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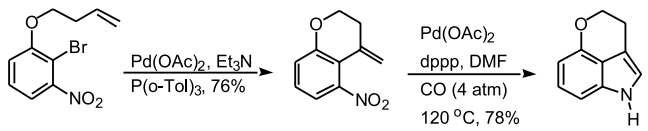
Contents

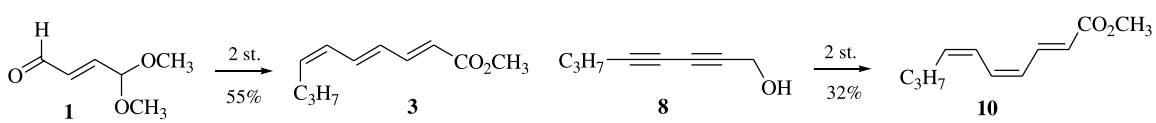
REPORT

$\Delta V_i^* = \Delta V_0^* + \Delta V_\sigma^*$
(ΔV_0^*: activation volume of the unhindered reaction, ΔV_σ^*: steric volume component)

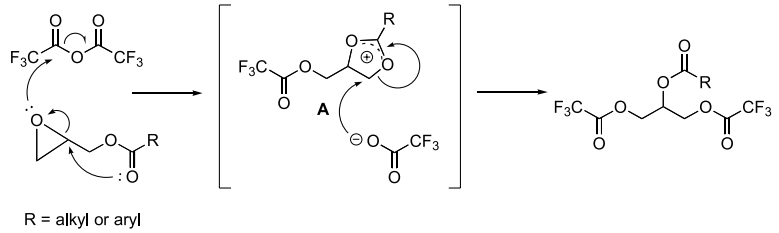
The paper reviews the recent progress made in the high-pressure relief of steric inhibition in congested reactions. The correlation between pressure and steric interactions is illustrated by comprehensive examples and rationalized via useful Hammond postulate. The report contains 96 references.

ARTICLES

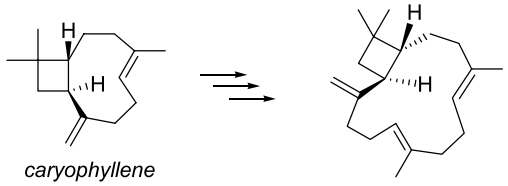


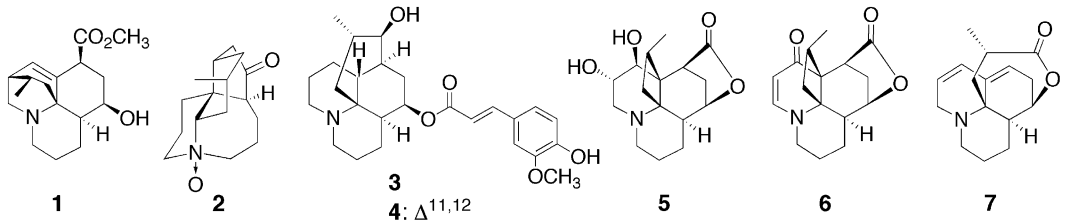


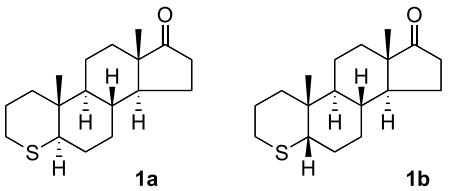
All eight stereoisomers of methyl 2,4,6-decatrienoate, among them sex pheromones of stink bugs, were synthesized by fully exploiting Wittig-type olefinations, including in situ MnO_2 oxidation–Wittig reaction.

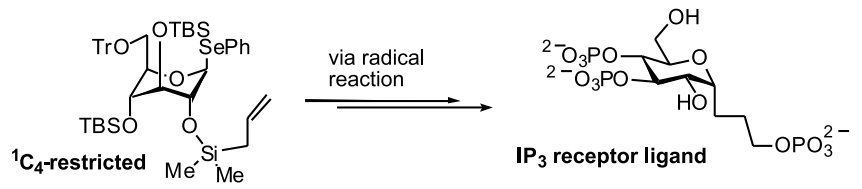


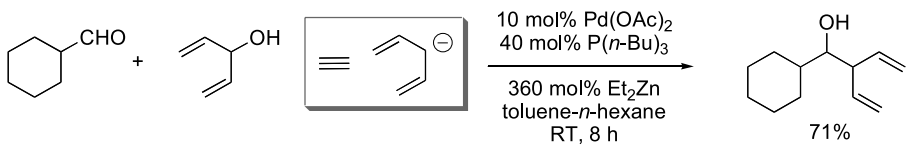
Efficient, one pot synthesis of 2-acyl- and 1,3-symmetrical triglycerides based on regioselective opening of an oxirane ring with TFAA in glycidol esters was developed.

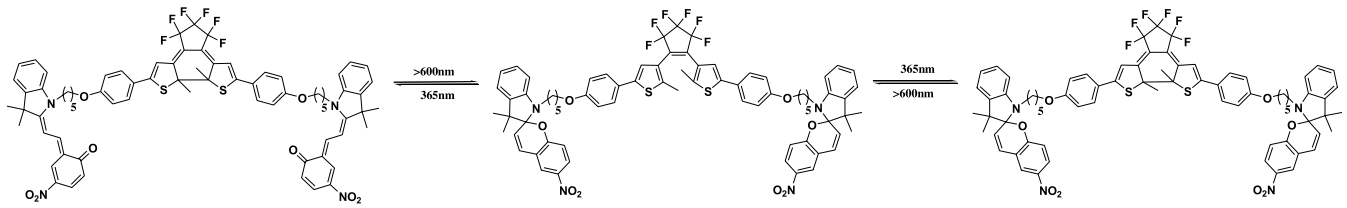


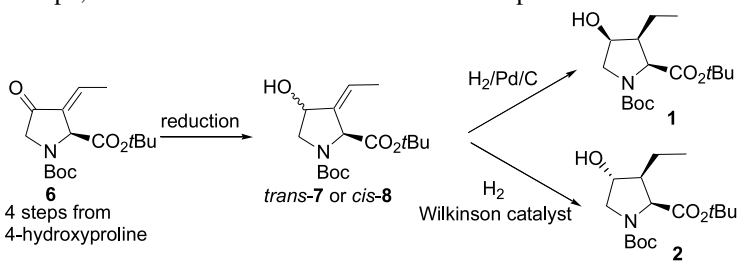


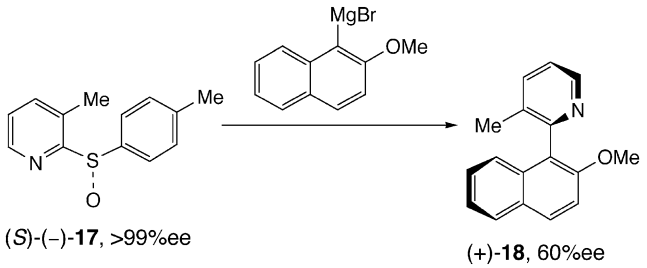


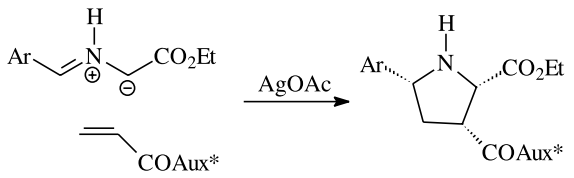


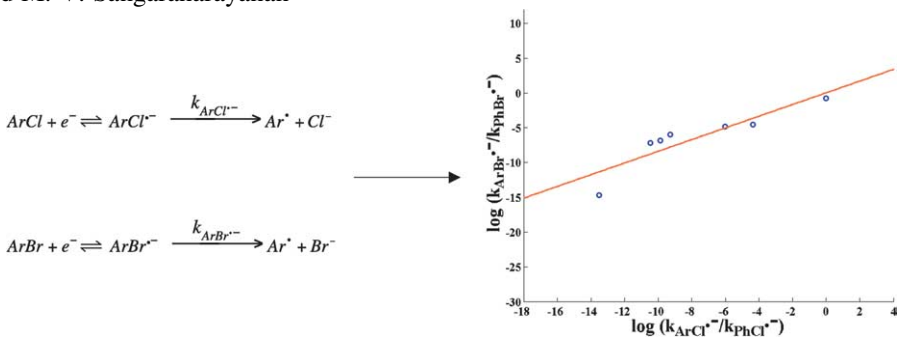


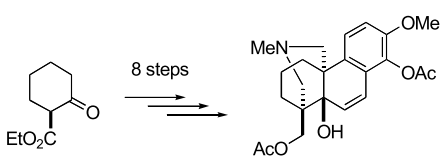


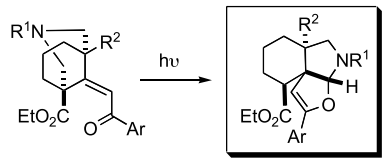


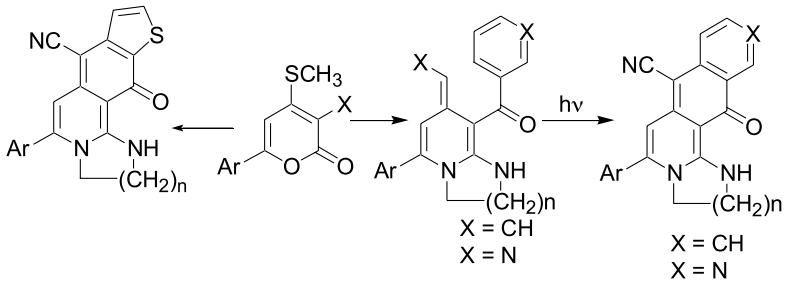


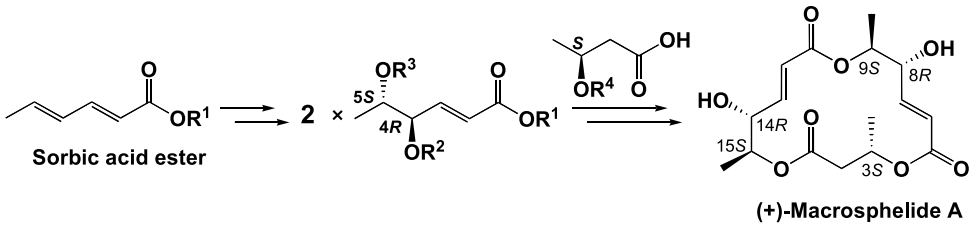


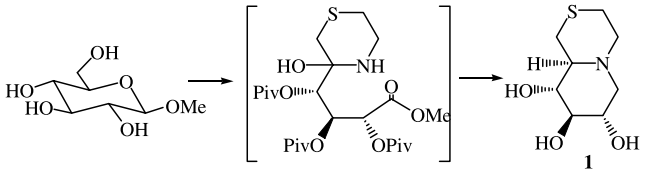




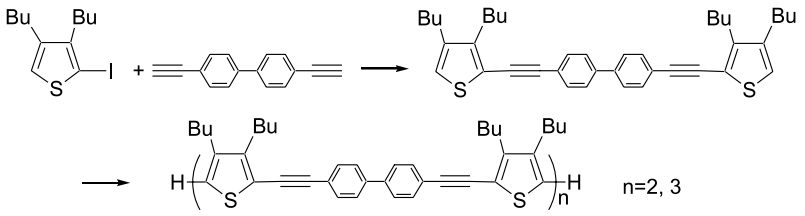




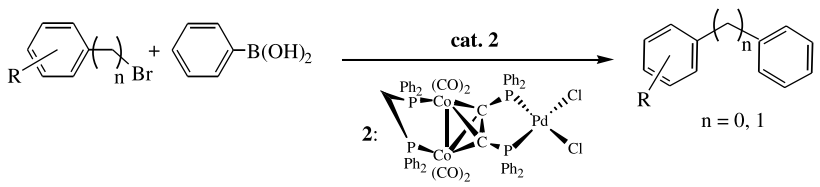




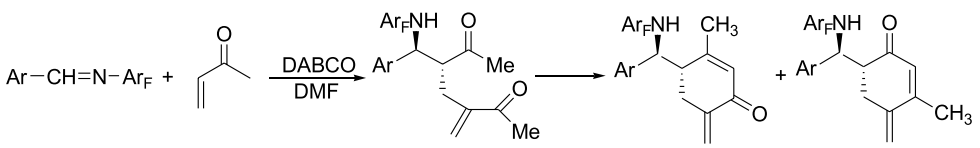
7(*S*),8(*R*),9(*R*)-Trihydroxy-2-thiaquinolizidine a new bicyclic dideoxy-iminohexitol glycosidase inhibitor is selective for α-glucosidases.

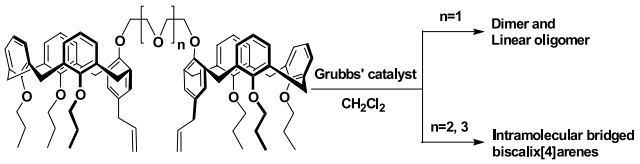


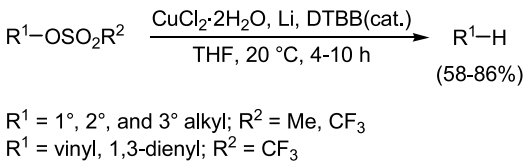
A new solid-supported oxazolidinone efficiently functions in Evans' asymmetric alkylation.

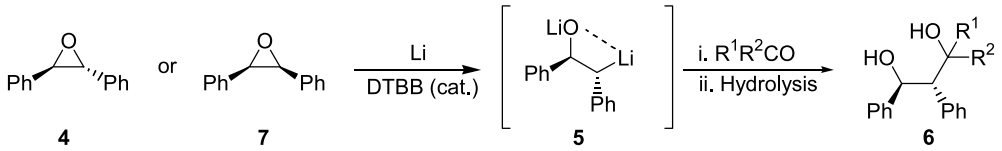


Biphasic Suzuki-coupling reactions of aryl and benzyl bromides employing catalyst **2** were carried out in designed conditions. Better yields were commonly observed while a phase-transfer agent TBAB was participated in the reactions.

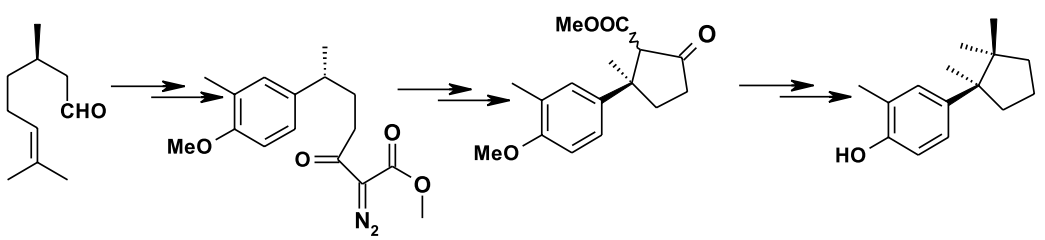








[Electrophile: Bu^tCHO, c-$C_6H_{11}CHO$, PhCHO, Me_2CO, Et_2CO, $(CH_2)_5CO$, $Pr^i{}_2CO$, $(c$-$C_3H_5)_2CO$].



OTHER CONTENTS

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ⓘ+ Supplementary data available via ScienceDirect

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Correlation between pressure and steric interactions in organic reactions

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Contents

1. Introduction

Amid numerous parameters, the rate of a chemical reaction may be influenced by structural changes of the reagents through polar, resonance and steric effects. Steric hindrance is a wide concept encompassing the effect of bulkiness of reactants and the steric accessibility of reaction centres on reagent approach. As a very general rule, steric effects decrease rate constants, although there are some examples illustrating an opposite effect.[1] Conceptually, it is common practice to distinguish between primary steric effects (steric hindrance to the approach of reagents, steric hindrance to solvation…) and secondary steric effects (moderation of a polar or a resonance effect by non-bonded compression).[2] The quantitative treatment of the kinetic rate constant k of a reaction relates basically to two main parameters: the resonance and field effect and the steric effect. It is a well-known fact that k obeys linear free energy relationships.[3] It is not the aim of this paper to review the relationships (Taft–Hammett, Grunwald–Winstein…) governing sterically congested reactions. We examine here the effect of an external factor on such reactions.

Steric effects are intimately related to volume effects. Accordingly, the velocity of hindered versus unhindered reactions can be affected differently by pressure. Intermolecular distances decrease under pressure, leading to an increase in the potential energy. The molecules try to adjust to the new situation by taking a more crowded conformation

Keywords: Activation volume; Steric hindrance; Pressure; Hammond postulate.
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which occupies a smaller volume.[4] Every reaction is described by two profiles: the well-known energy diagram which in the transition state theory shows the successive transition states and intermediates and the volume profile which is less evident to determine as it requires the determination of the individual volumes, virtual as for transition states and real as for intermediates.[5] The components of the volume profile are measurable only via high-pressure kinetics. A particularly instructive profile determined in this way has been recently pictured in the Baeyer–Villiger (B–V) oxidation of aliphatic ketones showing two transition states with one intermediate (Fig. 1).[6] Sterically hindered B–V reactions are reported at the end of this review.

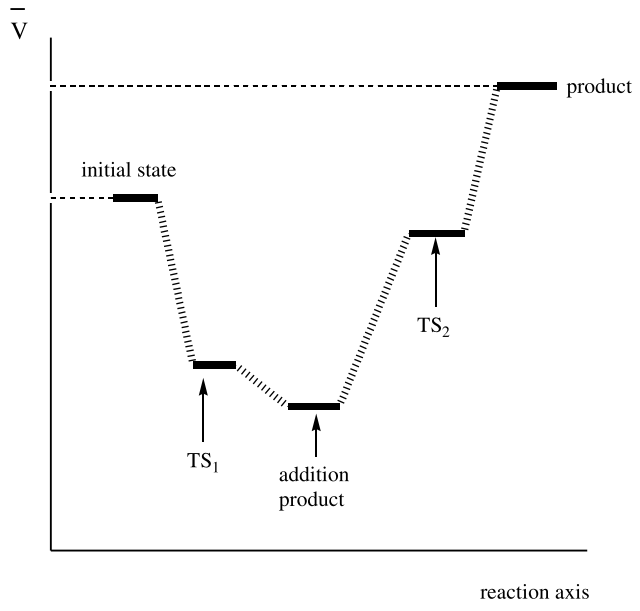
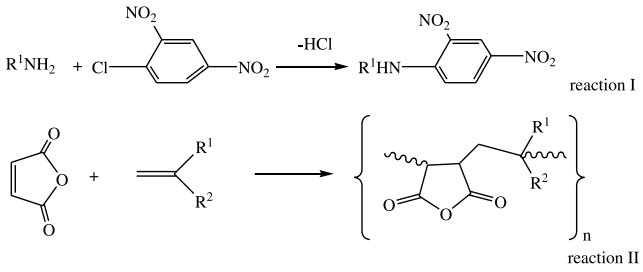


Figure 1. Volume profile of the Baeyer–Villiger reaction.

The influence of pressure on reaction rates was already considered towards the end of the nineteenth century.[7] Some fifty years later, Perrin et al. observed that reactions involving bulky reagents were accelerated by pressure more than their unhindered analogs.[8] Later, two groups examined the pressure effect in Menshutkin reactions of α-methyl substituted pyridines[9,10] and both confirmed Perrin's result, although these were differently rationalized. Gonikberg suggested a preferred more compact spatial arrangement of bulky molecules within the transition state under the influence of pressure,[10] whereas the other authors interpreted the phenomenon via Hammond postulate, according to which the less endothermic activated complex involves less volume contraction and, therefore, should occur earlier. Conversely, a more congested hindered reaction will be shifted to the final product with a late transition state. This view was proposed for the first time by Brower in his study of the pressure effect on aromatic nucleophilic substitutions.[11] In our first review detailing the pressure effect on strained transition states, we reported a correlation between steric hindrance and the activation volume ΔV^*.[12] The purpose of the present paper is to report the recent synthetic advances in the subject and its interpretation based on the activation volume.[13]

2. Correlation between pressure and steric hindrance

We begin with two examples, a nucleophilic aromatic substitution (reaction I in Scheme 1)[14] and the radical copolymerisation of maleic anhydride with *gem*-substituted alkenes (reaction II in Scheme 1)[15] (Table 1). Under similar pressure conditions, the rate constant ratio in both reactions increases when the reaction centres are substituted by more compressive groups.



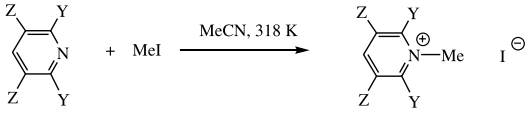
Scheme 1.

Table 1. Effect of steric bulk on rate constant ratios k_P:$k_{0.1}$ in reactions I and II

Reaction	R^1	R^2	Pressure (MPa)		
			0.1	150	200
I[a]	Bu	—	1	—	3.29
	t-Bu	—	1	—	7.52
II[b]	Me	Ph	1	4.2	—
	Ph	Ph	1	7.1	—
	Me	*t*-Bu	1	15.1	—

[a] In ethanol at 308 K.
[b] In chloroform at 343.4 K; lauroyl peroxide was the initiator.

As another illustrative example, the pressure effect has been clearly evidenced in the Menshutkin reaction of buttressed pyridines (Scheme 2 and Table 2).[16] Whereas the rate constant under ambient pressure conditions is abysmally decreased with increasing bulk of Z and Y, the most hindered reactions are more accelerated by pressure, meaning more negative activation volumes ΔV^*.



Scheme 2.

Table 2. Menshutkin reactions of methyl iodide with buttressed pyridines

Z	Y	Rate constant ratio[a]	ΔV^* ($cm^3\ mol^{-1}$)
H	H	1	-28.2 ± 0.2
H	Me	0.0354	-30.8 ± 0.2
t-Bu	Me	0.0036	-32.5 ± 0.5

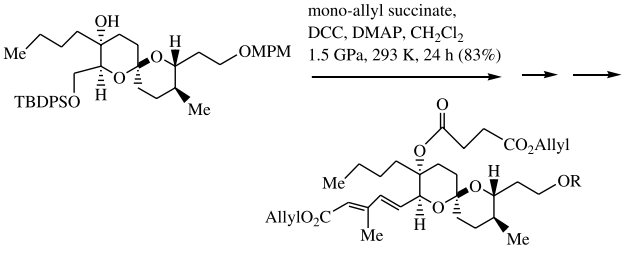
[a] In acetonitrile at 318 K and 0.1 MPa.

There are numerous other examples reporting this interesting effect. A large pressure-induced rate increase was noticed in the Wittig reaction of ylides with hindered cyclohexanones.[17,18] The Michael addition can be very sensitive to steric hindrance. The reaction is also subjected to electrostriction.[19] Successful sterically hindered

additions were achieved only under pressure such as Michael reactions involving steroidal systems[20] and the synthesis of congested β-aminoesters.[21]

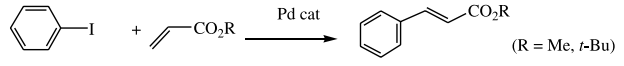
The asymmetric conjugate Michael-like addition of amines to chiral bulky crotonates is essentially accessible only under high pressure.[22] Interestingly, efficient stereo- and enantioselectivity are achieved at 1.4 GPa since the diastereoisomeric excess increases from 10% at ambient pressure to 98% at high pressure. Very recently, hindered quaternary centers have been made accessible via high-pressure asymmetric Michael addition of chiral imines to crotonates.[23]

Reactions involving sterically hindered tertiary alcohols are generally promoted to some extent by pressure. The reaction of these alcohols with cyclic anhydrides occurs successfully under 1.5 GPa to afford dicarboxylic monoesters.[24,25] As a recent prominent example, in the total synthesis of reveromycin A, a potent inhibitor of eukaryotic cell growth, the crucial step leading to spiroketals involves succinylation of the molecule harbouring a tertiary alcohol function. This could be accomplished under 1.5 GPa (Scheme 3).[26]

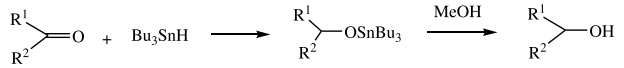


Scheme 3.

The phenomenon has also been observed in high-pressure organometallic reactions. In the Heck coupling of iodobenzene with alkyl acrylates (Scheme 4), the activation volume varies from -5 to $-12\ cm^3mol^{-1}$ when R changes from methyl to *tert*-butyl. The same correlation applies for the leaving group ($\Delta\Delta V^{*}=28\ cm^3\ mol^{-1}$) when the voluminous triflate group is substituted for iodine.[27]



Scheme 4.



Scheme 5.

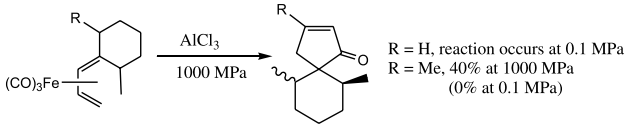
Table 3. Hydrostannation of ketones according to Scheme 5[a]

R^1	R^2	Yield at 0.1 MPa (%)	β_{1000}[b]
PhCHMe	*t*-Bu	0	>57
PhCHMe	*i*-Pr	2	32
PhCHMe	Et	12	6
$PhCH_2$	*i*-Pr	15	4

[a] 328 K, 24 h.
[b] Yield ratio at 1000 and 0.1 MPa, respectively.

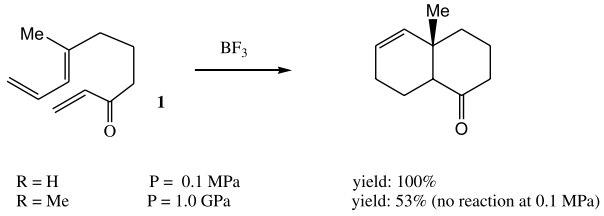
Hydrostannation and hydroboration of alkenes and ketones are very sensitive to the bulkiness of the reacting molecules. The pressure effect is larger when the size of R^1 and R^2 is increased (Scheme 5 and Table 3).[28]

Cyclocarbonylation via decomplexation of sterically congested iron-complexed conjugated dienes occurred only under high pressure in the presence of hard Lewis acids (Scheme 6).[29]



Scheme 6.

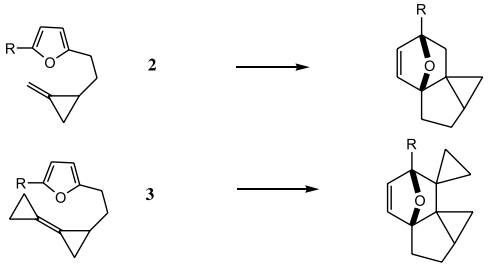
Sterically hindered cycloadditions were reported to be affected by pressure in an enhanced manner compared to normal cycloadditions (see, however, case B_2 in the following section). They include the cycloaddition of Danishefsky's diene and a sterically congested dienophile angularly substituted by a trifluoromethyl group,[30] and the Diels–Alder reactions of methyl palustrate with unsaturated anhydrides,[31] and of acyclic dienes with cycloalkenones.[32] Sterically rigid macrocycles of shaped cavities could be synthesized only under high pressure.[33] The intramolecular Lewis acid-catalyzed Diels–Alder reaction of ketone **1** leads to a precursor in the synthesis of brassinosteroids.[34] The reaction is very sensitive to the size of R (Scheme 7).



Scheme 7.

Sterically strained intramolecular Diels–Alder reactions have been investigated under pressure. They involved furans tethered by bicyclopropylidene and methylene cyclopropane moieties (Scheme 8).[35–37] When R in **2** and **3** is changed from H to OMe, the pressure sensitivity of the cycloaddition increases (Table 4).

The activation volumes are dependent on the additional strain (**2** vs **3**), as well as on steric hindrance introduced by



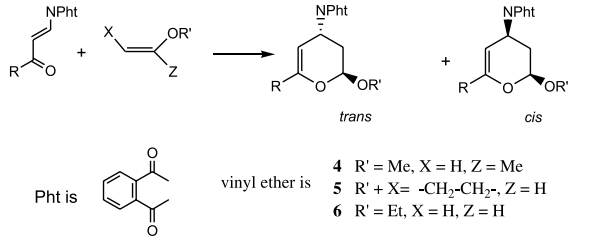
Scheme 8.

Table 4. Effect of pressure on the intramolecular Diels–Alder reactions of **2** and **3**

Furan	R	T (K)	ΔV^* (± 2 cm^3 mol^{-1})	ΔS^* (± 2 to 7 J mol^{-1} K^{-1})
2	H	383	−28.4	−92
3	H	383	−31.9	−84
2	OMe	353	−35.8	−75
3	OMe	353	−40.8	−78

the cyclopropane ring, leading to enhanced rigidity of the transition state. The ΔH^* (not shown in Table 4) and ΔS^* values are, however, not significantly altered. This is explained by the compensation between steric hindrance and strain release originating from the C_3 ring. Table 4 shows that ΔV^* is more informative with regard to steric hindrance than ΔS^*.

The same observation holds true for the hetero-Diels–Alder reaction between unsaturated aminoketones and vinyl ethers **4–6** (Scheme 9).[38–41] Changes in diastereoselectivity due to steric hindrance may be expected with an increase in pressure. Large $\Delta\Delta V^*$ values (up to -11 cm^3 mol^{-1}) were determined in these cycloadditions.[39] Table 5 reports the activation volume and enthalpy differences for *cis* and *trans* isomers.[39] The evident variation in size between the CF_3 and CCl_3 group is reflected in the $\Delta\Delta V^*$ values, but less in the $\Delta\Delta H^*$ values.

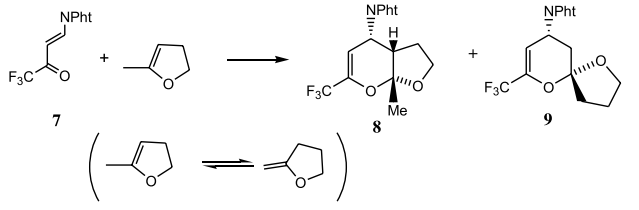


Scheme 9.

Table 5. Effect of pressure on hetero-Diels–Alder reactions (Scheme 9)

Vinyl ether R	R	T (°C)	$\Delta\Delta V^*$ (cm^3 mol^{-1})	$\Delta\Delta H^*$ (kJ mol^{-1})
4	CF_3	50	+4.1	−6.2
4	CCl_3	50	−0.6	−5.7
5	CF_3	60	−3.9	−8.3
5	CCl_3	90	−7.3	−6.6
6	CF_3	45	−6.0	−8.7
6	CCl_3	90	−9.2	−8.2

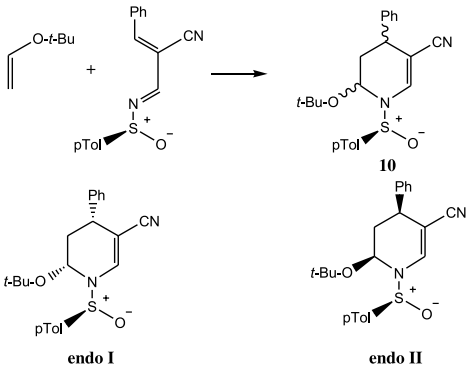
Similar reactions were studied by Tietze's and Buback's groups with analogous conclusions, and $\Delta\Delta V^*$ correlates with the steric bulk at the reaction centers.[42–44] A surprising effect was reported in the cycloaddition of **7** and 2-methyldihydrofuran (Scheme 10).[39] The reaction afforded



Scheme 10.

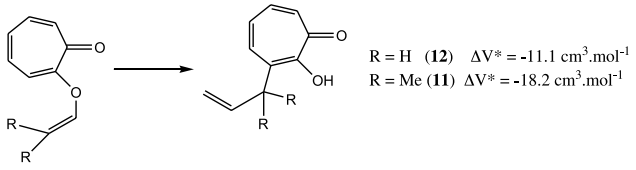
the annulated **8** and the spiro **9** compounds. The formation of **9** is assumed to proceed via *endo*-E-*syn* transition state with involvement of an isomeric vinyl ether species (Scheme 10). At 0.1 MPa, the **8:9** ratio is 1:5.2, which changed to 1:2.3 at higher pressure. Compound **8** results from a sterically more demanding transition structure and is, therefore, stabilised under pressure. The difference in activation volumes $\Delta V^*(\mathbf{8}) - \Delta V^*(\mathbf{9})$ was calculated to be -10.5 cm^3 mol^{-1}.

A thorough description of the correlation between pressure and steric constraints regarding diastereoselectivity has been published recently.[42] The aza-Diels–Alder reaction of an α,β-unsaturated sulfinimine with *t*-butyl vinyl ether leads to four diastereoisomers of **10** (Scheme 11; only the *endo* isomers are shown).[45] High pressure stabilises the *endo* I cycloadduct through the attack of the dienophile *anti* to the tolyl group which is a sterically more hindered approach (*endo* I:*endo* II:*exo* I + II = 1.46:1.00:0.93 at 0.1 MPa and 2.77:1.00:0.85 at 1100 MPa).



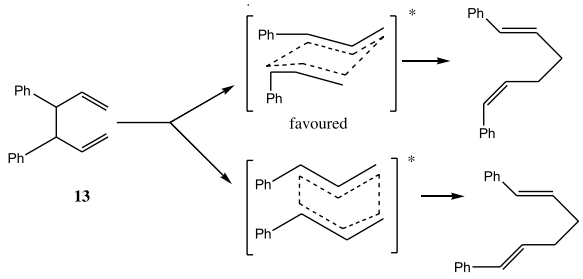
Scheme 11.

Relatively few studies on the pressure effect on hindered pericyclic rearrangements are available. In the sigmatropic transposition involving tropones, the reaction involving the more sterically hindered tropone **11** is characterized by a more negative activation volume than the corresponding sigmatropy of **12** (Scheme 12).[46] The transition state is certainly late as in every concerted Claisen rearrangement.[47] The activation volumes and probably also the reaction volumes (which, unfortunately, have not been measured) are, however, different as a reactant having a bulky substituent must be contracted to a greater extent (cf. case B_2 in Section 3).



Scheme 12.

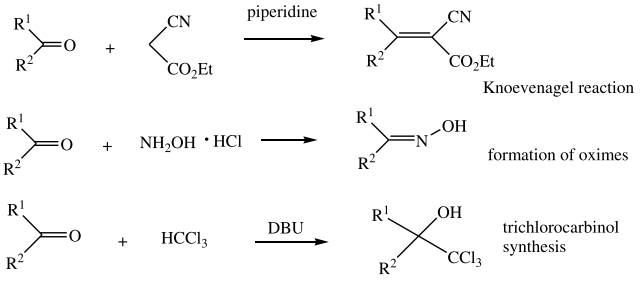
High pressure may even affect the chain-boat conformation. In the Cope rearrangement of 3,4-diphenyl-1,5-hexadiene **13**, pressure promotes the more compact chair-like transition state caused by the axial position of one phenyl group (Scheme 13).[48]



Scheme 13.

All examples shown above refer to pressure acceleration of the rate in sterically demanding reactions. There are, however, a few counter-examples. In the hydrolysis of sterically hindered cycloalkyl arenesulfonates[49] and benzyl chlorides,[50] the results were not conclusive, due to the apparent insensitivity of the ΔV^* values on steric congestion. The latter group reported[50] an interesting result in the solvolysis of 2,4,6-tri-*tert*-butylbenzyl chloride, which was less accelerated by pressure than the 2,4,6-trisubstituted methyl and isopropyl analogs. This result was rationalized by steric acceleration resulting in less negative ΔV^* and ΔS^* values.

Many other sterically demanding reactions have been examined under pressure and our laboratory has amply contributed in the last few years to this aspect of high-pressure chemistry. We examined the Knoevenagel condensation between ketones and ethyl cyanoacetate (Scheme 14 and Table 6),[51] the nucleophilic addition of alcohols to activated alkenes,[52] the synthesis of oximes and of trihalocarbinols[53] (Scheme 14), the thiazolium salt-catalyzed acyloin condensation and the Stetter reaction involving aldehydes and acrylonitrile (Scheme 15),[54] as well as multicomponent reactions (Scheme 16).[55–57] The pressure effect can be portrayed in many ways. For example, in the nucleophilic addition of linear primary alcohols to cinnamonitrile at 323 K in the presence of tri-*n*-butylphosphine,[52]

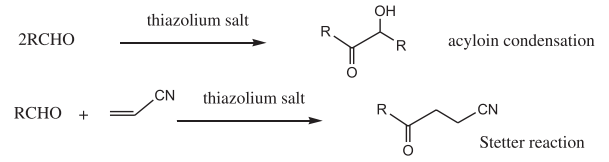


Scheme 14.

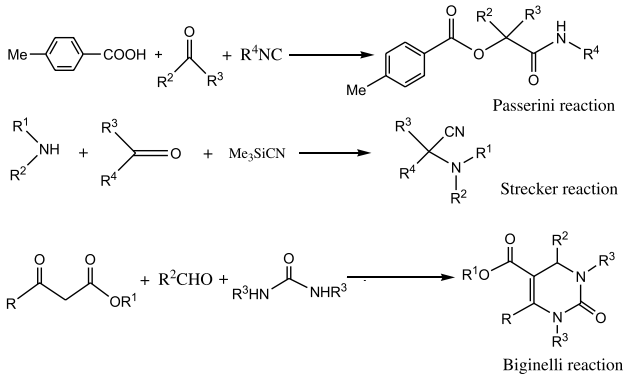
Table 6. Effect of pressure on Knoevenagel condensations with ethyl cyanoacetate[a] (Scheme 14)

R^1	R^2	Yield (%)	
		0.1 MPa	300 MPa
H	*s*-Bu	82	82
H	*t*-Bu	62	60
Me	Me	38	59
Et	Et	6	30
Me	*i*-Bu	5	55

[a] 296 K, 2 h, cat (piperidine), medium (keto compound).



Scheme 15.



Scheme 16.

the yields of β-cyanoethers are 31, 10, and 4% at 300 MPa when the alkyl group in the alcohol is ethyl, *n*-propyl, and *n*-butyl, respectively, whereas no reaction occurs at ambient pressure. Raising the pressure to 800 MPa led to yields of 100, 96, and 80%, respectively. In these reactions, pressure clearly removes the steric inhibition.

In the Knoevenagel condensation between ethyl cyanoacetate and keto compounds (Table 6),[51] pressure has no effect when $R^1 = H$ (aldehydes). When methyl ketones are the reagents, however, although increasing bulkiness of R^2 lowers the yields at ambient pressure, the pressure effect is more pronounced. The high-pressure method is thus confirmed as particularly adapted to the synthesis of sterically hindered alkenes which are notoriously difficult to prepare (Table 7).

Table 8 reports the pressure effect in thiazolium

Table 7. High-pressure synthesis of alkenes via Knoevenagel condensations[a]

R^1	R^2	*P* (MPa)	*T* (°C)	Time (h)	Yield (%)
Et	Pr	600	60	16.5	52
Et	Bu	600	60	16.5	46
Me	*s*-Bu	850	65	24	48
Et	*i*-Pr	900	65	24	86
Pr	Pr	900	65	24	33

[a] No reaction at 0.1 MPa.

Table 8. Effect of pressure on Stetter-like reactions (Scheme 15)[a]

R	β_{300}[b]	
	Acyloin synthesis	γ-Ketonitrile synthesis
Et	1	1
i-Pr	4	1.6
PrMeCH	5	2
t-Bu	—	High

[a] 353 K, 16 h, cat (thiazolium salt), ethanol.
[b] Yield ratio at 300 and 0.1 MPa, respectively.

salt-catalyzed acyloin condensations and the Stetter synthesis of γ-ketonitriles (Scheme 15).[54] Again, sterically hindered reactions are more pressure sensitive.

Some of the salient features of the reactions shown in Scheme 14 are portrayed in Figure 2, which reports the variations of β_{300} (yield ratio at 300 and 0.1 MPa, respectively) as a function of the steric bulk of R^2 in the corresponding reactions involving methyl ketones (R^1= Me). Figure 2 is a straightforward illustration of the pressure effect on steric hindrance. If no other effect is expected, the β_{300} values should be located on a line parallel to the Ω_S axis (Ω_S: steric factor defined by Isizawa et al.).[58] In fact, the results show a marked dependence of β_{300} on the space filling of the two alkyl groups of the ketone: β_{300} increases with the steric bulk of R^2. When Ω_S takes high values for R^2 (Ω_S=0.3044 for *i*-Pr, 0.3315 for CH_2*t*-Bu, and 0.3518 for *t*-Bu), β_{300} increases exponentially.

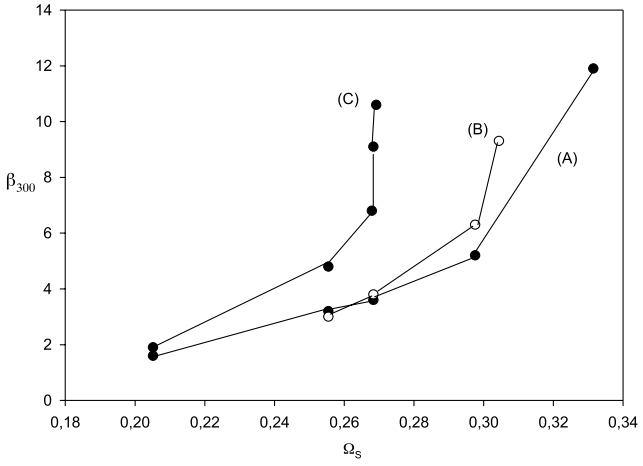


Figure 2. Variation of β_{300} as a function of Ω_S for three reactions involving methyl ketones (Ω_S refers to the steric bulk of R^2) (A: Knoevenagel reaction; B: synthesis of oximes; C: synthesis of trichlorocarbinols).

There is also a correlation between pressure and steric congestion in one-pot multicomponent reactions including Passerini,[55] Strecker,[56] and Biginelli reactions[57] (Scheme 16). A common feature of the reactions depicted in Scheme 16 is the low, or even zero, pressure effect as long as unhindered reagents are involved. With increasing bulkiness, however, the effect of pressure becomes significant.

Figure 3 portrays another example highlighting the inhibition of steric hindrance by pressure in the Passerini reaction involving *p*-toluic acid, 2-butanone and an isocyanide (Scheme 16).[55] At normal pressure, as expected, the yield of the Passerini product obtained from butyl isocyanide (graph B) is much higher than the corresponding adduct synthesized from *t*-butyl isocyanide (graph A). At pressures higher than 300 MPa, however, the reaction involving the more crowded isocyanide affords a higher yield. In the latter reaction, a near-quantitative yield is observed at 450 MPa.

A three-component double Strecker reaction was shown to occur under 600 MPa[59] in which 1,4-diacetylbenzene reacts with two molar amounts of aniline and TMSCN to yield the

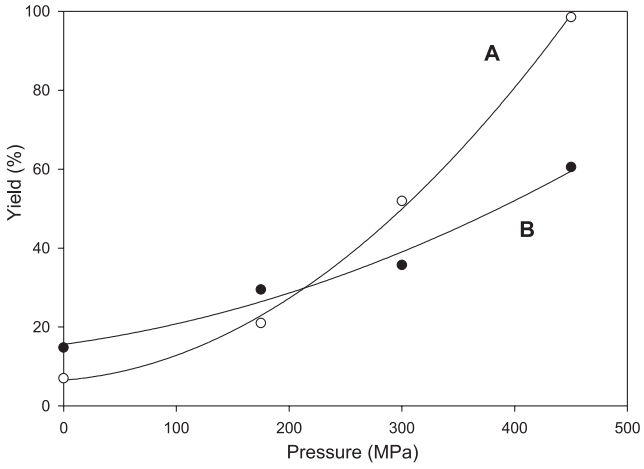
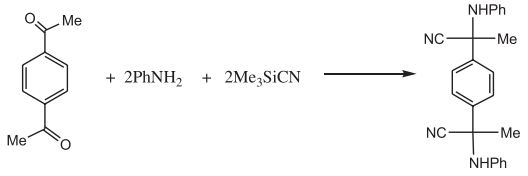


Figure 3. Effect of pressure in Passerini reactions involving *p*-toluic acid, 2-butanone and isocyanides (A: with *t*-butyl isocyanide; B: with butyl isocyanide).



Scheme 17.

α-diaminonitrile in 93% yield (303 K, 24 h, MeCN) vs 5% at 0.1 MPa in 72 h (other conditions identical) (Scheme 17).

The pressure sensitivity of Biginelli reactions is shown in Figure 4, in the condensation of aldehydes with urea and ethyl acetoacetate.[57] The highest pressure dependence, expressed as β_P (ratio of yields at pressure *P* and 0.1 MPa, respectively), is observed in the case of pivalaldehyde, whereas β_P barely varies in the isovaleraldehyde reaction.

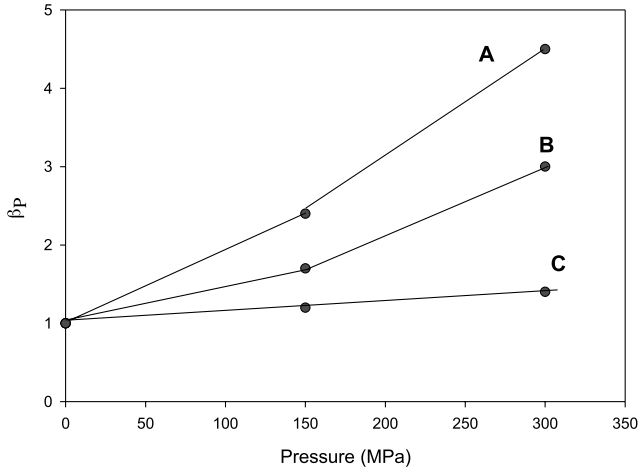


Figure 4. Effect of pressure in Biginelli reactions (353 K, 4 h, ZnI_2 as catalyst).

3. Theoretical aspects

Pressure affects the free energy and the activation energy through the $P\Delta V$ and $P\Delta V^*$ terms, respectively, and the various changes in the solute-solvent and solvent-solvent interactions. When the reaction progresses from the initial to transition state, it involves a change in energy, entropy, and enthalpy. The volume is, evidently, also affected, yielding the activation volume ΔV^*, which is, in fact, the resultant of all volume terms (Eq. 1):

$$\Delta V^* = \Sigma \Delta V_i^* \tag{1}$$

The kinetic quantities ΔG^*, ΔH^* and ΔS^* are related to ΔV^* according to the relationships:

$$(\partial \Delta G^*/\partial P)_T = \Delta V^*$$

$$(\partial \Delta S^*/\partial P)_T = -(\partial \Delta V^*/\partial T)_P$$

$$(\partial \Delta H^*/\partial P)_T = \Delta V^* - T(\partial V^*/\partial T)_P$$

A comprehensive description of (Eq. 1) has been given in a previous review.[60] Although the general expression reported should be used to take into account all volume occurrences, for our purpose, a simplified version of (Eq. 1) summarizing only structural (ΔV_S^*) and electrostatic ΔV_ε^* volume terms (Eq. 2) is sufficient.

$$\Delta V* = \Delta V_S^* + \Delta V_\varepsilon^* \tag{2}$$

(ΔV_S^*) is the volume variation due to changes in the nuclear positions of the reactants during the formation of the transition state. ΔV_ε^* is the volume variation due to changes in solute-solvent interactions when the reaction reaches the transition state. ΔV_ε^* is the electrostriction component due to volume shrinkage accompanying the formation of ions, zwitterions or, simply, polarized species. (ΔV_σ^*) is the only term permitting the localisation of the transition state. If we define $\theta = \Delta V_S^*/\Delta V_R$ (ΔV_R being the reaction volume based on partial molar volumes), θ is an indicator of the progression of the transition state along the reaction coordinate. This is obviously a simplified picture, since the relation between volume and coordinate is not strictly linear.

What is the effect of space filling by bulky substituents on ΔV^*? Since many studies have demonstrated a correlation between the kinetic pressure effect and steric hindrance, this would mean that more congested reactions are characterised by more negative ΔV^*. In this respect, we introduced, some time ago, a steric volume component (ΔV_σ^*) accommodating the extra volume change due to steric interactions (Eq. 3) within the same reaction series.[61]

$$\Delta V^* = \Delta V_0^* + \Delta V_\sigma^* \tag{3}$$

ΔV_0^*: activation volume of the unhindered reaction.

While steric hindrance is usually related to spatial crowding of the reaction sites, hindrance can also be attributable to the solvation sheath of polar substituents. Increased crowdedness changes the degree of incipient ionic charges in the transition state. This is naturally affected by pressure which induces electrostriction, a volume-decreasing event. Therefore, both activation volume terms shown in (Eq. 2) reflect the general problem of the separation of steric and polar effect.[62]

In order to clearly investigate the progression of the transition state on the reaction axis as a function of the severity of steric hindrance, (Eq. 1) should be nearly equivalent to the one-component expression, free of electrostriction (ΔV_ε^* is more complex and, therefore, less accessible than ΔV_S^*) (Eq. 4):

$$\Delta V^* \sim \Delta V_S^* \tag{4}$$

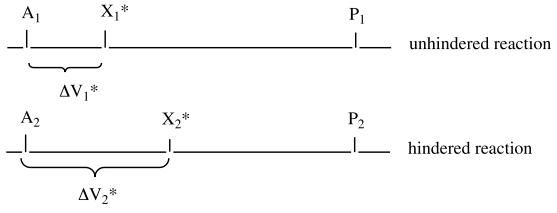
Steric interactions between the substrates increase the energy of a chemical species in which they are present. This implies a change of the position of the transition state in the energy profile and is illustrated by the useful Hammond postulate. Such transition-state variability would also be reflected in the volume profile. Consequently, the modification of steric interactions between the initial and transition state would lead to a progressive shrinking of the transition state which becomes more product like. The activation volume is, therefore, more negative (cf. Table 2) as well as the activation entropy referring to a more compact transition state, in harmony with the Hammond postulate.[9] According to this postulate, when two similar reactions differ by their activation energy, the more endothermic activated complexes are related to later transition states and should involve higher contraction along the reaction coordinate and more electrostriction of solvent owing to the corresponding stronger polarization.

One may, however, wonder whether this statement is verified in every case. Let us consider a simplified representation of the progression of a reaction along the reaction axis in a linear fashion. Several possibilities may be envisaged, depending on the mechanism (position of the transition state) and occurrence of electrostriction.

3.1. Case A. Early transition state, no electrostriction

In this case, (Eq. 4) applies, there exists a large propensity for X* to migrate on the reaction coordinate. This could occur for reactions which are slightly sensitive to pressure, when steric hindrance is low.

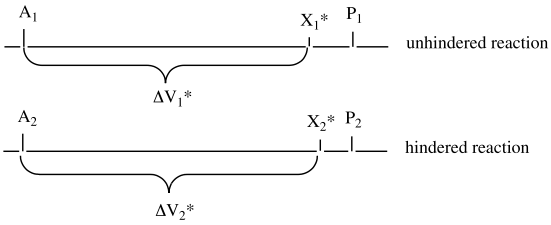
$$|\Delta V_2^*| > |\Delta V_1^*| \quad \text{with} \quad \Delta V_2^* = \Delta V_1^* + \Delta V_\sigma^* \quad \text{and} \quad \theta_2 > \theta_1$$



3.2. Case B. Late transition state, no electrostriction

In this case, (Eq. 4) applies, the transition state is close to the final state, the pressure effect on such reactions should hardly depend on steric hindrance.

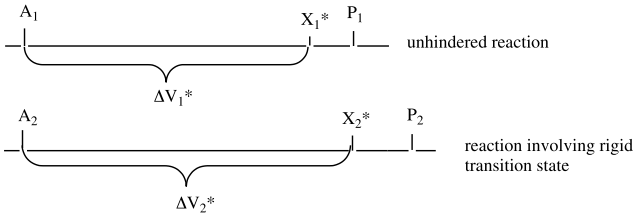
3.2.1. Normal case. This is case B_1.



$$|\Delta V_2^*| \sim |\Delta V_1^*| \quad \text{with} \quad \Delta V_\sigma^* \sim 0 \quad \text{and} \quad \theta_2 \sim \theta_1$$

3.2.2. Reactions involving rigid or strained substrates. This is case B_2.

$$|\Delta V_2^*| > |\Delta V_1^*| \quad \text{with} \quad \Delta V_\sigma^* \sim 0 \quad \text{and} \quad \theta_2 \sim \theta_1$$



This situation occurs, for example, in reactions involving acetylenic compounds which exhibit rigid structures due to the linearity of the triple bond. With increasing rigidity of the molecular skeleton, the number of molecular motions is reduced. This has an impact on molecular as well as transition state volumes. Such reactions are more sensitive to pressure compared to the corresponding reactions involving ethylenic reagents.[63,64] However, they also show larger ΔV_R in such way that the position of the transition state is not, or only barely, modified with similar θ values. Representative data are given in Table 9.

The increased sensitivity to pressure for the Diels–Alder reactions reported in Schemes 8–11 and for the Cope rearrangement in Scheme 13 with increasing ring strain or bulkiness of the substituting groups may fall into case B_2. Although the ΔV_R values were not available, they could probably be related also to steric strain or hindrance.

3.3. Case C. Early transition state with electrostriction

In this case, (Eq. 2) applies. ΔV_σ^* may result from the progression of the transition state due to mere steric hindrance or/and from steric inhibition to ionisation.

3.4. Case D. Late transition state with electrostriction

In this case, (Eq. 2) applies. ΔV_σ^* results from modification of ΔV_ε^* due to steric inhibition to ionisation.

The above reasoning is based on reaction and activation volumes. Another parameter may also be used, the packing coefficient η, defined as the ratio between the Van der Waals and molar volumes.[65] Despite empirical methods to determine the Van der Waals volumes,[66] these approximations are not possible for transition states, so that η is less accessible, since it has to be determined from molecular mechanics or quantum mechanical calculations.

4. Applications

It appears, therefore, that the best way to study the correlation between pressure and steric effects is to select a reaction relevant to case A. The difficulty is to find a reaction in which (i) the isopolarity of the initial and transition state is secured, and (ii) the transition state occurs early. This difficulty is highlighted, for example, even in radical reactions such as the hydrogen transfer from mercaptans to diphenylpicryl hydrazyl, which is strongly affected by the polarity of the solvent (Table 10).[67]

Reactions such as Knoevenagel, Biginelli, Passerini, Strecker, and Stetter reactions would apparently be candidates, but their kinetics are not simple and have not been investigated under pressure. Kinetic studies attempting to describe volume profiles as a function of steric effects have been made for a number of other reactions and Table 10 presents an almost exhaustive list.

According to Table 10, the activation volume of most reactions acknowledges the electrostatic term ΔV_ε^*. Two reactions are seemingly isopolar, Diels–Alder cycloadditions and sigmatropic rearrangements. They are both pericyclic processes for which concertedness has been demonstrated,[68,69] meaning that their transition state is late, apparently precluding any analysis of steric factors via ΔV^* (case B). Non-concerted pericyclic processes would exhibit θ values more or less far from unity and occur, therefore, via

Table 9. Pressure effect in concerted addition reactions involving acetylenic substrates (homogenized for $T=298$ K)

Type	Reaction	ΔV_{298}^* ($cm^3\ mol^{-1}$)	θ_{298}
[4+2]	Cyclopentadiene+methyl acrylate	−28.5	0.84
	Cyclopentadiene+DMAD	−32.0	0.89
[4+2]	Isoprene+methyl acrylate	−31.5	0.85
	Isoprene+methyl propiolate	−34.5	0.88
[4+2]	Dimethylbutadiene+methyl acrylate	−28.5	0.82
	Dimethylbutadiene+DMAD	−34.0	0.88
[2+2+2]	Norbornadiene+methyl acrylate	−28.0	0.86
	Norbornadiene+DMAD	−32.0	0.89
[2+2+2]	Quadricyclane+acrylonitrile	−25.0	0.86
	Quadricyclane+methyl propiolate	−34.0	0.87
	Quadricyclane+DMAD	−35.0	0.89
Ene	β-Pinene+diethyl ketomalonate	−29.4	1.06
	β-Pinene+DMAD	−35.5	1.12

Table 10. Reactions examined kinetically under pressure in relation to steric hindrance

Reaction	ΔV_R ($cm^3\ mol^{-1}$)	$\Delta V^*_{measured}$ ($cm^3\ mol^{-1}$)	Occurrence of ΔV_ε^*	Ref.
H transfer from mercaptans to DPPH	−12	−14 to −21	Yes	67
Radical copolymerization of maleic anhydride and alkenes	−18 to −20	−14 to −60	Probably	61
Hetero-Diels–Alder reactions (Scheme 9)	nd	−31 to −43	No	39,40
Intramolecular Diels–Alder reactions (Scheme 8)	nd	−28 to −41	No	36
Sigmatropic rearrangements	nd	−11to −18	No	46
Base-catalysed hydrolysis of nitrophenyl esters	nd	−3 to −10	Yes	71
Menshutkin reactions	nd	−20 to −47	Yes	10
Menshutkin reactions	−46 to −60	−22 to −50	Yes	9
Menshutkin reactions	nd	−22 to −50	Yes	72
Menshutkin reactions	?	−27 to −54	Yes	73
Menshutkin reactions	nd	−21 to −33	Yes	16
Nucleophilic addition of alcohols to acrylic compounds	−15 to −17	−40 to −75	Yes	74

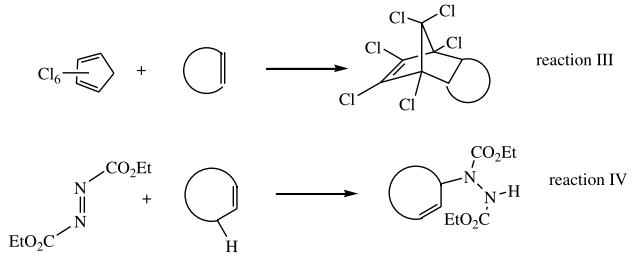
two-step mechanistic pathways. Their isopolarity should make them potential candidates for a steric study (case A).[70]

A new difficulty arises as the mechanism of pericyclic processes may be completely altered when steric constraints vary during the progression of the reaction.[75] Illustrative examples are portrayed in the [4+2] cycloaddition of hexachlorocyclopentadiene with *cis*-cycloalkenes[76] (Table 11, and reaction III in Scheme 18) and in the cyclodimerization of 2,3-dimethyl-1,3-butadiene (Table 12).[77] Another example is provided by the [4+2] and [4+4] cyclodimerization of a highly substituted 4,5-bis(methylene)-cyclopentane which proceeds via stepwise mechanism at variance with the route involving the unhindered monomer.[78]

Table 11. Effect of ring strain on the degree of concertedness in addition reactions in Scheme 18 involving cycloalkenes

Alkene	Strain energy (kJ mol^{-1})	θ value[a]	
		Reaction III	Reaction IV
Cyclopentene	28.8	1.05±0.08	0.65±0.05
Cyclohexene	10.9	0.97	0.58
Cycloheptene	30.1	0.76	0.76
Cyclooctene	36.8	0.75	0.79
Cis-cyclodecene	48.5	0.64	0.78

[a] III: [4+2] cycloaddition of hexachlorocyclopentadiene and cycloalkenes. IV: ene reaction of diethyl azodicarboxylate and cycloalkenes.



Scheme 18.

In the Diels–Alder reaction of hexachlorocyclopentadiene, θ decreases with increasing ring strain. The variation is ascribed to the possible intrusion of a two-step mechanism (see Ref. 76). In the cyclodimerization of dimethylbutadiene, the pressure effect is lower than the corresponding effect in the parent reaction of the less hindered isoprene.[79] In view of the correlation between steric hindrance and pressure, we would expect the opposite effect or, at least, an analogous θ value. The transition state in the dimethylbutadiene reaction, however, is very probably highly asynchronous, leading to a partial non-concerted process supported by a lower θ value and higher ΔH^* and ΔS^* values (a two-step mechanism is more endothermic and has a less-ordered transition state).

4.1. Case A

Reaction IV in Table 11 refers to the ene reaction of diethyl azodicarboxylate with *cis*-cycloalkenes (Scheme 18).[80] Ene reactions have been found to exhibit a large mechanistic spectrum, from pure concerted to stepwise mechanisms, with even the possibility of coexistence of several mechanistic types[68] Reaction IV has been established as being free of polar effects.[81] We demonstrated, or more exactly, confirmed the diradical two-step process[80] based on θ values of 0.68 and 0.58 for the addition of the azodicarboxylate with cyclopentene and cyclohexene, respectively. With increasing ring strain, however, the transition state moves towards the final state as shown in Table 11, although the trend is not linear. At the time we published our paper,[80] in accordance with our results found in the pressure study of reaction III, we hypothesised an alteration of the mechanism with a gradual increase of concertedness when the ring is enlarged. Simultaneously, we suggested that the higher θ values might also be ascribed to the strain increase in agreement with the Hammond postulate. Retrospectively, we now strongly support the latter interpretation for two reasons: (i) the diradical character of ene processes involving diethyl azodicarboxylate has been generalized,[63] with only one exception when the azo compound was reacted with 1,4-cyclohexadiene (in that case, the reaction would follow

Table 12. Pressure effect in the [4+2] cyclodimerization of conjugated dienes (T: 243 K)

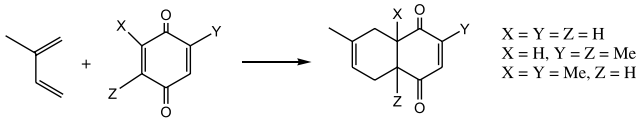
Diene	ΔV^* at 243 K ($cm^3\ mol^{-1}$)	θ value (±0.05)	ΔH^* (kJ mol^{-1})	ΔS^* (J $mol^{-1}\ K^{-1}$)
Isoprene	−42	0.88	79.0	−171
Dimethylbutadiene	−33	0.73	106.0	−119

a concerted pathway due to the quasi planar structure of the diene favoring a rigid transition state,[82]) and (ii) the analogy of the pressure effect on cyclic strain with the pressure effect on mere steric hindrance, as demonstrated in the radical copolymerisation of maleic anhydride and cycloalkenes.[83]

4.2. Case B

Is there a correlation between pressure and steric hindrance in case B ($\Delta V_\sigma^* \sim 0$)? At least, through activation enthalpies? Since X* cannot be shifted beyond the final state P (see, however, below when concerted ene reactions are featured with angular hydrogen abstraction), the pressure effect should be nearly identical whatever the magnitude of the steric hindrance. It should be the normal pressure effect expected for the reaction considered. To verify this assertion, we selected the Diels–Alder reactions of isoprene and diversely substituted quinones [*p*-benzoquinone, toluquinone, 2,5-dimethylbenzoquinone (5-DMBQ), and 2,6-dimethylbenzoquinone (6-DMBQ)] (Scheme 19) and measured the solvent effect, as well as the pressure and the temperature effect, on the second-order rate constant (Table 13).[84]

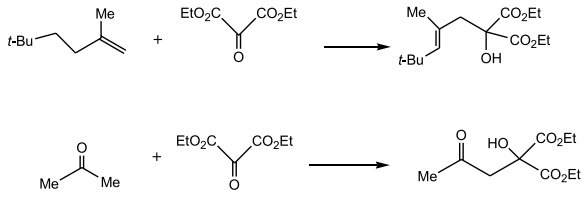
The solvent effect was found to be small, showing an amplification ratio of 2–5 from low polar solvents to ethanol. Visibly, the reactions are quasi isopolar, as expected. Remarkably, the ΔV^* values are nearly constant in the benzoquinone and toluquinone reactions. They are a little more negative in the DMBQ cycloadditions, but the reaction volume based on partial molar volumes of adduct and reactants is also more negative (case B_2), in such way that θ does not show any change in the three quinone cycloadditions and, therefore, is independent of the steric requirements in the transition state. Interestingly, the ΔV^* values do not vary within uncertainties according to the solvent and, accordingly, are free of any electrostatic volume term. Finally, it may be observed that θ is close to unity, demonstrating the lateness of the transition state for the four cycloadditions in the volume profile. Inspection of *E*-values shows little change, even for the sterically hindered 5-DMBQ and 6-DMBQ reactions. The ΔS^* values are also in the same range of magnitude, with even a more ordered transition state for the DMBQ [4+2] cycloadditions.



Scheme 19.

From these results, it is clear that hindered isopolar and concerted Diels–Alder reactions are no more endothermic than their unhindered analogs. Steric hindrance is manifested only in reduced rate constants for the DMBQ reactions. It is, therefore, concluded that pressure shows the normal acceleration effect, independently of any steric constraint, according to the Hammond postulate.

There are some cases (within case B) where $\theta > 1$, independently of solvent effects. Such a result may be perceived as astonishing, even improbable. This phenomenon is not an artefact, and it is met in some ene reactions occurring according to concerted processes.[85,86] We selected two ene reactions previously investigated under pressure in our laboratory and measured the temperature dependence of their rate constants. These are the addition of diethyl ketomalonate (DEKM) to the hindered 2,4,4-trimethyl-1-pentene[86] and to the unhindered acetone,[87] respectively (Scheme 20 and Table 14). Here, too, the solvent effect was found to be negligible.[86,87]



Scheme 20.

Table 14. Kinetic parameters of DEKM ene reactions

	Second reactant	
	2,4,4-Trimethyl-1-pentene[a]	Acetone[b]
E (± 3 kJ mol^{-1})	83.0	67.5
Ln A (± 1.2)	4.0	8.6
ΔS^* (± 10 J mol^{-1} K^{-1})	−131	−174
ΔV_{298}^* (± 1.5 cm^3 mol^{-1})	−32.0	−30.0
θ_{298} (± 0.04)	1.04	0.88

[a] Solvent (CCl_4).
[b] Acetone is also the medium.

The reaction involving 2,4,4-trimethyl-1-pentene is a (C–H–O) hydrogen transfer with angular hydrogen abstraction, whereas the ene reaction involving acetone is a (O–H–O) hydrogen transfer process with linear hydrogen abstraction.[70,86] The activation energy is higher in the first case as is also the case for θ. These values are indicative of a strained transition state which is more compressed than the final state. Compared to the values obtained in the ene addition of DEKM to the unhindered 1-pentene, the *E* and θ

Table 13. Kinetic parameters of Diels–Alder reactions of isoprene and quinones

Reaction	*p*-Benzoquinone	Toluquinone		5-DMBQ		6-DMBQ	
	EtOH	EtOH	$CHCl_3$	EtOH	$CHCl_3$	EtOH	$CHCl_3$
ΔV_{298}^* (± 2 cm^3 mol^{-1})	−37.2	−35.2	−37.2	−32.3	−35.3	−38.1	−35.6
θ (± 0.10)	nd[a]	0.94	1.02	nd[a]	0.97	1.08	nd[a]
E (± 2.5 kJ mol^{-1})	67.1	66.2	68.1	64.4	68.1	69.5	70.9
ΔS^* (± 9 J mol^{-1} K^{-1})	−118	−118	−117	−159	−143	−133	−137

[a] Not determined.

values are hardly modified, meaning that, like the Diels–Alder reactions of quinones, the magnitude of the pressure effect on ene additions is similar for hindered and unhindered reactions. The two modes of hydrogen abstraction show, however, noticeable differences as, expectedly, angular hydrogen abstraction should require more energy. The ordering of the transition state should be higher, but this is not reflected in the ΔS^* value, which is less negative than in the linear case.

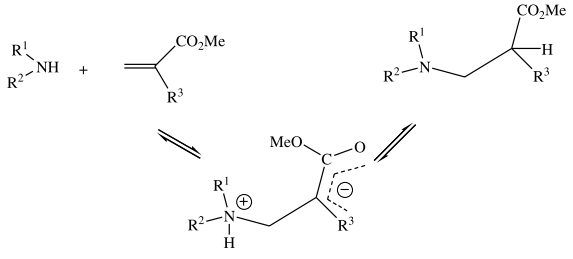
4.3. Case C

Case C is relevant for reactions subject to electrostriction and having early transition states. There is strong evidence that the transition state in Menshutkin reactions occurs early.[88–91] In this case, it is impossible to determine clearly the respective volume contributions of ΔV_σ^* in ΔV_S^* and ΔV_ε^*. Le Noble's results do not permit to ascertain that ΔV_σ^* is uniquely traceable to ΔV_S^* [9]. In fact, for the most hindered reaction involving the *t*-butyl group, $\Delta V_\sigma^* \sim -50\ \mathrm{cm^3\ mol^{-1}}$ with $\theta \sim 0.9$–1.0. A former study concluded that there was no steric term in ΔV_ε^*, only in ΔV_S^*.[73]

4.4. Case D

A number of reactions with electrostriction have late transition states (case D). ΔV_σ^* should contribute to ΔV_ε^* in such way that steric effects in hindered reactions are manifested as steric inhibition to ionisation. It is a well-known fact that pressure is a powerful parameter to generate electrostriction in apolar solvents[92] and the formation of oximes is an example.[53] We report here the results from two of our former studies, the conjugate addition of amines to acrylates[19] and the phosphine-catalysed nucleophilic addition of alcohols to unsaturated nitriles.[74]

The simplified mechanism of the addition of amines to activated double bonds is given in Scheme 21. The rate-limiting step would be the nucleophilic addition generating the C–N bond and the formation of a zwitterion. Electrostatic stabilisation of the electronic charges depends on the delocalisation of the negative charge. The latter is very probably affected by the size of R_1, R_2 and R_3. With increasing bulkiness, the sensitivity to pressure should be increased with an enhanced pressure-induced electrostriction. This is apparently the case, since ΔH^* increases and ΔV^* becomes more negative (Table 15), in harmony with the interpretation via Hammond postulate.



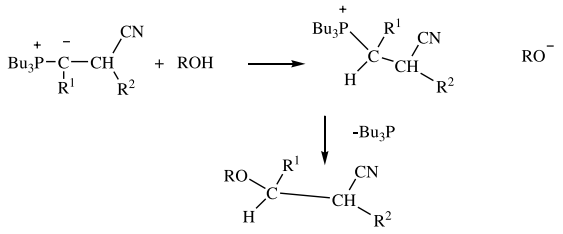
Scheme 21.

Table 15. Effect of pressure on the conjugate addition of amines to acrylates[a]

R^1	R^2	R^3	ΔH^* (kJ mol^{-1})	ΔS^* (J mol^{-1} K^{-1})	ΔV^* (cm^3 mol^{-1})
t-Bu	H	H	29.3	−176	−42
t-Bu	H	Me	35.1	−217	−53
Pr	Pr	Me	49.3	−163	−51

[a] Solvent (acetonitrile), *T* (309 K).

In the phosphine-catalysed cyanoalkylation of linear monohydric alcohols with methacrylonitrile and crotononitrile, the rate-determining step would be deprotonation of the alcohol and addition of the alkoxy moiety on the β carbon, with concomitant elimination of the phosphine (Scheme 22).[74] During the reaction, steric effects are manifested in the blockage of the attack of the nucleophile on the β carbon of the nitrile. This explains why the reaction occurs more readily with methacrylonitrile (R^1=H, R^2=Me) than with crotononitrile (R^1=Me, R^2=H). The size of the alkyl group R in the alcohol is of overwhelming importance for the reactivity. Due to the overall steric



Scheme 22.

Table 16. Activation volumes in the phosphine-catalysed addition of alcohols to acrylic nitriles[a]

R	ΔV^* (cm^3 mol^{-1})	
	Methacrylonitrile	Crotononitrile
Et	−40	−52
Pr	−40	−56
Bu	−45	−68
Pentyl	−52	−75

[a] Cat (Bu_3P), ROH is reactant and medium, *T* (303 K).

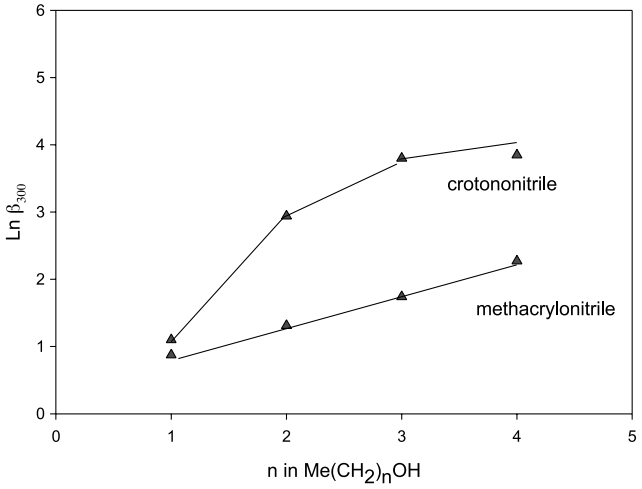


Figure 5. Dependence of β_{300} (yield ratio at 300 and 0.1 MPa, respectively), on chain length of alcohol in the phosphine-catalysed addition of alcohols to acrylic nitriles (323 K, 4 h).

congestion imposed by R, R^1, and R^2, the pressure effect expressed by ΔV^* is very significant with crotononitrile and with increasing bulkiness of R (Table 16).

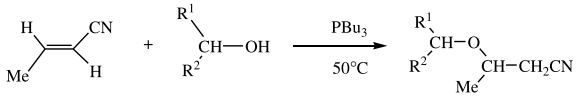
Figure 5 is particularly informative. It is clear that reactions involving crotonitrile are more pressure accelerated than the corresponding methacrylonitrile reactions. The ΔV^* values are among the most negative values known for the pressure dependence of organic reactions. As the structural activation volume (ΔV_S^*) for a late transition state in this reaction should amount to -15 to $-20\ cm^3\ mol^{-1}$, the remaining volume must be ascribed to electrostriction (ΔV_ε^*) and to steric hindrance to ionisation (ΔV_σ^*).

The very large ΔV^* values can be exploited for the synthesis of β-cyano ethers and Table 17 reports the yields obtained in the PBu_3-catalyzed addition of alcohols to crotononitrile (Scheme 23).[74] It is evident that these reactions are possible essentially at 300 MPa.

Table 17. PBu_3-catalysed addition of alcohols to crotononitrile[a]

R^1	R^2	Time (h)	Yield (%)	
			0.1 MPa	300 MPa
H	*i*-Pr	8	4	81
H	Et(Me)CH	22	1	92
H	Cy	24	2	58
H	*t*-Bu	24	1	92
Me	Me	20	0	65
Et	Me	20	0	38

[a] ROH is reactant and medium, *T* (323 K).



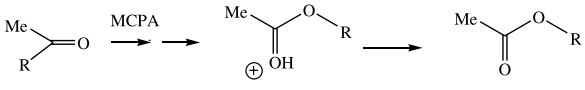
Scheme 23.

It is important to emphasize that reactions which have less steric requirements display a similar pressure behavior, even if bulky substrates are involved. This is highlighted in Baeyer–Villiger reactions (Table 18 and Scheme 24).[6]

Table 18. Pressure effect in the Baeyer–Villiger oxidation of aliphatic ketones

R	10^5k ($M\ s^{-1}$)[a]	β_{200}[b]	ΔV_{323}^* ($cm^3\ mol^{-1}$)
nBu	3.89	3.1	−6.5
s-Bu	3.36	1.6	−5.0
CH_2-*t*-Bu	1.56	3.2	−8.0
t-Bu	9.34	2.4	−5.0

[a] At 0.1 MPa and 323 K in $CHCl_3$.
[b] Yield ratio at 200 and 0.1 MPa, respectively.



Scheme 24.

The migration of R to O^+ should be sensitive to the size of R. If the bulkiness of R increases, the rate should be accelerated and this is, in fact, the case (cf. the *k* value when R = *t*-Bu). The less stringent steric demand in the Baeyer–Villiger oxidation, however, makes it less sensitive to pressure, which is exemplified in the β and ΔV^* values listed in Table 18.

5. Conclusions

High pressure is a fundamental parameter in sterically hindered reactions as it favors more compact transition states. This is due to the fact that steric interactions are in their quasi totality repulsive interactions leading to the destabilisation of the system. From this point of view, pressure contributes to reduce the destabilisation.

As demonstrated in this paper, the pressure acceleration increases with the complexity of the reactants and the steric approach to the reaction centres. Pressure is a rare, remarkable method capable of alleviating and, even, of removing steric inhibition. This inherent property, however, is valid only if:

(i) the rate constant is affected by the steric bulk or steric approach of reactants at ambient pressure
(i) the transition state has some aptitude to migrate on the reaction coordinate before reaching the final state
(i) the eventual ionogenic character of the reaction may involve steric inhibition to resonance or ionisation. This may occur even if the lateness of the transition state precludes any additional structural activation volume and
(iv) the reaction mechanism is not altered by steric constraints in the transition state.

It is anticipated that, in the light of the considerations developed in this paper, emphasis will be placed on pressure every time steric effects play a determining kinetic role. This may be the case in biological studies, where specific interactions or recognition processes of the bioactive substance-receptor site complex are important.[93] A further step could be to study the pressure effect on attractive steric interactions.[50,94–96]

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Biographical sketch

Gérard Jenner received his PhD in 1966 from the University of Strasbourg. His scientific interest has been high pressure chemistry and thermodynamics covering various fields such as macromolecular science, *P–V–T* relationships, homogeneous catalysis, and physical and synthetic organic chemistry. After two years spent as professor of physics in Tunisia, he joined the Centre National de la Recherche Scientifique where he is now director of research and head of laboratory. In 1980, he took a position as Research Associate at the State University of New York at Stony Brook with Professor W. J. le Noble. He was a member of the Board of the International Association of High Pressure Science and Technology (AIRAPT), of the Board of the European Physical Society (Condensed Matter Division) and chaired the European High Pressure Research Group (1988–91). He was previously visiting lecturer in Poland, Japan and Tunisia. He is presently Regional Editor for Current Organic Synthesis and Mini-Reviews in Organic Chemistry. His current interests focus on multiactivation processes with pressure as the basic parameter, mechanistic studies using pressure kinetics, correlations between pressure and steric inhibition, crystallisation of proteins under hyperbaric conditions.

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Synthesis of fused indoles by sequential palladium-catalyzed Heck reaction and *N*-heteroannulation

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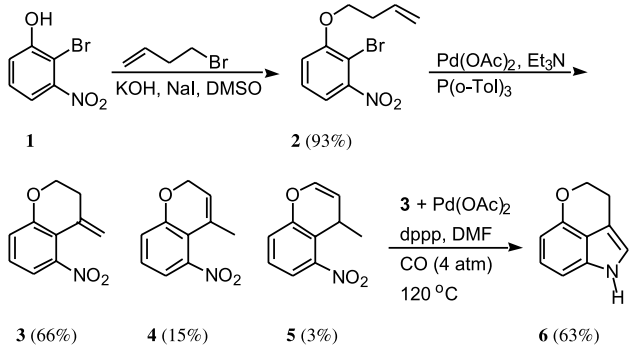
Abstract—A route to 3,4-fused indoles via two consecutive palladium-catalyzed reactions; an intramolecular Heck reaction followed by a reductive *N*-heteroannulation is described. Using this route, a number of indoles have been prepared having a variety of ring sizes anchored to the 3- and 4-position of the indole nucleus. Furthermore, a number of functional groups, both carbon and heteroatom substituents can be introduced in (and on) the additional ring without any detrimental effects on the two reactions.

1. Introduction

The palladium-catalyzed reductive *N*-heteroannulation of 2-(1-alkenyl)nitrobenzenes have been utilized to prepare indoles and carbazoles,[1–7] 2,2′-biindoles,[8] 1*H*-indol-2-yl-1*H*-quinolinones,[9] β-carbolines,[10] and 1,2-dihydro-4(3*H*)-carbazolones.[11,12] We have communicated a novel route to 3,4-fused indoles consisting of two consecutive palladium-catalyzed reactions, an intramolecular Heck reaction followed by a reductive *N*-heteroannulation.[13] For example, compound **2**, prepared by *O*-alkylation of 2-bromo-3-hydroxy-1-nitrobenzene (**1**) with 1-bromo-3-butene, was reacted under standard Heck condition to give a mixture of three isomeric 5-nitro-1-benzopyrans (**3**–**5**) in an 18:4:1 ratio (Scheme 1). Reductive *N*-heteroannulation of **3** using 10 mol % palladium diacetate ($Pd(OAc)_2$), 20 mol % 1,3-bis(diphenylphosphino)propane (dppp) in DMF at 120 °C and 4 atm of carbon monoxide gave an acceptable 63% yield of the fused indole **6** after 70 h.



Scheme 1.

Based on the results shown in Scheme 1, a systematic survey of this reaction sequence to fused indoles was undertaken. The starting materials for the Heck reaction were prepared by benzylic nucleophilic substitution using 2-bromo-3-nitrobenzylbromide (**7**) and a variety of unsaturated alkoxides and phenoxides. Compounds **8**–**15**, prepared in this fashion were used directly in Heck reactions (Table 1). The benzylic bromide **7** was also reacted with allyl amine, allyl sulfide, and the anion of dimethyl malonate to give **16**–**18**, respectively (Scheme 2). Compound **16** was reacted with acetic anhydride to give the amide **20**, the allyl sulfide **17** was oxidized to the sulfoxide **20** using sodium periodate and to the sulfone **21** using a urea–hydrogen peroxide complex. Finally, the malonate adduct **18** was deprotonated and alkylated with allyl bromide to give **22**.

The allylic amide **23** was prepared from 2-bromo-3-nitrobenzoic acid (**24**) via the corresponding acid chloride (Scheme 3). Transformation of **24** to the isocyanate **25** using diphenylphosphoryl azide followed by reaction with sodium methoxide furnished the expected methyl carbamate (Scheme 3). Deprotonation and alkylation using 4-bromo-1-butene gave **26** albeit in low overall yield.

With a number of precursors in hand, the intramolecular Heck reaction was examined.[14] Facile Heck reaction was

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observed in most cases using palladium diacetate, tris-(*o*-tolyl)phosphine (TTP), in triethyl amine (TEA). In some cases, the cyclization afforded products derived from exo to endo double bond migration during the reaction (entries 1, 2, 9, 10, and 12, Table 1). The isomers were readily separated on silica gel and the exocyclic product was always the major isomer. Exclusive or highly selective formation of the exo isomer has been reported in related systems.[15,16] A vinyl-substituted cyclization product was exclusively obtained in one case (entry 3). This result can be explained mechanistically via insertion of the alkene into the oxidative addition intermediate **44** to give a new σ-palladium complex **45** having a *cis*-relationship between the palladium moiety and the newly formed carbon–carbon bond. β-Hydride elimination requires a *cis*-geometry between the metal and the proton. Due to the presence of the sterically demanding nitro group, rotation of the metal is slow compared to the competing β-hydride elimination toward the methyl group forming **31** (Scheme 4). For compounds with two potential directions for the β-hydride elimination, the vinyl-substituted product is usually the major or sole isomer formed.[14] A single stereoisomer was formed upon cyclization of **11** (entry 4). Although the alkene geometry of the product **32** is unknown, the depicted geometry is consistent with a *syn* alkene insertion, σ-bond rotation, and *syn* β-hydride elimination sequence. Trans substituted alkenes related to **11** have previously been shown to give products with the same stereochemistry.[14,17,18]

Non-regioselective Heck reactions forming products derived from insertion into the internal or terminal position of the alkene was observed using a longer tether between the bromide and the alkene (entries 7–8). Both 7-exo and 8-endo (entry 7)[19] and 8-exo and 9-endo (entry 8) cyclizations were observed. The isomers were in both cases inseparable and were used in the next step as a mixture. Compound **13** did not furnish either a 9- or 10-membered cyclization product but gave a complex mixture of unidentified products. Similar results have been reported by Ma and Negishi using 9-membered ring precursors.[20]

Attempted Heck reaction of allylic amine **16** did not produce the anticipated cyclization products but gave, in addition to recovered starting material, a complex mixture of unidentified products. Poor yields of products has previously been reported using *N*-allyl *N*-(2-halo)benzylamines in intramolecular Heck reactions.[21,22] It is not unlikely that the initial σ-complex, formed by oxidative addition of palladium(0) into the aryl-bromine bond in **16**, is coordinated to the pendant amine, forming a relatively stable complex.[23–26] This effectively removes palladium from the catalytic cycle, and the reaction is quenched. The amide **19**, having a substantially lower ability to coordinate to the metal, cyclized to form the expected products **38** and **39**. Finally, unsuccessful cyclizations were observed using sulfide **17**, sulfoxide **20**, and sulfone **21**. Intramolecular Heck reactions of allyl aryl sulfides have been reported. To our knowledge, no examples of allyl benzyl sulfides, sulfones, or sulfoxides have been reported in the literature.

Palladium-catalyzed *N*-heteroannulation of the Heck products having an exocyclic double bond was examined next. We initially studied the reductive *N*-heteroannulation of **3** using conditions previously employed for substituted styrenes. Thus, reaction of **3** with 6 mol % $Pd(OAc)_2$ and 24 mol % PPh_3 in acetonitrile at 70 °C and 3 atm of carbon monoxide for 19.5 h, gave the expected indole **6** in low isolated yield (11%) together with recovered starting material (51%). Reaction of **3** for 70 h at 100 °C, using the same solvent and catalyst system, improved the yield of product (**6**) to 37% but a significant amount of starting material still remained (32%). After some optimization, a catalyst system consisting of 10 mol % $Pd(OAc)_2$, 12 mol % of 1,3-bis(diphenylphosphino)propane in dimethylformamide at 4 atm of CO and 120 °C gave **6** in 63% yield. The last reaction proved to be very clean, and no other organic products was observed by ^1H NMR of the crude reaction mixture. It is interesting to note that no detectable amount (by ^1H NMR at 270 MHz) of isomerization to the endocyclic benzopyranes **4**–**5** was observed in the initial reactions wherein the starting material **3** was not completely consumed. We have recently shown that better yields are obtained in some cases using bis(dibenzylidenacetone)palladium in combination with 1,10-phenanthroline. The reason for the need for two ligands is not clear at this point in time. Most of the reactions presented in Table 1 utilize the latter catalyst system. For the methylene and benzylidene substituted substrates, *N*-heteroannulation to form a 3,4-fused indole was observed in moderate to good yields (33–83%) in all cases examined. Compound **31** did not afford any cyclized product under any of the cyclization conditions described above. Attempts to isomerize the double bond of **31** using basic (potassium *t*-butoxide or triethylamine) or acidic conditions (*p*-toluenesulfonic acids) were fruitless.

The mixtures of tricyclic compounds **34**:**35** and **36**:**37** were also subjected to the reductive *N*-heteroannulation reaction (entries 7–8, respectively). In both cases, a moderate amount of fused indoles was isolated derived from cyclization of the exocyclic isomer. Curiously, reduction of the nitro group to an amine was observed for the two endocyclic compounds **35** and **37**.[27]

In conclusion, a novel route to fused indoles has been developed based on two palladium-catalyzed reactions. This methodology has been used to prepare indoles having a 6–8-membered rings anchored to the 3- and 4-postion of the indole nucleus. Nitrogen- and oxygen-containing rings as well as an example of a carbocyclic ring have been prepared. Applications of this sequence in total synthesis are currently underway in our laboratories.

2. Experimental

2.1. General procedures

All NMR spectra were determined in $CDCl_3$ and the chemical shifts are expressed in δ values relative to Me_4Si (0.0 ppm, ^1H and ^{13}C) or $CDCl_3$ (77.0 ppm, ^{13}C) internal standards. ^1H–^1H coupling constants are reported as calculated from spectra; thus a slight difference between $J_{a,b}$ and $J_{b,a}$ is usually obtained. Results of APT (attached proton test)—^{13}C NMR experiments are shown in

Table 1. Intramolecular Heck reaction and *N*-heteroannulation

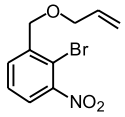
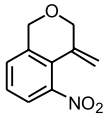
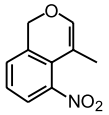
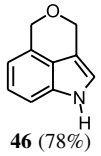
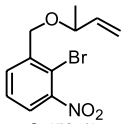
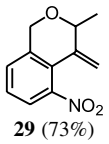
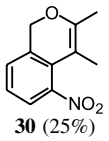
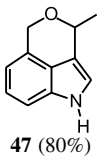
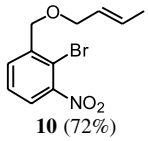
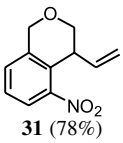
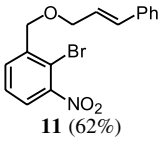
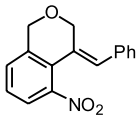
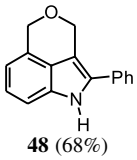
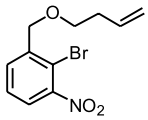
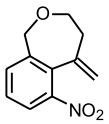
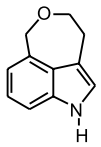
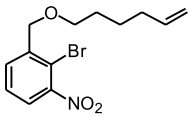
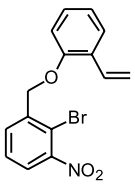
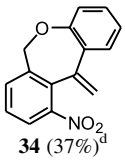
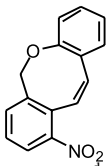
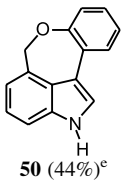
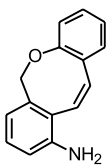
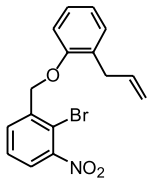
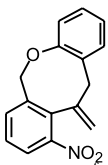
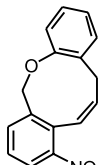
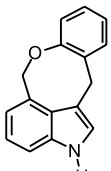
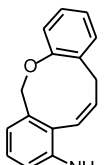
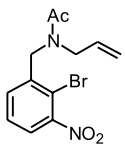
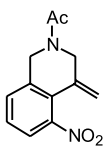
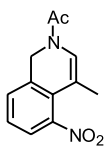
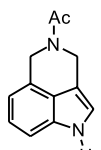
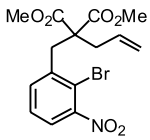
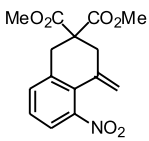
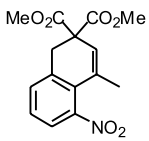
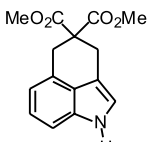
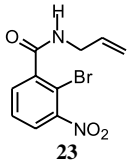
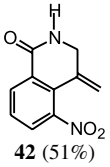
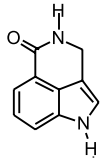
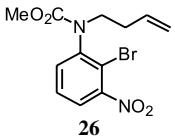
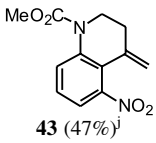
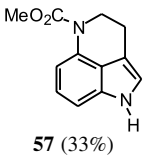
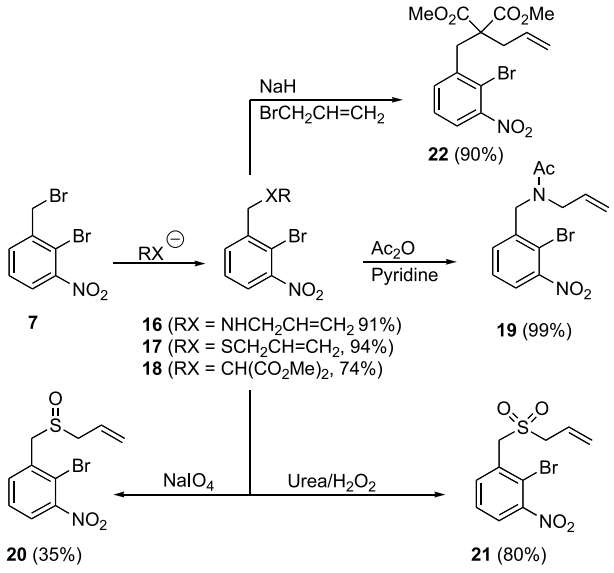
Entry	Bromoalkene[a,b]	Coupling product(s)[a,b]		Indole[a,b]	
1	 **8** (67%)	 **27** (76%)	 **28** (20%)	 **46** (78%)	
2	 **9** (50%)	 **29** (73%)	 **30** (25%)	 **47** (80%)	
3	 **10** (72%)	 **31** (78%)	Complex mixture of products		
4	 **11** (62%)	 **32** (82%)[c]		 **48** (68%)	
5	 **12** (67%)	 **33** (81%)		 **49** (83%)	
6	 **13** (46%)		Complex mixture of products		
7	 **14** (65%)	 **34** (37%)[d]	 **35** (60%)[d]	 **50** (44%)[e]	 **51** (64%)[e]
8	 **15** (91%)	 **36** (18%)[f]	 **37** (13%)[f]	 **52** (44%)[g]	 **53** (15%)[g,h]
9	 **19**	 **38** (69%)	 **39** (26%)	 **54** (41%)	
10	 **22**	 **40** (72%)	 **41** (14%)	 **55** (65%)	

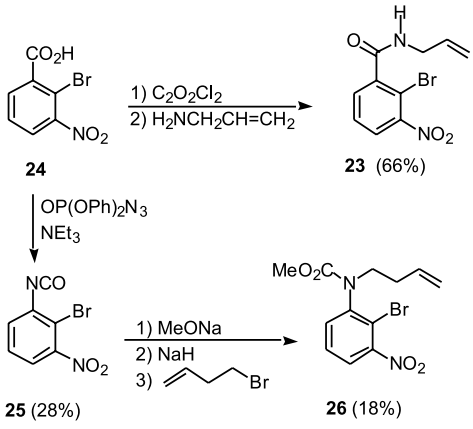
Table 1 (*continued*)

Entry	Bromoalkene[a,b]	Coupling product(s)[a,b]	Indole[a,b]
11	 **23**	 **42** (51%)	 **56** (61%)[i]
12	 **26**	 **43** (47%)[j]	 **57** (33%)

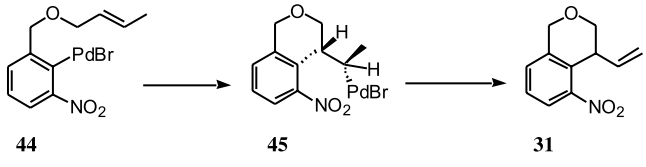
[a] See Section 2 for details.
[b] Isolated yield of pure compound given in parenthesis.
[c] Only one alkene isomer was obtained, however, the stereochemistry is not known.
[d] Calculated yield from an inseparable 1:1.6 mixture of **34** and **35**.
[e] Calculated yields starting from a mixture of **34** and **35**.
[f] Calculated yields from an inseparable 1.37:1 mixture of **36** and **37**.
[g] Calculated yields from a mixture of **36** and **37**.
[h] This product was tentatively assigned from a mixture of **52** and **53**.
[i] Minor amounts of impurity remained after extensive purification.
[j] Minor amount of products tentatively assigned as endocyclic isomers were also isolated.



Scheme 2.



Scheme 3.



Scheme 4.

parentheses, where relative to $CDCl_3$, (+) denotes CH_3 or CH and (−) denotes CH_2 or C.

Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Pyridine, hexanes, acetonitrile, and ethyl acetate were distilled from calcium hydride. Chemicals prepared according to literature procedures have been footnoted first time used; all other reagents were obtained from commercial sources and used as received. All reactions were performed under an argon atmosphere in oven-dried glassware unless otherwise stated. Solvents were removed from reaction mixtures and products on a rotary evaporator at water aspirator pressure. Elemental Analyses were performed by Atlantic Microlab, Inc., Norcross, GA. High Resolution Mass Spectra (HRMS) were performed at University of California Riverside Mass Spectrometry Center.

2.1.1. 2-Bromo-3-nitro-1-(3-butenyloxy)benzene (2). To a solution of 2-bromo-3-nitrophenol[28] (**1**) (1.09 g, 5.00 mmol) in DMSO (31 mL) was added KOH (3.00 g, 20.0 mmol). After 5 min of stirring, 4-bromo-1-butene (2.00 mL, 20.0 mmol) was added to the resulting red solution. After 43 h, water (150 mL) was added, and the

mixture was extracted with diethyl ether (4×150 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvents were removed. Purification by chromatography (hexanes/EtOAc, 9:1) gave **2** (1.27 g, 4.67 mmol, 93%) as a pale yellow oil that solidified upon storage in freezer (−20 °C). Mp 27–28 °C; ^{1}H NMR (270 MHz) δ 7.37 (t, J=8.1 Hz, 1H), 7.30 (dd, J=8.1, 1.6 Hz, 1H), 7.05 (dd, J=8.1, 1.6 Hz, 1H), 5.94 (tdd, J=17.0, 10.3, and 6.4 Hz, 1H), 5.21 (dd, J=17.0, 1.4 Hz, 1H), 5.15 (br d, J=10.3 Hz, 1H), 4.12 (t, J=6.5 Hz, 2H), 2.62 (q, J=6.7 Hz, 2H); ^{13}C NMR (67.5 MHz) δ 156.3 (−), 151.4 (−), 133.4 (+), 128.5 (+), 117.4 (−), 116.1 (+), 115.4 (+), 104.3 (−), 69.0 (−), 33.0 (−); IR (neat) 3080, 2935, 1588, 1535, 1456, 1363, 1276, 1040 cm^{-1}; Anal. Calcd for $C_{10}H_{10}BrNO_3$: C, 44.14; H, 3.70. Found: C, 44.43; H, 3.73.

2.1.2. 2-Bromo-3-nitro-1-[(2-propen-1-yloxy)methyl]-benzene (8). In a conical vial was placed 2-propen-1-ol (210 μL, 3.09 mmol) and small pieces of sodium (52 mg, 2.24 mmol). After 3 h, the resulting alkoxide was added via pipette to a solution of 2-bromo-3-bromomethyl-1-nitro-benzene (**7**)[1] (300 mg, 1.02 mmol), tetrabutylammonium iodide (39 mg, 0.11 mmol) in THF (10 mL). The conical vial was rinsed with THF (9 mL total). The resulting mixture was stirred at ambient temperature (27 h), diluted with water (15 mL), and extracted with diethyl ether (3× 15 mL). The combined organic phases were dried ($MgSO_4$), and filtered, and the solvents were removed. Purification by chromatography (hexanes/EtOAc, 4:1) gave **8** (186 mg, 0.68 mmol, 68%) as a faint yellow oil. ^{1}H NMR (270 MHz) δ 7.75 (d, J=7.7 Hz, 1H), 7.64, (d, J=7.9 Hz, 1H), 7.47 (t, J=7.9 Hz, 1H), 5.99 (10 line pattern, J=17.2, 10.3, 5.3 Hz, 1H), 5.37 (dd, J=17.2, 1.6 Hz, 1H), 5.27 (dd, J=10.3, 1.4 Hz, 1H), 4.16 (td, J=5.5, 1.4 Hz, 2H), 4.63 (s, 2H); ^{13}C NMR (67.5 MHz) δ 150.7 (+), 141.1 (+), 133.9 (−), 131.2 (−), 127.8 (−), 123.5 (−), 117.5 (+), 113.1 (+), 71.5 (+), 71.0 (+); IR (neat) 3081, 2858, 1532, 1353, 1102 cm^{-1}; Anal. Calcd for $C_{10}H_{10}BrNO_3$: C, 44.14; H, 3.70. Found: C, 44.14; H, 3.66.

2.1.3. 2-Bromo-3-nitro-1-[(2-buten-1-yloxy)methyl]ben-zene (9). Reaction of sodium (95 mg, 4.11 mmol) with 2-butene-1-ol (1.00 mL, 11.72 mmol) for (3.5 h) followed by reaction of the formed alkoxide with **7** (294 mg, 1.00 mmol) and tetrabutylammonium iodide (40 mg, 0.11 mmol) in THF (total 20 mL) for 66 h, as described for **8**, gave after chromatography (hexanes/EtOAc, 4:1) **9** (206 mg, 0.72 mmol, 72%) as a faint yellow oil. ^{1}H NMR (270 MHz) δ 7.74 (d, J=6.9 Hz, 1H), 7.63, (d, J=7.9 Hz, 1H), 7.45 (t, J=7.9 Hz, 1H), 5.81 (dq, J=15.2, 6.3 Hz, 1H), 6.64 (dtq, J=15.2, 5.9, 1.2 Hz, 1H), 4.60 (s, 2H), 4.08 (dd, J=6.1, 1.0 Hz, 2H), 1.75 (dd, J=6.3, 1.2 Hz, 3H); ^{13}C NMR (67.5 MHz) δ 150.8 (+), 141.3 (+), 131.4 (−), 130.4 (−), 127.8 (−), 126.8 (−), 123.5 (−), 113.2 (+), 71.8 (+), 70.8 (+), 17.8 (−); IR (neat) 1537, 1360 cm^{-1}.

2.1.4. 2-Bromo-3-nitro-1-[(3-buten-2-yloxy)methyl]ben-zene (10). Reaction of sodium (95 mg, 4.12 mmol) with 3-butene-2-ol (0.52 mL, 6.00 mmol) in THF (1 mL) for 66 h followed by addition of the formed alkoxide to a solution of **7** (298 mg, 1.01 mmol) and tetrabutylammonium iodide (38 mg, 0.10 mmol) in THF (total 20 mL), as described for **8**, gave after chromatography (hexanes/EtOAc, 7:3) **10** (144 mg, 0.51 mmol, 50%) as a faint yellow oil. ^{1}H NMR (270 MHz) δ 7.75 (dd, J=7.7, 0.78 Hz, 1H), 7.61 (d, J=7.9 Hz, 1H), 7.45 (t, J=7.9 Hz, 1H), 5.81 (ddd, J=17.4, 10.3, 7.5 Hz, 1H), 5.27 (d, J=18.0 Hz, 1H), 5.21 (d, J=11.1 Hz, 1H), 4.63 (d, J=14.0 Hz, 1H), 4.51 (d, J=14.0 Hz, 1H), 4.01 (pent, J=6.3 Hz, 1H), 1.35 (d, J=6.5 Hz, 3H); ^{13}C NMR (67.5 MHz) δ 150.7 (+), 141.5 (+), 139.4 (−), 131.4 (−), 127.8 (−), 123.4 (−), 116.6 (+), 113.1 (+), 77.4 (−), 69.2 (+), 21.2 (−); IR (neat) 1535, 1361, 1104, 912, 729 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{12}BrNO_3$ 285.0001, found 284.9996.

2.1.5. 2-Bromo-3-nitro-1-[(3-phenyl-2-propen1-1yloxy)-methyl]benzene (11). To a slurry of hexane washed sodium hydride (77 mg, 3.22 mmol) in THF (10 mL) was added 3-phenyl-2-propen-1-ol (347 mg, 2.59 mmol) via syringe. The reaction mixture was stirred until no more gas was evolved (1 h). The formed alkoxide was cooled to − 78 °C and added via pipette to a solution of **7** (502 mg, 1.70 mmol) and tetrabutylammonium iodide (64 mg, 0.17 mmol) in THF (10 mL). The resulting mixture was stirred (44 h) in the cold bath while warming to ambient temperature. Workup as described for **8** and purification by chromatography (hexanes/EtOAc, 19:1) gave **11** (369 mg, 1.06 mmol, 62%) as a faint yellow oil. ^{1}H NMR (270 MHz) δ 7.75 (d, J=7.5 Hz, 1H), 7.68, (d, J=8.1 Hz, 1H), 7.50 (t, J=7.9 Hz, 1H), 7.42–7.21 (m, 5H), 6.72 (d, J=15.8 Hz, 1H), 6.38 (dt, J=16.0, 6.1 Hz, 1H), 4.66 (s, 2H), 4.29 (dd, J=5.9, 1.2 Hz, 2H); ^{13}C NMR (67.5 MHz) δ 150.5 (+), 140.9 (+), 136.2 (+), 132.6 (−), 131.1 (−), 128.3 (−), 127.7 (−), 127.6 (−), 126.3 (−), 125.0 (−), 123.3 (−), 112.9 (+), 71.3 (+), 70.9 (+); IR (neat) 1537, 1265, 739 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{14}BrNO_3$ 347.0157, found 347.0161.

2.1.6. 2-Bromo-3-nitro-1-[(3-buten-1-yloxy)methyl]ben-zene (12). Reaction of sodium hydride (118 mg, 4.92 mmol) and 3-butene-1-ol (0.30 mL, 3.49 mmol) in THF (10 mL, 2 h) followed by reaction of the formed alkoxide with **7** (590 mg, 2.00 mmol) in THF (10 mL, 42 h), as described for **11**, gave after workup and chromatography (hexanes then hexanes/EtOAc, 49:1) **12** (345 mg, 1.35 mmol, 67%) as a faint yellow oil. ^{1}H NMR (270 MHz) δ 7.73 (d, J=7.7 Hz, 1H), 7.63 (d, J=7.9 Hz, 1H), 7.46 (t, J=7.7 Hz, 1H), 5.88 (ddt, J=17.0, 10.3, 6.7 Hz, 1H), 5.14 (d, J=17.8 Hz, 1H), 5.09 (d, J=11.3 Hz, 1H), 4.62 (s, 2H), 3.66 (t, J=6.7 Hz, 2H), 2.44 (q, J=6.5 Hz, 2H); ^{13}C NMR (67.5 MHz) δ 150.7 (+), 141.2 (+), 134.8 (−), 131.2 (−), 127.8 (−), 123.5 (−), 116.7(+), 113.1 (+), 71.8 (+), 70.5 (+), 34.1 (+); IR (neat) 1534, 1352, 1119, 796 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{12}BrNO_3$ 285.0001, found 284.9996.

2.1.7. 2-Bromo-3-nitro-1-[(5-hexen-1-yloxy)methyl]ben-zene (13). *t*-Butyl lithium (1.7 M, 2.4 mL, 4.08 mmol) was added to a solution of 5-hexene-1-ol (0.50 mL, 4.16 mmol) in THF (20 mL) and the reaction mixture was stirred until no more gas was evolved (2 h). The formed alkoxide was added to a solution of **7** (598 mg, 2.03 mmol) and tetrabutylammonium iodide (77 mg, 0.21 mmol) in THF (10 mL) that had been stirred for 1 h. The resulting solution was stirred (89.5 h) at ambient temperature. The mixture was diluted with water (30 mL) and extracted with

dichloromethane (4×20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (hexanes/EtOAc, 9:1) gave **13** (291 mg, 0.93 mmol, 46%) as a faint yellow oil. ^{1}H NMR (600 MHz) δ 7.72 (d, J=7.8 Hz, 1H), 7.63 (d, J=7.8 Hz, 1H), 7.46 (t, J=7.8 Hz, 1H), 5.82 (ddt, J=17.4, 10.2, 6.6 Hz, 1H), 5.02 (d, J=16.8 Hz, 1H), 4.97 (d, J=10.2, 1H), 4.61 (s, 2H), 3.60 (t, J=6.6 Hz, 2H), 2.10 (q, J=7.2 Hz, 2H), 1.70 (pentet, J=6.6 Hz, 2H), 1.52 (pentet, J=7.2 Hz, 2H); ^{13}C NMR (150 MHz) δ 150.9 (+), 141.5 (+), 138.6 (−), 131.3 (−), 127.9 (−), 123.6 (−), 114.7 (+), 113.3 (+), 71.9 (+), 71.3 (+), 33.5 (+), 29.1 (+), 25.5 (+); IR (neat) 2937, 2863, 1639, 1535, 1117, 733, 643 cm^{-1}; HRMS (DCI, CH_4) calcd for $C_{13}H_{18}BrNO_3$ (MH^+) 314.0392, found 314.0389.

2.1.8. 2-Bromo-3-nitro-1-[(2-ethenyl)phenoxy]methyl]-benzene (14). Reaction of sodium hydride (26 mg, 1.08 mmol) and 2-ethenylphenol (102 mg, 0.76 mmol) in THF (10 mL, 1.5 h) followed by reaction of the formed alkoxide with **7** (128 mg, 0.44 mmol) in THF (10 mL, 44 h), as described for **11**, gave after work up and chromatography (hexanes then hexanes/EtOAc, 9:1) **14** (95 mg, 0.28 mmol, 65%) as a faint yellow solid. Mp 68–71 °C; ^{1}H NMR (270 MHz) δ 7.77 (d with further fine splitting, J=7.7 Hz, 1H), 7.67 (dd, J=7.9, 1.6 Hz, 1H), 7.53 (dd, J=7.5, 1.6 Hz, 1H), 7.47 (t, J=7.9 Hz, 1H), 7.23 (t, J=6.4 Hz, 1H), 7.14 (q, J=17.8, 11.1 Hz, 1H), 6.99 (t, J=7.5 Hz, 1H), 6.86 (d, J=8.1 Hz, 1H), 5.77 (dd, J=17.8, 1.4 Hz, 1H), 5.31 (dd, J=11.3, 1.4 Hz, 1H), 5.18 (s, 2H); ^{13}C NMR (67.5 MHz) δ 154.8 (+), 150.8 (+), 139.7 (+), 131.2 (−), 131.1 (−), 129.0 (−), 128.2 (−), 127.2 (+), 126.6 (−), 124.0 (−), 121.7 (−), 114.9 (+), 113.1 (+), 112.3 (−), 69.5 (+); IR (neat) 1536, 1486, 1361, 1111, 907, 850, 733 cm^{-1}.

2.1.9. 2-Bromo-3-nitro-1-[2-(2-propen-1-ylphenoxy)-methyl]benzene (15). Reaction of sodium hydride (158 mg, 6.56 mmol) with 2-(2-propen-1-yl)phenol in THF (25 mL, 1H) followed by reaction of the formed alkoxide with **7** (1.02 g, 3.44 mmol) and tetrabutylammonium iodide (127 mg, 0.35 mmol) in THF (25 mL, 42.5 h), as described for **11**, gave after work up and chromatography (hexanes/EtOAc, 49:1) **15** (1.09 g, 3.14 mmol, 91%) as a faint yellow oil. ^{1}H NMR (270 MHz) δ 7.78 (d, J=7.7 Hz, 1H), 7.64 (dd, J=7.9, 1.2 Hz, 1H), 7.45 (t, J=7.9 Hz, 1H), 7.20–7.15 (m, 2H), 6.94 (t, J=7.5 Hz, 1H), 6.85 (d, J=8.3 Hz, 1H), 6.03 (ddq, J=17.6, 9.5, 6.5 Hz, 1H), 5.14 (s, 2H), 5.11–5.04 (m, 2H), 3.49 (d, J=6.5 Hz, 2H); ^{13}C NMR (67.5 MHz) δ 155.4 (+), 150.7 (+), 139.8 (+), 136.6 (−), 131.0 (−), 130.1 (−), 128.7 (+), 128.1 (−), 127.4 (−), 123.9 (−), 121.5 (−), 115.6 (+), 112.9 (+), 111.5 (−), 69.1 (+), 34.4 (+); IR (neat) 3078, 1534, 1492, 1364, 1236 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{12}BrNO_3$ 347.0157, found 347.0170.

2.1.10. 2-Bromo-3-nitro-*N*-(2-propenyl)benzenemethanamine (16). To a solution of **7** (1.00 g, 3.39 mmol) dissolved in THF (15 mL) was added 2-propen-1-ylamine (509 μL, 6.78 mmol) and triethylamine (950 μL, 6.78 mmol) via syringe. The resulting mixture was stirred at ambient temperature (36 h), diluted with water (15 mL), and extracted with diethyl ether (3×25 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvents were removed. Purification by chromatography (hexanes/EtOAc, 9:1) gave **16** (853 mg, 3.15 mmol, 93%) as an orange oil. ^{1}H NMR (270 MHz) δ 7.69 (dd, J=7.5, 1.4 Hz, 1H), 7.58 (dd, J=7.9, 1.6 Hz, 1H), 7.43 (t, J=7.9 Hz, 1H), 5.93 (ddt, J=17.2, 10.3, 5.9 Hz, 1H), 5.22 (dd with further fine splitting, J=17.2, 1.6 Hz, 1H), 5.14 (dd, J=10.3, 1.4 Hz, 1H), 3.94 (s, 2H), 3.29 (d with further fine splitting, J=5.9 Hz, 2H), 1.62 (br s, 1H); ^{13}C NMR (67.5 MHz) δ 151.0 (+), 142.5 (+), 136.1 (−), 132.4 (−), 127.7 (−), 123.1 (−), 116.2 (+), 114.5 (+), 52.7 (+), 51.2 (+); IR (neat) 3324, 1534, 1360 cm^{-1}; Anal. Calcd for $C_{10}H_{11}BrN_2O_2$: C, 44.30; H, 4.09. Found: C, 44.38; H, 4.07.

2.1.11. 2-Propen-1-yl 2-bromo-3-nitrobenzyl sulfide (17). Reaction sodium hydride (60 mg, 2.50 mmol) and 2-propenyl-1-thiol (140 μL mL, 1.81 mmol) in THF (10 mL, 1 h) followed by reaction of the formed thiolate with **7** (587 mg, 1.99 mmol) in THF (10 mL, 25 h), as described for **11**, gave after work up (extracted with dichloromethane (4×15 mL)) and chromatography (hexanes then hexanes/EtOAc, 49:1) a mixture of product (**17**) and starting material. The mixture was dissolved in chloroform (20 mL) and triphenylphosphine (61 mg, 0.23 mmol) was added. The resulting mixture was stirred (21.25 h) at 70 °C. The solvents were removed at reduced pressure and the crude material was purified by chromatography (hexanes/EtOAc, 9:1) to give **17** (425 mg, 1.86 mmol, 94%) as a faint yellow solid. Mp 35–38 °C; ^{1}H NMR (270 MHz) δ 7.59 (dd, J=3.6, 1.6 Hz, 1H), 7.56 (dd, J=3.8, 1.6 Hz, 1H), 7.41 (t, J=7.7 Hz, 1H), 5.83 (ddt, J=16.4, 10.5, 7.1 Hz, 1H), 5.20–5.12 (m, 2H), 3.86 (s, 2H), 3.13 (dt, J=7.1, 1.0 Hz, 2H); ^{13}C NMR (67.5 MHz) δ 151.3 (+), 140.9 (+), 133.5 (−), 133.2 (−), 127.6 (−), 123.1 (−), 117.7 (+), 115.4 (+), 35.3 (+), 34.5 (+); IR (neat) 1535, 1426, 1360, 1225, 990, 649 cm^{-1}; GCMS (EI) *m/z* 288.

2.1.12. Dimethyl 2-(2-bromo-3-nitrophenyl)-1,1-ethanedicarboxylate (18). To slurry of NaH (80% in mineral oil, 0.33 g, 11.0 mmol) in THF (25 mL) was added dimethylmalonate (1.14 mL, 10.0 mmol) via syringe. The reaction mixture was stirred (2H) until no more gas was evolved and a clear red solution was formed. A solution of **7** (2.95 g, 10.0 mmol) in THF (15 mL) was added to the formed anion. The solution slowly turned milky and a yellowish precipitate was formed. The resulting mixture was stirred at ambient temperature (2 h), diluted with H_2O (40 mL) and extracted with diethyl ether (3×50 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvents were removed. Purification by chromatography (hexanesEtOAc, 4:1) gave **18** (2.55 g, 7.37 mmol, 74%) as pale yellow crystals. Mp 68–70 °C; ^{1}H NMR (270 MHz) δ 7.59 (dd, J=7.9, 1.8 Hz, 1H), 7.50 (dd, J=7.7, 1.8 Hz, 1H), 7.37 (t, J=7.9 Hz, 1H), 3.88 (t, J=7.7 Hz, 1H), 3.73 (s, 3H), 3.46 (d, J=7.7 Hz, 2H); ^{13}C NMR (67.5 MHz) δ 168.5 (+), 151.5 (+), 140.2 (+), 134.4 (−), 127.9 (−), 123.6 (−), 115.6 (+), 52.8 (−), 50.7 (−), 35.4 (+); IR (neat) 1749, 1721, 1528, 1231 cm^{-1}; Anal. Calcd for $C_{12}H_{12}BrNO_6$: C, 41.64; H, 3.49. Found: C, 41.75; H, 3.45.

2.1.13. *N*-2-propen-1-yl-*N*-(2-bromo-3-nitrophenyl)-methyl ethanamide (19). To a solution of **16** (0.78 g,

2.88 mmol) in pyridine (1.18 mL, 14.6 mmol) was added acetic anhydride (1.66 mL, 17.4 mmol) via syringe. The yellow mixture was stirred at ambient temperature (overnight) then heated to 100 °C (oil-bath temperature, 1.5 h). The solvent was removed and the crude product was purified by chromatography (hexanes/EtOAc, 9:1) affording **19** (0.89 g, 2.85 mmol, 99%) as a pale yellow solid. Analytical data from a *ca* 3:1 mixture of rotamers. Mp 53–55 °C; ^{1}H NMR (270 MHz) δ 7.71–7.34 (m, 3H), 5.82 (br m), 5.3–5.1 (m), 4.73 (s, major), 4.63 (s, minor), 4.05 (d, J=5.7 Hz, minor), 3.97 (br s, major), 2.23 (s, major), 2.09 (s, minor); ^{13}C NMR (major) δ 171.1 (+), 150.9 (+), 139.4 (+), 131.6 (−), 130.9 (−), 123.2 (−), 117.0 (+), 113.9 (+), 50.8 (+), 48.8 (+), 20.9 (−); ^{13}C NMR (67.5 MHz) (minor) δ 170.6 (+), 151.0 (+), 138.8 (+), 132.0 (−), 129.3 (−), 123.7 (−), 117.9 (+), 113.4 (+), 51.6 (+), 48.0 (+), 21.1 (−); IR (neat) 1650, 1536 cm^{-1}; Anal. Calcd for $C_{12}H_{13}BrN_2O_3$: C, 46.02; H, 4.18. Found: C, 45.98; H, 4.21.

2.1.14. 2-Propen-1-yl 2-bromo-3-nitrobenzyl sulfoxide (20). To a solution of 1:1 water/ethanol solution (4 mL) was added sodium metaperiodate (289 mg, 1.35 mmol) and cooled to 0 °C. Compound **17** (250 mg, 1.10 mmol) dissolved in water/ethanol (1:1, 2 mL) was added to the cooled solution via pipette. The resulting solution was stirred at 0 °C (25 h). The mixture was then extracted with dichloromethane (4×15 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and the solvents were removed at reduced pressure. Crude H^1 NMR showed some remaining starting material. Sodium metaperiodate (265 mg, 1.24 mmol) was added to a solution of water/ethanol (1:1, 6 mL) and the crude product at 0 °C. The resulting solution was stirred (69.75 h) while warming from 0 °C to ambient temperature. The mixture was then extracted with dichloromethane (4×15 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and the solvents were removed at reduced pressure. Purification by chromatography (in sequence: hexanes/EtOAc, 1:1, hexanes/EtOAc, 3:7, and hexanes/EtOAc, 1:9) gave **20** (117 mg, 0.38 mmol, 35%) as a faint yellow solid. Mp 79–80 °C; ^{1}H NMR (270 MHz) δ 7.71 (dd, J=7.9, 1.8 Hz, 1H), 7.62 (dd, J=7.7, 1.6 Hz, 1H), 7.48 (t, J=7.7 Hz, 1H), 6.00 (ddt, J=17.0, 10.1, 7.5 Hz, 1H), 5.53 (d, J=9.1 Hz, 1H), 5.49 (dd, J=17.0, 1.2 Hz, 1H), 4.42 (d, J=12.9 Hz, 1H), 4.07 (d, J=12.9 Hz, 1H), 3.67 (dd, J=12.9, 7.3 Hz, 1H), 3.52 (dd, J=13.0, 7.5 Hz, 1H); ^{13}C NMR (67.5 MHz) δ 151.4 (+), 135.3 (−), 134.0 (+), 128.2 (−), 125.2 (−), 124.7 (−), 124.2 (+), 116.0 (+), 57.6 (+), 56.0 (+); IR (neat) 1533, 1362, 1038, 930, 805, 733 cm^{-1}; HRMS (DEI) calcd for $C_{10}H_{10}BrNO_3S$ 302.9565, found 302.9557.

2.1.15. 2-Propen-1-yl 2-bromo-3-nitrobenzyl sulfone (21). To a solution of trifluoroacetic anhydride (0.64 mL, 4.53 mmol) and acetonitrile (10 mL) was added urea/hydrogen peroxide[29] (UHP) crystals (565 mg, 6.00 mmol) and the mixture was stirred (20 min) at ambient temperature. To the solution was added **17** (370 mg, 1.62 mmol) and the resulting solution was stirred at ambient temperature (21.5 h). The mixture was diluted with water (10 mL) and extracted with dichloromethane (4×5 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure. Purification by chromatography (hexanes/EtOAc, 6:4) gave **21** (337 mg, 1.30 mmol, 80%) as a faint yellow solid. Mp 139–143 °C; ^{1}H NMR (270 MHz) δ 7.79 (dd, J=7.7, 1.6 Hz, 1H), 7.73 (dd, J=8.1, 1.8 Hz, 1H), 7.53 (t, J=7.9 Hz, 1H), 5.93 (ddt, J=16.8, 10.3, 7.3 Hz, 1H), 5.54 (dd with further fine splitting, J=10.3, 0.8 Hz, 1H), 5.51 (dd with further fine splitting, J=16.8, 1.2 Hz, 1H), 4.63 (s, 2H), 3.80 (d, J=7.3 Hz, 2H); ^{13}C NMR (67.5 MHz) δ 151.6 (+), 135.7 (−), 130.8 (+), 128.4 (−), 125.4 (−), 125.4 (+), 123.8 (−), 116.9 (+), 58.1 (+), 57.2 (+); IR (neat) 1737, 1537, 1362, 1122, 942, 737 cm^{-1}; GCMS (EI) m/z 214 ($M^+ - NO_2$); HRMS (DEI) calcd for $C_{10}H_{11}BrNO_4S$ 319.9592, found 319.9603.

2.1.16. Dimethyl 1-(2-bromo-3-nitrophenyl)-2,2-pent-4-ene-dicarboxylate (22). Sodium hydride (80% in mineral oil, 0.21 g, 7.0 mmol) was added, at ambient temperature, to a solution of **18** (2.20 g, 6.36 mmol) in THF (20 mL). The reaction mixture was stirred (1 h) until no more gas was evolved and a clear orange solution was formed. To the solution was added 3-bromo-propene (606 mL, 7.00 mmol), via syringe. The solution slowly turned milky and a yellowish precipitate was formed. The resulting mixture was stirred at ambient temperature (16 h), diluted with H_2O (40 mL) and extracted with diethyl ether (3×50 mL). The combined organic phases were dried ($MgSO_4$) and filtered, and the solvents were removed. Purification by chromatography (hexanes/EtOAc, 9:1 followed by hexanes/EtOAc, 4:1) gave **22** (2.20 g, 5.71 mmol, 90%) as faint yellow crystals. Mp 57–60 °C; ^{1}H NMR (270 MHz) δ 7.59–7.48 (m, 2H), 7.35 (t, J=7.9 Hz, 1H), 5.93 (ddt, J=17.0, 9.9, 7.1 Hz, 1H), 5.2–5.1 (m, 2H), 3.69 (s, 3H), 3.57 (s, 2H), 2.70 (d, J=7.1 Hz, 2H); ^{13}C NMR (67.5 MHz) δ 170.6 (+), 151.8 (+), 139.9 (+), 134.2 (−), 132.2 (−), 127.6 (−), 123.1 (−), 119.6 (+), 116.8 (+), 58.7 (+), 52.6 (−), 38.8 (+), 38.2 (+); IR (neat) 1732, 1536, 1215 cm^{-1}; Anal. Calcd for $C_{15}H_{16}BrNO_6$: C, 46.65; H, 4.18. Found: C, 46.74; H, 4.19.

2.1.17. 2-Bromo-3-nitro-1-(*N*-(2-propen-1-yl)benzenamide (23). To a solution of 2-bromo-3-nitrobenzoic acid (**24**) (1.00 g, 4.07 mmol) in dichloromethane (20 mL) was added oxallyl chloride (1.00 mL, 11.46 mmol) via syringe. The resulting mixture was heated at reflux (3 h) where after the remaining solvent and excess reagent was removed. The crude product was dissolved in dichloromethane (20 mL), pyridine (1.0 mL, 12.36 mmol) was added via pipette, and the resulting mixture was stirred (18 min) at ambient temperature. The solution was cooled (−20 °C) and 2-propen-1-ylamine (440 μL, 5.86 mmol) was added via syringe. The resulting mixture was stirred while warming to ambient temperature (20 h). The solvents were removed on under reduced pressure to give, after chromatography (hexanes/EtOAc, 6:4), **23** (769 mg, 2.70 mmol, 66%) as a faint yellow solid. Mp 120–121 °C; ^{1}H NMR (270 MHz) δ 7.75 (d, J=7.7 Hz, 1H), 7.62 (d, J=7.3 Hz, 1H), 7.51 (t, J=7.9 Hz, 1H), 6.13 (broad s, 1H), 5.93 (ddt, J=16.0, 10.9, 5.7 Hz, 1H), 5.31 (d, J=17.2 Hz, 1H), 5.23 (d, J=10.1 Hz, 1H), 4.09 (broad s, 2H); ^{13}C NMR (67.5 MHz) δ 166.2 (+), 150.6 (+), 141.0 (+), 132.9 (−), 131.2 (−), 128.3 (−), 125.3 (−), 116.8 (+), 111.1 (+), 42.2 (+); IR (neat) 3053,

2986, 1264, 895, 738 cm^{-1}; HRMS (EI) calcd for $C_{10}H_9BrN_2O_3$ 283.9797, found 283.9808.

2.1.18. 2-Bromo-3-nitrophenyl isocyanate (25). To a solution of diphenylphosporyl azide (2.00 mL, 9.28 mmol), triethylamine (2.4 mL, 17.22 mmol), and benzene (40 mL) was added **24** (1.99 g, 8.13 mmol). The resulting solution was stirred at ambient temperature (3 h) followed by stirring at 100 °C (3 h). The mixture was then diluted with ammonium chloride (sat. aqueous. 40 mL) and extracted with dichloromethane (3×30 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure. Purification by chromatography (in sequence: hexanes/EtOAc, 8:2, 1:1, and 3:7) gave **25** (558 mg, 2.30 mmol, 28%) as a faint yellow oil. ^{1}H NMR (270 MHz) δ ($CDCl_3$ and DMSO-d_6) 8.12 (d with other fine splitting, J=8.1 Hz, 1H), 8.02 (dd, J=7.9, 1.4 Hz, 0.7H), 7.91 (dd, J=7.9, 1.3 Hz, 0.3H), 7.81 (d, J=7.3 Hz, 1H); ^{13}C NMR (67.5 MHz) δ ($CDCl_3$ and DMSO-d_6) 149.5 (+), 144.6 (+), 133.03 (−), 132.98 (+), 128.1 (−), 125.1 (−), 114.5 (+); IR (neat) 1717, 1540, 1028, 1008, 952, 644 cm^{-1}; HRMS (EI) calcd for $C_7H_3BrN_2O_3$ 241.9327, found 241.9319.

2.1.19. Methyl *N*-(2-bromo-3-nitrophenyl) carbamate. To a solution of **25** (191 mg, 0.78 mmol) in methanol (5 mL) was added via pipette a solution of sodium methoxide prepared from sodium (20 mg, 0.86 mmol) and methanol (5 mL). The resulting mixture was stirred at ambient temperature (91 h). The mixture was diluted with HCl (aqueous 5%, 20 mL) and extracted with dichloromethane (3×20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure. Purification by chromatography (hexanes/EtOAc, 8:2) gave methyl *N*-(2-bromo-3-nitrophenyl)-carbamate (153 mg, 0.56 mmol, 71%) as a faint yellow solid. Mp 96–98 °C; ^{1}H NMR (270 MHz) δ (DMSO-d_6) 9.43 (bs, 1H), 7.78 (dd, J=3.6, 1.6 Hz, 1H), 7.75 (dd, J=3.8, 1.4 Hz, 1H), 7.58 (t, J=7.9 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR (67.5 MHz) δ 153.4 (+), 150.7 (+), 137.9 (+), 128.6 (−), 122.8 (−), 119.1 (−), 104.2 (+), 52.9 (−); IR (neat) 3401, 3278, 1746, 1530, 1225, 1077, 957, 796 cm^{-1}; GCMS (EI) m/z 275; HRMS (EI) calcd for $C_8H_7BrN_2O_4$ 273.9589, found 273.9589.

2.1.20. Methyl *N*-(2-bromo-3-nitrophenyl)-*N*-3-buten-1-yl carbamate (26). To a slurry of hexane washed sodium hydride (50 mg, 2.06 mmol) in THF (20 mL) was added methyl *N*-(2-bromo-3-nitrophenyl) carbamate (299 mg, 1.09 mmol). The reaction mixture was stirred until no more gas was evolved (1 h). To the resulting solution was added 4-bromo-1-butene (170 μL, 1.68 mmol) and the mixture was heated at reflux (80 °C, 138 h). The mixture was diluted with water (20 mL) and extracted with dichloromethane (4×15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvents were removed on a rotary evaporator at water aspirator pressure. Purification by chromatography (in sequence: hexanes/EtOAc, 95:5 then 9:1) gave **26** (93 mg, 0.28 mmol, 26%) as a faint yellow oil. ^{1}H NMR (600 MHz) δ 7.71 (d, J=7.8 Hz, 1H), 7.48 (t, J=8.4 Hz, 1H), 7.45 (d, J=7.2 Hz, 1H), 5.76 (dt, J=16.2, 6.6 Hz, 1H), 5.12–5.06 (m, 2H), 4.00 (pentet, J=7.2 Hz, 1H), 3.80 (br s, 1H), 3.65 (s, 3H), 3.40 (pentet, J=6.9 Hz, 1H), 2.41–2.29 (m, 2H); ^{13}C NMR (150 MHz, APT at 67.5 MHz) δ 155.2 (+), 151.8 (+), 143.0 (+), 134.7 (−), 133.9 (−), 128.4 (−), 124.0 (−), 117.3 (+), 116.9 (+), 53.3 (−), 49.3 (+), 32.5 (+); IR (neat) 1712, 1537, 1383, 908, 650 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{13}BrN_2O_4$ 328.0059, found 328.0055.

2.1.21. Dihydro-4-methylene-5-nitro-2*H*-1-benzopyrane (3), 4-methyl-5-nitro-2*H*-1-benzopyrane (4), and 4-methyl-5-nitro-4*H*-1-benzopyrane (5). A solution of **2** (1.27 g, 4.67 mmol), $Pd(OAc)_2$ (52 mg, 0.23 mmol), and tri(*o*-tolyl)phosphine (TTP, 142 mg, 0.47 mmol) in triethylamine (TEA, 23 mL) was heated at 125 °C (1.5 h). The reaction mixture was filtered (Celite), the filtrate was diluted with CH_2Cl_2 (50 mL), and the resulting solution was washed with HCl (10% aqueous, 3×50 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvents were removed by evaporation. Purification of the crude product by chromatography (hexanes/EtOAc, 19:1) gave, in order of elution, **5** (30 mg, 0.17 mmol, 3%), a mixture of **4** and **5** (1:1 mixture by ^{1}H NMR, 257 mg, 1.34 mmol, 29%), as yellow oils and **3** (462 mg, 2.42 mmol, 52%) as pale yellow crystals. Data for **3**. Mp 30–32 °C; ^{1}H NMR (270 MHz) δ 7.20 (t, J=8.1 Hz, 1H), 7.00 (dd, J=7.7, 1.0 Hz, 1H), 6.74 (dd, J=8.3, 1.2 Hz, 1H), 5.14 (s, 1H), 5.08 (s, 1H), 4.35 (t, J=5.7 Hz, 2H), 2.69 (t, J=5.8 Hz, 2H); ^{13}C NMR (67.5 MHz) δ 155.1 (+), 149.1 (+), 132.3 (+), 128.7 (−), 120.1 (−), 115.2 (−), 114.7 (+), 114.1 (+), 68.0 (+), 31.7 (+); IR (neat) 1527, 1308, 1248, 1042, 811 cm^{-1}; Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74. Found: C, 62.72; H, 4.72.

Data for **4** from a 1:1 mixture of **4** and **5**: ^{1}H NMR δ 7.26–7.17 (m, 2H), 7.08 (dd, J=6.5, 2.8 Hz, 1H), 5.83 (m, 1H), 4.48 (m, 2H), 1.93 (s, 3H); ^{13}C NMR δ 128.4 (−), 122.7 (−), 116.7 (−), 64.7 (+), 17.8 (−); ^{13}C NMR δ 156.1 (+), 148.3 (+), 128.6 (+), 128.3 (−), 122.6 (−), 119.9 (−), 118.8 (+), 116.7 (−), 64.5 (+), 17.5 (−); IR (neat) 1525, 1468, 1444, 1360, 1301, 1253 cm^{-1}; MRMS (EI) m/z 191.0575 (191.0582 calcd for $C_{10}H_9NO_3$).

Data for **5**. ^{1}H NMR (270 MHz) δ 7.52 (dd, J=8.1, 1.4 Hz, 1H), 7.19 (t, J=8.1 Hz, 1H), 7.06 (dd, J=8.3, 1.4 Hz, 1H), 6.46 (d, J=6.1 Hz, 1H), 5.00 (t, J=5.7 Hz, 1H), 4.05 (dq, J=6.7, 5.3 Hz, 1H), 1.18 (d, J=6.7 Hz, 3H); ^{13}C NMR (67.5 MHz) δ 152.3 (+), 149.0 (+), 139.0 (−), 127.2 (−), 121.6 (−), 121.1 (+), 119.8 (−), 107.2 (−), 25.0 (−), 24.8 (−); IR (neat) 1673, 1526, 1352, 1298, 1264, 1191, 1046 cm^{-1}; Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74. Found: C, 63.07; H, 4.93.

2.1.22. 3,4-Dihydro-4-methylene-5-nitro-1*H*-2-benzopyrane (27), and 4-methyl-5-nitro-1*H*-2-benzopyrane (28). Reaction of **8** (630 mg, 2.32 mmol), $Pd(OAc)_2$ (26 mg, 0.12 mmol), and TTP (71 mg, 0.23 mmol) in TEA (12 mL), as described for **2** (125 °C, 1.5 h), gave after chromatography (hexanes/EtOAc, 19:1) in order of elution, **28** (90 mg, 0.47 mmol, 20%) and **27** (338 mg, 1.77 mmol, 76%) both as yellow crystals.

Analytical data for **27**. Mp 67–70 °C; ^{1}H NMR (270 MHz) δ 7.44 (d, J=7.9 Hz, 1H), 7.33 (t, J=7.7 Hz, 1H), 7.22 (d, J=7.7 Hz, 1H), 5.33 (s, 1H), 5.32 (s, 1H), 4.81 (s, 2H), 4.45

(s, 2H); ^{13}C NMR (67.5 MHz) δ 148.6 (+), 138.1 (+), 133.3 (+), 127.8 (−), 127.4 (−), 125.1 (+), 122.1 (−), 115.2 (+), 70.61 (+), 67.8 (+); IR (CCl_4) 3084, 2845, 1523, 1361, 1094, 917 cm^{-1}; Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74. Found: C, 62.69; H, 4.82.

Analytical data for **28**. Mp 58–61 °C; ^{1}H NMR δ 7.39 (dd, J=7.5, 2.0 Hz, 1H), 7.26–7.17 (m, 2H), 6.63 (q, J=1.4 Hz, 1H), 4.96 (s, 2H), 1.81 (d, J=1.4 Hz, 3H); ^{13}C NMR δ 147.3 (−), 145.7 (+), 132.7 (+), 126.7 (−), 126.6 (−), 123.1 (−), 124.8 (+), 109.4 (+), 68.1 (+), 12.8 (−); IR (neat) 1518 cm^{-1}; Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74. Found: C, 62.53; H, 4.84.

2.1.23. 3-Methyl-4-methylene-5-nitro-isochroman (29) and 3,4-dimethyl-5-nitro-1*H*-isochromene (30). Reaction of **9** (108 mg, 0.38 mmol), $Pd(OAc)_2$ (6 mg, 0.03 mmol), and TTP (34 mg, 0.11 mmol) in TEA (13 mL), as described above for **2** (120 °C, 24 h), gave after chromatography (hexanes/EtOAc, 9:1) in order of elution **30** (19 mg, 0.09 mmol, 25%) and **29** (56 mg, 0.27 mmol, 73%) as faint yellow oils.

Analytical data for **29**: ^{1}H NMR (270 MHz) δ 7.50 (d, J=7.9 Hz, 1H), 7.33 (t, J=7.7 Hz, 1H), 7.25 (d, J=10.7 Hz, 1H), 5.30 (s, 1H), 5.26 (s, 1H), 4.77 (d, J=14.6 Hz, 1H), 4.66 (d, J=14.6 Hz, 1H), 4.57 (pent, J=6.3 Hz, 1H), 1.46 (d, J=6.5 Hz, 3H); ^{13}C NMR (67.5 MHz) δ 148.9 (+), 139.1 (+), 138.6 (+), 127.5 (−), 127.3 (−), 126.7 (+), 122.4 (−), 113.9 (+), 73.9 (−), 66.2 (+), 20.2 (−); IR (neat) 1529, 1369, 1090, 909, 732 cm^{-1}.

Spectral data for **30**: ^{1}H NMR (270 MHz) δ 7.48 (dd, J=7.1, 2.6 Hz, 1H), 7.23–7.15 (m, 2H), 4.87 (s, 2H), 2.01 (d, J=0.8 Hz, 3H), 1.81 (d, J=0.8 Hz, 3H); ^{13}C NMR (67.5 MHz) δ 156.3 (+), 145.3 (+), 133.6 (+), 127.4 (+), 126.7 (−), 125.4 (−), 123.7 (−), 104.7 (+), 68.0 (+), 17.0 (−), 13.0 (−); IR (neat) 1625, 1525, 1361, 1183, 1056; GCMS (EI) m/z 159 (M^+).

2.1.24. 4-Ethenyl-5-nitroisochroman (31). Reaction of **10** (436 mg, 1.53 mmol), Pd(OAc)2(26 mg, 0.12 mmol), and TTP (135 mg, 0.44 mmol) in TEA (13 mL), as described for **2** (120 °C, 23 h), gave after chromatography (hexanes/EtOAc, 8:2) **31** (242 mg, 1.19 mmol, 78%) as a faint yellow oil. ^{1}H NMR (270 MHz, $CDCl_3$ and DMSO-d_6) δ 7.73 (d, J=7.7 Hz, 1H), 7.35 (t, J=7.7 Hz, 1H), 7.26 (d, J=7.5 Hz, 1H), 5.94 (ddd, J=17.4, 10.3, 7.5 Hz, 1H), 5.10 (d, J=10.3 Hz, 1H), 4.95–4.78 (m, 3H), 4.24–4.21 (m, 1H), 3.96 (d, J=11.5 Hz, 2H); ^{13}C NMR (67.5 MHz) δ ($CDCl_3$ and DMSO-d_6) 148.0 (+), 135.9 (−), 135.6 (+), 127.9 (−), 127.1 (+), 125.6 (−), 121.3 (−), 114.9 (+), 67.2 (+), 65.8 (+), 35.8 (−); IR (neat) 1526, 1352, 1113, 924 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{11}NO_3$ 205.0739, found 205.0739.

2.1.25. 3,4-Dihydro-4-phenylmethylene-5-nitro-1*H*-2-benzopyrane (32). Reaction of **11** (244 mg, 0.70 mmol), Pd(OAc)2(11 mg, 0.05 mmol), and TTP (60 mg, 0.20 mmol) in TEA (13 mL), as described for **2** (120 °C, 43 h), gave after chromatography (hexanes/EtOAc 9:1) **32** (153 mg, 0.57 mmol, 82%) as a faint yellow solid. Mp 79–81 °C; ^{1}H NMR (270 MHz) δ 7.56 (d, J=7.7 Hz, 1H), 7.38–7.17 (m, 7H), 6.69 (s, 1H), 4.82 (s, 2H), 4.57 (s, 2H); ^{13}C NMR (67.5 MHz) δ 148.7 (+), 140.0 (+), 135.3 (+), 131.0 (−), 129.3 (−), 128.4 (+), 128.3 (−), 128.0 (−), 127.7 (+), 127.3 (−), 127.1 (−), 123.1 (−), 67.1 (+), 66.2 (+); IR (neat) 1529, 1359, 908, 732 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{13}NO_3$ 267.0895, found 267.0894.

2.1.26. 5-Methylene-6-nitro-1,3,4,5-tetrahydrobenzo-[*cd*]oxepine (33). Reaction of **12** (870 mg, 3.04 mmol), $Pd(OAc)_2$ (48 mg, 0.22 mmol), and TTP (260 mg, 0.85 mmol) in TEA (13 mL), as described for **2** (120 °C, 22.5 h), gave after chromatography (hexanes/EtOAc, 9:1) **33** (506 mg, 2.47 mmol, 81%) as a faint yellow oil. ^{1}H NMR (270 MHz) δ 7.60 (dd, J=7.9, 1.4 Hz, 1H), 7.38 (dd, J=7.3, 1.4 Hz, 1H), 7.31 (t, J=7.7 Hz, 1H), 5.26 (s, 1H), 4.99 (s, 1H), 4.65 (s, 2H), 4.07 (t, J=5.2 Hz, 2H), 2.66 (t, J=5.4 Hz, 2H); ^{13}C NMR (67.5 MHz) δ 149.9 (+), 143.9 (+), 139.8 (+), 137.4 (+), 131.1 (−), 127.5 (−), 122.6 (−), 116.3 (+), 75.4 (+), 74.3 (+), 38.3 (+); IR (neat) 1530, 1362, 908, 733 cm^{-1}; GCMS (EI) m/z 159 (M^+); HRMS (EI) calcd for $C_{11}H_{11}NO_3$ 205.0739, found 205.0740.

2.1.27. 11-Methylene-10-nitro-6,11-dihydro-dibenzo-[*b*,*e*]oxepine (34) and 10-nitro-6*H*-5-oxa-dibenzo[*a*,*e*]-cyclooctene (35). Reaction of **14** (202 mg, 0.61 mmol), $Pd(OAc)_2$ (10 mg, 0.04 mmol), and TTP (53 mg, 0.18 mmol) in TEA (13 mL), as described for **2** (120 °C, 18.5 h), gave after chromatography (hexanes/EtOAc, 9:1) a 1.7:1 ratio (^{1}H NMR) of an inseparable mixture of **35** and **34** (149 mg, 0.59 mmol, 97%) as a faint yellow solid. Analytical data for the inseparable mixture of **34** and **35**. Mp 142–153 °C; ^{1}H NMR (270 MHz) δ 8.01 (d, J=8.3 Hz), 7.74 (d, J=7.9 Hz), 7.55 (d, J=7.5 Hz), 7.45–7.38 (m), 7.21 (d, J=7.3 Hz), 7.08–6.97 (m), 6.88–6.74 (m), 5.63 (s), 5.46 (s), 5.15 (s); ^{13}C NMR (67.5 MHz) δ 155.1 (+), 154.5 (+), 142.3 (+), 137.4 (+), 136.9 (+), 136.0 (−), 134.3 (+), 133.7 (−), 133.0 (−), 131.4 (−), 130.6 (−), 130.3 (−), 129.0 (−), 128.3 (−), 128.1 (−), 125.1 (−), 124.3 (+), 124.0 (−), 123.7 (−), 122.3 (+), 121.8 (−), 121.0 (−), 120.1 (−), 119.0 (−), 118.4 (+), 70.1 (+), 69.6 (+); IR (neat) 1524, 1481, 1345, 758.

2.1.28. 11-Methylene-10-nitro-11,12-dihydro-6*H*-5-oxa-dibenzo[*a*,*e*]cyclooctene (36) and 6,13-dihydro-10-nitro-5-oxa-dibenzo[*a*,*e*]cyclononene (37) and 3-[2-(2-propen-1-yl)phenoxymethyl]-1-nitrobenzene. Reaction of **15** (454 mg, 1.30 mmol), $Pd(OAc)_2$ (21 mg, 0.09 mmol), and TPP (114 mg, 0.37 mmol) in TEA (13 mL), as described for **2** (120 °C, 20.5 h), gave after chromatography (hexanes/EtOAc, 9:1) a 1.37:1 ratio (by ^{1}H NMR) of an inseparable mixture of **36** and **37** (106 mg, 0.40 mmol, 31%) and 3-[2-(2-propen-1-yl)phenoxymethyl]-1-nitrobenzene (30 mg, 0.11 mmol, 8%) as faint yellow solids. Analytical data for the inseparable mixture of **36** and **37**. Mp 116–119 °C; ^{1}H NMR (270 MHz) δ 7.89–6.95 (m, 14H, major and minor), 6.41 (d, J=11.1 Hz, 1H, minor), 6.26 (dt, J=10.9, 7.7 Hz, 1H, minor), 5.31–4.91 (m, 6H, major and minor), 4.01 (s, 2H, major), 3.43 (d, J=7.3 Hz, 2H, minor); ^{13}C NMR (67.5 MHz) δ 156.8 (+), 156.6 (+), 151.1 (+), 149.9 (+), 144.9 (+), 140.1 (+), 138.5 (+), 136.5 (+), 134.1 (+), 133.3 (+), 133.1 (−), 131.4 (−), 130.3 (−), 130.2 (−), 129.2 (−), 128.9 (−), 128.6 (+), 128.2 (−), 127.8 (−), 127.0 (−), 125.7 (−), 124.9 (−), 124.7 (−),

123.6 (−), 123.3 (−), 121.5 (−), 119.9 (−), 114.1 (+), 75.8 (+, major), 74.8 (+, minor), 41.0 (+, major), 31.1 (+, minor); IR (neat) 1530, 1489, 1359, 1104, 1013.

Spectral data for 3-[2-(2-propen-1-yl)phenoxymethyl]-1-nitrobenzene. Mp 43–46 °C; ^{1}H NMR (270 MHz) δ 8.33 (s, 1H), 8.19 (d, J=8.3 Hz, 1H), 7.78 (dd, J=7.5, 0.6 Hz, 1H), 7.57 (t, J=7.9 Hz, 1H), 7.23–7.16 (m, 2H), 6.96 (dt, J=7.3, 1.0 Hz, 1H), 6.88 (d, J=8.3 Hz, 1H), 6.02 (ddt, J=17.6, 9.5, 6.5 Hz, 1H), 5.17 (s, 2H), 5.10–5.09 (m, 1H), 5.06–5.03 (m, 1H), 3.47 (d, J=6.5 Hz, 2H); ^{13}C NMR (67.5 MHz) δ 155.8 (+), 148.4 (+), 139.5 (+), 136.7 (−), 132.8 (−), 130.2 (−), 129.5 (−), 128.9 (+), 127.4 (−), 122.7 (−), 121.9 (−), 121.4 (−), 115.6 (+), 111.5 (−), 68.6 (+), 34.4 (+); IR (neat) 3055, 1733, 1532, 1493, 1049; HRMS (EI) calcd for $C_{16}H_{15}NO_3$ 269.1052, found 269.1044.

2.1.29. 2-Acetyl-4-methylene-5-nitro-1,2,3,4-tetrahydroisoquinoline (38), and 2-acetyl-4-methyl-5-nitro-1,2-dihydroisoquinoline (39). A solution of **19** (2.13 g, 6.80 mmol), $Pd(OAc)_2$ (76 mg, 0.34 mmol), and TTP (207 mg, 0.68 mmol) in TEA (25 mL) was heated at 100 °C (1.5 h). The reaction mixture was filtered (Celite) and the solvent was removed. The residue was dissolved in CH_2Cl_2 (30 mL), and the resulting solution was washed with HCl (10% aqueous, 4×25 mL). The organic phase was dried ($MgSO_4$), filtered, followed by removal of solvent. Purification of the crude product by chromatography (hexanes/EtOAc, 3:7) gave, in order of elution, **39** (410 mg, 1.77 mmol, 26%) and **38** (1.093 g, 4.71 mmol, 69%) both as yellow crystals.

Analytical data for **38**. Mp 89–92 °C; ^{1}H NMR δ 7.6–7.3 (m, 3H), 5.47 (s, minor), 5.45 (major), 5.29 (s, 1H), 4.72 (s, major), 4.57 (s, minor), 4.40 (s, minor), 4.33 (s, major), 2.20 (s, minor), 2.17 (major); ^{13}C NMR δ 169.5, 137.6 (+), 133.6 (+), 133.5, 129.6 (−), 128.7 (−), 128.4 (−), 128.2 (−), 128.1, 122.8 (−), 122.5 (−), 117.6 (+), 117.2 (+), 51.2 (+), 48.0 (+), 47.7 (+), 43.5 (+), 21.8 (−), 21.7 (−); IR (neat) 1647, 1528, 1420 cm^{-1}; Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 52.06. Found: C, 61.93; H, 5.21.

Analytical data for **39**. Mp 103–105 °C; ^{1}H NMR δ 7.45–7.24 (m, 3H), 6.69 (s, 1H), 4.86 (s, 2H), 2.21 (s, 3H), 1.96 (s, 3H); ^{13}C NMR δ 168.1 (+), 147.1 (+), 135.1 (+), 128.6 (−). 128.5 (−), 127.3 (−), 125.5 (+), 122.9 (−), 114.8 (+), 44.0 (+0, 21.1 (−), 15.6 (−); IR (neat) 1672, 1624, 1524, 1397, 1347 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{12}N_2O_3$ 232.0848, found 232.0843.

2.1.30. Dimethyl 3,4-dihydro-4-methylene-5-nitro-2,2,(1*H*)-naphthalenedicarboxylate (40), and dimethyl 4-methyl-5-nitro-2,2,(1*H*)-naphthalenedicarboxylate (41). A solution of **22** (1.16 g, 3.00 mmol), $Pd(OAc)_2$ (34 mg, 0.15 mmol), and TTP (91 mg, 0.30 mmol) in TEA (10 mL) was heated at 100 °C (2 h). The reaction mixture was filtered (Celite), the filtrate was diluted with CH_2Cl_2 (50 mL), and the resulting solution was washed with HCl (10% aqueous, 3×50 mL). The organic phase was dried ($MgSO_4$), and filtered, followed by solvent evaporation. Purification of the crude product by chromatography (hexanes/EtOAc, 9:1) gave, in order of elution, a mixture of **41**:**40** and **40** (367 mg, 1.20 mmol, 40%) both as yellow crystals. The mixture was repurified by chromatography (hexanes/EtOAc, 9:1) affording **41** (94 mg, 0.31 mmol, 10%), a mixture of **41**:**40** (71 mg, 23 mmol, 8%, *endo–exo*, 1:1) and **40** (261 mg, 0.85 mmol, 28%).

Analytical data for **40**. Mp 97–100 °C; ^{1}H NMR δ 7.38 (dd, J=7.3, 1.6 Hz, 1H), 7.34 (d with further fine splitting, J=5.9 Hz, 1H), 7.28 (t, J=7.7 Hz, 1H), 5.25 (s, 1H), 5.17 (s, 1H), 3.72 (s, 6H, 3.35 (s, 2H), 3.11 (s, 2H); ^{13}C NMR δ 170.5 (+), 148.8 (+), 136.8 (+), 134.7 (+), 131.4 (−), 128.0 (+), 127.8 (−), 121.7 (−), 117.4 (+), 54.8 (+), 52.9 (−, 2C), 37.8 (+), 34.9 (+); IR (neat) 1735, 1528, 1259 cm^{-1}; Anal. Calcd for $C_{15}H_{15}NO_6$: C, 59.02; H, 4.95. Found: C, 59.08; H, 5.01.

Analytical data for **41**. Mp 104–106 °C; ^{1}H NMR δ 7.5–7.2 (m, 3H), 6.25 (s, 1H), 3.73 (s, 6H), 3.36 (s, 2H), 2.00 (s, 3H); ^{13}C NMR δ 169.7 (+), 148.5 (+), 136.5 (+), 131.8 (+), 130.9 (−), 127.9 (−), 127.3 (+), 127.1 (−), 122.6 (−), 53.9 (+), 53.1 (−, 2C), 34.9 (+), 18.8 (−); IR (neat) 1736, 1528, 1274, 1235 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{15}NO_6$ 305.0899, found 305.0887.

2.1.31. 4-Methylene-5-nitro-3,4-dihydro-2*H*-isoquinolin-1-one (42). Reaction of **23** (287 mg, 1.01 mmol), $Pd(OAc)_2$ (17 mg, 0.07 mmol), and TTP (87 mg, 0.29 mmol) in TEA (13 mL), as described for **2** (ambient temp. 5.5 h then 120 °C, 74 h), gave after chromatography (in sequence hexanes/EtOAc, 6:4, 1:1, and 3:7) **42** (105 mg, 0.52 mmol, 51%) as a faint yellow solid. Mp 185–187 °C; ^{1}H NMR (270 MHz) δ 8.25 (d, J=7.5 Hz, 1H), 7.70 (d, J=7.7 Hz, 1H), 7.48 (t, J=7.3 Hz, 1H), 7.20 (s, 1H), 5.44 (s, 1H), 5.28 (s, 1H), 4.16 (s, 2H); ^{13}C NMR (67.5 MHz) δ 163.2 (+), 148.0 (+), 131.6 (+), 131.4 (−), 130.3 (+), 129.8 (+), 128.8 (−), 127.1 (−), 119.5 (+), 47.5 (+); IR (neat) 2962, 1678, 1534, 1261, 907, 650.

2.1.32. 4-Methylene-5-nitro-3,4-dihydro-2*H*-quinoline-1-carboxylic acid methyl ester (43) and 4-methyl-5-nitro-4*H*-quinoline-1-carboxylic acid methyl ester and 4-methyl-5-nitro-2*H*-quinoline-1-carboxylic acid methyl ester. Reaction of **26** (93 mg, 0.28 mmol), $Pd(OAc)_2$ (5 mg, 0.02 mmol), and TTP (26 mg, 0.09 mmol) in TEA (13 mL), as described for **2** (120 °C, 39.75 h), gave after chromatography (hexanes/EtOAc, 95:5) 4-methyl-5-nitro-4*H*-quinoline-1-carboxylic acid methyl ester (4 mg, 0.02 mmol, 6%), 4-methyl-5-nitro-2*H*-quinoline-1-carboxylic acid methyl ester (4 mg, 0.02 mmol, 6%), and **43** (33 mg, 0.13 mmol, 47%) as a faint yellow oil.

Spectral data for **43**: ^{1}H NMR (270 MHz) δ 7.83 (dd, J=6.2, 3.6 Hz, 1H), 7.33–7.31 (m, 2H), 5.23 (t, J=1.4 Hz, 1H), 5.19 (s, 1H), 3.85 (t, J=6.9 Hz, 2H), 3.81 (s, 3H), 2.85 (t, J=7.1 Hz, 2H); ^{13}C NMR (150 MHz, APT at 67.5 MHz) δ 154.8 (+), 148.7(+), 140.1 (+), 134.3 (+), 127.5 (−), 127.0 (−), 124.5 (+), 119.1 (−), 115.6 (+), 53.3 (−), 44.8 (+), 32.9 (+); IR (neat) 1708, 1528, 1439, 1376, 1218, 909; GCMS (EI) m/z 248 (M^+).

Analytical data for 4-methyl-5-nitro-4*H*-quinoline-1-carboxylic acid methyl ester. ^{1}H NMR (270 MHz) δ 8.21 (d, J=8.5 Hz, 1H), 7.66 (dd, J=8.1, 1.2 Hz, 1H), 7.35 (t, J=8.3 Hz, 1H), 6.96 (d, J=7.3 Hz, 1H), 5.48 (t, J=6.9 Hz,

1H), 3.92 (pent, $J=6.9$ Hz, 1H), 3.91 (s, 3H), 1.30 (d, $J=6.9$ Hz, 3H); ^{13}C NMR (150 MHz) δ 152.9, 148.6, 138.2, 128.6, 126.4, 126.4, 125.8, 120.8, 116.0, 53.7, 28.6, 22.0.

Analytical data for 4-methyl-5-nitro-2*H*-quinoline-1-carboxylic acid methyl ester. ^{1}H NMR (270 MHz) δ 7.83 (d, $J=7.7$ Hz, 1H), 7.42 (dd, $J=7.9$, 1.2 Hz, 1H), 7.32 (t, $J=8.1$ Hz, 1H), 6.04 (dt, $J=5.3$, 1.6 Hz, 1H), 4.25 (dd, $J=5.2$, 1.4 Hz, 2H), 3.82 (s, 3H), 1.94 (d, $J=1.4$ Hz, 3H); ^{13}C NMR (150 MHz) δ 154.2, 148.4, 139.4, 130.1, 127.7, 127.1, 126.8, 124.6, 120.1, 53.7, 42.6, 18.0.

2.1.33. 3,5-Dihydro-2*H*-pyrano[4,3,2-*cd*]indole (6). To an oven-dried threaded ACE glass pressure tube was added **3** (81 mg, 0.42 mmol), $Pd(OAc)_2$ (10 mg, 0.042 mmol), dppp (42 mg, 0.10 mmol), and DMF (3 mL). The tube was fitted with a pressure head where after the solution was saturated with CO (four cycles to 4 atm of CO), and the reaction mixture was heated to 120 °C (oil bath temperature) under CO (4 atm, 70 h). The black reaction mixture was diluted with HCl (10% aqueous, 10 mL), and extracted with Et_2O (3×10 mL). The combined organic phases were washed with HCl (10% aqueous, 10 mL), and dried ($MgSO_4$), and the solvents were removed. The crude product was purified by chromatography using hexanes/EtOAc (19:1) as eluent to give **6** (42 mg, 0.265 mmol, 63%) as faint yellow crystals.

A similar reaction of **3** (345 mg, 1.80 mmol), $Pd(OAc)_2$ (24 mg, 0.11 mmol), and triphenylphosphine (112 mg, 0.43 mmol) in MeCN (4 mL) under CO (4 atm, 100 °C, 70 h) gave after work up and chromatography, in order of elution, **3** (110 mg, 0.57 mmol, 32%), and **6** (107 mg, 0.67 mmol, 37%) as faint yellow crystals. Mp 54–57 °C; ^{1}H NMR (270 MHz) δ 8.04 (br s, 1H), 7.19 (t, $J=7.9$ Hz, 1H), 6.96 (d, $J=8.1$ Hz, 1H), 6.78 (br s, 1H), 6.64 (d, $J=7.5$ Hz, 1H), 4.48 (t, $J=5.5$ Hz, 2H), 3.13 (t, $J=4.9$ Hz, 2H); ^{13}C NMR δ 150.9 (+), 135.1 (+), 123.6 (−), 117.9 (+), 116.0 (−), 107.6 (+), 103.7 (−), 101.9 (−), 68.2 (+), 23.2 (+); IR (neat) 3406, 1631, 1610, 1504, 1341, 1267, 1234 cm^{-1}; Anal. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70. Found: C, 75.24; H, 5.78.

2.1.34. 1,5-Dihydro-3*H*-pyrano[3,4,5-*cd*]indole (46). Reaction of **27** (109 mg, 0.57 mmol), $Pd(OAc)_2$ (13 mg, 0.058 mmol), dppp (136 mg, 0.14 mmol) in DMF (5 mL), as described for **6** (4 atm CO, 120 °C, 120 h), gave after chromatography (hexanes/EtOAc, 19:1 followed by 9:1) **46** (71 mg, 0.45 mmol, 78%) as faint pink crystals. Mp 168–170 °C; ^{1}H NMR (270 MHz) δ 7.96 (br s, 1H), 7.19 (d, $J=8.1$ Hz, 1H), 7.15 (t, $J=6.5$ Hz, 1H), 6.87 (s, 1H), 6.82 (d, $J=6.7$ Hz, 1H), 5.04 (s, 2H), 4.95 (s, 2H); ^{13}C NMR (67.5 MHz) δ 133.5 (+), 129.4 (+), 124.1 (−), 115.6 (−), 112.6 (−), 111.3 (+), 109.1 (−), 66.7 (+), 64.5 (+); IR (neat) 3308, 1445, 1086 cm^{-1}; HRMS (EI) calcd for $C_{10}H_9NO$ 159.0684, found 159.0678.

2.1.35. 1,5-Dihydro-2-methyl-3*H*-pyrano[3,4,5-*cd*]indole (47). Reaction of **29** (141 mg, 0.69 mmol), $Pd(dba)_2$ (25 mg, 0.04 mmol), dppp (18 mg, 0.04 mmol), and 1,10-phenanthroline monohydrate (16 mg, 0.09 mmol) in DMF (5 mL), as described for **6** (6 atm CO, 120 °C, 29 h), gave after chromatography (hexanes/EtOAc, 9:1) **47** (95 mg, 0.55 mmol, 80%) as a faint yellow solid. Mp 127–130 °C; ^{1}H NMR (270 MHz) δ 8.08 (broad s, 1H), 7.16–7.09 (m, 2H), 6.81–6.70 (m, 1H), 6.76 (t, $J=1.8$ Hz, 1H), 5.07 (dq, $J=6.4$, 1.2 Hz, 1H) overlapping peak centered at 5.01 (m, 2H), 1.63 (d, $J=6.5$ Hz, 3H); ^{13}C NMR (67.5 MHz) δ 133.6 (+), 129.6 (+), 124.2 (+), 123.0 (−), 117.0 (+), 115.4 (−), 112.6 (−), 109.0 (−), 70.5 (−), 66.6 (+), 20.5 (−); IR (neat) 3293, 1448, 1340, 1016, 908, 731; GCMS (EI) *m/z* 173; HRMS (EI) calcd for $C_{11}H_{11}NO$ 173.0842, found 173.0842.

2.1.36. 1,5-Dihydro-2-phenyl-3*H*-pyrano[3,4,5-*cd*]indole (48). Reaction of **32** (105 mg, 0.39 mmol), $Pd(dba)_2$ (14 mg, 0.03 mmol), dppp (12 mg, 0.03 mmol), and 1,10-phenanthroline monohydrate (10 mg, 0.05 mmol) in DMF (5 mL), as described for **6** (6 atm CO, 120 °C, 22 h), gave after purification by chromatography (hexanes/EtOAc, 8:2) **48** (63 mg, 0.27 mmol, 68%) as a faint yellow solid. Mp 189–192 °C; ^{1}H NMR (600 MHz) δ 8.13 (broad s, 1H), 7.47–7.41 (m, 4H), 7.32 (dt, $J=6.6$, 2.4 Hz, 1H), 7.22 (d, $J=7.8$ Hz, 1H), 7.16 (dt, $J=7.8$, 1.2 Hz, 1H), 6.83 (d, $J=6.6$ Hz, 1H), 5.21 (s, 2H), 4.98 (s, 2H); ^{13}C NMR (150 MHz) δ 134.0, 132.5, 129.7, 129.6, 129.2, 127.3, 125.8, 125.6, 123.3, 113.0, 109.1, 109.0, 66.6, 65.0; IR (neat) 1601, 1448, 864, 737, 692 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{13}NO$ 235.0997, found 235.0998.

2.1.37. 2,6,8,9-Tetrahydro-7-oxa-2-aza-benzo[*cd*]azulene (49). Reaction of **33** (412 mg, 2.01 mmol), $Pd(dba)_2$ (74 mg, 0.13 mmol), dppp (52 mg, 0.13 mmol), 1,10-phenanthroline monohydrate (45 mg, 0.25 mmol) in DMF (5 mL), as described for **6** (6 atm CO, 120 °C, 24 h), gave after chromatography (hexanes/EtOAc, 9:1) **49** (287 mg, 1.66 mmol, 83%) as a faint yellow solid. Mp 115–116 °C; ^{1}H NMR (270 MHz) δ 8.35 (broad s, 1H), 7.09–6.98 (m, 2H), 6.79–6.67 (m, 2H), 5.07 (s, 2H), 4.02 (t, $J=4.9$ Hz, 2H), 3.03 (t, $J=5.5$ Hz, 2H); ^{13}C NMR (67.5 MHz) δ 136.5 (+), 134.0 (+), 124.8 (+), 121.3 (−), 121.2 (−), 114.3 (−), 113.7 (+), 109.3 (−), 76.4 (+), 73.3 (+), 29.7 (+); IR (neat) 3413, 2934, 1432, 908, 731 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{11}NO$ 173.0841, found 173.0836.

2.1.38. 2,6-Dihydro-7-oxa-2-aza-dibenzo[*cd*,*h*]azulene (50) and 6*H*-5-oxa-dibenzo[*a*,*e*]cyclooctene-10-ylamine (51). Reaction of a 1.7:1 mixture (estimated by ^{1}H NMR) of **34** and **35** (266 mg, 1.05 mmol), $Pd(dba)_2$ (37 mg, 0.06 mmol), dppp (27 mg, 0.07 mmol), and 1,10-phenanthroline monohydrate (24 mg, 0.13 mmol) in DMF (5 mL), as described for **6** (6 atm CO, 120 °C, 20.5 h), gave after chromatography (hexanes/EtOAc acetate, 9:1 then hexanes/EtOAc, 1:1) two fractions containing **50** and **51**, respectively. However, both fractions contained residual DMF. The fraction containing **51** was each dissolved in diethyl ether (10 mL) and washed with water (4×10 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure to give **51** (98 mg, 0.42 mmol, 64%) as a faint yellow solid. The fraction containing **50** was dissolved in diethyl ether (10 mL) and washed with water (4×10 mL). The organic phase was dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by chromatography (hexanes/EtOAc, 7:3) affording **50** (38 mg, 0.17 mmol, 44%) as a faint yellow solid.

Analytical data for **50**. Mp 197–198 °C; ^{1}H NMR (600 MHz) δ 8.35 (broad s, 1H), 7.70 (dd, J=6.6, 1.8 Hz, 1H), 7.54 (d, J=2.4 Hz, 1H), 7.34 (d, J=7.8 Hz, 1H), 7.21–7.12 (m, 4H), 6.95 (d, J=6.6 Hz, 1H), 5.28 (s, 2H); ^{13}C NMR (150 MHz, APT at 67.5 MHz) δ 158.3 (+), 136.0 (+), 133.5 (+), 128.0 (+), 126.5 (−), 126.1 (−), 124.6 (−), 124.2 (−), 122.8 (−), 122.3 (−), 120.2 (−), 116.6 (−), 115.3 (+), 110.7 (+), 75.2 (+); IR (neat) 908, 732, 650; HRMS (EI) calcd for $C_{15}H_{11}NO$ 221.0841, found 221.0837.

Analytical data for **51**. Mp 99–102 °C; ^{1}H NMR (270 MHz) δ 7.12–6.98 (m, 4H), 6.90–6.79 (m, 3H), 6.64–6.49 (m, 1H), 6.27 (d, J=12.7 Hz, 1H), 5.25 (s, 2H), 3.68 (broad s, 2H); ^{13}C NMR (67.5 MHz) δ 156.1 (+), 144.6 (+), 135.2 (+), 134.2 (−), 131.3 (−) 128.5 (−), 128.4 (−), 124.3 (+), 123.1 (+), 122.9 (−), 120.60 (−), 120.58 (−), 120.3 (−), 115.6 (−), 71.4 (+); IR (neat) 3373, 2955, 1618, 1486, 1437, 1255, 1114, 909; GCMS (EI) m/z 223; HRMS (EI) calcd for $C_{15}H_{13}NO$ 223.0997, found 223.1001.

2.1.39. Compound 52 and 10-amino-6*H*-dibenz[*b*,*f*]-oxocine (53). Reaction of a 1.37:1 mixture (estimated by ^{1}H NMR) of **36** and **37** (106 mg, 0.40 mmol), Pd(dba)$_2$ (13 mg, 0.02 mmol), dppp (10 mg, 0.02 mmol), and 1,10-phenanthroline monohydrate (10 mg, 0.05 mmol) in DMF (5 mL), as described for **6** (6 atm CO, 120 °C, 98 h), gave after chromatography (in sequence: hexanes/EtOAc, 9:1, 1:1, 0:1) a mixture of **52** and **53**. The mixture was purified by chromatography (hexanes/EtOAc, 98:2 followed by hexanes/EtOAc, 95:5) to give **52** (20 mg, 0.09 mmol, 37%) as a faint yellow solid followed by a 1:1.7 mixture of **52** to **53** (10 mg, ca. 0.02 mmol **52**, 0.03 mmol **53**, 7% **52**, 15% **53**) as a faint yellow solid.

Analytical data for **52**. Mp 173–175 °C; ^{1}H NMR (270 MHz) δ 7.88 (broad s, 1H), 7.20–6.94 (m, 7H), 6.80 (dd, J=7.3, 1.2 Hz, 1H), 5.71 (s, 2H), 4.11 (s, 2H); ^{13}C NMR (67.5 MHz) δ 158.3 (+), 138.4 (+), 135.0 (+), 132.7 (+), 129.2 (−), 127.8 (−), 123.8 (−), 123.5 (+), 122.0 (−), 121.6 (−), 120.6 (−), 117.2 (+), 116.1 (−), 109.9 (−), 76.7 (+), 31.0 (+); IR (neat) 911, 728, 650 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{12}NO$ 234.0919, found 234.0914.

Analytical data for **53** from the mixture of **52** and **53**: ^{1}H NMR (270 MHz) δ 6.37 (d, J=11.3 Hz, 1H), 6.07 (dt, J=11.1, 8.1 Hz, 1H), 5.21 (broad s, 2 Hz, 1H), 3.76 (broad s, 2H), 3.21 (d, J=7.7 Hz, 2H).

2.1.40. 4-Acetyl-1,3,4,5,-tetrahydropyrrolo[4,3,2-*de*]isoquinoline (54).[30] Reaction of **38** (350 mg, 1.51 mmol), Pd(OAc)$_2$ (34 mg, 0.151 mmol), dppp (124 mg, 0.302 mmol) in MeCN (5 mL), as described for **6** (4 atm CO, 120 °C, 2 h), gave after chromatography (EtOAc) **54** (124 mg, 0.62 mmol, 41%) as a light yellow crystals followed by **38** (21 mg, 0.092 mmol, 9%) Analytical data for **54**. Mp 207–209 °C, ^{1}H NMR (270 MHz) δ 8.02 (br s, 1H), 7.22–7.13 (overlapping m, 2H), 6.94 (s, 1H), 6.88 (d, J=6.9 Hz, 1H), 5.02 (d, J=1.8 Hz, 2H), 4.83 (s, 1H), 4.82 (s, 1H), 2.20 (s, 3H); ^{13}C NMR (67.5 MHz) δ 169.2 (+), 133.0 (+), 132.9 (+), 126.6 (+), 125.8 (+), 124.7 (+), 124.6 (+), 121.9 (−), 121.6 (−), 116.8 (−), 116.3 (−), 112.9 (−), 112.2 (−), 109.1 (−), 108.6 (−), 108.1 (+), 107.7 (+), 46.8 (+), 43.6 (+), 41.9 (+), 38.8 (+), 21.6 (−), 21.5 (−); IR (neat) 3294, 1626, 1606, 1444, 1441, 1248, 767 cm^{-1}. The compound decompose relatively fast at ambient temperature forming highly colored products.

2.1.41. Dimethyl 1,3-dihydro-4,4(5*H*)-benz[*cd*]indole-5,5-dicarboxylate (55). Reaction of **40** (225 mg, 0.74 mmol), Pd(OAc)$_2$ (17 mg, 0.074 mmol), and dppp (75 mg, 0.18 mmol) in MeCN (5 mL), as described for **6** (4 atm CO, 120 °C, 48 h), gave after chromatography (hexanes/EtOAc, 9:1) gave **55** (131 mg, 0.48 mmol, 65%) as a white solid. Mp 154–155 °C; ^{1}H NMR (270 MHz) δ 7.94 (br s, 1H), 7.08–6.92 (m, 2H), 6.78 (d, J=6.4 Hz, 1H), 6.68 (s, 1H), 3.53 (s, 6H), 3.45 (s, 2H), 3.38; ^{13}C NMR (67.5 MHz) δ 171.6 (+), 133.4 (+), 127.5 (+), 125.4 (+), 122.8 (−), 118.3 (−), 115.9 (−), 109.4 (+), 108.7 (−), 56.2 (+), 52.7 (−), 33.8 (+), 28.7 (+); IR (neat) 3391, 1721 cm^{-1}; Anal. Calcd for $C_{15}H_{15}O_4$: C, 65.92; H, 5.53. Found: C, 65.81; H, 5.59.

2.1.42. 3,4-Dihydro-1*H*-pyrrolo[4,3,2-de]isoquinoline-5-one (56). Reaction of **42** (145 mg, 0.71 mmol), Pd(dba)$_2$ (26 mg, 0.05 mmol), dppp (20 mg, 0.05 mmol), and 1,10-phenanthroline monohydrate (16 mg, 0.09 mmol) in DMF (5 mL), as described for **6** (6 atm, 120 °C, 26.5 h), gave after purification by chromatography (hexanes/EtOAc, 2:8 followed by EtOAc) **56** (74 mg, 0.43 mmol, 61%) as a faint yellow solid. Mp 207–210 °C; ^{1}H NMR (270 MHz, $CDCl_3$ and DMSO-d_6) δ 10.81 (broad s, 1H), 7.47 (d, J=2.8 Hz, 1H), 7.44 (d, J=4.0 Hz, 1H), 7.33 (s, 1H), 7.17 (t, J=7.3 Hz, 1H), 7.05 (s, 1H), 4.90 (s, 2H); ^{13}C NMR δ ($CDCl_3$ and DMSO-d_6) 163.9 (+), 132.1 (+), 127.5 (+), 120.9 (−), 119.2 (+), 117.6 (−), 114.2 (−), 113.4 (−), 103.9 (+), 41.0 (+); IR (neat) 1657, 1054, 911, 644; HRMS (EI) calcd for $C_{10}H_7N_2O$ 171.0558, found 171.0555.

2.1.43. 3,4-Dihydro-1*H*-pyrrolo[4,3,2-*de*]quinoline-5-carboxylic acid methyl ester (57). Reaction of **43** (36 mg, 0.15 mmol), Pd(dba)$_2$ (5 mg, 0.01 mmol), dppp (4 mg, 0.01 mmol), and 1,10-phenanthroline monohydrate (3 mg, 0.02 mmol) in DMF (5 mL), as described for **6** (6 atm CO,120 °C, 43.5 h), gave after chromatography (hexanes/EtOAc, 9:1) **57** (10 mg, 0.05 mmol, 33%) as a faint yellow oil. ^{1}H NMR (270 MHz) δ 7.98 (broad s, 1H), 7.36 (broad s, 1H), 7.15 (t, J=7.9 Hz, 1H), 7.5 (d, J=8.1 Hz, 1H), 6.84 (s, 1H), 4.11 (t, J=5.5 Hz, 2H), 3.86 (s, 3H), 3.01 (dt, J=6.3, 1.0 Hz, 2H); ^{13}C NMR (67.5 MHz) δ 155.4 (+), 134.5 (+), 132.7 (+), 123.1 (−), 120.6 (+), 116.9 (−), 110.3 (+), 109.9 (−), 106.0 (−), 52.9 (−), 45.6 (+), 22.9 (+); IR (neat) 1696, 1439, 1385, 1215, 907, 732, 650; GCMS (EI) m/z 216; HRMS (EI) calcd for $C_{12}H_{12}N_2O_2$ 216.0899, found 216.0896.

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Supplementary data

^{1}H NMR and ^{13}C NMR spectra of all new compounds are available.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.02.033

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The geometric isomers of methyl-2,4,6-decatrienoate, including pheromones of at least two species of stink bugs

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Abstract—All eight geometric isomers of methyl 2,4,6-decatrienoate were synthesized from readily accessible starting materials by fully exploiting Wittig-type olefinations, and taking advantage of an easy separation of 2*E* and 2*Z* unsaturated esters. The aggregation pheromone of the brown-winged green bug, *Plautia stali*, methyl (*E*,*E*,*Z*)-2,4,6-decatrienoate (also a cross-attractant for the brown marmorated stink bug, *Halyomorpha halys*), was expediently produced in two easy steps from (*E*)-4,4-dimethoxy-2-butenal in 55% yield. The sex pheromone of the red-shouldered stink bug, *Thyanta pallidovirens*, methyl (*E*,*Z*,*Z*)-2,4,6-decatrienoate, was conveniently synthesized from 2,4-octadiyn-1-ol in 32% yield using in situ manganese dioxide oxidation–Wittig condensation in a key step.
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1. Introduction

2,4,6-Decatrienoic acid does not appear to commonly occur in nature. Mixtures of several geometric isomers esterified with diterpenols and triterpenols have been found in the lattices of several *Euphorbia* plant species,[1–3] with the *E*,*E*,*Z* isomer being perhaps the most abundant. Methyl (*E*,*Z*,*Z*)-2,4,6-decatrienoate (**10**) was identified as a thermally unstable male-produced sex pheromone of the red-shouldered stink bug, *Thyanta pallidovirens*.[3,4] Methyl (*E*,*E*,*Z*)-2,4,6-decatrienoate (**3**) was isolated from males of the brown-winged green bug, *Plautia stali*, and was demonstrated to be responsible for the aggregation of conspecific males and females in orchards.[5] Reports indicated that yet another bug, the brown marmorated stink bug, *Halyomorpha halys*, was cross-attracted to ester **3** in field trials.[6,7] Although the explanation of this cross-attraction is still unknown, the trapping of *H. halys* with ester **3** was of particular interest to us because this invasive bug has recently become established in the Northeast U.S. and poses a potential threat to many commercial crops and ornamental plants.[8] The availability of an attractant for monitoring the spread of *H. halys* in the U.S. would be invaluable to extension and pest management programs.

Our preliminary studies showed that *H. halys* was cross-attracted to not only the *E*,*E*,*Z* ester **3** but also to the *E*,*Z*,*Z* ester **10**, and, importantly, that both esters readily isomerized under daylight to produce primarily mixtures of geometric isomers. The most attractive blend of esters for *H. halys* is yet to be found, so easy access to ester **3** and other isomers is a prerequisite for our future biological studies. Synthesis of ester **3** as an attractant for *P. stali* was patented in Japan[9] and used a partial hydrogenation of methyl (*E*,*E*)-2,4-decadien-6-ynoate with Lindlar catalyst in a key step. Not only was the starting material not readily available, the yield of **3** from the reduction step was only 12%. To our knowledge, the only other reported preparation of ester **3** produced it as a by-product in an unspecified yield.[10] The existing synthesis of ester **10** featured a one-pot double-carbocupration of acetylene with subsequent additon of methylpropiolate and provided the desired compound in 13% yield after reverse phase HPLC purification.[3]

In this paper, we report syntheses of all geometric isomers of methyl 2,4,6-decatrienoate by fully exploiting Wittig-type olefinations. Two stink bug pheromones, **3** and **10**, were conveniently prepared in 55 and 32% yields from easily accessible starting materials, (*E*)-4,4-dimethoxy-2-butenal and 2,4-octadiyn-1-ol, respectively.

2. Results and discussion

2.1. Synthesis of 4*E* isomers

All four isomers with a 4*E* configuration were easily synthesized from the same precursor, (*E*)-4,4-dimethoxy-2-butenal (**1**). The starting material for the preparation of **1**,

Keywords: Methyl 2,4,6-decatrienoate; Geometric isomers; Wittig reaction; Pheromone; *Plautia stali*; *Thyanta pallidovirens*; *Halyomorpha halys*.
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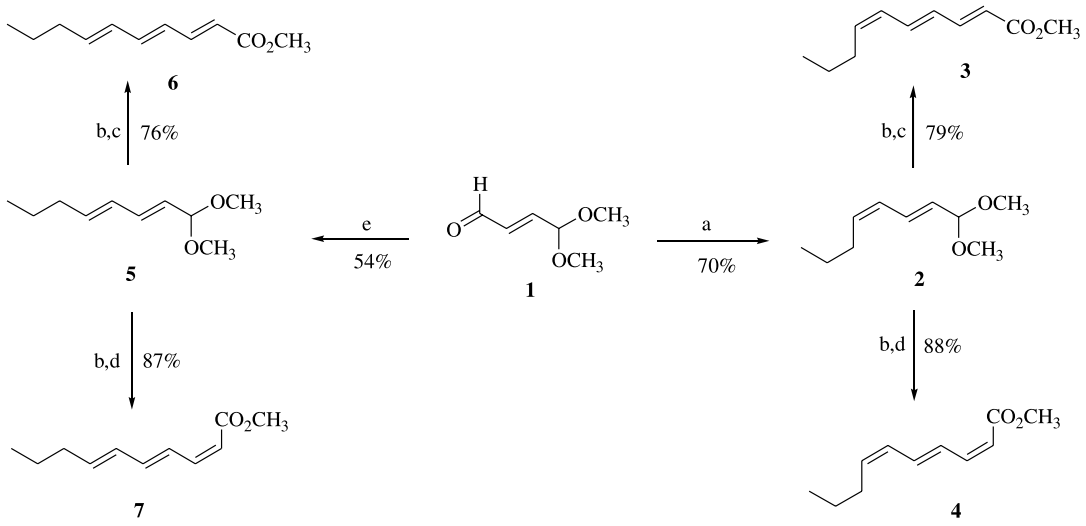


Scheme 1. Reagents and conditions: (a) $(Ph_3PC_4H_9)Br/[(CH_3)_3Si]_2NNa$, −70 °C; (b) PTSA, acetone–H_2O, 0–5 °C; (c) $(CH_3O)_2P(O)CH_2CO_2CH_3$, K_2CO_3–H_2O; (d) $(CF_3CH_2O)_2P(O)CH_2CO_2CH_3/[(CH_3)_3Si]_2NK$, 18-crown-6, −70 °C; (e) $(Ph_3PC_4H_9)Br/2BuLi$, THF.

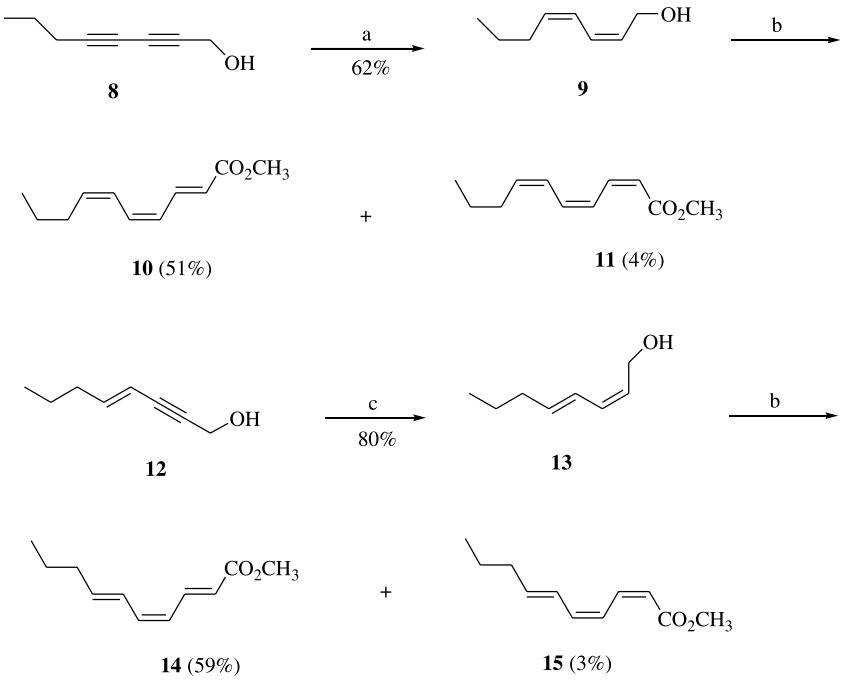
fumaraldehyde bis(dimethylacetal), is commercially available, or can be straightforwardly prepared from furan.[11] Earlier, we used this compound in the syntheses of conjugated dienic insect pheromones using stereoselective Wittig olefination.[12] In fact, this approach has already been applied to make the acetals **2** and **5**,[13] key intermediates in this synthesis. For *cis*-olefination of **1**, we deprotonated *n*-butyltriphenylphosphonium bromide with bis(trimethylsilyl)amide; condensation with **1** provided a 70% yield and a 96:4 ratio of **2** and **5**. *Trans*-olefination of **1** was accomplished by using 2 equiv of butyllithium as the base[14] and gave a 54% yield with a 94:6 ratio of **5**:**2**. Acetals **2** and **5** were deprotected under mild conditions (*p*-TSA, acetone-water, 0–5 °C) to avoid *cis-trans* isomerizations[12,13] and the unsaturatred aldehydes were used in the next steps without purification. A Horner–Wadsworth–Emmons *trans*-olefination with trimethyl phosphonoacetate was employed to convert **2** and **5**, respectively, to esters **3** and **6**. We selected the most straightforward, solvent-free protocol using potassium carbonate in water[15] and obtained a 79% yield for ester **3** (**3**:**6**, 96:4) and 76% yield for **6** (**6**:**3**, 95:5). The condensations were not entirely *trans*-stereoselective, but the minor *cis*-olefination products were successfully separated by flash chromatography on SiO_2. Importantly, the configurations of the existing double bonds in **2** and **5** essentially did not change during the course of the reaction, though we did find it useful to protect the reaction vessels from light to avoid photo-induced isomerizations. Whereas 2*E* olefinic esters could be easily prepared from aldehydes, there are not many procedures to reliably make 2*Z* olefinic esters. We were pleased to find that dienic aldehydes made from acetals **2** and **5** could be converted to esters **4** and **7** with *cis*-stereoselectivity under the modified Horner–Wadsworth–Emmons olefination[16] conditions utilizing electrophilic $(CF_3CH_2O)_2P(O)CH_2COOCH_3$ and a strongly dissociated base system, $KN(TMS)_2$/18-crown-6. The yields of the esters **4** and **7**, after purification from trace amounts of 2*E* esters by flash chromatography, were 88 and 87%, respectively, and the stereochemical purities (% of **7** in **4** and vice versa) 93 and 95%, respectively. Some loss of the geometry (from 96 to 93%) of the 6*Z* double bond in **4** was perhaps due to using a fairly large amount of 18-crown-6 (5 equiv). This could significantly increase the polarity of the medium and promote *cis-trans* isomerizations of the existing double bonds in the aldehyde.[17] Despite this minor limitation, the *cis*-olefination method seems viable for syntheses of **4** and **7** because of high yields and availability of all components (Scheme 1).

2.2. Synthesis of 4*Z* isomers

For syntheses of the isomers with 4*Z* double bonds, we intended to utilize the same strategy that had been successful for 4*E* isomers: that is, to assemble the sensitive trienoic esters in the last step by capitalizing on high yielding stereoselective *cis* and *trans* Horner-Wadsworth–Emmons olefinations. The main challenge of this pathway was the instability of the intermediate 2*Z* dienals, which were expected to be even more labile than *Z*-enals, which are themselves known to undergo rapid isomerizations[18] (Scheme 2).

Octadiyn-1-ol (**8**) was converted to a THP–ether and hydroborated with dicyclohexylborane[19] to furnish, after protonolysis and deprotection, dienol **9** in 62% yield and 99% selectivity. First, we examined a sequential one-pot Swern oxidation–Wittig reaction protocol that has proved useful for unstable aldehydes.[20] The oxidation of dienol **9** was conducted under standard Swern oxidation conditions (see Section 3), followed by the addition of methyl (triphenylphosphoranylidene)acetate to provide esters **10** and **11** which were separated by flash chromatography. Whereas the by-product all-*cis* isomer **11** was sufficiently pure to be fully characterized by ^1H and ^{13}C NMR spectra, ester **10** was significantly (~15%) contaminated with isomer **3**, judged by ^1H NMR (δ 6.84 and 7.35).

We next explored an in situ alcohol oxidation–olefination reaction utilizing manganese dioxide and a stabilized Wittig reagent, which reportedly proceeded without a change of the geometry of a pre-existing *Z* double bond in starting allylic alcohols.[21] Oxidation of **9** with activated MnO_2 was



Scheme 2. Reagents and conditions: (a) DHP, PPTS/dicyclohexylborane/AcOH/MeOH, PPTS; (b) MnO_2, CH_2Cl_2, $(Ph)_3P{=}CHCO_2Me$; (c) Zn(Cu/Ag), MeOH–H_2O.

conducted in the presence of methyl (triphenylphosphoranylidene)acetate in methylene chloride[21] and gave a mixture of esters (70% yield) separated by flash chromatography into individual stereoisomers **10** (51%) and **11** (4%). ^1H and ^{13}C NMR spectra of **10** were in close agreement with literature values.[3] Ester **10** was unstable under GC conditions[3,22] to asses its purity but the ^1H NMR spectrum revealed only traces (total 3–5%) of esters **3** and **14** (δ 6.27). A slight isomerization of 4*Z* or 6*Z* double bonds may have occurred during the course of olefination of the intermediate (*Z*,*Z*)-2,4-octadienal, which appeared to be a limiting step and required a 12 h reaction time at room temperature with 20% excess of the Wittig reagent. (Attempts to invigorate the olefination by increasing the temperature to 40 °C, or using THF instead of CH_2Cl_2, resulted in lower yields and decreased stereochemical purity of ester **10**). Thus, the in situ version of alcohol **9** oxidation–Wittig reaction proved efficient for synthesis of ester **10**, the pheromone of *T. pallidovirens*, because of its simplicity and reasonably good overall yield (32%) from the known diyne alcohol **8**.

The second part of Scheme 2 depicts the syntheses of the remaining two 4*Z* esters **14** and **15**. A CuI/$[(Ph)_3P]_4Pd$ catalyzed condensation[23] of (*E*)-1-iodo-1-pentene[24] with propargyl alcohol provided enynol **12** in 69% yield. Partial *cis*-hydrogenation of **12** was accomplished in 80% yield and >98% stereoselectivity using a Zn(Cu/Ag) reagent that proved handy in the reduction of enynols.[25] Dienol **13** underwent in situ MnO_2 oxidation–Wittig reaction similar to **9** and furnished esters **14** and **15** in 59 and 3% yields, respectively. Ester **15** was 93% pure and was contaminated with esters **7** and **14**, and ester **14** was 96% pure by GC. Despite appearing as a by-product, isomer **15** was sufficiently pure (as was ester **11**) to be fully characterized by ^1H and ^{13}C NMR. Because esters **11** and **15** were not target molecules and will be required as reference compounds in our bioassays, we did not pursue more economical synthetic routes. (An attempted synthesis of **15** by oxidation of **13** with MnO_2 and *cis*-olefination of the crude aldehyde with a fluorinated Horner–Wadsworth–Emmons reagent, as described above, resulted in a product of 88% stereochemical purity).

The structure assignments of the geometric isomers of methyl 2,4,6-decatrienoate were based on the expected ^1H chemical shifts, ^1H–^1H coupling constants, and specifically ^1H–^1H COSY NMR recordings. In general, interactions of vicinal protons across double bonds were of expected values, with J_{cis}=11.0–12.1 Hz, and J_{trans}=14.7–15.5 Hz. Yet, in the *E*,*Z*,*Z* isomer **10**, *cis* coupling constants J_{4-5} and J_{6-7} were anomalously low, 9.4 and 9.1 Hz, respectively.

All stereoisomeric methyl 2,4,6-decatrienoates but one (**10**[3]) survived GC conditions, as judged by the integrity and sharpness of their peaks and a close similarity of their mass spectra in the GC-MS analyses. Besides a strong molecular ion at *m*/*z* 180 (39–71%), they display a notable peak at 149 *m*/*z* (11–26%) apparently due to $(M\text{-}OCH_3)^+$ ion. However, the GC and GC–MS analyses of ester **14** performed at the injection temperature 260 °C showed an additional peak with a significantly shorter retention time but the same molecular ion (180 *m*/*z*) as the main compound, and thus could be misleading in the determination of its purity. However, at lower injection temperatures (e.g., 130 °C) the extra peak (apparently arising from an intramolecular Diels–Alder reaction) was absent. Although we did not pursue methodical photochemical studies, all geometric isomers of methyl 2,4,6-decatrienoates seemed unstable under daylight, not surprising given a strong UV absorption at ~300 nm (see Section 3). Thus, the attractant of *H. halys*, *E*,*E*,*Z*-ester **3**, left unprotected under

room conditions as a hexane solution (1 mg/mL) in a Pyrex vial for two days decreased in purity from 95 to 78%, with *Z*,*E*,*Z*-ester **4** and *E*,*E*,*E*-ester **6** being the main by-products. A similar trend was noticed when rubber septa impregnated with ester **3** were exposed to sunlight. The pheromone of *T. pallidovirens*, *E*,*Z*,*Z*-ester **10**, both in a hexane solution and rubber septa formulations, isomerized in sunlight producing a mixture of geometric isomers, among which esters **3** and **6** were most abundant. The role of esters **3** and **10**, or their combinations with other isomers, in trapping *H. halys* stink bug is under investigation.

3. Experimental

3.1. General

Boiling points are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ with TMS as an internal standard on a Bruker QE-300 spectrometer. Chemical shifts are reported in δ, and J coupling constants in Hz. ^{1}H–^{1}H COSY was used to assign signals of trienoates. GC analyses were performed on a Shimadzu 17A gas chromatograph with a flame ionization detector using a 60 m×0.25 mm RTX-1701 column (Restek Corporation), or a 15 m×0.25 mm DB-5 column (J&W Scientific), and H_2 as carrier gas. Electron impact ionization mass spectra (70 eV) were obtained with an Agilent Technologies 5973 GC-MS equipped with a 30 m× 0.25 mm HP-5MS column. High resolution electron impact mass spectra were measured on a Shimadzu GC-17A coupled with JEOL JMS-SX102A mass spectrometer using a 15 m×0.25 mm OV-5 capillary column (Ohio Valley Specialty Chemicals, Marietta, OH). UV spectra were recorded in hexane on a Shimadzu UV-160 spectrophotometer. Flash chromatography was carried out with 230–400 mesh silica gel (Whatman), and neutral alumina (Brockman Activity I, 60–325 mesh, Fisher Scientific, acetals **2** and **5**). The reagents were purchased from Aldrich Chemical Co. unless otherwise specified. THF was freshly distilled from sodium-benzophenone ketyl under N_2. Methylene chloride and benzene were distilled from P_2O_5. (*E*)-4,4-dimethoxy-2-butenal (**1**) was prepared from (*E*)-1,1,4,4-tetramethoxy-2-butene.[11] Mention of a proprietary company or product does not imply endorsement by the U.S. Department of Agriculture.

3.1.1. (*Z*,*E*)-2,4-Octadienal dimethyl acetal (2). To a suspension of butyltriphenylphosphonium bromide (7.98 g, 20 mmol) in dry THF (30 mL) was added a THF solution of sodium bis(trimethylsilyl)amide (20 mL of 1.0 M, 20 mmol) at −40 °C. The mixture was allowed to warm to room temperature, stirred for 2 h, and then cooled to −75 °C. Aldehyde **1** (2.860 g, 22 mmol) dissolved in dry THF (10 mL) was slowly added while maintaining the temperature between −75 and −65 °C. The resulting mixture was stirred at this temperature for 2 h and warmed to rt. The mixture was poured into ice-water, extracted with hexane/ether, 1:1, and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography with hexanes/ethyl acetate, 95:5, afforded **2** (2.370 g, 70%) consisting of 92% **2**, 3% *E*,*E*-acetal **5** and 3% of the deacetalization product, (*Z*,*E*)-2,4-octadienal. No deacetalization was observed when chromatography was conducted on neutral alumina (Brockman Activity I, 60–325 mesh, Fisher Scientific) as described.[12] MS (*m*/*z*): 170 (M^+, 35), 141 (34), 139 (100), 127 (81), 109 (40), 97 (57), 88 (59), 79 (63), 67 (46), 45 (52). ^{1}H NMR: 0.91 (t, J=7.3 Hz, H-8), 1.41 (sextet, J= 7.3 Hz, H-7), 2.17 (dtd, J=7.3, 7.3, 1.1 Hz, H-6), 3.32 (s, 6H, OCH_3), 4.85 (br d, J=4.9 Hz, H-1), 5.50 (dt, J=10.5, 7.5 Hz, H-5), 5.59 (dd, J=15.6, 4.9 Hz, H-2), 6.00 (br dd, J=11.0, 11.0 Hz, H-4), 6.63 (dd, J=15.5, 11.0 Hz, H-3). The data are a close match with reported values.[13]

3.1.2. (*E*,*E*)-2,4-Octadienal dimethyl acetal (5). To a suspension of butyltriphenylphosphonium bromide (1.197 g, 3 mmol) in dry THF (10 mL) was added butyllithium (1.2 mL, 2.5 M in hexanes, 3 mmol) at −40 °C. The mixture was stirred 2 h at −20 to (−30) °C, cooled to −65 °C, and treated with a solution of aldehyde **1** (390 mg, 3 mmol) in THF (3 mL). After decolorization, the second equivalent of BuLi (1.2 mL) was added at −65 °C, and the dark-brown mixture was allowed to warm to −40 °C. After stirring 1 h, methanol (200 μL) was added and the mixture was poured into water and extracted with hexanes/ether, 1:1. The organic extracts were washed with NH_4Cl solution, water, dried, and concentrated. Flash chromatography on neutral alumina with 2% ethyl acetate in hexanes afforded **5** (276 mg, 54%) of 98% chemical purity and **5**:**2** ratio 94:6. ^{1}H NMR: 0.89 (t, J=7.5 Hz, H-8), 1.41 (sextet, J=7.3 Hz, H-7), 2.06 (br dt, J=6.8, 7.2 Hz, H-6), 3.31 (s, 6H, OCH_3), 4.80 (br d, J=4.9 Hz, H-1), 5.50 (dd, J=15.5, 5.0 Hz, H-2), 5.75 (dt, J=15.1, 6.8 Hz, H-5), 6.04 (br dd, J=15.1, 10.2 Hz, H-4), 6.31 (dd, J=15.5, 10.2 Hz, H-3). The data are in close agreement with those reported.[13]

3.1.3. Methyl (*E*,*E*,*Z*)-2,4,6-decatrienoate (3). Acetal **2** (2.125 g, 12.5 mmol) was stirred with *p*-toluenesulphonic acid monohydrate (47 mg, 0.25 mmol) in a water–acetone (5 mL+13 mL) solution at 0–5 °C. After 0.5 h, dry potassium carbonate (~500 mg) was added to bring the pH to ~9–10. The mixture was evaporated on a rotary evaporator, extracted with hexane/ether, 3:1, dried (Na_2SO_4) for 0.5 h, and concentrated to give crude (*Z*,*E*)-2,4-octadienal (1.570 g). This was added to a mixture of trimethyl phosphonoacetate (3.035 mL, 18.75 mmol), potassium carbonate (4.174 g, 30.2 mmol) and water (3 mL). The mixture was stirred at rt overnight protected from light by wrapping the flask in an aluminum foil. The mixture was diluted with water, extracted with hexanes/ether, 1:1, the organic extract was washed with brine and dried. After evaporation of the solvent, the crude product was purified by flash chromatography with hexanes/ethyl acetate, 95:5. A low-polar fraction (27 mg, 92% *Z*,*E*,*Z*-ester **4**, 6% **7**, and 2% **3**) was isolated followed by the main fraction (1.784 g, 79%), **3**:**6**, 96:4. MS (*m*/*z*): 180 (M^+, 53), 151 (9), 149 (19), 138 (18), 121 (22), 120 (16), 119 (44), 111 (20), 107 (27), 106 (15), 105 (19), 91 (83), 79 (100), 77 (38). ^{1}H NMR: 0.92 (t, J=7.2 Hz, H-10), 1.43 (sextet, J=7.3 Hz, H-9), 2.21 (qd, J=7.4, 1.3 Hz, H-8), 3.73 (s, OCH_3), 5.68 (dt, J=10.6, 8.0 Hz, H-7), 5.86 (d, J=15.5 Hz, H-2), 6.09 (br dd, $J_1 \sim J_2$=11.0 Hz, H-6), 6.28 (dd, J=14.7, 11.4 Hz, H-4), 6.84 (dd, J=14.7, 11.3 Hz, H-5), 7.35 (dd, J=15.1, 11.3 Hz, H-3). ^{13}C NMR: 13.7 (C-10), 22.7 (C-9), 30.1 (C-8), 51.4 (OCH_3), 120.0, 128.1, 129.6, 136.1, 137.6, 145.0

(C-2–C-7), 167.5 (CO_2CH_3). UV: λ_{max} 295 nm (ε 45716). ^{1}H NMR and mass-spectrum of **3** were in a close agreement with reported.[5]

3.1.4. Methyl (*Z,E,Z*)-2,4,6-decatrienoate (4). Bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate (954 mg, 3 mmol), 18-crown-6 (3.96 g, 15 mmol) and dry THF (40 mL) were loaded into the flask, and the mixture was cooled to −70 °C. Potassium bis(trimethylsilyl)amide (6.0 mL, 0.5 M in toluene, 3 mmol) was added, and the pale-yellow suspension was stirred for 15 min at this temperature. Crude (*Z,E*)-2,4-octadienal, prepared from acetal **2** (510 mg, 3 mmol) as described in the previous experiment, was dissolved in 5 mL THF and added to the reaction mixture at −75 °C. The mixture was stirred for 1 h (or until GC analysis showed completion of the reaction) at that temperature, poured into saturated NH_4Cl solution, extracted with ether/hexanes, 1:1, then the organic layer was washed with water, dried, concentrated, and flash chromatographed with hexanes/ethyl acetate, 97:3. (*Z,E,Z*)-ester **4** (473 mg, 88%) containing 7% (*Z,E,E*)-ester **7** was isolated from a low-polar fraction. MS (*m/z*): 180 (M^+, 60), 151 (13), 149 (26), 138 (30), 121 (29), 120 (20), 119 (61), 111 (25), 107 (30), 106 (17), 105 (22), 91 (88), 79 (100), 77 (38). ^{1}H NMR: 0.92 (t, J=7.3 Hz, H-10), 1.43 (sextet, J=7.2 Hz, H-9), 2.22 (br q, J=7.3 Hz, H-8), 3.72 (s, OCH_3), 5.63 (d, J=11.0 Hz, H-2), 5.68 (dt, J=11.0, 7.5 Hz, H-7), 6.18 (br dd, $J_1 \sim J_2$=11.0 Hz, H-6), 6.64 (dd, $J_1 \sim J_2$=11.3 Hz, H-3), 6.78 (dd, J=15.1, 11.4 Hz, H-5), 7.47 (dd, J=15.0, 11.5 Hz, H-4). ^{13}C NMR: 13.7 (C-10), 22.7 (C-9), 30.1 (C-8), 51.1 (OCH_3), 116.3, 128.3, 128.6, 136.9, 137.5, 145.0 (C-2–C-7), 166.9 (CO_2CH_3). UV: λ_{max} 299 nm (ε 37656). HRMS for $C_{11}H_{12}O$ calcd 180.1150, found 180.1153.

3.1.5. Methyl (*E,E,E*)-2,4,6-decatrienoate (6). Acetal **5** (215 mg, 1.26 mmol) was deprotected with *p*-toluenesulphonic acid monohydrate (5 mg) in a mixture of water (2.5 mL) and acetone (6 mL) at 0–5 °C as described for acetal **2**. Crude (*E,E*)-2,4-octadienal (143 mg) was added to a mixture of trimethyl phosphonoacetate (306 μL, 1.9 mmol), potassium carbonate (435 mg, 3.15 mmol) and water (315 μL). The mixture was stirred overnight protected from light, diluted with water, and extracted with hexanes/ether, 1:1. The organic extracts were washed with brine and dried with Na_2SO_4. After evaporation of the solvent, the crude product was purified by flash chromatography with hexanes/ethyl acetate, 95:5, to afford ester **6** (172 mg, 76%) containing 5% **3**. MS (*m/z*): 180 (M^+, 57), 151 (10), 149 (19), 138 (19), 121 (24), 120 (17), 119 (49), 111 (20), 107 (31), 106 (15), 105 (19), 91 (84), 79 (100), 77 (38). ^{1}H NMR: 0.91 (t, J=7.2 Hz, H-10), 1.44 (sextet, J=7.3 Hz, H-9), 2.12 (br q, J=7.1 Hz, H-8), 3.73 (s, OCH_3), 5.83 (d, J=15.5 Hz, H-2), 5.93 (dt, J=15.1, 6.8, H-7), 6.13 (br dd, J=10.6, 15.1 Hz, H-6), 6.20 (dd, J=14.8, 11.3 Hz, H-4), 6.53 (dd, J=14.8, 10.5 Hz, H-5), 7.29 (dd, J=15.5, 11.4 Hz, H-3). ^{13}C NMR: 13.7 (C-10), 22.1 (C-9), 35.0 (C-8), 51.4 (OCH_3), 119.5, 127.7, 129.9, 140.5, 141.3, 145.1 (C-2–C-7), 167.6 (CO_2CH_3). UV: λ_{max} 292 nm (ε 45216). HRMS for $C_{11}H_{12}O$ calcd 180.1150, found 180.1159.

3.1.6. Methyl (*Z,E,E*)-2,4,6-decatrienoate (7). Crude (*E,E*)-2,4-octadienal, prepared from acetal **5** (266 mg, 1.56 mmol) as described in the previous experiment, was dissolved in 5 mL THF and added to a Horner–Wadsworth–Emmons reagent prepared from bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate (332 μL, 1.57 mmol), 18-crown-6 (2.068 g, 7.83 mmol), potassium bis(trimethylsilyl)amide (3.13 mL 0.5 M in toluene, 1.57 mmol), and dry THF (40 mL) as described for ester **4**. The mixture was stirred for 1 h, then worked-up, and flash chromatographed with hexanes/ethyl acetate, 97:3, to provide (*Z,E,E*)-ester **7** (245 mg, 87%) containing 5% ester **4**. MS (*m/z*): 180 (M^+, 39), 151 (7), 149 (17), 138 (18), 121 (19), 119 (44), 107 (28), 91 (82), 79 (100), 77 (37). ^{1}H NMR: 0.91 (t, J=7.4, H-10), 1.43 (sextet, J=7.3 Hz, H-9), 2.12 (br q, J=7.2 Hz, H-8), 3.72 (s, OCH_3), 5.60 (d, J=11.3 Hz, H-2), 5.92 (dt, J=14.8, 7.2 Hz, H-7), 6.21 (dd, J=14.9, 10.8 Hz, H-6), 6.46 (dd, J=14.8, 10.8 Hz, H-5), 6.58 (dd, $J_1 \sim J_2$=11.3 Hz, H-3), 7.40 (dd, J=15.0, 11.8 Hz, H-4). ^{13}C NMR: 13.7 (C-10), 22.1 (C-9), 35.0 (C-8), 51.0 (OCH_3), 115.7, 126.5, 130.4, 140.4, 142.2, 145.2 (C-2–C-7), 167.0 (CO_2CH_3). UV: λ_{max} 297 nm (ε 35521). HRMS for $C_{11}H_{12}O$ calcd 180.1150, found 180.1154.

3.1.7. 2,4-Octadiyn-1-ol (8). 3-Bromo-1-propyn-1-ol was prepared from propargyl alcohol (11.20 g, 0.20 mol) and sodium hypobromide.[26] The crude product was extracted with ether, dried (Na_2SO_4), concentrated under reduced pressure and used in Cadiot–Chodkiewicz[27] condensation without further purification. The reaction flask was charged under N_2 atmosphere with a 30% solution of *n*-$BuNH_2$ (167 mL), cooled to 0–5 °C and CuCl (1.00 g, 10.1 mmol) and NH_2OH hydrochloride (3–4 g) were added. 1-Pentyne (16.32 g, 0.24 mol) was added at once followed by slow addition of 3-bromo-1-propyn-1-ol at 5–15 °C. More NH_2OH hydrochloride was added (total 16.68 g, 0.24 mol) throughout the addition of bromopropynol to prevent the solution from turning blue. The reaction mixture was stirred another 45 min after the addition of bromopropynol, then the layers were separated, and the aqueous phase was extracted with ether. The combined ethereal extracts were washed with NH_4Cl, 3% HCl, brine and dried (Na_2SO_4). After evaporation of the solvent, the crude material was filtered through silica gel aided with hexane/ethyl acetate, 10:1, to give pure 2,4-octadiyn-1-ol (12.51 g, 51% from propargyl alcohol). MS (*m/z*): 122 (M^+, 46), 107 (18), 91 (25), 79 (44), 77 (100), 65 (30), 63 (26), 51 (15), 39 (32). ^{1}H NMR: 0.98 (t, J=7.4 Hz, H-8), 1.55 (sextet, J=7.3 Hz, H-7), 1.83 (OH), 2.25 (t, J=7.2 Hz, H-6), 4.30 (br s, H-1). The data are in close agreement with those reported.[28]

3.1.8. (*Z,Z*)-2,4-Octadien-1-ol (9). Compound **8** (2.44 g, 20.0 mmol) was stirred with 3,4-dihydro-2*H*-pyran (2.52 g, 30.0 mmol) in the presence of pyridinium *p*-toluenesulfonate (503 mg, 2.0 mmol) in a methylene chloride solution (50 mL) at 25 °C for 4 h. Evaporation of the volatiles and subsequent flash chromatography with hexanes/ethyl acetate, 12:1, gave tetrahydro-2-[(2,4-octadiynyl)oxy]-2*H*-pyran (3.74 g, 18.1 mmol, 91% yield). This was dissolved in dry THF (10 mL) and added at −20 °C to a suspension of dicyclohexylborane in THF prepared as follows: Borane–methyl sulfide complex (4.03 mL of 10 M in THF, 40.3 mmol) was added under N_2 atmosphere to dry THF (55 mL) at 0 °C, followed by addition of cyclohexene (8.2 mL, 81 mmol) and stirring for 0.5 h at 5–10 °C and 2 h

at rt. After the addition of the THP ether, the mixture was warmed to rt, stirred for 22 h, quenched with glacial acetic acid (20 mL) at 0 °C, and stirred at rt for 20 h. The solution was cooled to 0 °C and treated with 5 M NaOH (82 mL), then 30% H_2O_2 (10 mL) upon which the temperature went up and was maintained at ~30 °C for 1 h. The mixture was poured into water (100 mL), extracted with hexanes/ether, 1:1, then the combined organic extracts were washed with NH_4Cl solution and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography with hexanes/ethyl acetate, 20:1, afforded (2*Z*,4*Z*)-tetrahydro-2-[(2,4-octadienyl)oxy]-2*H*-pyran (2.889 g, 76%), which was deprotected by heating with pyridinium *p*-toluenesulfonate (340 mg) in methanol (20 mL) at 50–55 °C. The solution was concentrated, dissolved in ether/hexanes, 1:1, washed with brine, dried, and flash chromatographed with pentane/ethyl acetate, 5:2, to yield (*Z*, *Z*)-2,4-octadien-1-ol (1.560 g, 90%; 62% yield from 2,4-octadiyn-1-ol, 99% purity by GC). MS (EI, *m/z*): 126 (M^+, 23), 108 (19), 93 (21), 82 (36), 83 (100), 84 (60), 79 (87), 77 (42), 70 (39), 69 (30), 67 (84), 55 (89). ^{1}H NMR ($CDCl_3$): 0.90 (t, J=7.3 Hz, H-8), 1.40 (sextet, J~7.4 Hz, H-7), 2.15 (br q, J=7.4 Hz, H-6), 4.31 (br d, J=6.8 Hz, H-1), 5.49–5.64 (m, 2H, H-2, H-5), 6.23 (dd, $J_1 \sim J_2$=11.3 Hz, H-3), 6.37 (dd, J=11.7, 10.6 Hz, H-4). ^{13}C NMR (76 MHz, $CDCl_3$): 13.7 (C-8), 22.7 (C-7), 29.4 (C-6), 58.6 (C-1), 122.9, 125.8, 129.1, 134.4 (C-2–C-5). HRMS for $C_8H_{14}O$ calcd 126.1045, found 126.1043.

3.1.9. Methyl (*E*,*Z*,*Z*)-2,4,6-decatrienoate (10) and methyl (*Z*,*Z*,*Z*)-2,4,6-decatrienoate (11). Activated manganese dioxide (Alfa Aesar, technical grade, Ward Hill, MA, 1.74 g, 20 mmol) was added under N_2 to a solution of dienol **9** (252 mg, 2 mmol) and methyl (triphenylphosphoranylidene)acetate (803 mg, 2.4 mmol) in dry methylene chloride (30 mL). The flask was protected from light by wrapping in aluminum foil, and the mixture was stirred for 12 h at 25 °C, or until TLC showed no intermediate aldehyde present. The mixture was filtered through a short pad of Celite under N_2 pressure aided with an additional amount of CH_2Cl_2 (3×10 mL). The filtrate was then concentrated and flash chromatographed with hexanes/CH_2Cl_2, 1:1. A mixture of **10** and **11** (253 mg, 70%) was isolated and carefully re-chromatographed using hexanes/ethyl acetate, 19:1, to first afford ester **11** (13 mg). MS (*m/z*): 180 (M^+, 63), 151 (10), 149 (11), 138 (20), 137 (11), 121 (25), 120 (18), 119 (44), 111 (18), 107 (28), 105 (30), 93 (21), 91 (100), 79 (87), 77 (38). ^{1}H NMR: 0.92 (t, J=7.3 Hz, H-10), 1.43 (sextet, J=7.3 Hz, H-9), 2.22 (br q, H-8), 3.72 (s, OCH3), 5.69 (d, J=11.2 Hz, H-2), 5.72 (m, H-7), 6.55 (dd, $J_1 \sim J_2$=11.3 Hz, H-3), 6.67 (dd, $J_1 \sim J_2$= 11.5 Hz, H-5), 7.10 (dd, J=12.1, 11.3 Hz, H-6), 7.27 (br dd, $J_1 \sim J_2$=11.5 Hz, H-4). ^{13}C NMR: 13.7 (C-10), 22.6 (C-9), 29.7 (C-8), 51.1 (OCH_3), 117.2, 122.7, 123.8, 132.1, 137.5, 138.6 (C-2-C-7), 166.8 (CO_2CH_3). UV: λ_{max} 303 nm (ε 26674). HRMS for $C_{11}H_{12}O$ calcd 180.1150, found 180.1146. Further elution provided a mixture of esters **11** and **10** (25 mg), and finally pure **10** (182 mg, 51%). MS (*m/z*): 180 (M^+, 68), 151 (7), 149 (7), 138 (8), 121 (21), 120 (16), 119 (26), 107 (24), 106 (30), 105 (36), 93 (27), 91 (100), 79 (73), 77 (35). ^{1}H NMR: 0.91 (t, J=7.4 Hz, H-10), 1.43 (sextet, J=7.3 Hz, H-9), 2.21 (br q, J=7.6 Hz, H-8), 3.75 (s, OCH_3), 5.73 (dt, J=9.1, 8.0 Hz, H-7), 5.88 (d, J= 15.2 Hz, H-2), 6.08 (dd, J=11.2, 9.4 Hz, H-4), 6.60 (m, 2H, H-5, H-6), 7.77 (dd, J=15.2, 11.7 Hz, H-3). ^{13}C NMR ($CDCl_3$): 13.7 (C-10), 22.6 (C-9), 29.7 (C-8), 51.5 (OCH_3), 121.1, 123.3, 125.9, 132.1, 137.4, 139.3 (C-2–C-7), 167.5 (CO_2CH_3). ^{1}H and ^{13}C NMR data matched those reported.[3] UV: λ_{max} 299 nm (ε 29214).

3.1.10. Swern oxidation–Wittig reaction of 9. To a stirred solution of oxalyl chloride (214 μL, 2.45 mmol) in CH_2Cl_2 (15 mL) was added methyl sulfoxide (348 μL, 4.95 mmol) at −60 °C. After stirring for 20 min, a solution of alcohol **9** (252 mg, 2 mmol) in CH_2Cl_2 (10 mL) was added. After 20 min, triethylamine (1.393 mL, 10 mmol) was added at −60 °C, and the mixture was allowed to warm to 0 °C. Methyl (triphenylphosphoranylidene)acetate (2.00 g, 6.0 mmol) was added at once and the mixture was stirred at room temperature for 3 h, or until TLC (CH_2Cl_2) showed essentially no intermediate aldehyde present. The mixture was poured into ice-water (30 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were washed with water, dried (Na_2SO_4), concentrated, and chromatographed using hexanes/CH_2Cl_2, 1:1. *Z*,*Z*,*Z*-Isomer **11** (19 mg) was isolated in the first fraction and *E*,*Z*,*Z*-isomer **10** (196 mg) in the most polar fraction. ^{1}H NMR did not reveal any significant impurities in **11**, but it showed 15% contamination of **10** with *E*,*E*,*Z* isomer **3**.

3.1.11. (*E*)-4-Octen-2-yn-1-ol (12). Tetrakis(triphenylphosphine)palladium (3.11 g, 2.0 mmol) was added under N_2 to a solution of (*E*)-1-iodo-1-pentene[23] (7.84 g, 40.0 mmol) in benzene (100 mL). After 45–50 min, a solution of cuprous iodide (1.52 g, 8.0 mmol) and propargyl alcohol (3.36 g, 60.0 mmol) in *n*-butylamine (40 mL) was added over 15–20 min maintaining the temperature 20–25 °C by cooling. The resulting dark-brown mixture was stirred for 2.5 h and poured into sat. NH_4Cl (400 mL) then extracted with ether (200 mL). The organic layer was separated and the aqueous phase was extracted with ether:hexane, 1:1 (3×100 mL). The combined extracts were washed with sat. NH_4Cl, ammonium hydroxide, brine, and dried with sodium sulfate. After evaporation of the solvent, the residue was distilled under vacuum (bp 69–70 °C/0.05 mmHg) to give 4*E*-octen-2-yn-1-ol containing 4–5% of the homo-coupling product, 4,6-decadiene (MS: 138 (M^+, 45), 109 (25), 95 (28), 82 (19), 81 (30), 67 (100), 55 (13), 54 (14). The product was further purified by flash chromatography with hexane/ethyl acetate, 3:1, to give 98% pure **12** (3.482 g, 69%). MS (*m/z*): 124 (M^+, 100), 95 (39), 91 (43), 81 (96), 79 (50), 77 (41), 67 (30), 65 (56), 55 (35). ^{1}H NMR: 0.89 (t, J=7.2 Hz, H-8), 1.41 (sextet, J=7.2 Hz, H-7), 2.07 (br q, J=7.2 Hz, H-6), 4.35 (br s, H-1), 5.48 (dm, H-4), 6.15 (dt, J=15.5, 7.2 Hz, H-5). HRMS for $C_8H_{12}O$ calcd 124.0888, found 124.0888. **12** was described in the literature[29] as a mixture with *Z* isomer.

3.1.12. (*Z*,*E*)-2,4-Octadien-1-ol (13). Alcohol **12** (1.84 g, 14.8 mmol) was reduced with Zn(Cu/Ag) prepared from zinc (29.25 g, 0.447 mol), copper(II) acetate hydrate (2.925 g) and silver nitrate (2.925 g) in methanol at 40–43 °C for 8 h as described.[24] The crude product (1.695 g) was distilled under vacuum to provide >98% pure 2*Z*,4*E*-octadien-1-ol (1.495 g, 80%). Bp 53 °C/0.05 mmHg. MS (*m/z*): 126 (M^+, 32), 108 (16), 93 (14) 91 (14), 84 (51), 83 (100), 82 (29), 79 (65), 77 (33), 70 (36), 69 (28), 67 (72), 55

(83). ^{1}H NMR: 0.90 (t, J=7.4 Hz, H-8), 1.41 (sextet, J=7.3 Hz, H-7), 2.08 (q, H-6), 4.29 (br d, J=6.9 Hz, H-1), 5.48 (dt, J=10.6, 7.1 Hz, H-2), 5.74 (dt, J=14.4, 7.2 Hz, H-5), 6.06 (dd, J_1=J_2=10.7 Hz, H-3), 6.30 (dd, J=14.7, 11.0 Hz, H-4). HRMS for $C_8H_{14}O$ calcd 126.1045, found 126.1041. **13** was described in the literature as a mixture with *Z*,*Z* isomer and characterized by ^{13}C NMR.[29]

3.1.13. Methyl (*E*,*Z*,*E*)-2,4,6-decatrienoate (14) and methyl (*Z*,*Z*,*E*)-2,4,6-decatrienoate (15). Manganese dioxide (3.82 g, 43.9 mmol) was added under N_2 in five portions over 5 h to a solution of dienol **13** (553 mg, 4.39 mmol) and methyl (triphenylphosphoranylidene)acetate (1.91 g, 5.71 mmol) in dry methylene chloride (60 mL). The mixture was stirred for another 16 h at 25 °C and filtered through a short pad of Celite. The filtrate was concentrated and flash chromatographed with hexanes/CH_2Cl_2, 1:1 to afford: *Z*,*Z*,*E* ester **15** (24 mg, 3%), a mixture of **15** and **14** (164 mg) and *E*,*Z*,*E* ester **14** (467 mg, 59%).

Ester **15** was 93% pure by GC and was contaminated with isomers **14** and **7**. Spectral data for **15**: MS (*m*/*z*): 180 (M^+, 71), 151 (13), 149 (14), 138 (27), 137 (15), 121 (29), 119 (70), 111 (25), 107 (37), 91 (100), 79 (87), 77 (36). ^{1}H NMR: 0.91 (t, J=7.3 Hz, H-10), 1.45 (sextet, J=7.4 Hz, H-9), 2.14 (br q, J=6.9 Hz, H-8), 3.72 (s, OCH_3), 5.66 (br d, J=11.7 Hz, H-2), 5.97 (dt, J=15.0, 7.2 Hz, H-7), 6.33 (dd, $J_1 \sim J_2$=11.3 Hz, H-5), 6.58 (dd, J=14.8, 11.3 Hz, H-6), 7.09 (dd, H-3), 7.15 (br dd, H-4). ^{13}C NMR: 13.7 (C-10), 22.2 (C-9), 35.1 (C-8), 51.1 (OCH_3), 116.5, 122.3, 124.9, 137.9, 138.9, 140.7 (C-2–C-7), 166.9 (CO_2CH_3). UV: λ_{max} 298 nm (ε 35197). HRMS for $C_{11}H_{12}O$ calcd 180.1150, found 180.1145.

Isomer **14** was thermally unstable at GC injection temperature 260 °C but at 130 °C showed purity of 96%. MS (*m*/*z*): 180 (M^+, 68), 151 (12), 149 (14), 138 (18), 137 (15), 121 (27), 119 (49), 111 (20), 107 (32), 91 (100), 79 (95), 77 (36). ^{1}H NMR: 0.91 (t, J=7.4 Hz, H-10), 1.44 (sextet, J=7.3 Hz, H-9), 2.16 (br q, J=6.9 Hz, H-8), 3.74 (s, OCH3), 5.84 (d, J=15.1 Hz, H-2), 5.90 (dt, H-7), 5.96 (dd, H-4), 6.27 (dd, $J_1 \sim J_2$=11.2 Hz, H-5), 6.62 (ddm, J=14.7, 11.5 Hz, H-3), 7.74 (ddd, J=15.1, 11.7, 0.8 Hz, H-3). ^{13}C NMR ($CDCl_3$): 13.7 (C-10), 22.2 (C-9), 35.1 (C-8), 51.5 (OCH_3), 120.3, 124.2, 125.5, 137.8, 139.6, 140.6 (C-2–C-7), 167.6 (CO_2CH_3). UV: λ_{max} 296 nm (ε 32984). HRMS for $C_{11}H_{12}O$ calcd 180.1150, found 180.1144.

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Regioselective opening of an oxirane system with trifluoroacetic anhydride. A general method for the synthesis of 2-monoacyl- and 1,3-symmetrical triacylglycerols

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Abstract—A trifluoroacetic anhydride-catalyzed opening of the oxirane system of glycidyl esters with a simultaneous migration of the acyl group provides a new, efficient entry to either 2-monoacylglycerols (2-MAG) or 1,3-symmetrical triglycerides (1,3-STG) as potential prodrug frameworks.

1. Introduction

2-Monoacylglycerols (Fig. 1) have recently attracted research interest as unique carriers of fatty acids through intestinal mucosa,[1,2] as metabolic precursors of structured triglycerides having particular fatty acid residues at 2-position in the glycerol backbone[2] as well as biomolecules of importance to human nutrition.[3] Moreover, it was found[4] that a homologue from the same class of lipid mediators, namely 2-arachidonoylglycerol (2-AG), might be an intrinsic, natural ligand for central and peripheral cannabinoid receptors (CB1 and CB2), which had previously been identified as specific targets for a major psychoactive ingredient of marijuana, δ^9-tetrahydrocannabinol. Other 2-MAG, bearing linoleoyl- or palmitoyl fragments, have been suggested 'entourage' co-factors for enhancing the endogenous cannabinoid potential of 2-AG.[5]

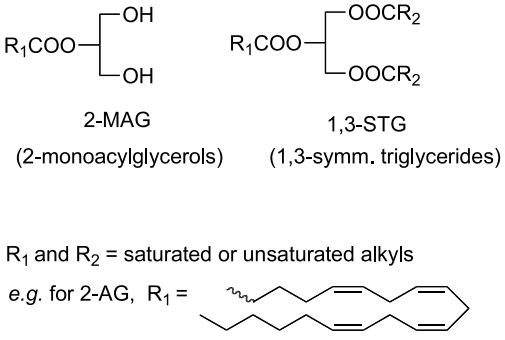

Figure 1. Structures of 2-MAG and 1,3-STG.

Complementary to their dual function as carrier molecules and biological effectors per se, 2-monoacylglycerols could be an attractive alternative of the currently employed 1,3-diacylglycerols as key-intermediates in the rational design of prodrugs representing symmetrically substituted 1,3-diacyl isosters of 2-MAG with requisite pharmaceutical moieties at the incipient glycerol 2-position.[2,6] In view of their resemblance to endogenous triglycerides, such a type of micromolecular vectors have already been used in order to confer various drugs to the metabolic pathways of natural lipids thus achieving therapeutic indices better than those of the starting substances (e.g., higher oral bioavailability, reduced ulcerogenity, first-pass metabolism resistance, etc.).[7] Also, 1,3-symmetrical triglycerides have founding interesting applications (e.g., in enzymatic synthesis of structurally modified lipids,[2] molecular modeling,[8] analytical studies,[9] etc.), but the potential of these conjugates has not been exploited to any significant extent due to unsatisfactory efficacy of the known methods of their preparation (e.g., multistep reaction sequences, lengthy isolation and purification steps, etc.).[9,10]

In spite of high demand for isomerically pure 2-MAG for biological studies or as starting material in the synthesis of

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other lipid derivatives, these compounds are often isolated from natural sources,[11] as chemical[12] and enzymatic methods[13] for their preparations are rather inefficient.

Searching for an alternative methodology that would circumvent shortcomings in the present methods of chemical synthesis of 2-monoacylglycerols, in this paper we describe an efficient and highly regioselective transformation of glycidyl esters **1**–**7** into 2-acyl-1,3-bis(trifluoroacetyl)glycerol derivatives **8**–**14** (Chart 1), from which 2-monoacylglycerols **15**–**21** can be obtained directly without recourse to any additional purification techniques whatsoever.[14] One can also envisage triglycerides **8**–**14** as convenient storage forms of 2-MAG (protection of 1- and 3-hydroxyl groups as trifluoroacetyl esters should prevent scrambling of the acyl moiety) or starting material for the preparation of other lipid mediators, for example, 1,3-STG **22**–**26**.

2. Results and discussion

There are two problems that make synthesis of 2-MAG most difficult. First, due to the presence of two adjacent primary hydroxyl functions, 2-monoacylglycerols show high propensity towards isomerisation (acid, base and heat promoted migration of an acyl group)[15] and this poses severe limitations in the choice of synthetic methods as well as means of their isolation, storage, etc. Secondly, a problem specific to 2-MAG with polyunsaturated systems is the pronounced susceptibility to autoxidation affecting integrity of the corresponding, native olefinic system that further reducing the number of available procedures for their preparation.

In this context, 2-AG is probably the most typical synthetic target to which similar acute complications seem to be inherent. Two chemical methods described in literature for the synthesis of this compound are based on the same chemistry: acylation of suitable 1,3-protected glycerol precursors with an arachidonic acid derivative, followed by deprotection and separation of the isomeric arachidonoylglycerols. In the original method developed by Martin[16] and its two most recent modifications,[12,17] 1,3-benzylideneglycerol is used as a substrate and, after introduction of the arachidonoyl moiety, the acetal group is removed using boric acid derivatives. In the other approach,[18] triisopropylsilyl (TIPS) groups are employed for the protection of 1-and 3-hydroxyl functions of glycerol and their removal from 1,3-bissilyl-2-arachidonoyl intermediate is effected by a prolonged treatment with tetra-*n*-butylammonium fluoride (TBAF) and acetic acid at low temperature. The use of 1,3-dibenzyloxy-2-propanol as starting material and β-chlorocatecholborane as a reagent for cleavage of the benzyl group are the latest improvements which do not affect the core of the same strategy.[19]

One should note that these methods provide only fragmentary solution to synthetic drawbacks, for example, extended reaction time, acidic or basic conditions required for the removal of protecting groups, necessity for an aqueous workup after each synthetic step or separation of the intermediates from the accompanying by-products etc, that have frequently been reported to contribute to isomerisation and oxidative or hydrolytic side-reactions during the synthesis of 2-MAGs. To lessen the problem of acyl migrations, in these synthetic procedures, the deprotection steps were either not taken to completion,[18] or the produced isomeric compounds were separated by various chromatographic techniques.[12,18,19] Although useful in general sense, the above approaches have not been evaluated on substances with other structural variations, and thus scope and generality of these methods are unclear.

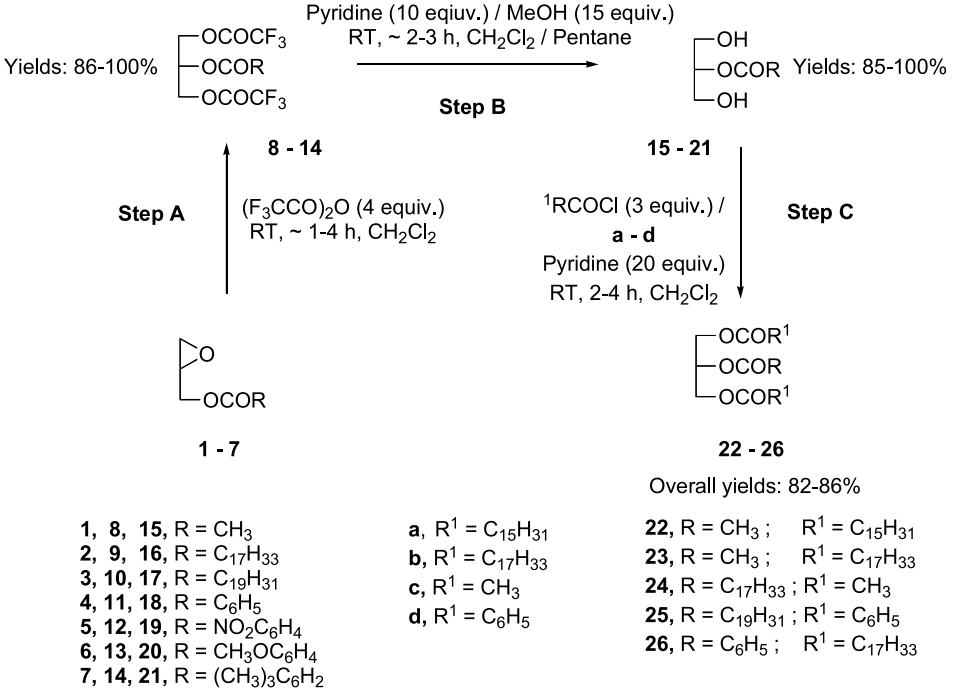


Chart 1.

In these studies, therefore, we adopted another strategy and investigated the regioselectivity of a trifluoroacetic anhydride-catalyzed opening of the oxirane system[14] of glycidyl esters **1**–**7** to produce the corresponding 1,3-bis(trifluoroacetyl)-2-acylglycerols as a novel approach to the synthesis of 2-monoacylglycerols (2-MAG) and also 1,3-symmetrical triglycerides (1,3-STG).

The starting materials were chosen to include model substrates bearing bioactive acyl fragments[4,11,18,20,21] with variable chain length and different degree of unsaturation in the acyl moiety [e.g., 2-(acetyloxymethyl)oxirane **1**, 2-(oleoyloxymethyl)oxirane **2**, and 2-(arachidonoyloxymethyl)oxirane **3**] or aromatic acyl residues with electron-withdrawing and electron-donating groups, and with different steric requirements [e.g., 2-(benzoyloxymethyl)-oxirane **4**, 2-(4-nitrobenzoyloxymethyl)oxirane **5**, and 2-(4-methoxybenzoyloxymethyl)oxirane **6**, and 2-(2,4,6-trimethylbenzoyloxymethyl)-oxirane **7**] (see Chart 1). The choice of palmitoyl **a**, oleoyl **b**, acetyl **c**, and benzoyl **d** chlorides as acylating agents was justified by accessibility of these compounds and their common use in the synthesis of acyl bioconjugates based on glycerol chemistry.[7,21]

At first, the ring-opening of glycidyl esters **1**–**7** with TFAA to produce triacylglycerols **8**–**14** was investigated under various experimental conditions (type of solvents, ratio of reactants, temperature; Chart 1, Step A). The best results were obtained when glycidol derivatives **1**–**7** were allowed to react with TFAA (4 equiv) in CH_2Cl_2 at rt for 1–4 h. The rate of the epoxide opening in **1**–**7** was not appreciably affected by electronic and structural features of the acyl group present and the reactions usually were complete within 1 h. The only exception was 2-(4-nitrobenzoyloxymethyl)oxirane **5** whose conversion to **12** required ca. 4 h. ^1H and ^{13}C NMR analysis revealed that under the investigated reaction conditions the conversion of **1**–**7** to 1,3-bis(trifluoroacetyl)-2-acylglycerols **8**–**14** did not involve any detectable intermediates, and it was quantitative and completely regioselective (>99%). The produced bis(trifluoroacetyl) derivatives **8**–**14** could thus be either directly used for a subsequent reactions, or isolated (~86–96% yields, see Section 3) and stored for several months (−20 °C, under argon) without detectable alterations of their spectral characteristics (^1H and ^{13}C NMR spectroscopy).

Since trifluoroacetate esters are known to undergo smooth transesterification with alcohols,[18] as the next step of this synthetic protocol trifluoroacetyl-conjugates **8**–**14** in pentane–CH_2Cl_2 were treated with methanol (15 equiv) in the presence of pyridine (10 equiv) (Chart 1, Step B). The reaction was quantitative (completion within 2–3 h) and after removal of volatile products via evaporation, isomerically homogenous 2-monoacylglycerols **15**–**21** (purity >99%, ^1H and ^{13}C NMR spectroscopy) were obtained in 85–99% overall yields (calculated on **1**–**7**) without any additional purification.

Due to high purity of the monoacylglycerols **15**–**21** produced, these could be directly used for the acylation to afford 1,3-symmetrical triacylglycerols **22**–**26** (Chart 1, Step C) To this end, 2-monoacylglycerols **15**–**18** in dichloromethane were treated with acyl chlorides **a**–**d** (3 equiv) in the presence of pyridine (20 equiv).

Under these conditions, the acylation proceeded without detectable acyl migration[22] and was complete within 2–4 h to give the target products, triglycerides **22**–**26**, in consistently high overall yields (82–86% after silica gel chromatography, see Section 3).

Regarding a possible mechanism for the regioselective epoxide opening, some additional observations are pertinent. Thus, in preliminary model experiments it was established that in methylene chloride at rt other carboxylic anhydrides (e.g., acetic-, benzoic anhydride, etc) were completely unreactive and only trichloroacetic anhydride could act in a similar way as TFAA to give regioselectively the isosteric 1,3-bis(trichloroacetates), although in a significantly slower reaction (ca. 24 h for the completion). The use of trifluoroacetic acid alone afforded variable proportions of 1-acyl- and 2-acyl glycerols under the same conditions. Additional studies (Table 1) revealed that the oxirane system became extremely resistant towards TFAA when the acyl group was replaced by an alkyl one (entry 1). Synthons from the traditional pool of acylated glycerol acetals (e.g., entries 2 and 3) remained unaffected under the same conditions, as well.

In all instances where mixtures of TFAA with up to three equivalent excess of non-halogenated carboxylic acids or carboxylic anhydrides were used, 1,3-bis(trifluoroacetyl)-2-acylglycerols were still formed as the only products of the reaction (e.g., entries 4 and 5).

Organic bases were shown to completely inhibit the epoxide opening, irrespective of their potential to act as nucleophiles or base catalysts, despite the presence of excess TFAA in the reaction mixtures (entries 6, 8–10). All these reactions could be rescued by the addition of trifluoroacetic acid providing the expected products (entry 7). A similar effect was observed for the reaction using tetrabutylammonium trifluoroacetate with TFAA (entry 11).

These data are consistent with a mechanism depicted in Scheme 1, which involves initial coordination of the epoxide oxygen by a strongly electrophilic TFAA, followed by the opening of the activated oxirane ring via an intramolecular attack of the adjacent carbonyl group to form cyclic acyliumglycerol cation **A**. This is apparently the rate-determining step of the reaction as opening of the oxirane ring does not occur under these conditions without assistance of the neighbouring carbonyl group. The produced acylium ion **A** then collapses in a fast reaction to the corresponding 1,3-bis(trifluoroacetyl)-2-acylglycerol by a regioselective attack of a trifluoroacetate ion on the primary carbon atom of the dioxolane ring.

A mechanism by which amines inhibit this reaction is not clear. It is possible that acid catalysis by traces of trifluoroacetic acid most likely present in the reaction mixture is essential for the formation of cyclic intermediate **A**, for example, to facilitate the departure of trifluoroacetoxy group during opening of the oxirane ring. An

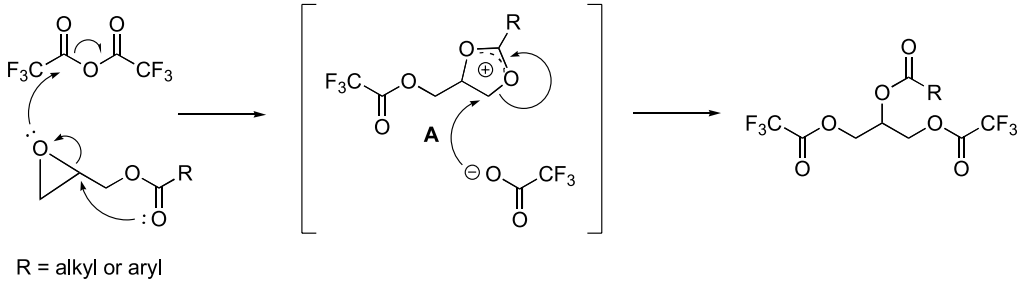
Table 1. Mechanistic studies

No.	Reaction conditions: methylene chloride, rt	Reaction time (remarks)
1.	TFAA (4.0 eq) → No reaction	rt/24 h
2.	TFAA (4.0 eq) → No reaction	rt/24 h
3.	TFAA (4.0 eq) → No reaction	rt/24 h
4.	TFAA (4.0 eq), ^{1}RCOOH (3.0 eq)	rt/∼4 h (quantitative yield)
5.	TFAA (4.0 eq), (^{1}RCO)$_2$O (4.0 eq)	rt/∼4 h (quantitative yield)
6.	Py (1.0 eq) / TFAA (4.0 eq) → No reaction	80 °C/∼4 h
7.	Py (1.0 eq) / TFAA (4.0 eq) / F_3CCOOH / (2.0 eq)	rt/∼4 h (quantitative yield)
8.	2,6-Lutidine (1.0 eq) / TFAA (4.0 eq) → No reaction	rt/24 h
9.	Bu_3N (2.0 eq) / TFAA (4.0 eq) / F_3CCOOH / (2.0 eq) → No reaction	rt/24 h
10.	$Bu_4N(TFA^-)$ (2.0 eq) / TFAA (4.0 eq) → No reaction	rt/24 h
11.	$Bu_4N(TFA^-)$ (2.0 eq) / TFAA (4.0 eq) / F_3CCOOH / (2.0 eq)	rt/∼4 h (quantitative yield)

R=$C_{16}H_{33}$; RCO=oleoyl; ^{1}RCO=Acetyl, benzoyl, etc. TFA^-=F_3CCOO^-; TFAA=$(F_3CCO)_2O$; Py=pyridine.

alternative scenario could be that due to increased acylating properties of TFAA in the presence of bases, the carbonyl function of the ester group is acylated and thus converted into tetrahedral species that cannot provide an intramolecular nucleophilic assistance necessary for the opening of the oxirane ring. Elucidation of these mechanistic aspects needs further studies.

In conclusion, we have developed an efficient synthetic strategy based on a novel, regioselective transformation of glycidyl esters **1**–**7** into 2-acyl-1,3-bis(trifluoroacetyl)-glycerols **8**–**14**, from which 2-monoacylglycerols **15**–**21** can be retrieved under mild conditions. The main features of this new synthetic protocol are: (i) highly effective and practically quantitative, one-pot synthesis of



Scheme 1.

2-monoacylglycerols **15–21** under mild reaction conditions; (ii) the produced compounds **8–14** and **15–21** are of high purity, which alleviates problems of their additional purification, and thus the extent of acyl migration (and of other side-reactions) is minimized; (iii) 2-acyl-1,3-bis(trifluoroacetyl)glycerols **8–14** can be envisaged either as convenient storage forms of 2-MAG or prospective prodrug frameworks for this class of lipid mediators; (iv) the general strategy also introduces 2-monoacylglycerols as common intermediates in the direct synthesis of prodrug isosters that typically represent triglycerides 1,3-STG (e.g., **22–26**); (v) the method makes use of commercially available reactants and it is easy to scale-up.

3. Experimental

3.1. General

All reagents were commercial grade (Fluka, Lancaster, Merck, Sigma) with purity >98% and were used as provided without further purification. Solvents were dried and distilled prior to use according to standard protocols.[23] Reaction conditions were kept strictly anhydrous.

Column chromatography (CC) was carried out on silica gel 60 (70–230 mesh ASTM, Merck) using the following mobile phases: system A, pentane–toluene–ethyl acetate (40:50:10, v/v/v); system B, pentane–toluene–ethyl acetate (30:20:50, v/v/v); system C, pentane–ethyl acetate (90:10, v/v); system D, dichloromethane–methanol (90:10, v/v); system E, pentane–toluene–ethyl acetate (60:35:5, v/v/v); system F, pentane–ethyl acetate (70:30, v/v). Progress of the reactions was monitored by analytical thin-layer chromatography (TLC) on pre-coated glass plates of silica gel 60 F_{254} (Merck) using the same solvent systems as for CC. The spots were visualized using the commercially available 3.5% molybdatophosphoric acid spray reagent (Merck) or 50% sulphuric acid followed by heating at 140 °C.

^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 MHz machine and chemical shifts are reported in ppm relative to TMS. The assignment of proton and carbon resonances of **1–26** was done on the basis of known or expected chemical shifts in conjunction with ^{1}H–^{1}H, ^{1}H–^{13}C, and DEPT correlated NMR spectroscopy. The melting points were determined on a Kofler melting point apparatus and are uncorrected.

Glycidyl esters **1–7** (see below), were obtained in one step from (±)-glycidol (Fluka) and appropriate acyl-donors (e.g., free fatty acids, fatty acid anhydrides, or acyl chlorides), in 74–95% yields as described elsewhere[14] or analogously to conventional approaches.[18,24] No attempts were made to optimize these particular procedures.

3.1.1. 2-(Acetyloxymethyl)oxirane (1). To a solution of (±)-glycidol (3.7 g; 50 mmol) and 4-dimethylaminopyridine (4-DMAP, 6.1 g; 50 mmol) in CH_2Cl_2 (15 mL) at rt was added acetic anhydride (6.1 g; 60 mmol). After 12 h, the solution was passed through a silica gel pad (~5 g) prepared in CH_2Cl_2. The support was washed with CH_2Cl_2 (150 mL) and the solvent evaporated in vacuo. Purification of the crude product by flash chromatography (CH_2Cl_2) gave the title compound **1** (4.3 g, 74%) as a colorless oil. [Found: C, 51.66; H, 7.00. $C_5H_8O_3$ (116.11) requires C, 51.72; H, 6.94%]; R_f (system A)=0.39; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 4.37 (1H, dd, J=2.9, 2.9 Hz, $OCH_2CHCH_aH_bOCO$); 3.87 (1H, dd, J=6.6, 6.2 Hz, $OCH_2CHCH_aH_bOCO$); 3.17 (1H, m, $C(O)CH_2CHCH_2O$); 2.81 (1H, t, J=4.4 Hz, $C(O)CH_2CHCH_aH_bO$); 2.61 (1H, dd, J=2.6, 2.6 Hz, $C(O)CH_2CHCH_aH_bO$); 2.06 (3H, s, 2-CH_3); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 170.88 (C1); 20.90 (C2): acetyl fragment; 65.20 (C3); 49.48 (C2); 44.82 (C1): oxirane-2-methyl fragment.

3.1.2. 2-(Oleoyloxymethyl)oxirane (2). To a solution of (±)-glycidol (1.1 g; 15 mmol) and 4-DMAP (2.2 g; 18 mmol) in CH_2Cl_2 (15 mL) at rt was added oleoyl chloride (5.4 g; 18 mmol). After 4 h, the solution was passed through a silica gel pad (~5 g) prepared in CH_2Cl_2. The support was washed with CH_2Cl_2 (150 mL) and the solvent evaporated in vacuo. Purification of the crude product by flash chromatography (toluene) gave the title compound **2** (4.4 g, 86%) as a colorless oil. [Found: C, 74.58; H, 11.28. $C_{21}H_{38}O_3$ (338.52) requires C, 74.51; H, 11.31%]; R_f (system C)=0.52; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 5.34 (2H, m, CH=CH); 4.40 (1H, dd, J=2.9, 2.9 Hz, $OCH_2CHCH_aH_bOCO$); 3.91 (1H, dd, J=5.9, 6.2 Hz, $OCH_2CHCH_aH_bOCO$); 3.20 (1H, m, $C(O)CH_2CHCH_2O$); 2.84 (1H, dd, J=4.0, 4.4 Hz, $C(O)CH_2CHCH_aH_bO$); 2.63 (1H, dd, J=2.6, 2.6 Hz, $C(O)CH_2CHCH_aH_bO$); 2.34 (2H, t, J=7.3 Hz, 2-CH_2); 2.01 (4H, m, 8-CH_2, 11-CH_2); 1.63 (2H, m, 3-CH_2); 1.30 (20H, m, 4-7-CH_2, 12-17-CH_2); 0.87 (t, J=7.0 Hz, 18-CH_3, 3H); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 173.73 (C1); 129.95 and 130.23 (C9 andC10); 34.28 (C2); 32.12 (C16); 29.30–29.98 (C4-C7, C12-C15); 27.38 and 27.43 (C11 and C8); 25.08 (C3); 22.90 (C17); 14.32 (C18): oleoyl fragment; 64.97 (C3); 49.60 (C2); 44.88 (C1): oxirane-2-methyl fragment.

3.1.3. 2-(Arachidonoyloxymethyl)oxirane (3). To a solution of (±)-glycidol (0.22 g; 3.0 mmol), 4-DMAP (0.49 g; 4.0 mmol) and arachidonic acid (1.22 g; 4.0 mmol) in CH_2Cl_2 (15 mL) at rt was added *N*,*N*′-dicyclohexylcarbodiimide (DCC, 0.82 g; 4.0 mmol) and the reaction system was stirred under these conditions for 12 h. After filtration, the solution was passed through a silica gel pad (~5 g) prepared in CH_2Cl_2. The support was washed with CH_2Cl_2 (150 mL) and the solvent evaporated under reduced pressure. Purification of the crude product by flash chromatography (system C) afforded the target compound **3** (1.03 g, 95%) as a yellowish oil. [Found: C, 76.70; H, 10.04. $C_{23}H_{36}O_3$ (360.54) requires C, 76.62; H, 10.06%]; R_f (system C)=0.33; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 5.36 (8H, m, CH=CH); 4.40 (1H, dd, J=3.3, 2.9 Hz, $OCH_2CHCH_aH_bOCO$); 3.91 (1H, dd, J=6.2, 6.2 Hz, $OCH_2CHCH_aH_bOCO$); 3.19 (1H, m, $C(O)CH_2CHCH_2O$); 2.82 (7H, m, 7, 10, 13-CH_2, $C(O)CH_2$-$CHCH_aH_bO$); 2.64 (1H, dd, J=2.6, 2.6 Hz, $C(O)CH_2$-$CHCH_aH_bO$); 2.36 (2H, t, J=7.5 Hz, 2-CH_2); 2.11, 2.05 (4H, m, 16-CH_2, 4-CH_2); 1.71 (2H, p, J=7.5 Hz, 3-CH_2); 1.31 (6H, m, 17-19-CH_2); 0.88 (3H, t, J=6.8 Hz, 20-CH_3); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 173.47 (C1); 130.71, 129.19, 129.04, 128.80, 128.45, 128.35, 128.07 and

127.76 (C5-6, C8-9, C11-12, C14-15); 33.62 (C2); 31.73 (C17); 29.54 (C18); 27.43 (C4); 26.73 (C16); 25.83 (C7, C10, C13); 24.91 (C3); 22.78 (C19); 14.28 (C20): arachidonoyl fragment; 65.05 (C3); 49.56 (C2); 44.87 (C1): oxirane-2-methyl fragment.

3.1.4. 2-(Benzoyloxymethyl)oxirane (4). Obtained from (±)-glycidol (1.1 g; 15 mmol), 4-DMAP (2.2 g; 18 mmol) and benzoyl chloride (2.5 g; 18 mmol) at rt (reaction time: 4 h) and then purified (system C) in the same way as described for **2**. Yield: 2.3 g (85%, colorless oil). [Found: C, 67.50; H, 5.70. $C_{10}H_{10}O_3$ (178.19) requires C, 67.41; H, 5.66%]; R_f (system C)=0.34; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 8.06 (2H, m, Aryl); 7.57 (1H, m, Aryl); 7.44 (2H, m, Aryl); 4.65 (1H, dd, J=2.9, 2.9 Hz, $OCH_2CHCH_aH_b$-OCO); 4.17 (1H, dd, J=6.2, 6.2 Hz, $OCH_2CHCH_aH_b$-OCO); 3.34 (1H, m, C(O)CH_2CHCH_2O); 2.89 (1H, dd, J=4.0, 4.4 Hz, C(O)$CH_2CHCH_aH_bO$); 2.73 (1H, dd, J=2.6, 2.6 Hz, C(O)$CH_2CHCH_aH_bO$); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 166.48 (–C(O)O); 133.44 (C4); 129.97 (C2, C6); 129.89 (C1); 128.64 (C3 and C5): benzoyl fragment; 65.66 (C3); 49.70 (C2); 44.92 (C1): oxirane-2-methyl fragment.

3.1.5. 2-(4-Nitrobenzoyloxymethyl)oxirane (5). Obtained from (±)-glycidol (1.1 g; 15 mmol), 4-DMAP (2.2 g; 18 mmol) and 4-nitrobenzoyl chloride (3.3 g; 18 mmol) at rt (reaction time: 5 h) and then purified (system F) as described for **2** and **4**. Yield: 2.8 g (85%, yellowish crystals, mp 60.3–61.9 °C, from system F; a commercial sample from Fluka: mp 59.9–62 °C). [Found: C, 53.75; H, 3.97; N, 6.19. $C_{10}H_9NO_5$ (223.18) requires C, 53.82; H, 4.06; N, 6.28%]; R_f (system F)=0.42; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 8.28 (4H, m, Aryl); 4.74 (1H, dd, J=2.6, 2.9 Hz, $OCH_2CHCH_aH_bOCO$); 4.18 (1H, dd, J=6.6, 6.6 Hz, $OCH_2CHCH_aH_bOCO$); 3.37 (1H, m, C(O)CH_2-$CHCH_2O$); 2.93 (1H, t, J=4.4 Hz, C(O)$CH_2CHCH_aH_bO$); 2.74 (1H, dd, J=2.9, 2.6 Hz, C(O)$CH_2CHCH_aH_bO$); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 164.63 (–C(O)O); 150.92 (C4); 135.22 (C1); 131.15 (C2, C6); 123.85 (C3 and C5): 4-nitrobenzoyl fragment; 66.70 (C3); 49.43 (C2); 44.91 (C1): oxirane-2-methyl fragment.

3.1.6. 2-(4-Methoxybenzoyloxymethyl)oxirane (6). Obtained from (±)-glycidol (1.5 g; 20 mmol), 4-DMAP (2.9 g; 24 mmol) and 4-methoxybenzoyl chloride (4.1 g; 24 mmol) at rt (reaction time: 6 h) and purified (system F) identically as described for **5**. Yield: 3.5 g (83%, colorless oil). [Found: C, 63.55; H, 5.75. $C_{11}H_{12}O_4$ (208.21) requires C, 63.45; H, 5.81%]; R_f (system F)=0.51; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 8.01 (2H, m, Aryl); 6.90 (2H, m, Aryl); 4.62 (1H, dd, J=2.9, 2.9 Hz, $OCH_2CHCH_aH_bOCO$); 4.12 (1H, dd, J=6.2, 6.2 Hz, $OCH_2CHCH_aH_bOCO$); 3.85 (3H, s, CH_3O); 3.32 (1H, m, C(O)CH_2CHCH_2O); 2.88 (1H, dd, J=4.0, 4.4 Hz, C(O)$CH_2CHCH_aH_bO$); 2.71 (1H, dd, J=2.6, 2.6 Hz, C(O)$CH_2CHCH_aH_bO$, 1); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 166.23 (–C(O)O); 163.78 (C4); 132.03 (C2 and C6); 122.24 (C1); 113.89 (C3 and C5); 55.67 (4-OCH_3): 4-methoxybenzoyl fragment; 65.39 (C3); 49.83 (C2); 44.94 (C1): oxirane-2-methyl fragment.

3.1.7. 2-(2,4,6-Trimethylbenzoyloxymethyl)oxirane (7). Obtained from (±)-glycidol (1.5 g; 20 mmol), 4-DMAP (3.7 g; 30 mmol), 2,4,6-trimethylbenzoic acid (4.9 g; 30 mmol) and DCC (6.2 g; 30 mmol) at rt (reaction time: 24 h) and purified (system C) as described for **3**. Yield: 3.6 g (82%, colorless oil). [Found: C, 70.95; H, 7.40. $C_{13}H_{16}O_3$ (220.26) requires C, 70.89; H, 7.32%]; R_f (system C)=0.31; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 6.86 (2H, s, Aryl); 4.63 (1H, dd, J=3.3, 3.3 Hz, $OCH_2CHCH_aH_bOCO$); 4.15 (1H, dd, J=6.2, 6.6 Hz, $OCH_2CHCH_aH_bOCO$); 3.32 (1H, m, C(O)CH_2CHCH_2O); 2.88 (1H, dd, J=4.4, 4.7 Hz, C(O)$CH_2CHCH_aH_bO$); 2.71 (1H, dd, J=2.6, 2.6 Hz, C(O)$CH_2CHCH_aH_bO$); 2.32 (6H, s, 2-CH_3, 6-CH_3); 2.28 (3H, s, 4-CH_3); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 169.94 (–C(O)O); 139.83 (C4); 135.61 (C2 and C6); 130.49 (C1); 128.73 (C3 and C5); 21.37 (4-CH_3); 20.11 (2-CH_3 and 6-CH_3): 2,4,6-trimethylbenzoyl fragment; 65.39 (C3); 49.83 (C2); 44.94 (C1): oxirane-2-methyl fragment.

3.2. General procedure for the preparation of 2-acyl-1,3-bis(trifluoroacetyl)glycerols 8–14 (step A)

To a solution of a glycidyl ester **1–7** (1.00 mmol), in dichloromethane (3.0 mL), trifluoroacetic anhydride (TFAA, 4.00 mmol), in CH_2Cl_2 (3.0 mL), was added at −20 °C, and the reaction mixture was kept at rt for 1–4 h. The solvent and unreacted TFAA were removed under reduced pressure (bath temperature 40–60 °C). Traces of TFAA were removed by co-evaporation with toluene (3× 25 mL) under the same conditions and the residue was kept under vacuum at rt for 2 h to give the target compound **8–14**, in practically quantitative yield.

If necessary, the thus obtained intermediate could additionally be purified by flash, solid-phase filtration through a silica gel pad (~ 5 g) utilizing an appropriate eluant (e.g., toluene or dichloromethane).

3.2.1. 2-Acetyl-1,3-bis(trifluoroacetyl)glycerol (8). Obtained from 2-(acetyloxymethyl)oxirane (**1**; 0.116 g; 1.00 mmol) and trifluoroacetic anhydride (0.840 g; 4.00 mmol) according to the above general procedure. After 1 h, solid-phase filtration using dichloromethane as eluant gave **8** as a colorless oil (0.280 g, 86%). [Found: C, 33.20; H, 2.50. $C_9H_8O_6F_6$ (326.15) requires C, 33.14; H, 2.47%]; R_f (system C)=0.45; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 5.40 (1H, m, CH_2CHCH_2); 4.63 (2H, dd, J=4.4, 4.0 Hz, C(O)$OCH_bH_aCHCH_aH_bOCO$); 4.46 (2H, dd, J=5.5, 5.5 Hz, C(O)$OCH_bH_aCHCH_aH_bOCO$); 2.10 (3H, s, 2-CH_3); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 170.07 (C1); 20.62 (C2): acetyl fragment; 157.19 (C1, q, J=43.5 Hz); 114.49 (C2, q, J=285.3 Hz): trifluoroacetyl fragment; 67.45 (C2); 64.86 (C1, C3): glycerol fragment.

3.2.2. 2-Oleoyl-1,3-bis(trifluoroacetyl)glycerol (9). Obtained by reacting 2-(oleyloxymethyl)oxirane (**2**; 0.169 g; 0.50 mmol) and trifluoroacetic anhydride (0.420 g; 2.00 mmol) for 1 h. Solvents were evaporated in vacuo to give **9** as a yellowish/colorless oil (0.274 g, 100%). [Found: C, 54.62; H, 7.00. $C_{25}H_{38}O_6F_6$ (548.57) requires C, 54.74; H, 6.98%]; R_f (system A)=0.59; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 5.41 (1H, m, OCH_2CHOCO); 5.34 (2H, m, $CH{=}CH$); 4.63 (2H, dd, J=4.0, 4.4 Hz, C(O)$OCH_bH_aCHCH_aH_bOCO$); 4.46 (2H, dd, J=5.5, 5.5 Hz, C(O)$OCH_bH_aCHCH_aH_bOCO$); 2.34 (2H, t,

J=7.3 Hz, 2-CH_2); 2.00 (4H, m, 8-CH_2, 11-CH_2); 1.62 (2H, m, 3-CH_2); 1.30 (20H, m, 4-7-CH_2, 12-17-CH_2); 0.88 (3H, t, J=6.6 Hz, 18-CH_3); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 172.72 (C1); 130.25 and 129.90 (C9 and C10); 34.06 (C2); 32.12 (C16); 29.14–29.98 (C4-C7, C12-C15); 27.42 and 27.36 (C11 and C8); 24.87 (C3); 22.89 (C17); 14.30 (C18): oleoyl fragment; 157.18 (C1, q, J=43.5 Hz); 114.51 (C2, q, J=285.3 Hz): trifluoroacetyl fragment; 67.15 (C2); 64.94 (C1, C3): glycerol fragment.

3.2.3. 2-Arachidonoyl-1,3-bis(trifluoroacetyl)glycerol (10). Obtained from 2-(arachidonyloxymethyl)oxirane (**3**; 0.180 g; 0.50 mmol) and trifluoroacetic anhydride (0.420 g; 2.00 mmol) for 1 h. Evaporation of solvents followed by solid-phase filtration (toluene) afforded **10** as a yellowish oil (0.267 g, 94%). [Found: C, 56.93; H, 6.30. $C_{27}H_{36}O_6F_6$ (570.57) requires C, 56.84; H, 6.36%]; R_f (system A)=0.57; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 5.36 (9H, m, CH=CH, CH_2CHCH_2); 4.63 (2H, dd, J=4.2, 4.4 Hz, C(O)OCH_bH$_a$CHCH$_a$H$_b$OCO); 4.46 (2H, dd, J=5.5, 5.5 Hz, C(O)OCH$_b$H$_a$CHCH$_a$H$_b$OCO); 2.81 (6H, m, 7, 10, 13-CH_2); 2.36 (2H, t, J=7.5 Hz, 2-CH_2); 2.12, 2.05 (4H, m, 16-CH_2, 4-CH_2, 4H); 1.70 (2H, p, J=7.3 Hz, 3-CH_2); 1.31 (6H, m, 17-19-CH_2); 0.89 (3H, t, J=6.9 Hz, 20-CH_3); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 172.51 (C1); 130.72, 129.44, 128.83, 128.68, 128.54, 128.22, 128.03 and 127.73 (C5-6, C8-9, C11-12, C14-15); 33.41 (C2); 31.73 (C17); 29.53 (C18); 27.43 (C4); 26.57 (C16); 25.81 (C7, C10, C13); 24.70 (C3); 22.78 (C19); 14.26 (C20): arachidonoyl fragment; 157.17 (C1, q, J=43.5 Hz); 114.50 (C2, q, J=285.3 Hz): trifluoroacetyl fragment; 67.22 (C2); 64.92 (C1, C3): glycerol fragment.

3.2.4. 2-Benzoyl-1,3-bis(trifluoroacetyl)glycerol (11). Obtained by reacting 2-(benzyloxymethyl)oxirane (**4**; 0.089 g; 0.50 mmol) and trifluoroacetic anhydride (0.420 g; 2.00 mmol) for 1 h. Solvents were removed under reduced pressure to give **11** as a colorless oil (0.194 g, 100%). [Found: C, 43.43; H, 2.60. $C_{14}H_{10}O_6F_6$ (388.22) requires C, 43.31; H, 2.60%]; R_f (system A)=0.55; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 8.00 (2H, m, Aryl); 7.60 (1H, m, Aryl); 7.47 (2H, m, Aryl); 5.66 (1H, m, CH_2CHCH_2); 4.75 (2H, dd, J=4.4, 4.4 Hz, C(O)OCH_bH$_a$-CHCH$_a$H$_b$OCO); 4.63 (2H, dd, J=5.1, 5.3 Hz, C(O)OCH$_b$-H$_a$CHCH$_a$H$_b$OCO); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 165.44 (–C(O)O); 134.16 (C4); 130.05 (C2, C6); 128.88 (C3 and C5); 128.66 (C1): benzoyl fragment; 157.22 (C1, q, J=43.5 Hz); 114.52 (C2, q, J=285.3 Hz): trifluoroacetyl fragment; 67.92 (C2); 64.97 (C1, C3): glycerol fragment.

3.2.5. 2-(4-Nitrobenzoyl)-1,3-bis(trifluoroacetyl)glycerol (12). Obtained from 2-(4-nitrobenzyloxymethyl)oxirane (**5**; 0.112 g; 0.50 mmol) and trifluoroacetic anhydride (0.420 g; 2.00 mmol) for 4 h. Solid-phase filtration using dichloromethane as eluant gave **12** (0.187 g, 86%) as yellowish crystals, mp 104.9 - 105.8 °C (from CH_2Cl_2). [Found: C, 39.00; H, 2.05; N, 3.23. $C_{14}H_9NO_8F_6$ (433.22) requires C, 38.82; H, 2.09; N, 3.23%]; R_f (system A)=0.44; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 8.30 (2H, m, Aryl); 8.20 (2H, m, Aryl); 5.69 (1H, m, CH_2CHCH_2); 4.79 (2H, dd, J=4.2, 4.2 Hz, C(O)OCH_bH$_a$CHCH$_a$H$_b$OCO); 4.65 (2H, dd, J=5.5, 5.3 Hz, C(O)OCH$_b$H$_a$CHCH$_a$H$_b$OCO); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 163.73 (–C(O)O); 151.28 (C4); 133.92 (C1); 131.22 (C2 and C6); 124.08 (C3 and C5): 4-nitrobenzoyl fragment; 157.21 (C1, q, J=44.2 Hz); 114.46 (C2, q, J=285.3 Hz): trifluoroacetyl fragment; 69.02 (C2); 64.77 (C1, C3): glycerol fragment.

3.2.6. 2-(4-Methoxybenzoyl)-1,3-bis(trifluoroacetyl)glycerol (13). Obtained from 2-(4-methoxybenzyloxymethyl)-oxirane (**6**; 0.208 g; 1.00 mmol) and trifluoroacetic anhydride (0.840 g; 4.00 mmol) for 2 h. Solid-phase filtration employing toluene as the mobile phase provided **13** as a colorless oil (0.401 g, 96%). [Found: C, 43.13; H, 2.92. $C_{15}H_{12}O_7F_6$ (418.25) requires C, 43.08; H, 2.89%]; R_f (system A)=0.50; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 7.92 (2H, m, Aryl); 6.86 (2H, m, Aryl); 5.62 (1H, tt, J=4.8, 5.1 Hz, CH_2CHCH_2); 4.73 (2H, dd, J=4.4, 4.4 Hz, C(O)OCH_bH$_a$CHCH$_a$H$_b$OCO); 4.62 (2H, dd, J=5.3, 5.1 Hz, C(O)OCH$_b$H$_a$CHCH$_a$H$_b$OCO); 3.87 (3H, s, 4-CH_3OC$_6$H$_4$); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 165.08 (–C(O)O); 164.38 (C4); 132.21 (C2 and C6); 114.17 (C3 and C5); 55.73 (4-CH_3): 4-methoxybenzoyl fragment; 157.22 (C1, q, J=43.5 Hz); 114.53 (C2, q, J=284.6 Hz): trifluoroacetyl fragment; 67.57 (C2); 65.03 (C1, C3): glycerol fragment.

3.2.7. 2-(2,4,6-Trimethylbenzoyl)-1,3-bis(trifluoroacetyl)glycerol (14). Obtained from 2-(2,4,6-Trimethylbenzyloxymethyl)oxirane (**7**; 0.110 g; 0.50 mmol) and trifluoroacetic anhydride (0.420 g; 2.00 mmol) for 2 h. Solid-phase filtration (toluene) afforded **14** as a colorless oil (0.201 g, 93%). [Found: C, 47.52; H, 3.70. $C_{17}H_{16}O_6F_6$ (430.30) requires C, 47.45; H, 3.75%]; R_f (system A)=0.53; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 6.88 (2H, m, Aryl); 5.69 (1H, m, CH_2CHCH_2); 4.74 (2H, dd, J=3.8, 3.8 Hz, C(O)OCH_bH$_a$CHCH$_a$H$_b$OCO); 4.56 (2H, dd, J=5.9, 6.0 Hz, C(O)OCH$_b$H$_a$CHCH$_a$H$_b$OCO); 2.28, 2.29 (9H, s, s, CH_3-C$_6$H$_2$); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 168.97 (–C(O)O); 140.56 (C4); 135.74 (C2 and C6); 129.25 (C1); 128.91 (C3 and C5); 21.36 (4-CH_3); 19.86 (2-, 6-CH_3): 2,4,6-trimethylbenzoyl fragment; 157.16 (C1, q, J=43.5 Hz); 114.48 (C2, q, J=285.3 Hz): trifluoroacetyl fragment; 67.96 (C2); 65.31 (C1, C3): glycerol fragment.

3.3. General procedure for the preparation of 2-monoacylglycerols 15–21 (step B)

To a solution of **8–14** (1.00 mmol) in pentane–CH_2Cl_2 (3:1, v/v. 5.0 mL), a mixture of pyridine (10.0 mmol) and methanol (15.0 mmol) in the same solvent (5.0 mL) was added at −20 °C, and the reaction mixture was left at rt for 2–3 h. Solvents were evaporated under reduced pressure (bath 40–60 °C) and the residue was kept under vacuum at rt for 2–3 h to give the target 2-monoacylglycerol **15–21**.

The product could also be retrieved from the corresponding bis(trifluoroacetyl)-intermediate **8–14** directly in a one-pot procedure.

3.3.1. 2-Acetylglycerol (15). Synthesized in a one-pot procedure comprising:

Step A. Reaction of 2-(acetyloxymethyl)oxirane (**1**; 0.116 g; 1.00 mmol) and trifluoroacetic anhydride (0.840 g;

4.00 mmol) in CH_2Cl_2 at rt for 1 h followed by evaporation of volatile products in vacuo to give 2-acetyl-1,3-bis(trifluoroacetyl)glycerol **8** as described above.

Step B. Direct treatment of the thus obtained intermediate **8** with pyridine (0.79 g; 10 mmol) and methanol (0.48 g; 15 mmol) in pentane–CH_2Cl_2 (3:1, v/v) at rt for 2 h and then removing solvents under reduced pressure to give the title compound **15** as a colorless oil (0.134 g, 100%). [Found: C, 44.71; H, 7.57. $C_5H_{10}O_4$ (134.13) requires C, 44.77; H, 7.51%]; R_f (system D)=0.33; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 4.89 (1H, tt, J=4.8, 4.8 Hz, OCH_2CHOCO); 3.80 (4H, d, J=4.6 Hz, OCH_2CHCH_2O); 2.11 (3H, s, 2-CH_3); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 171.58 (C1); 21.32 (C2): acetyl fragment; 75.31 (C2); 62.30 (C1, C3): glycerol fragment.

3.3.2. 2-Oleoylglycerol (16). Synthesized in a one-pot procedure from 2-(oleyloxymethyl)oxirane (**2**; 0.338 g; 1.00 mmol), (Step B: rt/3 h), as described for **15**. Yield: 0.356 g (100%, yellowish/colorless oil). [Found: C, 70.71; H, 11.35. $C_{21}H_{40}O_4$ (356.55) requires C, 70.74; H, 11.31%]; R_f (system B)=0.32; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 5.34 (2H, m, C*H*=C*H*); 4.92 (1H, tt, J=4.8, 4.8 Hz, OCH_2CHOCO); 3.83 (4H, d, J=4.8 Hz, OCH_2CHCH_2O); 2.36 (2H, t, J=7.7 Hz, 2-CH_2); 1.99 (4H, m, 8-CH_2, 11-CH_2); 1.63 (2H, m, 3-CH_2); 1.30 (20H, m, 4-7-CH_2, 12-17-CH_2); 0.87 (3H, t, J=7.0 Hz, 18-CH_3); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 174.29 (C1); 130.26 and 129.92 (C9 and C10); 34.55 (C2); 32.12 (C16); 29.98–29.29 (C4-C7, C12-C15); 27.43 and 27.37 (C8 and C11); 25.16 (C3); 22.90 (C17); 14.32 (C18): oleoyl fragment; 75.22 (C2); 62.70 (C1, C3): glycerol fragment.

3.3.3. 2-Arachidonoylglycerol (17). Synthesized in two steps: (a) treatment of 2-(arachidonyloxymethyl)oxirane (**3**; 0.180 g; 0.50 mmol) with trifluoroacetic anhydride (0.420 g; 2.00 mmol) in CH_2Cl_2 (reaction time: rt/1 h); b) isolation of intermediate **10** by solid-phase filtration (toluene) followed by its hydrolysis (reaction time: rt/3 h) in pentane–CH_2Cl_2 (3:1, v/v) using pyridine (0.39 g; 5.0 mmol) and methanol (0.24 g; 7.5 mmol). Yield: 0.175 g (92%, yellowish oil). [Found: C, 73.00; H, 10.18. $C_{23}H_{38}O_4$ (378.56) requires C, 72.98; H, 10.12%]; R_f (system B)=0.33; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 5.37 (8H, m, C*H*=C*H*); 4.92 (1H, tt, J=4.6, 4.6 Hz, OCH_2CHOCO); 3.82 (4H, d, J=4.8 Hz, OCH_2CHCH_2O); 2.81 (6H, m, 7, 10, 13-CH_2); 2.39 (2H, t, J=7.6 Hz, 2-CH_2); 2.13, 2.05 (4H, m, 4-CH_2, 16-CH_2); 1.73 (2H, p, J=7.3 Hz, 3-CH_2); 1.32 (6H, m, 17-19-CH_2); 0.88 (3H, t, J=6.8 Hz, 20-CH_3); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 174.03 (C1); 130.76, 129.26, 128.99, 128.85, 128.54, 128.32, 128.06 and 127.75 (C5-6, C8-9, C11-12, C14-15); 33.90 (C2); 31.74 (C17); 29.54 (C18); 27.43 (C4); 26.71 (C16); 25.83 (C7, C10, C13); 24.97 (C3); 22.78 (C19); 14.29 (C20): arachidonoyl fragment; 75.28 (C2); 62.67 (C1, C3): glycerol fragment.

3.3.4. 2-Benzoylglycerol (18). Obtained from 2-(benzyloxymethyl)oxirane (**4**; 0.089 g; 0.50 mmol) in the same way as described for **17**. Yield: 0.094 g (96%, colorless oil). [Found: C, 61.19; H, 6.20. $C_{10}H_{12}O_4$ (196.20) requires C, 61.22; H, 6.16%]; R_f (system B)=0.21; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 8.04 (2H, m, Aryl); 7.56 (1H, m, Aryl); 7.43 (2H, m, Aryl); 5.16 (1H, tt, J=4.8, 4.8 Hz, OCH_2CHOCO); 3.95 (4H, d, J=4.9 Hz, OCH_2CHCH_2O); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 166.89 (–C(O)O); 133.57 (C4); 129.99 (C2 and C6); 128.66 (C1, C3, C5): benzoyl fragment; 75.97 (C2); 62.60 (C1, C3): glycerol fragment.

3.3.5. 2-(4-Nitrobenzoyl)glycerol (19). Obtained from 2-(4-nitrobenzyloxymethyl)oxirane (**5**; 0.112 g; 0.50 mmol) identically with **17** and **18**. Yield: 0.109 g (90%, yellowish crystals, mp 115.9–117.8 °C, from pentane–CH_2Cl_2=3:1, v/v). [Found: C, 49.75; H, 4.67; N, 5.78. $C_{10}H_{11}NO_6$ (241.20) requires C, 49.80; H, 4.60; N, 5.81%]; R_f (system B)=0.15; ^{1}H NMR δ_H (in ppm, CD_3OD, 400 MHz) 8.31 (4H, m, Aryl); 5.18 (1H, tt, J=4.9, 4.9 Hz, OCH_2CHOCO); 3.83 (4H, m, OCH_2CHCH_2O); ^{13}C NMR δ_C (in ppm, CD_3OD, 100 MHz) 164.76 (–C(O)O); 150.88 (C4); 135.95 (C1); 130.80 (C2 and C6); 123.34 (C3 and C5): 4-nitrobenzoyl fragment; 77.20 (C2); 60.47 (C1, C3): glycerol fragment.

3.3.6. 2-(4-Methoxybenzoyl)glycerol (20). Obtained from 2-(4-Methoxybenzyloxy-methyl)oxirane (**6**; 0.104 g; 0.50 mmol) in a synonymous way as described for **17**–**19**. Yield: 0.107 g (95%, white crystals, mp 78.9–80.1 °C, from pentane–CH_2Cl_2=3:1, v/v). [Found: C, 58.48; H, 6.30. $C_{11}H_{14}O_5$ (226.23) requires C, 58.40; H, 6.24%]; R_f (system B)=0.17; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 7.95 (2H, m, Aryl); 6.85 (2H, m, Aryl); 5.12 (1H, tt, J=4.8, 4.8 Hz, OCH_2CHOCO); 3.93 (4H, d, J=4.8 Hz, OCH_2CHCH_2O); 3.85 (3H, s, 4-$CH_3OC_6H_4$); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 166.70 (–C(O)O); 163.94 (C4); 132.09 (C2, C6); 122.25 (C1); 113.93 (C3 and C5); 55.69 (4-CH_3): 4-methoxybenzoyl fragment; 75.79 (C2); 62.72 (C1, C3): glycerol fragment.

3.3.7. 2-(2,4,6-Trimethylbenzoyl)glycerol (21). Obtained from 2-(2,4,6-trimethylbenzyloxymethyl)oxirane (**7**; 0.110 g; 0.50 mmol) identically with **17**–**20**. Yield: 0.113 g (95%, white crystals, mp 85.9–90.5 °C, from pentane–CH_2Cl_2=3:1, v/v). [Found: C, 65.50; H, 7.69. $C_{13}H_{18}O_4$ (238.29) requires C, 65.53; H, 7.61%]; R_f (system B)=0.35; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 6.85 (2H, m, Aryl); 5.18 (1H, tt, J=4.8, 4.8 Hz, OCH_2CHOCO); 3.93 (4H, m, OCH_2CHCH_2O); 2.28, 2.30 (9H, s, s, CH_3-C_6H_2); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 170.35 (–C(O)O); 139.83 (C4); 135.28 (C2 and C6); 130.77 (C1); 128.69 (C3 and C5); 21.34 (4-CH_3); 19.97 (2-, 6-CH_3): 2,4,6-trimethylbenzoyl fragment; 75.88 (C2); 62.59 (C1, C3): glycerol fragment.

3.4. General procedure for the preparation of 1,3-symmetrical triacylglycerols 22–26 (step C)

A solution of 2-monoacylglycerol **15**–**18** (1.00 mmol) and pyridine (20.0 mmol), in dichloromethane (10.0 mL), was treated with a solution of acyl chloride **a**–**d** (3.00 mmol) in dichloromethane (10.0 mL) at −20 °C, and the reaction mixture was kept at rt for 2–4 h. Solvents were removed under reduced pressure. The residue was taken in dichloromethane (10.0 mL), solution was passed through a dichloromethane-filled aluminium oxide pad (~20 g) and the

support was washed with the same solvent (~150 mL). Dichloromethane was removed under reduced pressure and triglyceride formed **22**–**26** was isolated in pure state by flash column chromatography (CC).

The latter compound could also be obtained via a one-pot procedure by conveniently combining steps A, B and C.

3.4.1. 1,3-Dipalmitoyl-2-acetylglycerol (22). Synthesized in a one-pot procedure by consecutively performing:

Step A. Transformation of 2-(acetyloxymethyl)oxirane (**1**; 0.058 g; 0.50 mmol) by means of trifluoroacetic anhydride (0.420 g; 2.00 mmol) to 2-acetyl-1,3-bis(trifluoroacetyl)-glycerol **8** (reaction time: rt/1 h).

Step B. Direct hydrolysis of the thus obtained intermediate **8** with pyridine (0.39 g; 5.0 mmol) and methanol (0.24 g; 7.5 mmol) to 2-acetylglycerol **15** (reaction time: rt/2 h).

Step C. Treatment of **15** in the presence pyridine (0.79 g; 10.0 mmol) with palmitoyl chloride (**a**; 0.412 g; 1.50 mmol) (reaction time: rt/4 h). Finally, purification of the crude triglyceride by flash column chromatography (system E) gave the title compound **22** (0.254 g, 83%) as a white solid, mp 58.2–60.9 °C (from system E). [Found: C, 72.74; H, 11.60. $C_{37}H_{70}O_6$ (610.97) requires C, 72.74; H, 11.55%]; R_f (system E)=0.36; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 5.24 (1H, m, OCH_2CHOCO); 4.29 (2H, dd, J=4.2, 4.2 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 4.15 (2H, dd, J=5.9, 5.9 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 2.31 (4H, t, J=7.3 Hz, 2-CH_2); 2.07 (3H, s, CH_3CO); 1.60 (4H, m, 3-CH_2); 1.28 (48H, m, 4-15-CH_2); 0.87 (6H, t, J=6.8 Hz, 16-CH_3); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 173.54 (C1); 34.26 (C2); 32.14 (C14); 29.91–29.32 (C4-13); 25.07 (C3); 14.33 (C16): palmitoyl fragment; 170.28 (C1); 21.09 (C2): acetyl fragment; 69.40 (C2); 62.23 (C1, C3): glycerol fragment.

3.4.2. 1,3-Dioleoyl-2-acetylglycerol (23). Synthesized in a one-pot, three-step procedure from 2-(acetyloxymethyl)-oxirane (**1**; 0.058 g; 0.50 mmol), pyridine (0.79 g; 10.0 mmol), and oleoyl chloride (**b**; 0.451 g; 1.50 mmol) as described for **22**. The crude product was purified by flash CC (system E) to give the title compound **23** (0.271 g, 82%) as a colorless oil. [Found: C, 74.32; H, 11.22. $C_{41}H_{74}O_6$ (663.04) requires C, 74.27; H, 11.25%]; R_f (system E)=0.35; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 5.35 (4H, m, CH=CH); 5.24 (1H, m, OCH_2CHOCO); 4.30 (2H, dd, J=4.4, 4.4 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 4.14 (2H, dd, J=5.9, 5.9 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 2.31 (4H, t, J=7.5 Hz, 2-CH_2); 2.07 (3H, s, CH_3CO); 2.00 (8H, m, 8-CH_2, 11-CH_2); 1.61 (4H, m, 3-CH_2); 1.30 (40H, m, 4-7-CH_2, 12-17-CH_2); 0.87 (6H, t, J=6.9 Hz, 18-CH_3); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 173.49 (C1); 130.23, 129.93 (C9, C10); 34.24 (C2); 32.12 (C16); 29.98–29.29 (C4-C7, C12-C15); 27.43 and 27.38 (C8 and C11); 25.06 (C3); 22.90 (C17); 14.32 (C18): oleoyl fragment; 170.26 (C1); 21.09 (C2): acetyl fragment; 69.40 (C2); 62.24 (C1, C3): glycerol fragment.

3.4.3. 1,3-Diacetyl-2-oleoylglycerol (24). Synthesized in a one-pot procedure from 2-(oleyloxymethyl)oxirane (**2**; 0.169 g; 0.50 mmol), pyridine (0.79 g; 10.0 mmol), and acetyl chloride (**c**; 0.118 g; 1.50 mmol) in CH_2Cl_2 (rt/2 h), as described for **22**–**23**. Purification of the crude product by flash CC (system A) afforded the title compound **24** (0.187 g, 85%) as a colorless oil. [Found: C, 68.20; H, 10.10. $C_{25}H_{44}O_6$ (440.63) requires C, 68.15; H, 10.07%]; R_f (system A)=0.37; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 5.33 (2H, m, CH=CH); 5.26 (1H, m, OCH_2CHOCO); 4.27 (2H, dd, J=4.4, 4.4 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 4.14 (2H, dd, J=6.0, 6.0 Hz, $C(O)OCH_bH_aCHCH_aH_b$-OCO); 2.32 (2H, t, J=7.3 Hz, 2-CH_2); 2.06 (6H, s, CH_3CO); 1.99 (4H, m, 8-CH_2, 11-CH_2); 1.62 (2H, m, 3-CH_2); 1.30 (20H, m, 4-7-CH_2, 12-17-CH_2); 0.87 (3H, t, J=7.0 Hz, 18-CH_3); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 173.12 (C1); 130.25 and 129.90 (C10 and C9); 34.39 (C2); 32.11 (C16); 29.97–29.22 (C4-C7, C12-C15); 27.43 and 27.37 (C8 and C11); 25.08 (C3); 22.88 (C17); 14.32 (C18): oleoyl fragment; 170.70 (C1); 20.89 (C2): acetyl fragment; 68.95 (C2); 62.53 (C1, C3): glycerol fragment.

3.4.4. 1,3-Dibenzoyl-2-arachidonoylglycerol (25). Obtained according to the general procedure from 2-arachidonoylglycerol (**17**; 0.189 g; 0.50 mmol), pyridine (0.79 g; 10.0 mmol), and benzoyl chloride (**d**; 0.211 g; 1.50 mmol) in CH_2Cl_2 (reaction time: rt/4 h). The crude triglyceride was purified by flash CC (system A) to give the target compound **25** (0.252 g, 86%) as a colorless oil. [Found: C, 75.63; H, 7.95. $C_{37}H_{46}O_6$ (586.78) requires C, 75.74; H, 7.90%]; R_f (system A)=0.60; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 8.03 (4H, m, Aryl); 7.57 (2H, m, Aryl); 7.44 (4H, m, Aryl); 5.60 (1H, m, OCH_2CHOCO); 5.36 (8H, m, CH=CH); 4.63 (2H, dd, J=4.4, 4.4 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 4.52 (2H, dd, J=5.9, 5.9 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 2.90–2.70 (6H, m, 7, 10, 13-CH_2); 2.37 (2H, t, J=7.5 Hz, 2-CH_2); 2.07 (4H, m, 16-CH_2, 4-CH_2); 1.70 (2H, p, J=7.3 Hz, 3-CH_2); 1.30 (6H, m, 17-19-CH_2); 0.88 (3H, t, J=6.8 Hz, 20-CH_3); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 172.96 (C1); 130.71, 129.72, 129.72, 128.96, 128.80, 128.47, 128.32, 128.07, 127.76 (C5-6, C8-9, C11-12, C14-15); 33.85 (C2); 31.73 (C17); 29.54 (C18); 27.43 (C4); 26.70 (C16); 25.86, 25.83 and 25.80 (C13, C7 and C10); 24.98 (C3); 22.78 (C19); 14.29 (C20): arachidonoyl fragment; 166.26 (–C(O)O); 133.53 (C4); 129.95 (C6, C2); 129.10 (C1); 128.71 (C5, C3): benzoyl fragment; 69.23 (C2); 63.18 (C1, C3): glycerol fragment.

3.4.5. 1,3-Dioleoyl-2-benzoylglycerol (26). Obtained in a one-pot procedure from 2-(benzyloxymethyl)oxirane (**4**; 0.089 g; 0.50 mmol), pyridine (0.79 g; 10.0 mmol), and oleoyl chloride (**b**; 0.451 g; 1.50 mmol) followed by purification of the crude product (CC system E) as described for **22**–**24**. Overall yield of **26**: 0.308 g (85%, colorless oil). [Found: C, 76.32; H, 10.60. $C_{46}H_{76}O_6$ (725.11) requires C, 76.20; H, 10.56%]; R_f (system E)=0.43; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 8.04 (2H, m, Aryl); 7.58 (1H, m, Aryl); 7.44 (2H, m, Aryl); 5.52 (1H, m, OCH_2CHOCO); 5.35 (4H, m, CH=CH); 4.39 (2H, dd, J=4.4, 4.4 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 4.33 (2H, dd, J=6.0, 6.0 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 2.31 (4H, t, J=7.5 Hz, 2-CH_2); 1.99 (8H, m, 8-CH_2, 11-CH_2); 1.60 (4H, m, 3-CH_2); 1.30 (40H, m, 4-7-CH_2, 12-17-CH_2); 0.88 (6H, t, J=7.0 Hz, 18-CH_3); ^{13}C NMR δ_C (in ppm, $CDCl_3$,

100 MHz) 173.53 (C1); 130.21, 129.96 (C10, C9); 34.28 (C2); 32.12 (C16); 29.98–29.29 (C12-C15, C4-C7); 27.44, 27.38 (C8 and C11); 25.07 (C3); 22.90 (C17); 14.33 (C18): oleoyl fragment; 165.84 (–C(O)O); 133.53 (C4); 130.01 (C2, C6); 129.82 (C1); 128.65 (C3, C5): benzoyl fragment; 70.00 (C2); 62.36 (C1, C3): glycerol fragment.

3.4.6. 2-Oleoyl-1,3-bis(trichloroacetyl)glycerol. Obtained from 2-(oleyloxymethyl)oxirane (**2**; 0.169 g; 0.50 mmol) and trichloroacetic anhydride (0.617 g; 2.00 mmol) according to the general procedure (reaction time: rt/24 h). Flash CC using toluene–EtOAc (95:5, v/v) as eluant gave the pure trichloroacetylated product (0.317 g, 98%) as a colorless oil. [Found: C, 46.44; H, 6.00. $C_{25}H_{38}O_6Cl_6$ (647.28) requires C, 46.39; H, 5.92%]; R_f (system A)=0.64; ^{1}H NMR δ_H (in ppm, $CDCl_3$, 400 MHz) 5.47 (1H, m, OCH_2CHOCO); 5.34 (2H, m, $CH{=}CH$); 4.64 (2H, dd, J=4.4, 4.4 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 4.50 (2H, dd, J=5.7, 5.5 Hz, $C(O)OCH_bH_aCHCH_aH_bOCO$); 2.34 (2H, t, J=7.7 Hz, 2-CH_2); 2.00 (4H, m, 8-CH_2, 11-CH_2); 1.62 (2H, m, 3-CH_2); 1.30 (20H, m, 4-7-CH_2, 12-17-CH_2); 0.87 (3H, t, J=7.1 Hz, 18-CH_3); ^{13}C NMR δ_C (in ppm, $CDCl_3$, 100 MHz) 172.69 (C1); 130.27 and 129.90 (C10 and C9); 34.16 (C2); 32.12 (C16); 29.98–29.22 (C12-C15, C4-C7); 27.44 and 27.37 (C8 and C11); 24.91 (C3); 22.90 (C17); 14.33 (C18): oleoyl fragment; 161.74 (s, C1): trichloroacetyl fragment; 67.70 (C2); 65.99 (C1, C3): glycerol fragment.

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22. Isomeric purity of triglycerides can be assessed by examining ^{13}C NMR spectra in the region of absorption of carbonyl carbons. For acetyl-containing derivatives, both ^{1}H or ^{13}C NMR can be used for this purpose as methyl protons and the carbonyl carbons of the acetyl groups have distinctive chemical shifts depending on the position of the acetyl group

in the glycerol backbone. For example, for compounds **23** and **24**, the relevant chemical shifts in $CDCl_3$ are: 2.07 ppm (CH_3); 170.26 ppm (1-C) and 2.06 ppm (CH_3-) and 170.70 ppm (1-C), respectively.

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Synthesis of a caryophyllene isoprenologue, a potential diterpene natural product

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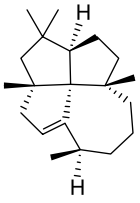
Abstract—(−)-β-Caryophyllene has been converted into three stereoisomers of a new bicyclic compound that is structurally related to the known macrocyclic diterpene, flexibilene, in the same way β-caryophyllene is related to humulene. Key steps are selective cleavage of caryophyllene, addition of a five carbon component by a Wittig reaction and McMurry cyclization.

1. Introduction

During our studies of the tetracyclic diterpene, laurenene (**1**)[1,2] we have been drawn to the similarity of its peripheral methylation pattern with that of the monocyclic diterpene, flexibilene (**2**).[3] We have also noted structural similarities to the triquinane sesquiterpenes, and have entertained the idea that the biosynthesis of laurenene might involve a pathway analogous to that proposed for the biosynthesis of silphenene (**3**) which proceeds through an intermediate with a caryophyllene framework.[4] For this reason we became interested in compound **4** which bears the same relationship to flexibilene (**2**) as caryophyllene (**5**) does to humulene (**6**). Although **4** has not been encountered as a natural product, this relationship to flexibilene renders it a worthwhile synthetic target and the putative connection to laurenene adds further impetus to its synthesis. Here we describe our synthesis of **4** and two of its geometric isomers **7** and **8**.



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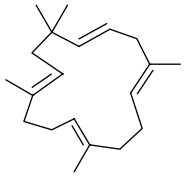
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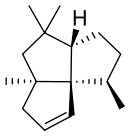

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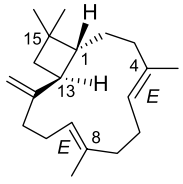

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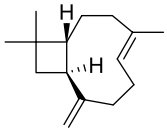

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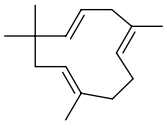
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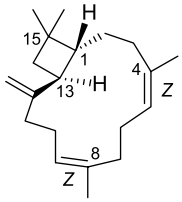

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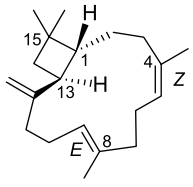

8

2. Results and discussion

The readily available (−)-β-caryophyllene (**5**) presented itself as an ideal starting point for our synthesis. The

Keywords: Bicyclic diterpene; Flexibilene; Wittig reaction; Warren modification; McMurry cyclization.
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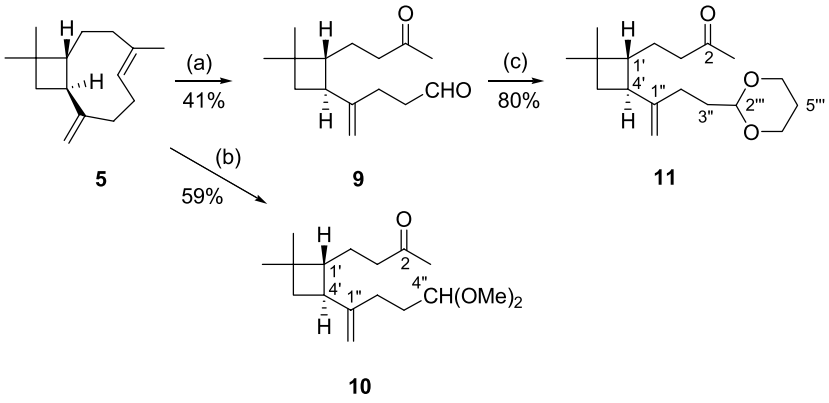
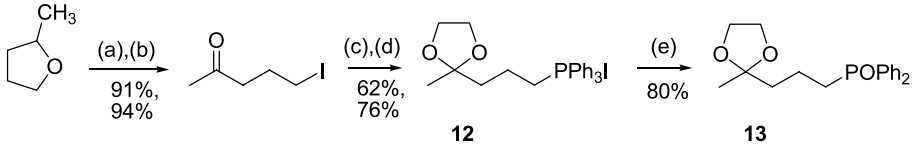


Scheme 1. Selective cleavage of (−)-β-caryophyllene **5**. (a) O_3/MeOH then $(CH_3)_2S$; (b) O_3/MeOH then $(CH_3)_2S$/K-10 clay/MeOH; (c) $HO(CH_2)_3OH/H^+$.



Scheme 2. Synthesis of five carbon subunits **12** and **13**. (a) $AlCl_3$/NaI; (b) $COCl_2$/DMSO; (c) Ph_3P; (d) $(CH_2OH)_2$/PTSA; (e) NaOH.

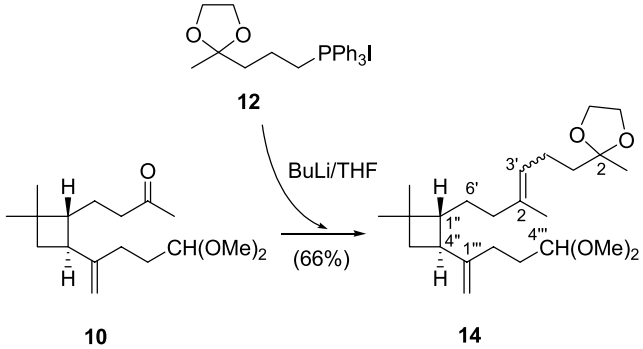
gem-dimethyl substituted cyclobutane, with a *trans* fused ring junction and the exocyclic double bond are already in place. Transformation of diene **5** into triene **4** requires enlargement of the nine-membered ring by insertion of an appropriately functionalized five-carbon unit, to produce the desired 13-membered ring.

Odinokov et al. have reported the selective ozonolysis of β-caryophyllene (**5**) at the endocyclic double bond.[5] This gave ketoaldehyde **9** which was converted into its dimethyl acetal **10**. We found it most convenient to form **10** directly by carrying out the ozonolysis in methanol and treating the resulting solution with both dimethyl sulfide and K-10 clay (Scheme 1). Alternative protection for the aldehyde function was obtained by treatment of **9** with 1,3-propanediol and *p*-toluenesulfonic acid in boiling benzene under Dean–Stark conditions to give acetal **11**.

Conversion of **9** or an equivalent into **4** required the addition of a 1,4-difunctionalised pentane unit with the attachment of the 1-position to the ketone function of **9** and the 4-position to the aldehyde. We chose to commence with functionalization of the ketone. Literature methods, involving ring opening of 2-methyltetrahydrofuran with aluminium trichloride/sodium iodide,[6] Swern oxidation[7,8] to 5-iodo-2-pentanone[9] and reaction with triphenylphosphine and acetal-protection, yielded the desired phosphonium salt **12**.[10,11] Treatment of **12** with boiling aqueous sodium hydroxide solution gave an alternative five-carbon source, the diphenylphosphinoyl derivative **13**[12] (Scheme 2).

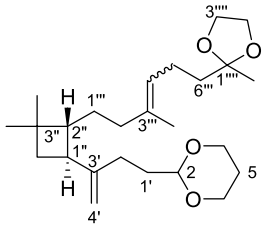
Wittig reaction of phosphonium salt **12** with ketoacetal **10** using *n*-butyl lithium as base in THF gave a 69% yield of an (*E*)/(*Z*) mixture of alkenes **14** (1:2.4 by GC) (Scheme 3). Although the MS of the product, which was isolated in 65% yield, showed no parent ion for $C_{24}H_{42}O_2$, peaks for ions corresponding to loss of CH_3, CH_3OH, and CH_3CH_2OH were noted. ^1H and ^{13}C NMR signals associated with the *gem*-dimethylcyclobutane system, the exocyclic methylene and the methoxy groups were well resolved, and relatively unchanged in chemical shift compared with those of the starting material. Peaks consistent with the dioxolane-protected methyl ketone system [δ_H 1.32 (s), 3.93 (m, $W_{h/2}=7$ Hz); δ_C 23.5 (q), 109.9 (s), 110.0 (s)] indicated that the five-carbon unit had been incorporated as desired. Furthermore, trisubstituted double bond formation was evidenced by olefinic methine [δ_H 5.03–5.15 (m); δ_C 123.8 (d), 124.1 (d)] and methyl peaks [δ_H 1.67 (d, $J=$ 1 Hz), 1.59 (s); δ_C 23.9 (q), 15.9 (q)]. The number of signals observed in these spectra confirmed the formation of both the (*E*)- and the (*Z*)-forms of alkene **14**. Comparison with literature data[13,14] indicated that the (*Z*)-form [δ_H 1.67 (d, $J=1$ Hz), δ_C 23.9 (q)] was dominant and GC indicated a ratio of 5:11. Other Wittig modifications gave lower yields.

Attempts to separate the isomers of **14** were only partially successful. Silica gel radial chromatography provided an enrichment of the major isomer by repeated elution, but neither silver nitrate impregnated plates nor reverse phase C_{18} column chromatography proved effective. An attempt to improve the (*E*)/(*Z*) ratio of the geometric isomers of **14** by



Scheme 3. Wittig reaction of keto acetal **10**.

irradiation in the presence of diphenyldisulphide[15,16] gave very little change in the isomer distribution. In similar fashion, Wittig reaction of ketone **11** gave the previously unreported **15** as an (*E*)/(*Z*) mixture (40%).



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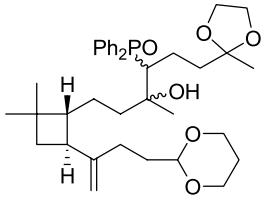
In an attempt to avoid isomeric mixtures, the Warren modification of the Wittig reaction[12,17,18] was attempted. Here the diastereoisomeric mixtures of phosphinoyl alcohols that are generated are frequently separable and able to be transformed stereospecifically into either the (*E*)- or (*Z*)-alkene. Reaction of diphenylphosphinoyl derivative **13** with ketone **10** gave a solid. The IR spectrum of the mixture indicated that an alcohol (ν_{max} 3350 cm^{-1}) was present, and a distinctive band at 1460 cm^{-1} was consistent with the diphenylphosphinoyl group. NMR spectra were complicated, but various resonances supported the expected gross structure **16**. Signals for the geminal methyl groups (δ_H 0.84, 0.88), the exocyclic C=CH_2 unit (δ_H 4.52–5.00, 2H, m; δ_C 106.5, 106.6, 106.7, 106.8, 151.8 and 152.0), the dioxolane grouping (δ_H 3.59–4.28, 4H, m; δ_C 64.2, 64.4 and 67.7), the methoxy groups (δ_H 3.31, 6H, s; δ_C 52.6) and the phenyl groups (δ_H 7.48, 6H, m and 7.79, 4H) were noted. Comparison with reported ^{1}H NMR data[12] enabled the assignment of a two proton multiplet at 2.32 ppm to both the phosphorus-bearing methine and one of the ring-junction methine groups. A group of singlets at δ 0.96, 0.98 and 1.04 was assigned to the CH_3–COH system and a pair of peaks at 1.24 and 1.27 ppm was assigned to the methyl group attached to the dioxolane ring (Scheme 4).

Although the anticipated phosphinoyl alcohols **16** should exist in four diastereoisomeric forms we did not separate these. Reaction of the mixed isomers of **16** in dimethyl formamide with sodium hydride generated the desired alkenes **14**, but only in 30% yield based on transformed starting material. A promising aspect of this reaction was that more of the (*E*)-isomer was formed with a 1:1 ratio of isomers. This was useful in later studies of the McMurry cyclisation (vide infra). However, a considerable amount of keto acetal **10** (35% based on transformed starting material) was also formed. It was noted that a bright red colour was formed upon addition of sodium hydride to the diphenylphosphinoyl alcohol. This suggested that fragmentation may be occurring.

The same sequence was repeated with the alternative substrate **11**. A low yield (15%) of phosphinoyl alcohol diastereoisomers **17** was again obtained, but these were separable by centrifugal chromatography into two fractions of different R_f on silica. By analogy with Warren's findings on similar systems[17] it was anticipated that the two isolated components would correspond to the *erythro* and *threo* forms about the newly created bond. However, when either of these fractions was treated with sodium hydride in dimethyl formamide, a 6:5 mixture of alkene **15** (*E*) and (*Z*)-geometric isomers was obtained. Again, a bright red colour was generated. Lawrence[19] has noted that such loss of stereoselectivity may occur if the alkene is sterically compressed (tri- or tetra-substituted).



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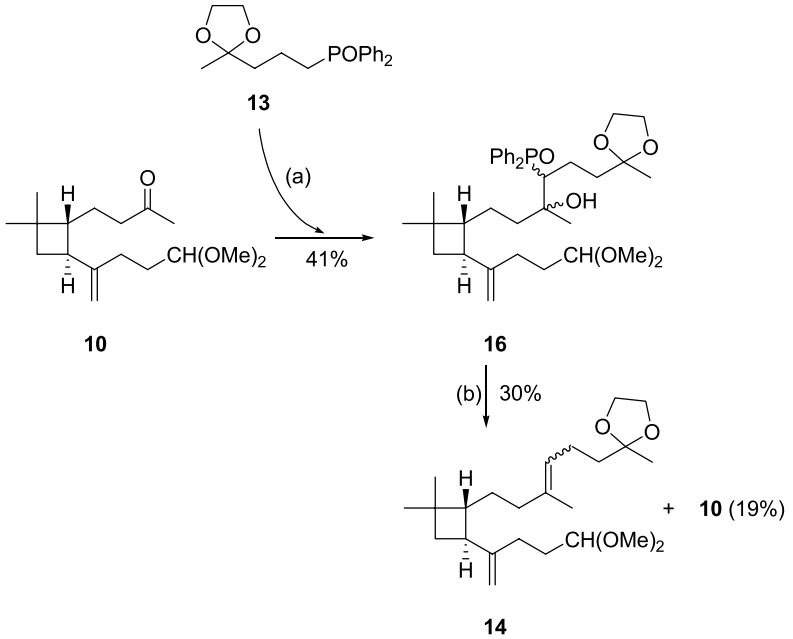
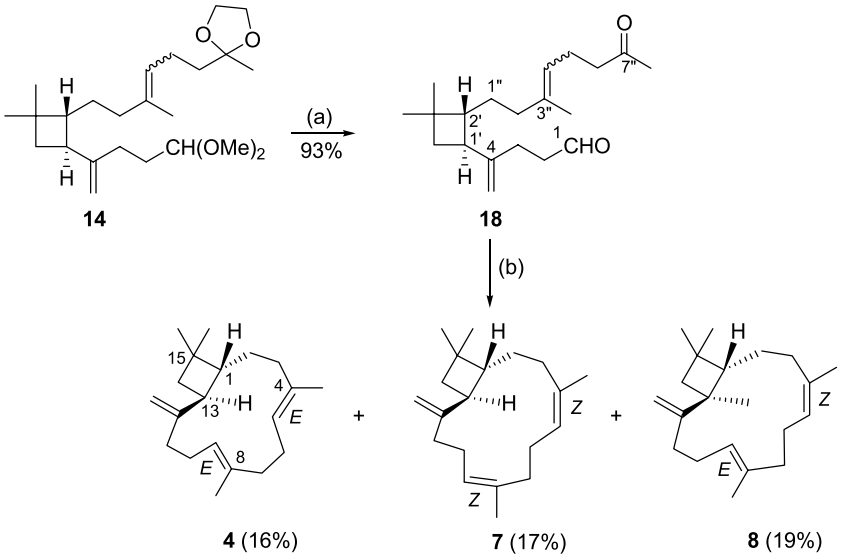


Scheme 4. Warren modification of the Wittig reaction of **10**. (a) BuLi/THF; (b) NaH/DMF.



Scheme 5. Synthesis of trienes **4**, **7** and **8**. (a) $HCl_{(aq)}$/THF; (b) Ti(0)/DME.

Removal of the acetal functions of **14** by acid hydrolysis proceeded efficiently, yielding inseparable (*E*) and (*Z*) isomers of product **18** (Scheme 5). Regeneration of the carbonyl groups was shown by the IR (ν_{max} 2725 (HC═O), 1714 (C═O) cm^{-1}) and NMR spectra (δ_H 2.13, 3H, s and 9.77, 1H, t, $J=2$ Hz; δ_C 202.3, 208.8). The olefinic methyl groups of the two isomers gave rise to ^1H NMR signals at δ_H 1.59 and 1.66 for the (*E*) and (*Z*) alkenes respectively. Isomeric ratios of isomers determined by integration of these signals concurred with those determined by gas chromatography, and (*E*)/(*Z*) mixtures of both 1:1 (from **14** formed by Warren reaction of **10** and **13**) and 5:11 (from Wittig reaction of **10** and **12**) were prepared.

McMurry coupling (Scheme 5) was initially achieved by using a modification of the procedures reported for the synthesis of humulene[20] and cyclotridecene,[21] and employed 8 equivalents of titanium trichloride with a 3.1:1 ratio of Zn/Cu couple to titanium trichloride. Keto aldehyde **18** with an (*E*)/(*Z*) ratio of 1:2.4 was added via syringe pump. GC of the product revealed approximately equal amounts of three components of similar retention index. GC/MS showed similar mass spectra for each peak, with the highest ion recorded at 257 Da, corresponding to a loss of CH_3 (β-caryophyllene (**5**) exhibits similar facile loss of CH_3). The ^1H NMR spectrum, though complicated by peak overlap, suggested that cyclization had taken place as desired. Although no starting material or pinacol species were detected, the isolated yield of trienes was only 20%.

The synthesis of casbene[22] appeared to offer a good analogy for the cyclization of **18**. This synthesis involved the coupling of a methyl ketone with an aldehyde, a 14-membered ring fused to a small ring with a *gem*-dimethyl unit was formed, and apart from the two reacting carbonyls, only alkene functional groups were present. Cyclization of **18** was achieved in a 30% yield by the use of 40 equivalents of titanium trichloride. This was increased to 52% by increasing the reagent preparation time and by adding the substrate more slowly.

With the notable exception of the keto-ester cyclization that enabled formation of the cyclononene ring in an attempted synthesis of β-caryophyllene,[23] the McMurry reaction conditions have not been reported to induce geometric isomerization of existing double bonds. No geometrical or positional isomerization has been observed during the intramolecular coupling reactions of keto-aldehyde reactants.[24] Thus the three products of the McMurry coupling of **18** were expected to retain the (*E*)/(*Z*) ratio of the substrate in the pre-existing double bond. Given the dominance of the (*Z*) isomer in the substrate and the approximate 1:1:1 ratio of triene products, it seemed likely that the (*Z*)-form of **18** had reacted to yield the (4*Z*,8*Z*)-triene **7** and the (4*Z*,8*E*)-triene **8**, while the (*E*)-isomer of **18** had reacted with a high degree of stereoselectivity to yield either the desired (4*E*,8*E*)-triene **4** or its (4*E*,8*Z*)-isomer. This hypothesis was consistent with the results of a dicarbonyl coupling reaction completed with a 1:1 mixture of the isomers of **18**. Here, GC revealed a ca. 1:1:2 ratio of the same triene products.

Although reverse phase chromatography has been applied successfully to the separation of the geometric isomers of casbene,[22] no such separation of **4**, **7** and **8** was attained. However, the three isomers were separated by centrifugal chromatography on silver nitrate impregnated silica. Two components eluted with 3:97 ethyl acetate/hexanes, and the third with 3:17 ethyl acetate/hexanes. This latter component, the (4*Z*,8*E*)-triene **8**, had the greatest signal dispersion in the ^1H NMR spectrum and proved to be the most amenable to full structural characterization.

HRMS data for triene **8** were consistent with the expected molecular formula, $C_{20}H_{32}$. The solution IR spectrum was compatible with an unsaturated hydrocarbon and ^1H and ^{13}C NMR spectroscopy (Table 1) revealed the presence of 1,1-disubstituted and trisubstituted (×2) double bonds in accord with a bicyclic structure.

Long range correlations from the proton resonances at δ_H 1.04, 1.02 to a quaternary carbon signal at δ_C 33.3 were

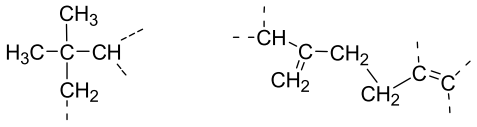
Table 1. NMR data for isomeric trienes **4**, **7** and **8**[a]

Position	δ_C			δ_H[b] [LRHETCOR[c]]
	4 (4*E*,8*E*)	**7** (4*Z*,8*Z*)	**8** (4*Z*,8*E*)	
1	45.3	50.7	47.1	1.92, ddd, 9.5, 10, 10 [n.o.]
2	27.3	28.0	25.1	2.12 [n.o.]; 2.29 [C-3]
3	35.4	28.8	29.1	1.73 [n.o.]; 2.27 [C-4, 4-Me]
4	133.5	137.9†	136.2	—
5	124.2	124.5‡	125.3	5.12, br dd, 7,7 [n.o.]
6	24.5*	30.9	29.6	1.73 [n.o.]
7	39.1	31.5	38.3	1.82 [n.o.]; 2.12 [n.o.]
8	133.7	136.9†	136.9	—
9	125.6	124.0‡	124.6	5.05, br dd, 6.5, 11 [n.o.]
10	25.0*	33.2	30.5	2.10 [n.o.]
11	31.4	37.3	34.4	2.17 [C-10, C-12, 12-=CH_2]
12	149.7	153.7	152.4	—
13	43.5	41.2	41.2	2.34 [C-2]
14	36.3	39.4	41.0	1.35, dd, 9.5, 10 [C-12, 15β-Me]; 1.85, dd, 10, 10 [n.o.]
15	33.7	33.3	33.3	—
15β-Me	31.4	30.8	30.6	1.04, s [C-1, C-15, 15α-Me]
15α-Me	23.3	23.0	22.6	1.02, s [C-14, C-15, 15β-Me]
12-=CH_2	108.6	108.4	108.7	4.78, s [C-13]; 4.87, d, 1.5 [C-11]
4-Me	15.1	23.8*	22.6	1.64, s [C-3, C-4, C-5]
8-Me	16.9	23.6*	19.1	1.61, s [C-7, C-8, C-9]

*,†,‡Values marked with the same symbol within a column may be interchanged.
[a] Recorded in $CDCl_3$ at 75 MHz (^{13}C) or 300 MHz (^1H), referenced to TMS.
[b] Chemical shift in ppm, multiplicity, coupling constants in Hz.
[c] Correlations from proton to signal to designated carbon signal, n.o.—none observed.

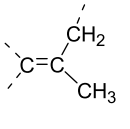
consistent with a *gem* dimethyl unit. Generation of substructure **8a** was enabled by LRHETCOR correlations from the methyl proton signal at δ 1.02 to a methylene carbon signal at δ_C 41.0, and from that at δ 1.04 to a methine carbon signal at δ_C 47.1.

A further substructure **8b** was generated based on chemical shift data, and LRHETCOR correlations. A correlation from one of the olefinic methylene proton signals (δ_H 4.78) to a methine carbon signal at δ_C 41.2 and one from the allylic methylene proton signal at δ_H 2.17 to the olefinic carbon resonances at δ_C 108.7 (t) and 152.4 (s) established the nature of the carbons adjacent to the 1,1-disubstituted double bond. The proton signal at δ_H 2.17 also correlated to a further methylene carbon (δ_C 30.5) associated with an allylic proton signal (δ_H 2.10).

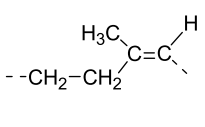


8a

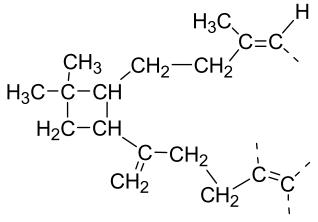
8b



8c



8d



8e

The ^1H NMR spectrum displayed two allylic methyl signals at δ_H 1.61 and 1.64. Each showed LRHETCOR correlation to a methylene carbon signal (δ_C 38.3 and 29.1 respectively). A proton signal associated with the latter of these (δ_H 2.27) correlated to the carbon signal of a further methylene group (δ_C 25.1). This gave rise to two further subunits **8c** and **8d**. The carbon chemical shifts of the two allylic methyl groups were consistent with an (*E*) geometry for the double bond of **8c** and a (*Z*) geometry for that of **8d**.[14] These four substructures **8a–d** encompassed 19 of the 20 carbons.

NMR shift data for the carbons of subunit **8a** indicated that it was, as expected, part of a four-membered ring. The structure of the starting material implied the union of fragments **8a** and **8b** to form a cyclobutane ring. The coupling pattern observed for the ring methylene proton signals (δ_H 1.35, dd, J=9.5, 10 Hz; 1.85, dd, J=10, 10 Hz) concurred with this proposal. LRHETCOR correlation between the proton signal of the methine group of **8b** (δ_H 2.34) and the carbon signal of the terminal methylene unit of **8d** (δ_C 25.1) added further weight to this assertion and

allowed the addition of subunit **8d** as in substructure **8e**. The methylene group in substructure **8c** is not part of substructure **8e** and this, together with only unplaced methylene group (δ_H 1.73, δ_C 29.6), was required to complete the ring as in structure **8**.

The first isomer to elute from the silver nitrate plate, had very similar HRMS and IR spectra to those of **8**. The most significant difference between the ^{13}C NMR spectra of the two isomers was the chemical shift of the peaks assigned to the methyl groups of the trisubstituted double bonds (δ_C 15.1 and 16.9 compared to δ_C 19.1 and 22.6 for **8**). Thus, both double bonds have the (*E*) geometry as in the desired structure **4**.[14] Observed LRHETCOR correlations were consistent with this structure.

The remaining isomer was assigned the (4*Z*,8*Z*) stereochemistry **7** on the basis of the chemical shifts of the two olefinic methyl carbon signals (δ_C 23.6, 23.8). Resonances (Table 1) were assigned with the aid of LRHETCOR correlations and by comparison of chemical shifts with those of **4** and **8**.

3. Conclusions

The synthesis of the caryophyllene isoprenologue **4** with the (4*E*,8*E*) geometry has now been completed. This has also yielded the (4*Z*,8*Z*) and (4*Z*,8*E*) isomers **7** and **8**. Overall, (−)-β-caryophyllene (**5**) has been converted into a 1:1:1 mixture of **4**, **7** and **8** in a 25% yield. Compound **4** is a potential natural product, structurally related to the marine metabolite, flexibilene **2**[3] as humulene **6** is to caryophyllene **5**. The GC retention, MS and NMR data presented here will allow rapid identification of **4**, or isomers **7** and **8**, from natural sources. However, any intention to explore possible connections between **4** and laurenene **1**, must await a synthesis that is more amenable to scale-up.

NMR spectra of the bicycle [11.2.0] compounds **4**, **7** and **8** showed no significant line broadening in contrast to the bicyclic [7.2.0] compound, caryophyllene (**5**)[25,26] where the smaller ring resulted in slowly exchanging rotational isomers.

4. Experimental

4.1. General methods

4.1.1. Chromatography. TLC was performed on silica gel 60 F_{254} 0.2 mm coated aluminium foil. Centrifugal chromatography was performed on a Harrison Research 7942T Chromatotron with plates coated with 1, 2 or 4 mm layers of silica gel 60 PF_{254} with $CaSO_4 \cdot ½H_2O$ applied as a slurry and dried. 4 mm Silver (I) impregnated plates were made by including $AgNO_3$ (5 g) into the slurry. Column chromatography used silica gel 60. GC was performed using a Hewlett–Packard HP 6890 series capillary gas chromatograph fitted with a programmable temperature injector (250 °C) and a flame ionisation detector (260 °C). A 30 m × 0.32 mm HP-1 column (0.25 μm film thickness) was used with helium as carrier gas at 8 PSI with a flow rate of 30 mL min^{-1}. Sample size was 0.1 μL and a sample split ratio of ~20:1 was used. Kovats retention indices[27] were determined from isothermal runs at 170 and 190 °C.

4.1.2. Instrumentation. NMR spectra were recorded on a Varian VXR-300 spectrometer operating at 300 MHz for ^1H and 50 MHz for ^{13}C. Spectra were obtained at 25 °C on ca. 0.075 M $CDCl_3$ solutions and were referenced to the $CHCl_3$ peak (δ 7.26) for ^1H, or to the centre line of the $CDCl_3$ signal (δ 77.08) for ^{13}C. LRHETCOR spectra were optimised for long range coupling of 6–10 Hz. IR spectra were recorded on a Perkin–Elmer 1600 series FT IR instrument. Optical rotations were measured as $CHCl_3$ solutions using a Jasco DIP-370 digital polarimeter.

4.1.3. Inert gas purification. Dry, oxygen free argon (1 to 10 ppm O_2) was prepared by passing argon (NZIG gas code 130) through a column (45 × 500 mm) packed with BASF R 3-11 catalyst. The catalyst was reduced prior to use by slowly passing a stream of H_2 through the pellets and increasing the temperature to 140 °C over 4 h, then maintaining this temperature for 12 h. The catalyst was then dried (200 °C/0.2 mm Hg, 12 h) and the column was connected to the two stage argon cylinder valve. H_2O was removed by a second column (35 × 240 mm) packed with Drierite indicator and powdered P_2O_5. All solvent transfers requiring dry conditions were done using Schlenck apparatus under dry argon and using standard vacuum line techniques. Glassware was flame dried three times. For the McMurry reaction, glassware was also heated overnight at 120 °C and ground glass joints were immediately fitted with a Teflon® sleeve and connected to vacuum prior to flame drying. Molecular sieves (new and recycled) were dried (180 °C, 0.2 mm Hg) for 10 h prior to use.

4.1.4. Solvent purification. For the Wittig reactions, THF was refluxed for 2 h and freshly distilled from Na/K amalgam under an argon atmosphere. DMSO was distilled under reduced pressure, shaken overnight with 4 Å molecular sieves then redistilled on to fresh molecular sieve and stored under dry argon. For the McMurry reactions, potassium was cut under hexane and transferred quickly to a distillation apparatus that had been heated overnight in an oven (120 °C) and then purged with dry argon. DME was then refluxed for 10 h over potassium under dry argon and then distilled onto fresh potassium. The DME was then refluxed over potassium under dry argon for a further 4 h before use in subsequent reactions. Acetone was distilled from 4 Å molecular sieves onto fresh sieve and stored under dry argon for 1 week prior to use. Et_2O was freshly distilled from $LiAlH_4$ under dry argon.

4.1.5. Zn/Cu couple. Zinc dust (489 g) was stirred with aqueous HCl solution (2%, 1500 mL) for 5 min then washed with aqueous HCl solution (2%, 1000 mL), H_2O (3 × 500 mL), EtOH (2 × 750 mL) then Et_2O (2 × 500 mL). The solvents were decanted from the dust in each case. The resultant light grey powder was dried (100 °C/12 mm Hg) for 3 h. A portion was weighed into a conical flask (127.08 g, 2 mol), and a glass filter tube with sinter (grade 4) was fitted. The vessel was evacuated for 1 h and then an argon atmosphere introduced and the equipment evacuated and flushed with argon three times. H_2O (500 mL) was

introduced and the slurry purged with argon for 10 min. $CuSO_4 \cdot 5H_2O$ (11.2 g, 63 mmol) was added and the reaction mixture shaken. After 5 min the solids were collected by filtration and washed with acetone (200 mL), then Et_2O (200 mL), and the dark grey material was dried (100 °C/0.2 mm Hg, 5 h) before being stored under dry argon.

4.1.6. (−)-β-Caryophyllene (5). Commercial β-caryophyllene (*ex* BDH) was purified by silica column chromatography, eluting with hexanes, to remove humulene and oxidised material.

4.2. Synthetic methods

4.2.1. (1′*S*,2′*R*)-3,3-Dimethyl-4-methylene-2-(3-oxobutyl)cyclobutanebutanal (9).[5] {CN 101979-01-5} A solution of (−)-β-caryophyllene (**5**) (5.0 g, 24.3 mmol) in EtOAc (50 mL) was dissolved in MeOH (500 mL) containing hexadecane (0.1 g) and treated with dry, ozonised oxygen at −78 °C. The reaction was monitored by GC. After 35 min there was no diene present with respect to the internal standard (hexadecane). After excess ozone had been removed by purging with nitrogen, Me_2S (5 mL) was added, and the reaction mixture was stirred for 12 h. Evaporation followed by column chromatography, eluting with Et_2O, gave **9** (2.4 g, 41%) as a clear oil; IR as in Ref. 5; ^{1}H NMR δ 1.05 (s, 2×3′-Me), 1.41 (dd, J=7, 8 Hz, H-4′), 1.63 (m, $W_{h/2}$=13 Hz, 2×H-4″), 1.80 (H-4′), 1.86 (m, H-2′), 2.12 (s, 3×H-1″), 2.31 (m, 2×H-2, 2×H-3 and H-1′), 2.57 (m, $W_{h/2}$=7 Hz, 2×H-3″), 4.69 (s, 4-=CH_2), 4.78 (s, 4-=CH_2), 9.75 (s, H-1); ^{13}C NMR δ 22.0 (3′-Me), 24.2 (C-4″), 26.2 (C-3), 29.5 (C-1″), 30.7 (3′-Me), 33.3 (C-3′), 39.3 (C-4′), 41.2 (C-1′), 41.5 (C-3″), 41.5 (C-2), 47.4 (C-2′), 107.2 (4-=CH_2), 150.3 (C-4), 201.7 (C-1), 208.3 (C-2″).

4.2.2. (1′*R*,4′*S*)-4-[4-(4, 4-Dimethoxy-1-methylenebutyl)-2, 2-dimethylcyclobutyl]-butan-2-one (10).[5] {CN 101927-11-1} MeOH (170 mL) was added to a solution of commercial (−)-β-caryophyllene **5** (3.0 g, 70% **5** by GC, 10.2 mmol) in EtOAc (10 mL) and the mixture was treated with dry, ozonised oxygen at −78 °C for 10 min. After excess ozone had been removed by purging with nitrogen and the solution had warmed to room temperature, Me_2S (5 mL) and Montmorillonite K-10 clay (3 g) were added, and the reaction mixture was stirred for 48 h. Filtration, evaporation, followed by column chromatography on silica, eluting with Et_2O/hexanes, 1:1, gave **10** (1.6 g, 59%) as a clear oil, distilled 85 °C/0.02 mm Hg; $[\alpha]_D^{24}$ 51.2° ($CHCl_3$, *c* 1.0); IR as in Ref. 5; ^{1}H NMR δ 1.04 (s, 2′-Me), 1.05 (s, 2′-Me), 1.43 (dd, J=10.5, 10.5 Hz, H-3′), 1.65 (m, 2×H-4), 1.72 (m, 2×H-2″), 1.80 (m, H-3′), 1.88 (m, H-1′), 2.01 (m, $W_{h/2}$=19 Hz, 2×H-3″), 2.11 (s, 3×H-1), 2.35 (m, 2×H-3), 2.38 (m, H-4′), 3.32 (s, 2×OMe), 4.36 (t, J=6 Hz, H-4″), 4.72 (s, 1″-=CH_2), 4.75 (s, 1″-=CH_2); ^{13}C NMR δ 22.4 (2′-Me), 24.7 (C-4), 29.4 (C-3″), 30.0 (C-1), 30.8 (2′-Me), 31.1 (C-2″), 33.6 (C-2′), 39.9 (C-3′), 41.6 (C-4′), 42.1 (C-3), 47.9 (C-1′), 52.7 (2×OMe), 104.2 (C-4″), 107.0 (1″-=CH_2), 151.9 (C-1″), 209.0 (C-2). Anal. Calcd for $C_{17}H_{30}O_2$: C, 72.3; H, 10.7. Found C, 72.5; H, 10.4.

4.2.3. (1′*R*,4′*S*)-4-[4-(3-[1, 3]Dioxan-2-yl-1-methylenepropyl)-2,2-dimethylcyclobutyl]-butan-2-one (11). To a mixture of benzene (30 mL), *p*-toluenesulfonic acid (32 mg, 0.017 mmol) and 1,3 propanediol (0.647 g, 8.5 mmol) was added keto-aldehyde **9** (2.0 g, 8.5 mmol). The reaction was fitted with a Dean–Stark trap and heated under reflux for 2 h. The reaction mixture was cooled, washed with satd aqueous $NaHCO_3$ solution (35 mL), the aqueous layer extracted with ether (2×10 mL) and the combined organic portions dried. Evaporation gave an oil (2.40 g) which, on centrifugal chromatography (Et_2O/hexanes; 1:1) gave **11** (1.9 g, 80%) as a clear liquid; ^{1}H NMR δ 0.99 (s, 2′-Me), 1.00 (s, 2′-Me), 1.30 (m, $W_{h/2}$=2 Hz, H-5‴), 1.39 (t, J=10 Hz, H-3′), 1.54 (dt, J=8, 8 Hz, 2×H-4), 1.64 (m, 2×H-3″), 1.75 (m, H-3′), 1.82 (m, H-1′), 2.00 (m, 2×H-2″), 2.05 (m, H-5‴), 2.07 (s, 3×H-1), 2.29 (m, 2×H-3), 2.32 (m, H-4′), 3.70 (ddd, J=3, 12, 12 Hz, H-4‴, 6‴), 4.05 (dd, J=5, 12 Hz, H-4‴, 6‴), 4.47 (t, J=5.5 Hz, H-2‴), 4.65 (brs, 1″-=CH_2), 4.69 (brs, 1″-=CH_2); ^{13}C NMR δ 22.4 (q, 2′-Me), 24.7 (t, C-4), 25.8 (t, C-5‴), 28.7 (t, C-2″), 29.8 (q, C-1), 31.0 (q, 2′-Me), 33.5 (s, C-2′), 33.5 (t, C-3″), 39.9 (t, C-3′), 41.6 (d, C-4′), 42.0 (t, C-3), 47.8 (d, C-1′), 66.9 (t, C-3‴, 6‴), 101.9 (d, C-2‴), 106.9 (t, 1″-=CH_2), 151.9 (s, C-1″), 208.8 (s, C-2). Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.4; H, 10.3. Found C, 73.1; H, 10.2.

4.2.4. (3′*E*,1″*R*,4″*S*)- and (3′*Z*,1″*R*,4″*S*)-2-{6-[4-(4,4-Dimethoxy)-1-methylenebutyl)-2, 2-dimethylcyclobutyl]-4-methyl-3-hexenyl}-2-methyl-1,3-dioxolane (14). (a) *n*-BuLi (871 μL, 1.4 M, 1.22 mmol) was added dropwise over 5 min to a stirred suspension of phosphonium salt **12**[10,11] {CN 21955-58-8} (0.580 mg, 1.11 mmol) in THF (20 mL) at −85 °C. After stirring for 5 min the solution was warmed to room temperature. After stirring for 10 min the bright orange/red solution was cooled to −85 °C and keto acetal **10** (0.300 g, 1.12 mmol) in THF (3 mL) was added dropwise over 5 min. The mixture was warmed to room temperature and stirred for 3 h before being diluted with H_2O (35 mL) and extracted with Et_2O (3×10 mL). Drying over anhyd. $MgSO_4$ and evaporation gave a yellow oil (0.350 g). Centrifugal SiO_2 chromatography (hexanes to Et_2O/hexanes; 1:1) gave a mixture of the (*E*) and (*Z*) isomers of **14** (5:11 by GC) (0.292 g, 66%). Further centrifugal chromatography on a sub-sample (×2, hexanes to Et_2O/hexanes; 3:1) yielded an enriched fraction of **14** with a 1:6 (*E*)/(*Z*) ratio by GC; IR (neat) ν_{max} 1039 (C–O), 924 (CH=C), 875 (CH_2=C) cm^{-1}; MS (EI) *m*/*z* (%) 379 ($M^+ - CH_3$, 5%), 362 ($M^+ -$MeOH, 5%), 347 ($M^+ - C_2H_7O$, 5%), 330 ($M^+ -$2MeOH, 5%). NMR spectra of mixtures of various compositions allowed assignment of most of the resonances for the two isomers. The (*Z*)-isomer had: ^{1}H NMR δ 1.06 (s, 2″-Me), 1.07 (s, 2″-Me), 1.32 (s, 2-Me), 1.67 (d, J=1 Hz, 4′-Me), 2.36 (ddd, J=9.5, 9.5, 9.5 Hz, H-4″), 3.32 (s, 2×OMe), 3.93 (m, $W_{h/2}$=7 Hz, 2×H-4 and 2×H-5), 4.37 (t, J=8 Hz, H-4‴), 4.71 (dd, J=1, 1 Hz, 1‴-=CH_2), 4.76 (s, 1‴-=CH_2), 5.08 (ddd, J=1, 8, 8 Hz, H-3′); ^{13}C NMR δ 22.4 (2″-Me), 22.7 (C-6′), 23.5 (2-Me), 23.9 (4′-Me), 29.5, 29.7, 30.6, 30.9 (C-1′, C-2′, C-2‴ and C-3‴), 31.4 (2″-Me), 33.8 (C-2″), 39.5, 39.6 (C-5′ and C-3″), 41.6 (C-4″), 49.3 (C-1″), 52.8 (2×OMe), 64.7 (C-4 and C-5), 104.3 (C-4‴), 106.9 (1‴-=CH_2), 110.0 (C-2), 124.1 (C-3′), 136.0 (C-4′), 152.2 (C-1‴). The (*E*)-isomer had: ^{1}H NMR δ 1.04 (s, 2″-Me), 1.05 (s, 2″-Me), 1.32 (s, 2-Me), 1.59 (s, 4′-Me), 2.35 (m, H-4″), 3.32 (s, 2×OMe), 3.93 (m, 2×H-4 and

2×H-5), 4.37 (m, H-4‴), 4.70–4.78 (m, 1‴-=CH_2), 5.06 (m, H-3′); ^{13}C NMR δ 15.9 (4′-Me), 33.7 (C-2″), 41.6 (C-4″), 48.5 (C-1″), 52.8 (2×OMe), 64.7 (C-4 and C-5), 104.3 (C-4‴), 106.8 (1‴-=CH_2), 109.9 (C-2), 123.7 (C-3′), 135.5 (C-4′), 152.2 (C-1‴) (other peaks obscured by overlaps with signals of the (*Z*)-isomer). A microanalytical sample was prepared by prep. TLC ($CHCl_3$) followed by microdistillation at 90 °C/4×10^{-4} mm Hg). Anal. Calcd for $C_{24}H_{42}O_4$: C, 73.1; H, 10.7. Found C, 73.1; H, 11.0.

(b) *n*-BuLi in hexanes (1.0 mL, 1.54 M, 1.52 mmol) was added dropwise over 5 min to a stirred solution of phosphine oxide **13**[12] {CN 87109-17-9} (0.456 g, 1.38 mmol) in THF (20 mL) at −78 °C. After stirring for 2 min the solution was warmed to 0 °C. After stirring for 15 min the deep red solution was cooled to −78 °C and a solution of keto acetal **10** (0.390 g, 1.38 mmol) in THF (7 mL) was added dropwise over 2 min. The solution decolourised, was warmed to room temperature, stirred for 5 min then quenched with saturated NH_4Cl (20 mL) and extracted with Et_2O (3×15 mL). Drying of the combined organic phases over anhyd. $MgSO_4$ and evaporation gave a pale yellow solid (0.964 g). Centrifugal chromatography (EtOAc to EtOH/EtOAc; 1:9) gave: (i) a mixture of diastereoisomers of the diphenylphosphinoyl alcohols **16** (0.350 g, 41%); IR (nujol) ν_{max} 3350 (OH), 1549, 1481, 1460, 1261, 1170, 750 cm^{-1}; ^{1}H NMR† δ 0.84, 0.88 (both s, 2″-Me), 0.96, 0.98, 1.04 (all s, 4′-Me), 1.24, 1.27 (both s, 2-Me), 1.25–2.25 (m, unassigned), 2.32 (m, $W_{h/2}$=9 Hz, H-3′ and H-4″), 3.31 (s, 2×OMe), 3.59–4.28 (m, H-4 and H-5), 4.34 (m, $W_{h/2}$=15, H-4‴), 4.52–5.00 (m, 1‴-CH_2), 7.48 (m, $W_{h/2}$=14 Hz, Ph, 6H), 7.79 (m, $W_{h/2}$=36 Hz, Ph, 4H); ^{13}C NMR† δ 20.3–49.2 (multiple peaks, unassigned), 52.6 (OMe), 64.2, 64.4, 67.7 (C-4 and C-5), 75.8, 75.9 (C-4′), 104.06, 104.11 (C-4‴), 106.5, 106.6, 106.7, 106.8 (C-1‴), 109.0 (C-2), 128.3–131.5 (several peaks, Ph), 151.8, 152.0 (C-1‴); (ii) starting material **10** (0.200 g, 55%). The reaction was repeated on scales up to 1.0 g of **10**.

To a stirred solution of the phosphinoyl alcohol mixture **16** (0.525 g, 0.858 mmol) in DMF (5 mL) was added NaH (0.041 g, 60% in oil, 1.7 mmol) and the mixture was stirred at 50 °C. After 1 h, TLC indicated that the starting material had not been fully converted and additional NaH (0.040 g, 1.7 mmol) was added. After a further 1.5 h the mixture was cooled, diluted with Et_2O (10 mL), quenched with saturated NaCl (50 mL) and extracted with Et_2O (3×10 mL). Drying over anhyd. $MgSO_4$ and evaporation gave a brown oil (0.569 mg) that on centrifugal chromatography (hexanes to EtOH/EtOAc; 1:9) gave; (i) a mixture of the (*E*) and (*Z*) isomers of **14** (1:1 by GC) (0.050 g, 16%); (ii) keto acetal **10** (0.045 g, 19%); (iii) unchanged **16** (0.240 g, 46%).

4.2.5. (3‴*E*,1″*S*,2*R*″)- and (3‴*Z*,1″*S*,2*R*″)-2-(3-{3, 3-Dimethyl-2-[3-methyl-6-(2-methyl-[1, 3]dioxolan-2-yl)-hex-3-enyl]-cyclobutyl}-but-3-enyl)-[1,3]dioxane (15). (a) Keto acetal **11** (0.100 g, 0.25 mmol) in THF (1 mL) was reacted with phosphonium salt **12**[10,11] as for the reaction of **10**. The ylide was prepared from *n*-BuLi (177 μL, 1.55 M, 0.27 mmol), **12** (0.130 mg, 0.25 mmol) in THF (4 mL). A yellow oil (0.200 g) was separated by centrifugal SiO_2 chromatography (Et_2O/hexanes; 1:9 to 1:1) to give a mixture of the (*E*) and (*Z*) isomers of **15** (1:2.3 by GC) (0.0.041 g, 40%); IR (neat) ν_{max} 1042 (C–O), 922 (CH=C), 875 (CH_2=C) cm^{-1}; ^{1}H NMR δ 1.03, 1.04, 1.06, 1.07 (each s, 3″-Me), 1.33 (s, 2‴′-Me), 1.58 (brs, 3‴-Me (*E*)-isomer), 1.66 (brs, 3‴-Me (*Z*)-isomer), 2.36 (brddd, *J*=9.5, 9.5, 9.5 Hz, H-1″), 3.72 (ddd, *J*=3, 12, 12 Hz, H-4, 6), 3.93 (m, $W_{h/2}$=6 Hz, 2×H-4⁗, 2×5⁗), 4.10 (dd, *J*=5, 12 Hz, H-4, 6), 4.50 (t, *J*=8 Hz, H-2), 4.70 (m, $W_{h/2}$=13 Hz, 2×H-4′), 5.05–5.15 (m, H-4‴); ^{13}C NMR δ 15.9 (3‴-Me (*E*)-isomer), 48.5, 49.3 (C-2″), 64.7 (C-4⁗, 5⁗), 66.9 (C-4, 6), 102.1 (C-2), 106.9 (C-2⁗), 109.9, 110.0 (C-4′), 123.7, 124.1 (C-4‴), 135.6, 136.1 (C-3‴), 152.2, 152.3 (C-3′). Anal. Calcd for $C_{25}H_{42}O_4$: C, 73.9; H, 10.4. Found C, 73.6; H, 10.7.

(b) Keto acetal **11** (0.100 g, 0.25 mmol) in THF (1 mL) was reacted with the phosphine oxide **13** as for the reaction of **10**. The anion was prepared from *n*-BuLi in hexanes (177 μL, 1.55 M, 0.27 mmol), **13**[12] (0.082 g, 0.25 mmol) in THF (4 mL). A semi-solid (0.188 g) was separated by centrifugal chromatography (EtOAc to EtOH/EtOAc; 1:9) to give: (i) phosphinoyl alcohol **17** isomer fraction 1 (0.028 g, 15%); ^{1}H NMR† δ 1.00, 0.96 (each 3H, s, 3″-Me), 1.02 (3H, s, 3‴-Me), 1.17 (3H, s, 2⁗-Me), 1.25–2.45 (m), 3.10–3.35 (6H, m, H-4, 6, 4⁗, 5⁗), 4.10 (2H, dd, *J*=5, 12 Hz, H-4, 6), 4.50 (1H, t, *J*=6.5 Hz, H-2), 4.69 (2H, brs, H-4′), 7.48 (6H, m, $W_{h/2}$=18 Hz, Ph), 7.82 (4H, m, $W_{h/2}$=32 Hz, Ph); ^{13}C NMR δ 20.5–46.5 (multiple peaks), 48.9 (C-2″), 64.4 (C-4⁗, 5⁗), 66.9 (C-4, 6), 76.1, 76.2 (C-3‴), 102.1 (C-2), 106.6 (C-4′), 109.2 (C-2⁗), 134.0–128.5 (multiple peaks, Ph), 152.2 (C-3′); (ii) phosphinoyl alcohol **17** isomer fraction 2 (0.028 g, 15%); ^{1}H NMR† δ 0.98, 0.95 (each 3H, s, 3″-Me), 1.01 (3H, s, 3‴-Me), 1.19 (3H, s, 2⁗-Me), 1.20–2.45 (m), 3.70 (6H, m, $W_{h/2}$=41 Hz, H-4, 6, 4⁗, 5⁗), 4.09 (2H, $W_{h/2}$=26 Hz, H-4, 6), 4.50 (1H, t, *J*=7 Hz, H-2), 4.69 (2H, $W_{h/2}$=8 Hz, H-4′), 7.50 (6H, m, $W_{h/2}$=18 Hz, Ph), 7.81 (4H, m, $W_{h/2}$=28 Hz, Ph); ^{13}C NMR δ 20.5–46.5 (multiple peaks), 48.9 (C-2″), 64.4 (C-4⁗, 5⁗), 66.9 (C-4, 6), 76.5, 76.5 (C-3‴), 102.0 (C-2), 106.9 (C-4′), 109.1 (C-2⁗), 134–128.5 (multiple peaks, Ph), 152.1 (C-3′); (iii) unchanged keto acetal **10b** (0.075 g, 72%).

The less polar phosphinoyl alcohol **17** fraction (0.028 g, 0.039 mmol) in DMF (0.5 mL) was treated with NaH (1.6 mg, 60% in oil, 0.039 mmol) as for the reaction of **16**. GC of the crude product revealed a 5:6 ratio of the (*Z*) to (*E*) isomers of **15**. The same ratio was obtained from the more polar **17** fraction.

4.2.6. (1′*S*,2′*R*,3″*E*)- and (1′*S*,2′*R*,3″*Z*)-3,3-Dimethyl-4-methylene-2-(3-methyl-7-oxoocta-3-enyl)cyclobutane-butanal (18). A solution of the (*E*) and (*Z*) isomers of **14** (0.649 g, 1.65 mmol, ratio 1:1) in THF (30 mL) containing aqueous HCl (2 M, 3 mL) was heated under reflux for 10 min. The mixture was cooled, quenched with saturated Na_2CO_3 (30 mL), and extracted with Et_2O (3×15 mL). Drying and evaporation gave the (*E*) and (*Z*) isomers of **18** (1:1 ratio by GC) as a clear oil (0.467 g, 93%); IR (neat) ν_{max} 2725 (HC=O), 1714 (C=O), 1634 (C=C) cm^{-1}; ^{1}H NMR δ 1.05, 1.07 (both s, 3′-Me), 1.59 (brs, 3″-Me, (*E*)-isomer), 1.66 (brd, *J*=1 Hz, 3″-Me, (*Z*)-isomer), 2.13 (s,

† Numbering as for **14**.

3×H-8″), 4.67, 4.78, 4.80 (all brs, γ-=CH_2), 5.00–5.09 (m, H-4″), 9.77 (t, J=2 Hz, H-1); ^{13}C NMR low-field signals at δ 107.4, 107.5 (γ-=CH_2), 122.4, 122.8 (C-4″), 136.6, 137.0 (C-3″), 150.8 (C-4), 202.3 (C-7″), 208.8 (C-1). A microanalytical sample was prepared by prep. TLC (CH_2Cl_2) followed by microdistillation at 90 °C/1×10^{-3} mm). Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.9; H, 10.6. Found C, 78.6; H, 10.7. A 5:11 mixture of the (*E*) and (*Z*) isomers of **16** was formed similarly.

4.2.7. (1*R*,4*E*,8*E*,13*S*)-, (1*R*,4*Z*,8*Z*,13*S*)- and (1*R*,4*Z*,8*E*,13*S*)-4,8,15,15-Tetramethyl-12-methylenebicyclo-[11.2.0]pentadeca-4, 8-dienes (4), (7) and (8). To a stirred mixture of $TiCl_3$ (8.14 g, 52.8 mmol) and Zn/Cu couple (11 g, M_r=65.5, 169 mmol) was added dry dimethoxyethane (120 mL). The mixture was gently simmered with vigorous stirring for 17 h. At first a blue-green colour was visible, but after ~5 h a black suspension predominated. A 5:11 mixture of (*E*) and (*Z*) isomers of keto aldehyde **18** (0.408 g, 1.32 mmol) was first dried for 4 h under vacuum at ambient temperature then dissolved in dry dimethoxyethane (49 mL) and added to the reaction via syringe pump at a rate of 0.54 mL h^{-1}. After 4 days, the addition was complete. The mixture was heated for a further 4 h, cooled, filtered through a pad of Florisil® and evaporated to give a yellow oil (0.482 g) containing three major components (1:1:1 ratio) by GC. Centrifugal chromatography on $AgNO_3$ impregnated silica (×2, hexane to EtOAc/hexane; 7:13) gave the following trienes listed in order of elution: (i) with EtOAc/hexanes; 3:97, (4*E*,8*E*)-diene **4** (0.056 g, 16%); $[\alpha]^{24}$ +42° (589 nm); +44° (577 nm); +50° (546 nm); +83° (435 nm); +93° (405 nm); +61° (365 nm) ($CHCl_3$, *c* 1.33); GC RI 1886 (170 °C), 1908 (190 °C); IR (CCl_4) ν_{max} 2928, 2860, 1461, 1381 (C–H), 1635, 921, 902 (C=C) cm^{-1}; ^{1}H NMR [LRHETCOR] δ 1.02 (s, 15α-Me) [15β-Me], 1.05 (s, 15β-Me) [15α-Me], 1.40 (m, $W_{1/2}$=19 Hz, H-2), 1.54 (s, 4-Me) [C-4, C-5], 1.55 (m, H-2), 1.58 (s, 8-Me) [C-8, C-9], 1.63 (m, 2×H-14) [15α-Me, C-12], 1.74 (m, H-3) [C-2, C-5], 1.87 (ddd, J=5.5, 9.5, 9.5 Hz, H-1), 2.01 (m, H-11), 2.04 (m, H-3), 2.08 (m, 2×H-7), 2.13 (m, 2×H-6), 2.21 (m, H-11), 2.28 (m, 2×H-10), 2.50 (ddd, J=9.5, 9.5, 9.5 Hz, H-13) [C-2], 4.74 (s, 12-=CH_2), 4.83 (s, 12-=CH_2) [15β-Me], 4.89 (dd, J=6.5, 6.5 Hz, H-5), 5.21 (dd, J=6.5, 6.5 Hz, H-9); ^{13}C NMR see Table 1; MS (EI) *m/z* [%] 272 [11], 257 [17], 216 [15], 201 [10], 161 [19], 147 [19], 137 [10], 135 [20], 133 [29]; HRMS [M^+] calcd for $C_{20}H_{32}$ 272.2504, found 272.2507; (ii) with EtOAc/hexanes; 3:97, (4*Z*,8*Z*)-diene **7** (0.063 g, 17%); $[\alpha]^{24}$ −23° (589 nm); −25° (577 nm); −29° (546 nm); −61° (435 nm); −78° (405 nm); −31° (365 nm) ($CHCl_3$, *c* 1.06); GC RI 1879 (170 °C), 1901 (190 °C); IR (CCl_4) ν_{max} 2958, 2861, 1461, 1379 (C–H), 1636, 900 (C=C) cm^{-1}; ^{1}H NMR [LRHETCOR] δ 1.03 (s, 15β-Me), 1.04 (15α-Me), 1.27 (m, $W_{1/2}$=23 Hz, H-6), 1.56 (dd, J=12, 12 Hz, H-14) [C-12, 15α-Me, 15β-Me], 1.62 (m, H-7), 1.70 (s, 4-Me and 8-Me), 1.72 (m, H-1), 1.81 (m, H-6), 1.83 (dd, J=12, 12 Hz, H-14) [15α-Me], 1.84 (m, H-10), 1.85 (m, H-2), 1.90 (ddd, J=3, 10, 10 Hz, H-3), 2.09 (m, 2×H-11) [C-12], 2.10 (m, H-10), 2.11 (m, H-3) [C-2], 2.36 (dd, J=15, 15 Hz, H-7) [C-4], 2.37 (m, H-2) [15α-Me], 2.52 (ddd, J=9, 9.5, 9.5 Hz, H-13) [C-12, 15β-Me], 4.71 (dd, J=2, 2 Hz, 12-=CH_2) [C-11], 4.75 (d, J=1 Hz, 12-=CH_2) [C-13], 5.21 (dd, J=8, 8 Hz, H-9), 5.23 (dd, J=8, 8 Hz, H-5); COSY correlations observed between δ 1.27 (H-6) and both δ 1.62 and 2.36 (H-7); ^{13}C NMR see Table 1; MS (EI) *m/z* [%] 272 [9], 257 [8], 216 [10], 201 [6], 161 [12], 147 [10], 137 [5], 135 [12], 133 [22]; HRMS [M^+] calcd for $C_{20}H_{32}$ 272.2504, found 272.2506; (iii) with EtOAc/hexanes; 3:17, (4*Z*,8*E*)-diene **8** (0.069 g, 19%); $[\delta]^{24}$ −84° (589 nm); −88° (577 nm); −103° (546 nm); −194° (435 nm); −245° (405 nm); −175° (365 nm) ($CHCl_3$, *c* 0.99); GC RI 1839 (170 °C), 1860 (190 °C); IR (CCl_4) ν_{max} 2955, 2923, 2859, 1453, 1381 (C–H), 1640, 912 (C=C) cm^{-1}; ^{1}H NMR see Table 1; ^{13}C NMR see Table 1; MS (EI) *m/z* [%] 272 [14], 257 [10], 216 [18], 201 [8], 161 [15], 147 [18], 137 [5], 135 [16], 133 [26]; HRMS [M^+] calcd for $C_{20}H_{32}$ 272.2504, found 272.2505.

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Lannotinidines A–G, new alkaloids from two species of *Lycopodium*

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Abstract—Seven new *Lycopodium* alkaloids, lannotinidines A–G (**1**–**7**), have been isolated from the club moss *Lycopodium annotinum* and *L. annotinum* var. *acrifolium*. Stereochemistry of **1**–**7** was elucidated by combination of NOESY correlations and chemical transformation. Lannotinidines B–E (**2**–**5**) elevated NGF mRNA expression.

A number of *Lycopodium* alkaloids continue to be of interest from biogenetic[1,2] and biological[3] points of view as well as challenging targets for total synthesis.[4] For example, huperzine A has been shown to be a potent reversible inhibitor of acetylcholine esterase.[2] Our interest has been focused on isolation of structurally interesting *Lycopodium* alkaloids and biosynthetic intermediates to clarify the biogenetic pathway.[5–13] Investigation on extracts of *Lycopodium annotinum* and *L. annotinum* var. *acrifolium* (Lycopodiaceae) resulted in the isolation of seven new alkaloids, lannotinidines A–G (**1**–**7**), in which **2**–**5** elevated activity of NGF biosynthesis. This paper describes the isolation and structure elucidation of **1**–**7**, and its effects on neurotrophic factor biosynthesis.

1. Isolation of lannotinidines A–G (1–7)

The club moss of *L. annotinum* was extracted with MeOH, and the extract was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials, which were adjusted at pH 10 with satd Na_2CO_3, were extracted with $CHCl_3$. $CHCl_3$-soluble materials were subjected to an amino silica gel column (hexane/EtOAc, 1:0→2:3, and then $CHCl_3$/MeOH, 1:0→0:1), in which a fraction eluted with hexane/EtOAc (1:1) was purified by a silica gel column ($CHCl_3$/MeOH, 1:0→0:1) followed by C_{18} HPLC (26% CH_3CN/0.1% TFA) to afford lannotinidines A (**1**, 0.0002%), B (**2**, 0.0002%), F (**6**, 0.00002%), and G (**7**, 0.0001%) together with known alkaloids, annotinine (**8**),[14] lycodoline (**9**),[15] and lyconnotine (**10**).[16] In the previous silica gel column, another fraction eluted with $CHCl_3$/MeOH (7:3) was purified by a silica gel column ($CHCl_3$/MeOH, 1:0→0:1) to give lannotinidines C (**3**, 0.002%) and D (**4**, 0.001%).

The club moss of *L. annotinum* var. *acrifolium* was extracted with MeOH, and $CHCl_3$ soluble materials of the extract were subjected to an amino silica gel column (hexane/EtOAc, 1:0→0:1, and then $CHCl_3$/MeOH, 1:0→0:1), in which the fraction eluted with hexane/EtOAc (4:1) was separated by C_{18} HPLC to afford lannotinidine A (**1**, 0.01%), and that eluted with $CHCl_3$/MeOH (4:1) was purified by a silica gel column ($CHCl_3$/MeOH, 1:0→0:1) to give lannotinidine E (**5**, 0.01%) and annotinine (**8**).[14]

Lannotinidine A {**1**, $[\alpha]_D^{23}$ +47° (*c* 1.0, MeOH)} showed the pseudomolecular ion peak at *m/z* 292 $(M+H)^+$ in the FABMS, and the molecular formula, $C_{17}H_{25}NO_3$, was established by HRFABMS [*m/z* 292.1910, $(M+H)^+$, Δ −0.3 mmu]. IR absorptions implied the presence of hydroxyl and ester carbonyl (3392 and 1733 cm^{-1}, respectively) functionalities. ^1H and ^{13}C NMR data (Tables 1 and 3, respectively) revealed seventeen carbon signals due to one ester carbonyl carbon, one sp^2 quaternary carbon, one sp^3 quaternary carbon, one sp^2 methine, five sp^3 methines, six sp^3 methylenes, and two methyl groups. Among them, two methylenes (δ_C 50.4; δ_H 3.41; δ_C 49.7; δ_H 3.01 and 3.14) and one quaternary carbon (δ_C 62.6) were ascribed to those

Keywords: Alkaloids; *Lycopodium*; Lannotinidines A–G; NGF biosynthesis.
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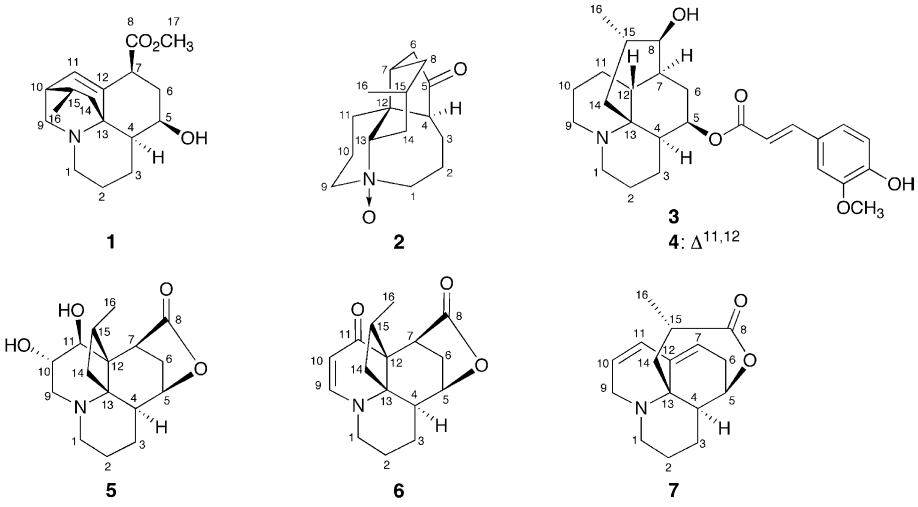


bearing a nitrogen. Since two out of six elements of unsaturation were accounted for, **1** was inferred to possess four rings. Partial structures (C-1 to C-7, C-9 to C-11, C-10 to C-15, and C-14 to C-16) were deduced from detailed analyses of 2D NMR data (^{1}H–^{1}H COSY and HOHAHA) of **1** (Fig. 1). Connections among the partial structures as shown in Figure 1, one isolated methyl (C-17) which was attached to an oxygen, and one carbonyl carbon at C-8 (δ_C 173.7) were implied by HMBC cross-peaks for H_3-17 and H-7 to C-8, H-11 to C-7, H_2-6 to C-12, H-5 and H_2-14 to C-13, respectively. HMBC correlations of H_2-1 to C-13 (δ_C 62.6) through a nitrogen revealed that the nitrogen was attached to C-1 and C-13. These data suggested that **1** possessed annopodine[16] skeleton with a hydroxyl at C-5, a methoxy carbonyl group at C-7, and a $\Delta^{11(12)}$ double bond. The relative stereochemistry of **1** was elucidated by NOESY

Table 1. ^{1}H NMR data [δ_H (*J*, Hz)] of lannotinidines A–D (**1–4**) in CD_3OD at 300 K

	1	2	3	4
1a	3.41 (2H, br d, 9.1)	3.61 (1H, m)	2.54 (1H, m)	3.19 (1H, m)
1b		3.93 (1H, m)	3.31 (1H, m)	3.73 (1H, m)
2a	1.76 (1H, m)	1.94 (1H, m)	1.39 (1H, d, 12.7)	1.85 (1H, m)
2b	2.06 (1H, m)	2.30 (1H, m)	2.02 (1H, m)	1.99 (1H, m)
3a	1.65 (1H, dddd, 13.4, 3.3, 3.3, 3.3)	1.70 (1H, m)	1.35 (1H, m)	1.52 (1H, m)
3b	1.90 (1H, m)	2.00 (1H, m)	1.80 (1H, m)	1.87 (1H, m)
4	2.03 (1H, m)	2.28 (1H, m)	2.71 (1H, m)	2.71 (1H, m)
5	4.21 (1H, ddd, 11.8, 6.6, 5.2)		5.21 (1H, t, 6.4)	2.35 (1H, m)
6a	1.52 (2H, m)	1.90 (1H, m)	1.96 (1H, m)	2.05 (1H, ddd, 16.2, 6.9, 6.9)
6b	2.53 (1H, m)	2.87 (1H, m)	2.02 (1H, m)	2.31 (1H, d, 16.2)
7	3.49 (1H, ddd, 14.1, 3.1, 3.1)	2.26 (1H, m)	1.81 (1H, m)	2.67 (1H, m)
8a		1.09 (1H, m)	3.31 (1H, m)	3.27 (1H,dd, 12.1, 4.6)
8b		1.55 (1H, br d, 14.2)		
9a	3.01 (1H, d, 12.1)	3.65 (1H, m)	2.51 (1H, m)	3.18 (1H, m)
9b	3.14 (1H, br d, 12.1)	3.43 (1H, d, 13.9)	3.31 (1H, m)	3.84 (1H, m)
10a	2.55 (1H, m)	2.04 (1H, m)	1.41 (1H, m)	2.33 (1H, m)
10b		2.02 (1H, m)	1.44 (1H, m)	2.61 (1H, m)
11a	6.42 (1H, dd, 6.9, 2.5)	1.74 (1H, m)	1.33 (1H, d, 12.2)	5.75 (1H, m)
11b		2.26 (1H, m)	1.77 (1H, m)	
12			1.41 (1H, m)	
13a		3.59 (1H, m)		
13b				
14a	1.94 (1H, m)	1.96 (1H, m)	0.97 (1H, t, 12.2)	1.30 (1H, m)
14b	2.06 (1H, m)	2.46 (1H, br d, 13.2)	2.74 (1H, m)	2.94 (1H, m)
15a	1.85 (1H, m)	2.19 (1H, m)	2.71 (1H, m)	2.83 (1H, m)
15b				
16	1.19 (3H, d, 7.1)	1.12 (3H, d, 7.2)	1.11 (3H, d, 6.1)	1.15 (3H, d, 5.5)
17a	3.77 (3H, s)			
17b				
18			6.33 (1H, d, 15.6)	6.35 (1H, d, 15.9)
19			7.64 (1H, d, 15.6)	7.61 (1H, d, 15.9)
20				
21			7.32 (1H, m)	7.19 (1H, s)
22				
23				
24			6.84 (1H, d, 8.2)	6.83 (1H, d, 8.1)
25			7.10 (1H, d, 8.2)	7.09 (1H, d, 8.1)
26			3.89 (3H, s)	3.90 (3H, s)

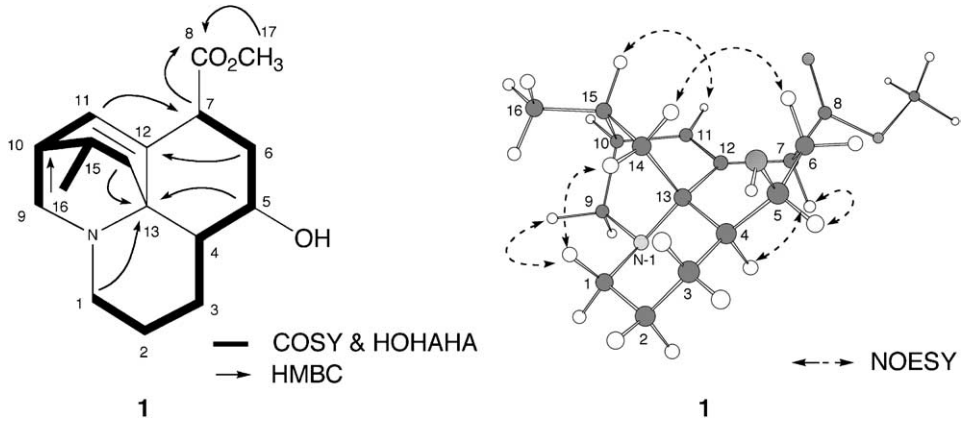


Figure 1. Selected 2D NMR correlations and relative stereochemistry for lannotinidine A (**1**).

correlations as shown in computer-generated 3D drawing (Fig. 1). The α-configurations of H-4, H-5, and H-7 were elucidated by NOESY correlations among H-4, H-5, and H-7. The relative stereochemistry of C-15 was assigned as shown in Figure 1 by the NOESY correlation between H-15 and H-11. NOESY correlations of H-6 to H-14a, H-1 to H-14b, and H-1 to H-9 supported the relative stereochemistry of C-13. Isomerization of double bond at $\Delta^{11(12)}$ in **1** by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave a compound with $\Delta^{7(12)}$ double bond, whose spectroscopic data were identical with those of annopodine.[16] Thus, the relative stereochemistry of lannotinidine A (**1**) was assigned as shown.

Lannotinidine B {**2**, $[\alpha]_D^{24}$ −62° (*c* 1.0, MeOH)} was revealed to have the molecular formula, $C_{16}H_{25}NO_2$, by HRFABMS [*m/z* 264.1960 $(M+H)^+$, Δ −0.3 mmu]. IR absorptions implied the presence of carbonyl (1731 cm^{-1}) group. ^1H and ^{13}C NMR data (Tables 1 and 3, respectively) suggested the presence of one ketone, nine sp^3 methylenes, four sp^3 methines, one methyl, and one sp^3 quaternary carbon. Among them, one methine (δ_c 78.6) and two methylenes (δ_c 72.1 and 69.2) were ascribed to those bearing a nitrogen oxide.[17]

^1H–^1H COSY and HOHAHA correlations of **2** clearly revealed the presence of two structural units **a** (C-1–C-4) and **c** (C-9–C-11) as shown in Figure 2. HMBC correlations for H_3-16 of C-8 (δ_c 37.6) indicated the presence of partial unit **b** (C-6–C-8 and C-13–C-16). Connections among three units **a**–**c**, C-5 (δ_C 218.0), and C-12 (δ_C 46.3) were suggested by HMBC correlations as follows. HMBC correlations for H-4, H-7, H-11, and H-13 of C-12 gave rise to connectivities of the three units through C-12. The connectivity between C-4 and C-6 through C-5 was elucidated by HMBC cross-peaks for H-6a (δ_H 1.90) and H-4 (δ_H 2.28) of C-5. Connectivities among C-1, C-9, and C-13 through N-1 were provided by HMBC correlations for H-1 to C-9 (δ_C 69.2) and C-13 (δ_C 78.6), H-9 to C-1 (δ_C 72.1) and C-13, and H-13 to C-1 and C-9. Thus, the gross structure of lannotinidine B was elucidated to be **2**.

The relative stereochemistry of **2** was deduced from cross-peaks observed in the phase sensitive NOESY spectrum as shown in computer-generated 3D drawing (Fig. 2). Chair conformations of a cyclohexane ring (C-7, C-8, and C-12–C-15) and a piperidine ring (N-1 and C-9–C-13) were suggested by NOESY correlations of H-9b to H-13 and H-11a, H-13 to H-11a and H_3-16, and H-7 to H-11a and H_3-16. NOESY correlations of H-4 to H-2a and H-10a indicated an α-configuration of H-4. NOESY cross-peaks of H-3b to H-8 and H-14a suggested that H-3b, H-8, and H-14a were oriented to the same side on the ring.

HRFABMS data [**3**: *m/z* 442.2579, $(M+H)^+$, Δ −1.4 mmu; **4**: *m/z* 440.2458, $(M+H)^+$, Δ −2.1 mmu] of

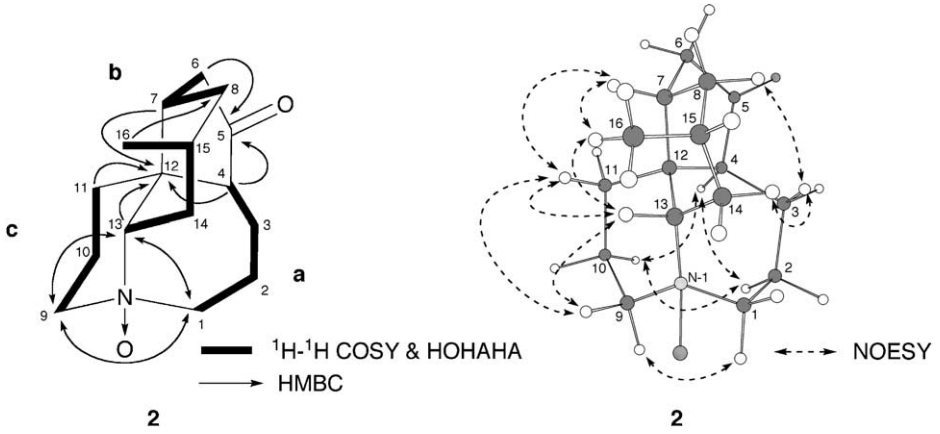


Figure 2. Selected 2D NMR correlations and relative stereochemistry for lannotinidine B (**2**).

Table 2. ^{1}H NMR data [δ_H (J, Hz)] of lannotinidines E–G (**5**–**7**) in CD_3OD at 300 K

	5	6	7
1a	2.57 (1H, ddd, 14.3, 4.3, 4.3)	3.42 (1H, dd, 13.8, 5.3)	3.43 (2H, dt, 17.0, 13.2, 3.8)
1b	3.15 (1H, ddd, 14.3, 11.2, 3.8)	3.80 (1H, ddd, 16.7, 13.8, 5.3)	
2a	1.48 (1H, m)	1.75 (2H, m)	1.94 (1H, m)
2b	1.59 (1H, m)		2.08 (1H, m)
3a	1.48 (1H, m)	1.67 (1H, dt, 12.1, 4.4)	1.83 (1H, dd, 8.2, 3.3)
3b	1.59 (1H, m)	1.73 (1H, m)	
4	1.90 (1H, m)	1.93 (1H, d, 12.1)	2.30 (1H, m)
5	4.53 (1H, d, 6.0)	4.63 (1H, d, 5.0)	4.75 (1H, dd, 8.9, 4.3)
6a	2.07 (1H, d, 12.5)	1.80 (1H, d, 12.4)	2.67 (1H, m)
6b	2.40 (1H, ddd, 12.5, 6.0, 5.8)	2.52 (1H, dt, 6.2, 5.8)	3.07 (1H, m)
7	2.87 (1H, d, 5.8)	3.30 (1H, d, 5.5)	6.10 (1H, t, 3.7)
9a	2.63 (1H, dd, 11.2, 10.5)	7.19 (1H, s), 6.83 (1H, d, 7.6)[a]	3.80 (1H, d, 4.6)
9b	2.68 (1H, dd, 11.2, 4.8)		3.87 (1H, m)
10	3.83 (1H, ddd, 10.5, 8.4, 4.8)	4.72 (1H, d, 7.6)[a]	5.79 (1H, m)
11	3.30 (1H, m)		6.40 (1H, d, 10.2)
14a	1.80 (1H, dd, 11.4, 11.1)	2.41 (1H, t, 12.1)	1.76 (1H, dd, 13.8, 2.1)
14b	1.86 (1H, dd, 11.4, 8.6)	2.71 (1H, dd, 12.6, 8.6)	2.44 (1H, t, 13.1)
15	2.81 (1H, m)	3.04 (1H, m)	2.67 (1H, m)
16	1.28 (3H, d, 7.4)	1.20 (3H, d, 7.3)	1.20 (3H, d, 6.6)

[a] In $CDCl_3$.

lannotinidines C {**3**, $[\alpha]_D^{24}$ −5° (*c* 1.0, MeOH)} and D {**4**, $[\alpha]_D^{24}$ −24° (*c* 1.0, MeOH)} revealed the molecular formula, $C_{26}H_{35}NO_5$ and $C_{26}H_{33}NO_5$, respectively. The ^{1}H and ^{13}C NMR (Tables 1 and 3, respectively) spectra of **3** revealed signals due to five quaternary carbons ($sp^2\times4$ and $sp^3\times1$), eleven methines ($sp^2\times5$ and $sp^3\times6$), eight methylenes, and two methyls, suggesting that **3** had a similar backbone skeleton to that of lycodoline (**9**) with a ferulic acid. In the ^{13}C NMR spectrum of **3**, signals due to two oxygen-bearing carbons at δ_C 70.6 (d) and 79.4 (d), three nitrogen-bearing carbons at δ_C 47.4 (t), 48.3 (t), and 57.3 (s), and one ester carbonyl carbon at δ_C 167.5 (s) appeared. The structure of **3** was elucidated by 2D NMR (^{1}H–^{1}H COSY, HOHAHA, HMQC, and HMBC) data (Fig. 3). The ^{1}H–^{1}H COSY and HOHAHA spectra revealed connectivities as shown in Figure 3. The partial unit (C-1–C-8, C-9–C-12, and C-14–C-16) was connected to C-13 on the basis of HMBC correlations of H-1a, H-5, H-7, H-9a, and H-14a to C-13 (δ_C 57.3). The presence of a ferulic acid ester at C-5 was revealed by HMBC correlations of H-5 and H-18 to C-17 (δ_C 167.5).

The relative stereochemistry of **3** was deduced from NOESY correlations (Fig. 3). NOESY cross-peaks of H-7/H-11b, H-14a/H-12, H-4/H-9a, and H-3a/H-5 suggested the stereochemistry at C-4, C-5, C-7, C-12, and C-13 as shown in Figure 3. The configuration of β-oriented ferulic acid ester at C-5 was also supported by the $^3J_{H-H}$ values (6.4 Hz each) between H-4 and H-5, and between H-5 and H-6. Hydrolysis of **3** with sodium methoxide gave a compound whose spectral data and $[\alpha]_D$ value were identical with those of deacetylfawcettiine.[18] Thus, the absolute configuration of lannotinidine C was assigned as **3**.

The molecular formula of lannotinidine D (**4**) was smaller than that of lannotinidine C (**3**) by an H_2 unit. ^{1}H and ^{13}C NMR data (Tables 1 and 3, respectively) of **4** were analogous to those of **3** with a hydroxyl at C-8 and a ferulic acid ester at C-5, although signals of trisubstituted olefin carbons (δ_H 5.75; δ_C 117.4 and 141.3) at C-11 and C-12 were observed for **4**. The gross structure of **4** was elucidated by 2D NMR (^{1}H–^{1}H COSY, HOHAHA, HMQC, and HMBC) data. Treatment of **4** with sodium methoxide afforded a hydrolysate whose spectral data and $[\alpha]_D$ value were identical with those of lycofoline.[19] Thus, the structure of lannotinidine D was assigned as **4**.

Lannotinidine E (**5**) was shown to have the molecular

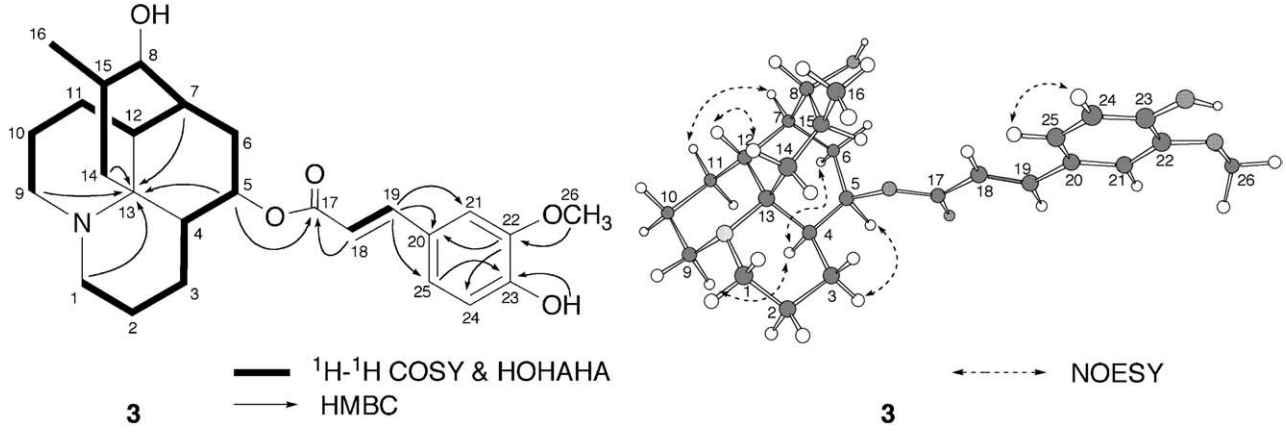


Figure 3. Selected 2D NMR correlations and relative stereochemistry for lannotinidine C (**3**).

Table 3. ^{13}C NMR data (δ_C) of lannotinidines A–G (**1**–**7**) in CD_3OD at 300 K

	1	2	3	4	5	6	7
1	50.4	72.1	48.3	50.3	49.9	49.9	49.6
2	24.8	22.7	20.6	20.1	24.8	28.8	24.1
3	20.7	39.6	25.2	22.1	25.5	24.3	21.8
4	42.2	57.0	32.5	44.0	38.1	47.9	43.8
5	67.0	218.0	70.6	70.0	82.6	81.1	75.2
6	35.0	44.9	24.8	31.0	36.1	37.2	32.7
7	42.2	39.1	42.8	47.8	43.6	40.4	130.9
8	173.7	37.6	79.4	77.8	182.2	181.3	177.2
9	49.7	69.2	47.4	46.0	53.8	153.6	49.8
10	36.0	26.6	23.4	23.5	73.4	92.7[a]	119.9
11	131.6	24.8	24.8	117.4	77.2	190.8	127.1
12	141.4	46.3	44.6	141.3	53.6	55.7	133.1
13	62.6	78.6	57.3	63.8	63.9	66.6	62.0
14	28.8	28.7	41.5	37.9	35.6	40.3	28.3
15	30.1	28.2	32.4	32.1	33.2	37.0	34.2
16	18.0	17.5	21.1	20.1	14.2	12.9	18.8
17	52.5		167.5	168.1			
18			115.6	115.6			
19			145.6	147.1			
20			134.6	127.7			
21			112.7	112.0			
22			149.5	149.4			
23			153.0	150.8			
24			116.7	116.6			
25			124.3	124.2			
26			56.4	56.5			

[a] In $CDCl_3$.

formula of $C_{16}H_{23}NO_4$ by HRFABMS [*m/z* 294.1712, $(M+H)^+$, Δ +0.7 mmu]. The IR spectrum was indicative of the presence of hydroxyl (3385 cm^{-1}) and butanolide (1767 cm^{-1}) functionalities. ^1H and ^{13}C NMR data including DEPT experiments (Tables 2 and 3, respectively) disclosed the presence of one ketone, two sp^3 quaternary carbons, six sp^3 methines, six sp^3 methylenes, and one methyl group. The ^1H–^1H COSY and HOHAHA spectra revealed connectivities of three partial structures **a** (C-1–C-7), **b** (C-9–C-11) with 1,2-diol at C-10 and C-11, and **c** (C-14–C-16) as shown in Figure 4. HMBC correlations were observed for H-6a, H-11, and H_3-16 to C-12 (δ_C 53.6), suggesting that C-7 and C-11 were connected to each other through C-12. The connectivity of C-4–C-13 was implied by an HMBC correlation for H-5 to C-13 (δ_C 63.9). HMBC cross-peaks for H-5 and H-6a to C-8 (δ_C 182.2), H-1a and H_2-9 to C-13, and H_2-1 to C-9 indicated that a γ-lactone ring was formed between C-8 and a hydroxyl at C-5, and that C-1, C-9, and C-13 were attached to a nitrogen atom.

The relative stereochemistry of **5** was elucidated from NOESY correlations as shown in computer-generated 3D drawing (Fig. 4). The α- and β- configurations of hydroxyls at C-10 and C-11 were elucidated by NOESY correlations of H-10/H-15 and H-6a/H-11, respectively. The $^3J_{H-H}$ coupling value ($J_{10/11}$ = 8.4 Hz) supported these configurations. In addition, NOESY correlations as shown in Figure 4 indicated that **5** possessed a similar stereostructure to that of annotinine (**8**). Treatment of annotinine (**8**) with sulfuric acid gave a dihydroxy derivative, whose spectral data and $[\alpha]_D$ value were identical with those of lannotinidine E (**5**). Thus, the absolute stereochemistry of lannotinidine E (**5**) was assigned as shown.

Lannotinidine F {**6**, $[\alpha]_D^{24}$ −22° (*c* 1.0, MeOH)} was revealed to have the molecular formula, $C_{16}H_{19}NO_3$, by HRFABMS [*m/z* 274.1432 $(M+H)^+$, Δ −1.1 mmu]. IR absorptions implied the presence of carbonyl (1770 and 1680 cm^{-1}) groups. ^1H and ^{13}C NMR data (Tables 2 and 3)

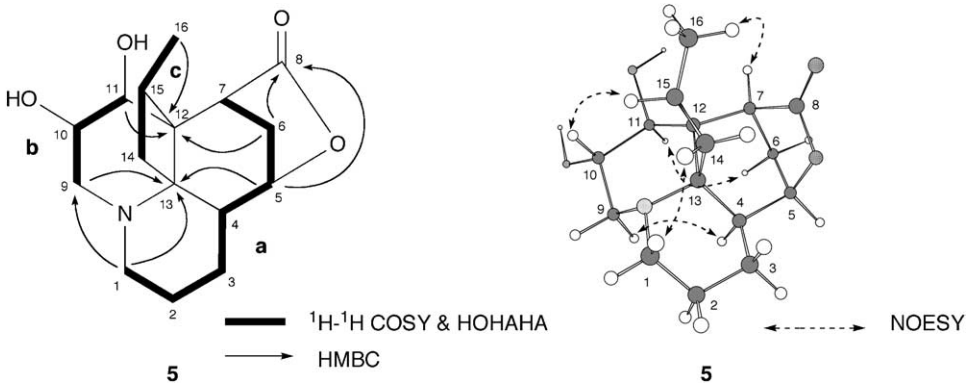


Figure 4. Selected 2D NMR correlations and relative stereochemistry for lannotinidine E (**5**).

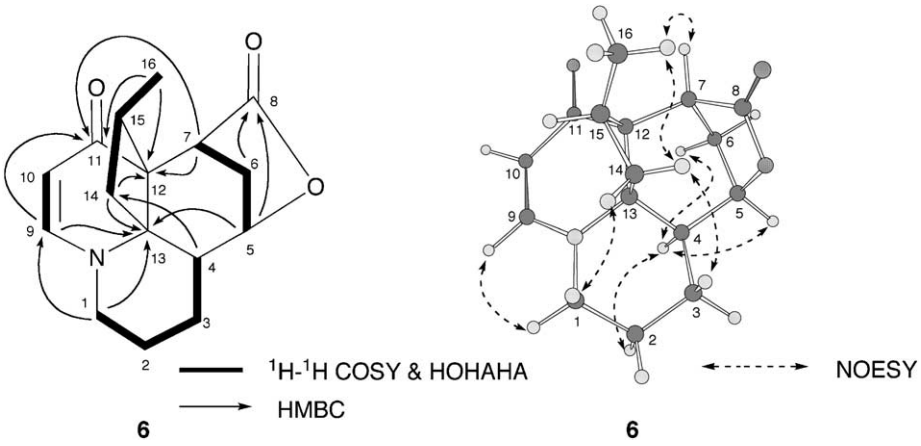


Figure 5. Selected 2D NMR correlations and relative configurations for lannotinidine F (**6**).

suggested the presence of two ketones, two sp^2 methines, five sp^3 methylenes, four sp^3 methines, one methyl, and two sp^3 quaternary carbon. Among them, one sp^2 methine (δ_c 153.6), one methylene (δ_c 49.9), and one quaternary carbon (δ_c 66.6) were ascribed to those bearing a nitrogen.

The ^1H–^1H COSY and HOHAHA spectra of **6** revealed four structural units as shown in Figure 5. The presence of 2,3-dihydro-4-pyridinone and γ-lactone moieties was suggested by HMBC correlations for H-9 of C-11 and C-13, H-5 and H-6 of C-8, respectively. Connectivities among C-1, C-9, and C-13 through a nitrogen were elucidated by HMBC cross-peaks for H-1 of C-9 and C-13. HMBC correlations for H-1, H-5, and H-14 of C-13, H-7, H-14, and H-16 of C-12, H-7 and H-16 of C-11, and H-4 of C-14 gave rise to connectivities among the four units through a nitrogen atom, C-11, C-12, and C-13. Thus, the gross structure of lannotinidine F was elucidated to be **6**. The relative stereochemistry of **6** was deduced from cross-peaks observed in the phase sensitive NOESY spectrum as shown in computer-generated 3D drawing (Fig. 5).

Lannotinidine G (**7**) was revealed to have the molecular formula, $C_{16}H_{21}NO_2$, by HRFABMS [*m/z* 260.1653 $(M+H)^+$, Δ +0.3 mmu]. IR absorptions implied the presence of carbonyl (1685 cm^{-1}) group. ^1H and ^{13}C NMR data (Tables 2 and 3, respectively) suggested the presence of one ketone, three sp^2 methines, one sp^2 quaternary carbon, six sp^3 methylenes, three sp^3 methines, one methyl, and one sp^3 quaternary carbon. Among them, signals due to three nitrogen-bearing carbons at δ_c 49.6, 49.8, and 62.0, and an oxygen-bearing carbon at δ_c 75.2 appeared.

The structure of **7** was elucidated by 2D NMR (^1H–^1H COSY, HOHAHA, HMQC, and HMBC) data (Fig. 6). The ^1H–^1H COSY and HOHAHA spectra revealed connectivities of C-1–C-7, C-9–C-11, and C-14–C-16. These three partial units were connected to one another on the basis of HMBC correlations as shown in Figure 6. Lannotinidine G (**7**) was identical with a compound produced by hydrolysis of lyconnotine (**10**) with KOH/MeOH followed by acidification.[16] The relative stereochemistry of **7** was deduced from NOESY correlations[16] (Fig. 6).

2. Plausible biogenesis of lannotinidines A–G (1–7)

A plausible biogenetic pathway for lannotinidines A–G (**1**–**7**), annotinine (**8**), lycodoline (**9**), and lyconnotine (**10**) is proposed as shown in Scheme 1. Lannotinidine B (**2**), which is the fawcettidane-type alkaloid without a hydroxy group or an olefin at C-13, may be derived through rearrangement (path **a**) from lycodoline (**9**).[9] Biogenetically, lannotinidines A (**1**), E (**5**), F (**6**), and G (**7**) may be derived from lycodoline (**9**). Cleavage of the C-8–C-15 bond (path **b**) followed by bond formation at C-12–C-15, formation of a γ-lactone ring, and epoxidation may produce annotinine (**8**), and then

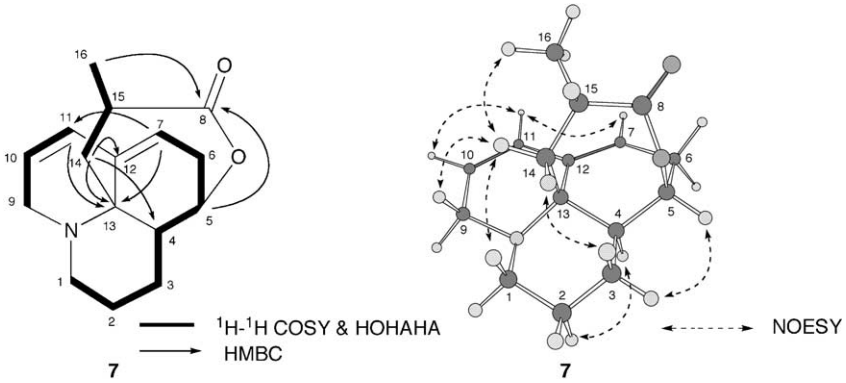
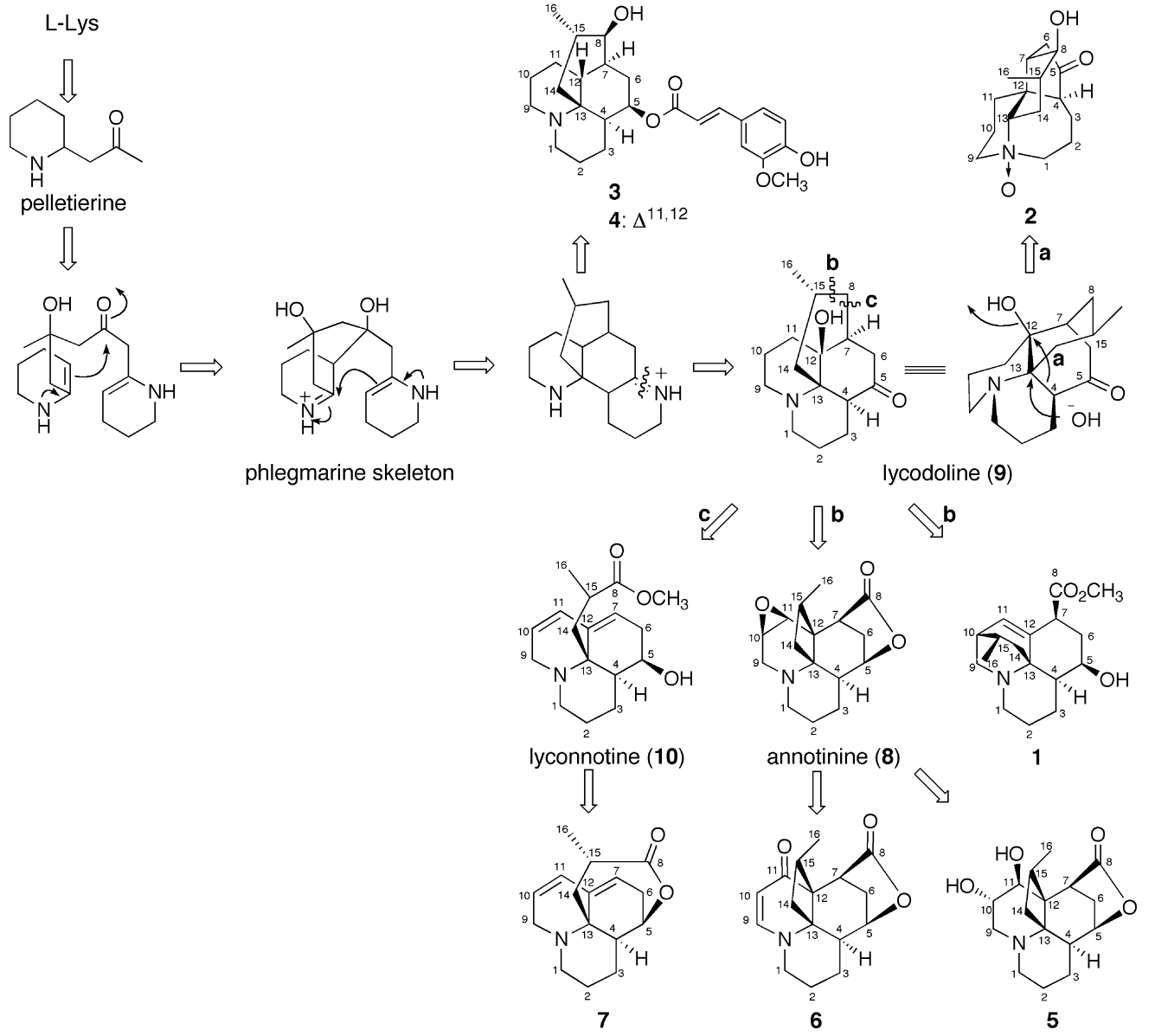


Figure 6. Selected 2D NMR correlations and relative stereochemistry for lannotinidine G (**7**).



Scheme 1.

cleavage of the epoxide ring and/or oxidation to produce lannotinidines E (**5**) and F (**6**). Bond formation at C-10–C-15 (path **b**) may produce lannotinidine A (**1**). On the other hand, lannotinidine G (**7**) may be derived through formation of a lactone ring from lyconnotine (**10**), which may be produced by cleavage of C-7–C-8 bond of lycodoline (**9**) (path **c**).

3. Bioactivity of lannotinidines A–F (1–6)

Effects of lannotinidines A–F (**1**–**6**) on neurotrophic factor biosynthesis in 1321N1 human astrocytoma cells were examined by determining NGF mRNA expression. 1321N1 cells were incubated with 30 μg/ml each of lannotinidines A–F (**1**–**6**) for 6 h, and the mRNA expressions of NGF in 1321N1 cells were examined by a semiquantitative RT-PCR method.[20] The mRNA expressions for NGF were enhanced by lannotinidines B–E (**2**–**5**) (Fig. 7), among which **2** was the most potent.

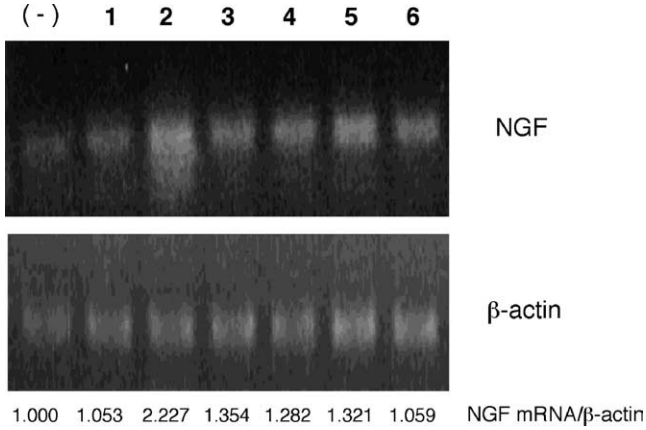


Figure 7. Effects of lannotinidines A–F (**1**–**6**) on NGF mRNA expression in 1321N1 cells. The cells were stimulated by the compounds for 6 h, and then total RNA from 132 1N1 cells was reverse transcribed, followed by PCR as described under Section 4. The amount of β-actin mRNA in each cell condition was also shown.

4. Experimental

4.1. General methods

^{1}H 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. Each NMR sample of lannotinidines A–G (**1**–**7**) was prepared by dissolving 1.0 mg in 30 μL of CD_3OD in 2.5 mm micro cells (Shigemi Co. Ltd) and chemical shifts were reported using residual CD_3OD (δ_H 3.31 and δ_C 49.0) as an internal standard. Standard pulse sequences were employed for the 2D NMR experiments. ^{1}H–^{1}H 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.

4.2. Material

The club moss *Lycopodium annotinum* and *L. annotinum* var. *acrifolium* were collected in Hokkaido in 2002. The botanical identification was made by Mr. N. Yoshida, Health Sciences University of Hokkaido. Each voucher specimen has been deposited in the herbarium of Hokkaido University.

4.3. Extraction and isolation

The club moss of *L. annotinum* (2.5 kg) was extracted with MeOH, and the extract was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials, which were adjusted at pH 10 with satd Na_2CO_3, were extracted with $CHCl_3$. $CHCl_3$-soluble materials (9.2 g) were subjected to an amino silica gel column (hexane/EtOAc, 1:0→2:3, and then $CHCl_3$/MeOH, 1:0→0:1), in which a fraction eluted with hexane/EtOAc (1:1) was purified by a silica gel column ($CHCl_3$/MeOH, 1:0→0:1) followed by C_{18} HPLC (Phenomenex LUNA C18, 5 μm, Shimadzu GLC LTD, 10×250 mm; eluent, 26% CH_3CN/0.1% TFA; flow rate, 2 mL/min; UV detection at 210 nm) to afford lannotinidines A (**1**, 5.2 mg, 0.0002%), B (**2**, 4.7 mg, 0.0002%), F (**6**, 0.5 mg, 0.00002%), and G (**7**, 2.6 mg, 0.0001%), annotinine (**8**),[14] lycodoline (**9**),[15] and lyconnotine (**10**),[16] and that eluted with $CHCl_3$/MeOH (7:3) was purified by a silica gel column ($CHCl_3$/MeOH, 1:0→0:1) to afford lannotinidines C (**3**, 49.1 mg, 0.002%) and D (**4**, 26.3 mg, 0.001%).

The club moss (50 g) of *L. annotinum* var. *acrifolium* was extracted with MeOH (500 mL×3). The MeOH extract (7 g) was partitioned between EtOAc and 3% tartaric acid. Water-soluble materials, after being adjusted at pH 10 with satd Na_2CO_3, were partitioned with $CHCl_3$. $CHCl_3$ soluble materials (0.42 g) were subjected to an amino silica gel column (hexane/EtOAc, 1:0→0:1, and then $CHCl_3$/MeOH, 1:0→0:1). The fraction eluted with hexane/EtOAc (4:1) was separated by C_{18} HPLC (Phenomenex LUNA C18, 5 μm, Shimadzu GLC LTD., 10×250 mm; eluent, 20% CH_3CN/0.1% TFA; flow rate, 2 mL/min; UV detection at 210 nm) to afford lannotinidine A (**1**, 5.3 mg, 0.01%), and that eluted with $CHCl_3$/MeOH (4:1) was purified by a silica gel column ($CHCl_3$/MeOH, 1:0→0:1) to give lannotinidine E (**5**, 4.8 mg, 0.01%) and annotinine (**8**).

4.3.1. Lannotinidine A (1). Colorless solid; $[\alpha]_D^{23}$ +47° (*c* 1.0, MeOH); IR (neat) ν_{max} 3392, 2950, and 1733 cm^{-1}; ^{1}H and ^{13}C NMR data (Table 1); FABMS *m/z* 292 (M+H)$^+$; HRFABMS *m/z* 292.1910 (M+H; calcd for $C_{17}H_{26}NO_3$, 292.1913).

4.3.2. Lannotinidine B (2). Colorless solid; $[\alpha]_D^{24}$ −62° (*c* 1.0, MeOH); IR (neat) ν_{max} 2933 and 1731 cm^{-1}; ^{1}H and ^{13}C NMR data (Table 1); FABMS *m/z* 264 (M+H)$^+$; HRFABMS *m/z* 264.1960 (M+H; calcd for $C_{16}H_{26}NO_2$, 264.1963).

4.3.3. Lannotinidine C (3). Colorless solid; $[\alpha]_D^{24}$ −5° (*c* 1.0, MeOH)[21]; IR (neat) ν_{max} 3450, 2937, and 1687 cm^{-1}; ^{1}H and ^{13}C NMR data (Table 1); FABMS *m/z* 442 (M+H)$^+$; HRFABMS *m/z* 442.2579 (M+H; calcd for $C_{26}H_{36}NO_5$, 442.2593).

4.3.4. Lannotinidine D (4). Colorless solid; $[\alpha]_D^{24}$ −24° (*c* 1.0, MeOH); IR (neat) ν_{max} 3450, 2940, and 1685 cm^{-1}; ^{1}H and ^{13}C NMR data (Table 1); FABMS *m/z* 440 (M+H)$^+$; HRFABMS *m/z* 440.2458 (M+H; calcd for $C_{26}H_{34}NO_5$, 440.2479).

4.3.5. Lannotinidine E (5). Colorless solid; $[\alpha]_D^{18}$ −7° (*c* 0.2, MeOH)[21]; IR (neat) ν_{max} 3385, 2928, and 1767 cm^{-1}; ^{1}H and ^{13}C NMR data (Table 1); FABMS *m/z* 294 (M+H)$^+$; HRFABMS *m/z* 294.1712 (M+H; calcd for $C_{16}H_{24}NO_4$, 294.1705).

4.3.6. Lannotinidine F (6). Colorless solid; $[\alpha]_D^{24}$ −22° (*c* 1.0, MeOH); IR (neat) ν_{max} 2955, 1770, 1680, and 1570 cm^{-1}; ^{1}H and ^{13}C NMR data (Table 1); FABMS *m/z* 274 (M+H)$^+$; HRFABMS *m/z* 274.1432 (M+H; calcd for $C_{16}H_{20}NO_3$, 274.1443). UV λ_{max} (MeOH): 335 nm (ε 9600).

4.3.7. Lannotinidine G (7). Colorless solid; $[\alpha]_D^{18}$ −2° (*c* 1.0, MeOH)[21]; IR (neat) ν_{max} 2920, 1685, 1205, 1180, and 1130 cm^{-1}; ^{1}H and ^{13}C NMR data (Table 1); FABMS *m/z* 260 (M+H)$^+$; HRFABMS *m/z* 260.1653 (M+H; calcd for $C_{16}H_{22}NO_2$, 260.1650).

4.3.8. Chemical transformation of lannotinidine A (1) to annopodine. To a solution of **1** (1 mg) in THF (75 μL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.75 μL). The mixture was allowed to stand at 80 °C for 12 h. After cooling, the mixture was extracted with $CHCl_3$. After evaporation of solvent, the residue was applied to a silica gel column ($CHCl_3$/MeOH, 1:0→0:1) followed by C_{18} HPLC (YMC-Pack ODS-AM, S-5 μm, YMC LTD, 10×250 mm; eluent, 15% CH_3CN/0.1% TFA; flow rate, 2 mL/min; UV

detection at 254 nm) to give a compound (0.7 mg), whose spectral data were identical with those of annopodine.[16] ^{1}H NMR (CD_3OD) δ 3.45 (1H, m, H-1a), 3.48 (1H, m, H-1b), 1.77 (1H, d, 10.8, H-2a), 1.98 (1H, m), 1.59 (1H, br d, 11.2, H-3a), 1.95 (1H, m, H-3b), 1.77 (1H, d, 10.8, H-4), 4.07 (1H, m, H-5), 2.63 (1H, m, H-6a), 2.65 (1H, m, H-6b), 3.08 (1H, d, 10.3, H-9a), 3.53 (1H, m, H-9b), 1.83 (1H, m), 2.71 (1H, m, H-11a), 3.16 (1H, m, H-11b), 1.88 (1H, m, H-14a), 2.88 (1H, dd, 15.1, 11.3, H-14b), 1.88 (1H, m, H-15), 1.13 (3H, d, 5.5, H-16), and 3.76 (3H, s, H-17). ^{13}C NMR (CD_3OD) δ 53.3 (C-1), 25.3 (C-2), 23.3 (C-3), 44.7 (C-4), 68.4 (C-5), 36.4 (C-6), 136.5 (C-7), 168.6 (C-8), 53.8 (C-9), 32.0 (C-10), 35.5 (C-11), 127.3 (C-12), 63.1 (C-13), 30.0 (C-14), 30.1 (C-15), 19.2 (C-16), and 52.2 (C-17).

4.3.9. Chemical transformation of lannotinidine C (3) to deacetylfawcettiine. To a solution of **3** (2.6 mg) in MeOH (8.5 μL) was added 28% MeONa (1.5 μL). The mixture was allowed to stand at 40 °C for 48 h. After cooling, the mixture was extracted with $CHCl_3$. After evaporation of solvent, the residue was applied to a silica gel column ($CHCl_3$/MeOH, 1:0→0:1) to give a compound (0.7 mg), whose spectral data were identical with those of deacetylfawcettiine.[18] $[\alpha]_D^{21}$ −21° (*c* 0.2, MeOH); ^{1}H NMR (CD_3OD) δ 2.57 (1H, m, H-1a), 3.34 (1H, m, H-1b), 1.48 (1H, d, 12.2, H-2a), 2.02 (1H, d, 12.2, H-2b), 1.83 (2H, m, H-3), 2.44 (1H, m, H-4), 3.91 (1H, m, H-5), 1.89 (2H, m, H-6), 1.81 (1H, m, H-7), 3.22 (1H, m, H-8), 2.58 (1H, m, H-9a), 3.39 (1H, m, H-9b), 1.66 (1H, d, 11.1, H-10a), 1.78 (1H, m, H-10b), 1.31 (1H, d, 12.0, H-11a), 1.76 (1H, m, H-11b), 1.38 (1H, d, 11.5, H-12), 0.88 (1H, t, 12.9, H-14a), 2.63 (1H, m, H-14b), 2.91 (1H, m, H-15), and 1.02 (1H, d, 3.1, H-16). ^{13}C NMR (CD_3OD) δ 48.3 (C-1), 20.8 (C-2), 27.9 (C-3), 34.0 (C-4), 84.9 (C-5), 26.3 (C-6), 43.4 (C-7), 79.9 (C-8), 47.7 (C-9), 23.6 (C-10), 24.8 (C-11), 45.2 (C-12), 66.2 (C-13), 41.6 (C-14), 32.3 (C-15), and 20.8 (C-16).

4.3.10. Chemical transformation of lannotinidine D (4) to lycofoline. To a solution of **4** (4.0 mg) in MeOH (11.2 μL) was added 28% MeONa (1.8 μL). The mixture was allowed to stand at 40 °C for 48 h. After cooling, the mixture was extracted with $CHCl_3$. After evaporation of solvent, the residue was applied to a silica gel column ($CHCl_3$/MeOH, 1:0→0:1) to give a compound (0.7 mg), whose spectral data were identical with those of lycofoline.[19] $[\alpha]_D^{21}$ −23° (*c* 0.1, MeOH); ^{1}H NMR (CD_3OD) δ 2.98 (1H, m, H-1a), 3.45 (1H, m, H-1b), 1.85 (1H, m, H-2a), 1.90 (1H, m, H-2b), 1.55 (1H, d, 8.7, H-3a), 1.92 (1H, m, H-3b), 2.71 (1H, m, H-4), 4.00 (1H, t, 5.7, H-5), 1.89 (1H, m, H-6a), 2.23 (1H, d, 15.3, H-6b), 2.58 (1H, m, H-7), 3.16 (1H, m, H-8), 3.64 (1H, m, H-9a), 3.89 (1H, m, H-9b), 2.37 (1H, m, H-10a), 2.79 (1H, m, H-10b), 5.62 (1H, m, H-11), 1.13 (1H, m, H-14a), 2.58 (1H, m, H-14b), 3.08 (1H, m, H-15), and 1.03 (1H, d, 6.0, H-16).

4.4. Chemical transformation of annotinine (8) to lannotinidine E (5)

To a solution of annotinine (**8**, 6 mg) in dioxane/H_2O (150 μL/15 μL) was added 15% H_2SO_4 (21 μL). The mixture was allowed to stand at 80 °C for 48 h. After cooling, the mixture was extracted with $CHCl_3$. After evaporation of solvent, the residue was applied to a silica gel column ($CHCl_3$/MeOH, 1:0→0:1) to give a compound (0.8 mg), $[\alpha]_D^{20}$ −8° (*c* 0.1, MeOH), whose spectral data were identical with those of lannotinidine E (**5**).

4.5. Semiquantitative RT-PCR

Total RNA from 1321N1 cells was extracted by using a total RNA extraction kit, and semiquantitative RT-PCR was carried out by using a RT-PCR kit. NGF mRNA expression was examined as described previously.[20]

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Shielding effect of thioether C–S bond from proton chemical shifts of 4-thia-5α- and 4-thia-5β-androstane-17-ones

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Abstract—4-Thia-5α- and 4-thia-5β-androstan-17-ones (**1a** and **1b**) were synthesized in order to obtain the NMR shielding parameters for the thioether C–S bond. The complete NMR assignment of both the proton and carbon atoms for these compounds and substituent-induced shifts (SIS) from the corresponding androstanones (**2a** and **2b**) are presented. A combination of the electric field effect and the anisotropy of the magnetic susceptibility of the C–S bond can successfully reproduced the observed SIS values for these androstanones.

1. Introduction

NMR has played an important role in the field of chemistry NMR techniques, such as distance-dependent NOE[1] and torsion angle-dependent $^3J_{HH}$ coupling constants,[2] were extensively utilized for conformational analysis and determination of stereochemistry of flexible organic compounds. NOE gives the information of the distance between nuclei, therefore it has been widely applied for structure analysis not only of small molecule but also of macromolecule,[3] such as DNA, polypeptide and oligosaccharides. However, NOE is not always obtainable since it is in inversely proportional to the sixth power of the distance between nuclei. It causes serious problem in the conformational analysis of flexible molecules, in which a conformational dynamic equilibrium among many different structures is operative.[4] It is difficult to determine exactly which conformer affords the observed NOE. Therefore, the structure analysis based on the NOE occasionally gives misleading result.[4] By contrast, the chemical shift, which is the most fundamental data of NMR, is not extensively used for conformational analysis of flexible compounds, although chemical shift gives invaluable information of molecular structure.

NMR chemical shifts reflect molecular structure. Hence, variation in the local environment affects chemical shieldings, and the change in chemical shifts of nuclei caused by adjacent substituents provides valuable information about the relative arrangement of the nuclei under study with respect to these nearby substituents, such as C–H bond,[5a] C–C bond,[5a] C=C double bond,[5b,i] halogen,[5i] hydroxy,[5i] carbonyl,[5c,d,i] cyano,[5f] ethylen-ketal and -thioketal,[5e] amide in peptide.[5g,h,j,k,l] The chemical shift changes caused by the nearby substituents can thus be applicable for conformational analysis. From this point of view, we have developed an efficient method for conformational analysis of flexible organic compounds by using chemical shift simulation technique.[6] For this method, information is necessary not only on the structures of dynamically equilibrating conformers but also on the calculated chemical shifts of the protons of these conformers. The chemical shift calculation can be achieved by the estimation of the change in chemical shifts of protons produced by nearby substituents. We also have succeeded to develop the induced magnetic shielding parameters for aromatic ring,[6a,7] ether,[8] carbonyl,[9] lactone,[10] amine, and ammonium.[11] In order to widen the applicability of the conformational analysis by using chemical shift simulation technique to a variety of organic molecules, it is necessary to obtain the shielding parameters for other substituents. In this paper, we report the induced magnetic shielding parameters for the thioether group S–C, which is ubiquitous in organic compounds.

To obtain the reliable shielding parameters of thioether C–S bond, steroid skeleton was chosen because of its skeletal rigidity and well-known geometry. Hence, we synthesized 4-thia-5α- (**1a**) and 4-thia-5β-androstanone (**1b**), and compared the chemical shifts of the associated protons with those of the corresponding reference compounds[8] (**2a**, **2b**) (Fig. 1).

Keywords: Thioether; Shielding effect.
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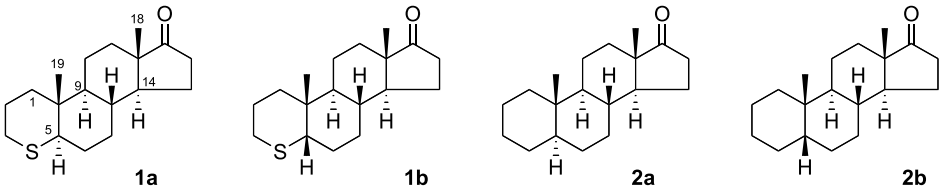
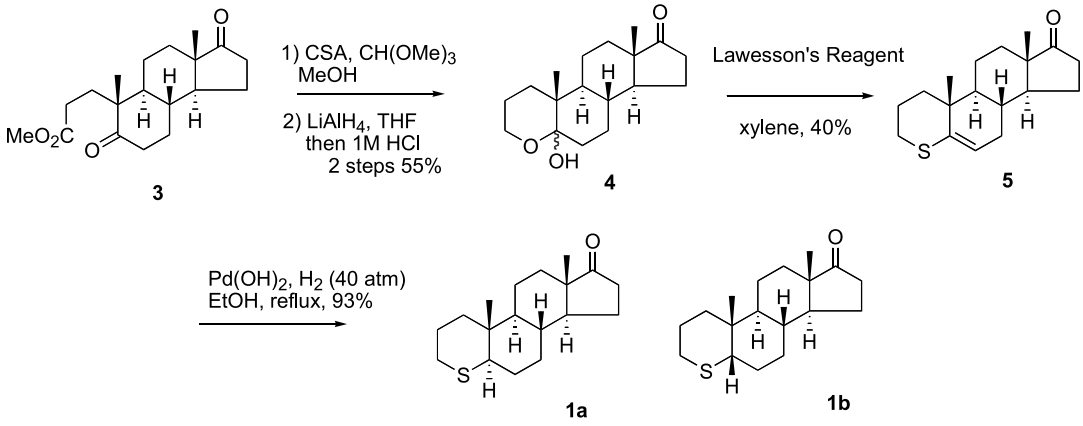


Figure 1. Thia-steroids (**1a**, **1b**) and steroids[8] (**2a**, **2b**).



Scheme 1. Synthesis of 4-thia-5α- (**1a**) and 5β-androstanone (**1b**).

2. Synthesis

The synthesis of thia-steroid is shown in Scheme 1. Protection of carbonyl groups of keto ester **3**,[12] which was obtained from 4-androstene-3,17-dione, followed by reduction of the ester group with $LiAlH_4$ in THF gave the corresponding primary alcohol. Deprotection of dimethyl acetal afforded diastereo mixture of lactol **4**. Treatment with Laweson's reagent of **4** gave cyclized product **5**. Reduction of **5** using $Pd(OH)_2$ in EtOH under high-pressure hydrogen atmosphere (40 atm) gave desired mixture of thioether epimers at C5 position. HPLC separation of the mixture afforded **1a** and **1b** in a ration of 3:2. The structures and the stereochemistry of **1** were confirmed by NOE experiment and X-ray crystallographic analysis (Fig. 2).

3. Results and discussions

3.1. Assignment NMR

Assignment of ^{1}H and ^{13}C NMR signals was mainly based on connectivity information from homo- and heteronuclear scalar couplings. Assignment of ^{1}H signals for **1a** and **1b** in $CDCl_3$ solution was made using a combination of phase sensitive DQF-COSY, NOESY, HMQC and HMBC experiments (Table 1). Assignment of ^{13}C signals was carried out using a combination of DEPT, HMQC and HMBC. The stereochemistry of C5 position was determined by NOE experiments and supported by X-ray crystallographic analysis of **1a** (Fig. 2). The observed substituent-induced shifts (SIS) can be obtained by the chemical shift difference between **1** and **2**.

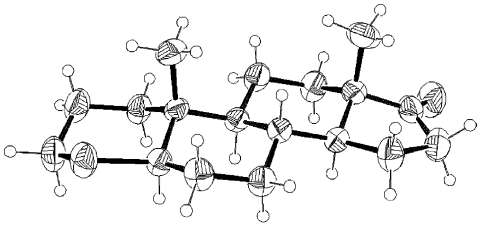


Figure 2. X-ray crystal structure of **1a**.

3.2. Molecular structure of androstan-17-ones

In order to obtain the magnetic shielding parameters of thioether, we have to get accurate geometrical factors of all protons in **1** and **2**. While the X-ray crystal structure of **1a** was obtained, a suitable crystal of **1b** for X-ray analysis was not prepared. In addition, it is known that the structure obtained by an X-ray crystallographic analysis has lesser positional accuracy of protons than that of heavier elements. We therefore applied MM3 calculation[13] to obtain geometrical factors of the protons for these compounds (Fig. 3). The reliability of the calculated structures can be estimated by comparison of the coordinates of the heavier atoms with those of the observed. A superimposed analysis of the two structures for **1a** was carried out, in which the root mean square deviations of the 20 non-hydrogen atoms between the calculated and observed structures are 0.037 Å. The result suggested that the structures obtained by MM3 calculation are nearly completely identical with those of the observed and can be used to calculate the shielding effect of the thioether C–S bond.

3.3. Calculation of the substituent-induced chemical shift for thioether C–S bond

Replacement of a CH_2 group by other functionalities may cause appreciable chemical shift changes of nearby protons. The substituent-induced chemical shift change can be

Table 1. [1]H NMR shifts in 5α- and 5β-androstanones[a]

Position	**1a**	**2a**[b]	$\Delta\delta_{\mathbf{1a}}$[c]	**1b**	**2b**[b]	$\Delta\delta_{\mathbf{1b}}$[d]
1α	0.97	0.89	0.08	1.84	1.75	0.09
1β	1.84	1.67	0.17	0.99	0.91	0.08
2α	[e]	1.50		[e]	1.27	
2β	[e]	1.41		[e]	1.37	
3α	2.52	1.22	1.30	2.57	1.72	0.85
3β	2.68	1.65	1.03	2.72	1.21	1.51
4α		1.29			1.72	
4β		1.29			1.22	
5	2.68	1.07	1.61	2.96	1.31	1.65
6α	1.58	1.25	0.33	1.56	1.27	0.29
6β	1.41	1.25	0.16	2.11	1.90	0.21
7α	1.08	0.97	0.11	[e]	1.18	
7β	1.84	1.78	0.06	[e]	1.52	
8	1.63	1.55	0.08	1.64	1.58	0.06
9	0.80	0.72	0.08	2.25	1.47	0.78
11α	1.73	1.67	0.06	1.53	1.55	−0.02
11β	1.30	1.27	0.03	1.26	1.26	0.00
12α	1.24	1.23	0.01	1.33	1.27	0.06
12β	1.81	1.79	0.02	1.82	1.80	0.02
14	1.28	1.27	0.01	1.47	1.36	0.11
15α	1.93	1.91	0.02	1.93	1.93	0.00
15β	1.50	1.60	−0.10	1.49	1.49	0.00
16α	2.06	2.03	0.03	2.08	2.06	0.02
16β	2.44	2.45	−0.01	2.43	2.43	0.00
18	0.87	0.86	0.01	0.86	0.85	0.01
19	1.10	0.81	0.29	1.01	0.95	0.06

[a] Measured in $CDCl_3$ at 25 °C (500 MHz) and in ppm.
[b] Ref. 8.
[c] $\Delta\delta_{\mathbf{1a}}=\delta_{\mathbf{1a}}-\delta_{\mathbf{2a}}$.
[d] $\Delta\delta_{\mathbf{1b}}=\delta_{\mathbf{1b}}-\delta_{\mathbf{2b}}$.
[e] These chemical shifts are not accurately assigned due to overlapped signals.

described by classical screening mechanisms as

$$\Delta\delta = \Delta\delta_{\mathrm{el}} + \Delta\delta_{\mathrm{magn}} + \Delta\delta_{\mathrm{others}} \quad (1)$$

where $\Delta\delta_{el}$ and $\Delta\delta_{\mathrm{magn}}$ are the chemical shifts difference from electric field effect due to the dipole moment of the substituent, and the contribution of the anisotropy of the magnetic susceptibility. $\Delta\delta_{\mathrm{others}}$ is the contribution of other factors mainly derived from van der Waals interaction between the substituent and the proton and solvent effect. The electric contribution for substituent-induced chemical shift (SIS) value, $\Delta\delta_{\mathrm{el}}$, can be estimated by using the Buchingham equation 2,[14]

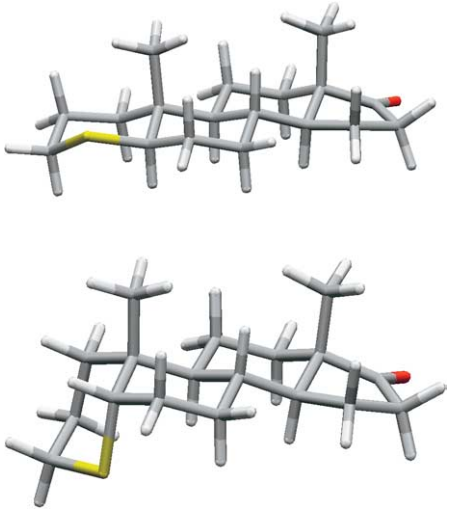


Figure 3. The calculated structures of **1a**, (top) and **1b**, (bottom).

$$\Delta\delta_{\mathrm{el}} = \kappa e_{\mathrm{CH}} \quad (2)$$

where κ is a constant to be determined by experiment and e_{CH} is the geometrical factor for the proton. The geometrical factor can be estimated by relative arrangement of the vector from the carbon to the hydrogen atom with respect to the unit vector of the substituent dipole moment.[15]

The contribution of the anisotropy of the magnetic susceptibility, $\Delta\delta_{\mathrm{magn}}$ can be represented by using an Eq. (3),[15]

$$\Delta\delta_{\mathrm{magn}} = \left\{\sum_{i=1}^{3} \chi_i(1-3\cos^2\theta_i)\right\}/3r^3 \quad (3)$$

where χ_i's are magnetic susceptibilities along the three principal axes of the substituent, r is the distance between the proton and the centre of the induced magnetic dipole of the substituent and θ_i's are the angles between the distance vector of the proton and the axes of the three principal magnetic susceptibilities χ_i. The Eq. 3 can be transformed to

$$\Delta\delta_{\mathrm{magn}} = \{(\Delta\chi_1(1-3\cos^2\theta_1) + \Delta\chi_2(1-3\cos^2\theta_2))/3r^3 \quad (4)$$

with $\Delta\chi_1=\chi_1-\chi_3$, $\Delta\chi_2=\chi_2-\chi_3$.

We set three axes as shown in Figure 4 in the same way for obtaining the shielding parameters of the ether C–O bond: *X* axis is on the C–S bond, *Y* axis is vertical to the C–S

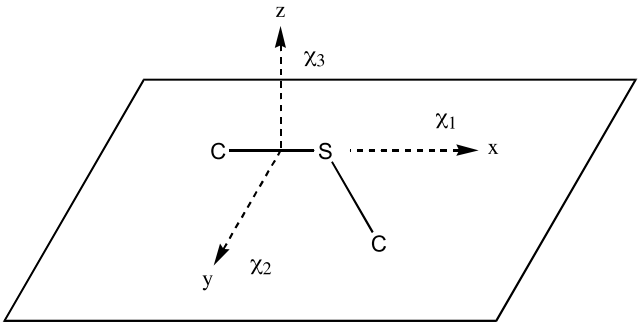


Figure 4. The axes for calculation.

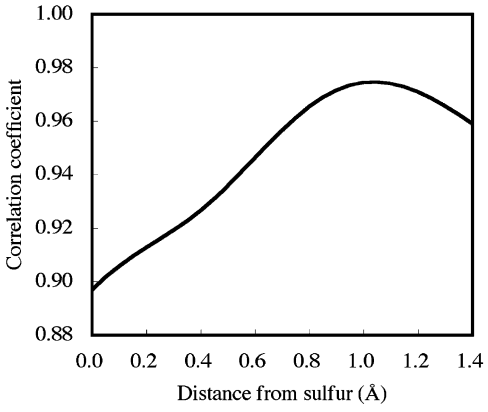


Figure 5. Correlation coefficients as a function of the distance of the sulfur atom from the origin along the C–S axis.

bond and in the C–S–C plane, and *Z* axis is vertical to the C–S–C plane. The origin of the three axes can be moved along the C–S bond to find best fit parameters.

The reproduction of the observed SIS values was carried out by a multiple least-squares regression analysis using the above mentioned equations and the geometrical factors obtained by the MM3 calculations.

The correlation coefficients between the observed and calculated SIS values within the multiple regression analyses are dependent on the distance of the sulfur atom from the origin (assumed center of the electric and induced magnetic dipole) along one of the C–S bonds. As is clearly seen in Figure 5, a maximum is obtained at the distance of 1.05 Å from the sulfur atom. The values obtained for the best fit set are:

$$\kappa = -4.29 \times 10^{12} \text{ esu}$$

$$\Delta\chi_1 = -9.28 \times 10^{-30} \text{ cm}^3/\text{molecule}$$

$$\Delta\chi_2 = -5.67 \times 10^{-30} \text{ cm}^3/\text{molecule}$$

$$\Delta\delta_{\text{others}} = 0.045 \times 10^{-6}$$

With the best fit NMR shielding parameters, we calculated the SIS values for all the protons of 4-thia-5α- and 4-thia-5β-androstan-17-ones and compared with those of observed. In Table 2, the observed and calculated induced shift for all the protons of the thiasteroids are listed. Excellent correlation of these data is obtained in a linear regression analysis (Fig. 6): (for **1a** and **1b**, 30 data set (range of the observed SIS values −0.02 to 1.65 ppm) $\Delta\delta_{\text{calc}} = a\Delta\delta_{\text{obs}} + b$; $a = 0.975$, $b = 0.009$, $R^2 = 0.975$, rmsd = 0.083).

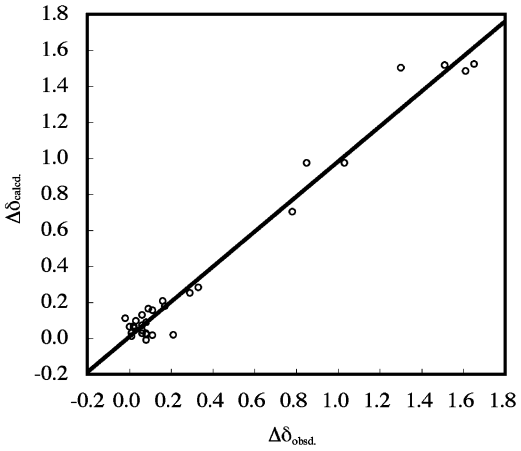


Figure 6. Plot of observed and calculated SIS values of **1**.

Table 2. The observed and calculated induced shifts of **1a** and **1b**

Position	1a		1b	
	Obsd	Calcd	Obsd	Calcd
1α	0.08	0.03	0.09	0.17
1β	0.17	0.18	0.08	0.02
3α	1.30	1.50	0.85	0.98
3β	1.03	0.97	1.51	1.52
5	1.61	1.49	1.65	1.52
6α	0.33	0.28	0.29	0.25
6β	0.16	0.21	0.21	0.02
7α	0.11	0.02	[a]	
7β	0.06	0.07	[a]	
8	0.08	0.09	0.06	0.03
9	0.08	−0.01	0.78	0.70
11α	0.06	0.04	−0.02	0.11
11β	0.03	0.10	0.00	0.07
12α	0.01	0.03	0.06	0.13
12β	0.02	0.06	0.02	0.07
14	0.01	0.01	0.11	0.16

[a] These data were not used for obtaining the shielding parameters because they were not obtained.

4. Conclusion

By use of 2D NMR techniques such as HMQC, HMBC, DQF-COSY, NOESY, the complete assignments of ^{1}H and ^{13}C for the thiasteroids **1a** and **1b**, were successfully carried out. A new set of shielding parameters for thioether C–S bond was obtained, with which a high correlation coefficient (0.976) between the observed and calculated SIS values for these androstanones was given.

5. Experimental

5.1. General procedures

The ^{1}H and ^{13}C NMR spectra at high field were recorded with a JEOL-Lambda 500 and Varian-Mercury 300 NMR spectrometer at 500 and 300 MHz (^{1}H NMR) and 125.65 and 75 MHz (^{13}C NMR). Sample concentrations in $CDCl_3$ were 0.05–0.1 M for most 1D experiments for NOE and 2D measurements. All NMR experiments were obtained using the standard pulse programs and sequences. All melting points were determined with a micro melting apparatus (Yanagimoto) and are uncorrected. HPLC were operated with a CCPS (TOSOH). IR spectra were measured using a Hitachi 260-10s infrared spectrophotometer. The mass spectra were taken with a JEOL JMS-SX 102A high-resolution double-focusing mass spectrometer at the Instrument center for Chemical Analysis, Hiroshima University. The elemental analysis was taken with a Perkin Elmer 2004 Series II CHNS/O Analyzer at the Instrument center for Chemical Analysis, Hiroshima University.

5.1.1. A mixture of 5-hydorodxy-4-oxa-androstane-17-one (4). To a solution of methyl 5,1-dioxo-A-nor-3,4-androstane-3-oate (**3**) (1.60 g, 4.99 mmol) and trimethyl orthoformate (10 ml) in dry methyl alcohol was added a catalytic amount of camphorsulfonic acid under argon. After stirring for 1 h under reflux condition, the reaction mixture was poured into an ice-cooled aqueous sodium bicarbonate. The aqueous layer was extracted with ether. The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent in vacuo, the crude acetal was obtained and used in the next reaction without further purification.

To a suspension of $LiAlH_4$ (200 mg, 5.26 mmol) in dry THF (50 mL) was added dropwise the crude acetal in the THF (20 ml) at 0 °C. After stirring for 1 h at the same temperature under argon, the reaction mixture was quenched with saturated sodium sulfate and added 1 M HCl (20 ml) after stirring for 1 h, the mixture was extracted with ether. The extracts were washed with saturated aqueous sodium bicarbonate, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo. The residual oil was chromatographed on silica gel (elution with 20% ethyl acetate in hexane) to give a mixture of lactol (**4**, 800 mg, 2.74 mmol, 55%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.2–3.9 (m, 1H), 3.62 (m, 1H), 2.43 (m, 2H) 2.1–1.2 (m, 18H), 0.93 (s, 3H), 0.84 (s, 3H).

5.1.2. 4-Thia-5-androstene-17-one (5). The mixture of the hemiacetal (**4**, 250 mg, 0.74 mmol) and Laweson's reagent (190 mg, 0.56 mmol) in dry xylene (4 ml) was boiled under reflux for 2 h. The solvent was removed under reduced pressure and residue was chromatographed on silica gel (elution with 5% ethyl acetate in hexane) to give 4-thia-5-androstene-17-one (5, 100 mg, 0.30 mmol, 40%) as colorless powder. mp 108–110 °C. ^{1}H NMR (300 MHz, CDCl3) δ 5.88 (dd, $J=5.6$, 2.0 Hz, 1H), 2.72 (ddd, $J=12.6$, 12.6, 3.0 Hz, 1H), 2.46 (m, 1H), 2.2–1.1 (m, 17H), 1.28 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.8, 138.5, 125.7, 51.7, 50.3, 47.4, 38.5, 38.4, 35.8, 31.7, 31.4, 31.1, 30.9, 23.4, 21.8, 20.4, 20.3, 13.5. HRMS (positive FAB, glycerin matrix) *m/z* found 290.1707 [$(M)^+$; calcd for $C_{18}H_{26}OS$; 290.1704]. Anal. Calcd for $C_{18}H_{26}OS$; C, 74.43; H, 9.02; S, 11.04. Found: C, 74.30; H, 9.05; S, 11.34.

5.1.3. 4-Thia-androstane-17-one (1a, 1b). To a solution of 4-thia-5-androstene-17-one (**5**, 160 mg, 0.55 mmol) in ethanol (10 ml) was added a catalytic amount of palladium hydroxide on carbon. After stirring for 8 h at 80 °C under hydrogen (40 atm), the resulting suspension was filtered on Celite. After removal of the solvent in vacuo, the residue was chromatographed on silica gel (elution with 10% ethyl acetate in hexane) to give sulfide 3:2 mixture (**1a**, **1b**, 150 mg, 0.51 mmol, 93%). The mixture was separated by HPCL column chromatographed. **1a**: mp 114–116 °C. ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 220.8, 53.9, 52.0, 51.2, 47.6, 38.8, 36.6, 35.7, 34.8, 31.5, 30.8, 30.3, 27.6, 23.6, 21.6, 20.3, 13.1, 12.4. HRMS (positive FAB, mNBA matrix) *m/z* found 292.1862 [$(M)^+$; calcd for $C_{18}H_{28}OS$; 292.1861]. Anal. Calcd for $C_{18}H_{26}OS$; C, 73.92; H, 9.65; S, 10.96. Found: C, 73.74; H, 9.76; S, 11.19. **1b**: mp 106–107 °C. ^{13}C NMR (125.65 MHz, $CDCl_3$) δ 221.6, 51.6, 47.9, 43.7, 40.9, 37.6, 36.0, 35.6, 35.5, 31.8, 27.2, 27.1, 27.0, 25.5, 24.2, 21.8, 21.3, 20.1, 13.8. HRMS (positive FAB, mNBA matrix) *m/z* found 292.1862 [$(M)^+$; calcd for $C_{18}H_{28}OS$; 292.1861]. Anal. Calcd for $C_{18}H_{26}OS$; C, 73.92; H, 9.65; S, 10.96. Found: C, 73.85; H, 9.73; S, 11.08.

5.2. X-ray diffraction analysis of 1a

The crystal data for **1a** are as follows; **1a**: $C_{18}H_{28}OS$, FW=292.48, Orthorhombic, space group $P2_12_12_1$ with $a=8.3910(3)$ Å, $b=10.5490(5)$ Å, $c=18.5850(5)$ Å, $V=1645.08(11)$ Å^3, and $Z=4$. Data were collected at 293 K on a Mac Science DIP2030 imaging plate equipped with graphite-monochromated Mo Kα radiation ($\lambda=0.71073$ Å). Unit cell parameters were determined by autoindexing several images in each data set separately with the program DENZO. For each data set, rotation images were collected in 3° increments with a total rotation of 180° about ϕ. Data were processed by using SCALEPACK. (The programs DENZO and SCALEPACK are available from Mac Science Co., Z. Otwinowski, University of Texas, Southwestern Medical Center). Of 2205 total unique reflections, 1847 were considered observed at the level of $|F_o|>4.0\sigma|F_o|$. On WinGX (Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837–838), the structures were solved by the direct method and refined by full-matrix least squares refinements on F^2 (SHELXL-97, Sheldrick, G. M. Program for the Refinement of Crystal Structures, University of Gottingen, Gottingen, Germany, 1997.). All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were placed using AFIX instructions. The structure converged

with $R=0.0808$, $wR=0.2062$. Crystallographic results have been deposited with the Cambridge Crystallographic Data Centre, UK as supplementary publication number CCDC No. 257342. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033 or e-mail: data_request@ccdc.cam.ac.uk.

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Synthesis of 4,8-anhydro-D-*glycero*-D-*ido*-nonanitol 1,6,7-trisphosphate as a novel IP_3 receptor ligand using a stereoselective radical cyclization reaction based on a conformational restriction strategy

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Abstract—4,8-Anhydro-D-*glycero*-D-*ido*-nonanitol 1,6,7-trisphosphate (**9**), designed as a novel IP_3 receptor ligand having an α-*C*-glycosidic structure, was synthesized via a radical cyclization reaction with a temporary connecting allylsilyl group as the key-step. Phenyl 2-*O*-allyldimethylsilyl-3,4-bis-*O*-TBS-1-seleno-β-D-glucopyranoside (**10a**), conformationally restricted in the unusual $^1C_4$-conformation, was treated with Bu_3SnH/AIBN to form the desired α-cyclization product **16a** almost quantitatively. On the other hand, when a conformationally unrestricted *O*-benzyl-protected 2-*O*-allyldimethylsilyl -1-selenoglucoside **15** was used as the substrate, the radical reaction was not stereoselective and gave a mixture of the α-and β-products. From **16a**, the target *C*-glucoside trisphosphate **9** was synthesized via phosphorylation of the hydroxyls by the phosphoramidite method. During the synthetic study, an efficient procedure for the oxidative C–Si bond cleavage, via a nucleophilic substitution at the silicon with *p*-MeOPhLi followed by Fleming oxidation, was developed. The *C*-glycoside **9** was found to be a full agonist for Ca^{2+} mobilization, although its activity was weaker than that of the natural ligand IP_3. Thus, the α-*C*-glucosidic structure was shown to be a useful mimic of the *myo*-inositol backbone of IP_3.

1. Introduction

D-*Myo*-inositol 1,4,5-trisphosphate (IP_3, **1**, Fig. 1)[1] is a biologically important intracellular Ca^{2+}-mobilizing second messenger whose analogues have been extensively synthesized for the development of specific ligands for IP_3 receptors. These ligands have been shown to be effective in investigating the mechanism of IP_3-mediated Ca^{2+} signaling pathways. They may also be useful as leads for the development of potentially beneficial drugs.[2,3]

Adenophostin A (**2**), isolated from *Penicillium brevicompactum*, is a very potent IP_3 receptor agonist,[4] and several groups, including ours, have been performing synthetic studies of novel IP_3 receptor ligands based on its structure.[5–7] 2-Hydroxyethyl α-D-glucopyranoside 3,4,2′-trisphosphate (**4**) was originally designed and synthesized as a highly simplified analogue of adenophostin A, and was demonstrated to be an agonist of the IP_3 receptor.[5,7a,b,l] These studies indicated that the α-D-glucopyranoside structure is a good bioisostere of the *myo*-inositol backbone of IP_3 and that the three-dimensional positioning of the three phosphate moieties and, in particular, the lone 'auxiliary' phosphate group, is significant to affect the activity.[5,6b] It has also been shown that the adenine moiety of adenophostin A can be replaced by other aromatic rings as a bioisostere; e.g. the uracil congener **5** *inter alia* has a strong Ca^{2+}-mobilizing activity close to that of adenophostin A (Fig. 1).[5,7k]

We are interested in *C*-glycosidic analogues having the α-D-glucopyranoside structure as potential IP_3 receptor ligands, since *C*-glycosides are known to be biologically stable mimics of the corresponding *O*-glycosides.[8] Thus, we have synthesized the *C*-glycosidic analogue **3** of adenophostin A and also its uracil congener **6**,[6d,e] which proved to be very potent IP_3-receptor agonists.[9] The α-*C*-glucoside

Keywords: *C*-Glycosides; Conformation; Fleming oxidation; Inositol trisphosphate; Radical reactions.
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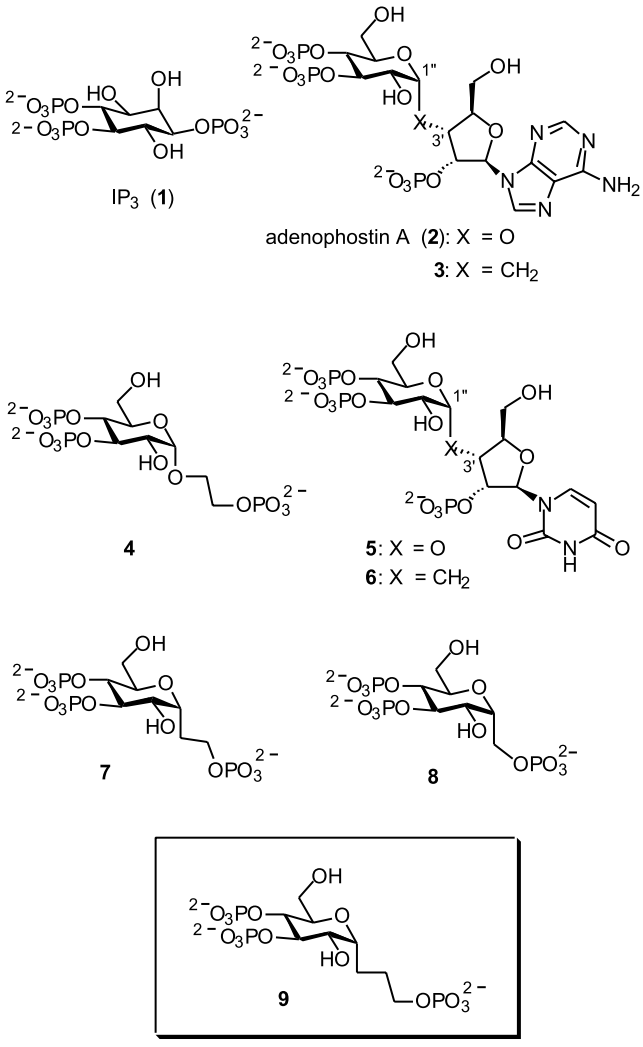


Figure 1. IP_3 receptor ligands.

trisphosphate **7**, having a C2-chain at the anomeric position, was also designed and synthesized as a simplified *C*-gycosidic IP_3 receptor ligand, the binding affinity of which was only about 2-fold lower than that of IP_3 itself.[6f] Interestingly, the *O*-glucoside trisphosphate **4**, having a structure similar to the *C*-glycoside **7**, was 25-fold lower than IP_3 in its affinity for the receptor.[5,7a,b,l] The significantly different activity between the *C*-glycoside **7** and the *O*-glycoside **4** may be due to the relative properties of the *O*- and the *C*-glycosidic linkage.[10] A second explanation for the difference may be due to the longer side-chain length of **4** compared with that of **7**, since the three-dimensional location of the phosphate groups of IP_3 receptor ligands seems to be a critical factor for their biological activity[3,5] Another shorter chain, C1-type α-*C*-glucoside trisphosphate **8**, was also synthesized; however, its Ca^{2+}-mobilizing activity was about 17-fold lower than IP_3,[7h] suggesting that the anomeric C1-unit might be too short for the effective binding of the molecule to the receptor. On the basis of these findings, we decided to synthesize another α-*C*-glucoside trisphosphate, i.e. 4,8-anhydro-D-*glycero*-D-*ido*-nonanitol 1,6,7-trisphosphate (**9**), whose anomeric C3-side-chain length is similar to that of **4**, in order to further clarify the structure–activity relationship of these *C*-and *O*-glucoside trisphosphates.

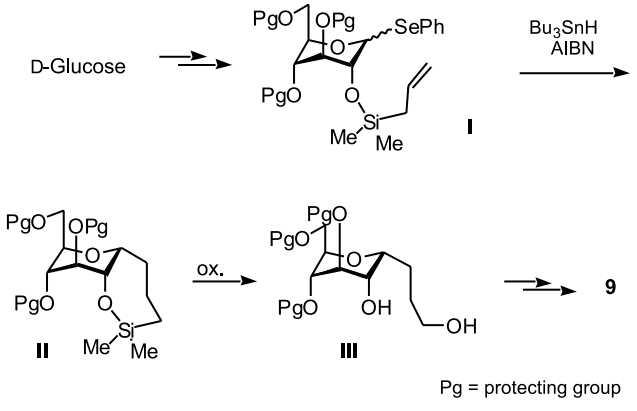
2. Result and discussion

2.1. Synthetic plan

Due to their unique biological activities, considerable effort has been devoted to the development of useful methods for the preparation of *C*-glycosides.[8,11] The use of radical reactions is one of the most efficient methods for constructing *C*-glycosidic bonds; therefore we have been working on the development of stereoselective intramolecular and intermolecular radical *C*-glycosidation reactions.[6d-f,11c,d]

The allylsilyl group was originally used as a very effective radical acceptor tether for the stereoselective introduction of a C_3 unit by Chattopadohyaya and co-workers.[12a] A branched thymidine derivative having an aminopropyl group at the 4′-posistion, which proved to be an effective nucleoside unit in antisense studies, was synthesized using the radical reaction with this tether as the key step.[12b] We planned to develop a procedure for introducing a C3 unit stereoselectively at the anomeric α-position of D-glucose via the radical cyclization reaction with the allylsilyl group as a temporary connecting tether[13] and apply it to the synthesis of the target *C*-glycoside trisphosphate **9**.

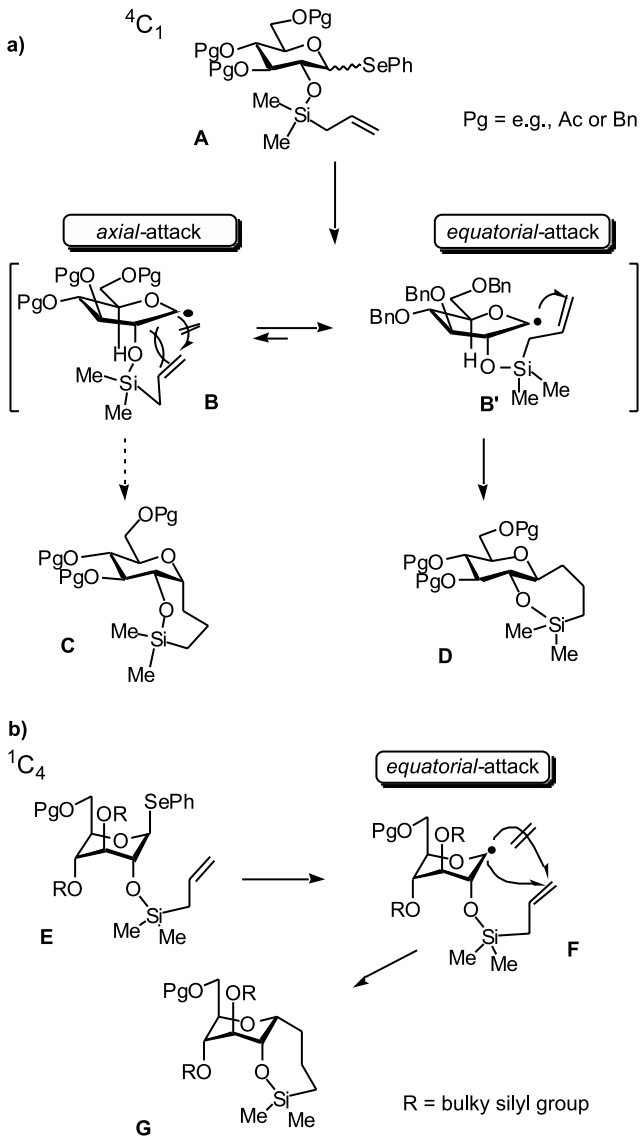
Scheme 1 shows our synthetic plan. We chose the phenyl 1-seleno-D-glucopyranoside **I** with an allylsilyl group at the 2-hydroxyl as the substrate for the radical reaction, because it seemed to be stable and easy to prepare. The radical cyclization reaction of **I** under reductive conditions gives the 7-endo *cis*-cyclized product **II**. Subsequent oxidative cleavage of the C–Si bond would give the desired α-*C*-glycoside **III**, which could then be converted into the target trisphosphate **9** via introduction of the three phosphate groups using the phosphoramidite method.



Scheme 1.

In this synthetic plan, the key would be whether the radical cyclization occurred stereoselectively to form the desired α-product. The stereoselectivity of the radical cyclization is significantly influenced by the conformation of the substrates.[14] Giese and co-workers previously clarified the

conformation of the anomeric radical intermediate produced from a tetra-*O*-acetyl-protected glucose derivative using ESR spectroscopy:[15] the glucosyl radical assuming a $B_{2,5}$-boat-like conformation is maximally stabilized in the conformation due to an effective interaction of the radical orbital (SOMO) with the σ^*-orbital of the adjacent C_2–O_2 bond and also with the p-orbital of a lone pair of the ring oxygen in their periplanar arrangement. Accordingly, as shown in Scheme 2, the anomeric radical, derived from the 2-*O*-allylsilyl substrate **A** assuming a usual $^4C_1$-chair conformation, would prefer such a $B_{2,5}$-boat-like conformation **B** (**B′**). Approach of the tether terminal to the anomeric position from the α-axial direction forming **C** might be disfavored because of the significant 1,2- and 1,5-steric repulsion (**B**) due to the axial orientation of the 2-*O*-silyl and the 5-H substituents, and consequently cyclization via the β-equatorial-attack (**B′**) might preferentially occur to result in the formation of *trans*-cyclized product **D**.



Scheme 2.

Based on these considerations, we designed substrate **E** for the radical reaction, the conformation of which should be restricted to an unusual $^1C_4$-chair form. We recently demonstrated by ab initio calculations that the anomeric radical intermediate preferentially assumes the substrate-like $^1C_4$-form when the conformation of the precursors of the radical is restricted in an unusual $^1C_4$-chair form.[11d] Hence we expected that the radical cyclization using the conformationally $^1C_4$-restricted substrate **E** would give stereoselectively the desired α-cyclization product **G**, via $^1C_4$-chair-like anomeric radical intermediate **F**, where 1,2-*trans*-cyclization would be sterically impossible because of the axial orientation of the 2′-tether, as shown in Scheme 2b.[16] The conformational restriction of the substrate to the desired $^1C_4$-form was thought to be possible by employing the significantly bulky silyl protecting groups as described bellow.

2.2. Design and preparation of the conformationally flipped 3,4-*O*-silyl substrates

Based on the above considerations, the 3,4-bis-*O*-silyl-protected substrates **10a**, **10b**, and **10c**, were designed for the radical reaction (Fig. 2). It is known that introducing a significantly bulky protecting group at the 3,4-*trans*-hydroxyl groups of pyranoses causes a flip of their conformation leading to a $^1C_4$-form, in which the bulky substituents are in axial positions due to mutual steric repulsion.[11b–e,17–20] Accordingly, the 3,4-*O*-silyl substrates **10a–c** would assume an unusual $^1C_4$-conformation due to the significant steric repulsion between the bulky silyl groups.

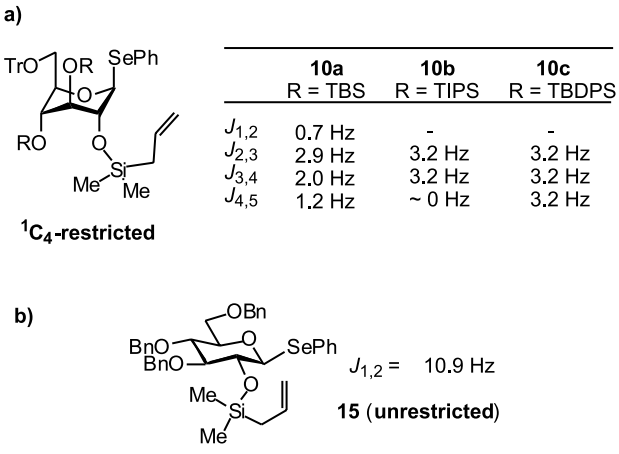
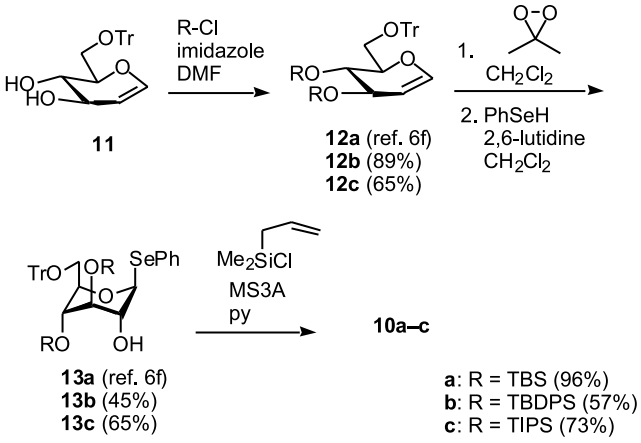


Figure 2. Conformationally restricted (a) and unrestricted (b) substrates of the radical cyclization reaction.

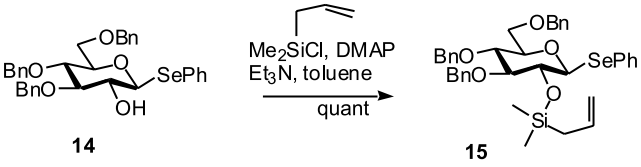
On the other hand, there was concern that the radical reaction might not be initiated if the silyl group was too bulky, since attack of the tin radical at the anomeric selenium might be prevented due to significant steric hindrance. In fact, we have experienced such decrease in reactivity at the anomeric position due to the extreme steric hindrance by bulky silyl groups in $^1C_4$-restricted substrates.[11c,d] Therefore, we planned to examine three $^1C_4$-restricted substrates **10a**, **10b**, and **10c**, with different silyl protecting groups as the radical reaction substrates.

The substrates **10a–c** were prepared from the known glucal **11**[21] as shown in Scheme 3. TBS, TBDPS, or TIPS groups were introduced at the 3,4-*trans*-hydroxyls of **11** by the usual method to give **12a–c**, respectively. The TBS-protected glucal **12a** was successively treated with dimethyldioxirane and with PhSeH/Et_3N in CH_2Cl_2 to give 1-β-phenylselenide **13a** along with the corresponding α-anomer. When 2,6-lutidine was used instead of Et_3N as a base in the phenylselenation step, the β-phenylselenide **13a** was obtained as the sole product. Similarly, β-phenylselenides **13b** and **13c** were stereoselectively prepared. An allyldimethylsilyl group was then introduced at the 2-hydroxyl of the anomeric phenylselenides **13a–c** to provide the radical reaction substrates **10a–c**.



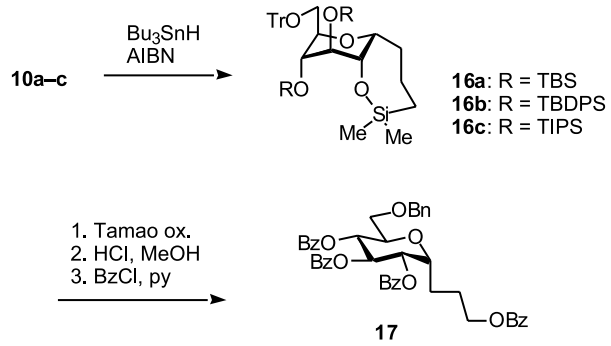
Scheme 3.

We also prepared a conformationally unrestricted substrate **15**, i.e. the 2-*O*-allyldimethylsilyl ether of phenyl 3,4,6-tri-*O*-benzyl-1-seleno-β-D-glucose (Fig. 2b) to clarify whether the conformational restriction of the substrate in the $^1C_4$-form was in fact essential for the α-selective radical cyclization. Phenyl 3,4,6-tri-*O*-benzyl-1-seleno-β-D-glucose (**14**)[22] was treated with allyldimethylchlorosilane, DMAP, and Et_3N in toluene at room temperature to give quantitatively the corresponding 2-*O*-silyl ether **15** (Scheme 4).



Scheme 4.

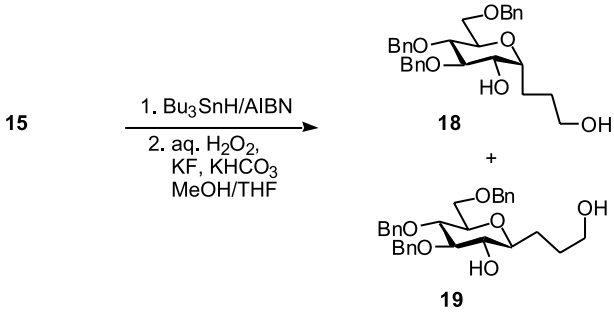
The conformation of the substrates **10a–c** and **15** was investigated by ^1H NMR (Fig. 2). The unrestricted substrate **15** has large coupling constants (ca. 10 Hz) between the ring protons showing its $^4C_1$-chair-like conformation. On the other hand, considerably smaller coupling constants (0–3.2 Hz) in the 3,4-*O*-silyl-protected substrates **10a–c** indicate their preference for the flipped $^1C_4$-conformation, as expected.



Scheme 5.

2.3. Radical reaction of the conformationally restricted and unrestricted substrates

The radical reactions of the $^1C_4$-restricted substrates **10a–c** and also the unrestricted substrate **15** were performed by slow addition of a mixture of Bu_3SnH and AIBN to a refluxing solution of the substrate in benzene (80 °C), toluene (110 °C), or *t*-butylbenzene (130 °C) (Schemes 5 and 6). The results are summarized in Table 1. First, the reaction was examined by slow addition of 2 equiv of Bu_3SnH and 0.67 equiv of AIBN to the 0.005 M solution of the bis-*O*-TBS substrate **10a** in benzene. However, the radical reaction was not initiated under the conditions, and substrate **10a** was completely recovered (entry 1). This suggests that the bulky silyl groups hindered the approach of the tin radical to the anomeric selenium, as indicated above. When **10a** was treated with 2.0 equiv of Bu_3SnH under higher substrate concentration conditions (0.05 M), the radical reaction occurred to produce the desired α-*C*-glucoside **16a** almost quantitatively (entry 2), the structure of which was confirmed after its conversion into the corresponding penta-*O*-benzoate **17**, by successive treatment under Tamao oxidation conditions,[23] HCl/MeOH, and BzCl/pyridine (Scheme 5). The corresponding α-cyclized products **16b** and **16c** were also exclusively obtained in high yield by the radical reactions (entries 3 and 4), when the other two $^1C_4$-restricted substrates, TBDPS-protected **10b** and TIPS-protected **10c**, were treated under identical conditions as for those of entry 2 for **10a**.



Scheme 6.

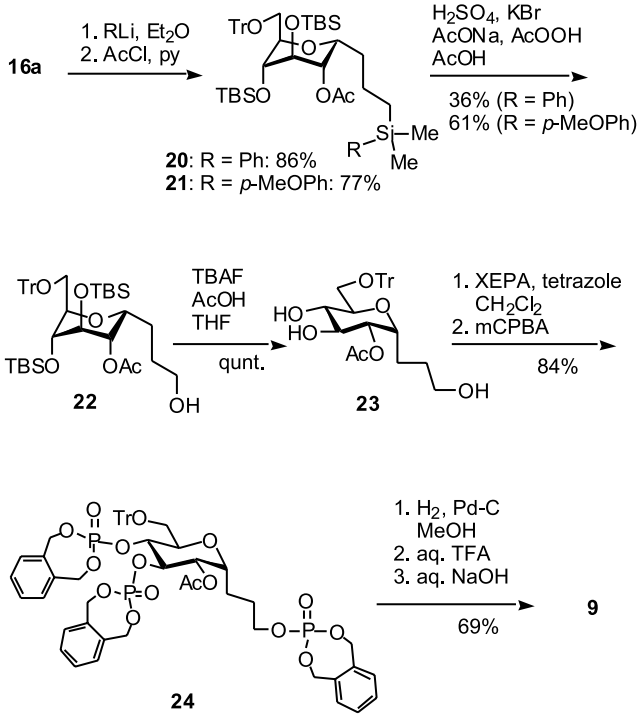
We next examined the radical cyclization with the conformationally unrestricted tri-*O*-benzyl substrate **15** by a similar procedure with Bu_3SnH and AIBN, followed by the Tamao oxidation (Scheme 6). First, the reaction was carried out in benzene under reflux under conditions

Table 1. Synthesis of *C*-glycosides by the radical reactions with 2-*O*-allylsilyl-tethered substrates[a]

Entry	Substrate (concn, M)	Solvent	Temp (°C)	Product	Yield (%)	α/β ratio
1	**10a** (0.005)	Benzene	80	No reaction	—	—
2	**10a** (0.05)	Benzene	80	**16a**	97[b]	Only α
3	**10b** (0.05)	Benzene	80	**16b**	85	Only α
4	**10c** (0.05)	Benzene	80	**16c**	84	Only α
5	**15** (0.005)	Benzene	80	**18**, **19**	73	1:2.9[c]
6	**15** (0.005)	Toluene	110	**18**, **19**	80	1:4.1[c]
7	**15** (0.005)	*t*-BuPhH	130	**18**, **19**	62	1:3.1[c]

[a] To a heating solution of the substrate in benzene, toluene, or *t*-BuPhH, a mixture of Bu_3SnH (entries 1, 5–7, 1.3 equiv; entries 2–4, 2 equiv;) and AIBN (0.67 equiv) in the same solvent was added slowly (entries 1, 5–7, over 4 h; entries 2–4, over 2 h).
[b] Mean value of three experiments.
[c] After treatment of a mixture of the radical reaction products under Tamao oxidation conditions, the α/β ration was determined by HPLC.

identical to those of entry 1 for **10a**. The radical reaction took place in spite of the lower concentration of the substrate (0.005 M) to give, after the Tamao oxidation, a mixture of the α-*C*-glucoside **18** and the β-*C*-glucoside **19** (entry 5: yield 73%). After isolation of the both anomers, ^{1}H NMR analyses proved that the major product was not the α-anomer **18** but the β-anomer **19** ($\alpha/\beta=1:2.9$). When the reaction was performed at 110 °C in toluene, the β-selectivity was further increased (entry 6: yield 80%, $\alpha:\beta=1:4.1$). At further higher temperature, the yield and the β-stereoselectivity decreased (entry 7). Therefore, the desired α-*C*-glycoside **18** was not obtained as the major product via the radical reaction of the unrestricted tri-*O*-benzyl substrate **15**. However, it should be noted that the reaction with the substrate **15** gave the *trans*-cyclized β-*C*-glycoside as the major product, since intermolecular anomeric radical reactions of glucose derivatives have been demonstrated to produce the corresponding α-product selectively probably because of the anomeric effect.



Scheme 7.

These results clearly indicate that the conformational restriction strategy is highly effective for realizing stereoselective radical cyclization at the anomeric position.

2.4. Synthesis of the target *C*-glucoside trisphosphate via the novel C–Si bond fission

The 3,4-*O*-TBS-protected radical reaction product **16a**, the overall yield of which was the highest among the series, was used for further derivatization, as shown in Scheme 7. To convert **16a** into the target *C*-glucoside trisphosphate **9**, oxidative C–Si bond fission in **16a** was required without cleaving the 3,4-*O*-TBS groups. The usual Tamao oxidation conditions, including use of the fluoride ion, would likely remove the silyl protecting groups, at least to some extent. Consequently, **16a** was exposed to conditions with H_2O_2/$KHCO_3$/KBr in aqueous MeOH/THF at room temperature. Although, the desired C–Si bond fission occurred selectively under these conditions, the reaction was extremely slow to require one month of stirring. Furthermore, the reaction was not reproducible. Thus, an alternative method was sought.

It is known that aromatic carbon–Si bonds are much more readily cleaved via an electrophilic substitution at the silicon center than aliphatic ones;[24] therefore, the arylsilyl groups could be a useful latent hydroxy group. Thus, **16a** was treated with PhLi in Et_2O at −78 °C followed by acetylation of the 2-hydroxyl to produce, in 86% yield, the ring-opened derivative **20** having a Ph–Si bond (Scheme 7). Although Fleming oxidation of **20** was examined under various conditions, detritylation was unavoidable under these conditions and resulted in a lower yield of the desired primary alcohol **22**.

Considerable acidic conditions are required for the Fleming oxidation, because *ipso*-protonation is essential to proceed the oxidation.[24] We speculated that if an electron-donating substituent were attached at the *ortho*- or *para*-position of the phenyl moiety, the *ipso*-protonation could effectively took place even under mild acidic conditions so that the oxidation would progress without removal of the trityl group. Thus, another ring-opening intermediate **21** having a *p*-MeOPhSi group was prepared by treating **16a** with *p*-MeOPhLi in THF followed by acetylation. When **21** was treated under Fleming oxidation conditions with AcOOH/AcOH/AcONa/H_2SO_4/KBr,[25] the desired primary alcohol **22** was successfully obtained in 61% yield, as expected.

The two *O*-silyl groups of **22** were simultaneously removed with TBAF in the presence of AcOH to give **23**. Using the phosphoramidite method with *o*-xylene *N*,*N*-diethylphosphoramidite (XEPA) developed by Watanabe and co-workers,[26] the phosphate units were next introduced. Thus, **23** was treated with XEPA and tetrazole in CH_2Cl_2, followed by oxidation with *m*-CPBA to give the desired trisphosphate derivative **24** in 84% yield. Finally, the *o*-xylene, trityl, and acetyl protecting groups were successively removed by hydrogenation, acidic hydrolysis, and basic hydrolysis to furnish the target **9** in 69% yield as the sodium salt, after treatment with ion-exchange resin.

As described above, we have synthesized the *C*-glucosidic trisphosphate **9** via the radical cyclization reaction using the conformationally restricted substrate as the key step. During the study, we also developed an efficient procedure for oxidative C–Si bond cleavage via nucleophilic substitution at the silicon atom with *p*-MeOPhLi. There has been growing interest in the use of silicon-containing tethers for intramolecular radical cyclization reactions, which are very useful for the regio- and stereoselective introduction of a carbon substituent based on a temporary silicon connection.[27] One drawback of this kind of temporary silicon-connecting radical reaction methods is that silyl protecting groups, which may be the most versatile protecting groups in recent organic chemistry, do not survive the subsequent oxidative Si–C bond cleavage step under normal Tamao oxidation conditions. As a result, the two-step method described here, i.e. the nucleophilic ring-opening with *p*-MeOPhLi followed by Fleming oxidation, could be of significant utility.

2.5. Biological effects

The ability of synthesized **9** to stimulate opening of the pore of recombinant rat type 1 IP_3 receptors expressed in chicken B cells that otherwise lack IP_3 receptors was measured using a fluorescent Ca^{2+} indicator trapped within the lumen of the intracellular Ca^{2+} store.[28–31] The results are shown in Table 2 and are presented as relative potency to those obtained using both IP_3 (**1**) and adenophostin A (**2**). The *C*-glycoside **9** having a C3-chain was found to be a full agonist for Ca^{2+} mobilization with a potency about 8-fold lower than that of IP_3. The activity of **9** seems to be somewhat stronger than **8** having a C1-chain, which was about 16-fold less potent than IP_3.[5,7i] By contrast, the binding affinity of **7**, having a C2-chain, for IP_3 receptors was shown to be only about 2-fold lower than that of IP_3 itself.[6f] These results clearly show that *C*-glycoside chain length can have a marked effect upon biological activity with an optimum chain length of C2 in this series. All of the compounds studied were clearly significantly weaker than adenophostin A.

Thus, the three-dimensional positioning of the three phosphate moieties and, in particular, that of the lone 'auxiliary' phosphate group, was effectively investigated, and the *myo*-inositol backbone of IP_3 was shown to be replaced by the α-D-*C*-glucosidic structure. It should be noted that this strategy, employing a series of *C*-glycosides as stable mimics of the *O*-glycoside, is essential because the corresponding *O*-glycoside trisphosphates, e.g. **25** and **26** (Fig. 3), could not be provided due to their predictable instability due to the O–C–O–O–P (**25**) or O–C–O–C–O–P (**26**) structure. Full details of *C*-glycoside based IP_3 analogue structure–activity relationships will appear elsewhere.

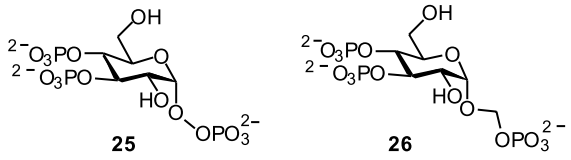


Figure 3. Putatively unstable α-*O*-glucoside trisphosphates.

3. Experimental

3.1. General methods

Chemical shifts are reported in ppm downfield from tetramethylsilane (^1H and ^{13}C) or H_3PO_4 (^{31}P), and *J* values are given in hertz. The ^1H NMR assignments described were in agreement with COSY spectra. Thin-layer chromatography was done on Merck coated plate $60F_{254}$. Silica gel chromatography was done on Merck silica gel 7734 or 9385. Reactions were carried out under an argon atmosphere.

3.1.1. (2*R*,3*R*,4*R*)-3,4-Bis-(*tert*-butyldiphenylsilyloxy)-3,4-dihydro-2-(triphenylmethoxymethyl)-2*H*-pyran (12b). A mixture of **11**[21] (1.94 g, 5 mmol), TBDPSCl (3.90 mL, 15 mmol) and imidazole (20.0 g, 30 mmol) in DMF (40 mL) was stirred at 60 °C for 20 h. The resulting mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2, 20–33% benzene in hexane) to give **12b** (3.90 g, 89%) as a white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 7.53–7.13 (m, 35H), 6.39 (d, 1H, *J*=6.2 Hz), 4.45 (m, 1H), 4.24 (m, 1H), 3.84 (dd, 1H, *J*=8.7, 10.8 Hz), 3.81 (s, 1H), 3.18 (d, 1H, *J*=5.0 Hz), 2.97 (dd, 1H, *J*=2.6, 10.8 Hz), 0.89 (s, 9H), 0.71 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 142.7, 135.5, 135.5, 135.4, 135.4, 133.7, 133.4, 133.2, 129.5, 129.5, 129.4, 129.4, 129.3, 128.6, 127.5, 127.5, 127.4, 127.2, 126.6, 100.3, 86.4, 78.1, 70.8, 64.7, 62.3, 26.9, 26.8, 19.3, 19.0; LRMS (FAB, positive) *m/z* 887 (MNa^+). Anal. Calcd for $C_{57}H_{60}O_4Si_2$: C, 79.12; H, 6.99. Found: C, 79.16; H, 7.17.

Table 2. Ca^{2+} release by rat type 1 IP_3 receptors expressed in DT40 cells

Compound	EC_{50}, nM	Hill slope	Ca^{2+} release, %	*n*	Relative potency	
					IP_3	Adenophostin A
IP_3 (**1**)	24.8±2.1	1.21±0.06	78±2	11	1	0.087±0.009
Adenophostin A (**2**)	2.1±0.2	1.54±0.13	76±1	12	12.77±4.46	1
9	213±37	1.39±0.27	69±2	5	0.12±0.01	0.009±0.001

3.1.2. (2*R*,3*R*,4*R*)-3,4-Bis-(triisopropylsilyloxy)-3,4-dihydro-2-(triphenylmethoxymethyl)-2*H*-pyran (12c). Compound **12c** (2.30 g, 65%) was obtained as a colorless oil from **11** (1.94 g, 5.0 mmol) as described above for the synthesis of **12b**, after purification by column chromatography (SiO_2, 20–33% benzene in hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, 6H, J=7.1 Hz), 7.44–7.15 (m, 9H), 6.36 (d, 1H, J=6.3 Hz), 4.72 (m, 1H), 4.30 (m, 1H), 3.81–3.74 (m, 3H), 3.07 (dd, 1H, J=2.4, 11.1 Hz), 1.01 (m, 21H), 0.87 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 142.5, 128.6, 127.5, 126.6, 100.4, 86.5, 78.7, 70.6, 64.8, 62.4, 18.2, 18.6, 18.1, 12.6, 12.4; LRMS (FAB, positive) m/z 723 (MNa^+). Anal. Calcd for $C_{43}H_{64}O_4Si_2$: C, 73.66; H, 9.20. Found: C, 73.45; H, 9.25.

3.1.3. Phenyl 3,4-Bis-*O*-*tert*-butyldiphenylsilyl-6-*O*-triphenylmethyl-1-seleno-β-D-glucopyranoside (13b). A mixture of **12b** (864 mg, 1.0 mmol) and dimethyldioxilane (ca. 0.1 M in acetone, 14 mL, ca. 1.4 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 1 h and then dried (Na_2SO_4) and evaporated. A mixture of the residue, PhSeH (128 μL, 1.2 mmol) and 2,6-lutidine (800 μL, 6.9 mmol) in CH_2Cl_2 (5 mL) was stirred at 0 °C for 12 h and then evaporated. The residue was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (SiO_2, 0–1% AcOEt in hexane) to give **13b** (467 mg, 45%) as a white foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–6.99 (m, 40H), 5.47 (d, 1H, J=5.0 Hz), 4.09 (dd, 1H, J=4.8, 7.2 Hz), 3.94 (brs, 1H), 3.78 (m, 1H), 3.75 (dd, 1H, J=7.2, 9.9 Hz), 3.65 (d, 1H, J=2.9 Hz), 3.04 (d, 1H, J=9.1 Hz), 2.89 (dd, 1H, J=4.7, 9.9 Hz), 0.87 (s, 9H), 0.72 (s, 9H); HRMS calcd $C_{63}H_{66}NaO_5SeSi_2$: 1061.3521 (MNa^+), found 1061.3510.

3.1.4. Phenyl 3,4-bis-*O*-triisopropylsilyl-6-*O*-triphenylmethyl-1-seleno-β-D-glucopyranoside (13c). Compound **13c** (1.7 g, 65%) was obtained as a colorless oil from **12c** (2.2 g, 3.0 mmol) as described above for the synthesis of **13b**, after purification by column chromatography (SiO_2, 0–1% AcOEt in hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.23 (m, 20H), 5.53 (d, 1H, J=5.1 Hz), 4.07–3.51 (m, 7H), 1.39 (m, 21H), 0.99 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 143.9, 143.7, 133.4, 132.3, 130.7, 128.7, 128.7, 128.6, 128.4, 127.6, 127.5, 127.0, 126.8, 126.7, 87.1, 80.7, 77.6, 77.2, 71.2, 71.0, 38.8, 30.5, 29.0, 23.9, 23.1, 18.4, 18.3, 18.3, 18.2, 18.1, 18.1, 18.0, 17.9, 14.2, 12.5, 12.4, 12.4, 12.3, 12.2, 11.1; LRMS (FAB, positive) m/z 897 (MNa^+). Anal. Calcd for $C_{49}H_{70}O_5SeSi_2$: C, 67.32; H, 8.07. Found: C, 67.68; H, 8.37.

3.1.5. Phenyl 2-*O*-allyldimethylsilyl-3,4-bis-*O*-*tert*-butyldimethylsilyl-6-*O*-triphenylmethyl-1-seleno-β-D-glucopyranoside (10a). A mixture of **13a**[6f] (1.2 g, 1.5 mmol), allyldimethylchlorosilane (438 μL, 3.0 mmol) and MS 3A (20 mg) in pyridine (10 mL) was stirred at room temperature for 1 h. The mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (SiO_2, 2–5% AcOEt in hexane) to give **10a** (1.3 g, 97%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.17 (m, 20H, aromatic), 5.84–5.69 (m, 1H, allyl-CH), 5.29 (d, 1H, 1-CH, J=5.7 Hz), 5.25–4.79 (m, 2H, allyl-CH_2), 3.97 (dd, 1H, 2-CH, J=2.9, 5.7 Hz), 3.95 (ddd, 1H, 5-CH, J=1.2, 5.2, 6.7 Hz), 3.80 (dd, 1H, 3-CH, J=2.0, 2.9 Hz), 3.76 (dd, 1H, 4-CH, J=1.2, 2.0 Hz), 3.48 (dd, 1H, 6-CH, J=6.7, 9.6 Hz), 3.24 (dd, 1H, 6-CH, J=5.2, 9.6 Hz), 1.67–1.60 (m, 2H, allyl-CH_2), 0.82 (s, 9H, –*t*Bu), 0.81 (s, 9H, –*t*Bu), 0.18 (s, 3H, –$SiCH_3$), 0.17 (s, 3H, –$SiCH_3$), 0.13 (s, 3H, –$SiCH_3$), 0.00 (s, 6H, –$SiCH_3$ x 2), −0.06 (s, 3H, –$SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 133.9, 133.1, 132.5, 131.4, 128.8, 128.7, 128.7, 127.6, 127.5, 126.7, 126.6, 113.6, 86.7, 83.5, 81.5, 75.9, 71.0, 65.3, 60.4, 26.0, 26.0, 25.3, 21.2, 18.1, 18.0, 14.8, −1.4, −4.2, −4.3, −4.6; LRMS (FAB, positive) m/z 911 (MNa^+). Anal. Calcd for $C_{48}H_{68}O_5SeSi_3$: C, 64.90; H, 7.72. Found: C, 64.85; H, 7.88.

3.1.6. Phenyl 2-*O*-allyldimethylsilyl-3,4-bis-*O*-*tert*-butyldiphenylsilyl-6-*O*-triphenylmethyl-1-seleno-β-D-glucopyranoside (10b). Compound **10b** (1.2 g, 57%) was obtained as a white foam from **13b** (1.9 g, 1.8 mmol) as described above for the synthesis of **10a**, after purification by column chromatography (SiO_2, 2–5% AcOEt in hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05–8.02 (m, 2H, aromatic), 7.93–7.24 (m, 38H, aromatic), 5.91–5.80 (m, 1H, allyl-CH), 5.55 (d, 1H, 1-CH, J=7.6 Hz), 5.00–4.95 (m, 2H, allyl-CH_2), 4.36 (d, 1H, 2-CH, J=7.6 Hz), 4.23–4.17 (m, 2H, 3-CH, 5-CH), 3.72 (d, 1H, 4-CH, J=3.2 Hz), 3.71 (t, 1H, 6-CH_2, J=9.5 Hz), 2.68 (dd, 1H, 6-CH_2, J=2.5, 9.5 Hz), 1.50–1.46 (m, 2H, allyl-CH_2), 1.11 (s, 9H, –*t*Bu), 0.93 (s, 9H, –*t*Bu), 0.10 (s, 3H, –$SiCH_3$), 0.09 (s, 3H, –$SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 135.8, 135.7, 135.5, 134.2, 132.9, 132.9, 132.8, 132.8, 131.0, 129.4, 129.4, 128.8, 128.7, 127.5, 127.4, 127.4, 127.3, 127.3, 126.8, 126.5, 113.2, 86.3, 84.1, 84.0, 76.2, 75.8, 71.1, 66.9, 26.9, 25.4, 19.2, 19.1, −1.6, −1.7; LRMS (FAB, positive) m/z 1159 (MNa^+). Anal. Calcd for $C_{68}H_{76}O_5SeSi_3$: C, 71.86; H, 6.74. Found: C, 71.62; H, 6.72.

3.1.7. Phenyl 2-*O*-allyldimethylsilyl-3,4-bis-*O*-triisopropylsilyl-6-*O*-triphenylmethyl-1-seleno-β-D-glucopyranoside (10c). Compound **10c** (1.4 g, 73%) was obtained as a colorless oil from **13c** (1.7 g, 1.9 mmol) as described above for the synthesis of **10a**, after purification by column chromatography (SiO_2, 2–5% AcOEt in hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.18 (m, 20H, aromatic), 5.81–5.70 (m, 1H, allyl-CH), 5.23 (d, 1H, 1-CH, J=7.6 Hz), 4.86–4.79 (m, 2H, allyl-CH_2), 4.12 (dd, 1H, 2-CH, J=4.5, 7.6 Hz), 3.98–3.94 (m, 2H, 3-CH, 5-CH), 3.86 (brs, 1H, 4-CH), 3.56 (dd, 1H, 6-CH, J=7.9, 9.4 Hz), 3.05 (dd, 1H, 6-CH, J=4.7, 9.4 Hz), 1.65 (m, 2H, allyl-CH_2), 1.03–0.84 (m, 42H, –$CH(CH_3)_2$), 0.15 (s, 3H, –$SiCH_3$), 0.11 (s, 3H, –$SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0, 134.3, 132.9, 130.6, 128.7, 128.7, 127.5, 127.4, 126.8, 126.6, 126.5, 113.3, 86.6, 83.7, 83.3, 77.1, 71.4, 66.4, 25.9, 18.5, 18.5, 18.3, 18.3, 12.8, 12.7, 12.3, −1.1, −1.3; HRMS calcd $C_{54}H_{80}NaO_5SeSi_3$: 995.4376 (MNa^+), found 995.4352.

3.1.8. Phenyl 2-*O*-allyldimethyl-3,4,6-tri-*O*-benzyl-1-seleno-β-D-glucopyranoside (15). A mixture of **14** (800 mg, 1.37 mmol), Et_3N (190 μL, 2.06 mmol), DMAP (17 mg, 0.137 mmol) and allyldimethylchlorosilane (300 μL, 2.06 mmol) was stirred at room temperature for 3 h. The mixture was partitioned between AcOEt and

H_2O, and the organic layer was washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (SiO_2, 2–5% AcOEt in hexane) to give **15** (923 mg, 98%) as a colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.66–7.07 (m, 20H, aromatic), 5.75 (m, 1H, allyl-H), 4.95 (d, 1H, benzyl-CH_2, J=11.5 Hz), 4.83 (d, 2H, allyl-CH_2, J=12.3 Hz) 4.83 (d, 2H, benzyl-CH_2, J=12.5 Hz), 4.78 (d, 1H, 1-CH, J=10.9 Hz), 4.59 (d, 1H, benzyl-CH_2, J=11.9 Hz), 4.55 (d, 1H, benzyl-CH_2, J=11.5 Hz), 4.51 (d, 1H, benzyl-CH_2, J=11.9 Hz), 3.74 (dd, 1H, 5-CH, J=9.7, 3.6 Hz), 3.74 (dd, 1H, 3-CH, J=10.9, 9.5 Hz), 3.73 (dd, 1H, 2-CH, J=10.9, 10.9 Hz), 3.73 (dd, 1H, 4-CH, J=9.5, 9.7 Hz), 3.49 (dd, 2H, 6-CH_2, J=3.6, 8.9 Hz), 1.67 (dd, 2H, Si–CH_2–, J=1.3, 7.6 Hz), 0.15 (s, 3H, Si–CH_3), 0.11 (s, 3H, Si–CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 138.2, 137.9, 134.2, 133.7, 129.3, 128.9, 128.4, 128.3, 128.2, 127.9, 127.7, 127.6, 127.5, 127.2, 126.8, 113.7, 87.0, 85.47, 80.3, 78.3, 75.2, 74.9, 74.8, 73.5, 68.9, 25.4, −1.3, −1.4; LRMS (FAB, positive) m/z 711 (MNa^+).

3.2. General procedure for the radical reactions of 10a–c

To a refluxing solution of **10a–c** (0.30 mmol) in benzene (6 mL), a solution of Bu_3SnH (161 μl, 0.6 mmol) and AIBN (33 mg, 0.2 mmol) in benzene (1.5 mL) was added dropwise by a syringe pump over 2 h. The mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (SiO_2, 2–5% AcOEt in hexane) to give **16a–c** as colorless oil. **16a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.15 (m, 15H), 3.98 (ddd, 1H, J=3.2, 3.7, 9.9 Hz), 3.85 (d, 1H, J=3.7 Hz), 3.63 (d, 1H, J=3.7 Hz), 3.52 (dd, 1H, J=3.2, 9.9 Hz), 3.39 (d, 1H, J=9.9 Hz), 3.35 (d, 1H, J=3.7 Hz), 3.02 (d, 6H, J=3.7 Hz), 2.03 (m, 2H), 0.76 (s, 9H), 0.74 (s, 9H), 0.15 (s, 3H), 0.05 (s, 3H), −0.02 (s, 3H), −0.05 (s, 6H), −0.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 128.6, 127.5, 126.6, 86.1, 77.5, 77.3, 74.4, 72.2, 71.2, 70.4, 63.3, 33.6, 26.1, 26.0, 25.9, 18.5, 18.1, 18.1, 18.0, 0.0, −1.0, −3.7, −3.9, −4.2, −4.3; LRMS (FAB, positive) m/z 755 (MNa^+). Anal. Calcd for $C_{42}H_{64}O_5Si_3$: C, 68.80; H, 8.80. Found: C, 68.52; H, 8.98. **16b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.08 (m, 35H), 4.08 (ddd, 1H, J=1.3, 2.9, 9.5 Hz), 3.97 (t, 1H, J=4.6 Hz), 3.89 (d, 1H, J=1.3 Hz), 3.69 (t, 1H, J=9.5 Hz), 3.41 (t, 1H, J=1.3 Hz), 3.39 (t, 1H, J=1.3 Hz), 2.43 (dd, 1H, J=2.9, 9.5 Hz), 2.16–2.08 (m, 1H), 2.02–1.96 (m, 1H), 1.76–1.69 (m, 1H), 1.38–1.26 (m, 1H), 0.91 (s, 9H), 0.84–0.78 (m, 1H), 0.73 (s, 9H), 0.58–0.52 (m, 1H), 0.07 (s, 3H), −0.22 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 144.1, 135.7, 135.5, 135.4, 133.7, 133.6, 133.1, 133.0, 129.5, 129.4, 129.2, 129.1, 128.6, 127.4, 127.3, 127.3, 127.1, 126.5, 85.9, 79.1, 72.2, 70.3, 70.1, 66.8, 62.1, 34.7, 27.0, 26.8, 19.3, 19.2, 17.7, 16.9, −0.1, −1.0; LRMS (FAB, positive) m/z 1003 (MNa^+). Anal. Calcd for $C_{62}H_{72}O_5Si_3$: C, 75.87; H, 7.39. Found: C, 75.58; H, 7.58. **16c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.43 (m, 2H), 7.27–7.18 (m, 9H), 4.24 (m, 1H), 3.86 (brs, 2H), 3.68 (t, 1H, J=9.9 Hz), 3.53 (brs, 2H), 2.86 (dd, 1H, J=3.2, 9.9 Hz), 2.06–2.03 (m, 1H), 1.98–1.95 (m, 1H), 1.73–1.69 (m, 1H), 1.03–0.87 (m, 44H), 0.11 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 128.8, 128.6, 127.5, 127.4, 126.5, 86.1, 79.7, 72.7, 71.4, 70.2, 66.9, 62.2, 34.7, 18.3, 18.2, 18.1, 17.8, 16.9, 12.6, 12.6, 12.5, 12.4, 12.4, −0.1, −0.4; LRMS (FAB, positive) m/z 839 (MNa^+). Anal. Calcd for $C_{48}H_{76}O_5Si_3$: C, 70.53; H, 9.37. Found: C, 70.61; H, 9.45.

3.2.1. 4,8-Anhydro-6,7,9-tri-*O*-benzyl-2,3-dideoxy-D-*glycero*-D-*ido*-nonitol (18) and 4,8-anhydro-6,7,9-tri-*O*-benzyl-2,3-dideoxy-D-*glycero*-D-gulo-nonitol (19). To a refluxing solution of **15** (206 mg, 0.3 mmol) in a solvent (60 mL), a solution of Bu_3SnH (97 μL, 0.36 mmol) and AIBN (30 mg, 0.18 mmol) in the same solvent (8.4 mL) was added dropwise by a syringe pump over 4 h. The mixture was evaporated, and a mixture of the resulting residue, KF (349 mg, 6.0 mmol), $KHCO_3$ (180 mg, 1.8 mmol) and aqueous H_2O_2 (30%, 2.2 mL) in MeOH (1.7 mL) and THF (1.7 mL) was stirred at room temperature for 12 h. Aqueous saturated $Na_2S_2O_3$ was added, and the resulting mixture was filtrated through Celite. The filtrate was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (SiO_2, 20–35% AcOEt in $CHCl_3$) to give a mixture of **18** and **19** (yield, see Table 1) as a white solid. The α/β ratio was determined by HPLC analysis [YMC Pack R-ODS-5A; 85% aqueous MeOH, 1.0 mL/min, room temperature, 260 nm; retention time, 11 min (**18**), 13.5 min (**19**)]. From a mixture of **18** and **19** (78 mg, **18**:**19**=1:2.9), **18** (12 mg, white solid) and **19** (35 mg, white solid) were obtained in a pure form by preparative HPLC (YMC Pack D-ODS-5A, 20×250 mm; 95% aqueous MeOH, 10 mL/min, room temperature, 260 nm). **18**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.21 (m, 15H, aromatic), 4.68–4.52 (m, 6H, benzyl-CH_2), 4.03 (q, 1H, 8-CH_2, J=5.0 Hz), 3.91 (ddd, 1H, 4-CH, J=3.3, 3.6, 5.0 Hz), 3.78–3.58 (m, 7H, 1-, 9-CH_2, 5-, 6-, 7-CH), 1.68 (m, 4H, 2-, 3-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 137.5, 137.0, 128.2, 128.2, 128.0, 127.6, 127.6, 127.6, 127.5, 127.4, 127.3, 77.7, 74.9, 73.3, 73.1, 73.1, 72.8, 71.7, 69.8, 67.9, 62.5, 29.2, 24.8; LRMS (FAB, positive) m/z 493 (MH^+). Anal. Calcd for $C_{30}H_{36}O_6\cdot 1/2H_2O$: C, 71.83; H, 7.43. Found: C, 71.84; H, 7.44. **19**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.17 (m, 15H, aromatic), 4.97–4.52 (m, 6H, benzyl-CH_2), 3.69 (dd, 1H, 9-CH_2, J=2.0, 10.8 Hz), 3.68–3.62 (m, 3H, 1-CH_2, 9-CH_2), 3.58 (dd, 1H, 7-CH, J=9.4, 9.4 Hz), 3.46 (dd, 1H, 6-CH, J=8.8, 9.4 Hz), 3.43 (ddd, 1H, 8-CH, J=2.0, 4.5, 9.4 Hz), 3.32 (dd, 1H, 5-CH, J=8.8, 9.1 Hz), 3.22 (ddd, 1H, 4-CH, J=2.1,2.1, 9.1 Hz), 1.98 (m, 1H, 3-CH_2), 1.72 (m, 2H, 2-CH_2), 1.55 (m, 1H, 3-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 137.6, 137.5, 128.3, 128.1, 128.0, 127.6, 127.6, 127.5, 127.3, 86.5, 79.2, 78.5, 78.1, 76.5, 75.0, 74.6, 73.4, 73.3, 68.7, 62.5, 28.7, 28.5; LRMS (FAB, positive) m/z 493 (MH^+). Anal. Calcd for $C_{30}H_{36}O_6\cdot 1/2H_2O$: C, 71.83; H, 7.43. Found: C, 71.84; H, 7.44.

3.2.2. (2*R*,3*S*,4*R*,5*R*,6*R*)-3-acetoxy-6-(triphenylmethoxy)-methyl-4,5-di-*tert*-butyldimethylsilyloxy-2-[(3-dimethylphenylsilyl)propyl)tetrahydropyran (20). A mixture of **16a** (655 mg, 0.73 mmol) and PhLi (0.72 M in Et_2O, 5 mL, 3.6 mmol) in THF (14 mL) was stirred at −20 °C for 5 min, and then aqueous saturated NH_4Cl was added. The resulting mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4) and evaporated. A mixture of the residue and AcCl (142 μL, 2.0 mmol) in pyridine (10 mL) was stirred at room

temperature for 12 h. The mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (SiO_2, 0–1% AcOEt in hexane) to give **20** (524 mg, 86%) as yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.08 (m, 20H), 4.21 (s, 1H), 4.04 (dd, 1H, J=3.5, 8.7 Hz), 3.70 (s, 1H), 3.65 (s, 1H), 3.48 (dd, 1H, J=8.7, 10.1 Hz), 3.28 (s, 1H), 2.98 (dd, 1H, J=3.5, 10.1 Hz), 1.97 (s, 3H), 1.70–1.40 (m, 2H), 1.36–1.18 (m, 2H), 0.89–0.79 (m, 2H), 0.78 (s, 9H), 0.62 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H), −0.05 (s, 3H), −0.06 (s, 3H), −0.07 (s, 3H), −0.11 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 144.3, 128.8, 128.7, 127.6, 126.7, 86.2, 77.6, 74.4, 72.2, 71.2, 70.2, 63.3, 33.6, 29.1, 27.4, 26.7, 26.2, 25.9, 18.3, 18.0, 18.0, 17.9, 13.7, 9.4, −0.1, −1.1, −3.9, −4.0, −4.4, −4.4; HRMS (FAB) calcd $C_{50}H_{72}O_6Si_3Na$ 875.4534 (MNa^+), found 875.4549.

3.2.3. (2*R*,3*S*,4*R*,5*R*,6*R*)-3-acetoxy-6-(triphenylmethoxy)-methyl-4,5-di-*tert*-butyldimethylsilyl-2-[3-(dimetyl-*p*-methoxyphenylsilyl)propyl]tetrahydropyrane (21). Compound **21** (328 mg, 77%) was obtained as yellow oil from **16a** (366 mg) as described above for the synthesis of **20** using *p*-MeOPhLi (prepared from *p*-lithioanisole and BuLi) instead of PhLi, after purification by column chromatography (SiO_2, 0–1% AcOEt in hexane): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.41 (m, 6H), 7.32–7.14 (m, 11H), 6.87 (t, 1H, J=7.2 Hz), 6.77 (d, 1H, J=8.2 Hz), 4.28 (s, 1H), 4.07 (dd, 1H, J=4.3, 9.5 Hz), 3.76 (s, 1H), 3.72 (brs, 4H), 3.55 (t, 1H, J=9.5 Hz), 3.34 (s, 1H), 3.02 (dd, 1H, J=4.3, 9.5 Hz), 2.03 (s, 3H), 1.68–1.66 (m, 1H), 1.43–1.41 (m, 1H), 1.27–1.23 (m, 2H), 0.84 (s, 9H), 0.77–0.73 (m, 2H), 0.67 (s, 9H), 0.18 (s, 3H), 0.17 (s, 3H), 0.00 (s, 3H), −0.01 (s, 3H), −0.03 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 170.8, 164.1, 144.0, 135.0, 130.5, 128.5, 127.6, 126.8, 126.7, 120.3, 109.3, 86.3, 79.1, 77.2, 71.2, 69.8, 68.6, 65.4, 61.5, 55.0, 34.8, 26.0, 25.8, 21.2, 20.3, 18.3, 17.8, 15.8, −2.5, −2.6, −4.5, −4.6, −4.8, −4.9; LRMS (FAB, positive) m/z 905 (MNa^+). Anal. Calcd for $C_{51}H_{74}O_7Si_3$: C, 69.34; H, 8.44. Found: C, 69.52, H, 8.52.

3.2.4. 4,8-Anhydro-4-*O*-acetyl-6,7-di-*O*-*tert*-butyldimethylsilyl-9-*O*-triphenylmethyl-2,3-dideoxy-D-*glycero*-D-*ido*-nonitol (22). To a mixture of **21** (54 mg, 0.060 mmol), KBr (15 mg, 0.12 mmol) and AcONa (50 mg, 0.61 mmol) in AcOH (12 mL) was added dropwise a mixture of AcOOH (32% in AcOH, 165 μL, 0.61 mmol) and H_2SO_4 (1.5 μL, 0.03 mmol) in AcOH at 0 °C, and the resulting mixture was stirred at room temperature for 14 h. After addition of aqueous saturated $Na_2S_2O_3$, the mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (SiO_2, 0–2% AcOEt in hexane) to give **22** (23 mg, 61%) as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.18 (m, 15H), 4.32 (s, 1H), 4.10 (dd, 1H, J=4.4, 9.1 Hz), 3.77 (brs, 2H), 3.62 (t, 2H, J=5.7 Hz) 3.56, (t, 1H, J=9.1 Hz), 3.34 (s, 1H), 3.10 (dd, 1H, J=4.4, 9.1 Hz), 2.05 (s, 3H), 1.73–1.68 (m, 2H), 1.45–1.43 (m, 2H), 0.88 (s, 9H), 0.84 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H), −0.01 (s, 3H), −0.05 (s, 3H); LRMS (FAB, positive) m/z 753 (MNa^+).

3.2.5. 4,8-Anhydro-4-*O*-acetyl-9-*O*-triphenylmethyl-2,3-dideoxy-D-*glycero*-D-*ido*-nonitol (23). A solution of **22** (32 mg, 44 μmol), TBAF (1 M in THF, 100 μL, 100 μmol) and AcOH (29 μL, 50 μmol) in THF (1 mL) was stirred at room temperature for 12 h. The mixture was partitioned between AcOEt and H_2O, and the organic layer was washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (SiO_2, 0–1% AcOEt in hexane) to give **23** (22 mg, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.43 (m, 6H), 7.33–7.23 (m, 9H), 4.88 (dd, 1H, J=5.9, 9.7 Hz), 4.15 (ddd, 1H, 2.6, 3.5, 5.9), 3.78 (m, 1H), 3.68 (d, 2H, J=2.7 Hz), 3.56–3.52 (m, 2H), 3.39 (dd, 2H, J=4.4, 11.4 Hz), 2.72 (brs, 1H), 2.44 (brs, 1H), 2.11 (s, 3H), 1.72 (m, 2H), 1.56 (m, 2H); HRMS (FAB) calcd $C_{30}H_{34}O_6Na$: 529.2202 (MNa^+), found 529.2224.

3.2.6. 4,8-Anhydro-2,3-dideoxy-D-*glycero*-D-*ido*-nonitol 1,6,7-trisphosphate derivative 24. A mixture of **23** (15 mg, 30 μmol), XEPA (29 mg, 120 μmol) and 1*H*-tetrazole (10 mg, 135 μmol) in CH_2Cl_2 was stirred at 0 °C for 30 min. After addition of H_2O (10 μL), the mixture was stirred at room temperature for further 10 min. The resulting mixture was cooled to −40 °C, and then *m*-CPBA (35 mg, 200 μmol) was added. The mixture was warmed to room temperature over 30 min and partitioned between AcOEt and aquerous saturated Na_2SO_3, and the organic layer was washed with H_2O, aqueous saturated $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. The residue was purified by preparative thin layer chromatography (SiO_2, 75% AcOEt in hexane) to give **24** (22 mg, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.35 (m, 6H), 7.28–7.13 (m, 20H), 7.07–7.05 (m, 1H), 5.39 (dd, 1H, J=8.9, 13.8 Hz), 5.23–4.80 (m, 11H), 4.69 (t, 1H, J=13.8 Hz), 4.54–4.38 (m, 2H), 4.24–4.15 (m, 3H), 3.78–3.75 (m, 1H), 3.42 (dd, 1H, J=1.2, 10.3 Hz), 3.34 (dd, 1H, J=7.3, 10.3 Hz), 2.12 (s, 3H), 1.94–1.77 (m, 2H), 1.70–1.65 (m, 2H); ^{31}P NMR (202 MHz, D_2O, H-decoupled) δ 0.32 (s), −2.19 (s), −3.82 (s); HRMS (FAB) calcd $C_{54}H_{55}O_{16}P_3Na$: 1075.2601 (MNa^+), found 1075.2530.

3.2.7. 4,8-Anhydro-2,3-dideoxy-D-*glycero*-D-*ido*-nonitol 1,6,7-trisphosphate hexasodium salt (9). A mixture of **24** (18 mg, 17 μmol) and Pd–C (10%, 20 mg) in MeOH (2 mL) was stirred at room temperature under atmospheric pressure of H_2 for 40 min. The catalysts were filtrated off with Celite, and the filtrate was evaporated. To a solution of the residue in MeOH (1 mL) was added TFA (1 μL, 13 μmol) and then the mixture was evaporated. A solution of the residue in H_2O was washed with AcOEt (three times) and evaporated. A solution of the residue in aqueous NaOH (1 M, 2 mL) was stirred at room temperature for 12 h. The resulting mixture was applied to Diaion PK-212 (H^+-form) column, and the column was developed with H_2O. The fractions containing **9** (acidic fractions) were evaporated. A solution of the residue in H_2O (1 mL) was applied to Daiaion WK-100 (Na^+-form) column, and the column was developed with H_2O. The fractions containing **9** were evaporated and dried in vacuo to give **9** (sodium salt, 12 mg, quant.) as a white solid. ^{1}H NMR (400 MHz, D_2O) δ 4.17 (dd, 1H, J=8.5, 17.3 Hz), 3.90 (dd, 1H, J=5.4, 10.6 Hz), 3.83–3.63 (m, 5H), 3.59–3.49 (m, 2H), 1.70–1.44 (m, 4H); ^{13}C NMR (100 MHz, D_2O) δ 77.46 (dd, $J_{c,p}$=3.3, 4.9 Hz), 75.18 (s), 73.26 (d, $J_{c,p}$=2.5 Hz), 73.03 (d, $J_{c,p}$=2.5 Hz), 71.72 (s), 65.53 (d,

$J_{c,p}$=5.8 Hz), 26.78 (d, $J_{c,p}$=6.6 Hz), 21.63 (s); ^{31}P NMR (202 MHz, D_2O, H-decoupled) δ 2.54 (s), 2.45 (s), 2.13 (s); HRMS (FAB) calcd $C_9H_{17}O_{15}Na_3P_3$: 526.9473 (M^-), found 526.9444.

3.3. Materials for the bioassay

RPMI 1640 medium, L-glutamine, 2-mercaptoethanol and G-418 were from Invitrogen (Paisley, UK), sera were from Sigma (Poole, UK) and Mag-fluo-4AM was from Molecular Probes (Leiden, The Netherlands).

3.3.1. Stable transfection of DT40 cells with rat type 1 IP_3R. The open reading frame of rat type 1 IP_3R (IP_3R1) was amplified by polymerase chain reaction (PCR) from the expression vector pCMVI-9-IP_3R1[28] using the following primers: 5′-AGGAATTCGCCACCATGTCTGACAAA ATG-3′ and 5′-CCGGTACCGAATTCTTAGGCTGGCTG CTGT-3′ and cloned as an *Eco*RI fragment into pcDNA3 (Invitrogen). The chicken β-actin hybrid promoter[29] was excised from the vector pAneo[31] and cloned in place of the CMV promoter upstream of the $InsP_3R1$ open reading frame to create the construct pcDNA3-IP_3R1. DT40 cells in which the genes for all three endogenous IP_3R subtypes have been deleted (DT40/IP_3R-KO)[30] were stably transfected by electroporation with linearized pcDNA3-IP_3R1 using a Gene Pulser apparatus (Bio-Rad Laboratories) at 330 V, 500 μF with 5 μg DNA/10^6 cells. Clonal isolation was carried out in the presence of 2 mg/ml G-418 and positive clones were amplified and screened for the presence of rat $InsP_3R1$ by western blotting using an anti-peptide antiserum[31] corresponding to the C-terminal 15-residues of rat IP_3R1.

3.4. Cell culture

DT40/IP_3R-KO cells stably expressing recombinant rat IP_3R1 (DT40/IP_3R1 cells) were cultured in suspension in RPMI 1640 medium supplemented with foetal bovine serum (10%), L-glutamine (2 mM), 2-mercaptoethanol (50 μM) and heat-inactivated chicken serum (1%). Cells were incubated in a humidified atmosphere (95% O_2; 5% CO_2 at 37 °C) and passaged every 2–3 days when they had reached a density of $\sim 2\times10^6$ cells/ml.

3.5. Measurement of Ca^{2+} release from permeabilized cells

The effects of $InsP_3$ on intracellular Ca^{2+} stores were measured using a low-affinity Ca^{2+}-indicator trapped within the intracellular stores of permeabilized cells. DT40/IP_3R1 cells were harvested (650× *g*; 2 min) and re-suspended (2–3×10^7 cells/ml) in Hepes-buffered saline (HBS: 135 mM NaCl, 5.9 mM KCl, 1.2 mM $MgCl_2$, 1.5 mM $CaCl_2$, 11.6 mM Hepes, 11.5 mM D-glucose, pH 7.3) supplemented with Mag-fluo-4AM (20 μM), Pluronic F-127 (0.05%) and bovine serum albumin (1 mg/ml). After 1 h at 20 °C in the dark, the Mag-fluo-4-loaded cells were harvested (650×*g*; 2 min) and re-suspended ($\sim 2\times10^6$ cells/ml) in Ca^{2+}-free cytosolic-like medium (CLM: 140 mM KCl, 20 mM NaCl, 2 mM $MgCl_2$, 1 mM EGTA, 20 mM Pipes, pH 7.0). The cells were permeabilized by incubation with saponin (10 μg/ml, 4 min at 37 °C), harvested (650×*g*; 2 min) and resuspended in Mg^{2+}-free CLM (140 mM KCl, 20 mM NaCl, 1 mM EGTA, 375 μM $CaCl_2$ ($\sim$200 nM free [Ca^{2+}]), 20 mM Pipes, pH 7.0). The permeabilized cells (with Mag-fluo-4 trapped within the lumen of the endoplasmic reticulum, ER) were then attached to 96-well plates ($\sim 8\times10^5$ cells/well) coated with poly-L-lysine (0.01%) and centrifuged onto the plate (300×*g*; 2 min). Immediately before an experiment, the cells were washed twice in Mg^{2+}-free CLM to remove cytosolic Mag-fluo-4 and the plates were then mounted in a FlexStation fluorescence plate reader (Molecular Devices, Sunnyvale, CA), which allows automated additions to the sample wells while recording fluorescence. Mag-fluo-4 fluorescence was monitored by excitation at 485 nm with emission detected at 520 nm. Active Ca^{2+} uptake into the ER was initiated by addition of Mg^{2+}-ATP (1.5 mM) and after 150 s, when the stores had loaded to a steady-state Ca^{2+} content, IP_3 was added. The amount of Ca^{2+} released by IP_3 was expressed as a fraction of the total Ca^{2+} content of the ER as assessed by addition of 1 μM ionomycin. Data are presented as means ±s.e. means from at least three independent experiments, each performed in triplicate. Concentration–effect relationships were fitted to four-parameter logistic equations using non-linear curve-fitting procedures (GraphPad Prism, San Diego, CA).

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Pd-catalyzed nucleophilic allylic alkylation of aliphatic aldehydes by the use of allyl alcohols

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Abstract—Under catalysis of $Pd(OAc)_2$-(P-*n*-$Bu)_3$, Et_2Zn promotes a variety of allyl alcohols to undergo nucleophilic allylation of aliphatic aldehydes and ketones at room temperature and provides homoallyl alcohols in 60–90 and ca. 60% isolated yield, respectively. The reaction is irreversible and kinetically controlled, and unique regio- and stereoselectivities observed for the allylation with unsymmetrically substituted allyl alcohols are discussed.

1. Introduction

Nucleophilic alkylation of aldehydes and ketones is among the most fundamental and useful methods to elaborate molecules, and many methodologies, especially allylation using a variety of allyl metals (Li, Mg, etc.) and metalloids (B, Si, Sn, etc.), have been explored.[1] Allylating agents are basically prepared from allyl halides derived from allyl alcohols by treatment with a stoichiometric amount of hazardous hydrogen halides or anhydrides of hydrogen halides–organic and inorganic acids. As allyl metalloids, despite their toxicity and instability, allylstannanes have been most widely studied and utilized owing to their good performance in reactivity and selectivity.[2]

Needless to say, the use of allyl alcohols themselves as allylation agents has many advantages from an economical and environmental points of view: no need for additional steps to convert to other allylating agents and production of water instead of strong acids as a side-product. Furthermore, from a practical point of view, ready availability of a wide structural variety, moderate stability withstanding purification by distillation and storage, and wide abundance in nature, all combine to make allyl alcohols suitable and ideal for small- to large-scale experiments.

2. Results and discussion

The allylation with allyl alcohols was first realized and studied extensively by Masuyama et al.,[3] who used a Pd–$SnCl_2$ catalytic system. At a first glance, heterolytic cleavage of the C–O bond of an allyl alcohol to generate an allyl anion and a hydroxy cation species ($CH_2{=}CHCH_2OH \rightarrow CH_2{=}CHCH_2^- + OH^+$) may seem to be unrealistic; however, this task could be realized by virtue of capability of a palladium(0) species to undergo oxidative addition upon an allyl alcohol, probably being activated by coordination to a Lewis acid, to form a π-allylpalladium species ($CH_2{=}CHCH_2OH + Pd(0) \rightarrow CH_2{=}CHCH_2Pd^+OH^-$) and capability of $SnCl_2$ to reduce a cationic π-allylpalladium species to an anionic allylstannane species ($CH_2{=}CHCH_2Pd^+OH^- + Sn^{2+}Cl_2 \rightarrow CH_2{=}CHCH_2Sn^{4+}Cl_2OH + Pd(0)$). From an environmental view point, however, this method suffers from hazardous nature of hydrogen chloride, ultimately formed by hydrolysis of chlorostannanes used in an excess amount.

Recently, we have disclosed that nucleophilic allylation of aromatic aldehydes can be successfully performed by using allyl alcohols under a Pd–Et_3B catalytic system, where Et_3B not only serves as a Lewis acid to activate an allyl alcohol, but it reacts with a π-allylpalladium intermediate to exchange the ethyl and allyl ligands to each other to give a nucleophilically active allylborane species and an unstable ethylpalladium(II) species, which might readily decompose in many ways, e.g. via β-hydrogen elimination generating ethylene and water molecules together with a catalytically active Pd(0) species (Scheme 1a).[4] Unfortunately, however,

Keywords: Palladium; Allyl alcohols; Allylation; Aldehydes; Ketones.
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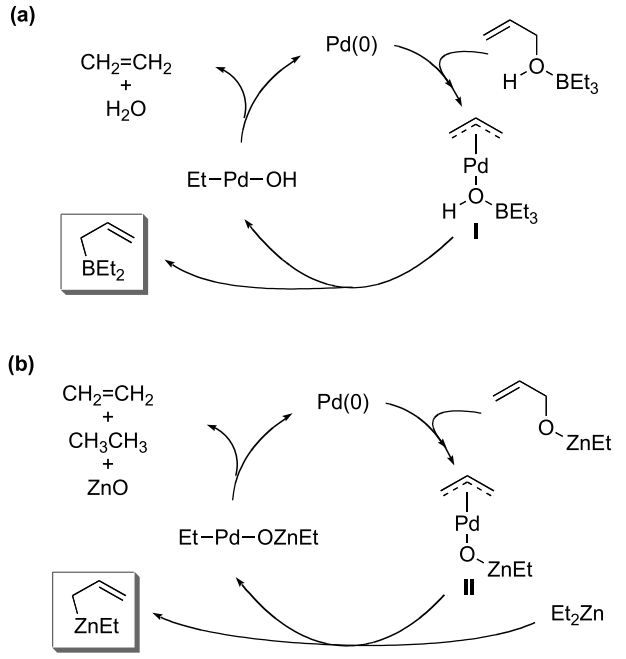


Scheme 1. Catalytic cycles for the generation of allylborane (a) and allylzinc (b) from allyl alcohol in the presence of a palladium(0) species.

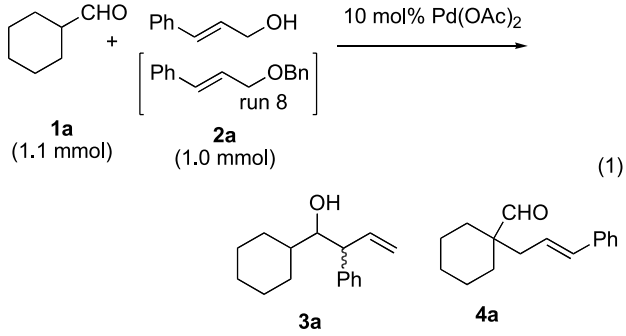
the reaction was not applicable to aliphatic aldehydes; nucleophilic allylation was accompanied by electrophilic allylation at the α-carbons of aliphatic aldehydes.[5]

For example, under the catalysis of Pd(0)–Et_3B, the reaction of cyclohexanecarboxaldehyde (**1a**) and cinnamyl alcohol (**2a**) provided a mixture of **3a** and **4a** in almost equal amounts (Eq. 1 and runs 1, Table 1) or **4a** selectively (run 2). The selective α-allylation giving rise to **4a** could be realized by using LiCl (facilitating the exchange of the counter ion of **I**: Et_3BOH^- to Cl^-) and Et_3N (increasing the concentration of an aldehyde enolate) as additives.[5] However, we have not been successful yet to modify the reaction to selectively undergo nucleophilic allylation at the carbonyl carbons of aldehydes.

Our working hypothesis (Scheme 1) suggested that organometallic species of higher migratory aptitude might promote the allyl–ethyl exchange process and hence facilitate the generation of an allylmetal species. Accordingly, we reexamined the reaction of **1a** and **2a** using Et_2Zn in place of Et_3B (Scheme 1b).[6] As was expected, **4a** was eliminated completely (run 3, Table 1); however, the reaction was very sluggish (45% conversion, 20 h at room temperature) and provided the expected **3a**, albeit in low yield. Application of *n*-Bu_3P, in place of Ph_3P, dramatically increased not only the yield of **3a**, but the reaction rate (run 4). Interestingly, non-polar solvents seemed to give the better results (runs 5 and 7). The solvent system in these reactions is rather unique and consists of non-polar solvents: toluene (0.5 mL) and *n*-hexane (3.6 mL, the solvent of Et_2Zn) for a 1 mmol scale reaction. The amount of toluene was set as small as possible to make the initial reaction mixture homogeneous at 0 °C (Section 4). Loading of 4 equiv of *n*-Bu_3P relative to $Pd(OAc)_2$ brought about higher diastereoselectivity (runs 5 and 7).

The diastereoselectivity is largely affected by the amount and the kind of phosphine ligands as well as by the solvent systems. In *n*-hexane–toluene solvent, there seems to be a

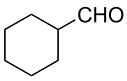
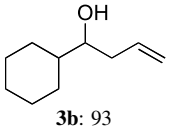
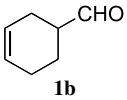
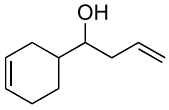
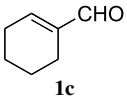
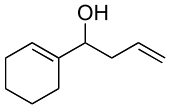
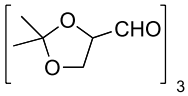
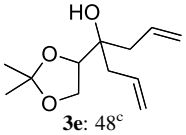
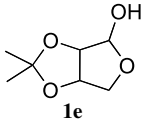
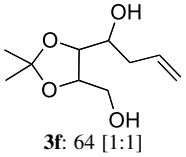
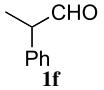
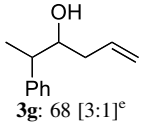
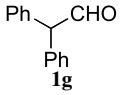
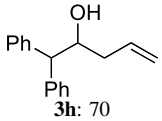
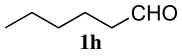
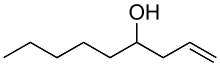
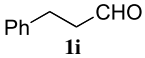
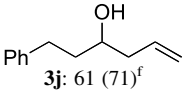
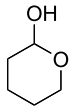
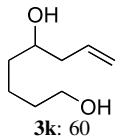
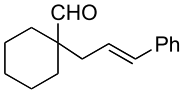
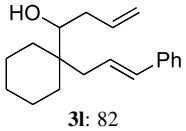
Table 1. Effects of organometallics (RM), ligands, and solvents on the Pd-catalyzed allylation of **1a** with allyl alcohol[a]



Run	RM (mol%)	Phosphine (mol%)	Solvent (ml)	Time (h)	% Yield [*anti*:*syn*][b]	
					3a	**4a**
1	Et_3B (240)	PPh_3(20)	THF (5)	4	39 [–]	30[c]
2	Et_3B (240)	P(*n*-Bu)$_3$(20)	THF (5)	23	21 [18:1]	51
3	Et_2Zn (360)	PPh_3(20)	THF (5)	20[d]	18 [7:1]	0
4	Et_2Zn (360)	P(*n*-Bu)$_3$(20)	THF (5)	10	53 [14:1]	0
5	Et_2Zn (360)	P(*n*-Bu)$_3$(20)	Tol (0.5)[e]	30	72 [2:1]	0[c]
6	Et_2Zn (360)	PPh_3(20)	Tol (0.5)	20	63 [1:1]	0
7	Et_2Zn (360)	P(*n*-Bu)$_3$(40)	Tol (0.5)	6	75 [18:1]	0
8[f]	Et_2Zn (360)	P(*n*-Bu)$_3$(40)	Tol (0.5)	1	93 [10:1]	0

[a] Reaction conditions: cinnamyl alcohol (**2a**) (1.0 mmol), cyclohexanecarboxaldehyde (1.2 mmol), $Pd(OAc)_2$ (10 mol%), Et_3B or Et_2Zn (indicated amount), phosphine (indicated amount) at room temperature under N_2.
[b] Yields refer to the isolated spectroscopically homogeneous materials. The diastereomer ratios were determined on the basis of ^1H NMR (400 MHz).
[c] 1,4-Diphenyl-1,5-hexadiene was isolated in 20% (run 1) and 10% yields (run 5), respectively.
[d] 45% conversion.
[e] tol = dry toluene.
[f] Benzyl cinnamyl ether was used in place of **2a**.

Table 2. Allylation of a variety of aldehydes **1** with allyl alcohol **2b**[a]

Run	Aldehyde	Time (h)	% isolated yield[b]
1	 **1a**	6	 **3b**: 93
2	 **1b**	8	 **3c**: 74
3	 **1c**	6	 **3d**: 73
4	 **1d**	10	 **3e**: 48[c]
5[d]	 **1e**	20	 **3f**: 64 [1:1]
6	 **1f**	7	 **3g**: 68 [3:1][e]
7	 **1g**	6	 **3h**: 70
8	 **1h**	8	 **3i**: 78
9	 **1i**	6	 **3j**: 61 (71)[f]
10[d]	 **1j**	18	 **3k**: 60
11	 **1k**	8	 **3l**: 82

[a] Reaction conditions: allyl alcohol (**2b**) (1.0 mmol), an aldehyde (1.2 mmol), $Pd(OAc)_2$ (10 mol%), Et_2Zn (3.6 mmol, 1M *n*-hexane solution), P(*n*-Bu)$_3$ (40 mol%) at room temperature under N_2.
[b] Yields refer to the isolated spectroscopically homogeneous materials.
[c] Yield is based on allyl alcohol, hence 0.24 mmol of **3e** was isolated.
[d] Et_2Zn (4.6 mmol) was used.
[e] Diastereomer ratio of *syn* to *anti*.
[f] Under the conditions of run 4 (Table 1); rt., 10 h.

general trend that the more electron donating and the more the amounts of the phosphine ligands, the higher the *anti*-selectivities (runs 5∼7). This may be accounted for as follows. The polarity of the solvent system is such that allylzinc would form aggregate with itself or with other zinc species (e.g., Et_2Zn, zinc alkoxide); hence, it hardly forms a putative six-membered chair-like transition state leading to an *anti*-isomer (vide infra, cf. **VI**, Scheme 3). In the presence of *n*-Bu_3P, on the other hand, it may loosen the aggregate to form an allylzinc monomer by coordination to Zn^{2+}; hence, a monomeric allylzinc species may participate in the reaction and undergo allylation via a transition state like **VI**, resulting in increasing the *anti*-selectivity.

Under the same conditions as run 7, using 1 mol% of $Pd(OAc)_2$ and 4 mol% of *n*-Bu_3P, one tenth of the amounts of the standard conditions (room temperature for 22 h), **3a** was obtained in 55% isolated yield as a mixture with 1-cyclohexylpropanol (14%).

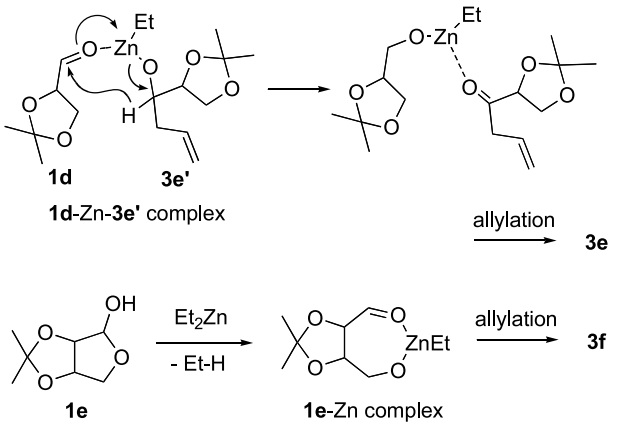
With respect to the chemical yields of homoallyl alcohols, it is apparently better to use allyl ethers (run 8, Table 1) or acid esters (e.g., acetate, benzoate, or phosphate) of allyl alcohols;[7] however, as mentioned above, there are many beneficial aspects for using allyl alcohols themselves.[8] In this paper, we disclose a full scope of the nucleophilic allylation of aliphatic aldehydes and ketones promoted by a Pd–Et_2Zn catalytic system.

2.1. Allylation of aliphatic aldehydes with allyl alcohol promoted by Pd–Et_2Zn

Table 2 reveals that allyl alcohol itself can be used as an allyl anion equivalent for a variety of aliphatic aldehydes encompassing primary (runs 8–10), secondary (runs 1–7) and tertiary aldehydes (run 11). All reactions were undertaken uniformly under the conditions established in run 7 of Table 1 (footnote a, Table 2). The yields range within a level of practical use (more than 60–70%) for all aldehydes examined except for **1d**, which produced an unexpected diallylation product **3e** (run 4) in modest yield.

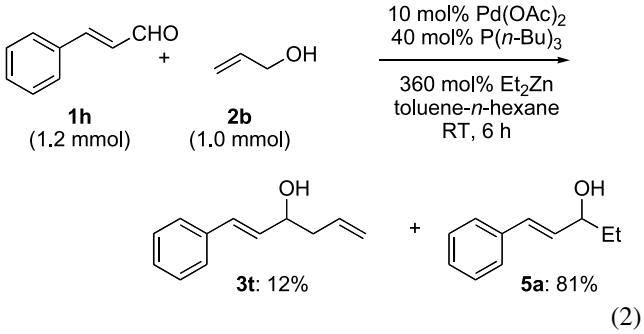
The formation of **3e** may be rationalized supposing the Meerwein–Pondorf–Verley (M–P–V) oxidation[9] of the primary allylic alkylation product **3e′** with the starting aldehyde **1d** (Scheme 2). The special feature about this substrate may be primarily attributed to the enhanced electrophilic reactivity of **1d** caused by the electron-withdrawing inductive effects by both the α- and β-oxygens.[10] In this context, the usual reactivity observed for **1e** (run 5) may deserve some comments. For the reactions of cyclic hemiacetals **1e** and **1j**, an additional 1 equiv Et_2Zn is used, since 1 equiv Et_2Zn is consumed to convert acidic hydroxy group into its zinc salt. Under such conditions, **1e** and **1j** might form a seven- and an eight-membered cyclic intermediate, respectively (e.g., **1e**-Zn complex, Scheme 2). The carbonyl oxygen of **1e**-Zn complex might be so weakly Lewis basic that it were no longer capable of forming such a complex like **1d**-**Zn**-**3e′**, being essential for the M–P–V reaction to proceed.

The reaction feature of α,β-unsaturated aldehyde **1c** (run 3) is in sharp contrast to those of cinnamaldehyde (Eq. 2) and

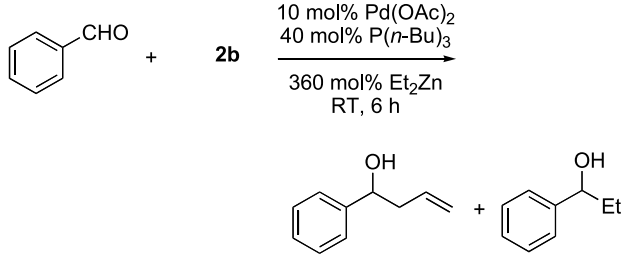


Scheme 2. Contrasting reactivity of **1d** and **1e**. The former undergoes M–P–V reduction through a complex **1d**-**Zn**-**3e**′.

benzaldehyde (Eq. 3). While the latter two react directly with Et_2Zn and provide the ethylation products, **5a** and **5b**, respectively, as major products, **1c** selectively undergoes allylation and provides no ethylation product at all.



(2)



toluene (0.5 ml)-*n*-hexane (3.6 ml)	**3u**: 29%	**5b**: 66%
THF (5 ml)-*n*-hexane (3.6 ml)	**3u**: 80%	**5b**: 0%

(3)

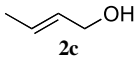
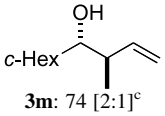
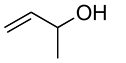
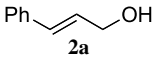
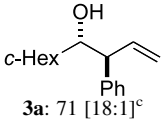
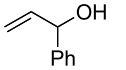
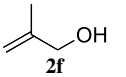
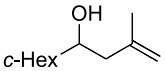
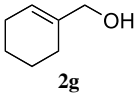
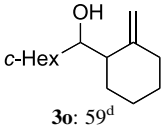
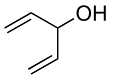
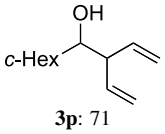
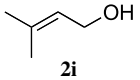
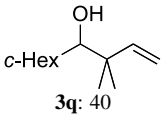
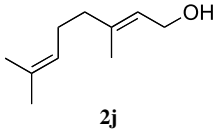
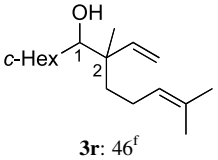
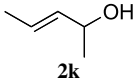
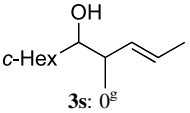
The allylation–ethylation competition seems to be a subject of large solvent effects, and the reaction of benzaldehyde and allyl alcohol in THF-*n*-hexane furnished an allylation product **3u** exclusively in 80% isolated yield (Eq. 3).

It is worth noting that, despite in situ formation of zinc alkoxides, no aldol-, Cannizzaro-, or Tischchenko-type products were detected at all in these reactions.

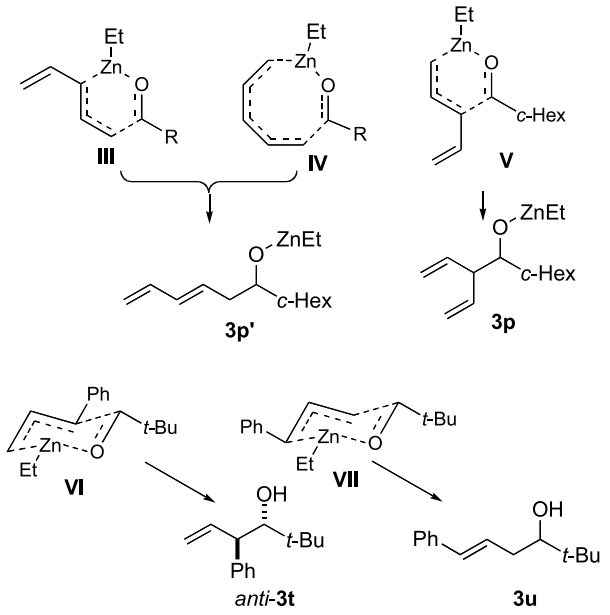
2.2. Allylation of cyclohexanecarboxaldehyde (1a) with a variety of allyl alcohols 2a–k promoted by Pd–Et_2Zn

Next, the reaction scope with respect to the structural variation of allyl alcohols was examined and the results examined using cyclohexanecarboxaldehyde as a probe are summarized in Table 3. Generally, unsymmetrically substituted allyl alcohols underwent C–C bond formation at the most substituted allylic termini, giving rise to branched homoallyl alcohols exclusively. All these results, particularly the results of run 7, strongly suggest that 1) allylzincs

Table 3. Allylation of cyclohexanecarboxaldehyde (**1a**) with substituted allyl alcohols **2**[a]

Run	Allylic alcohol **2**	Time (h)	% Isolated yield[b]
1	 **2c**	6	 **3m**: 74 [2:1][c]
2	 **2d**	6	**3m**: 78 [2:1]
3	 **2a**	6	 **3a**: 71 [18:1][c]
4	 **2e**	6	**3a**: 71 [12:1][c]
5	 **2f**	8	 **3n**: 68
6	 **2g**	11	 **3o**: 59[d]
7	 **2h**	8	 **3p**: 71
8	 **2i**	38[e]	 **3q**: 40
9	 **2j**	48[e]	 **3r**: 46[f]
10	 **2k**	6	 **3s**: 0[g]

[a] Reaction conditions: an allyl alcohol (1.0 mmol), **1a** (1.2 mmol), $Pd(OAc)_2$ (10 mol%), Et_2Zn (3.6 mmol, 1 M *n*-hexane solution), P (*n*-Bu)$_3$ (40 mol%) at room temperature under N_2.
[b] Yields refer to the isolated spectroscopically homogeneous materials.
[c] Diastereomer ratio of *anti* to *syn*.
[d] Single diastereomer, the stereochemistry unknown.
[e] At 50 °C.
[f] (1*S*′,2*S*′):(1*R*′,2*S*′)=5:1.
[g] 1-Cyclohexylpropanol (59%) was isolated.



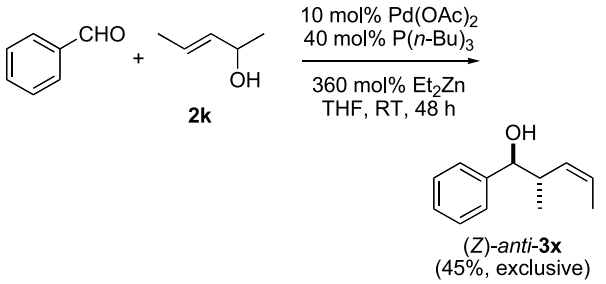
Scheme 3. Transition state models rationalizing regio- and stereoselectivities observed for the allylation of aldehydes with unsymmetrically substituted allyl alcohols.

are fluxional and 2) the allylzinc species with C–Zn σ-bonds bound to the least substituted allylic carbons participates in the reactions through a six-membered chair-like transition state **V** (Scheme 3). An isomeric product **3p′**, which might be derived through transition states **III** (characterized by an allylzinc bearing a *sec*-C–Zn bond) or **IV** (characterized by an eight-membered cyclic structure), was not detected at all.

The yields turned out to be dependent on the substitution patterns of allyl alcohols. The α-(runs 2, 4, 7), β-(run 5), γ-mono-substituted (runs 1, 3), and β,γ-disubstituted allyl alcohols (run 6), all recorded yields at an acceptable level; however, γ,γ-disubstituted allyl alcohols (runs 8 and 9) showed apparently diminished yields and reactivities, and for complete disappearance of the starting alcohols, heating for a long period of time was required. α,γ-Disubstituted allyl alcohols, **2k** and 2-cyclohexenol, did not participate in the reaction at all and ethylation with Et_2Zn was only the reaction detected, furnishing 1-cyclohexylpropanol in 59% (run 10).

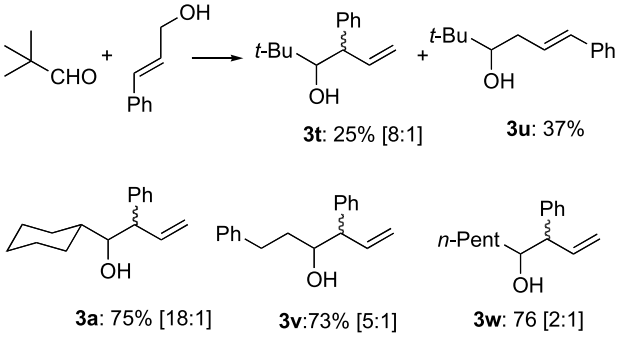
In order to address the possibility that **2k** might inhibit or retard generation of an active Pd(0) species, we examined the reaction of run 10 using a small amount of allyl alcohol (**2b**) (0.1 mmol) as an initiator; however, only **3b** and 1-cyclohexylpropanol were formed and no expected **3s** was detected at all, indicating **2k** being intrinsically unreactive toward aliphatic aldehydes under the conditions.

It should be noted that **2k** is reactive toward benzaldehyde, though requiring a long period of reaction time, and provides an allylation product **3x** as a single stereoisomer, the stereochemistry being *anti* with respect to the C1–C2 stereocenters and *Z* with respect to the double bond (Eq. 4).



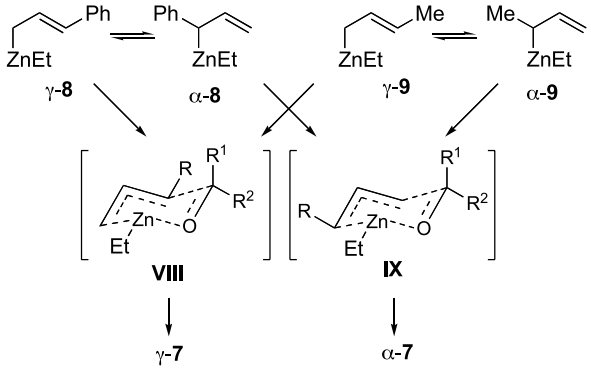
(4)

The same ratio of stereoisomers of **3m** was observed for the reactions with γ-methyl- (**2c**) and α-methylallyl alcohols (**2d**) (runs 1 and 2, Table 3). The phenyl analogues, **2a** and **2e**, provided **3a** in somewhat different ratios, but with much higher diastereoselectivity, furnishing *anti*-**3a** as a major product (12–18:1, runs 3 and 4). As is expected, the diastereoselectivity is a subject of the steric size of aldehydes and decreases as the size becomes small. In Scheme 4 are shown the results examined with cyclohexanecarbaldehyde, dihydrocinnamaldehyde and hexanal together with those examined with pivalaldehyde.



Scheme 4. Regio- and diastereoselectivities observed for the allylation of aliphatic aldehydes of different steric bulk with *trans*-cinnamyl alcohol under the conditions shown in footnote a in Table 2. In blankets are indicated isomer ratios of *anti* to *syn*.

Interestingly, pivalaldehyde turned out to be exceptional with respect to both regioselectivity and stereoselectivity; cinnamyl alcohol reacted to provide an expected isomer **3t** as a minor product together with its regioisomer **3u** as a major product. Furthermore, the stereoselectivity of **3t** was apparently lower than that of **3a**. These results may be rationalized by a close analysis of a transition state **VI**



Scheme 5. Fluxional behavior of allylzincs **8** and **9** and regioselectivity for the allylation of ketones.

(Scheme 3), otherwise being the most favored and responsible for the formation of *anti*-**3t**. For the particular case of pivalaldehyde, a gauche repulsion between Ph and *t*-Bu is such that preference of a transition state **VI** over others might be diminished, resulting in a low diastereoselectivity. In addition, in order to circumvent steric repulsion, an otherwise unstable allylzinc species (α-phenylallylzinc, cf., α-**8** in Scheme 5, vide infra) participates in the reaction to provide **3u** as a major product through a transition state **VII**. The trans structure of **3u** was determined on the basis of ^{1}H NMR and IR spectra.

2.3. Allylation of aliphatic ketones with allyl alcohols 2 promoted by Pd–Et_2Zn

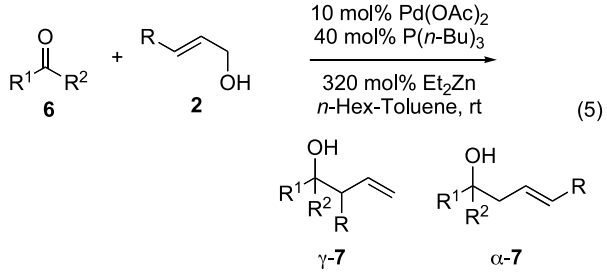
In Table 4 are summarized the results for the reactions of aliphatic ketones with allyl alcohols **2a–c**, performed under the identical conditions to those indicated in footnote a, Table 2. For reference, alkyl aryl and diaryl ketones were also examined under the identical conditions (runs 8–14). For the all combinations of ketones and allyl alcohols, the yields are modest and range from 50 to 70%, irrespective of the kinds of ketones, either aliphatic or aromatic.

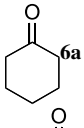
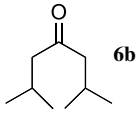
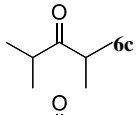
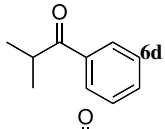
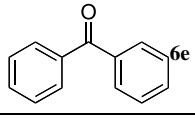
Interestingly, the regioselectivity (α- vs. γ-allylation) depends on the steric bulk of substituents of ketones and the kind of allylating agents. Cinnamyl alcohol undergoes nucleophilic addition to cyclohexanone (**6a**) at the most substituted allylic terminus to furnish γ-**7a** exclusively (run 1, Table 4), while it reacts with di-isobutyl ketone (**6b**) and di-isopropyl ketone (**6c**) at the least substituted allylic terminus, giving rise to α-**7d** and α-**7f**, respectively (runs 4 and 6). Similar, but less drastic change in the regioselectivity was observed for the reaction of crotyl alcohol with **6a–6c** (runs 2, 5, and 7).

The fact that cinnamyl alcohol tends to give the α-**7** isomers, while crotyl alcohol does the γ-**7** isomers might be partly ascribed to a larger steric repulsion that a phenyl group of **8** experiences against R^1 and R^2 than a methyl group of **9** does in a transition state **VIII** (Scheme 5), which might guide **8** to react with a ketone through a transition state **IX**. Another factor may be due to a higher population of α-**8** in an equilibrium between α-**8** and γ-**8**, as compared with α-**9** in an equilibrium between α-**9** and γ-**9**, owing to delocalization stabilization of the anionic charge on the carbon bearing Zn by a phenyl group.

Very clear-cut and contrasting results were observed for the allylation of aromatic ketones; cinnamyl alcohol provided exclusively α-**7**, while crotyl alcohol furnished the other regioisomers γ-**7** exclusively for the reactions with

Table 4. Allylation of ketone with allyl alcohols **2a–c**[a]



Run	Ketone **8**	**2**	Time (h)	% Isolated yield[b]	
				γ-**7**	α-**7**
1	 **6a**	**2a**: R=Ph	6	γ-**7a**: 58	α-**7a**: 0
2		**2c**: R=Me	7	γ-**7b**: 52	α-**7b**: 0
3	 **6b**	**2b**: R=H	8	**7c**: 58	
4		**2a**: R=Ph	8	γ-**7d**: 0	α-**7d**: 52
5		**2c**: R=Me	9	γ-**7e**: 53	α-**7e**: 5
6	 **6c**	**2b**: R=Ph	6	γ-**7f**: 0	α-**7f**: 52
7		**2c**: R=Me	7	γ-**7g**: 10	α-**7g**: 54
8	 **6d**	**2b**: R=H	6	**7h**: 66	
9		**2a**: R=Ph	8	γ-**7i**: 0	α-**7i**: 55
10		**2c**: R=Me	6	γ-**7j**: 55[c]	α-**7j**: 0
11	 **6e**	**2b**: R=H	4	**7k**: 70	
12		**2a**: R=Ph	6	γ-**7l**: 0	α-**7l**: 50
13		**2c**: R=Me	9	γ-**7m**: 53	α-**7m**: 0
14		**2c**: R=Me	32	γ-**7m**: 54	α-**7m**: 0

[a] Reaction conditions: an allyl alcohol (1.0 mmol), a ketone (1.2 mmol), $Pd(OAc)_2$ (10 mol%), Et_2Zn (3.6 mmol, 1 M *n*-hexane solution), P (*n*-Bu)$_3$ (40 mol%) at room temperature under N_2.
[b] Yields refer to the isolated spectroscopically homogeneous materials.
[c] A mixture of diastereomers (1:1).

isopropyl phenyl ketone (runs 9 and 10) and benzophenone (runs 12 and 13).

Finally, it should be noted that the reactions compiled in runs 1–13 are irreversible, and α- and γ-**7** are kinetically controlled products. This was confirmed by exposing the kinetic product γ-**7m** under the conditions for a long period of time (run 14), where no thermodynamic product α-**7m** was produced at all. This is primarily due to the low polarity of the solvents used in these reactions. In polar solvents, crotyl and cinnamylzincs react with sterically congested ketones reversibly and selectively provide γ-**7** under kinetic control and α-**7** under thermodynamic control.[11]

3. Conclusion

A variety of allyl alcohols, except for 1,3-disubstituted ones (e.g., 1,3-dimethylallyl alcohol and 2-cyclohexenol), serve as nucleophilic allylating agents for the allylation of aliphatic aldehydes and aliphatic ketones under the catalysis of $Pd(OAc)_2$ (10 mol%) -P(*n*-Bu)$_3$ (40 mol%) in the presence of Et_2Zn (360 mol%). The isolated yields of allylation products of primary, secondary, and tertiary aldehydes range from 60 to 90% and those of ketones about 60%. Almost all reactions proceed at room temperature and attain completion within 10 h. 1,3-Disubstituted allyl alcohols failed to react with aliphatic aldehydes.

Allylzinc intermediates, e.g. **8** and **9**, are fluxional and equilibrate between α- and γ-isomers (Scheme 5) and react with aldehydes, except for pivalaldehyde, through α-isomers to give rise to branched homoallyl alcohols exclusively with diastereomeric ratios (2:1–18:1), providing *anti*-isomers preferentially over *syn*-isomers. Cyclohexanone selectively reacts with **8** and **9** through the α-isomers to furnish branched homoallyl alcohols γ-**7**, while sterically more congested ketones tend to react with **8** and **9** through the γ-isomers giving rise to straight-chain homoallyl alcohols α-**7**. Pivalaldehyde behaves like sterically congested ketones and provides a mixture of straight-chain and branched homoallyl alcohols.

The synthetic utility of the reaction presented here may be augmented by 1) the ease with which the reactions can be performed, 2) ready availability and stability of allyl alcohols of a wide structural variety, 3) production of no hazardous side products, and 4) the catalytic nature of the reaction with respect to palladium.

4. Experimental

4.1. Solvents and reagents

Tetrahydrofuran was dried and distilled from benzophenone and sodium immediately prior to use under nitrogen atmosphere. Toluene was distilled over calcium hydride. $Pd(OAc)_2$ (purity 97.0%, Nakarai), Ph_3P (purity 97+%, Wako Pure Chemical Industries, Ltd), *n*-Bu_3P (purity 90.0+%, Tokyo Kasei Kogyo Co., Ltd), 2,3-*O*-isopropylidene-D-erythronolactone (Aldrich), Et_3B (1.0 M hexane solution, KANTO CHEMIKAL Co., INC.) and Et_2Zn (1.0 M hexane solution, KANTO), DIBAL (1.0 M hexane solution, KANTO) were purchased and used as received. The following allyl alcohols, aldehydes, and ketones were purchased and distilled prior to use by Kugelrohr apparatus: cinnamyl alcohol, allyl alcohol, crotyl alcohol, but-3-en-2-ol, α-phenylallyl alcohol, 2-methyl-2-propen-1-ol, divinylcarbinol, prenyl alcohol, geraniol, 2-cyclohexenol, 3-penten-2-ol, cyclohexanecarboxaldehyde, hexanal, dihydrocinnamaldehyde, α-phenylpropionaldehyde, diphenylacetaldehyde, 3-cyclohexenecarboxaldehyde, 1-cyclohexenecarboxaldehyde, pivalaldehyde, cyclohexanone, di-isobutyl ketone, di-isopropyl ketone, isopropyl phenyl ketone, benzophenone.

4.1.1. 2,2-Dimethyl-1,3-dioxolane-4-carboxaldehyde unsymmetric trimer (1d). To a solution of 2,2-dimethyl-1,3-dioxolane-4-methanol (1.32 g, 10 mmol) in CH_2Cl_2 (10 mL) was added pyridinium chlorochromate (4.33 g, 20 mmol) and sodium acetate (0.66 g, 8 mmol), each in one portion, at room temperature. After stirring for 12 h at room temperature, the mixture was extracted with ether (2× 100 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by means of column chromatography over silica gel (eluent; hexane/ethyl acetate=4:1) to give **1d** in 34% yield. IR (neat) 2986, 2939, 2885, 1759, 1458, 1373, 1211, 1103, 842 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.41 (s, 3H), 1.43 (s, 3H), 1.51 (s 3H), 3.76 (ddd, 8.0, 5.8, 1.9 Hz, 1H), 4.06–4.30 (m, 5H), 4.34 (quint, J=5.8 Hz, 1H), 4.63 (dt, J=1.9, 5.8 Hz, 1H).

4.1.2. 2,3-*O*-Isopropylidene-D-erythronolactol (1e). A solution of DIBAL (40.7 mmol, 1.0 M toluene solution) was added dropwise into a well-stirred solution of 2,3-*O*-isopropylidene-D-erythronolactone (3.0 g, 19 mmol) in CH_2Cl_2 (60.0 mL) kept at −78 °C over 0.5 h. After the mixture was stirred for 4 h at −78 °C, methanol (15 mL) and then water (15 mL) were added dropwise. After being allowed to warm to room temperature, ether (150 mL) and $MgSO_4$ were added into the mixture containing white precipitate. The mixture was filtrated and the filter cake was washed with ether (60 mL). The extracts were concentrated in vacuo and the residue was purified by means of a column chromatography over silica gel (AcOEt–hexane, 1/16 v/v) to give **1e** in 81% yield. IR (neat) 3425, 2986, 2947, 2885, 1458, 1380, 1335, 1211, 1165, 1072, 987, 910, 856 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.47 (s, 3H), 3.53 (br, 1H), 4.02 (d, J=10.2 Hz, 1H), 4.07 (dd, J=10.2, 3.3 Hz, 1H), 4.57 (d, J=5.8 Hz, 1H), 4.84 (dd, J=5.8, 3.3 Hz, 1H), 5.42 (s, 1H).

4.1.3. Tetrahydro-2*H*-pyran-2-ol (1j). To a solution of 3,4-dihydro-2*H*-pyran (8.28 g, 100 mmol) in water (90 mL) was added 2 M—HCl (1.7 mL, 20 mmol) at 0 °C over 30 min period. The mixture was allowed to warm to room temperature and stirred for an additional 1 h. Then the reaction mixture was neutralized with satd $NaHCO_3$ and extracted with CH_2Cl_2 (20 mL). The extract was dried ($MgSO_4$), filtered, and concentrated in vacuo, and the residue was purified by Kugelrohr distillation (80 °C/2.0 mm Hg) to give **1j** in 93% yield. IR (neat) 3387, 2939, 2855, 1736, 1442, 1358, 1272, 1196, 1080, 1026, 979, 903, 864 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.29–1.55 (m,

4H), 1.58–1.88 (m, 2H), 3.44 (dt, J=6.0, 5.5 Hz, 1H), 3.94 (m, 1H), 4.05 (s, 1H), 4.81 (s, 1H).

4.1.4. 1-(*trans*-Cinnamyl)cyclohexanecarbaldehyde (1k).[5] To a solution of $Pd(OAc)_2$ (43.2 mg, 0.2 mmol), Ph_3P (116.0 mg, 0.4 mmol) and LiCl (88.0 mg, 2.0 mmol) in dry THF (10 mL) were successively added cyclohexanecarboxaldehyde (249.2 mg, 2.2 mmol), cinnamyl alcohol (268.3 mg, 2.0 mmol), triethylamine (249.8 mg, 2.4 mmol), and triethylborane (4.8 mmol, 1.0 M hexane solution) via syringe at ambient temperature under N_2. The mixture was stirred at ambient temperature for 48 h. The mixture was washed with satd $NaHCO_3$ and then brine, and the organic phase was dried ($MgSO_4$) and concentrated in vacuo to give an yellow oil, which was purified by means of column chromatography over silica gel (AcOEt–hexane, 1/30 v/v) to give **1k** in 78% yield.

4.1.5. (1-Cyclohexenyl)methanol (2g). To a solution of lithium aluminum hydride (0.23 g, 6 mmol) in dry ether (20 mL) was added 1-cyclohexenecarboxaldehyde (1.10 g, 10 mmol) at 0 °C over 10 min. The mixture was stirred under nitrogen at room temperature for 5 h. After addition of H_2O (20 mL) and removal of white solid by filtration, the filtrate was concentrated in vacuo and the residue was purified by means of column chromatography over silica gel (hexane/ethyl acetate=7:1) to give **2g** in 97% yield. IR (neat) 3325, 2924, 2862, 1142, 1011, 918, 802 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.21–1.34 (m, 1H), 1.69–1.84 (m, 3H), 1.90–2.14 (m, 4H), 3.52 (s, 2H), 5.68 (s, 1H).

The following products were characterized by comparison of ^1H NMR spectral data with those of literature: 1-cyclohexyl-2-phenyl-3-buten-1-ol (**3a**),[5] 1-cyclohexyl-3-buten-1-ol (**3b**),[5] 1-(3-cyclohexenyl)-3-buten-1-ol (**3c**),[12] 2-phenyl-5-hexen-3-ol (**3g**),[13] 1,1-diphenyl-4-penten-2-ol (**3h**),[14] 1-nonen-4-ol (**3i**),[15] 6-phenyl-1-hexen-4-ol (**3j**),[16] 7-octene-1,5-diol (**3k**),[6] 1-cyclohexyl-2-methyl-3-buten-1-ol (**3m**),[16] 1-cyclohexyl-3-methyl-3-buten-1-ol (**3n**),[17] 1-cyclohexyl-2-vinyl-3-buten-1-ol (**3p**),[18] 1-cyclohexyl-2,2-dimethyl-3-buten-1-ol (**3q**),[17] 1-cyclohexyl-2,6-dimethyl-2-vinyl-5-hepten-1-ol (**3r**),[19] 1-phenyl-1,5-hexadien-3-ol (**3t**),[20] 1-phenyl-3-buten-1-ol (**3u**),[21] 1,4-diphenyl-5-hexen-3-ol (**3v**),[22] 3-phenyl-1-nonen-4-ol (**3w**),[22] (*Z*)-*anti*-2-methyl-1-phenyl-3-pentenol (**3x**), (*E*)-1-phenyl-1-penten-3-ol (**5a**),[5] 1-phenylpropan-1-ol (**5b**),[21] 1-(1-phenylallyl)cyclohexanol (γ-**7a**),[21] 1-(1-methylallyl)cyclohexanol (γ-**7b**),[21] (*E*)-3-isopropyl-2-methyl-6-phenyl-5-hexen-3-ol (α-**7f**),[23] 3-isopropyl-2,4-dimethyl-5-hexen-3-ol (γ-**7g**),[23] (*E*)-3-isopropyl-2-methyl-5-hepten-3-ol (α-**7g**),[23] 5-methyl-4-phenyl-1-hexen-4-ol (**7h**),[24] 2,4-dimethyl-3-phenyl-5-hexen-3-ol (γ-**7j**),[23] 1,1-diphenyl-3-buten-1-ol (**7k**).[25]

4.2. General procedure: allylation of cyclohexanecarboxaldehyde with *trans*-cinnamyl alcohol (run 3, Table 3)

Diethylzinc (3.2 mmol, 1.0 M *n*-hexane solution) and cinnamyl alcohol (1.0 mmol) was added successively by syringe to a homogeneous solution of $Pd(OAc)_2$ (22.6 mg, 0.1 mmol), *n*-Bu_3P (98 μl, 0.4 mmol) and cyclohexanecarboxaldehyde (1.1 mmol) in toluene (0.5 mL) at 0 °C under nitrogen. After completion of addition, the mixture was allowed to warm to room temperature and stirred for an additional 2 h, during which time a copious amount of a white precipitate appeared and the reaction mixture became sludgy. The mixture was diluted with EtOAc and washed with HCl (0.2 M), satd $NaHCO_3$, and brine, and then the organic phase was dried ($MgSO_4$) and concentrated in vacuo to give an yellow oil, which was purified by column chromatography over silica gel (AcOEt/hexane, 1/30 v/v) to give **3a** in 75% isolated yield.

4.2.1. 1-(1-Cyclohexenyl)-3-buten-1-ol (3d). IR (neat) 3361, 2930, 2858, 2837, 1641, 1436, 1138, 989, 914, 842 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.48–1.71 (m, 6H), 1.85–2.10 (m, 3H), 2.29 (ddd, J=14.0, 5.2, 7.4 Hz, 1H), 2.33 (ddd, J=14.0, 7.4. 5.2 Hz, 1H), 4.01 (s, 1H), 5.10 (dd, J=10.2, 1.7 Hz, 1H), 5.12 (dd, J=17.0, 1.7 Hz, 1H), 5.68 (s, 1H), 5.78 (ddt, J=17.0, 10.2, 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 22.7, 23.9, 24.9, 39.8, 75.2, 117.4, 122.9, 134.8, 139.1; HRMS calcd for $C_{10}H_{16}O$ 152.1201, found *m*/*z* (relative intensity): 152.1175 (M^+, 49), 151 (16), 140 (92), 136 (27), 135 (100).

4.2.2. 4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-1,6-heptadien-4-ol (3e). IR (neat) 3481, 3076, 2983, 2935, 2900, 1639, 1438, 1371, 1217, 1070, 999, 916, 864, 796, 661 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.43 (s, 3H), 2.06 (s, 1H), 2.10 (dd, J=14.4, 8.0 Hz, 1H), 2.27 (dd, J=13.9, 6.8 Hz, 1H), 2.32 (dd, J=13.9, 6.8 Hz, 1H), 2.37 (dd, J=13.9, 8.0 Hz, 1H), 3.89 (t, J=7.8 Hz, 1H), 3.95 (dd, J=7.8, 6.3 Hz, 1H), 4.03 (t, J=7.8, 6.3 Hz, 1H), 5.09 (d, J=10.7 Hz, 1H), 5.11 (d, J=15.7 Hz, 1H), 5.12 (d, J=15.7 Hz, 1H),5.14 (d, J=10.7 Hz, 1H), 5.88 (dddd, J=15.7, 10.7, 8.0, 6.8 Hz, 1H); HRMS calcd for M^+-OH $C_{12}H_{19}O_3$ 195.1390, found *m*/*z* (relative intensity): 195.1367 (M^+-OH, 100), 172 (10), 171 (95), 141 (13).

4.2.3. 1-[5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-buten-1-ol (3f, 1:1 mixture of diastereomers). IR (neat) 3396, 3078, 2986, 2937, 2359, 2341, 1643, 1456, 1380, 1246, 1217, 1167, 1042, 918, 874, 797 cm^{-1}; One isomer: ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.52 (s, 3H), 2.29–2.45 (m, 2H), 2.82–2.92 (br, 2H), 3.78–3.99 (m, 3H), 4.11 (dd, J=6.9, 3.0 Hz, 1H), 4.23 (dt, J=6.9, 5.0 Hz, 1H), 5.13 (dd, J=10.2, 1.4 Hz, 1H), 5.16 (dd, J=17.3, 1.4 Hz, 1H), 5.86 (ddt, J=17.3, 10.2, 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.02, 27.24, 39.58, 61.26, 68.58, 77.30, 78.39, 108.36, 118.05, 134.28 (C2); the other isomer: ^1H NMR (300 MHz, $CDCl_3$): δ1.36 (s, 3H), 1.41 (s, 3H), 2.21 (dt, J=14.3, 8.4 Hz, 1H), 2.60–2.66 (m, 2H), 2.80 (br, 1H), 3.76 (ddd, J=11.7, 7.0, 5.1 Hz, 1H), 3.81–3.90 (m, 2H), 3.99 (dd, J=9.2, 5.1 Hz, 1H), 4.32 (dt, J=8.1, 5.1 Hz, 1H), 5.20 (dd, J=14.7, 1.5 Hz, 1H), 5.21 (dd, J=11.7, 1.5 Hz, 1H), 5.86 (dddd, J=14.7, 11.7, 8.4, 6.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.34, 27.95, 38.84, 61.03, 68.54, 77.41, 79.36, 108.39, 119.21, 133.93; HRMS calcd for $C_{10}H_{19}O_4$ 203.1302, found *m*/*z* (relative intensity): 203.1283 (M^+, 3), 188 (10), 187 (100), 171 (23), 169 (1).

4.2.4. 1-[(1-Cinnamyl)cyclohexyl]-3-buten-1-ol (3l). IR (neat) 3463, 3024, 2923, 2862, 1643, 1596, 1497, 1389, 1281, 1041, 972, 910, 856, 748, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.27–1.58 (m, 11H), 2.06–2.17 (m, 1H), 2.28 (dd, J=14.1, 7.4 Hz, 1H), 2.40–2.45 (m, 1H),

2.46 (dd, $J=14.1$, 7.4 Hz, 1H), 3.52 (ddd, $J=10.5$, 4.0, 1.9 Hz, 1H), 5.13 (d, $J=10.0$ Hz, 1H), 5.14 (d, $J=16.8$ Hz, 1H), 5.86 (dddd, $J=16.8$, 10.0, 8.5, 5.9 Hz, 1H), 6.30 (dt, $J=15.9$, 7.3 Hz, 1H), 6,41 (d, $J=15.9$ Hz, 1H), 7.18–7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=21.4$, 21.5, 26.2, 30.9, 31.4, 35.8, 36.0, 40.5, 75.4, 117.6, 125.9, 126.8, 127.5, 128.3, 131.8, 136.6, 137.7; HRMS calcd $C_{19}H_{26}O$ 270.1984, found *m/z* (relative intensity): 270.1978 (M^+, 100), 269 (2), 268 (7).

4.2.5. Cyclohexyl (2-methylenecyclohexyl)methanol (3o). IR (neat) 3489, 3069, 2852, 2795, 1643, 1448, 1390, 1259, 1085, 980, 893, 866, 682, 642 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.19–1.78 (m, 18H), 2.17–2.29 (m, 3H), 3.60 (d, $J=9.9$ Hz, 1H), 4.77 (s, 1H), 4.85 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 24.2, 26.4, 26.6, 27.0, 28.1, 28.8, 31.2, 32.7, 38.9, 46.5, 72.5, 109.9, 150.1; HRMS calcd $C_{14}H_{24}O$ 208.1827, found *m/z* (relative intensity): 208.1788 (M^+, 20), 207 (11), 206 (53), 191 (61), 190 (100).

4.2.6. Mixture of 2,2-dimethyl-4-phenyl-5-hexen-3-ol (3t) and (*E*)-2,2-dimethyl-6-phenyl-5-hexen-3-ol (3u). IR (neat) 3456, 3024, 2955, 2869, 2361, 1597, 1474, 1366, 1180, 1072, 1011, 972, 918, 741, 694 cm^{-1}; ^{1}H NMR (**3t**, 300 MHz, $CDCl_3$): δ 0.93 (s, 9H, *anti*-isomer), 0.97 (s, 9H, *syn*-isomer), 1.45 (d, $J=4.1$ Hz, 1H, *syn*–isomer), 1.75 (d, $J=4.6$ Hz, 1H, *anti*-isomer), 3.53–3.66 (m, 2H, *anti*+*syn*-isomers), 5.03 (d, $J=10.2$ Hz, 1H, *syn*-isomer), 5.06 (d, $J=17.6$ Hz, 1H, *syn*-isomer), 5.12 (d, $J=17.6$ Hz, 1H, *anti*-isomer), 5.18 (d, $J=10.3$ Hz, 1H, *anti*-isomer), 6.16 (ddd, $J=17.6$, 10.2, 8.2 Hz, 1H, *syn*-isomer), 6.31 (ddd, $J=17.6$, 10.3, 8.2 1H, *anti*-isomer), 7.18–7.39 (m, 5H, *anti*+*syn*-isomers); ^{13}C NMR (**3t**, 100 MHz, $CDCl_3$): δ 26.6 (*anti*-isomer), 26.7 (*syn*-isomer), 35.6 (*anti*-isomer), 35.8 (*syn*-isomer), 52.7 (*anti*-isomer), 53.7 (*syn*-isomer), 81.3 (*syn*-isomer), 81.4 (*anti*-isomer), 114.6 (*syn*-isomer), 117.0 (*anti*-isomer), 126.1 (*anti*-isomer), 126.5 (*syn*-isomer), 127.7 (*anti*-isomer), 128.2 (*syn*-isomer), 128.3 (*anti*-isomer), 128.7 (*syn*-isomer), 138.6 (*anti*+*syn*-isomers), 141.3 (*syn*-isomer), 144.2 (*anti*-isomer); ^{1}H NMR (**3u**, 300 MHz, $CDCl_3$): δ 1.00 (s, 9H), 1.67 (s, 1H), 2.21 (dddd, $J=14.2$, 10.5, 8.3, 1.4 Hz, 1H), 2.55 (ddt, $J=14.2$, 6.1, 1.4 1H), 3.38 (d, $J=10.5$ Hz, 1H), 6.31 (ddd, $J=15.9$, 8.3, 6.1 1H), 6.53 (d, $J=15.9$ Hz, 1H), 7.23–7.41 (m, 5H); ^{13}C NMR (**3u**, 100 MHz, $CDCl_3$): δ 25.8, 34.7, 35.7, 78.6, 125.9, 127.0, 127.9, 128.4, 132.6, 137.1; HRMS calcd $C_{14}H_{20}O$ 204.1514, found *m/z* (relative intensity): 204.1516 (M^+, 26), 129 (6), 119 (36), 118 (100), 117 (43).

4.2.7. 4-Isobutyl-6-methylhept-1-en-4-ol (7c). IR (neat) 3485, 3076, 2954, 2927, 2869, 1709, 1639, 1468, 1367, 1261, 1097, 1018, 914, 866, 804, 661 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (d, $J=6.6$, 6H), 0.91 (d, $J=6.6$, 6H), 1.23 (s, 1H), 1.36 (d, $J=6.6$, 4H), 1.75 (sept, $J=6.6$, 2H), 2.21 (d, $J=7.4$, 2H), 5.05 (d, $J=17.2$ Hz, 1H), 5.07 (d, $J=10.4$ Hz, 1H), 5.77 (ddt, $J=17.2$, 10.4, 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.9, 24.7. 24.8, 44.8, 48.4, 75.1, 118.5, 134.2; HRMS calcd $C_{12}H_{24}O$ 184.1827, found *m/z* (relative intensity): 184.1792 (M^+, 4), 169 (3), 157 (18), 143 (100).

4.2.8. 4-Isobutyl-6-methyl-1-phenylhept-1-en-4-ol (α-7d). IR (neat) 3487, 3024, 2955, 2360, 1466, 1366, 964, 740, 694 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.92 (d, $J=6.6$ Hz, 6H, *Z*-isomer), 0.93 (d, $J=6.6$ Hz, 6H, *Z*-isomer), 0.98 (d, $J=6.6$ Hz, 6H, *E*-isomer), 0.99 (d, $J=6.6$ Hz, 6H, *E*-isomer), 1.43 (d, $J=6.6$ Hz, 4H), 1.85 (sept, $J=6.6$ Hz, 2H, *E*-isomer), 2.42 (d, $J=7.4$ Hz, 2H, *E*-isomer), 2.56 (dd, $J=7.4$, 1.9 Hz, 2H, *Z*-isomer), 5.74 (dt, $J=11.5$, 7.4 Hz, 1H, *Z*-isomer), 6.23 (dt, $J=15.9$, 7.4 Hz, 1H, *E*-isomer), 6.45 (d, $J=15.7$ Hz, *E*-isomer), 6.56 (d, $J=11.5$ Hz, 1H, *Z*-isomer); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.9, 24.8, 24.9, 44.1, 48.6, 75.6, 125.8, 125.9, 127.0, 128.4, 133.4, 137.3; HRMS calcd for $C_{18}H_{28}O$ 260.2140, found *m/z* (relative intensity): 260.2087 (M^+, 1), 245 (1), 243 (4), 204 (16), 203 (100).

4.2.9. Mixture of 4-Isobutyl-3,6-dimethyl-1-hepten-4-ol (γ-7e) and (*E*)-4-isobutyl-2-methyl-6-octen-4-ol (α-7e). IR (neat) 3495, 3070, 2951, 2933, 2859, 1729, 1640, 1469, 1261, 1108, 914, 804, 722, 668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (d, $J=6.3$ Hz, 3H, α-isomer), 0.80 (d, $J=6.3$ Hz, 3H, α-isomer), 0.81 (d, $J=6.3$ Hz, 3H, α-isomer), 0.82 (d, $J=6.3$ Hz, 3H, α-isomer), 0.83 (d, $J=6.3$ Hz, 3H, α-isomer), 0.88 (d, $J=6.8$ Hz, 3H), 0.89 (d, $J=6.8$ Hz, 3H), 0.90 (d, $J=6.8$ Hz, 3H), 0.91 (d, $J=6.8$, 3H), 0.92 (d, $J=6.8$ Hz, 3H), 1.20 (s, 1H), 1.21 (dd $J=14.4$, 6.8 Hz, 1H), 1.29 (dd $J=14.4$, 6.8 Hz, 1H), 1.30 (dd $J=14.4$, 6.8 Hz, 1H), 1.37 (dd $J=14.4$, 6.8 Hz, 1H), 1.56–1.65 (m, 2H, α-isomer), 1.75 (sept, $J=6.8$ Hz, 1H), 1.76 (sept, $J=6.8$ Hz, 1H), 2.15–2.23 (m, 2H, α-isomer), 2.36 (dq, $J=8.3$, 6.8 Hz, 1H), 5.01 (dd, $J=10.5$, 1.9 Hz, 1H), 5.02 (dt, $J=17.1$, 1.9 Hz, 1H), 5.31–5.40 (m, 1H, α-isomer), 5.55 (dt, $J=17.3$ Hz, 1H), 5.76 (ddd, $J=17.1$, 10.5, 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.5, 22.6, 23.5, 23.6, 23.7, 24.1, 44.1, 44.2, 45.0, 75.5, 115.2, 139.5; HRMS calcd for M^+-Me_2 $C_{11}H_{21}O$ 169.1590, found *m/z* (relative intensity): 169.1590 (M^+-Me_2, 5), 167 (4), 143 (100), 141 (8).

4.2.10. (*E*)-2-Methyl-3,6-diphenylhex-5-en-3-ol (α-7i). IR (neat) 3560, 3487, 3058, 3026, 2964, 2875, 2795, 1598, 1495, 1447, 1384, 1238, 1173, 1003, 970, 891, 764, 746, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.79 (d, $J=6.8$ Hz, 3H), 0.97 (d, $J=6.8$ Hz, 3H), 1.95 (s, 1H), 2.07 (sept, $J=6.8$ Hz, 1H), 2.70 (dd, $J=14.0$, 9.3 Hz, 1H), 2.93 (ddd, $J=14.0$, 5.6, 1.7 Hz, 1H), 5.86 (ddd, $J=15.6$, 9.3, 5.6 Hz, 1H), 6.46 (d, $J=15.6$ Hz, 1H), 7.15–7.41 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.8, 17.6, 37.8, 43.2, 78.2, 125.2, 125.9, 126.0, 126.3, 127.2, 127.9, 128.3, 134.3, 136.9, 144.9; HRMS calcd for $C_{19}H_{22}O$ 266.1671, found *m/z* (relative intensity): 266.1646 (M^+, 19), 251 (3), 248 (3), 224 (19), 223 (100).

4.2.11. (*E*)-1,1,4-Triphenyl-3-buten-1-ol (α-7l). IR (KBr) 3541, 3456, 3021, 2839, 1596, 1488, 1357, 1203, 1057, 972, 910, 748, 694 cm$^{-1;}$ ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.60 (s, 1H), 3.21 (d, $J=7.4$ Hz, 2H), 6.04 (dt, $J=15.9$, 7.4 Hz, 1H), 6.56 (d, $J=15.9$ Hz, 1H), 7.20–7.49 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.1, 77.4, 124.5, 126.0, 126.2, 126.9, 127.5, 128.2, 128.4, 135.3, 136.8, 146.4; HRMS calcd for $C_{22}H_{20}O$ 300.1514, found *m/z* (relative intensity): 300.1498 (M^+, 10), 283 (85), 282 (100).

4.2.12. 2-Methyl-1,1-diphenyl-3-buten-1-ol (γ-7m). IR (neat) 3514, 3058, 2977, 1598, 1578, 1493, 1448, 1319, 1278, 1153, 1001, 941, 810, 766, 748, 702 cm^{-1}; ^{1}H NMR

(300 MHz, $CDCl_3$): δ 0.99 (d, $J=6.6$ Hz, 3H), 2.27 (s, 1H), 3.54 (quint, $J=6.6$ Hz, 1H), 5.12 (dd, $J=10.7$, 1.7 Hz, 1H), 5.17 (dd, $J=17.3$, 1.7 Hz, 1H), 5.86 (ddd, $J=17.3$, 10.7, 6.6 Hz, 1H), 7.14–7.60 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4, 44.3. 79.2, 117.1, 125.5, 125.7, 126.3, 126.4, 127.9, 128.0,128.1, 129.9,132.2, 139.1, 145.6, 146.6; HRMS calcd for $C_{17}H_{18}O$ 238.1358, found *m/z* (relative intensity): 238.1329 (M^+, 2), 221 (100), 206 (15).

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Selective photoswitching of a dyad with diarylethene and spiropyran units

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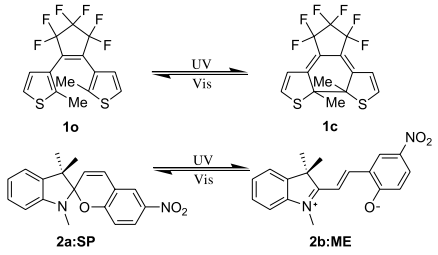
Abstract—A dyad bearing diarylethene and spiropyran units were synthesized. Ultraviolet light, visible light, H^+, and Fe^{3+} inputs induce the multiple interconversion among the colorless diarylethene with spiropyran form (**3**), the colored closed form of diarylethene with spiropyran form (**4**), ME (**5**), MEH (**6**, **7**) and MEH·Fe^{3+} (**8**). The efficient energy transfer from the anthracene emission to MEH·Fe^{3+} or ME·Fe^{3+} form was achieved. Using multi-mode photo switching in a dyad **3**, logic gates may be built.

1. Introduction

Photochromic compounds undergo reversible transformation between two distinct chemical isomers by different colors of light. The two isomers may show distinct physicochemical properties, which can be exploited to molecular electronics and information storage. One of the most promising candidates of photochromic materials is 1,2-diarylethene derivatives due to their remarkable thermal stability and fatigue resistance.[1] Another photochromic compound, spiropyran, has been investigated for various applications, such as recording, copying, and optical data storage.[2] The photoreaction of these kinds of photochromic compounds is depicted in Scheme 1. The functionalization of the spiropyran is a major issue because of some reasons, such as tuning the absorption wavelength or creating a system that can be used for information storage.[3] Such photoinduced isomerization of spiropyran derivatives has been exploited to design multi-addressable switches by communicating intra-[4] and intermolecular[5] signals to a fluorescent probe. The limitation of such compounds is that photogenerated isomers are thermally unstable and return to the initial isomers. To inhibit the thermal reversion of the MC form to the SP, several groups have introduced a chelating moiety[6] and crown spirobenzopyran[7] on the SP indoline ring and amino acids.[8] Recently, Yamazaki group[9] reported the relative stability of diarylethene in LB film through a comparative study with spiropyran/merocyanine.



Scheme 1.

One can thus envision that the incorporation of 1,2-diarylethene with spiropyran offers wide opportunities for the direct comparison of a thermal stability of both photochromic units or varying optical properties of such materials under the action of multiple external stimulations.

In this paper, we present the selective photoswitching of a dyad containing diarylethene and spiropyran units under external inputs such as light, proton, and metal ion.

2. Results and discussion

Dyad **3** was synthesized by reaction of 1,2-bis[2-methyl-5-(4-hydroxyphenyl)-3-thienyl]per-fluorocyclopentene[10] and 1′-(5-bromopentyl)-3′,3′-dimethyl-6-nitroindolinospirobenzopyran[11] in the presence of K_2CO_3 and crown ether in acetone and was fully characterized by NMR and MS spectrometry and elemental analysis. The compound in toluene is colorless (Scheme 2). The electronic absorption

Keywords: Photoswitch; Spiropyran; Diarylethene; Multiple interconversion.
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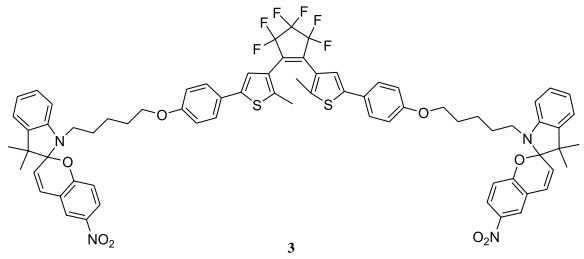


Scheme 2.

spectra of **3** and **4** in toluene are shown in Figure 1. Figure 1A shows a typical absorption spectral change of **3** in toluene upon ultraviolet light irradiation. Irradiation of toluene solution of **3** at 365 nm light resulted in an immediate increase in the absorption intensity at 602 nm, **4** (Scheme 3). In the photostationary state, 92% of **3** is converted into the closed form **4**. The photostationary state was easily analyzed with ^{1}H NMR spectroscopy by comparing the relative intensities of methyl proton signals. The closed-ring isomer **4** was stable and isolated from the blue colored solution by HPLC. The isomer **4** was identified with NMR and mass spectra and elemental analysis. In the ^{1}H NMR spectrum of **3**, one methyl resonance was observed at 1.96 ppm. In the blue isomer **4**, a distinct new absorption band was appeared at 2.26 ppm. After visible light irradiation ($\lambda > 600$ nm) for 3 min, the colored solution was completely bleached. Spiropyran unit in **3** shows the

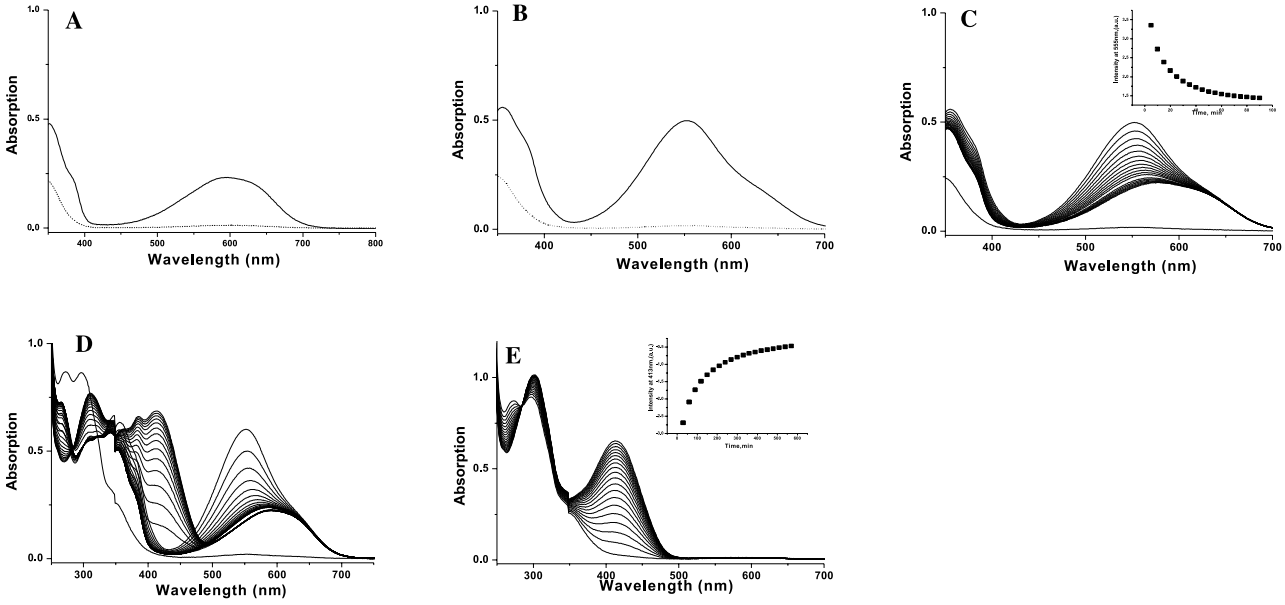
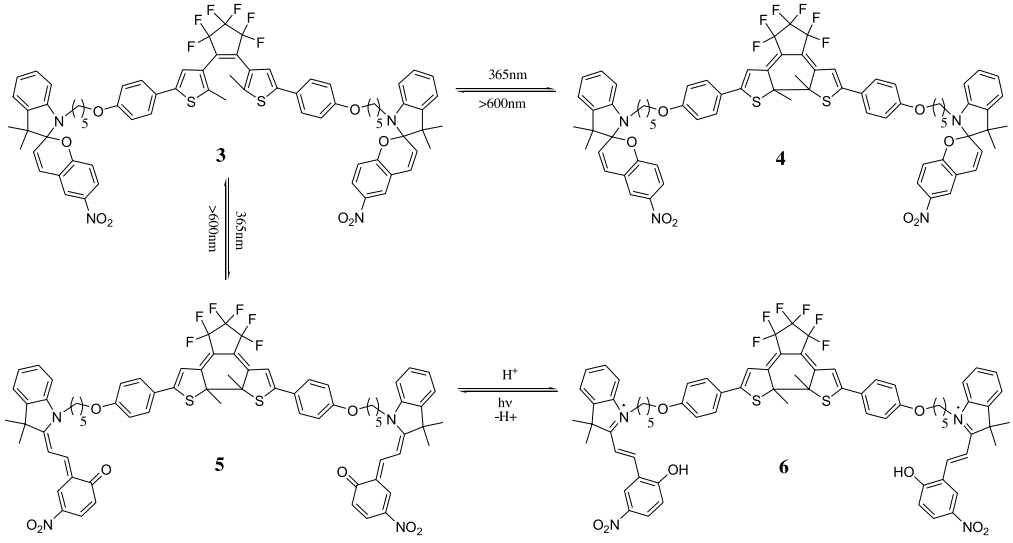


Figure 1. A. UV–vis spectra of compound **3** (·····) and a solution of **3/4** in the photostationary state (—) in toluene upon irradiation with 365 nm light. B. UV–vis spectra of compound **3** (·····) and a solution of **3/4/5** in the photostationary state (—) in EtOH upon irradiation with 365 nm light. C. Spectra illustrating the first order thermal reversion of the merocyanine form **5** with closed-ring isomer of the diarylethene at 25 °C (scanning at 5 min intervals for 70 min, the scanning at 30 min for 3 h). Inset curve shows the gradual intensity change of thermal reversion in **5**. D. Spectra showing the formation of merocyanine (MEH) **6** upon addition of CF_3COOH to **5** with closed-ring isomer of the diarylethene (scanning at 5 min intervals for 70 min, then scanning at 30 min intervals). E. Spectra showing the formation of merocyanine (MEH) **7** with open-ring isomer of the diarylethene.



Scheme 3.

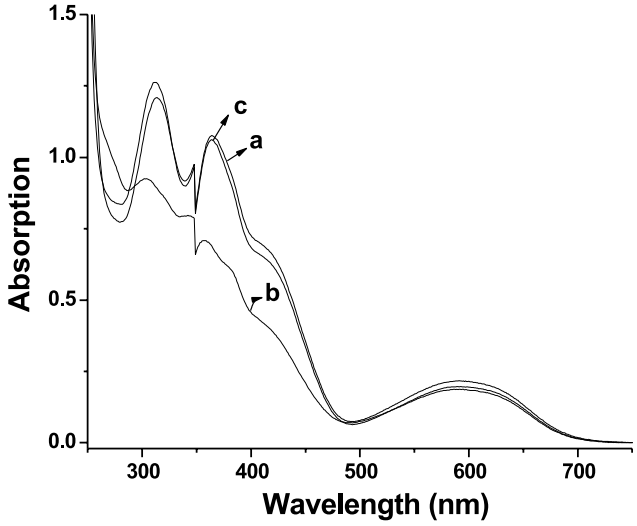
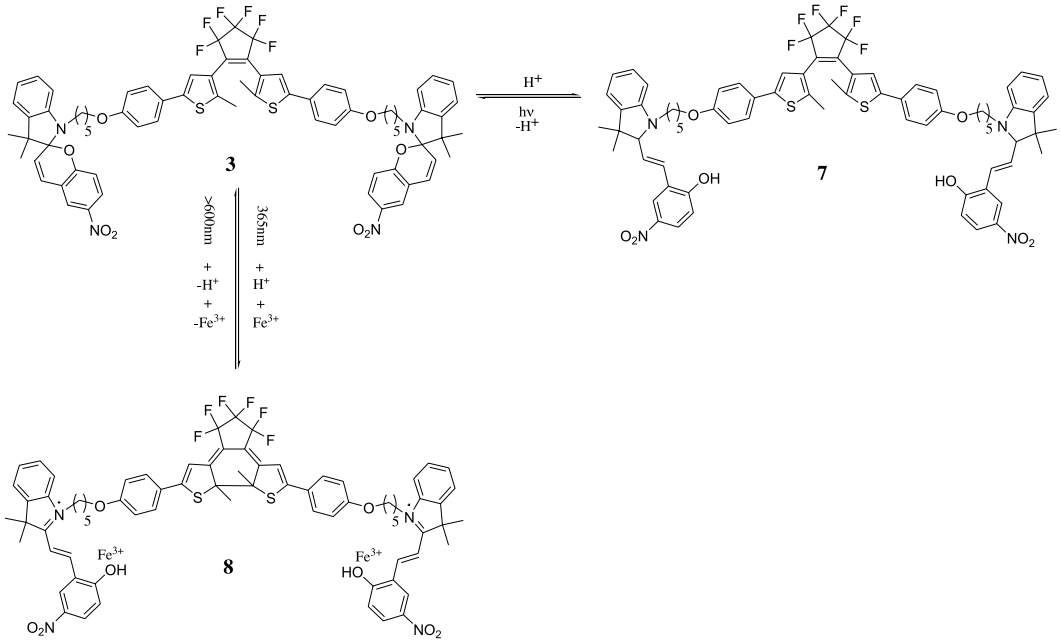


Figure 2. The absorption spectra of **3** in EtOH (a) upon sequential addition of CF_3COOH (2 equiv) and $Fe(ClO_4)_3$ (10 equiv) immediately after irradiation with 365 nm light, (b) upon addition of $Fe(ClO_4)_3$ (10 equiv) and (c) upon sequential addition of $Fe(ClO_4)_3$ (10 equiv) and CF_3COOH (2 equiv) after irradiation with 365 nm light.

selective photoswitch behavior under the specified condition. The spiropyran units are shown to be sensitive to the solvents. Upon irradiation with 365 nm light for 3 min, the closed form of spiropyran unit in EtOH is photoisomerized to the open form (ME), **5** as indicated by the appearance of its characteristic absorption band with $\lambda_{max}=548$ nm, together with the formation of the closed form of diarylethene ($\lambda_{max}=602$ nm) (Fig. 1B) and an emission band at 628 nm accompanies this process. After visible light irradiation ($\lambda>600$ nm) for 5 min, the photogenerated isomer **5** returns to the initial colorless one, **3**. The photostable isomer **5** was found to persist for at least two days at 0 °C in the dark. Our control thermal reversion experiment at 25 °C on the decay of the ME→SP conversion of **5** showed a first order process, $k_{obs}=1.30\times10^{-3}\ s^{-1}$, five times slower than that of spiropyran system studied by Buncel et al.[12] (Fig. 1C), but exposure to visible light resulted in rapid decay on the spectrum of the colored isomer. This result is quite interesting in that there was a significant decrease in the rate constant for MC decay. The value is comparable to that obtained from the thermally stable ME→SP photo-switch via intramolecular bidentate metal ion chelation.[12] It has been reported that electron-rich moieties on spiropyran would rise to an inhibiting effect on the rate of ME→SP thermal reversion.[13] Therefore, such decrease may be attributable to the mutual interaction of merocyanine and electron rich diarylethene. The observed absorption bands and derived first order rate constants for the ME→SP reversion in the solvents THF (592 nm, $3.77\times10^{-3}\ s^{-1}$), acetone (578 nm, $2.10\times10^{-3}\ s^{-1}$) and benzonitrile (588 nm, $2.78\times10^{-3}\ s^{-1}$) were obtained. For all the merocyanines, a hypsochromic shift of the absorption band is observed as the polarity of the solvent increases.[13a] The rate of the thermal reversion also decreases as the polarity of the solvent increases. The addition of acid into the merocyanine was reported to undergo the blue-shift of the absorption spectrum.[14] As expected, upon addition of CF_3COOH to **5**, a new absorption maximum at 422 nm grew in, corresponding to MEH, **6** with closed-ring isomer of the central diarylethene (Fig. 1D) and the emission band at 628 nm disappears. Upon addition of CF_3COOH to **3**, the dyad **3** was easily converted to corresponding to MEH, **7** with open-ring isomer of the central diarylethene (Fig. 1E). A characteristic absorption maximum of 422 nm demonstrates the formation of MEH, **7**. The kinetic on the formation of MEH displayed a first order with $k_{obs}=2.21\times10^{-4}\ s^{-1}$. Treatment of a blue solution of MEH, **7** with K_2CO_3 switches completely to ME and a characteristic absorption band at 548 nm appears. The ME form displays a high tendency to coordinate with metal ions.[15] Therefore, it is possible to control the electronic properties of spiropyran by light in the presence of metal ions. As expected, the



Scheme 4.

addition of $Fe(ClO_4)_3$ to a solution of **3** immediately after irradiation of ultraviolet led to an absorption enhancement in the range of 360–410 nm (Fig. 2b), concomitant with the disappearance of the characteristic absorption band, $\lambda_{max}=548$ nm which corresponds to the ME. As the addition of metal ions to the ME solution was well established to undergo the blue-shift of the absorption band,[7,5c] the above result was due to the formation of $ME\cdot Fe^{3+}$ complex. A similar absorption enhancement in the range of 400–450 nm was observed in the addition of $Fe(ClO_4)_3$ to the spiropyran-perylene diimide-spiropyran.[4a] When the above solution is treated by visible light ($\lambda>600$ nm), $ME\cdot Fe^{3+}$ complex is rapidly switched back to the SP form (Scheme 4). The sequential addition of CF_3COOH and $Fe(ClO_4)_3$ after irradiation with ultraviolet light exhibits an absorption band with $\lambda_{max}=394$ nm corresponding to $MEH\cdot Fe^{3+}$, **8** (Fig. 2a). Similar result was obtained by changing the addition order, namely the addition of $Fe(ClO_4)_3$ followed by CF_3COOH after irradiation of ultraviolet light (Fig. 2c). The absorption band of the colored form **8** and the fluorescence band of anthracene ($\lambda=401$ nm) show substantial spectral overlap, and the Förster excitation energy transfer can take place from the photogenerated anthracene to the ground state colored form **8**. As a result of two spectral hysochromic shift, the fluorescence intensity of anthracene is reduced to 37% of the initial value at 401 nm (Fig. 3c and d). Similar energy transfer from the anthracene emission to SP and MEH was observed by Raymo et al.[5] The fluorescence quantum yields of the mixture solution of **3** and anthracence upon the addition of $Fe(ClO_4)_3$ and no additives are 0.1302 and 0.0062, respectively, and are consistent with the results of the spectral studies.

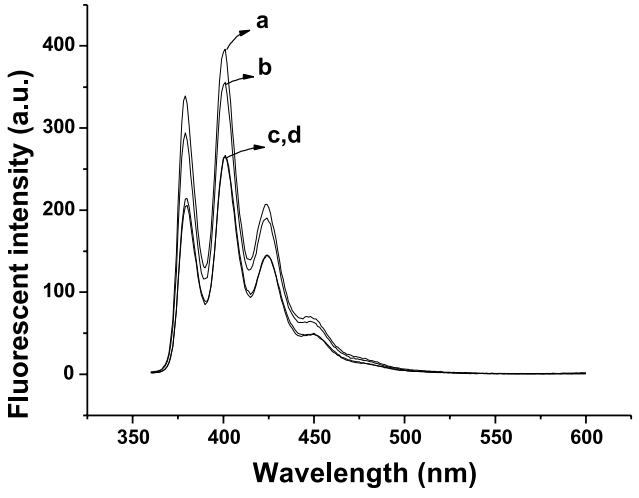


Figure 3. The emission spectra of the mixture solution of **3** and anthracene (**3**: anthracene =1:1, 1.0×10^{-6} M in EtOH, 25 °C, $\lambda_{exc}=357$ nm, DMF stock solution $=1.0\times10^{-3}$ M) (a) before and (b) after irradiation with ultraviolet light and (c) upon addition of 10 equiv of $Fe(ClO_4)_3$ and (d) upon sequential addition of CF_3COOH (2 equiv) and $Fe(ClO_4)_3$ (10 equiv) after irradiation with ultraviolet light.

In summary, we have prepared a dyad bearing diarylethene and spiropyran units. Ultraviolet light, visible light, H^+, and Fe^{3+} inputs induce the multiple interconversion among the colorless diarylethene with spiropyran form (**3**), the colored closed form of diarylethene with spiropyran form (**4**), ME (**5**), MEH (**6**, **7**) and $MEH\cdot Fe^{3+}$ (**8**). In addition, the efficient energy transfer from the anthracene emission to $MEH\cdot Fe^{3+}$ or $ME\cdot Fe^{3+}$ form was achieved. Using multimode photo switching in a dyad **3**, logic gates may be built.

3. Experimental

3.1. General

All reactions were carried out under an argon atmosphere. Solvents were distilled from appropriate reagents. Perfluorocyclopenthene was purchased from Fluorochem. 1,2-Bis[2-methyl-5-(4-hydroxyphenyl)-3-thienyl]perfluorocyclopentene and 1′-(5-bromopentyl)-3′,3′-di-methyl-6-nitroindolinospirobenzopyran were synthesized using a modified procedure of previous references.[10,11] ^1H and ^{13}C NMR spectra were recorded on a Varian Mercurry 300 spectrometer. The absorption and photoluminescence spectra were recorded on a Perkin–Elmer Lambda 2S UV–visible spectrometer and a Perkin LS fluorescence spectrometer, respectively. The fluorescence quantum yields using 9,10-diphenylanthracene as the standard were determined by the dilution method.[16]

3.1.1. Dyad 3. A heterogeneous solution of 1,2-bis[2-methyl-5-(4-hydroxyphenyl)-3-thienyl]perfluo-rocyclopentene (0.10 g, 0.18 mmol), 1′-(5-bromopentyl)-3′,3′-dimethyl-6-nitroindolinospiro-benzopyran (0.24 g, 0.54 mmol), K_2CO_3 (0.15 g, 1.08 mmol) and 18-crown-6 (0.03 g, 0.10 mmol) in acetone (40 ml) was heated at reflux with vigorous stirring for 3 days. The solution was evaporated to dryness and extracted with methylene chloride. The colorless solution was concentrated and purified by chromatography on silica gel (1:5 ethyl acetate/hexane) in 75% yield. Mp 123 °C; ^1H NMR ($CDCl_3$): δ 8.02–7.99 (m, 4H), 7.46 (d, $J=7.2$ Hz, 4H), 7.23–7.18 (m, 4H), 7.11 (s, 2H), 6.92–6.85 (m, 8H), 6.74 (d, $J=9.6$ Hz, 2H, vinylic *H*), 6.61 (d, $J=6.3$ Hz, 2H), 5.88 (d, $J=9.6$ Hz, 2H, vinylic *H*), 3.96 (t, $J=6.1$ Hz, 4H, OCH_2), 3.21 (t, $J=6.3$ Hz, 4H, NCH_2), 1.96 (s, 6H, CH_3), 1.80–1.31 (m, 12H, CH_2), 1.30 (s, 6H, CH_3), 1.20 (s, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 159.7, 158.9, 147.1, 142.1, 140.9, 140.3, 136.0, 127.2, 126.7, 125.8, 123.0, 122.7, 122.0, 121.1, 118.5, 116.4, 115.2, 114.2, 106.8, 52.7, 31.7, 29.1, 28.8, 26.3, 25.8, 23.9, 22.7, 20.3, 14.7. MS: *m/z* 1305 [M^+]. Anal. Calcd for $C_{73}H_{66}F_6N_4O_8S_2$: C, 67.16; H, 5.09. Found: C, 66.8; H, 4.98.

3.1.2. Closed-ring isomer of 3 (4). Compound **4** was isolated by chromatographing a photostationary solution containing **3** and **4** through a HPLC (silica gel column) with hexane as the eluent to yield a pale blue powder. Mp 123–124 °C; δ 8.04–7.82 (m, 4H), 7.38 (d, $J=7.4$ Hz, 4H), 7.20–7.15 (m, 4H), 6.58–6.84 (m, 8H), 6.72 (s, 2H), 6.66 (d, $J=9.6$ Hz, 2H), 6.60 (d, $J=6.3$ Hz, 2H), 6.02 (d, $J=9.6$ Hz, 2H), 3.92 (t, $J=6.1$ Hz, 4H, OCH_2), 3.18 (t, $J=6.3$ Hz, 4H), 2.26 (s, 6H, CH_3), 1.81–1.33 (m, 12H, CH_2), 1.32(s, 6H, CH_3), 1.22 (s, 6H, CH_3). Anal. Calcd for $C_{73}H_{66}F_6N_4O_8S_2$: C, 67.16; H, 5.09. Found: C, 66.76; H, 4.94.

Acknowledgements

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Stereoselective synthesis of (3*S*,4*S*)-*tert*-butyl-*N*-Boc-3-ethyl-4-hydroxy-L-prolinate and (3*S*,4*R*)-*tert*-butyl-*N*-Boc-3-ethyl-4-hydroxy-L-prolinate

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Abstract—Diastereomers of *tert*-butyl-*N*-Boc-3-ethyl-4-hydroxy-L-prolinate **1** and **2** have been synthesized in six steps starting from readily available Boc-protected *trans*-4-hydroxy-L-proline. The key reactions in the synthesis are asymmetric reductions, firstly on the 4-ketoproline intermediate **6** and secondly on the 3-exocyclic olefin bond of the resulting allylic alcohol **7** or **8**. Reaction conditions were optimized in order to control the stereochemistry of the three chiral centers.

1. Introduction

The stereospecific synthesis of non-natural amino acids has assumed great interest because of the use of these compounds as synthons for a wide variety of natural products, providing drugs and tools for the understanding of crucial biological reactions. In this respect, because of its unique conformational properties, the proline residue represents one of the most interesting targets.[1] Substituted prolines have been used extensively to influence the conformation of a peptide backbone and to induce desired turns in host structures.[2] Although many methods for the stereoselective synthesis of substituted prolines have been reported,[3] there is still a need for a new, efficient, stereoselective routes to these compounds. In our search for novel constrained amino acids to design selective and potent ligands, we have developed and optimized a method to obtain 3-substituted-4-hydroxy-L-proline analogues from *trans*-*N*-Boc-4-hydroxy-L-proline **3**, a naturally abundant amino acid. In the present work, we provide a practical pathway in terms of efficiency and potential for stereocontrol in the syntheses of diastereopure *cis* and *trans tert*-butyl-*N*-Boc-3-ethyl-4-hydroxy-L-prolinate analogues **1** and **2** (Fig. 1).

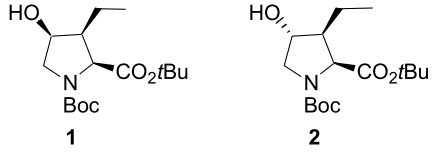
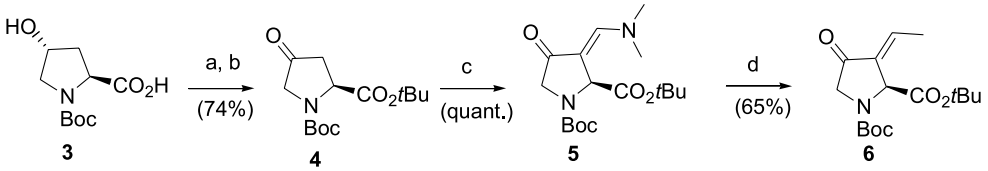


Figure 1. 4-Hydroxyproline analogues **1** and **2**.

2. Results and discussion

Our synthesis begins with the known Boc-protected



Scheme 1. (a) *O*-*tert*-butyl *N*,*N*′-diisopropylisourea, DCM, rt, 20 h; (b) TEMPO, NaOCl, KBr, $NaHCO_3$, DCM, rt; (*c*) Bredereck reagent, DME, 70 °C, 4 h; (d) MeMgBr, Et_2O, −78 °C then 5 h rt.

Keywords: Asymmetric reduction; 4-Hydroxyproline derivatives; Luche reagent.
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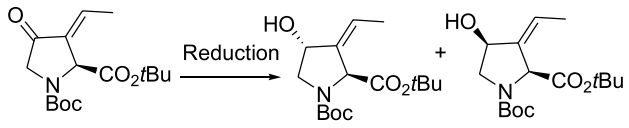


6 **7** (*trans*) **8** (*cis*)

Luche conditions $NaBH_4$, $CeCl_3$, $7H_2O$ (MeOH, -78°C, 1h10, 99%)	83%	17%
DIBAL-H ($AlH(iBu)_2$) (DCM, -90°C, 3h, 52%)	29%	71%
Superhydride® ($LiBHEt_3$) (THF, -78°C, 15min, 88%)	<5%	>95%
Superhydride® , $CeCl_3$ (THF, -78°C, 30 min, 71%)	<5%	>95%

Scheme 2.

trans-4-hydroxy-L-proline **3**, which was first esterified with *O*-*tert*-butyl *N*,*N*′-diisopropylisourea[4] and then converted into the corresponding ketoproline **4** via TEMPO oxidation (Scheme 1).[5] This two-step synthesis is shortened compared to the route of Barraclough et al.,[6] which involves benzyl esterification, oxidation, hydrolysis and finally esterification with *tert*-butanol. Preparation of enaminone **5** was achieved using Bredereck's reagent [bis(dimethylamino)-*tert*-butoxymethane][7], followed by reaction with the MeMgBr Grignard reagent to yield enone **6**. Stereoselective keto-reduction studies of **6** under various conditions allowed us to obtain preferentially either one of both diastereomers: *trans*-**7** and *cis*-**8** (Scheme 2). In each case diastereomers, *trans*-**7** and *cis*-**8**, were not chromatographically separable and the stereochemistry of these analogues was determined by 2D ^1H–^1H NOESY. Since the use of $NaBH_4$ alone led to 1,4-reduction products, Luche conditions[8] ($NaBH_4$, $CeCl_3 \cdot 7H_2O$) provided the major allylic alcohol *trans*-**7** (Scheme 2). As shown in Table 1, Luche reaction conditions were optimized based on temperature, enone concentration, solvent and reaction time. It appeared that the best conditions were at −78 °C under diluted enone concentration in MeOH (Table 1, entry 9). At −78 °C, the use of isopropanol as solvent was detrimental and when the temperature was higher at −15 °C an inversion of the stereoselectivity was observed (Table 1, entry 3 and 4). These results can be rationalized with the aid of computer modeling.[9] Indeed, as shown in Figure 2 (left side), cerium chloride complexing to the keto group through a molecule of MeOH on the less hindered side of **6** (*si* face) allows the borohydride $HB(OMe)_3$ to react on the opposite *re* face, leading preferentially to the *trans* allylic alcohol **7**. However, we hypothesize that when isopropanol is used, the resulting bulky borohydride complex can only react on the less hindered side (*si* face) of **6** leading preferentially to the formation of the *cis* alcohol **8** (Table 1, entry 4). This hypothesis is consistent with the inverse *cis* stereoselectivity observed when standard bulky hydride donors such as DIBAL-H were used in the reaction (Fig. 2, right side). Moreover, the use of Superhydride® with[10] or without $CeCl_3$ afforded the best yield and total stereoselectivity (Scheme 2). Indeed, only the *cis* allylic alcohol **8** was obtained in this reaction and no trace of the *trans* analogue **7** was observed by ^1H NMR analysis.

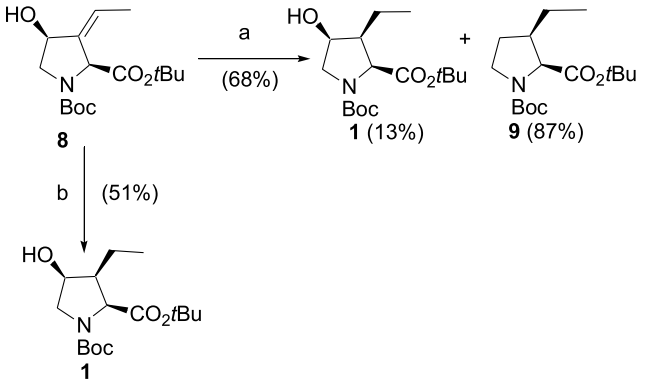
Stereoselective hydrogenation studies of **8** obtained from **6** with Superhydride® as reducing agent were undertaken. When 10% Pd/C catalyst was used, mainly hydrogenolysis

Table 1. Diastereomeric ratios of **7**:**8** obtained with Luche reagent ($NaBH_4$, $CeCl_3 \cdot 7H_2O$) under different reaction conditions

Entry	Temperature (°C)	Concentration of **6** (M)	Solvent	Reaction time	Yield (%)	Diastereomeric ratios of *trans*-**7**: *cis*-**8**[a]
1	−78	0.01	MeOH	45in	87	76/24
2	−78	0.01	EtOH	6 h	70	68/32
3	−78	0.01	*i*-PrOH	3 h	0	—
4	−15	0.01	*i*-PrOH	6 h	50	17/63
5	−95	0.05	MeOH	3 h	84	75/25
6	−78	0.05	MeOH	3 h	74	80/20
7	−78	0.05	MeOH	30in	79	64/36
8	20	0.05	MeOH	1.15 h	87	63/37
9	−78	0.005	MeOH	1.15 h	99	83/17

[a] Ratios determined by ^1H NMR experiments.

Figure 2. Stereoselective reduction of exo-enone **6** with Luche reagent (left) and DIBAL-H (right).



Scheme 3. (a) H_2 1 bar, Pd/C (5%), EtOAc, rt, 1.25 h; (b) H_2 1 bar, $RhCl(PPh_3)_3$, toluene, rt, 3 days.

product **9** was obtained along with some single diastereomer **1** (ratio 87:13, Scheme 3). We hypothesize that the complexation between the hydroxyl group and palladium (*si* face, Fig. 3, left side) together with steric hindrance of the *tert*-butyl group, by making the addition of hydrogen on olefin difficult, favored the formation of hydrogenolysis product **9**. Therefore, in order to avoid this hydrogenolysis, we chose Wilkinson's catalyst ($RhCl(PPh_3)_3$).[11] The reaction proceeded slowly, but stereoselectively, and after 3 days the single diastereomer **1** was obtained (Scheme 3). Whilst the slowness of the reaction was probably due to the presence of the tri-substituted alkene bond, the high stereoselectivity observed was governed by steric factors. Indeed, as shown in Figure 3 (right side), because of the sterically hindered *si* face of **8**, Wilkinson's catalyst acts selectively through the *re* face leading to the single *cis* diastereomer **1** (Scheme 3). These conclusions were further supported by examination of 2D ^1H–^1H NOESY spectra for **1** and **2** as well as crystallographic data for **1** (Fig. 4).[12] Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 259964.

Hydrogenation of **7**, previously obtained under Luche conditions, with 10% Pd/C allowed access to the major *trans* allylic alcohol diastereomer **2** (68%). Since **7** and **8** were not chromatographically separable, the mixture of both *trans* and *cis* diastereomers (ratio **7**:**8** 83/17) was hydrogenated on Pd/C (Scheme 4). Three compounds, **1**, **2** and **9**

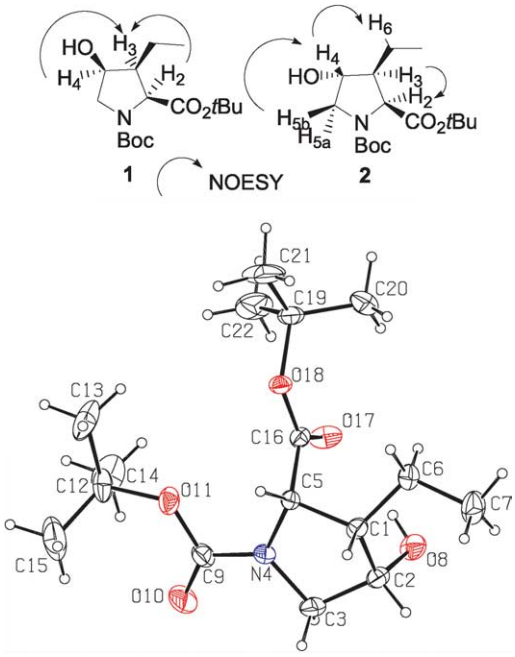


Figure 4. NOESY correlations for compounds **1** and **2** and ORTEP diagram of compound **1**.

were isolated and characterized. We have shown that hydrogenation of the *cis* allylic alcohol **8** on Pd/C led to **1** and **9** (Scheme 3). It is likely that hydrogenation of the *trans* alcohol **7** afforded specifically the *trans* diastereomer **2**. The rationale for these results is shown in Figure 5. Since no steric hindrance occurred with Boc and *tert*-butyl ester groups, the orientation of **7** could be governed by the ease of complexation of the hydroxyl group on Pd. Consequently, hydrogenation would occur specifically through the *re* face of **7** (Fig. 5) providing the final compound **2** (Scheme 4).

3. Conclusion

In summary, we have presented the diastereoselective syntheses of 3-ethyl-4-hydroxyprolinate derivatives **1** and **2**. The synthesis involving a 1,4-Grignard reagent addition followed by two asymmetric reductions, represents a new practical route for the design of numerous diastereopure *cis* and *trans* 3-substituted 4-hydroxyproline analogues of biological interest.

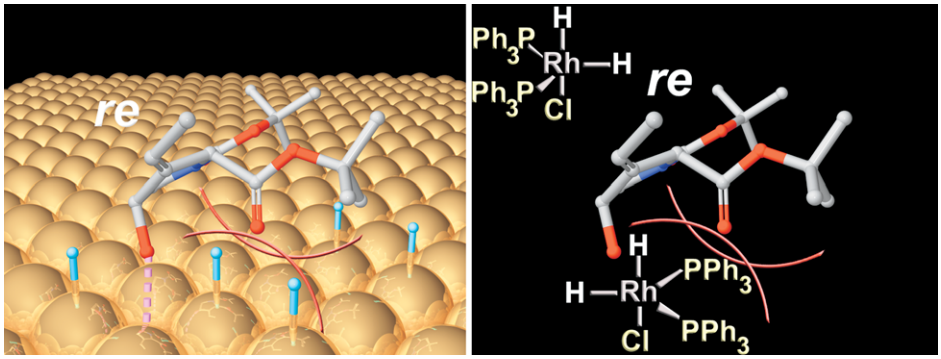
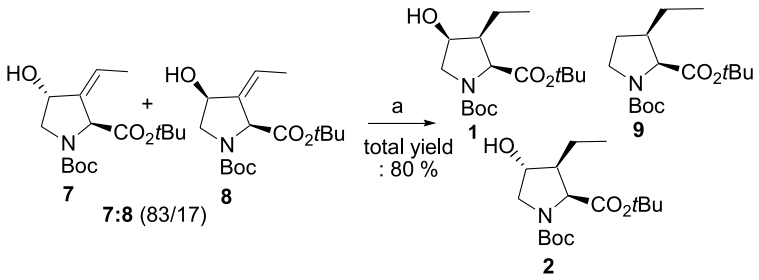


Figure 3. Stereoselective hydrogenation of **8** either on Pd (yellow, left) or with Wilkinson catalyst (right).



Scheme 4. (a) H_2, Pd/C (5%), EtOAc, 1 bar, 36 h, rt, yield for **2**: 68%.

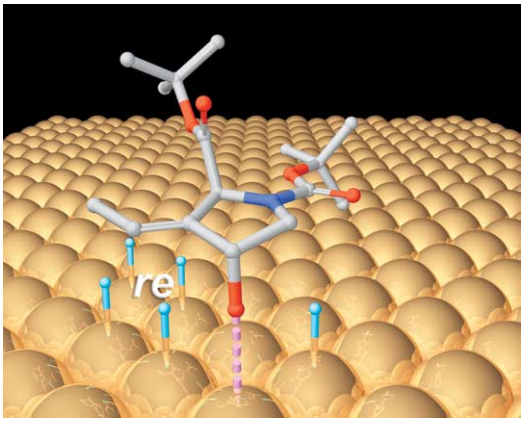


Figure 5. Stereoselective hydrogenation of **7** with H_2 on Pd (yellow).

4. Experimental

4.1. General

Building blocks, reagents and solvents that were commercially available were used as received. Anhydrous solvents were distilled: tetrahydrofuran and diethyl ether were purified by distillation from sodium and benzophenone, methylene chloride was dried by distillation from $CaCl_2$. Flash columns chromatography were performed on silica gel (40–60 μm) purchased from Merck. ^{1}H NMR spectra were recorded at 250 MHz (unless otherwise stated) on a Bruker instrument and chemical shifts were reported in δ (ppm, internal reference TMS). Low-resolution mass spectra were acquired using JEOL DX-100 instrument with positive (+) mode 'Fast Atom Bombardment' (FAB). The used matrixes are NBA: meta-nitrobenzylic alcohol or GT: glycerol–thioglycerol. High-resolution mass spectra were performed using the FAB method. Melting points (Mp) were not corrected. HPLC was carried out using a BDS HYPERSIL C18 (ThermoHypersil-Keystone) column (50×2,1 mm 3 μm) at rt (room temperature). The solvent system was a binary system: water containing 0.1% TFA and acetonitrile containing the same amount of TFA. The flow rate was 0.2 μL/min. Optical rotations were measured on a Perkin-Elmer 241 polarimeter in a 1-dm cell.

4.1.1. (2*S*, 4*R*)-*tert*-butyl-*N*-*tert*-butyloxycarbonyl-4-hydroxyprolinate. To *tert*-butanol (1 mL, 6.09 mmol, 7 equiv) under argon, were added diisopropylcarbodiimide (0.9 mL, 5.2 mmol, 6 equiv) and copper chloride (I) (5 mg, 0.05 mmol, 0.06 equiv). The resulting mixture was then left to stir at rt for 3 days, diluted with anhydrous dichloromethane (DCM) (3 mL) and added to a solution of Boc-L-Hyp-OH **3** (200 mg, 0.87 mmol, 1 equiv) in anhydrous DCM (3 mL) under argon and the resulting mixture stirred at rt for 20 h. The urea formed was filtered through a Celite® pad and solvents were evaporated under reduced pressure. The crude product was purified by flash column chromatography (cyclohexane/EtOAc: 70/30). The title compound was obtained as a colorless oil (216 mg, 87% yield from **3**).

^{1}H NMR ($CDCl_3$) δ 4.38 (1H, m, H_4); 4.21 (1H, t, J= 7.7 Hz, H_2); 3.42–3.60 (2H, m, H_5); 3.30 (1H, ls, –O*H*); 2.15–2.40 (1H, m, H_3); 1.90–2.10 (1H, m, H_3); 1.42 (18H, 2×s, Boc and *t*Bu) ^{13}C NMR (CDCl3) δ 172.00 (C_1); 154.48 and 154.27 (C=O Boc); 81.20 (Cq Boc); 81.17 (Cq *t*Bu); 69.92 and 69.05 (C_4); 58.56 (C_2); 54.62 (C_5); 39.11 and 38.35 (C_3); 28.32 and 27.97 (Boc and *t*Bu). MS (FAB$^+$, GT): 288 $(M+1H)^+$, 575 $(2M+1H)^+$. $[\alpha]_D^{25}$ −51.3 (*c* 1.28; $CHCl_3$). R_f: 0.26 (cyclohexane/EtOAc: 60/40).

4.1.2. (2*S*)-*tert*-butyl-*N*-*tert*-butyloxycarbonyl-4-oxoprolinate 4. To a solution of (2*S*, 4*R*)-*tert*-butyl-*N*-*tert*-butyloxycarbonyl-4-hydroxyprolinate (620 mg, 2.16 mmol, 1 equiv) in anhydrous DCM (14 mL) were added a saturated aqueous solution of $NaHCO_3$ (4.5 mL), TEMPO (17 mg, 0.11 mmol, 0.05 equiv), potassium bromide (26 mg, 0.22 mmol, 0.1 equiv) and four drops of Aliquat 336. The mixture was cooled to 0 °C and an aqueous solution of sodium hypochlorite was added dropwise until no starting material traces remained. (The sodium hypochlorite solution was buffered at pH 8.6 with an aqueous solution of 1 N HCl). Brine was then added to the mixture and the aqueous layer extracted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness. The crude product was purified by flash column chromatography (cyclohexane/EtOAc: 90/10). The title compound **4** was obtained as a yellow oil (465 mg, 85% yield).

^{1}H NMR ($CDCl_3$) δ 4.53–4.65 (1H, m, H_2); 3.82 (2H, d, J= 8.6 Hz, H_5); 2.86–2.93 (1H, m, H_3); 2.49 (1H, dd, J=18.8, 2.3 Hz, H_3); 1.45 (18H, 2×s, Boc and *t*Bu) ^{13}C NMR ($CDCl_3$) δ 208.83 and 208.05 (C_4); 170.88 (C_1); 154.37 and 153.52 (C=O Boc); 82.24 (Cq Boc); 80.90 (Cq ester); 56.99 and 56.57 (C_2); 52.88 and 52.46 (C_5); 41.32 and 40.79 (C_3); 28.17 and 27.82 (*t*Bu and Boc). HRMS (FAB$^+$) calculated for $C_{14}H_{24}NO_5$ $(M+H)^+$ 286.1654, found 286.1645. $[\alpha]_D^{25}$ +6.5 (*c* 0.77; $CHCl_3$). R_f: 0.27 (cyclohexane/EtOAc: 90/10).

4.1.3. (2*S*)-*tert*-butyl-*N*-*tert*-butyloxycarbonyl-3-dimethylaminomethylene-4-oxoprolinate 5. To a solution of

(2*S*)-*tert*-butyl-*N*-*tert*-butyloxycarbonyl-4-oxoprolinate **4** (30 mg, 0.1 mmol, 1 equiv) in anhydrous dimethoxyethane (1.25 mL) under argon was added bis-(dimethylamino)-*tert*-butoxymethane (Bredereck reagent)[7] (0.04 mL, 0.2 mmol, 2 equiv). The resulting solution was left to stir at 70 °C for 4 h. The reaction mixture was then concentrated under reduced pressure and the crude product purified by flash column chromatography (EtOAc 100%). The title compound **5** was obtained as a yellow solid (34 mg, 99% yield from **4**).

^{1}H NMR ($CDCl_3$) δ 7.33 (1H, s, H_6); 5.30 and 5.15 (1H, 2× s, H_2); 3.83 (m, 2H, H_5); 3.18 (6H, s, N–CH_3); 1.38 and 1.45 (18H, 2×s, Boc and *t*Bu); ^{13}C NMR ($CDCl_3$) δ 171.35 (C_4); 154.61 (C_1); 153.52 (C=O Boc); 147.36 (C_6); 98.64 and 98.38 (C_3); 81.78 and 81.65 (Cq Boc); 80.50 and 80.30 (Cq *t*Bu); 61.68 and 61.22 (C_2); 53.18 and 52.73 (C_5); 28.36 and 27.86 (*t*Bu and Boc) MS (FAB+, NBA): 341 $(M+1H)^+$, 681 $(2M+1H)^+$. $[\alpha]_D^{23}$ +31.7 (*c* 0.25; MeOH). R_f: 0.43 (EtOAc). Mp: 88 °C (lit. 94 °C).[6] Elemental analysis calculated for $C_{17}H_{28}N_2O_5$: C, 59.98; H, 8.29; N, 8.23. Found: C, 59.82; H, 8.12; N, 7.80.

4.1.4. (2*S*) *tert*-butyl-*N*-*tert*-butyloxycarbonyl-3-ethylidene-4-oxoprolinate 6. A solution of (2*S*)-*tert*-butyl-*N*-*tert*-butyloxycarbonyl-3-dimethylaminomethylene-4-oxoprolinate **5** (5.60 g, 16.45 mmol, 1 equiv) in freshly distilled Et_2O (323 mL) was cooled to −78 °C and a solution of methylmagnesium bromide (3 M in Et_2O) (17 mL, 51.0 mmol, 3.1 equiv) was added dropwise. The resulting mixture was stirred at −78 °C for 1 h, and the solution was then allowed to warm gently to rt and left to stir for 2 h. A saturated aqueous solution of NH_4Cl was added and layers were separated. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over anhydrous $MgSO_4$ and concentrated to dryness. The crude product was purified by flash column chromatography (cyclohexane/EtOAc: 90/10) and the title compound **6** was obtained as a colorless oil (3.31 g, 65% yield from **5**).

^{1}H NMR ($CDCl_3$) δ 6.90 (1H, 2×q, J=7.42 Hz, H_6); 5.14 and 5.06 (1H, 2×s, H_2); 3.95 (2H, m, H_5); 2.01 (3H, d, J=7.4 Hz, H_7); 1.47 and 1.40 (18H, 2×s, Boc and *t*Bu) ^{13}C NMR ($CDCl_3$) δ 197.60 and 196.94 (C_4); 168.96 (C=O *t*Bu); 154.51 and 153.73 (C=O Boc); 137.50 (C_6); 133.52 and 133.13 (C_3); 82.59 (Cq Boc); 81.17 (Cq *t*Bu); 61.24 and 60.86 (C_2); 53.62 and 53.14 (C_5); 28.05 and 27.00 (*t*Bu and Boc); 15.72 (C_7). MS (FAB^+, NBA): 312 $(M+1H)^+$. HRMS (FAB^+) calculated for $C_{16}H_{26}NO_5$ $(M+H)^+$ 312.1811, found 312.1795. $[\alpha]_D^{24}$ +82.2 (*c* 0.33; $CHCl_3$). R_f: 0.43 (cyclohexane/EtOAc: 80/20).

4.1.5. (2*S*, 4*S*)-*tert*-butyl-*N*-*tert*-butyloxycarbonyl-3-ethylidene-4-hydroxyprolinate 8 and (2*S*, 4*R*)-*tert*-butyl-*N*-*tert*-butyloxycarbonyl-3-ethylidene-4-hydroxyprolinate 7.

4.1.5.1. Procedure A: reduction with DIBAL-H. A solution of (2*S*) *tert*-butyl-*N*-*tert*-butyloxycarbonyl-3-ethylidene-4-oxoprolinate **6** (101 mg, 0.32 mmol, 1 equiv) in anhydrous DCM (1 mL) under argon was cooled to -90 °C and a solution of DIBAL-H (1 M in cyclohexane) (0.96 mL, 0.96 mmol, 3 equiv) was added dropwise. The resulting mixture was left to stir for 3 h at −90 °C. The reaction was quenched with methanol (10 mL) and a solution of saturated potassium sodium tartrate tetrahydrate. The mixture was allowed to warm to rt overnight and extracted with EtOAc. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (cyclohexane/EtOAc: 90/10 to 70/30) and the title compounds **7** and **8** (not separable by chromatography) obtained as yellow oils (52 mg, 52% yield from **6**). ^{1}H NMR analysis showed that the mixture was composed of 71% of **8** and 29% of **7**.

^{1}H NMR ($CDCl_3$) (500 MHz) δ 5.88 (0.71H, 2×q, J=7.1 Hz, H_6 (**8**)); 5.79 (0.29H, 2×q, J=7.1 Hz, H_6 (**7**)); 4.86 and 4.77 (0.29H, 2×s, H_2 (**7**)); 4.74 and 4.67 (0.71H, 2×s, H_2 (**8**)); 4.70 (0.29H, m, H_4 (**7**)); 4.34 (0.71H, t, J=5.4 Hz, H_4 (**8**)); 3.97 et 3.90 (0.29H, 2×dd, J=10.50, 7.91, 10.70, 7.70 Hz, H_5 (**7**)); 3.69 (0.71H, m, H_5 (**8**)); 3.47 (0.71H, m, H_5 (**8**)); 3.15 (0.29H, m, H_5 (**7**)); 1.90 (ls, –O*H*); 1.81 and 1.77 (3H, 2×d, J=6.8 Hz, H_7 (**8** and **7**)); 1.64 (ls, –O*H*); 1.44 (18H, m, Boc+*t*Bu) ^{13}C NMR ($CDCl_3$) δ 172.12 and 171.95 (C=O ester); 154.48 and 153.92 (C=O Boc); 138.43 and 137.71 (C_3); 125.87 and 124.77 (C_6); 82.81 (Cq Boc); 80.55 and 80.30 (Cq *t*Bu); 74.62 and 743.73 (C_4); 60.69 (C_2); 55.69 and 55.15 (C_5); 28.14 and 28.03 (Boc and *t*Bu); 14.86 (C_7). MS (FAB^+, GT): 314 $(M+1H)^+$, 627 $(2M+1H)^+$. R_f: 0.31 (cyclohexane/EtOAc: 70/30). HPLC assay: 92% by area %.

4.1.5.2. Procedure B: reduction with $NaBH_4$, $CeCl_3 \cdot 7H_2O$ (Luche reagent). To a solution of (2*S*) *tert*-butyl-*N*-*tert*-butyloxycarbonyl-3-ethylidene-4-oxoprolinate **6** (122 mg, 0.4 mmol, 1 equiv) in methanol (5.3 mL) and THF (1.4 mL) under argon, was added heptahydrate cerium chloride (229 mg, 0.6 mmol, 1.6 equiv). The solution was cooled to 0 °C, sodium borohydride (25 mg, 0.6 mmol, 1.6 equiv) was added in small portions and the mixture was stirred at 0 °C for 3 h. The reaction product was hydrolysed by addition of saturated aqueous solution of NH_4Cl and the mixture extracted with EtOAc. Organic layers were washed by brine, dried on anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (cyclohexane/EtOAc: 70/30) and the title compounds **7** and **8** (not separable by chromatography) obtained as a yellow oil (106 mg, 85% yield from **6**). ^{1}H NMR analysis showed that the mixture was composed of 35% of **8** and 65% of **7**.

^{1}H NMR ($CDCl_3$) (400 MHz) δ 5.92 (0.35H, 2×q, J=7.0 Hz, H_6 (**8**)); 5.82 (0.65H, 2×q, J=7.1 Hz, H_6 (**7**)); 4.89 and 4.80 (0.65H, H_2 (**7**)); 4.77 and 4.70 (0.35H, s, H_2 (**8**)); 4.72 (0.65H, m, H_4 (**7**)); 4.36 (0.35H, m, H_4 (**8**)); 4.00 and 3.94 (0.65H, 2×dd, J=10.8, 7.7 Hz, H_5 (**7**)); 3.74 (0.35H, m, H_5 (**8**)); 3.50 (0.35H, m, H_5 (**8**)); 3.19 (0.65H, dd, J=6.5, 10.7 Hz, H_5 (**7**)); 2.00 (ls, –O*H*); 1.84 and 1.81 (3H, 2×d, J=7.0 Hz, H_7 (**8** et **7**)); 1.70 (ls, –O*H*); 1.49 (18H, m, Boc+*t*Bu) ^{13}C NMR ($CDCl_3$) δ 172.14 and 169.70 (C=O ester); 154.52 and 153.92 (C=O Boc); 138.72 and 138.00 and 137.64 (C_3); 125.97 and 121.79 (C_6); 82.81 and 81.54 and 80.36 (Cq Boc, *t*Bu); 70.77 and 69.88 (C_4); 61.20 and 60.70 (C_2); 53.35 and 52.85 (C_5); 28.37 and 28.00 (Boc and *t*Bu);

14.65 (C_7). R_f: 0.31 (cyclohexane/EtOAc: 70/30). HPLC assay: 85% by area %.

4.1.6. (2*S*, 4*S*)-*tert*-butyl-*N*-*tert*-butyloxycarbonyl-3-ethylidene-4-hydroxyprolinate 8.

4.1.6.1. Procedure C: reduction with Superhydride®. To a solution of (2*S*) *tert*-butyl-*N*-*tert*-butyloxycarbonyl-3-ethylidene-4-oxoprolinate **6** (1.5 g, 4.82 mmol, 1 equiv) in freshly distilled THF (60 mL) under argon, was added at −78 °C Superhydride® ($LiBHEt_3$, 1 M in THF) (9.64 mL, 9.64 mmol, 2 equiv). The mixture was stirred at −78 °C for 15 min and quenched with 10% aqueous citric acid (60 mL). It was then diluted and extracted with EtOAc (200 mL). The combined organic layers were dried on anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (cyclohexane/EtOAc: 80/20) and the title compound **8** was obtained as a colorless oil (1.32 g, 88% yield from **6**).

^{1}H NMR ($CDCl_3$) δ 5.90 (1H, 2×q, J=7.0 Hz, H_6); 4.76 and 4.70 (1H, 2×s, H_2); 4.37 (1H, m, H_4); 3.65–3.76 (1H, dd, J=11.9, 16.0 Hz, H_5); 3.40–3.53 (1H, 2×dd, J=11.9, 16.0 Hz, H_5); 3.30 (1H, ls, −O*H*); 1.79 (3H, d, J=7.0 Hz, H_7); 1.49 and 1.46 (18H, 2×s, Boc and *t*Bu) ^{13}C NMR ($CDCl_3$) δ 171.89 (C=O ester); 154.43 and 153.87 (C=O Boc); 138.43 and 137.71 (C_3); 125.77 (C_6); 82.65 and 80.47 (Cq Boc, *t*Bu); 74.51 and 73.63 (C_4); 60.74 (C_2); 55.17 and 55.07 (C_5); 28.34 and 27.86 (Boc and *t*Bu); 14.75 (C_7). HRMS (FAB^+) calculated for $C_{16}H_{27}NO_5$ $(M+H)^+$ 314.1967, found 314.1964. $[\alpha]_D^{24}$ +85.5 (*c* 1.18; $CHCl_3$). R_f: 0.31 (cyclohexane/EtOAc: 70/30). HPLC assay: 96% by area %.

4.1.6.2. Procedure D: reduction with Superhydride®, $CeCl_3$. $CeCl_3 \cdot 7H_2O$ (216 mg, 0.55 mmol, 3.2 equiv) was dried for 2 h under vacuum at 110 °C then THF (2 mL) was added under argon at rt. The mixture was stirred overnight and a solution of (2*S*) *tert*-butyl-*N*-*tert*-butyloxycarbonyl-3-ethylidene-4-oxoprolinate **6** (55 mg, 0.18 mmol, 1 equiv) in THF (2 mL) added dropwise at rt. The resulting mixture was cooled to −78 °C and Superhydride® (1 M in THF) (0.36 mL, 0.36 mmol, 2 equiv) added. The solution was left to stir for 30 min, then 10% aqueous citric acid (5 mL) was added. The mixture was allowed to warm to rt and then extracted with EtOAc. The combined organic layers were washed with brine, dried on anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (cyclohexane/EtOAc: 80/20) and the title compound **8** was obtained as a colorless oil (40 mg, 71% yield from **6**).

4.1.7. (2*S*, 3*R*)-*tert*-butyl-*N*-*tert*-butyloxycarbonyl-3-ethylprolinate 9, (2*S*, 3*R*, 4*R*)-*tert*-butyl-*N*-*tert*-butyloxycarbonyl-3-ethyl-4-hydroxyprolinate 2, (2*S*, 3*R*, 4*S*)-*tert*-butyl-*N*-*tert*-butyloxycarbonyl-3-ethyl-4-hydroxyprolinate 1 via hydrogenation on Pd/C of a mixture of 7 and 8.

To a solution of (2*S*, 4*S*)-*tert*-butyl-*N*-*tert*-butyloxycarbonyl-3-ethylidene-4-hydroxyprolinate **8** and (2*S*, 4*R*)-*tert*-butyl-*N*-*tert*-butyloxycarbonyl-3-ethylidene-4-hydroxyprolinate **7** (83/17 obtained from Luche reduction, procedure B) (40 mg, 0.13 mmol) in EtOAc (4.5 mL) was added Pd/C (5%) (15 mg). The resulting mixture was left to stir for 36 h at rt under H_2 pressure (1 bar), then the Pd was filtered off through a Celite® pad, and solvent evaporated under reduced pressure. The crude product was purified by flash column chromatography (cyclohexane/EtOAc: 95/5 to 60/40) to give the title compounds **9** (7 mg, 18% yield from **7**+**8**, colorless oil, less polar product), **2** (28 mg, 68% yield from **7**+**8**, colorless oil, most polar product) and **1** (5 mg, 12% yield from **7**+**8**, colorless oil).

4.1.8. Compound 9. ^{1}H NMR ($CDCl_3$) (400 MHz) δ 4.19 and 4.12 (1H, 2×d, J=8.2 Hz, H_2); 3.63 (1H, m, H_4); 3.30 (1H, m, H_4); 2.23 (1H, m, H_3); 1.98 (1H, m, H_4); 1.71 (1H, m, H_4); 1.56 (1H, m, H_6); 1.48 (18H, m, Boc+*t*Bu); 1.29 (1H, m, H_6); 1.00 (3H, t, J=7.4 Hz, H_7) ^{13}C NMR ($CDCl_3$) δ 171.22 (C=O ester); 155.00 (C=O Boc); 81.19 and 79.73 (Cq Boc and *t*Bu); 63.13 (C_2); 45.81 and 45.16; 44.15 (C_3); 28.55 (C_4); 28.35 (Boc and *t*Bu); 23.41 (C_6); 12.97 (C_7). HRMS (FAB^+) calculated for $C_{16}H_{30}NO_4$ $(M+H)^+$ 300.2175, found 300.2167. $[\alpha]_D^{23}$ −3.2 (*c* 0.63; $CHCl_3$). R_f: 0.60 (cyclohexane/EtOAc: 70/30).

4.1.9. Compound 2. ^{1}H NMR ($CDCl_3$) (500 MHz) δ 4.28 and 4.22 (1H, 2×d, J=8.4 Hz, H_2); 4.14 (1H, q, J=7.2 Hz, H_4); 3.84 (1H, 2×dd, J=10.6, 7.5 Hz, H_5); 3.10 (1H, 2×dd, J=10.6, 7.0 Hz, H_5); 2.06 (1H, m, H_3); 1.61 (1H, m, H_6); 1.43, 1.42, 1.41 and 1.39 (18H, m, Boc+*t*Bu); 1.26 (1H, m, H_6); 1.02 (3H, t, J=7.4 Hz, H_7) ^{13}C NMR ($CDCl_3$) δ 170.86 (C=O ester); 154.53 and 153.92 (C=O Boc); 81.65 and 80.23 (Cq Boc and *t*Bu); 72.60 and 72.42 (C_4); 62.53 and 62.33 (C_2); 52.45 and 52.41 (C_5); 51.11 and 51.21 (C_3); 28.47 and 28.27 (Boc and *t*Bu); 21.10 (C_6); 12.74 (C_7). HRMS (FAB^+) calculated for $C_{16}H_{30}NO_5$ $(M+H)^+$ 316.2124, found 316.2134. MS (FAB^+, NBA): 316 $(M+1H)^+$, 631 $(2M+1H)^+$. $[\alpha]_D^{26}$ +20.74 (*c* 1.65; $CHCl_3$). R_f: 0.26 (cyclohexane/EtOAc: 70/30). HPLC assay: 97% by area %.

4.1.10. Compound 1. ^{1}H NMR ($CDCl_3$) δ 4.06–4.16 (2H, m, H_2 and H_4); 3.65 (1H, 2×d, J=12.1 Hz, H_5); 3.35–3.50 (1H, m, H_5); 2.10 (1H, m, H_3); 1.43 and 1.38 (18H, 2×s, Boc and *t*Bu); 1.37 (1H, m, H_6); 0.96 (3H, t, J=7.3 Hz, H_7) ^{13}C NMR ($CDCl_3$) δ 174.13 (C=O ester); 153.82 (C=O Boc); 83.04 and 80.23 (Cq Boc and *t*Bu); 72.48 and 71.59 (C_4); 62.44 (C_2); 56.30 and 55.86 (C_5); 49.29 and 48.21 (C_3); 28.40 and 27.91 (Boc and *t*Bu); 18.11 and 17.94 (C_6); 12.37 (C_7). $[\alpha]_D^{26}$ +19.77 (*c* 1.2; $CHCl_3$). R_f: 0.40 (cyclohexane/EtOAc: 70/30). Mp: 99 °C (EtOAc). Elemental analysis calculated for $C_{16}H_{29}NO_5$: C, 60.93; H, 9.27; N, 4.44, found: C, 61.34; H, 9.24; N, 4.16.

4.1.11. (2*S*, 3*R*, 4*S*)-*tert*-butyl-*N*-*tert*-butyloxycarbonyl-3-ethyl-4-hydroxyprolinate 1 via hydrogenation of 8 with the use of Wilkinson's catalyst). To a solution of (2*S*, 4*S*)-*tert*-butyl-*N*-*tert*-butyloxycarbonyl-3-ethylidene-4-hydroxyprolinate **8** (200 mg, 0.64 mmol, 1 equiv) in anhydrous toluene (7 mL) was added Wilkinson's catalyst (118 mg, 0.13 mmol, 20 mol %). The resulting mixture was stirred at rt under H_2 pressure (1 bar) for 3 days. The solution was filtered on a Celite® pad and the toluene evaporated under reduced pressure. The crude product was purified by flash column chromatography (cyclohexane/EtOAc: 90/10 to 80/20) to give the title compound **1** (102 mg, 51% yield from **8**, brown solid) which was recrystallised from EtOAc.

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Supplementary data

^{1}H NMR, 2D NOESY, ^{13}C NMR for compounds **1**, **2**, **7**, **8**, **9** and COSY for compounds **2**, **7** and **8**. Computer modeling details.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.02.006

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12. Since compound **2** was always obtained as an oil, X-ray studies were impossible to undertake.

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Enantioselective synthesis of axially chiral 1-(1-naphthyl)isoquinolines and 2-(1-naphthyl)pyridines through sulfoxide ligand coupling reactions

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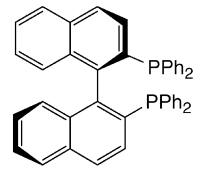
Abstract—Racemic 1-(1′-isoquinolinyl)-2-naphthalenemethanol *rac*-**12** was prepared through a ligand coupling reaction of racemic 1-(*tert*-butylsulfinyl)isoquinoline *rac*-**7** with the 1-naphthyl Grignard reagent **10**. Resolution of *rac*-**12** was achieved through chromatographic separation of the Noe-lactol derivatives **14** and **15**, providing (*R*)-(−)-**12** of >99% ee and (*S*)-(+)-**12** of 90% ee. The ligand coupling reaction of optically enriched sulfoxide (*S*)-(−)-**7** (62% ee) with Grignard reagent **10** furnished *rac*-**12**, with the absence of stereoinduction resulting from competing rapid racemisation of the sulfoxide **7**. Reaction of optically enriched (*S*)-(−)-**7** with 2-methoxy-1-naphthylmagnesium bromide was also accompanied by racemisation of the sulfoxide **7**, and furnished optically active (+)-1-(2′-methoxy-1′-naphthyl)isoquinoline (+)-**3b** in low enantiomeric purity (14% ee). The absolute configuration of (+)-**3b** was assigned as *R* using circular dichroism spectroscopy, correcting an earlier assignment based on the Bijvoet method, but in the absence of heavy atoms. Optically active 2-pyridyl sulfoxides were found not to undergo racemisation analogous to the 1-isoquinolinyl sulfoxide **7**, with the ligand coupling reactions of (*R*)-(+)- and (*S*)-(−)-2-[(4′-methylphenyl)sulfinyl]-3-methylpyridines, (*R*)-(+)-**17** and (*S*)-(−)-**17**, with 2-methoxy-1-naphthylmagnesium bromide providing (−)- and (+)-2-(2′-methoxy-1′-naphthyl)-3-methylpyridines, (−)-**18** and (+)-**18**, in 53 and 60% ee, respectively. The free energy barriers to internal rotation in **3b** and **18** have been determined, and the isoquinoline (*R*)-(−)-**12** examined as a ligand in the enantioselectively catalysed addition of diethylzinc to benzaldehyde; (*R*)-(−)-**12** was also converted to (*R*)-(−)-*N*,*N*-dimethyl-1-(1′-isoquinolinyl)-2-naphthalenemethanamine (*R*)-(−)-**19**, and this examined as a ligand in the enantioselective Pd-catalysed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate.

1. Introduction

The last three decades have seen the emergence of the synthesis of enantiomerically pure organic compounds as an important field of endeavour and the most economically attractive method is asymmetric catalysis.[1] Axially chiral bidentate ligands have proved to be fruitful candidates for this purpose and examples include the C_2-symmetric ligand BINAP **1**[2] (homobidentate) and C_1-symmetric ligands with different coordinating groups (heterobidentate), such as **2**.[3]



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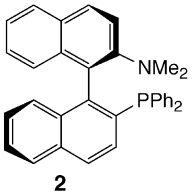

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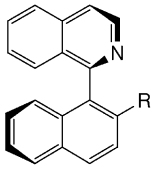

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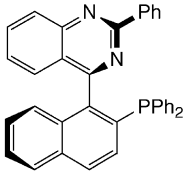
3b R = OMe
3c R = SMe
3d R = NHMe



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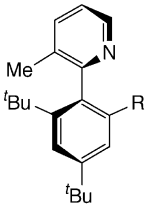

5a R = PPh_2
5b R = OH

Keywords: Axial chirality; Isoquinoline; Pyridine; Sulfoxide; Ligands; Catalysis.
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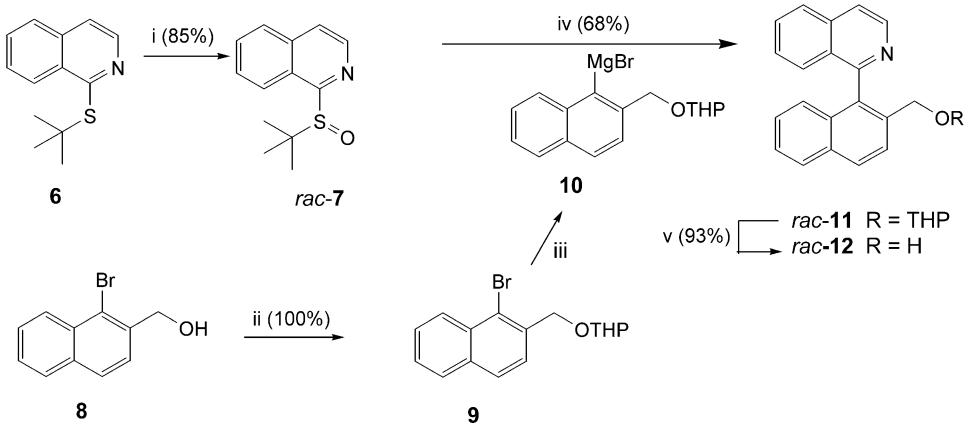
In 1993 Brown and his co-workers reported the synthesis and resolution of the *P*,*N*-heterobidentate ligand QUINAP **3a**,[4] where the coordinating nitrogen is incorporated in an axially chiral isoquinoline. The synthesis involved *rac*-**3b**, which was converted into *rac*-**3a** by demethylation, trifluoromethanesulfonation, Pd-catalysed coupling with diphenylphosphine oxide, and then reduction. Transition metal complexes of ligand **3a** have been used in a number of asymmetric catalytic reactions.[5] Some analogues of QUINAP **3a** have been described, including the axially chiral quinazoline **4**[6] and the pyridine **5a**,[7] as well as axially chiral azaheteroaromatics containing pendant heteroatoms other than phosphorus, for example, **3b** and **3c**,[8] **3d**[9] and **5b**.[10]

One potential problem with these isoquinoline and similar azaheteroaromatic ligands is their low barriers to atropisomerisation since the lone pair of electrons on the nitrogen now occupies one of the four blocking positions at the rotational axis. 1,1′-Biisoquinoline has not been resolved into atropisomers; its salt with tartaric acid undergoing rapid mutarotation at 0 °C.[11] 8,8′-Alkyl disubstitution raises the barrier to rotation to $\Delta G^{\ddagger}_{303} \sim 100$ kJ mol^{-1} so that resolution can only be achieved with difficulty.[12] The barrier in 1,1′-binaphthalene,[13] where the lone pairs are replaced by hydrogen atoms, is $\Delta G^{\ddagger}_{323} \sim 100$ kJ mol^{-1}, but diminishes to $\Delta G^{\ddagger}_{253}$ 80 kJ mol^{-1} in 1-(1′-naphthalenyl)isoquinoline.[14] Hence, 1-(2′-diphenylphosphino-3′,6′-dimethoxyphenyl)-isoquinoline, an analogue of **3a**, undergoes ready atropisomerisation at room temperature.[15]

At the present juncture all of the axially chiral nitrogen heterocycles mentioned above have been obtained in enantiomerically enriched form through resolution involving either the separation of diastereoisomeric palladacycles in the cases of ligands **3a**, **3b**, **3c**, **4** and **5a**, or the separation of the diastereoisomeric camphorsulfonate esters of **5b**, or through separation by HPLC on a chiral stationary phase for **3d**.

As an extension of our work on the asymmetric synthesis of 1,1′-binaphthalenes through ligand coupling reactions of sulfoxides[16] we were interested in the synthesis of axially chiral nitrogen heterocycles. Oae and Furakawa and their co-workers have performed extensive studies on the reactions of Grignard reagents with aryl and heteroaryl sulfoxides.[17] Thus treatment of methyl 2-pyridyl sulfoxide with half a molar equivalent of phenylmagnesium bromide gave 2,2′-bipyridine (79%) and methyl phenyl sulfoxide (36%).[18] The reaction involves an initial ligand exchange to form methyl phenyl sulfoxide and 2-pyridylmagnesium bromide which then attacks the original sulfoxide forming a σ-sulfurane which then undergoes ligand coupling of the two 2-pyridyl groups generating 2,2′-bipyridine. On the other hand, when *tert*-butyl 2-pyridyl sulfoxide is treated with phenylmagnesium bromide the product is 2-phenylpyridine (85%), the result of direct ligand coupling. With ethyl and *iso*-propyl 2-pyridyl sulfoxides both 2,2′-bipyridine and 2-phenylpyridine are formed in proportions which reflect the steric bulk of the alkyl substituents. The bulkiness of the sulfoxide alkyl group influences the trajectory of attack by the Grignard reagent and thus whether the alkyl group adopts an equatorial or axial position in the intermediate σ-sulfuranes. In the case of the *tert*-butyl sulfoxide, attack by phenylmagnesium bromide occurs solely along a trajectory opposite the *tert*-butyl group, placing the *tert*-butyl and phenyl groups in axial positions, so that the phenyl group and equatorial 2-pyridyl group undergo ligand coupling; the ligand exchange reaction generating 2-pyridylmagnesium bromide is suppressed, since attack along this trajectory can be likened to an S_N2 reaction at a neopentyl centre. Furthermore, Furakawa and co-workers[19] have described the diastereoselective formation of an atropisomeric 1-naphthyl-2-pyridyl system by a ligand coupling reaction of a 2-pyridyl sulfoxide, containing a chiral 3-substituent, with a 1-naphthyl Grignard reagent. However, the origin of the diasteroselectivity of this reaction could be attributed to either the carbon-centred chirality of the 3-substituent or that of the sulfoxide.[16] We were thus encouraged to explore the reaction of enantiomerically enriched 1-(*tert*-butylsulfinyl)isoquinoline.[20] In the case of 1-(2′-diphenylphosphino-3′,6′-dimethoxyphenyl)isoquinoline[15] the X-ray structure of the $PdCl_2$ complex revealed a Pd–N bond 26° out of the isoquinoline ring plane, this distortion being required to accommodate the constraints of the chelate unit. Molecular modelling revealed that similar compounds having an additional methylene group within the chelating



Scheme 1. Reagents and conditions: (i) *m*-CPBA (1 equiv), CH_2Cl_2, 0 °C, 4 h; (ii) 3,4-dihydro-2*H*-pyran (1.5 equiv), pyridinium *p*-toluenesulfonate (0.1 equiv), CH_2Cl_2, rt, 20 h; (iii) Mg (1.05 equiv), THF, rt, 20 h; (iv) **10** (2.3 equiv), THF–benzene, 40–45 °C, 48 h; (v) pyridinium *p*-toluenesulfonate (0.6 equiv), ethanol, reflux, 4 h.

unit, hence seven-membered, would be free from distortion, and so might be expected to show differences in reactivity and stereoselectivity. Our initial experiments were thus directed towards establishing whether the reaction of the naphthyl Grignard reagent **10** (Scheme 1) with the sulfoxide *rac*-**7** would provide a useful route to the *N*,*O*-ligand **12**. Some of these results have been described in a preliminary communication.[21]

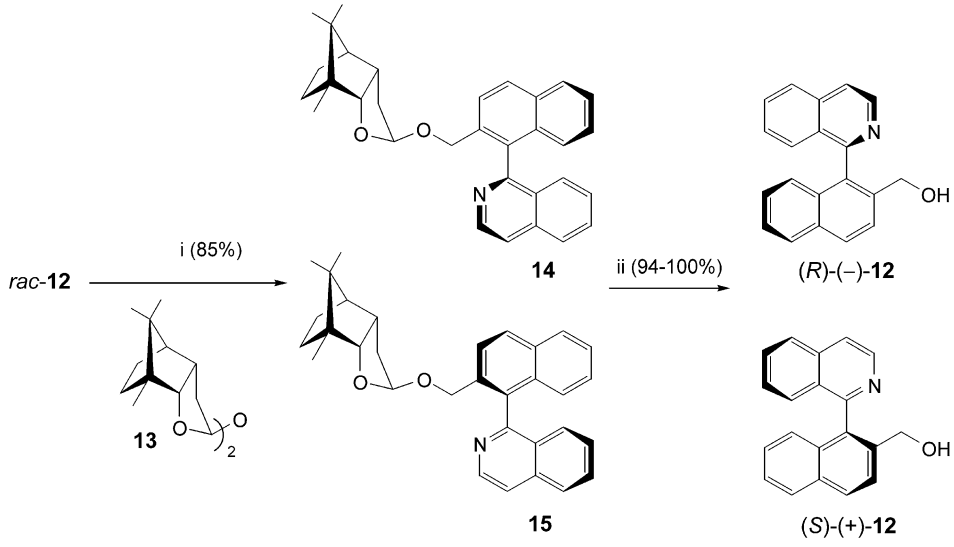
2. Results and discussion

Oxidation of 1-(*tert*-butylthio)isoquinoline **6** (prepared from 1-chloroisoquinoline and sodium *tert*-butylthiolate[22]) with *m*-chloroperbenzoic acid furnished *rac*-1-(*tert*-butylsulfinyl)isoquinoline *rac*-**7** in 85% yield. 1-Bromo-2-naphthalenemethanol **8** was protected as the tetrahydropyranyl ether **9** and the Grignard reagent **10** (ca. 2 mol equiv) was prepared in THF solution and allowed to react during 48 h at 40–45 °C with the sulfoxide *rac*-**7** in benzene–THF. The coupled product *rac*-**11** was isolated in 68% yield and on deprotection it afforded 1-(1′-isoquinolinyl)-2-naphthalenemethanol *rac*-**12** in 93% yield.

Attempts to resolve *rac*-**12** by fractional crystallisation of the 10-camphorsulfonate or the 3-bromocamphor-8-sulfonate salts were not successful nor could the *O*-methylmandelate or camphanate esters be separated by fractional crystallisation or chromatography. Resolution was finally achieved through the (+)-Noe-lactol derivatives (Scheme 2).[23] The resulting diastereoisomers were separated by radial chromatography. The earlier eluting fractions, of >99% de by HPLC analysis, consisted of diastereomer **14** isolated in 31% yield, based on the lactol-dimer **13**. Methanolysis provided (*R*)-(−)-**12** in >99% ee, estimated by ^{1}H NMR spectroscopy in the presence of (*S*)-(+)-2,2,2-trifluoro-1-(9-anthracenyl)ethanol [(*S*)-(+)-TFAE)], in quantitative yield. The *R*-absolute configuration was established by a single crystal X-ray diffraction structural determination on the *p*-bromobenzoate.[21] Later eluting fractions, isolated in 29% yield (based on **13**), largely consisted of the diastereomer **15**. HPLC analysis revealed that this material was contaminated by 1.5% of **14**. However, methanolysis of **15** gave (*S*)-(+)-**12** in 94% yield and with only 90% ee. Examination of the ^{1}H NMR spectrum of **15** revealed the presence of two additional diastereomers (each present in ca. 4%) which are presumably the β/*endo* anomers of **14** and **15**, which are chromatographically coincident with **15**. Since compound **15** was obtained as a gum, purification by crystallisation was not possible.

Heating the resolved ligand (*R*)-(−)-**12** in boiling benzene for 24 h did not result in any racemisation as shown by the ^{1}H NMR spectrum in the presence of the above-mentioned chiral shift reagent. Similarly, no racemisation was evident after heating in boiling toluene for a period of 6 d, and the compound underwent decomposition in boiling xylene. Thus, it was not possible to determine the barrier to atropisomerisation.

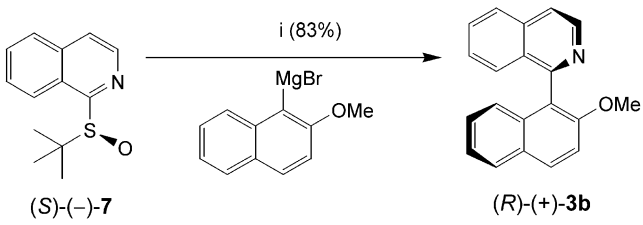
We now attempted the asymmetric synthesis of this ligand. When the ligand coupling reaction was repeated under exactly the same conditions except (*S*)-(−)-1-(*tert*-butylsulfinyl)isoquinoline **7**[20] of 62% ee was used as substrate, surprisingly the product obtained after deprotection was *rac*-**12**. This reaction was repeated for only 15 min at room temperature when the reaction was terminated by the addition of aqueous ammonium chloride. The sulfoxide **7** was recovered near quantitatively and proved to be completely racemic, accounting for the lack of asymmetric induction observed above. Sulfoxides have been shown to undergo disproportion and racemisation through rapid ligand exchange reactions on treatment with organolithium or Grignard reagents.[24] This mechanism for racemisation is very unlikely on account of the presence of the *tert*-butylsulfoxide (see above). A more likely explanation is provided by the work of Durst et al.[25] These authors have described the rapid racemisation of *tert*-butylsulfinylbenzene on treatment in THF solution at −78 °C with *tert*-butyllithium, which they propose may occur through reversible electron transfer between the organolithium and



Scheme 2. Reagents and conditions: (i) **13** (0.4 equiv), pyridinium *p*-toluenesulfonate (1.3 equiv), 3 Å molecular sieves, CH_2Cl_2, reflux, 16 h; (ii) pyridinium *p*-toluenesulfonate (1.5 equiv), methanol, 40 °C, 24 h.

the sulfoxide, with the intermediate sulfoxide radical anion having either an achiral geometry or being configurationally unstable.

We now sought to explore the reaction of the enantiomerically enriched sulfoxide **7** with 2-methoxy-1-naphthalenemagnesium bromide (Scheme 3). The effective van der Waals radius of the hydroxymethyl is estimated to be 1.82 Å whereas that for the methoxy group is 1.52 Å[26] so it was argued that this Grignard reagent would be less sterically hindered and, therefore, may undergo ligand coupling at a increased rate compared to the Grignard derived from the THP–ether **10**. In the event when (*S*)-(−)-1-(*tert*-butylsulfinyl)isoquinoline **7** of 62% ee was allowed to react with an excess of 2-methoxy-1-naphthalenemagnesium bromide at room temperature during 30 min the coupled product (*R*)-(+)-**3b** (Scheme 3) was isolated in 83% yield and its ee was shown to be 14% by ^{1}H NMR analysis in the presence of (*S*)-(+)-TFAE. When this experiment was repeated with only 0.5 mol equiv of the Grignard reagent the recovered sulfoxide was fully racemised; thus the low ee of coupled product is probably a consequence of competing rapid racemisation of sulfoxide **7**.



Scheme 3. Reagents and conditions: (i) 2-methoxy-1-naphthylmagnesium bromide (3.5 equiv), THF, rt, 30 min.

Recently, Cherlucci and co-workers[8] have resolved racemic **3b** by flash chromatography of diastereomeric palladacycles. An X-ray diffraction study on the laevorotatory atropomer of **3b** by use of the Bijvoet method allowed the assignment of the *R*-absolute configuration. Such determinations in the absence of heavy atoms are notoriously prone to error and there are examples of this recorded in the literature.[27] In order to confirm the absolute configuration of the enantiomerically enriched **3b** synthesised above, which was dextrorotatory in both chloroform and toluene solutions, we applied the exciton chirality method which is, like the Bijvoet method, a non-empirical method.[28] The requirements for exciton chirality to be manifest in CD spectra of atropomers are that the electron delocalisation between the two chromophores should be minimal and that the directions of the electric transition moments of these chromophores should be known. The magnitude ($\Sigma\Delta\varepsilon$) of the bisignate Cotton effect couplet should be significant (≥ 50) and the dihedral angle between the planes of the two chromophores should be $<110°$. The exciton chirality method was applied to the assignment of the absolute configuration of a number of naphthylisoquinoline alkaloid derivatives, namely *O*-methyldidehydroancistrocladine,[29] dideydroancistrocladisine and didehydroancistrocladidine.[30] The correctness of the assignments has been vindicated by X-ray and degradative studies. Similarly, the CD spectrum of the (*S*)-(+)-**12** (Fig. 1) is consistent with the X-ray structure determined by the *p*-bromobenzoate of (*R*)-(−)-**12**.[21] The X-ray crystal structure of the *p*-bromobenzoate of (*R*)-(−)-**12** showed that the dihedral angle between the two aromatic nuclei is 77° so that there is likely to be little electron delocalisation between the two chromophores for which the electron transition moments are directed along their long axes. The longer wavelength extremum ($\Delta\varepsilon+330$) is positive and the shorter extremum ($\Delta\varepsilon-200$) is negative, which indicates that the chirality of the long axes is positive so that the absolute configuration is *S* in keeping with the assignment based on the X-ray crystal structure. Similarly, the shape and extinction coefficients of the electronic spectrum of dextrorotatory atropomer of **3b**, λ_{max} 219, 227 nm, indicates that the molecule contains overlapping naphthalene and isoquinoline chromophores. The magnitude of the dihedral angles in the crystal structure (69°)[8] and the bisignate couplet (Fig. 1, $\Sigma\Delta\varepsilon=180$) indicate that the requirements for exciton chirality are met. The chirality of the long axes is negative so that the absolute configuration of dextrorotatory **3b** is *R*.

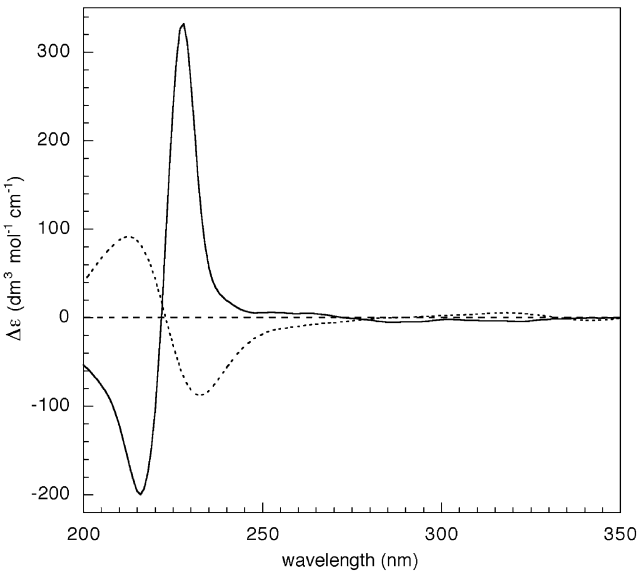


Figure 1. CD spectra (corrected to enantiomeric purity) of (*S*)-(+)-**12** (full line) and (*R*)-(+)-**3b** (dashed line).

A plausible rationalisation of the sense of asymmetric coupling is shown in Figure 2. The initial attack of

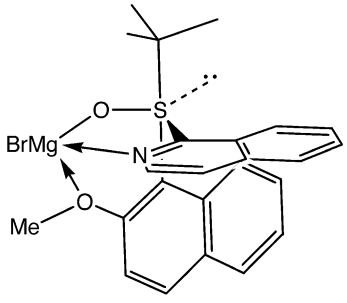
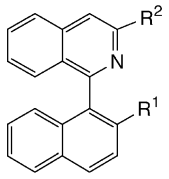


Figure 2. Proposed intermediate σ-sulfurane formed from reaction of 2-methoxy-1-naphthylmagnesium bromide with sulfoxide (*S*)-(−)-**7**.

2-methoxy-1-naphthalenemagnesium bromide on the sulfoxide (*S*)-(−)-**7** occurs axially from the side opposite the *tert*-butyl ligand thus avoiding non-bonding repulsions with the bulky *tert*-butyl group. The resultant σ-sulfurane thus has the oxy-magnesium bromide ligand in an equatorial position in which the magnesium is chelated with the methoxy oxygen in a six-membered ring. The nitrogen electron lone pair of the equatorial isoquinoline is thus able to form a five-membered chelate. These orientations then govern the stereochemical outcome of the coupling reaction.

The assignment of the signals in the ^{1}H NMR spectrum (500 MHz) of **3b** was assisted by the use of the COSY technique and differs from that of Brown and co-workers.[4] The spectrum exhibits an AB system with signals centred at δ_H 8.76 and 7.76 with $J_{3,4}=5.7$ Hz which is ascribed to the 3- and 4-protons on the isoquinoline ring, the signal at lower field being ascribed to the 3-proton on account of its proximity to nitrogen. Another AB system at δ_H 7.44 and 8.02 with $J_{3',4'}=9.1$ Hz was ascribed to the 3′- and 4′-protons on the naphthalene ring, that at lower field being the *peri*-proton. Application of the COSY technique allowed the assignment of the signal at δ_H 7.53 to the 8-proton since it is coupled ($J_{4,8}=0.7$ Hz) to the 4-proton through four bonds. Such a long-range coupling has been observed in the spectrum of isoquinoline.[31] A similar long-range coupling was exhibited between the 4′- and 8′-protons so that the latter is assigned to the signal at δ 7.05. These assignments for the 8- and 8′-*peri* protons are different to those made by Brown and co-workers. In isoquinoline the 8-proton (δ_H 7.92) is at lower field than the 5-proton (δ_H 7.78)[32] but in **3b** the situation is reversed. The shift of 8- and 8′-protons to higher field in **3b** can be ascribed to the conformation of the molecule which allows these protons to experience the shielding effect of the π-electrons of the neighbouring aromatic ring.

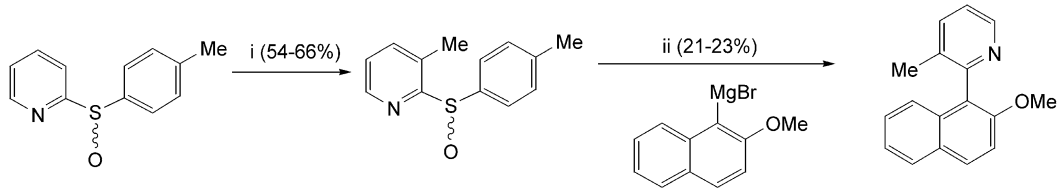
The rate of racemisation of **3b** in refluxing trichloroethene solution (87 °C) was determined through polarimetry, adopting the method of Meyers and Himmelsbach.[33] The rate constant was found to be $k=(7.0\pm1.4)\times10^{-5}$ s^{-1} at the 95% confidence level from least-squares analysis. This corresponds to a Gibbs energy of activation of $\Delta G^{\ddagger}_{360}=$ 117 kJ mol^{-1}. This value is similar to that determined for related compounds reported in the literature (**13** and **14**,[34] and **15**[35]).



13 R^1 = OH, R^2 = H; $\Delta G^{\ddagger}_{298}$ = 112 kJ mol^{-1}
14 R^1 = OH, R^2 = CH_2Br; $\Delta G^{\ddagger}_{298}$ = 119 kJ mol^{-1}
15 R^1 = OMe, R^2 = 2-pyridyl; $\Delta G^{\ddagger}_{357}$ = 113 kJ mol^{-1}

We now sought to explore the ligand coupling reactions of 2-pyridyl sulfoxides. An attempt to couple (*R*)-(+)-2-(*tert*-butylsulfinyl)-3-methylpyridine of 60% ee[20] with an excess of 2-methoxy-1-naphthalenemagnesium bromide in THF at room temperature during 5 h resulted in no coupled product, but the recovered sulfoxide did retain its optical activity, indicating that the 2-pyridyl sulfoxide does not undergo racemisation analogous to the isoquinoline sulfoxide **7**. The absence of coupling was unexpected since **7** had undergone coupling with the same Grignard reagent. It is unlikely, in view of this, that the lack of reactivity of the 2-pyridyl sulfoxide is steric in nature and may be attributed to partial bond fixation in the isoquinoline ring of sulfoxide **7** increasing its propensity to undergo ligand coupling. We next turned to 2-[(4′-methylphenyl)sulfinyl]-3-methylpyridine as a substrate. Both enantiomers of this compound were prepared by independent methylation of (*R*)-(−)- and (*S*)-(+)-2-[(4′-methylphenyl)sulfinyl]pyridine **16**[36] by sequential treatment with LDA and iodomethane at −78 °C in THF solution (Scheme 4). The enantiomeric purity of the products (*R*)-(+)-**17** (97% ee) and (*S*)-(−)-**17** (>99% ee) was established by HPLC on a chiral stationary phase. If the temperature during the methylation was allowed to rise above −78 °C some racemisation occurred.

Each of the sulfoxides (*R*)-(+)- and (*S*)-(−)-**17** was allowed to react with an excess of 2-methoxynaphthalenemagnesium bromide during 5 h in THF solution at room temperature (Scheme 4); the coupled products (−)-**18** (23%) and (+)-**18** (21%), respectively, were obtained as gums and their optical purity was established from their ^{1}H NMR spectra determined in the presence of the chiral shift reagent (*S*)-(+)-TFAE. The ee of (−)-**18** proved to be 53% and that of (+)-**18** proved to be 60%. The CD spectrum of (−)-**18** is shown in Figure 3. It appears to show an exciton



(*R*)-(−)-**16** (*R*)-(+)-**17** (97% ee) (−)-**18** (53% ee)

(*S*)-(+)-**16** (*S*)-(−)-**17** (>99% ee) (+)-**18** (60% ee)

Scheme 4. Reagents and conditions: (i) LDA (1.2 equiv), THF, −78 °C, 2 h; CH_3I (1.2 equiv), THF, −78 °C, 2 h; (ii) 2-methoxy-1-naphthylmagnesium bromide (3 equiv), THF, rt, 5 h.

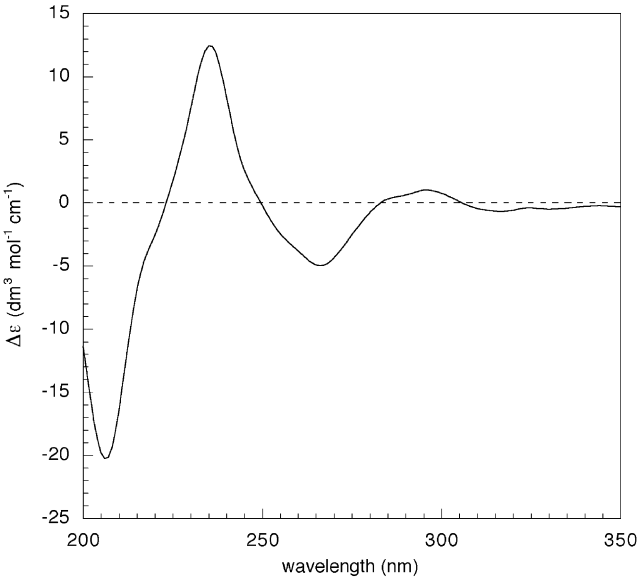


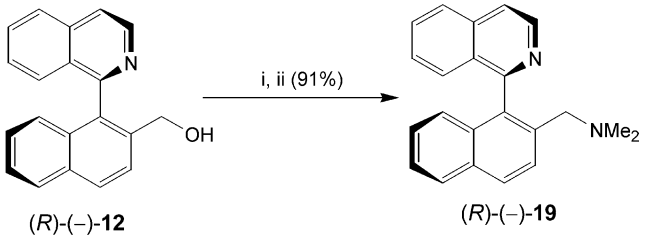
Figure 3. CD spectrum (corrected to enantiomeric purity) of (−)-**18**.

split couplet but the small value of $\Sigma\Delta\varepsilon$ (32.7) and the uncertainty of the direction of the electric transition moment of the relevant pyridine electronic transition preclude the assignment of the absolute configuration on this basis. In our previous work on the enantioselective synthesis of 1,1′-binaphthyls through sulfoxide ligand coupling reactions,[16] both *p*-tolyl and *tert*-butyl sulfoxides gave the same sense of asymmetric induction. Assuming this is also the case here, we have tentatively assigned the absolute configurations to (+)-**18** and (−)-**18** as *R* and *S*, respectively, based on the sense of asymmetric induction observed in the reaction of (*S*)-(−)-1-(*tert*-butylsulfinyl)isoquinoline **7**.

The rate of racemization of (+)-**18** was determined by heating a solution of the compound in d_8-toluene at 90 °C in the presence of the chiral shift reagent (*S*)-(+)-TFAE and monitoring the change in enantiomeric excess by ^{1}H NMR spectroscopy. After several half-lives the ratio of (−)-**18** and (+)-**18** was 50:50, confirming that the presence of the chiral shift reagent did not have a differential effect on the rates of atropisomerisation. The rate constant was found to be $k=(6.42\pm0.61)\times10^{-4}$ s^{-1} at the 95% confidence level from least-squares analysis. This corresponds to Gibbs energy of activation of $\Delta G^{\ddagger}_{363}=112$ kJ mol^{-1}.

We have performed some experiments on enantioselective catalysis using the ligand (*R*)-(−)-**12**. Thus, the addition of diethylzinc (1.2 mol equiv) to benzaldehyde[37] in toluene during 20 h at room temperature was catalysed by (*R*)-(−)-**12** (>98% ee, 0.05 mol equiv) and gave (*S*)-(−)-1-phenyl-1-propanol in 91% yield and 68% ee as estimated from its specific rotation.[38] The catalyst was recovered in quantitative yield without diminution of optical purity. The reaction displayed chiral amplification typical of amino alcohol-promoted alkylation with organozincs.[37] Thus performing the reaction with (*R*)-(−)-**6** of 53% ee, as estimated by the ^{1}H NMR spectrum determined in the presence of (*S*)-(+)-TFAE, gave (*S*)-(−)-1-phenyl-1-propanol of 53% ee.

We have also explored the conversion of the naphthalenemethanol ligand *rac*-**12** into the naphthalenemethanamine analogue *rac*-**19** (Scheme 5). This was accomplished in 85% overall yield by first chlorination with thionyl chloride and then displacement of chloride by dimethylamine. Repetition of this method with (*R*)-(−)-**12** (>98% ee) gave (*R*)-(−)-**19** as a crystalline solid in 91% yield and in >98% ee, as demonstrated by its ^{1}H NMR spectrum determined in the presence of (*S*)-(+)-TFAE. The ligand (*R*)-(−)-**19** proved to provide a reactive palladium catalyst in the allylic substitution[39] of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate in the presence of *N*,*O*-bis(trimethylsilyl)acetamide and potassium acetate.[40] When the reaction was carried out in acetonitrile at room temperature for 16 h in the presence of 0.06 mol equiv of (*R*)-(−)-**19** (>98% e.e) an 83% yield of methyl (3*S*,4*E*)-(−)-2-carbomethoxy-3,5-diphenylpent-4-enoate was obtained. The absolute configuration was based on its sign of rotation[41] and the ee was shown to be 19% by ^{1}H NMR analysis in the presence of Eu(hfc)$_3$. Whilst the ee in this reaction is modest, other applications of the ligands described in this paper are possible and the methodology may be adapted to provide further ligands of interest.



Scheme 5. Reagents and conditions: (i) thionyl chloride (excess), rt, 1 h; (ii) 27% aq $(CH_3)_2NH$ (excess), CH_2Cl_2, rt, 16 h.

3. Experimental

3.1. General

M.p.s were determined using a Kofler hot-stage apparatus and are uncorrected. All experiments involving the use of organometallic species were conducted under dry nitrogen or argon using the Schlenk technique. Anhydrous THF and toluene were distilled prior to use from sodium-benzophenone. Anhydrous dichloromethane (DCM) and acetonitrile were distilled prior to use from calcium hydride. Light petroleum was a hexane fraction. All organic extracts were dried over anhydrous sodium sulfate prior to evaporation under reduced pressure. Analytical TLC was carried out using Merck Kieselgel 60 PF_{254} precoated aluminium sheets visualised under UV light at 254 nm. Flash chromatography was performed on BDH silica gel (particle size 0.040–0.063 mm) and radial chromatography was performed on a Harrison Research Chromatotron by using plates coated with Merck Kieselgel 60 PF_{254}. ^{1}H and ^{13}C NMR spectra were obtained using either a Bruker AM300 (^{1}H, 300 MHz; ^{13}C, 75 MHz), Bruker AMX400 (^{1}H, 400 MHz; ^{13}C, 100 MHz) or Bruker ARX500 (^{1}H, 500 MHz; ^{13}C, 125 MHz) instrument, with *J*-values given in Hz. Mass spectra were recorded at 70 eV using either a Hewlett–Packard 5986 GC-MS instrument or a VG Autospec spectrometer. Optical rotations were measured

at ambient temperature on a Perkin–Elmer 141 polarimeter with a 10 cm microcell and are given in units of 10^{-1} deg cm^2 g^{-1}. Electronic spectra were determined using a GBC 918 UV/visible spectrophotometer. Circular dichroism (CD) spectra were recorded with a JASCO J-710 spectropolarimeter. Analytical HPLC was carried out using an ICI LC1500 solvent-delivery system and an ICI Kortec K95 variable-wavelength absorbance detector operating at 254 nm.

3.1.1. *rac*-1-(*tert*-Butylsulfinyl)isoquinoline *rac*-7. To a solution of 1-(*tert*-butylsulfanyl)isoquinoline **6**[22] (1.00 g, 4.6 mmol) in DCM (30 ml) at 0 °C was added *m*-chloroperbenzoic acid (0.85 g, 93% purity, 4.6 mmol) and the solution stirred for 4 h. The solution was diluted with DCM and washed in turn with saturated aq sodium hydrogen carbonate and water. Radial chromatography eluting with 1:1 ethyl acetate–DCM afforded the sulfoxide *rac*-**7** (0.91 g, 85%) as a pale yellow solid, mp 98 °C (dec) (lit.[20] mp 90–93 °C for (*S*)-**7** of 62% ee). The spectroscopic properties were identical to those previously reported for the optically enriched sulfoxide.[20]

3.1.2. *rac*-1-(1′-Isoquinolinyl)-2-naphthalenemethanol *rac*-12. A solution of 1-bromo-2-naphthalenemethanol **8**[42] (2.00 g, 8.4 mmol), 3,4-dihydro-2*H*-pyran (1.06 g, 12.7 mmol) and pyridinium *p*-toluenesulfonate (210 mg, 0.84 mmol) in dry DCM (15 ml) was stirred 20 h at rt under an atmosphere of nitrogen. The solution was diluted with DCM and washed with water. The oily crude product (2.71 g, 100%) was dried under high vacuum for several hours, then used directly in the next step.

A small portion (ca. 2 ml) of a solution of the THP–ether **9** prepared above in dry THF (15 ml) was added to stirred Mg turnings (215 mg, 8.8 mmol) together with a crystal of iodine under an atmosphere of argon. After initiation of the reaction (gentle warming may be required), the remainder of the solution was added dropwise at rt over 30 min. After stirring 20 h at rt the orange Grignard solution was added via cannula to a stirred solution of the sulfoxide *rac*-**7** (0.87 g, 3.7 mmol) in dry benzene (30 ml) under an atmosphere of argon. The reaction mixture was stirred at 40–45 °C for 48 h and then quenched by addition of 10% aq ammonium chloride solution. The mixture was diluted with DCM and the separated organic phase washed with water. Radial chromatography eluting with 10% ethyl acetate–DCM afforded the THP-protected coupled product *rac*-**11** (0.94 g, 68%) as a gum. A solution of this THP–ether *rac*-**11** and pyridinium *p*-toluenesulfonate (400 mg, 1.6 mmol) in ethanol (20 ml) was heated under reflux for 4 h. The reaction mixture was diluted with DCM and washed with water. Radial chromatography eluting with 30% ethyl acetate–DCM afforded the alcohol *rac*-**12** (674 mg, 93%) as a solid, mp 105–106 °C (from DCM–light petroleum) (found: C, 75.41; H, 4.83; N, 4.24. $C_{20}H_{15}NO$. 0.5 CH_2Cl_2 requires C, 75.11; H, 4.92; N, 4.27%); δ_H ($CDCl_3$, 500 MHz) 8.65 (1H, d, $J_{3',4'}=5.8$ Hz, 3′-H), 7.96 (1H, d, $J_{4,3}=8.4$ Hz, 4-H), 7.94 (1H, br d, $J_{5',6'}=8.3$ Hz, 5′-H), 7.91 (1H, br d, $J_{5,6}=8.2$ Hz, 5-H), 7.79 (1H, d, $J_{4',3'}=5.8$ Hz, 4′-H), 7.69 (1H, d, $J_{3,4}=8.4$ Hz, 3-H), 7.68 (1H, ddd, $J_{6',5'}=8.3$ Hz, $J_{6',7'}=5.8$ Hz, $J_{6',8'}=2.4$ Hz, 6′-H), 7.43 (1H, ddd, $J_{6,5}=8.2$ Hz, $J_{6,7}=6.9$ Hz, $J_{6,8}=1.1$ Hz, 6-H), 7.38–7.33 (2H, m, 8′- and 7′-H), 7.23 (1H, ddd, $J_{7,8}=8.5$ Hz, $J_{7,6}=6.9$ Hz, $J_{7,5}=1.2$ Hz, 7-H), 7.01 (1H, br d, $J_{8,7}=8.5$ Hz, 8-H), 5.28 (s, 0.5 equiv CH_2Cl_2), 4.32 and 4.26 (2H, AB, $J=12.4$ Hz, CH_2O) and 3.58 (1H, br s, OH); δ_C($CDCl_3$, 125 MHz) 159.4 (C), 142.1 (CH), 138.1, 136.3, 135.0, 132.8, 132.4 (each C), 130.7, 129.4 (each CH), 128.5 (C), 128.2 (CH), 127.7 (2×CH), 127.1, 127.0, 126.4, 126.1, 125.8, 120.9 (each CH), 63.7 (CH_2) and 53.4 (CH_2Cl_2); λ_{max}(MeCN)/nm 221 (ε/dm^3 mol^{-1} cm^{-1} 88,900) and 282 (10,300); *m*/*z* 285 (M^+, 75%), 284 (58), 268 (30), 267 (33), 266 (22), 256 (23), 254 (51), 253 (22), 130 (100), 129 (36) and 128 (36).

3.1.3. (*R*)-1-[2′-[[([2″*S*-(2″α,3a″α,4″α,7″α,7a″α)]-Octahydro-7″,8″,8″-trimethyl-4″,7″-methanobenzofuran-2″-yl)oxy]methyl]-1′-naphthalenyl]isoquinoline 14. A solution of the alcohol *rac*-**12** (1.00 g, 3.5 mmol), (+)-Noelactol dimer **13** (526 mg, 1.4 mmol) and pyridinium *p*-toluenesulfonate (1.14 g, 4.5 mmol) in dry DCM (15 ml) was heated under reflux in the presence of 3 Å molecular sieves (ca. 4 g) for 16 h. The reaction mixture was diluted with DCM, filtered to remove the sieves, and then washed with water. Flash chromatography eluting with 10% ethyl acetate–DCM provided recovered alcohol *rac*-**12** (268 mg) and the mixture of lactol derivatives **14** and **15** (1.10 g, 85%) as a gum. Radial chromatography eluting with 5% ethyl acetate–DCM substantially separated the epimeric lactol derivatives. The (*R*)-lactol derivative **14** (404 mg, 31%) was eluted first and obtained as a gum, $[\alpha]_D$ +6.5 (*c* 1.3, toluene), >99% de by ^{1}H NMR analysis (found: M^+ 463.2517. $C_{32}H_{33}NO_2$ requires M^+ 463.2511); δ_H($CDCl_3$, 500 MHz) 8.71 (1H, d, $J_{3,4}=5.7$ Hz, 3-H), 7.99 (1H, d, $J_{4',3'}=8.5$ Hz, 4′-H), 7.92 (1H, br d, $J_{5,6}=8.1$ Hz, 5-H), 7.91 (1H, br d, $J_{5',6'}=8.1$ Hz, 5′-H), 7.76 (1H, d, $J_{4,3}=5.7$ Hz, 4-H), 7.72 (1H, d, $J_{3',4'}=8.5$ Hz, 3′-H), 7.67 (1H, ddd, $J_{6,5}=8.1$ Hz, $J_{6,7}=6.8$ Hz, $J_{6,8}=1.2$ Hz, 6-H), 7.44–7.41 (2H, m, 8- and 6′-H), 7.36 (1H, ddd, $J_{7,8}=7.9$ Hz, $J_{7,6}=6.8$ Hz, $J_{7,5}=1.2$ Hz, 7-H), 7.24 (1H, ddd, $J_{7',8'}=8.5$ Hz, $J_{7',6'}=6.9$ Hz, $J_{7',5'}=1.2$ Hz, 7′-H), 7.03 (1H, br d, $J_{8',7'}=8.5$ Hz, 8′-H), 4.81 (1H, d, $J_{2'',\beta\text{-}3''}=5.0$ Hz, 2″-H), 4.58 and 4.18 (2H, AB, $J=12.0$ Hz, CH_2O), 4.03 (1H, dd, $J_{7a'',3a''}=9.4$ Hz, $J_{7a'',exo\text{-}6''}=1.3$ Hz, 7a″-H), 2.77–2.71 (1H, m, 3a″-H), 1.56–1.40 (4H, m, β-3″-, 4″-, *exo*-5″- and *exo*-6″-H), 1.29 (1H, dd, $J_{\alpha\text{-}3'',\beta\text{-}3''}=13.5$ Hz, $J_{\alpha\text{-}3'',3a''}=10.0$ Hz, α-3″-H), 1.23–1.18 and 1.08–1.01 (each 1H, m, *endo*-5″- and *endo*-6″-H), 0.92, 0.86 and 0.75 (each 3H, CH_3); δ_C($CDCl_3$, 125 MHz) 159.6 (C), 142.5 (CH), 136.1, 135.2, 134.8, 133.0, 132.6 (each C), 130.3 (CH), 128.7 (C and CH), 127.9, 127.6, 127.2, 126.7, 126.5, 126.3, 126.0, 125.7, 120.2, 108.2, 89.3 (each CH), 67.0 (CH_2), 52.4, 48.5 (each C), 47.3, 39.9 (each CH), 31.9, 26.4 (each CH_2), 20.8 (CH_3), 20.3 (CH_2), 18.7 and 14.6 (each CH_3); *m*/*z* 463 (M^+, 1.4%), 435 (3.4), 286 (14), 285 (41), 284 (100), 270 (26), 269 (66), 268 (80), 267 (41), 266 (28), 265 (22) and 254 (16).

3.1.4. (*S*)-1-[2′-[[([2″*S*-(2″α,3a″α,4″α,7″α,7a″α)]-Octahydro-7″,8″,8″-trimethyl-4″,7″-methanobenzofuran-2″-yl}oxy]methyl]-1′-naphthalenyl]isoquinoline 15. Later eluting fractions from radial chromatography of the foregoing mixture of lactol derivatives were enriched in the (*S*)-lactol derivative **15**, isolated as a gum (377 mg, 29%). This material by ^{1}H NMR analysis was contaminated by 1% of the (*R*)-derivative (δ_H 4.58 and 4.18 [AB,

J=12.0 Hz, CH_2O]), and by two other diasteroisomers (δ_H 4.79 and 4.16 [AB, J=11.9 Hz, CH_2O], and δ_H 4.59 and 4.32 [AB, J=12.5 Hz, CH_2O]), each present in 4% (found: M^+ 463.2516. $C_{32}H_{33}NO_2$ requires M^+ 463.2511); δ_H (major diastereoisomer, $CDCl_3$, 500 MHz) 8.71 (1H, d, $J_{3,4}$=5.8 Hz, 3-H), 8.00 (1H, d, $J_{4',3'}$=8.5 Hz, 4′-H), 7.92 (1H, br d, $J_{5,6}$=8.2 Hz, 5-H), 7.91 (1H, br d, $J_{5',6'}$=8.2 Hz, 5′-H), 7.76 (1H, dd, $J_{4,3}$=5.8 Hz, $J_{4,8}$=0.6 Hz, 4-H), 7.74 (1H, d, $J_{3',4'}$=8.5 Hz, 3′-H), 7.66 (1H, ddd, $J_{6,5}$=8.2 Hz, $J_{6,7}$=6.8 Hz, $J_{6,8}$=1.2 Hz, 6-H), 7.44–7.41 (2H, m, 8- and 6′-H), 7.35 (1H, ddd, $J_{7,8}$=7.9 Hz, $J_{7,6}$=6.8 Hz, $J_{7,5}$=1.2 Hz, 7-H), 7.23 (1H, ddd, $J_{7',8'}$=8.5 Hz, $J_{7',6'}$=6.9 Hz, $J_{7',5'}$=1.2 Hz, 7′-H), 6.99 (1H, dd, $J_{8',7'}$=8.5 Hz, $J_{8',6'}$=0.8 Hz, 8′-H), 5.14 (1H, d, $J_{2'',\beta\text{-}3''}$=5.1 Hz, 2″-H), 4.48 and 4.25 (2H, AB, J=11.7 Hz, CH_2O), 3.47 (1H, dd, $J_{7a'',3a''}$=9.5 Hz, $J_{7a'',exo\text{-}6''}$=1.6 Hz, 7a″-H), 2.57–2.51 (1H, m, 3a″-H), 1.70 (1H, ddd, $J_{\beta\text{-}3'',\alpha\text{-}3''}$=13.5 Hz, $J_{\beta\text{-}3'',3a''}$=6.8 Hz, $J_{\beta\text{-}3'',2''}$=5.1 Hz, β-3″-H), 1.55–1.39 (4H, m, α-3″-, 4″-, *exo*-5″- and *exo*-6″-H), 1.27–1.21 and 1.07–1.00 (each 1H, m, *endo*-5″- and *endo*-6″-H), 0.83, 0.79 and 0.64 (each 3H, CH_3); δ_C (major diastereoisomer, $CDCl_3$, 125 MHz) 159.5 (C), 142.6 (CH), 136.1, 135.1, 134.7, 133.0, 132.6 (each C), 130.3 (CH), 128.9 (C), 128.8, 127.9, 127.7, 127.1 (each CH), 126.8 (2×CH), 126.3, 126.0, 125.7, 120.2, 108.1, 89.1 (each CH), 66.8 (CH_2), 52.3, 48.4 (each C), 47.3, 39.9 (each CH), 32.2, 26.3 (each CH_2), 20.8 (CH_3), 20.3 (CH_2), 18.7 and 14.5 (each CH_3); *m*/*z* 463 (M^+, 1.3%), 435 (2.8), 286 (8.1), 285 (49), 284 (100), 270 (7), 269 (36), 268 (73), 267 (45), 266 (23), 265 (14) and 254 (9.0).

3.1.5. (*R*)-(−)-1-(1′-Isoquinolinyl)-2-naphthalenemethanol (*R*)-(−)-12. The (*R*)-lactol derivative **14** (250 mg, 0.54 mmol) and pyridinium *p*-toluenesulfonate (200 mg, 0.8 mmol) were dissolved in methanol (15 ml) and the solution stirred at 40 °C under an argon atmosphere for 24 h. The mixture was diluted with DCM and washed with water. Radial chromatography eluting with 40% ethyl acetate–DCM afforded the alcohol (*R*)-(−)-**12** (155 mg, 100%) as a solid, mp 100–102 °C, $[\alpha]_D$ −325 (*c* 1.44, $CHCl_3$). The ee was shown to be >98% by ^{1}H NMR analysis in the presence of (*S*)-(+)-TFAE (ca. 0.6 equiv, ca. 40 mmol dm^{-3}); δ_H($CDCl_3$, 300 MHz) 8.55 and 8.65 (each d, J=5.8 Hz) for the isoquinoline 3-H of the (*S*)- and (*R*)-enantiomers, respectively.

3.1.6. (*S*)-(+)-1-(1′-Isoquinolinyl)-2-naphthalenemethanol (*S*)-(+)-12. The (*S*)-lactol derivative **15** (250 mg, 0.54 mmol) was converted to (*S*)-(+)-**12** using the same procedure described for the preparation of (*R*)-(−)-**12**. Radial chromatography eluting with 40% ethyl acetate–DCM afforded the alcohol (*S*)-(+)-**12** (145 mg, 94%) as a gum, $[\alpha]_D$+290 (*c* 1.67, $CHCl_3$). The ee was shown to be 90% by ^{1}H NMR analysis in the presence of (*S*)-(+)-TFAE. CD (MeCN, ee corrected) λ/nm 216 (Δε/dm^3 mol^{-1} cm^{-1} −200) and 228 (+330).

3.1.7. (*R*)-(+)-1-(2′-Methoxy-1′-naphthyl)isoquinoline (*R*)-(+)-3b. A mixture of 1-bromo-2-methoxynaphthalene (1.0 g, 4.2 mmol) and magnesium (120 mg, 5.1 mmol) in dry THF (30 ml) was stirred at 40 °C and 1,2-dibromoethane (320 mg, 1.7 mmol) was added to initiate the reaction. The reaction mixture was then heated under reflux for 2 h and then stirred at 40 °C for 12 h. The molarity was determined by back titration (0.28 mol dm^{-3}). A portion of the foregoing Grignard solution (8.5 ml, 2.4 mmol) was added dropwise to a solution of (*S*)-(−)-1-(*tert*-butylsulfinyl)isoquinoline (*S*)-(−)-**7**[20] (158 mg, 0.68 mmol, 62% ee) in dry THF (10 ml) over a period of 5 min at room temperature under Ar. The reaction mixture was stirred for 30 min and next quenched by the addition of 10% aq ammonium chloride solution. The mixture was then diluted with DCM and washed with water. Radial chromatography eluting with 20% ethyl acetate–hexane gave the isoquinoline (*R*)-(+)-**3b** (160 mg, 83%) as a solid, mp 125–126 °C (lit.[4] mp 130–133 °C for racemic material), $[\alpha]_D$ +29.7 (*c* 0.585, toluene). The ee was shown to be 14% by ^{1}H NMR analysis in the presence of (*S*)-(+)-TFAE (ca. 0.8 equiv, ca. 50 mmol dm^{-3}); δ_H($CDCl_3$, 300 MHz) 3.72 and 3.67 (each s) for the CH_3O signal of the (*S*)- and (*R*)-enantiomer, respectively. δ_H($CDCl_3$, 500 MHz) 8.76 (1H, d, $J_{3,4}$=5.7 Hz, 3-H), 8.02 (1H, br d, $J_{4',3'}$=9.1 Hz, 4′-H), 7.92 (1H, br d, J=8.3 Hz, 5-H), 7.82 (1H, br d, $J_{5',6'}$=8.2 Hz, 5′-H), 7.76 (1H, dd, $J_{4,3}$=5.7 Hz, $J_{4,8}$=0.7 Hz, 4-H), 7.66 (1H, ddd, $J_{6,5}$=8.2 Hz, $J_{6,7}$=6.8 Hz, $J_{6,8}$=1.2 Hz, 6-H), 7.53 (1H, br d, $J_{8,7}$=8.4 Hz, 8-H), 7.44 (1H, d, $J_{3',4'}$=9.1 Hz, 3′-H), 7.39 (1H, ddd, $J_{7,8}$=8.4 Hz, $J_{7,6}$=6.8 Hz, $J_{7,5}$=1.1 Hz, 7-H), 7.33 (1H, ddd, $J_{6',5'}$=8.2 Hz, $J_{6',7'}$=6.8 Hz, $J_{6',8'}$=1.2 Hz, 6′-H), 7.25 (1H, ddd, $J_{7',8'}$=8.2 Hz, $J_{7',6'}$=6.8 Hz, $J_{7',5'}$=1.3 Hz, 7′-H), 7.05 (1H, br d, $J_{8',7'}$=8.2 Hz, 8′-H) and 3.77 (3H, s, OCH_3); δ_C($CDCl_3$, 125.8 MHz) 56.5 (OCH_3), 113.3 (C-3′), 120.1 (C-4), 121.6 (C-1′), 123.6 (C-6′), 124.7 (C-8′), 126.7 (C-7′), 126.8 (C-5), 127.1 (C-7), 127.4 (C-8), 127.8 (C-5′), 128.7 (C-8a), 128.9 (C-4′a), 130.1 (C-4), 130.4 (C-4′), 133.7 (C-8′a), 136.2 (C-4a), 142.4 (C-3), 154.7 (C-2′), 158.0 (C-1); CD (MeCN, ee corrected) λ/nm 213 (Δε/dm^3 mol^{-1} cm^{-1} +92) and 232 (−88); λ_{max}(MeCN)/nm 219 (ε/dm^3 mol^{-1} cm^{-1} 94,000), 227 sh (84,000), 279 (7300) and 322 (3400); *m*/*z* 285 (M^+, 77%), 284 (100), 270 (17), 269 (42), 268 (12), 254 (16), 241 (21), 240 (18), 171 (20), 149 (26), 135 (11), 127 (18), 120 (20), 73 (12) and 69 (13).

3.2. Kinetics of racemisation of (*R*)-(+)-3b

A sample of (*R*)-(+)-**3b** (10 mg) was dissolved in trichloroethene (10 ml) and was heated under an argon atmosphere at reflux (87 °C). The specific rotation was monitored every 30 min by first immersing the reaction vessel in an ice bath. The solvent was then removed under reduced pressure and the sample was redissolved quantitatively in trichloroethene and the optical activity measured. The sample solution was then transferred quantitatively to the flask and reflux resumed. The time involved in this operation was not counted in the reaction time. This procedure was carried out until the rotation remained constant for 5 measurements and the data were then fitted to the expression: $2kt=\ln[(\alpha_0-\alpha_\infty)/(\alpha_t-\alpha_\infty)]$, where k is the first-order rate constant, t is the time, and α_0, α_t, and α_∞ are the optical rotations at the kinetic zero, time t, and after 10 half lives, respectively.

3.3. (*R*)-(+)-2-[(4′-Methylphenyl)sulfinyl]-3-methylpyridine (*R*)-(+)-17

Butyllithium (1.81 mol dm^{-3} in hexane, 2.1 ml, 3.8 mmol) was added at 0 °C to a stirred solution of diisopropylamine

(0.58 ml, 4.2 mmol) in dry THF (5 ml). After 15 min the solution was added dropwise to a solution of (*R*)-(−)-2-[(4′-methylphenyl)sulfinyl]pyridine, (*R*)-(−)-**16**[36] (640 mg, 3.18 mmol), in dry THF (15 ml) at −78 °C under argon and the reaction mixture stirred for 2 h. Methyl iodide (0.24 ml, 3.8 mmol) was added and stirring was continued for 2 h at −78 °C. Water was then added, and the mixture then diluted with DCM and the organic phase washed with water. Radial chromatography eluting with 30% ethyl acetate–hexane gave the sulfoxide (*R*)-(+)-**17** (450 mg, 66%) as needles, mp 74 °C, $[\alpha]_D$ +58 (*c* 0.5, $CHCl_3$). The ee was shown to be 97% by chiral HPLC analysis [25 cm× 4.6 mm ID covalent (*R*)-(−)-*N*-(3,5-dinitrobenzoyl)phenylglycine Pirkle column (E.S. industries), eluting with 30% isopropanol–hexane at 1.0 ml min^{-1}]; t_R = 23.0 and 24.2 min for the (*S*)- and (*R*)-enantiomers of **17**, respectively, (found: M^+ 231.0726. $C_{13}H_{13}NO^{32}S$ requires M^+ 231.0719); δ_H ($CDCl_3$, 500 MHz) 8.56 (1H, br d, $J_{6,5}$ = 4.2 Hz, 6-H), 7.59 and 7.23 (4H, AA'BB′, 2′-, 3′-, 5′- and 6′-H), 7.48 (1H, ddq, $J_{4,5}$ = 7.7 Hz, $J_{4,6}$ = 1.6 Hz, $J_{4,Me}$ = 0.7 Hz, 4-H), 7.26 (1H, dd, $J_{5,4}$ = 7.7 Hz, $J_{5,6}$ = 4.2 Hz, 5-H), 2.43 (3H, s, 3-CH_3) and 2.34 (3H, s, 4′-CH_3); δ_C ($CDCl_3$, 125 MHz) 160.7 (2-C), 147.7 (6-C), 141.6 (1′-C), 140.1 (4-C), 139.7 (4′-C), 129.9 (2′- and 6′-C), 125.6 (3-C), 125.4 (3′- and 5′-C), 125.2 (5-C), 21.3 (4′-CH_3), 16.7 (3-CH_3); *m*/*z* 231 (M^+, 13%), 220 (19), 215 (30), 214 (100), 205 (73), 167 (31), 149 (89), 123 (20), 112 (30).

3.4. (*S*)-(−)-2-[(4′-Methylphenyl)sulfinyl]-3-methylpyridine (*S*)-(−)-17

When the above procedure was applied to (*R*)-(+)-2-[(4′-methylphenyl)sulfinyl]pyridine, (*S*)-(+)-**16**[36] (400 mg, 3.18 mmol), the sulfoxide (*S*)-(−)-**17** (230 mg, 54%) was obtained, mp 77 °C, $[\alpha]_D$ −64 (*c* 1.0, $CHCl_3$). The ee was shown to be >99% by chiral HPLC analysis.

3.5. (−)-2-(2′-Methoxy-1′-naphthyl)-3-methylpyridine (−)-18

A THF solution of 2-methoxy-1-naphthylmagnesium bromide (19 ml of 0.28 mol dm^{-3}, 5.3 mmol) was added dropwise to a solution of (*R*)-(+)-**17** (410 mg, 1.77 mmol, 97% ee) in dry THF (10 ml) over a period of 5 min at room temperature under argon. The reaction mixture was stirred for 5 h and next quenched by the addition of 10% aq ammonium chloride solution. The mixture was diluted with DCM and the organic phase washed with water. Radial chromatography eluting with 30% ethyl acetate–hexane afforded the pyridine (−)-**18** as a gum (101 mg, 23%), $[\alpha]_D$ −43 (*c* 1.0, $CHCl_3$). The ee was shown to be 53% by ^1H NMR analysis in the presence of (*S*)-(+)-TFAE (ca. 1.8 equiv, ca. 0.3 mol dm^{-3}); δ_H (d_8-toluene, 500 MHz) 3.27 and 3.13 (each s) for the CH_3O signal of the (−)- and (+)-enantiomer, respectively, (found: M^+ 249.1148. $C_{17}H_{15}NO$ requires 249.1154); δ_H ($CDCl_3$, 500 MHz) 8.62 (1H, dd, $J_{6,5}$ = 4.9 Hz, $J_{6,4}$ = 1.7 Hz, 6-H), 7.93 (1H, br d, $J_{4',3'}$ = 9.1 Hz, 4′-H), 7.85–7.81 (1H, m, 5′-H), 7.71 (1H, ddq, $J_{4,5}$ = 7.7 Hz, $J_{4,6}$ = 1.7 Hz, $J_{4,Me}$ = 0.8 Hz, 4-H), 7.37 (1H, d, $J_{3',4'}$ = 9.1 Hz, 3′-H), 7.35–7.31 (2H, m, 6′- and 7′-H), 7.31 (1H, dd, $J_{5,4}$ = 7.7 Hz, $J_{5,6}$ = 4.9 Hz, 5-H), 7.12–7.08 (1H, m, 8′-H), 3.85 (3H, s, OCH_3) and 2.05 (3H, br s, 3-CH_3); δ_C($CDCl_3$, 75 MHz) 155.5 (2-C), 153.8 (2′-C), 146.8 (6-C), 137.8 (4-C), 134.0, 132.9 and 130.0 (each C), 129.0, 127.9, 126.7, 124.2 and 123.5 (each CH), 122.7 (1′-C), 122.4 (CH), 113.2 (3′-C), 56.5 (OCH_3) and 18.6 (3-CH_3); CD (MeCN, ee corrected) λ/nm 206 ($\Delta\varepsilon$/dm^3 mol^{-1} cm^{-1} −20.3), 235 (+12.4), 267 (−5.0) and 296 (+1.0); λ_{max}(MeCN)/nm 229 (ε/dm^3 mol^{-1} cm^{-1} 49,300), 281 (5700) and 335 (2600); *m*/*z* 249 (M^+, 61%), 248 (71), 234 (49), 233 (28), 220 (26), 205 (85), 167 (31), 149 (100) and 112 (28).

3.6. (+)-2-(2′-Methoxy-1′-naphthyl)-3-methylpyridine (+)-18

When the above procedure was applied to (*S*)-(−)-**17** (200 mg, 0.87 mmol, >99% ee), the pyridine (+)-**18** (46 mg, 21%) was obtained as a gum, $[\alpha]_D$ +47.8 (*c* 2.2, $CHCl_3$). The ee was shown to be 60% by ^1H NMR analysis in the presence of (*S*)-(+)-TFAE.

3.7. Kinetic of racemisation of (+)-18

The pyridine (+)-**18** (20 mg) was dissolved in d_8-toluene (0.5 ml) together with (*S*)-(+)-TFAE (40 mg) and the ^1H NMR spectrum (500 MHz) acquired at 363 K (measured using the chemical shift dependence of ethylene glycol) at intervals ranging from 4 to 15 min. The enantiomeric excess was determined through integration of the OCH_3 signals at δ_H 3.27 and 3.13 for the (−)- and (+)-enantiomer, respectively. The spectrum acquired after 2 h showed a 50:50 mixture of the two enantiomers. The data was fitted to the expression: $2kt = \ln[ee_0/ee_t]$, where k is the first-order rate constant, t is the time, and ee_0 and ee_t are the enantiomeric excesses determined at the kinetic zero and time t, respectively.

3.7.1. (*S*)-(−)-1-Phenyl-1-propanol. The alcohol (*R*)-(−)-**12** (>98% ee, 28 mg, 98 μmol) was dissolved in dry toluene (5 ml) under an argon atmosphere and benzaldehyde (200 mm^3, 2.0 mmol) was then added, followed by diethylzinc (1.15 ml of a 2.1 mol dm^{-3} solution in toluene, 2.4 mmol). The mixture was stirred at rt for 20 h and then quenched by addition of 10% aq ammonium chloride solution. The mixture was then diluted with DCM and the organic phase washed with water. Radial chromatography eluting with 5% ethyl acetate–DCM afforded (*S*)-(−)-1-phenyl-1-propanol (245 mg, 91%) as an oil, $[\alpha]_D$ −32.9 (*c* 5.72, $CHCl_3$) (lit.[38] $[\alpha]_D$ −47.6 (*c* 6.11, $CHCl_3$) for the (*S*)-enantiomer of 98% ee). The ^1H NMR spectrum of this material was identical to that of an authentic sample. Further elution with 40% ethyl acetate–DCM afforded recovered (*R*)-(−)-**12** (>98% ee by ^1H NMR analysis, 28 mg, 100%).

Repetition of this reaction using a mixture of (*R*)-(−)-**12** (>98% ee, 15 mg, 53 μmol) and *rac*-**12** (15 mg, 53 μmol) as the catalyst afforded (*S*)-(−)-1-phenyl-1-propanol (256 mg, 95%) as an oil, $[\alpha]_D$ −25.5 (*c* 6.54, $CHCl_3$) and recovered (*R*)-(−)-**12** (53% ee by ^1H NMR analysis, 30 mg, 100%).

3.7.2. *rac*-*N*,*N*-Dimethyl-1-(1′-isoquinolinyl)-2-naphthalenemethanamine *rac*-19. The alcohol *rac*-**12** (300 mg, 1.05 mmol) was added to thionyl chloride (3 ml, 41 mmol) and the mixture stirred at rt for 1 h. The reaction mixture

was diluted with dry toluene (15 ml) and the excess thionyl chloride and toluene evaporated under reduced pressure. The residue was dissolved in DCM (15 ml), aqueous dimethylamine solution (6 ml, 27%) was added, and the mixture was stirred vigorously at room temperature for 16 h. The reaction mixture was diluted with DCM and the organic phase washed with water. Flash chromatography eluting with 5% methanol–DCM, followed by crystallisation from DCM–light petroleum, afforded the amine *rac*-**19** (285 mg, 85%) as prisms, mp 101–102 °C (found: C, 84.43; H, 6.54; N, 9.00. $C_{22}H_{20}N_2$ requires C, 84.64; H, 6.41; N, 8.97%); δ_H ($CDCl_3$, 400 MHz) 8.71 (1H, d, $J_{3',4'}=5.8$ Hz, 3′-H), 7.98 (1H, d, $J_{4,3}=8.6$ Hz, 4-H), 7.94 (1H, br d, $J_{5',6'}=8.3$ Hz, 5′-H), 7.90 (1H, br d, $J_{5,6}=8.3$ Hz, 5-H), 7.86 (1H, d, $J_{3,4}=8.6$ Hz, 3-H), 7.77 (1H, d, $J_{4',3'}=5.8$ Hz, 4′-H), 7.68 (1H, ddd, $J_{6',5'}=8.3$ Hz, $J_{6',7'}=5.2$ Hz, $J_{6',8'}=2.8$ Hz, 6′-H), 7.41 (1H, ddd, $J_{6,5}=8.3$ Hz, $J_{6,7}=6.8$ Hz, $J_{6,8}=1.2$ Hz, 6-H), 7.39–7.34 (2H, m, 8′- and 7′-H), 7.22 (1H, ddd, $J_{7,8}=8.4$ Hz, $J_{7,6}=6.8$ Hz, $J_{7,5}=1.2$ Hz, 7-H), 6.97 (1H, br d, $J_{8,7}=8.4$ Hz, 8-H), 3.20 and 3.12 (2H, AB, $J=13.6$ Hz, CH_2N) and 2.04 (6H, s, $N[CH_3]_2$); δ_C ($CDCl_3$, 100 MHz) 160.0 (C), 142.5 (CH), 136.1, 135.8, 135.1, 132.72, 132.68 (each C), 130.3 (CH), 128.8 (C), 128.7, 127.9, 127.33, 127.31, 126.9, 126.8, 126.2, 126.0, 125.5, 120.1 (each CH), 61.2 (CH_2) and 45.5 ($2\times CH_3$); *m/z* 312 (M^+, 19%), 297 (10), 269 (41), 268 (100), 267 (33), 266 (16) and 265 (11).

3.7.3. (*R*)-(−)-*N*,*N*-Dimethyl-1-(1′-isoquinolinyl)-2-naphthalenemethanamine (*R*)-(−)-19. The alcohol (*R*)-(−)-**12** (>98% ee, 149 mg, 0.52 mmol) was converted to the amine (*R*)-(−)-**19** using the same procedure described for the preparation of *rac*-**10**. Flash chromatography eluting with 5% methanol–DCM afforded the amine (*R*)-(−)-**19** (148 mg, 91%) as a solid, mp 78–80 °C, $[\alpha]_D$ −38.1 (*c* 1.1, toluene). The ee was shown to be >98% by ^{1}H NMR analysis in the presence of (*S*)-(+)-TFAE (ca. 1 equiv, ca. 70 mmol dm^{-3}); δ_H (C_6D_6, 400 MHz) 7.88 and 7.73 (each d, $J=5.8$ Hz) for the isoquinoline 3′-H of the (*R*)- and (*S*)-enantiomers, respectively.

3.7.4. Methyl (3*S*,4*E*)-(−)-2-carbomethoxy-3,5-diphenylpent-4-enoate. Under an atmosphere of argon di-μ-chloro-bis(π-allyl)dipalladium (6.4 mg, 20 μmol) was added to a solution of the ligand (*R*)-(−)-**19** (15 mg, 48 μmol) in dry degassed acetonitrile (2 ml). After stirring 15 min at rt, potassium acetate (8 mg, 82 μmol), dimethyl malonate (160 mm^3, 185 mg, 1.4 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (245 mm^3, 200 mg, 1.0 mmol) and (*E*)-1,3-diphenylallyl acetate (245 mm^3, 210 mg, 0.83 mmol) were added and the mixture was stirred at rt for 16 h. The mixture was then diluted with DCM and the organic phase washed with water. Flash chromatography eluting with 2:48:50 ethyl acetate–DCM–light petroleum afforded methyl (3*S*,4*E*)-(−)-2-carbomethoxy-3,5-diphenylpent-4-enoate (225 mg, 83%) as an oil, $[\alpha]_D$ −3.7 (*c* 1.8, ethanol) (lit.[41] $[\alpha]_D$ −18.4 (*c* 1.1, ethanol) for the (*S*)-enantiomer of 99% ee). The ^{1}H NMR spectrum of this material was in accord with that reported in the literature.[43] The ee was shown to be 19% by ^{1}H NMR analysis in the presence of $Eu(hfc)_3$ (ca. 0.35 equiv, ca. 40 mmol dm^{-3}); δ_H($CDCl_3$, 400 MHz) 3.87 and 3.85 (each s) for the lower field CO_2CH_3 signals of the (*R*)- and (*S*)-enantiomers, respectively.

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Silver acetate-catalysed asymmetric 1,3-dipolar cycloadditions of imines and chiral acrylamides

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Abstract—*N*-Metallated azomethine ylides were generated by the reaction of arylidene glycine imines with AgOAc and triethylamine. These azomethine ylides undergo cycloaddition to chiral acrylamides with excellent diastereoselectivity. The configuration of two of the cycloadducts was confirmed by X-ray crystallography.

1. Introduction

1,3-Dipolar cycloadditions are very important tools for the construction of five membered heterocycles.[1] The ease of generation of 1,3-dipoles, coupled with the highly regio-, and stereoselective nature of their cycloaddition reactions, has resulted in a number of syntheses which utilize such a reaction as a key step.[2] One of the major challenges now for 1,3-dipolar cycloadditions is the preparation of optically active compounds.[3]

The proline structure is present in many compounds with interesting biological features. The most direct strategy for the synthesis of functionalized proline derivatives is the 1,3-dipolar cycloaddition reaction of in situ generated carboxy-stabilized azomethine ylide and a dipolarophile. The asymmetric version of this reaction allows the synthesis of enantiomerically enriched prolines with the simultaneous creation of up to four stereochemically defined centers. Chiral acrylate esters and amides, have been widely evaluated as chirality sources in asymmetric Diels–Alder reactions.[4] In contrast fewer examples of chiral inductions in the 1,3-dipolar cycloadditions of azomethine ylides have been reported. To date, most attention has been devoted to the use of chiral esters (mainly menthyl-esters,[5] or those with a chiral controller at the β-position[6]), chiral α,β-unsaturated ketones,[7] and bicyclic lactams,[8] with use of *N*-acryloyl-(*S*)-proline esters as the only chiral alkenes.[9] Thus, the wide range of easily available and cheap chiral amines[10] and amino acids still remained unexplored as chiral auxiliaries in cycloadditions reactions. In this paper[11] we demonstrate the utilization of these chiral elements in the 1,3-dipolar cycloadditions of azomethine ylides to acrylamides.

2. Results and discussion

Starting from the corresponding amines,[12] acrylamides **2a**,[13] **2b**,[14] **2c**,[15] **2d**,[12b] were prepared by simple acylation with acryloyl chloride in dichloromethane in the presence of triethylamine. The acrylamide **2e** was prepared by the modification of a literature procedure[16] since, in this case, the simple acylation of ephedrine (**1**) with acryloyl chloride, led to a mixture of the *N*-acylated **2e** and *N*,*O*-diacylated product (**2f**). When acrylic acid was activated by ethyl chloroformate, however, the secondary nitrogen of the intermediate was acylated selectively, to give **2e** as a single product (Scheme 1).

These alkenes were then reacted with azomethine ylides, derived from arylidene glycine imines **3** in the presence of AgOAc and triethylamine at room temperature, employing

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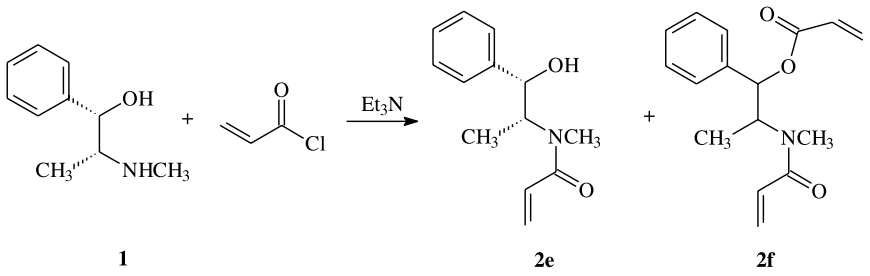
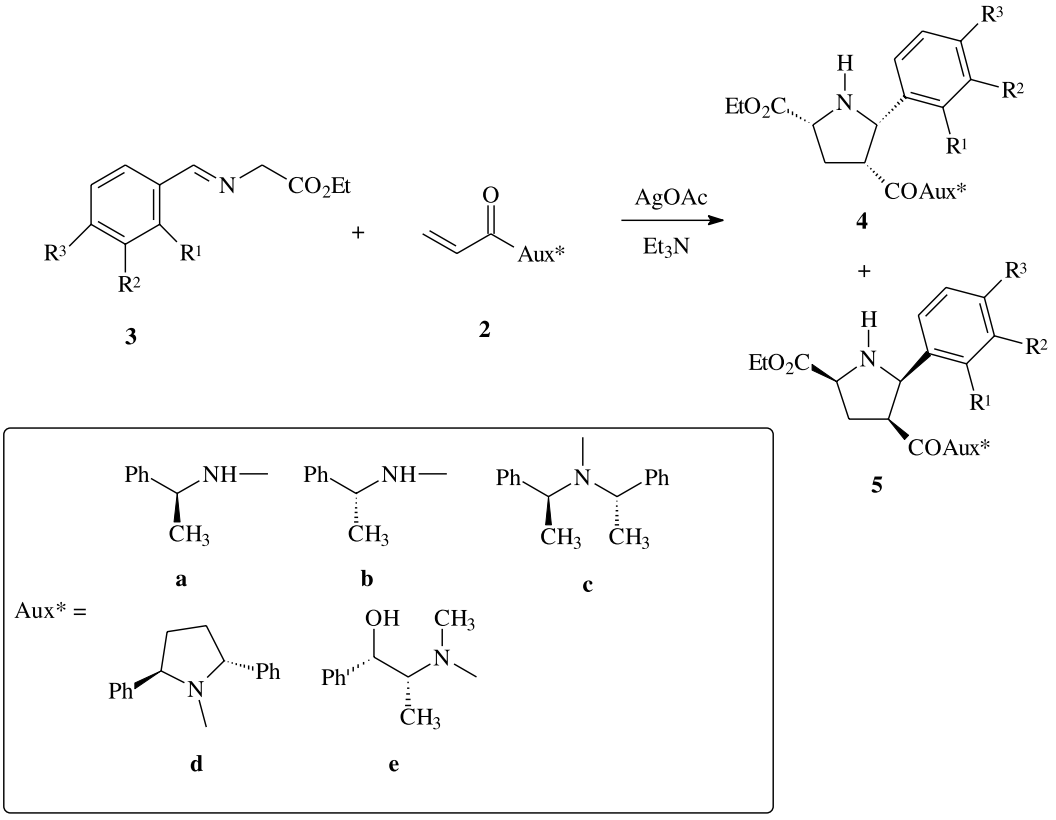


1 2e 2f

Scheme 1.



3 2 4 5 a b c d e

Scheme 2.

dry toluene as the solvent (Scheme 2). In accordance with previous results,[5a] this metallo-azomethine ylide cycloaddition exhibited regio- and stereospecific formation of the expected *syn-endo* cycloadducts, but the diastereoselectivities and yields varied depending upon the nature of the chiral auxillary and the substituents on the aryl group (Table 1).

The acrylamides **2a** and **2b**, derived from the corresponding α-phenylethylamine reacted only with moderate diastereoselectivity (entry 1–4), but in most cases both pyrrolidine isomers were readily obtained, in pure form, from these cycloadduct mixtures after repeated recrystallisations. The chiral dipolarophile **2c** based on (*R*,*R*)-*bis*-α-phenylethylamine as the chiral auxillary also resulted in the formation of diastereoisomeric mixtures. In contrast, the cyclic C_2-symmetric pyrrolidine derivative **2d** (R=H) showed complete diastereoselectivity in all cases.

The most promising results were achieved using (1*R*,2*S*)-(−)-ephedrine as the chiral element: the corresponding alkene **2e** gave, in most of the cycloadditions studied, a single diastereoisomer in good yield.

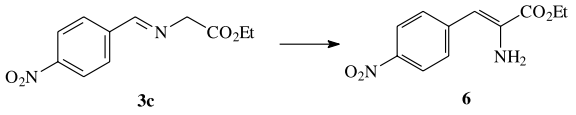
In the case of imine **3c** in all cases, depending on the reaction time a small amount of didehydroaminoacid **6** was always isolated from the reaction mixture. The formation of this compound has been observed and explained in our earlier papers (Scheme 3).[17]

The relative configuration of the cycloadducts of series **4** and **5** were determined by NOE studies of representative examples. The all-*cis* configuration of these pyrrolidines in all cases has been confirmed by the observed NOE effects between H-2 and H-5 (2–4%) and H-5 and H-4 (3–6%). The absolute configuration of two cycloadducts (**4a$_1$** and **4c$_1$**) has been established by X-ray crystallography. To compare

Table 1. Synthesis of pyrrolidines **3** and **4** from acrylamides **2** and glycine imines **1**

Entry	Acrylamide	Imine	R^1	R^2	R^3	Products	Reaction time	Yield (%)	Ratio (**4**:**5**)
1	**2a**	**3a**	H	H	H	**4a$_1$**, **5a$_1$**	48 h	77[a]	1.8:1
2	**2b**	**3a**	H	H	H	**4b$_1$**, **5b$_1$**	48 h	74[a]	1:1.8
3	**2b**	**3b**	Cl	H	Cl	**4b$_2$**, **5b$_2$**	36 h	70[a]	1:1.5
4	**2b**	**3c**	H	H	NO_2	**4b$_3$**, **5b$_3$**	24 h	82[a]	1:1
5	**2b**	**3d**	H	MeO	MeO	**4b$_4$**, **5b$_4$**	24 h	71[a]	1:1.2
6	**2c**	**3a**	H	H	H	**4c$_1$**, **5c$_1$**	36 h	65[a]	1:1
7	**2c**	**3b**	Cl	H	Cl	**4c$_2$**, **5c$_2$**	80 h	51[a]	1:2
8	**2c**	**3c**	H	H	NO_2	**4c$_3$**, **5c$_3$**	24 h	67[a]	1:1.7
9	**2d**	**3a**	H	H	H	**4d$_1$**, **5d$_1$**	24 h	78[b]	1:0
10	**2d**	**3b**	Cl	H	Cl	**4d$_2$**, **5d$_2$**	48 h	66[a]	1:0
11	**2d**	**3c**	H	H	NO_2	**4d$_3$**, **5d$_3$**	24 h	85[b]	1:0
12	**2e**	**3a**	H	H	H	**4e$_1$**, **5e$_1$**	24 h	76[b]	1:0
13	**2e**	**3b**	Cl	H	Cl	**4e$_2$**, **5e$_2$**	48 h	57[b]	10:1
14	**2e**	**3e**	H	H	MeO	**4e$_3$**, **5e$_3$**	24 h	75[b]	1:0
15	**2e**	**3d**	H	MeO	MeO	**4e$_4$**, **5e$_4$**	24 h	81[b]	1:0

[a] Isolated yield after flash chromatography.
[b] Isolated yield after recrystallisation.

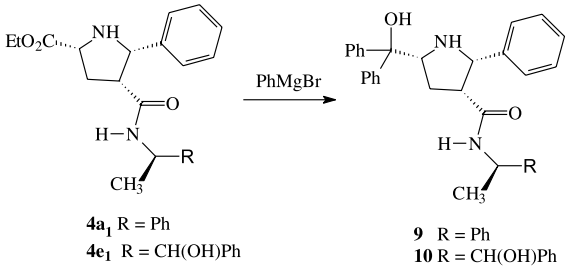


Scheme 3.

the configurations of the other products to those of these configurations, the cycloadducts were hydrolysed to the diacids **6** by ethanolic hydrochloric acid and re-esterified by the means of thionyl chloride in dry EtOH. The diesters **7** were then purified by chromatography and the optical rotations were compared (Scheme 4).

In an earlier attempt for the comparison of the absolute stereochemistry of the resulted cycloadducts, the reaction of **4a$_1$** and **4e$_1$** with PhLi and PhMgBr was attempted. To our surprise in spite of the large excess of organometallic reagents (PhMgCl or PhLi) the amide functions remained intact and in both cases, only transformation of the carbethoxy functionality was observed (Scheme 5).

In summary, *N*-metallated azomethine ylides were generated by the reaction of arylidene glycine imines **3** with AgOAc and triethylamine. These azomethine ylides undergo cycloaddition to chiral acrylamides **2** to give chiral pyrrolidines, **4** and **5**, with excellent diastereoselectivity. Single diastereoisomers were obtained from the reaction of the ylides with the dipolarophiles **2d** and **2e** (Figs. 1 and 2).



Scheme 5.

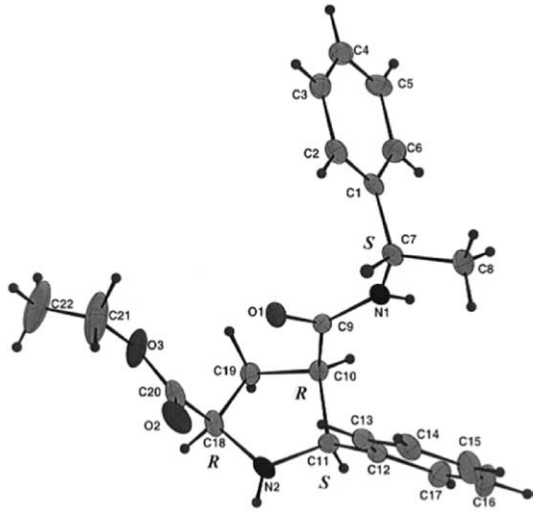
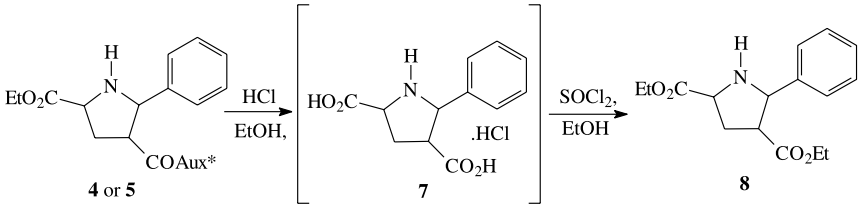


Figure 1. Crystal structure of **4a$_1$**.



Scheme 4.

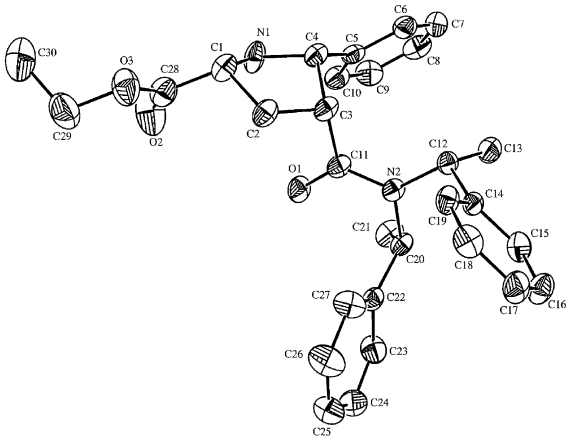


Figure 2. Crystal structure of $\mathbf{4c_1}$.

3. Experimental

3.1. General

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Elemental analyses were performed on a Perkin–Elmer 240 °C or Carlo Erba 1106 Elemental Analyser. IR spectra were recorded on a Perkin–Elmer 1600 series FTIR or Unicam research series FTIR spectrophotometer using sodium chloride plates. ^{1}H NMR spectra were acquired on a Jeol GSX 270 FT NMR at 270 MHz. Coupling constants are given in Hz and all chemical shifts are relative to an internal standard of tetramethylsilane. ^{13}C NMR spectra were obtained on a Jeol GFX 270 FT NMR (68 MHz) spectrometer. Low resolution electron impact mass spectra were obtained on a Trio 2000 VG. High resolution spectra were obtained on a VG ZAB-E spectrometer (E.P.S.R.C. Mass Spectrometry Service Centre, Swansea). Thin layer chromatography was performed on Merck silica gel $60F_{254}$. All solvents were purified according to standard procedures.

3.1.1. *S*-(*R,*R**)]-(−)-*N*,*N*-Bis-(1-phenyl-ethyl)-acrylamide (2c).** [*S*-(*R**,*R**)]-(−)-*bis*-(α-Phenyl-ethyl)-amine (0.50 g, 1.90 mM) has been dissolved in dry CH_2Cl_2 (10 mL) and at 0 °C triethylamine (0.70 mL, 5 mmol) was added. After 5 min acroyl chloride (0.25 g, 0.23 mL, 2.8 mM) was added dropwise. After 12 h stirring at room temperature the mixture was washed with saturated sodium hydrocarbonate solution (2×5 mL), water (5 mL), brine (5 mL) and dried over magnesium sulfate. The evaporation yielded a colourless oil (0.49 g, 92%); $[\alpha]_D^{23} = +213$ (*c* 1, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.2 (m, 10H, Ph), 6.28 (dd, 1H, *J*=2.6, 16.5 Hz, CH_2=), 6.11 (dd, 1H, *J*=9.9, 16.5 Hz, CH_2=), 5.97 (br s, 1H, CH), 5.40 (dd, 1H, *J*=2.6, 9.9 Hz, CH=), 4.98 (br s, 1H, CH), 1.74 (br d, 6H, *J*=6.6 Hz, 2×CH_3), ^{13}C NMR: 166.7 (C=O), 141.1 (CH), 130.6 (2×q), 128.3 (overlapping CHs), 127.6 (overlapping CHs), 126.7 (overlapping CHs), 55.2 (CH), 20 (broad, CH_3); IR (film, cm^{-1}): 3058, 3037, 2976, 2936, 1642, 1601, 1428, 1303, 1246, 1204, 1163, 1086, 1059; CIMS (*m*/*z*, rel intensity %): 280 (M^{+1}, 3), 174 (83), 120 (51), 105 (100), 55 (49); HRMS: Calcd: 279.1623 for $C_{19}H_{21}NO$; Found: 279.1628.

3.1.2. (*R*,*R*)-2,5-Diphenyl-1-acroyl-pyrrolidine (2d, R=H). (*R*,*R*)-2,5-Diphenyl-pyrrolidine (0.30 g, 1.35 mmol) has been dissolved in dry CH_2Cl_2 (10 mL) and at 0 °C triethylamine (0.28 mL, 2 mmol) was added. After 5 min acroyl chloride (0.24 g, 0.22 mL, 2.7 mM) was added dropwise. After 12 h stirring at room temperature the mixture was washed with saturated sodium hydrocarbonate solution (2×5 mL), water (5 mL), brine (5 mL) and dried over magnesium sulfate. The evaporation of the solvent followed by flash chromatography has yielded the product as a white solid (0.35 g, 93%). Mp 111–2 °C; $[\alpha]_D^{23} = +106$ (*c* 0.83, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.20–6.85 (m, 10H, Ph), 6.00 (m, 2H, CH=), 5.35 (d, 1H, *J*=7.9 Hz, CH=), 5.17 (t, 2H, *J*=9.9 Hz, C*H*-Ph), 2.34 (m, 1H, CH_2), 2.13 (m, 1H, CH_2), 1.56 (m, 2H, CH_2); ^{13}C NMR: 165.0, 143.7, 142.8, 128.8 (3×C), 128.4 (2×C), 128.0, 127.4, 126.7, 125.4 (2×CH), 125.3 (2×CH), 62.2, 62.1, 33.1, 30.3; IR (KBr, cm^{-1}): 3061, 2986, 2929, 1651, 1609, 1391, 1306, 1074; CIMS (*m*/*z*, rel intensity %): 278 (M^{+1}, 100), 146 (10), 73 (10); HRMS: Calcd: 277.1467 for $C_{19}H_{19}NO$; Found: 277.1470.

3.1.3. (1*R*,2*S*)-*N*-(2-Hydroxy-1-methyl-2-phenyl-ethyl)-*N*-methyl-acrylamide (2e) and (1*R*,2*S*)-*N*-(2-acroyloxy-1-methyl-2-phenyl-ethyl)-*N*-methyl-acrylamide (2f). *Method A*. (−)-Ephedrine hydrochloride (4.0 g, 20 mmol) was suspended in dry dichlormethane (50 mL) and triethylamine (4.22 g, 5.8 mL) was added in one portion. After 10 min stirring the mixture was cooled down to 0 °C and acryloyl chloride (2.64 g, 2.81 mL, 21 mM) was added dropwise. The reaction mixture was allowed to warm up to room temperature and it was stirred for 5 h. Then it was washed with water (25 mL), saturated $NaHCO_3$ solution (25 mL), brine (25 mL), dried over magnesium sulfate and evaporated to yield an oil which is a mixture of **2e** and **2f**. These products were separated by column chromatography (eluent: petrolether–ethyl acetate 1:1) to yield **2e** (1.38 g, 31.5%), and **2f** (2.18 g, 40%).

Method B. Acrylic acid (6.30 g, 6.0 mL, 87.5 mM) was dissolved in dry CH_2Cl_2 (30 mL) and triethylamine (8.8 g, 12.5 mL) was added. The mixture was cooled down to 0 °C and methyl chlorofomate (9.5 g, 8.4 mL) was added dropwise. After an hour stirring at 0 °C this mixture was slowly transferred to a flask containing (−)-ephedrine hydrochloride (8.0 g, 39.8 mM) and triethylamine (5.7 mL) in dry CH_2Cl_2 (50 mL). The reaction mixture was stirred at room temperature overnight and then washed with 2% aqueous NaOH (40 mL), water (30 mL) and brine (30 mL). The organic phase was dried over magnesium sulfate, evaporated to yield a yellow oil which was purified by flash chromatography to yield the product (**2e** only) as a colourless oil (7.67 g, 88%).

Compound **2e**. Colourless oil; $[\alpha]_D^{23} = -162$ (*c* 2.4, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.37–7.21 (m, 5H, Ph), 6.48 (dd, 1H, *J*=10.5, 16.5 Hz,=CH_2-trans), 6.29 (dd, 1H, *J*=2.6, 16.5 Hz, CH=), 5.88 (dd, 1H, *J*=2.6, 10.5 Hz,=CH_2-*cis*), 4.88 (d, 1H, *J*=3.3 Hz, H-2), 4.50 (dq, 1H, *J*=3.3, 7.3 Hz, H-1), 2.79 (s, 3H, NMe), 1.20 (d, 1H, *J*=7.3 Hz, CH_3); ^{13}C NMR: 168.0 (C=O), 141.8 (Ph-1′C), 128.2 and 128.1 (overlapping, 4×CH), 127.4 (CH), 126.2 (2×CH), 76.5 (C-2), 58.1 (NMe), 33.1 (C-1), 11.7 (CH_3); IR (film,

cm^{-1}): 3386 (br, OH), 3035, 2982, 2942, 1639, 1588, 1480, 1450, 1412, 1334, 1275, 1250, 1125, 1042; CIMS (*m/z*, rel intensity %): 220 (M^{+1}, 38), 202 (base peak), 148 (17), 112 (12); HRMS: Calcd: 219.1259 for $C_{13}H_{17}NO_2$; Found: 219.1257.

Compound **2f**. Colourless oil; $[\alpha]_D^{23}=-198$ (*c* 2.0, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.40–7.26 (m, 5H, Ph), 6.51–5.70 (m, 7H), 5.60 (dd, 1H, *J*=2, 10 Hz), 5.12 (m, 1H, CH), 2.90 (s, 3H, NMe), 1.25 (d, 3H, *J*=7 Hz, CH_3); ^{13}C NMR: 166.7, 165.0, 137.7, 131.7, 131.3, 128.6, 128.3, 128.1, 127.8, 126.7, 56.5, 52.5, 30.8, 12.8; IR (film, cm^{-1}): 3480, 3034, 2904, 2910, 1726, 1646, 1611, 1478, 1437, 1412, 1266, 1187, 1046, 979; CIMS (*m/z*, rel intensity %): 274 (M^{+1},18), 230 (10), 202 (base peak), 148 (10), 112 (22); HRMS: Calcd: 273.1365 for $C_{16}H_{19}NO_3$; Found: 273.1360.

3.2. AgOAc catalysed cycloaddition reactions—general procedure

A mixture of imine (1.2 equiv) AgOAc (1.5 equiv), appropriate dipolarophile (1 equiv) and Et_3N (1.1 equiv) in dry toluene (5 mL for 1 mmol of imine) protected from the light with aluminium was stirred at room temperature for 12–48 h. The reaction was then quenched by addition of saturated aqueous ammonium chloride solution and ether. The mixture was filtered through a pad of Celite. The organic layer was separated, washed with water, brine and dried over magnesium sulfate, filtered and the solvent evaporated. The residue was purified by flash chromatography and/or recrystallisation to afford the cycloadducts.

3.2.1. Ethyl,5-phenyl-4-[(1′-phenylethyl)carbamoyl]-pyrrolidine-2-carboxylate ($4a_1$ and $5b_1$). Colourless crystals; ^{1}H NMR (270 MHz, $CDCl_3$): 7.27–7.15 (m, 8H, Ph), 6.95—6.92 (m, 2H, Ph), 6.58 (broad d, 1H, *J*=7.3 Hz, N*H*CO), 4.71 (m, 1H, CH_3CH), 4.41 (d, 1H, *J*=5.9 Hz, H-5), 4.27 (dq, 2H, OCH_2), 3.98 (dd, 1H, *J*=6.0, 9.9 Hz, H-2), 3.06 (ddd, 1H, *J*=2.6, 5.9, 6.6 Hz, H-4), 2.76 (broad s, 1H, NH), 2.60 (ddd, 1H, *J*=6.6, 9.9, 13.9 Hz, H_2-3), 2.38 (ddd, 1H, *J*=2.6, 6.0, 13.9 Hz, H_2-3), 1.32 (t, 3H, *J*=7.3 Hz, Me), 1.11 (d, 1H, *J*=7.3 Hz, Me); ^{13}C NMR: 173.5 (C=O), 171.7 (C=O), 143.2 (Ph-1′C), 138.2 (Ph-1′C), 128.4 (4×CH), 127.3 (CH), 128.8 (CH), 126.4 (2×CH), 126.2 (2×CH), 65.1, 61.1, 58.1, 50.0, 48.3, 33.8, 21.3, 14.2; CIMS (*m/z*, rel intensity %): 367 (M^+, base peak), 293 (12), 246 (8), 105 (10); IR (nujol, cm^{-1}): 3322, 1737, 1648, 1526, 1214, 1059, 1009.

(*R*,*R*,*R*,*S*)-**$4a_1$**. Mp 145–6 °C; $[\alpha]_D^{23}=-100$ (*c* 1.0, $CHCl_3$) HRMS: Calcd: 366.1943 for $C_{22}H_{26}N_2O_3$; Found: 366.1933.

(*S*,*S*,*S*,*R*)-**$5b_1$**: Mp 143–4 °C; $[\alpha]_D^{23}=+100$ (*c* 1.0, $CHCl_3$); HRMS: Calcd: 366.1943 for $C_{22}H_{26}N_2O_3$; Found: 366.2074.

3.2.2. (*R*,*R*,*R*,*R*)-Ethyl,5-phenyl-4-[(1′-phenylethyl)carbamoyl]-pyrrolidine-2-carboxylate ($4b_1$). White powder; mp 151–2 °C; $[\alpha]_D^{23}=+130$ (*c* 1.7, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.39—7.17 (m, 8H, Ph), 7.04 (dd, 2H, *J*=1.4, 7.5 Hz, Ph), 6.81 (broad d, 1H, *J*=7.9 Hz, N*H*CO), 4.71 (m, 1H, CH_3CH), 4.45 (d, 1H, *J*=6.6 Hz, H-5), 4.15 (q, *J*=7.3 Hz, 2H, OCH_2), 3.99 (dd, 1H, *J*=6.6, 9.9 Hz, H-2), 3.10 (ddd, 1H, *J*=3.3, 5.9, 6.6 Hz, H-4), 2.76 (broad s, 1H, NH), 2.61 (ddd, 1H, *J*=6.6, 9.9, 13.9 Hz, H_2-3), 2.29 (ddd, 1H, *J*=3.3, 6.6, 13.9 Hz, H_2-3), 1.32 (t, 3H, *J*=7.3 Hz, Me), 1.11 (d, 1H, *J*=7.3 Hz, Me); ^{13}C NMR: 173.4 (C=O), 171.9 (C=O), 143.5 (Ph-1′C), 138.3 (Ph-1′C), 127.4 (4×CH), 126.8 (CH), 126.4 (CH), 126.2 (2×CH), 126.1 (2×CH), 64.7, 61.1, 58.0, 49.9, 48.1, 33.5, 21.5, 14.1; CIMS (*m/z*, rel intensity %): 367 (M^+, base peak), 293 (19), 105 (20); IR (nujol, cm^{-1}): 3332, 1738, 1648, 1527, 1214, 1059, 1011; HRMS: Calcd: 366.1943 for $C_{22}H_{26}N_2O_3$; Found: 366.2015.

3.2.3. (*S*,*S*,*S*,*R*)-Ethyl,5-(2,4-dichlorophenyl)-4-[(1′-phenylethyl)carbamoyl]-pyrrolidine-2-carboxylate ($5b_2$). White powder; mp 171–2 °C; $[\alpha]_D^{23}=+116$ (*c* 1.2, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.51 (d, 1H, *J*=7.9 Hz, Ar), 7.33–7.12 (m, 5H, Ar), 6.93 (dd, 1H, *J*=1.8, 7.9 Hz, Ar), 6.42 (d, 1H, *J*=7.9 Hz, Ar), 4.73 (m, 1H, C*H*CH_3), 4.57 (d, 1H, *J*=6.0 Hz, H-5), 4.29 (q, 2H, *J*=7.3 Hz, OCH_2), 3.96 (dd, 1H, *J*=6.1, 9.5 Hz, H-2), 3.35 (ddd, 1H, *J*=3.2, 6.0, 6.7 Hz, H-4), 2.70 (br s, 1H, NH), 2.53 (ddd, 1H, *J*=6.7, 9.5, 13.8 Hz, H_2-3), 2.35 (ddd, 1H, *J*=3.2, 6.1, 13.8 Hz, H_2-3), 1.29 (t, 3H, *J*=7.3 Hz, Me), 1.08 (d, 3H, *J*=8.6 Hz, Me); ^{13}C NMR: 173.4 (C=O), 170.9 (C=O), 143.0 (q), 134.5 (q), 133.8 (q), 133.3 (q), 129.1 (2×CH), 128.6 (2×CH), 127.6 (CH), 127.6 (CH), 126.4 (CH), 125.9 (CH), 62.6, 61.2, 58.1, 47.3, 33.6, 21.0, 14.2; IR (nujol, cm^{-1}): 3306, 1734, 1644, 1527, 1213, 1123, 1090, 1050, 1019; CIMS (*m/z*, rel intensity %): 477 (M^+, 4), 463 (12), 435 (base peak), 401 (15), 361 (14), 262 (17), 140 (20), 105 (34); HRMS: Calcd: 434.1164 for $C_{22}H_{24}Cl_2N_2O_3$; Found: 434.1152.

3.2.4. (*R*,*R*,*R*,*R*)-Ethyl,5-(2,4-dichlorophenyl)-4-[(1′-phenylethyl)carbamoyl]-pyrrolidine-2-carboxylate ($4b_2$). White powder; mp 162–3 °C; $[\alpha]_D^{23}=+78$ (*c* 0.8, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.52 (d, 1H, *J*=7.9 Hz, Ar), 7.37–7.10 (m, 5H, Ar), 6.94 (dd, 1H, *J*=1.9, 7.9 Hz, Ar), 6.27 (d, 1H, *J*=7.9 Hz, Ar), 4.73 (quintet, 1H, C*H*CH_3), 4.52 (d, 1H, *J*=6.0 Hz, H-5), 4.31 (q, 2H, *J*=7.3 Hz, OCH_2), 3.98 (dd, 1H, *J*=6.5, 9.8 Hz, H-2), 3.31 (ddd, 1H, *J*=3.2, 6.0, 6.7 Hz, H-4), 2.70 (br s, 1H, NH), 2.55 (ddd, 1H, *J*=6.7, 9.8, 13.9 Hz, H_2-3), 2.39 (ddd, 1H, *J*=3.2, 6.5, 13.9 Hz, H_2-3), 1.34 (t, 3H, *J*=7.3 Hz, Me), 1.30 (d, 3H, *J*=8.6 Hz, Me); ^{13}C NMR: 173.3 (C=O), 171.1 (C=O), 143.0 (q), 134.5 (q), 133.6 (q), 133.3 (q), 128.9 (2×CH), 128.4 (2×CH), 127.7 (CH), 127.5 (CH), 126.4 (CH), 125.9 (CH), 62.4, 61.2, 58.4, 47.4, 33.8, 21.8, 14.2; CIMS (*m/z*, rel intensity %): 477 (M^+, 14), 435 (base peak), 401 (5), 361 (24), 262 (37); HRMS: Calcd: 434.1164 for $C_{22}H_{24}Cl_2N_2O_3$; Found: 434.1174.

3.2.5. (*S*,*S*,*S*,*R*)-Ethyl,5-(4-nitrophenyl)-4-[(1′-phenylethyl)carbamoyl]-pyrrolidine-2-carboxylate ($5b_3$). White needles; mp 189–90 °C; $[\alpha]_D^{23}=+148$ (*c* 1.5, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.87 (d, 1H, *J*=8.6 Hz, Ar-3′H and 5′H), 7.31 (d, 1H, *J*=8.6 Hz, Ar-2′H and 6′H), 7.21 (m, 3H, Ph), 7.03 (m, 2H, Ph), 4.78 (sextett, 1H, PhCH), 4.51 (d, 1H, *J*=6.6 Hz, H-5), 4.29 (dq, 2H, OCH_2), 4.05 (dd, 1H, *J*=5.9, 10.6 Hz, H-2), 3.17 (ddd, 1H, *J*=2.5, 6.6, 8.6 Hz, H-4), 2.71 (ddd, 1H, *J*=5.9, 8.6, 14 Hz, H_2-3), 2.35 (ddd, 1H, *J*=2.5, 5.9, 14 Hz, H_2-3), 1.35 (t,

3H, J=6.6 Hz, CH_3), 1.26 (d, 3H, J=6.6 Hz, CH_3); ^{13}C NMR: 173.8 (C=O), 170.7 (C=O), 145.7 (Ar-1′H), 132.0 (Ph-1′C), 128.4 (2×CH), 127.3 (3×CH), 126.4 (2×CH), 123.3 (2×CH), 64.2, 61.5, 57.6, 50.1, 48.2, 33.5, 21.1 (Me), 14.2 (Me); IR (nujol, cm^{-1}): 3290, 1726, 1642, 1548, 1521, 1343, 1262, 1203, 1106, 1021; CIMS (*m/z*, rel intensity %): 412 (M^+, base peak), 382 (29), 338 (7), 289 (10), 167 (10), 105 (13); HRMS: Calcd: 411.1794 for $C_{22}H_{25}N_3O_5$; Found: 411.1808.

3.2.6. (*R*,*R*,*R*,*R*,*R*)-Ethyl,5-phenyl-4-[[*bis*(1′-phenylethyl)]carbamoyl]-pyrrolidine-2-carboxylate (4c$_1$). Colourless needles; mp 172–3 °C; $[\alpha]_D^{23}=-158$ (*c* 0.96, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 7.31–7.02 (m, 11H, Ph), 6.77–6.71 (m, 4H, Ph), 5.31 (broad d, 1H, J=6.6 Hz, PhC*H*), 4.70 (q, 1H, J=7.3 Hz, PhC*H*), 4.23 (dq, 2H, OCH_2), 3.95 (d, 1H, J=7.3 Hz, H-5), 3.87 (t, 1H, J=8.6 Hz, H-2), 3.43 (dd, 1H, J=5.3, 7.3 Hz, H-4), 2.53–2.02 (m, 2H, H_2-3), 1.46 (d, 3H, J=7.3 Hz, CH_3), 1.42 (d, 3H, J=7.3 Hz, CH_3), 1.29 (t, 3H, J=7.3 Hz, CH_3); ^{13}C NMR: 173.9 (C=O), 173.1 (C=O), 141.1 (2×Ph-1′C), 138.7 (Ph-1′C), 128.4, 128.3, 128.0, 127.8, 127.2, 126.9 (15×CH, overlapping), 67.4, 61.0, 52.4, 52.1, 47.2, 36.9, 30.0, 19.5, 16.9, 14.3; IR (nujol, cm^{-1}): 1737, 1627, 1604, 1453, 1293, 1262, 1195, 1177, 1102, 1025, 949; CIMS (*m/z*, rel intensity %): 471 (M^+, base peak), 397 (10), 367 (15), 280 (12), 246 (9), 105 (22); HRMS: Calcd: 470.2569 for $C_{30}H_{34}N_2O_3$; Found: 470.2573.

3.2.7. (*S*,*S*,*S*,*R*,*R*)-Ethyl,5-phenyl-4-[[*bis*(1′-phenylethyl)]carbamoyl]-pyrrolidine-2-carboxylate (5c$_1$). White powder; mp 156–8 °C; $[\alpha]_D^{23}=-121$ (*c* 0.42, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 7.35–7.12 (m, 11H, Ph), 6.78–6.73 (m, 4H, Ph), 5.38 (broad d, 1H, J=6.9 Hz, PhC*H*), 4.66 (q, 1H, J=6.8 Hz, PhC*H*), 4.27 (dq, 2H, OCH_2), 3.98 (d, 1H, J=7.6 Hz, H-5), 3.91 (t, 1H, J=8.6 Hz, H-2), 3.48 (dd, 1H, J=5.1, 7.6 Hz, H-4), 2.35–2.22 (m, 2H, H_2-3), 1.47 (d, 3H, J=6.8 Hz, CH_3), 1.41 (d, 3H, J=6.8 Hz, CH_3), 1.31 (t, 3H, J=7.5 Hz, CH_3); ^{13}C NMR: 174.8, 172.9, 141.8, 140.9, 138.1, 129.1, 128.1, 127.9, 127.6, 127.4, 127.1, 126.8, 126.3, 125.9, 68.0, 51.7, 50.7, 48.6, 35.8, 30.1, 21.0, 17.4, 14.2; IR (nujol, cm^{-1}): 1739, 1625, 1604, 1452, 1296, 1197, 1109, 1027, 949; CIMS (*m/z*, rel intensity %): 471 (M^+, base peak), 397 (15), 367 (25), 105 (36); HRMS: Calcd: 470.2569 for $C_{30}H_{34}N_2O_3$; Found: 470.2573.

3.2.8. (*S*,*S*,*S*,*R*,*R*)-Ethyl,5-(2,4-dichlorophenyl)-4-[[*bis*(1′-phenylethyl)]carbamoyl]-pyrrolidine-2-carboxylate (5c$_2$). White powder; mp 184–6 °C; $[\alpha]_D^{23}=-102$ (*c* 0.88, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 7.61 (d, 1H, J=8.6 Hz, Ar), 7.39—7.03 (m, 8H, Ar), 6.78–6.77 (m, 4H, Ar), 5.64 (br s, 1H, PhC*H*), 4.90 (q, 1H, J=6.6 Hz, PhC*H*), 4.48 (d, 1H, J=6.0 Hz, H-5), 4.25 (dq, 2H, OCH_2), 3.70 (br dd, 1H, H-2), 3.42 (br s, 1H, H-4), 1.90 (broad ddd, 1H, H_2-3), 1.75 (broad ddd, 1H, H_2-3), 1.54 (d, 3H, J=6.6 Hz, Me), 1.30 (t, 3H, J=7.2 Hz, Me), 1.22 (d, 3H, J=6.6 Hz, Me); ^{13}C NMR: 173.6 (C=O), 172.7 (C=O), 141.3 (q), 141.1 (q), 134.8 (q), 133.5, 133.1, 128.9, 128.4, 128.0, 127.7, 127.3, 126.8, 126.7 (15×C, overlapping), 66.9, 61.1, 51.9, 47.6, 36.3, 29.6, 20.5, 17.8, 14.3; CIMS (*m/z*, rel intensity %): 539 (M^+, base peak), 505 (10), 435 (12), 280 (30), 105 (70); IR (film, cm^{-1}): 2976, 2931, 1738, 1629, 1445, 1378, 1279, 1201, 1178, 1102; HRMS: Calcd 538.1790 for $C_{30}H_{32}Cl_2N_2O_3$; Found: 538.1791.

3.2.9. (*S*,*S*,*S*,*R*,*R*)-Ethyl,5-(2,4-dichlorophenyl)-4-[[*bis*(1′-phenylethyl)]carbamoyl]-pyrrolidine-2-carboxylate (4c$_2$). White powder; mp 170 °C; $[\alpha]_D^{23}=-95$ (*c* 0.25, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 7.56 (d, 1H, J=8.5 Hz, Ar), 7.33–7.01 (m, 8H, Ar), 6.75–6.71 (m, 4H, Ar), 4.99 (br s, 1H, PhC*H*), 4.65 (q, 1H, J=6.6 Hz, PhC*H*), 4.48 (d, 1H, J=6.0 Hz, H-5), 4.23 (dq, 2H, OCH_2), 3.89 (dd, 1H, J=7.3, 9.3 Hz, H-2), 3.10 (br s, 1H, H-4), 2.51 (ddd, 1H, J=7.9, 9.3, 13.2 Hz, H_2-3), 2.27 (ddd, 1H, J=4.0, 7.3, 13.2 Hz, H_2-3), 1.38 (d, 3H, J=6.6 Hz, Me), 1.34 (t, 3H, J=7.3 Hz, Me), 1.25 (d, 3H, J=6.6 Hz, Me); ^{13}C NMR: 173.5 (C=O), 172.5 (C=O), 141.4 (q), 141.1 (q), 134.7 (q), 133.9, 133.4, 129.0, 128.7, 128.0, 127.7, 127.5, 127.1, 126.8, 126.6 (15×C, overlapping), 66.7, 61.3, 51.9, 47.7, 36.6, 31.2, 20.5, 17.9, 14.1; CIMS (*m/z*, rel intensity %): 539 (M^+, base peak), 105 (80); IR (film, cm^{-1}): 2979, 2938, 1737, 1626, 1452, 1377, 1211, 1109; HRMS: Calcd 538.1790 for $C_{30}H_{32}Cl_2N_2O_3$; Found: 538.1786.

3.2.10. (*S*,*S*,*S*,*R*,*R*)-Ethyl,5-(4-nitrophenyl)-4-[[*bis*(1′-phenylethyl)]carbamoyl]-pyrrolidine-2-carboxylate (5c$_3$). White powder; mp 212–3 °C; $[\alpha]_D^{23}=-179$ (*c* 1.2, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 8.03 (d, 2H, J=8.6 Hz, Ar), 7.25–7.04 (m, 10H, Ph), 6.49 (d, 2H, J=8.6 Hz, Ar), 5.82 (broad q, 1H, J=6.6 Hz, C*H*Ph), 4.65 (q, 1H, J=7.2 Hz, C*H*Ph), 4.25 (dq, 2H, OCH_2), 3.90 (t, 1H, J=8.6 Hz, H-2), 3.79 (d, 1H, J=7.9 Hz, H-5), 3.42 (ddd, 1H, J=1.4, 5.3, 7.9 Hz, H-4), 2.57 (ddd, 1H, J=5.3, 8.6, 13.5 Hz, H_2-3), 2.32 (ddd, 1H, J=1.4, 8.6, 13.5 Hz, H_2-3), 1.68 (d, 3H, J=6.5 Hz, Me), 1.47 (d, 3H, J=6.5 Hz, Me), 1.31 (t, 3H, J=7.3 Hz, Me); ^{13}C NMR: 173.8 (C=O), 172.7 (C=O), 146.8 (q), 141.0 (q), 140.7 (q), 128.7, 128.6, 128.5, 128.3, 128.2, 127.8, 127.6 (overlapping CHs), 127.2 (CH), 122.8 (CH), 66.1, 61.1, 51.6, 51.0, 48.6, 37.0, 29.6, 20.1, 16.4, 14.2; IR (KBr, cm^{-1}): 2977, 2933, 1734, 1626, 1517, 1494, 1442, 1345, 1240, 1201, 1105, 1035, 841; CIMS (*m/z*, rel intensity %): 516 (M^{+1}, 100), 486 (10), 412 (9), 280 (10), 105 (30); HRMS: Calcd 515.2402 for $C_{30}H_{33}N_3O_5$; Found: 515.2407.

3.2.11. (*R*,*R*,*R*,*R*,*R*)-Ethyl,5-(4-nitrophenyl)-4-[[*bis*(1′-phenylethyl)]carbamoyl]-pyrrolidine-2-carboxylate (4c$_3$). White powder; mp 201–3 °C; $[\alpha]_D^{23}=-142$ (*c* 0.34, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 8.14 (d, 2H, J=8.6 Hz, Ar), 7.29–7.02 (m, 10H, Ph), 6.73 (d, 2H, J=8.6 Hz, Ar), 5.70 (broad s, 1H, C*H*Ph), 4.65 (q, 1H, J=7.2 Hz, C*H*Ph), 4.27 (dq, 2H, OCH_2), 3.70 (t, 1H, J=8.6 Hz, H-2), 3.76 (d, 1H, J=7.0 Hz, H-5), 3.05 (broad q, 1H, H-4), 1.97 (broad m, 1H, H_2-3), 1.72 (broad m, 1H, H_2-3), 1.59 (d, 3H, Me), 1.32 (d, 3H, Me), 1.29 (t, 3H, J=6.9 Hz, Me); ^{13}C NMR: 173.8 (C=O), 172.6 (C=O), 146.8 (q), 141.1 (q), 140.6 (q), 128.7, 128.6, 128.4, 128.3, 128.2, 127.9 (overlapping CHs), 126.1 (CH), 123.0 (CH), 66.8, 61.2, 51.6, 51.3, 47.4, 35.6, 29.9, 21.2, 17.7, 14.2; CIMS (*m/z*, rel intensity %): 516 (M^{+1}, 100), 412 (13), 105 (30); HRMS: Calcd 515.24022 for $C_{30}H_{33}N_3O_5$; Found: 515.240545.

3.2.12. (*R*,*R*,*R*,*R*,*R*)-Ethyl,4-[(2′,5′-*trans*-diphenylpyrrolidinyl)-1-carbonyl]-5-phenyl-pyrrolidine-2-carboxylate (4d$_1$). White powder; mp 203 °C; $[\alpha]_D^{23}=+262$ (*c* 2.2,

$CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 7.39 (m, 10H, Ph), 7.20 (d, 1H, $J=7.2$ Hz, Ph), 7.02 (m, 2H, Ph), 6.28 (d, 2H, $J=7.8$ Hz, Ph), 5.26 (d, 1H, $J=7.9$ Hz) and 5.17 (d, 1H, $J=7.9$ Hz, H-2′ and H-5′), 4.20 (q, 2H, $J=6.6$ Hz, OCH_2), 4.19 (d, 1H, $J=7.3$ Hz, H-5), 3.70 (t, 1H, $J=8.6$ Hz, H-2), 3.20 (dt, 1H, $J=4.5$, 7.9 Hz, H-4), 2.24 (m, 2H, CH_2), 2.11 (m, 1H, CH_2), 1.90 (m, 1H, CH_2), 1.67 (d, 1H, $J=6.6$ Hz, CH_2), 1.50 (d, 1H, $J=6.6$ Hz, CH_2), 1.25 (t, 3H, $J=6.6$ Hz, CH_3); ^{13}C NMR: 173.4 (C=O), 172.5 (C=O), 143.6 (Ph-1′C), 142.6 (Ph-1′C), 138.5 (Ph-1′C), 128.9 (2×CH), 128.7 (2×CH), 128.5 (2×CH), 127.4 (CH), 127.3 (CH), 126.9 (2×CH), 125.9 (CH), 125.4 (2×CH), 124.8 (2×CH), 66.5, 62.9, 62.0, 60.9, 60.1, 47.8, 36.5, 32.7, 30.4, 14.1 (CH_3); IR (nujol, cm^{-1}): 1737, 1622, 1424, 1318, 1260, 1169, 1090, 1031; CIMS (*m/z*, rel intensity %): 469 (M^{+1}, base peak), 395 (10), 278 (12), 192 (10); HRMS: Calcd: 468.2413 for $C_{30}H_{32}N_2O_3$; Found: 468.2400.

3.2.13. (*R*,*R*,*R*,*R*,*R*)-Ethyl,5-(2,4-dichlorophenyl)-4-[(2′,5′-*trans*-diphenylpyrrolidinyl)-1-carbonyl]-pyrrolidine-2-carboxylate (4d$_2$). White powder; mp 211 °C; $[\alpha]_D^{23}=+47$ (*c* 0.2, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 7.52 (d, 1H, $J=2.6$ Hz, Ar), 7.51–7.01 (m, 10H, Ar), 6.42 (dd, 2H, $J=2.0$, 8.2 Hz, Ar), 5.31 (d, 1H, $J=7.2$ Hz, NC*H*Ph), 5.27 (d, 1H, $J=7.2$ Hz, *NCH*Ph), 4.20 (d, 1H, $J=7.2$ Hz, H-5), 4.19 (q, 2H, $J=7.0$ Hz, OCH_2), 3.65 (t, 1H, $J=8.6$ Hz, H-2), 3.47 (ddd, 1H, $J=1.9$, 3.7, 7.2 Hz, H-4), 2.33 (m, 2H, CH_2), 1.93 (m, 1H, CH_2), 1.81 (m, 1H, CH_2), 1.70 (m, 1H, CH_2), 1.55 (m, 1H, CH_2), 1.26 (t, 3H, $J=7.0$ Hz, CH_3); ^{13}C NMR: 173.2 (C=O), 172.7 (C=O), 143.5 (q), 142.8 (q), 133.3, 132.9, 129.2, 128.8, 128.7, 128.6, 127.5, 127.4, 127.0, 125.8, 124.9 (16×C, overlapping), 66.3, 63.0, 62.1, 61.0, 60.1, 47.9, 36.4, 32.8, 30.2, 14.1; IR (nujol, cm^{-1}): 1735, 1624, 1427, 1269, 1204, 1178, 1095, 1031; CIMS (*m/z*, rel intensity %): 537 (M^+, 100), 503/501 (14), 278 (38), 205 (17), 149 (60), 85 (99); HRMS: Calcd: 536.1633 for $C_{30}H_{30}Cl_2N_2O_3$; Found: 536.1636.

3.2.14. (*R*,*R*,*R*,*R*,*R*)-Ethyl,5-(4-nitrophenyl)-4-[(2′,5′-*trans*-diphenylpyrrolidinyl)-1-carbonyl]-pyrrolidine-2-carboxylate (4d$_3$). White powder; mp 222–3 °C; $[\alpha]_D^{23}=+34$ (*c* 0.17, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 8.09 (d, 2H, $J=8.6$ Hz, Ar), 7.44–7.31 (m, 5H, Ar), 7.18 (d, 2H, $J=6.6$ Hz, Ar), 7.07 (t, 1H, $J=7.3$ Hz, Ar), 6.95 (t, 2H, $J=7.3$ Hz, Ar), 6.52 (d, 2H, $J=7.3$ Hz, Ar), 5.25 (d, 1H, $J=7.3$ Hz, C*H*Ph), 5.16 (d, 1H, $J=7.3$ Hz, C*H*Ph), 4.24 (d, 1H, $J=7.3$ Hz, H-5), 4.20 (q, 2H, $J=7.3$ Hz, OCH_2), 3.69 (t, 1H, $J=8.6$ Hz, H-2), 3.25 (ddd, 1H, $J=3.3$, 4.6, 7.9 Hz, H-4), 2.51–2.19 (m, 2H, CH_2), 2.01 (ddd, 1H, $J=4.6$, 7.3, 13.2 Hz, H_2-3), 1.88–1.72 (m, 2H, CH_2), 1.58 (dd, 1H, $J=5.3$, 11.9 Hz, CH_2), 1.27 (t, 3H, $J=7.3$ Hz, CH_3); ^{13}C NMR:172.9 (C=O), 172.2 (C=O), 147.1 (q), 146.2 (q), 143.6 (q), 142.6 (q), 129.0 (2×CH), 127.9 (2×CH), 127.8 (2×CH), 127.7 (2×CH), 126.6 (CH), 125.4 (2×CH), 125.1 (2×CH), 123.6 (2×CH), 66.1, 63.2, 62.0, 61.1, 60.2, 47.8, 36.3, 33.4, 30.0, 14.2; IR (nujol, cm^{-1}): 1736, 1611, 1511, 1416, 1353, 1309, 1272, 1187, 1171, 1063, 1028; CIMS (*m/z*, rel intensity %): 514 (M^{+1}, base peak), 484 (12), 440 (8), 278 (10), 237 (12); HRMS: Calcd: 513.2264 for $C_{30}H_{31}N_3O_5$; Found: 513.2259.

3.2.15. (*R*,*R*,*R*,*R*,*S*)-Ethyl,4-[(2′-hydroxy-1′-methyl-2′-phenyl-ethyl)carbamoyl]-5-(2,4-dichlorophenyl)-pyrrolidine-2-carboxylate (4e$_1$). White powder; mp 182–3 °C; $[\alpha]_D^{23}=-101$ (*c* 1.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 7.40–7.15 (m, 8H, Ar), 4.61 (d, 1H, $J=6.6$ Hz, C*H*OH), 4.40 (d, 1H, $J=4.0$ Hz, H-5), 4.27 (dq, 2H, OCH_2), 4.10 (broad m, 2H, OH + C*H*-CH_3), 3.84 (t, 1H, $J=7.9$ Hz, H-2), 3.57 (ddd, 1H, $J=4.0$, 7.3, 10.7 Hz, H-4), 2.80 (m, 1H, H_2-3), 2.47 (s, 3H, NMe), 2.35 (m, 1H, H_2-3), 1.33 (t, 3H, $J=7.1$ Hz, CH_3), 0.72 (d, 3H, $J=7.3$ Hz, CH_3); ^{13}C NMR: 173.6 (C=O), 172.8 (C=O), 141.7, 134.7, 133.7, 133.2, 129.2, 128.5, 127.9 (2×CH), 127.3, 127.1, 126.1 (2×CH), 76.5, 62.3, 59.8, 56.8, 43.5, 34.8, 32.5, 14.2, 11.4; IR (KBr, cm^{-1}): 3377, 2987, 1736, 1621, 1476, 1449, 1413, 1374, 1206, 1104, 1048; CIMS (*m/z*, rel intensity %): 479 (M^+, base peak), 463 (20), 314 (31), 280 (15), 176 (10), 148 (52), 135 (22), 107 (25); HRMS: Calcd: 478.1426 for $C_{24}H_{28}Cl_2N_2O_4$; Found: 478.1409.

3.2.16. (*R*,*R*,*R*,*R*,*S*)-Ethyl,4-[(2′-hydroxy-1′-methyl-2′-phenyl-ethyl)carbamoyl]-5-(2,4-dichlorophenyl)-pyrrolidine-2-carboxylate (4e$_2$). White powder; mp 182–3 °C; $[\alpha]_D^{23}=-101$ (*c* 1.0, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 7.40–7.15 (m, 8H, Ar), 4.61 (d, 1H, $J=6.6$ Hz, C*H*OH), 4.40 (d, 1H, $J=4.0$ Hz, H-5), 4.27 (dq, 2H, OCH_2), 4.10 (broad m, 2H, OH+C*H*–CH_3), 3.84 (t, 1H, $J=7.9$ Hz, H-2), 3.57 (ddd, 1H, $J=4.0$, 7.3, 10.7 Hz, H-4), 2.80 (m, 1H, H_2-3), 2.47 (s, 3H, NMe), 2.35 (m, 1H, H_2-3), 1.33 (t, 3H, $J=7.1$ Hz, CH_3), 0.72 (d, 3H, $J=7.3$ Hz, CH_3); ^{13}C NMR: 173.6 (C=O), 172.8 (C=O), 141.7, 134.7, 133.7, 133.2, 129.2, 128.5, 127.9 (2×CH), 127.3, 127.1, 126.1 (2×CH), 76.5, 62.3, 59.8, 56.8, 43.5, 34.8, 32.5, 14.2, 11.4; IR (film, cm^{-1}): 3377, 2987, 1736, 1621, 1476, 1449, 1413, 1374, 1206, 1104, 1048; CIMS (*m/z*, rel intensity %): 479 (M^+, base peak), 463 (20), 314 (31), 280 (15), 176 (10), 148 (52), 135 (22), 107 (25); HRMS: Calcd: 478.1426 for $C_{24}H_{28}Cl_2N_2O_4$; Found: 478.1419.

3.2.17. (*R*,*R*,*R*,*R*,*S*)-Ethyl,5-(4-methoxyphenyl)-4-[(2′-hydroxy-1′-methyl-2′-phenyl-ethyl)carbamoyl]-pyrrolidine-2-carboxylate (4e$_3$). White needles, mp. 134–5 °C; $[\alpha]_D^{23}=-59$ (*c*, 1.3, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 7.28–7.14 (m, 7H, Ar), 6.80 (d, 2H, $J=7.5$ Hz, Ar), 4.55 (br s, 1H, OH), 4.41 (d, 1H, $J=4$ Hz, H-5), 4.28 (m, 3H, C*H*OH and, CH_2CH_3), 4.11 (m, 1H, $CHCH_3$), 3.81 (t, 1H, $J=8.0$ Hz, H-2), 3.73 (s, 3H, OMe), 3.33 (dd, 1H, $J=7$, 13 Hz, H-4), 2.75 (br s, 1H, NH), 2.45 (m, 1H, H_2-3), 2.35 (s, 3H, NCH_3), 2.27 (m, 1H, H_2-3), 1.33 (t, 3H, $J=8.7$ Hz, CH_3), 0.72 (d, 3H, $J=$Hz, CH_3); ^{13}C NMR: 173.4 (q), 173.3 (q), 159.1 (q), 141.9 (q), 130.6 (q), 128.2 (2×CH), 127.9 (2×CH), 127.1 (CH), 126.1 (2×CH), 113.5 (2×CH), 76.5, 65.6, 60.9, 59.9, 57.0, 55.2, 46.6, 34.6, 32.4, 14.1, 11.0; IR (nujol, cm^{-1}): 3184, 1739, 1609, 1521, 1402, 1259, 1231, 1104, 1027; EIMS (*m/z*, rel intensity %): 441 (M^{+1}, 6), 367 (10), 333 (10), 307 (19), 276 (base peak), 174 (34), 147 (49), 105 (38); HRMS: Calcd: 442.2467 for $C_{25}H_{34}N_2O_5$; Found: 442.2463.

3.2.18. (*R*,*R*,*R*,*R*,*S*)-Ethyl,5-(3,4-dimethoxyphenyl)-4-[(2′-hydroxy-1′-methyl-2′-phenyl-ethyl)carbamoyl]-pyrrolidine-2-carboxylate (4e$_4$). White needles, mp. 155 °C; $[\alpha]_D^{23}=-46$ (*c*, 1.5, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): 7.29–7.18 (m, 5H, Ph), 6.87 (d, 1H, $J=2.0$ Hz, Ar-2′H), 6.82 (dd, 1H, $J=2.0$, 8.0 Hz, Ar-6′H), 6.76 (d, 1H, $J=8.0$ Hz, Ar-5′H), 4.47 (d, 1H, $J=3.3$ Hz, C*H*OH), 4.37–4.22

(m, 4H, OCH_2, H-2 and H-4), 4.11 (dq, 1H, $J=3.3$, 7.3 Hz, C*H*–CH_3), 3.85 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.38 (ddd, 1H, $J=2.0$, 5.3, 7.9 Hz, H-4), 2.39 (ddd, 1H, $J=2.0$, 7.9, 13.2 Hz, H_2-3), 2.34 (s, 3H, NMe), 2.32 (ddd, 1H, $J=5.3$, 8.6, 13.2 Hz, H_2-3), 1.34 (t, 3H, $J=7.3$ Hz, CH_3), 0.78 (d, 3H, $J=7.3$ Hz, CH_3); ^{13}C NMR: 173.9 (C═O), 173.4 (C═O), 148.8 (2×q), 141.8 (q), 131.6 (q), 128.0 (2×CH), 127.4 (CH), 126.2 (2×CH), 119.5 (CH), 110.8 (CH), 110.5 (CH), 76.9 (*C*HOH), 66.1, 61.0, 60.1, 57.9, 55.9 (2×MeO), 46.8, 34.8, 32.9, 14.2, 11.4; IR (nujol, cm^{-1}): 3181, 1737, 1608, 1519, 1402, 1305, 1256, 1238, 1195, 1141, 1104, 1023; CIMS (*m*/*z*, rel intensity %): 471 (M^{+1}, base peak), 453 (18), 397 (8), 337 (10), 306 (28), 252 (12), 202 (18), 166 (20), 148 (42), 107 (13);HRMS: Calcd: 470.2417 for $C_{26}H_{34}N_2O_6$; Found: 470.2415.

3.2.19. (*R*,*R*,*R*)- or (*S*,*S*,*S*)-Diethyl, 5-phenyl-pyrrolidine-2,4-dicarboxylate (8). *Preparation from homochiral cycloadducts—General procedure*. The corresponding cycloadduct (**3** or **4**, 1.0 mM) was dissolved in ethanol (20 mL) and concentrated hydrochloric acid (3 mL) was added. The reaction mixture was refluxed overnight, then all the solvents were removed, and the residue was dried in vacuo. The obtained white powder was suspended in dry ethanol (10 mL) and thionyl chloride was added (0.2 mL). After 1 h reflux, when all the solids dissolved again the solvents were removed in vacuo and the residue was redissolved in ether–triethylamine mixture (25 mL/1 mL). This solution was washed with water and brine, dried over magnesium sulfate and evaporated in vacuo. The remaining oil was purified by column chromatography to yield the corresponding enantiomer of the title diester as a colurless oil; $[\alpha]_D^{23}=\pm 88$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.30 (m, 5H, Ph), 4.54 (d, 1H, $J=7.9$ Hz, H-5), 4.29 (q, 2H, $J=6.6$ Hz, OCH_2), 3.96 (t, 1H, $J=7.9$ Hz, H-2), 3.70 (dq, 2H, OCH_2), 3.31 (dd, 1H, $J=7.3$, 13.8 Hz, H-4), 2.78 (br s, 1H, NH), 2.41 (m, 2H, H_2-3), 1.33 (t, 3H, CH_3), 0.82 (t, 3H, $J=6.6$ Hz, CH_3); ^{13}C NMR: 173.3 (C═O), 172.6 (C═O), 139.2 (Ph-1′C), 128.1 (2×CH), 127.5 (Ph-4′C), 126.9 (2×CH), 65.9, 61.2, 60.2, 60.1, 49.7, 33.6, 14.2, 13.6; IR (film, cm^{-1}): 3351, 2980, 2905, 1732, 1451, 1378, 1198, 1166, 1111, 1037; CIMS (*m*/*z*, rel intensity %): 292 (M+1, 100), 246 (22), 218 (55), 191 (13), 144 (10), 117 (9), 29 (41); HRMS: Calcd: 291.1470 for $C_{16}H_{21}NO_4$; Found: 291.1463.

3.3. Grignard reaction

A Grignard reagent, freshly prepared from the addition of Mg (0.52 g, 21.6 mmol) to benzyl bromide (2.6 mL, 21.6 mmol) in anhyd Et_2O (50 mL) at room temperature for 1 h, was transferred to a solution of **4a$_1$** (0.73 g, 2 mmol) or **4e$_1$** (0.79 g, 2 mmol) in anhyd Et_2O (25 mL) at 0 °C via a cannula. The reaction mixture was refluxed under N_2 for 2 h, quenched by H_2O (15 mL). The organic layer was washed with H_2O (50 mL) brine (50 mL), dried ($MgSO_4$) and rotary evaporated to give a crude product which was purified by column chromatography (30% EtOAc/petroleum ether).

3.3.1. 2-(Diphenyl-hydroxy-methyl)-5-phenyl-4-[(1′-phenylethyl)carbamoyl]-pyrrolidine (9). Yield: 0.79 g, (84%); white powder; mp 219–20 °C; $[\alpha]_D^{23}=-22$ (*c* 0.16, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.67 (d, 2H, $J=$ 7.3 Hz, Ph), 7.61 (d, 2H, $J=7.3$ Hz, Ph), 7.35–7.12 (m, 14H, Ph), 7.03 (d, 2H, $J=7.9$ Hz, Ph), 5.78 (s, 1H, NHCO), 5.21 (d, 1H, $J=7.9$ Hz, H-5), 4.68 (quintet, 1H, CH_3CH), 4.49 (t, 1H, $J=7.0$ Hz, H-2), 2.84 (ddd, 1H, $J=2.6$, 7.9, 9.2 Hz, H-4), 2.27 (ddd, 1H, $J=2.6$, 7.0, 14.5, H_2-3), 2.00 (ddd, 1H, $J=7.0$, 9.2, 14.5 Hz, H_2-3), 0.82 (d, 1H, $J=$ 6.6 Hz, Me), ^{13}C NMR: 172.3 (C═O), 147.5 (Ph-1′C), 146.4 (Ph-1′C), 142.9 (Ph-1′C), 139.2 (Ph-1′C), 128.4, 128.2, 127.7, 127.2, 126.9, 126.4, 126.1, 126.0, 125.8, (overlapping CHs), 112.1, 76.2, 65.8, 63.6, 50.4, 48.4, 37.3, 29.7, 20.6; IR (nujol, cm^{-1}): 3152, 1591, 1301, 1259, 1203, 1128, 1035; CIMS (*m*/*z*, rel intensity %): 477 (M^{+1},3), 459 (6), 293 (10), 257 (18), 229 (18), 183 (90), 159 (50), 85 (87), 57 (100); HRMS: Calcd: 476.2464 for $C_{32}H_{32}N_2O_2$; Found: 476.2467.

3.3.2. 2-(Diphenyl-hydroxy-methyl)-4-[(2′-hydroxy-1′-methyl-2′-phenyl-ethyl)carbamoyl]-5-phenyl-pyrrolidine (10). Yield: 0.92 g (91%); white powder; mp 232 °C; $[\alpha]_D^{23}=-15$ (*c* 0.26, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): 7.65 (d, 2H, $J=6.6$ Hz, Ph), 7.63 (d, 2H, $J=7.3$ Hz, Ph), 7.37–7.10 (m, 16H, Ph), 6.14 (br s, 1H, OH), 4.49–4.43 (m, 3H, H-2, H-5 and C*H*OH), 4.05 (br m, 1H, CH_3CH), 3.40 (dt, 1H, $J=4.0$, 7.9 Hz, H-4), 2.35 (ddd, 1H, $J=4.0$, 7.3, 13.9 Hz, H_2-3), 2.21 (s, 3H, NMe), 1.91 (ddd, 1H, $J=7.3$, 8.0, 13.9, H_2-3), 0.63 (d, 2H, $J=6.8$ Hz, CH_3); ^{13}C NMR: 175.3 (C═O), 147.5 (q), 146.7 (q), 141.7 (q), 139.1 (q), 128.1, 127.5, 127.0, 126.4, 126.1, (overlapping CHs), 77.7, 65.9, 63.9, 58.2, 45.6, 33.0, 30.6, 11.0; IR (nujol, cm^{-1}): 3164, 1594, 1309, 1253, 1203, 1128, 1024; CIMS (*m*/*z*, rel intensity %): 521 (M^+,2), 337 (4), 319 (5), 211 (7), 183 (base peak), 148 (32), 105 (27); HRMS: Calcd MH^+: 521.2804 for $C_{34}H_{37}N_2O_3$; Found: MH^+ 521.2805.

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Hammett-type relationship for the cleavage of radical anions of aromatic chlorides and bromides

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Abstract—A Hammett-type correlation pertaining to the cleavage of radical anions of aromatic halides has been formulated. The expression has been verified using the reaction series of aromatic chlorides and bromides. The correlation reveals the sensitive nature of the carbon–chlorine bond to the polar effects of the substituents in comparison to the carbon–bromine bond. The cleavage rate constants of radical anions of some aromatic chlorides and bromides have been deduced using the correlation. The standard potentials for formation of radical anions of aromatic chlorides and bromides have been estimated based on the correlation.

1. Introduction

In the past few decades, the data collected on rates and equilibria of reactions have resulted in the formulation of a number of empirical relationships. The introduction of a substituent may alter the reactivity of a compound, for example, toluene is nitrated more rapidly than benzene and less rapidly than nitrobenzene. The structure–reactivity correlations are influenced by a number of factors, of which the polar effect is important. In this context, the Hammett equation[1] describes a linear correlation between the logarithms of rate or equilibrium constants of one reaction series with those of another reaction series which has been subjected to the same variations of substrate structure.

Aromatic molecules with a suitable leaving group (ArX) undergo electron transfer at the electrode surface and are capable of hosting transitorily the incoming electron in their π^* orbitals leading to the radical anions ($ArX^{\cdot -}$, reaction 1)

$$ArX + e^- \rightleftharpoons ArX^{\cdot -} \quad (E^0_{ArX/ArX^{\cdot -}}) \tag{1}$$

$$ArX^{\cdot -} \xrightarrow{k} Ar^{\cdot} + X^- \tag{2}$$

The radical anion $ArX^{\cdot -}$ readily undergoes decomposition to yield neutral radical $Ar^{\cdot}$ and anion X^- (reaction 2) and the cleavage rate constant varies significantly with the nature of Ar and X. Reaction 1 is simply an outer-sphere electron transfer where no bonds are broken or formed and the kinetics of the reaction can be analyzed using the Marcus–Hush theory of outer-sphere electron transfer.[2] Semi-empirical quantum mechanical calculations suggest that the cleavage of radical anion may be viewed as an intramolecular concerted electron transfer-bond breaking process.[3] When the breaking bond begins stretching, the unpaired electron present in the π^* orbital of the ring is transferred to the σ^* orbital of the stretching bond simultaneous with its cleavage. The activation–driving force relationship for the intramolecular concerted electron transfer-bond breaking reactions is described by a relationship similar to the activation–driving force relationship of the Marcus–Hush model of outer-sphere electron transfer.[4]

The purpose of this paper is to report the formulation of a Hammett-type relationship for the reaction 2 and illustrate the correlation using the cleavage of radical anions of aromatic chlorides and bromides for which the first order cleavage rate constant data are available. As an application of the correlation, the cleavage rate constants of radical anions of some aromatic chlorides and bromides have been predicted. The standard potentials for formation of radical anions of aromatic chlorides and bromides, which are difficult (or impossible) to estimate in the case of irreversible voltammetric reductions, have also been deduced based on the correlation in conjunction with a previous report.[4]

2. Formulation of the relationship

The reduction of a large number of aromatic molecules

Keywords: Hammett equation; Aromatic halides; Reductive cleavage; Radical anion; Reaction constant; Cleavage rate constant; Standard potential.
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involving the cleavage of an aromatic carbon–heteroatom σ-bond leads to the formation of radical anions and the widely investigated family of compounds in this connection are aromatic halides. In the reductive cleavage reactions of aromatic halides, electron transfer and bond breaking are two distinct steps and the dissociation of radical anions may be viewed as an intramolecular dissociative electron transfer. According to the nature of the halogen and of the aromatic moiety, the life time of the radical anions spans between several minutes and nanoseconds.[3] The polar effects of the substituents on the cleavage rate constant of the carbon–halogen bond should be equal for two different series of molecules having the same aromatic moieties but different halogens. Hence it follows that, the polar effects of the substituents on the cleavage of radical anions of aromatic halides can be studied, more suitably, using a Hammett-type relationship. Considering a reaction series of cleavage of radical anions of aromatic halides ($k^i_{ArX^{\cdot-}}$ as the first order cleavage rate constant of the *i*th radical anion) and another series with different halogen ($k^i_{ArX'^{\cdot-}}$ as the first order cleavage rate constant of the *i*th radical anion), a linear relationship between the logarithms of cleavage rate constants of the two series can be postulated as shown in Eq. 3.

$$\log k^i_{ArX^{\cdot-}} = \rho \log k^i_{ArX'^{\cdot-}} + c \tag{3}$$

where ρ is the slope and c, the intercept. For a special case where there is no substituent (i.e., hydrogen as the substituent) Eq. 3 may be rewritten as Eq. 4.

$$\log k^0_{ArX^{\cdot-}} = \rho \log k^0_{ArX'^{\cdot-}} + c \tag{4}$$

The constant c in the Eq. 3 can be eliminated by subtracting Eq. 4 from Eq. 3, to yield Eq. 5.

$$\log \frac{k^i_{ArX^{\cdot-}}}{k^0_{ArX^{\cdot-}}} = \rho \log \frac{k^i_{ArX'^{\cdot-}}}{k^0_{ArX'^{\cdot-}}} \tag{5}$$

Eq. 5 can be employed for any pair of series of aromatic halides. It is possible to relate any two series by correlating them to a standard series, for example to that of ArX'. Denoting $\log(k^i_{ArX'^{\cdot-}}/k^0_{ArX'^{\cdot-}})$ values as σ, Eq. 5 becomes Eq. 6.

$$\log \frac{k^i_{ArX^{\cdot-}}}{k^0_{ArX^{\cdot-}}} = \rho\sigma \tag{6}$$

Eq. 6 is the Hammett-type relationship pertaining to the cleavage of radical anions of aromatic halides with ρ as the reaction constant and σ as the substituent constant. The reaction constant ρ is dependent on the carbon–halogen bond being cleaved and on the nature of the solvent, since the cleavage of $ArX^{\cdot-}$ was found to be sensitive to the polarity of the solvent.[6] The substituent constant σ represents a quantitative measure of the polar effects of the substituents relative to hydrogen.

For a given reaction series, the driving force of the cleavage of radical anions (reaction 2) is influenced by (a) the strength of the bond being cleaved, viz. the bond dissociation energy and (b) the standard potential of the radical anion ($E^0_{ArX/ArX^{\cdot-}}$). A linear relationship between the standard potential of the radical anions (which are a measure of the π* orbital energy of the aromatic rings[7]) and $\log k_{ArX^{\cdot-}}$ was reported and was rationalized invoking a linearized version of activation–driving force relationship which requires, for a given halogen, the assumption that the bond dissociation energy does not vary much with the aromatic moiety.[4] Relationship 3, however, is more general and does not require the bond dissociation energy to be constant for each series. The influence of variation in bond dissociation energy on $\log k^i_{ArX^{\cdot-}}$ (lhs of Eq. 3) is proportionately compensated by the influence of variation in bond dissociation energy on $\log k^i_{ArX'^{\cdot-}}$ (rhs of Eq. 3), hence the polar effects of the substituents (which govern the π* energy level of the ring where the unpaired electron is located) are reflected in the cleavage rate constants with high fidelity.

3. Cleavage of radical anions of aromatic chlorides and bromides

Aromatic chlorides and bromides follow a stepwise mechanism for reductive cleavage.[8] Experimentally, direct and indirect electrochemical methods are used to determine the cleavage rate constants of radical anions, which span more than 10 orders of magnitude.[3] For example, in the 10^{-1}–$10^{7}\ s^{-1}$ range of $k_{ArX^{\cdot-}}$, direct electrochemical methods, viz. cyclic voltammetry or double potential step chronoamperometry is used. In the 10^{6}–$10^{9}\ s^{-1}$ range, redox catalysis which is an indirect electrochemical method, is used to estimate $k_{ArX^{\cdot-}}$. The rate constant data for the cleavage of radical anions of aromatic chlorides and bromides are available[4,9] and can be employed to verify Eq. 6. Chlorobenzene and bromobenzene have been selected as the unsubstituted compounds of the respective series. The reaction series of chlorides and bromides have phenyl, 4-nitrophenyl, 4-benzoylphenyl, 3-acetylphenyl, 4-acetylphenyl, 1-naphthyl and 9-anthracenyl moieties. The cleavage rate constants of the chlorobenzene and bromobenzene were obtained using the respective standard potentials[8] ($E^0_{ArX/ArX^{\cdot-}}$) and the linear variation of $\log k_{ArX^{\cdot-}}$ versus $E^0_{ArX/ArX^{\cdot-}}$ plots for the aromatic chlorides and

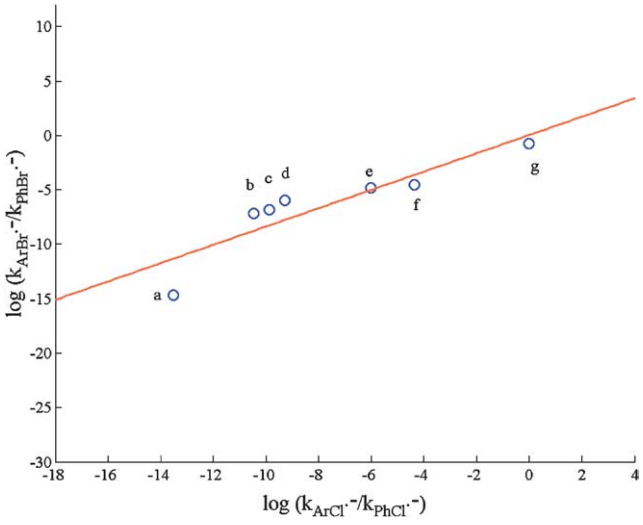

Figure 1. Correlation between $\log(k_{ArBr^{\cdot-}}/k_{PhBr^{\cdot-}})$ and $\log(k_{ArCl^{\cdot-}}/k_{PhCl^{\cdot-}})$ values for the aromatic moieties (a) 4-nitrophenyl, (b) 4-benzoylphenyl, (c) 9-anthracenyl, (d) 4-acetylyphenyl, (e) 3-acetylphenyl, (f) 1-naphthyl and (g) phenyl.

Table 1. Logarithmic cleavage rate constants and standard potentials of radical anions of aromatic chlorides estimated using Eq. 6

Aromatic moieties	Logarithmic cleavage rate constants ($\log k_{ArCl^{\cdot-}}$) predicted from Eq. 6	$E^0_{ArCl/ArCl^{\cdot-}}$ (vs SCE) estimated using $\log k_{ArCl^{\cdot-}}$ values and the correlation reported in Ref. 4
2-Methyl-4-nitrophenyl	−5.30	−731
2-Methyl-3-nitrophenyl	−4.24	−860
2-Isopropyl-4-nitrophenyl	−3.89	−902
1-Fluorenoyl	−3.89	−902
3-Fluorenoyl	−3.65	−932
2,6-Dimethly-4-nitrophenyl	−3.05	−1004
3-Benzoylphenyl	0.51	−1437

Table 2. Logarithmic cleavage rate constants and standard potentials of radical anions of aromatic bromides estimated using Eq. 6

Aromatic moieties	Logarithmic cleavage rate constants ($\log k_{ArBr^{\cdot-}}$) predicted from Eq. 6	$E^0_{ArBr/ArBr^{\cdot-}}$ (vs SCE) estimated using $\log k_{ArBr^{\cdot-}}$ values and the correlation reported in Ref. 4
2-Nitrophenyl	0.93	−1271
1-Anthracenyl	3.49	−1554
2-Anthracenyl	4.17	−1629
4-(2-(4-Pyridyl)vinyl)phenyl	3.58	−1564
2-Quinolyl	7.62	−2011
4-Quinolyl	7.62	−2011
4-Cyanophenyl	9.34	−2201

bromides.[4,5] From the above data, the variation between $\log(k_{ArBr^{\cdot-}}/k_{PhBr^{\cdot-}})$ and $\log(k_{ArCl^{\cdot-}}/k_{PhCl^{\cdot-}})$ has been deduced and is shown in Figure 1. The plot is satisfactorily linear with a slope of 0.841 (correlation coefficient = 0.91), thus validating Eq. 6. The slope of the plot represents the reaction constant (ρ) and its value is less than unity indicating that the reactivity of the cleavage of the carbon–bromine bond is less than that of the carbon–chlorine bond. In other words, the sensitivity of the aromatic bromides to the polar effects of the substituents is 0.841 times that of the aromatic chlorides. The expression 6 could not be verified more extensively on account of the lack of data on cleavage rate constants.

The correlation proposed here offers a way to predict the cleavage rate constant of radical anion of an aromatic bromide when that of the radical anion of the aromatic chloride is known and vice versa—which is very useful in selecting radical anions for redox catalysis.[10,11] Furthermore, using the correlation reported by Saveant, viz. linear variation of $\log k_{ArX^{\cdot-}}$ with $E^0_{ArX/ArX^{\cdot-}}$ for aromatic chlorides and bromides,[4,5] it is possible to estimate the standard potential for formation of the radical anion ($E^0_{ArX/ArX^{\cdot-}}$) of either aromatic chloride or bromide if the cleavage rate constant ($\log k_{ArX^{\cdot-}}$) of the other aromatic halide is known and vice versa. The significance of the above application lies in the fact that for irreversible voltammetric reduction of an aromatic halide, it is seldom possible to estimate $E^0_{ArX/ArX^{\cdot-}}$ using direct methods.[11] Moreover, if the reduction does not obey the quadratic activation–driving force relationship, $E^0_{ArX/ArX^{\cdot-}}$ cannot be estimated even using convolution potential sweep voltammetry.[12,13] Table 1 shows the logarithmic cleavage rate constants of radical anions of some aromatic chlorides ($\log k_{ArCl^{\cdot-}}$) obtained using the values of logarithmic cleavage rate constants of radical anions of respective aromatic bromides[4,9] and the correlation 6. Table 1 also gives the predicted $E^0_{ArCl/ArCl^{\cdot-}}$ values estimated using the linear $\log k_{ArCl^{\cdot-}}$ versus $E^0_{ArCl/ArCl^{\cdot-}}$ plot of Saveant.[4,5] Analogously, Table 2 gives the logarithmic cleavage rate constants of radical anions of some aromatic bromides for which the data on logarithmic cleavage rate constants of radical anions of respective aromatic chlorides are available.[4,9] Combining the above data and the linear variation of $\log k_{ArBr^{\cdot-}}$ with $E^0_{ArBr/ArBr^{\cdot-}}$ plot of Saveant,[4,5] $E^0_{ArBr/ArBr^{\cdot-}}$ values of respective aromatic bromides have been deduced and are shown in Table 2.

4. Summary

A Hammett-type linear correlation which describes the effects of polar factors on reactivity in aromatic compounds has been suggested and formulated for the cleavage of radical anions of aromatic halides. The correlation has been illustrated using the cleavage of radial anions of aromatic chlorides and bromides which reveals the sensitive nature of the carbon–chlorine bond to the polar effects of the substituents in comparison to the carbon–bromine bond. The cleavage rate constants of radical anions of some aromatic chlorides and bromides have been predicted using the correlation. Another interesting possibility consists in estimating the standard potentials for the formation of radial anions of aromatic chlorides and bromides when $\log k_{ArX^{\cdot-}}$ values for the other halide become available.

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Investigating direct routes to an advanced intermediate for the synthesis of C-20 diterpene alkaloids

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Abstract—Rapid access to the ABCE ring system of the C-20 diterpene alkaloids was achieved by silver (I) promoted intramolecular Friedel–Crafts arylation of a functional group specific 5-bromo-3-azabicyclo[3.3.1]nonane derivative.

1. Introduction

Diterpene alkaloids have been isolated from a range of plants including *Aconitum*, *Delphinium*, *Consolida*, *Thalictrum* and *Spiraea* species.[1,2] There has been some interest in their biological activity,[3] but it is their complex highly functionalised skeletons that have attracted the attention of numerous synthetic[4] chemists. Of particular note is the work of the Wiesner,[5] Masamune,[6] Fukumoto,[7] and Nagata groups[8] all of whom have shown enormous creativity and ingenuity in their efforts to assemble these complex structures. The construction of the highly bridged structures of the kobusine[9] (**1**)–hetisine[10] (**2**) family[11] (Fig. 1) of alkaloids, however, has remained elusive. Some progress has been made[12–14] and these reports prompt us to disclose our own endeavours in the field.

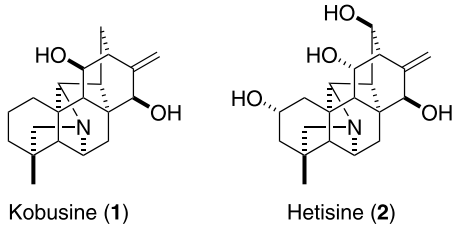
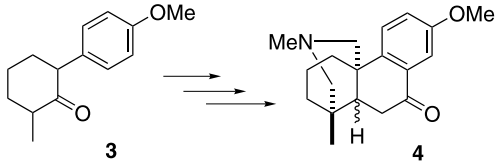


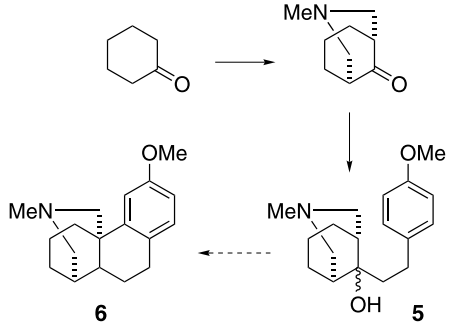
Figure 1.

In designing our approach, we were mindful of the formidable logistical challenges that were likely to develop in pursuing a target possessing such a complex skeleton and were consequently drawn to the double Mannich strategy developed by Shimizu et al.[15] The rapid assembly of 3-azabicyclo[3.3.1]nonan-7-ones on cyclohexanone based starting materials,[16] provides a particularly direct and efficient method for assembling the E-ring of these alkaloids and when applied to the aryl substituted cyclohexanone **3**, afforded a particularly direct synthesis of the tetracyclic intermediate **4**, although with poor stereochemical control (Scheme 1).[17]



Scheme 1.

Shimizu et al. also prepared 3-methyl-9-(4-methoxyphenyl-ethyl)-3-azabicyclo[3.3.1]nonan-9-ol **5** by a similar approach, but were unable to convert it into the target phenanthrene derivative **6** (Scheme 2).[15]



Scheme 2.

Keywords: Diterpene alkaloids; Silver (I); Intramolecular Friedel–Crafts arylation; 3-Azabicyclo[3.3.1]nonane.
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Although equivalent arene carbinols have been cyclised to give hydrophenanthrenes this must occur *via* alkene formation or a 1,2-hydride shift to give cation **7** (Fig. 2).[18] With the azabicyclononane, however, the formation of the necessary bridgehead alkene or cation would constitute a violation of Bredt's rule.[19]

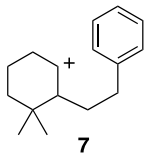


Figure 2.

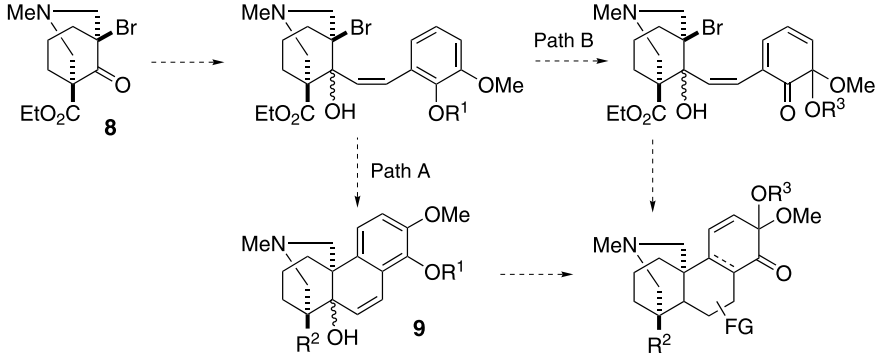
To address the problem, we elected to begin with the bromo-3-azabicyclo[3.3.1]nonanone **8** (the *N*-methyl analogue of an intermediate that had been prepared previously by Kraus and Shi[20]) in the knowledge that intermolecular bridgehead arylation had been achieved with 1-bromoadamantane using palladium (Pd/C) at high temperature (de Meijere[21]) and with 1-bromobicyclo[2.2.2]octane using silver (I) salts at room temperature (Kraus[22]). As an alternative coupling strategy, we could also envisage a free radical based approach initiated by loss of a bromine radical.[23] For the elaboration of the C- and D-rings, we planned to utilise an aromatic C-ring that would serve as a precursor to an *ortho*-quinonoid moiety in anticipation of the addition of the D-ring by means of a [4+2] cycloaddition, a tactic that has been used so effectively by Wiesner.[24] If we could combine these various elements into a viable strategy, then there was a reasonable expectation of restricting the complete sequence to a manageable length. Thus, we arrived at the synthetic plan outlined in Scheme 3 and now describe in full our investigations, which have culminated in an exceptionally direct approach to the advanced intermediate **9**.[25]

2. Results and discussion

Attempts were made to prepare **10** either by treating **8** with the metalated *cis*-styrene[26] **11**, derived from the telluride **12**, or the less sterically demanding alkyne analogue **13**[27] followed by reduction. It was hoped that the *cis* stereochemistry of the alkene bond in **10** would reduce the degrees of freedom relative to the saturated analogue and maximize the chances of the planned cyclisation. Both reagents were synthesised from *ortho*-vanillin in good overall yield, using Comasseto–Marino[26] and Corey–Fuchs methodology,[28] respectively. The robust isopropylether masking function as developed by Banwell[29] had been chosen for both of these approaches so as to allow for selective de-alkylation at the appropriate juncture without the risk of premature deprotection. In the event, only small amounts of the rearranged product **14** were obtained when **11** was employed (Fig. 3).

We therefore deprotonated arylacetylene **13** with methylmagnesium bromide (i.e., **15**) and added it to bicycle **8** dissolved in toluene, thereby affording a 3:2 mixture of diastereomers **16** and **17**, respectively, in 94% yield. With THF as solvent, however, mainly the desired epimer[30] **16** (64% yield) was obtained, accompanied this time by the by-product **18** from rearrangement of **17** (Scheme 4). This kind of rearrangement had also been observed by Kraus and put to good effect in the synthesis of epi-modhephene.[20]

Catalytic hydrogenation of the alkyne bond in **16** without hydrogenolysis of the bridgehead bromo substitutent proved, not surprisingly, to be unattainable, but could be achieved with diimide, generated in situ from 1,3,5-triisopropylbenzenesulfonylhydrazide,[31] to afford the *cis*-alkene **10** in 74% yield as the sole product (Fig. 3). With this intermediate in hand we embarked upon the cyclisation



Scheme 3.

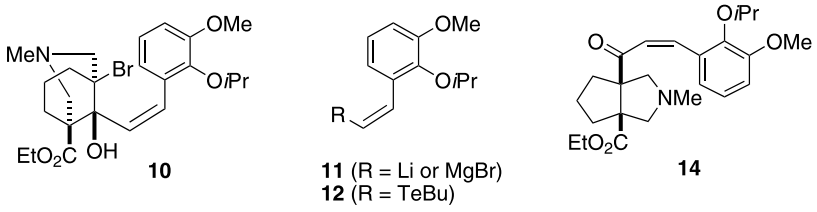
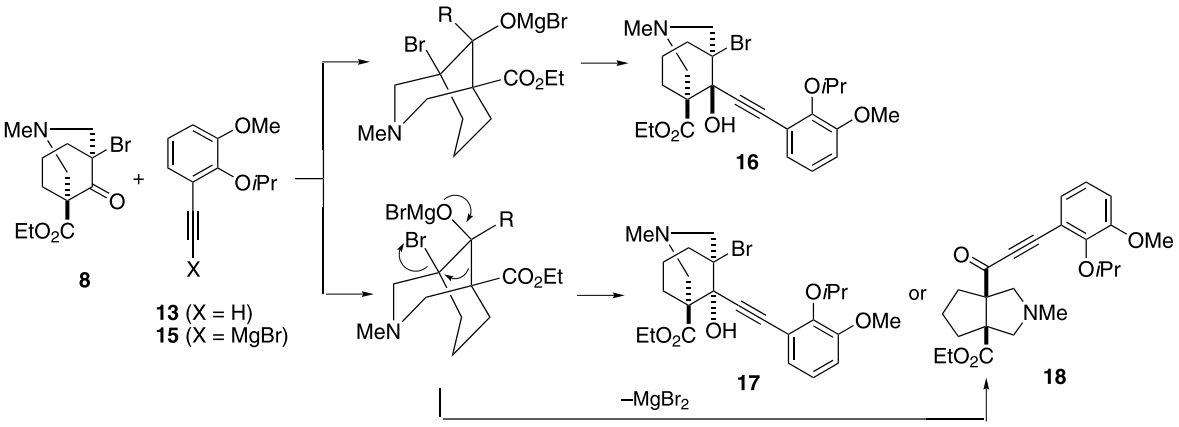
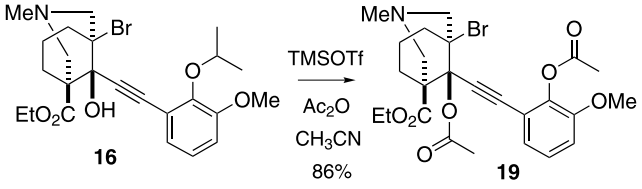


Figure 3.



Scheme 4.

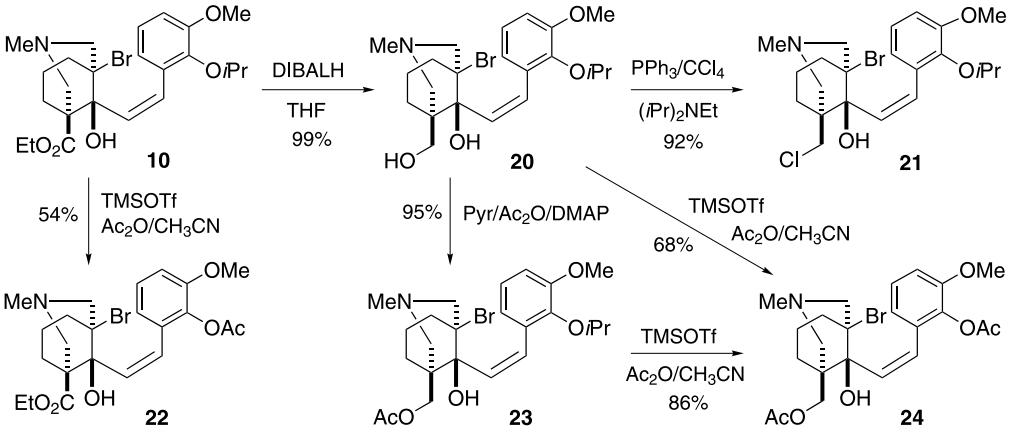
studies. Treatment of **10** with silver trifluoroacetate at various temperatures or with palladium (Pd/C), however, resulted in rearrangement[32] to ketone **14** (Fig. 3). Although, acylation of the hydroxyl could be expected to retard the rearrangement, this deceptively simple step proved to be surprisingly difficult.[33] Nevertheless, when **16** was treated with acetic anhydride and trimethylsilyl triflate, the desired acylation was achieved (i.e., **19**). While replacement of the isopropyloxy function by acetate also occurred[34] (Scheme 5), it was considered to be of no significance as the acetylene was resistant to hydrogenation.



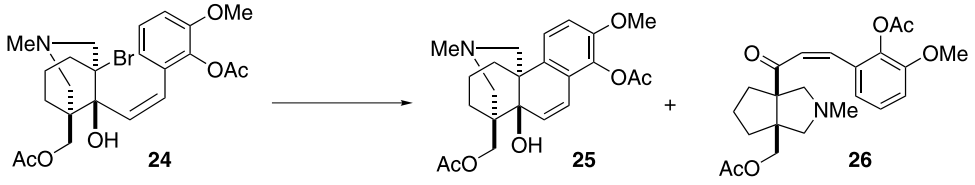
Scheme 5.

Further modification of the functionality in these intermediates by routine procedures to afford substrates **20–23** (Scheme 6) and subsequent treatment with silver trifluoroacetate still failed to result in cyclisation, affording only rearranged products.

However, when both ester and isopropyl functionality were modified, that is, as in diacetate **24**, intramolecular arylation induced by treatment with silver trifluoroacetate was at last observed, producing **25**, albeit in only 18% yield, the remainder consisting of the rearranged product **26** (Scheme 7). Then, after extensive small scale experimentation with different solvents and silver salts [e.g., $AgOCOCF_3$, $AgBF_4$, $AgB(C_6F_5)_4$[35]] we found that the yield of cyclisation could be increased to 53% using silver 2,4,6-trinitrobenzenesulfonate[36] in nitromethane. Changing the solvent system and investigating solvent mixtures gave no improvement on nitromethane. Although it is not entirely clear as to why silver 2,4,6-trinitrobenzenesulfonate



Scheme 6.



Scheme 7.

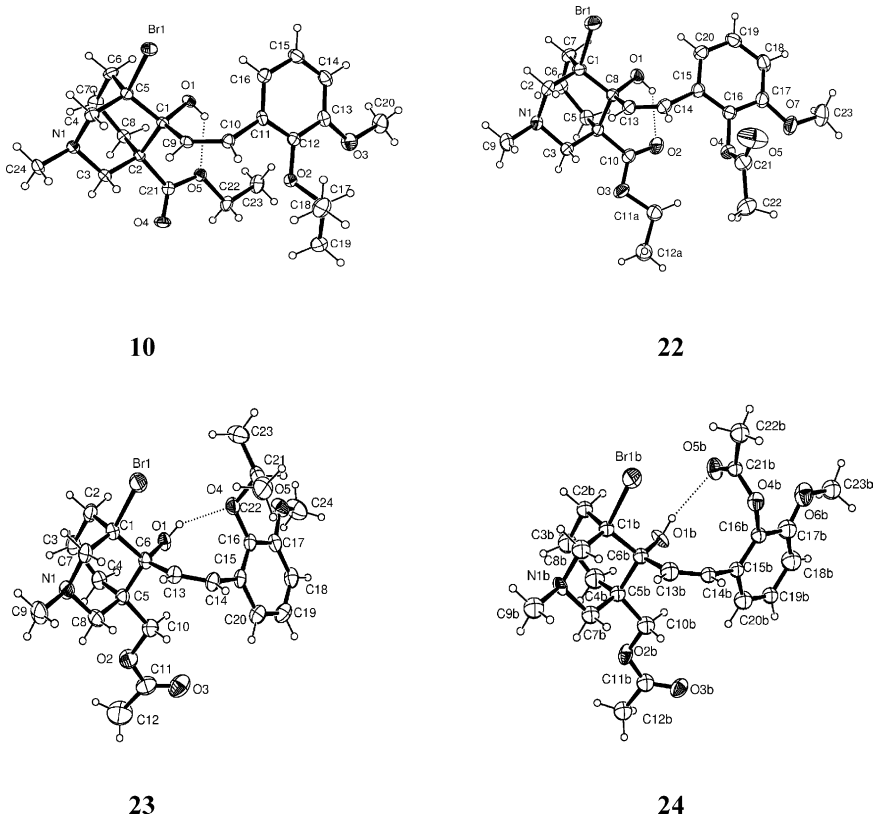


Figure 4. X-ray crystal structure diagrams for compounds **10**, **22**, **23** and **24**. In the case of **24** only one of the two crystallographically independent molecules is shown for this structure.

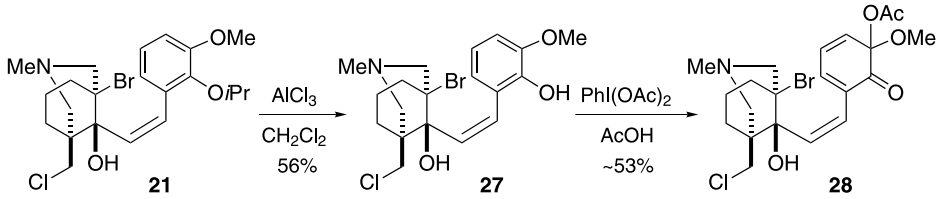
provides such a dramatic improvement in yield it is conceivable, however, that the 2,4,6-trinitrobenzenesulfonate counter ion provides increased silver(I) solubility.

In an attempt to understand why **24** is amenable to cyclisation while derivatives **10** and **20**–**23** fail to bridgehead arylate X-ray crystal structure analysis was performed and data obtained for compounds **10**, **22**, **23** and **24** (Fig. 4).

On close inspection of the ^{1}H NMR spectrum, sharp O*H* singlets are observed for the hydroxyl proton [**10** (5.01 ppm), **20** (4.26 ppm), **21** (4.05 ppm), **22** (3.63 ppm) and **23** (4.46 ppm)] suggesting strong intramolecular hydrogen bonding interactions have formed, but for compound **24** the OH peak is not observed. In the solid state hydrogen bonding is seen for all compounds **10**, **22**, **23** and **24**, but, **24** maintains the longest non-covalent hydrogen–oxygen bond length (2.14–2.19 Å). In the case of strong intramolecular hydrogen bonding (e.g., **10**, **20**, **21**, **22** and **23**) this has two implications: restricted aryl rotation and increasing electron density on the hydroxyl oxygen both favouring the undesired pinacol-type rearrangement.

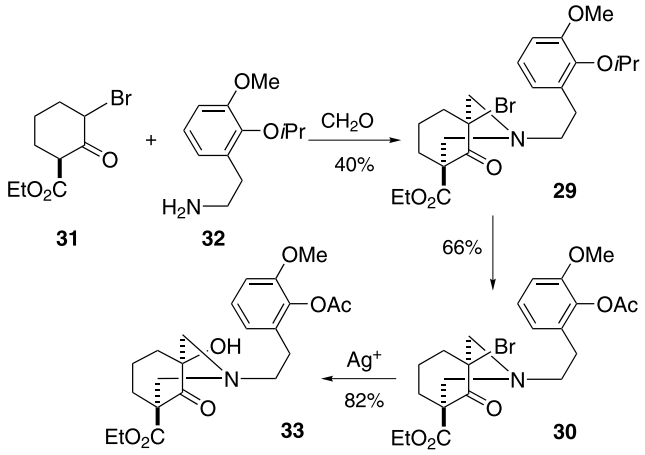
Attempts were made to circumvent the medium yielding silver (I) induced cyclisation by investigating radical based processes. As aromatic rings are generally not amenable to radical mediated substitution (addition/elimination) reactions the aryl ring was firstly dearomatised. Treatment of **21** with aluminium trichloride[29] removed the isopropyl protecting group affording the phenol **27** (56%), which underwent oxidation to the unstable *ortho*-quinone acetal **28** (~53%) with phenyliododiacetate[37] (Scheme 8). Using radical inducing conditions applicable to the azabicyclo-[3.3.1]nonane system[23] (Vitamin B_{12}) resulted in rapid decomposition. Tin based procedures gave similar results.

Finally, in view of the results above *N*-phenethyl derivatives **29** and **30** were synthesised to further probe silver (I) mediated bridgehead arylation. Derivative **29**, obtained in 40% yield from a double Mannich reaction of bromide **31** and amine **32** in the presence of formaldehyde, afforded no



Scheme 8.

cyclised products when subjected to a variety of silver (I) salts. Conversion of **29** into **30** proceeded smoothly (66%) using the TMSOTf/Ac_2O/CH_3CN protocol developed above. Treatment with silver (I) 2,4,6-trinitrobenzenesulfonate[36] in nitromethane, did not lead to a cyclised product but gave instead, alcohol **33** (82%) (Scheme 9).



Scheme 9.

3. Conclusion

We have demonstrated that intramolecular bridgehead arylation of a functional group specific 5-bromo-3-azabicyclo[3.3.1]nonane derivative (**24**) affords a viable route to a highly functionalized, advanced intermediate (**25**), the brevity of the route (the longest linear sequence is only 8 steps) compensating for the modest yield of cyclization. While the kobusine family of alkaloids (>100 in number[11]) remain our main objective, we note that **25** and its analogues may also have the potential to serve as an intermediate for the synthesis of denudatine[38] and dictysine[39] type alkaloids (Fig. 5).

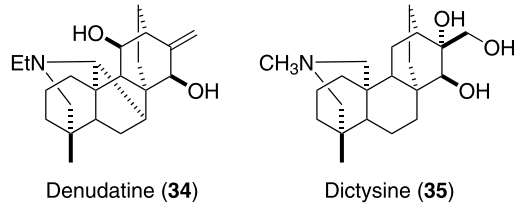


Figure 5.

4. Experimental

4.1. General experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AV400 (400.13 MHz; 100.62 MHz) or a Bruker AC200 (200.13 MHz; 50.32 MHz) in deuteriochloroform ($CDCl_3$). Coupling constants are given in Hz and chemical shifts are expressed as δ values in ppm. High and low resolution EI mass spectral data were obtained on a KRATOS MS 25 RFA. Microanalyses were performed by the University of Queensland Microanalytical Service. Column chromatography was undertaken on silica gel (Flash Silica gel 230–400 mesh), with distilled solvents. Anhydrous solvents were prepared according to Perin and Armarego, 'Purification of laboratory solvents', 3rd Ed. Melting points were determined on a Fischer Johns Melting Point apparatus and are uncorrected. Methylmagnesium bromide was purchased from the Aldrich Chem. Co.

4.2. X-ray crystallography

Data for compounds **22**, **23** and **24** were collected at 293 K on an Enraf-Nonius CAD4 diffractometer. Data reduction, structure solution and refinement (SHELX97[40]) were performed with the WINGX package.[41] For compound **10** data were collected at 200 K on a Nonius Kappa CCD diffractometer. Structure solution and refinement of this structure was carried out with the teXsan package.[42] Drawings of all molecules were created with ORTEP3.[43] Data in CIF format have been deposited with the Cambridge Crystallographic Data Centre (CCDC Deposition Nos. 247761–247764). Copies of the data can be obtained free of charge upon request to deposit@ccdc.cam.ac.uk.

4.2.1. Ethyl 5-bromo-3-methyl-9-oxo-3-azabicyclo-[3.3.1]nonanecarboxylate 8. To a solution of ethyl 6-bromocyclohexanone-2-carboxylate[44] **31** (10 g, 0.040 mol) and formaldehyde (39.1 mL, 0.482 mol, 37% in water) in methanol (160 mL) at 0 °C was added a solution of methylamine (9.35 mL, 0.120 mol, 40% in water) in methanol (90 mL) dropwise over 3 h. The solution was then allowed to warm to room temperature over 20 h followed by refluxing for 30 min. On cooling the volatiles were removed in vacco and the residue diluted with water (100 mL) and extracted with diethyl ether (3×50 mL). The ether layers were dried (Na_2SO_4) and evaporated affording an oil which was passed through a plug of alumina. The residue was then purified by distillation (116°/0.01 mmHg) affording a pale yellow solid (8.30 g, 68%) on cooling, mp 49–51 °C. Five fold scale-up afforded ethyl 5-bromo-3-methyl-9-oxo-3-azabicyclo[3.3.1]nonanecarboxylate in 50% yield. ^1H NMR (400 MHz, $CHCl_3$) δ 1.27 (t, 3H, J=7.2 Hz), 1.56–1.63 (m, 1H), 2.21–2.27 (m, 1H), 2.27 (s, 3H), 2.54–2.60 (m, 2H), 2.72–2.82 (m, 1H), 2.96 (dd, 1H, J=11.1, 2.3 Hz), 3.03–3.17 (m, 3H), 3.50 (dd, 1H, J=11.1, 2.3 Hz), 4.20 (q, 2H, J=7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 36.4, 44.3, 46.3, 59.9, 61.5, 63.7, 68.9, 71.2, 169.7, 201.9. Near IR (Nujol) υ (cm^{-1}) 1747, 1736. MS m/z (EI) 305 ($M^{+\cdot}$, 20%), 303 ($M^{+\cdot}$, 20%), 288 (13), 286 (13), 260 (19), 258 (16), 232 (8), 224 (100), 206 (8), 197 (15), 178 (74), 150 (37), 135 (11), 125 (15), 122 (14), 108 (10), 94 (10), 86 (43), 84 (68), 79 (27). Anal. Calcd for $C_{12}H_{18}BrNO_3$: C, 47.38; H, 5.96; N, 4.60; $M^{+\cdot}$ 305.0451. Found: C, 47.26; H, 6.00; N, 4.47; 305.0451.

4.2.2. 2-Isopropoxy-3-methoxyphenylacetylene 13.[27] The procedure of Banwell[29] was used. To a suspension of *o*-vanillin (20 g, 131 mmol) and potassium carbonate (63.6 g, 460 mmol) in *N*,*N*-dimethylformamide (200 mL) was added isopropyl bromide (15.4 mL, 164 mmol). The mixture was then heated at 100 °C for 4 h. On cooling the reaction mixture was diluted with water (~500 mL) and washed with diethyl ether (3×100 mL). The ether layers were combined, dried (Na_2SO_4) and evaporated. The residue (>90% yield) was dried under high vacuum and used in the next step without purification. Spectral data was

in agreement with that reported.[45] ^{1}H NMR (400 MHz, TMS) δ 1.30 (d, J=6.4 Hz, 6H), 3.86 (s, 3H), 4.61 (sep, J=6.4 Hz, 1H), 7.05–7.12 (m, 2H), 7.38–7.41 (m, 1H), 7.43 (s, 1H). ^{13}C NMR (400 MHz, $CHCl_3$) δ 22.3, 56.0, 76.2, 117.8, 118.9, 123.6, 130.9, 150.6, 153.2, 190.9. MS *m/z* (EI) 194 ($M^{+\cdot}$, 11%), 152 (100), 122 (12), 106 (47), 84 (6), 62 (18), 51 (6), 45 (38). Anal. Calcd for $C_{11}H_{14}O_3$: $M^{+\cdot}$ 194.0943. Found: 194.0942.

Following the method of Corey and Fuchs[28] triphenylphosphine (108.0 g, 412 mmol) was dissolved in dichloromethane (400 mL) at 0 °C and to this was added carbontetrabromide (68.3 g, 206 mmol) portionwise. After 15 min the aldehyde above was added to the mixture portionwise over 10 min and allowed to stir for a further 10 min at 0 °C followed by stirring at room temperature for 30 min. The mixture was then preabsorbed onto silica gel (~400 g) and the pure product eluted from the silica gel plug (diethyl ether/light petroleum; 1:1) (600–700 mL). Evaporation of the eluent afforded a pale yellow oily residue (22 g, 61%) after distillation (105°/0.01 mm). ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.27 (d, J=6.2 Hz, 6H), 3.82 (s, 3H), 4.37 (sep, J=6.2 Hz, 1H), 6.89 (dd, J=8.15, 1.4 Hz, 1H), 7.02 (t, J=8.15 Hz, 1H), 7.25–7.27 (m, 1H), 7.63 (s, 1H). ^{13}C NMR (400 MHz, $CHCl_3$) δ 22.5, 55.8, 76.0, 89.9, 112.6, 120.9, 123.2, 130.8, 134.1, 144.9, 152.9. Near IR (film) υ (cm^{-1}) 1577. MS *m/z* (EI) 350 ($M^{+\cdot}$, 9%), 308 (26), 228 (5), 226 (5), 214 (8), 212 (9), 199 (1), 185 (4), 183 (5), 170 (1), 155 (1), 148 (100), 133 (2), 105 (9), 89 (5), 76 (10), 63 (2). Anal. Calcd for $C_{12}H_{14}Br_2O_2$: C, 41.17; H, 4.03; $M^{+\cdot}$ 347.9361. Found: C, 41.08; H, 4.01; 347.9363.

The above material (20 g, 57.1 mmol) was dissolved in anhydrous tetrahydrofuran (450 mL) and cooled to −78 °C under nitrogen. To this was added *n*-BuLi (82 mL, 123 mmol, 1.5 M in hexanes) dropwise over 15 min. The reaction mixture was stirred at −78 °C for 1 h and then removed from the cold bath and stirred for 2 h. The flask was then placed in an ice-bath and the reaction quenched with saturated ammonium chloride solution (200 mL). The phases were partitioned and the aqueous phase washed with diethyl ether (100 mL). The combined ether phases were dried (Na_2SO_4) and evaporated affording the product, which was purified by distillation (75°/0.1 mm) giving the pure product (8.30 g, 76%) as a colourless oil. The oil slowly solidified on refrigeration as a colourless solid, mp 48–50 °C. ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.31 (d, J=6.2 Hz, 6H), 3.20 (s, 1H), 3.81 (s, 3H), 4.56 (sep, J=6.2 Hz, 1H), 6.88 (dd, J=8.2, 1.7 Hz, 1H), 6.94 (t, J=8.2 Hz, 1H), 7.03 (dd, J=8.2, 1.7 Hz, 1H). ^{13}C NMR (400 MHz, $CHCl_3$) δ 22.6, 55.9, 76.2, 80.6, 80.8, 113.3, 117.9, 123.4, 125.6, 149.3, 153.2. Near IR (Nujol) υ (cm^{-1}) 1917, 1836. MS *m/z* (EI) 190 ($M^{+\cdot}$, 24%), 148 (100), 133 (10), 118 (8), 105 (14), 91 (8), 84 (8), 77 (15). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42; $M^{+\cdot}$ 190.0994. Found: C, 76.06; H, 7.61; 190.0997.

4.2.3. Ethyl 5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenylethynyl]-3-azabicyclo-[3.3.1]nonanecarboxylate 16. *Method A*. Phenylacetylene **13** (5.16 g, 27.1 mmol) was dissolved in anhydrous tetrahydrofuran (40 mL) and placed in an ice-bath under nitrogen. Methylmagnesium bromide (21 mL, 24.4 mmol, 1.16 M, tetrahydrofuran/toluene) was then added and the flask taken out of the bath and stirred at room temperature for 2.5 h. In a separate flask azabicyclo[3.3.1]nonane **8** (3.91 g, 12.9 mmol) was dissolved in anhydrous tetrahydrofuran (130 mL) and cooled to −78 °C (dry-ice/acetone bath) under nitrogen. To this was added the above solution dropwise over 5 min. The reaction mixture was then allowed to reach 15–20 °C over 80 min in the bath before being quenched with acetic acid (1 mL) in tetrahydrofuran (16 mL). After 5 min saturated sodium hydrogencarbonate solution (5 mL) was added followed by extraction into diethyl ether, drying (Na_2SO_4) and evaporation in vacco. The residue was subjected to column chromatography (*t*-butylmethylether/light petroleum; 3:7), which firstly eluted recovered excess phenyl acetylene **13** followed by the titled compound (4.54 g, 71%) as a mixture of diasteroisomers [9(**16**):1(**17**)]. Flushing the column with ethyl acetate afforded ethyl 3-methyl-5-[2-(3-methoxy-2-isoproxy)phenylethynyl]-oxo-3-azabicyclo[3.3.0]octane-carboxylate **18**.

Method B. Phenylacetylene **13** (0.136 g, 0.714 mmol) was reacted with methylmagnesium bromide (0.47 mL, 0.655 mmol, 1.4 M, THF) as above in toluene (2 mL). This was added to azabicyclo[3.3.1]nonane **8** (0.181 g, 0.595 mmol) as above in toluene (7 mL) and quenched with acetic acid (0.6 mL) in tetrahydrofuran (2 mL) followed by saturated sodium hydrogencarbonate solution (1 mL). Work up as above gave **16** and **17** (3:2) (0.275 mg, 94%).

Ethyl 5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenylethynyl]-3-azabicyclo[3.3.1]nonane-carboxylate **16** (major diasteromer reported only). ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.22 (t, J=7.1 Hz, 3H), 1.29 (d, J=6.2 Hz, 6H), 1.47–1.62 (m, 1H), 1.72–1.83 (m, 1H), 2.22 (s, 3H), 2.21–2.36 (m, 2H), 2.72–2.90 (m, 2H), 2.98 (dd, J=12.0, 2.5 Hz, 1H), 3.13 (d, J=12 Hz, 1H), 3.19 (d, J=11.1 Hz, 1H), 3.28 (dd, J=11.1, 12.0 Hz, 1H), 3.79 (s, 3H), 4.13–4.23 (m, 2H), 4.67 (sep, J=6.2 Hz, 1H), 5.04 (s, 1H, OH), 6.83 (dd, J=8.1, 1.7 Hz, 1H), 6.91 (t, J=8.1 Hz, 1H), 6.97 (dd, J=8.1, 1.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.50, 22.54, 23.1, 29.1, 36.8, 44.8, 53.2, 55.8, 59.2, 61.5, 67.1, 69.1, 74.8, 75.3, 85.1, 92.5, 112.8, 118.2, 123.2, 125.6, 148.0, 153.2, 175.1. MS *m/z* (EI) 495 ($M^{+\cdot}$, 2%), 493 ($M^{+\cdot}$, 2%), 478 (6), 476 (6), 458 (1), 452 (2), 450 (2), 436 (1), 414 (100), 370 (11), 368 (10), 340 (18), 326 (10), 324 (7), 298 (17), 190 (14), 177 (64), 161 (10), 148 (30), 134 (9), 122 (36), 105 (9). Anal. Calcd for $C_{24}H_{32}BrNO_5$: $M^{+\cdot}$ 495.1444. Found: 495.1432.

Ethyl 3-methyl-5-[2-(3-methoxy-2-isoproxy)phenylethynyl]-oxo-3-azabicyclo[3.3.0]octanecarboxylate **18** was obtained as a pale yellow oil. ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.16 (t, J=7.1 Hz, 3H), 1.30 (d, J=6.2 Hz, 6H), 1.80–1.94 (m, 4H), 2.29–2.39 (m, 1H), 2.33 (s, 3H), 2.49–2.57 (m, 1H), 2.79 (d, J=6.0 Hz, 1H), 2.81 (d, J=6.0 Hz, 1H), 2.91 (d, J=9.4 Hz, 1H), 3.00 (d, J=9.4 Hz, 1H), 3.82 (s, 3H), 4.05 (q, J=7.1 Hz, 2H), 4.59 (sep, J=6.2 Hz, 1H), 6.94 (m, 3H), 7.00–7.09 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.8, 22.5, 26.0, 38.0, 39.5, 42.0, 55.9, 60.9, 64.1, 66.5, 67.3, 70.3, 76.4, 90.0, 90.1, 115.0, 116.0, 123.7, 126.0, 149.9, 153.1, 174.5, 188.3. Near IR (film) υ (cm^{-1}) 2192, 1729, 1664, 1572. MS *m/z* (EI) 413 ($M^{+\cdot}$, 12%), 398 (2),

370 (14), 354 (6), 340 (13), 324 (2), 312 (2), 298 (10), 281 (3), 260 (3), 242 (2), 224 (6), 209 (8), 196 (8), 182 (9), 175 (15), 161 (27), 142 (18), 122 (44), 110 (14), 94 (15), 84 (45), 72 (100). Anal. Calcd for $C_{24}H_{31}NO_5$: $M^{+\cdot}$ 413.2202. Found: 413.2189.

4.2.4. Ethyl 5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenyl-*Z*-ethenyl]-3-azabicyclo-[3.3.1]nonanecarboxylate 10. *Method A*. Acetylene **16** (213 mg, 0.14 mmol) was dissolved in distilled methanol (9 mL) and to this was added pyridine (9 drops) and palladium on carbon (21 mg, 10%). The mixture was degassed/gassed three times with hydrogen and stirred under a hydrogen atmosphere for 24–27 h. Filtration of the reaction mixture through celite followed by evaporation afforded an oily residue which was subjected to column chromatography (*t*-butylmethylether/light petroleum; 1:17) affording recovered starting material (~50 mg), ethyl 5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenyl-*Z*-ethenyl]-3-azabicyclo[3.3.1]nonanecarboxylate (100 mg, 47%) and a mixture of unidentified products (20 mg).

Method B. Acetylene **16** (4.32 g, 8.74 mmol) was dissolved in anhydrous tetrahydrofuran (200 mL) and to this was 1,3,5-triisopropylbenzenesulfonohydrazide[31] (5.48 g, 18.4 mmol). The mixture was refluxed for 2 h. To the hot mixture was added a solution of sodium acetate (1 M, 18.5 mL) and reflux continued for 5 min. Tetrahydrofuran was evaporated and the residue diluted with saturated sodium hydrogen carbonate (100 mL) and extracted with diethyl ether (3×50 mL). The organic layer was dried (Na_2SO_4), and evaporated in vacco afforded an oily residue, which was dried under high vacuum for 30 min. The above procedure was repeated two more times and the resulting residue subjected to column chromatography (*t*-butylmethylether/ethyl acetate/light petroleum; 2:1:7) affording recovered starting material (0.786 g, 18%) and ethyl 5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenyl-*Z*-ethenyl]-3-azabicyclo[3.3.1]nonanecarboxylate (3.21 g, 74%) (91% based on starting material recovery). Mp 123–125 (diethyl ether). ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.98 (t, J=7.1 Hz, 3H), 1.21 (d, J=6.2 Hz, 3H), 1.27 (d, J=6.2 Hz, 3H), 1.66–1.77 (m, 2H), 2.10–2.21 (m, 1H), 2.21–2.27 (m, 1H), 2.58–2.63 (m, 1H), 2.93–3.03 (m, 1H), 2.96 (s, 3H), 3.60 (dd, J=13.6, 2.4 Hz, 1H), 3.67 (dd, J=13.6, 2.4 Hz, 1H), 3.72 (dq, J=10.7, 7.1 Hz, 1H), 3.81 (s, 3H), 3.99 (d, J=13.5 Hz, 1H), 4.01 (dq, J=10.7, 7.1 Hz, 1H), 4.42 (d, J=13.5 Hz, 1H), 4.51 (sep, J=6.2 Hz, 1H), 5.01 (s, 1H), 5.87 (d, J=13.1 Hz, 1H), 6.72 (d, J=13.1 Hz, 1H), 6.79–6.85 (m, 1H), 6.96–7.01 (m, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 13.6, 20.0, 22.4, 22.6, 27.1, 35.8, 47.0, 52.3, 55.6, 57.5, 61.5, 62.3, 67.3, 75.6, 75.8, 77.3, 111.8, 122.3, 123.0, 126.7, 130.8, 132.2, 152.4, 170.4. MS *m/z* (EI) 497 ($M^{+\cdot}$, 15%), 495 ($M^{+\cdot}$, 12%), 454 (2), 452 (2), 438 (1), 436 (1), 416 (51), 398 (11), 372 (16), 370 (13), 356 (7), 354 (5), 342 (17), 340 (9), 313 (7), 300 (9), 288 (6), 286 (7), 284 (5), 282 (7), 238 (20), 224 (37), 195 (25), 177 (47), 162 (10), 150 (40), 142 (14), 122 (100), 94 (20). Anal. Calcd for $C_{24}H_{34}BrNO_5$: $M^{+\cdot}$ 495.1620. Found: 495.1612.

4.2.5. Ethyl 5-bromo-3-methyl-9-*exo*-acetoxy-9-[2-(3-methoxy-2-acetoxy)phenylethynyl]-3-azabicyclo[3.3.1]-nonanecarboxylate 19. Acetylene **16** (63 mg, 0.127 mmol) was dissolved in anhydrous acetonitrile (0.2 mL) and anhydrous acetic anhydride (0.2 mL) under a nitrogen atmosphere. To this solution was added one half portion of trimethylsilyltrifluoromethanesulfonate (0.1 mL, 0.51 mmol) dropwise over 1 min. After 10 min the remaining half portion was added and the reaction mixture stirred for 10 min. The reaction flask was placed in an ice-bath and the reaction quenched with saturated sodium hydrogen carbonate solution (1–2 mL) followed by solid sodium hydrogen carbonate (~300 mg) and dilution with water (3 mL). Extraction with diethyl ether (3×5 mL), drying (Na_2SO_4), and evaporation in vacco afforded a residue which was subjected to column chromatography (diethyl ether/light petroleum; 7:3) affording ethyl 5-bromo-3-methyl-9-*exo*-acetoxy-9-[2-(3-methoxy-2-acetoxy)phenylethynyl]-3-azabicyclo[3.3.1]nonanecarboxylate as a colourless glass (59 mg, 87%) and trace amounts of a triacetylated derivative. Compound **19** was crystallised by slow evaporation from chloroform, mp 98–100 °C (white crystals). ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.21 (t, J=7.2 Hz, 3H), 1.47–1.62 (bm, 1H), 1.78 (bdd, J=14.0, 5.2 Hz, 1H), 2.11 (s, 3H), 2.20 (bs, 3H), 2.29–2.50 (m, 2H), 2.35 (s, 3H), 2.68–2.90 (m, 3H), 3.10–3.40 (bm, 3H), 3.79 (s, 3H), 4.04–4.18 (m, 2H), 6.89–6.95 (m, 1H), 7.10–7.15 (m, 2H). Near IR (Nujol) υ (cm^{-1}) 1764, 1756, 1716. MS *m/z* (EI) 537 ($M^{+\cdot}$, 15%), 535 ($M^{+\cdot}$, 12%), 478 (56), 476 (54), 456 (93), 414 (40), 396 (100), 382 (13), 368 (16), 354 (17), 340 (12), 324 (21), 308 (14), 280 (25), 246 (12), 206 (16), 175 (23), 161 (14), 148 (24), 122 (22), 94 (12). Anal. Calcd for $C_{25}H_{30}Br_1N_1O_7$: C, 55.98; H, 5.64; N, 2.61; $M^{+\cdot}$ 535.1206. Found: C, 55.72; H, 5.65; N, 2.52; $M^{+\cdot}$ 535.1206.

4.2.6. 5-Bromo-1-hydroxymethyl-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenyl-*Z*-ethenyl]-3-azabicyclo[3.3.1]nonane 20. Alkene **10** (3.21 g, 6.48 mmol) was dissolved in anhydrous tetrahydrofuran (120 mL) under nitrogen and the flask placed in an ice-bath. Diisobutylaluminium hydride (31.1 mL, 31.1 mmol, 1 M solution in hexanes) was added dropwise over 5 min. The reaction was stirred for 1 h and then at room temperature for 1 h before quenching with saturated ammonium chloride solution (50 mL). Tetrahydrofuran was evaporated in vacco and the aqueous extracted with diethyl ether (3×50 mL). The organic layer was partitioned, dried (Na_2SO_4), and evaporation in vacco afforded a residue which was subjected to column chromatography (*t*-butylmethylether/light petroleum; 6:4) on silica gel affording a white solid (2.92 g, 99%), mp 134–136 °C. ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.19 (d, J=6.1 Hz, 3H), 1.34 (d, J=6.1 Hz, 3H), 1.41–1.50 (bm, 1H), 1.66–1.84 (m, 2H), 2.07–2.15 (m, 1H), 2.23 (bs, 3H), 2.32 (bd, J=11.4 Hz, 1H), 2.6–2.75 (bm, 1H), 2.77–2.87 (m, 1H), 2.96 (bd, J=11.4 Hz, 1H), 3.18 (bd, J=11.2 Hz, 1H), 3.31 (bd, J=11.2 Hz, 1H), 3.40 (AB, J=11.1 Hz, 2H), 3.81 (s, 3H), 4.45 (bs, 1H), 4.48 (sep, J=6.1 Hz, 1H), 6.17 (d, J=13.0 Hz, 1H), 6.54 (d, J=13.0 Hz, 1H), 6.69 (d, J=7.7 Hz, 1H), 6.79 (d, J=7.7 Hz, 1H), 7.00 (t, J=7.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 22.7, 23.1, 27.5, 38.8, 45.0, 47.1, 52.8, 55.6, 60.2, 66.5, 75.9, 77.5, 78.4, 111.0, 120.9, 123.7, 128.5, 131.6, 133.5, 142.7, 153.0. Near IR (Nujol) υ (cm^{-1}) 3447, 3381, 1569. MS *m/z* (EI) 455 ($M^{+\cdot}$, 12%), 453 ($M^{+\cdot}$, 13%), 412 (2), 410 (2), 396 (10), 394 (10), 374 (100), 356 (12), 332 (10), 314 (48), 282 (5),

244 (9), 196 (8), 177 (28), 164 (25), 150 (12), 137 (18), 122 (25), 91 (8). Anal. Calcd for $C_{22}H_{32}BrNO_4$: C, 58.15; H, 7.09; N, 3.08; $M^{+\cdot}$ 453.1515. Found: C, 58.35; H, 7.20; N, 3.14; 453.1526.

4.2.7. 5-Bromo-1-chloromethyl-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenyl-*Z*-ethenyl]-3-azabicyclo[3.3.1]nonane 21. Diol **20** (1.0 g, 2.20 mmol) from above and triphenylphosphine (2.31 g, 8.80 mmol) were dissolved in anhydrous carbon tetrachloride (50 mL) under a nitrogen atmosphere and to this was added *N*,*N*-diisopropylethylamine (6.13 mL, 35.2 mmol). The mixture was then refluxed for 14 h. On cooling the solvent was removed and the residue dissolved in dichloromethane (50 mL) and washed with saturated sodium hydrogen carbonate solution (100 mL). The organic layer was then partitioned, dried (Na_2SO_4), and evaporation in vacco afforded a white solid residue which was subjected to column chromatography (dichloromethane) affording a white amorphous solid (960 mg, 92%), mp 168–170 °C. ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.16–1.22 (m, 1H), 1.27 (d, J=6.2 Hz, 6H), 1.4–1.54 (m, 1H), 2.04–2.14 (m, 1H), 2.15–2.25 (m, 1H), 2.22 (bs, 3H), 2.39 (AB, J=11.7 Hz, 2H), 2.65–2.85 (m, 3H), 3.07 (AB, J=8.2 Hz, 1H), 3.23 (AB, J=11.4 Hz, 2H), 3.52–3.57 (m, 1H), 3.80 (s, 3H), 4.05 (s, 1H), 4.53 (sep, J=6.2 Hz, 1H), 6.24 (d, J=12.8 Hz, 1H), 6.56 (d, J=12.8 Hz, 1H), 6.79 (d, J=8.0 Hz, 1H), 6.88–6.91 (m, 1H), 7.02 (t, J=8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4, 22.6, 23.2, 27.9, 38.9, 45.0, 46.2, 55.6, 60.2, 66.3, 68.4, 75.8, 80.2, 111.1, 121.2, 123.9, 127.8, 132.2, 133.6, 142.1, 152.6. Near IR (Nujol) υ (cm^{-1}) 3400, 1569. MS *m*/*z* (EI) 473 ($M^{+\cdot}$, 37%), 471 ($M^{+\cdot}$, 26%), 438 (58), 436 (56), 394 (38), 392 (100), 374 (5), 350 (18), 314 (21), 262 (22), 246 (93), 244 (92), 214 (24), 200 (19), 183 (5), 177 (39), 164 (56), 150 (18), 137 (38), 122 (30), 91 (14). Anal. Calcd for $C_{22}H_{31}BrClNO_3$: C, 55.88; H, 6.61; N, 2.96; $M^{+\cdot}$ 471.1176. Found: C, 55.73; H, 6.59; N, 2.70; $M^{+\cdot}$ 471.1184.

4.2.8. Ethyl 5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-acetoxy)phenyl-*Z*-ethenyl]-3-azabicyclo-[3.3.1]nonanecarboxylate 22. Alcohol **10** (104 mg, 0.209 mmol) was dissolved in anhydrous acetonitrile (0.7 mL), anhydrous dichloromethane (0.35 mL) and acetic anhydride (0.35 mL) under a nitrogen atmosphere. To this solution was added trimethylsilyltrifluoromethanesulfonate (0.14 mL, 0.733 mmol) dropwise over 1 min. The reaction mixture was stirred for 15 min then quenched with saturated sodium hydrogen carbonate solution (1–2 mL) followed by solid sodium hydrogen carbonate (~300 mg) and dilution with water (3 mL). Extraction with diethyl ether (3×5 mL), drying (Na_2SO_4), and evaporation in vacco afforded a residue which was subjected to column chromatography (dichloromethane/ethyl acetate; 24:1) on silica gel affording a colourless glass which was crystallised from diethyl ether as transparent prisms (56 mg, 54%), mp 169–171 °C. ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.13 (t, J=7.2 Hz, 3H), 1.44–1.64 (m, 2H), 2.10–2.20 (m, 1H), 2.25 (s, 3H), 2.28 (bs, 3H), 2.33–2.44 (m, 1H), 2.70–2.83 (bm, 1H), 2.84–3.40 (m, 3H), 3.12–3.35 (bm, 2), 3.63 (bs, 1H), 3.79 (s, 3H), 4.04 (dq, J=10.8, 7.2 Hz, 1H), 4.17 (dq, J=10.8, 7.2 Hz, 1H), 6.18 (bd, J=12.6 Hz, 1H), 6.39 (bd, J=12.6 Hz, 1H), 6.85 (bd, J=8.0 Hz, 1H), 7.12 (t, J=8.0 Hz, 1H), 7.38 (bd, J=8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 20.6, 23.0, 30.4, 38.2, 44.9, 53.4, 55.9, 58.8, 61.3, 66.2, 71.7, 78.3, 111.1, 123.0, 125.4, 127.0, 130.8, 131.1, 137.5, 150.6, 168.4, 174.0. Near IR (Nujol) υ (cm^{-1}) 3447, 1752, 1701. MS *m*/*z* (EI) 497 ($M^{+\cdot}$, 43%), 495 ($M^{+\cdot}$, 44%), 454 (1), 434 (1), 424 (1), 416 (83), 398 (17), 374 (17), 356 (9), 342 (11), 324 (8), 314 (9), 305 (15), 303 (15), 288 (21), 286 (21), 257 (7), 248 (18), 238 (23), 232 (6), 224 (100), 206 (8), 195 (28), 177 (43), 162 (10), 150 (36), 137 (12), 122 (67), 94 (13), 84 (66). Anal. Calcd for $C_{23}H_{30}BrNO_6$: C, 55.65; H, 6.09; N, 2.82; $M^{+\cdot}$ 495.1256. Found: C, 55.56; H, 6.14; N, 2.77; $M^{+\cdot}$ 495.1259.

4.2.9. 1-Acetoxymethyl-5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenyl-*Z*-ethenyl]-3-azabicyclo[3.3.1]nonane 23. Diol **20** (201 mg, 0.442 mmol) was dissolved in anhydrous dichloromethane (3 mL) under an argon atmosphere. The solution was cooled in an ice-bath and acetic anhydride (0.33 mL, 3.54 mmol), pyridine (0.11 mL, 1.37 mmol) and 4-(dimethylamino)pyridine (10 mg) were added. After 2 h at room temperature the reaction was heated at 40 °C for 3 h. Solvents were then removed and the residue subjected to column chromatography (diethyl ether/light petroleum, 1:1) affording 1-acetoxymethyl-5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenyl-*Z*-ethenyl]-3-azabicyclo-[3.3.1]nonane (210 mg, 95%) which solidified on standing, mp 117–118 °C. ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.19 (d, J=6.1 Hz, 3H), 1.33 (d, J=6.1 Hz, 3H), 1.39–1.48 (m, 1H), 1.51–1.58 (m, 1H), 1.77–1.90 (m, 1H), 1.92 (s, 3H), 2.06–2.15 (m, 1H), 2.21 (s, 3H), 2.36 (dd, J=11.6, 2.5 Hz, 1H), 2.59–2.79 (m, 1H), 2.70 (d, J=12.1 Hz, 1H), 2.78–2.89 (m, 1H), 3.17 (dd, J=11.6, 2.5 Hz, 1H), 3.31 (d, J=11.8 Hz, 1H), 3.59 (d, J=11.1 Hz, 1H), 3.79 (s, 3H), 4.03 (d, J=11.1 Hz, 1H), 4.46 (s, OH), 4.46 (sep, J=6.1 Hz, 1H), 6.17 (d, J=13.0 Hz, 1H), 6.53 (d, J=13.0 Hz, 1H), 6.76–6.84 (m, 2H), 7.01 (t, J=8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 22.2, 22.7, 23.1, 27.5, 38.9, 45.0, 46.2, 55.5, 60.3, 66.5, 69.9, 75.9, 77.2, 77.5, 110.9, 121.6, 123.5, 128.3, 131.6, 133.5, 142.6, 152.7, 170.9. MS *m*/*z* (EI) 497 ($M^{+\cdot}$, 7%), 495 ($M^{+\cdot}$, 9%), 454 (4), 452 (2), 438 (4), 436 (4), 415 (5), 372 (8), 356 (17), 342 (35), 314 (8), 312 (13), 300 (15), 282 (12), 270 (10), 240 (15), 195 (29), 177 (54), 164 (25), 150 (38), 137 (28), 122 (100). Anal. Calcd for $C_{24}H_{34}BrNO_5$: C, 58.07; H, 6.90; N, 2.82; $M^{+\cdot}$ 495.1621. Found: C, 58.00; H, 7.15; N, 2.64; $M^{+\cdot}$ 495.1614.

4.2.10. 1-Acetoxymethyl-5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-acetoxy)phenyl-*Z*-ethenyl]-3-azabicyclo[3.3.1]nonane 24. *Method A*. The diol **20** (86 mg, 0.189 mmol) was dissolved in anhydrous acetonitrile (0.35 mL), and acetic anhydride (0.35 mL) under a nitrogen atmosphere. To this solution was added one half portion of trimethylsilyltrifluoromethanesulfonate (0.22 mL, 1.15 mmol) dropwise over 30 s. After 10 min the remaining half portion was added and the reaction mixture stirred for 10 min. The reaction flask was placed in an ice-bath and the reaction quenched with saturated sodium hydrogen carbonate solution (2–3 mL) followed by solid sodium hydrogen carbonate (~400 mg) and dilution with water (5 mL). Extraction with diethyl ether (3×5 mL), drying (Na_2SO_4), and evaporation in vacco afforded a residue which was subjected to column chromatography

(diethyl ether/light petroleum; 6:4) affording 1-acetoxymethyl-5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-acetoxy)phenyl-*Z*-ethenyl]-3-azabicyclo[3.3.1]nonane as a white solid (64 mg, 68%) and triacetylated material (8 mg, 8%).

Method B. Compound **23** (56 mg, 0.113 mmol) was reacted, as above in method A, with acetic anhydride (0.3 mL), anhydrous acetonitrile (0.3 mL) and trimethylsilyltrifluoromethanesulfonate (0.14 mL, 0.677 mmol). Column chromatography as above afforded 1-acetoxymethyl-5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-acetoxy)phenyl-*Z*-ethenyl]-3-azabicyclo[3.3.1]nonane (48 mg, 86%) as a white solid, mp 127–129 °C. ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.45–1.63 (m, 1H), 1.84–1.94 (m, 1H), 1.98 (s, 3H), 2.10–2.17 (m, 1H), 2.23 (s, 3H), 2.28 (s, 3H), 2.43–2.48 (m, 1H), 2.44 (s, OH), 2.62–2.79 (m, 1H), 2.77 (d, J=11.8 Hz, 1H), 3.16 (dd, J=11.5 Hz, 1H), 3.28 (d, J=11.5 Hz, 1H), 3.79 (s, 3H), 3.93 (bd, J=11.0 Hz, 1H), 4.13 (d, J=11.0 Hz, 1H), 6.22 (d, J=12.8 Hz, 1H), 6.50 (d, J=12.8 Hz, 1H), 6.86 (d, J=8.0 Hz, 1H), 7.06 (d, J=8.0 Hz, 1H), 7.16 (t, J=8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 20.8, 23.1, 27.6, 39.0, 44.9, 45.2, 55.8, 60.2, 66.4, 69.9, 76.6, 78.9, 110.96, 121.0, 126.2, 126.8, 131.9, 132.7, 136.6, 150.9, 169.6, 170.9. Near IR (Nujol) υ (cm^{-1}) 3452, 1745, 1731, 1725. MS *m/z* (EI) 497 ($M^{+\cdot}$, 14%), 495 ($M^{+\cdot}$, 14%), 454 (2), 452 (2), 438 (3), 436 (2), 416 (92), 398 (10), 374 (14), 356 (26), 342 (15), 328 (5), 314 (4), 300 (9), 286 (17), 272 (5), 246 (16), 195 (25), 177 (56), 164 (70), 150 (19), 136 (19), 134 (17), 122 (90), 105 (22). Anal. Calcd for $C_{23}H_{30}Br_1N_1O_6$: C, 55.65; H, 6.09; N, 2.82; $M^{+\cdot}$ 495.1257. Found: C, 55.75; H, 6.23; N, 2.68; $M^{+\cdot}$ 495.1257.

4.2.11. 7-Acetoxy-4a-*exo*-hydroxy-8-methoxy-2-methyl-4-acetoxymethyl-2,3,4,4a-tetrahydro-1*H*-4,10b-propanobenz[h]isoquinoline 25. *Method A*. Diacetate **24** (33 mg, 0.066 mmol) was dissolved in anhydrous dichloromethane (2 mL) under a nitrogen atmosphere and the reaction flask covered with aluminium foil. The reaction flask was cooled in an ice-bath and solid silver trifluoroacetate (31 mg, 0.140 mmol) added to the vigorously stirring solution. After 1 h the reaction was quenched with concd ammonia solution (15 drops) followed by addition of solid sodium sulfate. Filtration through glass wool and evaporation of the filtrate afforded an oily residue which was subjected to column chromatography (*t*-butyl methyl ether). The 7-acetoxy-4a-*exo*-hydroxy-8-methoxy-2-methyl-4-acetoxymethyl-2,3,4,4a-tetrahydro-1*H*-4,10b-propanobenz[h]isoquinoline **25** (5 mg, 18%) was eluted first followed by the more polar by-product **26**, which underwent significant isomerization on the column (ethyl acetate/methanol).

Method B. Diacetate **24** (10 mg, 0.020 mmol) was dissolved in anhydrous nitromethane (2 mL) under an argon atmosphere and the reaction flask covered with aluminium foil. The reaction flask was cooled in an ice-bath and solid silver 2,4,6-trinitrobenzenesulfonate[36] (24 mg, 0.060 mmol) added to the vigorously stirring solution. The reaction was allowed to reach room temperature over 14 h. The solvent was removed under high vacuum, the residue redissolved in dichloromethane (~ 2–3 mL) and concd ammonia solution (20 drops) added followed by addition of solid sodium sulfate. The dichloromethane layer was removed (Pastuer Pipette) and the solid residue washed three times with dichloromethane. The combined dichloromethane extracts were passed through glass wool and evaporated. Column chromatography (dichloromethane/ethyl acetate, 3:1) afforded 7-acetoxy-4a-*exo*-hydroxy-8-methoxy-2-methyl-4-acetoxymethyl-2,3,4,4a-tetrahydro-1*H*−4,10b-propanobenz[h]isoquinoline **25** (4.5 mg, 54%) ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.56 (bs, 1H), 1.57–1.72 (m, 2H), 1.89–2.31 (m, 5H), 2.02 (s, 3H), 2.07 (s, 3H), 2.33 (s, 3H), 2.57 (d, J=11.3 Hz, 1H), 2.73 (d, 11.3, 1H), 2.77 (m, 1H), 3.79 (s, 3H), 4.18 (AB, 2H), 6.38 (d, J=10.1 Hz, 1H), 6.64 (d, J=10.1 Hz, 1H), 6.84 (d, J=8.6 Hz, 1H), 7.21 (d, J=8.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.40, 20.43, 21.0, 28.8, 28.9, 40.2, 42.6, 45.5, 56.0, 61.0, 66.2, 67.7, 71.5, 111.5, 122.1, 123.6, 124.7, 130.9, 133.2, 135.9, 149.8, 168.8, 171.0. Near IR (Nujol) υ (cm^{-1}) 3463, 1743. MS *m/z* (EI) 415 ($M^{+\cdot}$, 22%), 372 (17), 356 (8), 330 (42), 282 (11), 240 (31), 203 (12), 71 (11), 43 (100). Anal. Calcd for $C_{23}H_{29}NO_6$: $M^{+\cdot}$ 415.1995. Found: $M^{+\cdot}$ 415.1989.

4.2.12. *o*-Quinone acetal 28. To a solution of **21** (20 mg, 0.042 mmol) in anhydrous dichloromethane (2 mL) under a nitrogen atmosphere was added solid aluminium chloride (7 mg, 0.055 mmol) in one portion. The mixture was then stirred at room temperature for 16 h. The reaction was quenched with saturated sodium hydrogencarbonate solution (2 mL) and extracted with dichloromethane/diether ether (1:1) (5 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was subjected to column chromatography (*t*-butyl methyl ether/light petroleum, 3:7), which afforded two fractions. The first (8 mg) was recovered starting material and the second was 5-bromo-1-chloromethyl-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-hydroxy)phenyl-*Z*-ethenyl]-3-azabicyclo[3.3.1]-nonane **27** (10 mg, 56%) as an orange oil. ^{1}H NMR (300 MHz, $CHCl_3$) δ 1.45–1.60 (m, 1H), 1.74–1.97 (m, 3H), 2.16–2.25 (m, 1H), 2.32 (s, 3H), 2.50 (dd, 1H), 2.69–2.87 (m, 2H), 3.07 (d, J=12 Hz, 1H), 3.24–3.39 (m, 2H), 3.65 (AB, 2H), 3.95 (s, 3H), 5.96 (bs, OH), 6.31 (d, J=13 Hz, 1H), 6.68 (d, J=13 Hz, 1H), 6.78–6.94 (m, 3H).

Phenol **27** (68 mg, 0.158 mmol) was dissolved in anhydrous dichloromethane (2 mL) under a nitrogen atmosphere and added dropwise to a solution of iodobenzene diacetate (51 mg, 0.158 mmol) in anhydrous dichloromethane (1.5 mL) and acetic acid (0.5 mL) all at room temperature. After 1.5 h the reaction was quenched with excess solid sodium hydrogen carbonate followed by saturated sodium hydrogen carbonate solution (5 mL). Extraction with dichloromethane, drying (Na_2SO_4) and evaporation afforded the crude product (~48 mg, 53%), which was found to decompose on silica gel and hence was used without further purification. ^{1}H NMR (300 MHz, $CHCl_3$) δ 1.46–1.60 (m, 1H), 1.85–1.95 (m, 2H), 2.14 (s, 3H), 2.10–2.30 (m, 1H), 2.28 (s, 3H), 2.46 (dd, 1H), 2.65 (d, 1H), 2.67–2.85 (m, 2H), 3.00–3.10 (bdd, 1H), 3.12–3.50 (m, 2H), 3.53 (s, 3H), 3.64 (s, 1H), 3.39 (d, 1H), 6.20–6.50 (m, 3H), 6.80–6.88 (m, 1H), 7.07–7.14 (m, 1H).

4.2.13. Ethyl 5-bromo-3-[2-(3-methoxy-2-isopropoxy)-ethyl]-9-oxo-3-azabicyclo[3.3.1]nonanecarboxylate 29. To a solution of ethyl 6-bromocyclohexanone-2-carboxylate **31** (0.30 g, 1.20 mmol) and formaldehyde

(1.2 mL, 14.5 mmol, 37% in water) in methanol (2.0 mL) at 0 °C was added a solution of 2-(3-methoxy-2-isopropoxy)-ethylamine[46] **32** (0.756 mg, 3.61 mmol) in methanol (2.0 mL) dropwise over 1 h. The solution was then allowed to warm to room temperature over 22 h followed by refluxing for 10 min. On cooling the volatiles were removed in vacco and the residue subjected to column chromatography (dichloromethane) affording a colourless oil (231 mg, 40%). ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.15–1.34 (m, 9H), 1.34–1.44 (m, 1H), 2.10–2.18 (m, 1H), 2.41–2.53 (m, 1H), 2.60–2.76 (m, 2H), 2.78–2.87 (m, 1H), 2.98 (dd, J=11.0, 1.8 Hz, 1H), 3.07 (dd, J=11.5, 1.8 Hz, 1H), 3.30 (dd, J=11.5, 2.2 Hz, 1H), 3.65 (dd, J=11.0, 2.2 Hz, 1H), 3.80 (s, 3H), 4.16–4.24 (m, 2H), 4.50 (sep, J=6.2 Hz, 1H), 6.73–6.77 (m, 2H), 6.93 (t, J=7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.4, 22.63, 22.67, 28.1, 36.2, 46.2, 55.6, 56.6, 60.0, 61.2, 61.4, 68.7, 69.4, 74.4, 110.5, 121.9, 123.2, 134.1, 145.1, 152.9, 169.8, 202.2. MS *m/z* (EI) 483 ($M^{+\cdot}$, 5%), 481 ($M^{+\cdot}$, 5%), 466 (4), 438 (20), 436 (21), 402 (5), 304 (98), 302 (100), 226 (10), 224 (5), 222 (11), 194 (3), 164 (4), 150 (14), 137 (8), 122 (7), 107 (5). Anal. Calcd for $C_{23}H_{32}BrNO_5$: $M^{+\cdot}$ 483.1444. Found: $M^{+\cdot}$ 483.1431.

4.2.14. Ethyl 5-bromo-3-[2-(3-methoxy-2-acetoxy)ethyl]-9-oxo-3-azabicyclo[3.3.1]nonanecarboxylate 30. Ethyl 5-bromo-3-[2-(3-methoxy-2-isopropoxy)ethyl]-9-oxo-3-azabicyclo[3.3.1]nonanecarboxylate **29** (58 mg, 0.12 mmol) was dissolved in anhydrous acetonitrile (0.3 mL) and acetic anhydride (0.3 mL) under a argon atmosphere. To this solution was added one half portion of trimethylsilyltrifluoromethanesulfonate (0.13 mL, 0.733 mmol). After 5 min the remaining half portion was added and the reaction mixture stirred for 5 min. The reaction was then transferred to a separatory funnel containing saturated sodium hydrogen carbonate solution (10 mL). Extraction with diethyl ether (3×5 mL), drying (Na_2SO_4), and evaporation in vacco afforded a residue which was subjected to column chromatography (dichloromethane) affording the title compound as a pale yellow oil (38 mg, 66%). ^{1}H NMR (200 MHz, $CHCl_3$) δ 1.27 (t, J=7.1 Hz, 3H), 1.34–1.51 (m, 1H), 2.07–2.22 (m, 1H), 2.33 (s, 3H), 2.39–2.84 (m, 8H), 2.99 (dd, J=11.0, 1.6 Hz, 1H), 3.07 (dd, J=11.5, 2.2 Hz, 1H), 3.25 (dd, J=11.5, 2.2 Hz, 1H), 3.60 (dd, J=11.0, 2.2 Hz, 1H), 3.79 (s, 3H), 4.20 (q, J=7.1 Hz, 2H), 6.76–6.86 (m, 2H), 7.12 (dd, J=7.3, 8.5 Hz, 1H). MS *m/z* (EI) 483 ($M^{+\cdot}$, 5%), 481 ($M^{+\cdot}$, 5%), 438 (2), 436 (2), 402 (5), 356 (1), 342 (1), 330 (1), 328 (1), 304 (95), 302 (100), 222 (13), 210 (2), 164 (2), 162 (2), 150 (12), 137 (8), 122 (5), 107 (5), 91 (5). Anal. Calcd for $C_{22}H_{28}BrNO_6$: $M^{+\cdot}$ 483.1081. Found: $M^{+\cdot}$ 483.1069.

4.2.15. Ethyl 5-hydroxy-3-[2-(3-methoxy-2-acetoxy)-ethyl]-9-oxo-3-azabicyclo[3.3.1]nonanecarboxylate 33. Ethyl 5-bromo-3-[2-(3-methoxy-2-acetoxy)ethyl]-9-oxo-3-azabicyclo[3.3.1]nonanecarboxylate **30** (38 mg, 0.079 mmol) was dissolved in anhydrous nitromethane (2 mL) under an argon atmosphere and the flask covered with aluminium foil. The reaction flask was then placed in an ice-bath and solid silver 2,4,6-trinitrobenzenesulfonate[36] (95 mg, 0.236 mmol) added in one portion. The mixture was allowed to reach room temperature in the bath over 24 h. The solvent was then removed under high vacuum and the solid residue redissolved in dichlormethane (~2 mL) and concd ammonia solution (50 drops) added. After 5 min solid Na_2SO_4 was added and the dichloromethane removed (Pasteur Pipette) followed by multiple dichloromethane washes. The combined extracts were evaporated and the residue subjected to column chromatography [dichloromethane then dichloromethane/ethyl acetate (95:5)], which afforded recovery of starting material (~5 mg) and the titled compound as a pale yellow oil (27 mg, 82%). ^{1}H NMR (200 MHz, $CHCl_3$) δ 1.27 (t, J=7.3 Hz, 3H), 1.38–1.54 (m, 1H), 1.76–1.96 (m, 1H), 2.08–2.47 (m, 4H), 2.32 (s, 3H), 2.47–2.79 (m, 5H), 2.96–3.06 (m, 1H), 3.21–3.35 (m, 2H), 3.61 (s, OH), 3.80 (s, 3H), 4.21 (q, J=7.3 Hz, 2H), 6.78–6.87 (m, 2H), 7.11 (t, 7.9, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1, 19.8, 20.1, 20.5, 27.9, 36.6, 42.1, 55.9, 56.5, 58.6, 61.5, 61.8, 66.4, 75.0, 110.3, 121.9, 126.3, 133.1, 138.3, 151.2, 168.9, 169.9, 211.5. MS *m/z* (EI) 419 ($M^{+\cdot}$, 3%), 402 (1), 374 (2), 332 (1), 302 (1), 286 (1), 254 (1), 240 (100), 212 (1), 194 (1), 176 (5), 164 (1), 151 (2), 136 (1), 107 (1), 91 (1). Anal. Calcd for $C_{22}H_{29}NO_7$: $M^{+\cdot}$ 419.1944. Found: $M^{+\cdot}$ 419.1955.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.02.014. Both ^{1}H and ^{13}C NMR spectra of compounds **8**, **10**, **13**, **16**, **18**, **20–25**, **29–30** and **33** are available.

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Nitrogen is a requirement for the photochemical induced 3-azabicyclo[3.3.1]nonane skeletal rearrangement!

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Abstract—Specific 3-azabicyclo[3.3.1]nonane derivatives undergo skeletal cleavage when subjected to light or Lewis acidic conditions affording novel heterotricycles, which is in stark contrast to 3-oxabicyclo[3.3.1]nonanes.

1. Introduction

The 3-azabicyclo[3.3.1]nonane (3-ABN) skeleton **1** is well known[1] to both natural product[2,3] and synthetic[4] chemists alike as it appears as the AE ring motif in the prolific C_{19}- (e.g., chasmanine **2**) and C_{20}- (e.g., atisine **3**) diterpene alkaloid series[5,6] (Fig. 1).

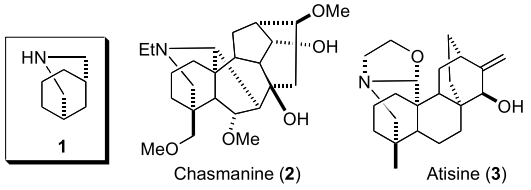
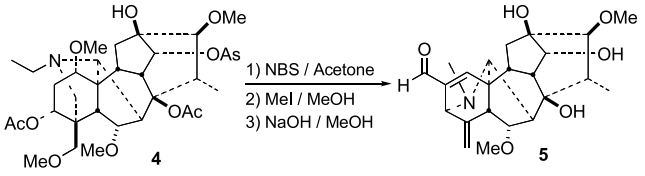


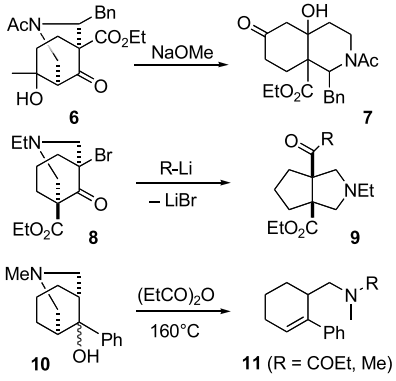
Figure 1.

In comparison, however, rearrangement of the 3-ABN skeleton is not so well known. For example, biosynthetic rearrangement is seldom observed (e.g., arcutin[7]), although, 3-acetylyunaconitine **4** affords AE ring rearranged products (e.g., **5**) when treated chemically (1. NBS; 2. MeI; 3. NaOH) (Scheme 1).[8]



Scheme 1.

Furthermore, synthetic 3-ABNs have been observed in only three instances to undergo rearrangement [i.e., retroaldol[9] (**6** to **7**), pinacol-type[10] (**8** to **9**) and thermal[11] (**10** to **11**)] (Scheme 2).



Scheme 2.

Recently, however, during the course of attempting to optimise our direct route to C_{19}- and C_{20}-diterpene alkaloid advanced intermediate **12**,[12] we discovered that certain 3-ABNs (e.g., **14**) undergo unprecedented photochemical rearrangement affording novel heterotricycles **15** (Scheme 3).[13] Unfortunately, however, photochemical rearrangement is not general and we herein disclose these results in full.

2. Results and discussion

Paramount to studying the photochemical rearrangement of

Keywords: Photochemistry; 3-Azabicyclo[3.3.1]nonane.
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† To whom correspondence should be made regarding X-ray crystal structure analysis.

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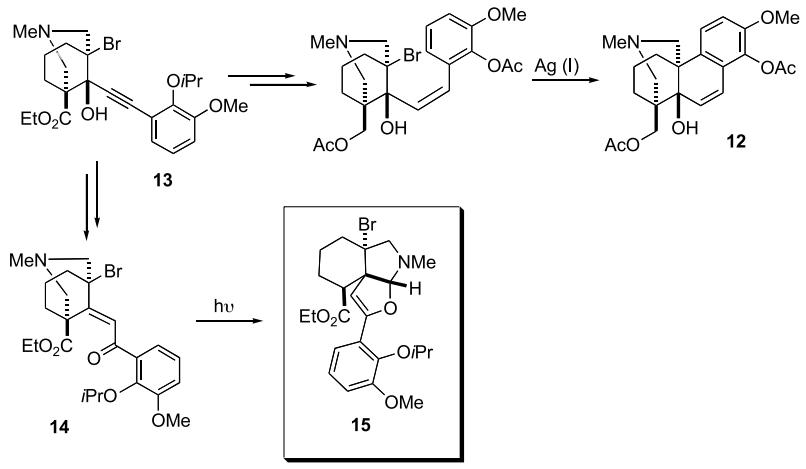
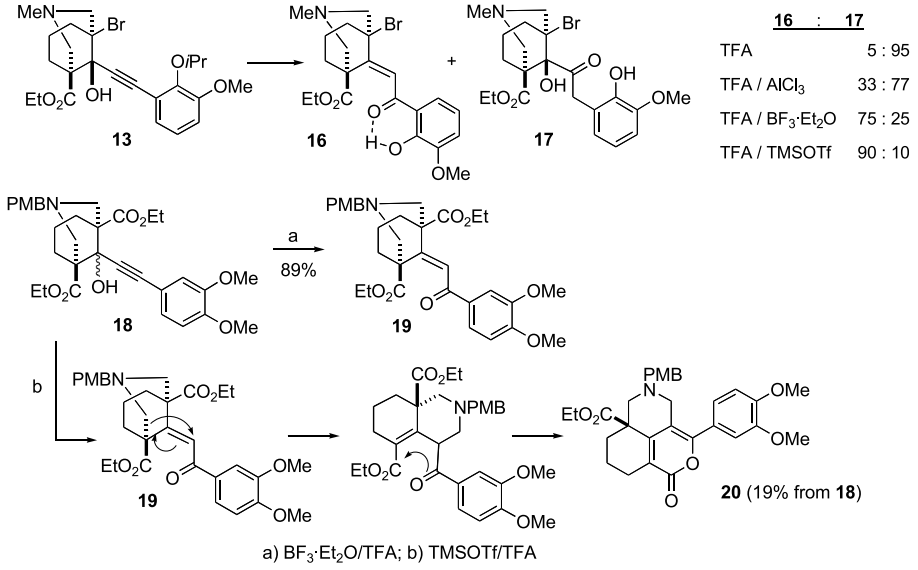


Scheme 3.



Scheme 4.

3-ABNs of type **14** was their synthesis and in this regard a Meyer–Schuster rearrangement[14] was found to be the method of choice. Treatment of the propargylic alcohol **13**[12] with a selection of Lewis acids in trifluoroacetic acid (TFA) gave the isopropyl deprotected enone **16** (Meyer–Schuster product) and the corresponding deprotected α-hydroxyketone **17** (triple bond hydration) in varying ratios (Scheme 4). Trimethylsilyl trifluorosulfonate (TMSOTf) in TFA was found to be the optimum conditions affording a 9:1 ratio in favour of the enone **16**. In stark contrast treatment of propargylic alcohol **18** using the successful conditions (TMSOTf/TFA) developed for **13**, gave the Meyer–Schuster product **19** only in low yield (13%) along with pyranone **20** (19%) [confirmed by X-ray crystal analysis (Fig. 2)], derived from a sequential [1,3]-sigmatropic shift followed by enolic ring closure. Changing the Lewis acid to borotrifluoride etherate, however, gave **19** in 89% (Scheme 4).

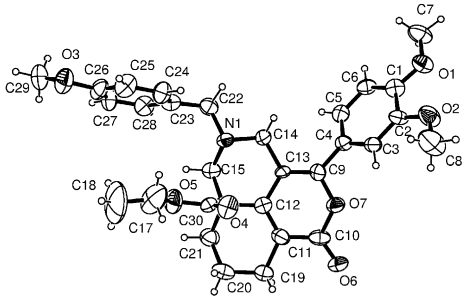
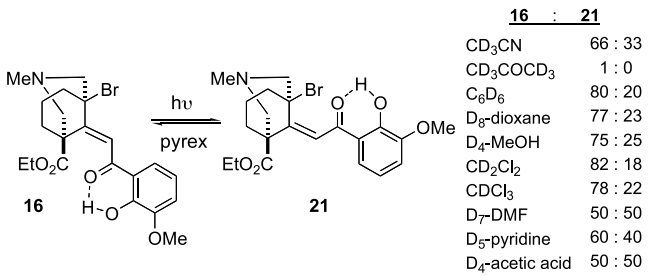


Figure 2.

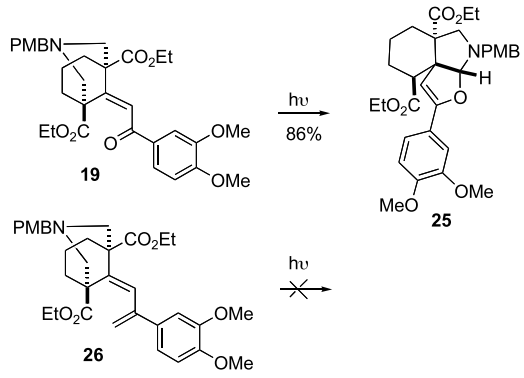
Photochemical rearrangement of 3-ABNs seem to be very functional group specific, for example, photolysis of **16** at 300 nm in various oxygen free deuterated solvents results in photochemical isomerization (*cis* to *trans*) of enone **16** to enone **21** without the formation of any rearranged product (Scheme 5). This is not easily explained, but maybe due to one of a number of processes, which prevent n to π* transitions, for example, nitrogen or oxygen protonation, or hydrogen bonding.[15]



Scheme 5.

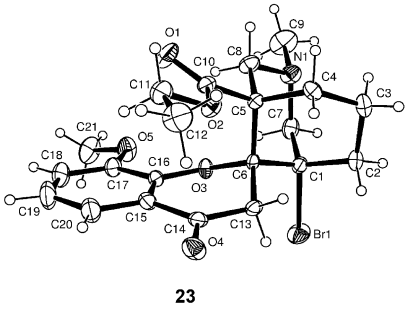
Whereas conversion of the phenol to an isopropyl ether followed by photolysis afforded rearranged products (e.g., **14** to **15**). However, the etherfication procedure of Banwell[16] gave in addition to the isopropyl ether [i.e., **14** (48%)] pyranones **22** and **23** (29%) (Fig. 3), which was easily circumvented using the procedure of Sargent[17] in conjunction with a large excess of *iso*-propylbromide (93%) (Scheme 6). Pyranones **22** and **23** could be obtained in 26 and 61% yields, respectively, in the absence of isopropyl bromide. Irradiation of **14**, gave the rearranged product **15** (18%) along with a mixture (2:8) of **15** and **24** (51%) (Scheme 4). Unfortunately, conversion to **15** cannot be driven to completion, extended radiation leads to substantial decomposition mostly likely due to complications arising from the single electron susceptible bridgehead bromide function. A photochemical equilibrium between **14/24** and **15** was dismissed when pure **15** was irradiated affording slow decomposition.

In contrast, irradiation of **19** gave the rearranged product **25** in very high yield (86%) (Scheme 7). To evaluate the scope of this process the ketone functionality of **19** was replaced with CH_2 (e.g., **26**), in an attempt to emulate α-hydrogen abstraction reported by Grainger[18] and Reddy (Scheme 7)[19] and the ring *N* substituted with oxygen (**27**) (Scheme 8). Conversion to diene **26** via standard Wittig methodology (CH_2=PPh_3) proceeded smoothly (64%), however, photolysis at 254 and 300 nm resulted in decomposition.



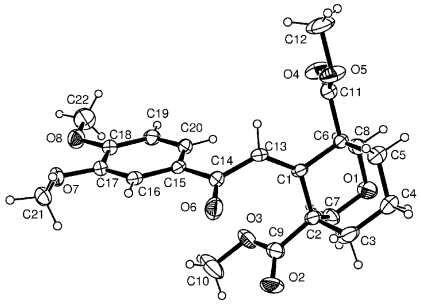
Scheme 7.

Construction of **27**, confirmed by X-ray crystal structure analysis (Fig. 4), was achieved following similar protocols used to synthesise **19**, except starting from dimethyl 9-oxo-3-oxabicyclo[3.3.1]nonane-1,5-dicarboxylate.[20]



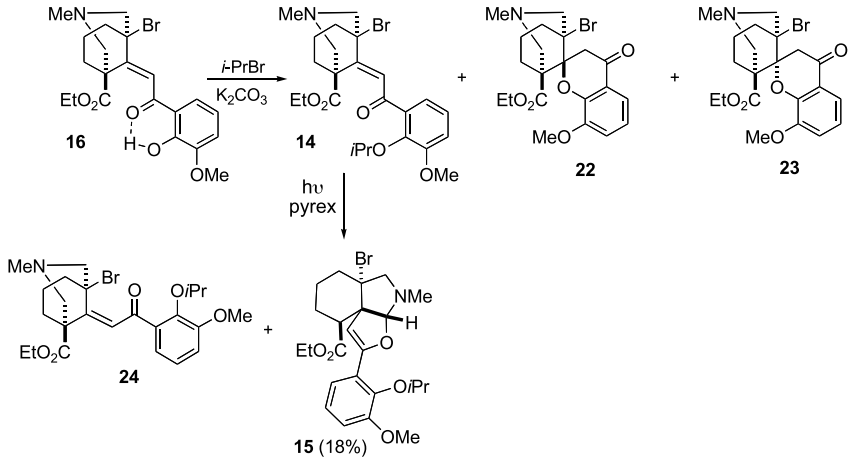
23

Figure 3.

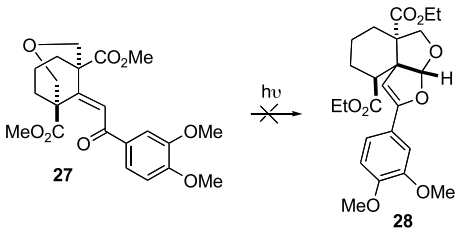


27

Figure 4.



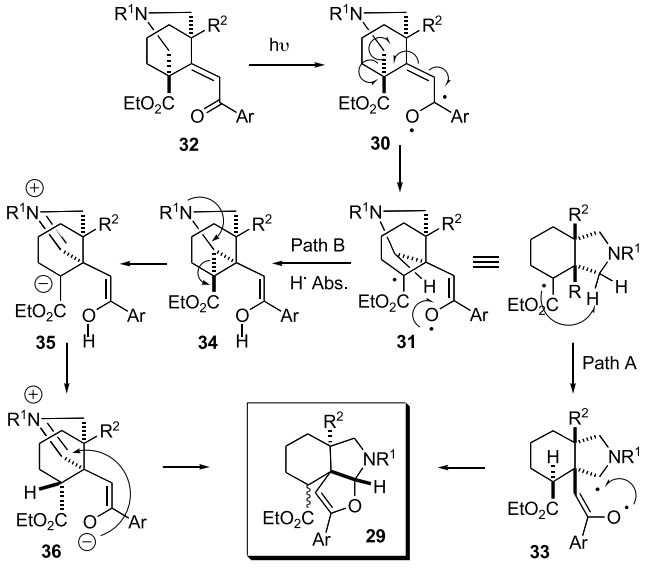
Scheme 6.



Scheme 8.

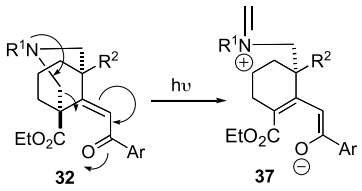
Unfortunately, however, photolysis of **27** at 300 nm returned starting material and irradiation at 254 nm resulted in slow decomposition (Scheme 8).

Two mechanistic pathways to **15** and **25** (e.g., **29**) are proposed of which only mechanistic pathway B arrives at the observed stereochemistry for the non-bridgehead ester group [**29** (β)] whereas pathway A would afford stereochemistry opposite [**29** (α)] to that seen in the X-ray crystal structures of **15** and **25** (Scheme 9). Both mechanisms involve a 1,2-sigmatropic shift (**30** to **31**) initiated by ketone **32** excitation (triple state). The subsequent formation of radical **33** (Path A) appears justified on the basis of recent data provided by Croft et al.[21] Ring closure of **33** leads to the final tricycle **29**. Alternatively, rearrangement of radical **31** (Path B) leads to the unstable cyclopropane intermediate **34**. Anionic ring opening of **34** would afford **35**, which undergoes immediate proton exchange on the less hindered face with concomitant ring closure, via the oxyanion **36**, affording **29**. An intermolecular pathway has been ruled out in this instance as deuterium atom abstraction from d_7-DMF was not observed.



Scheme 9.

The observation that oxabicyclo **27** does not undergo photochemical reaction suggests that the oxa substituent cannot suitably stabilise the 1,2-shift (i.e., **30** to **31**), which, if radical in nature would concur with recent calculations[22] (i.e., nitrogen has the greatest stabilisation of lone pair donor groups). It is also conceivable that photochemical induced heterolytic sigma bond cleavage may occur to give intermediate **37**, which would be favoured by aza more than oxa groups, however, it is difficult to transpose intermediate **37** into product (e.g., **15** and **25**) (Scheme 10).



Scheme 10.

3. Conclusion

We have discovered for the first time a photochemical rearrangement of the 3-ABN skeleton, which affords a unique heterotricyclic system. It should be noted that all attempts to ring open the aminal moiety of **15** and **25** so as to gain access to alkaloid type skeletons have failed.

4. Experimental

4.1. General experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV400 (400.13 MHz; 100.62 MHz) or a Bruker AC200 (200.13 MHz; 50.32 MHz) in deuteriochloroform ($CDCl_3$). Coupling constants are given in Hz and chemical shifts are expressed as δ values in ppm. High and low resolution EI mass spectral data were obtained on a KRATOS MS 25 RFA. Microanalyses were performed by the University of Queensland Microanalytical Service. Column chromatography was undertaken on silica gel (Flash Silica gel 230–400 mesh), with distilled solvents. Anhydrous solvents were prepared according to Perin and Armarego, 'Purification of laboratory solvents', 3rd Ed. Melting points were determined on a Fischer Johns Melting Point apparatus and are uncorrected. Methylmagnesium bromide and *n*-BuLi was purchased from the Aldrich Chem. Co.

4.2. X-ray crystallography

Data for all compounds were collected at 293 K on an Enraf-Nonius CAD4 diffractometer. Data reduction, direct methods structure solution and full least squares refinement (SHELX97[23]) were performed with the WINGX package.[24] Drawings of all molecules were created with ORTEP3.[25] Data in CIF format have been deposited with the Cambridge Crystallographic Data Centre (CCDC Deposition Nos. 248300–248302). Copies of the data can be obtained free of charge upon request to deposit@ccdc.cam.ac.uk

4.2.1. Ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-hydroxy-3-methoxyphenyl)-*E*-ethylidene]-3-azabicyclo[3.3.1]nonanecarboxylate 16. Ethyl 5-bromo-3-methyl-9-*exo*-hydroxy-9-[2-(3-methoxy-2-isopropoxy)phenylethynyl]-3-azabicyclo[3.3.1]nonanecarboxylate[12] **13** (0.205 g, 0.041 mmol) was rapidly dissolved in trifluoroacetic acid (3 mL) at room temperature. The solution was cooled in an ice-bath and trimethylsilyltrifluorosulfonate (0.23 mL, 1.29 mmol)

added rapidly. After addition the flask was taken out of the bath and stirred at room temperature for 1 h. The reaction mixture was then transferred, via Pasteur pipette, to a separatory funnel containing a saturated solution of sodium hydrogen carbonate (50 mL) and extracted with dichloromethane (3×10 mL). The residue was dried under vacuum, redissolved in anhydrous THF (3 mL) and sodium hydride added until effervescence ceased. The mixture was quenched with saturated ammonium chloride solution and extracted with dichloromethane (3×10 mL). Column chromatography (ethyl acetate/dichloromethane, 5:95) afforded the title compound as a bright yellow viscous oil (0.13 g, 70%). ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.83 (t, J=7.1 Hz, 3H), 1.56–1.65 (m, 1H), 2.20 (s, 3H), 2.21–2.28 (m, 2H), 2.40–2.51 (m, 1H), 2.63 (d, J=11.1 Hz, 1H), 2.69–2.76 (m, 1H), 2.85 (dd, J=10.6, 2.4 Hz, 1H), 2.93–3.07 (m, 2H), 3.50 (dd, J=10.6, 1.3 Hz, 1H), 3.66–3.85 (m, 2H), 3.89 (s, 3H), 6.87 (t, J=8.1 Hz, 1H), 7.03–7.07 (m, 1H), 7.38 (s, 1H), 7.42 (dd, J=8.1, 1.4 Hz, 1H), 12.26 (s, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 23.6, 36.3, 44.6, 47.3, 52.4, 56.2, 60.9, 64.1, 71.1, 71.5, 117.1, 118.4, 120.1, 122.6, 123.0, 148.7, 152.7, 153.0, 172.3, 199.5. MS *m/z* (EI) 453 ($M^{+\cdot}$, 4%), 451 ($M^{+\cdot}$, 5%), 408 (2), 406 (2), 372 (80), 326 (20), 302 (20), 300 (21), 298 (14), 286 (6), 283 (6), 279 (15), 256 (8), 222 (17), 220 (30), 206 (19), 167 (39), 151 (98), 149 (100), 129 (11), 113 (18). Anal. Calcd for $C_{21}H_{26}BrNO_5$: $M^{+\cdot}$ 451.0995. Found: 451.0989.

4.2.2. Photolysis of ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-hydroxy-3-methoxyphenyl)-*E*-ethylidene]-3-azabicyclo[3.3.1]nonanecarboxylate 16. Ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-hydroxy-3-methoxyphenyl)-*E*-ethylidene]-3-azabicyclo[3.3.1]nonanecarboxylate **16** (0.020 g, 0.044 mmol) was dissolved in oxygen free D_7-*N*,*N*-dimethylformamide (1 mL) in a 5 mm NMR tube (PP-528) and irradiated with a Hanovia high pressure mercury–xeon vapour lamp (1000 W). [*Note*. The light was passed through a ~5 °C water filter (30 cm long) and the sample placed 10 cm from the end of the cooling tube.] The isomerization was monitored by ^{1}H NMR every 15 min until a 1:1 mixture of **16** and **21** was evident. The solvent was removed and the residue subjected to column chromatography (dichloromethane) affording an inseparable 1:1 mixture of **16** and **21** (0.015 g, 75%).

The relevant ^{1}H NMR values for **21** are listed only and are a result from subtracting isolated peaks observed from a spectrum of pure **16**.

^{1}H NMR (200 MHz, $CHCl_3$) δ 1.27 (t, J=7.4 Hz, 3H), 3.32 (AB, 1H), 3.885 (s, 3H), 4.12–4.26 (m, 2H), 5.80 (s, 1H).

4.2.3. Ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-isopropoxy-3-methoxyphenyl)-*E*-ethylidene]-3-azabicyclo-[3.3.1]nonanecarboxylate 14. Ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-hydroxy-3-methoxyphenyl)-*E*-ethylidene]-3-azabicyclo[3.3.1]nonanecarboxylate **16** (0.156 g, 0.345 mmol) was dissolved in *N*,*N*-dimethylformamide (1.5 mL) followed by addition of 2-bromopropane (0.97 mL, 10.3 mmol) and potassium carbonate (0.095 g, 0.69 mmol). The mixture was then stirred at room temperature for 16 h. Excess 2-bromopropane and *N*,*N*-dimethylformamide were removed under high vacuum and the residue suspended in dichloromethane (5 mL) and passed through celite. Column chromatography (diethyl ether/light petroleum, ~1:4) of the residue on silica gel afforded the title compound (0.159 g, 93%) and **22** (0.004 g, 3%) both as pale yellow oils. ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.22–1.30 (m, 9H), 1.54–1.63 (m, 1H), 1.96–2.05 (m, 1H), 2.17 (s, 3H), 2.36–2.49 (m, 2H), 2.51–2.60 (m, 1H), 2.79 (dd, J=10.7, 2.4 Hz, 1H), 2.87 (dd, J=11.1, 2.4 Hz, 1H), 2.89–3.03 (m, 1H), 2.97 (dd, J=11.1, 1.3 Hz, 1H), 3.28 (dd, J=10.7, 1.3 Hz, 1H), 3.82 (s, 3H), 4.13–4.25 (m, 2H), 4.59 (sept, J=6.2 Hz, 1H), 6.99–7.07 (m, 2H), 7.42 (AB, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.3, 22.4, 23.6, 35.9, 44.8, 46.2, 54.9, 56.1, 61.2, 63.1, 65.4, 71.3, 76.1, 116.1, 122.8, 123.7, 125.7, 134.3, 142.4, 147.0, 153.5, 172.7, 195.3. Near IR (Nujol) ν (cm^{-1}) 1729, 1713, 1681, 1666. MS *m/z* (EI) 494 ($M^{+\cdot}$, 0.5%), 492 ($M^{+\cdot}$, 0.5%), 414 (77), 368 (7), 354 (7), 340 (2), 326 (9), 315 (1), 302 (11), 300 (12), 283 (2), 256 (2), 220 (27), 208 (5), 206 (8), 193 (49), 174 (2), 151 (100), 148 (6), 146 (5), 134 (6), 120 (4). Anal. Calcd for $C_{24}H_{32}BrNO_5$: $M^{+\cdot}$ 414.2280 (−HBr). Found: 414.2277.

4.2.4. Pyranones 22 and 23. Ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-hydroxy-3-methoxyphenyl)-*E*-ethylidene]-3-azabicyclo[3.3.1]nonanecarboxylate **16** (0.023 g, 0.051 mmol) was dissolved in *N*,*N*-dimethylformamide (2.0 mL) followed by addition of potassium carbonate (0.021 g, 0.15 mmol). The mixture was then heated at 80 °C for 15 min. On cooling *N*,*N*-dimethylformamide was removed under high vacuum and the residue suspended in dichloromethane (5 mL) and passed through celite. Column chromatography (dichloromethane/ethyl acetate, gradient) of the residue on silica gel afforded two fractions. Fraction one (**22**) (6 mg, 26%) was obtained as colourless crystals. Mp 116–118 °C (diethyl ether/dichloromethane) ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.89 (t, J=7.2 Hz, 3H), 1.63–1.78 (m, 2H), 2.22 (s, 3H), 2.31–2.38 (m, 1H), 2.67–2.97 (m, 5H), 3.15–3.27 (m, 2H), 3.34 (d, J=14.7 Hz, 1H), 3.52–3.73 (m, 3H), 3.88 (s, 3H), 6.86 (t, J=8.0 Hz, 1H), 7.03 (dd, J=8.0, 1.6 Hz, 1H), 7.37 (dd, J=8.0, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 23.2, 29.4, 39.0, 41.3, 44.7, 52.8, 56.7, 59.7, 61.3, 65.5, 74.6, 83.1, 117.2, 117.9, 120.1, 120.4, 149.3, 150.7, 172.2, 189.8. MS *m/z* (EI) 453 ($M^{+\cdot}$, 30%), 451 ($M^{+\cdot}$, 32%), 408 (8), 372 (74), 328 (46), 315 (7), 298 (34), 283 (14), 270 (4), 255 (27), 220 (27), 151 (57), 138 (17), 136 (21), 122 (21), 105 (13). Anal. Calcd for $C_{21}H_{26}BrNO_5$: $M^{+\cdot}$ 451.0995. Found: 451.0992. Fraction two (**23**) (14 mg, 61%) was obtained as colourless needles. Mp 131–133 °C (diethyl ether/dichloromethane) ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.94 (t, J=7.2 Hz, 3H), 1.48–1.58 (m, 1H), 1.84 (dd, J=14.9 Hz, 6.5, 1H), 2.26 (s, 3H), 2.32–2.48 (m, 3H), 2.72 (d, J=11.6 Hz, 1H), 2.85–3.02 (m, 1H), 3.16 (d, J=10.8 Hz, 1H), 3.32 (dd, J=11.6, 2.6 Hz, 1H), 3.47–3.65 (m, 5H), 3.88 (s, 3H), 6.86 (t, J=7.9 Hz, 1H), 7.01 (dd, J=7.9, 1.5 Hz, 1H), 7.38 (dd, J=7.9, 1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 22.7, 32.1, 39.8, 40.5, 45.1, 52.3, 56.8, 57.7, 61.2, 64.4, 74.8, 83.1, 117.1, 117.9, 120.2, 120.6, 149.3, 149.9, 172.3, 189.9. MS *m/z* (EI) 453 ($M^{+\cdot}$, 30%), 451 ($M^{+\cdot}$, 29%), 372 (43), 328 (27), 298 (14), 283 (10), 255 (13), 227 (4), 220 (7), 194 (6), 151 (32), 138 (10), 136 (9), 122 (11), 105 (6). Anal. Calcd for $C_{21}H_{26}BrNO_5$: C, 55.76; H, 5.79; N, 3.10; $M^{+\cdot}$ 451.0995. Found: C, 55.53; H, 5.76; N, 3.07; $M^{+\cdot}$ 451.0986.

4.2.5. Photolysis of ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-isopropoxy-3-methoxyphenyl)-*E*-ethylidene]-3-azabicyclo[3.3.1]nonanecarboxylate 14. Ethyl 5-bromo-3-methyl-9-[2-oxo-2-(2-isopropoxy-3-methoxyphenyl)-*E*-ethylidene]-3-azabicyclo[3.3.1]nonanecarboxylate **14** (0.171 g, 0.346 mmol) was dissolved in oxygen free *N*,*N*-dimethylformamide (150 mL) and irradiated through pyrex in a 1 L Hanovia photochemical reactor using a 4 W arc lamp for 10 days. The solvent was then removed under high vacuum using an in-line trap and the residue subjected to column chromatography (diethyl ether/light petroleum, 3:7–6:4), which afforded tricycle **15** (0.030 g, 18%) in fraction one and a mixture of **14** and **24** (1:1) (0.088 g, 51%) in fraction two.

Ethyl 3a-bromo-2-methyl-1,3,3a,4,5,6,7,7a-octahydro-9-(2-isopropoxy-3-methoxyphenyl)-isoindolo[1,7a-b]furan-7-carboxylate **15**. ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.00 (t, J=7.1 Hz, 3H), 1.23 (d, J=6.2 Hz, 3H), 1.29 (d, J=6.2 Hz, 3H), 1.54–1.82 (m, 3H), 1.84–1.91 (m, 1H), 2.19–2.26 (m, 1H), 2.34–2.44 (m, 1H), 2.51 (s, 3H), 2.83–2.92 (m, 2H), 3.35 (d, J=8.0 Hz, 1H), 3.81 (s, 3H), 3.84–4.00 (m, 2H), 4.67 (sept, J=6.2 Hz, 1H), 5.63 (s, 1H), 5.67 (s, 1H), 6.80–6.84 (m, 1H), 6.96 (t, J=16 Hz, 1H), 7.22–7.27 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.3, 22.2, 22.5, 26.3, 34.3, 40.0, 45.9, 55.9, 60.4, 65.18, 65.25, 69.5, 74.2, 94.4, 107.4, 112.7, 119.6, 122.9, 125.2, 144.7, 152.95, 153.04, 173.8. Near IR (Nujol) ν (cm^{-1}) 1731. MS *m*/*z* (EI) 494 ($M^{+\cdot}$, 0.5%), 492 ($M^{+\cdot}$, 0.5%), 414 (100), 368 (29), 326 (6), 298 (5), 282 (2), 270 (2), 256 (2), 220 (63), 208 (10), 193 (87), 175 (2), 151 (89), 148 (6), 146 (8), 134 (22), 120 (8). Anal. Calcd for $C_{24}H_{32}BrNO_5$: $M^{+\cdot}$ 414.2280 (−HBr). Found: 414.2279.

4.2.6. Diethyl 3-(4-methoxyphenylmethyl)-9-[2-oxo-2-(3,4-dimethoxyphenyl)ethylidene]-3-azabicyclo[3.3.1]-nonane-1,5-dicarboxylate 19. Following the procedure of Fukumoto.[4g,h] Diethyl cyclohexanone-2,6-dicarboxylate (3.20 g, 13.2 mmol) was dissolved in distilled ethanol (120 mL) and *p*-methoxybenzylamine (2.16 mL, 16.5 mmol) added followed by formaldehyde (4.8 mL, 54.2 mmol, 37% in water). After stirring the solution in the dark at room temperature for 48 h the solvent was removed in vacuo and the residue subjected to column chromatography (diethyl ether/light petroleum, ~1:4) affording diethyl 3-(4-methoxyphenylmethyl)-9-oxo-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylate as a viscous colourless oil (4.67 g, 88%). ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.24 (t, J=7.2 Hz, 6H), 1.58–1.67 (m, 1H), 2.16–2.24 (m, 2H), 2.53–2.62 (m, 2H), 2.83–2.99 (m, 1H), 2.98–3.03 (m, 2H), 3.11–3.17 (m, 2H), 3.48 (s, 2H), 3.79 (s, 3H), 4.10–4.21 (m, 4H), 6.81–6.90 (m, 2H), 7.18–7.27 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.2, 36.3, 55.2, 58.4, 61.2, 61.4, 61.7, 113.8, 129.9, 130.0, 158.9, 170.4, 207.3. Near IR (film) ν (cm^{-1}) 1730, 1611, 1510. MS *m*/*z* (EI) 403 ($M^{+\cdot}$, 5%), 398 (1), 386 (2), 358 (2), 330 (4), 302 (1), 282 (2), 272 (1), 254 (2), 242 (8), 226 (2), 209 (7), 196 (25), 168 (30), 140 (19), 135 (17), 121 (100). Anal. Calcd for $C_{22}H_{29}NO_6$: $M^{+\cdot}$ 403.1995. Found: 403.1986.

3,4-Dimethoxyphenylacetylene[26] (0.442 g, 2.73 mmol) was dissolved in anhydrous tetrahydrofuran (3 mL) and placed in an ice-bath under argon. Methylmagnesium bromide (2 mL, 2.86 mmol, 1.4 M, tetrahydrofuran/toluene) was then added and the flask taken out of the bath and stirred at room temperature for 1.3 h. In a separate flask diethyl 3-(4-methoxyphenylmethyl)-9-oxo-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylate (1.0 g, 2.48 mmol) was dissolved in anhydrous tetrahydrofuran (30 mL) and cooled to −78 °C (dry-ice/acetone bath) under argon. To this was added the above solution dropwise via cannular over 5 min. The reaction mixture was then allowed to reach 15–20 °C over 1.5 h and was stirred at room temperature for 1 h, before quenching with saturated ammonium chloride solution. The phases were partitioned and the aqueous washed with diethyl ether (2×20 mL). The combined organic layers were evaporated and the residue subjected to column chromatography (diethyl ether/light petroleum, gradient) affording diethyl 3-(4-methoxyphenylmethyl)-9-*exo*-hydroxy-9-[2-(3,4-dimethoxy)phenylethynyl]-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylate (1.0 g, 71%) (pale yellow oil) as a mixture of diastereomers [7(*exo*):3(*endo*)]. Near IR (film) ν (cm^{-1}) 3468, 3272, 1725, 1511. MS {mixture of diastereomers [7(*exo*):3(*endo*)]} *m*/*z* (EI) 565 ($M^{+\cdot}$, 31%), 547 (1), 536 (2), 519 (3), 492 (10), 474 (6), 464 (1), 444 (4), 424 (3), 416 (3), 398 (4), 378 (3), 370 (4), 342 (1), 324 (4), 309 (1), 296 (2), 282 (2), 269 (1), 256 (2), 248 (4), 232 (1), 218 (2), 204 (1), 189 (8), 175 (3), 162 (5), 154 (9), 149 (3), 136 (3), 121 (100). Anal. Calcd for $C_{32}H_{39}NO_8$: $M^{+\cdot}$ 565.2676. Found: 565.2674.

Method A. To diethyl 3-(4-methoxyphenylmethyl)-9-*exo*-hydroxy-9-[2-(3,4-dimethoxy)phenylethynyl]-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylate [7(*exo*):3(*endo*)] (0.430 g, 0.76 mmol) at room temperature was added a mixture of trifluoroacetic acid (0.5 mL) and borontriflouride diethyl etherate (0.3 mL, 2.36 mmol). After stirring at room temperature for 1 h the reaction mixture was then transferred, via Pasteur pipette, to a separatory funnel containing a saturated solution of sodium hydrogen carbonate (50 mL) and extracted with dichloromethane (3×10 mL). The residue was subjected to column chromatography (diethyl ether/dichloromethane/light petroleum, gradient) afforded diethyl 3-(4-methoxyphenylmethyl)-9-[2-oxo-2-(3,4-dimethoxyphenyl)ethylidene]-3-azabicyclo-[3.3.1]nonane-1,5-dicarboxylate **19** (0.381 g, 89%), as a colourless crystals, mp 168–170 °C. ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.74 (t, J=7.2 Hz, 3H), 1.29 (t, J=7.1 Hz, 3H), 1.60–1.71 (m, 1H), 1.99–2.08 (m, 1H), 2.13–2.22 (m, 1H), 2.24–2.42 (m, 2H), 2.66 (dd, J=11.1, 1.6 Hz, 1H), 2.82 (dd, J=11.1, 1.6 Hz, 1H), 2.90–3.07 (m, 3H), 3.41 (AB, 2H), 3.57–3.74 (m, 2H), 3.79 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 4.14–4.26 (m, 2H), 6.24 (s, 1H), 6.82–6.87 (m, 3H), 7.19–7.22 (m, 2H), 7.46 (d, J=1.9 Hz, 1H), 7.54 (dd, J=8.3 Hz, 1.9, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 14.3, 20.9, 36.6, 36.9, 49.9, 53.2, 55.22, 55.97, 55.05, 60.3, 61.0, 61.9, 62.0, 62.5, 109.9, 110.2, 113.8, 119.7, 123.9, 129.8, 130.3, 130.6, 149.1, 152.4, 153.3, 158.7, 173.0, 173.7, 191.5. MS *m*/*z* (EI) 565 ($M^{+\cdot}$, 13%), 536 (2), 520 (3), 492 (10), 474 (2), 444 (4), 429 (2), 416 (2), 400 (16), 385 (2), 370 (3), 354 (4), 343 (2), 330 (1), 312 (3), 297 (1), 278 (1), 263 (2), 206 (1), 191 (1), 180 (2), 165 (26), 121 (100). Anal. Calcd for $C_{32}H_{39}NO_8$: C, 67.95; H, 6.95; N, 2.48; $M^{+\cdot}$ 565.2676. Found: C, 68.05; H, 7.07; N, 2.34; 565.2676.

Method B. Diethyl 3-(4-methoxyphenylmethyl)-9-*exo*-hydroxy-9-[2-(3,4-dimethoxy)phenylethynyl]-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylate [7(*exo*):3(*endo*)] (0.069 g, 0.122 mmol) was rapidly dissolved in trifluoroacetic acid (1 mL) at 0 °C (ice-bath) under argon. Trimethylsilyltrifluorosulfonate (0.07 mL, 0.378 mmol) was added rapidly and the flask then taken out of the bath and stirred at room temperature for 1 h. The reaction mixture was then transferred, via Pasture pipette, to a separatory funnel containing a saturated solution of sodium hydrogen carbonate (50 mL) and extracted with dichloromethane (3×10 mL). The residue was dried under vacuum and subjected to column chromatography (ethyl acetate/dichloromethane, 1:9) affording two fractions. Fraction one contained the title compound **19** (0.009 g, 13%) and fraction two afforded ethyl 1-(3,4-dimethoxyphenyl)-8-(4-methoxyphenylmethyl)-4,5,6,6a,7,9-hexahydro-3*H*-pyrano[4,4*a*,5,*d*-*e*]isoquinolin-3-on-6a-carboxylate **20** (0.012 g, 19%) as a yellow amorphous solid. ^{1}H NMR (400 MHz, $CHCl_3$) δ 1.15 (t, J=7.1 Hz, 3H), 1.40–1.65 (m, 2H), 1.87–1.98 (m, 1H), 2.06–2.14 (m, 1H), 2.18 (d, J=11.2 Hz, 1H), 2.42–2.55 (m, 1H), 2.63–2.74 (m, 1H), 3.17 (d, J=14.6 Hz, 1H), 3.28–3.35 (m, 1H), 3.42–3.55 (AB, 2H), 3.76 (s, 3H), 3.79 (s, 3H), 3.89 (s, 3H), 3.91–3.98 (m, 1H), 4.00–4.21 (m, 2H), 6.76–6.87 (m, 3H), 6.97 (d, J=2.0 Hz, 1H), 7.03 (dd, J=8.4, 2.0 Hz, 1H), 7.08–7.13 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 18.1, 23.1, 29.3, 49.8, 53.0, 55.2, 55.89, 55.93, 58.1, 61.3, 61.8, 110.4, 110.5, 111.4, 113.6, 121.0, 121.6, 125.0, 129.3, 130.0, 148.7, 148.9, 150.0, 152.3, 158.9, 163.0, 173.4. MS *m*/*z* (EI) 519 ($M^{+\cdot}$, 5%), 504 (1), 490 (2), 474 (1), 446 (1), 398 (100), 370 (4), 354 (4), 324 (4), 297 (2), 269 (1), 165 (6), 121 (55). Anal. Calcd for $C_{30}H_{33}NO_7$: $M^{+\cdot}$ 519.2257. Found: 519.2261.

4.2.7. Diethyl 2-(4-methoxyphenylmethyl)-1,3,3a,4,5,6,7,7a-octahydro-9-(3,4-dimethoxyphenyl)-isoindolo-[1,7*a*-*b*]furan-3a,7-dicarboxylate 25. Diethyl 3-(4-methoxyphenylmethyl)-9-[2-oxo-2-(3,4-dimethoxyphenyl)ethylidene]-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylate **19** (0.100 g, 0.177 mmol) was dissolved in oxygen free *N*,*N*-dimethylformamide (10 mL) under argon in a 10 mm NMR tube (PP-528) and irradiated for 1 h with a Hanovia high pressure mercury–xeon vapour lamp (1000 W). [*Note*. The light was passed through a water filter (30 cm long) at ~5 °C and the sample placed 10 cm from the end of the cooling tube.] The solvent was then removed under high vacuum using an in-line trap and the residue subjected to column chromatography (diethyl ether/dichloromethane/light petroleum, gradient), which afforded the title compound **25** (0.076 g, 76%), as a pale yellow solid, and recovered starting material **19** (0.012 g, 12%) in that order. Yield based on recovered starting material 86%, mp 109–111 °C (partial), 115–116 °C. ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.99 (t, J=7.1 Hz, 3H), 1.23 (t, J=7.1 Hz, 3H), 1.55–1.73 (m, 3H), 1.78–1.91 (m, 2H), 2.01–2.11 (m, 1H), 2.52 (d, J=8.7 Hz, 1H), 3.10 (d, J=8.7 Hz, 1H), 3.14–3.20 (m, 1H), 3.72 (d, J=13.6 Hz, 1H), 3.78 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 3.88–4.03 (m, 2H), 4.09–4.17 (m, 2H), 4.16 (d, J=13.6 Hz, 1H), 4.90 (s, 1H), 5.90 (s, 1H), 6.78–6.88 (m, 3H), 7.03 (d, J=2.0 Hz, 1H), 7.14 (dd, J=2.0, 8.3 Hz, 1H), 7.23–7.28 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.2, 21.4, 25.6, 33.1, 46.8, 51.2, 54.4, 55.2, 55.90, 55.93, 56.3, 60.1, 60.3, 60.8, 96.7, 97.9, 108.6, 110.7, 113.7, 118.4, 123.4, 129.6, 131.1, 148.6, 149.5, 157.1, 158.6, 173.9, 174.5. Near IR (Nujol) ν (cm^{-1}) 1729, 1715. MS *m*/*z* (EI) 565 ($M^{+\cdot}$, 13%), 520 (11), 492 (10), 474 (5), 444 (4), 424 (2), 416 (3), 400 (16), 165 (26), 121 (100). Anal. Calcd for $C_{32}H_{39}NO_8$: C, 67.95; H, 6.95; N, 2.48; $M^{+\cdot}$ 565.2676. Found: C, 67.79; H, 6.90; N, 2.41; 565.2674.

4.2.8. Diethyl 3-(4-methoxyphenylmethyl)-9-[2-methylene-2-(3,4-dimethoxyphenyl)ethylidene]-3-azabicyclo-[3.3.1]nonane-1,5-dicarboxylate 26. Methylphosphonium bromide (0.047 g, 0.133 mmol) was predried under high vacuum and suspended in anhydrous THF (0.5 mL) under argon. The flask was placed in an ice-bath and *n*-BuLi (0.08 mL, 1.5 M in hexanes) added. After 15 min diethyl 3-(4-methoxyphenylmethyl)-9-[2-oxo-2-(3,4-dimethoxyphenyl)ethylidene]-3-azabicyclo[3.3.1]nonane-1,5-dicarboxylate **19** (0.050 g, 0.088 mmol) was introduced, via cannular, to the flask as a solution in THF (0.5 mL). The mixture was stirred at room temperature for 1.5 h followed by addition of saturated ammonium chloride solution (20 drops). The solvent was then removed under vacuum and the residue extracted with dichloromethane (10 mL). Evaporation of the organic layer and column chromatography (dichloromethane/ethyl acetate, gradient) afforded the title compound **26** (0.023 g, 46%) and recovered starting material **19** (0.014 g, 28%) in that order. The yield based on recovered starting material is 64%. ^{1}H NMR (400 MHz, $CHCl_3$) δ 0.68 (t, J=7.1 Hz, 3H), 1.22 (t, J=7.2 Hz, 3H), 1.62–1.74 (m, 1H), 1.94–2.10 (bm, 2H), 2.17–2.28 (m, 1H), 2.31–2.43 (m, 1H), 2.61–2.67 (m, 1H), 2.80 (bd, J=10.6 Hz, 1H), 2.87–3.09 (m, 3H), 3.32–3.66 (vbm, 2H), 3.41 (s, 2H), 3.79 (s, 3H), 3.867 (s, 3H), 3.875 (s, 3H), 4.04–4.21 (m, 2H), 4.80 (s, 1H), 5.34 (s, 1H), 5.67 (s, 1H), 6.78–6.88 (m, 3H), 7.00–7.06 (m, 2H), 7.18–7.25 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 14.2, 21.0, 37.0, 48.7, 52.6, 55.2, 55.81, 55.88, 60.1, 60.8, 62.3, 62.5, 63.4, 109.5, 110.7, 111.3, 113.7, 119.5, 122.2, 126.4, 129.8, 130.6, 131.2, 141.6, 142.2, 148.5, 148.9, 158.7, 174.3, 174.4. MS *m*/*z* (EI) 563 ($M^{+\cdot}$, 30%), 518 (1), 490 (4), 471 (1), 442 (17), 414 (1), 414 (1), 396 (2), 368 (3), 340 (2), 324 (1), 294 (2), 267 (3), 253 (1), 165 (6), 151 (2), 135 (1), 121 (100). Anal. Calcd for $C_{33}H_{41}NO_7$: $M^{+\cdot}$ 563.2883. Found: 563.2878.

4.2.9. Dimethyl 9-[2-oxo-2-(3,4-dimethoxyphenyl)ethylidene]-3-oxabicyclo[3.3.1]nonane-1,5-dicarboxylate 27. 3,4-Dimethoxyphenylacetylene[26] (0.211 g, 1.30 mmol) was dissolved in anhydrous THF (4 mL) and cooled to −78 °C (dry-ice/acetone bath) under argon. To this solution was added *n*-butyllithium (1.0 mL, 1.40 mmol, 1.4 M solution in *n*-hexane) via syringe during 2 min and the mixture was stirred at −78 °C for 1 h. After removing the cooling-bath the mixture was allowed to reach 20 °C over 2 h and was stirred at room temperature for 1 h. After cooling this mixture to −78 °C a solution of dimethyl 9-oxo-3-oxabicyclo[3.3.1]nonane-1,5-dicarboxylate[20] (0.308 g, 1.20 mmol) in anhydrous THF (3 mL) was quickly added (1 s) and stirred at −78 °C. After 1 h at −78 °C the reaction mixture was allowed to reach room temperature over 2–3 h, before quenching with saturated ammonium chloride solution (25 mL). The phases were partitioned and the aqueous washed with diethyl ether (5×25 mL). The combined organic layers were washed with distilled water (2×20 mL) and brine (1×20 mL), dried (Na_2SO_4) and

evaporated. The residue was then purified by flash chromatography (light petroleum/ethyl acetate, 3:1) affording dimethyl 9-(3,4-dimethoxyphenylethynyl)-9-hydroxy-3-oxabicyclo[3.3.1]nonane-1,5-dicarboxylate (0.402 g 80%) (colourless oil) as a mixture of diastereomeres (*exo*/*endo*=94: 6, detected by ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59–1.65 (m, 1H), 1.81–1.85 (m, 2H), 2.35–2.55 (m, 3H), 3.72 (s, 6H), 3.84 (s, 3H), 3.86 (s, 3H), 4.08 (d, J= 12.2 Hz, 2H), 4.25 (dd, J=12.1, 2.3 Hz, 2H), 4.75 (s, 1H, OH), 6.77 (d, J=8.3 Hz, 1H), 6.84 (d, J=1.8 Hz, 1H), 6.97 (dd, J=8.3, 1.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 27.7, 31.3, 49.7, 51.8, 55.5, 70.4, 71.4, 85.9, 88.1, 110.6, 113.8, 113.9, 124.7, 148.2, 149.4, 173.1.

Cooled (−15 °C) trifluoroacetic acid (1.5 mL) was rapidly added, under argon at −15 °C via syringe, to dimethyl 9-(3,4-dimethoxyphenylethynyl)-9-hydroxy-3-oxabicyclo-[3.3.1]nonane-1,5-dicarboxylate (0.230 g, 0.55 mmol). The reaction mixture was vigorously stirred while warming to room temperature over 2 h. The reaction was quenched with saturated sodium hydrogen carbonate solution and extracted with dichloromethane (5×15 mL). After solvent evaporation, the residue (pale yellow oil) was crystallised by adding diethyl ether. Recrystallisation from anhydrous methanol afforded the titled compound (0.197 g, 86%) as colourless crystals, mp 169.5–170.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.68–1.75 (m, 1H), 2.13–2.17 (m, 1H), 2.25–2.43 (m, 3H), 2.52–2.66 (m, 1H), 3.24 (s, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 3.93 (s, 3H), 3.97–4.07 (m, 2H), 4.09–4.21 (m, 2H), 6.24 (s, 1H), 6.87 (d, J=8.0 Hz, 1H), 7.45 (d, J=1.9 Hz, 1H), 7.52 (dd, J=8.3 Hz, 1.9, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 36.2, 36.6, 50.1, 51.3, 52.2, 52.9, 56.0, 56.1, 75.3, 75.8, 110.1, 110.2, 120.0, 124.0, 130.3, 149.1, 150.2, 153.4, 172.0, 172.9, 191.4. Near IR (Nujol) ν (cm^{-1}) 1738, 1717. Anal. Calcd for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26. Found: C, 63.16; H, 6.31.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.02.013.

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Synthesis of annelated [*a*]aza-anthracenones and thieno[3,2-*g*]aza-naphthalenones through ring transformation of 2*H*-pyran-2-one followed by photocyclization☆

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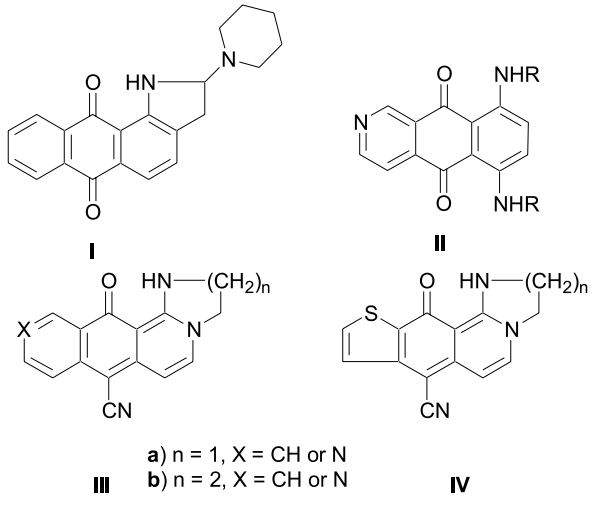
Abstract—A concise synthesis of some new classes of heterocycles (4-aryl-11-oxo-1,2,3,11-tetrahydro-1,3a-diaza-cyclopenta[*a*]anthracen-6-carbonitriles and 5-aryl-12-oxo-1,3,4,12-tetrahydro-2*H*-1,4a-diazabenzo[*a*]anthracene-7-carbonitriles) has been developed by the ring transformation of suitably functionalized 2*H*-pyran-2-one with α-oxoketene cyclic aminals to intermediates (8-aroyl-5-aryl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridine-7-ylidene)-acetonitriles and (9-aroyl-6-aryl-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-8-ylidene)-acetonitriles) followed by their photocyclization either in $CHCl_3$ or acetonitrile. This reaction was further explored for the synthesis of methyl 4-aryl-11-oxo-1,2,3,11-tetrahydro-1,3a,9-triaza-cyclopenta[*a*]anthracene-6-carboxylate, 4-aryl-11-oxo-1,2,3,11-tetrahydro-1,3a,9-triaza-cyclopenta[*a*]anthracene-6-carbonitriles, 5-aryl-12-oxo-1,3,4,12-tetrahydro-2*H*-1,4a,10-triazabenzo[*a*]anthracene-7-carbonitriles, 4-aryl-10-oxo-1,2,3,10-tetrahydro-9-thia-1,3a-diazadicyclopenta[*a*,*g*]naphthalene-6-carbonitriles and 5-aryl-11-oxo-1,3,4,11-tetrahydro-2*H*-10-thia-1,4a-diazacyclopenta[*b*]phenanthrene-7-carbonitriles from the similar reactions.

1. Introduction

Protein tyrosine kinases including Src[1] are key elements that regulate numerous cell functions such as cell growth and differentiation through signal transduction. Over activation and expression of Src is responsible for various diseases including cancer.[2] 4-Anilino-1-azaanthracene-3-carbonitrile and aza analogs of quinoline have been found highly effective as Src kinase inhibitors in the treatment of cancer and other diseases.[3] Various compounds with anthracene (**I**) and azaanthracene (**II**) basic skeletons have been used in the clinical management of leukemia, breast and ovarian cancer.[4] The development of resistance against clinically used anticancer drugs, necessitated the design and synthesis of a new class of heterocycles, which could not only improve the therapeutic efficacy against multiple drug resistance but were also less toxic.[5] The therapeutic significance of 9,10-anthraquinone highlightened our interest in the synthesis of annelated [*a*]aza-anthracenone (**III**), and thieno[3,2-*g*]aza-naphthalenone (**IV**) not previously reported in the literature.



Non-annelated azaanthraquinones have been synthesized either by Diels–Alder reaction of azanaphthoquinone with an appropriate diene,[6] classical Friedel–Crafts[7] reactions or oxidation of 9,10-dihydroazaanthracene.[8] Considering the electronic aspects of prototype structures **I** and **II**, annelated [*a*] azaanthracenone (**III**) and thieno [3,2-*g*]

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Keywords: Azaanthracenones; Thieno[3,2-*g*]azanaphthalenone; Ring transformation; Photocyclization.
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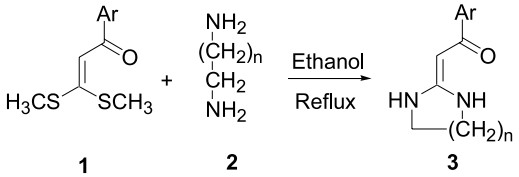
aza-naphthalenone (**IV**) were designed and by replacing the carbonyl oxygen with an electron withdrawing cyano substituent to retain an almost similar electronic status of the molecules.

The ubiquitous presence of 2*H*-pyran-2-one (**4**) in various natural products and its unique electronic topography led us to consider its suitability for ring transformation reactions to generate molecular diversity.[9] Herein, we report a concise and efficient synthesis of anneleted [*a*]aza-anthracenones (**6**), triaza-cyclopenta[*a*]anthracenones (**8**) and thieno[3,2-*g*]aza-naphthalenones (**9**) through ring transformation reaction of suitably functionalized 2*H*-pyran-2-one **4** with α-oxoketene cyclic aminals **3a–h** followed by photocyclization.

2. Results and discussion

Our strategy to synthesize 4-aryl-11-oxo-1,2,3,11-tetrahydro-1,3a-diazacyclopenta[*a*]anthracene-6-carbonitriles (**6a–e**) and 5-aryl-12-oxo-1,3,4,12-tetrahydro-2*H*-1,4a-diazabenzo[*a*]anthracene-7-carbonitriles (**6f,g**) was based on the ring transformation of 2*H*-pyran-2-ones[10] (**4**) with α-oxoketene cyclic aminals[11] (**3**), obtained from the reaction of α-oxoketene dithioacetal (**1**) with 1,2 or 1,3-diaminoalkanes (**2**) in alcohol at reflux temperature (Scheme 1).



1 **2** **3**

3	n	Ar	Yield (%)
a	1	C_6H_5	90
b	1	4-Cl.C_6H_4	85
c	1	4-Br.C_6H_4	88
d	1	2-thienyl	83
e	1	3-Pyridyl	83
f	2	4-Br.C_6H_4	80
g	2	2-thienyl	91
h	2	3-Pyridyl	79

Scheme 1. Preparation of α-oxoketene cyclic aminals (**3**).

Thus, stirring an equimolar mixture of **3** and **4** in the presence of powdered KOH in dry DMF for 24 h at ambient temperature in normal light provided **6** directly in poor yield (8%) after usual workup. Thus, attempts were made to trap the intermediate to understand the course of the reaction as well as to improve the yield of the final product.

The intermediate **5** was synthesized from the usual ring transformation of 2*H*-pyran-2-one (**4**) by **3** in the dark and purified by Si-gel column chromatography to isolate **5** as a pure product. The structure of intermediate (**5**) was confirmed by ^{1}H NMR spectroscopy and mass spectrometry. A solution of intermediate (**5**) was photochemically cyclized to **6** in 50% yield by irradiating its solution in chloroform with a 200 W electric bulb. The progress of the reaction was also monitored by recording the UV spectrum of **5** in DMSO. The initial absorption band at 435 nm disappeared after irradiation for 2 h with a hypsochromic shift and the appearance of a new absorption maxima at 385 nm (Fig. 1, Scheme 2).

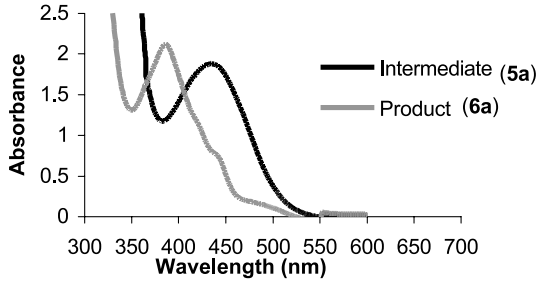


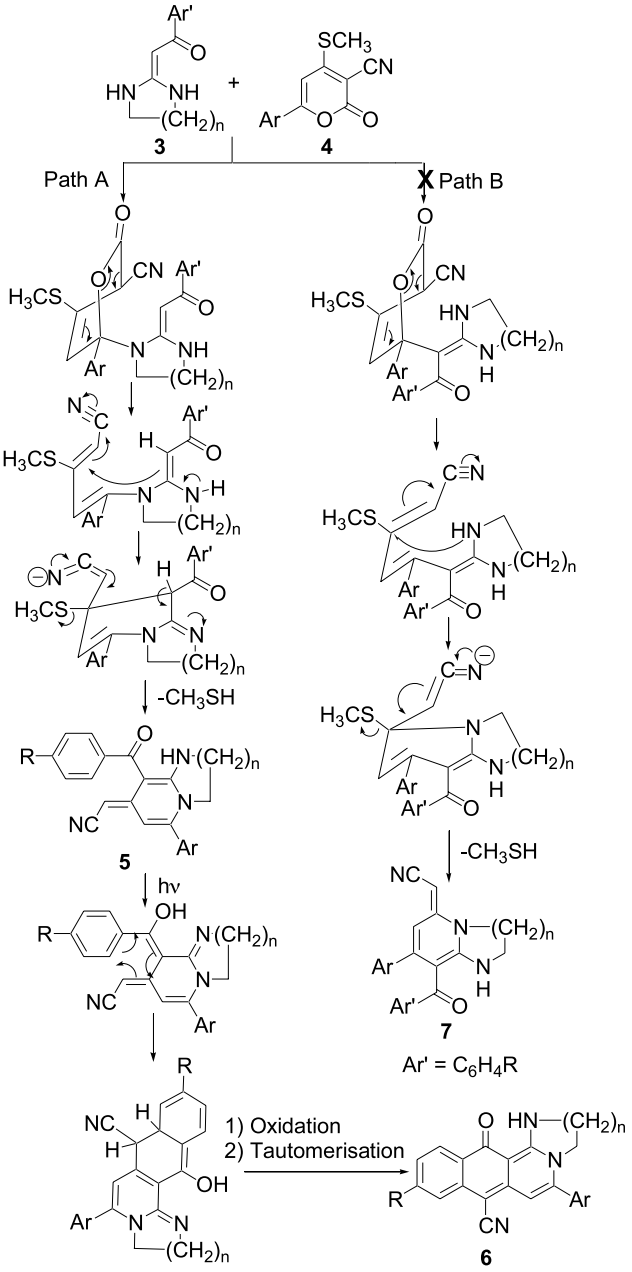
Figure 1. Absorption maxima of intermediate **5a** (435 nm) and product **6a** (385 nm) after irradiation (200 W electric bulb) for 2 h.

To generate molecular diversity, a reaction of **4** with different α-oxoketene cyclic aminals (**3e**,**h**) derived from 3,3-bis-methylsulfanyl-1-pyridin-3-yl-propanone was carried out analogously to obtain **8** as the major product (Scheme 3).

The ring transformation and photocyclization reactions were also achieved in a single step by simply irradiating a solution of a mixture of **3** and **4** in the presence of NaH in THF for 10–15 h.

In this reaction, there are two possible modes of photocyclization of the intermediate involving positions 2 and 4 of the pyridine ring and the α-vinylic carbon adjacent to the nitrile functionality. Isolation of only one product from this reaction, indicated the involvment of either C2 or C4 of the pyridine ring in the photocyclization. The proton NMR of **8f** showed one singlet for the C2 proton at δ 9.54 and confirmed the cyclization involving C4 of the pyridine ring. The downfield shift of the C2 proton was probably due to strong intramolecular H-bonding with the neighboring carbonyl oxygen. The two doublets for the C5 and C6 protons at δ 7.58 and 8.57, respectively, with 5.7 Hz coupling constant further supported cyclization involving C4. The scope of the reaction was further explored by synthesizing thieno[3,2-*g*]azanaphthalenones (**9**) directly by irradiating a solution of 2*H*-pyran-2-one (**4**) and α-oxoketene cyclic aminals **3** in the presence of NaH in THF for 15 h in moderate yield and produced a new class of heterocycle (Scheme 4).

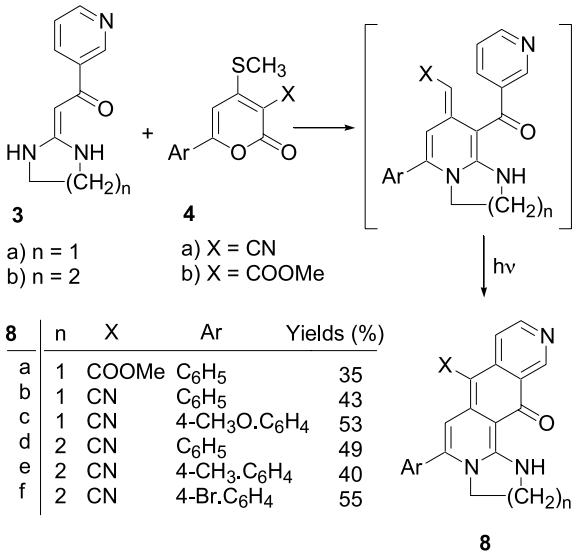
The nature of the substitutents present at positions 3 and 4 of the pyran ring greatly influence the ring transformation reactions. An electron withdrawing substituent, especially at position 3, is an essential requirement to enhance the electrophilicity of C6 of the pyran ring which facilitates the nucleophile induced ring transformation reactions. 2*H*-Pyran-2-ones (**4**) can be considered as a cyclic ketene hemithioacetal, prone to nucleophilic attack at C6 due to extended conjugation. α-Oxoketene cyclic aminals (**3**) are endowed with three nucleophilic centers, two of them due to the presence of two secondary amino groups and other due to the vinylic carbon, adjacent to the cyano function.



5/6	Ar	R	n	Yield (%) 5	6
a	C_6H_5	Cl	1	52	39
b	4-$CH_3OC_6H_4$	Cl	1	62	51
c	4-FC_6H_4	Cl	1	60	53
d	1-naphthyl	Cl	1	62	54
e	4-BrC_6H_4	Cl	1	62	62
f	4-BrC_6H_4	Br	2	64	52
g	4-$CH_3C_6H_4$	Br	2	65	55

Scheme 2. Proposed mechanism for the formation of aza-anthracenones.

Thus, the possibility for the formation of two products existed depending upon the initial involvement of either of the two secondary amino groups or vinylic carbon of the ring transformed product. The progress of the reaction through intermediate **7** (Scheme 2) was ruled out on the basis of the structure of the photochemically cyclized product **6** which can only be obtained from intermediate



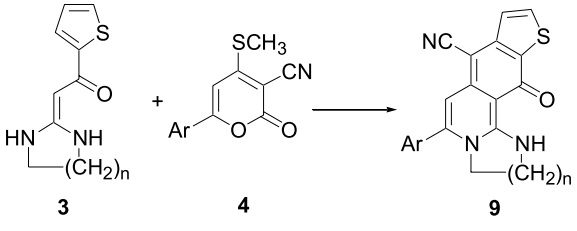
8	n	X	Ar	Yields (%)
a	1	COOMe	C_6H_5	35
b	1	CN	C_6H_5	43
c	1	CN	4-$CH_3O.C_6H_4$	53
d	2	CN	C_6H_5	49
e	2	CN	4-$CH_3.C_6H_4$	40
f	2	CN	4-$Br.C_6H_4$	55

Scheme 3. Preparation of triaza-cyclopenta[*a*]anthracene-6-carbonitriles **8**.

5.The structure was further confirmed by spectroscopy and also by single crystal X-ray diffraction analysis of **6f** (Fig. 2).[12] The presence of chloroform in the asymmetric unit of the crystal structure may be due to the presence of strong intermolecular H-bond between hydrogen atom of chloroform and N20 of the cyano group [C28–H28···N20A: H···A=2.36 Å, D···A=3.15(2) Å and ∠(DHA)=136.8°].

The possibility of a free radical mechanism for photocyclized product **6** was ruled out on the basis of formation of the same product in the presence of TEMPO. Thus, the reaction possibly proceeds through a photochemically allowed conrotatory cyclization[13] followed by aerial oxidation of dihydro intermediate to yield **6**.A plausible mechanism of this reaction is depicted in Scheme 2, where the nitrogen nucleophile attacks at C6 of the pyran ring with ring opening followed by decarboxylation and recyclization involving the vinylic carbon and C4 of the pyran ring with elimination of methyl mercaptan to yield **5** (Scheme 2, Fig. 3).

The stereoselectivity in the formation of intermediate **5** has possibly arised from strong intramolecular hydrogen bonding between the NH and CO functionalities or steric hindrance which plays a crucial role in restricting the



9	n	Ar	Yields(%)
a	1	C_6H_5	35
b	1	4-$CH_3O.C_6H_4$	51
c	2	4-$Br.C_6H_4$	48
d	2	4-$CH_3.C_6H_4$	52

Scheme 4. Preparation of thieno[3,2-*g*]azanaphthalenones (**10**).

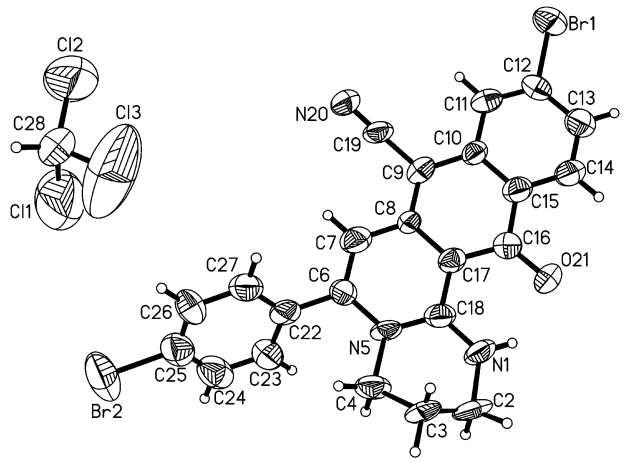


Figure 2. ORTEP diagram of **6f** showing the X-ray molecular structure in 50% probability level, solvent of crystallization 'chloroform' has been shown in the crystal structure.

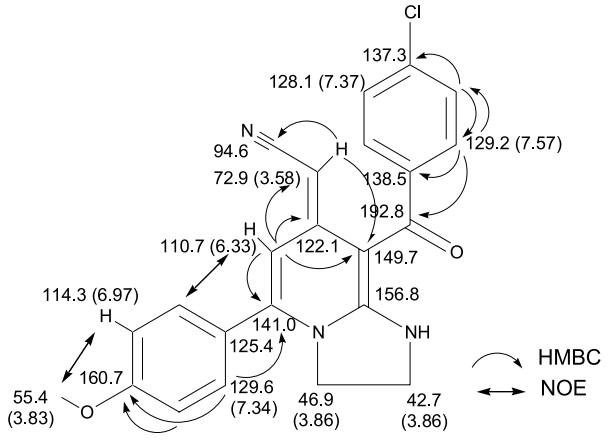


Figure 3. Chemical structure of **5b** showing HMBC and NOE.

rotation of the aroyl group, to attain *E*-geometry. The intermediates **5** isolated from the reaction were characterized by IR and NMR spectroscopy and mass spectrometry as (*E*)-2-(8-aroyl-5-aryl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridine-7-ylidene)acetonitrile (**5**, $n=1$) and pyrido[1,2-*a*]-pyrimidin-8-ylidene)acetonitrile (**5**, $n=2$). The proton NMR spectrum of **5b** showed two CH proton singlets at 6.33 and 3.59 ppm, a methyl singlet at 3.83 ppm and a set of aliphatic methylene protons as multiplet centered at 3.86 ppm, two sets of *ortho* coupled doublets at 7.34 and 7.57 and a broad singlet at 8.49 ppm for the NH proton. The ^{13}C NMR spectrum provided two methylene carbons at 42.7 and 46.9 ppm, one methyl carbon at 55.4 ppm, two methylene carbons at 72.9 and 110.7 ppm as shown in Figure 3. Three aromatic methyne carbons at 114.3, 129.0 and 129.6 ppm and the presence of two carbons at 129.6 ppm was corroborated in the HSQC experiment. Moreover, the ^{13}C assignments were carried out by the combined use of NOE difference, HSQC and HMBC experiments. The high field shift of the olefinic CH in the ^{1}H NMR spectrum at 3.59 ppm and at 72.7 ppm in the ^{13}C NMR was attributed to the shielding effect of the carbonyl and nitrile functionalities of **5b**.

In summary, our methodology provides a concerted approach to the synthesis of fused heterocyclic systems, using readily available starting materials under mild conditions. It opens as an efficient diversity-orientated synthetic route for the synthesis of complex nitrogen bridgehead aza-heterocycles.

3. Experimental

3.1. General

All reactions were conducted in flame dried glassware under nitrogen atmosphere. Pre-coated Merck TLC plates were used for monitoring reactions. Column chromatographic separations were performed on silica gel (60–120 mesh). IR spectra were taken on a Shimadzu 8201 PC FTIR Spectrophotometers. ^{1}H and ^{13}C NMR spectra were recorded, on Bruker DRX 300 or DPX 200 spectrometers. ^{13}C NMR assignments were obtained from DEPT and inverse H–C one bond and multiple bond correlation experiments. Mass spectra were recorded on JEOL SX-102 (FAB) spectrometers. Combustion analyses were performed on Elementar Vario EL III Carlo Erba 1108 analyzers.

3.2. General procedure for the synthesis of imidazo[1,2-*a*]-pyridines (5a–e) and pyrido[1,2-*a*]pyrimidine (5f,g)

A mixture of 2*H*-pyran-2-ones **4** (1 mmol), α-oxoketene cyclic aminal **3** (1 mmol) and NaH (60% suspension, 2.5 mmol) in dry THF (20 mL) was stirred for 2 h at 5–10 °C. After additional stirring for another 10 h at 20–25 °C, the reaction mixture was poured into ice-water (50 mL) and neutralized with 10% HCl. The separated solid was filtered, washed with water (50 mL) and dried. The entire reaction was carried out in the dark to prevent photocyclization. The crude solid obtained was further purified by column chromatography using 50% hexane–$CHCl_3$ as eluent in the dark.

3.2.1. [8-(4-Chlorobenzoyl)-5-phenyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridin-7-ylidene]-acetonitrile (5a). Yields 52%; brown-red solid; mp 185–190 °C dec.; IR (neat): $\nu_{max}=3352$, 2923, 2855, 2168, 1638, 1595, 1517, 1287, 1085, 1010 cm^{-1}; ^{1}H NMR (200 MHz, DMSO): δ 3.53 (s, 1H, CH), 3.62–3.67 (m, 2H, NCH_2), 3.83–3.87 (m, 2H, NCH_2), 6.01 (s, 1H, CH), 7.49–7.62 (m, 9H, ArH), 8.40 (bs, 1H, NH); FAB (MS) 374 ($M^+ +1$); $C_{22}H_{16}ClN_3O_2$ (373.10) calcd: C, 70.68; H, 4.31; N, 11.24; found: C, 70.51; H, 4.41; N, 11.39.

3.2.2. [8-(4-Chlorobenzoyl)-5-(4-methoxyphenyl)-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridin-7-ylidene]-acetonitrile (5b). Yields 62%; brown-red solid; mp 175–180 °C dec.; IR (neat) ν_{max} 3353, 3019, 2927, 2856, 2175, 1640, 1597, 1529, 1295, 1216, 1091, 1013 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.58 (s, 1H, CH), 3.83–3.89 (m, 7H, OCH_3 and $2NCH_2$), 6.32 (s, 1H, CH), 6.96 (d, $J=8.7$ Hz, 2H, ArH), 7.32–7.39 (m, 4H, ArH), 7.57 (d, $J=8.7$ Hz, 2H, ArH), 8.49 (bs, 1H, NH); ^{13}C NMR (75 MHz in ppm) δ 42.7, 46.9, 55.4, 72.9, 110.7, 114.3, 122.1, 125.4, 129.6, 138.5, 149.7, 156.8, 160.7, 192.8; FAB (MS) 404 ($M^+ +1$);

$C_{23}H_{18}ClN_3O$ (403.11) calcd: C, 68.40; H, 4.49; N, 10.40; found: C, 68.61; H, 4.38; N, 10.59.

3.2.3. [8-(4-Chlorobenzoyl)-5-(4-fluorophenyl)-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridin-7-ylidene]-acetonitrile (5c). Yields 60%; brown-red solid; mp 165–170 °C dec.; IR (neat) ν_{max} 3367, 3019, 2926, 2177, 1641, 1596, 1527, 1292, 1216, 1091, 1011 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.62 (s, 1H, CH), 3.84 (m, 4H, $2NCH_2$), 6.33 (s, 1H, CH), 7.11–7.72 (m, 8H, ArH), 8.51 (bs, 1H, NH); FAB (MS) 453 ($M^+ + 1$); $C_{22}H_{15}ClFN_3O$ (391.01) calcd: C, 67.44; H, 3.86; N, 10.72; found: C, 67.61; H, 3.78; N, 10.69.

3.2.4. [8-(4-Chlorobenzoyl)-5-naphthalen-1-yl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridin-7-ylidene]-acetonitrile (5d). Yields 62%; brown-red solid; mp 135–139 °C dec.; IR (neat) ν_{max} 3431, 3019, 2927, 2177, 1643, 1599, 1528, 1216, 1092, 1011 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.56–3.78 (m, 5H, $2NCH_2$ and CH), 6.49 (s, 1H, CH), 7.28–7.66 (m, 7H, ArH), 7.81–7.99 (m, 4H, ArH), 8.48 (bs, 1H, NH); FAB (MS) 424 ($M^+ + 1$); $C_{26}H_{18}ClN_3O$ (423.89) calcd: C 73.67; H, 4.28 N, 9.91; found: C, 73.49; H, 4.36; N, 10.01.

3.2.5. [5-(4-Bromophenyl)-8-(4-chlorobenzoyl)-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridin-7-ylidene]-acetonitrile (5e). Yields 62%; brown-red solid; mp 123–128 °C dec.; IR (neat) ν_{max} 3368, 3017, 2925, 2176, 1641, 1599, 1527, 1293, 1216, 1092, 1011 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.60 (s, 1H, CH), 3.83 (m, 4H, $2NCH_2$), 6.31 (s, 1H, CH), 7.11–7.59 (m, 8H, ArH), 8.50 (bs, 1H, NH); FAB (MS) 453 ($M^+ + 1$) $C_{22}H_{15}BrClN_3O$ (452.73) calcd: C, 58.36; H, 3.34; N, 9.28; found: C, 58.49; H, 3.50; N, 9.11.

3.2.6. [9-(4-Bromobenzoyl)-6-(4-bromophenyl)-1,2,3,4-tetrahydro-pyrido[1,2-*a*]pyrimidin-8-ylidene]-acetonitrile (5f). Yields 64%; brown-red solid; mp 157–162 °C dec.; IR (neat) ν_{max} 3430, 3016, 2926, 2177, 1644, 1591, 1528, 1216, 1073, 1010 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.98–2.08 (m, 2H, CH_2), 3.45–3.54 (m, 5H, $2NCH_2$ and CH), 6.32 (s, 1H, CH), 7.23–7.26 (m, 2H, ArH), 7.42–7.49 (m, 4H, ArH), 7.58–7.63 (m, 2H, ArH), 10.94 (bs, 1H, NH); FAB (MS) 512 ($M^+ + 1$) $C_{23}H_{17}Br_2N_3O$ (511.21) calcd: C, 54.04; H, 3.35; N, 8.22; found: C, 54.21; H, 3.50; N, 8.01.

3.2.7. [9-(4-Bromobenzoyl)-6-(4-methylphenyl)-1,2,3,4-tetrahydro-pyrido[1,2-*a*]pyrimidin-8-ylidene]-acetonitrile (5g). Yields 65%; brown-red solid; mp 195–200 °C dec.; IR (neat) ν_{max} 3018, 2927, 2177, 1645, 1590, 1530, 1216, 1072, 1010 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.97–2.02 (m, 2H, CH_2), 2.41 (s, 3H, CH_3), 3.43–3.56 (m, 5H, $2NCH_2$ and CH), 6.32 (s, 1H, CH), 7.24–7.60 (m, 8H, ArH), 10.90 (bs, 1H, NH); FAB (MS) 447 ($M^+ + 1$); $C_{24}H_{20}BrN_3O$ (446.34) calcd: C, 64.58; H, 3.34; N, 9.28; found: C, 64.39; H, 3.49; N, 9.11.

3.3. General procedure for the synthesis of aza-[*a*]anthracenones (6)

A solution of **5** (0.05 mmol) in acetonitrile (10 mL) was irradiated under stirring for 10 h by 200 W electric bulb. A yellow solid separated, was filtered and washed with methanol. The crude product was further purified by column chromatography using 1% methanol in chloroform as eluent.

3.3.1. 8-Chloro-11-oxo-4-phenyl-1,2,3,11-tetrahydro-1,3*a*-diaza-cyclopenta[*a*]anthracene-6-carbonitrile (6a). Yields 39%; yellow powder; mp >250 °C; IR (KBr) ν_{max} 3434, 2925, 2859, 2174, 1598, 1515 cm^{-1}; ^1H NMR (200 MHz, DMSO) δ 3.84–3.87 (m, 2H, NCH_2), 4.07–4.10 (m, 2H, NCH_2), 6.41 (s, 1H, CH), 7.21–7.59 (m, 7H, ArH), 8.17 (d, J=8.0 Hz, 1H, ArH), 10.00 (bs, 1H, NH); FAB (MS) 372 ($M^+ + 1$); $C_{22}H_{14}ClN_3O$ (371.08) calcd: C, 71.07; H, 3.80; N, 11.30; found: C 71.16; H, 3.71; N, 11.39.

3.3.2. 8-Chloro-4-(4-methoxyphenyl)-11-oxo-1,2,3,11-tetrahydro-1,3*a*-diaza-cyclopenta[*a*]anthracene-6-carbonitrile (6b). Yields 51%; yellow powder; mp >250 °C; IR (KBr) ν_{max} 3447, 3255, 2910, 2194, 1646, 1595, 1524, 1435, 1303, 1258, 1025 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.89 (s, 3H, OCH_3), 4.03–4.06 (m, 2H, NCH_2), 4.14–4.17 (m, 2H, NCH_2), 6.79 (s, 1H, CH), 7.01 (d, J=8.0 Hz, 2H, ArH), 7.33–7.42 (m, 3H, ArH), 7.89 (s, 1H, ArH), 8.35 (d, J=8.0 Hz, 2H, ArH), 10.11 (bs, 1H, NH); FAB (MS) 402 ($M^+ + 1$); $C_{23}H_{16}ClN_3O_2$ (401.84) calcd: C, 68.74; H, 4.01; N, 10.46; found: C, 68.91; H, 3.91; N, 10.45.

3.3.3. 8-Chloro-4-(4-fluorophenyl)-11-oxo-1,2,3,11-tetrahydro-1,3*a*-diaza-cyclopenta[*a*]anthracene-6-carbonitrile (6c). Yields 53%; yellow powder; mp >250 °C; IR (KBr) ν_{max} 3431, 3000, 2190, 1645, 1597, 1524, 1442, 1227, 1085 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.06–4.24 (m, 4H, $2NCH_2$), 6.74 (s, 1H, CH), 7.21–7.53 (m, 5H, ArH), 7.85 (s, 1H, ArH), 8.28 (d, J=8.7 Hz, 1H, ArH), 10.01 (bs, 1H, NH); FAB (MS) 390 ($M^+ + 1$); $C_{22}H_{13}ClFN_3O$ (389.81) calcd: C, 67.79; H, 3.36; N, 10.78; found: C, 67.81; H, 3.46; N, 10.92.

3.3.4. 8-Chloro-4-naphthalen-1-yl-11-oxo-1,2,3,11-tetrahydro-1,3*a*-diaza-cyclopenta[*a*]anthracene-6-carbonitrile (6d). Yield 54%; yellow powder; mp >250 °C; IR (KBr) ν_{max} 3433, 3055, 2193, 1645, 1591, 1523, 1430, 1310, 1256, 1084 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.83–4.09 (m, 4H, $2NCH_2$), 7.02 (s, 1H, CH), 7.31–7.36 (m, 1H, ArH), 7.57–7.72 (m, 5H, ArH), 7.93–8.01 (m, 3H, ArH), 8.38 (d, J=8.7 Hz, 1H, ArH), 10.01 (bs, 1H, NH); FAB (MS) 422 ($M^+ + 1$); $C_{26}H_{16}ClN_3O$ (421.88) calcd: C, 74.02; H, 3.82; N, 9.96; found: C, 74.12; H, 3.92; N, 9.11.

3.3.5. 4-(4-Bromophenyl)-8-chloro-11-oxo-1,2,3,11-tetrahydro-1,3*a*-diaza-cyclopenta[*a*]anthracene-6-carbonitrile (6e). Yield 62%; yellow powder; mp >250 °C; IR (KBr) ν_{max} 3330, 2183, 1642, 1593, 1516, 1219 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.06–4.23 (m, 4H, $2NCH_2$), 6.84 (s, 1H, CH), 7.28–7.40 (m, 4H, ArH), 7.67–7.71 (m, 3H, ArH); FAB (MS) 451 ($M^+ + 1$); $C_{22}H_{13}BrClN_3O$ (450.71) calcd: C, 58.63; H, 2.91; N, 9.32; found: C, 58.71; H, 3.05; N, 9.62.

3.3.6. 9-Bromo-5-(4-bromophenyl)-12-oxo-1,3,4,12-tetrahydro-2*H*-1,4*a*-diaza-benzo[*a*]anthracene-7-carbonitrile (6f). Yield 52%; yellow powder; mp >250 °C; IR (KBr) ν_{max} 3435, 2179, 1646, 1600, 1514, 1326, 1207 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.08–2.16 (m, 2H, CH_2),

3.65 (t, $J=6.0$ Hz, 2H, NCH_2), 3.80 (t, $J=6.0$ Hz, 2H, NCH_2), 6.84 (s, 1H, CH), 7.41–7.54 (m, 5H, ArH), 8.09 (s, 1H, ArH), 8.31 (d, $J=9.0$ Hz, 1H, ArH), 14.04 (bs, 1H, NH); FAB (MS) 510 ($M^+ +1$); $C_{23}H_{15}Br_2N_3O$ (509.19) calcd: C, 54.25; H, 2.97; N, 8.25; found: C, 54.35; H, 2.92; N, 8.32.

3.3.7. 9-Bromo-12-oxo-5-(4-methylphenyl)-1,3,4,12-tetrahydro-2*H*-1,4*a*-diaza-benzo[*a*]anthracene-7-carbonitrile (6g). Yield 55%; yellow powder; mp >250 °C; IR (KBr) ν_{max} 3430, 2193, 1738, 1641, 1598, 1515, 1325, 1208 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.07–2.13 (m, 2H, CH_2), 2.45 (s, 3H, CH_3), 3.63 (t, $J=5.5$ Hz, 2H, NCH_2), 3.79 (t, $J=5.5$ Hz, 2H, NCH_2), 6.80 (s, 1H, CH), 7.30–7.46 (m, 5H, ArH), 8.07 (s, 1H, ArH), 8.30 (d, $J=8.74$ Hz, 1H, ArH), 13.81 (bs, 1H, NH); FAB (MS) 445 ($M^+ +1$); $C_{24}H_{18}BrN_3O$ (444.32) calcd: C, 64.88; H, 4.08; N, 9.46; found: C, 65.06; H, 4.22; N, 9.41.

3.4. General procedure for the synthesis of triaza-cyclopenta[*a*]anthracene-6-carbonitriles (8) and thieno[3,2-*g*]-aza-naphthalenones (9)

A mixture of 2*H*-pyran-2-one (**4**, 1 mmol), α-oxoketene cyclic aminal (**3**, 1 mmol) and NaH (60% suspension, 2.5 mmol) in dry THF (15 mL) was stirred for 15 h under light irradiation by 200 W electric bulb. The reaction mixture was poured onto ice water (50 mL), neutralized with 10% HCl. The precipitate obtained was filtered, washed with water (50 mL) and dried. The crude solid was finally purified on Si-gel column chromatography using 4% methanol in chloroform as eluent.

3.4.1. 11-Oxo-4-phenyl-1,2,3,11-tetrahydro-1,3a,9-triaza-cyclopenta[*a*]anthracene-6-carboxylic acid methyl ester (8a). Yield 35%; yellow powder; mp >250 °C; IR (KBr) ν_{max} 3398, 2926, 2370, 1851, 1705, 1657, 1597, 1441 cm^{-1}; ^1H NMR (200 MHz, 2 drop CD_3OD in $CDCl_3$) δ 3.95 (s, 3H, $COOCH_3$), 4.16 (t, $J=5.6$ Hz, 2H, NCH_2), 4.35 (t, $J=5.6$ Hz, 2H, NCH_2), 7.28 (s,1H, CH), 7.51–7.56 (m, 5H, ArH), 8.07 (d, $J=6.0$ Hz, 1H, ArH), 8.2 (d, $J=6.0$ Hz, 1H, ArH), 9.24 (s, 1H, ArH); FAB (MS) 372 ($M^+ +1$); $C_{22}H_{17}N_3O_3$ (371.13) calcd: C, 71.15; H, 4.61; N, 11.31; found: C, 71.22; H, 4.73; N, 11.33.

3.4.2. 11-Oxo-4-phenyl-1,2,3,11-tetrahydro-1,3a,9-triaza-cyclopenta[*a*]anthracene-6-carbonitrile (8b). Yield 43%; yellow powder; mp >250 °C; IR (KBr) ν_{max} 3277, 2831, 2367, 2211, 1630, 1596, 1527, 1363 cm^{-1}; ^1H NMR (200 MHz, 2 drops CD_3OD in $CDCl_3$) δ 4.16–4.26 (m, 2H, NCH_2), 4.69–4.82 (m, 2H, NCH_2), 6.93 (s, 1H, CH), 7.52–7.61 (m, 5H, ArH), 7.91 (d, $J=6.2$ Hz, 1H, ArH), 8.32 (d, $J=6.2$ Hz, 1H, ArH), 9.26 (s, 1H, ArH); FAB (MS) 339 ($M^+ +1$); $C_{21}H_{14}N_4O$ (338.12) calcd: C, 74.54; H, 4.17; N, 16.56; found: C, 74.67; H, 4.23; N, 16.65.

3.4.3. 4-(4-Methoxyphenyl)-11-oxo-1,2,3,11-tetrahydro-1,3a,9-triaza-cyclopenta[*a*]anthracene-6-carbonitrile (8c). Yield 53%; yellow powder; mp >250 °C; IR (KBr) ν_{max} 3377, 2926, 2833, 2368, 2186, 1632, 1589, 1362 cm^{-1}; ^1H NMR (200 MHz, 2 drops CD_3OD in $CDCl_3$) δ 3.76 (s, 3H, OCH_3), 4.09–4.18 (m, 2H, NCH_2), 4.26–4.30 (m, 2H, NCH_2), 6.83 (s, 1H, CH), 7.07 (d, $J=8.5$ Hz, 2H, ArH), 7.45 (d, $J=8.5$ Hz, 2H, ArH), 7.67 (d, $J=5.1$ Hz, 1H, ArH), 8.49 (d, $J=5.2$ Hz, 1H, ArH), 9.42 (s, 1H, ArH); FAB (MS) 369 ($M^+ +1$); $C_{22}H_{16}N_4O_2$ (368.13) calcd: C, 71.73; H, 4.38; N, 15.21; found: C, 71.81; H, 4.42; N, 15.27.

3.4.4. 12-Oxo-5-phenyl-1,3,4,12-tetrahydro-2*H*-1,4a,10-triaza-benzo[*a*]anthracene-7-carbonitrile (8d). Yield 49%; yellow powder; mp >250 °C; IR (KBr) ν_{max} 3377, 2926, 2854, 2363, 2184, 1742, 1646, 1507, 1448, 1362 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.07–2.18 (m, 2H, CH_2), 3.64–3.66 (m, 2H, NCH_2), 3.78–3.84 (m, 2H, NCH_2), 6.84 (s,1H, CH), 7.40–7.45 (m, 2H, ArH), 7.52–7.56 (m, 3H, ArH), 7.65 (d, $J=5.8$ Hz, 1H, ArH), 8.57 (s, 1H, ArH), 9.62 (s, 1H, ArH); FAB (MS) 353 ($M^+ +1$); $C_{22}H_{16}N_4O$ (352.13) calcd: C, 74.98; H, 4.58; N, 15.90; found: C, 74.91; H, 4.62; N, 15.83.

3.4.5. 12-Oxo-5-(4-methylphenyl)-1,3,4,12-tetrahydro-2*H*-1,4a,10-triaza-benzo[*a*]anthracene-7-carbonitrile (8e). Yield 40%; yellow powder; mp >250 °C; IR (KBr) ν_{max} 3404, 2832, 2368, 2188, 1635, 1605, 1514, 1362 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.12–2.17 (m, 2H, CH_2), 2.47 (s, 3H, CH_3), 3.68 (t, $J=5.7$ Hz, 2H, NCH_2), 3.87 (t, $J=5.7$ Hz, 2H, NCH_2), 6.82 (s, 1H, CH), 7.35–7.41 (m, 4H, ArH), 7.67 (d, $J=5.7$ Hz, 1H, ArH), 8.48–8.49 (m, 1H, ArH), 9.51 (s, 1H, ArH); FAB (MS) 367 ($M^+ +1$); $C_{23}H_{18}N_4O$ (366.15) calcd: C, 75.39; H, 4.95; N, 15.29; found: C, 75.48; H, 5.08; N, 15.34.

3.4.6. 5-(4-Bromophenyl)-12-oxo-1,3,4,12-tetrahydro-2*H*-1,4a,10-triaza-benzo[*a*]anthracene-7-carbonitrile (8f). Yield 55%; yellow powder; mp >250 °C; IR (KBr) ν_{max} 3404, 2930, 2832, 2368, 2191, 1630, 1590, 1510, 1362 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.09–2.14 (m, 2H, CH_2), 3.61–3.63 (m, 2H, NCH_2), 3.75–3.80 (m, 2H, NCH_2), 6.69 (s, 1H, CH), 7.32 (d, $J=8.3$ Hz, 2H, ArH), 7.58 (d, $J=5.8$ Hz, 1H, ArH), 7.67 (d, $J=8.3$ Hz, 2H, ArH), 8.57 (d, $J=5.8$ Hz, 1H, ArH), 9.53 (s, 1H, ArH); FAB (MS) 432 ($M^+ +1$); $C_{22}H_{15}BrN_4O$ (430.04) calcd: C, 61.27; H, 3.51; N, 12.99; found: C, 61.39; H, 3.74; N, 13.11.

3.4.7. 10-Oxo-4-phenyl-1,2,3,10-tetrahydro-9-thia-1,3a-diaza-dicyclopenta[*a*,*g*]naphthalene-6-carbonitrile (9a). Yield 35%; yellow powder; mp >250 °C; IR (KBr) ν_{max} 2929, 2832, 2717, 2191, 1628, 1593, 1364 cm^{-1}; ^1H NMR (200 MHz, 2 drops CD_3OD in $CDCl_3$) δ 4.10–4.26 (m, 4H, $2NCH_2$), 6.93 (s, 1H, CH), 7.34 (s, 1H, ArH), 7.44–7.57 (m, 5H, ArH), 7.78 (d, $J=5.3$ Hz, 1H, ArH); FAB (MS) 344 ($M^+ +1$); $C_{20}H_{13}N_3OS$ (343.08) calcd: C, 69.95; H, 3.82; N, 12.24; found: C, 69.86; H, 3.91; N, 12.32.

3.4.8. 4-(4-Methoxyphenyl)-10-oxo-1,2,3,10-tetrahydro-9-thia-1,3a-diaza-dicyclopenta[*a*,*g*]naphthalene-6-carbonitrile (9b). Yield 51%; yellow powder; mp >250 °C; IR (KBr) ν_{max} 2936, 2832, 2717, 2363, 2210, 1705, 1648, 1592, 1364 cm^{-1}; ^1H NMR (200 MHz, 2 drops CD_3OD in $CDCl_3$) δ 3.9 (s, 3H, OCH_3), 4.10–4.28 (m, 4H, $2NCH_2$), 6.90 (s, 1H, CH), 7.05 (d, $J=8.5$ Hz, 2H, ArH), 7.42–7.46 (m, 3H, ArH), 7.79 (d, $J=5.3$ Hz, 1H, ArH); FAB (MS) 374 ($M^+ +1$); $C_{21}H_{15}N_3O_2S$ (373.08) calcd: C, 67.54; H, 4.05; N, 11.25; found: C, 67.69; H, 4.25; N, 11.32.

3.4.9. 5-(4-Bromophenyl)-11-oxo-1,3,4,11-tetrahydro-2*H*-10-thia-1,4a-diaza-cyclopenta[*b*]phenanthrene-7-carbonitrile (9c). Yield 48%; yellow powder; mp >250 °C; IR (KBr) ν_{max} 3424, 2365, 2197, 1635, 1593, 1528, 1351 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.07–2.13 (m, 2H, CH_2), 3.62 (t, J=5.8 Hz, 2H, NCH_2), 3.77 (t, J=5.9 Hz, 2H, NCH_2), 6.86 (s, 1H, CH), 7.31 (d, J=8.3 Hz, 2H, ArH), 7.43 (d, J=5.3 Hz, 1H, ArH), 7.67 (d, J=8.3 Hz, 2H, ArH), 7.71 (d, J=5.3 Hz, 1H, ArH); FAB (MS) 437 (M^++2); $C_{21}H_{14}BrN_3OS$ (435.00) calcd: C, 57.81; H, 3.23; N, 9.63; found: C, 57.89; H, 3.33; N, 9.82.

3.4.10. 11-Oxo-5-(4-methylphenyl)-1,3,4,11-tetrahydro-2*H*−10-thia-1,4a-diaza-cyclopenta[*b*]phenanthrene-7-carbonitrile (9d). Yield 52%; yellow powder; mp >250 °C; IR (KBr) ν_{max} 2832, 2379, 2192, 1634, 1586, 1526, 1361 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.05–2.14 (m, 2H, CH_2), 2.46 (s, 3H, CH_3), 3.82–3.87 (m, 4H, $2NCH_2$), 6.84 (s, 1H, CH), 7.20–7.38 (m, 4H, ArH), 7.41 (d, J=5.3 Hz, 1H, ArH), 7.46 (d, J=5.3 Hz, 1H, ArH); FAB (MS) 372 (M^++1); $C_{22}H_{17}N_3OS$ (371.11) calcd: C, 71.14; H, 4.61; N, 11.31; found: C, 71.16; H, 4.72; N, 11.45.

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12. Crystal data of **6f**: $C_{23}H_{15}Br_2N_3O\cdot CHCl_3$, M=628.57, triclinic, space group: P-1, a=7.796(1), b=10.726(1), c=15.686(1) Å, α=83.14(1), β=79.16(1), γ=73.58(1), V=1232.7(2) $Å^3$, T=293 K, Z=2, μ=3.64 mm^{-1}, $F(000)$=620.0, $R1$=0.1072 for 1919 $F_o > 4\text{sig}(F_o)$ and 0.2226 for all 4249 data. CCDC No. 260828 contains the supplementary crystallographic data. These data can be obtained free of charge from www.ccdc.cam.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK; fax: (internat.) +44 1223/336 033; E-mail: deposit@ccdc.cam.ac.uk]. Programs: XSCANS [Siemens Analytical X-ray Instrument Inc.: Madison, Wisconsin, USA 1996], SHELXTL-NT [Bruker AXS Inc.: Madison, Wisconsin, USA 1997].
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Absolute stereochemistries and total synthesis of (+)/(−)-macrosphelides, potent, orally bioavailable inhibitors of cell–cell adhesion

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Abstract—In the current studies, we used the single-crystal X-ray analysis and Kakisawa–Kashman modification of the Mosher NMR method to determine the complete relative and absolute stereochemistries of the (+)-macrosphelides A (+)-**1** and B (+)-**2**. The stereostructure of (+)-**2** was determined by chemical comparison with artificial (+)-**2** from (+)-**1**. We also report the convergent total synthesis of (+)-**1** and (+)-**3**, as well as their antipodes, utilizing an asymmetric dihydroxylation for introduction of chirality and Yamaguchi macrocyclization to form the 16-membered trilactone macrolides.

1. Introduction

Critical early events in inflammation,[1–3] the allergic response,[4–6] and tumor metastasis[7–9] involve interactions between leukocytes and endothelial cells. In particular, tumor metastasis is a multi-step process requiring detachment of malignant cells from primary tumor mass, infiltration and invasion to blood and/or lymph vessels, adhesion to endothelia of distant organs, and finally formation of new tumor colonies.[10] During the early stage of adhesion between endothelial cells and tumor cells, E-selectin is expressed on activated endothelial cells, which recognize sialyl Lewis X on the tumor cells.[11–13] Several groups have demonstrated that sialyl Lewis X and E-selectin molecules perform this important role in tumor cell adhesion to endothelial cells.[14,15]

We previously reported the isolation, determination of planar structures, and preliminary biological evaluation of (+)-macrosphelides A and B ((+)-**1** and (+)-**2**) as cell–cell adhesion inhibitors from *Microsphaeropsis* sp. FO-5050 (Fig. 1).[16] We have now extended this study to

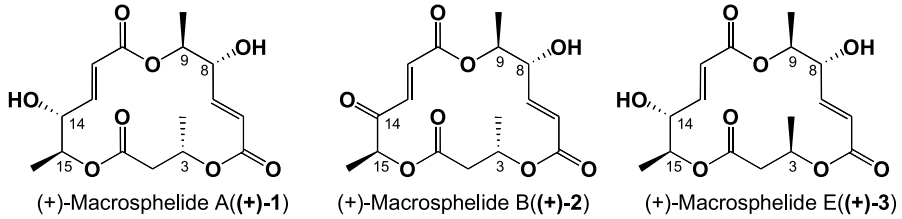

Figure 1. Structures of (+)-macrosphelide A, B and E.

Keywords: Kakisawa–Kashman modification; (+)/(−)-Macrosphelides; Cell–cell adhesion.
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the total synthesis and determination of the absolute stereochemistries of these compounds.[17]

Macrosphelides are the first 16-membered-ring antibiotics embodying three lactone linkages (i.e., macrotriolides). The IC_{50} values of (+)-**1** and (+)-**2** were 3.5 and 36 μM, respectively, for the adhesion of human-leukemia HL-60 cells to human-umbilical-vein endothelial cells (HUVEC).[16] Preliminary studies suggest that (+)-**1** and (+)-**2** prevent cell–cell adhesion by inhibiting the binding of sialyl Lewis X to E-selectin. (+)-**1** also proved to be orally active against lung metastasis of B16/BL6 melanoma in mice (50 mg/kg/day) without body weight loss.[18] On the other hand, Numata and co-workers have found that a strain of *Periconia byssoides* isolated from the seahare *Aplysia kurodai*, produces novel cytotoxic materials containing four new macrolides, macrosphelides E–H.[19] Macrosphelide E ((+)-**3**) is identical to (+)-macrosphelide A ((+)-**1**), differing only in the stereochemistry at C(3). Due to their attractive properties and unique structures, several synthetic approaches to macrosphelides have been reported.[20] In conjunction with our continuing investigations into the structure elucidation and synthesis of important bio-regulatory natural products, we report herein the determination of the complete relative and absolute stereochemistries of (+)-macrosphelides A and B ((+)-**1** and (+)-**2**). We also describe the first total synthesis of these compounds, together with an application of our synthetic route to the preparation of (+)-**3** and some enantiomers of natural macrosphelides.

2. Results and discussion

2.1. Determination of the absolute stereochemistry of (+)-macrosphelides A and B

Initially our attention was directed toward the structure elucidations of (+)-**1** and (+)-**2**. A series of NMR studies revealed the planar structures of (+)-**1** and (+)-**2**, which were also supported by FAB-MS, IR data, chemical characterizations of the derived di- and monoacetates, respectively.[16] The relative structure of (+)-**1** was confirmed by single-crystal X-ray diffraction[21] to be (3*S**,8*R**,9*S**,14*R**,15*S**) (Fig. 2).

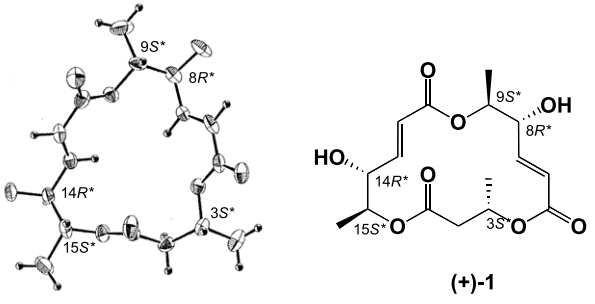


Figure 2. ORTEP plot of (+)-**1**.

The configurations at C(8) and C(14) in (+)-**1** were also elucidated using the Kakisawa–Kashman modification[22] of Mosher's method.[23] Thus, (+)-**1** was treated with (*S*)-(−)- and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA), dicyclohexylcarbodiimide (DCC), and 4-(dimethylamino)pyridine (DMAP) in THF at room temperature[22] to provide the 8,14-bis-*O*-(*S*)-(−)-MTPA ester (−)-**4** and 8,14-bis-*O*-(*R*)-(+)-MTPA ester (+)-**5**, respectively (Scheme 1).

The ^{1}H NMR spectra of (−)-**4** and (+)-**5** were completely assigned via selective ^{1}H decoupling. The *R* configurations at C(8) and C(14) were confirmed by application of the Kakisawa–Kashman test[22] to determine the ^{1}H $\Delta\delta$ values for (−)-**4** and (+)-**5** (Fig. 3). Thus, the absolute stereochemistry of macrosphelide A is (3*S*,8*R*,9*S*,14*R*,15*S*) as shown in Figure 1. This assignment was also confirmed by total synthesis.

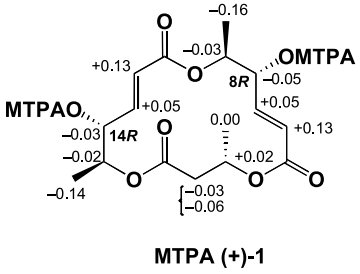
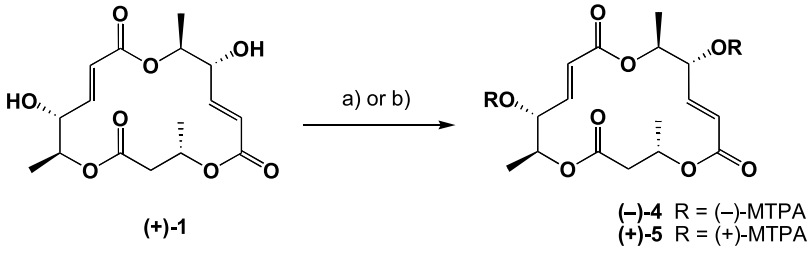
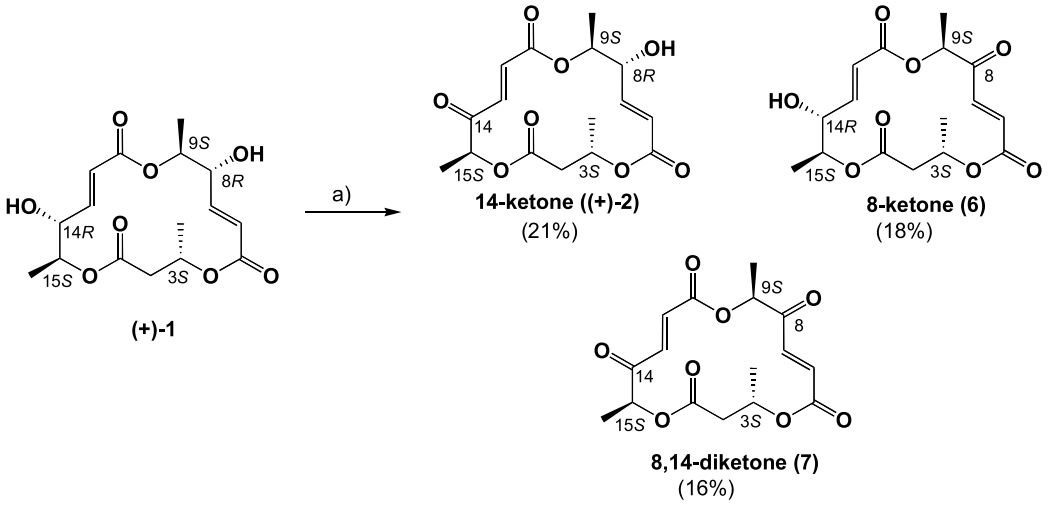


Figure 3. δ Values for the bis-MTPA ester derivatives of (+)-**1** ($\delta = \delta_{(-)} - \delta_{(+)}$).

Our next aim was to determine the absolute structure of (+)-**2**, anticipated to be the a C(14) oxidation product of (+)-**1** (Fig. 1). To prepare (+)-**2**, (+)-**1** was treated with pyridinium dichromate (PDC) in CH_2Cl_2 at room temperature for 3 h (Scheme 2). Initial separation of the reaction mixture gave three major fractions: (i) a mixture of the 14- and 8-monoketones, **2** and **6**, (ii) pure 8, 14-diketone **7** (16% yield), and (iii) recovered starting material (+)-**1** (45%). Further purification of the monoketone mixture (**2** and **6**) by HPLC then provided pure (+)-**2** and **6** in 21 and 18% yields, respectively. Synthetic (+)-**2** derived from (+)-**1** was identical with the natural product sample in all respects.



Scheme 1. Synthesis of bis(+)/(−)-MTPA ester. (a) (−)-MTPA, DCC, DMAP, THF, 100% yield; b) (+)-MTPA, DCC, DMAP, THF, 27% yield.



Scheme 2. PDC oxidation of (+)-**1** to provide (+)-**2**. (a) PDC, CH_2Cl_2.

Thus, the absolute stereochemistry of macrosphelide B ((+)-**2**) is (3*S*,8*R*,9*S*,15*S*) as shown in Scheme 2.

2.2. Synthetic strategy for the preparation of (+)-macrosphelide A

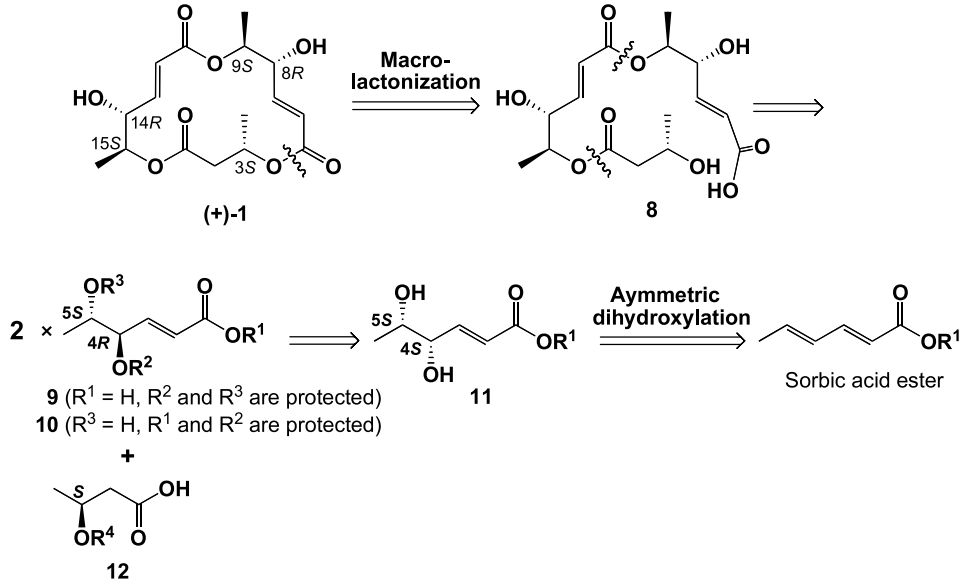
Disconnection of the three esters of (+)-macrosphelide A ((+)-**1**) reveals two trans-(4*R*,5*S*)-4,5-dihydroxyhexenoic acid components and (*S*)-3-hydroxybutanoic acid (commercially available). Thus, the strategy required the enantioselective preparation of *trans*-(4*R*,5*S*)-4,5-dihydroxyhexenoic acid, which was prepared by selective asymmetric dihydroxylation, followed by differential protection for two hydroxy groups and inversion of allyl alcohol (Scheme 3).

2.3. Preparation of building blocks 9 and 10

The starting point of our synthesis required preparation of the two differentially protected building blocks **9** and **10**, from known (*E*,*E*)-hexa-2,4-dienoic acid ester (sorbic acid ester) via the common enantio-active precursor **11** (Scheme 3).

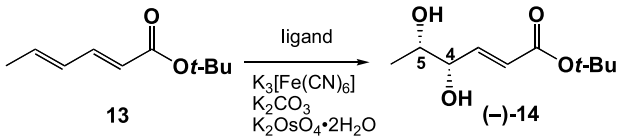
Initially, asymmetric Sharpless dihydroxylation[24] of sorbic *tert*-butyl ester **13**[25] using AD-mix-α, (which uses $(DHQ)_2$-PHAL as a chiral ligand), was employed to afford the corresponding diol (−)-**14** (62%, 85% ee) (Table 1). Three other chiral ligands were examined for the asymmetric dihydroxylation. The best result (71%, 88% ee) was obtained with Corey-AD-ligand-α without MeI salt (**15**)[26] (1,4-bis[(2*S*,8*S*,9*R*)-6′-(4-heptyloxy)-10,11-dihydrocinchonan-9-oxylnaphthopyridazine] (Table 1).

In order to study the biological structure–activity relationships of macrosphelides, preparation of select derivatives of their antipodes was desirable. To this end, the antipode of (−)-**14** was attempted. Four ligands, $(DHQD)_2PHAL$,[24] $(DHQD)_2AQN$,[27] Corey-AD-ligand-β (**18**)[26] and Corey-AD-ligand-β without MeI salt (**17**),[26] were examined for asymmetric dihydroxylation of **13** (Table 2), with **17** giving



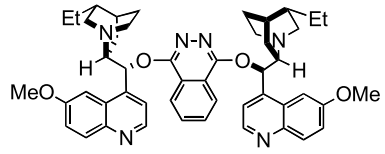
Scheme 3. Synthetic strategy for the preparation of (+)-**1**.

Table 1. Asymmetric dihydroxylation of sorbic acid *tert*-butyl ester using α-ligands

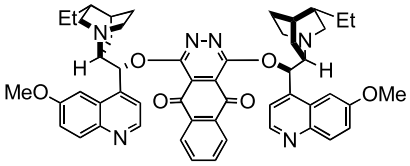


Ligand[a]	Yield of (−)-**14**[b]	%ee of (−)-**14**[c]
$(DHQ)_2PHAL$	62%	85%
$(DHQ)_2AQN$	67%	61%
15	71%	88%
16	66%	75%

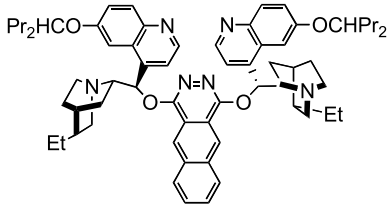
[a] All reactions were carried out with ligands (0.01 equiv), $K_3[Fe(CN)_6]$ (3.0 equiv), K_2CO_3 (3.0 equiv) and $K_2OsO_4 \cdot 2H_2O$ (0.01 equiv) in *t*-BuOH·H_2O (1/1 v/v).
[b] Yields were based on pure materials isolated by chromatography on SiO_2.
[c] The ee of the product was determined by ^1H NMR measurements of the MTPA ester of TBS ether (+)-**19**.



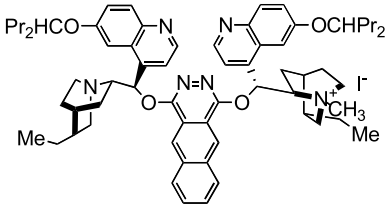
$(DHQ)_2PHAL$



$(DHQ)_2AQN$



Corey-AD-Ligand-α non MeI salt (15)



Corey-AD-Ligand-α (16)

the best result (74%, 98% ee). Interestingly, dihydroxylation with **18** afforded diol (+)-**14** in low yield (5.9%) with large amounts of tetraol products, as diastereomeric mixtures. The enantiomeric purities of (−)- and (+)-**14** were determined by Mosher analysis[23] of the silylated alcohol (**19**).

Selective protection of the C(5)–OH group of (−)-**14**, with TBSCl, Et_3N, and DMAP, provided the desired ether (+)-**19**, together with undesired C(4)–O–TBS ether (+)-**20** and starting material in 56, 11 and 30% yields, respectively, (Scheme 4). Mitsunobu inversion[28] of the C(4)–OH group in (+)-**19** with PPh_3, DEAD, and formic acid, followed by hydrolysis of the formyl ester in diluted NH_4OH/MeOH solution afforded (+)-**21** in 83% yield. Interestingly, the TBS protecting group at the C(5)–OH position was found to migrate to C(4)–OH position, when other carboxylic acids (e.g. AcOH, BzOH) were used for Mitsunobu inversion.

Stereochemistry at the C(4)-position in (+)-**21** was confirmed by the Kakisawa–Kashman[22] modified Mosher's method,[23] after esterification of (+)-**21**. The (−)- and (+)-MTPA esters of (+)-**21** were isolated in 100 and 91% yield, respectively (Scheme 5 and Fig. 4).

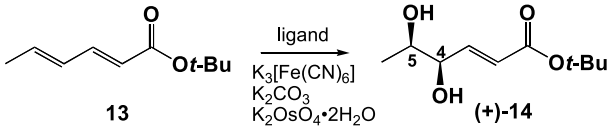
The other secondary hydroxyl group in TBS ether (+)-**21** was protected as β-methoxyethoxymethyl (MEM) ether to provide (−)-**22**. Hydrolysis in aqueous sodium hydroxide solution (0.2 N NaOH MeOH/THF/H_2O) afforded the first building block (−)-**23** (carboxylic acid) in 96% yield (Scheme 6). The second building block, (−)-**24** (secondary alcohol), was prepared by deprotection of TBS group of (−)-**22** with tetra-*n*-butylammonium fluoride (TBAF) in 100% yield (Scheme 6).

2.4. Completion of total synthesis of (+)-macrosphelide A

Condensation of carboxylic acid (−)-**23** and alcohol (−)-**24**, in the presence of DCC, DMAP, and camphorsulfonic acid (CSA) (Keck protocol[29]) furnished diester (−)-**25** in 92% yield. Subsequent desilylation of (−)-**25** was carried out with TFA to give the alcohol (−)-**26** in 99% yield. The requisite third building block (+)-**27**[30] was prepared by silylation of (*S*)-3-hydroxybutylic acid, and coupled by DCC accelerated condensation in the presence of DMAP and CSA (Keck protocol[29]) with the alcohol (−)-**26** to afford the triester (−)-**28** in 96% yield (Scheme 7).

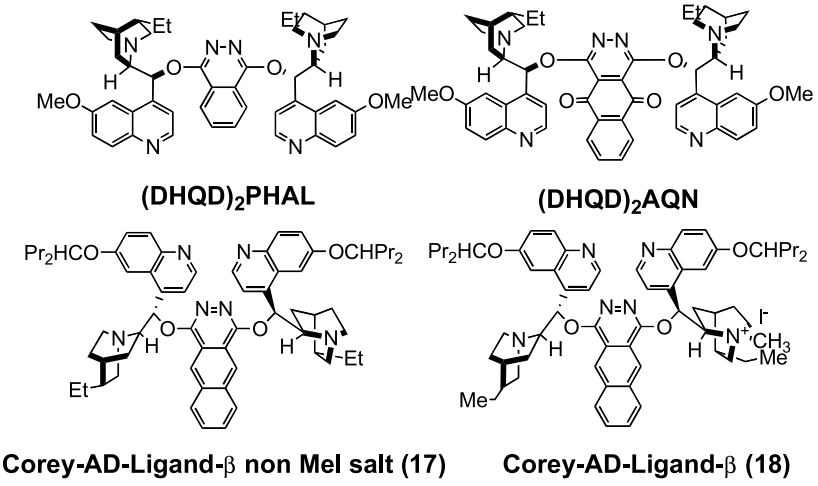
Selective, simultaneous removal of the TBS and *tert*-butyl groups, to convert (−)-**28** to seco acid (−)-**29**, was attempted under a variety of acidic conditions. The best result was obtained by treatment with thioanisole/TFA/CH_2Cl_2 (5:5:1),[31] to give seco acid (−)-**29** in 64% yield, with undesired mono MEM ether **31** in low yield (Table 3).

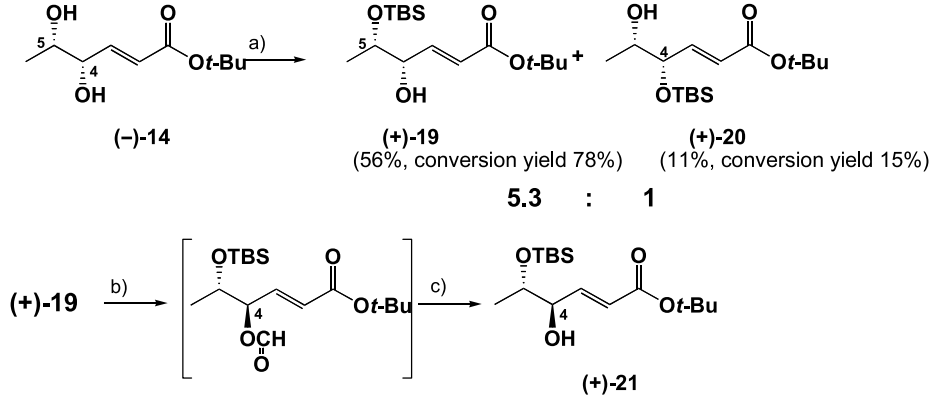
Table 2. Asymmetric dihydroxylation of sorbic acid *tert*-butyl ester using β-ligands



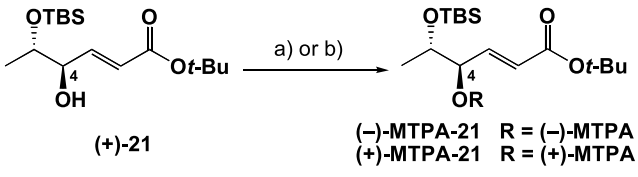
Ligand[a]	Yield of (+)-**14**[b]	%ee of (+)-**14**[c]
$(DHQD)_2PHAL$	68%	95%
$(DHQD)_2AQN$	61%	82%
17	74%	98%
18	5.9%	90%

[a] All reactions were carried out with ligands (0.01 equiv), $K_3[Fe(CN)_6]$ (3.0 equiv), K_2CO_3 (3.0 equiv) and $K_2OsO_4 \cdot 2H_2O$ (0.01 equiv) in *t*-BuOH·H_2O (1/1 v/v).
[b] Yields were based on pure materials isolated by chromatography on SiO_2.
[c] The ee of the product was determined by ^1H NMR measurements of the MTPA ester of TBS ether (−)-**19**.





Scheme 4. Preparation of (+)-**21**. (a) TBSCl, Et_3N, DMAP, CH_2Cl_2; (b) PPh_3, DEAD, HCOOH; (c) dil. NH_4OH, 83% yield for two steps.



Scheme 5. Synthesis of (−)/(+)-MTPA ester. (a) (−)-MTPA, DCC, DMAP, CH_2Cl_2, 100% yield; (b) (+)-MTPA, DCC, DMAP, CH_2Cl_2, 91% yield.

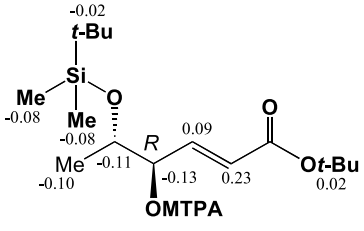
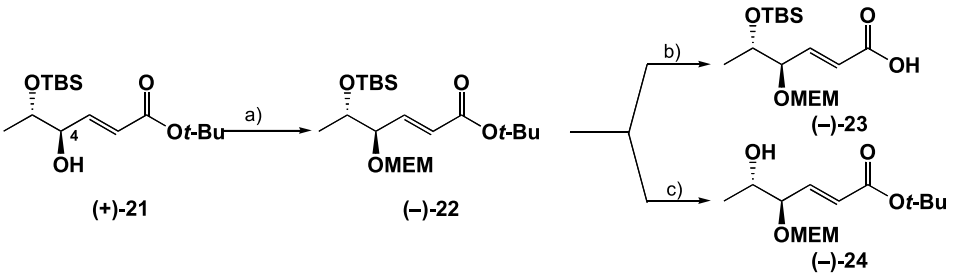
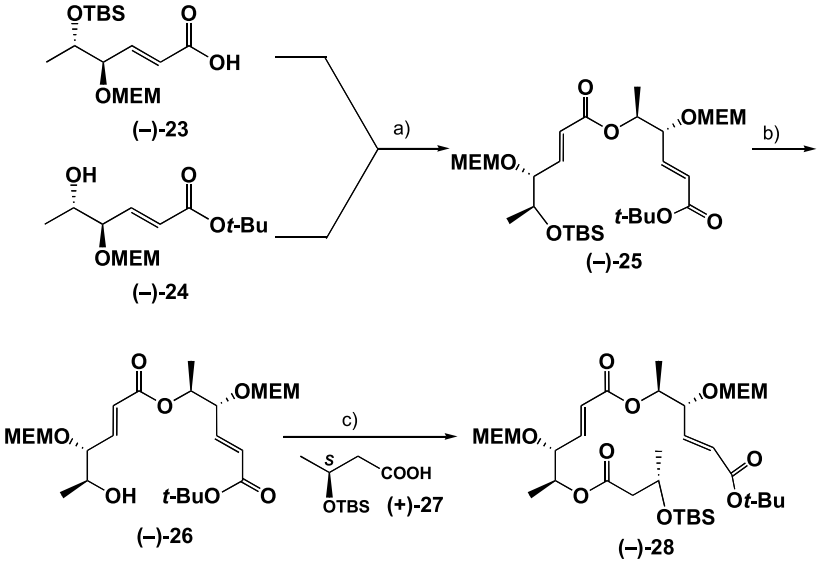


Figure 4. Stereochemistry identification: δ values for the MTPA ester derivatives of (+)-**21**.



Scheme 6. Preparation of acid (−)-**23** and alcohol (−)-**24**. (a) MEMCl, *i*-Pr_2NEt, CH_2Cl_2, 100% yield; (b) 0.2 N NaOH, 96% yield; (c) TBAF, 100% yield.

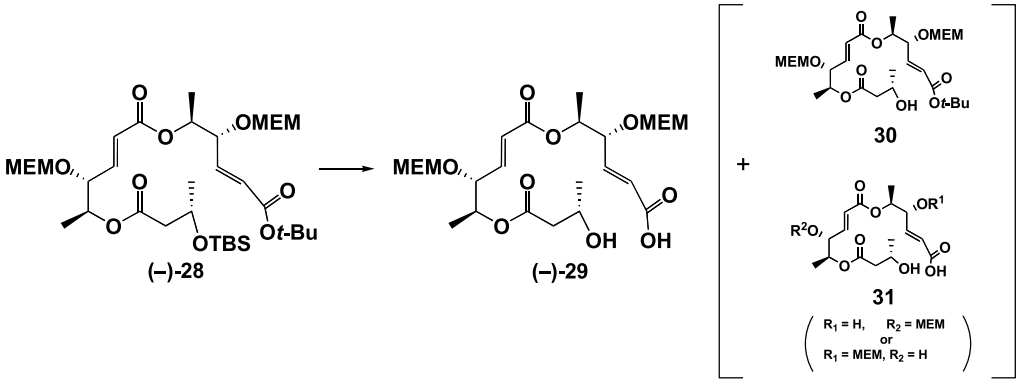


Scheme 7. Synthesis of triester (−)-**28**. (a) DCC, DMAP, CSA, 92% yield; (b) TFA, THF, H_2O, 99% yield; (c) (+)-**27**, DCC, DMAP, CSA, 96% yield.

Yamaguchi macrolactonization[32] of the seco acid (−)-**29** then proceeded in excellent yield (91%) to furnish (−)-**32**. Finally, deprotection of (−)-**32** in TFA/CH_2Cl_2 (1:1) provided totally synthetic (+)-macrosphelide A ((+)-**1**) in 90% yield (Scheme 8). Its spectral properties were identical in all respects (400 MHz ^1H and 100 MHz ^{13}C NMR, IR, HR-FABMS, optical rotation, melting point and mixed melting point, TLC, and HPLC in four solvent systems) to those of the natural product.

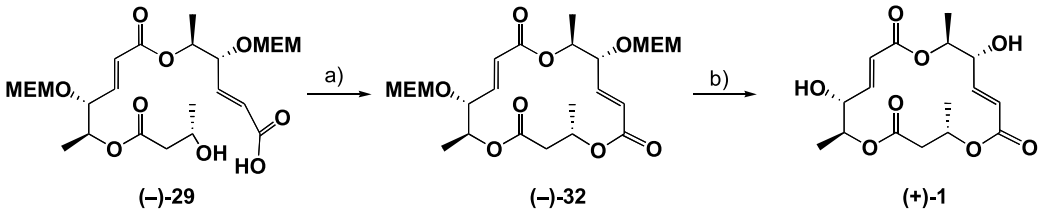
In summary, a highly convergent, stereocontrolled first total synthesis of (+)-macrosphelide A ((+)-**1**) has been

Table 3. Deprotection of TBS and *t*-butyl groups of (−)-**28**

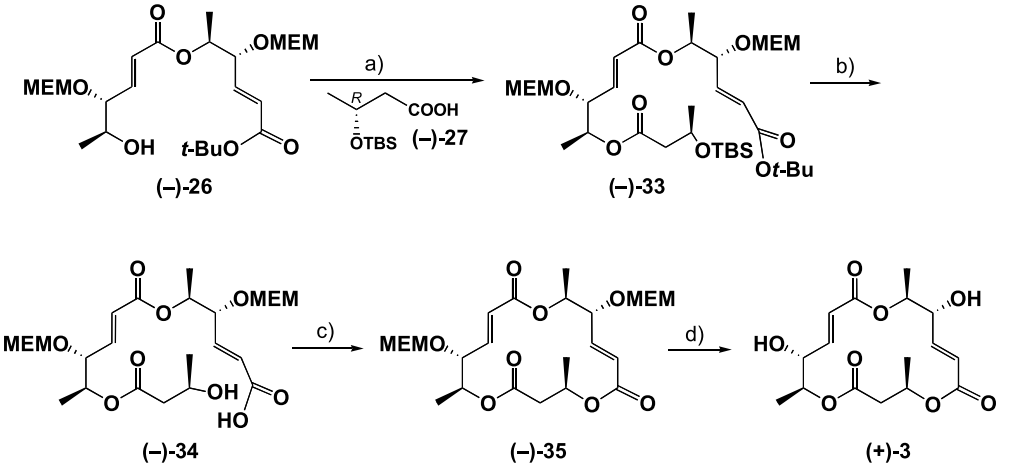


Reaction conditions	Results[a]
TFA·THF·H_2O (1:8:1)	**30** (83%)
HCOOH	(−)-**29** (23%)+**31** (20%)
AcOH·PrOH·H_2O (1:4:4)	(−)-**29** (19%)+**31** (29%)
TFA·thioanisole·CH_2Cl_2 (5:5:1)	(−)-**29** (64%)+**31** (24%)

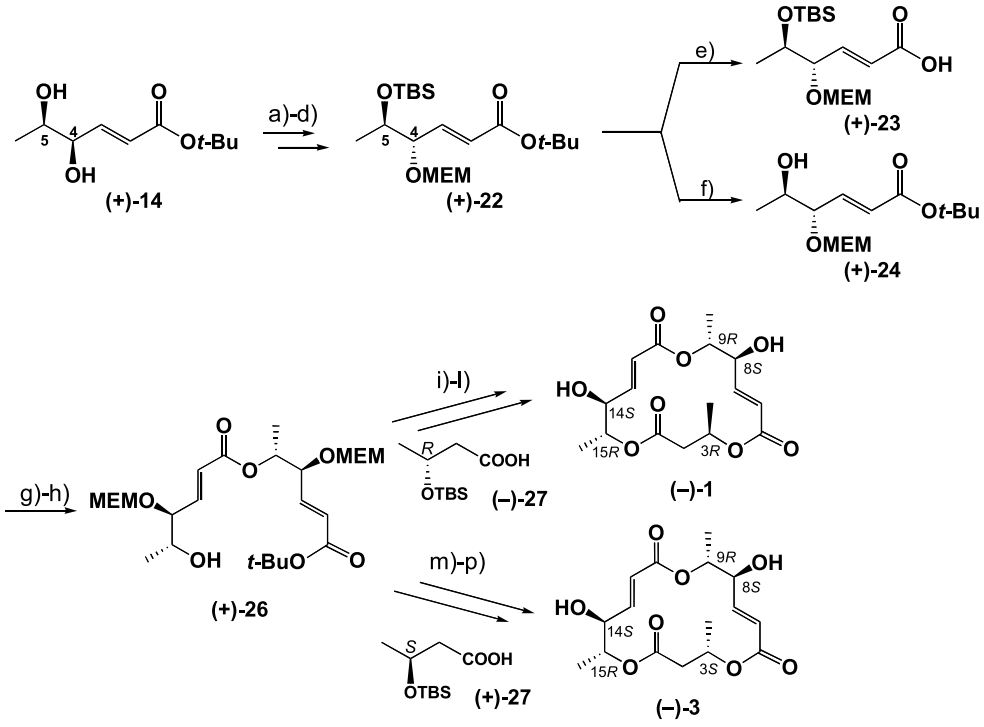
[a] Yields were based on pure materials isolated by chromatography on SiO_2.



Scheme 8. The end game for total synthesis of (+)-macrosphelide A ((+)-**1**). (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, 91% yield; (b) TFA, 90% yield.



Scheme 9. Synthesis of (+)-macrosphelide E ((+)-**3**). (a) (−)-**27**, DCC, DMAP, CSA, CH_2Cl_2, 100% yield; (b) TFA, thioanisole, CH_2Cl_2, 51% yield; (c) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, 66% yield; (d) TFA, 79% yield.



Scheme 10. Synthesis of (−)-macrosphelides A and E ((−)-**1** and (−)-**3**). (a) TBSCl, Et_3N, CH_2Cl_2, 35% yield; (b) PPh_3, DEAD, HCOOH; (c) dil NH_4OH, 73% yield for two steps; (d) MEMCl, *i*-Pr_2NEt, CH_2Cl_2, 96% yield; (e) 0.2 N NaOH, 85% yield; (f) TBAF, 98% yield; (g) DCC, DMAP, CSA, 62% yield; (h) AcOH, THF, H_2O, 97% yield; (i) (−)-**27**, DCC, DMAP, CSA, 77% yield; (j) TFA, thioanisole, CH_2Cl_2, 38% yield; (k) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, 86% yield; (l) TFA, 88% yield; (m) (+)-**27**, DCC, DMAP, CSA, 100% yield; (n) TFA, thioanisole, CH_2Cl_2, 41% yield; (o) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, 85% yield; (p) TFA, 64% yield.

achieved, in 11 steps, from sorbic acid ester, with a 20% overall yield. The synthetic scheme includes the use of a modified Sharpless asymmetric dihydroxylation for the effective introduction of two stereocenters.

2.5. Synthesis of (+)-macroshelode E, and (−)-macrosphelides A and E

We next sought to prepare the (+)-macrosphelide E ((+)-**3**), which was isolated from the gastrointestinal tract of the sea hare *Aplysia kurodai*. Its absolute structure was established via a series of NMR studies in conjunction with HREIMS, UV data, and chemical characterization of the fragmented 3-hydroxybutyric acid and 4,5-dihydroxy-2-*E*-hexenoic acid. Numata and co-workers[19] showed that (+)-macrosphelide E is the C(3) epimer of (+)-macrosphelide A. Synthesis of (+)-**3** was initiated using a Keck protocol[29] of the alcohol precursor (−)-**26** with building block (−)-**27**[30] (prepared by silylation of (*R*)-3-hydroxybutylic acid) to give (−)-**33** in 100% yield. Removal of the silyl and *tert*-butyl moieties from (−)-**33**, (under the same condition as for (−)-**28**[31]) furnished the seco acid (−)-**34**, which was then cyclized by Yamaguchi protocol[32] to give (−)-**35** in 66% yield. Finally, acid treatment of (−)-**35** to remove MEM protecting groups provided synthetic (+)-**3** in 79% yield (Scheme 9), which demonstrated identical, reported spectral data for the naturally occurring compound.[19]

(−)-Macrosphelides A and E, which are the antipodes of the naturally occurring products, were also prepared from (+)-**14** following the same procedure as for the syntheses of (+)-macrosphelides A and E (Scheme 10).

3. Conclusion

As described above, the determination of the absolute structures of (+)-macrosphelides ((+)-**1** and **2**) and the total syntheses of (+)/(−)-macrosphelides A and E were completed. The longest linear synthetic sequence for the synthesis of (+)-macrosphelide A comprised of 11 steps, and proceeded in 20% overall yield (corresponding to an 88% average yield per step). Our synthesis used a modified Sharpless-Asymmetric-Dihydroxylation for the introduction of the two asymmetric carbons. We have also demonstrated that this synthetic route can be applied to the preparation of macrosphelide derivatives, including enantiomers and diastereomers. Studies on the mode of action and the structure–activity relationships of macrosphelides are currently underway.

4. Experimental

4.1. General

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

4.1.1. (5*R*,6*S*,11*R*,12*S*,16*S*)-(3*E*,9*E*)-5,11-Bis[(*S*)-α-methoxy-α-trifluoromethylphenyl-acetoxy]-6,12,16-trimethyl-1,7,13-trioxacyclohexadeca-3,9-diene-2,8,14-trione (−)-4. At room temperature a solution of (+)-macrosphelide A (10.0 mg, 29.2 μmol) in dry THF (0.6 mL) was treated with *(S)*-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (41 mg, 175 μmol), dicyclohexylcarbodiimide (18 mg, 88 μmol), and 4-dimethylaminopyridine (3.6 mg, 29 μmol). A white precipitate formed immediately. The resultant mixture was stirred for 2 h, quenched with saturated aqueous $NaHCO_3$ (1 mL), and extracted with dichloromethane (3×1.5 mL). The combined extracts were dried over sodium sulfate, filtered and concentrated. To remove dicyclohexylurea the white solid was taken up in ether (1 mL) and filtered, the cake was washed with ether (1 mL), and the combined ethereal solutions were concentrated. Preparative TLC (250 μm×20×20 cm; 2:1 hexanes/EtOAc) gave (−)-**4** (26.2 mg, 100% yield) as a white powder: $[\alpha]_D^{20}=-20$ (*c* 0.86, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.27 (m, 10H), 6.75 (dd, *J*=15.9, 7.1 Hz, 1H), 6.69 (dd, *J*=15.7, 7.5 Hz, 1H), 5.98 (dd, *J*=15.8, 1.2 Hz, 2H), 5.38 (m, 1H), 5.32 (m, 1H), 5.30 (m, 1H), 5.12 (m, 1H), 5.10 (m, 1H), 3.53 (s, 3H), 3.50 (s, 3H), 2.53 (m, 1H), 2.49 (m, 1H), 1.30 (d, *J*=6.5 Hz, 3H), 1.21 (d, *J*=6.5 Hz, 3H), 1.13 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 17.2, 19.5, 40.6, 55.6 (2 C), 67.7, 69.3, 70.1, 75.3, 77.0, 121.7, 124.6, 125.5 (2 C), 125.6 (2 C), 127.1 (4 C) 128.6 (2 C), 129.9 (2 C), 131.5 (2 C), 140.3 (2 C), 140.4 (2 C) 163.4, 163.6, 165.4, 165.7, 169.1; HRMS (FAB, NaI matrix) *m/z* 797.2053 [$(M+Na)^+$; calcd for $C_{36}H_{36}O_{12}F_6Na$: 797.2009].

4.1.2. (5*R*,6*S*,11*R*,12*S*,16*S*)-(3*E*,9*E*)-5,11-Bis[(*R*)-α-methoxy-α-trifluoromethylphenyl-acetoxy]-6,12,16-trimethyl-1,7,13-trioxacyclohexadeca-3,9-diene-2,8,14-trione (+)-5. Following the procedure described above for the preparation of (−)-**4**, (+)-macrosphelide A (10.0 mg, 29.9 μmol) was acylated with *(R)*-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (41 mg, 175.2 μmol). Work-up and preparative TLC (250 μm×20×20 cm; 2:1 hexanes/EtOAc) afforded (+)-**5** (6.1 mg, 27% yield) as a white powder: $[\alpha]_D^{20}=+36$ (*c* 0.43, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.28 (m, 10H), 6.70 (dd, *J*=15.8, 6.1 Hz, 1H), 6.64 (dd, *J*=15.8, 7.0 Hz, 1H), 5.85 (dd, *J*=15.7, 1.2 Hz, 2H), 5.41 (m, 1H), 5.37 (m, 1H), 5.28 (m, 1H), 5.14 (m, 1H), 5.13 (m, 1H), 3.53 (s, 3H), 3.49 (s, 3H), 2.59 (m, 1H), 2.52 (m, 1H), 1.37 (d, *J*=6.5 Hz, 3H), 1.30 (d, *J*=6.5 Hz, 3H), 1.27 (d, *J*=6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 17.7, 19.4, 40.6, 55.5, 55.6, 67.7, 69.7, 70.4, 75.2, 76.9, 121.6, 124.5, 124.7 (2 C), 125.2 (2 C), 127.2

(2 C), 127.3 (2 C), 128.6 (2 C), 129.9 (2 C), 131.3, 131.4, 140.1 (4 C), 163.2, 163.5, 165.7 (2 C), 169.1; HRMS (FAB, NaI matrix) *m/z* 797.2000 [(M+Na)$^+$; calcd for $C_{36}H_{36}O_{12}F_6Na$: 797.2009].

4.1.3. (5*R*,6*S*,12*S*,16*S*)-(3*E*,9*E*)-5-Hydroxy-6,12,16-trimethyl-1,7,13-trioxacyclohexa-deca-3,9-diene-2,8,11,14-tetraone [macrosphelide B (+)-2]. A mixture of (+)-**1** (10.9 mg, 32 μmol), pyridinium dichromate (72 mg, 192 μmol) in CH_2Cl_2 (3 mL) was stirred at room temperature for 3 h, diluted with ether (3 mL), filtered and concentrated in vacuo. Preparative TLC (250 μm×20×20 cm; 9:1 chloroform/methanol) gave a mixture of monoketones (+)-**2** and 5-ketone (**6**) (5.1 mg) as a colorless oil, diketone (**7**) (1.7 mg, 16% yield) as a colorless oil, and recovered **1** (4.9 mg, 45% yield) as a white solid. Further purification by HPLC (Senshu Pak, PEGASIL ODS, 20×25 cm; 35% CH_3CN in H_2O, 0.8 mL/min) afforded pure (+)-**2** (2.3 mg, 21% yield) and **6** (1.9 mg, 18% yield) as colorless oils. (+)-**2**: $[\alpha]_D^{24}=+10.0$ (*c* 0.39, MeOH) [lit. +4.1 (*c* 0.99, MeOH); IR (KBr) 3437 (s), 1736 (s), 1267 (m), 1190 (m), 1130 (m), 1055 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J*=15.8 Hz, 1H), 6.92 (dd, *J*=15.8, 3.7 Hz, 1H), 6.74 (d, *J*=15.8 Hz, 1H), 6.08 (dd, *J*=15.8, 2.1 Hz, 1H), 5.46 (m, 1H), 5.07 (m, 1H), 5.05 (m, 1H), 4.32 (br s, 1H), 2.82 (dd, *J*=16.3, 11.0 Hz, 1H), 2.62 (dd, *J*=16.3, 2.3 Hz, 1H), 1.50 (d, *J*=6.9 Hz, 3H), 1.43 (d, *J*=6.9 Hz, 3H), 1.36 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 17.9, 19.8, 40.6, 67.7, 74.8, 75.8, 76.8, 122.6, 132.1, 132.5, 144.2, 164.1, 165.4, 170.3, 196.2; HRMS (FAB, m-NBA matrix) *m/z* 341.1212 [(M+H)$^+$; calcd for $C_{16}H_{21}O_8$: 341.1236].

Compound **6**. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.25 (d, *J*=15.8 Hz, 1H), 7.02 (dd, *J*=15.8, 5.3 Hz, 1H), 6.65 (d, *J*=15.8 Hz, 1H), 6.19 (dd, *J*=15.8, 1.3 Hz, 1H), 5.35 (m, 1H), 5.20 (q, *J*=6.9 Hz, 1H), 4.90 (m, 1H), 4.19 (m, 1H), 2.71 (dd, *J*=16.2, 10.6 Hz, 1H), 2.57 (dd, *J*=16.2, 2.6 Hz, 1H), 1.51 (d, *J*=7.3 Hz, 3H), 1.39 (d, *J*=6.3 Hz, 3H), 1.36 (d, *J*=6.3, 3H); HRMS (FAB, m-NBA matrix) *m/z* 341.1231 [(M+H)$^+$; calcd for $C_{16}H_{21}O_8$: 341.1236].

Compound **7** ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.29 (d, *J*=16.2 Hz, 1H), 6.78 (d, *J*=15.8 Hz, 1H), 7.09 (d, *J*=15.8 Hz, 1H), 6.56 (d, *J*=16.2 Hz, 1H), 5.20 (q, *J*=7.3 Hz, 1H), 5.12 (q, *J*=6.9 Hz, 1H), 5.31 (m, 1H), 2.84 (dd, *J*=16.5, 11.3 Hz, 1H), 2.61 (dd, *J*=16.5, 2.1 Hz, 1H), 1.51 (d, *J*=7.3 Hz, 3H), 1.39 (d, *J*=6.9 Hz, 3H), 1.34 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 15.9, 17.0, 19.5, 40.6, 69.2, 75.5, 76.3, 132.0, 132.2, 132.3, 134.3, 163.1, 163.5, 170.1, 195.6, 197.4; HRMS (FAB, m-NBA matrix) *m/z* 339.1075 [(M+H)$^+$; calcd for $C_{16}H_{19}O_8$: 339.1080].

4.1.6. 3.1.4. (4*S*, 5*S*)-(*E*)-4,5-Dihydroxyl-2-hexenoic acid *t*-butyl ester (−)-14. *Reaction of asymmetric dihydroxylation with AD-mix-α*. To a well-stirred solution of AD-mix-α (488 mg) in 3.2 mL of *t*-BuOH/H_2O (1/1 v/v) was added 30.4 mg (0.32 mmol) of methansulfonamide at ambient temperature. The clear yellow solution was cooled to 0 °C and added 53.8 mg (0.32 mmol) of unsaturated ester **13**. The solution was stirred vigorously at 0 °C. After stirring for 27 h, the reaction was quenched with 500 mg of solid Na_2SO_3, warmed to ambient temperature and stirred for 50 min. The mixture was extracted with 3×8 mL of CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated. Flash chromatography (50% EtOAc/hexane) provided 39.9 mg of diol (−)-**14** (0.20 mmol, 62%) as a colorless oil.

Reaction of asymmetric dihydroxylation with Corey AD-ligand-α non MeI salt (**15**). To a well-stirred solution of 588 mg (1.8 mmol) of potassium hexacyanoferrate, 247 mg (1.8 mmol) of potassium carbonate, 2.2 mg (6.0 μmol) of potassium osmate(VI) dihydrate and 5.9 mg (6.0 μmol) of Corey AD-ligand-α non MeI salt **15** in 3.2 mL of *t*-BuOH/H_2O (1/1 v/v) was added 57 mg (0.6 mmol) of methansulfonamide at ambient temperature. The clear yellow solution was cooled to 0 °C and added 100 mg (0.6 mmol) of unsaturated ester **13**. The solution was stirred vigorously at 0 °C. After stirring for 18.5 h, the reaction was quenched with 1.0 g of solid Na_2SO_3, warmed to ambient temperature and stirred for 50 min. The mixture was extracted with 3×20 mL of $CHCl_3$, dried over Na_2SO_4, filtered and concentrated. Flash chromatography (50% EtOAc/hexane) provided 86 mg of diol (−)-**14** (0.42 mmol, 71%) as a colorless oil: R_f 0.18 (1:1 hexane/EtOAc); $[\alpha]_D^{20}=-10.3$ (*c* 1.04, $CHCl_3$); IR (KBr) 3435 (s), 1716 (s), 1369 (m), 1157 (s) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.81 (dd, *J*=15.8, 5.3 Hz, 1H), 6.06 (dd, *J*=15.8, 1.7 Hz, 1H), 4.04 (m, 1H), 3.73 (m, 1H), 2.34 (d, *J*=4.6 Hz, 1H), 2.11 (d, *J*=4.0 Hz, 1H), 1.49 (s, 9H), 1.25 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 19.1, 28.1, 70.2, 75.7, 80.8, 124.3, 145.2, 165.7; HRMS (FAB, NBA matrix) *m/z* 203.1273 [(M+H)$^+$; calcd for $C_{10}H_{19}O_4$: 203.1283]. Anal. Calcd for $C_{10}H_{19}O_4$: C, 59.39; H, 8.97. Found: C, 59.12; H, 8.88.

4.1.7. (4*R*,5*R*)-(*E*)-4,5-Dihydroxyl-2-hexenoic acid *t*-butyl ester (+)-14. Following the procedure described above for the preparation of (−)-**14**, dihydroxylation of 100 mg (0.60 mmol) of **13** with Corey AD-ligand-β non MeI salt (**17**) afforded 89.3 mg of (+)-**14** (74%): $[\alpha]_D^{29}=+12.4$ (*c* 1.56, $CHCl_3$); HRMS (FAB, NBA matrix) *m/z* 203.1310 [(M+H)$^+$; calcd for $C_{10}H_{19}O_4$: 203.1283].

4.1.8. (4*S*,5*S*)-(*E*)-5-(*t*-Butyldimethylsiloxy)-4-hydroxyl-2-hexenoic acid *t*-butyl ester (+)-19. To a solution of 1.12 g (5.53 mmol) of diol (−)-**14**, 34 mg (0.28 mmol) of 4-dimethylaminopyridine and 1.84 g (12.2 mmol) of *tert*-butyldimethylsilyl chloride in 11.0 mL of CH_2Cl_2 at 0 °C was added 1.85 mL (13.3 mmol) of triethylamine. The reaction mixture was gradually warmed to ambient temperature for 5 h. After 7 h 15 min, the solution was quenched with 5 mL of H_2O. This mixture was extracted with 3×30 mL of $CHCl_3$, washed with 20 mL of saturated NaCl aqueous solution, dried over Na_2SO_4, filtered, and concentrated. Chromatography (1.6% EtOAc/hexane) provided 986 mg of (+)-**19** (3.12 mmol, 78% based on recovered (−)-**14**, 186 mg of 4-silyl ether (+)-**20** (0.59 mmol, 11%) and 316 mg of starting material (1.56 mmol, 30%). (+)-**19**: R_f 0.58 (3:1 hexane/EtOAc); $[\alpha]_D^{24}=+6.0$ (*c* 1.81, $CHCl_3$); IR (KBr) 3435 (s), 2978 (m), 2931 (m), 2858 (m), 1716 (s), 1369 (m), 1257 (m), 1157 (s), 1097 (m) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.79 (dd, *J*=15.8, 4.6 Hz, 1H), 6.02 (dd, *J*=15.8, 1.7 Hz, 1H), 3.99 (m, 1H), 3.76 (m, 1H), 2.56 (d, *J*=5.9 Hz, 1H), 1.48 (s, 9H), 1.21 (d, *J*=6.3 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s,

3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −4.9, −4.4, 18.0, 20.1, 25.7, 28.1, 71.1, 75.2, 80.3, 123.8, 146.0, 165.6; HRMS (FAB, NaI matrix) *m/z* 339.1978 [$(M+Na)^+$; calcd for $C_{16}H_{32}O_4SiNa$: 339.1968]. Anal. Calcd for $C_{10}H_{32}O_4Si$: C, 60.72; H, 10.19. Found: C, 60.88; H, 10.06.

4.1.9. (4*R*,5*R*)-(*E*)-5-(*t*-Butyldimethylsiloxy)-4-hydroxyl-2-hexenoic acid *t*-butyl ester (−)-19. Following the procedure described above for the preparation of (+)-**19**, silylation of 78 mg (0.39 mmol) of (+)-**14** afforded 89.3 mg of (−)-**19** (33%, 69% based on recovered (+)-**14**): $[\alpha]_D^{27}=-8.2$ (*c* 0.85, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 339.1968 [$(M+Na)^+$; calcd for $C_{16}H_{32}O_4SiNa$: 339.1968]. Anal. Calcd for $C_{10}H_{32}O_4Si$: C, 60.72; H, 10.19. Found: C, 60.38; H, 10.11.

4.1.10. (4*R*,5*S*)-(*E*)-5-(*t*-Butyldimethylsiloxy)-4-hydroxyl-2-hexenoic acid *t*-butyl ester (+)-19. At room temperature, to a solution of 836 mg (2.65 mmol) of (+)-**21** and 1.39 g (5.29 mmol) of triphenylphosphine in 5.0 mL of benzene was added a solution of 0.83 mL (5.29 mmol) of diethyl azodicarboxylate and 0.21 mL (5.56 mmol) of formic acid in 8.3 mL of benzene over 45 min. The reaction mixture was stirred for 3.5 h then quenched with 10 mL of H_2O. This mixture was extracted with 3×20 mL of $CHCl_3$, washed with 5.0 mL of saturated $NaHCO_3$ aqueous solution, dried over Na_2SO_4, filtered, and concentrated. This crude product was used directly in the subsequent reaction. To this product was added 13.0 mL of diluted NH_4OH solution (pH 10.0–10.2) in $MeOH\cdot H_2O$ (3:1), the solution was stirred for 1.5 h at ambient temperature, and then quenched with 40 mL of saturated NH_4Cl aqueous solution. This mixture was extracted with 3×50 mL of $CHCl_3$, dried over Na_2SO_4, filtered, and concentrated. Chromatography (5% EtOAc/hexane) provided 697 mg of (+)-**21** (2.21 mmol, 83%) as a colorless oil: R_f 0.42 (4:1 hexane/EtOAc); $[\alpha]_D^{25}=+17.9$ (*c* 2.58, $CHCl_3$); IR (KBr) 3435 (s), 2931 (m), 2858 (m), 1716 (s), 1369 (m), 1257 (m), 1157 (s), 1097 (m) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 6.77 (dd, *J*=15.8, 5.3 Hz, 1H), 6.00 (dd, *J*=15.8, 1.7 Hz, 1H), 4.16 (m, 1H), 3.90 (m, 1H), 2.36 (d, *J*=3.6 Hz, 1H), 1.48 (s, 9H), 1.09 (d, *J*=6.3 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −5.0, −4.5, 17.8, 18.0, 25.7, 28.1, 70.8, 74.9, 80.4, 123.6, 144.4, 165.6; HRMS (FAB, NaI matrix) *m/z* 339.1968 [$(M+Na)^+$; calcd for $C_{16}H_{32}O_4SiNa$: 339.1968]. Anal. Calcd for $C_{16}H_{32}O_4Si$: C, 60.72; H, 10.19. Found: C, 60.88; H, 10.23.

4.1.11. (4*S*,5*R*)-(*E*)-5-(*t*-Butyldimethylsiloxy)-4-hydroxyl-2-hexenoic acid *t*-butyl ester (−)-21. Following the procedure described above for the preparation of (+)-**21**, inversion of 777 mg of (−)-**19** afforded 89.3 mg of (−)-**21** (73%): $[\alpha]_D^{28}=-20.0$ (*c* 0.70, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 339.1970 [$(M+Na)^+$; calcd for $C_{16}H_{32}O_4SiNa$: 339.1968]. Anal. Calcd for $C_{16}H_{32}O_4Si$: C, 60.72; H, 10.19. Found: C, 60.40; H, 10.22.

4.1.12. (4*R*,5*S*)-(*E*)-5-(*t*-Butyldimethylsiloxy)-4-[(*S*)-α-methoxy-α-trifluoromethylphenyl-acetoxy]-2-hexenoic acid *t*-butyl ester (−)-MTPA-21. At room temperature a solution of (+)-**21** (6.9 mg, 0.02 mmol) in dry THF (0.4 mL) was treated with *(S)*-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (31 mg, 0.13 mmol), dicyclohexylcarbodiimide (14 mg, 0.07 mmol), and 4-dimethylaminopyridine (2.7 mg, 0.02 mmol). A white precipitate formed immediately. The resultant mixture was stirred for 15 min, quenched with H_2O (1 mL), and extracted with $CHCl_3$ (3×4.0 mL). The combined extracts were dried over sodium sulfate, filtered and concentrated. To remove dicyclohexylurea the white solid was taken up in ether (1 mL) and filtered, the cake was washed with ether (1 mL), and the combined ethereal solutions were concentrated. Preparative TLC (250 μm×20×20 cm; 6:1 hexanes/EtOAc) gave (−)-MTPA-**21** (11.3 mg, 100% yield) as a colorless oil: $[\alpha]_D^{27}=-20.5$ (*c* 1.00, $CHCl_3$); IR (KBr) 2858 (m), 1755 (s), 1720 (s), 1662 (w), 1254 (s), 779 (m), 719 (m) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.46 (m, 5H), 6.74 (dd, *J*=15.8, 6.3 Hz, 1H), 5.91 (dd, *J*=15.8, 1.3 Hz, 1H), 5.47 (m, 1H), 3.88 (m, 1H), 3.57 (s, 3H), 1.48 (s, 9H), 1.04 (d, *J*=6.3 Hz, 3H), 0.84 (s, 9H), −0.01, −0.04 (s, each 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −5.2, −4.7, 17.9, 19.2, 25.6, 28.1, 55.6, 69.5, 78.7, 78.7, 80.4, 126.6, 127.5, 128.4, 129.6, 132.1, 139.9, 164.8, 165.7; HRMS (FAB, m-NBA+NaI matrix) *m/z* 555.2367 [$(M+Na)^+$; calcd for $C_{26}H_{39}O_6F_3SiNa$: 555.2366].

4.1.13. (4*R*,5*S*)-(*E*)-5-(*t*-Butyldimethylsiloxy)-4-(*R*)-α-methoxy-α-trifluoromethylphenyl-acetoxy-2-hexenoic acid *t*-butyl ester (+)-MTPA-21. At room temperature a solution of (+)-**21** (8.9 mg, 0.03 mmol) in dry THF (0.6 mL) was treated with *(R)*-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (40 mg, 0.17 mmol), dicyclohexylcarbodiimide (17 mg, 0.08 mmol), and 4-dimethylaminopyridine (3.4 mg, 0.03 mmol). A white precipitate formed immediately. The resultant mixture was stirred for 20 min, quenched with H_2O (1 mL), and extracted with $CHCl_3$ (3×4.0 mL). The combined extracts were dried over sodium sulfate, filtered and concentrated. To remove dicyclohexylurea the white solid was taken up in ether (1 mL) and filtered, the cake was washed with ether (1 mL), and the combined ethereal solutions were concentrated. Preparative TLC (250 μm×20×20 cm; 6:1 hexanes/EtOAc) gave (+)-MTPA-**21** (13.1 mg, 91% yield) as a colorless oil: $[\alpha]_D^{27}=+21.7$ (*c* 1.00, $CHCl_3$); IR (KBr) 2858 (m), 1755 (s), 1718 (s), 1662 (w), 1255 (s), 779 (m), 719 (m) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.51 (m, 5H), 6.65 (dd, *J*=15.8, 5.6 Hz, 1H), 5.68 (dd, *J*=15.8, 1.7 Hz, 1H), 5.60 (m, 1H), 3.99 (m, 1H), 3.61 (s, 3H), 1.46 (s, 9H), 1.14 (d, *J*=6.3 Hz, 3H), 0.86 (s, 9H), 0.07, 0.04 (s, each 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −5.2, −4.7, 18.0, 18.5, 25.6, 28.0, 55.7, 69.5, 78.4, 78.7, 80.8, 125.5, 127.4, 128.4, 129.6, 132.2, 139.7, 164.8, 165.7; HRMS (FAB, m-NBA+NaI matrix) *m/z* 555.2370 [$(M+Na)^+$; calcd for $C_{26}H_{39}O_6F_3SiNa$: 555.2366].

4.1.14. (4*R*,5*S*)-(*E*)-5-(*t*-Butyldimethylsiloxy)-4-methoxyethoxymethoxy-2-hexenoic acid *t*-butyl ester (−)-22. At room temperature, to a solution of 368 mg (1.16 mmol) of (+)-**21** and 2.63 mL (15.08 mmol) of *N*-ethyldiisopropylamine in 6.0 mL of CH_2Cl_2 was added 1.32 mL (11.60 mmol) of β-methoxyethoxymethyl chloride, the reaction mixture was stirred for 66 h, and then quenched with 5.0 mL of water. This mixture was extracted with 3× 20 mL of CH_2Cl_2, washed with 10 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated. Chromatography (3.3% EtOAc/hexane) provided 410.4 mg

of (−)-**22** (1.02 mmol, 87%) as a colorless oil: R_f 0.58 (30:1 $CHCl_3$/MeOH); $[\alpha]_D^{26} = -28.4$ (*c* 0.62, $CHCl_3$); IR (KBr) 3435 (s), 2956 (m), 2931 (m), 2889 (m), 2858 (m), 1716 (s), 1369 (m), 1254 (m), 1155 (s), 1105 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.72 (dd, $J=15.8$, 6.6 Hz, 1H), 5.90 (dd, $J=15.8$, 1.0 Hz, 1H), 4.72 (s, 2H), 4.02 (dd, $J=11.2$, 6.9 Hz, 1H), 3.80 (m, 1H), 3.77 (m, 1H), 3.63 (m, 1H), 3.54 (m, 2H), 3.38 (s, 3H), 1.47 (s, 9H), 1.17 (d, $J=5.9$ Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −4.8, −4.6, 18.0, 20.0, 25.8, 27.9, 59.0, 67.1, 70.6, 71.6, 79.9, 80.3, 93.8, 125.4, 144.3, 165.3; HRMS (FAB, NBA matrix) *m/z* 405.2658 $[(M+H)^+$; calcd for $C_{20}H_{41}O_6Si$: 405.2672]. Anal. Calcd for $C_{20}H_{41}O_6Si$: C, 59.37; H, 9.96. Found: C, 59.34; H, 10.00.

4.1.15. (4*S*,5*R*)-(*E*)-5-(*t*-Butyldimethylsiloxy)-4-methoxyethoxymethoxy-2-hexenoic acid *t*-butyl ester (+)-22. Following the procedure described above for the preparation of (−)-**22**, MEM protection of 719 mg (2.3 mmol) of (−)-**21** afforded 884 mg of (+)-**22** (96%): $[\alpha]_D^{28} = +29.3$ (*c* 0.15, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 427.2488 $[(M+Na)^+$; calcd for $C_{20}H_{40}O_6Si$ Na: 427.2492]. Anal. Calcd for $C_{20}H_{40}O_6Si$: C, 59.37; H, 9.96. Found: C, 59.60; H, 9.86.

4.1.16. (4*R*,5*S*)-(*E*)-5-(*t*-Butyldimethylsililoxy)-4-methoxyethoxymethoxy-2-hexenoic acid (−)-23. At room temperature, 192 mg (0.48 mmol) of (−)-**22** was dissolved in 4.8 mL of 0.2 N NaOH in MeOH·THF·H_2O (3:1:1) solution, the mixture was stirred for 6 days, and then quenched with 5.0 mL of 0.2 N HCl aqueous solutin became neutral solution. This mixture was extracted with 4×15 mL of $CHCl_3$, dried over Na_2SO_4, and concentrated. Chromatography (5–9% MeOH/$CHCl_3$) provided 154 mg of (−)-**23** (0.44 mmol, 94%) as a colorless oil: R_f 0.35 (10:1 $CHCl_3$/MeOH); $[\alpha]_D^{22} = -30.0$ (*c* 0.62, $CHCl_3$); IR (KBr) 3435 (s), 2954 (m), 2931 (m), 2891 (m), 2858 (m), 1722 (m), 1703 (s), 1255 (m), 1111 (s), 1043 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.98 (dd, $J=15.8$, 6.3 Hz, 1H), 6.02 (dd, $J=15.8$, 1.0 Hz, 1H), 4.74 (dd, $J=10.9$, 6.9, 2H), 4.10 (m, 1H), 3.84 (m, 1H), 3.76 (m, 1H), 3.66 (m, 1H), 3.54 (m, 2H), 3.38 (s, 3H), 1.17 (d, $J=6.3$ Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −4.8, −4.6, 18.0, 19.9, 25.7, 59.0, 67.3, 70.5, 71.6, 79.9, 94.2, 122.4, 148.5, 170.8; HRMS (FAB, NaI matrix) *m/z* 371.1861 $[(M+Na)^+$; calcd for $C_{16}H_{32}O_6SiNa$: 371.1866]. Anal. Calcd for $C_{16}H_{32}O_6Si$: C, 55.14; H, 9.25. Found: C, 54.86; H, 9.18.

4.1.17. (4*S*,5*R*)-(*E*)-5-(*t*-Butyldimethylsililoxy)-4-methoxyethoxymethoxy-2-hexenoic acid (+)-23. Following the procedure described above for the preparation of (−)-**23**, hydrolysis of 27.1 mg (0.07 mmol) of (+)-**22** afforded 19.3 mg of (+)-**23** (85%): $[\alpha]_D^{28} = +33.2$ (*c* 0.62, $CHCl_3$); HRMS (FAB, NBA matrix) *m/z* 347.1888 $[(M-H)^-$; calcd for $C_{16}H_{31}O_6Si$: 347.1888]. Anal. Calcd for $C_{16}H_{31}O_6Si$: C, 55.14; H, 9.25. Found: C, 54.76; H, 9.31.

4.1.18. (4*R*,5*S*)-(*E*)-5-Hydroxy-4-methoxyethoxymethoxy-2-hexenoic acid *t*-butyl ester (−)-24. At room temperature, to a solution of 186 mg (0.46 mmol) of silyl ether (−)-**22** in 0.9 mL THF was added 1.4 mL of 1.0 M tetra-*n*-butylammonium fluorid in THF, the solution was stirred for 1 h, and then quenched with 2 mL of H_2O. This mixture was extracted with 3×20 mL of $CHCl_3$, dried over Na_2SO_4, filtered, and concentrated. Chromatography (50% EtOAc/hexane) provided 133 mg of (−)-**24** (0.46 mmol, 100%) as a colorless oil: R_f 0.20 (1:1 hexane/EtOAc); $[\alpha]_D^{27} = -51.3$ (*c* 1.01, $CHCl_3$); IR (KBr) 3435 (s), 2978 (m), 2933 (m), 2891 (m), 1716 (s), 1367 (m), 1308 (m), 1254 (m), 1155 (s), 1039 (m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.73 (dd, $J=15.8$, 6.3 Hz, 1H), 5.96 (dd, $J=15.8$, 1.3 Hz, 1H), 4.75 (dd, $J=15.5$, 6.9 Hz, 2H), 4.21 (m, 1H), 3.93 (m, 1H), 3.86 (m, 1H), 3.67 (m, 1H), 3.55 (m, 2H), 3.39 (s, 3H), 1.48 (s, 9H), 1.14 (d, $J=6.3$ Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 17.5, 28.1, 59.0, 67.5, 69.0, 71.6, 80.7, 80.8, 94.4, 125.8, 142.3, 165.2; HRMS (FAB, NaI matrix) *m/z* 313.1623 $[(M+Na)^+$; calcd for $C_{14}H_{26}O_6Na$: 313.1627]. Anal. Calcd for $C_{14}H_{26}O_6$: C, 57.91; H, 9.03. Found: C, 57.59; H, 8.93.

4.1.19. (4*S*,5*R*)-(*E*)-5-hydroxy-4-methoxyethoxymethoxy-2-hexenoic acid *t*-butyl ester (+)-24. Following the procedure described above for the preparation of (−)-**24**, desilylation of 437 mg (1.1 mmol) of (+)-**22** afforded 306 mg of (+)-**24** (98%): $[\alpha]_D^{31} = +63.9$ (*c* 0.51, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 313.1630 $[(M+Na)^+$; calcd for $C_{14}H_{26}O_6Na$: 313.1627]. Anal. Calcd for $C_{14}H_{26}O_6$: C, 57.91; H, 9.03. Found: C, 57.65; H, 9.06.

4.1.20. (4*S*,5*S*,10*R*,11*S*)-(2*E*,8*E*)-11-(*tert*-Butyldimethylsiloxy)-4,10-bis(2-methoxy-ethoxymethoxy)-5-methyl-6-oxa-1,7-dioxo-2,8-dodecadienoic acid *tert*-butyl ester (−)-25. At room temperature, to a solution of 300 mg (0.86 mmol) of (−)-**23**, 277 mg (0.78 mmol) of (−)-**24**, 23 mg (0.19 mmol) of 4-dimethylaminopyridine and 22 mg (0.093 mmol) of camphorsulfonic acid in 10.0 mL of CH_2Cl_2 was added 243 mg (1.18 mmol) of dicyclohexylcarbodiimide, the solution was stirred for 18 h 30 min, and then quenched with 10.0 mL of H_2O. This mixture was extracted with 3×10 mL of $CHCl_3$, washed with 10.0 mL of H_2O, dried over Na_2SO_4, filtered, and concentrated. Chromatography (17–25% EtOAc/hexane) provided 447 mg of (−)-**25** (0.71 mmol, 92%) as a colorless oil: R_f 0.44 (1:1 hexane/EtOAc); $[\alpha]_D^{23} = -40.4$ (*c* 0.50, $CHCl_3$); IR (KBr) 3435 (s), 2954 (w), 2931 (w), 2889 (w), 1718 (m), 1637 (w), 1255 (w), 1157 (m), 1038 (m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.82 (dd, $J=15.8$, 6.6 Hz, 1H), 6.71 (dd, $J=15.8$, 6.3 Hz, 1H), 5.98 (dd, $J=15.8$, 1.0 Hz, 1H), 5.97 (dd, $J=15.8$, 1.3 Hz, 1H), 5.09 (m, 1H), 4.72 (dd, $J=11.2$, 6.9 Hz, 2H), 4.71 (dd, $J=11.2$, 6.9 Hz, 2H), 4.34 (m, 1H), 4.05 (m, 1H), 3.74 (m, 1H), 3.65 (m, 2H), 3.60 (m, 2H), 3.52 (m, 4H), 3.37 (s, 3H), 3.36 (s, 3H), 1.47 (s, 9H), 1.22 (d, $J=6.3$ Hz, 3H), 1.15 (d, $J=6.4$ Hz, 3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −4.8, −4.7, 15.0, 18.0, 19.8, 25.7, 28.0, 59.0, 59.0, 67.1, 67.1, 70.4, 70.5, 71.4, 71.6, 71.6, 79.8, 80.7, 93.7, 93.9, 123.3, 126.2, 141.7, 146.1, 165.0, 165.2; HRMS (FAB, NaI matrix) *m/z* 643.3488 $[(M+Na)^+$; calcd for $C_{30}H_{56}O_{11}SiNa$: 643.3490]. Anal. Calcd for $C_{30}H_{56}O_{11}Si$: C, 58.04; H, 9.09. Found: C, 57.99; H, 9.12.

4.1.21. (4*R*,5*R*,10*S*,11*R*)-(2*E*,8*E*)-11-(*tert*-Butyldimethylsiloxy)-4,10-bis(2-methoxy-ethoxymethoxy)-5-methyl-6-oxa-1,7-dioxo-2,8-dodecadienoic acid *tert*-butyl ester (+)-25. Following the procedure described above for the preparation of (−)-**25**, condensation of 169 mg (0.5 mmol)

of (+)-**23** and 169 mg (0.6 mmol) of (+)-**24** afforded 186 mg of (+)-**25** (62%): $[\alpha]_D^{28}=+48.5$ (*c* 0.85, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 643.3515 $[(M+Na)^+$; calcd for $C_{30}H_{56}O_{11}SiNa$: 643.3490]. Anal. Calcd for $C_{30}H_{56}O_{11}Si$: C, 58.04; H, 9.09. Found: C, 57.94; H, 8.96.

4.1.22. (4*S*,5*S*,10*R*,11*S*)-(2*E*,8*E*)-11-Hydroxy-4,10-bis(2-methoxyethoxymethoxy)-5-methyl-6-oxa-1,7-dioxo-2,8-dodecadienoic acid *tert*-butyl ester (−)-26. 392 mg (0.63 mmol) of (−)-**25** was dissolved in 6.3 mL of TFA·THF·H_2O (2:8:1) and the solution was stirred for 22 h at ambient temperature, and then quenched with 15.0 mL of saturated $NaHCO_3$ aqueous solution. This solution was then extracted with 3×40 mL of $CHCl_3$, washed with 50 mL of saturated NaCl aqueous solution, dried over Na_2SO_4, filtered, and concentrated. Chromatography (6% MeOH/$CHCl_3$) provided 105 mg of (−)-**26** (0.21 mmol, 83%) as a colorless oil: R_f 0.54 (15:1 $CHCl_3$/MeOH); $[\alpha]_D^{27}=-58.5$ (*c* 0.66, $CHCl_3$); IR (KBr) 3440 (s), 2980 (w), 2933 (w), 2893 (w), 1716 (s), 1659 (w), 1369 (m), 1296 (m), 1255 (m), 1157 (s), 1039 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.86 (dd, *J*=15.8, 5.9 Hz, 1H), 6.71 (dd, *J*=15.8, 6.3 Hz, 1H), 6.04 (dd, *J*=15.8, 1.3 Hz, 1H), 5.97 (dd, *J*=15.8, 1.3 Hz, 1H), 5.09 (m, 1H), 4.75 (dd, *J*=20.1, 7.3 Hz, 2H), 4.72 (s, 2H), 4.36 (m, 1H), 4.22 (m, 1H), 3.93 (m, 1H), 3.82 (m, 2H), 3.65 (m, 2H), 3.53 (m, 4H), 3.38 (s, 3H), 3.37 (s, 3H), 2.93 (d, *J*=5.9 Hz, 1H), 1.48 (s, 9H), 1.24 (d, *J*=6.6 Hz, 3H), 1.14 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 15.0, 17.7, 28.1, 59.0, 59.0, 67.2, 67.2, 67.5, 67.5, 69.0, 71.6, 71.6, 80.8, 80.9, 93.7, 94.5, 123.6, 126.2, 141.7, 144.3, 165.0, 165.0; HRMS (FAB, NaI matrix) *m/z* 529.2632 $[(M+Na)^+$; calcd for $C_{24}H_{42}O_{11}Na$: 529.2625]. Anal. Calcd for $C_{24}H_{42}O_{11}$: C, 56.90; H, 8.36. Found: C, 56.53; H, 8.39.

4.1.23. (4*R*,5*R*,10*S*,11*R*)-(2*E*,8*E*)-11-Hydroxy-4,10-bis(2-methoxyethoxymethoxy)-5-methyl-6-oxa-1,7-dioxo-2,8-dodecadienoic acid *tert*-butyl ester (+)-26. Following the procedure described above for the preparation of (−)-**26**, desilylation of 178 mg (0.3 mmol) of (+)-**25** afforded 142 mg of (+)-**26** (97%): $[\alpha]_D^{28}=+76.8$ (*c* 0.87, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 529.2616 $[(M+Na)^+$; calcd for $C_{24}H_{42}O_{11}Na$: 529.2625]. Anal. Calcd for $C_{24}H_{42}O_{11}$: C, 56.90; H, 8.36. Found: C, 56.76; H, 8.44.

4.1.24. (4*R*,5*S*,10*R*,11*S*,15*S*)-(2*E*,8*E*)-15-(*tert*-Butyldimethylsiloxy)-4,10-bis(2-methoxyethoxy-methoxy)-5,11-dimethyl-6,12-dioxa-1,7,13-trioxo-2,8-hexadeca-dienoic acid *tert*-butyl ester (−)-28. At room temperature, to a solution of 89.7 mg (0.177 mmol) of (−)-**26**, 50.2 mg (0.230 mmol) of (*S*)-3-*tert*-butyldimethylsiloxybutylic acid (+)-**27**, 5.2 mg (0.043 mmol) of 4-dimethylaminopyridine and 4.9 mg (0.021 mmol) of camphorsulfonic acid in 2.0 mL of CH_2Cl_2 was added 54.9 mg (0.266 mmol) of dicyclohexylcarbodiimide, the solution was stirred for 14 h, and then quenched with 1.5 mL of H_2O. This mixture was extracted with 3×10 mL of $CHCl_3$, washed with 8 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated. Chromatography (50% EtOAc–hexane) provided 119.6 mg of (−)-**28** (0.169 mmol, 96%) as a colorless oil: R_f 0.47 (1:1 hexane/EtOAc); $[\alpha]_D^{28}=-28.3$ (*c* 0.48, $CHCl_3$); IR (KBr) 3435 (s), 2931 (w), 2895 (w), 1718 (s), 1654 (w), 1369 (w), 1304 (m), 1255 (m), 1155 (s), 1088 (m), 1065 (m), 1039 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.82 (dd, *J*=15.8, 6.3 Hz, 1H), 6.71 (dd, *J*=15.8, 6.6 Hz, 1H), 6.05 (dd, *J*=15.8, 1.3 Hz, 1H), 5.99 (dd, *J*=15.8, 1.3 Hz, 1H), 5.10 (m, 1H), 5.04 (m, 1H), 4.74 (s, 2H), 4.72 (dd, *J*=17.5, 6.9 Hz, 2H), 4.36 (m, 2H), 4.24 (m, 1H), 3.77 (m, 2H), 3.63 (m, 2H), 3.53 (m, 4H), 3.37 (s, 6H), 2.48 (dd, *J*=14.5, 6.6 Hz, 1H), 2.36 (dd, *J*=14.5, 6.3 Hz, 1H), 1.48 (s, 9H), 1.24 (d, *J*=6.6 Hz, 3H), 1.20 (d, *J*=6.6 Hz, 3H), 1.18 (d, *J*=5.9 Hz, 3H), 0.85 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −4.9, −4.5, 14.9, 15.0, 18.0, 23.7, 25.8, 28.1, 44.9, 59.0, 59.0, 65.6, 65.6, 67.2, 67.2, 71.1, 71.6, 71.6, 71.7, 80.8, 80.8, 93.7, 93.8, 124.0, 126.3, 141.7, 143.8, 165.0, 165.0, 170.7; HRMS (FAB, NaI matrix) *m/z* 729.3853 $[(M+Na)^+$; calcd for $C_{34}H_{62}O_{13}SiNa$: 729.3857]. Anal. Calcd for $C_{34}H_{62}O_{13}Si$: C, 57.77; H, 8.84. Found: C, 57.62; H, 8.80.

4.1.25. (4*S*,5*R*,10*S*,11*R*,15*R*)-(2*E*,8*E*)-15-(*tert*-Butyldimethylsiloxy)-4,10-bis(2-methoxyethoxy-methoxy)-5,11-dimethyl-6,12-dioxa-1,7,13-trioxo-2,8-hexadeca-dienoic acid *tert*-butyl ester (+)-28. Following the procedure described above for the preparation of (−)-**28**, condensation of 57.3 mg (0.1 mmol) of (+)-**26** and 29.6 mg (0.1 mmol) of (−)-**27** afforded 61.7 mg of (+)-**28** (77%): $[\alpha]_D^{28}=+42.9$ (*c* 0.55, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 729.3856 $[(M+Na)^+$; calcd for $C_{34}H_{62}O_{13}SiNa$: 729.3857]. Anal. Calcd for $C_{34}H_{62}O_{13}Si$: C, 57.77; H, 8.84. Found: C, 57.58; H, 8.97.

4.1.26. (4*R*,5*S*,10*R*,11*S*,15*S*)-(2*E*,8*E*)-15-Hydroxy-4,10-bis(2-methoxyethoxymethoxy)-5,11-dimethyl-6,12-dioxa-1,7,13-trioxo-2,8-hexadecadienoic acid (−)-29. At 0 °C, to a solution of 12.7 mg (0.018 mmol) of (−)-**28** in 0.82 mL of thioanisole and 0.16 mL of CH_2Cl_2 was added 0.82 mL of trifluoroacetic acid with stirring. After stirring for 35 min, the reaction mixture was warmed to room temperature, and the solvent was removed in vacuo. Chromatography (9% MeOH/$CHCl_3$) provided 6.2 mg of (−)-**29** (0.012 mmol, 64%) as a colorless oil: R_f 0.18 (10:1 $CHCl_3$/MeOH); $[\alpha]_D^{24}=-49.8$ (*c* 0.35, $CHCl_3$); IR (KBr) 3437 (s), 1718 (s), 1655 (w), 1304 (m), 1180 (m), 1065 (m), 1039 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.92 (dd, *J*=15.8, 6.3 Hz, 1H), 6.82 (dd, *J*=15.8, 6.3 Hz, 1H), 6.09 (dd, *J*=15.8, 1.3 Hz, 1H), 6.05 (dd, *J*=15.8, 1.3 Hz, 1H), 5.11 (m, 2H), 4.75 (dd, *J*=15.5, 6.9 Hz, 2H), 4.73 (dd, *J*=15.5, 6.9 Hz, 2H), 4.38 (m, 1H), 4.32 (m, 1H), 4.20 (m, 1H), 3.79 (m, 2H), 3.66 (m, 2H), 3.53 (m, 4H), 3.39 (s, 3H), 3.38 (s, 3H), 2.46 (d, *J*=5.6 Hz, 2H), 1.28 (d, *J*=6.3 Hz, 3H), 1.24 (d, *J*=6.3 Hz, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 15.2, 15.3, 22.5, 43.2, 59.0, 59.0, 64.4, 64.4, 67.3, 67.3, 71.4, 71.4, 71.5, 71.5, 71.5, 93.7, 93.9, 123.7, 124.2, 143.6, 145.3, 164.8, 169.7, 172.0; HRMS (FAB, NaI matrix) *m/z* 559.2346 $[(M+Na)^+$; calcd for $C_{24}H_{40}O_{13}Na$: 559.2367]. Anal. Calcd for $C_{24}H_{40}O_{13}$: C, 53.72; H, 7.51. Found: C, 53.80; H, 7.86.

4.1.27. (4*S*,5*R*,10*S*,11*R*,15*R*)-(2*E*,8*E*)-15-Hydroxy-4,10-bis(2-methoxyethoxymethoxy)-5,11-dimethyl-6,12-dioxa-1,7,13-trioxo-2,8-hexadecadienoic acid (+)-29. Following the procedure described above for the preparation of (−)-**29**, deprotection of 31.3 mg (0.04 mmol) of (+)-**28** afforded 8.9 mg of (+)-**29** (38%): $[\alpha]_D^{29}=+57.8$ (*c*

0.18, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 559.2333 [$(M+Na)^+$; calcd for $C_{24}H_{40}O_{13}Na$: 559.2367].

4.1.28. (5*R*,6*S*,11*R*,12*S*,16*S*)-(3*E*,9*E*)-5,11-Bis(2-methoxyethoxymethoxy)-6,12,16-trimethyl-1,7,13-trioxacyclohexadeca-3,9-diene-2,8,14-trione (−)-32. To a solution of 25.4 mg (0.047 mmol) of (−)-**29** was added 570 μl (0.284 mmol) of 0.5 M triethylamine in toluene and 470 μl (0.237 mmol) of 0.5 M 2,4,6-trichlorobenzoyl chloride in toluene at room temperature, and the solution was stirred for 1 h. This solution was diluted with 12.3 mL of toluene and added to a solution of 145 mg (1.18 mmol) of 4-dimethylaminopyridine in 4.7 mL of toluene at 80 °C over 2 h. The anhydride flask was washed with 6.2 mL of toluene and the washing added to the mixture over 30 mim. The reaction was then heated at 80 °C for a total of 3.5 h. After cooling, the white suspension was diluted with 16 mL of saturated $NaHCO_3$ aqueous solution became clear. The two layers were separated and aqueous layer was extracted with 3×25 mL of EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Chromatography (9% MeOH/$CHCl_3$) provided 22.3 mg of (−)-**32** (0.043 mmol, 91%) as a colorless oil: R_f 0.61 (10:1 $CHCl_3$/MeOH); $[\alpha]_D^{27}=-86.5$ (*c* 0.68, $CHCl_3$); IR (KBr) 1724 (s), 1252 (m), 1188 (s), 1138 (m), 1109 (m), 1055 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.71 (dd, $J=15.8$, 7.3 Hz, 1H), 6.69 (dd, $J=15.8$, 6.9 Hz, 1H), 5.96 (dd, $J=15.8$, 1.0 Hz, 1H), 5.89 (dd, $J=15.8$, 1.0 Hz, 1H), 5.29 (m, 1H), 5.02 (m, 1H), 4.92 (m, 1H), 4.70 (dd, $J=8.6$, 4.6 Hz, 2H), 4.67 (s, 2H), 4.08 (m, 2H), 3.76 (m, 2H), 3.62 (m, 2H), 3.53 (m, 4H), 3.37 (s, 6H), 2.58 (dd, $J=14.8$, 3.0 Hz, 1H), 2.47 (dd, $J=14.8$, 8.3 Hz, 1H), 1.39 (d, $J=6.3$ Hz, 3H), 1.30 (d, $J=6.3$ Hz, 3H), 1.28 (d, $J=6.3$ Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 18.1, 18.3, 20.0, 41.3, 59.5, 59.5, 67.7, 67.7, 67.9, 71.0, 72.0, 72.0, 72.1, 79.1, 79.1, 93.7, 94.3, 124.9, 125.0, 144.4, 145.5, 164.7, 164.8, 170.0; HRMS (FAB, NaI matrix) *m/z* 541.2272 [$(M+Na)^+$; calcd for $C_{24}H_{38}O_{12}Na$: 541.2261]. Anal. Calcd for $C_{24}H_{38}O_{12}$: C, 55.59; H, 7.39. Found: C, 55.83; H, 7.49.

4.1.29. (5*S*,6*R*,11*S*,12*R*,16*R*)-(3*E*,9*E*)-5,11-Bis(2-methoxyethoxymethoxy)-6,12,16-trimethyl-1,7,13-trioxacyclohexadeca-3,9-diene-2,8,14-trione (+)-32. Following the procedure described above for the preparation of (−)-**32**, lactonization of 11.6 mg (0.02 mmol) of (+)-**29** afforded 9.8 mg of (+)-**32** (86%): $[\alpha]_D^{29}=+94.5$ (*c* 0.22, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 541.2247 [$(M+Na)^+$; calcd for $C_{24}H_{38}O_{12}Na$: 541.2261].

4.1.30. (+)-Macrosphelide A (+)-1. To a solution of 2.7 mg (5.2 mmol) of (−)-**32** in 0.29 mL of CH_2Cl_2 was added 0.29 mL of trifluoroacetic acid. After stirring for 7.5 h at ambiemt temperature, the reaction mixture was concentrated in vacuo, and chromatographed (10% MeOH/$CHCl_3$) to provide 1.6 mg (4.7 mmol, 90%) of (+)-**1** as colorless solid: R_f 0.43 (10:1 $CHCl_3$/MeOH); mp 146–147 °C (MeOH) (lit. 141–142 °C); $[\alpha]_D^{27}=+82.0$ (*c* 0.10, MeOH) [lit. +84.1 (*c* 0.59, MeOH)]; IR (KBr) 3437 (s), 1713 (s), 1284 (m), 1190 (m), 1051 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.87 (dd, $J=15.8$, 5.8 Hz, 1H), 6.86 (dd, $J=15.8$, 5.8 Hz, 1H), 6.05 (dd, $J=15.8$, 1.7 Hz, 1H), 6.03 (dd, $J=15.8$, 1.7 Hz, 1H), 5.38 (m, 1H), 4.95 (m, 1H), 4.86 (m, 1H), 4.22 (m, 1H), 4.14 (m, 1H), 2.62 (dd, $J=15.5$, 8.5 Hz, 1H), 2.56 (dd, $J=15.5$, 3.5 Hz, 1H), 1.45 (d, $J=6.6$ Hz, 3H), 1.37 (d, $J=6.6$ Hz, 3H), 1.33 (d, $J=6.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 18.0, 19.7, 41.0, 67.7, 73.2, 74.1, 74.8, 75.0, 122.3, 122.8, 145.0, 146.0, 164.5, 165.7, 170.1; HRMS (FAB, NaI matrix) *m/z* 365.1219 [$(M+Na)^+$; calcd for $C_{16}H_{22}O_8Na$: 365.1212].

4.1.31. (−)-Macrosphelide A (−)-1. Following the procedure described above for the preparation of (+)-**1**, deprotection of 4.3 mg (0.008 mmol) of (+)-**32** afforded 2.5 mg of (−)-**1** (88%): $[\alpha]_D^{25}=-80.0$ (*c* 0.07, MeOH); HRMS (FAB, NaI matrix) *m/z* 365.1219 [$(M+Na)^+$; calcd for $C_{16}H_{22}O_8Na$: 365.1212].

4.1.32. (4*R*,5*S*,10*R*,11*S*,15*R*)-(2*E*,8*E*)-15-(*tert*-Butyldimethylsiloxy)-4,10-bis(2-methoxyethoxy-methoxy)-5,11-dimethyl-6,12-dioxa-1,7,13-trioxo-2,8-hexadeca-dienoic acid *tert*-butyl eter (−)-33. To a solution of 123 mg (0.24 mmol) of (−)-**26**, 63 mg (0.29 mmol) of (−)-**27**, 7 mg (0.06 mmol) of 4-dimethylaminopyridine and 7 mg (0.03 mmol) of camphorsulfonic acid in 2.0 mL of CH_2Cl_2 was added 75 mg (0.36 mmol) of dicyclohexylcarbodiimide at room temperature. The reaction mixture was stirred for 22 h, and then quenched with 2.0 mL of H_2O. The mixture was extracted with 3×20 mL of $CHCl_3$, the combined organic layers were washed with 15 mL of saturated NaCl solution, dried over Na_2SO_4, filtered, and concentrated. Chromatography (50% EtOAc/hexane) provided 171 mg of (−)-**33** (0.24 mmol, 100%) as a colorless oil: R_f 0.47 (1:1 hexane/EtOAc); $[\alpha]_D^{28}=-54.0$ (*c* 0.49, $CHCl_3$); IR (KBr) 3431 (s), 2931 (w), 2895 (w), 1720 (s), 1659 (w), 1369 (w), 1298 (m), 1255 (m), 1153 (s), 1038 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.78 (dd, $J=15.8$, 6.3 Hz, 1H), 6.68 (dd, $J=15.8$, 6.3 Hz, 1H), 6.02 (dd, $J=15.8$, 1.3 Hz, 1H), 5.95 (dd, $J=15.8$, 1.3 Hz, 1H), 5.06 (m, 1H), 5.00 (m, 1H), 4.71 (s, 2H), 4.69 (dd, $J=17.8$, 6.9 Hz, 2H), 4.31 (m, 2H), 4.22 (m, 1H), 3.74 (m, 2H), 3.61 (m, 2H), 3.49 (m, 4H), 3.34 (s, 6H), 2.45 (dd, $J=14.9$, 7.3 Hz, 1H), 2.31 (dd, $J=14.9$, 5.6 Hz, 1H), 1.45 (s, 9H), 1.21 (d, $J=6.6$ Hz, 3H), 1.17 (d, $J=6.6$ Hz, 3H), 1.09 (d, $J=6.6$ Hz, 3H), 0.82 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ −4.9, −4.6, 14.9(2C), 17.8, 23.7, 25.7(3C), 28.0(3C), 44.7, 58.9(2C), 65.6, 67.2(2C), 71.1, 71.6(2C), 71.8, 76.5, 80.7(2C), 93.6, 93.7, 124.0, 126.2, 141.6, 143.8, 164.9(2C), 170.8; HRMS (FAB, NaI matrix) *m/z* 729.3855 [$(M+Na)^+$; calcd for $C_{34}H_{62}O_{13}SiNa$: 729.3857].

4.1.33. (4*S*,5*R*,10*S*,11*R*,15*S*)-(2*E*,8*E*)-15-(*tert*-Butyldimethylsiloxy)-4,10-bis(2-methoxyethoxy-methoxy)-5,11-dimethyl-6,12-dioxa-1,7,13-trioxo-2,8-hexadeca-dienoic acid *tert*-butyl ester (+)-33. Following the procedure described above for the preparation of (−)-**33**, condensation of 53.8 mg (0.1 mmol) of (+)-**26** and 30.1 mg (0.1 mmol) of (+)-**27** afforded 81.6 mg of (+)-**33** (100%): $[\alpha]_D^{27}=+70.2$ (*c* 0.45, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 729.3881 [$(M+Na)^+$; calcd for $C_{34}H_{62}O_{13}SiNa$: 729.3857].

4.1.34. (4*R*,5*S*,10*R*,11*S*,15*R*)-(2*E*,8*E*)-15-Hydroxy-4,10-bis(2-methoxyethoxymethoxy)-5,11-dimethyl-6,12-dioxa-1,7,13-trioxo-2,8-hexadecadienoic acid (−)-34. To a solution of 29 mg (0.042 mmol) of (−)-**33** in 2.0 mL of thioanisole and 0.4 mL of CH_2Cl_2 was added 2.0 mL of

trifluoroacetic acid dropwise at 0 °C. After stirring for 30 min, the reaction was concentrated in vacuo. Chromatography (9% MeOH/$CHCl_3$) provided 12 mg of (−)-**34** (0.021 mmol, 51%) as a colorless oil: R_f 0.18 (10:1 $CHCl_3$/MeOH); $[\alpha]_D^{28} = -68.8$ (*c* 0.25, $CHCl_3$); IR (KBr) 3437 (s), 1720 (s), 1660 (w), 1300 (m), 1180 (m), 1039 (s) cm^{-1}; $_1H$ NMR (270 MHz, $CDCl_3$) δ 6.92 (dd, $J=15.8$, 6.3 Hz, 1H), 6.82 (dd, $J=15.8$, 6.3 Hz, 1H), 6.07 (dd, $J=15.8$, 1.3 Hz, 1H), 6.05 (dd, $J=15.8$, 1.3 Hz, 1H), 5.12 (m, 2H), 4.76 (dd, $J=15.5$, 6.8 Hz, 2H), 4.72 (dd, $J=15.5$, 6.8 Hz, 2H), 4.38 (m, 1H), 4.34 (m, 1H), 4.21 (m, 1H), 3.78 (m, 2H), 3.65 (m, 2H), 3.53 (m, 4H), 3.38 (s, 6H), 2.51 (dd, $J=15.8$, 8.6 Hz, 1H), 2.43 (dd, $J=15.8$, 4.0 Hz, 1H), 1.27 (d, $J=6.6$ Hz, 3H), 1.22 (d, $J=6.6$ Hz, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 15.3, 15.4, 22.4, 43.3, 59.0(2C), 64.3(2C), 67.3(2C), 71.6(3C), 76.5(2C), 93.8, 93.9, 124.3(2C), 143.5, 145.4, 164.9(2C), 171.8; HRMS (FAB, NaI matrix) *m/z* 559.2352 $[(M+Na)^+$; calcd for $C_{24}H_{40}O_{13}Na$: 559.2367].

4.1.35. (4*S*,5*R*,10*S*,11*R*,15*S*)-(2*E*,8*E*)-15-Hydroxy-4,10-bis(2-methoxyethoxymethoxy)-5,11-dimethyl-6,12-dioxa-1,7,13-trioxo-2,8-hexadecadienoic acid (+)-34. Following the procedure described above for the preparation of (−)-**34**, deprotection of 29.6 mg (0.04 mmol) of (+)-**33** afforded 9.2 mg of (+)-**34** (41%): $[\alpha]_D^{25} = +70.0$ (*c* 0.12, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 559.2363 $[(M+Na)^+$; calcd for $C_{24}H_{40}O_{13}Na$: 559.2367].

4.1.36. (5*R*,6*S*,11*R*,12*S*,16*R*)-(3*E*,9*E*)-5,11-Bis(2-methoxyethoxymethoxy)-6,12,16-trimethyl-1,7,13-trioxacyclohexadeca-3,9-diene-2,8,14-trione (−)-35. To a solution of 32.0 mg (0.060 mmol) of (−)-**34** was added 720 µl (0.36 mmol) of 0.5 M triethylamine in toluene and 600 µl (0.30 mmol) of 0.5 M 2,4,6-trichlorobenzoyl chloride in toluene at room temperature, and stirred for 1 h. The solution was then diluted with 15.0 mL of toluene and added to a solution of 180 mg (1.48 mmol) of 4-dimethylaminopyridine in 5.9 mL of toluene at 80 °C over 2 h. The anhydride flask was washed with 8.0 mL of toluene and the washing added to the mixture over 30 mim. The reaction was then heated at 80 °C for a total of 3.5 h. After cooling, the white suspension was diluted with 20 mL of saturated $NaHCO_3$ aqueous solution became clear. The two layers were separated and aqueous layer was extracted with 3× 25 mL of EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Chromatography (9% MeOH/$CHCl_3$) provided 20.0 mg of (−)-**35** (0.039 mmol, 66%) as a colorless oil: R_f 0.61 (10:1 $CHCl_3$/MeOH); $[\alpha]_D^{28} = -30.0$ (*c* 0.52, $CHCl_3$); IR (KBr) 1722 (s), 1191 (m), 1134 (m), 1111 (m), 1035 (m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.81 (dd, $J=15.8$, 5.9 Hz, 1H), 6.78 (dd, $J=15.8$, 6.9 Hz, 1H), 6.12 (dd, $J=15.8$, 1.0 Hz, 1H), 5.94 (dd, $J=15.8$, 1.0 Hz, 1H), 5.22 (m, 1H), 5.10 (m, 2H), 4.72 (dd, $J=15.5$, 6.9 Hz, 2H), 4.72 (s, 2H), 4.31 (m, 1H), 4.12 (m, 1H), 3.75 (m, 2H), 3.62 (m, 2H), 3.53 (m, 4H), 3.37 (s, 6H), 2.75 (dd, $J=14.9$, 3.0 Hz, 1H), 2.53 (dd, $J=14.9$, 6.6 Hz, 1H), 1.39 (d, $J=6.6$ Hz, 3H), 1.35 (d, $J=6.6$ Hz, 3H), 1.18 (d, $J=6.6$ Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 17.1, 17.5, 19.2, 40.6, 59.0(2C), 67.2, 67.3(2C), 71.2, 71.8(2C), 72.0, 77.2, 77.5, 93.4(2C), 124.6, 124.8, 142.9, 143.1, 164.4, 165.0, 169.4; HRMS (FAB, NaI matrix) *m/z* 541.2258 $[(M+Na)^+$; calcd for $C_{24}H_{38}O_{12}Na$: 541.2261].

4.1.37. (5*S*,6*R*,11*S*,12*R*,16*S*)-(3*E*,9*E*)-5,11-Bis(2-methoxyethoxymethoxy)-6,12,16-trimethyl-1,7,13-trioxacyclohexadeca-3,9-diene-2,8,14-trione (+)-35. Following the procedure described above for the preparation of (−)-**35**, lactonization of 11.8 mg (0.02 mmol) of (+)-**34** afforded 9.7 mg of (+)-**35** (85%): $[\alpha]_D^{25} = +37.3$ (*c* 0.22, $CHCl_3$); HRMS (FAB, NaI matrix) *m/z* 541.2261 $[(M+Na)^+$; calcd for $C_{24}H_{38}O_{12}Na$: 541.2261].

4.1.38. (+)-Macrosphelide E (+)-3. To a solution of 11 mg (0.02 mmol) of (−)-**35** in 0.15 mL of CH_2Cl_2 was added 0.45 mL of trifluoroacetic acid. After being stirred at ambiemt temperature for 2 h, the reaction mixture was concentrated in vacuo, and chromatographed (10% MeOH/$CHCl_3$) to provide 5.8 mg (0.017 mmol, 79%) of (+)-**3** as colorless solid: R_f 0.43 (10:1 $CHCl_3$/MeOH); $[\alpha]_D^{28} = +21.5$ (*c* 0.31, MeOH); IR (KBr) 3433 (s), 1716 (s), 1665 (w), 1645 (w), 1280 (m), 1192 (m), 1053 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (dd, $J=16.0$, 4.0 Hz, 1H), 6.80 (dd, $J=16.0$, 5.0 Hz, 1H), 6.13 (dd, $J=16.0$, 1.8 Hz, 1H), 6.06 (dd, $J=16.0$, 1.8 Hz, 1H), 5.32 (m, 1H), 5.12 (m, 1H), 4.97 (m, 1H), 4.37 (br s, 1H), 4.18 (br s, 1H), 2.73 (dd, $J=16.0$, 3.0 Hz, 1H), 2.60 (dd, $J=16.0$, 7.3 Hz, 1H), 1.42 (d, $J=6.7$ Hz, 3H), 1.39 (d, $J=6.7$ Hz, 3H), 1.31 (d, $J=6.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.3, 17.8, 19.6, 40.5, 66.6, 73.8, 75.2, 75.4, 76.0, 122.3, 123.0, 145.0, 145.3, 165.3, 166.7, 170.8; HRMS (FAB, NBA matrix) *m/z* 343.1381 $[(M+H)^+$; calcd for $C_{16}H_{23}O_8$: 343.1393].

4.1.39. (−)-Macrosphelide E (−)-3. Following the procedure described above for the preparation of (+)-**3**, deprotection of 5.9 mg (0.01 mmol) of (+)-**35** afforded 2.4 mg of (−)-**3** (64%): $[\alpha]_D^{28} = -25.0$ (*c* 0.20, MeOH); HRMS (FAB, NBA matrix) *m/z* 343.1394 $[(M+H)^+$; calcd for $C_{16}H_{23}O_8$: 343.1393].

Acknowledgements

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21. Compound (+)-**1**, $C_{16}H_{22}O_8$, crystallizes in the monoclinic space group $P2_1$ with $a=10.3502(4)$, $b=5.6291(3)$, and $c=16.0611(6)$ Å, $\beta=106.365(2)°$, $V=897.85(7)$ Å^3, $Z=2$, and $d_{calcd}=1.266$ g/cm^3. X-ray intensity data were collected on a SMART APEXII diffractometer employing Cu Kα radiation ($\lambda=1.54178$ Å) and the $\omega-2\theta$ scan technique. The structure was solved by direct methods. For refinement, 2747 unique reflections with $F^2>2\sigma(F^2)$ were used. Full-matrix least-squares refinement based on F, minimizing the quantity $\Sigma w(|F_o|-|F_c|)^2$ with $w=4F_o^2/\sigma^2(Fo^2)$, converged $R=0.055$ and $Rw=0.146$. Crystallographic data of (+)-**1** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 258197. Copies of the data can be obtained, free of charge, on application to CDCC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
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Trihydroxy-2-thiaquinolizidine derivatives as a new class of bicyclic glycosidase inhibitors

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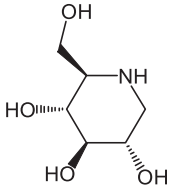
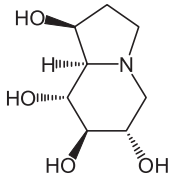
Abstract—Trihydroxy-2-thiaquinolizidines, a new class of bicyclic dideoxy-iminohexitol glycosidase inhibitor derivatives with nominally the D-*gluco*, L-*ido*, D-*manno* and L-*gulo* configurations were synthesized. X-ray analyses indicated that the preferred conformation for D-*gluco* and D-*manno* derivatives was a flat *trans*-fused system. Unlike deoxynojirimycin, the compound with D-*gluco* configuration was selective for α-glucosidases (yeast and rice) and showed no inhibitory activity towards β-glucosidase (almond), α-galactosidase (green coffee beans), α-galactosidase (*E. coli*) and α-mannosidase (jack bean), while the L-*ido* derivative was specific for β-glucosidase (almond).

1. Introduction

Despite their promise, glycosidase inhibitors such as deoxynojirimycin **1** and castanospermine **2**, (generally known as iminoalditols or aza-sugars) have not realized their full clinical potential. This is largely because of a lack of commercially viable syntheses and difficulty in preparing a comprehensive palette of variant structures. In some cases such as deoxynojirimycin there is also the problem of too low specificity.[1,2] Iminoalditols are typically plant alkaloids and many of the possible drug candidates are available in only small exploratory amounts. The potential medical applications for these compounds and their derivatives are numerous and range from diabetes[3–6] and other metabolic disorders through antimicrobials,[7–11] cancer,[12] autoimmune diseases,[13–18] neurological[19] and metabolic[20,21] disorders. Because of their rigidity and the added interaction of the second ring, bicyclic systems such as castanospermine **2** and swainsonine **3** are especially interesting.



1



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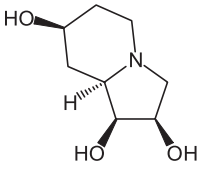

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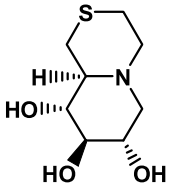
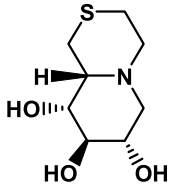
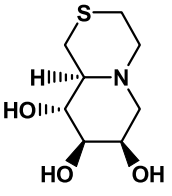


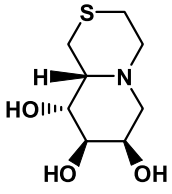
4a



4b



5a



5b

As part of our ongoing work on the development of strategies for the preparation of glycosidase inhibitors, we explored the possibility of synthesizing analogs of deoxynojirimycin **1** and related compounds in which O-6 were replaced by a sulfur atom. We also envisaged bridging the 6-position to the ring nitrogen with a 2-carbon fragment to form a trihydroxy-2-thiaquinolizidine ring system thus increasing rigidity and lipophilicity. Such systems have never been reported before but hold great promise because the formation of a carbon–carbon bond is circumvented as in **2** and **3**. The presence of sulfur (closely related to oxygen) at a position that is normally oxygenated is also a decided advantage. If such systems could be reached using a general strategy, analogs with differing configurations at the various

Keywords: Glycosidase inhibitors; Aza-sugars; Iminoalditols; Glucosidases; Mannosidases; Enzymology; Drugs.
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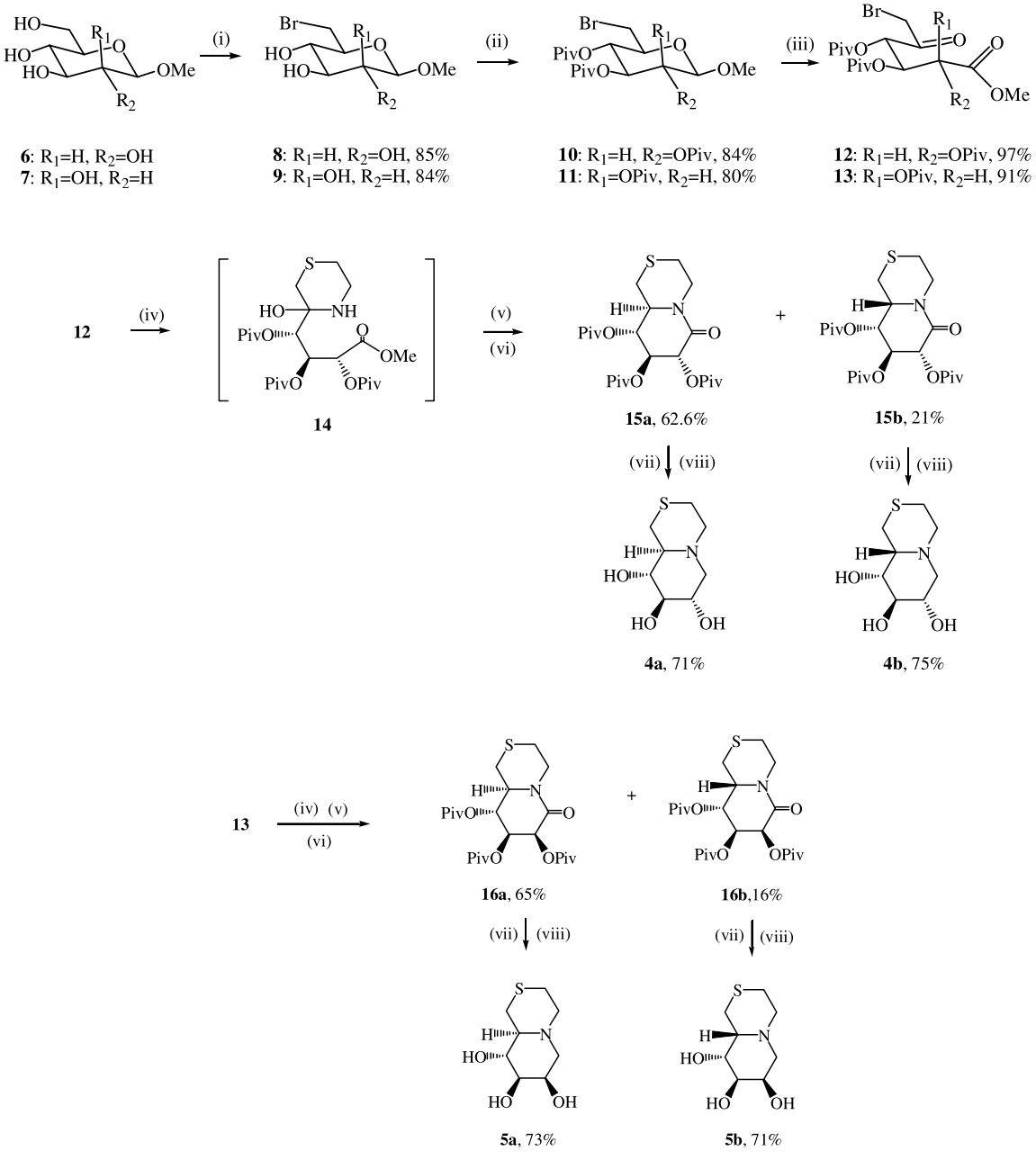
carbon centers and differing substitution patterns could be made, increasing the chance of obtaining compounds with useful therapeutic potential. The strategy could, in principle, be extended to iminopentitol analogs. A total of four such systems (**4a**, **4b**, **5a**, and **5b**) were prepared corresponding to the D-*gluco*, L-*ido*, D-*manno*, L-*gulo* configurations. The synthesis is illustrated below in Scheme 1.

The key feature of the reaction scheme is the oxidation of a 6-bromo β-glycoside to give a 6-bromo-5-ulosonic acid alkyl ester (Scheme 1). This oxidation has been reported to give the keto–ester functionality in high yield.[22] Reaction of this α-halo ketone with an α-aminothiol should lead to rapid thioether formation and immediate cyclization to an aminal which could quickly form an imine. Reduction of the aminal or imine by hydride (e.g., borane or cyanoborohydride) should yield an amine which could then be cyclized to form a lactam. Reduction of the lactam should yield the thiaquinolizidine system.

2. Results

The reaction sequence involved the preparation of a peracylated 6-bromo-6-deoxy-glycoside **10** which was obtained by selective conversion of the primary hydroxyl group of methyl β-D-glucoside to a bromo-group followed by treatment with pivaloyl chloride (trimethylacetyl chloride) in pyridine to protect the remaining hydroxyl groups. The pivaloyl group was selected over the acetyl



Scheme 1. Synthesis of trihydroxy-2-thiaquinolizidine derivatives. (i) Ph_3P, CBr_4, pyridine; (ii) PivCl, pyridine; (iii) CrO_3, Ac_2O, HOAc; (iv) $HS(CH_2)_2NH_2$, CH_3OH; (v) $NaCNBH_3$, CH_3OH; (vi) Na_2CO_3, $CHCl_3$; (vii) BH_3–THF; (viii) $NaOCH_3$, CH_3OH.

group because of the partial deacylation of acetates by aminoethanethiol, resulting in difficulty in purification and low yield. Oxidation of **10** with chromium trioxide in acetic acid afforded a 5-ulosonic acid ester **12**. The oxidation of acetylated β-glycopyranosides by chromium trioxide has been reported by Angyal and James[22] to afford 5-keto esters, independent of the configurations on C2, C3, or C4. The oxidation is specific to β-glycopyranosides, while α-glycopyranosides are not attacked. Treatment of **12** with 2-aminoethanethiol yielded the aminal **14** directly which underwent reduction by $NaBCNH_3$ and cyclization to the lactam **15a** and the L-*ido* isomer **15b**. There was some variability in the actual amount of lactam **15b** ranging from traces to 2.5:1 in favor of the D-*gluco* analog. Reduction of the lactams with borane and deacylation yielded the desired compounds **4a** and **4b**.The final and intermediate products were characterized by a very high degree of crystallinity.

The same reaction sequence was applied to methyl β-D-mannopyranoside (**7**), and the D-*manno* lactam **16a** and L-*gulo* lactam **16b** was obtained in 4:1 ratio in favor of the D-*manno* lactam. Reduction of lactams and deprotection yielded products **5a** and **5b** in good yields. X-ray analysis of **4a** and **5a** (Fig. 1) indicated two six-membered rings with relaxed chair conformation for both D-*gluco* and D-*manno* products. A *trans*-diequatorial type fusion between the rings gives the molecules an overall flat geometry. The expected intermediate oxocarbenium species is very flat because of the double bond character between the ring oxygen and C-1.

The inhibitory activity of four trihydroxy-2-thiaquinolizidines against a series of enzymes was tested. Enzymes were assayed according to standard procedures[23] by following the hydrolysis of nitrophenyl glycosides spectrophotometrically or by evaluating the reducing sugar formed in some glucosidase assays. The enzymes used were α-glucosidase (yeast and rice), β-glucosidase (almond), α-galactosidase (green coffee beans), β-galactosidase (*E. coli*) and α-mannosidase (jack beans).

Table 1 shows the inhibition constants (mM) for compounds **4a**, **4b**, **5a**, and **5b**. Compound **4a** displayed competitive inhibition against both yeast and rice α-glucosidase with K_i of 330 and 900 μM, respectively. No inhibitory activity towards β-glucosidase (almond), α-galactosidase (green coffee beans), β-galactosidase (*E. coli*) and α-mannosidase (jack bean) was observed. Compound **4b** was tested against α-glucosidase (yeast), β-glucosidase and α-mannosidase. It showed an opposite inhibition pattern to compound **4a**. It only inhibits β-glucosidase with K_i value 1 mM without inhibiting α-glucosidase and α-mannosidase. Compound **5a** and **5b** were also tested for α-mannosidase (jack beans), but no inhibition was observed.

3. Discussion

The synthetic strategy for the preparation of trihydroxy-2-thiaquinolizidines proved to be quite efficient and direct. The relative ease of preparation of these analogs and the generality of the method open the possibility for the preparation of a clinically relevant series of selective inhibitory compounds. The inhibition results indicated that compound **4a** was active only against α-glucosidases. No inhibition of β-glucosidases was observed. This is consistent with the observation that deoxynojirimycin type inhibitors with nitrogen atom at the ring oxygen position are more selective for α-glucosidase.[24–26] According to the stereoelectronic requirements, in α-glycosidases, the positively charged leaving group and the lone pair of the ring oxygen are positioned antiperiplanar and cooperatively facilitate the glycosidic bond cleavage. Thus, oxocarbenium ion can be formed directly, and this oxocarbenium ion with positive charge at ring oxygen is an important transition state for α-glucosidases. For β-glycosidases, the glycosidic bond cleavage cannot receive aid form the lone pair of the ring oxygen, so the ring could flip to a boat (**17**) or other conformations (**18**) to facilitate the bond cleavage. Substrate distortion is generally the case for β-glycosidases.[27–31]

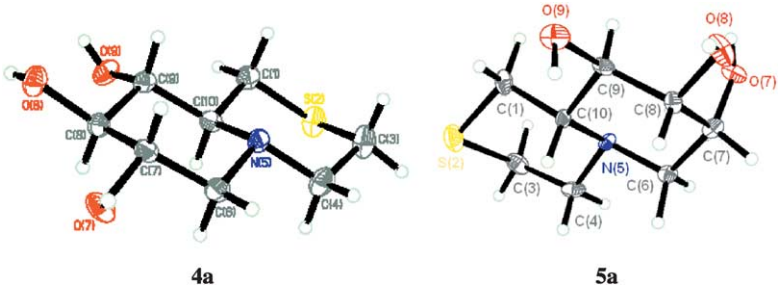


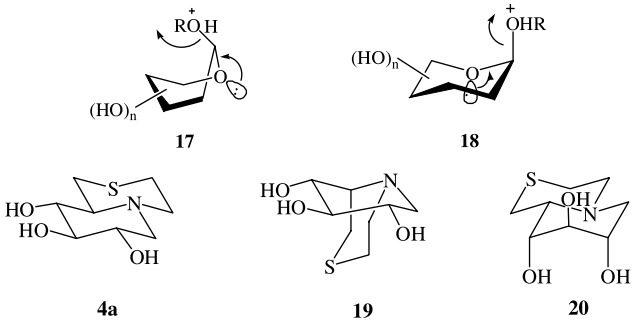
Figure 1. X-ray structures of 7(*S*),8(*R*),9(*R*),10(*S*)-trihydroxy-2-thiaquinolizidine **4a** and 7(*R*),8(*R*),9(*R*),10(*S*)-trihydroxy-2-thiaquinolizidine **5a** showing the *trans*-type ring junction and overall flat geometry.

Table 1. Inhibition constants (mM) for compounds **4a**, **4b**, **5a**, and **5b**

Enzymes	4a	4b	5a	5b
α-Glucosidase (yeast)	0.33	ni	—	—
α-Glucosidase (rice)	0.9	—	—	—
β-Glucosidase (almond)	ni	1.0	—	—
α-Galactosidase (green coffee beans)	ni	—	—	—
β-Galactosidase (*E. coli*)	ni	—	—	—
α-Mannosidase (jack beans)	ni	ni	ni	ni

ni, No inhibition observed in this concentration range; —, not determined.

Compound **4a**, with its rigid bicyclic structure, is locked in its *trans*-fused chair conformation, so it cannot flip or change to other conformations. Therefore, it showed no inhibition against β-glucosidase. In contrast, compound **4b** showed specific inhibition against β-glucosidase while no inhibition for α-glucosidase. This is almost certainly due to a difference in conformation to the D-*gluco* compound brought about by flattening or ring inversion to place the thiomethyl group in an equatorial position. Compound **4b** should be more stable in conformation **20** instead of conformation **19**. Conformation **20** corresponds to the one that matches the transition state for a β-glycoside undergoing hydrolysis under stereoelectronic control.



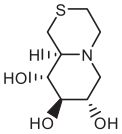
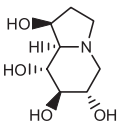
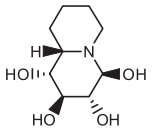
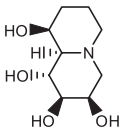
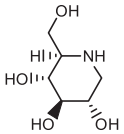
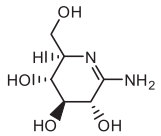
The activities and specificities of the known aza-bicyclic systems and key monocyclic systems are shown in Table 2. Compared to deoxynojirimycin **1**, compound **4a** is a relatively weak inhibitor, but it showed specificity for α-glucosidase. No inhibitory activity towards β-glucosidase (almond), α-galactosidase (green coffee beans), α-galactosidase (*E. coli*) and α-mannosidase (jack bean) was observed. One of the major problems with the use of iminosugars and their derivatives as inhibitors is the lack of specificity. Hence the last two entries in Table 2 have low K_i values but show poor specificity. Compound **4a** showed very specific activity against α-glucosidase, and **4b** showed specificity against β-glucosidase. The specificity comes from the structural rigidity, which prevents **4a** from distortion to boat or other conformations that are important for mimicking the β-glucosidase transition state. Compound **4b** is expected to exist in a conformation that favors β-glucosidase inhibition. Compound **5a** and **5b** showed no activity against α-mannosidase (jack beans). This is probably because of the rigid structure. It is also possible that the second 6-member ring might interfere with any change in ring geometry that might be necessary to facilitate binding of the inhibitor to the active site of the enzyme.

Castanospermine is one of the most active bicyclic systems. It showed poor activity against yeast α-glucosidase but strongly inhibited the rice enzyme. However, it showed non-selectivity by inhibiting almond β-glucosidase. It has relatively flexible structure compared to **4a** and **4b**, and it presented a twisted boat conformation of the 6-member ring when bounded to Exo-β-(1,3)-gluconase.[36] This distortion cannot be made for compound **4a** which has a *trans*-diequatorial type fusion between the rings. Compound **22**, which is the slightly ring-expanded version of the potent α-mannosidase inhibitor swainsonine (**3**) showed complete loss of inhibition of α-mannosidase (Table 2). As a general rule, decalin-type bicyclic systems show much reduced or no inhibitory activity compared to their acyclic or octahydroindene-type analogs. Therefore, one important conclusion that can be made is that structural flexibility leads to nonspecific inhibitory activity. Monocyclic systems generally showed poor specificity by inhibiting both α- and β-glycosidases because of their flexible structures. Castanospermine (**2**) and the thiaquinolizidine described here (**4a**) are the most impressive of the reported bicyclic aza-type iminosugar derivatives with a nitrogen atom at the ring junction. Compound **4a** was superior against and selective for α-glucosidases compared to castanospermine. Thiaquinolizidines, therefore represent a significant advancement in this area.

4. Conclusion

Trihydroxy-2-thiaquinolizidines are bicyclic systems where reasonable inhibitory activity and absolute specificity for one anomer were obtained. Although only modest inhibitory activity was observed, the specificity is extremely high. This is a very important point. For iminopentitol glycosidase inhibitors, the general rule is that high inhibitory activity always comes along with low specificity tremendously limiting their utility as drugs. Modest inhibitors combined

Table 2. Comparison of inhibition activity K_i, μM (IC_{50}, μM) for iminoalditol transition state analogs

Enzymes	 **4a**	 **2**[1]	 **21**[32]	 **22**[33]	 **1**[1]	 **23**[34,35]
α-Glucosidase (yeast)	330	>1500	—	IC_{50}>2000	12.6	~10
α-Glucosidase (rice)	900	0.015	—	—	0.01	—
β-Glucosidase (almond)	ni	1.5	ni	IC_{50}>2000	47	8
α-Galactosidase (green coffee beans)	ni	—	ni	—	—	~10
β-Galactosidase (*E. coli*)	ni	—	—	—	—	~10
α-Mannosidase (jack beans)	ni	—	—	IC_{50}>2000	—	9

—, Not determined; ni, no inhibition observed.

with efficient drug delivery strategies to keep local concentrations high enough would constitute an excellent therapeutic approach. This study also identifies a strategy for changing the specificity of an inhibitor by inverting the stereochemistry at a critical position to increase the stability of inverted ring structures. The thiaquinolizidines described here are relatively easily accessible. Their ease of preparation and specificity therefore represent significant potential for further therapeutic advancement.

5. Experimental

5.1. General procedures

Melting points were measured on a Ficher–Johns melting point apparatus. Optical rotations were measured ($\lambda=$ 589 nm) at room temperature using a Jasco P-1010 polarimeter. IR spectra were recorded on a FT-IR instrument. The ^{1}H (and ^{13}C) NMR spectra were recorded at 500 (125.5) MHz on a Varian VXR spectrometer. The HRFABMS mass spectra were obtained using a Jeol HX-110 double-focusing mass spectrometer operating in positive ion mode.

5.2. Inhibition assays

Inhibitory potency was determined by spectrophotometrically measuring the residual hydrolytic activities of the glycosidases against the corresponding nitrophenyl α- or β-D-glycopyranoside. The glycosidases used were α-glucosidase (yeast), α-glucosidase (rice), β-glucosidase (almond), α-galactosidase (green coffee beans), β-galactosidase (*E. coli*) and α-mannosidase (jack beans). All enzymes were purchased from Sigma. Each assay was performed in a phosphate or an acetate buffer at the optimal pH for each enzyme. Inhibition studies (except rice α-glucosidase) were performed by adding the inhibitor to a final concentration of 0.05–11 mM to the respective buffer solutions along with enzyme. The solutions were incubated at 37 °C before adding substrates to the reactions. The absorbance of the resulting mixture was determined at 400 nm (for *p*-nitrophenol).

For rice α-glucosidase inhibition, maltose was used as the substrate, and the assay was based on the glucose oxidase/peroxidase enzyme procedure. In this assay, the glucose released from maltose can be oxidized by glucose oxidase to generate D-gluconic acid and hydrogen peroxide. Under the catalysis of peroxidase, hydrogen peroxide reacts with dianisidine to give the oxidized form which forms a brown color. The absorbance of the solution was determined at 500 nm for oxidized *o*-dianisidine. The assay was performed in sodium acetate buffer at pH 4.0 at 37 °C. The inhibitor was added to a final concentration of 0.4 and 8.9 mM to the substrate solution. The enzyme was added to the solution at 37 °C, and the reaction was stopped after 10 and 30 min by adding dilute perchloric acid solution. The glucose oxidase/peroxidase solution was pipetted into the reaction mixture, and incubate at 37 °C for 30 min. The absorbance of the solution was determined at 500 nm.

5.3. Synthetic methods

5.3.1. Methyl 6-bromo-6-deoxy-β-D-glucopyranoside.[37] (8) To a stirred solution of methyl β-D-glucopyranoside **6** (10.15 g, 50 mmol) in anhydrous pyridine (300 mL) at 0 °C were added triphenylphosphine (26.2 g, 100 mmol) and carbon tetrabromide (24.87 g, 75 mmol). The resulting mixture was protected from moisture and stirred at 0 °C for 10 min. It was then allowed to warm to 65 °C and was stirred for an additional 4 h. Methanol (10 mL) was added to decompose any excess reagent. The solvent was removed by evaporation and the residue was purified by column chromatography (CH_2Cl_2, followed by 20:1 CH_2Cl_2/MeOH). Crystallization from methanol-hexanes afforded white crystalline solid (10.96 g, 85%), mp 149–150 °C, lit. mp[38] 154 °C, $[\alpha]_D^{20}$ −27.6° (*c* 0.22, H_2O).

5.3.2. Methyl 6-bromo-6-deoxy-2,3,4-tri-*O*-pivaloyl-β-D-glucopyranoside (10). Pivaloylation of **8** (6.73 g, 26 mmol) by trimethylacetyl chloride (28.8 mL, 32.4 mmol) in pyridine (300 mL) at room temperature for 2 days afforded an white solid **6** (11.2 g, 84%), mp 109–110 °C, $[\alpha]_D^{20}$ −2.4° (*c* 0.31, $CHCl_3$). IR (CH_3Cl) ν_{max} 2971.7, 1745.6, 1140.9 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.29 (1H, t, $J=9.5$ Hz), 4.99 (2H, t, $J=9.7$ Hz), 4.42 (1H, d, $J=$ 8.0 Hz), 3.70 (1H, m), 3.50 (3H, s), 3.39–3.12 (2H, m), 1.14 (9H, s), 1.13 (9H, s), 1.08 (9H, s); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 177.14, 176.63, 176.51, 101.36, 73.7, 71.9, 71.2, 70.8, 57.1, 38.8, 38.7, 30.6 ppm; HRFABMS ($M+H^+$) Calcd 509.1750, found 509.1736.

5.3.3. Methyl 6-bromo-2,3,4-tri-*O*-pivaloyl-5-keto-ester (12). To a solution of **10** (1 g, 1.96 mmol) in acetic acid (100 mL) and acetic anhydride (10 mL), chromium trioxide (1.18 g, 11.8 mmol) was added and the suspension was stirred at room temperature for 3 h. The mixture was then poured slowly into cold water (500 mL). The water was extracted 5 times with CH_2Cl_2 and the combined organic phase was washed with brine, saturated sodium bicarbonate and dried (Na_2SO_4), concentrated. The resulting residue was passed through a small pad of silica gel to give **12** as a colorless oil (1 g, 97%), $[\alpha]_D^{20}$ +36.5° (*c* 0.12 $CHCl_3$), IR (CH_2Cl_2) ν_{max} 2975.85, 1743.63, 1132.00 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72, (1H, t, $J=4.8$ Hz), 5.57 (1H, d, $J=4.5$ Hz), 5.23 (1H, d, $J=5.0$ Hz), 4.12 (1H, d, $J=$ 14.0 Hz), 4.01 (1H, d, $J=13.5$ Hz), 3.72 (3H, s), 1.25 (9H, s), 1.21 (9H, s), 1.18 (9H, s); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 194.5, 177.1, 176.9, 176.8, 167.1, 72.9, 70.2, 69.4, 52.7, 38.9, 38.8, 38.7, 31.6, 27.0, 26.9 ppm; HRFABMS ($M+H^+$) Calcd 523.1543, found 523.1530.

5.3.4. Lactam (15a) and (15b). A solution of **7** (7 g, 13.4 mmol) and 2-aminoethanethiol (1.24 g, 16.1 mmol) in methanol (250 mL) was stirred at room temperature for 1 h, followed by addition of sodium cyanoboron hydride (1.26 g, 20 mmol). The reaction mixture was stirred overnight and sodium carbonate was added to facilitate the lactam cyclization. After stirred for several hours, the suspension was filtered and acetic acid (2 mL) was added and concentrated. The residue was purified by column chromatography (10:1 hexanes/acetone) to yield two lactam diastereomers **15a** and **15b** (4.64 g, 73.6%), the ratio is 2.5:1.

Lactam **15a** (3.31 g, 52.6%) was given as a white solid, mp 188–190 °C, $[\alpha]_D^{20}$ +12.6° (*c* 0.1 $CHCl_3$), IR ($CHCl_3$) ν_{max} 1744.54, 1685.34 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 5.53 (1H, t, J=10.5 Hz), 5.30 (1H, d, J=11.0 Hz), 5.19 (1H, dd, J=10.5, 8 Hz), 4.94 (1H, dt, J=13.5, 3 Hz), 3.53 (1H, ddd, J=9.8, 8.4, 3.4 Hz), 2.87 (1H, td, J=14.3, 2.5 Hz Hz), 2.66 (1H, td, J=13.0, 3.0 Hz), 2.61–2.49 (3H, m); 1.21 (9H, s), 1.17 (9H, s), 1.12 (9H, s); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 177.4, 177.1, 176.6, 164.3, 70.4, 69.4, 67.8, 60.2, 44.7, 38.9, 38.7, 31.8, 27.1, 26.6 ppm. HRFABMS (M+H^+) calcd 472.2369, found 472.2379.

Lactam **15b** (1.33 g, 21.0%) was given as a white solid, mp 179–181 °C. IR (CH_2Cl_2) ν_{max} 1741.07, 1679.15, 1137.70 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.76 (1H, t, J=10.3 Hz), 5.27 (1H, dd, J=11.5, 6.3 Hz), 4.78 (1H, m), 4.02 (1H, ddd, J=11.8, 6.3, 2.0 Hz), 3.07 (1H, t, J=12.3 Hz), 2.98–2.88 (3H, m), 2.50 (1H, d, J=13.0 Hz), 2.35 (1H, m), 1.20 (9H, s), 1.17 (9H, s), 1.14 (9H, s); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 177.4, 176.8, 163.7, 67.7, 67.0, 59.2, 47.1, 38.9, 38.7, 27.7, 27.1, 27.1, 27.0, 26.3 ppm. HRFABMS (M+H^+) calcd 472.2369, found 472.2371.

5.3.5. 7(*S*),8(*R*),9(*R*),10(*S*)-Trihydroxy-2-thiaquinolizidine (4a). A solution of lactam **15a** (2 g, 4.24 mmol) and BH_3–THF (20 mL, 1.5 M) in anhydrous THF (30 mL) was refluxed for 4 h and the TLC and NMR showed the completion of the reduction. The solvent was removed and methanol was added and the mixture concentrated 3 times. The residue was dissolved in methanol (30 mL), followed by addition of NaOMe (0.15 g, 2.8 mmol). The reaction was stirred for 8 h to remove remaining ester groups and concentrated. The residue was applied to an ion exchange column (Dowex 50WX8-400, 30 g), which was washed with water (50 mL) and eluted with NH_4OH (50 mL). The elution was concentrated and purified by column chromatography (15:1 CH_2Cl_2/MeOH) to afford a white solid (0.62 g, 71%), mp 235–237 °C; $[\alpha]_D^{20}$ +20.2° (*c* 0.06 H_2O); IR (KBr) ν_{max} 3355.78, 3275.61 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.50 (1H, ddd, 11.0, 9.1, 4.9 Hz), 3.25 (1H, t, J=9.3 Hz), 3.12 (1H, dt, J=12.5, 3.0 Hz), 3.06 (1H, t, J=9.5 Hz), 2.93 (1H, dt, J=14.0, 2.5 Hz), 2.84 (1H, dd, J=11.5, 5.0 Hz), 2.75 (1H, td, J=13.0, 3.0 Hz), 2.52 (1H, m), 2.45 (1H, t, J=12.3 Hz), 2.43 (1H, m), 2.19 (1H, t, J=11.3 Hz), 2.13 (1H, td, J=10.0, 2.5 Hz); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 77.9, 74.1, 68.5, 65.6, 59.4, 55.7, 29.3, 26.3 ppm. HRFABMS (M+H^+) calcd 206.0851, found 206.0849.

5.3.6. 7(*S*),8(*R*),9(*R*),10(*R*)-Trihydroxy-2-thiaquinolizidine (4b). The title compound was obtained by the same method as **4a** from lactam **15b** (75% from **15b**). ^1H NMR (500 MHz, D_2O) δ 3.51–2.42 (2H, m), 3.06 (2H, d, J=10.0 Hz), 2.90 (4H, dd, J=26.0, 12.5 Hz), 2.82 (2H, t, J=10.5 Hz), 2.60 (2H, dd, J=12.0, 4 Hz), 2.20 (2H, d, J=14.0 Hz). HRFABMS (M+H^+) calcd 206.0851, found 206.0849.

Manno-derivatives were obtained in the same fashion as *gluco*-derivatives.

5.3.7. Methyl 6-bromo-6-deoxy-β-D-mannopyranoside (9). The title compound was obtained as a white solid (84%). ^1H NMR (500 MHz, D_2O) δ 3.91 (1H, d, J=2 Hz), 3.75 (1H, d, J=2.5 Hz), 3.73 (1H, d, J=2.5 Hz), 3.571 (2H, dd, J=11.8, 5.8 Hz), 3.569 (1H, d, J=1.5 Hz), 3.46 (3H, s), 3.43 (1H, m); ^{13}C NMR (125.5 MHz, D_2O) δ 101.41, 74.89, 72.83, 70.47, 68.96, 57.24, 32.95 ppm.

5.3.8. Methyl 6-bromo-6-deoxy-2,3,4-tri-*O*-pivaloyl-β-D-mannopyranoside (11). The title compound was obtained as white solid (80%), mp 130–132. ^1H NMR (500 MHz, $CDCl_3$) δ 5.41 (1H, dd, J=3, 0.75 Hz), 5.24 (1H, t, J=10 Hz), 5.08 (1H, dd, J=10, 3 Hz), 4.57 (1H, d, J=1 Hz), 3.68 (1H, m), 3.49 (3H, s), 3.47–3.39 (2H, m), 1.24 (9H, s), 1.15 (9H, s), 1.09 (9H, s); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 177.28, 177.22, 176.80, 99.74, 73.82, 70.85, 68.31, 68.21, 57.18, 39.06, 38.84, 38.75, 31.08, 27.16, 27.04, 27.02 ppm. HRFABMS (M+H^+) Calcd 509.1750, found 509.1748.

5.3.9. Methyl 6-bromo-2,3,4-tri-*O*-pivaloyl-5-keto-ester (13). The title compound was obtained as a colorless oil (91%). ^1H NMR (500 MHz, $CDCl_3$) δ 5.73 (1H, dd, J=8.5, 3 Hz), 5.71 (1H, d, J=2.5 Hz), 5.01 (1H, d, J=9 Hz), 4.13 (1H, d, J=14 Hz), 4.00 (1H, d, J=13.5 Hz) 3.69 (3H, s), 1.24 (9H, s), 1.21 (9H, s), 1.15 (9H, s); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 194.78, 176.90, 176.85, 176.59, 167.76, 73.16, 68.99, 68.85, 52.75, 38.91, 38.81, 38.69, 38.91, 38.81, 38.69, 31.38, 26.96, 26.86, 26.84 ppm. HRFABMS (M+H^+) Calcd 523.1543, found 523.1545.

5.3.10. Lactam 16a. The title compound was obtained as white solid (65%), mp 136–138. ^1H NMR (500 MHz, $CDCl_3$) δ 5.67 (1H, d, J=3.5 Hz), 5.39 (1H, m), 5.01 (1H, m), 4.99 (1H, t, J=3 Hz), 3.66 (1H, dt, J=11.5, 2 Hz), 2.99 (1H, m), 2.85 (1H, td, J=13, 2 Hz), 2.74 (1H, td, J=13, 2.5 Hz), 2.59 (1H, dt, J=13.5, 2 Hz), 2.46 (1H, m), 1.22 (9H, s), 1.21 (9H, s), 1.20 (9H, s); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 176.94, 176.86, 176.36, 163.27, 69.43, 68.18, 66.51, 62.75, 46.54, 38.91, 38.85, 38.81, 31.06, 27.18, 27.08, 26.98, 26.66 ppm. HRFABMS (M+H^+) calcd 472.2369, found 472.2366.

5.3.11. Lactam 16b. The title compound was obtained as white solid (16%), mp 182–184. ^1H NMR (500 MHz, $CDCl_3$) δ 5.65 (1H, d, J=2.5 Hz), 5.34 (1H, t, J=5 Hz), 5.31 (1H, m), 5.04 (1H, dt, J=8.5, 3 Hz), 3.77 (1H, m), 2.79 (1H, td, J=13.5, 2 Hz), 2.68 (2H, m), 2.53 (1H, m), 2.39 (1H, dt, J=13.5, 2 Hz), 1.25 (9H, s), 1.20 (9H, s), 1.18 (9H, s); ^{13}C NMR (125.5 MHz, $CDCl_3$) δ 177.12, 176.66, 176.23, 165.11, 67.13, 66.90, 66.34, 58.60, 44.57, 39.14, 38.94, 38.85, 28.78, 27.19, 27.11, 27.04 ppm. HRFABMS (M+H^+) calcd 472.2369, found 472.2367.

5.3.12. 7(*R*),8(*R*),9(*R*),10(*S*)-Trihydroxy-2-thiaquinolizidine (5a). The title compound was obtained as white solid (73% from **16a**), mp 144–145. ^1H NMR (500 MHz, D_2O) δ 3.93 (1H, m), 3.43 (1H, dd, J=10, 3.5 Hz), 3.35 (1H, t, J=9.5 Hz), 3.06 (1H, dt, J=12.5, 3 Hz), 2.90 (1H, dt, J=8.5, 2.5 Hz), 2.81–2.74 (2H, m), 2.51–2.44 (2H, m), 2.39–2.32 (2H, m), 2.05 (1H, t, J=9 Hz); ^{13}C NMR (125.5 MHz, D_2O) δ 73.90, 71.15, 67.48, 66.24, 59.37, 55.87, 28.77, 26.02 ppm. HRFABMS (M+H^+) calcd 206.0851, found 206.0851.

5.3.13. 7(*R*),8(*R*),9(*R*),10(*R*)-Trihydroxy-2-thiaquinolizidine (5b). The title compound was obtained by the same

way as **51a** (71% from **16b**). ^{1}H NMR (500 MHz, D_2O) δ 3.97 (1H, m), 3.87 (1H, s), 3.69 (1H, d, $J=2.0$ Hz), 3.10 (1H, d, $J=12.5$ Hz), 2.84 (2H, dd, $J=13.5$, 11.0 Hz), 2.76 (1H, m), 2.61 (2H, m), 2.44 (2H, t, $J=11.0$ Hz), 2.36 (1H, d, $J=14.0$ Hz). ^{13}C NMR (125.5 MHz, D_2O) δ 72.1, 70.5, 64.3, 60.4, 56.8, 54.4, 28.4, 26.0. HRFABMS ($M+H^+$) calcd 206.0851, found 206.0850.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 231490. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 36033 or e-mail: deposit@ccdc.cam.ac.uk].

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Syntheses, optical and electrochemical properties of 4,4′-bis-[2-(3,4-dibutyl-2-thienylethynyl)]biphenyl and its oligomers

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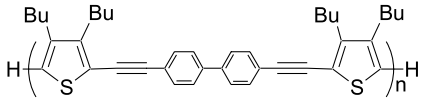
Abstract—New π-conjugated oligomers (**1**–**3**) combined of thiophene rings, C≡C units, and phenylene rings were synthesized. The monomer (**1**) was synthesized by Sonogashira cross-coupling reaction. Lithiation and oxidation of the monomer led to the formation of dimer (**2**) and trimer (**3**). Optical and electrochemical properties of compounds **1**–**3** were studied. The oligomers with thioacetyl moieties were synthesized for self-assembly.

1. Introduction

In 1975, Moore stated that chip densities would double every 2 years.[1] According to the statement, the reduction in size of circuits and increase in speed can only continue for some finite time. This forces us to consider other options. Many researches are focused towards molecular electronics. We seek to use the electronic properties intrinsic in the molecules to fabricate electric devices. π-Conjugated oligomers of defined length and constitution arise from new potential to act as molecular wires in molecular scale electronics. A variety of spectacular molecular architectures are resulted from the efforts aimed at the construction of such wires. In addition, modern synthetic organic and organometallic methodologies are providing powerful tools for the direct acquisition of the molecules and materials capable of fulfilling a huge variety of requirements in terms of mechanical, physical, and chemical properties.[2] Oligoynes,[3] oligothiophenes,[4] and oligophenylenes[5] have been intensively studied. Tour and co-workers have reported the syntheses of oligo(α-thiophene ethynylene)s and oligo(*p*-phenylene ethynylene)s.[6] But linear conjugated oligomers involving combination of three different sub-structures are seldom discussed. Here, we report the syntheses of π-conjugated molecules **1**–**3** consisting of thiophene rings, C≡C units, and phenylene rings as potential molecular wires. These compounds possess the following features that make them suitable for studies of molecular scale electronics: (1) these compounds are rigid in their frameworks so as to minimize conformational flexibility yet containing butyl groups for maintaining solubility and processability of the final products. The butyl groups have been preferred over long paraffinic chains because they afford better yields during the syntheses of the precursors;[7] (2) alkynyl units separate the aryl units, so ground state contiguous π-overlap will be minimally affected by rotational variations; (3) thiol end groups can be attached to the ends of the compounds; (4) they are stable to light and oxygen, so that they can be manipulated in the air.

Additionally, the syntheses of compounds (**4**, **5**) bearing one or two thioacetyl moieties at terminal positions were presented. On one hand, the thiols resulted from the hydrolyzation of thioacetyl moieties can serve as molecular scale alligator clips for adhesion of the molecular scale wires to the gold probes.[8,9] On the other hand, the molecule with one end-thiol group can be used as a ligand for the functionalizaion of noble metal nanoparticles. And molecules with end-thiol groups at both terminal positions can be used as rigid linkers for the assembly of noble metal nanoparitcles to form 2D structures.



1: n = 1
2: n = 2
3: n = 3

Keywords: Synthesis; π-Conjugated oligomers; Electrochemistry.
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2. Results and discussions

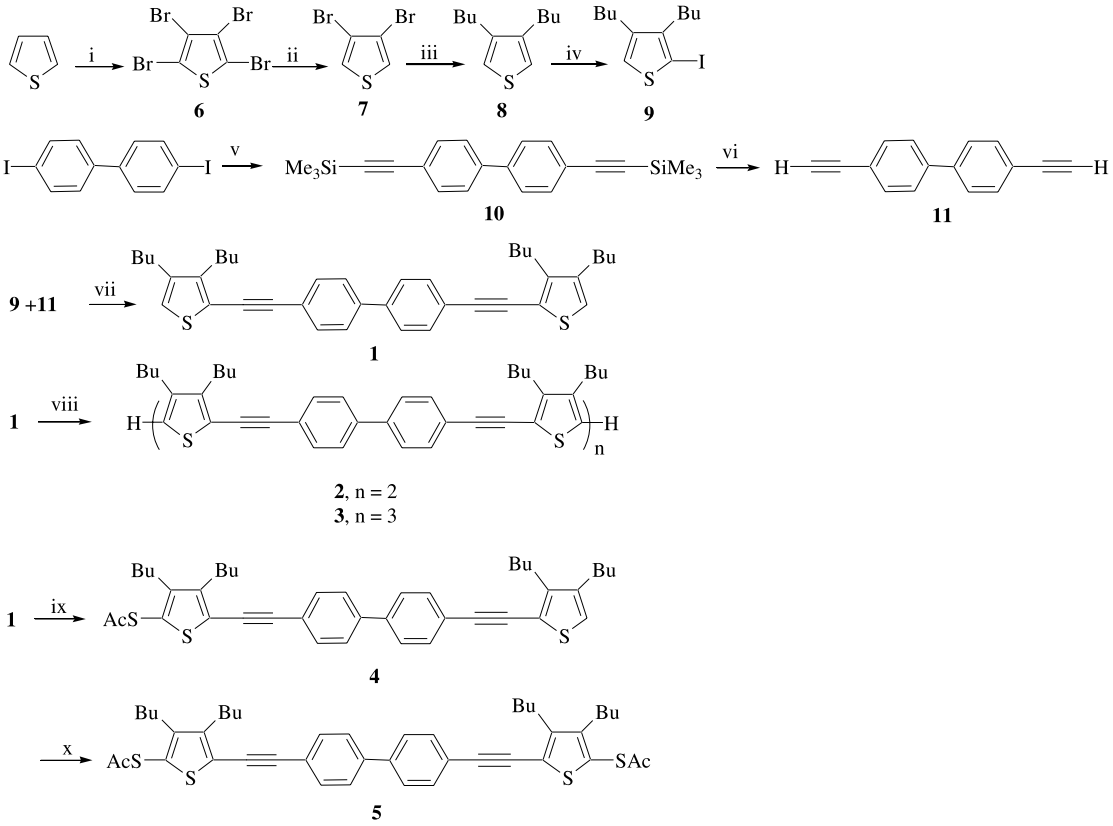
2.1. Molecular design and synthetic strategy

The synthetic strategy employed two reaction types to grow the conjugated chains rapidly. As a monomer unit, compound **1** was synthesized by Pd-mediated Sonogashira cross-coupling reaction. Oligomers **2** and **3** containing two or three monomer units were synthesized by lithiation of **1** and followed with oxidation coupling reactions, using $CuCl_2$ as the oxidant, which were depicted in Scheme 1. The starting material, 3,4-dibutylthiophene (**8**) was prepared according to the procedure described by Tour.[10] Then, it was subjected to react with iodine and mercury oxide, leading to **9** by an adopted procedure reported by Minnis.[11] Diiodide was obtained simultaneously, but it was no need to separate the iodide and diiodide. The iodide **9** intended to decompose in the air and should be used as soon as possible after workup. Commercially available 4,4′-diiodobiphenyl was coupled with (trimethylsilyl) acetylene via a Sonogashira–Hagihara reaction to afford the (trimethylsilyl)ethynyl derivative **10**,[12] which was then desilylated with potassium carbonate to afford the ethynyl derivative **11**. The aryl iodide **9** was coupled with the terminal alkyne **11** to afford compound **1** in a yield of 67% (Scheme 1). Pd/Cu coupling reactions required the strict exclusion of oxygen; degassing and use of a dry box was required to attain reasonable yields. Lithiation of **1** and followed with an oxidative coupling reaction in the presence of $CuCl_2$ led to the formation of dimer (**2**) and trimer (**3**) in yields of 33 and 30%, respectively.[13] Compounds **1**–**3** were stable in the air. They showed good solubilities in dichloromethane, chloroform, THF and benzene, yielding excellent processability for practical application.

Complementary thiol end groups, protected as thioester moieties, were attached to one or both ends of molecule **1** via a one-pot lithiation–sulfide-acetylation protocol.[14] The monothiol-terminated system could be used for self-assembly on gold surfaces. And α, ω-difunctionalized system could serve as a bridge between two gold probes. Thiol-terminated molecules could also be used for the functionalization of noble metal nanoparticles.

2.2. UV–vis and fluorescence spectral studies

The UV–vis absorption and fluorescence spectra of compounds **1**–**3** in dichloromethane were shown in Figures 1 and 2. In the UV–vis absorption spectra, broad bands with little vibronic structure were present. The shapes of the spectra were almost identical. There were two absorption bands for every compound. A weak band appeared around 270–280 nm. A strong band appeared at 352, 366 and 368 nm for **1**, **2** and **3**, respectively. Elongation of the conjugation length from **1** to **2** resulted in a red shift of 14 nm. However, only little red shift was observed from **2** to **3**. Similar chain length dependence was observed for their fluorescence spectra (Fig. 2). The spectroscopic measurements provided definite information on the effective conjugation length, that was, they exhibited a certain



Scheme 1. Preparation of compounds **1**–**5**. Reagents and conditions: (i) Br_2, 84%. (ii) *n*-BuLi, H_2O, 70%. (iii) C_4H_9MgBr, $Ni(dppp)Cl_2$, Et_2O, 61%. (iv) HgO, I_2, 94%. (v) $Me_3SiC{\equiv}CH$, $Pd(PPh_3)_4$, CuI, Et_3N, rt, 63%. (vi) K_2CO_3, MeOH, Et_2O, rt, 100%. (vii) $Pd(PPh_3)_4$, CuI, Et_3N, rt, 67%. (viii) LDA, $CuCl_2$, 33% for **2** and 30% for **3**. (ix) 1 equiv *n*-BuLi, S_8, AcCl, 23%. (x) 2 equiv *n*-BuLi, S_8, AcCl, 21%.

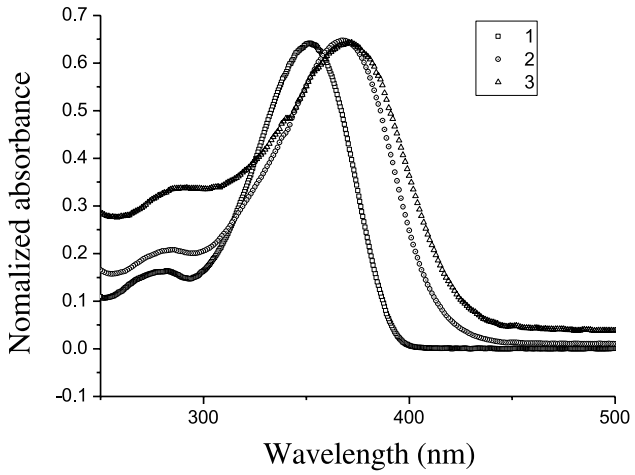


Figure 1. UV–vis absorption spectra of compounds **1**–**3** in CH_2Cl_2.

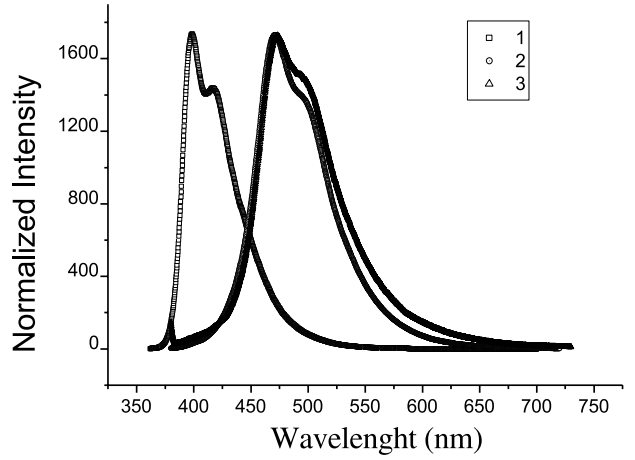


Figure 2. Fluorescence emission spectra of compounds **1**–**3** in CH_2Cl_2. Excited wavelengths are 352, 366 and 368 nm for molecules **1**, **2** and **3**, respectively.

limitation for the extensive conjugation. The saturation in λ_{max} was observed previously and arose because of the limitations to electron delocalization in the longer oligomers. There were several competing factors that must be considered. It has been known that with increasing of π-conjugation chain and more extensive electron delocalization, the absorption maxima should show bathochromic shifts. To enhance the solubility of the systems, the thiophene rings were substituted with *n*-butyl groups. The pendant butyl groups had two contrary effects on the π-systems. The butyl groups could cause distortions of the conjugated systems from planarity if steric interactions were severe enough. On the other hand, if steric interactions were not particularly severe, butyl groups could induce bathochromic shifts, which had been explained by inductive and hyperconjugative effects.[6] These two contradictory factors could take effect concurrently. With increase of chain length, the steric hindrance due to the butyl groups became overwhelmingly dominant, the effective conjugation reached saturation. The fluorescence quantum yields of **1**–**3** in dichloromethane were 62, 13 and 11%, respectively (Table 1). The quantum yields decreased as the conjugation length increased.

Table 1. The absorption λ_{max} (in CH_2Cl_2), emission λ_{max} (in CH_2Cl_2), and fluorescent quantum yields of oligomers **1**–**3**

Oligomer	UV λ_{max} (nm)	Em λ_{max} (nm)	Φ_F[a]
1	352	398	0.62
2	366	471	0.13
3	368	474	0.11

Excited wavelengths are 352, 366 and 368 nm for molecules **1**, **2** and **3**, respectively.
[a] Use 9,10-diphenylanthracene ($\Phi_F = 1.0$) to compare with in cyclohexane.

2.3. Electrochemical studies

The electrochemical behaviors of compounds **1**–**3** were studied by cyclic voltammetry. The oxidation wave was observed around 1.22 V for compound **1**, which showed no tendency for reduction under CV conditions but rather underwent irreversible oxidations in CH_2Cl_2, due to the fact that the corresponding radical cations were not stable. Electrochemical polymerization and film deposition for compound **1** was carried out using multiple scan cyclic voltammetry. Upon multiple cycling of **1** in CH_2Cl_2 solution, a new redox process developed at a lower potential (~0.4 V) due to the reversible redox process of the as-deposited polymer (Fig. 3). The current response of this new redox process continued to increase in intensity upon additional cycling consistent with the deposition of an electroactive polymer onto the surface of the working electrode. As for products **2** and **3**, quasi-reversible redox behaviors were observed with oxidation peaks at 1.18 and 1.16 V, respectively. And no evidence for dimerization or polymer growth could be observed with continued cyclic sweeping through oxidizing potentials (Fig. 4). The electrochemical behavior of compound **1** was similar with that of 3,4-dibutyl thiophene, which displayed a typical electrochemical polymerization on the surface of anode. The difference between compound **1** and its dimer and trimer was due to stabilizing of radical cations with the increasing of conjugating length. Oligo(thiophene)s also displayed different electrochemical behavior with the different conjugating length. Only oxidation waves could

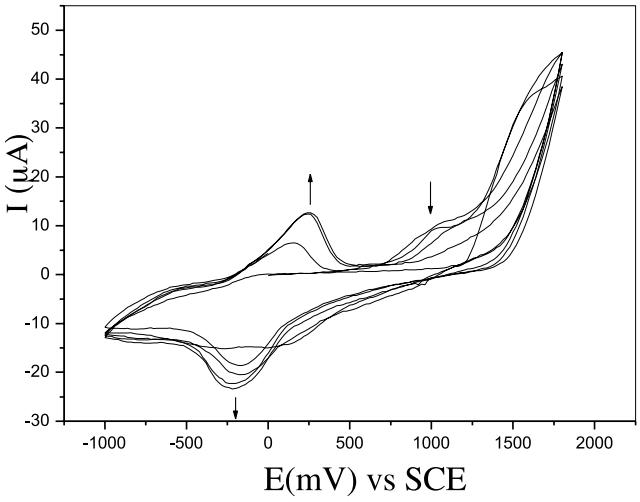


Figure 3. Cyclic voltammetric scanning electropolymerization of **1** (10^{-4} M in 0.1 M $Bu_4N^+PF_6^-/CH_2Cl_2$, 5 cycles. Pt working and counter electrodes, scan rate 100 mV s^{-1}).

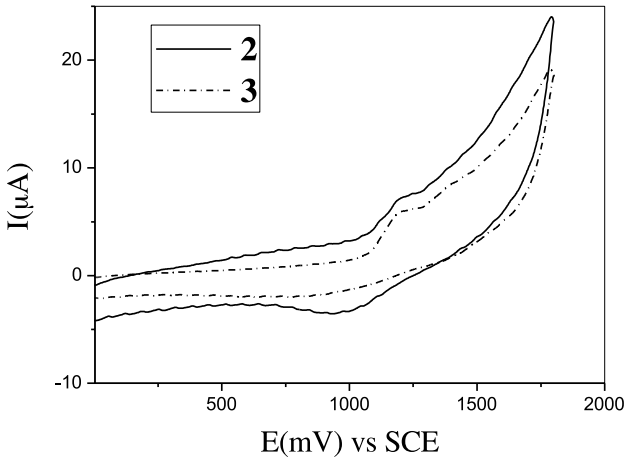


Figure 4. Cyclic voltammetric scanning electropolymerization of compounds **2** and **3**, 10^{-4} M in 0.1 M $Bu_4N^+PF_6^-/CH_2Cl_2$. Pt working and counter electrodes, scan rate 100 mV s^{-1}.

be observed for shorter oligomers, and reversible redox wave could be observed for longer oligomers.[15]

CVs of compounds **4** and **5** were also conducted for comparison. With masked thiol end-groups at the terminal positions, **4** and **5** presented peak oxidation potentials at 1.30 V, which were slightly higher than that of the parent molecule **1**. This should be due to the electron withdrawing effect of the thioacetyl groups.

3. Conclusions

We reported the synthesis of π-conjugated molecule **1** from the easy accessible materials with high efficiency. This molecule had a linear π-conjugated system with a length scale about 2 nm, and this π-conjugated system could be easily elongated by one-pot lithiation and oxidation coupling reaction. Dimer (**2**) and trimer (**3**) of compound **1** were obtained in moderate yields. These compounds could serve as building blocks for other functional molecular wires with precise conjugation lengths.

4. Experimental

4.1. General

Melting points were measured with a Buchi Melting Point B-540 instrument and uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker 300 MHz or Varian 200 MHz spectrometers. All chemical shifts were quoted in ppm relative to TMS. Infrared spectra were obtained on a Perkin–Elmer System 2000 FT-IR spectrometer. Mass spectra were determined with AEI-MS50-MS or MALDI-TOF-MS. Elemental analysis was performed on Carlo-Erba-1106 instrument. HRMS was performed on UK GCT-Micromass. Absorption spectra were measured with Hitachi (model U-3010) UV–vis spectrophotometer. Fluorescence measurements were carried out with a Hitachi (model F-4500) Spectrophotometer in a 1-cm quartz cell. Cyclic voltammetric experiments were performed on an EGDG PAR 370 system at a scan rate of 100 mV in CH_2Cl_2 using Bu_4NPF_6 as electrolyte, platinum electrodes as counter and work electrodes and SCE as reference electrode. *n*-Butyllithium (2.5 M solution in hexanes) and LDA (1.5 M in cyclohexane) were purchased from Acros or Aldrich Chemical Co., Inc. 4,4′-Diiodobiphenyl and (trimethylsilyl) acetylene were from Alfa Aesar. $Ni(dppp)Cl_2$, $Pd(PPh_3)_4$ from Aldrich Chemical Co., Inc. were used as received. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone immediately prior to use. All other reagents and solvents (standard grade) were used as received unless otherwise noted. All reactions involving *n*-BuLi or LDA were carried out under an atmosphere of dry N_2. Sonogashira cross-coupling reactions required the strict exclusion of oxygen and water.

4.1.1. 4,4′-Bis(trimethylsilyl)biphenyl 10. To a solution of 4,4′-diiodobiphenyl (2.00 g, 4.9 mmol), $Pd(PPh_3)_4$ (0.113 g, 0.098 mmol), CuI (0.037 g, 0.196 mmol) in THF (10 mL) was added 0.744 g (1 mL, 7.35 mmol) of triethylamine. A solution of 1.01 g (1.045 mL, 10.29 mmol) of (trimethylsilyl)acetylene in 5 mL of THF was then added slowly. The solution was stirred overnight at room temperature and white precipitate appeared, which was removed by filtration. The filtrate was evaporated, and the residue was purified by silica gel column chromatography (hexane) to give **10** (1.07 g, 63%) as a white solid. Mp 169 °C. IR (KBr, cm^{-1}): 2959, 2156, 1488, 1249, 861, 847, 824, 759. MS (EI): 346 (M^+). ^{1}H NMR: 7.53 (s, 8H), 0.27 (s, 18H).

4.1.2. 4,4′-Diethynylbiphenyl 11. To a solution of **10** (4.66 g, 13.47 mmol) in methanol (30 mL) and diethyl ether (30 mL) was added potassium carbonate (18.61 g, 134.68 mmol). The solution was allowed to stir for 6 h before being poured into water. The aqueous layer was extracted with dichloromethane, and the organic extracts were washed with brine. The combined organic layers were dried over magnesium sulfate. The solvent was removed by rotary evaporation. No further purification was necessary to afford 2.72 g (100%) of **11** as a white solid. Mp 167 °C. (lit.[16] Mp 165.5–166.5 °C). IR (KBr, cm^{-1}): 3277, 2104, 1488, 857, 825. MS (EI): 202 (M^+). ^{1}H NMR: 3.16 (s, 2H), 7.54–7.60 (m, 8H).

4.1.3. 4,4′-Bis-[2-(3,4-dibutyl-2-thienylethynyl)]biphenyl 1. Following the method used for the synthesis of **10**. Used were **9** (6.80 g, 21.6 mmol), $Pd(PPh_3)_4$ (0.499 g, 0.432 mmol), CuI (0.165 g, 0.864 mmol), THF (30 mL), triethylamine (4.5 mL), **11** (2.182 g, 10.8 mmol),THF (50 mL). The solvent was evaporated and the residue was purified by silica gel column chromatography (silica gel, petroleum/dichloromethane 4:1) to give compound **1**(4.27 g, 67%) as a pale-yellow solid. Mp 67 °C. IR (KBr, cm^{-1}): 2956, 2928, 2858, 2199, 1635, 1493, 1406, 868, 819, 743. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94–2.76 (m, 36H), 6.87 (s, 2H), 7.55–7.60 (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 14.0, 22.6, 22.7, 28.0, 28.8, 31.9, 32.2, 84.3, 94.6, 118.5, 121.5, 122.8, 126.9, 131.7, 139.8, 142.1, 147.1. MS (EI): 590 (M^+). Anal. Calcd for $C_{40}H_{46}S_2$: C, 81.30; H, 7.85; S, 10.85. Found: C, 81.51; H, 8.00; S, 11.06.

4.1.4. 5,5′-Bis[4′-(3,4-dibutyl-thien-2-ylethynyl)-biphenyl-4-ylethynyl]-3,4,3′,4′-tetrabutyl-[2,2′]-bithiophenyl 2. A solution of **1** (0.130 g, 0.22 mmol) in anhydrous

THF (10 mL) was added to lithium diisopropylamine (0.18 mL, 0.26 mmol, 1.5 M in cyclohexane) in 10 mL of anhydrous THF at −78 °C under nitrogen. The reaction mixture were stirred at −78 °C for 30 min, then anhydrous powered $CuCl_2$ (0.0296 g, 0.22 mmol) was added in one portion, upon which the color of the solution changed to black. The solution was stirred until it returned to rt then for an additional 30 min at 30 °C. The mixture was poured into 20 mL of water, containing 10 mL of 1 M hydrochloric acid. Then it was extracted twice with 100 mL of diethyl ether. The combined organic layers were washed with water, dried over sodium sulfate and concentrated in vacuo. The crude product was purified by silica gel column chromatography (petroleum/dichloromethane 2:1) to give 0.043 g (33%) of **2** as a yellow solid. Mp 97 °C. IR (KBr, cm^{-1}): 2956, 2929, 2862, 2197, 1687, 1602, 1491, 1460, 821, 740. MS (MALDI-TOF): 1177 (M^+). ^1H NMR (300 MHz, $CDCl_3$): δ 0.85–2.76 (m, 72H), 6.88 (s, 2H), 7.56–7.62 (m, 16H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 83.78, 84.34, 94.58, 95.88, 118.43, 118.92, 121.48, 122.60, 122.78, 126.84, 126.87, 130.12, 131.66, 139.73, 139.91, 141.86, 142.09, 147.05, 147.57. HRMS calcd for $C_{80}H_{90}S_4$: 1178.5925. Found: 1178.5919.

4.1.5. 4,4′-Bis-{5-[4′-(3,4-dibutyl-thien-2-ylethynyl)-biphenyl-4-yl-ethynyl]-[2,2′]-bithiophenyl-5′-ylethynyl}-biphenyl 3. 0.039 g (30%) of **3** was also isolated as a yellow solid. Mp 153 °C. IR (KBr, cm^{-1}): 2956, 2927, 2858, 2197, 1688, 1603, 1492, 1460, 821, 743. MS (MALDI-TOF): 1767 (M^+). ^1H NMR (300 MHz, $CDCl_3$): δ 0.90–2.82 (m, 108H), 6.93 (s, 2H), 7.64–7.65 (m, 24H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 13.80, 13.97, 14.01, 22.56, 22.67, 22.74, 22.79, 27.54, 27.96, 28.56, 28.71, 29.68, 31.87, 32.19, 32.46, 32.85, 83.76, 83.80, 84.32, 94.56, 95.86, 118.41, 118.90, 121.47, 122.59, 122.63, 122.77, 126.83, 126.86, 130.11, 131.66, 139.72, 139.86, 139.90, 141.85, 142.08, 147.04, 147.56. Anal. Calcd for $C_{120}H_{134}S_6$: C, 81.49; H, 7.64; S, 10.88. Found: C, 81.24; H, 7.50; S, 10.64.

4.1.6. [4-[2-(3,4-Dibutyl-2-thienylethynyl)-4′-[thioacetic acid-S-[2-(3,4-dibutyl-2-thienylethynyl)]ester]biphenyl 4. To a solution of **1** (0.198 g, 0.336 mmol) in THF (10 mL) at −78 °C was added dropwise *n*-butyllithium (0.201 mL, 0.503 mmol). The solution was stirred at −78 °C for 30 min then warmed to 0 °C and sulfur powder (0.011 g, 0.336 mmol) was added. The reaction remained at 0 °C for 30 min. The solution was recooled to −78 °C, and acetyl chloride (0.029 mL, 0.403 mmol) was added in one portion. The solution was allowed to warm to room temperature overnight. The mixture was extracted with dichloromethane and dried over magnesium sulfate. The solvent was removed by rotary evaporation, and the residue was purified by silica gel chromatography using 4:1 petroleum/dichloromethane as eluent to provide 0.051 g (23%) of **4** as a yellow solid. Mp 82.3–83.0 °C. MS (EI): 664 (M^+), 622 ($M-COCH_3+1$). IR (KBr, cm^{-1}): 2956, 2861, 2198, 1910, 1725, 1492, 1460, 1112, 821, 741, 605. ^1H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 3H), 0.89–2.79 (m, 36H), 6.89 (s, 1H), 7.57–7.63 (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 13.92, 14.04, 14.08, 22.63, 22.75, 22.78, 22.82, 22.94, 27.88, 28.03, 28.79, 29.63, 29.76, 31.94, 32.27, 32.43, 32.53, 32.79, 53.47, 83.26, 84.45, 91.65, 96.83, 118.50, 120.53, 121.56, 122.32, 122.90, 123.82, 126.90, 126.93, 127.38, 131.50, 131.71, 131.81, 139.71, 140.22, 142.13, 147.10, 147.37, 148.23, 194.23. HRMS calcd for $C_{42}H_{48}OS_3$: 664.2867. Found: 664.2870.

4.1.7. {4,4′-Bis-[2-thioacetic acid-S-(3,4-dibutyl-2-thienyl-ethynyl)]ester}biphenyl 5. It was prepared similarly as compound **4**. Used were **1** (0.296 g, 0.502 mmol), THF (10 mL), *n*-butyllithium (0.8 mL, 2.007 mmol), sulfur powder (0.048 g, 1.505 mmol), acetyl chloride (0.107 mL, 1.505 mmol). The residue was purified by silica gel chromatography by first using 4:1 petroleum/dichloromethane and then increasing to 2:1 petroleum/dichloromethane to provide 0.078 g (21%) of **5** as a yellow solid. Mp 93.7–95.0 °C. MS (EI): 738 (M^+), 696 ($M-COCH_3+1$), 654 ($M-COCH_3-COCH_3+2$), 622 ($M-COCH_3-COCH_3-S+2$). IR (KBr, cm^{-1}): 2956, 2862, 2197, 1911, 1726, 1492, 1461, 1113, 945, 821, 738. ^1H NMR (300 MHz, $CDCl_3$): δ 2.44 (s, 6H), 0.09–2.78 (m, 36H), 7.57–7.63 (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 13.84, 13.96, 22.72, 22.77, 27.83, 28.76, 29.56, 32.38, 32.47, 83.28, 96.74, 120.56, 122.42, 123.76, 126.92, 131.78, 140.11, 147.34, 148.17, 194.19. HRMS calcd for $C_{44}H_{50}O_2S_4$: 738.2694. Found: 738.2688.

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Design and synthesis of a new polymer-supported Evans-type oxazolidinone: an efficient chiral auxiliary in the solid-phase asymmetric alkylation reactions

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Abstract—Wang resin-supported Evans' chiral auxiliary (**23**) was designed based on a novel polymer-anchoring strategy, which utilizes the 5-position of the oxazolidinone ring, and its new synthetic route applicable to multi-gram preparation in just a day was developed. Solid-phase Evans' asymmetric alkylation on **23**-derived *N*-acylimide resin and following lithium hydroperoxide-mediated chemoselective hydrolysis afforded the corresponding α-branched carboxylic acids in desired high stereoselectivities (up to 97% ee) and moderate to good overall yield (up to 70%, for 3 steps), which were comparable to those of the conventional solution-phase methods. Furthermore, recovery and recycling of the polymer-supported chiral auxiliary were successfully achieved without decreasing the stereoselectivity of the product. Therefore, this is the first successful example that the solid-phase Evans' asymmetric enolate-alkylation was efficiently performed on the solid-support, and it is concluded that the connection to the solid-support via the 5-position of the oxazolidinone ring is an ideal strategy in the solid-phase Evans' chiral auxiliary.

1. Introduction

Evans' chiral oxazolidinone is one of the efficient auxiliaries for preparing chiral building blocks necessary to synthesize molecules possessing the accurate spatial configuration of specific functional groups.[1,2] Its generality and reliability with high optical purity have already been established in a variety of efficient asymmetric syntheses of low molecular weight chiral compounds and complicated natural products.[3–5] Moreover, its potential is expanding in the study of novel asymmetric reactions.[6]

Solid-phase organic synthesis has been developed as a rapid and diversified method in organic chemistry.[7] As compared to solution-phase, the solid-phase technology provides a simple procedure 'filtration' for rapidly achieving the isolation of desired compounds or recovering expensive reagents or catalysts attached onto the solid-support for recycling. Hence, many useful reagents or catalysts, especially those used in chiral synthesis, in solution-phase methods have been intensively and successfully applied to the solid-phase methods so far.[8] However, some solid-supported chiral auxiliaries are problematic in achieving high quality of stereoselective reactions.[9] One of such well-known examples is pseudoephedrine[10] grafted onto the Merrifield resin. This solid-supported auxiliary showed lower stereoselectivity in asymmetric alkylation (approx. 85% ee) in comparison to the corresponding solution-phase experiments.

Evans' oxazolidinone has also been applied to the solid-phase stereoselective reactions such as enolate-alkylation reaction,[11] aldol reaction,[12] Diels–Alder cycloaddition[13] and 1,3-dipolar cycloaddition.[14] However, undesired results similar to those observed in the solid-supported pseudoephedrine case were reported, especially in the fundamental solid-phase asymmetric enolate-alkylation reaction which prepares optically active α-branched carboxylic acid derivatives.[11b] Indeed, maximum stereoselectivity was 90% ee in asymmetric benzylation using the auxiliary resin **1** (Fig. 1A).[15] Moreover, a side reaction was reported in the preparation of solid-supported L-serine derived chiral oxazolidinone **2**.[16] Therefore, to improve the efficiency in stereoselective reactions, we previously reported a

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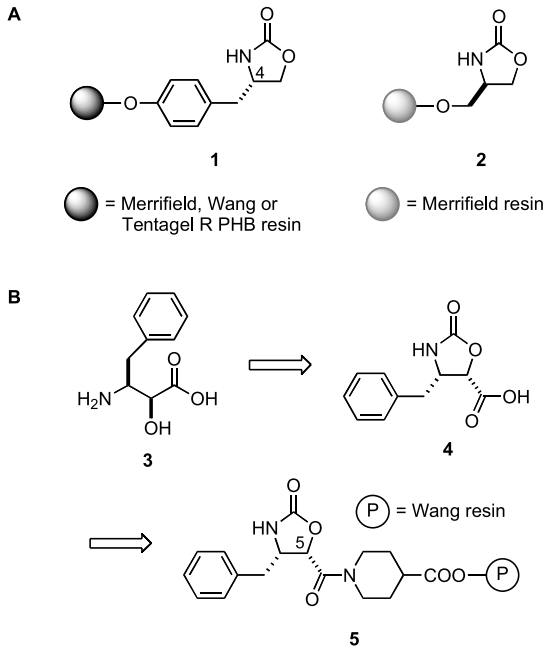


Figure 1. Reported polymer-supported Evans' chiral auxiliaries anchored at the 4-position of the oxazolidinone ring (A) and design of a new auxiliary anchored at the 5-position (B).

polymer-supported chiral Evans' oxazolidinone with a novel anchoring system onto the solid-support as a rapid communication.[17] In this article, we describe the detailed design and synthesis of the polymer-supported chiral Evans' oxazolidinone and its reusability in Evans' asymmetric alkylation.

2. Results and discussion

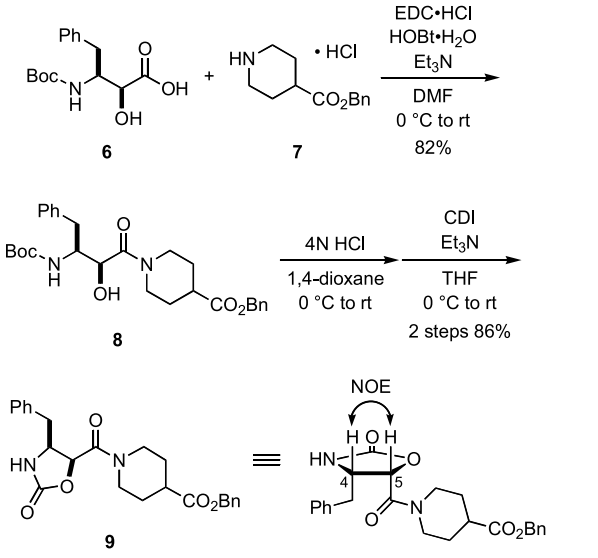
2.1. Design of a new polymer-supported chiral oxazolidinone

One of the common features of polymer-supported Evans' chiral auxiliary in all previous reports[11–14] is that a chiral 4-substituted oxazolidin-2-one was connected to the solid-support through the chiral discriminating moiety at the 4-position of the oxazolidinone ring (Fig. 1A). This made us suspect that chiral control ability of Evans' oxazolidinone is influenced by the polystyrene backbone of the solid-support, leading to the low stereoselectivity in the asymmetric alkylation.[11b] Hence, we proposed an alternative anchoring strategy, which leaves the crucial chiral discriminating moiety unmodified, and utilizes the external 5-position for connecting to the solid-support (Fig. 1B).

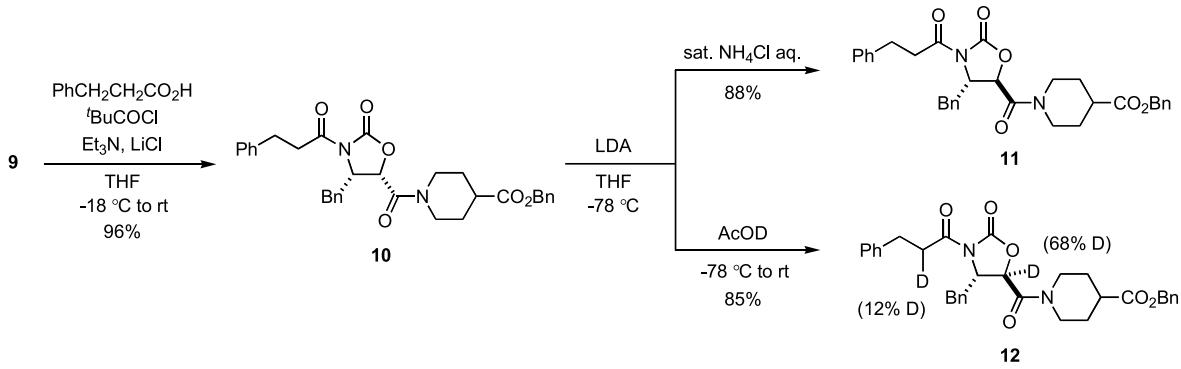
To prepare such a new oxazolidinone derivative, we focused on α-hydroxy-β-amino acids, which are routinely used in our laboratory as a core structure for the development of effective aspartic protease inhibitors.[18] The unique structure of α-hydroxy-β-amino acids, in which three different functional groups, i.e. amino, hydroxyl and carboxyl groups, are located on two adjacent asymmetric carbon atoms gave us the idea. Namely, the known oxazolidinone formation[19] at the 1,2-amino alcohol moiety of α-hydroxy-β-amino acid, (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid **3** (allophenylnorstatine, Apns),[18] can afford a desired oxazolidinone derivative **4** with a benzyl substituent at the 4-position as a chiral discriminating group and a free carboxyl group at the 5-position which can connect with the solid-support (Fig. 1B). In addition, Burgess et al. pointed out that Wang resin had a better enantiomeric excess than Merrifield resin in asymmetric benzylation.[11b] Since Wang resin has an additional benzyl moiety which has a space from the polystyrene backbone in comparison to Merrifield resin, we planned to employ both Wang resin and, as a further spacer, a piperidine-4-carboxylic acid. Thus, in the designed solid-supported auxiliary **5**, this spacer is connected to the carboxyl group at the 5-position of the oxazolidinone moiety by a tertiary-amide bond and to Wang resin by an ester bond. This tertiary-amide bond with no amide proton is stable under both acidic and basic conditions. The ester bond between the spacer and Wang resin can be formed by the standard methods.

2.2. Evaluation of new oxazolidinone derivatives in solution-phase model experiment

To understand the efficacy of designed solid-support chiral oxazolidinone **5** as a new chiral auxiliary, we first studied a solution-phase experiment, using a model oxazolidinone derivative **9** whose C-terminal is protected by a benzyl ester to mimic Wang resin. As Scheme 1 shows, **9** was synthesized by a three-step reaction. Namely, Boc-Apns-OH **6** was coupled to benzyl piperidine-4-carboxylate **7**[20] by the EDC–HOBt (EDC: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, HOBt: 1-hydroxybenzotriazole) method[21] to give dipeptide **8**,[22] followed by the removal of the Boc group and CDI (1,1′-carbonyldiimidazole) treatment[19] to afford the *cis*-configured oxazolidinone derivative **9** as a single isomer. During the cyclization reaction, neither aziridine nor 1,2-imidazoylamine byproduct formation was observed.[23] The *cis*-configuration of **9** was confirmed by the coupling constant[24] between H-4 and H-5, and NOE experiments (Scheme 1 and Ref. 25). Synthesized **9** had



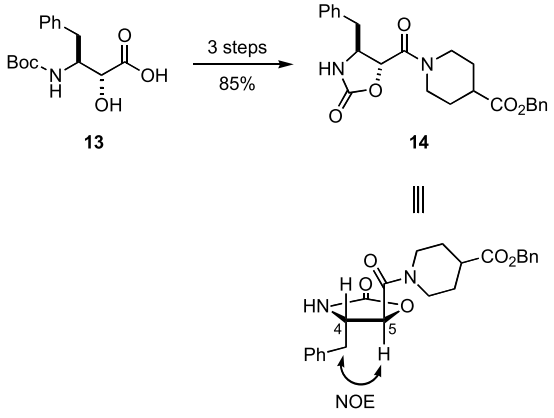
Scheme 1. Synthesis of a *cis*-configured oxazolidinone derivative **9** from Boc-Apns-OH **6**.



Scheme 2. Epimerization and deuterium incorporation to the *cis*-configured carboximide **9**.

coupling constants of $J_{4,5}=7.9$, 8.1 Hz, which corresponded to the representative value of the *cis*-configured oxazolidinone.

Next, oxazolidinone **9** was *N*-acylated with 3-phenylpropionic acid by the mixed anhydride method to obtain carboximide **10** (Scheme 2).[26] Although there are three α-protons in **10**, the newly introduced carboximide α-proton was expected to be most acidic. Since it was reported that the imide-selective enolization of substrates with the both carboximide and ester structures was accomplished by careful base addition,[27] and that after asymmetric reaction, *N*-acyl fragments were selectively cleaved from the auxiliary by the imide-specific lithium hydroperoxide-mediated hydrolysis,[28] we proposed **9** as a chiral auxiliary that could be recovered and reused. However, its enolate formation gave a new compound even with a careful addition of LDA (1.2 equiv) to the cooled THF solution of **10** and a subsequent stirring for 0.5 h. This compound was an epimerized *trans*-configured carboximide **11**.[29] This result suggests that the α-proton of the carboxamide moiety was predominantly deprotonated by LDA to diminish the steric repulsion caused by *cis*-configuration.[30] Indeed, quenching lithium enolate generated in situ from **10** with acetic acid-*d* (99at.% D) afforded the deuterized **12** in 85% yield. The deuterium was incorporated mainly at the α-position of the carboxamide moiety (68% D) along with the α-position of the *N*-acylimide moiety (12% D).



Scheme 3. Synthesis of a *trans*-configured oxazolidinone derivative **14** from Boc-Pns-OH **13**.

This unexpected result prompted us to suggest that stable *trans*-configured oxazolidinone **14** was suitable for the auxiliary (Scheme 3). We synthesized **14** according to the procedure shown in Scheme 1, starting from Boc-Pns-OH **13** (Pns: phenylnorstatine), a 2*R* isomer of **6**, in 85% yield (3 steps). The relative stereochemistry of **14** was analyzed by NMR. Coupling constants of $J_{4,5}$ were 5.1 and 5.3 Hz, which are well consistent with the known value in *trans*-configuration[24] and a strong NOE signal was observed between H-5 and two protons at the benzylic position.[25] In addition, the most stable conformation of **14** obtained from conformational analysis showed a dihedral angle of 136.4° between two methine hydrogens (H-4 and H-5). This value and Karplus curve reasonably supported the observed coupling constant. From these observations, the configuration between H-4 and H-5 in **14** was confirmed as *trans*. Furthermore, the absolute stereochemistry of **14** was confirmed as 4*S*,5*R* by the X-ray crystal structural analysis of (*R*)-phenylethylamide **15**[31] derived from **14** (Fig. 2). In addition, it was found that the piperidine-4-carboxylic acid spacer extended outside from the oxazolidinone core, suggesting that this spacer does not interfere with the asymmetric reaction.

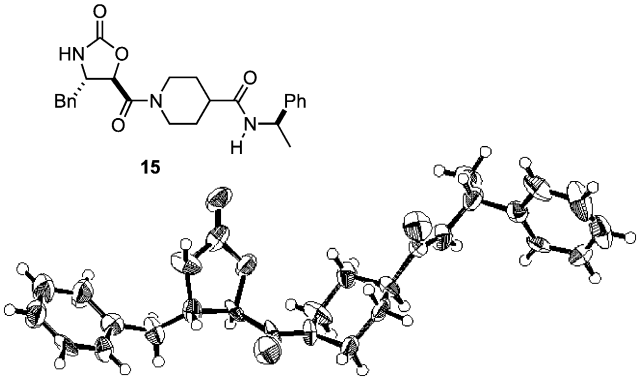
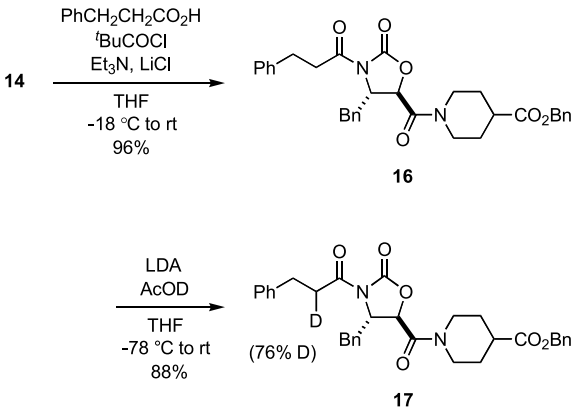


Figure 2. X-ray crystal structure of (*R*)-phenylethylamide **15**.

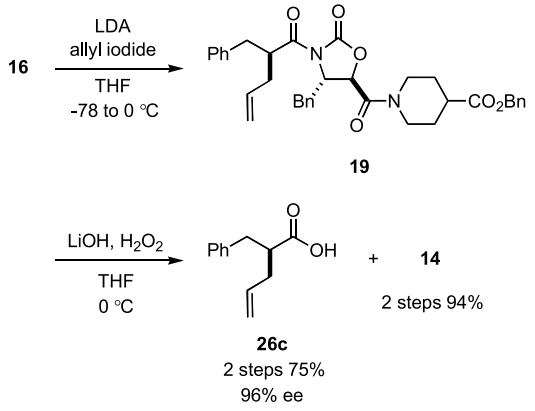
Next, we synthesized *N*-3-phenylpropionylated oxazolidinone **16** and subjected it to the deuterium labeling to confirm the enolization position (Scheme 4) by the same procedure described in Scheme 2. No particular change on TLC was observed during the enolization and the recovered product (88% yield) contained 76% of deuterized **17**, exclusively at the α-position of the desired carboximide moiety with unmodified **16**. This result suggests that the



Scheme 4. Deuterium incorporation to *trans*-configured carboximide **16**.

α-position of the imide *N*-acyl moiety in **16** has the most acidic α-proton, which is predominantly deprotonated by LDA. Self-condensation of **16** was not observed under this reaction condition.

With these positive observations, we examined the Evans' asymmetric allylation of the carboximide **16** as a model for alkylation (Scheme 5).[15] Briefly, to a solution of **16** in THF was added LDA (1.2 equiv) dropwise at −78 °C. After stirring for 0.5 h, the generated *Z*-*O*-enolate **18**[32] was treated with allyl iodide (3.0 equiv), and the temperature of the reaction mixture was gradually increased up to 0 °C over a period of 3 h. Resultant **19** was hydrolyzed by LiOOH without any purification.[28] The desired α-allylated carboxylic acid **26c** was obtained in good yield (2 steps 75%, an average of 87% for each of the two steps in the reaction sequence) and high stereoselectivity (96% ee),[33] which were comparable to the standard Evans' asymmetric allylation in solution-phase.[15] Oxazolidinone **14** was sufficiently recovered (94%) without epimerization, and no byproduct produced by the endocyclic cleavage of the oxazolidinone ring[28] was observed. These results proved that the *trans*-configured oxazolidinone **14** was effective as a chiral auxiliary and that the spacer moiety did not interfere with the asymmetric reaction.



Scheme 5. Asymmetric allylation of the *N*-3-phenylpropionylated carboximide **16**.

An energy minimization study of enolate intermediate **18** suggested that its conformation corresponds to that of the original chelation-controlled model proposed for standard Evans' chiral auxiliary system (Fig. 3).[15,34] Interestingly, this modeling also suggested that nucleophilic attack of the hydroperoxide anion to the oxazolidinone carbonyl for the endocyclic cleavage is effectively obstructed by the steric effect of the benzyl and carboxamide moieties.[35] From these data, we selected the structure of **14** originating from Pns as the candidate for solid-supported Evans' auxiliary.

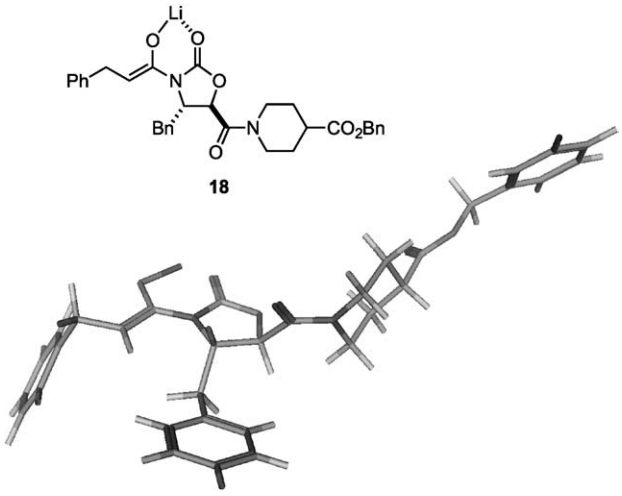


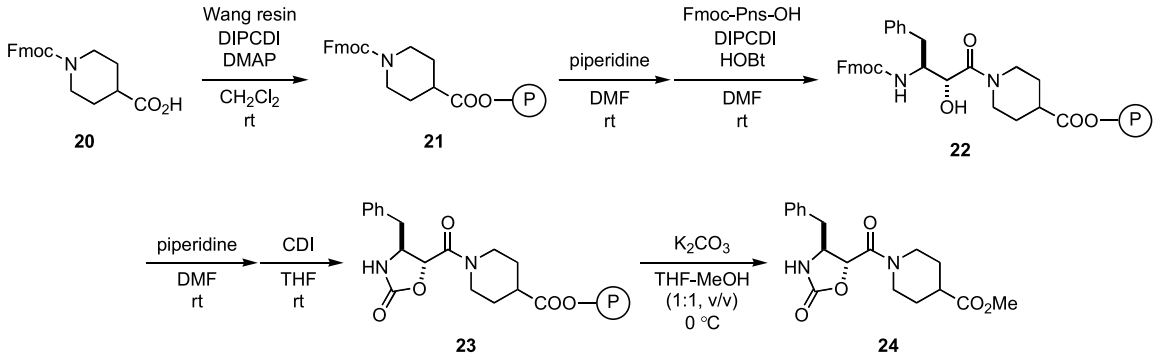
Figure 3. Energy minimization study of enolate intermediate **18**.

2.3. Solid-phase synthesis of Wang resin-supported chiral oxazolidinone 23

In our previous communication,[17] Wang resin-supported chiral oxazolidinone **23** was obtained by the carbodiimide-mediated coupling between Wang resin and the oxazolidinone-spacer unit prepared from **14** by hydrogenolysis. Since four-step solution-phase synthesis of this unit and its excess use (4 equiv) required for complete loading onto the resin were inefficient, in the present study we developed a more convenient synthetic route for **23** using Fmoc-based solid-phase method as shown in Scheme 6.[36] Namely, Fmoc-piperidine-4-carboxylic acid **20** was first loaded to Wang resin using the DIPCDI–DMAP (DIPCDI: 1,3-diisopropylcarbodiimide) method[37] in CH_2Cl_2. After Fmoc-deprotection of **21** with 20% piperidine, Fmoc-Pns-OH was coupled by the DIPCDI–HOBt method to give the dipeptide resin **22** followed by removal of the Fmoc group. The resultant 1,2-amino alcohol moiety was converted to oxazolidinone with CDI. Methanolysis of **23** with potassium carbonate in anhydrous THF–MeOH yielded the corresponding methyl ester **24** as a single isomer (95% for 6 steps). During this synthesis, neither epimerization at the 5-position nor byproduct formation such as aziridine and 1,2-aminoimidazole was observed.[23] It is noteworthy that all reactions in Scheme 6 proceeded smoothly at room temperature within a few hours, and multi-gram quantity of the oxazolidinone resin **23** with high loading yield was efficiently synthesized in just a day.

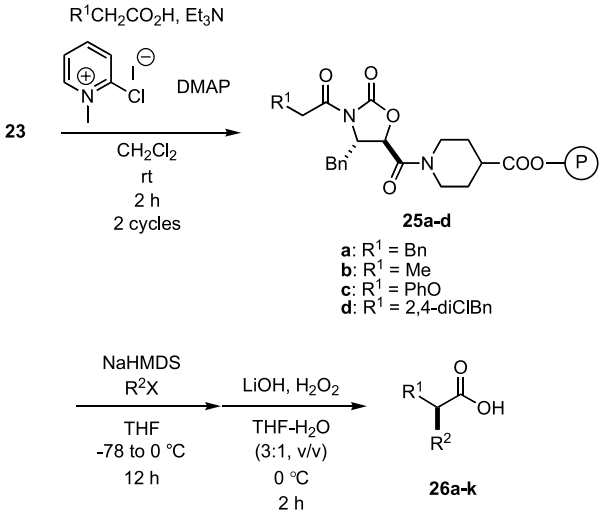
2.4. Solid-phase Evans' asymmetric alkylation with the oxazolidinone resin 23

At first, we investigated the solid-phase Evans' asymmetric allylation of the *N*-3-phenylpropionylated carboximide



Scheme 6. Solid-phase synthesis of Wang resin-supported oxazolidinone resin **23**.

resin **25a**, which was prepared from **23** by Mukaiyama method (Scheme 7).[38] It was found that the use of NaHMDS (3 equiv) as a base and gradual increase of the temperature of reaction mixture up to 0 °C over a period of 12 h in the alkylation reaction were quite effective.[39] After quenching the reaction mixture with saturated NH_4Cl aq, the allylated carboximide resin was recovered, washed, then subjected to the LiOOH-mediated hydrolysis. The desired chiral α-allylated carboxylic acid **26c** was obtained with high stereoselectivity (96% ee), which was equal to the model experiment in solution-phase (Table 1, entry 3). The absolute configuration of acid **26c** was determined in comparison to the reported specific rotation,[33] suggesting



Scheme 7. Solid-phase asymmetric Evans' alkylation.

that the asymmetric alkylation on resin **25a** also proceeded in the same chelation-controlled model as the solution-phase method.[15] During the hydrolytic cleavage, the ester linkage and oxazolidinone core were stable.[40] These encouraging results urged us to understand the generality of **23** in the Evans' asymmetric alkylation reaction. Several carboximide resins **25b–d** were prepared and subjected to the similar solid-phase alkylation reactions with a series of electrophiles (R^2X).[41] The results are summarized in Table 1. Favorably, not only highly reactive alkyl halides such as MeI and BnBr but also less reactive EtI reacted sufficiently under the same reaction conditions. Hydrolytic cleavage of the resultant resin afforded the corresponding chiral α-branched carboxylic acids **26a–k** with satisfying isolated yields (50–70%, for 3 steps) and enantiomeric excesses (84–97% ee).[42] Especially, in the asymmetric benzylation of carboximide resin **25b**, stereoselectivity was found to be 97% ee (Table 1, entry 6), which was better than the value reported by Burgess et al.,[11b] and was as high enough as in the corresponding solution-phase asymmetric alkylation utilizing the standard chiral 4-substituted oxazolidin-2-one.[15] The relatively lower yield was due to the fact that the yield includes the three-step process from the oxazolidinone resin **23** to the final alkylated product **26**. We consider that yield for two steps (alkylation and hydrolysis) is similar to that of the solution-phase method, and average yield calculated for each step was reasonably acceptable (79–89%). We assume that these successful results are attributed to our new polymer-anchoring strategy based on the connection at the 5-position of the oxazolidinone ring. This liberates the chiral differentiating benzyl group from the polystyrene backbone of the resin, freeing the auxiliary

Table 1. Results of the solid-phase asymmetric Evans' alkylations

Entry	25	R^1	R^2X	26	Yield[a] (%)	ee[b] (%)
1	**25a**	Bn-	MeI	**26a**	61(85)	85
2	**25a**	Bn-	EtI	**26b**	50(79)	88
3	**25a**	Bn-	Allyl-I	**26c**	68(88)	96
4	**25a**	Bn-	Propargyl-Br	**26d**	62(85)	96
5	**25a**	Bn-	$BrCH_2CO_2Et$	**26e**	62(85)	92
6	**25b**	Me-	BnBr	**26f**	70(89)	97
7	**25b**	Me-	4-BrBnBr	**26g**	68(88)	97
8	**25b**	Me-	4-NO_2BnBr	**26h**	55(82)	97
9	**25b**	Me-	2,4-diClBnI	**26i**	65(87)	97
10	**25c**	PhO-	Allyl-I	**26j**	50(79)	96
11	**25d**	2,4-diClBn-	MeI	**26k**	59(84)	84

[a] Combined yield of 3 steps starting from oxazolidinone resin **23**. Value in the parenthesis is the average yield for each step.
[b] Determined by chiral HPLC analysis after conversion to the corresponding (*S*)-α-methylbenzylamine-derived amides.

unit from the solid-support, which was not realized in the previous system based on the 4-position anchoring.

2.5. Recycling of the Wang resin-supported auxiliary 23

The recycling of the expensive auxiliary is one of the key points in the development of the polymer-supported chiral auxiliary. However, the recycling of the polymer-supported Evans' oxazolidinone has been reported in only one case of solid-phase 1,3-dipolar-cycloaddition,[14b] with a considerable reduction of regio- and stereo-selectivity depending on the cycle number up to three, although the reason was unclear.

Hence, the ability of recycling of the Wang resin-supported chiral auxiliary **23** was studied in the solid-phase asymmetric allylation, mentioned above, to obtain α-allylated carboxylic acid **26c** (Fig. 4). After the first cycle of allylation, the recovered chiral auxiliary resin **23** was washed and dried, then *N*-acylation with 3-phenylpropionic acid gave the corresponding carboximide resin **25a** again. After the continuous second to fourth solid-phase asymmetric allylation, the desired product **26c** was obtained in high enantioselectivity (96% ee each) (Table 2). Throughout these cycles, the product's stereoselectivity was maintained successfully, although the yield gradually decreased about

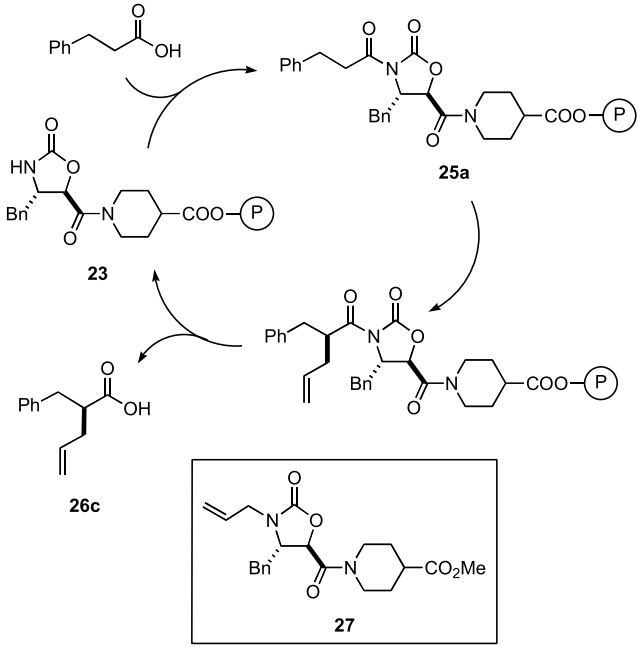


Figure 4. Recycling of the chiral auxiliary resin **23**.

Table 2. Recycling of the Wang resin-supported chiral oxazolidinone **23** in Evans' asymmetric allylation

Cycle	Yield[a] (%)	ee[b] (%)
1	68	96
2	59	96
3	49	96
4	42	96

[a] Combined yield of 3 steps starting from oxazolidinone resin **23**.
[b] Determined by chiral HPLC analysis after conversion to the corresponding (*S*)-α-phenylethylamides.

8% in each cycle. After the fourth cycle, the resin was cleaved by methanolysis to measure the amount of the residual auxiliary. Methyl ester **24**, which corresponds to the chiral auxiliary on the resin, was obtained in 71% yield along with the 22% of undesired *N*-allylated oxazolidinone **27**.[43] This indicated that the reduced yield obtained after recycling was due to the formation of byproduct **27**, in which the substrate-loading site was completely blocked by the allyl group (Fig. 4). It is thought that this unfavorable side reaction was induced by the partial elimination of the *N*-acyl moiety during enolate-alkylation steps. In fact, from detailed analysis of our solution-phase model experiment, 6% of *N*-allylated byproduct formation was detected. Therefore, the reaction conditions should be carefully adjusted to minimize unfavorable *N*-alkylation of the oxazolidinone resin.

3. Conclusion

In the development of an efficient tool to prepare versatile chiral synthon, we designed and synthesized Wang resin-supported Evans' chiral oxazolidinone derivative based on the novel polymer-anchoring strategy, which utilizes the 5-position of the oxazolidinone ring. Solid-phase asymmetric Evans' enolate-alkylation reaction on this auxiliary resin proceeded successfully and a series of chiral α-branched carboxylic acids was obtained in high stereoselectivities (up to 97% ee), which are parallel to those obtained in the comparative classical solution-phase experiments. Therefore, this is the first successful example that Evans' asymmetric alkylation reaction proceeded efficiently on a solid-support. Furthermore, recycling of this polymer-bound chiral auxiliary was achieved by maintaining stereoselectivity of the product. This newly developed solid-support auxiliary provides a variety of chiral α-branched carboxylic acid derivatives, which would be valuable synthetic building blocks in Medicinal Chemistry.[44] These results also suggest the significance of the polymer-anchoring strategy of chiral auxiliary to perform the satisfactory asymmetric induction in solid-phase organic synthesis. Further application studies to other solid-phase Evans' asymmetric reactions are now in progress.

4. Experimental

4.1. General

NMR spectra (^{1}H and ^{13}C) were recorded on a JEOL JNM-AL300 (^{1}H: 300 MHz; ^{13}C:75.5 MHz) or a Varian UNITY INOVA 400NB (^{1}H: 400 MHz; ^{13}C: 100 MHz) spectrometer and the chemical shift values were expressed in parts per million downfield from tetramethylsilane (TMS) as an internal standard. All coupling constants (*J* values) were reported in Hertz (Hz). Infrared (IR) spectra were recorded using a Shimadzu FT-IR-8300 Fourier Transform Infrared Spectrophotometer. Melting points were taken on a micro hot-stage apparatus (Yanagimoto) and were uncorrected. Mass spectra (MS) were obtained by electron impact (EI) ionization methods on JEOL GCmate MS-BU20. Elemental analyses were done on a Perkin–Elmer Series

CHNS/O Analyzer 2400. Specific rotations were recorded on a Horiba High-speed Accurate Polarimeter SEPA-300 with a sodium lamp and are reported as follows: $[\alpha]_D^T$ (c g/100 mL, solvent). The enantiomeric excess was determined by chiral HPLC analysis with JASCO HPLC systems consisting of the following: pump, 880-PU; detector, 875-UV, measured at 230 nm; column, Chiralcel® OD normal phase column (4.6×250 mm; Daicel Chemical Ind., Ltd, Tokyo, Japan); mobile phase, *n*-hexane/EtOH; flow rate, 1.0 mL/min. Solvents used for HPLC analysis were of HPLC grade. Organic extracts were dried over sodium sulfate (Na_2SO_4), filtered, and concentrated using a rotary evaporator at <40 °C bath temperature. Solids and involatile oils were vacuum dried at <2 mmHg. Solution- and solid-phase asymmetric alkylation reactions were carried out under Ar atmosphere, using anhydrous THF in flame-dried glassware. In the case of solid-phase asymmetric alkylation reactions, immobilized substrates were agitated by a slow stirring under Ar atmosphere.

4.2. Materials

Commercially available chemicals were obtained from Wako Pure Chemical Industries, Ltd (Osaka, Japan), Nacalai Tesque, Inc. (Kyoto, Japan), Aldrich Chemical Co., Inc. (Milwaukee, WI) and Tokyo Kasei Kogyo Co., Ltd (Tokyo, Japan), and used without further purification. Exceptionally, triethylamine was distilled from CaH_2 under Ar atmosphere and stored over KOH (pellet). Dehydrated MeOH and THF were purchased from Kanto Chemical Co., Inc. (Tokyo, Japan) and stored over pre-activated pellet-type molecular sieves 3A and 4A, respectively. Wang resin (0.80 mmol/g, styrene–1%DVB, 200–400 mesh) was purchased from Watanabe Chem. Ind., Ltd (Hiroshima, Japan). Boc-Apns-OH and H-Pns-OH were purchased from Nippon Kayaku (Tokyo, Japan). Boc- and Fmoc-Pns-OH were prepared from H-Pns-OH by the standard procedure. NaHMDS was used as supplied (Aldrich) as a solution in THF (1.0 M). Column chromatography was carried on Merck 107734 silica gel 60 (70–230 mesh). Analytical thin layer chromatography (TLC) was performed using Merck 105715 silica gel 60 F_{254} precoated plates (0.25 mm thickness) and compounds were visualized by UV illumination (254 nm) and by heating after dipping in 10% ethanolic solution of phosphomolybdic acid or after spraying ca. 0.7% ethanolic solution of ninhydrin. Preparative TLC was done with Merck 105717 silica gel 60 F_{254} plate (2.0 mm thickness).

4.3. Synthesis of *cis*-configured oxazolidinone 9 and *N*-3-phenylpropionylated carboximide 10

4.3.1. Benzyl *N*-{(2*S*,3*S*)-3-[(*tert*-butoxycarbonyl)-amino]-2-hydroxy-4-phenylbutanoyl}piperidine-4-carboxylate 8. To a solution of Boc-Apns-OH **6** (4.0 g, 13.5 mmol), benzyl piperidine-4-carboxylate HCl **7** (4.1 g, 16.2 mmol) and HOBt·H_2O (7.7 g, 16.2 mmol) in DMF (68 mL) was added EDC·HCl (3.1 g, 16.2 mmol) in parts at 0 °C. After stirring for 0.5 h at the same temperature, Et_3N (7.0 mL, 16.2 mmol) was added dropwise, then the reaction mixture was stirred overnight at room temperature. The solution was diluted with AcOEt and washed consecutively with 5% citric acid aq, 5% $NaHCO_3$ aq, water (×2) and brine. After the organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure. The resulting white powder **8** (5.5 g, 82%) was used for the next reaction without any purification. $R_f=0.44$ (*n*-hexane/AcOEt=1:1); mp 37–39 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.14 (m, 10H), 5.16, 5.13 (2d, 0.5×2H, $J=12.3$ Hz), 5.12 (s, 0.5×2H), 5.06 (br d, 0.5H, $J=8.4$ Hz), 5.02 (br d, 0.5H, $J=9.0$ Hz), 4.58 (d, 0.5H, $J=2.2$ Hz), 4.55 (d, 0.5H, $J=2.2$ Hz), 4.22–3.92 (m, 4H), 3.14, 3.06 (2ddd, 0.5×2H, $J=13.7$, 11.2, 3.1 Hz), 2.88, 2.54 (2ddd, 0.5×2H, $J=13.4$, 11.2, 3.1 Hz, partially overlapping with the next signal), 2.71–2.51 (m, 3H), 2.08–1.21 (m, 4H), 1.38 (s, 0.5×9H), 1.37 (s, 0.5×9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.5, 173.5, 169.9, 169.6, 155.6, 137.8, 135.7, 129.2, 129.1, 128.6, 128.4, 128.3, 128.2, 128.1, 126.5, 126.4, 79.6, 77.2, 69.9, 69.8, 66.5, 54.1, 53.4, 44.1, 42.0, 42.0, 40.7, 34.4, 34.2, 28.3, 27.6; $[\alpha]_D^{26}=+16.3$ (c 0.64, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 3690, 3441, 3038, 1728, 1699, 1639, 1497, 1367, 1238, 1169, 698 cm^{-1}; HRMS (EI): found M^+ 496.2576, $C_{28}H_{36}N_2O_6$ requires M^+ 496.2573. Anal. Calcd for $C_{28}H_{36}N_2O_6$: C, 67.72; H, 7.31; N, 5.64; found: C, 67.69; H, 7.46; N, 5.58.

4.3.2. Benzyl *N*-[(4*S*,5*S*)-4-benzyl-1,3-oxazolidin-2-one-5-carbonyl]piperidine-4-carboxylate 9. Compound **8** (5.4 g, 10.9 mmol) was treated with 4 M HCl/dioxane (45.0 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 2.5 h. After the solvent was removed under reduced pressure, the obtained colorless oil was dissolved in anhydrous THF (110 mL). To this solution was added Et_3N (2.3 mL, 16.4 mmol) dropwise at 0 °C, followed by CDI (2.7 g, 16.4 mmol). The cloudy reaction mixture was stirred overnight at room temperature, diluted with AcOEt, and washed consecutively with 5% citric acid aq, 5% $NaHCO_3$ aq, water and brine. After the organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was applied to silica-gel column chromatography (*n*-hexane/AcOEt=1:10) to yield **9** as a white powder (4.0 g, 86% for 2 steps). $R_f=0.27$ (*n*-hexane/AcOEt=1:10); mp 136–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.14 (m, 10H), 5.41 (d, 0.5H, $J=7.9$ Hz), 5.39 (d, 0.5H, $J=8.1$ Hz), 5.15 (s, 0.5×2H), 5.14 (s, 0.5×2H), 4.98 (br s, 0.5H), 4.92 (br s, 0.5H), 4.46, 4.23 (2dtd, 0.5×2H, $J=13.6$, 4.0,1.5 Hz, partially overlapping with the next signal), 4.28–4.18 (m, 1H), 3.76 (m, 0.5×2H), 3.25, 3.11 (2ddd, 0.5×2H, $J=13.6$, 10.3,3.3 Hz), 2.92–2.53 (m, 3H), 2.87–2.71 (m, 0.5×2H, partially overlapping with the next signal), 2.05–1.93 (m, 2H), 1.80–1.62 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.4, 173.4, 163.8, 163.7, 157.4, 157.3, 135.8, 135.6, 129.2, 129.1, 129.1, 128.9, 128.6, 128.4, 128.1, 127.3, 127.2, 75.1, 74.9, 66.5, 55.5, 55.4, 44.1, 43.9, 41.5, 41.2, 40.8, 40.0, 37.4, 37.3, 28.1, 28.1, 27.6, 27.4; $[\alpha]_D^{25}=-58.4$ (c 1.01, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 3030, 3020, 1774, 1730, 1666, 1231, 1207, 800, 791, 768, 714, 675 cm^{-1}; HRMS (EI): found M^+ 422.1843, $C_{24}H_{26}N_2O_5$ requires M^+ 422.1841. Anal. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63; found: C, 68.14; H, 6.28; N, 6.49.

4.3.3. Benzyl *N*-[(4*S*,5*S*)-4-benzyl-(3-phenylpropionyl)-1,3-oxazolidin-2-one-5-carbonyl]piperidine-4-carboxylate 10. To a solution of 3-phenylpropionic acid (1.8 g, 11.7 mmol) in anhydrous THF (30 mL) was added Et_3N

(3.1 mL, 22.5 mmol) and trimethylacetylchloride (1.3 mL, 10.8 mmol) dropwise at −18 °C. The reaction mixture was stirred at the same temperature for 0.5 h, then anhydrous LiCl (420 mg, 9.9 mmol) was added, followed by the slow addition of a solution of oxazolidinone **9** (3.8 g, 9.0 mmol) in anhydrous THF (20 mL). After the addition was completed, the reaction mixture was stirred overnight at room temperature. The solution was poured into ice-cold satd $NaHCO_3$ aq and the organic phase was extracted with AcOEt, washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting oil was applied to silica-gel column chromatography (*n*-hexane/AcOEt=4:1) to yield the desired compound **10** as a white solid (4.7 g, 95%). R_f= 0.48 (*n*-hexane/AcOEt=1:1); mp 153–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$). Major isomer δ 7.41–7.04 (m, 15H), 5.11–5.09 (m, 1H), 5.07 (s, 2H), 4.92–4.87 (m, 1H), 4.36–4.33 (m, 1H), 3.36–3.26 (m, 2H), 3.11–2.93 (m, 6H), 2.22 (tt, 1H, J=11.2, 3.7 Hz), 2.10 (td, 1H, J=12.6, 3.1 Hz), 1.89–1.85 (m, 1H), 1.63–1.38 (m, 3H); minor isomer δ 7.41–7.04 (m, 15H), 5.11–5.09 (m, 3H), 4.92–4.87 (m, 1H), 3.59 (ddd, 1H, J=13.6, 6.4, 4.0 Hz), 3.36–3.20 (m, 2H), 3.11–2.93 (m, 4H), 3.14, 2.87 (2ddd, 2H, J=13.4, 8.8, 3.7 Hz, partially overlapping with the next signal), 2.71–2.64 (m, 1H), 2.47–2.41 (m, 1H), 1.77–1.70 (m, 1H), 1.63–1.38 (m, 2H), 0.98–0.89 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.2, 172.9, 171.9, 171.9, 162.0, 161.9, 151.7, 151.6, 140.2, 135.7, 135.6, 135.5, 129.6, 129.5, 128.7, 128.6, 128.6, 128.5, 128.4, 128.4, 128.1, 127.2, 127.1, 126.3, 73.3, 66.5, 66.4, 57.6, 57.5, 43.3, 43.1, 41.1, 40.8, 40.4, 39.0, 36.9, 34.2, 34.2, 30.1, 27.5, 27.2, 26.8, 26.1; $[\alpha]_D^{25}=-25.2$ (c 1.16, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 1790, 1730, 1701, 1670, 1454, 1375, 1173, 718, 696 cm^{-1}; HRMS (EI): found M^+ 554.2410, $C_{33}H_{34}N_2O_6$ requires M^+ 554.2416. Anal. Calcd for $C_{33}H_{34}N_2O_6$: C, 71.46; H, 6.18; N, 5.05; found: C, 71.51; H, 6.40; N, 4.84.

4.3.4. Deuterium labeling study of the carboximide 10. Under Ar atmosphere, the solution of the carboximide **10** (146.5 mg, 0.264 mmol) in anhydrous THF (2.6 mL) was cooled to −78 °C (MeOH-dry ice bath), and LDA (1.8 M solution in heptane/THF/ethylbenzene, 0.18 mL, 0.32 mmol) was added dropwise. After stirring for 0.5 h at the same temperature, acetic acid-*d* (99at.% D) (0.31 mL, 5.28 mmol) was added slowly and the reaction mixture was stirred for 1 h at room temperature. The solution was poured into ice-cold satd NH_4Cl aq and the organic phase was extracted with AcOEt, washed with 5% $NaHCO_3$ aq, water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting oil was subjected to preparative TLC (*n*-hexane/AcOEt=3:2, 2 times development) to yield the products as a white powder (124.7 mg, 85%). The content of deuterium-incorporated **12** was detected by NMR. R_f=0.53 (*n*-hexane/AcOEt=1:1); mp 40–41 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.18 (m, 15H), 5.14, 5.10 (2d, 0.5×2H, J=12.3 Hz), 5.09 (s, 0.5×2H), 4.88 (d, 0.16H, J=4.6 Hz), 4.87 (d, 0.16H, J=4.4 Hz), 4.71–4.64 (m, 1H), 4.19 (dt, 0.5H, J=13.6, 4.2 Hz), 4.13 (dt, 0.5H, J=13.4, 4.2 Hz), 3.45–3.18 (m, 2.88H), 3.08–2.94 (m, 2H), 2.87–2.32 (m, 5H), 1.91–1.86 (m, 1H), 1.65–1.38 (m, 2H and 0.5H), 1.18–1.10 (m, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 173.3, 172.1, 172.1, 164.8, 164.7, 152.5, 152.4, 140.3, 140.3, 135.7, 135.6, 135.2, 129.6, 129.5, 129.3, 129.3, 128.6, 128.6, 128.5, 128.4, 128.4, 128.2, 128.1, 128.1, 127.7, 126.2, 71.8, 71.6, 71.5 (t, J=24.1 Hz), 66.5, 66.5, 59.2, 59.1, 58.9, 58.8, 43.5, 43.3, 41.7, 41.6, 40.4, 40.3, 37.8, 37.7, 37.1, 37.0, 30.2, 28.2, 28.0, 27.4, 27.3; $[\alpha]_D^{26}=-15.1$ (c 1.55, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 1796, 1732, 1703, 1661, 1454, 1379, 1198, 1173, 772, 756, 727, 700, 679, 667 cm^{-1}; HRMS (EI): found M^+ 555.2478, $C_{33}H_{33}DN_2O_6$ requires M^+ 555.2479. Anal. Calcd for $C_{33}H_{33}DN_2O_6$: C, 71.33; H+D, 6.35; N, 5.04; found: C, 71.26; H+D, 6.06; N, 4.99.

4.4. Synthesis of *trans*-configured oxazolidinone 14 and *N*-3-phenylpropionylated carboximide 16

4.4.1. Benzyl *N*-[(4*S*,5*R*)-4-benzyl-1,3-oxazolidin-2-one-5-carbonyl]piperidine-4-carboxylate 14. To a solution of Boc-Pns-OH **13** (12.4 g, 42.0 mmol), benzyl piperidine-4-carboxylate·HCl **7** (12.9 g, 50.4 mmol) and HOBt·H_2O (7.7 g, 50.4 mmol) in DMF (210 mL) was added EDC·HCl (9.7 g, 50.4 mmol) in parts at 0 °C. After stirring for 0.5 h at the same temperature, Et_3N (7.0 mL, 50.4 mmol) was added dropwise, then the reaction mixture was stirred overnight at room temperature. The solution was diluted with AcOEt and washed consecutively with 5% citric acid aq, 5% $NaHCO_3$ aq, water (×2) and brine. After the organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure. The resulting white powder (20.0 g, 96%) was used for the next reaction without any purification. R_f=0.52 (*n*-hexane/AcOEt=1:1); mp 34–36 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.21 (m, 10H), 5.17, 5.12 (2d, 0.5×2H, J=12.5 Hz), 5.10 (s, 0.5×2H), 4.87 (br d, 0.5H, J=10.8 Hz), 4.71 (br d, 0.5H, J=10.3 Hz), 4.28–4.01 (m, 4H), 3.13–2.68 (m, 5H), 2.62–2.47 (m, 1H), 2.08–1.33 (m, 4H), 1.39 (s, 0.5×9H), 1.38 (s, 0.5×9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.6, 173.3, 170.3, 155.3, 155.2, 137.9, 137.7, 135.8, 135.6, 129.3, 128.6, 128.5, 128.2, 128.1, 128.0, 126.7, 79.4, 66.9, 66.6, 66.3, 53.8, 53.1, 43.7, 43.3, 42.1, 41.7, 41.0, 40.2, 38.8, 38.6, 28.2, 27.5, 27.2, 27.1, 26.7; $[\alpha]_D^{25}=-20.0$ (c 0.47, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 3439, 3005, 1717, 1701, 1639, 1499, 1454, 1393, 1367, 1240, 1169, 700 cm^{-1}; HRMS (EI): found M^+ 496.2568, $C_{28}H_{36}N_2O_6$ requires M^+ 496.2573. Anal. Calcd for $C_{28}H_{36}N_2O_6$: C, 67.72; H, 7.31; N, 5.64; found: C, 67.65; H, 7.31; N, 5.90.

Obtained dipeptide (20.0 g, 40.3 mmol) was treated with 4 M HCl/dioxane (140 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 2.5 h. After the solvent was removed under reduced pressure, the colorless oil obtained was dissolved in anhydrous THF (400 mL). To this solution was added Et_3N (8.4 mL, 60.5 mmol) dropwise at 0 °C, followed by the addition of CDI (9.8 g, 60.5 mmol). The cloudy reaction mixture was stirred overnight at room temperature, diluted with AcOEt, and washed consecutively with 5% citric acid aq, 5% $NaHCO_3$ aq, water and brine. After the organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was applied to silica-gel column chromatography (*n*-hexane/AcOEt=1:2) to yield **14** as a white powder (15.0 g, 88% for 2 steps). R_f=0.55 (*n*-hexane/AcOEt=1:5); mp 91–93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.20 (m, 10H), 5.28 (br s, 0.5H,), 5.25 (br s, 0.5H), 5.14 (s, 0.5×2H), 5.12 (s, 0.5×2H), 4.80 (d, 0.5H, J=5.3 Hz), 4.79 (d, 0.5H, J=5.1 Hz),

4.69–4.64 (m, 1H), 4.40–4.37 (m, 0.5H), 4.19 (dt, 0.5H, J= 13.6, 4.2 Hz), 3.89–3.86 (m, 0.5H), 3.74–3.71 (m, 0.5H), 3.23, 3.0 (2br t, 0.5×2H, J=11.2 Hz, partially overlapping with the next signal), 3.06–2.77 (m, 3H), 2.67–2.55 (m, 1H), 1.99–1.59 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.7, 173.4, 164.4, 164.3, 156.9, 135.8, 135.8, 135.7, 129.1, 129.0, 128.6, 128.3, 128.3, 128.1, 127.3, 76.8, 76.6, 66.5, 55.3, 44.8, 44.5, 42.0, 41.8, 41.0, 41.0, 40.9, 40.3, 28.4, 28.2, 27.5, 27.5; $[\alpha]_D^{27}=-91.2$ (c 1.28, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 3452, 3036, 3007, 1771, 1730, 1653, 1456, 1387, 1313, 1271, 1238, 1209, 1173, 1038, 1011, 756, 737, 698, 667 cm^{-1}; HRMS (EI): found M^+ 422.1845, $C_{24}H_{26}N_2O_5$ requires M^+ 422.1842. Anal. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63; found: C, 67.99; H, 6.20; N, 6.55.

4.4.2. *N*-{*N*-[(4*S*,5*R*)-4-benzyl-1,3-oxazolidin-2-one-5-carbonyl]piperidine-4-carboxyl}-(*R*)-1-phenethyl amide 15. To a solution of oxazolidinone **14** (141.1 mg, 0.334 mmol) in MeOH (3.0 mL) and water (0.35 mL) was added 5% Pd-C (15.2 mg), and the reaction mixture was stirred for 3 h under H_2 atomosphere. The reaction mixture was purged with Ar, then filtered through a pad of Celite® with MeOH. After evaporation, the resulting oil was diluted with AcOEt, and washed consecutively with water and brine. After the organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure. To a solution of this carboxylic acid in DMF (4.0 mL) was added $HOBt\cdot H_2O$ (61.3 mg, 0.401 mmol) and EDC·HCl (61.3 mg, 0.401 mmol) at 0 °C. After the mixture was stirred for 0.5 h at the same temperature, (*R*)-α-methylbenzylamine (51.6 μL, 0.401 mmol) was added dropwise. The reaction mixture was stirred for overnight at room temperature, then diluted with AcOEt and washed with 5% citric acid aq, 5% $NaHCO_3$ aq, water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting crude product was purified by preparative TLC ($CHCl_3$/MeOH=10:1, 2 times development) to yield amide **15** as a white powder (133.7 mg, 92% for 2 steps). Recrystalization of the obtained white powder from $CHCl_3$ afforded the white needles, which was analyzed by X-ray crystallography. R_f=0.34 ($CHCl_3$/MeOH=10:1); mp 190–191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.20 (m, 10H), 5.75 (br d, 0.5H, J= 8.1 Hz), 5.72 (br d, 0.5H, J=8.4 Hz), 5.13 (q, 0.5H, J= 6.8 Hz), 5.11 (q, 0.5H, J=7.0 Hz), 5.06 (s, 0.5H), 5.05 (s, 0.5H), 4.81 (d, 0.5H, J=5.5 Hz), 4.79 (d, 0.5H, J=5.7 Hz), 4.69–4.64 (m, 1H), 4.56–4.52 (m, 0.5H), 4.45–4.39 (m, 0.5H), 3.95–3.99 (m, 0.5H), 3.87–3.82 (m, 0.5H), 3.16, 2.87 (2ddd, 0.5×2H, J=14.3, 11.5, 2.9 Hz, partially overlapping with the next signal), 3.01–2.67 (m, 3H), 2.39–2.29 (m, 1H), 1.94–1.54 (m, 4H), 1.50 (d, 0.5×3H, J= 7.0 Hz), 1.48 (d, 0.5×3H, J=6.8 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 172.8, 165.6, 165.5, 157.4, 145.0, 144.8, 136.3, 136.2, 129.6, 129.5, 128.6, 128.3, 126.8, 126.6, 125.8, 74.3, 74.1, 55.8, 55.5, 47.6, 44.0, 41.4, 41.3, 28.9, 28.1, 27.7, 22.5; $[\alpha]_D^{25}=+9.4$ (c 1.05, MeOH); HRMS (EI): found M^+ 435.2157, $C_{25}H_{29}N_3O_4$ requires M^+ 435.2158.

4.4.3. Crystallography of amide 15. Diffraction data for **15** were collected on a Rigaku AFC7R diffractometer with graphite monochromated Cu Kα radiation (λ=1.54178 Å) and a rotating anode generator. All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation. Formula $C_{25}H_{29}N_3O_4$, formula weight=435.52, orthorhombic, space group $P2_12_12_1$ (#19), a=17.986(2), b=23.841(2), c=5.269(3) Å, V=2259(1) Å^3, Z=4, D_{calc}=1.280 g/cm^3, F_{000}=928.00, μ(Cu Kα)=7.10 cm^{-1}. Total of 1554 unique reflections (complete for $2\theta<110°$) was used in the solution and refinement of structure. The structure was solved by direct methods using SAPI91,[45] and expanded using Fourier techniques with DIRDIF94 program.[46] The final refinement was done by the full-matrix least-squares method with anisotropic thermal parameters for all non-hydrogen atoms, and hydrogen atoms were included but not refined. The final R value was 0.238 (R_w=0.087).

4.4.4. Benzyl *N*-[(4*S*,5*R*)-4-benzyl-(3-phenylpropionyl)-1,3-oxazolidin-2-one-5-carbonyl]piperidine-4-carboxylate 16. To a solution of 3-phenylpropionic acid (6.8 g, 45.2 mmol) in anhydrous THF (100 mL) was added Et_3N (12.2 mL, 87.0 mmol) and trimethylacetylchloride (5.2 mL, 41.8 mmol) dropwise at -18 °C. The reaction mixture was stirred at the same temperature for 0.5 h, then anhydrous LiCl (1.6 g, 38.3 mmol) was added, followed by the slow addition of a solution of oxazolidinone **14** (14.7 g, 34.8 mmol) in anhydrous THF (75 mL). After the addition was completed, the reaction mixture was stirred overnight at room temperature. The solution was poured into ice-cold satd $NaHCO_3$ aq and the organic phase was extracted with AcOEt, washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting oil was applied to silica-gel column chromatography (*n*-hexane/AcOEt=4:1) to yield the desired compound **16** as a white solid (18.5 g, 96%). R_f= 0.52 (*n*-hexane/AcOEt=1:1); mp 39–41 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.18 (m, 15H), 5.14, 5.10 (2d, 0.5×2H, J=12.3 Hz), 5.09 (s, 0.5×2H), 4.88 (d, 0.5H, J= 4.4 Hz), 4.87 (d, 0.5H, J=4.4 Hz), 4.71–4.65 (m, 1H), 4.19 (dt, 0.5H, J=13.7, 4.0 Hz), 4.13 (dt, 0.5H, J=13.4, 4.2 Hz), 3.45–3.18 (m, 3H), 3.08–2.94 (m, 2H), 2.83–2.33 (m, 5H), 1.92–1.86 (m, 1H), 1.65–1.39 (m, 2H and 0.5H), 1.19–1.09 (m, 0.5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.1, 171.9, 164.7, 164.5, 152.4, 152.3, 140.2, 135.6, 135.5, 135.0, 129.4, 129.3, 129.2, 129.1, 128.4, 128.3, 128.3, 128.2, 128.2, 127.9, 127.9, 127.5, 126.0, 71.7, 71.5, 66.3, 59.2, 58.8, 43.3, 43.1, 41.5, 41.4, 40.2, 40.1, 37.6, 37.5, 36.9, 36.9, 30.0, 28.0, 27.9, 27.2; $[\alpha]_D^{26}=-16.7$ (c 2.09, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 3040, 3007, 1794, 1728, 1701, 1659, 1497, 1454, 1379, 1310, 1292, 1263, 1244, 1171, 1103, 1078, 1030, 694 cm^{-1}; HRMS (EI): found M^+ 554.2410, $C_{33}H_{34}N_2O_6$ requires M^+ 554.2416. Anal. Calcd for $C_{33}H_{34}N_2O_6$: C, 71.46; H, 6.18; N, 5.05; found: C, 71.28; H, 5.99; N, 5.34.

4.4.5. Deuterium labeling study of the carboximide 16. Under Ar atmosphere, the solution of the carboximide **16** (142.4 mg, 0.257 mmol) in anhydrous THF (2.6 mL) was cooled to −78 °C (MeOH-dry ice bath), and LDA (1.8 M solution in heptane / THF / ethylbenzene, 0.17 mL, 0.31 mmol) was added dropwise. After stirring for 0.5 h at the same temperature, acetic acid-*d* (99at.% D) (0.30 mL, 5.14 mmol) was added slowly, then cooling bath was removed and the reaction mixture was stirred for 1 h at room

temperature. The solution was poured into ice-cold satd NH_4Cl aq and the organic phase was extracted with AcOEt, washed with 5% $NaHCO_3$ aq, water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting oil was subjected to preparative TLC (*n*-hexane/AcOEt=1:1) to yield the products as a white powder (125.7 mg, 88%). The content of deuterium-incorporated **17** was detected by NMR. R_f=0.53 (*n*-hexane/AcOEt=1:1); mp 39–40 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.18 (m, 15H), 5.14, 5.10 (2d, 0.5×2H, J=12.3 Hz), 5.09 (s, 0.5×2H), 4.88 (d, 0.5H, J=4.6 Hz), 4.87 (d, 0.5H, J=4.6 Hz), 4.71–4.64 (m, 1H), 4.19 (dt, 0.5H, J=13.6, 4.0 Hz), 4.13 (dt, 0.5H, J=13.2, 4.0 Hz), 3.44–3.18 (m, 2.24H), 3.06–2.94 (m, 2H), 2.83–2.33 (m, 5H), 1.91–1.86 (m, 1H), 1.64–1.38 (m, 2H and 0.5H), 1.18–1.08 (m, 0.5H); ^{2}H NMR (400 MHz, $CHCl_3$) δ 3.32 (s, 0.76D); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.3, 172.1, 164.8, 164.6, 152.5, 152.4, 140.3, 135.7, 135.6, 135.2, 129.5, 129.5, 129.3, 129.3, 128.6, 128.5, 128.4, 128.4, 128.1, 127.7, 126.2, 71.8, 71.6, 66.5, 59.2, 58.9, 43.5, 43.3, 41.7, 41.6, 40.3, 37.8, 37.7, 37.1, 37.0, 36.7 (t, J=19.9 Hz), 30.1, 30.1, 28.2, 28.0, 27.3; $[\alpha]_D^{27}=-14.8$ (*c* 1.69, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 1792, 1732, 1703, 1661, 1454, 1371, 1236, 1196, 1186, 1173, 797, 725, 700, 673 cm^{-1}; HRMS (EI): found M^+ 555.2482, $C_{33}H_{33}DN_2O_6$ requires M^+ 555.2479. Anal. Calcd for $C_{33}H_{33}DN_2O_6$: C, 71.33; H+D, 6.35; N, 5.04; found: C, 71.17; H+D, 6.29; N, 5.01.

4.5. Preparation of the Wang resin-supported oxazolidinone 23 by Fmoc-based solid-phase synthesis

Wang resin (0.80 mmol/g resin) (5.0 g, 4.0 mmol) in a cap-fitted reaction vessel was washed with CH_2Cl_2 (20 mL, ×5), then Fmoc-piperidine-4-carboxylic acid **20** (4.2 g, 12.0 mmol) and CH_2Cl_2 (30 mL) were charged. DIPCDI (1.9 mL, 12.0 mmol) was added, followed by the addition of DMAP (48.7 mg, 0.4 mmol). The heterogeneous reaction mixture was vigorously shaken for 2 h at room temperature, then filtered and washed with DMF (20 mL, ×5). The obtained white resin **21** was then washed with piperidine in DMF (20%, v/v) (20 mL, ×5) and treated with piperidine in DMF (20%, v/v) (30 mL) for 0.5 h at room temperature. The solvent and reagent were drained and the resin was washed with DMF (20 mL), $CHCl_3$ (20 mL), DMF (20 mL) (×5, sequentially). Next, Fmoc-Pns-OH (5.0 g, 12.0 mmol), HOBt·H_2O (1.8 g, 12.0 mmol), DMF (30 mL) and DIPCDI (1.9 mL, 12.0 mmol) were added, and the heterogenious reaction mixture was vigorously shaken for 2 h at room temperature, then filtered and washed with DMF (20 mL, ×5). The aliquot of the resultant resin **22** was applied to the Kaiser-Test[47] to check the reaction progress. Starting secondary amine resin was positive (pale orange), whereas the dipeptide-bound resin **22** was negative (colorless). The obtained resin **22** was washed with piperidine in DMF (20%, v/v) (20 mL, ×5) and treated with piperidine in DMF (20%, v/v) (30 mL) for 0.5 h at room temperature. The solvent and reagent were drained and the resin was washed with DMF (20 mL), $CHCl_3$ (20 mL), DMF (20 mL) (×5, sequentially). The obtained amino alcohol resin was washed with THF (20 mL, ×5), then CDI (1.9 g, 12.0 mmol) and anhydrous THF (30 mL) were added. The heterogenious reaction mixture was vigorously shaken for 3 h at room temperature, then filtered and washed with THF (20 mL, ×5). Kaiser-Test of the starting primary amine resin was positive (blue), whereas the oxazolidinone resin **23** was negative (colorless). The obtained resin was washed with $CHCl_3$ (20 mL) and MeOH (20 mL) (×5, sequentially), then overnight drying in vacuo afforded the desired pale yellowish oxazolidinone resin **23** (6.3 g) with loading rate of 0.61 mmol/g.

4.5.1. *O*-Wang resin-supported *N*-[(9*H*-9-fluorenylmethoxy)carbonyl]piperidine-4-carboxylic acid 21. FT-IR (KBr) ν_{max} 1736, 1719 cm^{-1}.

4.5.2. *O*-Wang resin-supported *N*-((2*R*,3*S*)-3-{[(9*H*-9-fluorenylmethoxy)carbonyl]amino}-2-hydroxy-4-phenylbutanoyl)piperidine-4-carboxylic acid 22. FT-IR (KBr) ν_{max} 3398, 1733, 1718, 1638 cm^{-1}.

4.5.3. *O*-Wang resin-supported *N*-[(4*S*,5*R*)-4-benzyl-1,3-oxazolidin-2-one-3-carbonyl]piperidine-4-carboxylic acid 23. FT-IR (KBr) ν_{max} 1763, 1740, 1655 cm^{-1}.

4.5.4. Methanolysis of the oxazolidinone resin 23 to afford the methyl *N*-[(4*S*,5*R*)-4-benzyl-1,3-oxazolidin-2-one-5-carbonyl]piperidine-4-carboxylate 24. Oxazolidinone-loaded resin **23** (129.9 mg, 0.083 mmol) was swollen in anhydrous THF (0.85 mL) and anhydrous MeOH (0.85 mL), then potassium carbonate (22.9 mg, 0.166 mmol) was added in one portion at 0 °C. The heterogeneous reaction mixture was gently stirred for 2 h at room temperature. The reaction was quenched by the addition of satd NH_4Cl aq, and the resultant resin was removed by filtration. The filtrate was extracted with AcOEt, and washed with water and brine, then dried over Na_2SO_4. After solvent removal, the remaining crude oil was purified by preparative TLC (*n*-hexane/AcOEt=1:10) to yield the oxazolidinone methyl ester **24** as a white solid (27.4 mg, 95% in 6 steps from Wang resin). R_f=0.30 (*n*-hexane/AcOEt=1:5); mp 39–40 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.21 (m, 5H), 5.73 (br s, 1H), 4.82 (d, 0.5H, J=5.5 Hz), 4.80 (d, 0.5H, J=5.5 Hz), 4.67–4.62 (m, 1H), 4.39–4.34 (m, 0.5H), 4.19 (dt, 0.5H, J=13.6, 4.0 Hz), 3.83–3.79 (m, 0.5H), 3.70–3.65 (m, 0.5H, partially overlapping with the next signal), 3.70 (s, 0.5×3H), 3.68 (s, 0.5×3H), 3.20, 3.00 (2ddd, 0.5×2H, J=14.1, 10.6, 3.1 Hz, partially overlapping with the next signal), 2.99–2.78 (m, 3H), 2.61–2.50 (m, 1H), 1.96–1.54 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.3, 174.1, 164.5, 164.4, 157.1, 135.8, 135.7, 129.1, 128.8, 127.1, 76.4, 76.3, 55.4, 55.3, 51.8, 44.7, 44.4, 41.9, 41.7, 40.8, 40.7, 40.6, 40.1, 28.3, 28.1, 27.4; $[\alpha]_D^{25}=-104.4$ (*c* 0.55, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 3454, 3007, 2955, 1771, 1732, 1655, 1456, 1437, 1383, 1317, 1269, 1240, 1194, 1177, 1040, 1015, 760, 745 cm^{-1}; HRMS (EI): found M^+ 346.1526, $C_{18}H_{22}N_2O_5$ requires M^+ 346.1528. Anal. Calcd for $C_{18}H_{22}N_2O_5\cdot0.25H_2O$: C, 61.61; H, 6.46; N, 7.98; found: C, 61.99; H, 6.26; N, 7.96.

4.6. General procedure for *N*-acylation of the Wang resin-supported oxazolidinone resin 23, solid-phase asymmetric alkylation, lithium hydroperoxide-mediated hydrolysis, and the derivatization to the (*S*)-phenylethylamide for enantiomeric excess determination

Oxazolidinone-loaded resin **23** in a polystyrene reactor was washed with CH_2Cl_2 (×5), then the corresponding

carboxylic acid (3.0 equiv), 2-chloro-1-methylpyridinium iodide (3.0 equiv) and anhydrous CH_2Cl_2 (0.08 mmol resin/mL) were added. The mixture was shaken for 10 min, followed by the addition of Et_3N (5.0 equiv) and DMAP (0.3 equiv). The reaction mixture was shaken for 2 h at room temperature and filtered, then the resultant resin was washed with CH_2Cl_2 (×5). The reaction was repeated once again, and the obtained resin was washed with DMF, $CHCl_3$ and MeOH (×5, sequentially), then overnight drying in vacuo afforded the desired carboximide resin **25**. Under Ar atmosphere, carboximide resin **25** in a glass reaction vessel was swollen in THF (20 mL/mmol resin) for 10 min at room temperature, and the heterogeneous mixture was cooled to −78 °C (MeOH-dry ice bath), followed by the dropwise addition of 1.0 M THF solution of NaHMDS (3.0 equiv). After continuously stirring for 1 h at the same temperature, the corresponding alkyl halide (10.0 equiv) was added. The temperature of the reaction mixture was gradually increased up to 0 °C over 12 h with gentle stirring, then quenched by the addition of satd NH_4Cl aq, and tri-phase reaction mixture was stirred for additional 15 min. at 0 °C. The resultant resin was separated from the reaction mixture by filtration, followed by washing with THF-H_2O (1:1), THF and MeOH (×5, sequentially). Then, the resin was dried well in the desiccator under reduced pressure for 3 h. THF-H_2O (3:1, v/v) (0.05 mmol resin/mL) was added to the α-alkylated carboximide resin, and the resin was swollen for 10 min. at 0 °C. Next, 30% aqueous H_2O_2 (6.0 equiv) and $LiOH\cdot H_2O$ (3.0 equiv) were added. After gentle stirring for 2 h at the same temperature, the reaction was quenched by the addition of 1.5 N $NaHSO_3$ aq, and the deacylated resin was filtered off. The filtrate was acidified to pH 2 with 1 N HCl aq, and extracted with AcOEt. The extract was washed with brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative TLC to yield the desired α-alkylated carboxylic acids **26**. The recovered oxazolidinone resin **23** was washed with THF, $CHCl_3$ and MeOH (×5, sequentially), then dried in the desiccator under reduced pressure. Determination of the enantiomeric excess of the obtained carboxylic acids **26** was carried out by derivatization to the corresponding (*S*)-phenylethyl amides and chiral HPLC analysis. To a 0.05 M solution of the acids **26** in DMF was added $HOBt\cdot H_2O$ (1.2 equiv) and EDC·HCl (1.2 equiv) at 0 °C. The mixture was stirred for 0.5 h at the same temperature, and (*S*)-phenylethylamine (1.2 equiv) was added dropwise. The reaction mixture was stirred overnight at room temperature, then diluted with AcOEt and washed with 5% citric acid aq, 5% $NaHCO_3$ aq, water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting amide was subjected to the HPLC analysis without any purification. Enantiomeric excess was calculated from the peak areas of the corresponding two diastereomers.

4.6.1. (*S*)-2-Benzylpropanoic acid 26a. The title compound **26a** was obtained according to the general procedure using the oxazolidinone resin **23** (277.5 mg, 0.169 mmol). Purification by preparative TLC (*n*-hexane/AcOEt=1:1) gave **26a** as a colorless oil (16.8 mg, 61% yield in 3 steps from oxazolidinone resin **23**). R_f=0.63 (*n*-hexane/AcOEt=1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.17 (m, 5H), 3.08 (dd, 1H, J=13.0, 6.1 Hz), 2.83–2.71 (m, 1H), 2.67 (dd, 1H, J=13.0, 7.9 Hz), 1.18 (d, 3H, J=6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.7, 139.0, 129.0, 128.4, 126.4, 41.1, 39.3, 16.5; $[\alpha]_D^{28}$=+20.6 (*c* 0.87, $CHCl_3$): lit.,[48] $[\alpha]_D$=+25.5 (*c* 1.00, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 3038, 2980, 1709, 1454, 1238, 719, 698, 675 cm^{-1}; HRMS (EI): found M^+ 164.0838, $C_{10}H_{12}O_2$ requires M^+ 164.0837. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37; found: C, 73.25; H, 7.47. Enantiomeric excess was 85% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=30/1, 1.0 mL/min, 230 nm), major isomer=13.1 min, minor isomer=16.8 min.

4.6.2. (*S*)-2-Benzylbutanoic acid 26b. The title compound **26b** was obtained according to the general procedure using the oxazolidinone resin **23** (193.8 mg, 0.118 mmol). Purification by preparative TLC ($CHCl_3$/MeOH=10:1) gave **26b** as a colorless oil (10.6 mg, 50% yield in 3 steps from oxazolidinone resin **23**). R_f=0.53 ($CHCl_3$/MeOH=10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.16 (m, 5H), 2.98 (dd, 1H, J=13.6, 7.7 Hz), 2.75 (dd, 1H, J=13.6, 6.8 Hz), 2.66–2.57 (m, 1H), 1.72–1.54 (m, 2H), 0.96 (t, 3H, J=7.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.3, 139.1, 128.9, 128.4, 126.4, 48.8, 37.7, 24.7, 11.6; $[\alpha]_D^{26}$=+30.7 (*c* 0.86, benzene): lit.,[49] $[\alpha]_D^{24}$=+34.7 (*c* 8.45, benzene); FT-IR ($CHCl_3$) ν_{max} 1707, 1462, 1383, 1096, 899, 696, 652 cm^{-1}; HRMS (EI): found M^+ 178.0999, $C_{11}H_{14}O_2$ requires M^+ 178.0994. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; found: C, 73.99; H, 7.99. Enantiomeric excess was 88% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=30/1, 1.0 mL/min, 230 nm), major isomer=11.3 min, minor isomer=16.1 min.

4.6.3. (*S*)-2-Benzyl-4-pentenoic acid 26c. The title compound **26c** was obtained according to the general procedure using the oxazolidinone resin **23** (302.1 mg, 0.184 mmol). Purification by preparative TLC ($CHCl_3$/MeOH=10:1) gave **26c** as a colorless oil (23.8 mg, 68% yield in 3 steps from oxazolidinone resin **23**). R_f=0.50 ($CHCl_3$/MeOH=10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.16 (m, 5H), 5.78 (ddt, 1H, J=17.1, 10.3,7.0 Hz), 5.12–5.05 (m, 2H), 3.03–2.94 (m, 1H), 2.82–2.72 (m, 2H), 2.44–2.25 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.7, 138.8, 134.7, 128.9, 128.5, 126.5, 117.5, 46.9, 37.3, 35.6; $[\alpha]_D^{26}$=+24.0 (*c* 1.27, $CHCl_3$): lit.,[33] $[\alpha]_D^{25}$=+19.2 (*c* 12.2, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 3084, 3067, 3038, 1709, 922, 802, 775, 764, 746, 739, 729, 721, 700, 675, 667 cm^{-1}; HRMS (EI): found M^+ 190.0989, $C_{12}H_{14}O_2$ requires M^+ 190.0994. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42; found: C, 75.50; H, 7.50. Enantiomeric excess was 96% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=30/1, 1.0 mL/min, 230 nm), major isomer=11.6 min, minor isomer=15.2 min.

4.6.4. (*S*)-2-Benzyl-4-pentynoic acid 26d. The title compound **26d** was obtained according to the general procedure using the oxazolidinone resin **23** (206.9 mg, 0.126 mmol). Purification by preparative TLC ($CHCl_3$/MeOH=10:1) gave **26d** as a colorless oil (14.7 mg, 62% yield in 3 steps from oxazolidinone resin **23**). R_f=0.44 ($CHCl_3$/MeOH=10:1); ^{1}H

NMR (300 MHz, $CDCl_3$) δ 7.31–7.20 (m, 5H), 3.09 (dd, 1H, J=13.4, 6.6 Hz), 2.99–2.85 (m, 2H), 2.44 (dd, 2H, J=6.4, 2.6 Hz), 2.06 (t, 1H, J=2.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 179.5, 138.1, 129.0, 128.5, 126.7, 80.9, 70.6, 45.9, 36.3, 20.0; $[\alpha]_D^{26}=-10.9$ (c 1.24, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 3308, 1719, 1217, 1200, 770, 700, 671 cm^{-1}; HRMS (EI): found M^+ 188.0835, $C_{12}H_{12}O_2$ requires M^+ 188.0837. Anal. Calcd for $C_{12}H_{12}O_2\cdot 0.25H_2O$: C, 74.78; H, 6.54; found: C, 75.14; H, 6.57. Enantiomeric excess was 96% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=30/1, 1.0 mL/min, 230 nm), major isomer=16.4 min, minor isomer=18.6 min.

4.6.5. (*R*)-2-Benzyl-4-ethoxy-4-oxobutanoic acid 26e. The title compound **26e** was obtained according to the general procedure using the oxazolidinone resin **23** (259.8 mg, 0.158 mmol). Purification by preparative TLC ($CHCl_3$/MeOH=10:1) gave **26e** as a colorless oil (23.1 mg, 62% yield in 3 steps from oxazolidinone resin **23**). R_f=0.41 ($CHCl_3$/MeOH=10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.17 (m, 5H), 4.11 (q, 2H, J=7.2 Hz), 3.21–3.10 (m, 2H), 2.83–2.74 (m, 1H), 2.64 (dd, 1H, J=17.0, 8.9 Hz), 2.41 (dd, 1H, J=17.0, 4.6 Hz), 1.22 (t, 3H, J=7.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 179.5, 171.7, 137.9, 129.1, 128.6, 126.8, 60.8, 42.8, 37.4, 34.8, 14.1; $[\alpha]_D^{26}=+10.6$ (c 1.15, $CHCl_3$): lit.,[50] $[\alpha]_D^{28}=+10.0$ (c 2.9, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 1732, 1717, 910, 777, 754, 739, 721, 700, 679, 652 cm^{-1}; HRMS (EI): found M^+ 236.1051, $C_{13}H_{16}O_4$ requires M^+ 236.1048. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83; found: C, 65.93; H, 6.81. Enantiomeric excess was 92% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=30/1, 1.0 mL/min, 230 nm), major isomer=15.7 min, minor isomer=16.6 min.

4.6.6. (*R*)-2-Benzylpropanoic acid 26f. The title compound **26f** was obtained according to the general procedure using the oxazolidinone resin **23** (236.5 mg, 0.144 mmol). Purification by preparative TLC (*n*-hexane/AcOEt=1:1) gave **26f** as a colorless oil (16.6 mg, 70% yield in 3 steps from oxazolidinone resin **23**). R_f=0.63 (*n*-hexane/AcOEt=1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.17 (m, 5H), 3.08 (dd, 1H, J=13.0, 6.1 Hz), 2.80–2.70 (m, 1H), 2.67 (dd. 1H, J=13.0, 7.9 Hz), 1.18 (d, 3H, J=6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 182.3, 139.0, 129.0, 128.4, 126.4, 41.2, 39.3, 16.5; $[\alpha]_D^{28}=-30.7$ (c 1.04, $CHCl_3$): lit.,[51] $[\alpha]_D^{22}=-30.1$ (c 1.00, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 1707, 1464, 1381, 1231, 893, 800, 694, 648 cm^{-1}; HRMS (EI): found M^+ 164.0830, $C_{10}H_{12}O_2$ requires M^+ 164.0837. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37; found: C, 72.94; H, 7.31. Enantiomeric excess was 97% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=30/1, 1.0 mL/min, 230 nm), major isomer=16.8 min, minor isomer=13.1 min.

4.6.7. (*R*)-3-(4-Bromophenyl)-2-methylpropanoic acid 26g. The title compound **26g** was obtained according to the general procedure using the oxazolidinone resin **23** (185.5 mg, 0.113 mmol). Purification by preparative TLC ($CHCl_3$/MeOH=10:1) gave **26g** as a white powder (18.6 mg, 68% yield in 3 steps from oxazolidinone resin **23**). R_f=0.55 ($CHCl_3$/MeOH=10:1); mp 60–62 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, 2H, J=8.4 Hz), 7.06 (d, 2H, J=8.4 Hz), 3.01 (dd, 1H, J=13.0, 6.4 Hz), 2.77–2.68 (m, 1H), 2.64 (dd, 1H, J=13.0, 7.5 Hz), 1.18 (d, 3H, J=6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.1, 138.0, 131.5, 130.7, 120.3, 40.9, 38.7, 16.6; $[\alpha]_D^{26}=-26.4$ (c 1.02, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 3030, 1711, 1466, 1381, 1231, 1215, 1097, 893, 800, 787, 750, 733, 725, 696, 677, 654 cm^{-1}; HRMS (EI): found M^+ 241.9949, $C_{10}H_{11}BrO_2$ requires M^+ 241.9942. Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56; found: C, 49.56; H, 4.66. Enantiomeric excess was 97% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=50/1, 1.0 mL/min, 230 nm), major isomer=30.8 min, minor isomer=27.5 min.

4.6.8. (*R*)-3-(4-Nitrophenyl)-2-methylpropanoic acid 26h. The title compound **26h** was obtained according to the general procedure using the oxazolidinone resin **23** (256.2 mg, 0.156 mmol). Purification by preparative TLC ($CHCl_3$/MeOH=10:1) gave **26h** as a pale yellowish powder (21.2 mg, 65% yield in 3 steps from oxazolidinone resin **23**). R_f=0.44 ($CHCl_3$/MeOH=10:1); mp 101–103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, 2H, J=8.8 Hz), 7.36 (d, 2H, J=8.8 Hz), 3.15 (dd, 1H, J=16.5, 9.9 Hz), 2.86–2.77 (m, 2H), 1.23 (d, 3H, J=6.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.0, 146.9, 146.7, 129.8, 123.7, 40.8, 39.0, 16.8; $[\alpha]_D^{25}=-36.9$ (c 1.14, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 1713, 1607, 1522, 1464, 1381, 1348, 1231, 1097, 895, 733, 694, 648 cm^{-1}; HRMS (EI): found M^+ 209.0683, $C_{10}H_{11}NO_4$ requires M^+ for 209.0688. Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70; found: C, 57.58; H, 5.39; N, 6.72. Enantiomeric excess was 97% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=20/1, 1.0 mL/min, 230 nm), major isomer=33.2 min, minor isomer=37.5 min.

4.6.9. (*R*)-3-(2,4-Dichlorophenyl)-2-methylpropanoic acid 26i. The title compound **26i** was obtained according to the general procedure using the oxazolidinone resin **23** (251.2 mg, 0.153 mmol). Purification by preparative TLC ($CHCl_3$/MeOH=10:1) gave **26i** as a pale yellowish oil (25.3 mg, 71% yield in 3 steps from oxazolidinone resin **23**). R_f=0.56 ($CHCl_3$/MeOH=10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 1H), 7.16–7.15 (m, 2H), 3.12 (dd, 1H, J=12.8, 6.6 Hz), 2.90–2.82 (m, 1H), 2.79 (dd, 1H, J=12.8, 7.2 Hz), 1.22 (d, 3H, J=6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.9, 135.4, 134.9, 133.0, 132.0, 129.4, 127.0, 39.3, 36.3, 16.8; $[\alpha]_D^{27}=-44.9$ (c 1.00, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 1709, 1474, 1383, 1103, 901, 870, 802, 725, 712, 677, 652 cm^{-1}; HRMS (EI): found M^+ 232.0055, $C_{10}H_{10}Cl_2O_2$ requires M^+ 232.0058. Anal. Calcd for $C_{10}H_{10}Cl_2O_2$: C, 51.53; H, 4.32; found: C, 51.68; H, 4.44. Enantiomeric excess was 97% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=70/1, 1.0 mL/min, 230 nm), major isomer=24.2 min, minor isomer=21.7 min.

4.6.10. (*R*)-2-Phenoxy-4-pentenoic acid 26j. The title compound **26j** was obtained according to the general procedure using the oxazolidinone resin **23** (284.0 mg, 0.173 mmol). Purification by preparative TLC ($CHCl_3$/MeOH=10:1) gave **26j** as a white solid (16.7 mg, 50% yield in 3 steps from oxazolidinone resin **23**). R_f=0.48 ($CHCl_3$/MeOH=10:1); mp 30–31 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (br s, 1H), 7.31–7.25 (m, 2H), 7.02–6.98 (m, 1H), 6.90 (dd, 2H, J=8.8, 1.1 Hz), 5.91 (ddt, 1H, J=17.0, 10.3, 7.0 Hz), 5.21 (dd, 1H, J=17.0, 1.6 Hz), 5.16 (dd, 1H, J=10.3, 1.6 Hz), 4.72 (t, 1H, J=6.2 Hz), 2.72–2.76 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$)? δ 176.5, 157.4, 131.9, 129.6, 122.1, 119.0, 115.3, 75.9, 36.8; $[\alpha]_D^{28}$=+7.9 (*c* 1.96, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 1732, 1599, 1495, 1238, 771, 750, 735, 691 cm^{-1}; HRMS (EI): found M^+ 192.0782, $C_{11}H_{12}O_3$ requires M^+ 192.0786. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29; found: C, 68.49; H, 6.34. Enantiomeric excess was 96% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=50/1, 1.0 mL/min, 230 nm), major isomer=8.3 min, minor isomer=9.8 min.

4.6.11. (*S*)-3-(2,4-Dichlorophenyl)-2-methylpropanoic acid 26k. The title compound **26k** was obtained according to the general procedure using the oxazolidinone resin **23** (208.5 mg, 0.127 mmol). Purification by preparative TLC ($CHCl_3$/MeOH=10:1) gave **26k** as a colorless oil (17.4 mg, 59% yield in 3 steps from oxazolidinone resin **23**). R_f=0.52 ($CHCl_3$/MeOH=10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 1H), 7.17–7.16 (m, 2H), 3.12 (dd, 1H, J=12.8, 6.6 Hz), 2.90–2.80 (m, 1H), 2.79 (dd, 1H, J=12.8, 7.3 Hz), 1.22 (d, 3H, J=6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.8, 135.4, 134.9, 133.0, 132.1, 129.4, 127.0, 39.2, 36.3, 16.8; $[\alpha]_D^{27}$=+34.7 (*c* 0.95, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 1711, 1474, 901, 733, 698, 675, 667, 652 cm^{-1}; HRMS (EI): found M^+ 232.0054, $C_{10}H_{10}Cl_2O_2$ requires M^+ 232.0058. Anal. Calcd for $C_{10}H_{10}Cl_2O_2$: C, 51.53; H, 4.32; found: C, 51.93; H, 4.62. Enantiomeric excess was 85% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=70/1, 1.0 mL/min, 230 nm), major isomer=21.7 min, minor isomer=24.2 min.

4.6.12. Reuse of the oxazolidinone resin 23 in solid-phase Evans' asymmetric allylation, and methanolysis of the oxazolidinone resin recovered after three-times recycling. Starting from the oxazolidinone resin **23** (298.9 mg, 0.182 mmol), reaction sequence (*N*-acylation with 3-phenylpropionic acid, asymmetric allylation, and LiOOH-mediated hydrolysis) was repeated three times according to the procedure for synthesizing carboxylic acid **26c**. Then, oxazolidinone-loaded resin **23** recovered after three-times recycling was subjected to the methanolysis condition following the same procedure for synthesizing ester **24**. After the reaction, the resultant crude oil was purified by preparative TLC (*n*-hexane/AcOEt=1:5) to yield the methyl ester **24** (45.3 mg, 72% calculated from the loading rate of the starting oxazolidinone resin **23**) and *N*-allylated oxazolidinone methyl ester **27** as a pale yellowish viscous oil (16.1 mg, 23% calculated by the loading rate of the starting oxazolidinone resin **23**). R_f=0.47 (*n*-hexane/AcOEt=1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.17 (m, 5H), 5.78 (dddd, 1H, J=17.2, 10.3, 7.3, 4.8 Hz), 5.26–5.19 (m, 2H), 4.70 (d, 0.5H, J=4.4 Hz), 4.69 (d, 0.5H, J=4.6 Hz), 4.66–4.60 (m, 1H), 4.30 (dtd, 0.5H, J=3.4, 4.0, 1.5 Hz), 4.24–4.21 (m, 0.5H), 4.20–4.17 (m, 0.5H), 4.15–4.10 (m, 0.5H), 3.68–3.51 (m, 2H), 3.69 (s, 0.5×3H), 3.67 (s, 0.5×3H, partially overlapping with the next signal), 3.15–2.71 (m, 4H), 2.56–2.45 (m, 1H), 1.91–1.38 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.3, 174.0, 164.5, 164.4, 156.0, 155.9, 135.3, 135.2, 131.6, 129.2, 128.9, 128.9, 127.3, 127.2, 118.9, 118.8, 73.5, 73.3, 57.0, 56.9, 51.8, 45.2, 44.7, 44.4, 41.9, 41.7, 40.7, 40.2, 38.1, 37.9, 28.4, 28.1, 27.5, 27.4; $[\alpha]_D^{26}$=−85.9 (*c* 1.19, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 1753, 1746, 1655, 1456, 1437, 1175, 895, 648 cm^{-1}; HRMS (EI): found M^+ 386.1846, $C_{21}H_{26}N_2O_5$ requires M^+ 386.1841. Anal. Calcd for $C_{21}H_{26}N_2O_5$: C, 65.27; H, 6.78; N, 7.25; found: C, 64.99; H, 6.49; N, 7.47.

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25. In addition, in the most stable conformation of **9** calculated by conformational analysis,[34] the dihedral angle between two methine hydrogens (H-4 and H-5) was 38.1°. This value and Karplus curve also supported the observed coupling constant. Furthermore, irradiation of H-5 in NMR gave a strong NOE for H-4. For a related example, Carter, P. H.; LaPorte, J. R.; Scherle, P. A.; Decicco, C. P. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1237–1239.
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30. A steric repulsion between benzyl and carboxamide moieties in *cis*-configuration was thought to provide the ideal environment for chirality induction, because the conformation of benzyl moiety at the 4-position is restricted around *Re*-face of the enolate intermediate to avoid the steric repulsion by the carboxamide moiety at the 5-position.
31. Crystallographic data (excluding structural factors) for the structure **15** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 259416. Copies of the data can be obtained, free of charge, on application to CDCC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
32. The quenching study of lithium enolate generated from a similar derivative, *N*-propionylated carboximide, with TBSOTf, afforded the *O*-silyl enol ether as a single isomer in 82% yield. The irradiation to its olefinic methyl group gave a clear NOE enhancement for *tert*-butyldimethyl moiety (400 MHz, ^{1}H NMR, $CDCl_3$), suggesting that the reaction proceeded via a *Z*-configured lithium enolate intermediate.
33. The absolute stereochemistry of **26c** was determined in comparison of its $[\alpha]_D$ value with the reported authentic data in Kurth, M. J.; Decker, O. H. W.; Hope, H.; Yanuck, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 443–448. Enantiomeric excess of **26c** was determined by HPLC analysis after conversion to the corresponding (*S*)-phenethylamide. Vedejs, E.; Gingras, M. *J. Am. Chem. Soc.* **1994**, *116*, 579–588.
34. Energy minimization was performed by systematic conformation search on the MMFF94x force field using the Molecular Operating Environment modeling package (MOE 2004.03, Chemical Computing Group, Inc., Montreal, Canada), followed by MOPAC (PM3 program).
35. This effect may be similar to the shielding effect observed in 5,5-dimethyl-4-benzyloxazolidinone, so-called 'SuperQuats'. Davies, S. G.; Sanganee, H. J.; Szolcsanyi, P. *Tetrahedron* **1999**, *55*, 3337–3354.
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39. Other bases such as LiHMDS and KHMDS were less effective, and lower conversion was observed in the reaction below -20 °C.
40. (a) Preliminary stability test of **23** against LiOOH treatment revealed that ester linkage is sufficiently inert under the basic condition up to 8 h at 0 °C, and oxazolidinone ring was also stable enough. Kaiser-Test[47] of the recovered resin was completely negative, indicating that there is no free amino group caused by the oxazolidinone ring opening. Indeed, hydrolysis of the ester moiety was observed only in the H_2O_2 free condition. (b) Methanolysis of the recovered oxazolidinone resin **23** afforded the corresponding methyl ester **24** in 94% without any epimerization. Additionally there is no contamination of endo-cleavage byproduct as well as in the case of solution-phase model experiment.

41. 3-(2,4-Dichlorophenyl)propionic acid was prepared from *trans*-2,4-dichlorocinnamic acid in the following three-step reaction sequence (3 steps, 87%): (a) K_2CO_3, MeI, DMF, rt; (b) $NaBH_4$, CuCl, THF, 0 °C; (c) 1 N NaOH aq, MeOH, 50 °C. Unfortunately, simple hydrogenolysis of *trans*-2,4-dichlorocinnamic acid by H_2, 10% Pd–C in EtOH resulted in not only reduction of olefin moiety, but also de-chlorination at the 2-position on the aromatic ring. 2,4-Dichlorobenzyl iodide was prepared by iodination of the corresponding alcohol with NaI/Amberlyst. Tajbakhsh, M.; Hosseinzadeh, R.; Lasemi, Z. *Synlett* **2004**, *4*, 635–638.
42. Absolute configuration of the products was determined in comparison to the specific rotations in literature; otherwise, corresponding authentic samples were prepared using (*S*)-4-benzyl-2-oxazolidinone. Yields were calculated from the original loading of Wang resin.
43. This type of side reaction is known in the standard Evans' chemistry and thought that the enolate intermediate partially decomposes via a ketene-pathway, see Ref. 15.
44. (a) Carboxylic acid **26c** is known as a key component of α-chymotripsin inhibitor, see: Kim, D. H.; Li, Z.-H.; Lee, S. S.; Park, J.; Chung, S. J. *Bioorg. Med. Chem.* **1998**, *6*, 239–249. (b) Carboxylic acid **26e** is known as a key component of carboxypeptidase inhibitor, see: Byers, L. D.; Wolfenden, R. *Biochemistry* **1973**, *12*, 2070–2078. (c) Carboxylic acid **26i** and **26k** are known as a key acyl component of potent γ-secretase inhibitor, see: Churcher, I.; Ashton, K.; Butcher, J. W.; Clarke, E. E.; Harrison, T.; Lewis, H. D.; Owens, A. P.; Teall, M. R.; Williams, S.; Wrigley, J. D. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 179–183.
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Biphasic Suzuki coupling reactions of aryl or benzyl bromides employing cobalt-containing phosphine ligand coordinated palladium complex

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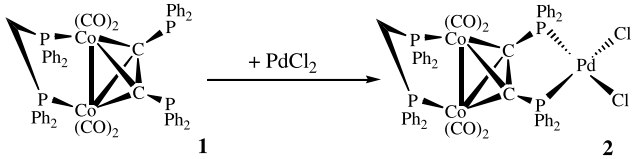
Abstract—Biphasic Suzuki-coupling reactions of aryl and benzyl bromides employing a cobalt-containing phosphine ligand chelated palladium complex **2** were carried out in various reaction conditions. Comparisons of the catalytic efficiencies in the presence/absence of a phase-transfer agent, TBAB, were presented. In addition, the effects of altering solvents, temperatures, catalysts, and substrates on the reactions were monitored and reported. Better yields were commonly observed while a phase-transfer agent TBAB was participated in the reactions. The factor of reaction time is more crucial than that of temperature in short reaction hour experiments. Obviously, an induction period for the reduction of Pd(II) to Pd(0) active species is needed for this type of reaction.

1. Introduction

Palladium-catalyzed Suzuki cross-coupling of haloarenes with arylboronic acid is among the most powerful C_{sp^2}–C_{sp^2} bond-formation available to synthetic organic chemists.[1] Although *N*-heterocyclic carbenes (NHC) have been emerged as potentially effective ligands for Suzuki reactions recently,[2] yet, phosphines remain the most employed ligands in accelerating or modifying the reactions.[3] Even though various synthetic methods have been extensively explored in searching of more versatile and efficient organic phosphine ligands in the palladium-catalyzed Suzuki–Miyaura cross-coupling reactions,[4] nevertheless, to our best knowledge, a systematical investigation of transition-metal-containing phosphines (TM-phosphines) has yet remained a relatively uncultivated territory.[5,6]

Our previous work had demonstrated the catalytic capacity of an unusual palladium complex **2**, which is coordinated by a cobalt-containing bidentate phosphine ligand [(μ-Ph_2-PCH_2PPh_2)$Co_2(CO)_4$(μ-$PPh_2C{\equiv}CPPh_2$)] **1**, on Suzuki cross-coupling reactions (Scheme 1).[7] The reactions, using bromobenzene (or bromothiophene) with phenylboronic acid as reaction substrates, were carried out by employing **2** as catalyst in organic as well as biphasic media and results were satisfactory.[8]



Scheme 1.

The reactants of the catalytic processes under investigation were composed of 1.00 mmol of aryl halide, 1.5 equiv of phenylboronic acid, 1 mol% of **2** (based on aryl halide), 1 mL toluene (or mixed solvent: THF/H_2O = 5 mL/1 mL), and 2.0 equiv of K_3PO_4 (based on aryl halide). The reaction mixture was stirred at 65 °C for 16 h then workup followed. In most of the cases, the reactions carried out in biphasic media are more efficient than that in pure organic phase. The fact that high efficiency was achieved for an alkyl bromide is noteworthy.[8,9]

As known, Suzuki–Miyaura coupling reactions are more efficient in organic phase while employing $Pd(OAc)_2$ as catalyst; on the contrary, it is more efficient in biphasic media for using $PdCl_2$.[10] The idea of using biphasic media in Suzuki–Miyaura coupling reaction is attractive because of the ecological and safety reason for using water as a major component of the reaction solvent.[11] In addition, water-soluble reagent such as NaOH, K_3PO_4 (bases using in Suzuki reaction) and NaCl (side product of Suzuki reaction) can be dissolved extensively in water. Besides, the disadvantage of low solubility of the metal catalysts in

Keywords: Biphasic Suzuki reaction; Palladium complex; Cobalt-containing phosphine; Phase-transfer agent.
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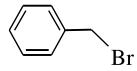
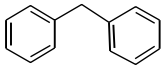
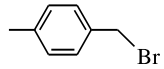
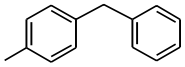
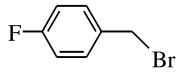
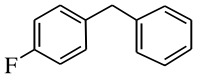
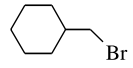
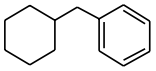
Table 1. Suzuki-coupling reactions of benzyl bromides employing catalyst **2**[a]

Entry	Halide	Product	Solvent	Yield (%)
1			THF–H_2O(5:1) Toluene	99.0 90.0
2			THF–H_2O(5:1) Toluene	79.2 64.9
3			THF–H_2O(5:1) Toluene	90.2 72.4
4			THF–H_2O(5:1) Toluene	NR NR

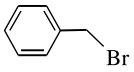
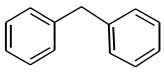
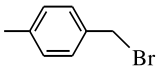
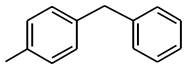
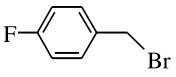
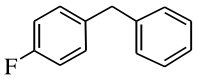
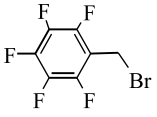
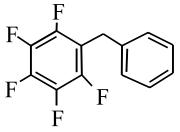
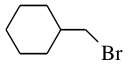
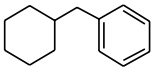
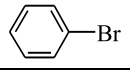
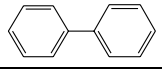
[a] Reactions were conducted in either THF with NaOH(aq) (3 M, 1.00 mL) or in toluene (1.00 mL) with K_3PO_4 (3 equiv) at 65 °C for 16 h employing 1 mol% of **1** with bromides (1.00 mmol) and phenylboronic acid (1.50 mmol).

biphasic media might be overcome either by employing phase-transfer agent or water-soluble phosphine ligands.[12] Phase transfer agent such as tetrabutylammonium bromide (TBAB) was reported frequently used in biphasic reactions.[13] Role played by the ammonium salt is thought to be two-folds. First, it facilitates the solvability of the organic substrates in the solvent medium. Second, it was thought to enhance the rate of the coupling reaction by activating the boronic acid through the formation of a boronate complex $[ArB(OH)_3]^-[R_4N]^+$. TBAB has been used recently in conjunction with a palladium oxime catalyst for the Suzuki coupling of aryl chlorides with phenylboronic acid in water[14] and as a promoter in the $Pd(PPh_3)_4$ catalyzed Suzuki coupling reaction of 4-bromobenzonitrile and phenylboronic acid in organic solvents.[15]

In principle, the carbon–halide bond, either C_{sp3}-, C_{sp2}-, or C_{sp}–X, are all subjected to the attack of deliberately chosen electrophiles while appropriate metal-containing catalysts were employed.[16] Nevertheless, difficulties are often encountered while inactivated alkyl halides and alkyl electrophiles are employed in Suzuki coupling reactions. First, alkyl halides (even CH_3I) react slowly with Pd^0 complexes, in contrast with the behavior observed for allyl, benzyl, alkenyl, and aryl halides.[17] Second, once the alkyl-Pd^{II} complex is formed, it should face the possibility of decomposition by a fast β-hydride elimination, which competes with the usually slower trans-metalation process. β-Hydride elimination process requires several conditions such as the existence of a vacant coordination site and the feasibility of arranging the M–C(α)–C(β)–H atoms in the same plane. This undesirable process may not be a problem in carbonylative couplings of $C(sp^3)$ centers since the fast CO insertion prevents decomposition of the alkyl-Pd intermediate.[18] Third, the reductive elimination process is normally slow for σ-alkyl-σ-aryl-Pd^{II} or di-σ-alkyl-Pd^{II} complexes.[19]

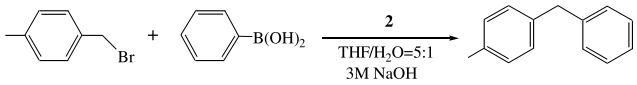
Reported herein are some notable results from biphasic Suzuki–Miyaura coupling reactions of aryl or benzyl

Table 2. Biphasic Suzuki-coupling reactions of benzyl bromides with phenylboronic acid employing catalyst **2** and adding TBAB[a]

Entry	Bromides	Product	Temperature (°C)	Time (h)	Yield (%)
1			40 65	0.5 16	98.2 99.0
2			40 65	0.5 16	72.0 86.8
3			40 65	0.5 16	74.2 90.2
4			40	0.5	47.8
5			40	0.5	37.4
6[b]			40	0.5	6.8

[a] Reactions were conducted in THF with 1 mol% of **2**, NaOH(aq) (3 M, 1.00 mL), bromides (1.00 mmol), TBAB (0.20 mmol) and phenylboronic acid (1.50 mmol).
[b] For comparison.

Table 3. Biphasic Suzuki coupling reactions employing **2** at various conditions[a]



Entry	TBAB (equiv)	Temperature (°C)	Time (h)	Yield (%)
1	—	65	16	>99
2	0.2	65	16	>99
3	—	65	0.5	10.8
4	0.2	65	0.5	16.2
5	—	40	16	75.4
6	0.2	40	16	87.5
7	—	40	0.5	10.5
8	0.2	40	0.5	6.8

[a] Reactions were conducted in THF with 1 mol% of **2**, NaOH(aq) (3 M, 1.00 mL), bromide (1.00 mmol) and phenylboronic acid (1.50 mmol).

bromides employing a cobalt-containing phosphine ligand coordinated palladium complex **2** in the presence/absence of a phase-transfer agent, TBAB.

2. Results and discussion

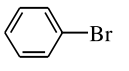
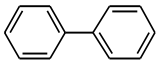
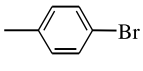
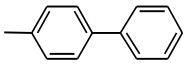
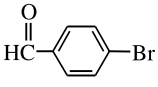
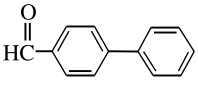
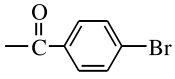
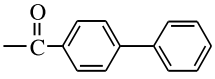
2.1. Suzuki reaction using cobalt-containing phosphine ligand chelated palladium complex 2

In our previous work,[8] an unusual high efficiency was achieved for a substituted alkyl bromide, benzylbromide, in a **2**-catalyzed Suzuki reaction. For comparison, the same reaction conditions were employed for several structural related substituted bromomethanes in either uni- or bi-phasic media (Table 1). The reactants of the catalytic reactions under investigation are consisted of 1.0 mmol of aryl halide, 1.5 equiv of phenylboronic acid, 1 mol% of **2** (based on aryl halide), 1.00 mL toluene (or mixed solvent: $THF/H_2O=5$ mL/1 mL), and 3.0 equiv of K_3PO_4. The reaction mixture was stirred at 65 °C for 16 h then workup followed. Encouraging results were obtained as shown (Table 1, entries 1–3). In these cases, reactions carried out in biphasic media are more efficient than that in pure organic solvent. Almost quantitative yield (99.0%) was obtained when bromobenzene is used as the halide source (entry 1). Nevertheless, the reaction was not very efficient (79.2% in THF/H_2O and 64.9% in toluene) when a less reactive 4-methyl-benzyl bromide, having a σ electron-donating group, was used (entry 2). The reaction with 4-fluoro-benzyl bromide, having a σ electron-withdrawing group at the *para*-position, gave a better yield, that is, 90.2% in THF/H_2O and 72.4% in toluene (entry 3). However, no reactivity was observed for using an aliphatic bromide as substrate (entry 4).

Biphasic Suzuki-coupling reactions, using benzyl bromides and phenylboronic acid as reaction substrates, were carried out employing catalyst **2** (Table 2, entries 1–5). A phase-transfer agent, TBAB, was intentionally added to enhance the reactivity of the reaction. Satisfactory results were obtained for using benzyl bromide or mono-substituted benzyl bromides as reaction substrates (entries 1–3). The substituent, either electron-withdrawing/donating, in the *para*-position does not affect the outcome notably (entries 2–3). Although having five strong σ electron-withdrawing groups at the *ortho*, *meta*, *para*-position for pentaflurobenzylbromide, as demonstrated in entry 4, the yield drops significantly, 47.8%. Obviously, the exceedingly strong electron-withdrawing effect from the five substituents as well as the steric effect caused by *ortho*-position substituent play major role in preventing the aryls from coupling. It is worthy of noting that the yield is improved from almost nothing (Table 1, entry 4) to 37.4% (Table 2, entry 5) while adding TBAB to the reaction system. On the contrary, the yield drops from 99.0% (Table 1, entry 1) to 6.8% (Table 2, entry 6) while the reaction time is shortened from 16 h to 30 min. It indicates that an induction period is needed before the reaction can be speeded up to a reasonable rate. In brief, the biphasic Suzuki coupling reactions are more efficient in the presence of phase-transfer agent TBAB than those without it.

Table 3 lists the results from the biphasic Suzuki coupling reactions, employing **2** as catalyst and with 4-methylbenzyl bromide and phenylboronic acid as substrates, in various reaction conditions. This study has shown the importance of two features. First, the yields are relatively lower for reactions without adding TBAB (entry 3 vs 4; 5 vs 6). Second, the factor of reaction time is more crucial than that of temperature. Low yield was observed commonly for short reaction time. Obviously, an induction period for the reduction of Pd(II) to Pd(0) active species is needed for this type of reaction.

Table 4. Biphasic Suzuki coupling reaction of aryl bromides employing catalyst **2** and adding TBAB[a]

Entry	Halide	Product	Yield (%)
1			6.8
2			Trace
3			12.3
4			27.2

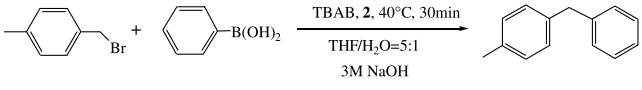
[a] Reactions were conducted in THF at 40 °C for 0.5 h employing 1 mol% of **2**, NaOH(aq) (3 M, 1.00 mL), bromides (1.00 mmol), TBAB (0.20 mmol) and phenylboronic acid (1.50 mmol).

The necessity of long reaction hours for this type of reaction is also demonstrated in the following experiments (Table 4). The following reactions were carried out for only 0.5 h rather than the commonly employed 16 h. A rather low yield, 6.8%, was obtained while bromobenzene is used as the halide source (Table 4, entry 1). By contrast, almost quantitative yield (99.0%) was obtained at higher temperature, 65 °C, and long reaction hours, 16 h (Table 1, entry 1). The account is also valid for entries 2–4 no matter which type of halides, with electron-withdrawing/donating substituents, are used. It is concluded here that longer reaction time is more crucial for aryl bromides (C_{sp^2} substituent) than benzyl bromides (C_{sp^3} substituent) to produce better yield in Suzuki coupling reaction employing the kind of catalyst like **2**.

2.2. Suzuki reactions using 3, 4, 5-chelated palladium complexes and 2

For comparison, biphasic Suzuki-coupling reaction of benzyl bromides employing a number of palladium catalysts were carried out (Table 5). Rather low yields were observed for using **3** as an acting diphosphine ligand in the cases or either $Pd(OAc)_2$ or $(COD)PdCl_2$ as the palladium source (entries 1–2). Slightly improved yields were obtained while a mono-dentate phosphine ligand **4** was used (entries 3–4). Better yields were seen while 2-(di-*tert*-butylphosphino)biphenyl **5**, the powerful phosphine ligand which was used by Buchwald,[20] were employed (entries 5 and 6). Not many differences were observed either using $Pd(OAc)_2$ or $(COD)PdCl_2$ as the palladium source. In summary, the catalytic efficiencies of these types of ligands are in the sequence of **5**>**4**>**3**. The best yield was found while **2** was used as the catalyst (entry 7).

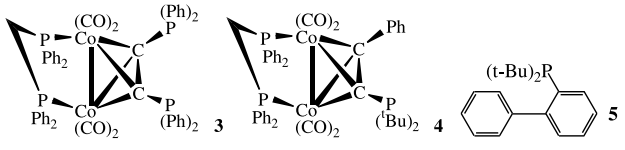
Table 5. Biphasic Suzuki-coupling reaction of benzyl bromides employing various palladium catalysts[a]



Entry	Pd	Ligand[b]	Isolated yield (%)
1	$Pd(OAc)_2$	3	6.4
2	$(COD)PdCl_2$	3	4.6
3	$Pd(OAc)_2$	4	12.9
4	$(COD)PdCl_2$	4	12.6
5	$Pd(OAc)_2$	5	43.5
6	$(COD)PdCl_2$	5	38.7
7	**2**	—	72.0

[a] Reactions were conducted in THF with 1 mol% of Pd catalysts, NaOH(aq) (3 M, 1 mL), bromides (1.00 mmol), TBAB (0.20 mmol) and phenylboronic acid (1.50 mmol).

[b]



3. Concluding remarks

We have demonstrated the catalytic capacity of a novel cobalt-containing phosphine chelated palladium complex **2** in either uni- or bi-phasic Suzuki's reactions. It has shown that Suzuki-coupling reactions of benzyl bromides (substrates of C_{sp^3} substituent) employing catalyst **2** was performed better than using aryl bromides (substrates of C_{sp^2} substituent). In most cases, the reactions carried out in biphasic media were much efficient than that in pure organic phase. Better yields were commonly observed while a phase-transfer agent TBAB was added in the reactions. The factor of reaction time is more crucial than that of reaction temperature. Not many differences were observed either using $Pd(OAc)_2$ or $(COD)PdCl_2$ as the palladium source.

4. Experimental

4.1. General

All operations were performed in a nitrogen flushed glove box or in a vacuum system. Freshly distilled solvents were used. ^1H NMR spectra were recorded over Varian-400 spectrometer at 400.00 MHz. The chemical shifts are reported in ppm relative to internal standard $CDCl_3$.

4.2. General procedures for the Suzuki cross-coupling reactions

Suzuki cross-coupling reactions were performed according to the following procedures.

4.2.1. Method I (conducted in a THF–H_2O biphasic medium). Complex **2** (0.012 mg, 0.01 mmol) and boronic acid (0.183 g, 1.50 mmol) were charged into a 20 mL Schlenk flask. The flask was evacuated and backfilled with nitrogen before adding THF (5 mL), 3 M NaOH solution (1 mL), aryl halide (1.00 mmol) and (in the presence/absence of) tetrabutylammonium bromide (TBAB, 0.65 g, 0.20 mmol). The solution was stirred at 65 °C for 30 min–16 h. The mixture was washed with aqueous NaOH (1 M, 20 mL), and then the aqueous layer was extracted with ether (30 mL). The combined organic layers were washed with brine (20 mL), and dried over with anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel.

4.2.2. Method II (conducted in a toluene medium). Complex **2** (0.012 mg, 0.01 mmol), the boronic acid (0.183 g, 1.50 mmol), and K_3PO_4 (0.425 g, 2.00 mmol), were charged into a Schlenk flask. The flask was evacuated and backfilled with nitrogen before adding toluene (1 mL) and the aryl halide (1.00 mmol). The solution was stirred at 65 °C, 16 h. The same procedures as Method I were followed from here accordingly.

4.2.3. Method III (conducted in a THF–H_2O biphasic medium). Ligand **1** (1.00 mmol), boronic acid (0.183 g, 1.50 mmol) and 1 mol% of Pd complex ($Pd(OAc)_2$ or $PdCl_2$), were charged into a Schlenk flask. The flask was evacuated and backfilled with nitrogen before adding THF (5 mL), 3 M NaOH solution (1 mL), tetrabutylammonium bromide (TBAB, 0.065 g, 0.20 mmol) and aryl halide (1.00 mmol). The flask was sealed with Teflon screw cap, and the solution was stirred at 40 °C for 0.5 h. The same

procedures as Method I were followed from here accordingly.

Acknowledgements

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An unexpected highly diastereoselective double Baylis–Hillman reaction of per- (or poly)fluorophenyl aromatic aldimines with methyl vinyl ketone

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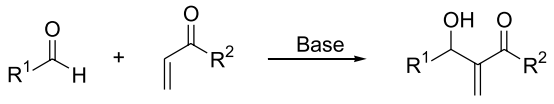
Abstract—Aza-Baylis–Hillman reaction of per- (or poly)fluorophenyl aromatic aldimines **1** with methyl vinyl ketone (MVK) was studied. It was found that both the used Lewis base and solvent can significantly affect the reaction. Using triphenylphosphine as a Lewis base, the reaction of **1** with MVK proceeded smoothly to give the normal Baylis–Hillman adduct **2** along with the double Baylis–Hillman adduct **3** as by-product in THF. When 1,4-diazabicyclo[2.2.2]octane was used as a Lewis base in DMF, the aza-Baylis–Hillman reaction of **1** with MVK gave the double aza-Baylis–Hillman adduct **3** exclusively in moderate to good yields with excellent diastereoselectivities. The double Baylis–Hillman adduct **3** was conveniently converted to fluorine-containing 4-alkylidene-2-cyclohexen-1-ones under mild reaction conditions in good yields.

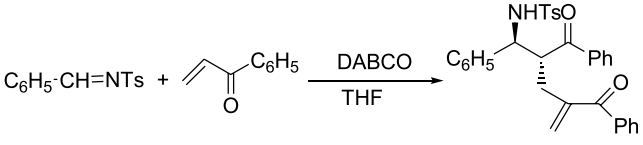
1. Introduction

Mild and selective carbon–carbon bond formations represent one of the major challenges in organic synthesis. In the same perspective, atom-economic reactions become more and more a need and a requirement.[1] One of the carbon–carbon bond forming reaction which fulfills the above criteria is the Baylis–Hillman reaction.[2,3] In this transformation, Michael acceptors are coupled with aldehydes to form highly functionalized α-methylene-β-hydroxycarbonyl compounds (Scheme 1).



Scheme 1.

Previously, Shi and co-workers reported that, in the reaction of sulfonated imines with phenyl vinyl ketone catalyzed by DABCO, the highly diastereselective double aza-Baylis–Hillman reaction products were formed in moderate to good yields. While using methyl vinyl ketone (MVK) as the active olefin, no such double aza-Baylis–Hillman reaction product could be formed at all (Scheme 2).[4] As part of our ongoing projects in fluorooganic chemistry,[5] we examined the Baylis–Hillman reaction of per- (or poly)fluorophenyl aromatic aldimines with MVK in the presence of different Lewis bases, and found that the double Baylis–Hillman reaction product could be exclusively formed with high diastereoselectivity in the presence of 1,4-diazabicyclo-[2.2.2]octane (DABCO).



Scheme 2.

It is well known that the biological properties of medicinal compounds can often be influenced by fluorine substitution.[6] The physical properties of several electronic and optical devices also depend immensely on the structure of fluoroorganic molecules.[7] Fluorine substitution provides organic chemists with an opportunity to study an extreme case of electronic effect in reactions.[6,7] Herein we report an unexpected highly diastereoselective double Baylis–

Keywords: Per- (or poly)fluorophenyl aromatic aldimines; Lewis base; Baylis–Hillman reactions; Methyl vinyl ketone.
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Hillman reaction of per- (or poly)fluorophenyl aromatic aldimines with methyl vinyl ketone (MVK).

2. Results and discussion

The promoters and solvents for the aza-Baylis–Hillman reaction of *N*-pentafluorophenyl-pentafluorophenyl aldimine (**1a**) with methyl vinyl ketone were systematically examined first, and the results were summarized in Table 1. We found that every parameter, such as solvent and catalyst influenced the reaction of *N*-pentafluorophenyl-pentafluorophenyl aldimine (0.5 mmol) with MVK (1 mmol) drastically (Scheme 3; Table 1). Using 20 mol % of triphenylphosphine as a Lewis base in THF, the reaction proceeded very well to give the normal aza-Baylis–Hillman adduct **2a** as a major product in good yield (Table 1, entry 1). In DMF and CH_2Cl_2, the corresponding normal aza-Baylis–Hillman adduct **2a** was obtained in 63% and 48% yield along with the double aza-Baylis–Hillman adduct **3a** in 27 and 31% yield, respectively (Table 1, entries 2 and 3). In CH_3CN, the aza-Baylis–Hillman reaction of *N*-pentafluorophenyl-pentafluorophenyl aldimine with MVK was sluggish because of the poor solubility of **1a** in the reaction media (Table 1, entry 4). For the influence of Lewis bases, a variety of Lewis base catalysts (20 mol %) were also screened. The use of tertiary amines such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a Lewis base gave the corresponding normal aza-Baylis–Hillman adduct in low yield along with many unidentified products (Table 1, entry 5). While using DABCO (20 mol %) as a Lewis base in DMF, we delightfully found that the double aza-Baylis–Hillman adduct **3a** was formed exclusively in good yield (Table 1, entry 7). In contrast to other Lewis base, no reaction of **1a** with MVK occurred to give the corresponding adduct **2a** or **3a**, but only **1a** by itself decomposed in the presence of stronger Lewis base such as tri-*n*-butylphosphine (PBu_3) to provide a mixture of compounds (Table 1, entry 8). On the other hand, using DMAP, Et_3N or Me_2S, no reaction occurred under the same reaction conditions due to their low catalytic activity as a Lewis base to initiate the aza-Baylis–Hillman reaction (Table 1, entries 9–11). Thus, PPh_3 is the best Lewis base for this version of normal aza-Baylis–Hillman reaction in THF, while DABCO is the best Lewis base for this version of double aza-Baylis–Hillman reaction in DMF. Moreover, on the basis of the ^1H, ^{19}F and ^{13}C NMR spectroscopic data and X-ray diffraction analysis, we were pleased to find that, in this aza-Baylis–Hillman reaction, the double aza-Baylis–Hillman reaction product **3a** was formed diastereoselectively in the *anti*-configuration (Fig. 1).

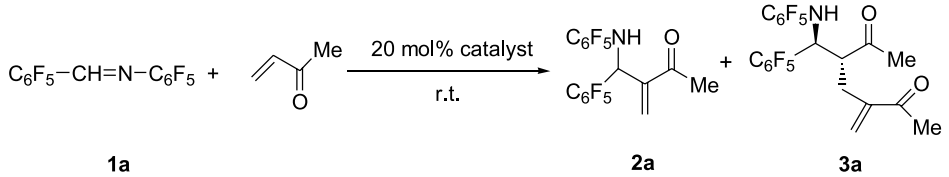
In Tables 2 and 3, the results of the aza-Baylis–Hillman reaction of per- (or poly)fluorophenyl aromatic aldimines with methyl vinyl ketone in the presence of Lewis bases PPh_3 and DABCO were summarized, respectively.

The other per- (or poly)fluorophenyl aromatic aldimines (**1b–1k**) (0.5 mmol) could react with MVK (1 mmol) smoothly in the presence of Lewis base PPh_3 under the optimized reaction conditions to give the corresponding normal aza-Baylis–Hillman adducts **2b–2k** and the double Baylis–Hillman adducts **3b–3h** in excellent to moderate yields; while the product ratio was dependent on electronic features of aryl substituents of the corresponding imines (Table 2). The aza-Baylis–Hillman adducts **2** and double Baylis–Hillman adducts **3** were formed in good yields in the reaction of MVK with imines with an electron-withdrawing group on the benzene ring (Table 2, entries 4–9), whereas an electron-donating substituent lowered the yields (entries

Table 1. Results of aza-Baylis–Hillman reactions of *N*-pentafluorophenyl-pentafluorophenyl aldimine with MVK[a]

Entry	Lewis base	Solvent	Time (h)	Yield of **2a**[b] (%)	Yield of **3a**[b] (%)
1	PPh_3	THF	12	80	18
2	PPh_3	DMF	12	63	27
3[c]	PPh_3	CH_2Cl_2	12	48	31
4	PPh_3	CH_3CN	12	Trace	Trace
5[c]	DBU	THF	6	30	0
6	DABCO	THF	12	12	72
7	DABCO	DMF	12	Trace	87
8[d]	PBu_3	THF	24	0	0
9	DMAP	THF	12	[e]	[e]
10	Et_3N	THF	12	[e]	[e]
11	Me_2S	THF	12	[e]	[e]

[a] All reactions carried out at room temperature; the molar ratio of **1a** to MVK was 1:2.
[b] Isolated yields.
[c] Determined by ^{19}F NMR.
[d] An unidentified mixture of products was obtained.
[e] No reaction occurred.



1a **2a** **3a**

Scheme 3.

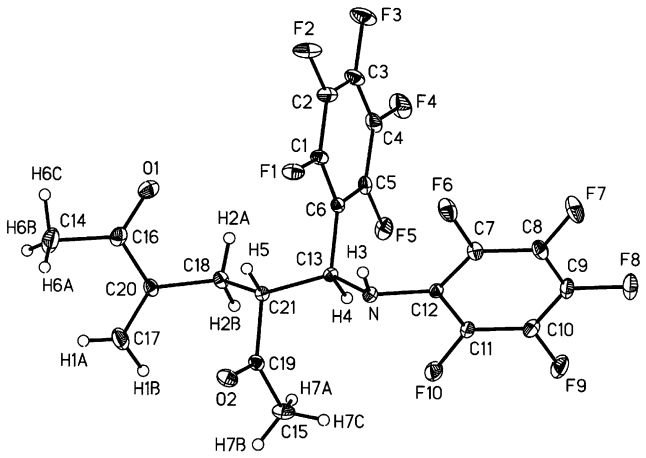
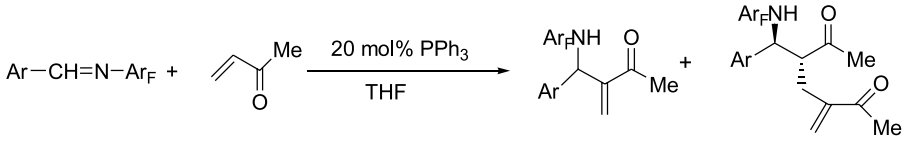


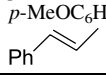
Figure 1. X-ray crystal structure of **3a**.

10–11). To our surprise, the aza-Baylis–Hillman reaction of *N*-(4-chloro-2,3,5,6-tetrafluoro) phenyl-4-nitrophenyl aldimine **1d** with MVK, under the similar reaction conditions, gave the normal Baylis–Hillman adduct **2d** exclusively (Table 2, entry 4). And decreasing the reaction temperature to 0 °C yielded 80% of the normal Baylis–Hillman adduct **2d** and no corresponding double aza-Baylis–Hillman adduct **3d** was isolated (entry 5). 4-Methylphenyl, 4-methoxyphenyl or 4-propenyl-phenyl aldimines **1i**–**1k** could also react with MVK to give the normal aza-Baylis–Hillman adducts **2i**–**2k** in moderate yields along with some unidentified products, respectively, but only if the reaction temperature was kept at 60 °C due to their low reactivity. None of the corresponding double aza-Baylis–Hillman adducts was formed, possibly due to the decomposition or side reaction at high reaction temperature (entries 10–12). The above results indicated that the substituents on Ar_F and

Table 2. Aza-Baylis–Hillman reactions of per- (or poly)fluorophenyl aromatic aldimines with MVK in THF in the presence of PPh_3[a]

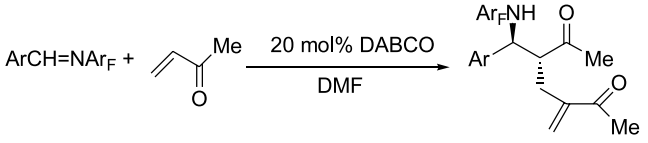


1(a-k) **2 (a-k)** **3(a-c, e-h)**

Entry	Ar	Ar_F	Time (h)	Temperature (°C)	Yield of **2**[b](%)	Yield of **3**[b](%)
1	C_6F_5	C_6F_5	12	rt	**2a**, 80	**3a**, 18
2	C_6H_5	C_6F_5	96	40	**2b**, 20	**3b**, 25
3	C_6H_5	4-ClC_6F_4	72	40	**2c**, 51	**3c**, 17
4	*p*-$NO_2C_6H_4$	4-ClC_6F_4	24	40	**2d**, 90	0
5	*p*-$NO_2C_6H_4$	4-ClC_6F_4	24	0	**2d**, 80	0
6	*o*-$NO_2C_6H_4$	4-ClC_6F_4	24	40	**2e**, 51	**3e**, 35
7	*p*-BrC_6H_4	4-ClC_6F_4	72	40	**2f**, 35	**3f**, 37
8	*o*-BrC_6H_4	4-ClC_6F_4	72	40	**2g**, 61	**3g**, 27
9	*o*-ClC_6H_4	4-ClC_6F_4	58	40	**2h**, 53	**3h**, 25
10	*p*-MeC_6H_4	4-ClC_6F_4	48	60	**2i**, 45	—[c]
11	*p*-$MeOC_6H_4$	4-ClC_6F_4	72	60	**2j**, 34	—[c]
12		4-ClC_6F_4	72	60	**2k**, 30	—[c]

[a] The molar ratio of imine with MVK was 1:2.
[b] Isolated yields.
[c] An unidentified mixture of products was obtained.

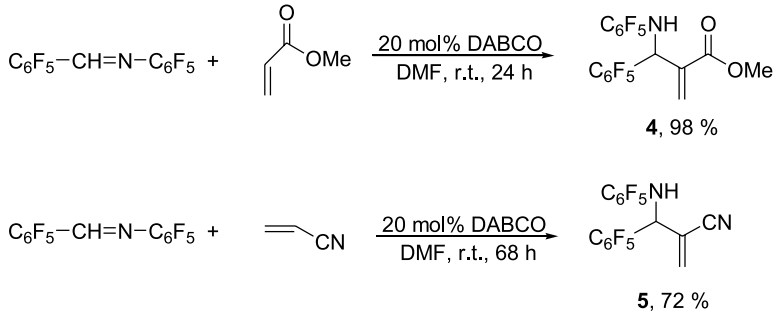
Table 3. Results of aza-Baylis–Hillman reactions of per- (or poly)fluorophenyl aromatic aldimines with MVK in DMF in the presence of DABCO[a]



1 **3**

Entry	Ar	ArF	Time (h)	Temperature (°C)	Yield of **3**[b] (%)[c]
1[d]	C_6F_5	C_6F_5	12	25	**3a**, 87
2	C_6H_5	C_6F_5	240	60	**3b**, 35
3	C_6H_5	4-ClC_6F_4	240	60	**3c**, 47
4	*p*-$NO_2C_6H_4$	4-ClC_6F_4	24	−78∼0	**3d**, 30
5	*o*-$NO_2C_6H_4$	4-ClC_6F_4	48	−78∼0	**3e**, 69
6	*p*-BrC_6H_4	4-ClC_6F_4	60	25	**3f**, 65
7	*o*-BrC_6H_4	4-ClC_6F_4	48	25	**3g**, 61
8	*o*-ClC_6H_4	4-ClC_6F_4	60	25	**3h**, 61

[a] The molar ratio of imine to MVK was 1:5.
[b] All the products **3** were *anti*-configuration.
[c] Isolated yields.
[d] The molar ratio of imine with MVK was 1:2.



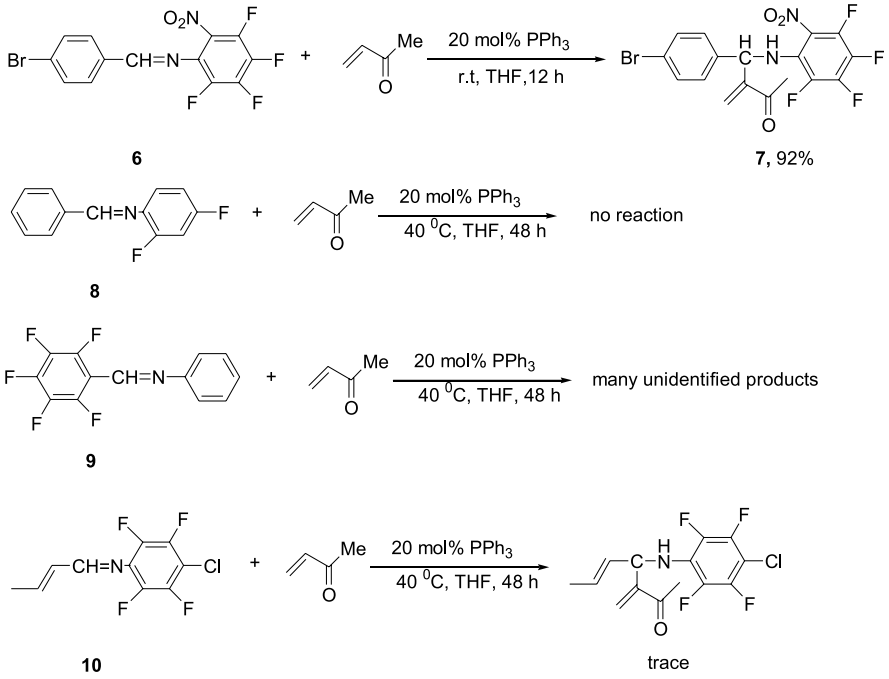
Scheme 4.

Ar affected the reactions, and electron-withdrawing substituents on the groups (Ar) would favor this version of the aza-Baylis–Hillman reaction.

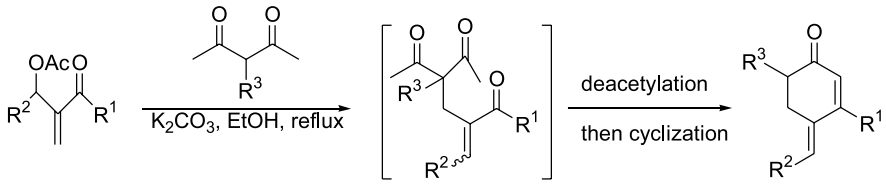
On the other hand, if using DABCO as a Lewis base in DMF, in all cases the corresponding double aza-Baylis–Hillman adducts were obtained exclusively as the sole product with the *anti*-configuration (Table 3). In order to obtain **3** in higher yields, 5 equiv of MVK was employed in all cases (Table 3). For substrates having an electron-withdrawing group on the benzene ring, the reaction proceeded very well to give **3** in good yields within shorter reaction time (Table 3, entries 5–8). Rising of the reaction temperature and prolonged reaction time were effective with less-reactive substrates like **1b**,**1c** (Table 3, entries 2–3). Specifically, when *N*-(4-chloro-2,3,5,6-tetrafluoro)phenyl-4-nitrophenyl aldimine **1d** bearing a strong electron-withdrawing nitro group on the benzene ring was used as the substrate, it was found that **1d** decomposed rapidly, and the corresponding double aza-Baylis–Hillman adduct **3d** could only be obtained in 30% yield along with many unidentified products, when the reaction temperature was kept at $-78\sim0$ °C (Table 3, entry 4).

It should be emphasized here that for other Michael acceptors such as methyl acrylate and acrylonitrile reacted with **1**, no such double aza-Baylis–Hillman reaction product could be observed at all. For example, the aza-Baylis–Hillman reaction of *N*-pentafluorophenyl-pentafluorophenyl aldimine **1a** with methyl acrylate in DMF in the presence of DABCO (20 mol %) was completed within 24 h to provide 98% yield of the product **4**. Under the same reaction conditions, it reacted with acrylonitrile within 68 h providing 2-(pentafluorophenyl-pentafluorophenylamino -methyl)-acrylonitrile **5** in 72% yield (Scheme 4).

This result stimulated us to seek out other versions of aza-Baylis–Hillman reactions using other fluorinated imines. Therefore, several fluorine-containing imines have been prepared and used as the substrates (Scheme 5). The reaction of [1-(4-bromophenyl)-meth-(*E*)-ylidene]-(2,3,4,5-tetrafluoro-6-nitrophenyl)-amine **6** which had an electron-withdrawing group (*o*-NO_2) on Ar_F with MVK proceeded smoothly under the same conditions as those described above, the corresponding normal aza-Baylis–Hillman adduct **7** was formed exclusively in 92% yield within 12 h. However, under the same reaction conditions,

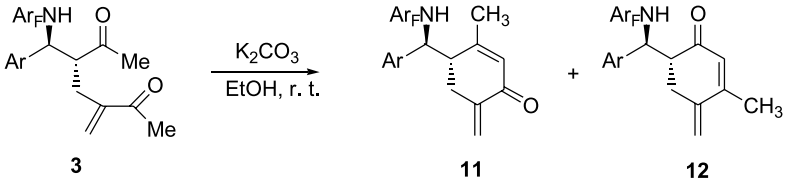


Scheme 5.



Scheme 6.

Table 4. Synthesis of fluorine-containing 4-alkylidene-2-cyclohexen-1-ones **11** and **12**



3 **11** **12**

Entry	Ar	ArF	Time (h)	Yield[a]/%	Ratio (**11**/**12**)
1	C_6F_5	C_6F_5	4	90	1:2[b]
2	*o*-BrC_6H_4	4-ClC_6F_4	4	79	37:42[c]
3	*o*-ClC_6H_4	4-ClC_6F_4	4	97	48:49[c]

[a] Isolated yield.
[b] Determined by ^{19}F NMR.
[c] Determined by isolated weight.

N-benzyliden-2, 4-difluor-anilin **8** did not react with MVK and even at higher temperature no reaction occurred to give the corresponding product due to its low reactivity. These results indicated that the electron-withdrawing nature of the *N*-substituent was necessary for a successful aza-Baylis–Hillman reaction. When *N*-phenyl-pentafluorophenyl aldimine **9** was subjected to similar reaction conditions, many unidentified products were formed, and none of the corresponding aza-Baylis–Hillman adduct was obtained. We also prepared trans-crotonaldehyde-4-chloro-2,3,5,6-tetrafluoro-phenylimine **10** which was very labile and must be used immediately for the reaction. In the aza-Baylis–Hillman reaction of **10** with MVK in the presence of PPh_3 under the same conditions, the corresponding normal aza-Baylis–Hillman adduct was formed in very low yield.

In 1998, Amri and co-workers reported a convenient synthesis of 4-alkylidene-2-cyclohexen-1-ones via the tandem three-step: S_N2' substitution–deacetylation–cyclization reactions (Scheme 6).[8] We intended to convert the double Baylis–Hillman adducts **3** to fluorine-containing 4-alkylidene-2-cyclohexen-1-ones, which represented the main structural feature of some natural and synthetic products[9–11] characterized by important biological activities[12] and considered as useful flavouring materials and perfumes.[13] However, under the reported reaction conditions, we found that the double aza-Baylis–Hillman adducts were transformed to the corresponding two isomers **11** and **12** in good yields at room temperature (Table 4). The structure of **12h** was determined by X-ray diffraction (Fig. 2). Specifically, when **3a** was used as a substrate, the aza-Baylis–Hillman adduct was transformed to the corresponding two isomers **11a** and **12a** in a ratio of 1:2 according to the ^{19}F NMR spectra which could not be separated by flash column chromatography. This transformation could provide a convenient method for the preparation of fluorine-containing 4-alkylidene-2-cyclohexen-1-one derivatives.

The double Baylis–Hillman reaction mechanism of electron deficient *N*-sulfonylimine and aldehyde had been proposed in Scheme 7.[4,14] The first mechanism is the Michael addition of enolate derived from DABCO and MVK to the Baylis–Hillman adduct, and the second is the aldol condensation reaction of enolate derived from DABCO and MVK (a MVK dimer type enloate) with the substrate.

To confirm the reaction mechanism of the formation of the

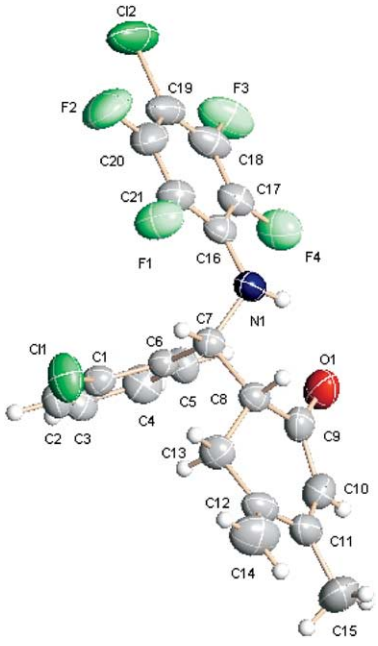
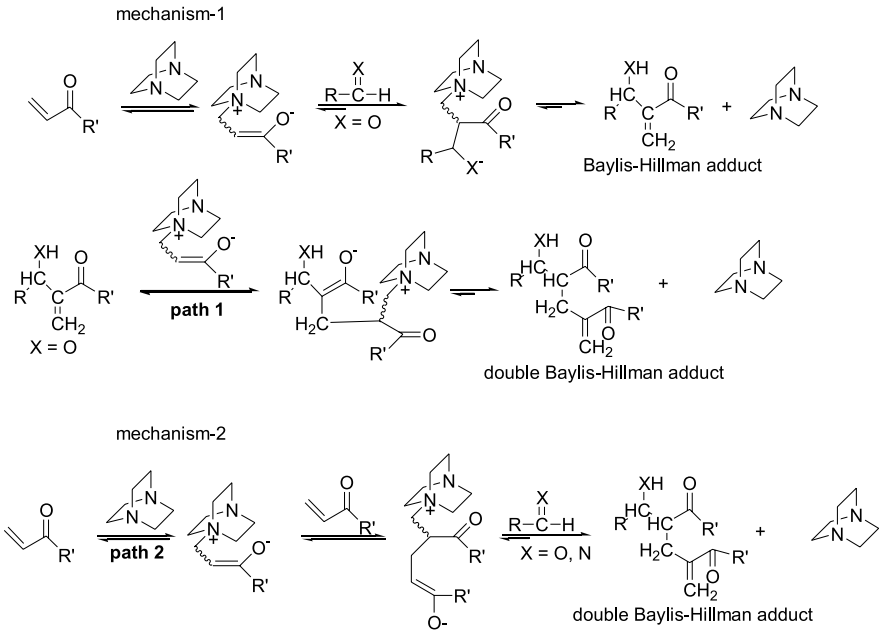
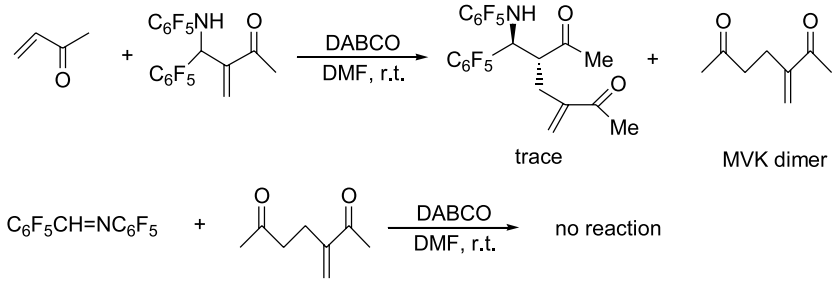


Figure 2. X-ray crystal structure of **12h**.



Scheme 7.



Scheme 8.

double aza-Baylis–Hillman product **3**, we conducted the reaction of MVK with the normal aza-Baylis–Hillman adduct **2a** under the same conditions (Scheme 8). To our surprise, only trace **3a** was obtained and the main product was the dimmer of MVK. We also confirmed that the MVK dimmer did not react with *N*-pentafluorophenyl-pentafluorophenyl aldimine **1a** in the presence of DABCO (Scheme 8). This was simply due to the fact that the MVK dimmer type enolate (show in mechanism 2 of Scheme 7) could not be formed from the MVK dimmer with DABCO. These results suggested that the double aza-Baylis–Hillman products **3** were not derived from the first mechanism as shown in Scheme 7, and this unexpected highly diastereoselective double aza-Baylis–Hillman reaction could only proceed via the second mechanism. Namely, a MVK dimmer type enolate was formed during the reaction which was further reacted with per- (or poly)fluorophenyl aromatic aldimines to give exclusively the double aza-Baylis–Hillman adduct (show in mechanism 2 of Scheme 7).

3. Conclusion

In conclusion, we have found that in the aza-Baylis–Hillman reaction of per- (or poly)fluorophenyl aromatic aldimines **1** with MVK, the Lewis base and solvent could significantly affect the reaction. Using triphenylphosphine as a Lewis base, the reaction of **1** with MVK proceeded smoothly to give the normal Baylis–Hillman adduct **2** along with the double Baylis–Hillman adduct **3** as by-product in THF. On the other hand, in the aza-Baylis–Hillman reaction of **1** with MVK using DABCO as a Lewis base, double aza-Baylis–Hillman adducts **3** were formed exclusively in the *anti*-configuration, which was confirmed to be derived from the Baylis–Hillman reaction of the enolate of the MVK dimmer induced by DABCO and MVK with per- (or poly)fluorophenyl aromatic aldimines. The double Baylis–Hillman adducts **3** were conveniently converted to fluorine-containing 4-alkylidene-2-cyclohexen-1-ones under mild reaction conditions in good yields. Further studies on applications of these aza-Baylis–Hillman reactions are underway.

4. Experimental

Unless otherwise stated, all reactions were carried out under an argon atmosphere. All per- (or poly)fluorophenyl aromatic aldimines[15] were prepared according to the literature. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in

$CDCl_3$ on Bruker AM-300 instruments with Me_4Si and $CFCl_3$ (with upfield negative) as the internal and external standards, respectively. IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Lower resolution mass spectrum or high-resolution mass spectra (HRMS) were obtained on a Finnigan GC-MS 4021 or a Finnigan MAT-8430 instrument using the electron impact ionization technique (70 ev), respectively. Elemental analyses were performed by this Institute. X-ray crystal structure analysis was performed on a Bruker P4 instrument. Melting points were measured in Temp-Melt apparatus and were uncorrected.

4.1. Typical reaction procedure for the triphenylphosphine-catalyzed Baylis–Hillman reaction of methyl vinyl ketone with per- (or poly)fluorophenyl aromatic aldimines

To a solution of *N*-pentafluorophenyl-pentafluorophenyl aldimine (181 mg, 0.5 mmol) and triphenylphosphine (26 mg, 0.1 mmol) in THF (1.0 mL) at room temperature was added methyl vinyl ketone (70 mg, 1 mmol). The reaction was monitored by TLC; when the imine disappeared, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography [SiO_2, EtOAc–petroleum ether (1:20)] to yield **2a** (172 mg, 80%) as a colorless liquid and **3a** (45 mg, 18%) as a colorless solid.

4.1.1. 3-(Pentafluorophenyl-pentafluorophenylamino-methyl)-but-3-en-2-one (2a). Colorless liquid; IR (film) υ 1678 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.39 (3H, s, Me), 4.29 (1H, d, $J=11.4$ Hz, NH), 6.03 (1H, d, $J=10.8$ Hz, CH), 6.24 (1H, s), 6.41 (1H, s); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −143.0 (2F, d, $^3J_{FF}=18.9$ Hz), −154.2 (1F, t, $^3J_{FF}=21.4$ Hz), −157.7 (2F, d, $^3J_{FF}=24.5$ Hz), −161.3 (2F, m), −163.2 (2F, t, $^3J_{FF}=22.0$ Hz), −167.5 (1F, t, $^3J_{FF}=17.2$ Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 26.1, 50.9, 114.2, 121.3, 126.8, 135.3 (m, $^1J_{CF}=288.2$ Hz), 136.3, 137.8 (m, $^1J_{CF}=239.1$ Hz), 139.1, 141.7 (m, $^1J_{CF}=211.6$ Hz), 144.9 (m, $^1J_{CF}=245.9$ Hz), 145.8, 197.6; MS (EI) *m/e* 431 (M^+, 7.05), 43 (M^+-388, 100). Anal. Calcd for $C_{17}H_7NOF_{10}$: C, 47.35; H, 1.64; N, 3.25. Found: C, 47.71; H, 1.79; N, 3.26.

4.1.2. 3-(Pentafluorophenylamino-phenyl-methyl)-but-3-en-2-one (2b). Colorless liquid (34 mg, 20%); IR (film) υ 1681 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.35 (3H, s, Me), 4.56 (1H, d, $J=9.3$ Hz, NH), 5.70 (1H, d, $J=9.6$ Hz, CH), 6.04 (1H, s), 6.26 (1H, s), 7.27–7.36 (5H, m, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −158.20 (2F, d, $^3J_{FF}=25.4$ Hz), −164.2 (2F, t, $^3J_{FF}=22.8$ Hz), −170.6 (1F, m); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 19.7, 60.6, 116.7, 122.6, 126.7, 126.8, 127.9, 128.8, 133.9 (m, $^1J_{CF}=241.9$ Hz), 138.3 (m, $^1J_{CF}=232.2$ Hz), 140.2, 148.3, 198.8; MS (EI) *m/e* 341 (M^+, 12.11), 159 (M^+-182, 61.39), 43 (M^+-298, 100). Anal. Calcd for $C_{17}H_{12}NOF_5$: C, 59.83; H, 3.54; N, 4.10. Found: C, 60.10; H, 3.48; N, 3.91.

4.1.3. 3-[(4-Chloro-2,3,5,6-tetrafluorophenylamino)-phenyl-methyl]-but-3-en-2-one (2c). Colorless liquid(91 mg, 51%); IR (film) υ 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.36 (3H, s, Me), 4.75 (1H, d, $J=9.6$ Hz, NH), 5.81 (1H, d, $J=9.3$ Hz, CH), 6.05 (1H, s), 6.28 (1H, s), 7.28–7.37 (5H, m, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −143.8 (2F, d, $^3J_{FF}=20.6$ Hz), −156.7 (2F, d, $^3J_{FF}=19.7$ Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 26.6, 60.1, 99.9, 125.7, 126.8, 127.1, 128.0, 128.7, 138.0 (m, $^1J_{CF}=241.3$ Hz), 140.1, 144.6 (m, $^1J_{CF}=244.2$ Hz), 148.2, 198.8; MS (EI) *m/e* 357 (M^+, 6.06), 43 (M^+-314, 100). Anal. Calcd for $C_{17}H_{12}NOF_4Cl$: C, 57.08; H, 3.36; N, 3.92. Found: C, 57.21; H, 3.56; N, 3.66.

4.1.4. 3-[(4-Chloro-2,3,5,6-tetrafluorophenylamino)-(4-nitrophenyl)-methyl]-but-3-en-2-one (2d). Yellow solid (181 mg, 90%); mp 97–99 °C; IR (film) υ 1681 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.37 (3H, s, Me), 4.90 (1H, d, $J=9.3$ Hz, NH), 5.75 (1H, d, $J=9.9$ Hz, CH), 6.13 (1H, s), 6.35 (1H, s), 7.56 (2H, d, $J=9.0$ Hz, Ar), 8.22 (2H, d, $J=8.7$ Hz, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −142.8 (2F, d, $^3J_{FF}=13.0$ Hz), −156.9 (2F, d, $^3J_{FF}=16.9$ Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 26.5, 60.6, 101.2, 123.9, 125.1, 127.4, 128.8, 138.3 (m, $^1J_{CF}=232.5$ Hz), 144.6 (m, $^1J_{CF}=247.0$ Hz), 147.1, 147.4, 147.6, 198.77; MS (EI) *m/e* 402 (M^+, 2.89), 43 (M^+-359, 100). Anal. Calcd for $C_{17}H_{11}N_2O_3F_4Cl$: C, 50.70; H, 2.75; N, 6.96. Found: C, 50.62; H, 2.87; N, 6.85.

4.1.5. 3-[(4-Chloro-2,3,5,6-tetrafluorophenylamino)-(2-nitrophenyl)-methyl]-but-3-en-2-one (2e). Yellow solid (103 mg, 51%); mp 109–111 °C; IR (film) υ 1683 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.37 (3H, s, Me), 4.46 (1H, d, $J=8.1$ Hz, NH), 5.90 (1H, s), 6.24 (1H, s), 6.43 (1H, d, $J=8.1$ Hz, CH), 7.49 (1H, m, Ar), 7.66 (1H, m, Ar), 7.76 (1H, m, Ar), 7.98 (1H, m, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ -143.2 (2F, d, $^3J_{FF}=18.8$ Hz), -157.9 (2F, d, $^3J_{FF}=16.6$ Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 26.0, 55.6, 100.4, 125.4, 125.6, 127.4, 128.4, 129.2,133.3, 135.3, 137.9 (m, $^1J_{CF}=241.1$ Hz), 144.4 (m, $^1J_{CF}=249.0$ Hz), 147.7, 148.1, 198.0; MS (EI) *m/e* 402 (M^+, 0.98), 43 (M^+-359, 100). Anal. Calcd for $C_{17}H_{11}N_2O_3F_4Cl$: C, 50.70; H, 2.75; N, 6.96. Found: C, 50.73; H, 3,04; N, 6.79.

4.1.6. 3-[(4-Bromophenyl)-(4-chloro-2,3,5,6-tetrafluorophenylamino)-methyl]-but-3-en-2-one (2f). Colorless liquid (76 mg, 35%); IR (film) υ 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.35 (3H, s, Me), 4.75 (1H, d, $J=9.0$ Hz, NH), 5.70 (1H, d, $J=9.0$ Hz, CH), 6.05 (1H, s), 6.27 (1H, s), 7.20 (2H, d, $J=8.1$ Hz, Ar), 7.47 (2H, d, $J=8.1$ Hz, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −143.2 (2F, d, $^3J_{FF}=21.4$ Hz), −157.3 (2F, d, $^3J_{FF}=22.8$ Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 26.5, 60.0, 101.7, 121.8, 125.4, 127.4, 128.4, 131.9, 139.2, 138.0 (m, $^1J_{CF}=236.2$ Hz), 139.2, 144.5 (m, $^1J_{CF}=262.15$ Hz), 147.8, 198.7; MS (EI) *m/e* 435 (M^+, 2.90), 43 (M^+-392, 100). HRMS (MALDI) *m/e* calcd for $C_{17}H_{12}N_2O_3F_4Br$ $(M+H)^+$ 435.9727, found 435.9746.

4.1.7. 3-[(2-Bromophenyl)-(4-chloro-2,3,5,6-tetrafluorophenylamino)-methyl]-but-3-en-2-one (2g). Colorless liquid(133 mg, 61%); IR (film) υ 1680 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.36 (3H, s, Me), 4.76 (1H, d, $J=9.3$ Hz, NH), 5.72 (1H, d, $J=9.0$ Hz, CH), 6.07 (1H, s), 6.30 (1H, s), 7.20–7.50 (4H, m, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −143.2 (2F, d, $^3J_{FF}=21.4$ Hz),

−157.3 (2F, d, $^3J_{FF}$=22.8 Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 26.6, 60.2, 102.7, 122.9, 125.3, 126.4, 127.6, 129.7, 130.3, 131.0, 138.0 (m, $^1J_{CF}$=243.5 Hz), 142.4, 144.9 (m, $^1J_{CF}$=292.9 Hz), 147.6, 198.6; MS (EI) *m/e* 435 (M^+, 3.69), 43 (M^+−392, 100). Anal. Calcd for $C_{17}H_{11}NOF_4ClBr$: C, 46.76; H, 2.54; N, 3.21. Found: C, 47.18; H, 2.81; N, 2.97.

4.1.8. 3-[(2-Chlorophenyl)-(4-chloro-2,3,5,6-tetrafluorophenylamino)-methyl]-but-3-en-2-one (2h). Colorless liquid (104 mg, 53%); IR (film) υ 1681 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.39 (3H, s, Me), 4.62 (1H, d, *J*=9.0 Hz, NH), 6.01 (1H, s), 6.23 (1H, d, *J*=8.7 Hz, CH), 6.32 (1H, s), 7.21–7.45 (4H, m, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −143.5 (2F, d, $^3J_{FF}$=14.9 Hz), −158.1 (2F, d, $^3J_{FF}$=12.7 Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 26.6, 56.7, 100.6, 125.6, 127.2, 127.9, 128.2, 129.2, 130.2, 133.6, 137.5, 137.9 (m, $^1J_{CF}$=239.9 Hz), 144.5 (m, $^1J_{CF}$=246.3 Hz), 147.4, 198.5; MS (EI) *m/e* 391 (M^+, 13.14), 43 (M^+−348, 100). Anal. Calcd for $C_{17}H_{11}NOF_4Cl_2$: C, 52.06; H, 2.83; N, 3.57. Found: C, 52.25; H, 2.88; N, 3.50.

4.1.9. 3-[(4-Chloro-2,3,5,6-tetrafluorophenylamino)-*p*-tolyl-methyl]-but-3-en-2-one (2i). Colorless liquid (84 mg, 45%); IR (film) υ 1680 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.34 (3H, s, Me), 3.35 (3H, s, Me), 4.71 (1H, d, *J*=8.7 Hz, NH), 5.78 (1H, d, *J*=9.3 Hz, CH), 6.04 (1H, s), 6.25 (1H, s), 7.16 (2H, d, *J*=7.8 Hz, Ar), 7.24 (2H, d, *J*=7.8 Hz, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −143.7 (2F, d, $^3J_{FF}$=16.9 Hz), −157.7 (2F, d, $^3J_{FF}$=18.3 Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 21.1, 26.7, 59.8, 99.9, 125.6, 126.4, 126.7, 129.5, 137.1, 137.8, 137.9 (m, $^1J_{CF}$=225.4 Hz), 144.6 (m, $^1J_{CF}$=248.0 Hz), 148.4, 198.8; MS (EI) *m/e* 371 (M^+, 7.14), 173 (M^+− 198, 54.03), 43 (M^+−328, 100). Anal. Calcd for $C_{18}H_{14}NOF_4Cl$: C, 58.16; H, 3.80; N, 3.78. Found: C, 58.43; H, 3.87; N, 3.55.

4.1.10. 3-[(4-Chloro-2,3,5,6-tetrafluorophenylamino)-(4-methoxy-phenyl)-methyl]-but-3-en-2-one (2j). Colorless liquid (68 mg, 35%); IR (film) υ 1680 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.35 (3H, s, Me), 3.80 (3H, s, Me), 4.67 (1H, d, *J*=8.7 Hz, NH), 5.78 (1H, d, *J*=8.7 Hz, CH), 6.03 (1H, s), 6.25 (1H, s), 6.88 (2H, d, *J*=6.6 Hz, Ar), 7.27 (2H, d, *J*=6.6 Hz, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −143.6 (2F, d, $^3J_{FF}$=26.2 Hz), −157.6 (2F, d, $^3J_{FF}$=23.4 Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 26.7, 55.3, 59.5, 100.0, 114.2, 125.6, 126.1, 128.2, 132.2, 137.8 (m, $^1J_{CF}$=235.4 Hz), 144.5 (m, $^1J_{CF}$=254.8 Hz), 148.4, 159.3, 198.8; MS (EI) *m/e* 387 (M^+, 3.47), 318 (M^+−69, 100), 43 (M^+−344, 57.65). Anal. Calcd for $C_{18}H_{14}NO_2F_4Cl$: C, 55.76; H, 3.64; N, 3.61. Found: C, 56.09; H, 3.83; N, 3.42.

4.1.11. 3-(4-Chloro-2,3,5,6-tetrafluorophenylamino)-3-methylene-6-(*trans*)-phenyl-hex-5-en-2-one (2k). Colorless liquid (58 mg, 30%); IR (film) υ 1678 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.39 (3H, s, Me), 4.78 (1H, d, *J*=9.9 Hz, NH), 5.23 (1H, dd, *J*=9.9, 7.2 Hz, CH), 6.06 (1H, s), 6.20 (1H, s), 6.34 (1H, dd, *J*=7.2, 6.9 Hz, CH), 6.59 (1H, d, *J*=6.9 Hz, CH), 7.23–7.39 (5H, m, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −143.3 (2F, d, $^3J_{FF}$=26.2 Hz), −156.5 (2F, d, $^3J_{FF}$=24.8 Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 26.6, 59.8, 100.0, 125.6, 126.6, 127.4, 128.0, 128.6, 132.3, 136.1, 137.9 (m, $^1J_{CF}$=239.9 Hz), 138.8, 144.5 (m, $^1J_{CF}$=246.3 Hz), 147.6, 199.1; MS (EI) *m/e* 383 (M^+, 10.13), 185 (M^+−198, 100), 43 (M^+−340, 93.02); HRMS *m/e* calcd for $C_{19}H_{14}NOF_4Cl$ 383.0700, found. 383.06837.

4.2. Typical reaction procedure for the DABCO-catalyzed Baylis–Hillman reaction of methyl vinyl ketone with per- (or poly)fluorophenyl aromatic aldimines.

To a solution of *N*-pentafluorophenyl-pentafluorophenyl aldimine (181 mg, 0.5 mmol) and DABCO (12 mg, 0.1 mmol) in DMF (1.0 mL) at room temperature was added methyl vinyl ketone(175 mg, 2.5 mmol) under an argon atmosphere and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was washed with water (3×10 mL) and extracted with dichloromethane (2×10 mL). The organic layer was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, the residue was purified on silica gel using ethyl acetate (hexane (V/V: 1:20) as an elute to give a white solid product **3a**, which was further recrystallized from dichloromethane-hexane (V/V: 1:1) to give the pure product **3a** (218 mg, 87%) as a colorless crystal.

4.2.1. (*4,5-trans*)-3-Methylene-5-(pentafluorophenyl-pentafluorophenylamino-methyl)-heptane-2,6-dione (3a). Colorless solid; mp 102–104 °C; IR (film) υ 1713 cm^{-1} (C=O); 1670 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.40 (3H, s, Me), 2.31 (1H, dd, *J*=13.8, 5.7 Hz), 2.34 (3H, s, Me), 2.50 (1H, dd, *J*=13.8, 9.0 Hz), 3.36 (1H, ddd, *J*=9.3, 9.0, 5.7 Hz), 4.56 (1H, d, *J*=11.7 Hz, NH), 5.27 (1H, dd, *J*=11.7, 9.3 Hz, CH), 5.82 (1H, s), 6.08 (1H, s); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −143.9 (2F, d, $^3J_{FF}$=17.2 Hz), −152.8 (1F, t, $^3J_{FF}$=20.3 Hz), −157.7 (2F, d, $^3J_{FF}$=20.6 Hz), −160.4 (2F, m), −163.1 (2F, t, $^3J_{FF}$=17.8 Hz), −167.3 (1F, t, $^3J_{FF}$=18.1 Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 25.5, 30.7, 31.8, 53.2, 54.8, 114.2, 121.3, 128.5, 135.3 (m, $^1J_{CF}$=288.2 Hz), 136.3, 137.8 (m, $^1J_{CF}$=239.1 Hz), 139.1, 141.7 (m, $^1J_{CF}$=211.6 Hz), 144.6, 144.9 (m, $^1J_{CF}$=245.9 Hz), 198.8, 209.0; MS (EI) *m/e* 501 (M^+, 0.53), 362 (M^+−139, 55.76), 43 (M^+−458, 100). Anal. Calcd for $C_{21}H_{13}NO_2F_{10}$: C, 50.31; H, 2.61; N, 2.79. Found: C, 50.32; H, 2.62; N, 2.66.

4.2.2. (*4,5-trans*)-3-Methylene-5-(pentafluorophenyl-amino-phenyl-methyl)-heptane-2,6-dione (3b). Colorless solid (72 mg, 35%); mp 86–87 °C; IR (film) υ 1717 cm^{-1} (C=O); 1662 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.92 (3H, s, Me), 2.37 (3H, s, Me), 2.56 (1H, dd, *J*=13.2, 6.3 Hz), 2.68 (1H, dd, *J*=13.2, 8.4 Hz), 3.24 (1H, ddd, *J*=8.4, 6.3, 5.7 Hz), 4.79 (1H, dd, *J*=10.5, 5.7 Hz, CH), 5.32 (1H, d, *J*=10.5 Hz, NH), 5.91 (1H, s), 6.13 (1H, s), 7.13–7.32 (5H, m, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −158.0 (2F, d, $^3J_{FF}$=23.1 Hz), −164.4 (2F, t, $^3J_{FF}$=17.5 Hz), −170.60 (1F, m); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 25.8, 31.7, 32.0, 56.1, 60.4, 116.7, 122.2, 126.2, 127.9, 128.7, 128.9, 133.9 (m, $^1J_{CF}$=241.9 Hz), 138.3 (m, $^1J_{CF}$=232.2 Hz), 140.4, 145.2,

199.4, 212.8; MS (EI) *m/e* 411 (M^+, 1.05), 272 (M^+-139, 100), 43 (M^+-368, 32.97). Anal. Calcd for $C_{21}H_{18}NO_2F_5$: C, 61.31; H, 4.41; N, 3.40. Found: C, 61.42; H, 4.31; N, 3.18.

4.2.3. (*4,5-trans*)-3-[(4-Chloro-2,3,5,6-tetrafluorophenylamino)-phenyl-methyl]-5-methylene-heptane-2,6-dione (3c). Colorless liquid (101 mg, 47%); IR (film) υ 1707 cm^{-1} (C=O); 1678 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.90 (3H, s, Me), 2.37 (3H, s, Me), 2.59 (1H, dd, $J=13.2$, 6.9 Hz), 2.71 (1H, dd, $J=13.2$, 8.1 Hz), 3.26 (1H, ddd, $J=8.1$, 6.9, 5.1 Hz), 4.87 (1H, dd, $J=11.1$, 5.1 Hz, CH), 5.66 (1H, d, $J=11.1$ Hz, NH), 5.91 (1H, s), 6.14 (1H, s), 7.10 - 7.32 (5H, m, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −143.8 (2F, d, $^3J_{FF}=25.4$ Hz), −157.3 (2F, d, $^3J_{FF}=25.9$ Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 25.9, 32.0, 32.1, 60.0, 65.9, 100.0, 125.5, 126.1, 127.9, 128.7, 129.0, 137.9 (m, $^1J_{CF}=241.1$ Hz), 142.9, 144.5 (m, $^1J_{CF}=248.0$ Hz), 145.2, 199.4, 213.0; MS (EI) *m/e* 427 (M^+, 4.26), 288 (M^+-139, 100), 43 (M^+-384, 55.18); HRMS (MALDI) *m/e* calcd for $C_{21}H_{18}NO_2F_4ClNa$ $(M+Na)^+$ 450.0860, found 450.0898.

4.2.4. (*4,5-trans*)-3-[(4-Chloro-2,3,5,6-tetrafluorophenylamino)-(4-nitrophenyl)-methyl]-5-methylene-heptane-2,6-dione (3d). Yellow solid (71 mg, 30%); mp 150–152 °C; IR (film) υ 1709 cm^{-1} (C=O); 1678 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.94 (3H, s, Me), 2.39 (3H, s, Me), 2.57 (1H, dd, $J=13.2$, 7.2 Hz), 2.70 (1H, dd, $J=13.2$, 7.8 Hz), 3.24 (1H, ddd, $J=7.8$, 7.2, 4.5 Hz), 4.82 (1H, dd, $J=9.6$, 4.5 Hz, CH), 5.74 (1H, d, $J=9.6$ Hz, NH), 5.92 (1H, s), 6.16 (1H, s), 7.04 (2H, d, $J=8.7$ Hz, Ar), 7.42 (2H, d, $J=8.4$ Hz, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −143.4 (2F, d, $^3J_{FF}=26.2$ Hz), −157.3 (2F, d, $^3J_{FF}=18.3$ Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 25.9, 31.8, 32.1, 55.5, 59.5, 100.2, 124.2, 125.5, 127.3, 127.4, 129.6, 137.9 (m, $^1J_{CF}=241.1$ Hz), 144.4 (m, $^1J_{CF}=249.0$ Hz), 144.7, 148.2, 199.5, 212.4; MS (EI) *m/e* 472 (M^+, 4.26), 333 (M^+-139, 88.90), 43 (M^+-429, 100); HRMS *m/e* calcd for $C_{21}H_{17}N_2O_4F_4Cl$ 472.0813, found 472.0815.

4.2.5. (*4,5-trans*)-3-[(4-Chloro-2,3,5,6-tetrafluorophenylamino)-(2-nitrophenyl)-methyl]-5-methylene-heptane-2,6-dione (3e). Yellow solid (163 mg, 69%); mp 144–146 °C; IR (film) υ 1704 cm^{-1} (C=O); 1678 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.08 (3H, s, Me), 2.51 (3H, s, Me), 2.61 (1H, dd, $J=13.2$, 10.5 Hz), 2.97 (1H, dd, $J=13.2$, 3.6 Hz), 3.44 (1H, ddd, $J=10.5$, 3.6, 3.0 Hz), 5.50 (1H, dd, $J=10.2$, 3.0 Hz, CH), 5.94 (1H, s), 6.25 (1H, s), 6.58 (1H, d, $J=10.2$ Hz, NH), 7.38–7.59 (3H, m, Ar), 7.96–7.99 (1H, m, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −143.1 (2F, d, $^3J_{FF}=23.1$ Hz), −158.7 (2F, d, $^3J_{FF}=22.3$ Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 25.8, 31.7, 32.0, 52.3, 53.8, 100.2, 125.5, 125.4, 128.5, 128.6, 129.0, 133.7, 136.7, 137.9 (m, $^1J_{CF}=241.1$ Hz), 144.4 (m, $^1J_{CF}=249.0$ Hz), 144.6, 148.2, 199.3, 213.8; MS (EI) *m/e* 333 (M^+-139, 20.47), 43 (M^+-429, 100). Anal. Calcd for $C_{21}H_{17}N_2O_4F_4Cl$: C, 53.35; H, 3.62; N, 5.92. Found: C, 52.93; H, 3.57; N, 5.70.

4.2.6. (*4,5-trans*)-3-[(4-Bromophenyl)-(4-chloro-2,3,5,6-tetrafluorophenylamino)-methyl]-5-methylene-heptane-2,6-dione (3f). Colorless solid (165 mg, 65%); mp 112–120 °C; IR (film) υ 1707 cm^{-1} (C=O); 1677 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.95 (3H, s, Me), 2.42 (3H, s, Me), 2.63 (1H, dd, $J=13.2$, 8.1 Hz), 2.76 (1H, dd, $J=13.2$, 6.6 Hz), 3.31 (1H, ddd, $J=8.1$, 6.6, 4.2 Hz), 4.95 (1H, dd, $J=9.3$, 4.2 Hz, CH), 5.94 (1H, d, $J=9.3$ Hz, NH), 5.95 (1H, s), 6.20 (1H, s), 7.36 (2H, d, $J=8.7$ Hz, Ar), 8.17 (2H, d, $J=8.7$ Hz, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −142.9 (2F, d, $^3J_{FF}=21.7$ Hz), −157.6 (2F, d, $^3J_{FF}=22.0$ Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 22.7, 29.7, 32.2, 55.1, 59.4, 100.1, 121.8, 125.5, 127.9, 129.1, 132.0, 138.1 (m, $^1J_{CF}=237.1$ Hz), 139.7, 144.5 (m, $^1J_{CF}=254.1$ Hz), 144.9, 199.4, 212.8; MS (EI) *m/e* 505 (M^+, 2.21), 366 (M^+-139, 69.72), 43 (M^+-462, 100); HRMS (MALDI) *m/e* calcd for $C_{21}H_{18}NO_2F_4ClBr$ $(M+H)^+$ 506.0146, found 506.0124.

4.2.7. (*4,5-trans*)-3-[(2-Bromophenyl)-(4-chloro-2,3,5,6-tetrafluorophenylamino)-methyl]-5-methylene-heptane-2,6-dione (3g). Colorless solid (155 mg, 61%); mp 124–126 °C; IR (film) υ 1705 cm^{-1} (C=O); 1673 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.94 (3H, s, Me), 2.45 (3H, s, Me), 2.67 (1H, dd, $J=13.2$, 9.3 Hz), 2.90 (1H, dd, $J=13.2$, 5.1 Hz), 3.40 (1H, ddd, $J=9.3$, 5.1, 3.6 Hz), 5.30 (1H, dd, $J=10.2$, 3.6 Hz, CH), 6.02 (1H, s), 6.24 (1H, s), 6.26 (1H, d, $J=10.2$ Hz, NH), 7.09–7.28 (3H, m, Ar), 7.53–7.56 (1H, m, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −143.5 (2F, d, $^3J_{FF}=26.2$ Hz), −158.2 (2F, d, $^3J_{FF}=22.0$ Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 25.6, 31.5, 32.2, 51.8, 58.0, 100.1, 122.6, 125.6, 127.5, 127.9, 128.7, 129.2, 133.5, 138.1 (m, $^1J_{CF}=239.5$ Hz), 139.3, 144.5 (m, $^1J_{CF}=262.2$ Hz), 145.0, 198.9, 213.2; MS (EI) *m/e* 505 (M^+, 2.21), 366 (M^+-139, 69.72), 43 (M^+-462, 100). Anal. Calcd for $C_{21}H_{17}NO_2F_4ClBr$: C, 49.78; H, 3.38; N, 2.76. Found: C, 49.76; H, 3.34; N, 2.55.

4.2.8. (*4,5-trans*)-3-[(2-Chlorophenyl)-(4-chloro-2,3,5,6-tetrafluorophenylamino)-methyl]-5-methylene-heptane-2,6-dione (3h). Colorless solid (141 mg, 61%); mp 88–90 °C; IR (film) υ 1706 cm^{-1} (C=O); 1674 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.94 (3H, s, Me), 2.42 (3H, s, Me), 2.63 (1H, dd, $J=13.2$, 9.3 Hz), 2.87 (1H, dd, $J=13.2$, 5.1 Hz), 3.36 (1H, ddd, $J=9.3$, 5.1, 3.6 Hz), 5.33 (1H, dd, $J=9.9$, 3.6 Hz, CH), 5.98 (1H, s), 6.18 (1H, d, $J=9.9$ Hz, NH), 6.21 (1H, s), 7.14–7.36 (4H, m, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −143.6 (2F, d, $^3J_{FF}=18.9$ Hz), −158.2 (2F, d, $^3J_{FF}=18.1$ Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 25.6, 31.5, 32.1, 51.9, 55.6, 99.6, 125.7, 125.3, 125.4, 128.8, 128.9, 130.2, 132.4, 137.8, 138.0 (m, $^1J_{CF}=224.9$ Hz), 144.5 (m, $^1J_{CF}=244.4$ Hz), 145.0, 199.0, 213.2; MS (EI) *m/e* 461 (M^+, 1.51), 322 (M^+-139, 100), 43 (M^+-458, 56.81). Anal. Calcd for $C_{21}H_{17}NO_2F_4Cl_2$: C, 54.56; H, 3.71; N, 3.03. Found: C, 54.86; H, 3.53; N, 2.95.

4.2.9. 2-(Pentafluorophenyl-pentafluorophenylamino-methyl)-acrylic acid methyl ester (4). Colorless liquid (219 mg, 98%); IR (film) υ 3408, 1728, 1525, 1504 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 3.78 (3H, s, Me), 4.44 (1H, d, $J=11.1$ Hz, NH), 6.00 (1H, s), 6.04 (1H, d, $J=11.7$ Hz, CH), 6.54 (1H, s); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −143.0 (2F, d, $^3J_{FF}=21.4$ Hz), −153.8 (1F, t, $^3J_{FF}=22.0$ Hz), −157.7 (2F, d, $^3J_{FF}=21.7$ Hz), −161.2 (2F, m), −163.2 (2F, t, $^3J_{FF}=20.9$ Hz), −167.5 (1F, t,

$^3J_{FF}$=21.7 Hz); MS (EI) *m/e* 447 (M^+, 91), 387 (60), 362 (100), 265 (50). Anal. Calcd for $C_{17}H_7N_2O_2F_{10}$: C, 45.66; H, 1.58; N, 3.13. Found: C, 45.85; H, 1.68; N, 3.11.

4.2.10. 2-(Pentafluorophenyl-pentafluorophenylamino-methyl)-acrylonitrile (5). Colorless liquid (149 mg, 72%); IR (film) υ 3396, 1510, 1505 cm^{-1}; ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 4.40 (1H, d, J=10.8 Hz, NH), 5.78 (1H, d, J=11.4 Hz, CH), 6.15 (1H, s), 6.25 (1H, s); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −142.8 (2F, d, $^3J_{FF}$=12.7 Hz), −150.7 (1F, t, $^3J_{FF}$=20.9 Hz), −156.7 (2F, d, $^3J_{FF}$=22.8 Hz), −159.3 (2F, m), −162.2 (2F, t, $^3J_{FF}$=23.1 Hz), −165.2 (1F, t, $^3J_{FF}$=22.6 Hz); MS (EI) *m/e* 414 (M^+, 81), 362 (80), 232 (100), 182 (31). Anal. Calcd for $C_{16}H_4N_2F_{10}$: C, 46.40; H, 0.97; N, 6.76. Found: C, 46.75; H, 1.35; N, 7.00.

4.2.11. 2-[(4-Bromophenyl)-(2,3,4,5-tetrafluoro-6-nitro-phenylamino)-methyl]-but-3-en-2-one (7). Yellow liquid (206 mg, 92%); IR (film) υ 1681 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.35 (3H, s, Me), 5.82 (1H, d, J=8.1 Hz, CH), 5.97 (1H, s), 6.27 (1H, s), 6.84 (1H, d, J=8.1 Hz, NH), 7.20 (2H, d, J=8.1 Hz, Ar), 7.48 (2H, d, J=8.7 Hz, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −144.2 (1F, m), −146.6 (1F, m); −153.2 (1F, m), −168.8 (1F, m); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 26.4, 59.6, 122.1, 127.2, 128.6, 130.4, 132.1, 134.7, 136.5, 138.8, 141.6, 143.2, 145.1, 148.2, 198.1; MS (EI) *m/e* 446 (M^+, 0.06), 43 (M^+−403, 100); HRMS (MALDI) *m/e* calcd for $C_{17}H_{12}N_2O_3F_4Br$ $(M+H)^+$ 446.9967, found 446.9973.

4.3. Typical experimental procedure for the synthesis of fluorine-containing 4-alkylidene-2-cyclohexen-1-ones 11 and 12

To absolute ethanol solution of anhydrous potassium carbonate was mixed with 3-methylene-5-(pentafluoro-phenyl-pentafluorophenylamino-methyl)-heptane-2,6-dione **3a**. The mixture was stirred at room temperature for a given time (TLC, see Table 4). After removed of ethanol in vacuo, the residue was shaken with water to dissolve the salts. The resulting mixture was extracted three times with 10 mL of ether. The organic phase was dried on $MgSO_4$, concentrated and the crude products **11a** and **12a** were purified by flash chromatogryphy (EtOAc/Hexane, 1:40).

4.3.1. 3-Methyl-4-methylene-6-(pentafluorophenyl-pentafluorophenylamino-methyl)-cyclohex-2-enone (12a). Yellow liquid (32 mg, 60%); IR (film) υ 1668 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.10 (3H, s, Me), 2.93–3.11 (3H, m), 4.35 (1H, d, J=10.8 Hz, NH), 5.13–5.21 (1H, m, CH), 5.45 (1H, s), 5.52 (1H, s), 5.84 (1H, s); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −143.7 (2F, d, $^3J_{FF}$=18.6 Hz), −154.2 (1F, t, $^3J_{FF}$=20.9 Hz), −157.5 (2F, d, $^3J_{FF}$=22.5 Hz), −161.6 (2F, m), −163.4 (2F, t, $^3J_{FF}$=21.4 Hz), −167.7 (1F, t, $^3J_{FF}$=20.3 Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 19.7, 34.1, 50.9, 51.8, 114.2, 118.3, 121.3, 126.8, 135.3 (m, $^1J_{CF}$=288.2 Hz), 136.3, 137.8 (m, $^1J_{CF}$=239.1 Hz), 139.0, 139.2, 141.7 (m, $^1J_{CF}$=211.6 Hz), 144.9 (m, $^1J_{CF}$=245.9 Hz), 154.8, 197.1; MS (EI) *m/e* 483 (M^+, 0.53), 362 (M^+−121, 61.10), 122 (M^+−361, 100), 107 (M^+−376, 53.12); HRMS (MALDI) *m/e* calcd for $C_{21}H_{11}NOF_{10}Na$ $(M+Na)^+$ 506.0579, found 506.0600.

4.3.2. 3-Methyl-6-methylene-4-(pentafluorophenyl-pentafluorophenylamino-methyl)-cyclohex-2-enone (11a). Yellow liquid (16 mg, 30%); IR (film) υ 1668 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.14 (3H, s, Me), 2.35–2.42 (1H, m), 2.86–2.93 (1H, m), 2.99–3.11 (1H, m), 4.48 (1H, d, J=9.6 Hz, NH), 5.13–5.21 (1H, m, CH), 5.35 (1H, s), 5.56 (1H, s), 5.95 (1H, s); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −142.9 (2F, d, $^3J_{FF}$=13.8 Hz), −153.5 (1F, t, $^3J_{FF}$=20.0 Hz), −158.0 (2F, d, $^3J_{FF}$=24.8 Hz), −161.0 (2F, m), −163.8 (2F, t, $^3J_{FF}$=15.6 Hz), −168.7 (1F, t, $^3J_{FF}$=17.2 Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 19.7, 34.6, 50.8, 52.0, 114.2, 118.3, 121.5, 126.1, 135.3 (m, $^1J_{CF}$=288.2 Hz), 136.3, 137.8 (m, $^1J_{CF}$=239.1 Hz), 138.8, 139.1, 141.7 (m, $^1J_{CF}$=211.6 Hz), 144.9 (m, $^1J_{CF}$=245.9 Hz), 154.4, 197.7; MS (EI) *m/e* 483 (M^+, 3.75), 362 (M^+−121, 61.10), 122 (M^+−361, 100), 107 (M^+−376, 53.12); HRMS (MALDI) *m/e* calcd for $C_{21}H_{11}NOF_{10}Na$ $(M+Na)^+$ 506.0579, found 506.0600.

4.3.3. 4-[(2-Bromophenyl)-(4-chloro-2,3,5,6-tetrafluoro-phenylamino)-methyl]-3-methyl-6-methylene-cyclohex-2-enone (11g). Colorless liquid (23 mg, 37%); IR (film) υ 1664 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.10 (3H, s, Me), 2.94–2.97 (2H, m), 3.12–3.19 (1H, m), 5.13–5.18 (1H, m, CH), 5.33 (1H, d, J=10.8 Hz, NH), 5.45 (1H, s), 5.50 (1H, s), 5.91 (1H, s), 7.08–7.14 (1H, m, Ar), 7.27–7.35 (1H, m, Ar), 7.50–7.63 (2H, m, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −143.6 (2F, d, $^3J_{FF}$=26.5 Hz), −156.5 (2F, d, $^3J_{FF}$=21.7 Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 19.6, 36.3, 51.4, 60.4, 100.9, 117.4, 123.2, 125.8, 127.5, 127.7, 129.0, 133.1, 133.2, 138.6 (m, $^1J_{CF}$=252.0 Hz), 141.1, 142.7, 144.4 (m, $^1J_{CF}$=237.9 Hz), 154.2, 200.0; MS (EI) *m/e* 487 (M^+, 0.84), 366 (M^+−121, 32.48), 210 (M^+−277, 27.63), 122 (M^+−365, 100), 107 (M^+−380, 44.84); HRMS (MALDI) *m/e* calcd for $C_{21}H_{15}NOF_4ClBrNa$ $(M+Na)^+$ 509.9859, found 509.9879.

4.3.4. 6-[(2-Bromophenyl)-(4-chloro-2,3,5,6-tetrafluoro-phenylamino)-methyl]-3-methyl-4-methylene-cyclohex-2-enone (12g). Colorless solid (26 mg, 42%); mp 127 °C; IR (film) υ 1652 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.05 (3H, s, Me), 2.61–2.69 (1H, m), 2.82–2.89 (1H, m), 3.15–3.22 (1H, m), 5.42 (2H, s), 5.62 (1H, brs, NH), 5.70–5.75 (1H, m), 5.96 (1H, s), 7.08–7.54 (4H, m, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −143.7 (2F, d, $^3J_{FF}$=16.9 Hz), −157.2 (2F, d, $^3J_{FF}$=19.5 Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 19.7, 32.6, 49.8, 58.2, 100.0, 117.2, 124.0, 125.8, 127.7, 128.4, 128.8, 129.2, 133.4, 138.6 (m, $^1J_{CF}$=252.0 Hz), 138.9, 140.9, 144.4 (m, $^1J_{CF}$=237.9 Hz), 154.6, 198.6; MS (EI) *m/e* 487 (M^+, 1.68), 366 (M^+−121, 34.82), 210 (M^+−277, 34.17), 122 (M^+−365, 100), 107 (M^+−380, 37.99); HRMS (MALDI) *m/e* calcd for $C_{21}H_{15}NOF_4ClBrNa$ $(M+Na)^+$ 509.9859, found 509.9883.

4.3.5. 4-[(2-Chlorophenyl)-(4-chloro-2,3,5,6-tetrafluoro-phenylamino)-methyl]-3-methyl-6-methylene-cyclohex-2-enone (11h). Colorless liquid (21 mg, 48%); IR (film) υ 1664 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 2.03 (3H, s, Me), 2.76–2.84 (2H, m), 3.00–3.07 (1H, m),

5.07–5.12 (1H, m), 5.18 (1H, brs, NH), 5.34 (1H, s), 5.43 (1H, s), 5.84 (1H, s), 7.10–7.27 (3H, m, Ar), 7.45–7.48 (1H, m, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −143.4 (2F, d, $^3J_{FF}$=22.8 Hz), −156.3 (2F, d, $^3J_{FF}$=19.5 Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.1, 35.9, 51.4, 58.2, 100.0, 117.6, 125.7, 127.0, 127.4, 128.4, 128.8, 129.9, 132.9, 138.2, 138.4 (m, $^1J_{CF}$=228.1 Hz), 140.9, 144.5 (m, $^1J_{CF}$=253.7 Hz), 154.3, 200.0; MS (EI) *m/e* 443 (M^+, 0.65), 322 (M^+-121, 39.24), 210 (M^+-233, 28.66), 122 (M^+-321, 100), 107 (M^+-336, 49.97); HRMS (MALDI) *m/e* calcd for $C_{21}H_{15}NOF_4Cl_2$ Na $(M+Na)^+$ 466.0365, found 466.0383.

4.3.6. 6-[(2-Chlorophenyl)-(4-chloro-2,3,5,6-tetrafluorophenylamino)-methyl]-3-methyl-4-methylene-cyclohex-2-enone (12h). Colorless solid (22 mg, 49%); mp 122 °C; IR (film) υ 1648 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 1.96 (3H, s, Me), 2.51–2.60 (1H, m), 2.75–2.82 (1H, m), 3.08–3.15 (1H, m), 5.33 (2H, s), 5.61–5.67 (1H, m), 5.85 (1H, s), 5.71 (1H, brs, NH), 7.06–7.30 (4H, m, Ar); ^{19}F NMR ($CDCl_3$, TMS, 282 MHz) δ −143.5 (2F, d, $^3J_{FF}$=23.4 Hz), −157.1 (2F, d, $^3J_{FF}$=22.8 Hz); ^{13}C NMR ($CDCl_3$, TMS, 75.44 MHz) δ 14.1, 32.9, 49.9, 56.9, 100.0, 117.2, 125.6, 127.2, 128.3, 128.8, 128.9, 130.0, 133.7, 137.2, 138.3 (m, $^1J_{CF}$=242.4 Hz), 140.9, 144.4 (m, $^1J_{CF}$=246.05 Hz), 154.7, 198.4; MS (EI) *m/e* 443 (M^+, 1.36), 322 (M^+-121, 42.69), 210 (M^+-233, 27.45), 122 (M^+-321, 100), 107 (M^+-336, 43.94); HRMS (MALDI) *m/e* calcd for $C_{21}H_{15}NOF_4Cl_2Na$ $(M+Na)^+$ 466.0365, found 466.0403.

4.4. X-ray crystal structure data of compounds (3a) and (12h)

Intensity data were collected at 293(2) K on Bruker P4 diffractometer with graphite monochromator and Mo Kα radiation (λ=0.71073 Å). The structure was solved by direct methods and explained using Fourier techniques. The nonhydrogen atoms were refined anisotropically, hydrogen atoms were included but not refined. The final cycle of full matrix least-squares refinement was based on F^2, respectively. All calculations were performed using SHELXS-97 and SHELXL-97 programs. X-ray data for compounds **3a** and **12h** are listed in Table 5.

Table 5. X-ray data collection and processing parameters for compounds **3a** and **12h**

Compound	**3a** CCDC 260807	**12h** CCDC 260807
Formula	$C_{21}H_{13}F_{10}NO_2$	$C_{21}H_{15}Cl_2F_4NO$
Size (mm)	0.27×0.22×0.16	0.51×0.44×0.41
Space group	*P*2 (1)/*C*	*P*2 (1)/*n*
Crystal system	Monoclinic	Monoclinic
a (Å)	9.748(2)	19.201(1)
b (Å)	25.814(5)	8.1936(5)
c (Å)	9.028(2)	26.4171(17)
α (°)	90.00	90.00
β (°)	111.00(3)	110.6980(10)
γ (°)	90.00	90.00
V (Å^3)	2120.9(7)	3887.8(4)
Z-value	4	8
D_{calc} (g cm^{-3})	1.570	1.518
μ (mm^{-1})	0.16	0.384
T (K)	293(2)	293(2)
2θ range (°)	3–55	4–54
Total reflections	6033	22164
F(000)	1008	1808
Independent reflections	4872	8430
R_{int}	0.0343	0.0756
$I>2\sigma$ (*I*)	1535	8430
Parameters	360	533
Goodness of fit	0.904	0.875
Final *R* indices ($I>2\sigma$ (*I*))	0.2000; 0.0530	0.0476; 0.1122
R indices (all data)	0.1479; 0.1062	0.0889; 0.1264

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Bis- and tetracalix[4]arenes in the partial cone conformation: synthesis, structure and RCM reactions

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Abstract—The synthesis, structure and ring-closing metathesis (RCM) reactions of polyether bridged biscalix[4]arenes **6** in the partial cone conformation with upper rim allyl substituents are reported. The RCM reaction modes depend on the length of polyether chain. Diethylene glycolic chain produced the dimer **7a** and linear oligomer **7a′** with multi-cavities, whereas triethylene and tetraethylene glycolic chains allowed direct cyclization through intramolecular head-to-tail pattern to yield novel bridged biscalix[4]arenes **7b–c**.

1. Introduction

Calixarenes[1] are a class of well defined macrocyclic oligomers of phenols bridged by methylene groups. Owing to their (1) convenient preparation in large quantities; (2) easy chemical modification on both lower and upper rims; (3) versatile complexation towards ions and molecules and (4) unique structural properties, they have been one of the most extensively studied synthetic receptors in recent years.

A permanent and challenging topic in supramolecular chemistry is the design and construction of sophisticated artificial receptors with defined multi-cavities which would show various supramolecular function.[2] Suitable calixarene derivatives have been used as building blocks for this purpose. One of particular interest in this regard are the construction of double- and multi-calixarenes,[3,4] consisting of more than two calixarene subunits, for their peculiar multi-cavity structures and molecular recognition abilities. Covalently linked double calixarenes could be constructed by intermolecular bridges in a head-to-head, tail-to-tail, or head-to-tail arrangement, in which the calixarene subunits adopt the cone or the 1,3-alternate conformation.[4] Similar cases occurred to covalently linked multi-calixarenes. To our knowledge, no double- and multi-calixarenes bridged by intramolecular head-to-tail arrangement of calixarenes in the partial cone conformation were reported so far,[5] although they could provide novel and efficient receptors with potential complexation towards complicated guests.[4a,c]

Ring-closing metathesis (RCM)[6] has been established as an efficient approach to macrocyclic systems and also found powerful applications in supramolecular chemistry.[7] In this regard, Grubbs' ruthenium catalyst ($RuCl_2(CHPh)(PCy_3)_2$, **1**) is particularly attractive due to its remarkable functional group tolerance, operational simplicity, high stability and commercial availability. Herein, we report the synthesis, structure and RCM reactions of polyether bridged biscalix[4]arenes **6** in the partial cone conformation with upper rim allyl substituents. Through different RCM reaction modes in the presence of Grubbs' catalyst **1**, novel bridged double- and tetra-calix[4]arenes with multi-cavities were obtained.

2. Results and discussion

As shown in Scheme 1. Tri(*n*-propoxy)calix[4]arene **3**,[8] prepared according to the reference, reacted with excess 3-bromopropene in dry THF in the presence of NaH to give allyloxy-substituted calix[4]arene **4** in 65% yield. **4** then underwent Claisen rearrangement in refluxing *N*,*N*-diethylaniline to yield calix[4]arene **5** in 85% yield with monoallyl substituent on the upper rim. The ^{1}H NMR spectrum of **5** showed two doublets at 4.44 and 4.38 ppm, and a AB signal at 3.26 ppm for the bridging methylene protons. Two signals at 30.7 and 30.5 ppm for the bridging methylene carbons in its ^{13}C NMR spectrum indicated that **5** adopts the cone conformation. This conformation was further confirmed by its crystal structure (Fig. 1).

Keywords: Multi-calix[4]arene; Partial cone conformation; RCM reaction; Synthesis; Structure.
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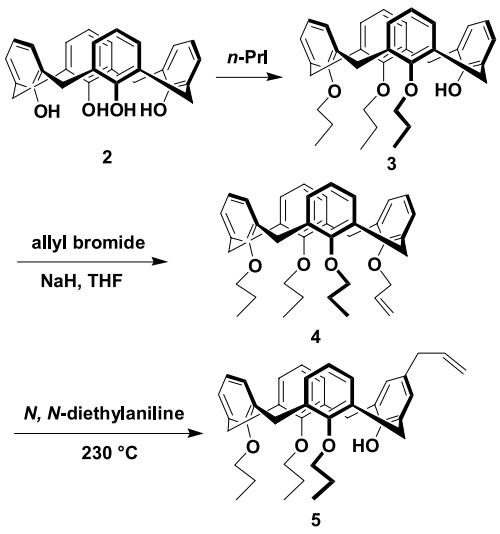


Scheme 1.

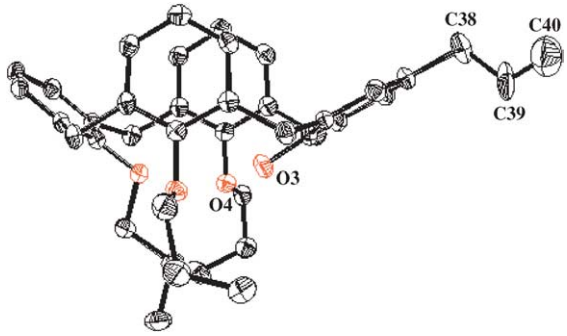
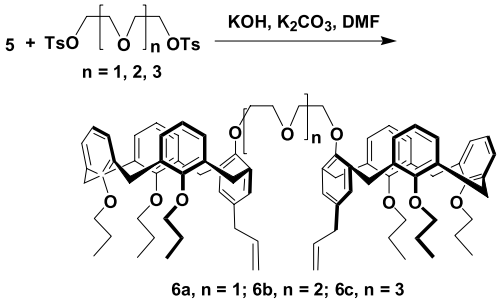


Figure 1. The crystal structure of **5**, hydrogen atoms are omitted for clarity. Selective bond lengths: C39–C40, 1.39 Å; C38–C39, 1.55 Å; O3–H…O4, 2.46 Å.

Treatment of compound **5** with diethylene glycol ditosylate in the presence of KOH and K_2CO_3 mixture in DMF, we exclusively isolated a single bridged biscalix[4]arene **6a** (56%) in which the two calix[4]arene subunits are in the partial cone conformation. The ^{1}H NMR spectrum of **6a** showed two doublets at δ 4.13 and 3.11 ppm and one AB signal at δ 3.69 ppm for the bridging methylene protons. Meanwhile, its ^{13}C NMR spectrum exhibited two signals at δ 35.6 and 30.4 ppm for the bridging methylene carbons, which demonstrated its partial cone conformer.[9] Under the same conditions as above, biscalix[4]arenes **6b** and **6c** in the partial cone conformation were synthesized by the reactions of compound **5** with triethylene or tetraethylene glycol ditosylate, respectively. In each case, the partial cone conformation of calix[4]arene skeleton in solution was determined by the NMR spectra (Scheme 2).



Scheme 2.

To determine the structure of the polyether bridged biscalix[4]arenes in the solid state, the single crystal X-ray analyses of **6a** and **6c** were undertaken. Crystals of compound **6a** were obtained by slow evaporation of a dichloromethane and *n*-hexane solution. As seen in Figure 2, the rings bearing allyl group are inverted relative to the other rings. Consequently, the calix[4]arenes in **6a** adopt the partial cone conformation, all of the propoxy groups point outwards from the center of the molecule and the two allyl groups are in opposite position. Moreover, the molecule **6a** resides on a crystallographic two-fold axis, and its two calix[4]arene subunits are related by symmetry in the crystal structure. For the subunits, the four linking methylene carbons are all coplanar to within 0.02 Å, and the interplanar angle between the two planes is 34.5°. The inclinations of rings A–D to the reference plane are 92.4, 98.4, 35.3 and 80.5°, respectively. The opposite aromatic rings A and C have an interplanar angle of 57.1°, while the rings B and D have an interplanar angle of 17.9°.

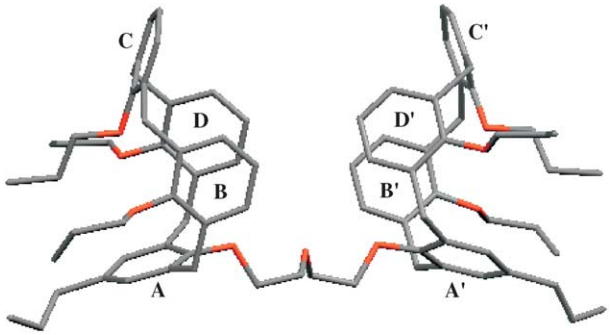


Figure 2. The crystal structure of **6a**, hydrogen atoms are omitted for clarity.

Crystals of **6c** were obtained by slow evaporation of a CH_2Cl_2/CH_3CN solution, and its X-ray structure is shown in Figure 3. Similar to **6a**, the two calix[4]arene subunits in **6c** all adopt the partial cone conformation, and the four linking methylene carbons are coplanar to within 0.01 Å for the two subunits. The interplanar angle between the two reference planes is 13.1°, which is obviously smaller than that of **6a** due to the long flexible chain in **6c**. The phenyl rings in **6c** are inclined by between 30.6 and 97.8°, to the reference planes. The interplanar angles between the opposite

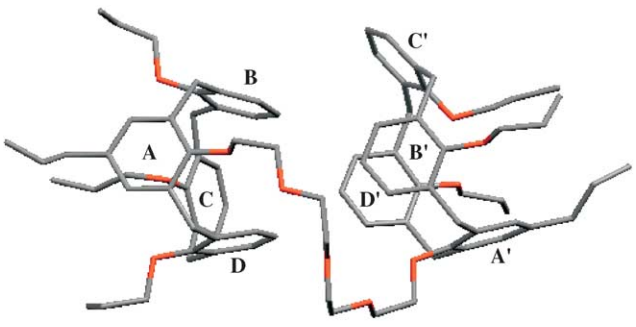
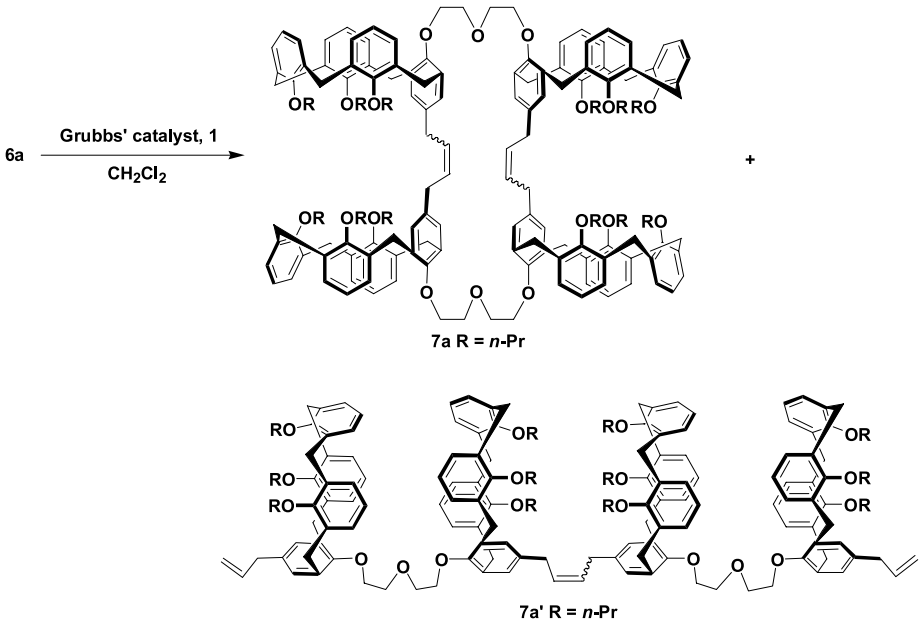


Figure 3. The crystal structure of **6c**, hydrogen atoms are omitted for clarity.

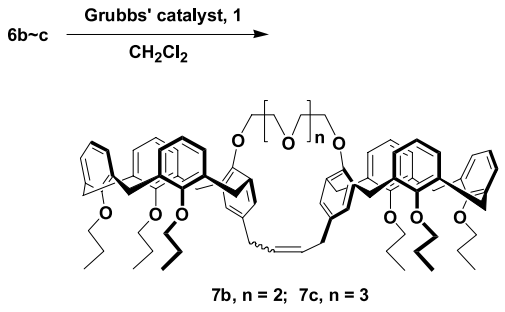


Scheme 3.

aromatic rings of A and C, B and D, A′ and C′ and B′ and D′ are 109.4, 154.5, 118.5 and 16.3°, respectively.

RCM reactions were carried out with 5 mol% Grubbs' catalyst **1** in dry CH_2Cl_2 under argon at room temperature. The biscalix[4]arene **6a** has shorter polyether chain and the direct cyclic reaction may suffer greater steric strain. So it should be possible that intermolecular metathesis competed with intramolecular bridging. In fact, only two intermolecular reaction products, dimer **7a** and linear oligomer **7a′** with multi-cavities were isolated from the metathesis reactions of compound **6a**. The structures of **7a** and **7a′** were demonstrated by their NMR and mass spectra. Compound **7a** showed similar NMR spectral features of calix[4]arene skeleton with those of its precursor **6a**, which suggested that it may be a single isomer of *E*,*Z* geometry, and the calix[4]arenes in **7a** all retained the partial cone conformation. The NMR spectra of **7a′** displayed the signals for one symmetric disubstituted alkene and two terminal vinyl groups, and also confirmed that the calix[4]arene units all kept the partial cone conformation. The MAIDL-TOF mass spectrum of **7a′** was also fully consistent with its oligomer structure (Scheme 3).

Under the same reaction conditions as **6a**, RCM reaction of compound **6b** with longer chain only produced a single cyclization product **7b** in 52% yield through intramolecular head-to-tail pattern of calix[4]arene. Same case occurred to compound **6c**, as a result, biscalix[4]arene **7c** was obtained in 66% yield. The NMR spectra of **7b** and **7c** showed that the signals for the terminal vinyl groups of **6b** and **6c** were replaced by those of a single disubstituted alkene, and the calix[4]arenes retained the partial cone conformation in solution. Their MAIDL-TOF MS confirmed the loss of two methylene groups and the formation of intramolecular RCM products (Scheme 4).



Scheme 4.

We also obtained the crystals of **7b** from a mixture of dichloromethane and *n*-hexane. Its X-ray structure analysis revealed that both of the calix[4]arene subunits retained the partial cone conformation, the double bond (C73 and C74) adopted the *E* conformation and all the propoxy groups are in the same direction (Fig. 4(a)). The four linking methylene carbon atoms for the two calix[4]arene subunits are coplanar to 0.01 and 0.02 Å, respectively, and the phenyl rings A–D (A′–D′) are inclined by 91.6, 97.5, 140.8, 84.8° (88.9, 95.8, 37.7, 86.6°), respectively, to the reference planes. The interplanar angle between the two reference planes is 44.4°, and the interplanar angle between phenyl rings A and A′ is 106.8°. Interestingly, we found that four molecules of biscalix[4]arene **7b** composed of an italics capital letter *N* along the *a* axis in its crystal cell, and their packing further formed a wave type structure with polychannels in the solid state (Fig. 4(b)).

In summary, polyether bridged bis-calix[4]arenes in the partial cone conformation with allyl substituents on the upper rim were synthesized, and their structures in solution and in the solid state were characterized. The RCM reaction modes were found to depend on the length of polyether chain. Diethylene glycolic chain produced the dimer and linear oligomer with multi-cavities, whereas the longer chains allowed direct cyclization through intramolecular head-to-tail pattern to yield novel bridged biscalix[4]arenes.

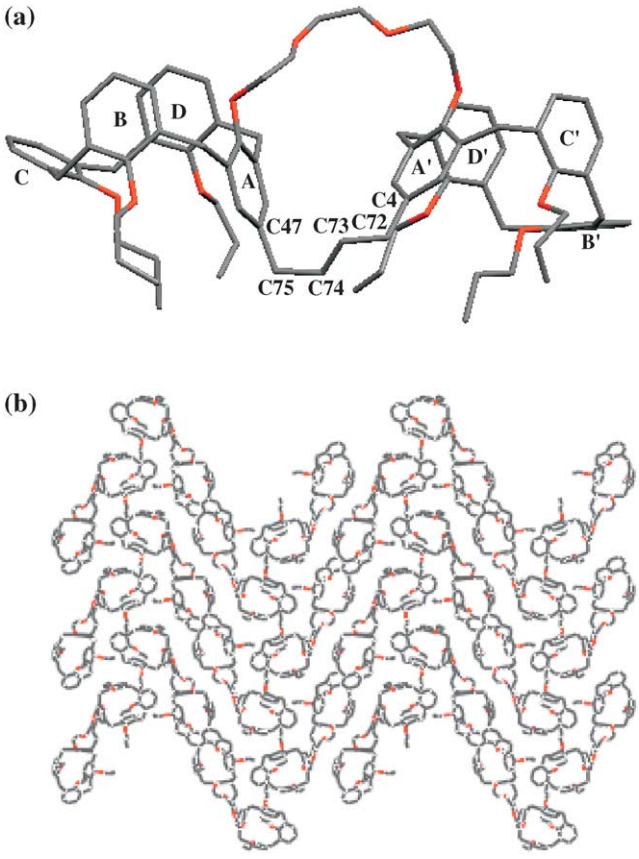


Figure 4. The crystal structure (a) and perspective view of the crystal lattice along the *a* axis of the cell (b) of **7b**, hydrogen atoms are omitted for clarity. Selective bond lengths: C4–C72, 1.51 Å; C72–C73, 1.48 Å; C73–C74, 1.38 Å; C74–C75, 1.51 Å; C75–C47, 1.51 Å.

3. Experimental

3.1. General

Melting points were determined on an electrothermal melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained at 300 MHz ($CDCl_3$, TMS as internal standard) on a Bruker DMX 300 NMR. MALDI-TOF MS were recorded on a Bruker BIFLEXIII mass spectrometer with CCA (2-cyano-4′-hydroxycinnamic acid) as the matrix. Elemental analyses were performed by the Analytical Laboratory of the Institute. IR Spectra were recorded on JASCO 480 spectrometer. NaH (60% dispersed in mineral oil, ACROS) was washed twice with petroleum ether (30–60 °C) and stored in a desiccator. Dichloromethane used in the RCM reactions was distilled from calcium hydride. DMF was dried over 4 Å molecular sieve. All other chemicals were reagent grade and were used without further purification. Column chromatography was performed with silica gel (200–300 mesh). Petroleum ether for column chromatography refers to that of 30–60 °C boiling range.

3.1.1. Synthesis of compound 4. To the solution of **3**[8] (550 mg, 1.0 mmol) in dry THF (30 mL) under argon atmosphere was added NaH (160 mg, 4.0 mmol). The mixture was stirred for 30 min at room temperature and then added dropwise allyl bromide (726 mg, 6.0 mmol) in dry THF (10 mL). The mixture was refluxed for 4 h, quenched by methanol (10 mL) and then concentrated. The residue was dissolved in CH_2Cl_2 (50 mL), washed with water (2×20 mL) and saturated NaCl (2×20 mL), respectively. The organic layer was dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the crude product was recrystallized from MeOH–CH_2Cl_2 to give **4** (384 mg, 65%) as a white power. Mp: 176–178 °C; ^{1}H NMR ($CDCl_3$): δ 6.86 (d, J=7.4 Hz, 4H), 6.78–6.72 (m, 2H), 6.64–6.60 (m, 2H), 6.45–6.44 (m, 4H), 6.27–6.34 (m, 1H), 5.17–5.25 (m, 2H), 4.56 (d, J=6.4 Hz, 2H), 4.48 (ABq, J=12.8 Hz, 4H), 3.98 (t, J=7.7 Hz, 2H), 3.82 (t, J=7.1 Hz, 4H), 3.19 (d, J=13.4 Hz, 4H), 2.02–1.91 (m, 6H), 1.05 (t, J=7.4 Hz, 6H), 0.96 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 157.2, 156.7, 156.5, 156.1, 136.2, 136.1, 135.2, 134.4, 129.4, 129.0, 128.5, 127.8, 122.3, 122.0, 116.5, 77.6, 76.7, 75.8, 31.3, 31.1, 23.5, 23.4, 10.5, 10.3. MALDI-TOF MS *m/z*: 613.6 ($M+Na^+$), 629.6 ($M+K^+$). Anal. Calcd for $C_{40}H_{46}O_4$: C, 81.32; H, 7.85. Found: C, 81.35; H, 7.91.

3.1.2. Synthesis of compound 5. A solution of compound **4** (500 mg, 0.85 mmol) in *N*,*N*-diethylaniline (10 mL) was refluxed for 3 h in an atmosphere of N_2. After cooling to rt, the mixture was poured into 2 N HCl (20 mL), and then filtrated. The crude product was recrystallized from MeOH–$CHCl_3$ to give **5** (425 mg, 85%) as a white solid. Mp: 112–113 °C; ^{1}H NMR ($CDCl_3$): δ 7.20 (d, J=7.4 Hz, 2H), 6.99 (t, J=7.4 Hz, 1H), 6.93 (s, 2H), 6.43–6.36 (m, 6H), 6.12–5.99 (m, 1H), 5.12 (d, J=4.6 Hz, 1H), 5.07 (s, 1H), 4.49 (s, 1H), 4.44 (d, J=13.3 Hz, 2H), 4.38 (d, J=13.7 Hz, 2H), 3.86 (t, J=8.4 Hz, 2H), 3.75 (t, J=6.7 Hz, 4H), 3.38 (d, J=6.5 Hz, 2H), 3.26 (ABq, J=12.8 Hz, 4H), 2.36–2.23 (m, 2H), 2.00–1.83 (m, 4H), 1.14 (t, J=7.3 Hz, 6H), 0.95 (t, J=7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 156.8, 154.4, 151.5, 138.5, 137.2, 133.3, 132.7, 131.2, 130.4, 129.3, 129.0, 128.4, 128.3, 127.7, 122.9, 115.0, 77.4, 76.5, 39.5, 30.7, 30.5, 23.4, 22.3, 10.8, 9.5. MALDI-TOF MS *m/z*: 613.3 ($M+Na^+$). Anal. Calcd for $C_{40}H_{46}O_4$: C: 81.32, H 7.85. Found: C: 81.27; H 7.97.

3.2. General procedure for synthesis of 6

To the mixture of compound **5** (590 mg, 1 mmol), KOH (72 mg, 1.29 mmol) and K_2CO_3 (72 mg, 0.52 mmol) in dry DMF (15 mL) under N_2 was added dropwise *p*-toluenesulfonate derivative (0.4 mmol) in dry DMF (10 mL). The reaction mixture was stirred at rt for 24 h. The solvent was then removed in vacuo and the residue was dissolved in CH_2Cl_2 (100 mL). The organic phase was washed with brine (2×30 mL) and water (2×30 mL), dried over anhydrous $MgSO_4$ and then concentrated to give a residue, which was separated by column chromatography with ethyl acetate and petroleum ether (1:4, v/v) as eluent to provide **6** as a white solid.

3.2.1. Compound 6a. Yield 56%; mp 197–199 °C; ^{1}H NMR ($CDCl_3$): δ 7.11–7.05 (m, 12H), 6.91 (t, J=7.6 Hz, 2H), 6.43 (t, J=7.5 Hz, 4H), 6.28 (d, J=7.5 Hz, 4H), 6.13–5.97 (m, 2H), 5.16 (d, J=16.1 Hz, 2H), 5.12 (d, J=9.0 Hz, 2H), 4.08 (d, J=13.1 Hz, 4H), 4.04–4.02 (m, 4H), 3.90 (t, J=4.7 Hz, 4H), 3.78–3.73 (m, 4H), 3.66 (ABq, J=12.8 Hz, 8H), 3.64–3.52 (m, 4H), 3.40 (d, J=6.9 Hz, 4H), 3.35 (t, J=8.4 Hz, 4H), 3.06 (d, J=13.3 Hz, 4H), 1.91–1.86 (m,

8H), 1.57–1.31 (m, 4H), 1.10 (t, J=7.3 Hz, 12H), 0.75 (t, J=7.5 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 156.7, 155.3, 155.0, 137.8, 136.9, 133.5, 133.0, 132.5, 131.8, 130.1, 129.2, 128.6, 128.1, 121.9, 121.2, 115.1, 75.7, 75.2, 71.1, 70.2, 39.6, 35.5, 30.2, 23.6, 21.6, 10.7, 9.5. MALDI-TOF MS *m/z*: 1273.8 ($M+Na^+$), 1289.8 ($M+K^+$). Anal. Calcd for $C_{84}H_{98}O_9\cdot 0.5H_2O$: C, 80.03; H, 7.92. Found: C, 80.01; H, 7.90.

3.2.2. Compound 6b. Yield 62%; mp 64–66 °C; ^{1}H NMR ($CDCl_3$): δ 7.11 (d, J=7.4 Hz, 4H), 7.05 (s, 4H), 7.04 (d, J=7.8 Hz, 4H), 6.92 (t, J=7.4 Hz, 2H), 6.42 (t, J=7.5 Hz, 4H), 6.28 (d, J=7.5 Hz, 4H), 6.15–6.01 (m, 2H), 5.17 (d, J=16.1 Hz, 2H), 5.13 (d, J=8.9 Hz, 2H), 4.08 (d, J=13.1 Hz, 4H), 3.99 (t, J=4.6 Hz, 4H), 3.85 (t, J=4.9 Hz, 4H), 3.84 (s, 4H), 3.79–3.72 (m, 4H), 3.68 (ABq, J=13.0 Hz, 8H), 3.53 (t, J=8.0 Hz, 4H), 3.41 (d, J=6.9 Hz, 4H), 3.35 (t, J=8.4 Hz, 4H), 3.06 (d, J=13.2 Hz, 4H), 1.94–1.82 (m, 8H), 1.50–1.42 (m, 4H), 1.12 (t, J=7.4 Hz, 12H), 0.75 (t, J=7.4 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 156.9, 155.5, 155.0, 138.0, 137.1, 133.7, 133.2, 132.7, 132.0, 130.4, 129.5, 128.9, 128.3, 122.2, 121.4, 115.4, 76.6, 76.0, 75.4, 71.5, 70.7, 39.9, 35.7, 30.5, 23.8, 21.8, 11.0, 9.8. MALDI-TOF MS *m/z*: 1318.4 ($M+Na^+$), 1334.3 ($M+K^+$). Anal. Calcd for $C_{86}H_{102}O_{10}$: C, 79.72; H, 7.93. Found: C, 79.76; H, 7.97.

3.2.3. Compound 6c. Yield 64%; mp 60–62 °C; ^{1}H NMR ($CDCl_3$): δ 7.15 (d, J=7.4 Hz, 4H), 7.11 (s, 4H), 7.08 (d, J=7.2 Hz, 4H), 6.96 (t, J=7.4 Hz, 2H), 6.48 (t, J=7.4 Hz, 4H), 6.33 (d, J=7.5 Hz, 4H), 6.17–6.08 (m, 2H), 5.22 (d, J=16.1 Hz, 2H), 5.18 (d, J=9.1 Hz, 2H), 4.13 (d, J=13.1 Hz, 4H), 4.01 (t, J=4.5 Hz, 4H), 3.86–3.77 (m, 16H), 3.69 (ABq, J=13.1 Hz, 8H), 3.57 (m, 4H), 3.47 (d, J=6.8 Hz, 4H), 3.40 (t, J=8.4 Hz, 4H), 3.11 (d, J=13.2 Hz, 4H), 1.99–1.88 (m, 8H), 1.56–1.45 (m, 4H), 1.17 (t, J=7.4 Hz, 12H), 0.82 (t, J=7.4 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 156.9, 155.5, 155.3, 138.0, 137.1, 133.7, 133.2, 132.7, 132.0, 130.4, 129.5, 128.8, 128.3, 122.2, 121.4, 115.4, 76.0, 75.4, 71.5, 70.8, 70.6, 39.8, 35.7, 30.5, 23.8, 21.8, 11.0, 9.8. MALDI-TOF MS *m/z*: 1362.2 ($M+Na^+$), 1378.2 ($M+K^+$). Anal. Calcd for $C_{88}H_{106}O_{11}$: C, 78.89; H, 7.97. Found: C, 78.89; H, 7.94.

3.3. General procedure for RCM reactions

To the solution of a calix[4]arene derivative **6** (0.05 mmol) in dry CH_2Cl_2 (10 mL) under argon was added the Grubbs' catalyst **1** (2.1 mg, 5 mol%). The mixture was stirred at room temperature and the reaction process was monitored by TLC. When the reaction was completed, the reaction mixture was quenched by exposure to air for 6 h. The solution was concentrated in vacuo and separated by column chromatography using ethyl acetate: petroleum ether (1:4, v/v) as the eluent to provide the product **7**.

3.3.1. Compound 7a. Yield 20%; mp>300 °C; ^{1}H NMR ($CDCl_3$): δ 7.11–7.01 (m, 24H), 6.92 (t, J=7.4 Hz, 4H), 6.45–6.38 (m, 8H), 6.27 (t, J=6.7 Hz, 8H), 5.76–5.72 (m, 4H), 4.09 (d, J=12.4 Hz, 16H), 3.89–3.83 (m, 8H), 3.75–3.51 (m, 32H), 3.40–3.29 (m, 16H), 3.07 (d, J=12.9, 4H), 3.05 (d, J=12.9, 4H), 1.92–1.70 (m, 16H), 1.57–1.43 (m, 8H), 1.04–1.01 (m, 24H), 0.75 (t, J=7.5 Hz, 12H). ^{13}C NMR ($CDCl_3$): δ 156.0, 154.7, 142.2, 137.2, 133.5, 133.2, 132.1, 130.6, 130.4, 129.8, 129.4, 128.8, 128.2, 122.1, 121.3, 75.9, 75.4, 71.3, 70.5, 38.8, 35.7, 30.5, 22.9, 21.8, 11.0, 9.8. MALDI-TOF MS *m/z*: 2467.3 ($M+Na^+$), 2483.3 ($M+K^+$). Anal. Calcd for $C_{164}H_{188}O_{18}$: C, 80.49; H, 7.74. Found: C, 80.32; H, 7.87.

3.3.2. Compound 7a′. Yield 32%; mp 124–126 °C; ^{1}H NMR ($CDCl_3$): δ 7.13–7.06 (m, 24H), 6.93 (t, J=7.4 Hz, 2H), 6.92 (t, J=7.4 Hz, 2H), 6.48–6.41 (m, 8H), 6.31 (t, J=6.1 Hz, 8H), 6.14–6.01 (m, 2H), 5.84 (t, J=4.8 Hz, 2H), 5.17 (d, J=17.1 Hz, 1H), 5.16 (d, J=17.1, 1H), 5.13 (d, J=9.1 Hz, 1H), 5.12 (d, J=9.1 Hz, 1H), 4.11–3.93 (m, 16H), 3.91 (t, J=4.7 Hz, 8H), 3.80–3.74 (m, 8H), 3.72–3.66 (m, 16H), 3.59–3.47 (m, 16H), 3.41 (d, J=6.8 Hz, 4H), 3.38–3.33 (m, 4H), 3.08 (d, J=13.1 Hz, 4H), 3.07 (d, J=13.3 Hz, 4H), 1.96–1.84 (m, 16H), 1.52–1.45 (m, 8H), 1.13 (t, J=7.4 Hz, 12H), 1.12 (t, J=7.4 Hz, 12H), 0.79–0.74 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 156.9, 155.6, 155.2, 138.0, 137.1, 133.8, 133.3, 132.8, 132.1, 130.4, 129.5, 128.9, 128.3, 122.2, 121.5, 115.4, 76.0, 75.4, 71.4, 70.5, 39.9, 35.8, 30.5, 23.88, 23.84, 21.8, 10.2, 9.8. MALDI-TOF MS *m/z*: 2495.1 ($M+Na^+$), 2511.1 ($M+K^+$). Anal. Calcd for $C_{166}H_{192}O_{18}$: C, 80.55; H, 7.82. Found: C, 80.41; H, 7.86.

3.3.3. Compound 7b. Yield 52%; mp 133–134 °C; ^{1}H NMR ($CDCl_3$): δ 7.12 (d, J=7.3 Hz, 6H), 6.95 (s, 4H), 6.95–6.92 (m, 4H), 6.43 (t, J=7.5 Hz, 4 H), 6.28 (d, J=7.5 Hz, 4H), 5.72 (t, J=6.1 Hz, 2H), 4.09 (d, J=13.1 Hz, 4H), 4.06–4.01 (m, 4H), 3.82–3.75 (m, 12H), 3.70 (s, 4H), 3.59–3.49 (m, 8H), 3.41–3.32 (m, 8H), 3.08 (d, J=13.2 Hz, 4H), 1.96–1.89 (m, 8H), 1.48–1.45 (m, 4H), 1.16 (t, J=6.3 Hz, 12H), 0.79 (t, J=7.5 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 157.1, 155.6, 137.1, 133.9, 133.3, 132.1, 131.4, 130.6, 129.0, 128.8, 128.2, 122.2, 121.4, 75.9, 75.6, 71.5, 70.8, 70.3, 37.6, 35.7, 30.4, 23.9, 21.9, 11.0, 9.7. MALDI-TOF MS *m/z*: 1290.6 ($M+Na^+$). Anal. Calcd for $C_{84}H_{98}O_{10}$: C, 79.59; H, 7.79. Found: C, 79.36; H, 7.91.

3.3.4. Compound 7c. Yield 66%; mp 128–130 °C; ^{1}H NMR ($CDCl_3$): δ 7.11–7.00 (m, 12H), 6.90 (t, J=7.5 Hz, 2H), 6.41 (t, J=7.5, 4H), 6.24 (d, J=7.4 Hz, 4H), 5.79 (t, J=6.1 Hz, 2H), 4.05 (d, J=13.1 Hz, 4H), 4.02–3.98 (m, 4H), 3.84 (d, J=13.0 Hz, 4H), 3.72–3.64 (m, 12H), 3.59–3.46 (m, 12H), 3.37 (d, J=6.1 Hz, 4H,), 3.32 (t, J=8.5 Hz, 4H,), 3.03 (d, J=13.2 Hz, 4H), 1.82–1.77 (m, 8H), 1.08–1.04 (m, 4H), 1.06 (t, J=7.3 Hz, 12H), 0.76 (t, J=7.3 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 157.1, 155.6, 154.8, 137.2, 133.7, 133.2, 132.3, 131.1, 130.9, 129.5, 128.9, 128.2, 122.2, 121.5, 76.0, 75.6, 71.4, 70.7, 70.4, 69.9, 38.1, 35.7, 30.5, 23.9, 21.9, 11.0, 9.9. MALDI-TOF MS *m/z*: 1333.6 ($M+Na^+$), 1349.5 ($M+K^+$). Anal. Calcd for $C_{86}H_{102}O_{11}$: C, 78.75; H, 7.84. Found: C, 78.89; H, 7.93.

3.4. X-ray crystallographic study

Crystals suitable for X-ray diffraction were grown from a mixture of dichloromethane and *n*-hexane for compounds **5**, **6a** and **7b**, or a mixture of dichloromethane and acetonitrile for compound **6c**. Data collection was performed at 293 K using a Rigaku R-AXIS RAPID IP detector, and SHELXS-97 and SHELXL-97 programs were used for structure solution and refinement. Crystallographic data for structures

reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-258734 (for compound **5**), CCDC-CCDC 258735 (for compound **6a**), CCDC-258736 (for compound **6c**), and CCDC-258737 (for compound **7b**). These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

3.4.1. Compound 5. $C_{40}H_{46}O_4$, MZ 590.77, crystal dimensions $0.79\times0.75\times0.08$ mm^3, orthorhombic, space group *Pna*21, $a=19.6494(7)$ Å, $b=18.1277(14)$ Å, $c=9.5362(12)$ Å, $U=3396.8(5)$ Å^3, $D_c=1.112$ Mg m^{-3}, $Z=4$, 4110 reflections collected, 2593 independent [R(int)=0.0000], giving $R_1=0.0527$ for observed unique reflection [$F^2>2$ s (F^2)] and $wR_2=0.1447$ for all data.

3.4.2. Compound 6a. $C_{84}H_{98}O_9$, MZ 1251.62, crystal dimensions $0.79\times0.44\times0.04$ mm^3, monoclinic, space group *P*2/*c*, $a=18.311(2)$ Å, $b=11.6641(12)$ Å, $c=18.060(2)$ Å, $\beta=104.258(5)°$, $U=3738.4(7)$ Å^3, $D_c=1.112$ Mg m^{-3}, $Z=2$, 8410 reflections collected, 2384 independent [R(int)=0.0000], giving $R_1=0.0947$ for observed unique reflection [$F^2>2$ s (F^2)] and $wR_2=0.3091$ for all data.

3.4.3. Compound 6b. $C_{88}H_{106}O_{11}\cdot H_2O$, MZ 1357.74, crystal dimensions $0.27\times0.81\times0.29$ mm^3, monoclinic, space group *P*2(*1*)/*c*, $a=14.109$ (3) Å, $b=34.077$ (7) Å, $c=16.963$ (3) Å, $\beta=102.25$ (3)°, $U=7970$ (3) Å^3, $D_c=1.132$ Mg m^{-3}, $Z=4$, 13011 reflections collected, 6086 independent [R(int)=0.0000], giving $R_1=0.0936$ for observed unique reflection [$F^2>2$ s (F^2)] and $wR_2=0.3125$ for all data.

3.4.4. Compound 7c. $C_{84}H_{98}O_{10}$, MZ 1267.62, crystal dimensions $0.672\times0.393\times0.288$ mm^3, monoclinic, space group *P*2(*1*)/*N*, $a=11.560$ (2) Å, $b=39.600$ (8) Å, $c=16.380$ (3) Å, $\beta=97.42$ (3)°, $U=7436$ (3) Å^3, $D_c=1.132$ Mg m^{-3}, $Z=4$, 47393 reflections collected, 3940 independent [R(int)=0.0652], giving $R_1=0.0769$ for observed unique reflection [$F^2>2$ s (F^2)] and $wR_2=0.2259$ for all data.

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Reduction of alkyl and vinyl sulfonates using the $CuCl_2 \cdot 2H_2O$–Li–DTBB(cat.) system

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Dedicated to Professor Johan Mulzer on occasion of his 60th birthday

Abstract—The reduction of a series of alkyl mesylates, dimesylates and triflates to the corresponding hydrocarbons was efficiently performed using a reducing system composed of $CuCl_2 \cdot 2H_2O$, an excess of lithium sand and a catalytic amount (5 mol%) of 4,4′-di-*tert*-butylbiphenyl (DTBB), in tetrahydrofuran at room temperature. The process was also applied to enol and dienol triflates affording alkenes and dienes, respectively. The use of the deuterated copper salt $CuCl_2 \cdot 2D_2O$ allowed the simple preparation of the corresponding deuterated products.

1. Introduction

Sulfonyl esters are very useful synthetic intermediates extensively used in two important transformations in synthetic organic chemistry: (a) indirect deoxygenation of alcohols;[1] and (b) reduction of carbonyl groups, via the corresponding vinyl sulfonates, to obtain alkanes or alkenes.[2] Concerning the deoxygenation of alcohols, one of the most practical methods involves the transformation of the hydroxyl group in a better leaving group such as a tosylate, followed by reaction with sodium iodide (to give the corresponding alkyl iodide) and final palladium-catalyzed hydrogenation or other reduction methodologies.[3] More sophisticated procedures involve the transformation of alcohols into isoureas,[4] thionocarbonates,[5] dithiocarbonates[6] or thiocarbonates,[7] and further reduction with a silane, stannane or potassium in a protic solvent. More recently, lithium aminoborohydride reagents proved to be effective in the reduction of alkyl mesylates.[8] On the other hand, the paramount importance of the carbonyl group in organic synthesis makes methods for its efficient removal of considerable relevance. Among the known methods utilized for the reduction of this functionality, the conversion of carbonyl groups into their enol triflates and further reduction to the corresponding alkenes or alkanes has been widely studied. One of the simplest procedures relies on the palladium-catalyzed reduction of the corresponding triflates by using hydrogen,[9] formic acid,[10] silanes or stannanes,[11] as some conventional reducing agents. These two-step reductions of carbonyl groups have been particularly useful in synthetic transformations of steroidal skeletons. In this field, enol and dienol triflates are key synthetic intermediates in the chemical transformation of a wide variety of steroidal α,β-unsaturated ketones.[10] Another method, treatment of the tosylhydrazone of an aldehyde or a ketone with a strong base, followed by hydrolysis, leads to the formation of an alkene (the so-called Shapiro reaction[12a]). This reaction has been applied to the obtention of alkenes or 1,3-dienes from aldehydes, ketones, or α,β-unsaturated ketones, respectively, via alkyllithium mediated decomposition of the tosylhydrazones under mild reaction conditions.[12]

On the other hand, in the recent years, we have worked about the development of new reducing systems of functional groups based on the use of activated transition metals, mainly active nickel.[13] In this sense, we first studied and reported the efficiency of the $NiCl_2 \cdot 2H_2O$–Li–arene(cat.) reducing system toward a wide variety of organic functionalities, among them alkenes,[14] alkynes,[15] carbonyl

Keywords: Reduction; Alkyl sulfonates; Enol triflates; Arene catalysis; Active copper.
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compounds and imines,[16] alkyl and aryl halides,[17] sulfonates, aromatic and heteroaromatic compounds,[18] hydrazines, azo compounds, azoxy compounds and amine *N*-oxides,[19] and nitrones.[20] More recently and taking into account the periodic table proximity and the little work published regarding copper-mediated reducing systems, we focused on the copper-based $CuCl_2 \cdot 2H_2O$–Li–Arene (cat.) combination, which was found to be very efficient in the reduction of carbonyl compounds and imines,[21] as well as in the hydrodehalogenation of aryl and alkyl halides.[22]

As part of our research in the field above described, we want to present herein the results obtained on the reduction of alkyl and vinyl sulfonates under very mild reaction conditions, based on the use of active copper, generated from commercially available copper(II) chloride dihydrate, lithium, and a catalytic amount of an arene (DTBB) as electron carrier.[23]

2. Results and discussion

The reduction of a series of sulfonates was successfully carried out under very mild conditions, using a mixture of copper(II) chloride dihydrate (1.0 mmol), an excess of lithium sand (1:8 molar ratio, referred to the copper salt) and a catalytic amount of DTBB (0.1 mmol/mmol of copper salt, 5.0 mol%) in tetrahydrofuran at room temperature. Thus, the reaction of primary, secondary and tertiary mesylates with the above mentioned reducing system, led to the formation of the corresponding hydrocarbons resulting from a sulfonyloxy/hydrogen exchange (Table 1, entries 1–3). Dimesylates could be reduced to the corresponding hydrocarbons under the same reaction conditions using 2 equiv of the reducing system (Table 1, entry 4).

The same process was successfully applied to a variety of trifluoromethanesulfonate derivatives. As shown in Table 1, primary and secondary alkyl triflates could be reduced to the corresponding alkanes in good yields (Table 1, entries 5, 6, and 8). The reaction with cyclic triflates proved to work nicely leading to the corresponding cycloalkanes also in good yields (Table 1, entries 9 and 10). One main advantage of this methodology consists in using the deuterated salt $CuCl_2 \cdot 2D_2O$ (prepared from anhydrous $CuCl_2$ and D_2O as previously described[14]) instead of the hydrated one, thus furnishing the corresponding deuterium-labeled hydrocarbons in a simple and economic way (Table 1, entry 7).[24] It is worthy to note that the triflate functionality was more reactive than the mesylate one, as it is shown by the shorter reaction times of the former.

When the same process was applied to enol triflates, the corresponding alkenes were obtained as major products in good yields (Table 2). Thus, the enol triflates derived from nonan-5-one, 4-*tert*-butylcyclohexanone, and decalone, were easily transformed into the corresponding olefins after 6 h (Table 2, entries 1, 2, and 4). The same methodology was successfully applied to the conjugate enol triflates derived from 3,4-dihydrophenanthren-1(2*H*)-one and pulegone (Table 2, entries 5 and 6). Moreover, dienol triflates, such as those derived from isophorone and cholest-5-en-3-one, were readily reduced to the corresponding dienes by using 1 equiv of the copper salt for 8–10 h at room temperature (Table 2, entries 7 and 8). It is worthy to note that no over-reduction was observed, even using an excess of the reducing system (2 equiv) or longer reaction times (Table 2, entries 1, 2, and 6). In contrast, some time depending over-reduction was observed in the reaction with the 3,4-dihydrophenanthren-1(2*H*)-one derived enol triflate (Table 2, entry 5), in which the carbon–carbon double bond is conjugated with the aromatic system. Finally, the use of the deuterated copper salt ($CuCl_2 \cdot 2D_2O$) in the reducing system allowed the preparation of deuterium labeled alkenes (Table 2, entry 3).[24]

By comparing the active copper reducing system with the equivalent one containing nickel, it can be concluded that the latter is more versatile since the degree of reduction (to the alkene or alkane) can be easily controlled by adjusting the stoichiometry of the nickel salt.[18] However, the high selectivity and commercial availability of the former makes it the reagent of choice to stop the reduction of enol and dienol triflates at the alkene and diene stage, respectively.

3. Conclusion

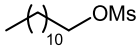
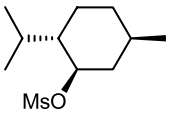
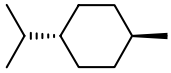
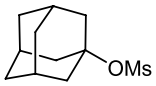
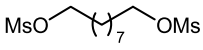
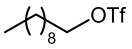
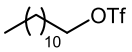
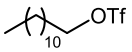
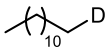
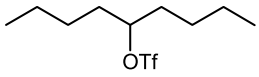
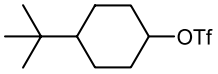
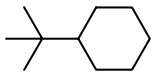
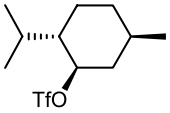
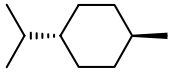
In conclusion, we have described herein a new procedure to reduce alkyl and vinyl sulfonates to the corresponding hydrocarbons under very mild reaction conditions, using the active copper-based reducing combination $CuCl_2 \cdot 2H_2O$–Li–DTBB(cat.). Some advantages of this reduction procedure should be noted, including its simple use and the clean reduction of enol and dienol triflates to alkenes and dienes, respectively. In contrast with the nickel-based analogous system,[18] no over-reduction has been detected even using an excess of the reducing combination or long reaction times. This last feature makes this copper-based reducing system an attractive alternative to the Shapiro reaction in the synthesis of olefins from carbonyl compounds. Finally, the use of the deuterated copper salt allowed the preparation of deuterium labeled alkanes or alkenes in a simple and economic way.

4. Experimental

4.1. General

All moisture sensitive reactions were carried out under nitrogen atmosphere. Anhydrous tetrahydrofuran was freshly distilled from sodium/benzophenone ketyl. Other solvents used were treated prior to use by standard methods.[25] All alcohols and carbonyl compounds for the synthesis of the corresponding sulfonates were of the best available grade (Aldrich, Fluka, Merck) and were used without further purification. Copper(II) chloride dihydrate was commercially available (Aldrich); its deuterated derivative was prepared by treating anhydrous copper(II) chloride with an excess of deuterium oxide and then by heating in vacuo (ca. 0.5 Torr) at 60 °C in Kugelrohr during 1 h. Column chromatography was performed with Merck silica gel 60 (0.040–0.063 μm, 240–400 mesh). Thin layer chromatography (TLC) was performed on precoated silica

Table 1. Reduction of alkylsulfonates

Entry	Sulfonate	Reaction conditions		Product[a]	
		$CuCl_2 \cdot 2H_2O$ (equiv)	t (h)	Structure	Yield (%)[b]
1		1	10		73
2		1	10		65
3		1	10		80
4		2	12		72[c]
5		1	4		79[c]
6		1	4		75
7		1[d]	4		70[e]
8		1	4		68[c]
9[f]		1	6		79
10		1	6		86

[a] All isolated products were >95% pure (GLC).
[b] Isolated yield after column chromatography (silica gel, hexane/EtOAc) unless otherwise stated, based on the starting sulfonate.
[c] GLC yield, high volatility compound.
[d] $CuCl_2 \cdot 2D_2O$ was used instead of $CuCl_2 \cdot 2H_2O$.
[e] ca. 70% deuterium incorporation (mass spectrometry, 300 MHz ^{1}H NMR).
[f] Starting alcohol commercially available as a *cis–trans* mixture.

gel plates (Merck 60, F254, 0.25 mm). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ARX-300 spectrophotometer using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal reference. Mass spectra (EI) were obtained at 70 eV on a Hewlett Packard HP-5890 GC/MS instrument equipped with a HP-5972 selective mass detector. Infrared (FT-IR) spectra were obtained on a Nicolet-Nexus spectrophotometer. The purity of volatile compounds and the chromatographic analyses (GC) were determined with a Shimadzu GC-9A instrument equipped with a flame-ionization detector and a 2 m column (1.5% OV17 9_A SUS Chrom 103 80/1000), using nitrogen as carrier gas.

4.2. Synthesis of the starting mesylates. General procedure[26]

To a solution of the corresponding alcohol (2.5 mmol) in methylene chloride (15 mL) containing triethylamine (1.1 mL, 4 mmol) at 0 to −10 °C, was added methanesulfonyl chloride (0.62 mL, 4 mmol) over a period of 5–10 min. Stirring was maintained until total conversion of the starting material (TLC, GLC). The reaction mixture was transfered to a separatory funnel with the aid of more methylene chloride (5–10 mL). The mixture was first extracted with ice water, followed by cold 10% hydrochloric acid, saturated sodium bicarbonate solution, and brine (10 mL each). Drying of the methylene chloride solution with anhydrous Na_2SO_4, followed by solvent removal gave the mesylate, which was pure enough (GLC) for its use in the reduction reactions. The following known compounds, included in Table 1, were characterised by comparison of their chromatographic and spectroscopic data (^{1}H and ^{13}C NMR, and MS) with those described in the literature: dodecyl methanesulfonate (entry 1),[27] (−)-menthyl methanesulfonate (entry 2),[28] 1-adamantyl methanesulfonate (entry 3),[26] 9-methylsulfonyloxynonyl methanesulfonate (entry 4).[29]

4.3. Synthesis of the starting alkyl triflates. General procedure[30]

To a solution of the corresponding alcohol (2.14 mmol) in pyridine (5 mL) at 0 °C was slowly added trifluoromethanesulfonyl anhydride (0.4 mL, 2.4 mmol). The solution was stirred at 0 °C for 5 min and then allowed to warm to room temperature and stirred for 25 h. The resulting mixture was poured into water and extracted with diethyl ether (2× 15 mL). The ether extract was washed sequentially with

water, cold 10% hydrochloric acid solution, water, and brine (2×10 mL each), dried over anhydrous Na_2SO_4, and concentrated to yield an oil. Chromatography (flash column, hexane/EtOAc) afforded the corresponding triflates as colorless oils. The following known compounds, included in Table 1, were characterized by comparison of their chromatographic and spectroscopic data (^1H and ^{13}C NMR, and MS) with those described in the literature: decyl trifluoromethanesulfonate (entry 5),[31] dodecyl trifluoromethanesulfonate (entries 6 and 7),[32] 4-(*tert*-butyl)cyclohexyl trifluoromethanesulfonate (entry 9),[33] (−)-menthyl trifluoromethanesulfonate (entry 10).[34] For new compound, physical and spectroscopic data follow:

4.3.1. 1-Butylpentyl trifluoromethanesulfonate. Colorless oil; t_r 14.24; IR (film): ν=2936, 2877, 1471, 1425, 1302, 1210, 1137, 1118, 968, 718 cm^{-1}; ^1H NMR: δ=0.76 (6H, t, J=6.8 Hz, 2×CH_3), 1.22 (8H, m, 2×$CH_2CH_2CH_3$), 1.96 (4H, m, 2×CH_2CH), 4.15 (1H, m, CH); ^{13}C NMR: δ_C= 12.6 (2×CH_3), 21.0 (2×CH_2CH_3), 26.7 (2×CH_2CH_2-CH_3), 34.2 (2×CH_2CH), 86.0 (CH), 119.7 (q, J=320.0 Hz, CF_3); MS: m/z=276 (M^+, 1%), 127 (10), 85 (77), 71 (93), 70 (11), 69 (43), 57 (100), 56 (18), 55 (48), 44 (62), 43 (92), 42 (15), 41 (79), 39 (25). HRMS: calcd for $C_{10}H_{19}F_3O_3S$ 276.3203, found 276.3209.

4.4. Synthesis of the starting enol triflates[35]

For all the starting enol triflates included in Table 2, except for enol triflate derived from cholest-5-en-3-one (Table 2, entry 8), a solution of the corresponding ketone (1.6 mmol) in THF (3 mL) was added to a solution of LDA (1.76 mmol) in THF (3 mmol) at −78 °C, and the resulting solution was allowed to be stirred for 2 h at the same temperature. A solution of *N*-phenyltrifluoromethanesulfonimide (0.63 g, 1.76 mmol) in THF (3 mL) was then added; the reaction mixture was stirred at 0 °C for 1 h and allowed to warm to room temperature. Stirring was maintained during 9 h. After solvent removal at the rotatory evaporator, the resultant yellow oil was purified by column chromatography on silica gel (hexane) to yield the enol triflate product. The following known compounds, included in Table 2, were characterized by comparison of their chromatographic and spectroscopic data (^1H and ^{13}C NMR, and MS) with those described in the literature: (*Z*)-1-butyl-1-pentenyl trifluoromethanesulfonate (entry 1),[36] 4-*tert*-butylcyclohexen-1-yl trifluoromethanesulfonate (entries 2 and 3),[35] *trans*-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl trifluoromethanesulfonate (entry 4),[9b] 3-methyl-6-(1-methylethylidene)cyclohexen-1-yl trifluoromethanesulfonate (entry 6),[37] 3,5,5-trimethyl-1,3-cyclohexadien-1-yl trifluoromethanesulfonate (entry 7).[38] For new compound, physical and spectroscopic data follow.

4.4.1. Dihydrophenanthrenyl trifluoromethanesulfonate. Pale brown oil; t_r 35.43; IR (film): ν=3067, 2970, 2890, 1650, 1596, 1491, 1394, 1207, 1133, 1067, 910, 815, 761, 695 cm^{-1}; ^1H NMR: δ=2.55 (2H, m, CH_2CH) 3.69 (2H, t, J=7.1 Hz, CH_2C), 6.01 (1H, t, J=4.8 Hz, $CHCH_2$), 7.11–7.51 (3H, m, ArH), 7.68 (1H, d, J=8.8 Hz, ArH), 7.74 (1H, d, J=7.6 Hz, ArH), 7.93 (1H, d, J=8.2 Hz, ArH); ^{13}C NMR: δ=22.6 (CH_2CH), 30.7 (CH_2C), 117.2 ($CHCH_2$), 119.1 (q, J=320.4 Hz, CF_3), 119.3, 124.1, 126.8, 127.2, 127.5, 129.4 (6×ArCH), 131.4, 133.0, 134.3, 137.3 (4×ArC), 147.2 (CO); MS: m/z=328 (M^+, 53%), 195 (32), 168 (14), 167 (100), 166 (28), 165 (75), 153 (10), 152 (43), 139 (20), 69 (27). HRMS: calcd for $C_{15}H_{11}F_3O_3S$ 328.3117, found 328.3111.

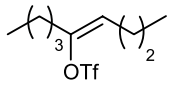
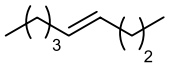
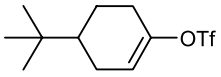
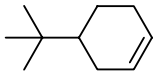
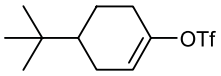
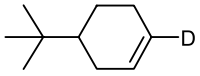
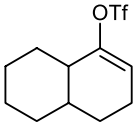
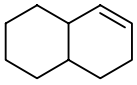
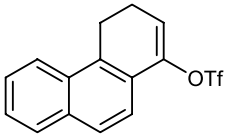
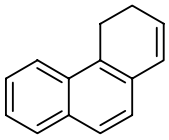
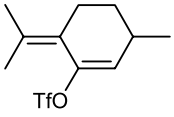
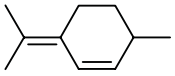
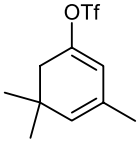
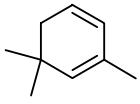
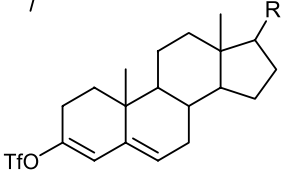
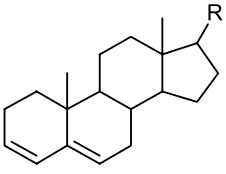
4.5. Synthesis of cholesta-3,5-dien-3-yl trifluoromethanesulfonate[39]

2,6-Di-*tert*-butylpyridine (0.226 g, 1.1 mmol) and triflic anhydride (0.186 mL, 0.111 g, 1.1 mmol) were added to a solution of cholest-5-en-3-one (0.384 g, 1 mmol) in chloroform (10 mL). The reaction mixture was stirred under reflux for 12 h. The reaction solvent was distilled and the crude reaction mixture was diluted with hexane (20 mL). The hexane solution was washed with water (20 mL) and brine (20 mL). The organic layer was filtered through basic alumina with hexane elution, and then solvents were removed by rotatory evaporation to yield the corresponding vinyl triflate pure enough to be used for the reduction reaction. The crystallized triflate (hexane) was characterized by comparison of its physical and spectroscopic data (^1H, ^{13}C NMR) with those described in the literature.[10c]

4.6. Reduction of sulfonates using the $CuCl_2\cdot 2H_2O$–Li–DTBB(cat.) combination. General procedure

A solution of the corresponding sulfonate (1 mmol) in THF (5 mL) was added to a mixture of $CuCl_2\cdot 2H_2O$ (170 mg, 1 mmol) or its deuterated salt (174 mg, 1 mmol), lithium sand (56 mg, 8.0 mmol) and DTBB (27 mg, 0.1 mmol) in THF (5 mL) at room temperature under a nitrogen atmosphere. The reaction mixture, which was initially dark green, changed to black, thus indicating the formation of activated copper(0). After total conversion of the starting material (TLC or GLC), the resulting suspension was diluted with diethyl ether (20 mL) and filtered off through a pad containing silica gel and celite (ca. 3:1). The filtrate was dried over anhydrous sodium sulfate, the solvents were evaporated (15 Torr), and the resulting residue was purified by column chromatography (silica gel, hexane/EtOAc). For volatile products, the dried organic layer was analyzed by GLC using an internal standard (dodecane for alkyl triflates and cycloocta-1,5-diene for enol triflates) (see Table footnotes). The reduction products in Tables 1 and 2, were fully characterized by comparison of their chromatographic and spectral data with those of the corresponding commercially available pure samples [*n*-dodecane (Table 1, entries 1 and 6), adamantane (Table 1, entry 3), *n*-nonane (Table 1, entries 4 and 8), *n*-decane (Table 1, entry 5), *tert*-butylcyclohexane (Table 1, entry 9), (*E*)-non-4-ene (Table 2, entry 1), cholesta-3,5-diene (Table 2, entry 8)]. For the rest of compounds included in Tables 1 and 2, literature references for all known compounds follow: *p*-menthane (Table 1, entries 2 and 10),[40] 1-deuteriododecane (Table 1, entry 7),[41] 4-*tert*-butylcyclohexene (Table 2, entry 2),[11a] 4-*tert*-butyl-1-deuteriocyclohexene (Table 2, entry 3),[42] 1,2,3,4,4a,5,6,8a-octahydronaphtalene (Table 2, entry 4),[43] 3,4-dihydrophenantrene (Table 2, entry 5),[44] 3-methyl-6-(1-methylethylidene)cyclohex-1-ene (isoterpinolene) (Table 2, entry 6),[45] 3,5,5-trimethylcyclohexa-1,3-diene (Table 2, entry 7).[46]

Table 2. Reduction of enol triflates

Entry	Sulfonate	Reaction conditions		Product[a]	
		$CuCl_2 \cdot 2H_2O$ (equiv)	t (h)	Structure	Yield (%)[b]
1		2	6		72
2		2	6		65
3		1[c]	6		69[d]
4		1	6		61
5		1	6		58
6		2	8		73
7		1	8		78[e]
8[f]		1	10		66

[a] All products were >95% pure (GLC).
[b] Isolated yield after column chromatography (silica gel, hexane) unless otherwise stated, based on the starting sulfonate.
[c] $CuCl_2 \cdot 2D_2O$ was used instead of $CuCl_2 \cdot 2H_2O$.
[d] ca. 73% deuterium incorporation (mass spectrometry, 300 MHz ^{1}H NMR).
[e] GLC yield, high volatility compound.
[f] R=1,5-dimethylhexyl.

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Reductive ring opening of *cis*- and *trans*-2,3-diphenyloxirane: a common intermediate

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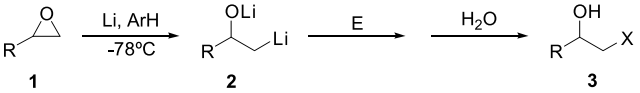
Abstract—The reaction of both *cis*- and *trans*-2,3-diphenyloxirane (**7** and **4**, respectively) with an excess of lithium and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB, 2.5 mol%) in the presence of different carbonyl compounds as electrophiles (Barbier conditions) in THF at temperatures ranging between −80 and −50 °C gives the same organolithium intermediate **5** and consequently, the same 1,3-diols **6**. In the case of *cis*-epoxide an inversion of the configuration at the benzylic carbanionic center can explain the obtained results. Only for the dicyclopropyl ketone derivative (**6h**) some amount (14%) of the corresponding epimer (**6′h**) resulting from a process with retention of the configuration of the intermediate is obtained. In representative cases, the structure of the final products (**6**) was unequivocally determined by X-ray diffraction analysis.

1. Introduction

In the last few years, functionalized organolithium compounds[1] have emerged as synthetically useful intermediates able to transfer their functionality to electrophilic reagents, making accessible polyfunctionalized molecules in only one synthetic operation. One problem associated to this type of compounds is that, due to their high reactivity, they have to be prepared and manipulated at low temperature, so the lithiation step is a crucial process. For this reason, about ten years ago, we developed an arene-catalyzed lithiation[2–5] as a convenient methodology in order to perform lithiation reactions under very mild reaction conditions. Among the different applications of this methodology is the ring opening of heterocycles, which is a direct way to generate functionalized organolithium intermediates.[6] For instance, epoxide **1** can be opened using a lithium-arene (stoichiometric version)[7] or lithium and a catalytic amount of an arene (catalytic version)[8] at low temperature, so a regioselective ring opening takes place to give the most stable primary β-oxide functionalized organolithium intermediate **2**, which by reaction with electrophiles gives, after hydrolysis, the expected products **3** (Scheme 1).



1 2 3

Scheme 1.

In this paper we describe the application of the arene-catalyzed lithiation to the ring opening of *cis*- and *trans*-2,3-diphenyloxirane in order to study the stereochemistry of the process, specially in the lithiation step.[9]

2. Results and discussion

The treatment of *trans*-2,3-diphenyloxirane (**4**) with an excess of lithium powder (1:7 molar ratio; theoretical 1:4) and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB, 1:0.05 molar ratio) in the presence of the corresponding carbonyl compound as electrophile[10] (1:2 molar ratio) in THF at temperatures ranging between −80 and −50 °C

Keywords: Epoxides; Reductive ring opening; DTBB-catalyzed lithiation; 1,3-Diols.
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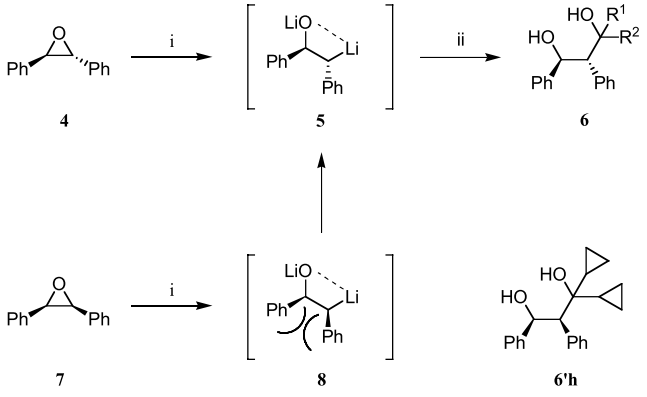
gave, after hydrolysis with water, the expected 1,3-diols **6** (Scheme 2). Both the intermediate **5** and the final products **6** keep the stereochemistry of the initial stereocenters of the starting material **4**. Surprisingly, when we started from *cis*-2,3-diphenyloxirane (**7**), the same process (under the same reaction conditions and using the same electrophiles) afforded the same products **6** with the same stereochemistry than before. In this reaction, the corresponding intermediate **8**, which (like in the case of **5**) possesses a rather rigid structure due to the coordination of the negatively charged oxide with the lithium atom (CIPE),[11] suffers a benzylic inversion at the carbanionic center[12] giving the more stable intermediate **5**, so the same products **6** obtained from the epoxide **4** were isolated (Scheme 2 and Table 1). Concerning reaction conditions, higher temperature (0 °C) gave worse results because variable amounts of the corresponding pinacol were obtained, their separation from the desired product being not easy. On the other hand, when the reaction shown in Scheme 2 was carried out step-by-step (Grignard conditions), yields were slightly lower than those obtained with Barbier conditions.



Scheme 2. Reagents and conditions: (i) Li, DTBB (2.5% molar), E (R^1R^2CO)=Bu′CHO, *c*-$C_6H_{11}CHO$, PhCHO, Me_2CO, Et_2CO, $(CH_2)_5CO$, $Pr^i{}_2CO$, $(c\text{-}C_3H_5)_2CO$, THF −78 to −50 °C; (ii) H_2O, −50 °C to rt.

As it can be seen in Table 1, yields are in general modest. In spite the complete conversion (total disappearance of the starting material at the end of the reaction), important amounts of the 'reduced' product 1,2-diphenyl-1-ethanol (resulting from a proton abstraction of intermediate **5** or/and **8** from the reaction media)[13] are obtained together with products **6**. Even so, the reaction can be used for synthetic purposes because the separation of both products is very easy by flash chromatography. On the other hand, it is worthy to note that no products having the configuration of the intermediate **8** (from the starting epoxide **7**) have been detected from the reaction crude, except in the case of using dicyclopropyl ketone as electrophile, in which a 7:1 mixture of diastereomers (**6h**:**6′h**) was obtained in favor of compound **6h**. The minor diastereomer **6′h** was isolated from the corresponding mixture mechanically (at the microscope plate) in order to get its whole characterization. Finally, when benzaldehyde was used as prostereogenic electrophile, only one diastereomer (**6c**) was isolated having (1*S**,3*S**) configuration, its structure having been determined by NMR experiments. We do not have any explanation for this result.

Due to the stereochemical aspects of the reaction shown in Scheme 2 the structure of some compounds **6** (and **6′h**) was determined not only by NMR experiments, but also by X-ray crystallography (Chart 1 and Table 2), in which a hydrogen-bond is observed in the solid state in all cases. The same observation was found by NMR in solution (see Section 4).

3. Conclusion

In conclusion, we report here that the DTBB-catalyzed lithiation of both *cis*- and *trans*-2,3-diphenyloxirane (**7** and **4**, respectively) gives the same intermediate **5**, so after reaction with different carbonyl compounds the same 1,3-diols **6** were stereoselectively obtained, these products being the expected ones coming from the *trans*- starting material **4** without changing the configuration of both oxiranyl stereocenters. In the case of the *cis*-epoxide **7**, a benzylic

Table 1. Preparation of compounds **6**

Entry	Electrophile	Product			Yield (%)[a]	
		No.	R^1	R^2	From **4**	From **7**
1	Bu′CHO	**6a**	H	Bu^t	35[b]	32[c]
2	*c*-$C_6H_{11}CHO$[d]	**6b**	H	*c*-C_6H_{11}[d]	20[e]	30[f]
3	PhCHO	**6c**	H	Ph	20[g]	31[g]
4	Me_2CO	**6d**	Me	Me	35	50
5	Et_2CO	**6e**	Et	Et	60	40
6	$(CH_2)_5CO$	**6f**	$(CH_2)_5$		41	38
7	$Pr^i{}_2CO$	**6g**	Pr^i	Pr^i	25	76
8	$(c\text{-}C_3H_5)_2CO$[h]	**6h**	*c*-C_3H_5	*c*-C_3H_5[h]	31	79[i]

[a] Isolated yield after flash chromatography (silica gel, hexane/ethyl acetate) based on the starting epoxides **4** or **7**.
[b] 2.8:1 Diastereomeric mixture (^1H NMR).
[c] 2.1:1 Diastereomeric mixture (^1H NMR).
[d] *c*-C_6H_{11}=cyclohexyl.
[e] 1.3:1 Diastereomeric mixture (^1H NMR).
[f] 1.5:1 Diastereomeric mixture (^1H NMR).
[g] Only the diastereomer with the (1*S**,3*S**) configuration was obtained (^1H NMR from the crude mixture).
[h] *c*-C_3H_5=cyclopropyl.
[i] A 7:1 mixture of compounds **6**:**6′h** was obtained (^1H NMR).

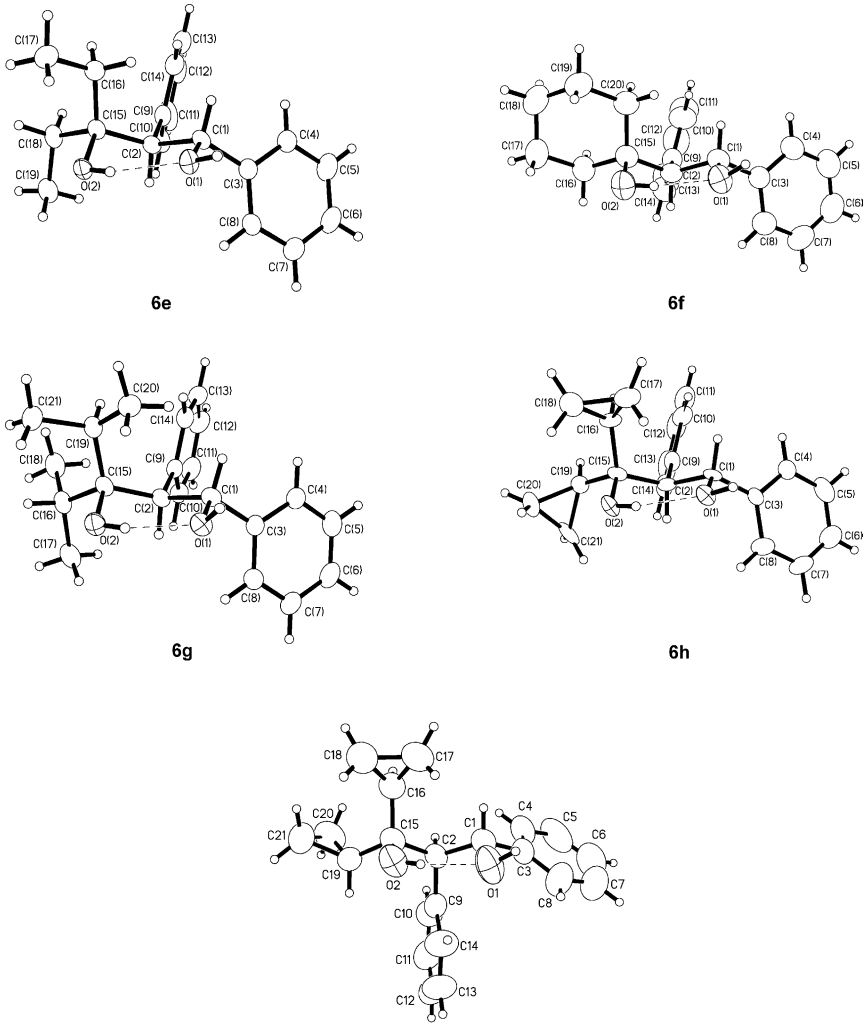


Chart 1.

inversion in the initially obtained organolithium intermediate **8** leads to the same intermediate **5**. Only in the case of the dicyclopropyl ketone an small amount (about 14%) of the corresponding product **6′h** without inversion was obtained.

4. Experimental

4.1. General

For general information see Ref. 5. X-ray analyses were performed at the Universities of Zaragoza and Purdue, the corresponding details being given below. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AC-300 using $CDCl_3$ as solvent and TMS as internal standard.

4.2. DTBB-catalyzed lithiation of *cis*- and *trans*-2,3-diphenyloxirane 4 and 7. Preparation of compounds 6

To a cooled green suspension of lithium (49 mg, 7 mmol) and DTBB (13 mg, 0.05 mmol) in THF (3 mL) at −80 °C was slowly added (ca. 45 min) a solution of the corresponding electrophile (2 mmol) and *cis* or *trans*-2,3-diphenyloxirane (200 mg, 1 mmol) in THF (2 mL). The resulting mixture was stirred for 2 h allowing the temperature to rise to −50 °C and then it was hydrolyzed with water (5 mL) allowing the temperature to rise to 20 °C. The resulting mixture was extracted with ethyl acetate (3×10 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting residue was then purified by flash chromatography (silica gel, hexane/ethyl acetate) to give the desired compounds **6**, which were recrystallized in hexane/ethyl acetate. Yields are given in Table 1; physical, analytical spectroscopic data as well as literature references for the known compounds **6c** and **6d** follow.

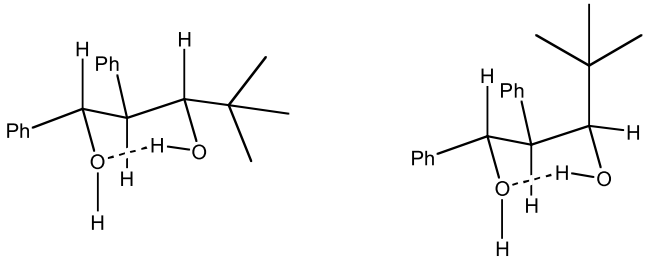
4.2.1. (1*S,2*R**,3*R**/*S**)-4,4-Dimethyl-1,2-diphenyl-1,3-pentanediol (6a).** Diastereomeric mixture. 1:2.78. t_r= 15.3 (major), 15.5 (minor) min; R_f (hexane/ethyl acetate 8:2)=0.13, 0.14; mp 166 °C; ν (film) 3261 (OH), 3085, 3060, 3026, 1603 cm^{-1} (C=CH); δ_H 0.69 [9H, s, $(CH_3)_3$, minor], 0.85 [9H, s, $(CH_3)_3$, major], 3.06–3.11 (2H, m,

Table 2. Crystallographic data of compounds **6e–h** and **6′h**

	6e	**6f**	**6g**	**6h**	**6′h**
Crystallized from	Hexane/ethyl acetate	Hexane/ethyl acetate	Hexane/ethyl acetate	Hexane/ethyl acetate	Hexane/ethyl acetate
Empirical formula	$C_{19}H_{24}O_2$	$C_{20}H_{24}O_2$	$4(C_{21}H_{28}O_2)$, C_6H_{14}	$C_{21}H_{24}O_2$	$C_{21}H_{24}O_2$
Formula weight [g mol^{-1}]	284.38	296.39	1335.91	308.40	308.40
Crystal color, habit	Colorless, plate	Colorless, block	Colorless, block	Colorless, block	Colorless, block
Crystal dimensions [mm]	0.20×0.12×0.07	0.18×0.13×0.11	0.22×0.21×0.13	0.20×0.150×0.125	0.15×0.07×0.06
Temperature [K]	100(1)	291(1)	100(1)	150(1)	291(1)
Crystal system	Orthorhombic	Monoclinic	Triclinic	Monoclinic	Monoclinic
Space group	$P2_12_12_1$	$C2/c$	$P\bar{1}$	Cc	$P2_1/c$
Z	4	8	2	4	4
Reflections for cell determination	2192	1453	3000	1475	575
2θ Range for cell determination [°]	4.62–42.68	5.2–40.10	4.48–49.94	5.7–49.32	4.8–31.4
Unit cell parameters					
a [Å]	9.8420(7)	23.324(2)	14.6635(10)	11.3406(17)	9.9482(11)
b [Å]	10.5542(8)	8.3651(8)	14.6931(10)	17.198(3)	20.549(2)
c [Å]	15.8826(12)	17.2572(17)	18.8287(13)	9.1699(14)	9.2011(10)
α, β, γ [°]	90, 90, 90	90, 100.457(2), 90	84.3680(10), 76.3420(10), 89.8380(10)	90, 102.953(10), 90	90, 110.290(2), 90
V [Å^3]	1649.8(2)	3311.1(5)	3922.1(5)	1742.9(5)	1764.2(3)
D_x [g cm^{-3}]	1.145	1.189	1.131	1.175	1.161
$\mu(MoK_\alpha)$ [mm^{-1}]	0.072	0.075	0.070	0.074	0.073
Transmission factors (min; max)	0.799; 0.995	0.9217; 0.9918	0.8875; 0.9909	—; —	0.9151; 0.9956
$2\theta_{max}$ [°]	50	50	50	49.32	50
Total reflections measured	12,196	11,828	29,044	1475	12,861
Symmetry-independent reflections	1691	2925	13,809	1475	3105
Reflections with $I>2\sigma(I)$	1479	1859	7715	1280	1064
Reflections used in refinement	1691	2925	13,809	1475	3105
Parameters refined	194	201	909	210	211
$R(F)$ [$I>2\sigma(I)$ reflections]	0.0367	0.0435	0.0568	0.0880	0.0647
$wR(F^2)$ (all data)	0.0905	0.1137	0.1213	0.2677	0.1264
Weighting parameters [a;b][a]	0.05; 0.0963	0.0539; 0.0722	0.0330; 0.0	0.2; 1.6929	0.03; 0.0
Goodness-of-fit	1.066	1.014	0.990	1.049	0.950
Secondary extinction coefficients	—	—	—	—	0.0058(10)
Final Δ_{max}/σ	0.005	0.000	0.001	0.013	0.008
$\Delta\rho$ (max; min) [eÅ^{-3}]	0124; −0.162	0.115; −0.170	0.214; −0.208	0.306; −0.321	0.151; −0.134

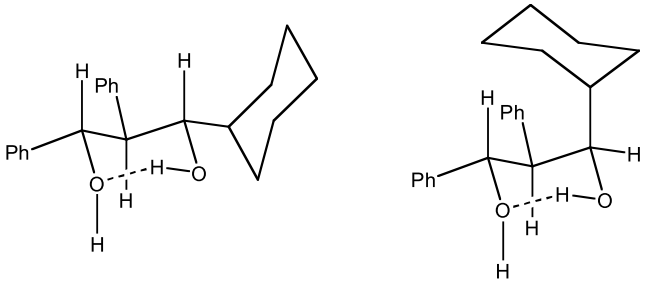
[a] $w=[\sigma^2(F_o^2)+(aP)^2+bP]^{-1}$, where $P=(F_o^2+2F_c^2)/3$.

PhC*H*COH), 3.62 (4H, br s, 2×OH), 3.99 (1H, d, J= 6.9 Hz, Me_3CCHOH, major), 4.02 (1H, d, J=1.9 Hz, Me_3CCHOH, minor), 4.98 (1H, d, J=9.5 Hz, PhC*H*OH, major), 5.03 (1H, d, J=7.1 Hz, PhC*H*OH, minor), 6.84–7.33 (20H, m, ArH); δ_C 26.1, 26.8 (CH_3), 35.5, 37.0 (Me_3C), 53.7, 54.7 (Ph*C*HCOH), 77.7, 79.0 (Me_3CCOH), 84.7 (Ph*C*HOH), 125.9, 126.3, 126.9, 127.0, 127.1, 127.6, 127.9, 128.0, 129.0, 130.5 (ArCH), 140.1, 142.6, 143.4 (ArC); *m/z* (minor) 251 (M^+-H_2O-Me, 1%), 181 (17), 180 (30), 179 (11), 160 (62), 146 (12), 145 (100), 105 (13), 91 (27), 79 (13), 77 (17), 57 (14); HRMS (minor): M^+-H_2O, found 266.1691. $C_{19}H_{22}O$ requires 266.1671; *m/z* (major) 266 (M^+-H_2O, 1%), 180 (27), 179 (11), 160 (59), 146 (12), 145 (100), 120 (10), 107 (17), 105 (10), 91 (28), 79 (16), 77 (18), 57 (15); HRMS (major): M^+-H_2O, found 266.1707. $C_{19}H_{22}O$ requires 266.1671. Anal. Calcd for $C_{19}H_{24}O_2\cdot H_2O$: C, 75.46; H, 8.67. Found: C, 75.69; H, 7.98%.



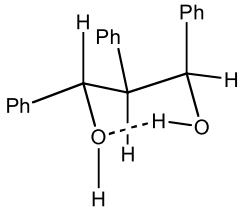
4.2.2. (1*S,2*R**,3*R**/*S**)-1-Cyclohexyl-2,3-diphenyl-1,3-propanediol (6b).** Diastereomeric mixture. 1:1.35. t_r= 17.5 (minor), 17.6 (major) min; R_f (hexane/ethyl acetate 8:2)=0.21, 0.22; mp 186 °C; ν (film) 3402 (OH), 3093, 3060, 3026 cm^{-1} (C=CH); δ_H 0.79–0.90, 1.02–1.48, 1.55–1.67 (22H, 3m, ringCH, 5×ringCH_2), 3.01–3.11 (2H, m,

PhC*H*COH), 3.24 (4H, br s, 2×OH), 4.04 (1H, br d, J=8.8 Hz, CyC*H*OH, minor), 4.15 (1H, br d, J=8.2 Hz, CyC*H*OH, major), 5.03 (1H, d, J=9.2 Hz, PhC*H*OH, major), 5.35 (1H, d, J=3.2 Hz, PhC*H*OH, minor), 6.81–7.17 (20H, m, ArH); δ_C 24.3, 25.4, 25.9, 26.3, 26.4, 29.4, 29.7, 30.5, 30.6 (ringCH_2), 40.2, 40.4 (ringCH), 54.8, 55.7 (Ph*C*HCOH), 74.9, 76.9 (Cy*C*OH), 80.6, 80.7 (Ph*C*HOH), 126.4, 126.9, 127.0, 127.2, 127.7, 127.8, 127.9, 128.1, 128.8, 129.9 (ArCH), 138.2, 139.2, 142.4, 142.8 (ArC); *m/z* (minor) 292 (M^+-H_2O, 1%), 186 (47), 180 (52), 179 (17), 129 (11), 107 (11), 105 (21), 104 (100), 95 (10), 91 (27), 79 (16), 77 (17), 55 (17); HRMS (minor): $M^+-2\times H_2O$, found 274.1680. $C_{21}H_{22}$ requires 274.1721; *m/z* (major) 274 ($M^+-2\times H_2O$, 1%), 186 (50), 180 (23), 129 (11), 107 (14), 105 (20), 104 (100), 95 (10), 91 (25), 79 (17), 77 (16), 55 (15); HRMS (major): $M^+-2\times H_2O$, found 274.1715. $C_{21}H_{22}$ requires 274.1721. Anal. Calcd for $C_{21}H_{26}O_2\cdot 1/3H_2O$: C, 79.71; H, 8.49. Found: C, 79.68; H, 8.29%.



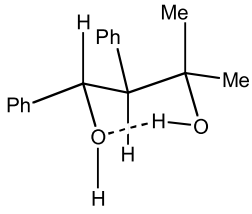
(major) **6b** (minor)

4.2.3. (1*S,3*S**)-1,2,3-Triphenyl-1,3-propanediol (6c).**[14] t_r=17.7 min; R_f (hexane/ethyl acetate 8:2)=0.13; mp 130 °C; ν (film) 3408 (OH), 3085, 3061, 3028, 1602 cm^{-1} (C=CH); δ_H 3.22 [1H, dd, J=3.2, 7.8 Hz, PhC*H*$(COH)_2$], 3.50 (2H, br s, 2×OH), 5.18 (1H, d, J=7.8 Hz, PhC*H*OH), 5.34 (1H, d, J=3.2 Hz, PhC*H*OH), 6.84–7.19 (15H, m, ArH); δ_C 59.2 [Ph*C*H$(COH)_2$], 74.2, 76.0 (Ph*C*HOH), 126.4, 126.5, 126.9, 127.0, 127.5, 127.7, 128.1, 130.1 (ArCH), 137.4, 142.1, 142.9 (ArC); *m/z* 268 ($M^+-2\times H_2O$, 1%), 181 (15), 180 (100), 179 (32), 178 (11), 165 (16), 107 (14), 105 (21), 91 (13), 79 (18), 77 (26); HRMS: M^+-H_2O, found 286.1315. $C_{21}H_{18}O$ requires 286.1358. Anal. Calcd for $C_{21}H_{20}O_2$: C, 82.85; H, 6.63. Found: C, 82.52; H, 6.40%.



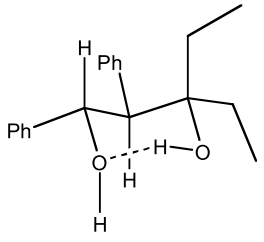
6c

4.2.4. (1*S,2*R**)-3-Methyl-1,2-diphenyl-1,3-butanediol (6d).**[15] t_r=14.6 min; R_f (hexane/ethyl acetate 8:2)=0.13; mp 98 °C; ν (film) 3328 (OH), 3026, 1602 cm^{-1} (C=CH); δ_H 0.94, 1.54 (3H, 3H, 2s, 2×CH_3), 3.09 (1H, d, J=10.8 Hz, PhC*H*COH), 4.45, 4.70 (2H, 2br s, 2×OH), 5.26 (1H, d, J=10.8 Hz, PhC*H*OH), 7.06–7.14 (10H, m, ArH); δ_C 24.4, 30.6 (CH_3), 62.6 (Ph*C*HCOH), 74.8 (Me_2*C*OH), 77.3 (Ph*C*HOH), 126.5, 127.1, 127.3, 127.9 (ArCH), 139.2, 143.1 (ArC); *m/z* 238 (M^+-H_2O, 1%), 181 (12), 180 (82), 179 (40), 178 (17), 165 (20), 133 (11), 132 (100), 117 (47), 115 (10), 107 (12), 105 (16), 91 (24), 79 (16), 77 (25), 59 (11); HRMS: $M^+-2\times H_2O$, found 220.1532. $C_{17}H_{16}$ requires 220.1552. Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.94; H, 7.94%.



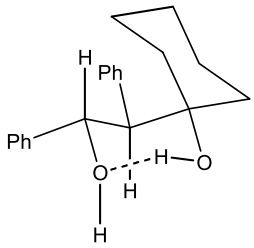
6d

4.2.5. (1*S,2*R**)-3-Ethyl-1,2-diphenyl-1,3-pentanediol (6e).** t_r=15.8 min; R_f (hexane/ethyl acetate 8:2)=0.76; mp 141 °C; ν (film) 3261 (OH), 3080, 3066, 3026, 1602 cm^{-1} (C=CH); δ_H 0.76 (3H, t, J=7.3 Hz, CH_3), 0.99 (3H, t, J=7.3 Hz, CH_3), 1.09, 1.57, 1.76, 2.12 (4H, 4m, 2×CH_2), 3.23 (1H, d, J=10.2 Hz, PhC*H*COH), 3.82 (2H, br s, 2×OH), 5.24 (1H, d, J=10.2 Hz, PhC*H*OH), 7.08 (10H, br s, ArH); δ_C 7.3, 7.6 (CH_3), 27.9, 30.0 (CH_2), 59.8 (Ph*C*HCOH), 77.4 (Et_2*C*OH), 78.2 (Ph*C*HOH), 126.4, 126.9, 127.1, 127.8 (ArCH), 139.2, 143.6 (ArC); *m/z* 266 (M^+-H_2O, 1%), 181 (15), 180 (100), 179 (32), 178 (13), 165 (16), 160 (51), 131 (15), 107 (10), 105 (13), 91 (24), 79 (14), 77 (18), 57 (30); HRMS: $M^+-2\times H_2O$, found 248.1580. $C_{19}H_{20}$ requires 248.1565.

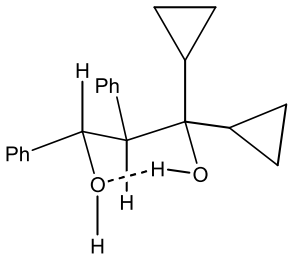


6e

4.2.6. (1*S,2*R**)-1-(2-Hydroxy-1,2-diphenylethyl)-1-cyclohexanol (6f).** t_r=17.2 min; R_f (hexane/ethyl acetate 8:2)=0.24; mp 205 °C; ν (film) 3248 (OH), 3087, 3026, 1602 cm^{-1} (C=CH); δ_H 0.82–1.04, 1.28–1.80, 2.14–2.17 (10H, 3m, 5×ringCH_2), 2.97 (2H, br s, 2×OH), 3.13 (1H, d, J=10.6 Hz, PhC*H*COH), 5.35 (1H, d, J=10.6 Hz, PhC*H*OH), 7.06–7.17 (10H, m, ArH); δ_C 21.2, 21.6, 25.6, 31.5, 38.0 (ringCH_2), 63.4 (Ph*C*HCOH), 75.4 [$(CH_2)_5$*C*OH], 76.8 (Ph*C*HOH), 126.5, 127.0, 127.4, 127.8, 127.9 (ArCH), 139.1, 143.4 (ArC); *m/z* 278 (M^+-H_2O, 1%), 181 (15), 180 (100), 179 (30), 178 (13), 172 (49), 165 (16), 129 (13), 107 (10), 105 (14), 104 (16), 91 (25), 81 (23), 79 (19), 77 (20); HRMS: $M^+-2\times H_2O$, found 260.1545. $C_{20}H_{20}$ requires 260.1565. Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.94; H, 8.40%.

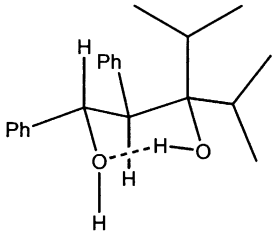


6f



6h

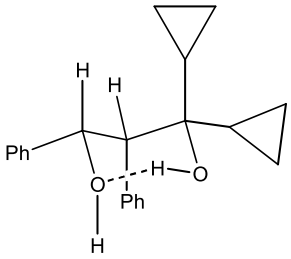
4.2.7. (1*S,2*R**)-3-Isopropyl-4-methyl-1,2-diphenyl-1,3-pentanediol (6g).** $t_r=16.7$ min; R_f (hexane/ethyl acetate 8:2)=0.45; mp 142 °C; ν (film) 3261 (OH), 3087, 3066, 3033, 1609 cm^{-1} (C=CH); δ_H 0.44 (3H, d, $J=6.9$ Hz, CH_3), 0.92 (3H, d, $J=6.7$ Hz, CH_3), 1.04 (3H, d, $J=6.9$ Hz, CH_3), 1.35 (3H, d, $J=6.7$ Hz, CH_3), 1.79, 2.52 (2H, 2m, 2×CH), 3.39 (1H, d, $J=10.3$ Hz, PhC*H*COH), 4.44 (2H, br s, 2×OH), 5.34 (1H, d, $J=10.3$ Hz, PhC*H*OH), 6.93–7.30 (10H, m, ArH); δ_C 17.6, 18.8, 19.3 (CH_3), 32.1, 37.0 (CH), 57.3 (Ph*C*HCOH), 79.6 (Ph*C*HOH), 82.1 (Pr^i_2COH), 126.2, 126.9, 127.5, 127.6 (ArCH), 139.2, 144.3 (ArC); *m*/*z* 276 ($M^+-2\times H_2O$, 1%), 188 (12), 181 (15), 180 (100), 179 (26), 178 (11), 165 (13), 146 (10), 145 (83), 107 (13), 105 (15), 91 (29), 79 (16), 77 (19), 71 (48); HRMS: $M^+-2\times H_2O$, found 276.1865. $C_{21}H_{24}$ requires 276.1878. Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.72; H, 9.04. Found: C, 80.09; H, 9.06%.



6g

4.2.8. (1*S,2*R**)-1,1-Dicyclopropyl-2,3-diphenyl-1,3-propanediol (6h).** $t_r=16.96$ min; R_f (hexane/ethyl acetate 8:2)=0.41; mp 115 °C; ν (film) 3335 (OH), 3087, 3060, 3006, 1690 cm^{-1} (C=CH); δ_H 0.13–0.19, 0.22–0.29, 0.35–0.41, 0.47–0.60, 0.74–0.78, 1.43–1.58 (10H, 6m, 2×ringCH, 4×ringCH_2), 3.27 (1H, d, $J=10.9$ Hz, PhC*H*COH), 1.58, 3.63 (2H, 2br s, 2×OH), 5.61 (1H, d, $J=10.9$ Hz, PhC*H*OH), 7.04–7.35 (10H, m, ArH); δ_C −1.3, −0.2, 1.2, 1.3 (ringCH_2), 15.8, 19.0 (ringCH), 62.3 (Ph*C*HCOH), 74.2 (Ph*C*HOH), 126.3, 127.3, 127.4, 127.9 (ArCH), 138.7, 143.1 (ArC); *m*/*z* 184 (17), 181 (15), 180 (100), 179 (28), 178 (10), 169 (19), 165 (16), 156 (10), 155 (26), 154 (11), 153 (13), 143 (28), 142 (14), 141 (41), 129 (18), 128 (45), 127 (11), 115 (33), 106 (47), 105 (51), 91 (37), 79(10), 78 (15), 77 (57), 69 (21), 51 (26); HRMS: $M^+-2\times H_2O$, found 272.1581. $C_{21}H_{20}$ requires 272.1565.

4.2.9. (1*R,2*R**)-1,1-Dicyclopropyl-2,3-diphenyl-1,3-propanediol (6′h).** $t_r=17.01$ min; R_f (hexane/ethyl acetate 8:2)=0.39; mp 156 °C; ν (film) 3335 (OH), 3089, 3058, 3003, 1690 cm^{-1} (C=CH); δ_H 0.01–0.09, 0.22–0.27, 0.33–0.40, 0.41–0.51, 0.54–0.61, 0.72–0.85 (10H, 6m, 2×ringCH, 4×ringCH_2), 2.94 (1H, d, $J=2.5$ Hz, PhC*H*COH), 2.48, 3.32 (2H, 2br s, 2×OH), 6.01 (1H, d, $J=2.3$ Hz, PhC*H*OH), 6.98–7.14 (10H, m, ArH); δ_C 0.0, 0.2, 1.2, 1.6 (ringCH_2), 16.7, 20.8 (ringCH), 62.6 (Ph*C*HCOH), 74.6 (Ph*C*HOH), 125.9, 126.3, 126.6, 127.2, 127.6, 131.4 (ArCH), 137.4, 143.0 (ArC); *m*/*z* (major) 249 ($M^+-H_2O-C_3H_5$, 1%), 184 (19), 181 (16), 180 (100), 179 (23), 169 (17), 165 (13), 154 (21), 143 (25), 142 (11), 141 (31), 129 (14), 128 (33), 115 (25), 111 (15), 106 (31), 105 (41), 91 (34), 79 (13), 78 (11), 77 (46), 69 (33), 51 (19); HRMS: $M^+-2\times H_2O$, found 272.1579. $C_{21}H_{20}$ requires 272.1565.



6'h

4.3. X-ray analysis

Diffraction data were taken in a Bruker Smart CCD diffractometer (for compounds **6e**, **6f**, **6g** and **6′h**) at the University of Zaragoza and in a Kappa CCD apparatus (for compound **6h**) at Purdue University. Crystal data are summarized in Table 2 and have been deposited at the Cambridge Crystallographic Data Centre.

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First enantiospecific synthesis of (+)-β-herbertenol

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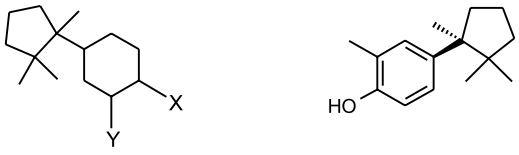
Abstract—The first enantiospecific synthesis of (+)-β-herbertenol, from naturally occurring *R*-(+)-citronellal, employing Taber's diazo decomposition protocol as the key step, is described.

1. Introduction

Numerous herbertene type sesquiterpenoids, an expanding group of natural products possessing a 3-methyl-1-(1,2,2-trimethylcyclopentyl) cyclohexane skeleton **1**, have been isolated from *Herbertous* species and other *liverworts*.[1,2] Recently, Asakawa and co-workers reported the isolation of seven new herbertanes and two new cuperanes from Japanese liverworts.[3] Many of these compounds, particularly those with an oxygenated aromatic six membered ring, show a wide spectrum of biological properties, which include potent antifungal, neurotrophic and anti-lipid peroxidation activities (Fig. 1).[1a,b,4,5]



X= H, Y= Me; Herbertene skeleton (**1**)

X= Me, Y= H; Cuparene skeleton (**2**)

(-)-β-Herbertenol (**3**)

Figure 1. Herbertene and cuparene skeleton.

Because of the difficulties associated with the construction of the vicinal quaternary carbons in the cyclopentane ring, herbertanes and cuparanes have become popular synthetic targets in recent years.[6] Although, there are synthetic strategies reported towards (±)-β-herbertenol, not a single asymmetric synthesis is reported. Our interest in these skeletons has led to the synthesis of cuparenones[6i,j] and recently in the facile synthesis of (±)-β-herbertenol.[6k] In continuation of our efforts towards the synthesis of homochiral β-herbertenol, we describe herein the first enantiospecific synthesis of (+)-β-herbertenol.

2. Results and discussion

The idea central to our synthetic route is to make use of naturally occurring chiral citronellal for asymmetric synthesis of β-herbertenol using Taber's protocol of diazo decomposition of α-diazo-β-ketoester **8** by $Rh_2(OAc)_4$ to provide the five membered ring with retention of configuration at the chiral center.[7,8]

To investigate the idea, *R*-(+)-citronellal was converted into α-diazo-β-ketoester **8** as depicted in Scheme 1. Enone **4a** was synthesized from *R*-(+)-citronellal.[9] It was then converted into its silyl enol ether using LDA as base,[10] and the resultant silyl enol ether was treated with NBS[11] to give the corresponding haloderivative **4b** as a mixture of diastereomers, and as we were going to destroy the centers during aromatization in the next step, we did not establish the diastereomeric ratio. Thus, the halo derivative **4b** on dehydrohalogenation[12] provided the phenol **5a** in 75% overall yield. The phenol thus obtained was then protected as methyl ether **5b** and converted into acid **6**, by Weinreb's method.[13] Acid **6** was then converted into β-ketoester **7** using Meldrum's acid in 78% yield. Diazotransfer was carried out by Regitz's protocol to give α-diazo-β-ketoester **8**.[14] The crucial insertion reaction was performed on **8** using rhodium catalyzed cyclization to furnish cyclized β-ketoester **9** as a diastereomeric mixture in 40% overall yield starting from **7**. Having secured the key

Keywords: Enantiospecific; Diazo decomposition; Citronellal.
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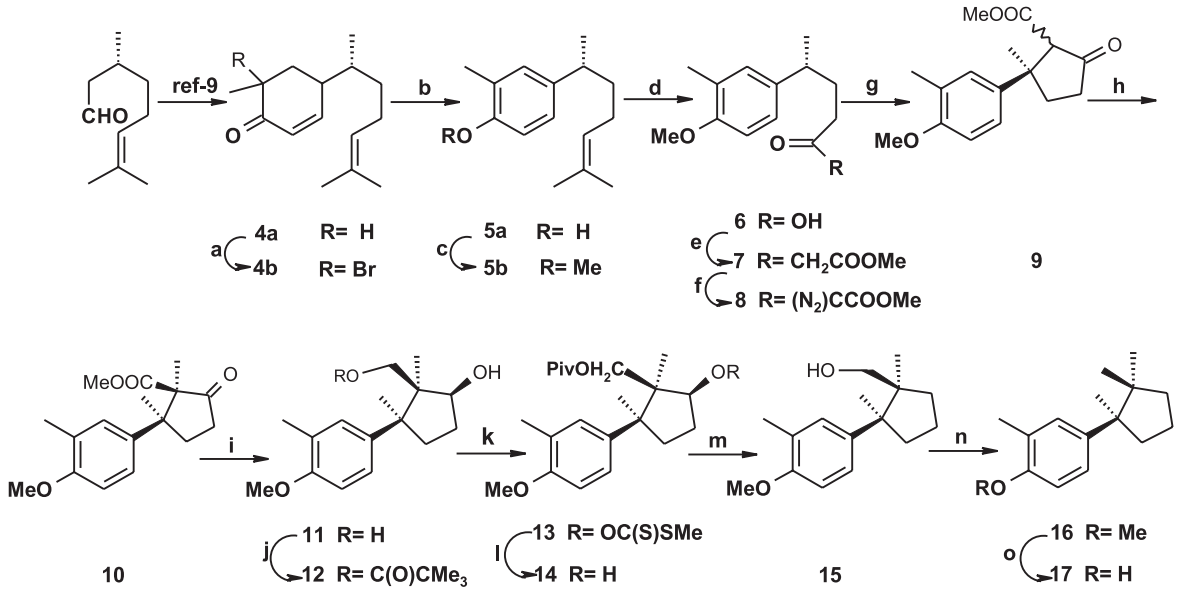

Scheme 1. Reagents and conditions: (a) (i) LDA, THF, −78 °C, TMSCl; (ii) NBS, THF, 0 °C, 0.5 h; (b) Li_2CO_3, LiBr, DMF, 135 °C, 4 h, 75% from **4a**; (c) K_2CO_3, Me_2SO_4, acetone, reflux, 12 h, 90%; (d) OsO_4 (cat), Jones' reagent, acetone, rt, 5 h, 80%; e) (i) $SOCl_2$, CH_2Cl_2, reflux, 2 h; (ii) Meldrum's acid, pyridine, CH_2Cl_2, 0 °C–rt, 2 h; (iii) MeOH, reflux, 4 h, 78%; (f) Et_3N, MsN_3, CH_2Cl_2, −10 °C–rt, overnight; (g) $Rh_2(OAc)_4$ (cat.), CH_2Cl_2, rt, 40% for 2 steps; (h) K_2CO_3, MeI, acetone, rt, 85%; (i) LAH, THF, 0 °C–rt, 5 h, 80%; (j) Pivaloyl chloride, Et_3N, CH_2Cl_2, −10 °C–rt, 4 h, 65%; (k) NaH, CS_2, THF, 0 °C, 1.5 h, then MeI, rt, 5 h, 95%; (l) TBTH, AIBN (cat), toluene, reflux, 2 h, 80%; (m) LAH, THF, rt, 2 h, 95%; (n) (i) PDC, CH_2Cl_2, 0 °C, 3 h; (ii) NH_2NH_2–H_2O, diethyleneglycol, 150 °C, 4 h, 190 °C, 3 h, 73% for 2 steps; (o) BBr_3, CH_2Cl_2, −78 °C–rt, overnight, 93%.

cyclopentanone in place, the remaining problem was to convert **9** into the geminal dialkylated cyclopentane skeleton. Accordingly, ester **9** was methylated using K_2CO_3, MeI in dry acetone, which gave single diasteteomer **10** in which methyl group and the aryl group on the adjacent quaternary carbon are anti to each other. The ^{1}H NMR spectrum of the compound **10** support this, in which the ester methyl signal appeared at 3.33 ppm because of the shielding of methoxy carbonyl group by the vicinal *cis* aryl group. The β-ketoester **10** was then reduced using LAH to the corresponding diol **11** as a single diastereomer. The stereochemistry of compound **11** was deduced by X-ray analysis of the racemic alcohol diol **11** (Fig. 2). The X-ray structure not only confirms the relative configuration of newly generated hydroxy group in **11**, but also the relative stereochemistry of methyl group in **10**. The primary alcohol of diol **11** was protected as a pivaloyl ester to give **12**. The secondary alcohol group was then deoxygenated by employing Barton's protocol[15] to give pivaloyl ester **14**, which on reduction using LAH gave the corresponding alcohol **15**. This alcohol was then oxidized to the corresponding aldehyde using PDC, followed by deoxygenation under Huang–Minlon conditions to give the methyl ether of β-herbertenol **16**, which on deprotection using BBr_3 gave the final product, that is, (+)-β-herbertenol **17**.

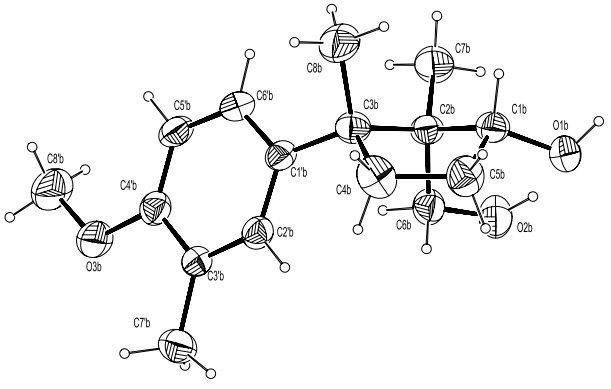

Figure 2. ORTEP view of *rac*-**11**.

3. Conclusion

Thus, (+)-β-herbertenol has been synthesized from naturally occurring *R*-(+)-citronellal employing carbene insertion as the key step. The same idea can be applicable to the synthesis of naturally occurring (−)-β-herbertenol and other herbertanes.

4. Experimental

4.1. General methods

All solvents were freshly distilled before use and dry solvents were distilled under argon from Na/benzophenone. Melting points are uncorrected. Chemical shifts in ^{1}H and ^{13}C NMR are reported relative to residual solvents. Abbreviations for ^{1}H NMR: s=singlet, d=doublet, m=multiplet. Progress of the reactions were monitored by TLC using Merck silica gel 60 F_{254} precoated plates and visualized by flourescence quenching or by charring after treatment with the mixture of *p*-anisaldehyde-H_2SO_4 in ethanol. The products were purified by column chromatography (SiO_2). Analytical data of all known compounds were compared with the literature, and new compounds were fully characterized.

4.1.1. 6-Bromo-4-(1,5-dimethyl-hex-4-enyl)-6-methyl-cyclohex-2-enone (4b). A 1 L round bottomed flask equipped with a magnetic stir bar and a condenser was charged with diisopropylamine (18.01 g, 178 mmol) and dry THF (250 mL) under N_2, and cooled to −78 °C. To this mixture, *n*-BuLi (102.5 mL of a 1.6 M solution in hexane, 164 mmol) was added dropwise and stirred for 10 min, followed by dropwise addition of the conjugated ketone (30 g, 136 mmol) in dry THF (50 mL). Reaction mixture was stirred for 1.5 h at −78 °C and then quenched with chlorotrimethylsilane (16.296 g, 150 mmol). The reaction mixture was allowed to come to 0 °C within 4 h and quenched with saturated $NaHCO_3$ solution (200 mL). The mixture was extracted with pet ether (250 mL×3) and combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated to give 38 g of crude silyl enol ether, which was confirmed by ^{1}H NMR and used directly for the next step. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.15 (s, 9H), 0.84–0.89 (m, 3H), 1.17–1.36 (m, 3H), 1.58 (s, 3H), 1.62 (s, 3H), 1.66 (s, 3H), 1.90–2.08 (m, 4H), 2.21–2.26 (m, 1H), 5.06 (t, J=6.4 Hz, 1H), 5.45–5.53 (m, 1H), 5.60–5.66 (m, 1H).

To an ice-cold solution of crude silyl enol ether (38 g) in dry THF (300 mL) was added *N*-bromosuccinimide (26.7 g, 150 mmol) portionwise and reaction mixture was stirred for 30 min at 0 °C and quenched with saturated $NaHCO_3$ solution (300 mL). The reaction mixture was then extracted with pet. ether (300 mL×2) and combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated to give 37 g of crude α-bromo enone **4b**, which was directly used for the dehydrohalogenation. IR (neat) ν_{max} (cm^{-1}): 2964, 1688, 1504, 1446, 1377, 1259.^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.84 (d, J=7.33 Hz, 1.5H), 0.87 (d, J=7.33 Hz, 1.5H), 1.16–1.40 (m, 2H), 1.56 (s, 3H), 1.63 (s, 3H), 1.71–1.78 (m, 2H), 1.81 (s, 3H), 1.89–2.05 (m, 2H), 2.14–2.27 (m, 1H), 2.60–2.74 (m, 1H), 5.02 (t, J=6.8 Hz, 1H), 5.92–5.99 (m, 1H), 6.69–6.78 (m, 1H). MS-ESI *m/z* 301 $(M+2)^+$. Anal. Calcd for $C_{15}H_{23}BrO$: C, 60.21%; H, 7.75%. Found: C, 60.47%; H, 7.49%.

4.1.2. 4-(1,5-Dimethyl-hex-4-enyl)-2-methyl-phenol (5a). To a solution of crude α-bromo enone in dry DMF (300 mL) under N_2 was added lithium carbonate (30.23 g, 409 mmol) and lithium bromide (23.69 g, 273 mmol) and the mixture was stirred at 130–135 °C for 3 h. The mixture was allowed to come to room temperature and DMF was removed under reduced pressure. The residue was diluted with water (300 mL) and extracted with CH_2Cl_2 (300 mL×3). The combined organic layer was washed with water (600 mL×2) and brine solution (600 mL×1), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue obtained was chromatographed using flash silica gel (pet. ether: EtOAc 96:4 as eluent) to provide phenol **5a** (22.2 g, 75% overall) as colorless oil. $[\alpha]_D^{25}$=−39.1 (c=0.92, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}): 3416, 2961, 1611, 1509, 1453, 1260. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.19 (d, J=6.8 Hz, 3H), 1.52 (s, 3H), 1.49–1.60 (m, 2H), 1.67 (s, 3H), 1.80–1.88 (m, 2H), 2.23 (s, 3H), 2.58 (m, 1H), 5.07 (t, J=5.9 Hz, 1H), 6.66 (d, J=7.8 Hz, 1H), 6.87–6.92 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.1 (CH_3), 17.9 (CH_3), 22.9 (CH_3), 25.9 (CH_3), 26.5 (CH_2), 38.9 (CH), 38.9 (CH_2), 115.1 (CH), 123.8 (CH), 125.0 (CH), 125.6 (C), 129.9 (CH), 131.4 (C), 140.1 (C), 151.9 (C). MS-ESI *m/z* 218 (M^+). Anal. Calcd for $C_{15}H_{22}O$: C, 82.52%; H, 10.16%. Found: C, 82.31%; H, 10.19%.

4.1.3. 4-(1,5-Dimethyl-hex-4-enyl)-1-methoxy-2-methyl-benzene (5b). To a stirred solution of phenol (**5a**) (21 g, 96 mmol) in dry acetone (200 mL) was added anhydrous K_2CO_3 (33.28 g, 241 mmol) and dimethyl sulphate (30.38 g, 241 mmol) under N_2. The mixture was refluxed for 12 h and then acetone was removed under reduced pressure followed by dilution with water. The mixture was stirred overnight and then extracted with CH_2Cl_2 (200 mL×3). The combined organic layer was washed with water, brine solution and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography using pet. ether/EtOAc 99:1 as eluent to provide the methyl ether **5b** (20.2 g, 90%) as colorless oil. $[\alpha]_D^{25}$=−44.2 (c=1.3, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}): 2957, 1609, 1505, 1463, 1376, 1251, 1135. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.20 (d, J=6.8 Hz, 3H), 1.50–1.60 (m, 2H), 1.55 (s, 3H), 1.70 (s, 3H), 1.83–1.94 (m, 2H), 2.23 (s, 3H), 2.60 (m, 1H), 3.80 (s, 3H), 5.10 (t, J=5.9 Hz, 1H), 6.74 (d, J=8.8 Hz, 1H), 6.94–6.98 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.6 (CH_3), 17.9 (CH_3), 22.9 (CH_3), 26.0 (CH_3), 26.5 (CH_2), 38.9 (CH), 38.9 (CH_2), 55.4 (CH_3), 110.0 (CH), 125.1 (CH) 125.2 (CH), 126.5 (C), 129.7 (CH), 131.3 (C), 139.5 (C), 156.2 (C). MS-ESI *m/z* 231 $(M-1)^+$. Anal. Calcd for $C_{16}H_{24}O$: C, 82.71%; H, 10.41%. Found: C, 82.58%; H, 10.80%.

4.1.4. 4-(4-Methoxy-3-methyl-phenyl)-pentanoicacid (6). A 500 mL round bottomed flask equipped with magnetic stir bar and 100 mL addition funnel was charged with olefin **5b** (16.34 g, 70.4 mmol) and acetone (200 mL). The mixture was cooled to 0 °C and catalytic amount of OsO_4 (2 mL of 1% solution in toluene) was added to it, which was stirred for 15 min followed by dropwise addition of Jones' reagent (94 mL). The reaction mixture was stirred at room temperature for 5 h before excess of Jones' reagent was quenched by isopropanol (15 mL). Acetone was removed under reduced pressure followed by dilution with water and extraction with CH_2Cl_2 (150 mL×3). The combined organic layer was washed with water and brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated. The product was purified by flash column chromatography using pet. ether/EtOAc 9:1 as eluent to give acid **6** (12.5 g, 80%) as colorless oil. $[\alpha]_D^{25}$=−19.5 (c=0.8, $CHCl_3$). IR (neat) ν_{max} (cm^{-1}): 2957, 1709, 1610, 1507, 1456, 1377, 1252, 1182. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.27 (d, J=6.9 Hz, 3H), 1.84–1.97 (m, 2H), 2.23 (s, 3H), 2.24–2.26 (m, 2H), 2.67 (m, 1H), 3.82 (s, 3H), 6.75 (d, J=8.2 Hz, 1H), 6.95–6.97 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.5 (CH_3), 22.8 (CH_3), 32.6 (CH_2), 33.4 (CH_2), 38.8 (CH), 55.5 (CH_3), 110.1 (CH), 125.3 (CH), 126.8 (C), 129.5 (CH), 137.9 (C), 156.5 (C), 180.6 (C). MS-ESI *m/z* 221 $(M-1)^+$. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24%; H, 8.16%. Found: C, 70.44%; H, 8.33%.

4.1.5. 6-(4-Methoxy-3-methyl-phenyl)-3-oxo-heptanoic-acidmethylester (7). To a solution of acid (**6**) (14 g, 63 mmol) in dry CH_2Cl_2 (150 mL) was added thionyl chloride (9 g, 75.6 mmol) and catalytic amount of DMF

(0.5 mL), under N_2. The reaction mixture was refluxed for 2 h and then CH_2Cl_2 was removed at atmospheric pressure. To remove the excess of thionyl chloride, dry benzene (25 mL) was added to the residue and distilled off under reduced pressure. The residue was as such used for the next step.

A 500 mL round-bottomed flask equipped with stir bar was charged with Meldrum's acid (9.54 g, 66.3 mmol) and dry CH_2Cl_2 (150 mL) under N_2. The mixture was cooled to −5 °C and pyridine (12.46 g, 158 mmol) was added to it. After stirring for 30 min at 0 °C, acid chloride in dry CH_2Cl_2 (20 mL) was added dropwise to it. The mixture was stirred at 0 °C for 1 h and at room temperature for an additional hour followed by dilution with CH_2Cl_2. The reaction mixture was poured to 2 N HCl solution (175 mL) containing crushed ice and aqueous layer was extracted with CH_2Cl_2 (150 mL×2). The combined organic layer was washed with 2 N HCl solution, water and finally with brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give crude acyl meldrum derivative, which was taken in dry methanol (300 mL) and refluxed for 4–5 h. Methanol was concentrated under reduced pressure and residue was chromatographed using flash silica gel (pet. ether/EtOAc 92:8 as eluent) to give β-keto ester (13.67 g, 78%) as yellow oil. $[\alpha]_D^{25} = -19.9$ ($c=1.95$, $CHCl_3$). IR (neat) ν_{max} (cm^{-1}): 2955, 1747, 1718, 1505, 1453, 1306, 1252. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.23 (d, $J=6.2$ Hz, 3H), 1.69–2.12 (m, 2H), 2.30–2.54 (m, 2H), 2.18 (s, 3H), 2.56–2.66 (m, 1H), 3.33 (s, 2H), 3.69 (s, 3H), 3.79 (s, 3H), 6.74 (d, $J=8.8$ Hz, 1H), 6.89–6.92 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.3 (CH_3), 22.7 (CH_3), 31.7 (CH_2), 38.3 (CH), 41.1 (CH_2), 48.8 (CH_2), 51.9 (CH_3), 55.0 (CH_3), 109.7 (CH), 124.9 (CH), 126.3 (C), 129.1 (CH), 137.7 (C), 158.1 (C), 167.4 (C), 202.3 (C). MS-ESI *m/z* 279 $(M+1)^+$. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04%; H, 7.97%. Found: C, 69.04%; H, 8.16%.

4.1.6. 2-(4-Methoxy-3-methyl-phenyl)-2-methyl-5-oxo-cyclopentanecarboxylic acid methylester (9). A 500 mL round-bottomed flask equipped with a magnetic stir bar was charged with ketoester (**7**) (9 g, 32.37 mmol) in dry CH_2Cl_2 (175 mL) and triethylamine (8.19 g, 80.9 mmol). The reaction mixture was cooled to −5 °C and mesyl azide (4.7 g, 38.8 mmol) in CH_2Cl_2 (25 mL) was added, dropwise. The reaction mixture was stirred overnight at room temperature, cooled to 0 °C and quenched with 5 M NaOH solution (100 mL); and extracted using CH_2Cl_2 (100 mL×2). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product, α-diazo-β-keto ester, was purified by filtering it through a short pad of silica gel using pet. ether/EtOAc 9:1 as eluent and confirmed by IR. IR (neat) ν_{max} (cm^{-1}): 2956, 2136, 1724, 1656, 1616, 1506, 1375, 1252, 1136.

The oil was transferred to a flame dried 1 L round-bottomed flask equipped with a magnetic stir bar and maintained under N_2. CH_2Cl_2 (500 mL), dried by filtering through anhydrous K_2CO_3 was added, followed by rhodium (II) acetate dimer (0.150 g, 2% by weight). The reaction mixture was stirred at room temperature until evolution of nitrogen ceased (30 min). The reaction mixture was concentrated in vacuo and product was purified by flash column chromatography using pet. ether/EtOAc 93:7 as eluent to give cyclized β-keto ester (**9**) (3.13 g, 40% yield) as colorless oil. IR (neat) ν_{max} (cm^{-1}): 2954, 1758, 1728, 1652, 1612, 1508, 1444, 1347, 1252, 1147. HRMS: M+, $C_{16}H_{20}O_4$ requires 276.1361, found 276.1363. As this product was unstable, it was used immediately for the next step.

4.1.7. 2-(4-Methoxy-3methyl-phenyl)-1,2-dimethyl-5-oxo-cyclopentanecarboxylic acid methyl ester (10). To a solution of β-keto ester **9** (1.5 g, 5.44 mmol) in dry acetone (20 mL) was added anhydrous K_2CO_3 (0.751 g, 5.44 mmol), followed by iodomethane (0.41 mL, 6.52 mmol) under N_2 at 20 °C and reaction mixture was stirred at room temperature for 24 h. Reaction mixture was, then, filtered through celite, solvent was evaporated under reduced pressure and residue was then chromatographed using flash silica gel (eluent; pet. ether/EtOAc 94:6) to give the desired product **10** (1.34 g, 85% yield) as colorless oil. $[\alpha]_D^{25} = +126.3$ ($c=0.6$, $CHCl_3$); IR (neat) ν_{max} (cm^{-1}): 2952, 1745, 1713, 1511, 1454, 1383, 1300, 1253, 1141. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.29 (s, 3H), 1.40 (s, 3H), 1.88–2.80 (m, 4H), 2.22 (s, 3H), 3.33 (s, 3H), 3.82 (s, 3H), 7.01–7.17 (m, 2H), 7.76 (d, $J=7.8$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.9 (CH_3), 16.6 (CH_3), 25.7 (CH_3), 31.5 (CH_2), 35.7 (CH_2), 49.4 (C), 51.7 (CH_3), 55.1 (CH_3), 64.7 (C), 109.5 (CH), 124.1 (CH), 126.1 (CH), 128.3 (C), 135.9 (C), 156.5 (C), 171.1 (C), 215.5 (C). MS-ESI *m/z* 291 $(M+1)^+$. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.30%; H, 7.64%. Found: C, 70.10%; H, 7.34%.

4.1.8. 2-Hydroxymethyl-3-(4-methoxy-3-methyl-phenyl)2,3-dimethyl-cyclopentandiol (11). A 50 mL two neck round-bottomed flask equipped with magnetic stir bar was charged with LAH (0.328 g, 8.6 mmol) and dry THF (10 mL) under N_2. Reaction mixture was cooled to 0 °C and ketoester **10** was added to it using dry THF (10 mL). It was stirred for additional 5 h at room temperature, cooled to 0 °C and excess of LAH was quenched by dilute HCl solution. THF was evaporated under reduced pressure and aqueous layer was extracted with CH_2Cl_2 (25 mL×3). The combined organic layer was washed with water (50 mL×2), brine solution (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography using pet ether/EtOAc 8:2 as eluent to give diol **11** (0.725 g, 80% yield) as white solid. MP 133–134 °C. $[\alpha]_D^{25} = +58.7$ ($c=1.1$, $CHCl_3$); IR ($CHCl_3$) ν_{max} (cm^{-1}): 3625, 3350, 3017, 2966, 1506, 1251. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.19 (s, 3H), 1.21 (s, 3H), 1.51–1.80 (m, 2H), 2.20 (s, 3H), 2.63–2.89 (m, 2H), 3.59 (d, $J=11.2$ Hz, 1H), 3.76 (d, $J=11.2$ Hz, 1H), 3.80 (s, 3H), 4.22 (dd, $J=6.4$, 8.8 Hz, 1H), 6.71 (d, $J=9.3$ Hz, 1H), 7.08 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.9 (CH_3), 17.4 (CH_3), 27.0 (CH_3), 30.9 (CH_2), 34.2 (CH_2), 48.9 (C), 50.2 (C), 55.4 (CH_3), 67.6 (CH_2), 82.7 (CH), 109.6 (CH), 125.0 (CH), 126.1 (C), 129.3 (CH), 137.4 (C), 156.2 (C). MS-ESI *m/z* 265 $(M+1)^+$. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69%; H, 9.15%. Found: C, 72.36%; H, 9.01%.

Diffraction analysis of racemic (**11**) *($C_{16}H_{24}O_3$, $M=264.35$).* Single crystal of compound **X** obtained from

ethyl acetate–petroleum ether mixture. X-ray intensity data were collected on a Bruker SMART APEX CCD diffractometer with graphite-monochromatized (Mo Kα= 0.71073 Å) radiation at room temperature. All the data were corrected for Lorentzian, polarization and absorption effects using Bruker's SAINT and SADABS programs. SHELX-97 (G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Gottingen, Germany, 1997) was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. Crystal data: crystal size, $0.40\times0.19\times0.12$ mm^3; temperature, 293(2) K; crystal system, triclinic; spce group $P1$; $a=7.606(5)$ Å; $b=9.793(6)$ Å; $c=10.946(7)$ Å; $\alpha=103.240(12)°$; $\beta=107.106(11)°$; $\gamma=96.723(15)°$; $V=743.5(8)$ Å^3; $Z=2$; $F(000)=288$; d calc [g cm^{-3}]$=1.181$; μ [mm^{-1}]$=0.080°$; absorption correction, multi-scan; $T_{min}=0.9688$; $T_{max}=0.9905$; reflection collected, 7089; unique reflections, 5082; observed reflections, 3305; index range, $-9\le h\le9$, $-11\le k\le11$, $-12\le l\le12$; R_1 [$I>2\sigma(I)$]$=0.0577$; WR2$=0.1323$; goodness of fit, 1.004; $\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})$=-0.155$, 0.160. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-254163. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: 144 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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4.1.9. 2,2-Dimethyl-propionicacid 5-hydroxy-2-(4-methoxy-3-methyl-phenyl)-1,2-dimethyl-cyclopentylmethyl ester (12). To a solution of diol **11** (0.59 g, 2.24 mmol) in dry CH_2Cl_2 (20 mL) was added triethylamine (0.27 g, 2.68 mmol), followed by cooling to -10 °C and addition of pivaloyl chloride (0.28 g, 2.35 mmol) in dry CH_2Cl_2 (5 mL). Reaction mixture was stirred at 0 °C for 2.5 h and diluted with water (50 mL). The aqueous layer was extracted using CH_2Cl_2 (25 mL×3), the combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography using pet. ether/EtOAc 9:1 as eluent to provide corresponding pivaloyl ester **12** (0.51 g, 65%) as colorless oil. $[\alpha]_D^{25}=+23.54$ ($c=0.9$, $CHCl_3$). IR (neat) ν_{max} (cm^{-1}): 3407, 3018, 2972, 1718, 1608, 1504, 1465, 1288, 1157. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.09 (s, 3H), 1.17 (s, 9H), 1.31 (s, 3H), 1.64–1.78 (m, 2H), 2.18 (s, 3H), 2.33–2.41 (m, 1H), 2.66–2.72 (m, 1H), 3.73 (d, $J=11.5$ Hz, 1H), 3.76 (d, $J=11.5$ Hz, 1H), 3.80 (s, 3H), 4.08 (dd, $J=4.8$, 8.7 Hz, 1H), 6.72 (d, $J=8.4$ Hz, 1H), 7.12–7.15 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.9 (CH_3), 18.5 (CH_3), 27.0 (CH_3), 27.5 (CH_3), 31.7 (CH_2), 35.0 (CH_2), 39.1 (C), 49.3 (C), 51.2 (C), 55.4 (CH_3), 68.0 (CH_2), 81.6 (CH), 109.6 (CH), 125.3 (CH), 126.1 (C), 129.7 (CH), 137.6 (C), 156.3 (C), 178.6 (C). MS-ESI m/z 349 $(M+1)^+$. Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38%; H, 9.26%. Found: C, 72.74%; H, 8.96%.

4.1.10. 2,2-Dimethyl-propionic acid 2-(4-methoxy-3-methyl-phenyl)-1,2-dimethyl-5-methylsulfanylthiocaboxyoxy-cyclopentylmethyl ester (13). A 50 mL two-necked round-bottomed flask equipped with a magnetic stir bar was charged with NaH (60%) (0.12 g, 3 mmol) and dry THF (7 mL). Alcohol (**11**) (0.7 g, 2 mmol) in dry THF (7 mL) was added to it at 0° under N_2 and reaction mixture was stirred for 30 min. Then, carbon disulphide (0.23 g, 3 mmol) was added to it at 0 °C and stirred for 2 h at room temperature followed by addition of iodomethane (0.85 g, 6 mmol) at 0 °C. The reaction mixture was stirred for additional 5 h at room temperature. After completion of reaction, mixture was diluted with ice water and extracted with ethyl acetate (20 mL×3). The combined organic layer was washed with water and brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography using pet. ether/EtOAc 98:2 as eluent to give xanthate derivative (0.83 g, 94%) as colorless oil. $[\alpha]_D^{25}=+11.4$ ($c=1.6$, $CHCl_3$). IR (neat) ν_{max} (cm^{-1}): 2971, 1725, 1608, 1508, 1479, 1397, 1252, 1151. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.16 (s, 3H), 1.16 (s, 9H), 1.39 (s, 3H), 1.76–1.82 (m, 1H), 1.90–1.96 (m, 1H), 2.19 (s, 3H), 2.30 (s, 3H), 2.55–2.63 (m, 1H), 2.76–2.82 (m, 1H), 3.59 (d, $J=11.1$ Hz, 1H), 3.80 (s, 3H), 3.86 (d, $J=11.1$ Hz, 1H), 5.75 (dd, $J=4.8$, 8.8 Hz, 1H), 6.72 (d, $J=8.3$ Hz, 1H), 7.08–7.11 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 16.9 (CH_3), 18.7 (CH_3), 19.0 (CH_3), 26.7 (CH_3), 27.6 (CH_3), 29.6 (CH_2), 36.4 (CH_2), 49.9 (C), 51.3 (C), 55.5 (CH_3), 66.8 (CH_2), 92.2 (CH), 109.6 (CH), 116.4 (C), 125.7 (CH), 126.0 (C), 129.9 (CH), 136.7 (C), 156.5 (C), 178.2 (C), 215.1 (C). MS-ESI m/z 440 $(M+2)^+$. Anal. Calcd for $C_{23}H_{34}O_4S_2$. C, 62.97%; H, 7.81%. Found: C, 63.32%; H, 7.53.

4.1.11. 2,2-Dimethyl-propionic acid 2-(4-methoxy-3-methyl-phenyl)-1,2-dimethyl-cyclopentylmethyl ester (14). To a stirred solution of xanthate (**13**) (0.53 g, 1.21 mmol) in dry toluene (20 mL) was added tributyltinhydride (0.39 g, 1.33 mmol) and AIBN (0.020 g, catalytic) under N_2. The mixture was stirred at reflux temperature for 2 h, the solvent was removed under reduced pressure and residue was chromatographed using flash silica gel (pet. ether/EtOAc 98:2 as eluent) to give required product (0.32 g, 80% yield) as colorless oil. $[\alpha]_D^{25}=+16.7$ ($c=1.05$, $CHCl_3$). IR (neat) ν_{max} (cm^{-1}): 2966, 1728, 1608, 1508, 1464, 1382, 1252, 1156. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.11 (s, 3H), 1.17 (s, 9H), 1.34 (s, 3H), 1.48–1.84 (m, 6H), 2.19 (s, 3H), 3.29 (d, $J=11.1$ Hz, 1H), 3.63 (d, $J=11.1$ Hz, 1H), 3.79 (s, 3H), 6.72 (d, $J=9.5$ Hz, 1H), 7.10–7.14 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.9 (CH_3), 19.9 (CH_3), 20.7 (CH_2), 25.5 (CH_3), 27.6 (CH_3), 35.2 (CH_2), 38.3 (CH_2), 39.1 (C), 48.1 (C), 49.9 (C), 55.5 (CH_3), 70.9 (CH_2), 109.6 (CH), 125.3 (CH), 125.9 (C), 129.7 (CH), 137.9 (C), 156.3 (C), 178.5 (C). MS-ESI m/z 231 $(M-OPiv.)^+$. Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86%; H, 9.7%. Found; C, 75.46%; H, 9.76%.

4.1.12. [2-(4-Methoxy-3methyl-phenyl)-1,2-dimethyl-cyclopentyl]-methanol (15). To a stirred solution of ester **14** (0.3 g, 0.9 mmol) in dry THF (10 mL) was added LAH (0.69 g, 1.8 mmol) portionwise at room temperature and reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, excess of LAH was quenched with dilute HCl solution, THF was evaporated

under reduced pressure and aqueous layer was extracted using CH_2Cl_2 (30 mL×3). The combined organic layer was washed with water and brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography using pet. ether/EtOAc 9:1 as eluent to give alcohol **15** (0.22 g, quantitative yield) as colorless oil. $[\alpha]_D^{25}=42.1$ ($c=0.75$, $CHCl_3$). IR (neat) ν_{max} (cm^{-1}): 3378, 2954, 1608, 1506, 1464, 1376, 1296, 1172. ^1H NMR ($CDCl_3$, 200 MHz) δ 1.14 (s, 3H), 1.30 (s, 3H), 1.48–1.87 (m, 6H), 2.22 (s, 3H), 3.06 (d, $J=11.1$ Hz, 1H), 3.15 (d, $J=11.1$ Hz, 1H), 3.82 (s, 3H), 6.76 (d, $J=8.4$ Hz, 1H), 7.07–7.17 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.9 (CH_3), 19.7 (CH_3), 20.5 (CH_2), 25.5 (CH_3), 35.2 (CH_2), 37.7 (CH_2), 49.3 (C), 49.4 (C), 55.4 (CH_3), 69.6 (CH_2), 109.6 (CH), 125.1 (CH), 126.1 (C), 129.4 (CH), 138.1 (C), 156.2 (C). MS-ESI *m/z* 230 $(M-H_2O)^+$. Anal. Calcd for $C_{16}H_{24}O_2$. C, 77.38%; H, 9.74%. Found: C, 77.19%; H, 9.58%.

4.1.13. 1-Methoxy-2-methyl-4-(1,2,2-trimethyl-cyclopentyl)-benzene (16). To a stirred solution of alcohol (**15**) (0.1 g, 0.4 mmol) in dry CH_2Cl_2 (10 mL) was added pyridinium dichromate (0.228 g, 0.6 mmol) portionwise at 0 C within 5 min and allowed to stir at room temperature for 3 h. Reaction mixture was then diluted with diethyl ether (25 mL) and filtered through a short pad of celite, which was washed with diethyl ether (25 mL×2). Organic layer was then washed with water and brine solution, dried over sodium sulphate and concentrated. The residue (0.11 g) was directly used for the next step, as aldehyde is unstable. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.25 (s, 1.5H), 1.31 (s, 1.5H), 1.34 (s, 1.5H), 1.40 (s, 1.5H), 1.56–1.63 (m, 2H), 1.77–1.94 (m, 2H), 2.11–2.41 (m, 2H), 2.21 (s, 3H), 3.81 (s, 3H), 6.76 (d, 1H, $J=7.86$ Hz), 7.09–7.12 (m, 2H), 9.04 (s, 1H).

To a stirred solution of crude aldehyde in diethylene glycol (4 mL) was added hydrazine monohydrate (0.024 g, 0.48 mmol) and sodium hydroxide (0.355 g, 8.875 mmol) at room temperature and mixture was stirred at 150 °C for 4 h and at 190 °C for additional 3 h. The reaction mixture was diluted with water (25 mL) and extracted using diethyl ether (15 mL×2). The combined organic layer was then washed with water and brine solution, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography (pet. ether/EtOAc, 99:1 as eluent) to give (**12**) (0.068 g, 73% for 2 steps) as colorless liquid. $[\alpha]_D^{25}=+56$ ($c=1.25$, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz) δ 0.59 (s, 3H), 1.08 (s, 3H), 1.27 (s, 3H), 1.53–1.86 (m, 5H), 2.25 (s, 3H), 2.43–2.60 (m, 1H), 3.84 (s, 3H), 6.76 (d, $J=7.9$ Hz, 1H), 7.14–7.18 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.8 (CH_3), 19.9 (CH_2), 24.5 (CH_3), 24.9 (CH_3), 26.7, (CH_3), 37.1 (CH_2), 39.9 (CH_2), 44.4 (C), 50.1 (C), 55.3 (CH_3), 109.1 (CH), 125.3 (CH), 129.8 (CH), 139.4 (C), 155.7 (C).

4.1.14. (+)-β-Herbertenol (17). BBr_3 (1 M solution in CH_2Cl_2, 0.251 g, ~1 mL, 1 mmol) was added dropwise to methyl ether **12** (0.045 g, 0.19 mmol) in dry CH_2Cl_2 (5 mL) at −78 °C. The reaction mixture was brought to room temperature and stirred for 30 min. The reaction was monitored by TLC. After completion, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and excess BBr_3 was quenched with saturated $NaHCO_3$ (1 mL). The organic layer was washed with water, brine, dried over anhydrous sodium sulphate, filtered and concentrated at reduced pressure to furnish crude (+)-β-herbertenol. It was purified by flash column chromatography (pet. ether/EtOAc 95:5 as eluent) to give pure (+)-β-herbertenol. (0.039 g, 93%). MP 79–80 °C. $[\alpha]_D^{25}=+61.2$ ($c=0.7$, $CHCl_3$). IR ($CHCl_3$) ν_{max} (cm^{-1}) 3450 (broad), 3020, 2960, 1610, 1215, 1106. ^1H NMR ($CDCl_3$, 200 MHz) δ 0.58 (s, 3H), 1.06 (s, 3H), 1.25 (s, 3H), 1.48–1.52 (m, 1H), 1.56–1.73 (m, 2H), 1.73–1.84 (m, 2H), 2.27 (s, 3H), 2.39–2.53 (m, 1H), 4.75 (bs, 1H), 6.72 (d, $J=7.9$ Hz 1H), 7.05–7.11 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.3 (CH_3), 20.0 (CH_2), 24.6 (CH_3), 24.8 (CH_3), 26.8 (CH_3), 37.3 (CH_2), 40.1 (CH_2) 44.5 (C), 50.3 (C), 114.3 (CH), 122.6 (C), 125.9 (CH), 129.9 (CH), 140.2 (C), 151.8 (C). Mass *m/z* 218 (M^+). HRMS: M^+, found 218.1669. $C_{15}H_{22}O$ requires 218.1671. [For (−)-β-herbertenol; MP 80–81 °C and $[\alpha]_D^{25}=-47$ (*c* 0.7, $CHCl_3$)].

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