro-4-methoxyphtalazine **12**



Scheme 3.



Scheme 4.



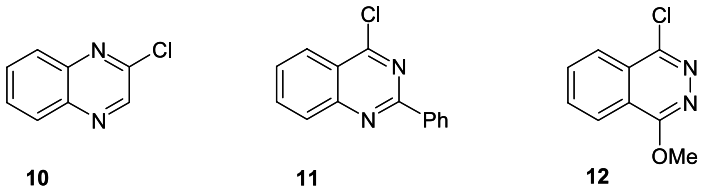
Scheme 5.

was prepared in 85% yield from commercial 1,4-dichlorophtalazine according to Druey and Ringier[33] (Scheme 5).

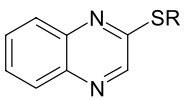
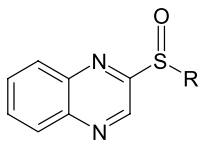
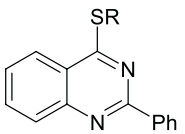
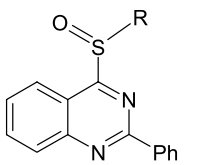
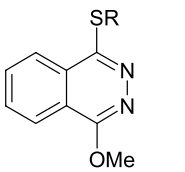
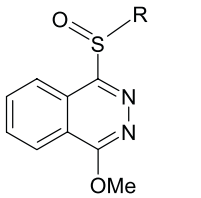
In the present work we describe an efficient synthesis of arylsulfanylbenzodiazines by aromatic substitution reaction of halogenobenzodiazines with the corresponding lithium thiolates. Thirteen alkyl and arylsulfanylbenzodiazines of which eleven are new **2a**–**b**, **13a**–**b**, **15**, **17**, **19a**–**b**, **21b**, **23**, **25** were obtained. These compounds have been oxidized with *m*-CPBA to afford the corresponding new substituted sulfinylbenzodiazines **3a**–**b**, **14a**–**b**, **16**, **18**, **20a**–**b**, **22b**, **24**, **26** as shown in Scheme 1 (Table 1 and Table 2) or for compound **2a** with potassium permanganate in acetic acid to obtain the 4-*tert*-butylsulfonylcinnoline **4** (Scheme 1). It must be noticed that yields obtained for each series were very satisfactory.

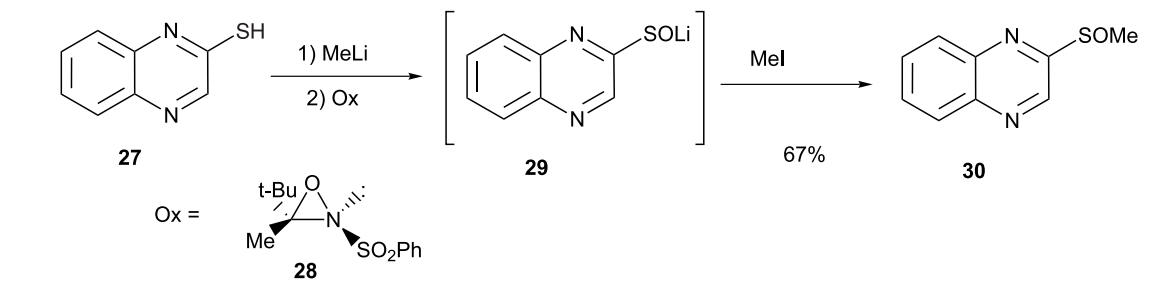
Starting from the 2-sulfanylquinoxaline **27**, we report also an improved synthesis of 2-methylsulfinylquinoxaline[34] **30** in one pot. By using the original method developed by Perrio[35] in the benzene series, we succeeded in obtaining the 2-methylsulfinylquinoxaline **30** in 67% yield (Scheme 6). The protocol developed involves three consecutive reactions carried out in one pot: deprotonation of the thiol **27** to generate the corresponding thiolate, oxidation with the *N*-sulfonyloxaziridine **28** into the corresponding sulfenate **29** and finally S-alkylation with methyl iodide. The present

Table 2. Synthesis of sulfanyl and sulfinylbenzodiazines



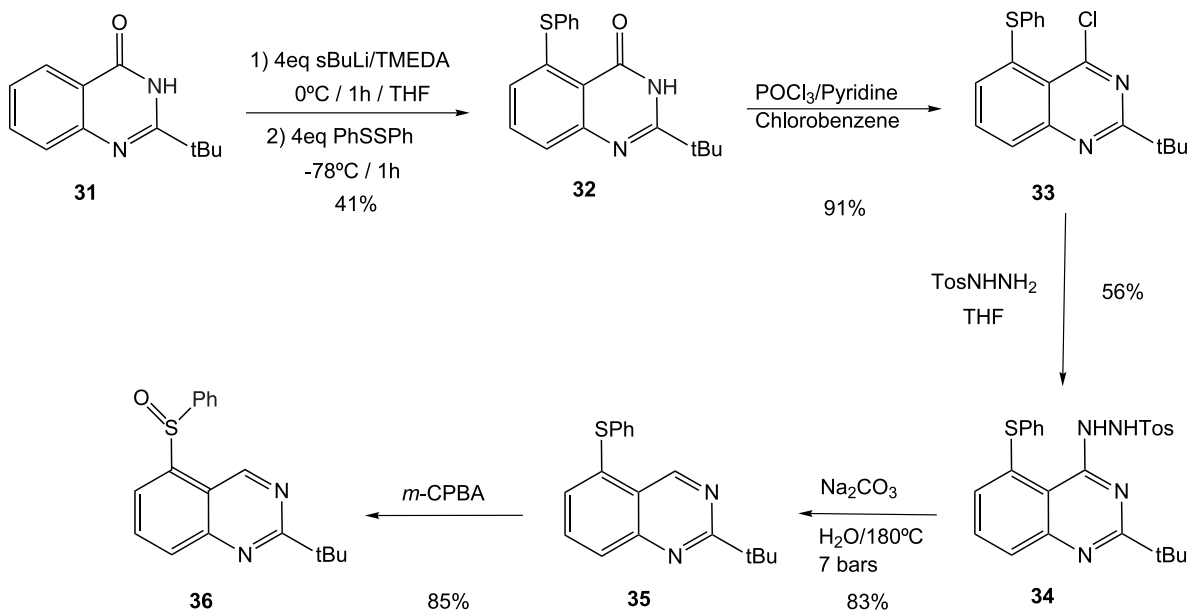
10 **11** **12**

Entry	Halodiazine	Sulfide substrate		Yield (%)	Sulfoxide substrate		Yield (%)
1	**10**		**21a** R=*t*-Bu	94		**22a** R=*t*-Bu	89
			21b R=*p*-Tol	87		**22b** R=*p*-Tol	90
2	**11**		**23** R=*t*-Bu	88		**24** R=*t*-Bu	77
3	**12**		**25** R=*t*-Bu	95		**26** R=*t*-Bu	83



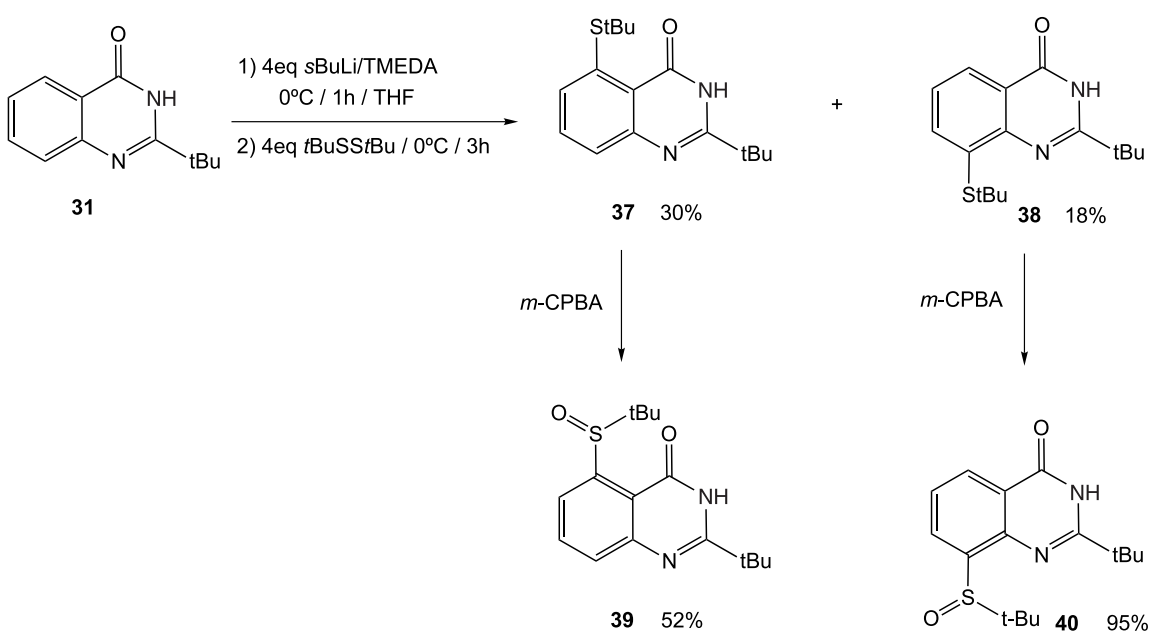
27 29 30 28

Scheme 6.



31 32 33 34 35 36

Scheme 7.



Scheme 8.

method could offer an efficient, simple and general synthetic procedure to access in one pot to sulfoxides of benzodiazines and their substituted derivatives, thus, complementing the known literature procedures for the synthesis of other benzodiazine derivatives.

All compounds synthesized so far, bear the sulfinyl moiety connected to the diazine ring of the benzodiazines. We also wished to prepare sulfoxides whose sulfur atom is connected to the benzene ring. In the quinazoline series, a new synthetic route (Scheme 7) and particularly the first metalation step has been developed in our group[36] to prepare 2-*tert*-butyl-5-phenylsulfanylquinazoline **35** with satisfactory yield from 2-*tert*-butyl-4(3*H*)-quinazolinone[37] **31**. The final oxidation step was achieved with *m*-CPBA, affording the corresponding 2-*tert*-butyl-5-phenylsulfinylquinazoline **36** with a yield of 85%.

By analogy (Scheme 8), metalation of the 2-*tert*-butyl-4(3*H*)-quinazolinone **31** followed by addition of *tert*-butyldisulfide allowed us to obtain 2-*tert*-butyl-5-*tert*-butylsulfanyl-4(3*H*)-quinazolinone **37** in 30% yield and 2-*tert*-butyl-8-*tert*-butylsulfanyl-4(3*H*)-quinazolinone **38** in 18% yield. Then, oxidation with *m*-CPBA afforded the corresponding 5- and 8-substituted sulfinyl-4(3*H*)-quinazolinone **39** and **40** with respective yields of 52% and 95%.

3. Conclusion

In conclusion, we report here a convenient synthesis of eleven new sulfinylbenzodiazines that employed halogenobenzodiazines as key intermediates. This route gave good yields and offered flexibility to introduce a variety of alkyl and/or aryl groups by choosing the appropriate alkylating agent (alkyl or arylthiolate) before the oxidation step with *m*-CPBA. Moreover, we have developed a one pot synthetic route to prepare the 2-methylsulfinylquinoxaline via the corresponding 2-sulfanylquinoxaline with satisfactory yield. We have also developed and improved a general method for the access to sulfinylquinazolines and sulfinyl-4(3*H*)-quinazolinones bearing the sulfinyl group in the benzene moiety. It used a metalation step to afford the corresponding alkyl and/or aryl sulfinyl-4(3*H*)-quinazolinone in moderate to good yields.

The study of metalation reactions of these sulfinylbenzodiazines is presently under investigation and will be reported soon.

4. Experimental

4.1. General

Melting points were measured on a Kofler hot-stage. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with a Bruker Avance 300 spectrometer (^1H at 300 MHz and ^{13}C at 75 MHz). IR spectra were obtained as potassium bromide pellets with a Perkin Elmer Paragon 500 spectrometer. Elemental analyses were performed on a Carlo Erba 1106 apparatus. Mass spectra were recorded with a Jeol JMS-AX500 spectrometer.

Tetrahydrofuran (THF) was distilled from benzophenone sodium and used immediately (water content <60 ppm). Column chromatography were performed with silica gel Merck (70–230 mesh ASTM) or neutral alumina gel Acros (0.0050–0.200 mm). *m*-CPBA (3-chloroperoxybenzoic acid, balance 3-chlorobenzoic acid and water, 70–75%) was purchased from Acros. 2-Chloroquinoxaline **10**, 4-chloro-2-phenylquinazoline **11** and 1,4-dichlorophtalazine are available from Aldrich.

4.2. General procedure for the preparation of sulfides

To a stirred solution of thiol or disulfide in THF cooled at 0 °C, under an atmosphere of dry nitrogen, was added *n*-butyllithium (1.6 or 2.5 M in hexanes). The solution was stirred at this temperature for 10 min, then a THF solution of halogeno compound was added, the temperature was warmed to the indicated temperature (θ) and the reaction mixture stirred for the indicated time (t). Hydrolysis was carried out at room temperature using water. The solvent was evaporated and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

4.3. General procedure for the oxidation reaction of sulfides

Into a round bottomed two necked flask provided with magnetic stirring bar and under an atmosphere of nitrogen was placed a CH_2Cl_2 solution of sulfide. After cooling to −10 °C, a CH_2Cl_2 solution of *m*-CPBA (0.5 equiv.) was added dropwise, and the reaction mixture was stirred at −10 °C for 30 min. Additional *m*-CPBA (0.5 equiv.) dissolved in dichloromethane was then added dropwise and the mixture was stirred at −10 °C during 30 min. the solution was washed with aqueous $Na_2S_2O_4$ (5%), aqueous $NaHCO_3$ (5%) and water. The organic layer was dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel.

4.3.1. 4-*tert*-Butylsulfanylcinnoline (2a). Synthesis of **2a** was performed according to the general procedure for preparation of sulfides with 2-methyl-2-propanethiol (2.8 ml, 25.4 mmol) in 50 ml of THF, *n*-butyllithium 1.6 M (15.9 ml, 25.4 mmol) and 4-chlorocinnoline **1** (2.79 g, 16.9 mmol) dissolved in 10 ml of THF. θ=66 °C, t=2 h 30 min. A purification by column chromatography on silica gel with ether petroleum/ethyl acetate (7/3) as eluent gave **2a** (3.44 g, 93%) as a yellow solid. Mp=70 °C. ^1H NMR ($CDCl_3$): δ=9.23 (s, 1H, H_3); 8.32 (m, 2H, H_5+H_8); 7.64 (m, 2H, H_6+H_7); 1.23 (s, 9H). ^{13}C NMR ($CDCl_3$): δ=150.8 (C); 150.6 (CH); 132.5 (C); 131.7 (CH); 131.1 (CH); 130.5 (CH); 129.9 (C); 125.7 (CH); 49.7 (C); 31.8 (CH_3). IR (KBr) (cm^{-1}): 2962, 1610, 1552, 1478, 1389, 1370, 1229, 1156, 765, 674. Anal. calcd for $C_{12}H_{14}N_2S$: C, 65.96; H, 6.41; N, 12.83; S, 14.70. Found: C, 66.04; H, 6.18; N, 12.62; S, 14.96%.

4.3.2. 4-Phenylsulfanylcinnoline (2b). Synthesis of **2b** was

performed according to the general procedure for preparation of sulfides with thiophenol (0.4 ml, 3.65 mmol) in 15 ml of THF, *n*-butyllithium 1.6 M (2.3 ml, 3.65 mmol) and 4-chlorocinnoline **1** (0.5 g, 3.04 mmol) dissolved in 10 ml of THF. θ=66 °C, t=2 h 30 min. A purification by column chromatography on silica gel with dichloromethane/ethyl acetate (8/2) as eluent gave **2b** (0.67 g, 93%) as a yellow solid. Mp=135 °C. ^{1}H NMR ($CDCl_3$): δ=8.54 (s, 1H, H_3); 8.40 (d, J_{8-7}=9.0 Hz, 1H, H_8); 8.06 (d, J_{5-6}=7.9 Hz, 1H, H_5); 7.74 (m, 2H, H_6+H_7); 7.55 (m, 2H, SPh); 7.44 (m, 3H, SPh). ^{13}C NMR ($CDCl_3$): δ=147.5 (C); 140.6 (CH); 137.7 (C); 134.3 (CH); 129.9 (CH); 129.7 (CH); 129.3 (CH); 129.2 (CH); 129.0 (CH); 126.5 (C); 122.8 (C); 121.6 (CH). IR (KBr) (cm^{-1}): 3058, 1614, 1555, 1480, 1396, 1225, 754, 672, 552. Anal. calcd for $C_{14}H_{10}N_2S$: C, 70.56; H, 4.23; N, 11.75; S, 13.46. Found: C, 70.38; H, 4.28; N, 11.67; S, 13.39%.

4.3.3. 4-Methylsulfanylcinnoline (2c). Synthesis of **2c** was performed according to the general procedure for preparation of sulfides with methyl disulfide (0.65 ml, 7.32 mmol) in 10 ml of THF, *n*-butyllithium 1.6 M (4.58 ml, 7.32 mmol) and 4-chlorocinnoline **1** (1 g, 6.1 mmol) dissolved in 10 ml of THF. θ=66 °C, t=1 h 10 min. A purification by column chromatography on silica gel with dichloromethane/ethyl acetate (1/1) as eluent gave **2c** (0.79 g, 74%) as a yellow solid. Mp=96 °C (lit.[38]= 98 °C). ^{1}H NMR ($CDCl_3$): δ=9.01 (s, 1H, H_3); 8.40 (d, J_{8-7}=8.5 Hz, 1H, H_8); 7.91 (d, J_{5-6}=8.2 Hz, 1H, H_5); 7.72 (m, 2H, H_6+H_7); 2.63 (s, 3H, CH_3).

4.3.4. 4-*tert*-Butylsulfinylcinnoline (3a). Oxidation of a solution of 4-*tert*-butylsulfanylcinnoline **2a** (3.27 g, 15 mmol), in dichloromethane (250 ml), was performed according to the general procedure with *m*-CPBA (2×1.85 g, 2×7.5 mmol) dissolved in dichloromethane (2×60 ml), giving after purification by column chromatography on silica gel with ethyl acetate as eluent, **3a** (3.12 g, 89%) as a orange solid. Mp=117 °C. ^{1}H NMR ($CDCl_3$): δ=9.57 (s, 1H, H_3); 8.59 (d, J_{7-8}=8.5 Hz, 1H, H_8); 8.14 (d, J_{5-6}=8.0 Hz, 1H, H_5,); 7.85 (m, 2H, H_6+H_7); 1.23 (s, 9H, $(CH_3)_3$). ^{13}C NMR ($CDCl_3$): δ=150.1 (C_9); 142.1 (C_3); 136.2 (C_4); 132.7 (C_6); 131.6 (C_7); 131.0 (C_8); 124.4 (C_{10}); 123.2 (C_5); 59.7 (C, *t*Bu); 23.7 (CH_3, *t*Bu). IR (KBr) (cm^{-1}): 2868–3100, 1611, 1552, 1483, 1397, 1366, 1167, 1048, 784, 670. Anal. calcd for $C_{12}H_{14}N_2OS$: C, 61.45; H, 5.97; N, 11.95; S, 13.70. Found: C, 61.22; H, 5.98; N, 11.92; S, 13.56%.

4.3.5. 4-Phenylsulfinylcinnoline (3b). Oxidation of a solution of 4-phenylsulfanylcinnoline **2b** (0.20 g, 0.84 mmol), in dichloromethane (20 ml), was performed according to the general procedure with *m*-CPBA (2×0.11 g, 2×0.42 mmol) dissolved in dichloromethane (2×5 ml), giving after purification by column chromatography on silica gel with a mixture of ethyl acetate/ether petroleum (1/1) as eluent, **3b** (94 mg, 44%) as a yellow solid. Mp=157 °C. ^{1}H NMR ($CDCl_3$): δ=9.72 (s, 1H, H_3); 8.56 (d, J_{7-8}=8.42 Hz, 1H, H_8); 8.10 (d, J_{5-6}=7.54 Hz, 1H, H_5); 7.76 (m, 4H, H_6+H_7 and 2H of SOPh); 7.39 (m, 3H, SOPh). ^{13}C NMR ($CDCl_3$): δ=150.5 (C); 143.3 (C); 140.0 (C); 139.6 (CH); 133.1 (CH); 132.6 (CH); 131.7 (CH); 131.4 (CH); 130.3 (CH); 125.9 (CH); 122.1 (CH); 121.8 (C). IR (KBr) (cm^{-1}): 3056, 1610, 1556, 1439, 1403, 1145, 1051, 767, 746, 685. Anal. calcd for $C_{14}H_{10}N_2OS$: C, 66.12; H, 3.96; N, 11.02; S, 12.61. Found: C, 66.22; H, 4.15; N, 10.91; S, 12.35%.

4.3.6. 4-*tert*-Butylsulfonylcinnoline (4). 4-*tert*-Butylsulfanylcinnoline **2a** (0.3 g, 1.37 mmol) in acetic acid (20 ml, 8 N) was stirred at room temperature while $KMnO_4$ (0.8 g, 5.06 mmol) in water (30 ml) was added during 30 min. the reaction mixture was chilled to 15 °C and decolourised by an aqueous solution of Na_2SO_3 (5%). 4-*tert*-butylsulfonylcinnoline **4** was collected to give (0.2 g, 59%) as a yellow solid. Mp=140 °C. ^{1}H NMR ($CDCl_3$): δ=9.59 (s, 1H); 8.82 (m, 1H); 8.64 (m, 1H); 7.91 (m, 2H); 1.34 (s, 9H). ^{13}C NMR ($CDCl_3$): δ=(152.2 (C); 145.8 (CH); 134.3 (CH); 131.9 (CH); 131.4 (CH); 128.4 (C); 125.0 (CH); 123.0 (C); 62.8 (C); 23.9 (CH_3). IR (KBr) (cm^{-1}): 2939–3091, 1483, 1374, 1306, 1147, 1116, 763, 693, 580, 489. Anal. calcd for $C_{12}H_{14}N_2O_2S$: C, 57.53; H, 5.59; N, 11.19; S, 12.82. Found: C, 57.42; H, 5.28; N, 11.17; S, 12.58%.

4.3.7. 6,7-Dimethoxy-4-*tert*-butylsulfinylcinnoline (6a). Oxidation of a solution of 6,7-dimethoxy-4-*tert*-butylsulfanylcinnoline **13a** (1.02 g, 3.59 mmol) in dichloromethane (60 ml), was performed according to the general procedure with *m*-CPBA (2×0.44 g, 2×1.8 mmol) dissolved in dichloromethane (2×5 ml), giving after purification by column chromatography on silica gel with ethyl acetate as eluent, **6a** (0.876 g, 83%) as yellow solid. Mp=172 °C. ^{1}H NMR ($CDCl_3$): δ=9.38 (s, 1H); 8.09 (s, 1H); 7.79 (s, 1H); 4.07 (s, 3H); 4.04 (s, 3H); 1.34 (s, 9H). ^{13}C NMR ($CDCl_3$): δ=156.2 (C); 154.1 (C); 145.1 (CH); 126.1 (C); 121.5 (C); 107.9 (CH); 101.4 (CH); 63.0 (C); 57.2 (CH_3); 57.0 (CH_3); 23.9 (CH_3). IR (KBr) (cm^{-1}): 2990–3120, 1495, 1298, 1117, 576. Anal. calcd for $C_{14}H_{18}N_2O_3S$: C, 57.12; H, 6.16; N, 9.52. Found: C, 56.65; H, 6.06; N, 9.27%.

4.3.8. 6,7-Dimethoxy-4-*p*-tolylsulfinylcinnoline (6b). Oxidation of a solution of 6,7-dimethoxy-4-*p*-tolylsulfanylcinnoline **13b** (0.15 g, 0.48 mmol) in dichloromethane (20 ml), was performed according to the general procedure with *m*-CPBA (2×0.06 g, 2×0.24 mmol) dissolved in dichloromethane (2×2 ml), giving after purification by column chromatography on silica gel with a mixture of dichloromethane/acetone (4/1) as eluent, **6b** (0.06 g, 37%) as yellow solid. Mp=242 °C. ^{1}H NMR ($CDCl_3$): δ=9.42 (s, 1H); 7.71 (s, 1H); 7.53 (d, J=8.3 Hz, 2H); 7.26 (s, 1H); 7.20 (d, J=7.9 Hz, 2H); 4.00 (s, 3H); 3.93 (s, 3H); 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$): δ=155.0 (C); 153.9 (C); 149.2 (C); 143.3 (C); 140.0 (C); 139.4 (CH); 137.1 (C); 130.8 (CH); 125.9 (CH); 119.6 (C); 108.0 (CH); 98.8 (CH); 57.0 (CH_3); 56.9 (CH_3); 21.8 (CH_3). IR (KBr) (cm^{-1}): 2854–3079, 14,989, 1428, 1297, 1258, 1216, 1055, 1011, 819, 510. Anal. calcd for $C_{17}H_{16}N_2O_3S$: C, 62.18; H, 4.91; N, 8.53. Found: C, 61.92; H, 4.53; N, 8.35%.

4.3.9. 4-Chloro-3-*tert*-butylcinnoline (6) and 3-*tert*-butylcinnolin-4-ol (7). A suspension of 2-(3,3-dimethyl-1-butynyl)-phenylamine (0.5 g, 2.89 mmol) in 5 ml of water was stirred and cooled to 0 °C. 5 ml of a 36% aqueous solution of aqueous hydrochloric acid was added then, dropwise, a solution of $NaNO_2$ (0.31 g, 4.49 mmol) dissolved in 1 ml of water. The reaction mixture was

warmed to room temperature and stirred for 2 h. After neutralization with a saturated aqueous solution of $NaHCO_3$ and extraction with dichloromethane, the organic layer was dried over magnesium sulfate and evaporated. A purification by column chromatography on silica gel with ether petroleum/ethyl acetate (8/2) as eluent gave **6** in a first fraction (0.38 g, 59%) as a yellow solid. Mp=113 °C. ^{1}H NMR ($CDCl_3$): δ=8.35 (d, J=6.7 Hz, 1H); 8.12 (d, J=7.5 Hz, 1H); 7.66 (m, 2H); 1.62 (s, 9H). ^{13}C NMR ($CDCl_3$): δ=159.3 (C); 150.2 (C); 134.3 (C); 132.0 (CH); 130.6 (CH); 130.0 (CH); 126.2 (C); 123.5 (CH); 39.3 (C); 29.7 (CH_3). IR (KBr) (cm^{-1}):2865–3100, 1458, 1338, 1160, 995, 850, 775, 706. Anal. calcd for $C_{12}H_{13}N_2Cl$: C, 65.31; H, 5.94; N, 12.69. Found: C, 65.70; H, 6.26; N, 13.14%.

A second fraction gave 3-*tert*-butylcinnolin-4-ol **7** (69 mg, 12%) as a white solid. Mp=244 °C. ^{1}H NMR (DMSO-d_6): δ=8.16 (d, J=7.2 Hz, 1H); 7.84 (dd, J=7.7, 7.7 Hz, 1H); 7.63 (d, J=8.7 Hz, 1H); 7.46 (dd, J=7.6, 7.6 Hz, 1H); 1.50 (s, 9H). ^{13}C NMR (DMSO-d_6): δ=169.8 (C); 154.9 (C); 141.1 (C); 133.5 (CH); 124.6 (CH); 124.2 (CH); 122.8 (C); 37.1 (C); 28.1 (CH_3). IR (KBr) (cm^{-1}): 2700–3200, 1554, 1478, 1360, 1146, 757. Anal. calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.23; H, 6.92; N, 13.37%.

3-*tert*-Butylcinnolin-4-ol **7** (0.1 g, 0.49 mmol) can be chlorinated by refluxing in phosphorus oxychloride (5 ml) for 1 h. After evaporation of phosphorus oxychloride, the mixture was poured into ice water (5 ml) and neutralized with a saturated aqueous solution of potassium carbonate. The aqueous layer was extracted with dichloromethane. The combined organic layer was dried over magnesium sulfate and evaporate A purification by column chromatography on silica gel with dichloromethane as eluent gave 4-chloro-3-*tert*-butylcinnoline **6** (98 mg, 91%).

4.3.10. 1-Chloro-4-methoxyphtalazine (12). Sodium (0.46 g, 20.10 mmol) was dissolved in 180 ml of dry methanol, then 1,4-dichlorophtalazine was added and the reaction mixture was refluxing for 30 min. The hot solution was filtered and evaporated. The crude product was crystallised from cyclohexane giving **12** (3.33 g, 85%) as a white solid. Mp=107 °C (lit.[33] 108 °C). ^{1}H NMR ($CDCl_3$): δ=8.14 (m, 2H, H_5+H_8); 7.86 (m, 2H, H_6+H_7); 4.20 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ=161.0 (C); 150.5 (C); 133.5 (CH); 132.1 (CH); 127.9 (C); 125.5 (CH); 123.9 (CH); 121.9 (C); 55.6 (CH_3). IR (KBr) (cm^{-1}): 2860–3079, 144.8, 1366, 1337, 1293, 964, 774, 661. Anal. calcd for $C_9H_7N_2OCl$: C, 55.54; H, 3.63; N, 14.39. Found: C, 55.29; H, 3.68; N, 14.48%.

4.3.11. 6,7-Dimethoxy-4-*tert*-butylsulfanylcinnoline (13a). Synthesis of **13a** was performed according to the general procedure for preparation of sulfides with 2-methyl-2-propanethiol (1.87 ml, 17.36 mmol) in 50 ml of THF, *n*-butyllithium 2.5 M (6.94 ml, 17.36 mmol) and 4-chloro-6,7-dimethoxycinnoline **5** (2.6 g, 11.57 mmol) dissolved in 10 ml of THF. θ=66 °C, t=2 h. A purification by column chromatography on silica gel with ethyl acetate as eluent gave **13a** (2.76 g, 86%) as a yellow solid. Mp=180 °C. ^{1}H NMR ($CDCl_3$): δ=9.06 (s, 1H, H_3); 7.57 (s, 1H); 7.50 (s, 1H); 3.99 (s, 3H); 3.97 (s, 3H); 1.26 (s, 9H). ^{13}C NMR ($CDCl_3$): δ=154.3 (C); 153.6 (C); 150.5 (CH); 129.2 (C); 127.8 (C); 107.1 (CH); 102.1 (CH); 56.8 (CH_3); 56.7 (CH_3); 49.7 (C); 31.7 (CH_3). IR (KBr) (cm^{-1}): 2837–2996, 1494, 1428, 1300, 1226, 1157, 1015, 857, 793. Anal. calcd for $C_{14}H_{18}N_2O_2S$: C, 60.41; H, 6.52; N, 10.06. Found: C, 60.39; H, 6.86; N, 9.94%.

4.3.12. 6,7-Dimethoxy-4-*p*-tolylsulfanylcinnoline (13b). Synthesis of **13b** was performed according to the general procedure for preparation of sulfides with *p*-toluenethiol (0.17 g, 1.36 mmol) in 15 ml of THF, *n*-butyllithium 1.6 M (0.85 ml, 1.36 mmol) and 4-chloro-6,7-dimethoxycinnoline **5** (0.2 g, 0.89 mmol) dissolved in 10 ml of THF. θ=66 °C, t=2 h. A purification by column chromatography on silica gel with ethyl acetate as eluent gave **13b** (0.26 g, 92%) as a pale yellow solid. Mp=177 °C. ^{1}H NMR ($CDCl_3$): δ=8.52 (s, 1H, H3); 7.69 (s, 1H); 7.49 (d, J=7.9 Hz, 2H, *p*-tol); 7.3 (d, J=8.3 Hz, 2H, *p*-tol); 7.22 (s, 1H); 4.11 (s, 3H); 4.08 (s, 3H); 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$): δ=153.8 (C); 153.7 (C); 147.1 (C); 142.1 (CH); 140.7 (C); 136.4 (C); 135.3 (CH); 131.4 (CH); 125.1 (C); 121.4 (C); 107.4 (CH); 100.0 (CH); 56.9 (CH_3); 56.8 (CH_3); 21.7 (CH_3). IR (KBr) (cm^{-1}): 2826–3027, 1496, 1424, 1252, 1159, 1017, 822, 791. Anal. calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.43; H, 5.25; N, 8.96%.

4.3.13. 3-*tert*-Butyl-4-*tert*-butylsulfanylcinnoline (15). Synthesis of **15** was performed according to the general procedure for preparation of sulfides with 2-methyl-2-propanethiol (1.02 ml, 9.32 mmol) in 50 ml of THF, *n*-butyllithium 1.6 M (5.83 ml, 9.32 mmol) and 4-chloro-3-*tert*-butylcinnoline **6** (1.37 g, 6.21 mmol) dissolved in 10 ml of THF. θ=20 °C, t=2 h. A purification by column chromatography on silica gel with dichloromethane as eluent gave **15** (1.59 g, 93%) as a yellow solid. Mp=86 °C. ^{1}H NMR ($CDCl_3$): δ=8.52 (d, J_{8-7}=8.0 Hz, 1H, H_8); 8.36 (d, J_{5-6}=8.1 Hz, 1H, H_5); 7.63 (m, 2H, H_6+H_7); 1.67 (s, 9H, *t*Bu); 1.13 (s, 9H, S-*t*Bu). ^{13}C NMR ($CDCl_3$): δ=166.0 (C); 149.6 (C); 132.0 (C); 131.3 (C); 130.3 (CH); 129.9 (CH); 129.6 (CH); 127.9 (CH); 51.9 (C); 40.5 (C); 32.8 (CH_3); 32.0 (CH_3). IR (KBr) (cm^{-1}): 2863–2987, 1459, 1364, 1158, 1071, 769. Anal. calcd for $C_{16}H_{22}N_2S$: C, 70.03; H, 8.08; N, 10.21. Found: C, 70.02; H, 8.03; N, 10.05%.

4.3.14. 3-*tert*-Butyl-4-*tert*-butylsulfinylcinnoline (16). Oxidation of a solution of 3-*tert*-butyl-4-*tert*-butylsulfanylcinnoline **15** (0.10 g, 0.36 mmol)), in dichloromethane (15 ml), was performed according to the general procedure with *m*-CPBA (2×0.05 g, 2×0.18 mmol) dissolved in dichloromethane (2×5 ml), giving after purification by column chromatography on silica gel with a mixture of ethyl cyclohexane/acetate (7/3) as eluent, **16** (0.05 g, 49%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ=9.42 (d, J=8.3 Hz, 1H); 8.47 (d, J=8.7 Hz, 1H); 7.75 (ddd, J=1.5, 8.5, 7.2 Hz, 1H); 7.64 (ddd, J=1.5, 8.7, 7.8 Hz, 1H); 1.68 (s, 9H); 1.14 (s, 9H). ^{13}C NMR ($CDCl_3$): δ=161.8 (C); 150.0 (C); 131.1 (CH); 130.9 (C); 130.6 (CH); 130.0 (CH); 126.7 (C); 126.2 (CH); 62.2 (C); 41.2 (C); 33.6 (CH_3); 26.3 (CH_3). IR (KBr) (cm^{-1}): 2967–3252, 1613, 1477, 1461, 1362, 1161, 1130, 760. HRMS (FAB$^+$) calcd for (MH^+) $C_{16}H_{23}N_2OS$: *m*/*z* 291.1531. Found: 291.1536.

4.3.15. 3-Methoxy-4-phenylsulfanylcinnoline (17). Synthesis of **17** was performed according to the general procedure for preparation of sulfides with thiophenol (0.14 ml, 1.24 mmol) in 15 ml of THF, *n*-butyllithium 1.6 M (0.77 ml, 1.24 mmol) and 4-iodo-3-methoxycinnoline **8** (0.29 g, 1.03 mmol) dissolved in 5 ml of THF. θ=20 °C, t=24 h. A purification by column chromatography on silica gel with ether petroleum/ethyl acetate (2/1) as eluent gave **17** (0.26 g, 93%) as a yellow solid. Mp=87 °C. ^{1}H NMR ($CDCl_3$): δ=8.32 (m, 1H); 8.17 (m, 1H); 7.54 (m, 2H); 7.10 (m, 5H); 4.17 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ=161.4 (C); 149.5 (C); 134.7 (C); 132.1 (CH); 131.3 (C); 130.6 (CH); 129.5 (CH); 128.4 (CH); 127.2 (CH); 124.7 (CH); 116.4 (C); 56.4 (CH_3). IR (KBr) (cm^{-1}): 2900–3056, 1616, 1550, 1523, 1459, 1324, 1112, 766, 741, 693. Anal. calcd for $C_{15}H_{12}N_2OS$: C, 67.15; H, 4.50; N, 10.44; S, 11.95. Found: C, 67.22; H, 4.56; N, 10.33; S, 11.53%.

4.3.16. 3-Methoxy-4-phenylsulfinylcinnoline (18). Oxidation of a solution of 3-methoxy-4-phenylsulfanylcinnoline **17** (0.21 g, 0.78 mmol)), in dichloromethane (20 ml), was performed according to the general procedure with *m*-CPBA (2×0.10 g, 2×0.39 mmol) dissolved in dichloromethane (2×5 ml), giving after purification by column chromatography on silica gel with a mixture of ether petroleum/ethyl acetate (1/2) as eluent, **18** (0.14 g, 63%) as a yellow solid. Mp=146 °C. ^{1}H NMR ($CDCl_3$): δ=9.01 (d, J=8.8 Hz 1H); 8.35 (d, J=8.2 Hz, 1H); 7.73 (d, J=7.7 Hz, 2H, SPh); 7.60 (m, 2H, H_6+H_7); 7.37 (m, 3H, SPh); 4.34 (s, 3H, OCH_3). ^{13}C NMR ($CDCl_3$): δ=157.4 (C); 150.4 (C); 143.9 (C, SOPh); 133.0 (CH); 131.5 (CH); 131.2 (CH); 129.7 (CH, SOPh); 128.8 (CH); 126.7 (C); 124.9 (CH, SOPh); 122.3 (CH); 122.0 (C). IR (KBr) (cm^{-1}): 2951–3022, 1610, 1556, 1528, 1458, 1319, 1117, 1046, 773, 743, 688. Anal. calcd for $C_{15}H_{12}N_2O_2S$: C, 63.38; H, 4.26; N, 9.85; S, 11.28. Found: C, 63.19; H, 4.24; N, 9.81; S, 11.12%.

4.3.17. 3-*tert*-Butylsulfanylcinnoline (19a). Synthesis of **19a** was performed according to the general procedure for preparation of sulfides with 2-methyl-2-propanethiol (1 ml, 9.11 mmol) in 50 ml of THF, *n*-butyllithium 1.6 M (5.69 ml, 9.11 mmol) and 3-chlorocinnoline **9** (1 g, 6.08 mmol) dissolved in 10 ml of THF. θ=66 °C, t=2 h. A purification by column chromatography on silica gel with dichloromethane/ethyl acetate (9/1) as eluent gave **19a** (1.21 g, 91%) as a yellow solid. Mp=69 °C. ^{1}H NMR ($CDCl_3$): δ=8.38 (d, J=8.3 Hz, 1H); 7.84 (s, 1H); 7.65 (m, 3H); 1.44 (s, 9H). ^{13}C NMR ($CDCl_3$): δ=155.0 (C); 149.3 (C); 131.8 (CH); 130.9 (CH); 130.0 (CH); 127.5 (CH); 126.5 (CH); 126.4 (C); 48.9 (C); 31.7 (CH_3). IR (KBr) (cm^{-1}): 2865–3042, 1424, 1366, 1166, 1140, 1105, 764, 750. Anal. calcd for $C_{12}H_{14}N_2S$: C, 66.02; H, 6.46; N, 12.83; S, 14.69. Found: C, 65.61; H, 6.66; N, 12.74; S, 14.34%.

4.3.18. 3-*p*-Tolylsulfanylcinnoline (19b). Synthesis of **19b** was performed according to the general procedure for preparation of sulfides with *p*-toluenethiol (0.23 g, 1.82 mmol) in 5 ml of THF, *n*-butyllithium 1.6 M (1.14 ml, 1.82 mmol) and 3-chlorocinnoline **9** (0.2 g, 1.22 mmol) dissolved in 5 ml of THF. θ=66 °C, t=2 h. A purification by column chromatography on silica gel with ether petroleum/ethyl acetate (7/3) as eluent gave **19b** (0.27 g, 87%) as a yellow solid. Mp=117 °C. ^{1}H NMR ($CDCl_3$): δ=8.37 (d, J=8.1 Hz, 1H); 7.60 (m, 2H); 7.47 (m, 3H); 7.20 (m, 3H); 2.36 (s, 3H). ^{13}C NMR ($CDCl_3$): δ=160.2 (C); 149.1 (C); 140.3 (C); 135.5 (CH); 131.9 (CH); 131.3 (CH); 130.1 (CH); 130.0 (CH); 127.1 (C); 126.9 (C); 126.2 (CH); 119.5 (CH); 21.8 (CH_3). IR (KBr) (cm^{-1}): 2906–3036, 1494, 1427, 1103, 1044, 809, 755, 515. Anal. calcd for $C_{15}H_{12}N_2S$: C, 71.40; H, 4.79; N, 11.10; S, 12.71. Found: C, 71.58; H, 4.95; N, 10.98; S, 12.46%.

4.3.19. 3-*tert*-Butylsulfinylcinnoline (20a). Oxidation of a solution of 3-*tert*-butylsulfanylcinnoline **19a** (5.34 g, 24.46 mmol)), in dichloromethane (300 ml), was performed according to the general procedure with *m*-CPBA (2×3.02 g, 2×12.23 mmol) dissolved in dichloromethane (2×50 ml), giving after purification by column chromatography on silica gel with a mixture of dichloromethane/ethyl acetate (4/1) as eluent, **20a** (8.81 g, 66%) as a beige solid. Mp=129 °C. ^{1}H NMR ($CDCl_3$): δ=8.60 (d, J_{8-7}=9.4 Hz, 1H, H_8); 8.48 (s, 1H, H_4); 7.94 (m, 2H, H_5+H-*Ar*); 7.86 (m, 1H, H-*Ar*); 1.29 (s, 9H, *t*Bu). ^{13}C NMR ($CDCl_3$): δ=160.6 (C); 151.2 (C); 132.6 (CH); 132.5 (CH); 130.3 (CH); 127.6 (CH); 126.7 (C); 122.2 (CH); 58.5 (C); 23.6 (CH_3). IR (KBr) (cm^{-1}): 2863–3100, 1389, 1365, 1174, 1060, 1034, 774. Anal. calcd for $C_{12}H_{14}N_2OS$: C, 61.45; H, 5.97; N, 11.95; S, 13.70. Found: C, 61.46; H, 6.23; N, 11.95; S, 13.43%.

4.3.20. 3-*p*-Tolylsulfinylcinnoline (20b). Oxidation of a solution of 3-*p*-tolylsulfanylcinnoline **19b** (0.21 g, 0.83 mmol)), in dichloromethane (20 ml), was performed according to the general procedure with *m*-CPBA (2×0.11 g, 2×0.42 mmol) dissolved in dichloromethane (2×5 ml), giving after purification by column chromatography on silica gel with a mixture of dichloromethane/ethyl acetate (8/2) as eluent, **20b** (0.17 g, 76%) as a beige solid. Mp=189 °C. ^{1}H NMR ($CDCl_3$): δ=8.59 (m, 2H); 7.94 (m, 5H); 7.30 (d, J=8.3 Hz, 2H); 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$): δ=163.6 (C); 151.2 (C); 142.5 (C); 140.8 (C); 132.7 (CH); 132.4 (CH); 130.4 (CH); 130.3 (CH); 127.6 (CH); 127.0 (C); 125.3 (CH); 119.1 (CH); 21.8 (CH_3). IR (KBr) (cm^{-1}): 2854–3040, 1389, 1085, 1057, 1035, 807, 755. Anal. calcd for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44. Found: C, 67.06; H, 4.72; N, 10.31%.

4.3.21. 2-*tert*-Butylsulfanylquinoxaline (21a). Synthesis of **21a** was performed according to the general procedure for preparation of sulfides with 2-methyl-2-propanethiol (3.33 ml, 30.44 mmol) in 100 ml of THF, *n*-butyllithium 2.5 M (12.18 ml, 30.44 mmol) and 2-chloroquinoxaline **10** (3.34 g, 20.29 mmol) dissolved in 50 ml of THF. θ=66 °C, t=2 h. A purification by column chromatography on silica gel with dichloromethane as eluent gave **21a** (4.42 g, 92%) as a pale yellow solid. Mp=63 °C (lit.[39]=60–61 °C). ^{1}H NMR ($CDCl_3$): δ=8.44 (s, 1H); 7.87 (m, 2H); 7.55 (m, 2H); 1.60 (s, 9H). ^{13}C NMR ($CDCl_3$): δ=157.6 (C); 146.4 (CH); 142.8 (C); 139.9 (C); 130.3 (CH); 129.6 (CH); 128.5 (CH); 49.4 (C); 30.7 (CH_3). IR (KBr) (cm^{-1}): 2901–3061, 1543, 1358, 1149, 1078, 962, 757. Anal. calcd for $C_{12}H_{14}N_2S$: C, 66.02; H, 6.46; N, 12.83. Found: C, 66.17; H, 6.57; N, 12.54%.

4.3.22. 2-*p*-Tolylsulfanylquinoxaline (21b). Synthesis of

21b was performed according to the general procedure for preparation of sulfides with *p*-toluenethiol (9.1 g, 72.92 mmol) in 150 ml of THF, *n*-butyllithium 2.5 M (29.2 ml, 73 mmol) and 2-chloroquinoxaline **10** (10 g, 60.77 mmol) dissolved in 50 ml of THF. θ=66 °C, t=2 h. A purification by column chromatography on silica gel with dichloromethane/ether petroleum (2/1) as eluent gave **21b** (14.47 g, 94%) as a yellow solid. Mp=61 °C. ^{1}H NMR ($CDCl_3$): δ=8.32 (s, 1H, H_3); 7.90 (dd, J=8.1, 1.5 Hz, 1H); 7.82 (dd, J=8.5, 1.5 Hz, 1H); 7.58 (m, 2H, H_6+H_7); 7.48 (d, J=8.3 Hz, 2H, *p*-tolyl); 7.20 (d, J=7.9 Hz, 2H, *p*-tolyl); 2.36 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$): δ=158.1 (C); 143.6 (CH); 142.5 (C); 140.5 (C); 140.2 (C); 135.5 (CH); 131.1 (CH); 130.8 (CH); 129.5 (CH); 129.0 (CH); 128.7 (CH); 125.5 (C); 21.8 (CH_3). IR (KBr) (cm^{-1}): 2916–3056, 1542, 1079, 961, 806, 756, 508. Anal. calcd for $C_{15}H_{12}N_2S$: C, 71.40; H, 4.79; N, 11.10. Found: C, 71.48; H, 4.54; N, 11.70%.

4.3.23. 2-*tert*-Butylsulfinylquinoxaline (22a). Oxidation of a solution of 2-*tert*-butylsulfanylquinoxaline **21a** (2 g, 8.41 mmol)), in dichloromethane (150 ml), was performed according to the general procedure with *m*-CPBA (2×1.04 g, 2×4.21 mmol) dissolved in dichloromethane (2×35 ml), giving after purification by column chromatography on silica gel with a mixture of dichloromethane/ethyl acetate (1/1) as eluent, **22a** (1.9 g, 89%) as a yellow solid. Mp=99 °C (lit.[39]=99–100 °C). ^{1}H NMR ($CDCl_3$): δ=9.33 (s, 1H); 8.02 (m, 2H); 7.81 (m, 2H); 1.25 (s, 9H). ^{13}C NMR ($CDCl_3$): δ=157.8 (C); 143.0 (C); 142.2 (CH); 141.2 (C); 131.9 (CH); 131.6 (CH); 130.1 (CH); 129.9 (CH); 58.9 (C); 23.7 (CH_3). IR (KBr) (cm^{-1}): 2923–3056, 1488, 1363, 1171, 1051, 767, 626. Anal. calcd for $C_{12}H_{14}N_2OS$: C, 61.45; H, 5.97; N, 11.95; S, 13.70. Found: C, 61.32; H, 6.03; N, 12.02; S, 13.62%.

4.3.24. 2-*p*-Tolylsulfinylquinoxaline (22b). Oxidation of a solution of 2-*p*-tolylsulfanylquinoxaline **21b** (0.45 g, 1.78 mmol)), in dichloromethane (40 ml), was performed according to the general procedure with *m*-CPBA (2×0.22 g, 2×0.89 mmol) dissolved in dichloromethane (2×10 ml), giving after purification by column chromatography on silica gel with a mixture of dichloromethane/ethyl acetate (4/1) as eluent, **22b** (0.43 g, 90%) as a yellow solid. Mp=124 °C. ^{1}H NMR ($CDCl_3$): δ=9.33 (s, 1H); 8.02 (m, 2H); 7.72 (m, 2H); 7.67 (d, J=8.3 Hz, 2H); 7.19 (d, J=8.3 Hz, 2H); 2.24 (s, 3H). ^{13}C NMR ($CDCl_3$): δ=160.7 (C); 143.1 (C); 142.6 (C); 141.6 (C); 140.3 (C); 140.3 (CH); 131.8 (CH); 131.6 (CH); 130.6 (CH); 130.0 (CH); 129.8 (CH); 125.1 (CH); 21.8 (CH_3). IR (KBr) (cm^{-1}): 2921–3055, 1488, 1049, 812, 764, 507. Anal. calcd for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44. Found: C, 67.65; H, 4.53; N, 10.36%.

4.3.25. 2-Phenyl-4-*tert*-butylsulfanylquinazoline (23). Synthesis of **23** was performed according to the general procedure for preparation of sulfides with 2-methyl-2-propanethiol (3.5 ml, 31.16 mmol) in 70 ml of THF, *n*-butyllithium 2.5 M (12.5 ml, 31.16 mmol) and 4-chloro-2-phenylquinazoline **11** (5 g, 20.77 mmol) dissolved in 30 ml of THF. θ=66 °C, t=2 h. A purification by column chromatography on silica gel with dichloromethane as eluent gave **23** (5.36 g, 88%) as a pale yellow solid. Mp=88 °C. ^{1}H NMR ($CDCl_3$): δ=8.50 (d, J=8.1 Hz, 1H); 7.97 (d, J=8.3 Hz, 1H); 7.85 (d, J=8.7 Hz, 1H); 7.64 (dd, J=8.5 Hz, 6.7 Hz, 1H); 7.37 (m, 4H); 1.72 (s, 9H). ^{13}C NMR ($CDCl_3$): δ=172.7 (C); 159.2 (C); 149.3 (C); 138.8 (C); 133.8 (CH); 130.8 (CH); 129.6 (CH); 129.0 (CH); 128.9 (CH); 126.9 (CH); 124.2 (CH); 123.3 (C); 49.3 (C); 30.7 (CH_3). IR (KBr) (cm^{-1}): 2912–3063, 1534, 1482, 1338, 1308, 1150, 990, 754, 707. Anal. calcd for $C_{18}H_{18}N_2S$: C, 73.43; H, 6.16; N, 9.51. Found: C, 73.48; H, 6.11; N, 9.36%.

4.3.26. 2-Phenyl-4-*tert*-butylsulfinylquinazoline (24). Oxidation of a solution of 2-phenyl-4-*tert*-butylsulfanylquinazoline **23** (0.51 g, 1.74 mmol)), in dichloromethane (40 ml), was performed according to the general procedure with *m*-CPBA (2×0.23 g, 2×0.87 mmol) dissolved in dichloromethane (2×10 ml), giving after purification by column chromatography on silica gel with a mixture of dichloromethane/ethyl acetate (9/1) as eluent, **24** (0.41 g, 77%) as a pale yellow solid. Mp=135 °C. ^{1}H NMR ($CDCl_3$): δ=9.09 (d, J=8.7 Hz, 1H); 8.53 (m, 2H); 8.06 (d, J=8.7 Hz, 1H); 7.86 (dd, J=7.7, 7.7 Hz, 1H); 7.53 (dd, J=7.7, 7.7 Hz); 7.45 (m, 3H); 1.33 (s, 9H). ^{13}C NMR ($CDCl_3$): δ=170.5 (C); 158.9 (C); 152.4 (C); 137.2 (C); 135.1 (CH); 131.6 (CH); 129.8 (CH); 129.2 (CH); 129.0 (CH); 128.1 (CH); 125.2 (CH); 124.3 (C); 60.4 (C); 24.6 (CH_3). IR (KBr) (cm^{-1}): 2959–3197, 1666, 1602, 1482, 1297, 1056, 768, 693. Anal. calcd for $C_{18}H_{18}N_2OS$: C, 69.65; H5.84; N, 9.02. Found: C, 69.19; H, 5.84; N, 9.03%.

4.3.27. 1-Methoxy-4-*tert*-butylsulfanylphtalazine (25). Synthesis of **25** was performed according to the general procedure for preparation of sulfides with 2-methyl-2-propanethiol (1.28 ml, 11.31 mmol) in 50 ml of THF, *n*-butyllithium 2.5 M (4.52 ml, 11.31 mmol) and 1-chloro-4-methoxyphtalazine **12** (2 g, 10.28 mmol) dissolved in 15 ml of THF. θ=66 °C, t=2 h. A purification by column chromatography on silica gel with dichloromethane as eluent gave **25** (2.43 g, 95%) as a white solid. Mp=61 °C. ^{1}H NMR ($CDCl_3$): δ=8.14 (m, 2H, H_5+H_8); 7.75 (m, 2H, H_6+H_7); 4.22 (s, 3H, OCH_3); 1.63 (s, 9H, *t*Bu). ^{13}C NMR ($CDCl_3$): δ=159.7 (C_1); 156.5 (C_4); 132.3 (CH); 132.1 (CH); 129.10 (C_{10}); 125.0 (CH); 123.6 (CH); 120.0 (C_9); 55.2 (CH_3); 49.2 (C); 31.3 (CH_3). IR (KBr) (cm^{-1}): 2966, 1538, 1452, 1361, 1326, 966, 763, 656, 620. Anal. calcd for $C_{13}H_{16}N_2OS$: C, 62.87; H, 6.49; N, 11.28. Found: C, 62.91; H, 6.54; N, 11.56%.

4.3.28. 1-Methoxy-4-*tert*-butylsulfinylphtalazine (26). Oxidation of a solution of 1-methoxy-4-*tert*-butylsulfanylphtalazine **25** (2 g, 8.05 mmol)), in dichloromethane (150 ml), was performed according to the general procedure with *m*-CPBA (2×0.99 g, 2×4.03 mmol) dissolved in dichloromethane (2×30 ml), giving after purification by column chromatography on silica gel with a mixture of dichloromethane/ethyl acetate (3/7) as eluent, **26** (1.76 g, 83%) as a pale yellow solid. Mp=147 °C. ^{1}H NMR ($CDCl_3$): δ=9.17 (m, 1H, H_5); 8.20 (m, 1H, H_8); 7.82 (m, 2H, H_6+H_7); 4.25 (s, 3H, OCH_3); 1.30 (s, 9H, *t*Bu). ^{13}C NMR ($CDCl_3$): δ=161.8 (C); 156.5 (C); 132.9 (CH, 2C); 129.6 (C); 124.7 (CH); 123.8 (CH); 120.7 (C); 59.7 (C); 55.8 (CH_3); 24.6 (CH_3). IR (KBr) (cm^{-1}): 2866–3077, 1493, 1457, 1375, 1048, 704, 529.8. Anal. calcd for

$C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60. Found: C, 58.04; H, 5.57; N, 10.63%.

4.3.29. 2-Methylsulfinylquinoxaline (30). To a solution of thioquinoxalinol **27** (0.158 g, 0.97 mmol) dissolved in THF (5 ml) was added dropwise, at −78 °C, MeLi 1.5 M (0.71 ml, 1.07 mmol). After stirring the solution at −78 °C for 15 min *trans*-3-(1,1-dimethylethyl)-3-methyl-2-(phenylsulfonyl)oxaziridine **28** (0.259 g, 1.00 mmol) dissolved in THF (2 ml) was added dropwise over a 1 min period. The reaction mixture was stirred at −78 °C for 30 min and then treated with methyl iodide (0.19 ml, 3.03 mmol). The reaction mixture was then warmed to −20 °C over 1.5 h and then the cold bath was removed. After stirring for a further 1.5 h at room temperature, the reaction mixture was treated with saturated aqueous NH_4Cl solution (3 ml) and the product extracted with dichloromethane (3×20 ml). The combined organic extracts were washed with brine (3×10 ml), dried over magnesium sulfate, filtered an then evaporated. A 7/1 pentane/dichloromethane mixture was added to precipitate the benzenesulfonamide by-product from the crude mixture. After filtration and concentration under reduced pressure the crude product was purified by column chromatography on silica gel with ether petroleum/ethyl acetate (85/15) as eluent gave **30** (0.116 g, 62%) as a white solid. Mp=96 °C. (lit.[34] 102–103 °C). ^{1}H NMR ($CDCl_3$): δ=9.43 (s, 1H); 8.16 (m, 1H); 8.04 (m, 1H); 7.82 (m, 2H); 2.97 (s, 3H). ^{13}C NMR ($CDCl_3$): δ=160.5 (C); 143.2 (C); 141.5 (C); 140.8 (CH); 132.0 (CH); 131.9 (CH); 130.2 (CH); 129.7 (CH); 41.8 (CH_3). IR (KBr) (cm^{-1}): 2906–3043, 1495, 1364, 1054, 962, 775. Anal. calcd for $C_9H_8N_2OS$: C, 56.23; H, 4.19; N, 14.57. Found: C, 55.86; H, 4.07; N, 14.46%.

4.3.30. 2-*tert*-Butyl-4(3H)-quinazolinone (31). To 10 g (73 mmol) of anthranilic acid dissolved in 120 ml of pyridine was added, at 0 °C, 27 ml (219 mmol) of trimethylacetyl chloride. The mixture was then refluxing for 1 h. After cooling, 300 ml of water was added. The aqueous layer was extracted with dichloromethane (3×100 ml). The organic extract was evaporated and the residue was stirred overnight in 200 ml of ammonia (30%). After evaporation of ammonia, 200 ml of a solution of aqueous sodium hydroxide (5%) was added and the solution was refluxing for 1 h. After cooling and acidification to pH=4 with HCl (1M), the precipitate was collected and washed with water to give **31** (14.33 g, 97%) as a white solid. Mp=185 °C. ^{1}H NMR (DMSO-d_6): δ=11.98 (s, 1H); 8.16 (dd, J=7.9, 1.1 Hz, 1H); 7.85 (m, 1H); 7.69 (d, J=7.9 Hz, 1H); 7.55 (m, 1H); 1.42 (s, 9H). ^{13}C NMR (DMSO-d_6): δ=163.0 (C); 162.7 (C); 148.6 (C); 134.6 (CH); 127.6 (CH); 126.5 (CH); 125.9 (CH); 121.0 (C); 37.6 (C); 28.1 (CH_3). IR (KBr) (cm^{-1}): 2873–3179, 1666, 1610, 1470, 1165, 972, 770. Anal. calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.24; H, 6.87; N, 13.78%.

4.3.31. 5-Phenylsulfanyl-2-*tert*-butyl-4(3H)-quinazolinone (32). A stirred solution of 2-*tert*-butyl-4(3H)-quinazolinone **31** (10 g, 49 mmol) and TMEDA (30 ml, 199 mmol), dissolved in 100 ml of tetrahydrofuran and under an atmosphere of dry nitrogen, was cooled to −78 °C. *sec*-butyllithium 1.3 M (153 ml, 199 mmol) was added dropwise and the mixture was warmed to 0 °C and kept at this temperature for 1 h. The solution was cooled to −78 °C and a solution of phenyl disulfide (43.2 g, 198 mmol) in 50 ml of tetrahydrofuran was added and the mixture was stirred for 1 h at −78 °C. Hydrolysis was then carried out at −78 °C using a mixture of water (20 ml) and ethanol (20 ml). The solution was gently warmed to room temperature and the solvent was removed under reduced pressure. The residue was extracted with dichloromethane (4×70 ml). The organic layer was dried over magnesium sulfate and evaporated. The residue was washed with dichloromethane (10 ml) and collected by filtration. A second wash with 10 ml of dichloromethane gave **32** after filtration (5.73 g, 37%) as a white solid. Mp>265 °C. ^{1}H NMR ($CDCl_3$): δ=10.85 (s, 1H, NH); 7.57 (m, 2H); 7.42 (m, 3H); 7.29 (m, 2H); 6.51 (m, 1H); 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$): δ=164.2 (C); 162.5 (C); 151.3 (C); 144.2 (C); 136.7 (CH); 133.9 (CH); 132.6 (C); 130.4 (CH); 129.9 (CH); 123.7 (CH); 123.3 (CH); 37.7 (C); 28.7 (CH_3). IR (KBr) (cm^{-1}): 2929–3166; 1648; 1620; 1585; 1549; 1455, 1304; 949. Anal. calcd for $C_{18}H_{18}N_2OS$: C, 69.65; H, 5.84; N, 9.02; S, 10.33. Found: C, 69.37; H, 5.93; N, 8.87; S, 10.58%.

4.3.32. 4-Chloro-5-phenylsulfanyl-2-*tert*-butylquinazoline (33). A mixture of 5-phenylsulfanyl-2-*tert*-butyl-4(3H)-quinazolinone **32** (3.9 g, 12.56 mmol), phosphorus oxychloride (1.95 ml, 20.92 mmol) pyridine (0.98 ml, 12.02 mmol) and chlorobenzene (100 ml) was heated at 130 °C for 5 h. after cooling to room temperature, 50 ml of water was added then the reaction mixture was neutralized with a saturated aqueous solution of potassium carbonate. The aqueous layer was extracted with dichloromethane. The organic layer was washed with 100 ml of an aqueous solution of sodium hydroxide (2 M), dried over magnesium sulfate and evaporated. A purification by column chromatography on neutral alumina with ether petroleum/ethyl acetate (95/5) as eluent gave **33** (3.89 g, 94%) as a yellow solid. Mp=73 °C. ^{1}H NMR ($CDCl_3$): δ=7.62 (d, J=8.3 Hz, 1H); 7.40 (m, 3H); 7.33 (m, 3H); 6.91 (d, J=7.9 Hz, 1H); 1.38 (s, 9H). ^{13}C NMR ($CDCl_3$): δ=172.5 (C); 160.5 (C); 154.3 (C); 139.2 (C); 135.3 (CH); 133.4 (CH); 133.3 (C); 130.5 (CH); 129.6 (CH); 128.2 (CH); 126.7 (CH); 120.8 (C); 29.6 (C); 29.7 (CH_3). IR (KBr) (cm^{-1}): 2921–3063, 1568, 1545, 1270, 1120, 881, 823, 755. Anal. calcd for $C_{18}H_{17}ClN_2S$: C,65.74; H, 5.21; N, 8.52; S, 9.75. Found: C, 65.57; H, 5.57; N, 8.28; S, 10.22%.

4.3.33. 5-Phenylsulfanyl-2-*tert*-butyl-4-toluene-*p*-sulphonylhydrazinoquinazoline (34). To 4-chloro-5-phenylsulfanyl-2-*tert*-butylquinazoline **33** (12.4 g, 34.7 mmol) dissolved in 500 ml of tetrahydrofuran was added toluene-*p*-sulphonylhydrazide (17.56 g, 94.26 mmol). The reaction mixture was refluxed. The pale yellow crystals of 5-phenylsulfanyl-2-*tert*-butyl-4-toluene-*p*-sulphonylhydrazinoquinazoline **34** formed were collected after 7 days (9.30 g, 56%). Mp=263 °C. ^{1}H NMR (DMSO-d_6): δ=10.65 (s, 1H, NH); 9.59 (s, 1H, NH); 8.00 (d, J=8.3 Hz, 2H); 7.59 (m, 5H); 7.40 (d, J=7.9 Hz, 2H); 7.19 (dd, J=7.9, 7.9 Hz, 1H); 7.08 (d, J=8.3 Hz, 1H); 6.36 (d, J=7.5 Hz, 1H); 2.39 (s, 3H); 1.37 (s, 9H). ^{13}C NMR (DMSO-d_6): δ=164.2 (C); 146.6 (C); 143.3 (C); 139.7 (C); 139.2 (C); 136.6 (C); 135.9 (CH)); 133.4 (C); 130.5 (CH); 130.3 (CH); 129.7 (CH); 129.5 (CH); 128.2 (CH); 122.2 (CH); 112.6 (C); 112.0

(CH); 37.5 (C); 28.0 (CH_3); 21.3 (CH_3). IR (KBr) (cm^{-1}): 3362, 3199, 1606, 1504, 1162, 706, 689, 560. Anal. calcd for $C_{25}H_{26}N_4O_2S_2$: C, 62.74; H, 5.47; N, 11.71; S, 13.40. Found: C, 62.52; H, 5.22; N, 11.76; S, 13.32%.

4.3.34. 5-Phenylsulfanyl-2-*tert*-butylquinazoline (35). 5-Phenylsulfanyl-2-*tert*-butyl-4-toluene-*p*-sulphonylhydrazinoquinazoline **34** (2.36 g, 4.9 mmol) was added to a stirred solution of sodium carbonate (3.12 g, 29.4 mmol) in 60 ml of water and warmed at 180 °C for 3 h under a pressure of 7 bars. The aqueous layer was extracted with dichloromethane and the organic layer was dried over magnesium sulfate and evaporated. A purification by column chromatography on silica gel with ether petroleum/dichloromethane (1/1) as eluent gave **35** (1.2 g, 83%) as a pale yellow solid. Mp=107 °C. ^{1}H NMR ($CDCl_3$): δ=9.76 (s, 1H); 7.85 (d, J=8.3 Hz, 1H); 7.67 (dd, J=7.9, 7.4 Hz, 1H); 7.47 (dd, J=7.2, 1.1 Hz, 1H); 7.21 (m, 5H); 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$): δ=174.7 (C); 155.5 (CH); 151.1 (C); 144.7 (C); 142.3 (C); 133.3 (CH); 132.6 (CH); 132.0 (CH); 130.1 (CH); 125.7 (CH); 124.8 (CH); 119.6 (C); 40.1 (C); 29.9 (CH_3). IR (KBr) (cm^{-1}): 2864–3058; 1602; 1574, 1552, 1480; 1112; 833; 745; 717. Anal. calcd for $C_{18}H_{18}N_2S$: C, 73.43; H, 6.16; N, 9.51. Found: C, 73.47; H, 6.21; N, 9.29%.

4.3.35. 5-Phenylsulfinyl-2-*tert*-butylquinazoline (36). Oxidation of a solution of 5-phenylsulfanyl-2-*tert*-butylquinazoline **35** (3.4 g, 11.55 mmol)), in dichloromethane (300 ml), was performed according to the general procedure with *m*-CPBA (2×1.41 g, 2×5.78 mmol) dissolved in dichloromethane (2×15 ml), giving after purification by column chromatography on silica gel with a mixture of ether petroleum/ethyl acetate (7/3) as eluent, **36** (3.22 g, 90%) as a pale yellow solid. Mp=137 °C. ^{1}H NMR ($CDCl_3$): δ=9.77 (s, 1H, H_4); 8.16 (d, J_{6-7}=7.2 Hz, 1H, H_6); 8.01 (d, J_{8-7}=8.7 Hz, 1H, H_8); 7.90 (dd, J_{7-6}=7.3 Hz, J_{7-8}= 8.5 Hz, 1H, H_7); 7.63 (m, 2H); 7.63 (m, 3H); 1.38 (s, 9H). ^{13}C NMR ($CDCl_3$): δ=174.7 (C_2); 155.5 (C_4); 151.1 (C_9); 144.8 (C); 142.3 (C_5); 133.3 (C_7); 132.6 (C_8); 131.9 (CH); 130.1 (CH); 125.7 (CH); 124.8 (C_6); 119.6 (C_{10}); 40.1 (C); 29.9 (CH_3). IR (KBr) (cm^{-1}): 2864–3063, 1577, 1552, 1438, 1057, 833, 693. Anal. calcd for $C_{13}H_{16}N_2O_2S$: C, 69.65; H, 6.26; N, 9.02. Found: C, 69.97; H, 6.14; N, 8.89%.

4.3.36. 2-*tert*-Butyl-5-*tert*-butylsulfanylquinazolin-4-one (37) and 2-*tert*-butyl-8-*tert*-butylsulfanylquinazolin-4-one (38). A stirred solution of 2-*tert*-butyl-4(3H)-quinazolinone **31** (5 g, 25 mmol) and TMEDA (15 ml, 100 mmol), dissolved in 50 ml of tetrahydrofuran and under an atmosphere of dry nitrogen, was cooled to −78 °C. *sec*-Butyllithium 1.3 M (77 ml, 100 mmol) was added dropwise and the mixture was warmed to 0 °C and kept at this temperature for 1 h. *tert*-Butyl disulfide (20 ml, 100 mmol) was added and the mixture was stirred for 3 h at 0 °C. Hydrolysis was then carried out at 0 °C with water (30 ml). The solution was gently warmed to room temperature and the solvent was removed under reduced pression. The residue was extracted with dichloromethane. The organic layer was dried over magnesium sulfate and evaporated. A purification by column chromatography on silica gel with dichloromethane/diethyl ether (9/1) as eluent gave **37** in a first fraction (2.02 g, 30%) as a white solid. Mp=200 °C. ^{1}H NMR ($CDCl_3$): δ=11.59 (s, 1H); 7.69 (m, 3H); 1.65 (s, 9H, S-*t*Bu); 1.64 (s, 9H, *t*Bu). ^{13}C NMR ($CDCl_3$): δ=163.9 (C_4); 162.7 (C_2); 152.0 (C_9); 140.0 (C_5); 133.1 (CH); 129.8 (CH); 125.7 (CH); 120.3 (C_{10}); 46.8 (C, S-*t*Bu); 37.7 (C, *t*Bu); 31.3 (CH_3, S-*t*Bu); 28.7 (CH_3, *t*Bu). IR (KBr) (cm^{-1}): 2956–3170, 1656, 1620, 1585, 1454, 1296, 980. Anal. calcd for $C_{16}H_{22}N_2OS$: C, 66.17; H, 7.63; N, 9.65. Found: C, 65.74; H, 7.61; N, 9.46%.

A second fraction gave **38** (1.27 g, 18%) as a white solid. Mp=165 °C. ^{1}H NMR ($CDCl_3$): δ=11.10 (s, 1H); 8.30 (d, J=7.9 Hz, 1H, H_5); 8.03 (d, J=7.2 Hz, 1H, H_7); 7.39 (dd, J=7.7, 7.7 Hz, 1H, H_6); 1.50 (s, 9H, *t*Bu); 1.33 (s, 9H, S-*t*Bu). ^{13}C NMR ($CDCl_3$): δ=164.4 (C_4); 162.0 (C_2); 151.6 (C_9); 144.9 (C_7); 132.7 (C_8); 127.7 (C_5); 126.1 (C_6); 121.9 (C_{10}); 47.8 (C, S-*t*Bu); 38.4 (C, *t*Bu); 31.7 (CH_3, S-*t*Bu); 28.7 (CH_3, *t*Bu). IR (KBr) (cm^{-1}): 2964–3176, 1665, 1614, 1590, 1422, 986, 784, 776. Anal. calcd for $C_{16}H_{22}N_2OS$: C, 66.17; H, 7.63; N, 9.65. Found: C, 65.78; H, 7.37; N, 9.46%.

4.3.37. 2-*tert*-Butyl-5-*tert*-butylsulfinylquinazolin-4-one (39). Oxidation of a solution of 2-*tert*-butyl-5-*tert*-butylsulfanylquinazolin-4-one **37** (0.15 g, 0.52 mmol) in dichloromethane (10 ml), was performed according to the general procedure with *m*-CPBA (2×64 mg, 2×0.26 mmol) dissolved in dichloromethane (2×5 ml), giving after purification by column chromatography on silica gel with a mixture of ethyl acetate/dichloromethane (8/2) as eluent, **39** (64 mg, 40%) as a pale yellow solid. Mp>265 °C. ^{1}H NMR ($CDCl_3$): δ=10.9 (s, 1H, NH); 8.11 (dd, J_{6-7}=7.4 Hz, J_{6-8}=1.3 Hz, 1H, H_6); 7.8 (m, 2H, H_7+H_8); 1.44 (s, 9H, *t*Bu); 1.15 (s, 9H, S(O)-*t*Bu). ^{13}C NMR ($CDCl_3$): δ=16.7 (C); 163.2 (C); 150.7 (C); 143.4 (C); 134.0 (CH); 131.1 (CH); 125.7 (CH); 119.3 (C); 59.8 (C); 38.1 (C); 28.8 (CH_3); 23.7 (CH_3). IR (KBr) (cm^{-1}): 2976–3172, 1658, 1613, 1592, 1456, 1042, 974, 823. HRMS (DCI^+) calcd for (MH^+) $C_{16}H_{23}N_2O_2S$: *m*/*z* 307.1480. Found: 307.1476.

4.3.38. 2-*tert*-Butyl-8-*tert*-butylsulfinylquinazolin-4-one (40). Oxidation of a solution of 2-*tert*-butyl-8-*tert*-butylsulfanylquinazolin-4-one **38** (0.7 g, 2.41 mmol), in dichloromethane (40 ml), was performed according to the general procedure with *m*-CPBA (2×0.3 g, 2×1.2 mmol) dissolved in dichloromethane (2×10 ml), giving after purification by column chromatography on silica gel with a mixture of ethyl acetate/dichloromethane (8/2) as eluent, **40** (0.7 g, 95%) as a pale yellow solid. Mp=162 °C. ^{1}H NMR ($CDCl_3$): δ=11.76 (s, 1H, NH); 8.32 (d, J_{5-6}=7.5 Hz, 1H, H_5); 8.22 (d, J_{7-6}=7.1 Hz, 1H, H_7); 7.57 (dd, J=7.7, 7.7 Hz, 1H, H_6); 1.42 (s, 9H, *t*Bu); 1.17 (s, 9H, S(O)-*t*Bu). ^{13}C NMR ($CDCl_3$): δ=163.9 (C_4); 163.3 (C_2); 147.4 (C_9); 138.9 (C_8); 133.6 (C_7); 129.3 (C_5); 126.5 (C_6); 121.0 (C_{10}); 58.7 (C, S(O)-*t*Bu); 38.4 (C, $_t$Bu); 28.6 (CH_3, *t*Bu); 23.9 (CH_3, S(O)-*t*Bu). IR (KBr) (cm^{-1}): 2960–3183, 1671, 1602, 1427, 1034, 782. Anal. calcd for $C_{16}H_{22}N_2O_2S$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.55; H, 6.84; N, 8.58%.

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