Tetrahedron

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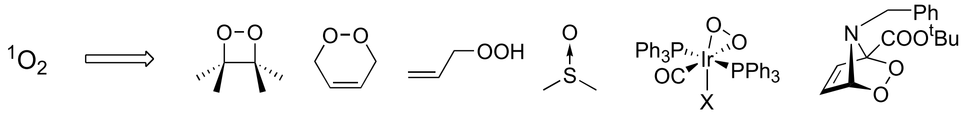
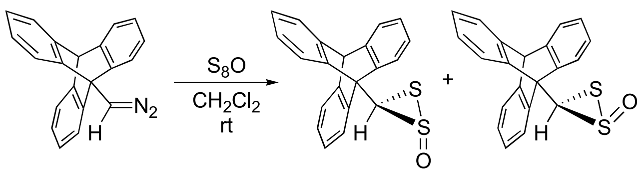
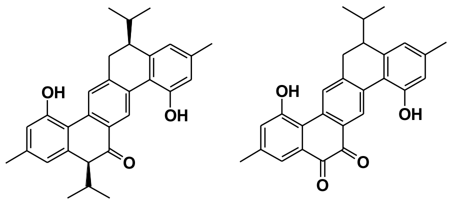
Contents

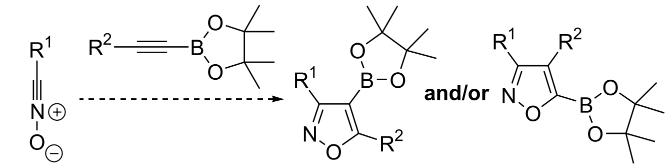
REPORT

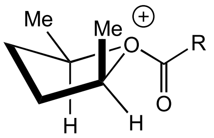


ARTICLES

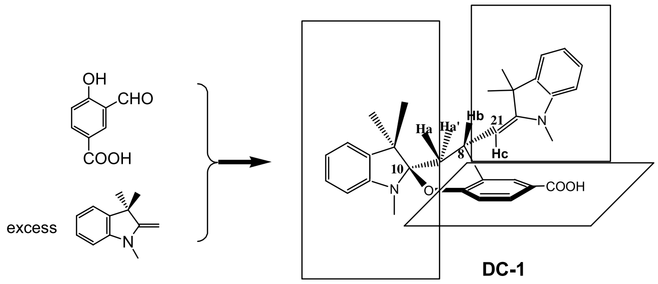


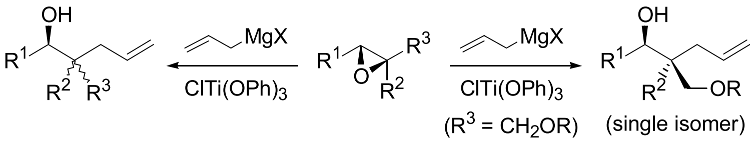


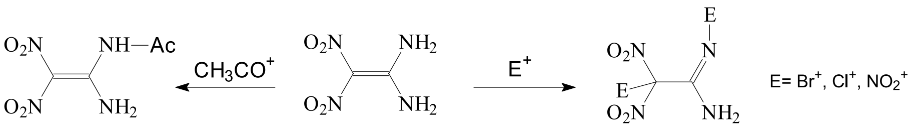


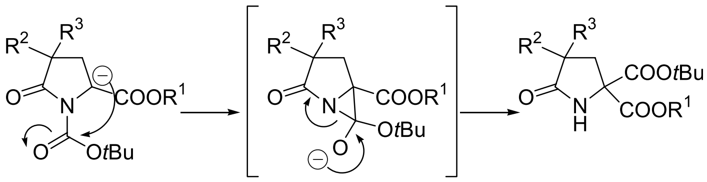


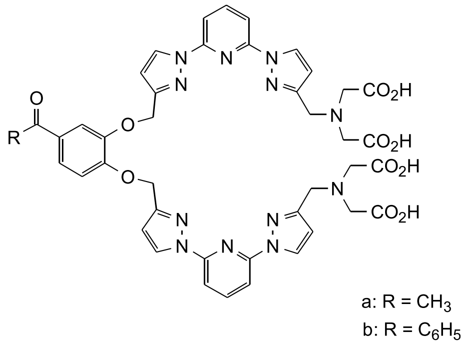
Cleavage of the proposed acyloxy cation with chloride anion is consistent with a concerted (A_ND_N) process when R = Me, and a stepwise (D_N+A_N) process when R = *t*-Bu.

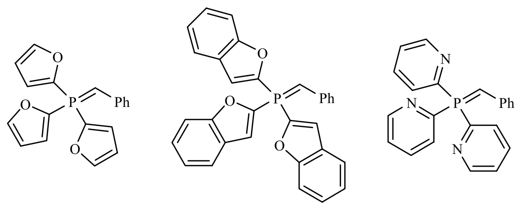


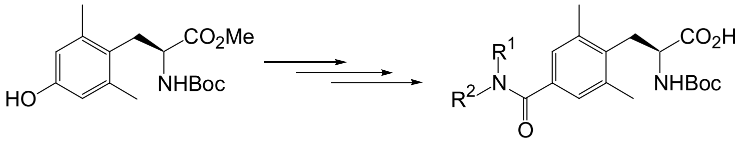


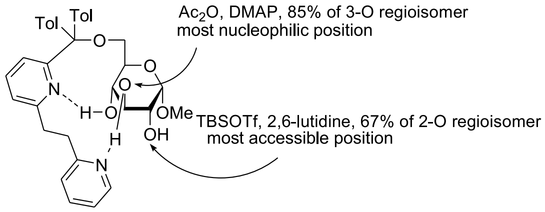

O_2N
NH—Ac
O_2N
NH_2
CH_3CO^+
O_2N
NH_2
O_2N
NH_2
E^+
E
N
O_2N
E
O_2N
NH_2
E= Br^+, Cl^+, NO_2^+

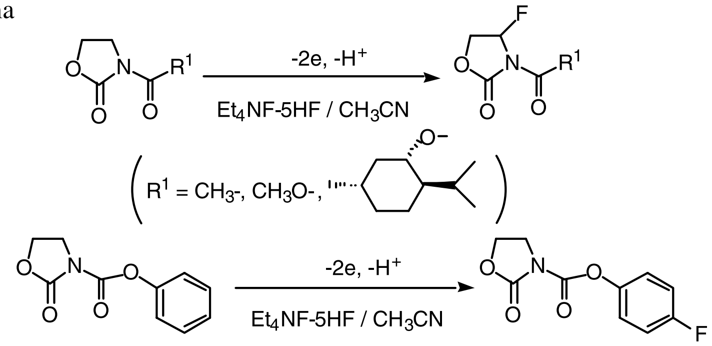

R^2
R^3
O
N
$COOR^1$
O
O*t*Bu
R^2
R^3
O
N
$COOR^1$
O*t*Bu
O
R^2
R^3
COO*t*Bu
O
N
H
$COOR^1$

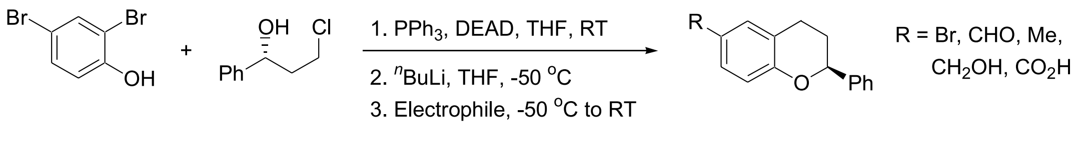

O
R
O
O
N
N
N
N
N
N
N
N
N
N
CO_2H
CO_2H
CO_2H
CO_2H
a: R = CH_3
b: R = C_6H_5

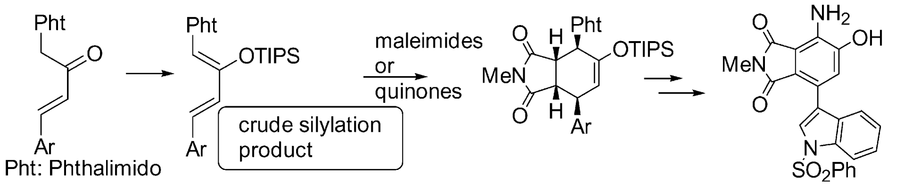

O
O
P
Ph
O
O
P
Ph
O
O
N
N
P
Ph
N

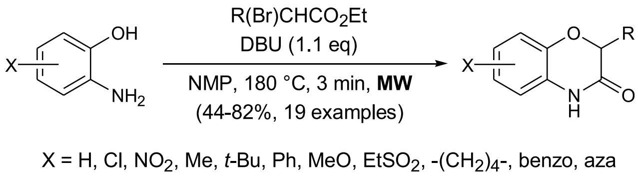


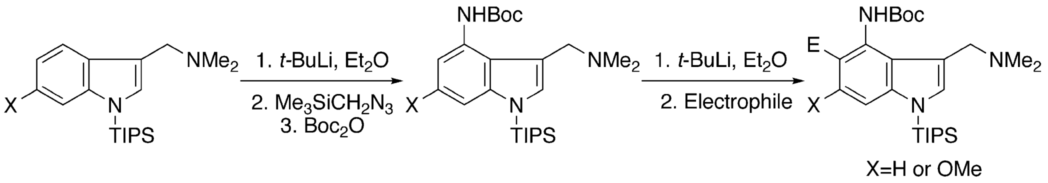

Ac2O, DMAP, 85% of 3-O regioisomer
most nucleophilic position
TBSOTf, 2,6-lutidine, 67% of 2-O regioisomer
most accessible position


-2e, -H+
Et4NF-5HF / CH3CN
R1 = CH3-, CH3O-,

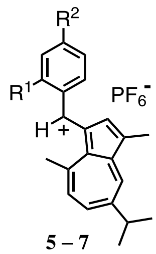

1. PPh3, DEAD, THF, RT
2. nBuLi, THF, -50 °C
3. Electrophile, -50 °C to RT
R = Br, CHO, Me,
CH2OH, CO2H



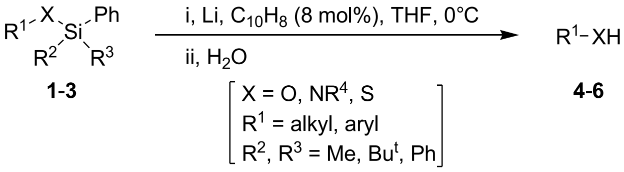




Reactions of guaiazulene (**1**) with methyl terephthalaldehydate (**2**) and 2-hydroxy- and 4-hydroxybenzaldehydes (**3** and **4**) in methanol in the presence of hexafluorophosphoric acid at 25 °C for 2 h under aerobic conditions give the corresponding monocarbocation compounds **5**–**7** in 94, 89 and 97% yields, respectively. The title studies are reported.



5 – 7



OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

The [3+2] cycloaddition reaction of alkynylboronates and nitrile oxides provides a rapid and regioselective method for the synthesis of isoxazole boronic esters. This technique allows access to a wide range of substitution patterns with selective incorporation of the boronate unit at C-4 or C-5. *Tetrahedron* **2005**, *61*, 6707–6714. Cover figure designed by Olivier Provoost.
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Advances in singlet oxygen chemistry

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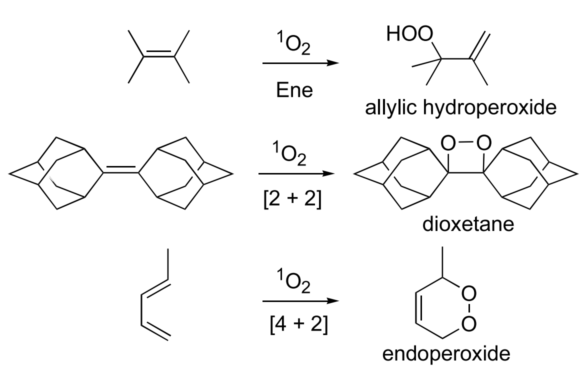
1. Introduction

Oxygen is ubiquitous. It comprises nearly 50% of the Earth's crust and is an essential component in metabolic pathways in all higher organisms.[1] It was first identified by Carl Wilhelm Scheele and by Joseph Priestly in the late 18th century. Its unpaired electronic structure and the possibility of a spin-paired electronic state was first predicted by Lewis in 1924. These seminal contributions, along with the Mulliken molecular orbital prediction of two low-lying oxygen excited states ($^1\Delta_g$ and $^1\Sigma_g^+$), and the demonstration by Katusky[2–4] of a metastable intermediate species in photooxygenation reactions in the 1930s, laid the foundation for the following 50 years of singlet oxygen research. These years, between 1940 and 1990, were characterized by delineation of the physical[5] and chemical[6] pathways of singlet oxygen formation and deactivation. The physical studies, with the aid of technological advances that have taken advantage of the luminescence of both the $^1\Delta_g$ and $^1\Sigma_g^+$ states, have demonstrated that only $^1\Delta_g$ (approximately 22.5 kcal/mol above the ground state triplet) has a sufficient lifetime to allow it to play a role in chemical reactions in solution. The chemical studies have identified the fundamental [2+2], [4+2], ene, and heteroatom oxidation reactions of $^1\Delta_g$ (referred to as singlet oxygen or $^1O_2$ throughout this review) and have established their basic mechanistic details. In a review published in 2000 we outlined the efforts initiated in the 1990s to influence the regio- and stereoselectivity of singlet oxygen reactions.[6] In this review we discuss the advances made in both mechanistic and synthetic aspects of the fundamental reactions discussed in our previous review.[6] In addition, we have also expanded the discussion to include new developments in heteroatom and heterocyclic photooxygenations. We have made no attempt to be exhaustive in our treatment of the singlet oxygen literature. In particular, advances in the photophysical and biological aspects of singlet oxygen chemistry, although briefly mentioned, are not discussed in detail. Recent excellent reviews should be consulted for more information on these aspects of singlet oxygen chemistry.[5,7,8]

2. Fundamental reaction types

2.1. Ene, [2+2] and [4+2] cycloadditions

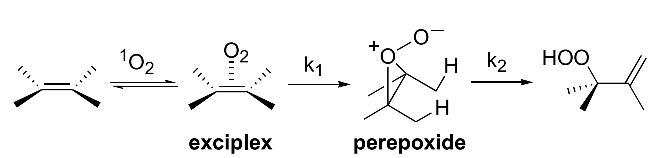
The ene, [2+2], and [4+2] reactions (Scheme 1) represent powerful protocols for the addition of molecular oxygen to organic substrates. The ene reaction generates allylic hydroperoxides which can be converted to synthetically valuable allylic alcohols (Scheme 1).[9] The [2+2] cycloaddition is observed with electron rich alkenes, and with alkenes devoid of, or those containing only geometrically inaccessible, allylic hydrogens.[10] The dioxetane products (Scheme 1) are often sensitive molecules that thermally decompose in a fascinating chemiluminescent process to carbonyl compounds.[10] The [4+2] cycloaddition leads to formation of endoperoxides (Scheme 1).[11] These endoperoxides are versatile intermediates that can be transformed via a variety of synthetic procedures to specifically oxygenated products.[12,13] Despite the inherent geometric control present in each of these fundamental reactions, the control of reaction regio- and stereochemistry remains a challenge as a result of the small size of the singlet oxygen molecule.



Scheme 1.

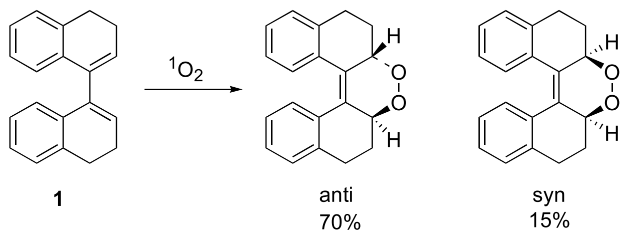
2.1.1. Historical perspective. The ene,[14] and [4+2] cycloaddition[15] reactions have been recognized for more than 50 years while the [2+2] cycloaddition[16] leading to isolable dioxetanes is a more recent addition to the arsenal of synthetic procedures. The mechanistic foundations that allow rational synthetic use of these reactions are well established.

The generally accepted mechanism[6,17,18] for the singlet oxygen ene reaction is depicted in Scheme 2. The stereochemical and regiochemical outcome of a singlet oxygen ene reaction can often be determined by evaluation of the conformational, steric, electronic, and hydrogen bonding interactions in the perepoxide traversed on the potential energy surface. The key features of the reaction include: (1) singlet oxygen functions as the electrophilic and the alkene as the nucleophilic component of the reaction, (2) it is a suprafacial process involving addition of oxygen and removal of hydrogen from the same face of the alkene, (3) only those hydrogens properly aligned to maximize overlap in the developing alkene linkage are subject to abstraction, (4) hydrogen abstraction occurs preferentially on the more crowded side of the alkene; a phenomenon known as the *cis* effect, (5) Markovnikov directing effects play little or no role in determining the end of the alkene from which hydrogen abstraction occurs, and (6) hydrogen bonding, electronic, and steric interactions with the trailing pendant oxygen in the perepoxide can be used to dictate the diastereoselectivity (facial and side selectivity) of perepoxide and subsequent product formation.



Scheme 2.

The majority of singlet oxygen [4+2] cycloadditions are considered to be concerted Diels–Alder like processes.[11,19] This assertion is supported by the suprafacial stereochemistry of the reaction[20,21] and by substituent effects.[22] Nevertheless, several non-stereospecific singlet oxygen [4+2] cycloadditions[23–25] as well as competitive formations of ene and [2+2] cycloaddition products[26–28] have been reported. These processes appear to be most important in 1,3-dienes which cannot readily attain the s-*cis* conformation. For example, force field calculations[29] indicate that 3,3′,4,4′-tetrahydro-1,1′-binaphthalene, **1**, prefers to exist overwhelmingly in a perpendicular (dihedral angle ∼89°) conformation and it reacts with singlet oxygen to give both the *anti*- and *syn*-cycloadducts (Scheme 3).[25] The [2+2] cycloadditions are also promoted in 1,3-dienes bearing electron rich substituents such as alkoxy groups.[30–34]



Scheme 3.

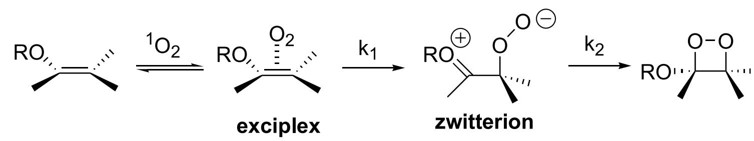
A myriad of experimental studies have suggested that singlet oxygen [2+2] cycloadditions occur via the mechanism depicted in Scheme 4.[35] For example, (1) both stereospecific[16] and non-stereospecific[34] dioxetane formations have been observed, (2) when ene and [2+2] adduct formation compete increasing solvent polarity favors dioxetane formation,[36] and (3) methanol trapping products are formed under conditions where the dioxetane product is stable arguing for interception of either an exciplex or zwitterion precursor.[36]

2.1.2. Recent advances. Advances in both mechanistic understanding and synthetic applications of the fundamental reactions have been made in the past 5 years. On the mechanistic front, high-level computational results[37–39] suggest that the perepoxide in the singlet oxygen ene reaction is a transition state rather than an intermediate as implicated by experimental evidence such as the Stephenson isotope effect test.[40–42] Recently, Singleton and co-workers[43,44] have provided both experimental and computational results which attempt to reconcile the conflicting evidence for a perepoxide intermediate. They have suggested that the singlet oxygen ene reaction proceeds via two transition states without an intervening intermediate. This topographical arrangement is made possible because these two maxima on the reaction pathway are saddle points on a three-dimensional energy surface. The first transition state does not involve hydrogen abstraction by the trailing oxygen but leads to the second perepoxide-like transition state. This second transition state lies near a valley-ridge inflection where a bifurcation to the isomeric allylic hydroperoxides occurs. Consequently, dynamic effects (i.e., the momentum of atoms) dictate the product ratio. However, it has recently been argued that non-statistical dynamic behavior does not occur near the valley-ridge inflection and that variational transition state theory can be used to calculate partitioning ratios.[45] Consequently, generation of massive numbers of dynamical trajectories can be circumvented in order to obtain statistically interpretable results. Regardless of whether statistical or non-statistical behavior is observed, it is clear that the two transition states are spatially isolated on the potential energy surface to a sufficient degree that it is possible to selectively influence one but not the other. As a result, minor perturbations, such as isotopic substitution in the Stephenson isotope effect experiment makes it appear that this concerted process proceeds via two kinetically distinguishable steps.

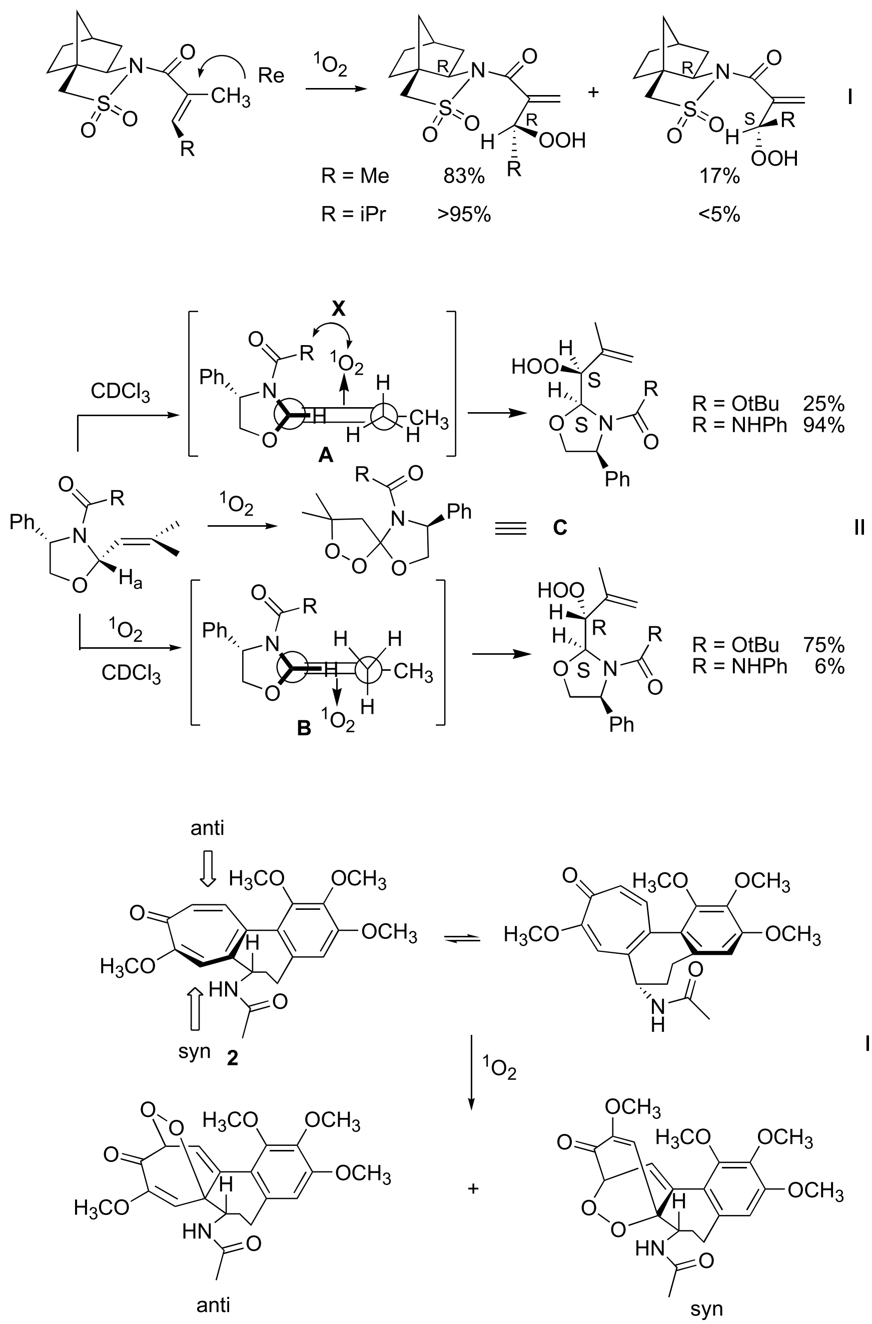
Ongoing synthetic efforts have focused on improving the π-facial diastereoselectivity of singlet oxygen addition to olefinic linkages; several examples are given in Scheme 5. In example I, high diastereoselectivity from the *Re* face was observed.[46] This stereochemical outcome was attributed to the steric and electronic features of the sultam functional group. The carbonyl group is electrostatically repelled by the sultam sulfonyl group dictating a geometry in which it points away from the sultam SO_2 group. This electronic effect coupled with steric shielding of the *Si* face in the preferred rotamer is responsible for diastereoselectivity in excess of 80% even when R=Me. In general, however, chiral auxiliary approaches relying exclusively on steric effects fail as a result of the small size of singlet oxygen. On the other hand, chiral auxiliaries that rely on hydrogen bonding as a directing element are spectacularly successful. For example, steric repulsion between singlet oxygen and the R=O*t*Bu group in complex **A** (interaction **X** example II; Scheme 5) leads to a modest diastereoselectivity of 75:25 for the *RS*-ene product.[47] When R=NHPh, however, hydrogen bonding to the trailing oxygen in the perepoxide-like complex **A** completely reverses the diastereoselectivity to 6:94 for the *SS*-ene product and dramatically suppresses the formation of regioisomer **C**. The efficacy of the chiral auxiliary was reduced in acetone consistent with its hydrogen bonding origin.

Example III illustrates preferential π-facial formation of a helimeric mixture of (M)-**2**/(P)-**2**-(−)-isocolchicine endoperoxide with a diastereoselectivity of 1:7 from the *anti* direction.[48] In this case, electrostatic repulsion between the amide functionality and the incoming singlet oxygen appears to protect the *syn* face.

Turro, Adam, and co-workers[49] have recently introduced the use of enecarbamates as chiral auxiliaries. The isopropyl substituent in enecarbamate **3Z** (Scheme 6) effectively shields the bottom face of the alkene and directs singlet oxygen to the top face to exclusively form the



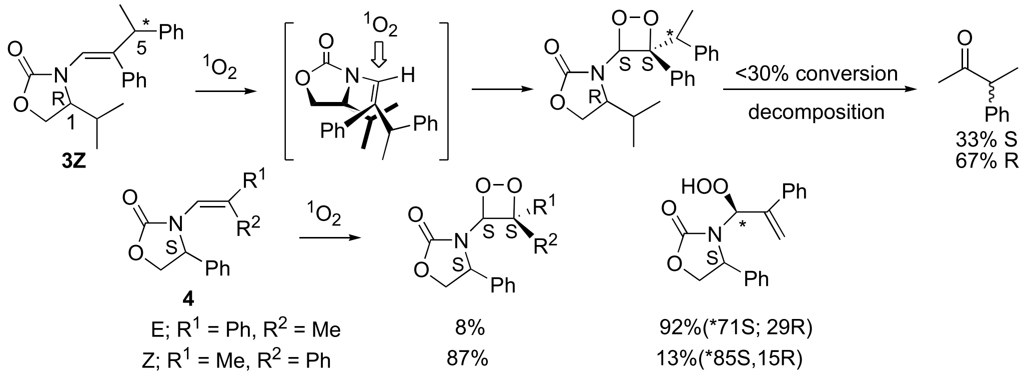
Scheme 4.



Scheme 5.

S,*S*-dioxetane.[50] The chirality at the phenethyl group (C-5) does not influence the π-facial selectivity but does influence the rate of reaction.[51] The 1*R*,5*R* substrate reacts more rapidly than the 1*R*,5*S* diastereomer to give 33% enantiomeric excess (ee) of the (*R*)-methyldesoxybenzoin (MDB) dioxetane decomposition product at less than 30% conversion. The enhanced reactivity of the 1*R*,5*R* in comparison to the 1*R*,5*S* substrate was attributed to the preferred population of the conformation which places the smaller methyl group in the 1*R*,5*R*, but the larger phenyl group in the 1*R*,5*S*, on the same face as the approaching singlet oxygen. The *E* isomer of **3** shows a remarkable temperature effect on the enantioselectivity of MDB formation.[52] In CD_3CN **3E** gives (*S*)-MDB in 64% ee at 50 °C and (*R*)-MDB in 58% ee at −40 °C. It was suggested that this temperature switching of stereoselectivity is evidence for a reversibly formed exciplex preceding collapse to the dioxetane. Despite the attractive features of this chiral auxiliary its usefulness is diminished by the fact that it effectively physically quenches singlet oxygen and as a result enecarbamate **3Z** produces product with a quantum yield of less than 0.1.[53]

The ene carbamate group can also be used to switch reaction selectivity from the [2+2] to the ene reaction as illustrated by enecarbamate substrate, **4** (Scheme 6). In the *E* isomer, the enecarbamate auxiliary and the methyl group are on the same side of the double bond and overwhelming ene reactivity is observed. On the other hand, in the *Z* isomer in which the phenyl group is on the same side of the double



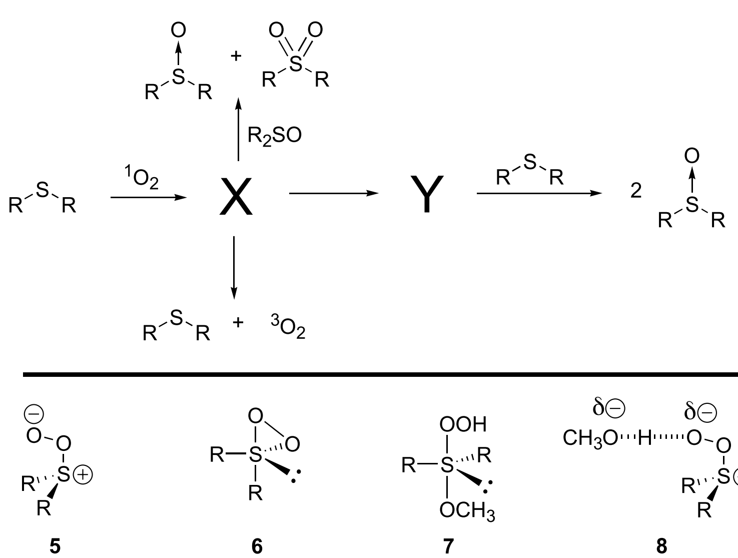
Scheme 6.

bond as the enecarbamate group [2+2] reactivity dominates. Orbital interaction between the HOMO of the enecarbamate and the LUMO of singlet oxygen directs reaction to the side of the alkene bearing the nitrogen atom. In the *Z* alkene, that has no allylic hydrogen *cis* to the enecarbamate group, only [2+2] cycloaddition can occur.[54,55] The ene product exhibits a preference for formation of the (*S*)-allylic hydroperoxide (71% in the *E* isomer and 85% in the *Z* isomer) consistent with the previously illustrated facial shielding.

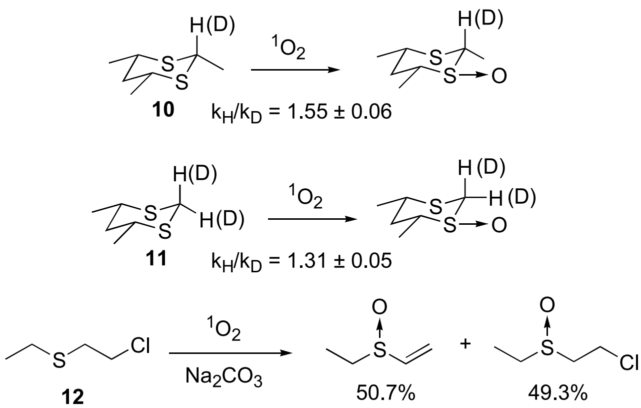
2.2. Heteroatom oxidations

Singlet oxygen by virtue of its potent electrophilic character reacts readily at electron pair bearing heteroatom centers. Consequently, singlet oxygen is known to interact with sulfur, selenium, phosphorus, and nitrogen compounds, and with some iridium and rhodium transition metal complexes. The interaction is often dominated by physical quenching, k_q, but can be accompanied by chemical quenching, k_r, leading to formation of covalent adducts involving transfer of one or two oxygen atoms to the heteroatom center.

2.2.1. Historical perspectives. Sulfide photooxidation, reported by Schenck[56] in the early 1960s, represents one of the earliest and most thoroughly studied examples of heteroatom oxidation. The key mechanistic features of this reaction were delineated by Foote and co-workers in the 1970s and early 1980s and are depicted in Scheme 7. The unique feature of the mechanism is the presence of two intermediates X and Y. Decomposition of the first intermediate, X, to sulfide and triplet oxygen is responsible for the inefficiency of the reaction (typically the quantum yield for sulfoxide formation $\Phi < 0.05$). The sulfide substrate reacts with the second intermediate, Y, to give the sulfoxide product. On the other hand, the sulfoxide product, as well as exogenous reagents such as phosphites[57–59] and selenoxides,[60] trap the first intermediate to generate phosphates, selenones, and sulfones, respectively. This observation along with studies designed to probe the electronic character of the reaction suggests that the first intermediate is a nucleophilic and the second intermediate an electrophilic oxygen donor. Consequently, the prevailing opinion was that X was best represented as a persulfoxide, **5**, and Y as a thiadioxirane, **6**. In polar protic solvents such as methanol only a single intermediate is kinetically required and speculation has resulted in its assignment as a hydrogen bonded persulfoxide, **7**, or as a hydroperoxy sulfurane, **8**. Compelling experimental evidence for this mechanistic suggestion has been difficult to generate since all attempts to spectroscopically identify intermediates in either protic or aprotic solvents have failed.



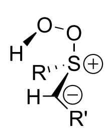
Scheme 7.



Scheme 8.

2.2.2. Recent advances.

2.2.2.1. Organosulfur compounds. Recent studies of sulfide photooxidations have focused on the question of the structural identities of the reactive intermediates. In 1992, Jensen published an extensive ab initio study of the reactions of singlet oxygen with organic sulfides.[61,62] He pointed out that the computed barrier separating the persulfoxide, **5**, and thiadioxirane, **6**, intermediates was nearly 20 kcal/mol and incompatible with the experimentally observed rapid interconversion of **X** and **Y** (Scheme 7). In 1998, Jensen and co-workers[63] suggested a revised mechanism of sulfide photooxidation that invoked hydroperoxy sulfonium ylide, **9**, rather than thiadioxirane, **6**, as intermediate **Y**. The computed barrier separating **5** and **9** is a more palatable 6 kcal/mol given the experimental ease of interconversion.

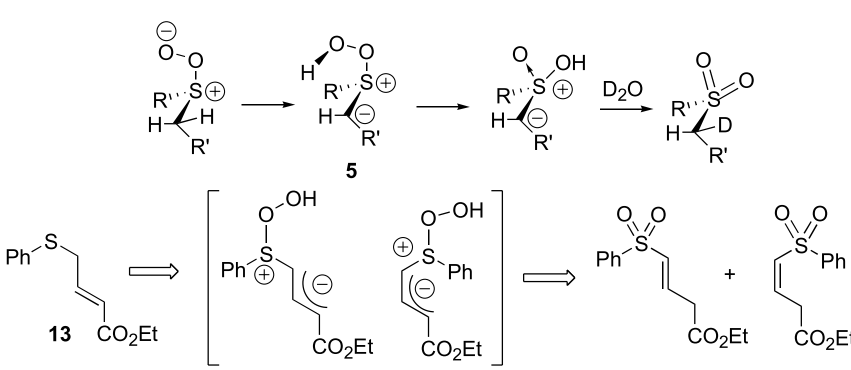


9

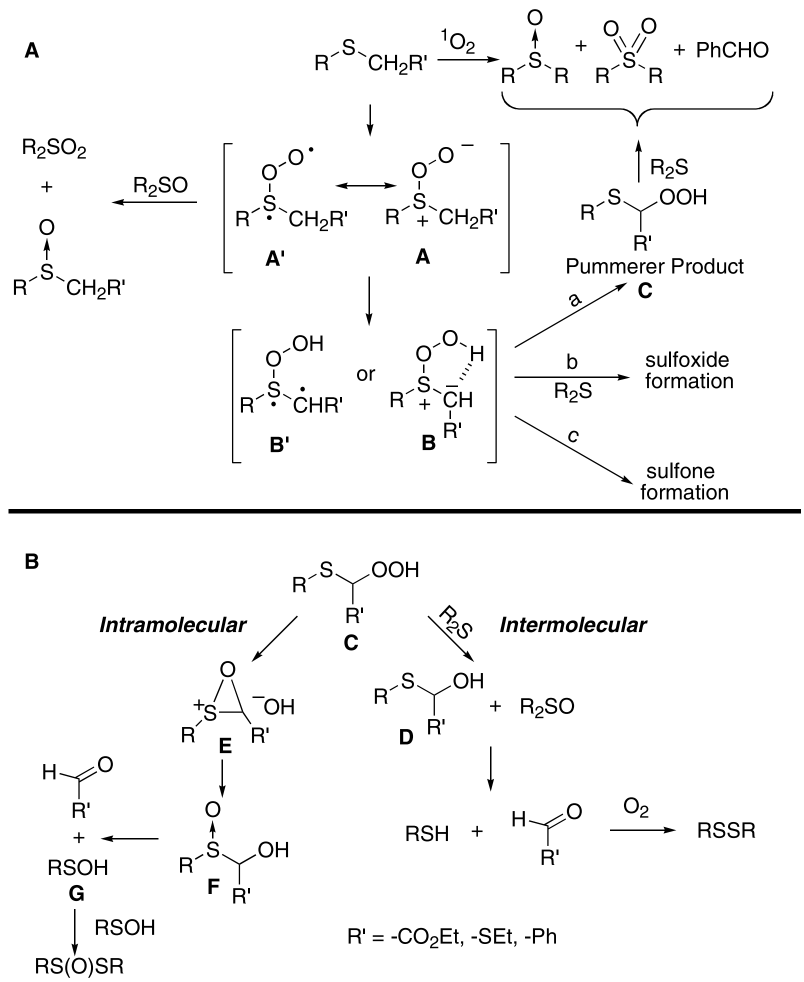
Compelling experimental evidence supporting the ab initio assignment of **9** as intermediate **Y** has been reported. In particular, reactions of singlet oxygen with 1,3-dithianes, **10** and **11**, and their 2-deuterated isotopomers, which react exclusively to give a single sulfoxide product, exhibited substantial isotope effects indicative of α-proton abstraction.[64] In addition, the formation of ethyl vinyl sulfide during photooxidation of 2-chloroethyl ethyl sulfide, **12**, can most easily be rationalized by invoking a β-elimination from a hydroperoxy sulfonium ylide intermediate (Scheme 8).[65] Finally, the extremely reluctant oxidations of sulfides devoid of α-hydrogens can also be explained within the framework of this mechanistic suggestion.[66] Parenthetically, the singlet oxygen inaccessible thiadioxirane has recently been implicated as an intermediate in electron transfer initiated molecular oxygenations of sulfides.[67]

Hydroperoxy sulfonium ylides have previously been implicated in sulfone formation, as shown in Scheme 9,[68] and as key intermediates in sulfur carbon bond cleavages[69] during photooxygenations of benzylic and five-membered ring sulfides.[70,71] Evidence for the intermediacy of the hydroperoxy sulfonium ylide included the observations that the two oxygen atoms in the sulfone product were derived from the same oxygen molecule and that isotopic exchange at the α-position accompanied sulfone formation. A subsequent report[72] that singlet oxygen induced double migration during reaction of singlet oxygen with a homoallylic sulfide, **13** (Scheme 9) also provides experimental verification of the intermediacy of **9** during sulfone formation. Alternatively, sulfone formation can occur by adventitious trapping of the persulfoxide, **X** in Scheme 7, by the sulfoxide product. This latter pathway requires an incubation period for formation of the sulfoxide product (trapping agent) and can be easily distinguished from the hydroperoxy sulfonium ylide route.

In a detailed study of the effect of radical and anion stabilizing groups, **R′** in Scheme 10A, Toutchkine and co-workers[73,74] suggested that there are both diradical, **B′**, and zwitterionic, **B**, isomers of the hydroperoxy sulfonium ylide, whose populations dictate partitioning between Pummerer, step a, sulfoxide, step b, and sulfone, step c, formation (Scheme 10A). The lack of an internal hydrogen bond in **B′** in particular appears to enhance Pummerer rearrangement. Albini and co-workers[75,76] have also noted during examinations of substitutent and isotope effects on C–S cleavages in benzyl sulfides that the α-hydrogen abstraction is best characterized as a homolytic rather than heterolytic process. Isolation of trace amounts of bibenzyl from photooxygenations of benzyl sulfides also provides support for the radical character of the Pummerer rearrangement.[76] The product of the Pummerer rearrangement, the α-hydroperoxy sulfide (**C**, Scheme 10) is normally not isolated but decomposes by both inter- and intramolecular pathways to the sulfur–carbon bond cleavage products.[73,74]



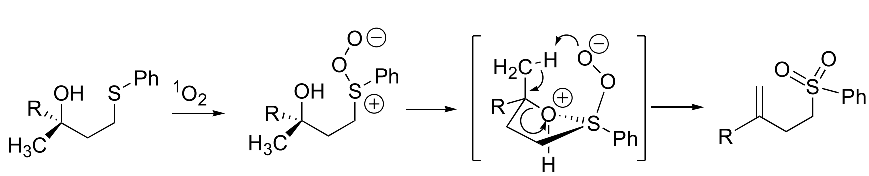
Scheme 9.



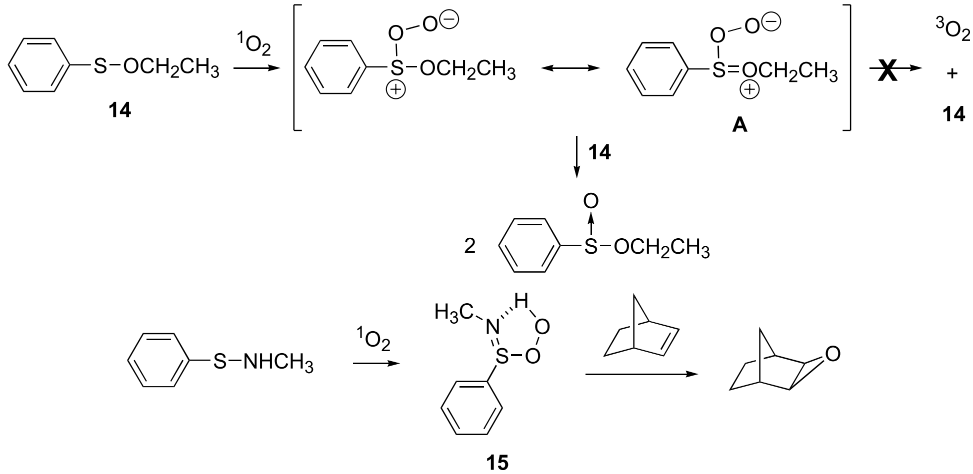
Scheme 10.

Sulfides exhibit distinctly different behavior in polar aprotic solvents. Rapid conversion of the persulfoxide to either a hydrogen bonded persulfoxide **8** or to a hydroperoxy sulfurane **9** (Scheme 7), as the only kinetically detected intermediate, competively inhibits both hydroperoxy sulfonium ylide formation and physical quenching. The viability of hydroperoxy sulfurane formation was compellingly demonstrated by formation of unusual oxidative elimination products during photooxygenations of a series of hydroxy tethered sulfides in aprotic solvents (Scheme 11).[77,78] However, their formations did not completely inhibit physical quenching as is the case in methanol as a solvent.[79] On the other hand, Albini and co-workers[75,80–82] in a series of manuscripts demonstrated that the rate constants for chemical reaction linearly correlate with the acid strengths of protic additives thereby providing a strong argument that it is formation of the hydrogen bonded persulfoxide, and not the hydroperoxy sulfurane, which is responsible for the unique behavior observed in polar protic solvents.

The reactions of singlet oxygen with a variety of other sulfur containing compounds including disulfides, sulfenamides,[83–85] and sulfenate esters[86] have also been investigated. In each case, with the possible exception of some disulfides, the persulfinate appears to be the initially formed intermediate whose fate is a sensitive function of the identity of the sulfur containing functional group and of the experimental conditions. For example, as anticipated, a kinetic study of the reaction of sulfenate ester, **14**, does not require a second intermediate because of the absence of an α-hydrogen.[86] On the other hand, it also reacts with 100% efficiency to give the sulfinate ester as the exclusive product. This unusual behavior was attributed to inhibition of physical quenching by the unique ability of the sulfenate ester to act as an electrophilic trapping agent for the persulfinate and its thermodynamic stabilization via resonance form **A** in Scheme 12.[86] A similar resonance stabilization of the intermediate formed during photooxygenation of the sulfenamide, 4-morpholinyl benzyl sulfide ($PhCH_2SN$



Scheme 11.



Scheme 12.

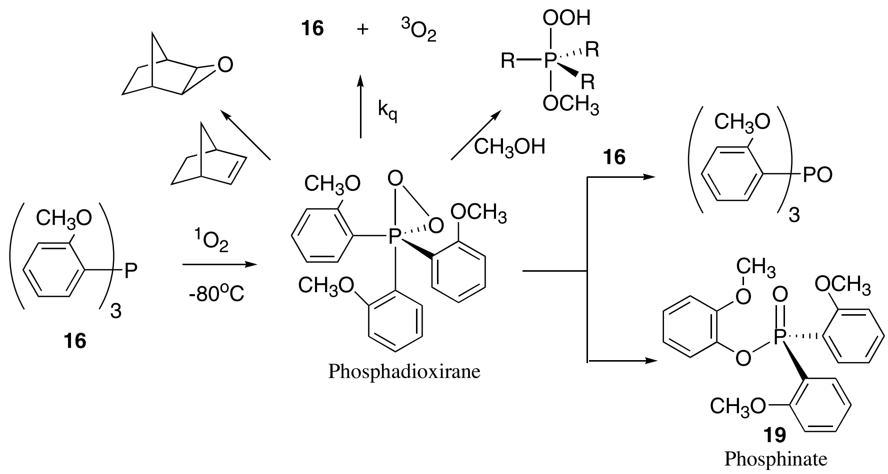
($(CH_2CH_2)_2O$) is perhaps also responsible for its inability to physically quench singlet oxygen.[83] However, in this case it is possible that the competitive abstraction of the benzylic hydrogens also contribute to inhibition of physical quenching since 45–55% physical quenching is still observed with 4-morpholinyl *tert*-butyl sulfide (t-$C_4H_9SN(CH_2CH_2)_2O$) which lacks these activated α-hydrogens. It has also been reported that photoxygenation of *N*-alkyl sulfenamides with labile N–H groups leads to iminopersulfinic acids, **15**, (isoelectronic to the hydroperoxy sulfonium ylide) capable of epoxidizing norbornene (Scheme 12).[84,85]

The biologically relevant disulfides (RSSR) exhibit several unique features.[87,88] These include: (1) a preference in aprotic solvents for thiosulfonate ($RS(O)_2SR$) rather than thiosulfinate (RS(O)SR) formation and a dramatic solvent dependent product ratio, (2) a decrease in efficiency of singlet oxygen quenching in comparison to sulfides, and (3) a remarkable dependence of quenching rate, k_T, on ionization potential, IP, rather than on steric effects as observed with simple dialkyl sulfides.[89] These phenomena have been attributed to predominant physical quenching of singlet oxygen by a charge transfer mechanism. Only those disulfides with small alkyl groups, MeSSMe, or with exposed disulfide linkages ($\Theta_{C-S-S-C} < 30°$ or smaller) can form a persulfinate at a reasonable rate which can either go on to chemically react or decompose in a physical quenching process to give triplet oxygen and the disulfide substrate.[90–94]

Several examples of organometallic complexes bearing thiolate ligands have recently been demonstrated to react with singlet oxygen at sulfur.[95–98] The mechanistic details of these reactions are still not clear, however, the intriguing suggestion that a long lived transient ($t_{1/2} > 1$ μs) observed during photooxidation of a platinum(II) diamine dithiolate complex might be the long sought after and elusive persulfoxide,[97] and reports of oxidative damage to sulfur rich metalloenzymes,[99] are likely to provide the impetus for further studies in this area.

2.2.2.2. Organophosphorus compounds. The ability of singlet oxygen to oxidize organophosphorus compounds was established in the early 1970s,[100] however, experimental studies to determine the mechanism of reaction were not undertaken until the 1990s[101,102] and have lagged far behind the effort in organosulfur chemistry. Sawaki and co-workers[102] examined sulfoxide trapping of the intermediates formed in the reaction of singlet oxygen with tri-*n*-butylphosphite and triphenylphosphine. They concluded that an electrophilic intermediate was involved in both reactions and that in the triphenylphosphine reaction it collapsed to produce both triphenylphosphine oxide (Ph_3PO) and diphenylphosphinate (Ph_2PO_2Ph). They also demonstrated that both oxygen atoms in the phosphinate had their origin in the same singlet oxygen molecule. Ando and co-workers[101,103] also established the electrophilic nature of the intermediate and demonstrated that it was capable of epoxidizing norbornene. Both research groups speculated, based on their results that the intermediate was a three-membered ring phosphadioxirane. This suggestion was supported by a computational study at several levels of theory which easily located the phosphadioxirane, O_2PH_3, as the only intermediate on the phosphine/singlet oxygen reaction surface.[104] The absence of an open intermediate isoelectronic to the persulfoxide, **5**, was attributed to the fact that the terminal oxygen is always *anti* to a P–H (or a P–R) bond allowing it to readily collapse to the trigonal bipyrimidal phosphadioxirane. The persulfoxide, however, adopts a conformation that places the terminal oxygen *anti* to the lone pair on sulfur that could only collapse to the energetically unfavorable trigonal bipyrimidal sulfurane with an apical lone pair. On the other hand, rotation of the terminal oxygen *anti* to the SH (or S–R) bond resulted in spontaneous formation of the thiadioxirane, O_2SH_3.

Selke and co-workers[105] have recently examined reactions of singlet oxygen with tris(*o*-methoxyphenyl)phosphine, **16**, tris(*m*-methoxyphenyl)phosphine, **17**, and tris(*p*-methoxyphenyl)phosphine, **18**. They report that all three phosphines react to produce the corresponding phosphine oxide but that only **16** produces the rearranged phosphinate, **19** (Scheme 13). They suggest that the *ortho*-methoxy groups in **16** sterically shield the peroxy linkage in a phosphadioxirane intermediate from bimolecular conversion to the phosphine oxide allowing unimolecular phosphonate formation to compete (Scheme 13). Indeed, a detailed kinetic study revealed that **19** and the phosphine oxide are formed from



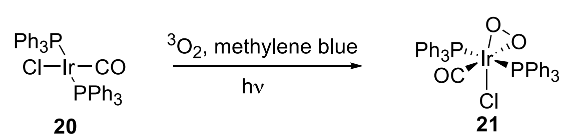
Scheme 13.

the same intermediate, that no detectable physical quenching of singlet oxygen is observed, and that these phosphines are two to three orders of magnitude better quenchers of singlet oxygen than $P(OCH_3)_3$ (i.e., k_T ($M^{-1}\,s^{-1}$) in benzene) **16**—$(5.0\pm0.2)\times10^6$; **17**—$(9.2\pm0.3)\times10^6$; **18**—$(3.31\pm0.43)\times10^7$; $P(OCH_3)_3$[57]—4.7×10^4. To rationalize all of these results they suggested the mechanism shown in Scheme 13. Direct observation of the phosphadioxirane at −80 °C by low temperature NMR, its ability to epoxidize alkenes, and its reaction with methanol all provide compelling support for this mechanistic suggestion.[106] These workers also report that at −80 °C formation of phosphine oxide and rearrangement of the phosphinate are sufficiently suppressed to allow decomposition of the phosphadioxirane to triplet oxygen (physical quenching) to compete.

2.2.2.3. Organometallic complexes. Organometallic complexes are known to react both physically and chemically with singlet oxygen and the chemical reactivity can either be ligand or metal centered. The ability to physically quench singlet oxygen[107–111] has been established for many years and an excellent complication of the quenching rates is available.[112] On the other hand, metal and ligand centered chemical reactions of singlet oxygen have only recently attracted attention (vide supra).

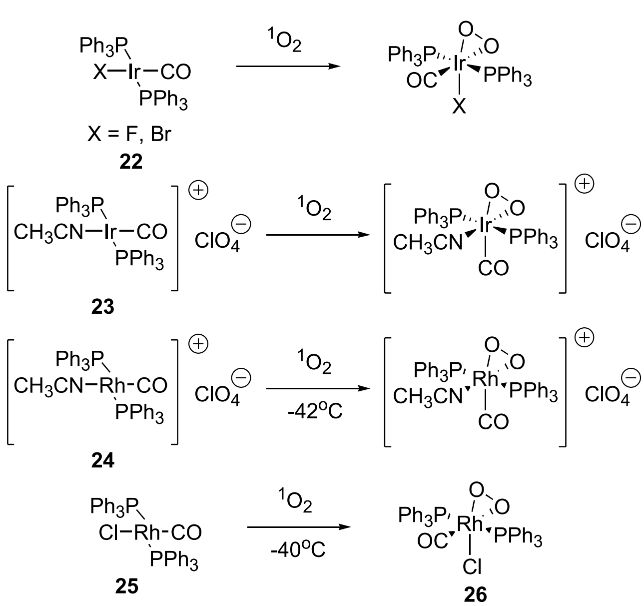
Ligand centered reactions have been investigated for both their mechanistic interest and their synthetic potential. Studies of the reactions of singlet oxygen with platinum II dithiolates has provided valuable mechanistic information on the photooxidative destruction of thiolate ligands (vide supra).[97] The ability of tricarbonyl iron to function as a protecting group and suppress reaction at the site of complexation has been exploited synthetically in order to direct oxidation to a remote site in the ligand.[113]

The first report of a metal centered reaction was that of Selke and Foote[114] who reported that Vaska's complex, **20**, reacted to produce metal–dioxygen complex, **21**. However, a detailed kinetic study revealed that physical deactivation of singlet oxygen by **20** is about an order of magnitude more important than its chemical reactivity. Nevertheless, the ratio of the chemical rate constants for reaction of singlet and triplet oxygen with **20** to give **21** is 10^9. This remarkable rate enhancement was attributed to the 22 kcal/mol excitation energy of singlet oxygen. These workers also demonstrated that peroxo complex **21** photochemically regenerates **20** and releases oxygen as a triplet, although formation of a small amount of singlet oxygen cannot be completely ruled out (Scheme 14).[115]



Scheme 14.

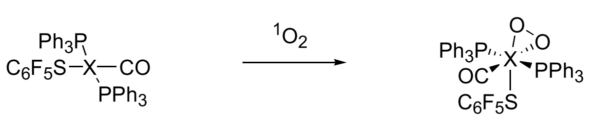
Since the initial Selke and Foote communication[114] a variety of other iridium and rhodium organometallic complexes have been reported to react with singlet oxygen to give the peroxo complexes as shown in Scheme 15. For example, the bromide and fluoride analogues of Vaska's



Scheme 15.

complex, **22**, and both Ir(I), **23**, and Rh(I), **24**, complexes[116] bearing the weakly bound acetonitrile ligand react with singlet oxygen to give isolable peroxo complexes. Especially noteworthy is Rh(I) complex, **25**, which does not react with triplet but does react with singlet oxygen to give the peroxo complex **26**.[117] The rhodium complexes are in general less stable than the iridium analogues and require low temperature irradiation for successful isolation. In addition, the singlet oxygen physical quenching rate constant for the iridium complex **20** ($2.4 \pm 0.3 \times 10^8\ M^{-1}\ s^{-1}$) is nearly identical to that observed for the rhodium complex **25** ($1.9 \pm 0.7 \times 10^8\ M^{-1}\ s^{-1}$) ruling out a spin–orbit coupling quenching mechanism which should be more important for iridium with its much higher atomic number. In contrast to the successful photooxygenations shown in Scheme 15, Crabtree's catalyst, [Ir(PPh_3)$_2$(1,5-cyclooctadiene)], was surprisingly unreactive towards singlet oxygen.

Ir(I) and Rh(I) thiolate complexes, **27** and **28**, respectively, react at the metal rather than at the sulfur ligand in sharp contrast to exclusive thiolate oxidation observed in Ni(II),[118] Pd(II),[96] Pt(II),[95,97] and Co(III)[98] thiolates (vide supra). On the other hand, even though the Pt(II) complex PtHCl(PEt_3)$_2$ does not chemically react it does physically quench singlet oxygen with a rate constant of $1.9 \times 10^7\ M^{-1}\ s^{-1}$.[119] It is possible that a Pt(IV) dioxygen complex could be an intermediate in this quenching process, however, attempts to directly observe it at temperatures as low as −79 °C were unsuccessful (Scheme 16).



27 X = Ir(I)
28 X = Rh(I)

Scheme 16.

2.2.2.4. Amines. The ability of amines to both chemically and physically quench singlet oxygen has been well established.[120,121] A considerable amount of data implicates a charge transfer complex between singlet oxygen and amines as a key component of these processes.[122–125] Berstein and Foote[126] recently reported compelling evidence that singlet oxygen mediates a novel cycloaddition of an amine and C_{60} (Scheme 17). Gan and co-workers[127] have extended this very useful reaction to cycloadditions of maleimides. Exclusive formation of pyrrolidine, **29**, with C_s symmetry led these workers to suggest the mechanism shown in Scheme 17.[128] Addition of singlet oxygen to methyl-iminodiacetate generates a *N*-peroxide, **A**, which collapses to a hydroperoxy anion iminium ion pair, **B**, which subsequently partitions to α-hydroperoxyamine, **C**, via a Pummerer-like rearrangment, and to *syn*-azomethine ylide, **D**, which adds to the maleimide to give the 1,3-*cis* isomer. The use of a polar solvent such as pyridine allows isomerization of the ylide to the *anti*-configuration and competitive formation of the 1,3-*trans* isomer. The α-amidoester, **30**, is a minor product except in the absence of any, or in the presence of an electron rich, 1,3-dipolarophile such as cyclohexene.

3. Heterocyclic photooxygenations

3.1. Five-membered rings

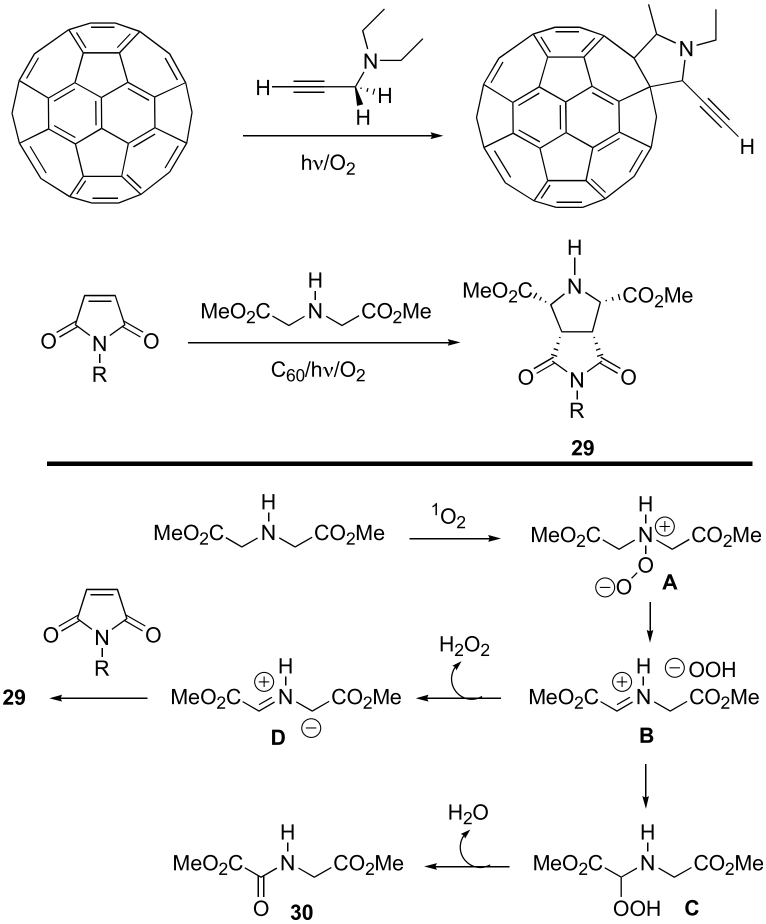
A significant number of articles regarding the reactions of singlet oxygen with heterocyclic systems have been published. The definition of heterocyclic system itself embraces a very wide class of organic compounds and as a consequence it is difficult to classify and summarize all the reported reactions in an organized manner. In fact, at the beginning of the preparation of this manuscript no recent comprehensive review on this topic was available.[129] Wasserman and Lipshutz in 1979[130] published a well-organized review on the reaction of singlet oxygen with several heterocyclic systems such as furans, pyrroles, indoles, imidazoles, purines, oxazoles, thiazoles and thiophenes. During the same period, George and Bhat[131] reviewed the photooxygenations of nitrogen heterocycles that also included examples involving singlet oxygen. In addition, studies that compare the singlet oxygen reactivity of different five-membered heterocycles have occasionally appeared in the literature.[132] We adopt the same approach as these previously published reviews and concentrate on reactions of five-membered rings which reflects the importance of this ring system in biological and heterocyclic chemistry.

3.1.1. Furans and benzofurans. The unabated intense interest in the reactions of furans with singlet oxygen reflects: (1) the widespread occurrence of this functionality both in biologically important substrates[133] and in pharmaceuticals;[134,135] (2) their use as probes for the presence of singlet oxygen both in aqueous[136,137] and microheterogenous media;[138] and, (3) the value of the singlet oxygen furan reaction in organic synthesis.[139]

3.1.1.1. Historical perspective. Reactions of singlet oxygen with furans typically occur by formation of a 2,5-endoperoxide (**II** in Scheme 18) that evolves into the final products. In the absence of stabilizing substituents the endoperoxide is generally very reactive (sometimes explosively) and its isolation can only be achieved at low temperatures under carefully controlled conditions.[140] For example, the parent system, 2,3,7-trioxabicyclo[2.2.1]hept-5-ene, has been prepared at −78 °C and its structure verified by microwave spectroscopy.[141] The endoperoxides can also be trapped in situ by reduction to the corresponding 2,3,7-trioxabicylco[2.2.1]heptanes (bicyclic ozonides) with diimide.[142]

The heterocyclic endoperoxide intermediates are formed via a mechanism reminiscent of the hydrocarbon analogues.[13] Symmetrically substituted furans react by a synchronous and asymmetrically substituted furans by an asynchronous concerted [4+2] cycloaddition of singlet oxygen across the 2,5-positions of the furan.[143–145] The reactions are entropy controlled[146] and, in the case of 1,3-diphenylisobenzofuran, excellent evidence has been collected to suggest the intervention of an exciplex intermediate.[147,148]

Previously recognized reactions and rearrangements of these endoperoxide intermediates are summarized in Scheme 18. Reduction (path a) occurs by cleavage of the



Scheme 17.

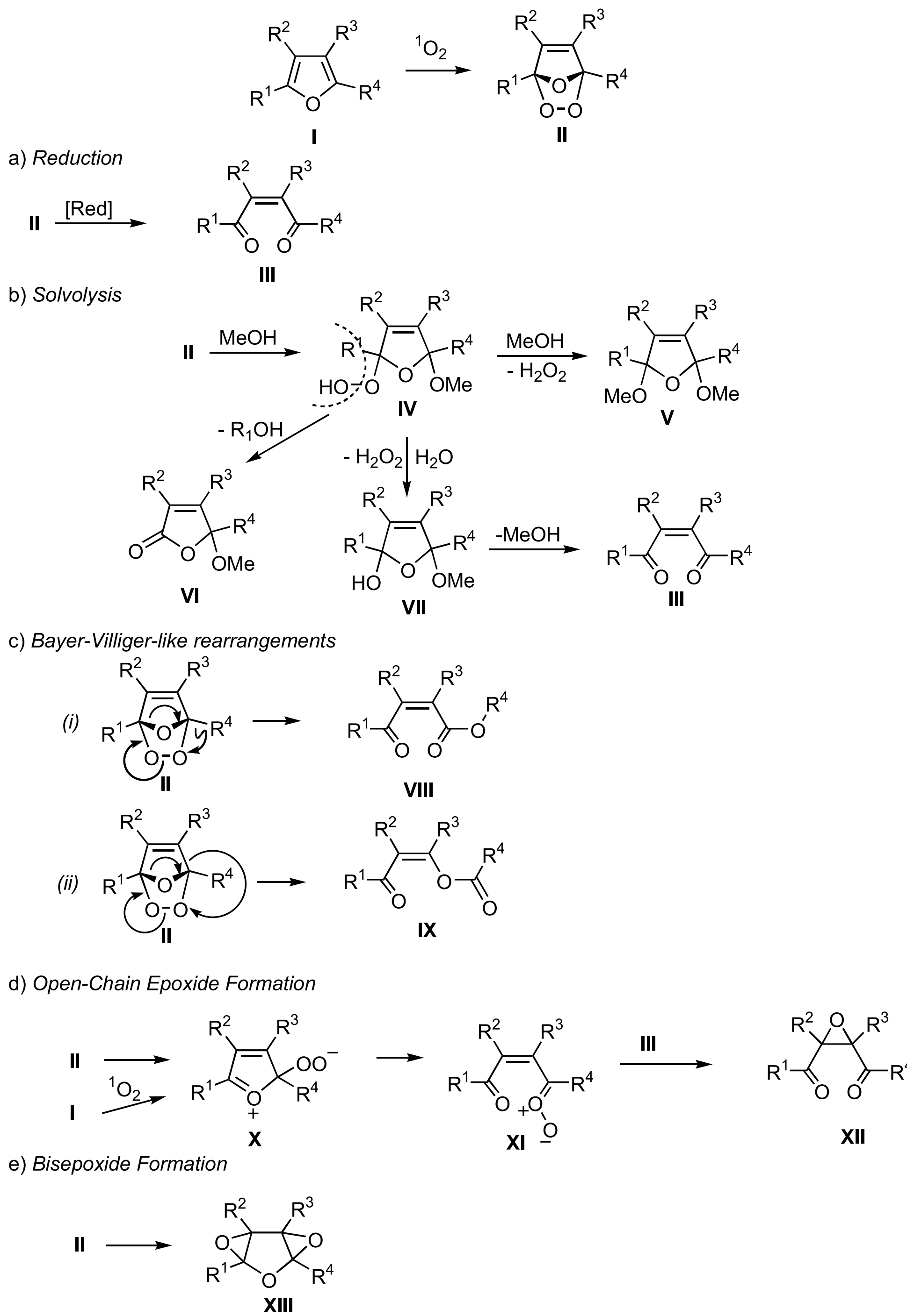
O–O bond and loss of oxygen. Solvolysis (path b), as exemplified by reaction with methanol (Scheme 18), can lead to a variety of products. Attack at C-1 or C-4 leads to formation of methanol addition product **IV** and further substitution to the bis-methanol adduct **V**. Loss of alcohol from **IV** leads to the cyclic lactone **VI**, or loss of hydrogen peroxide and addition of water, to the alkoxy-alcohol **VII** which can cleave with loss of methanol to the α,β-unsaturated carbonyl compound **III**. Baeyer–Villiger like rearrangements (path c) are initiated by O–O cleavage and migration of one of the bonds to the bridgehead carbons to give ester **VIII** or **IX**. This reaction can be made regioselective by incorporation of a trimethylsilyl group at either R_1 or R_4 leading to preferential formation of the trimethylsilyl ester.[149] This regioselective approach has been widely used for the synthesis of the butenolide [2(5*H*)-furanone] moiety.[150] Epoxide **XII** formation (path d), which can be initiated by decomposition of endoperoxide **II** or presumably by direct formation of zwitterion **X** from the furan, occurs by oxygen donation from carbonyl oxide intermediate **XI**. On the other hand, bisepoxide formation (path e) can occur by heterolytic cleavage of endoperoxide **II** or less likely by intermolecular epoxidation of the furan.

Endoperoxide formation across the 2,5-positions of benzofurans (**XIV**; Scheme 19) would lead to loss of a significant amount of aromatic resonance energy. As a consequence, 1,2-cycloaddition or, if appropriately substituted, exocyclic endoperoxide formation (**XVIII**→**XIX**) dominate their singlet oxygen chemistry (Scheme 19). The sensitive 2,3-dioxetane products formed in the 1,2-cycloaddition can either cleave thermally to form **XVI** or be reduced to the corresponding diol **XVII**.

The reactivity, or lack of reactivity, of benzofurans is a sensitive function of the identity of substituents and the substitution pattern. Electron-donating groups increase reactivity while electron-withdrawing substituents decrease reactivity and may even render the substrate inert to photooxidation. This effect is less important when the substituent is attached to the benzene ring. 2-Arylbenzofurans are less reactive than their 3-aryl-isomers presumably as a result of greater planarity in the 2-position leading to enhanced conjugative removal of electron density from the benzofuran nucleus.[151]

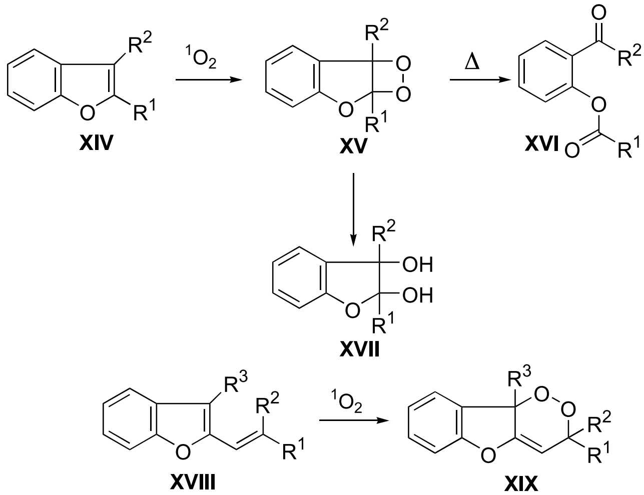
3.1.1.2. Recent advances. An exciplex intermediate has recently been implicated in the [4+2] cycloadditions of singlet oxygen to a series of furans by a study of pressure effects on the reactions.[152] In addition, a detailed kinetic study has demonstrated that the interaction of singlet oxygen is completely chemical in nature with no physical quenching component.[153]

On the product studies front, Gollnick and Griesbeck have reported the isolation of a series of ozonides as the primary



Scheme 18.

furan/singlet oxygen photoproducts and a detailed study of their subsequent reactions under a variety of conditions.[154] Their principal observations are summarized in Scheme 20 and include: (1) the primary unimolecular decomposition route in non-polar aprotic solvents involves homolytic cleavage of the O–O bond to give a bis-alkoxy radical, **A**. (2) The fate of the bis-alkoxy radical is a sensitive function of reaction conditions and the identities of the bridgehead substitutents. For example, when $R'=R=CH_3$ at temperatures between 50 and 60 °C dimer formation, **B**, is the predominant process. At higher temperatures, however, bis-epoxide, **C**, formation is observed. When one of the bridgehead substituents is hydrogen a 1,2-hydrogen shift can occur to give an epoxylactone, **D**. (3) Polar protic solvents can react as nucleophiles, acids or bases with furan endoperoxides. For example, formations of *cis*-alkoxy hydroperoxides, **E**, occur with the protic solvent functioning as both an acid to assist in the cleavage of the peroxy bridge and as a nucleophile adding with retention of stereochemistry to the bridgehead carbon. Consistent with this mechanistic formulation is the fact that the protic solvent adds to the bridgehead carbon best able to accommodate the developing positive charge. Formations of 5-hydroxy-2(5*H*)-furanones (4-hydroxybutenolides), **F**, can occur by

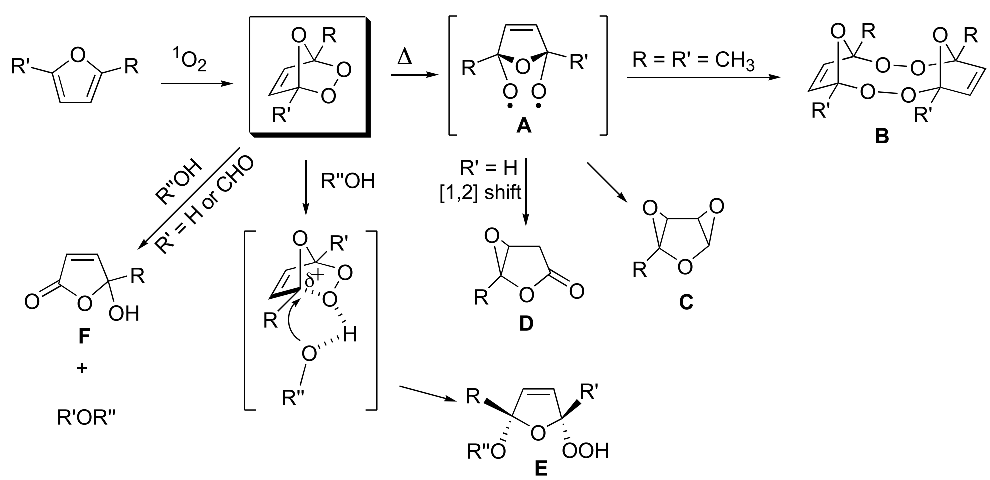


Scheme 19.

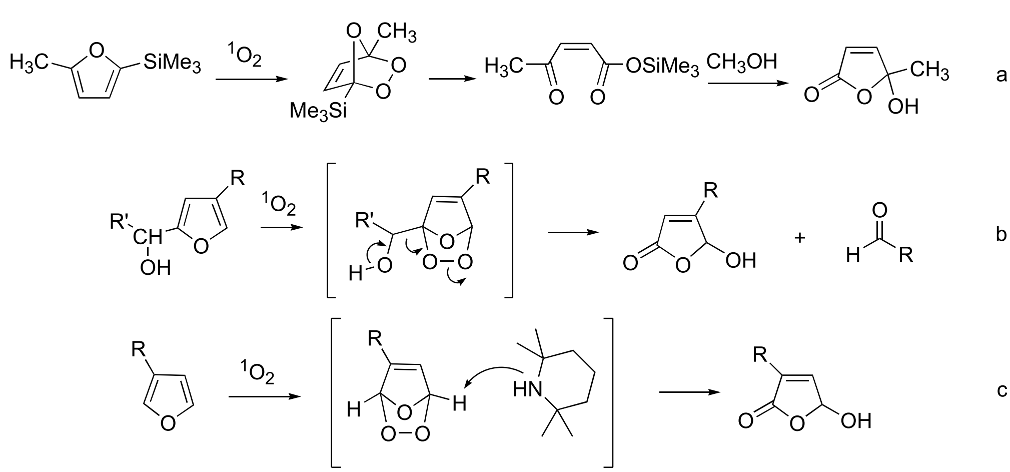
the protic solvent acting as a base to remove the bridgehead hydrogen or as a nucleophile to attack a bridgehead aldehyde which ultimately undergoes C–C cleavage to generate the butenolide, or alternatively (vide infra) via a Baeyer–Villiger like rearrangement.

A significant amount of work has been devoted to controlling the regio- and stereochemistry of 4-hydroxy-butenolide, **F**, formation as a result of the widespread occurrence of this functional group in natural products. Two very different approaches have been taken. In the first approach substituents have been used to direct the regiochemistry of the Baeyer–Villiger-like rearrangement (Scheme 20) In particular, Lee and co-workers[155] have developed the trialkylsilyl and 1-hydroxyalkyl groups in order to dictate the site of oxidation in the furan nucleus (Scheme 21a and b, respectively). In the second approach the site of oxidation is determined by the use of hindered bases that promote hydrogen abstraction from the sterically most accessible bridgehead in the furan endoperoxide intermediate (Scheme 21c).[156] These strategies have subsequently been implemented in an impressive array of natural product syntheses.[157–162] A particularly interesting natural product strategy uses protected hydroxy groups tethered to the furan nucleus that can be unmasked after oxidation of the furan for Michael addition to the butenolide and formation of oxacycles.[163,164]

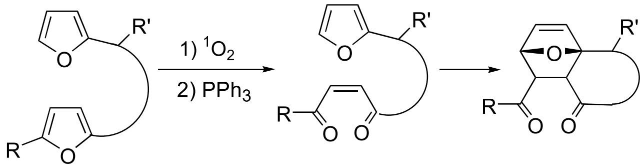
The reduction of furan endoperoxides with sulfides or phosphines to generate 2,3-unsaturated-1,4-dicarbonyl compounds has also attracted synthetic attention.[165] In a



Scheme 20.



Scheme 21.



Scheme 22.

very interesting application Feringa[166] reported a novel tandem photooxidation–intramolecular Diels–Alder reaction that takes advantage of the selectivity of singlet oxygen for the most electron rich furan in a tethered dyad (Scheme 22).

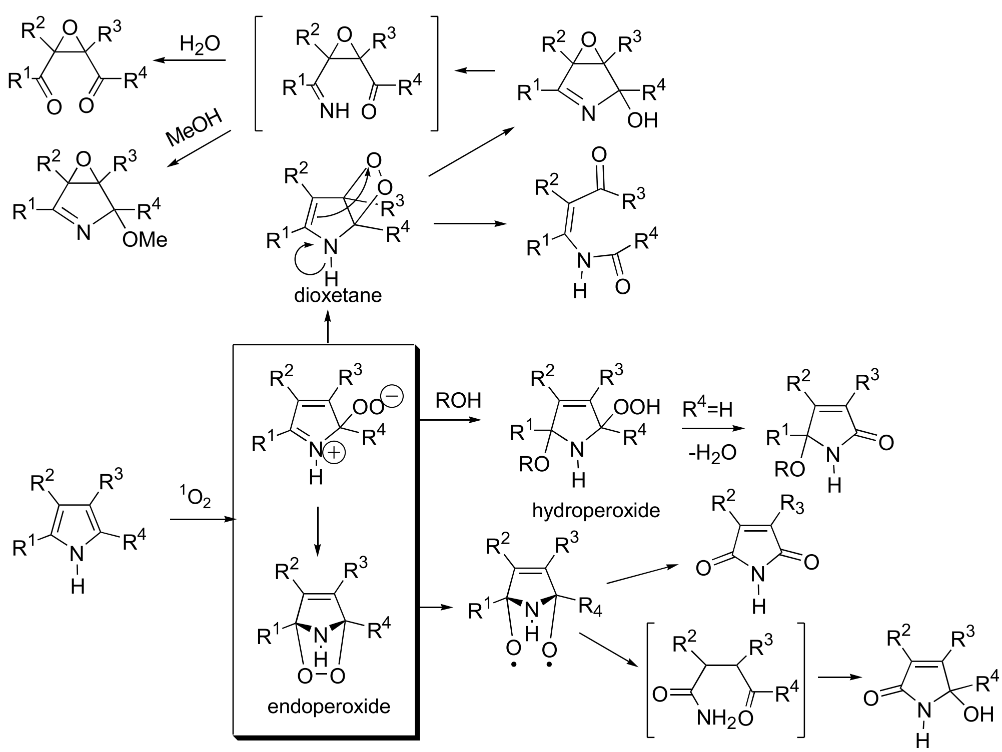
3.1.2. Pyrroles and indoles. The interest in the reactions of singlet oxygen with pyrroles and indoles has been driven by developments in phototherapeutic methods to treat neonatal jaundice[167] and in the hope that these reactions might serve as models for oxidations of important biological molecules such as tryptophan.

3.1.2.1. Historical perspective. The first photochemical oxidation of the parent heterocycle pyrrole was reported in 1912 by Ciamician and Silber.[168] Early studies report the formation of tarry products[169] which, unless carefully controlled, render pyrrole photooxidations useless for preparative purposes. Reactions conditions such as solvent, dilution, and temperature, and the substitution pattern on the pyrrole ring, play a significant role in determining the nature of the isolated products.

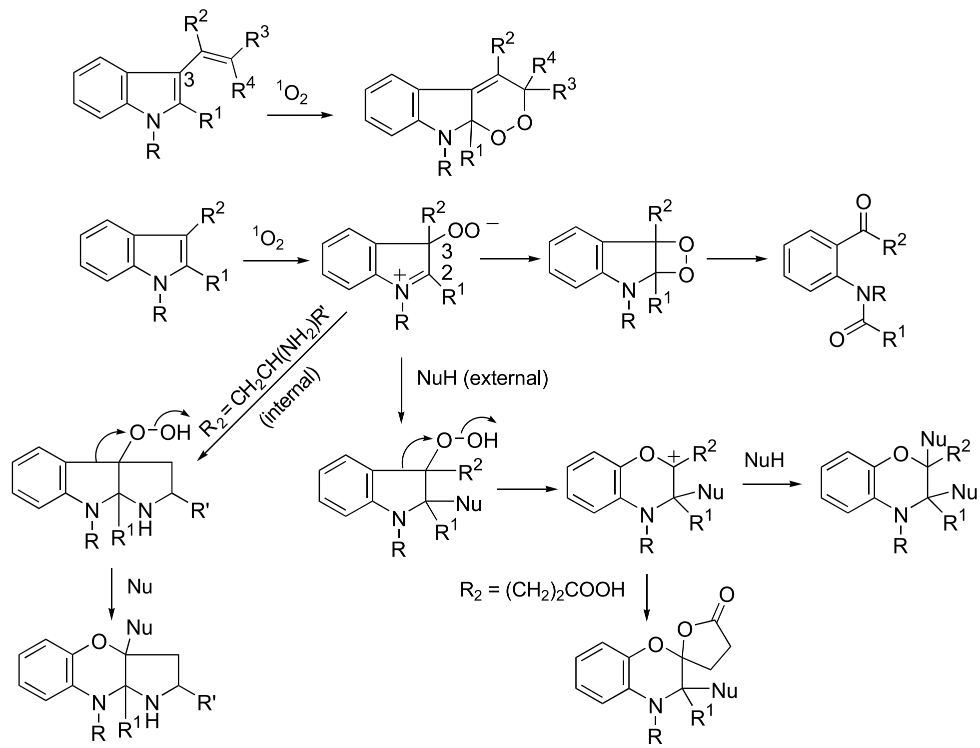
Endoperoxide, dioxetane, and hydroperoxide intermediates have all been implicated in reactions of pyrroles with singlet oxygen. A [4+2] cycloaddition to form the endoperoxide has often been suggested, however, the initial formation of a zwitterion that serves as a common precursor to all these intermediates is also possible (Scheme 23). In striking contrast to the reactions of furan derivatives, the pyrrole ring does not generally open by N(1)–C(2) or N(1)–C(5) bond cleavage (Scheme 23). Homolytic cleavages of the oxygen-oxygen bond in the endoperoxide preferentially produce maleimides or γ-hydroxy-α,β-unsaturated lactams. The dioxetane can either decompose with cleavage of the C(2)–C(3) bond or rearrange to an epoxide.[130,131]

Indoles, reminiscent of benzofurans, do not give the [4+2] cycloaddition products because of the concomitant loss of aromatic resonance energy and instead the site of attack is at the C2–C3 double bond. Only in the case of 3-vinyl indoles are [4+2] cycloadditions observed[170] (Scheme 24). The reactions at the C2–C3 bond occurs predominantly at C3 to give a zwitterionic intermediate[146,171] which is susceptible to nucleophilic attack (from an external or internal nucleophile) at C2 leading to subsequent rearrangements (Scheme 24).[130,131,171]

3.1.2.2. Recent advances. In 1991, both Wasserman[172] and Boger[173] discovered that attenuation of the reactivity of the pyrrole nucleus with a combination of electron donating and withdrawing groups allowed controlled synthetically useful singlet oxygenations (Scheme 25). Pyrrole **31** reacted with singlet oxygen to give a 45, 35, and 10% yield of **32**, **33**, and **34**, respectively.[172] Addition of 10% pyridine resulted in an increase in the yield of **32** to 80% consistent with its formation via base catalyzed decomposition of an endoperoxide intermediate. Concomitantly, the yields of both **32** and **34** decreased, which were formed by base independent decomposition of a dioxetane and deoxygenation of a perepoxide intermediate, respectively. Pyrrole **35**



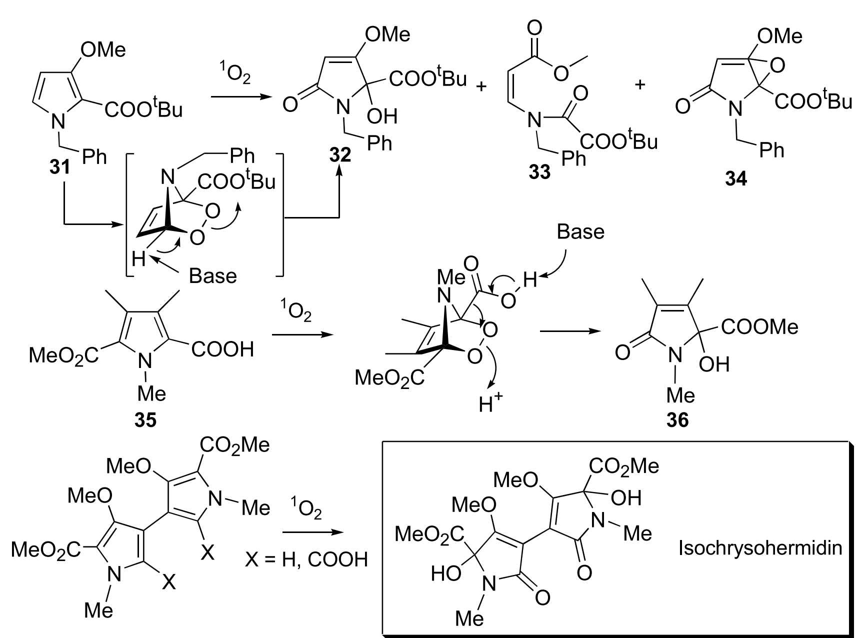
Scheme 23.



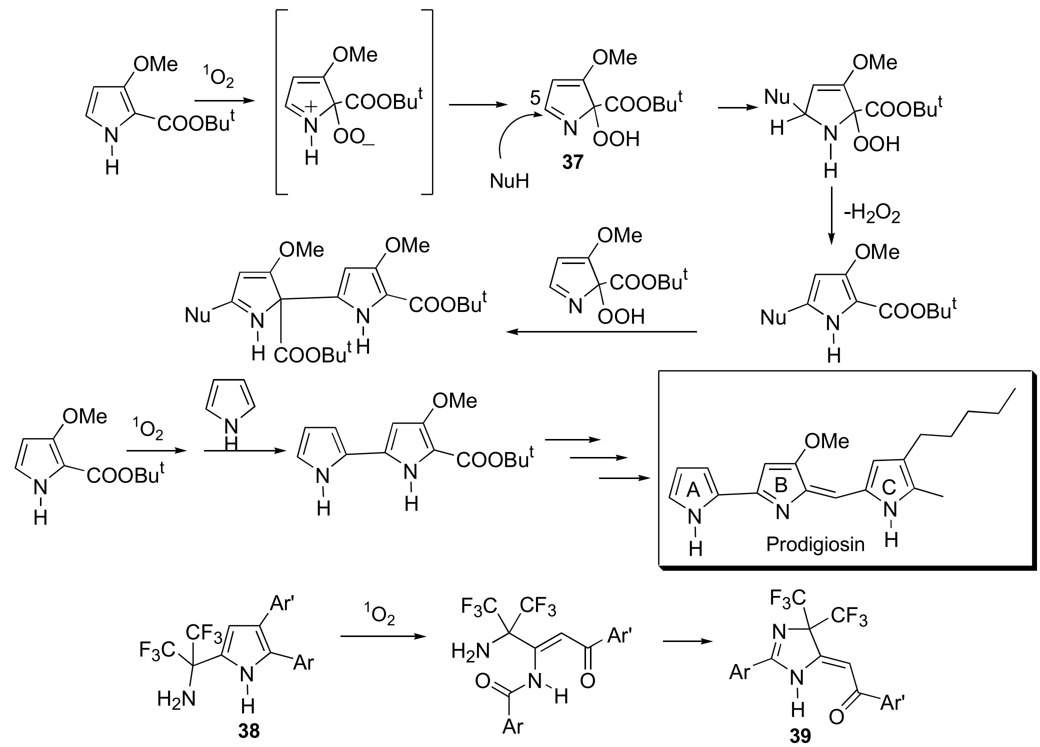
Scheme 24.

reacted via a novel oxidative decomposition, also via an endoperoxide intermediate to give **36**.[173] Both of these oxidations have subsequently been used in total syntheses of *d*,*l*- and *meso*-isochrysohermidin.[174–176]

Pyrroles without the *N*-alkyl group take a different reaction pathway to produce hydroperoxides such as **37**.[177] (Scheme 26) This hydroperoxide is electrophilic and will react with a wide variety of nitrogen and carbon centered nucleophiles, including pyrroles at C-5.[178,179] This behavior is undoubtedly responsible for the high molecular weight products formed in the singlet oxygen reactions of many pyrroles and the often-noted influence of substrate concentration on product distribution. This unique behavior has been elegantly utilized to synthesize the A and B rings of the potent antimicrobial and cytotoxic prodigiosin[180] (Scheme 26). When the C-5 position is blocked nucleophilic attack is impeded and alternative reactivity is observed. For example, pyrrole **38**, reacts via cleavage of the 2,3-bond to give imidazoline, **39**, in 69% yield (Scheme 26).



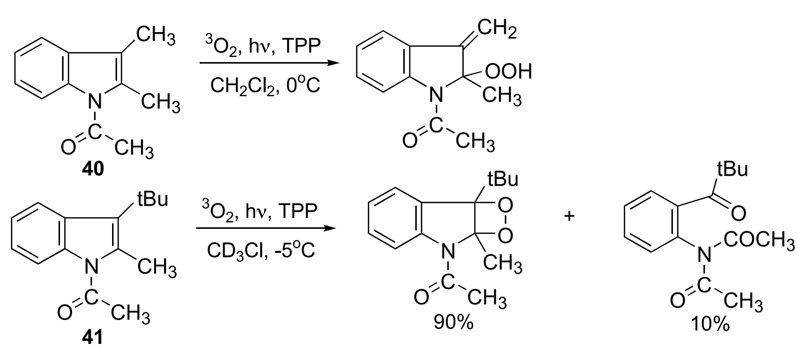
Scheme 25.



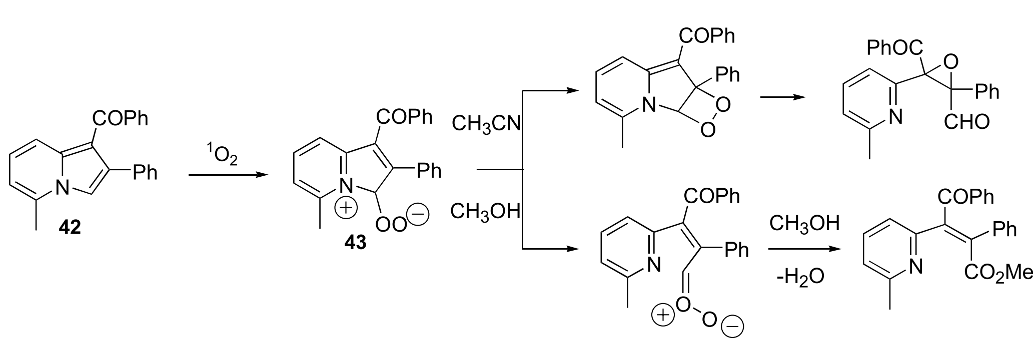
Scheme 26.

The dioxetane precursor for the oxidative ring opening of **38** was not directly observed, however, dioxetanes have been isolated during photooxygenations of acylated indoles.[181–185] (Scheme 27). In chlorinated solvents, indole **40** gives exclusively the ene product, however, **41**, which cannot undergo an ene reaction at the 3-position, give a remarkably stable dioxetane and a small amount of cleavage product.[181] In methanol, formation of the dioxetane is enhanced and even **40** gives 53% of the dioxetane accompanied by 37% of the ene and 10% of the cleavage product.[182]

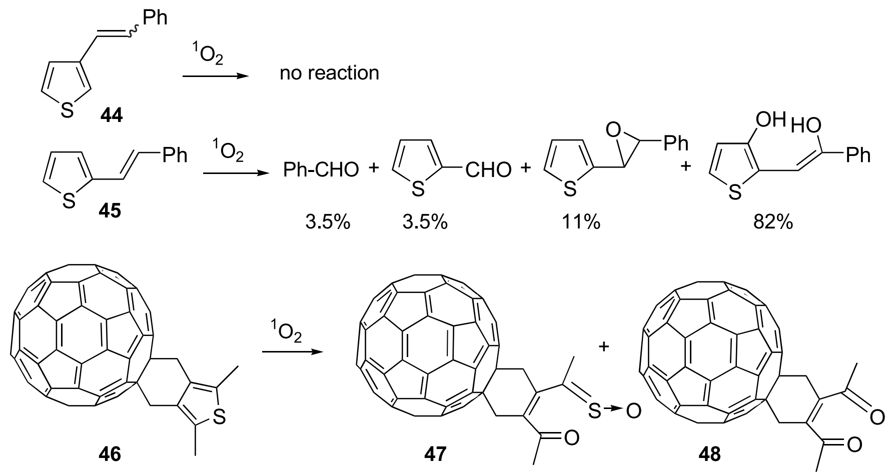
Indolizines, such as **42**, are isoelectronic to indole and also



Scheme 27.



Scheme 28.



Scheme 29.

react with singlet oxygen.[186,187] These reactions primarily result in cleavage of the N–C3 bond (Scheme 28). Zwitterion **43**, is a likely key intermediate in these reactions and can partition to give the various products as a function of reaction/solvent conditions.

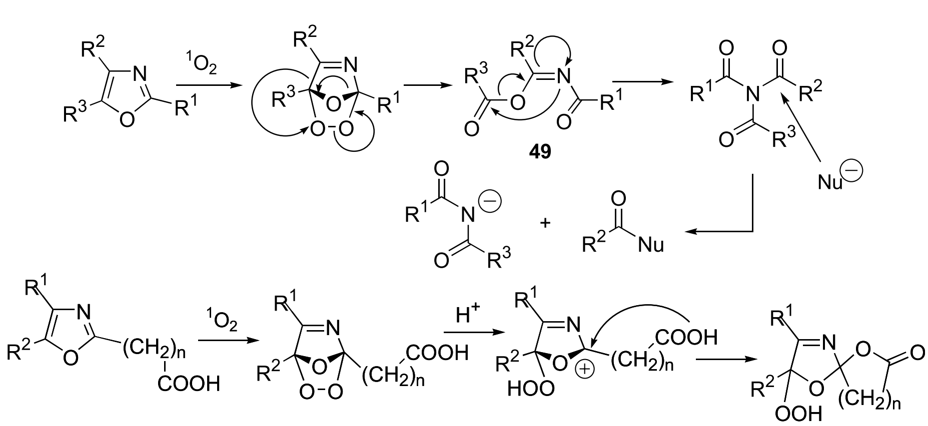
The high reactivity of electron rich pyrroles also makes them attractive for use in detection systems for singlet oxygen. Compounds such as *tert*-butyl-3,4,5-trimethylpyrrolecarboxylate (BTMPC) and *N*-benzyl-3-methoxy-2-*tert*-carboxylate (BMPC) have been employed as post-column mobile phase additives to detect elution of singlet oxygen sensitizers in HPLC.[188] In addition, the chemiluminescence of indole singlet oxygen products provides a convenient tool to monitor their reactions.[189]

3.1.3. Thiophenes. In comparison to furans and pyrroles, thiophene and monosubstituted thiophenes exhibit substantially reduced reactivity towards singlet oxygen. For example, *cis*- or *trans*-3-styrylthiophenes, **44**, (Scheme 29) do not react with singlet oxygen even after 10 h of irradiation.[190] However, a [4+2] cycloaddition involving the furan nucleus is responsible for the major product in the photooxygenation of **45** (Scheme 29).[191] Dialkyl substitution at the 2,5-positions increases the reactivity of the thiophene nucleus as illustrated by the recently reported reaction of the C-60 appended thiophene **46** (Scheme 29).[192] Most recent physical organic studies have focused on development of polythiophenes as singlet oxygen sensitizers[193] and little is known about the detailed mechanistic pathways for formation of sulfine (e.g., **47**) and α,β-unsaturated 1,4-dicarbonyl compounds (e.g., **48**) in these reactions.

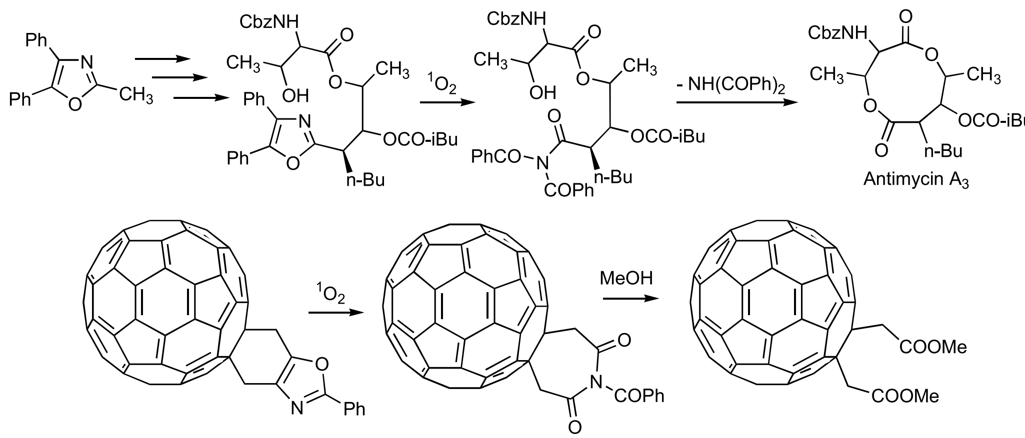
3.1.4. Oxazoles.

3.1.4.1. Historical perspective. Oxazoles are highly reactive singlet oxygen substrates that are converted in high yields to endoperoxides[194] which react by sequential Baeyer–Villiger like rearrangement and *O*- to *N*-acyl transposition to give triamides.[130,131] Consequently, oxazoles represent acyl synthons since the imide group is an activated leaving group (Scheme 30). In substrates that geometrically prevent the *O*- to *N*-acyl transposition the imino anhydride, **49**, can be isolated. In addition when a carboxylic acid group is tethered to the oxazole the endoperoxide can be diverted to form a spiro-hydroperoxy lactone[195] (Scheme 30).

3.1.4.2. Recent advances. Recent studies of oxazole photooxygenation have focused on modulation of the reactivities of the three carbonyls in the triamide product by manipulation of the substituents on the oxazole substrate. In an elegant demonstration of this strategy Wasserman and co-workers[196] showed that when two of the substituents are



Scheme 30.



Scheme 31.

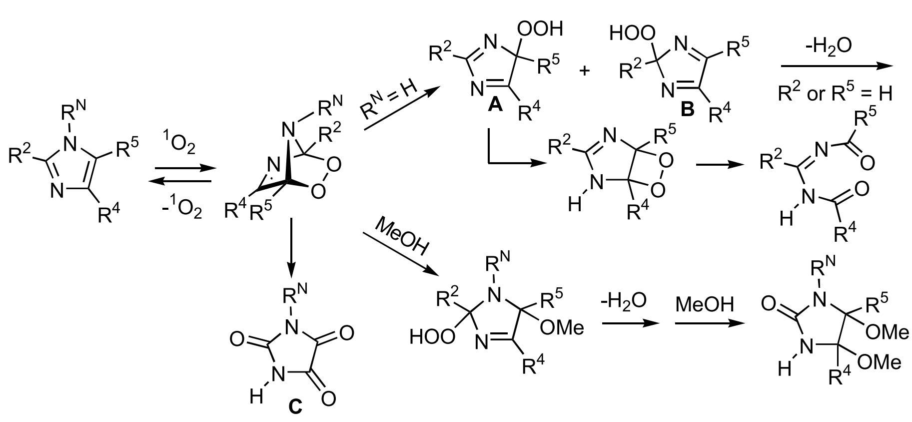
aryl and one alkyl nucleophilic addition to the triamide was regioselective for the acyl rather than the aroyl group. Intramolecular addition leading to ring formation is also possible when a nucleophile is appended to one of the substituents. Wasserman and co-workers used this strategy in the synthesis of Antimycin A_3[197] (Scheme 31) and of Pyrenolide C.[198,199] Oxazole photooxygenation has also been utilized to synthesize novel [60]fullerenes in a self-sensitization process (Scheme 31).[200]

3.1.5. Imidazoles. The reactions of imidazoles with singlet oxygen are of limited synthetic value but are of great mechanistic interest because of their prevalence in nucleic acids and proteins.

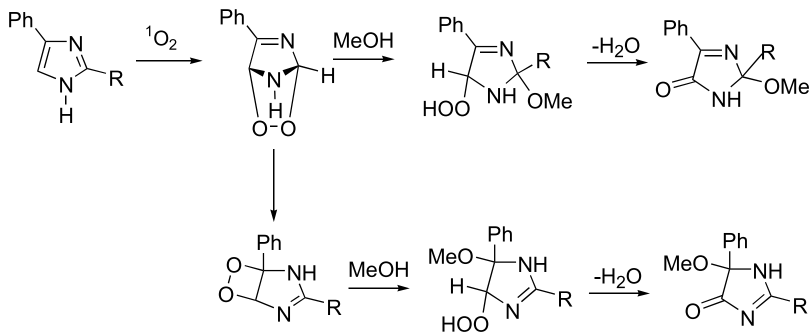
3.1.5.1. Historical perspective. In the 1960s and 70s, Wasserman and co-worker extensively investigated the photooxidations of a wide range of alkyl and aryl substituted imidazoles.[130] The endoperoxide is the key intermediate formed in these reactions and can be directly observed by low temperature NMR.[201] The decomposition of the endoperoxide is a sensitive function of the substitution pattern (Scheme 32). When R^N is hydrogen lone-pair assisted opening of the endoperoxide to give either hydroperoxides **A** or **B** can be observed. If the R group geminal to the –OOH group is hydrogen loss of water from these hydroperoxides produces the corresponding amide or urea, respectively. Hydroperoxide **A** has also been implicated in formation of diacylamidines. Presumably the chemiluminescence, first reported by Radziszewski[130] in 1877 during reaction of 2,4,5-triphenylimidazole (lophine) with singlet oxygen, is emitted during decomposition of the dioxetane precursor of the diacylamidine product. Methoxy-imidazolones have been observed by addition of methanol to the endoperoxides primarily by the process shown in Scheme 32. Interestingly, when R^2, R^4, and R^5 are good leaving groups such as halogen parabanic acid derivatives, **C**, are observed.[202]

3.1.5.2. Recent advances. In recent years, imidazole photooxygenation has been investigated from both theoretical[203] and experimental perspectives. For example, in developing synthetic strategies towards biologically active trifluoromethylated compounds, Li et al. have recently exploited the photooxidative ring opening-ring closure of imidazoles to obtain 4,4′-bis(trifluoromethyl)-imidazolines.[204] In a mechanistic study the formation of two imidazolinone isomers during photooxygenation of 2,4-disubstituted imidazoles has been attributed to nucleophilic attack by the solvent on both an endoperoxide and a dioxetane intermediate (Scheme 33).[205]

Kang and Foote[206] have reported the previously unobserved formation of CO_2 during photooxygenation of 4,5-diphenylimidazole. They also examined this reaction using low temperature NMR with a series of isotopically labeled (^{13}C and ^{15}N) isomers. They were able to spectroscopically



Scheme 32.

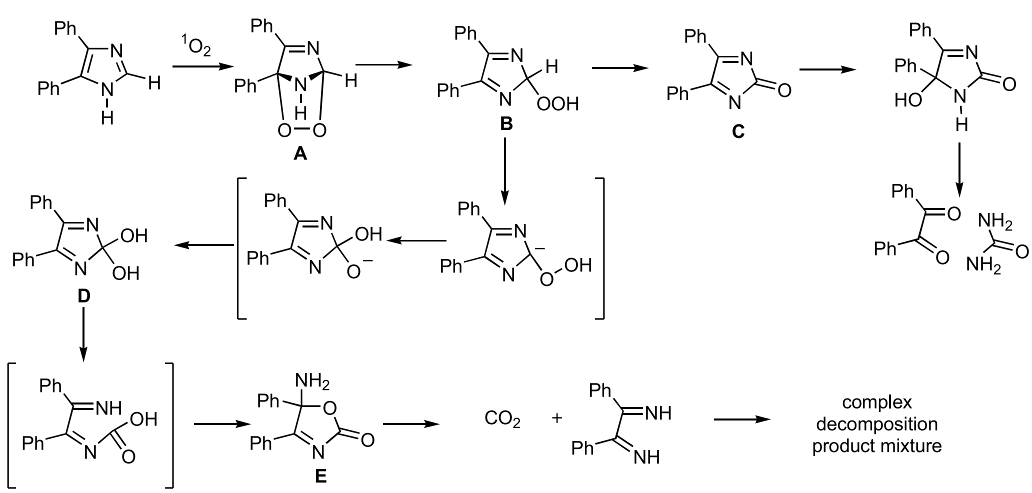


Scheme 33.

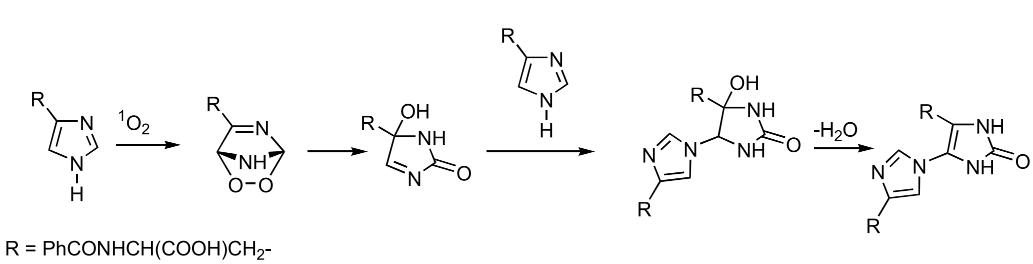
observe the time resolved formations of intermediates **A–E** (Scheme 34).

Several model studies to understand the photooxidative behavior of the imidazole containing nucleic acid base, guanine, have been reported.[207,208] This intense interest in guanine reflects the often-observed selective decomposition of this residue during photodynamic action. The most informative model studies have used soluble derivatives and low temperatures to prevent decomposition of primary photoproducts thereby circumventing the major obstacles that have prevented a detailed understanding of the mechanism of guanosine photooxygenation.[209–211] These studies have unambiguously demonstrated that the imidazole ring is the site of oxidative damage to guanosine and that [4+2] cycloaddition to form an endoperoxide is the initiating event in the singlet oxygen reaction. The photooxygenations of *N*-benzoyl-histidine have been examined under physiological conditions and have been shown to generate dimeric products (Scheme 35).[212] The proposed mechanism provides an elegant explanation for the photosensitized crosslinking of proteins observed during the photodynamic therapy (PDT) of tumors and other diseases[213] and during premature UV-induced skin aging.[214]

3.1.6. Thiazoles. Photooxygenations of thiazoles have rarely been used synthetically despite the fact that they have been reported to undergo reactions similar to oxazoles.[130] Nevertheless, Wasylyk and co-workers[215] have reported [4+2] cycloaddition of singlet oxygen to a thiazole moiety in a novel cyclic peptide and the decomposition of the thioozonide to an amide. The lack of synthetic interest has in part been a result of the impractical and troublesome work up encountered in these reactions. On the other hand, interest in this reaction persists as a result



Scheme 34.



Scheme 35.

of concern about the environmental impact of thiazole containing drugs[216] and of changes in biological activity due to modifications caused by such reactions.[217]

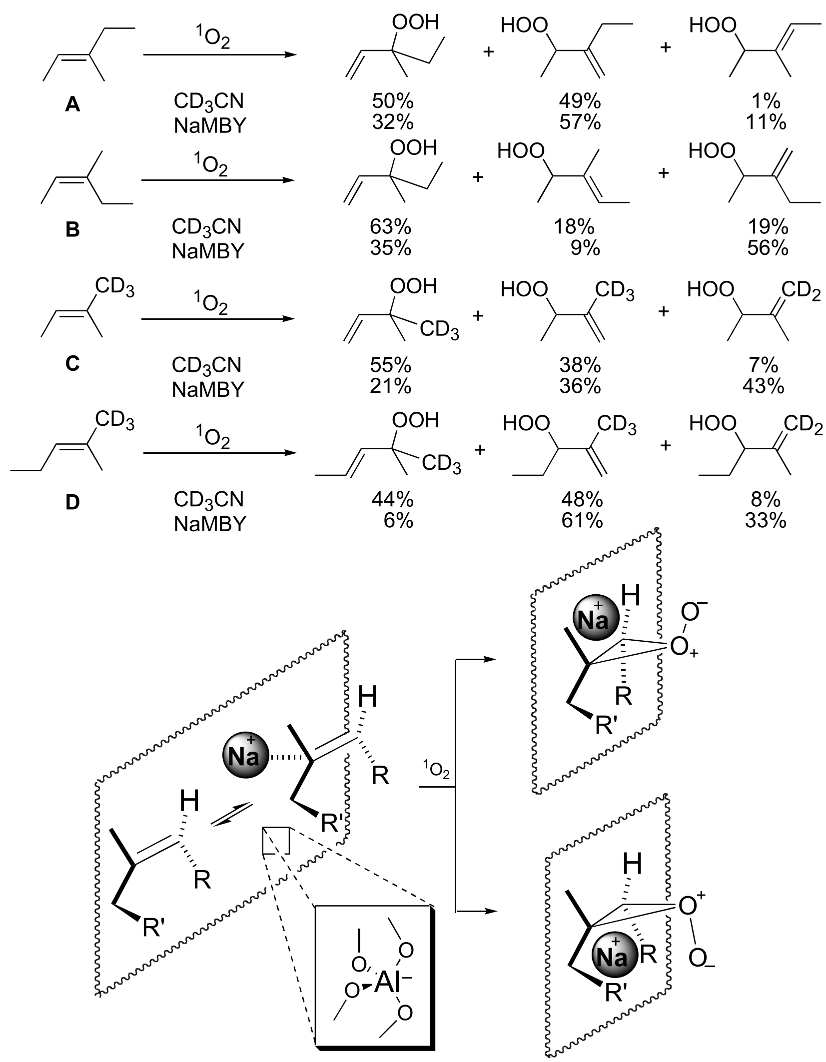
4. Formation and reactions of singlet oxygen in heterogeneous media

Photooxygenations in heterogeneous media have attracted considerable attention because of their relevance to biological and environmental oxidations and to the expectation that constrained environments could enhance regio- and stereochemistry of these synthetically useful reactions.[218]

4.1. Zeolites

The first report of an intrazeolite singlet oxygen reaction was made by Li and Ramamurthy in 1996.[219] In this seminal contribution these authors utilized thiazine exchanged zeolite Y as a reaction medium. Zeolite Y (e.g., NaY) is an aluminosilicate composed of catenated $[SiO_4]^{4-}$ and $[AlO_4]^{5-}$ tetrahedra connected to generate a honeycomb network of supercages that provide access to organic substrates via tetrahedrally arranged 7.4 Å windows. The cations present in the interior, needed to balance the negative charge on the tetravalent aluminum atoms, create a highly charged electrostatic and unique reaction environment.

Dramatic changes in the regiochemistry of the singlet oxygen ene reaction have been realized in the intrazeolite medium by the Ramamurthy group and others.[220–223] Several examples of the contrasting solution/zeolite behavior and a mechanistic model that provides a rationale for these changes are depicted in Scheme 36.[224] The unique features of these reactions which must be explained by any successful mechanistic model include: (1) the '*cis* effect', the propensity for hydrogen abstraction from the most substituted side of an alkene, which has been attributed to a secondary orbital interaction between the pendant oxygen on the persulfoxide and the allylic C–H orbitals, is dramatically diminished in the zeolite in comparison to solution (e.g., from 99 to 89% in **A**; from 81 to 43% in **B**; from 93 to 48% in **C**; and from 92 to 67% in **D**). (2) Markovnikov directing effects, the propensity for hydrogen abstraction from the most highly substituted end of the alkene, is enhanced in the zeolite (e.g., from 50 to 68% in **A**;



Scheme 36.

from 37 to 65% in **B**; from 45 to 79% in **C**; and from 56 to 94% in **D**). (3) Replacement of each of the unique methyl groups in **C** by an ethyl group decreases the extent of hydrogen abstraction at that position by a greater amount in the zeolite than in solution (e.g., intrazeolite hydrogen abstraction from the ethyl group is 11% in **A**, 9% in **B**, 6% in **D**, and 43, 36, and 21%, respectively, from the methyl groups in the analogous position in **C**) and, (4) reaction rates are dramatically faster in the zeolite than in solution. Ene reactions that require several hours of irradiation in solution have been reported to go to completion within 5 min in zeolite Y.[225]

The sodium ion has a profound influence on the potential energy surface for the intrazeolite singlet oxygen ene reaction and is invoked as an integral part of the mechanistic model depicted in Scheme 36.[6] In this model sodium ion complexation to the alkene[226,227] sterically force allylic substituents rather than allylic hydrogens (e.g., methyl in **A**, **B**, and **D**, Scheme 36) to occupy the face accessible to singlet oxygen thereby precluding hydrogen abstraction at these sites. As the singlet oxygen approaches the sodium ion moves preferentially to the least substituted side of the alkene to provide stabilization to the incipient perepoxide. This sterically constrained movement of the sodium ion and stabilization of the perepoxide provides an explanation for the diminished importance of the *cis* effect and for the counterintuitive observation of intrazeolite enhanced reactivity. In addition, the electropositive sodium ion pulls electron density away from the perepoxide increasing hydrogen abstraction from the allylic sites on the end of the alkene bearing the bulk of the cation-induced positive charge density. This model is supported by intrazeolite photooxidation of *Z*-2,3-dimethyl-1,1,1,2,2,2-hexadeutero-2-butene which exhibited an intramolecular isotope effect of 1.04 ± 0.02 which is consistent with a perepoxide but completely inconsistent with a zwitterion. In addition, dramatic substitutent effects on the regiochemistries of the singlet oxygen ene reactions of a series of aryl substituted trimethylstyrenes in the interior of NaY but not in solution are consistent with significant build up of positive charge on the carbon framework of the perepoxide.

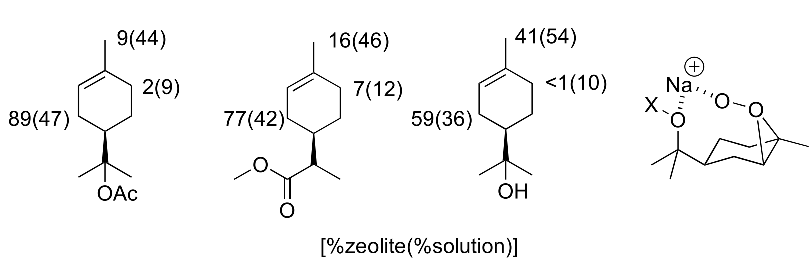
The mechanistic model given in Scheme 36 is not valid for substrates for which cation binding is electronically precluded[228] or for those in which alternative binding modes are facilitated.[226,229,230] For example, Stratakis and co-workers[231] report that photooxidations of a series of cyclohexenes lead to an intrazeolite increase in hydrogen abstraction from the least substituted end of the alkene linkage (Scheme 37). This is consistent with simultaneous binding of the sodium to remote oxygen functionality and the perepoxide (Scheme 37).

The report that allylic hydroperoxides are not stable to extended irradiation times reduces the synthetic potential of this intrazeolitic reaction.[232] On the other hand, introduction of a new experimental procedure that allows large scale reactions,[233] and the often observed reduced reaction times[225,234] and simplified reaction mixtures[225] suggests that the full potential of this reaction has not been realized. In particular, only a few enantioselective[235,236] and diastereoselective[229,237] intrazeolite singlet oxygen reactions have been reported.

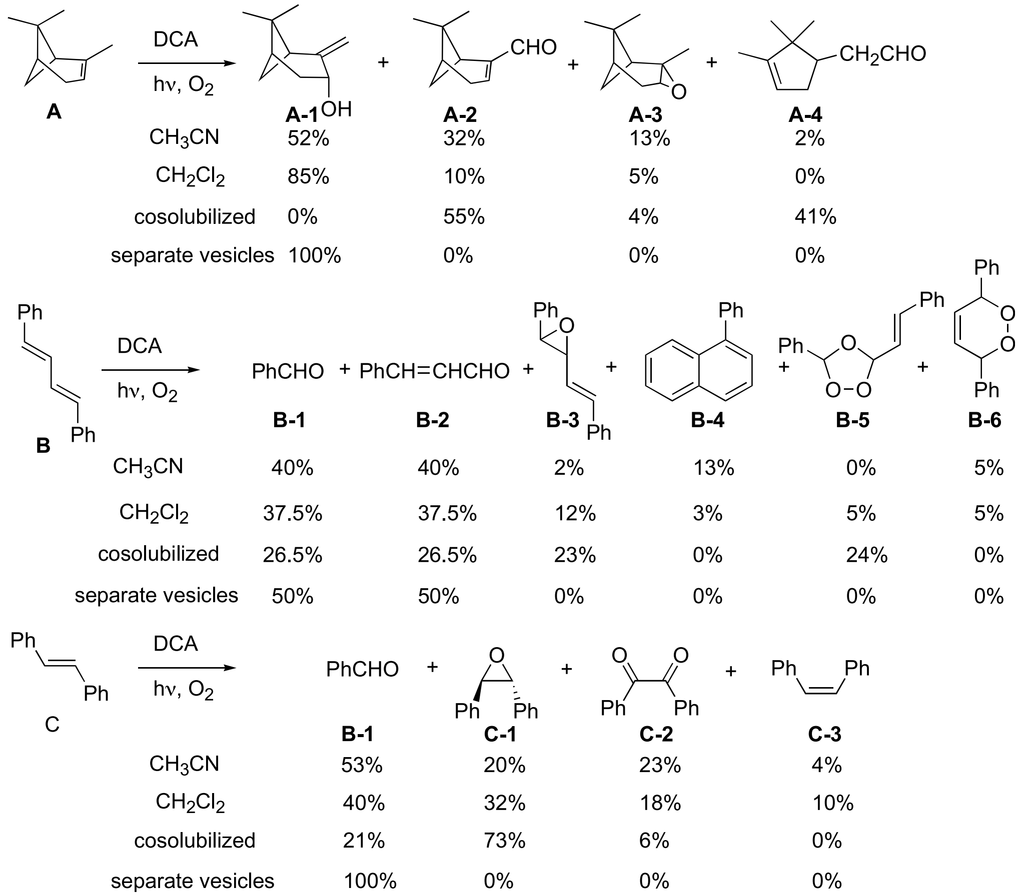
4.2. Micelles and vesicles

Photooxygenation reactions in micelles and vesicles have been examined extensively as models for the more complex microheterogeneous cellular environment, and to a lesser extent as a result of the expectation that these restrictive environments might influence reaction diastereoselectivity. The intense interest in photodynamic based therapies has provided the impetus for many of the cellular photooxygenation model studies. Singlet oxygen, a well-established oxidant in these photodynamic processes, has an average diffusion length of approximately 780 and 2500 nm in H_2O and D_2O, respectively, suggesting that cellular targets considerably removed from its loci of generation are susceptible to oxidative damage.[238] Indeed, inter-vesicle migration of singlet oxygen has been shown to occur with either neutral sensitizers like DCA or TPP that are located in the bilayer region of the vesicle or with charge sensitizers like methylene blue that are localized in the vesicle enclosed water pool.[239] The kinetic behavior of these model systems can be very complex since it is also well established that the quantum yield of singlet oxygen formation is a sensitive function of the sensitizers microheterogenous environment.[240] A detailed discussion of the complex kinetic treatments of photooxygenations in micelles and vesicles is beyond the scope of this manuscript, however, a recent expertly written review can be consulted for more details.[241]

Tung and co-workers[242,243] took advantage of the ability of vesicles to compartmentalize reagents and substrates to influence product distributions in photooxygenation reactions. Three examples using 9,10-dicyanoanthracene (DCA) as a sensitizer and vesicles composed of a 1:1 mixture of octyltrimethylammonium bromide and sodium laurate are shown in Scheme 38. DCA suffers from the feature that it acts both as a singlet oxygen and electron transfer sensitizer and consequently can produce very complicated product mixtures as shown for all three substrates in CH_3CN and



Scheme 37.



Scheme 38.

CH_2Cl_2. When the substrate and DCA are placed in the same vesicle formation of electron transfer products is preferred as a result of close contact of the sensitizer and substrate. On the other hand, when the substrate and sensitizer are placed in separate vesicles electron transfer products are completely suppressed in favor of the singlet oxygen products. This result is consistent with the fact that under the reaction conditions singlet oxygen has a sufficient lifetime to allow inter-vesicle migration while both the sensitizer and substrate are confined to their separate vesicles. In the case of substrate **A**, only product **A-1** is derived from singlet oxygen and it is the exclusive product when DCA and the substrate are physically separated but is completely suppressed when they are cosolubilized in the same vesicle. In the case of substrate **B**, products **B-2**, **B-3**, **B-4**, and **B-5** are derived from electron transfer and endoperoxide, **B-6**, from singlet oxygen, while **B-1** and **B-2** are formed in both electron transfer and singlet oxygen reactions. The absence of endoperoxide, **B-3**, even when DCA and **B** are in separate vesicles was attributed to the confined intra-vesicle environment which precluded population of the s-*cis* conformer needed for 4+2 cycloaddition of singlet oxygen. Finally, in the case of substrate **C** all four products are formed by electron transfer photooxygenation but only benzaldehyde is formed under singlet oxygen conditions. Consistent with that interpretation is the exclusive formation of benzaldehyde when *trans*-stilbene is physically isolated from DCA in separate vesicles.

5. Conclusion and future prospects

Efforts to understand the impact of the oxidative destruction of natural and manmade materials will continue to drive interest in singlet oxygen chemistry. In addition, increased emphasis on environmental and economic concerns will also generate significant synthetic interest in this readily available and green reagent to make novel natural products such as the litseaverticillols.[244] In particular, new methods to direct the stereo- and regiochemistry of singlet oxygen addition to organic and inorganic substrates are needed and the study of reactions in supramolecular systems will be at the forefront of this effort.

Acknowledgements

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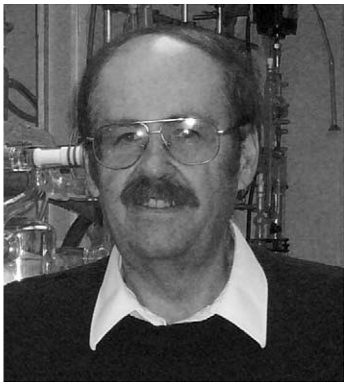
Biographical sketch



Edward L. Clennan was born in 1951 in St. Paul Minnesota. He received his BS degree in chemistry and mathematics from the University of Wisconsin at River Falls and his PhD from the University of Wisconsin at Madison. Prior to joining the faculty at the University of Wyoming he spent two years at Texas Christian University working as a postdoctoral fellow in the laboratory of Professor P. D. Bartlett. In addition, in recent years he spent a year at the National Science Foundation as a program officer and three years as Head of the Department of Chemistry at the University of Wyoming where he is currently a Professor of Chemistry. His research interests are in the area of oxidation chemistry in homogeneous and heterogeneous media. Current projects include the study of singlet oxygen reactions in zeolites and the development of new mechanistic tools to study organic reactions in homogeneous and heterogeneous media.

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Synthesis and reactions of a monosubstituted dithiirane 1-oxide, 3-(9-triptycyl)dithiirane 1-oxide

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Abstract—A 3-monosubstituted dithiirane 1-oxide, 3-(9-triptycyl)dithiirane 1-oxide, was prepared for the first time, by the reaction of (9-triptycyl)diazomethane and S_8O. The dithiirane 1-oxide was obtained as *cis*- and *trans*-isomers, and the structure of the *trans*-isomer was verified by X-ray crystallography. The *cis*-isomer isomerized gradually to the *trans*-isomer in solution. The divalent sulfur atom of the *cis*- and *trans*-dithiirane 1-oxides were removed on treatment with triphenylphosphine to give the corresponding *Z*- and *E*-sulfines, respectively. The reaction of the *trans*-dithiirane 1-oxide with $(Ph_3P)_2Pt(C_2H_4)$ provided the (sulfenato-thiolato)Pt^{II} complex, and that with Lawesson's reagent yielded the 1,3,4,2-trithiaphospholane and 1,2,4,5,3-tetrathiaphosphorinane derivatives.
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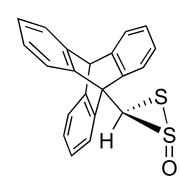
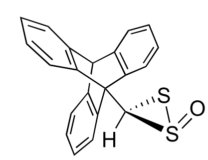
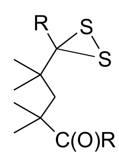
1. Introduction

We report here, the synthesis of 3-(9-triptycyl)dithiirane 1-oxide **1**, the first, isolable 3-monosubstituted dithiirane 1-oxide, and its physical and chemical properties. While dithiiranes had been recognized as elusive intermediates,[1–7] we discovered the formation of isolable dithiiranes **2** and dithiirane 1-oxides **3** by oxidative hydrolysis of bicyclic 1,3-dithietanes **4** and **5**, respectively.[8–14] We have also disclosed two routes for dithiirane oxides **6**: one is the elimination of S_2O from tetrathiolane 2,3-dioxides[15,16] and the other is the reaction of diazoalkanes with S_8O.[17] Dithiirane 1-oxides **6** can be led to the corresponding dithiiranes **7** by treatment with Lawesson's reagent (LR).[18] On the other hand, Shimada and co-workers succeeded in the synthesis of dithiiranes **8** and **9** by the reaction of the corresponding thioketone *S*-oxides (sulfines) with LR.[19] Mloston and Maier reported the isolation of the parent dithiirane in the argon matrix at 10 K together with the parent thioformaldehyde *S*-sulfide (thiosulfine).[20] Thus, dithiiranes isolated so far at room temperature in air are limited to 3,3-dialkyl- and 3-alkyl-3-aryldithiirane derivatives. 3-Monosubstituted dithiiranes are of great interest not only for their physical and chemical properties but also from the viewpoint of to what extent the steric demand of the substituent can be reduced for the intrinsically unstable dithiirane ring. Previously, we reported that reactions of (2,4,6-trimethyl-


trans-**1**


cis-**1**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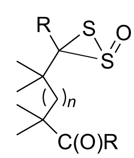
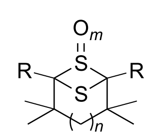
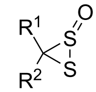

3: *n* = 0,1,2

R = aryl, *t*-Bu


4: *n* = 1; *m* = 0
5: *n* = 0,1,2; *m* = 1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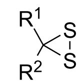
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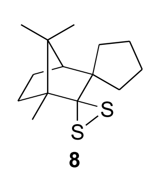
$R^1 = R^2$ = 1-adamantyl (1-Ad)
R^1 = 1-Ad; R^2 = *t*-Bu
R^1 = Ph; R^2 = *t*-Bu
R^1-R^2 = -$CMe_2CH_2CH_2CMe_2$-
R^1-R^2 = -CMe_2(*o*-C_6H_4)CMe_2-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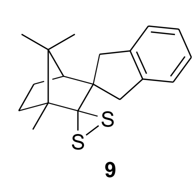
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Keywords: Dithiirane oxide; Steric protection; 9-Triptycyl; Diazo compound; Octasulfur monoxide.
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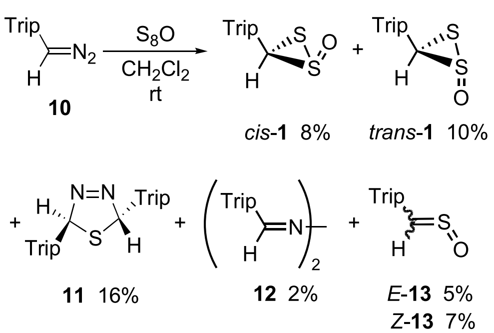
phenyl)- and (2,4,6-tri-*t*-butylphenyl)diazomathanes with S_8O failed to give the corresponding monosubstituted dithiirane 1-oxides.[17] Thus we next, employed 9-triptycyl as the substituent,[21] and the reaction of (9-triptycyl)diazomethane (**10**) with S_8O furnished the desired 3-monosubstituted dithiirane 1-oxide. Hereafter, the 9-triptycyl group is abbreviated to Trip for convenience.

2. Results and discussion

(9-Triptycyl)diazomethane (**10**), prepared by oxidation of the corresponding hydrazone ($TripCHNNH_2$), was treated with S_8O in dichloromethane at room temperature. After chromatographic purification, we obtained the desired *cis*-**1** [(1*R**,3*S**)-**1**] (8%) and *trans*-**1** [(1*S**,3*S**)-**1**] (10%) together with 1,3,4-thiadiazoline **11** (16%), azine **12** (2%), and sulfines *Z*-**13** (7%) and *E*-**13** (5%) (Eq. 1). The formation of **11** is explained by the reaction of **10** with TripCHS,[17,22] though TripCHS was not obtained in this reaction or in reactions reported later in this paper.[23] The stereochemistry of **11** was determined as *trans* by X-ray crystallography.[24] Azine **12** may be formed by the reaction of **10** with SO_2.[17,25–27] Sulfines **13** are the decomposition products of **1** on silica gel.



(1)

The structures of dithiirane 1-oxides, *cis*-**1** and *trans*-**1**, were elucidated by their spectroscopic data. In the ^1H NMR spectra (400 MHz) measured at 298 K, dithiirane ring protons of *cis*-**1** and *trans*-**1** appeared at δ 4.98 and 5.49, respectively. The low-field shift in *trans*-**1** is due to the anisotropic effect of the S=O group being *cis* to the proton.[28,29] At this temperature, three benzene rings of *cis*-**1** are not equivalent to each other, indicating that free rotation of the 9-triptycyl group in *cis*-**1** is slowed by the steric hindrance due to the *cis* oxygen atom.[30] In the ^{13}C NMR spectra, dithiirane ring carbons of *cis*-**1** and *trans*-**1** resonated at δ 66.7 and 66.9, respectively, and the ^1J (^{13}C–^1H) coupling constants determined with gated decoupling were 169 and 173 Hz, respectively. These ^1J (^{13}C–^1H) values are comparable to those of other three-membered cyclic compounds such as cyclopropane (161 Hz) and thiirane (171 Hz).[31] The stereochemistry of *trans*-**1** was verified by X-ray crystallography as depicted in Figure 1.

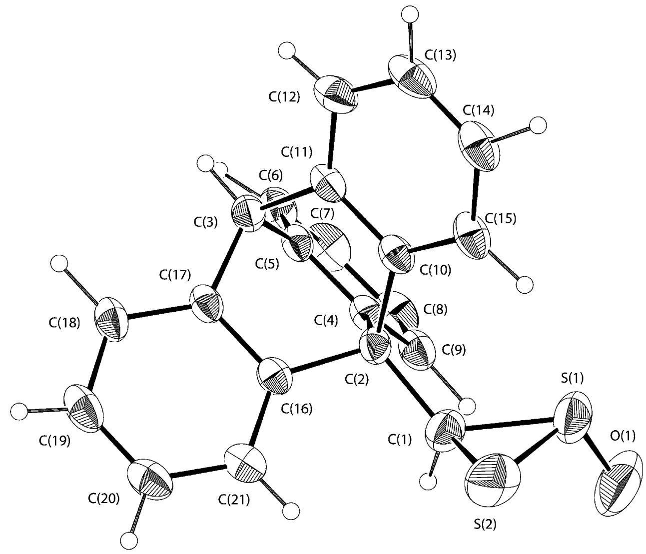
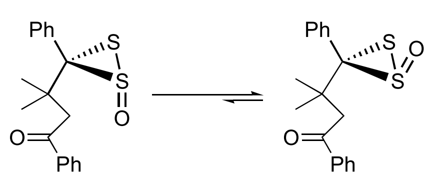


Figure 1. ORTEP drawing of *trans*-**1** (30% ellipsoidal probability). Relevant bond lengths (Å) and bond angles (deg) data: S1–O1 1.436(6), S1–C1 1.787(5), S1–S2 2.119(3), S2–C1 1.798(5), C2–C16 1.521(5), C2–C10 1.533(6), C2–C4 1.537(5), C2–C1 1.540(6), O1–S1–C1 113.2(3), O1–S1–S2 115.8(4), C1–S1–S2 54.01(18), C1–S2–S1 53.53(18), C16–C2–C10 105.7(3), C16–C2–C4 105.6(3), C10–C2–C4 105.9(3), C16–C2–C1 111.0(4), C10–C2–C1 119.7(4), C4–C2–C1 108.0(4), C2–C1–S1 123.4(4), C2–C1–S2 124.3(4), S1–C1–S2 72.5(2).

cis-**1** was not obtained in the pure form by chromatographic purification or recrystallization because of its gradual isomerization to *trans*-**1** in solution. The reverse isomerization from *trans*-**1** to *cis*-**1** was not observed under similar conditions. Standing a $CDCl_3$ solution of *cis*-**1** at room temperature in the dark for 3 months led to the complete disappearance of *cis*-**1** to leave *trans*-**1** (71%) and *Z*-**13** (29%) (Eq. 2). This isomerization apparently obeyed the first-order kinetics ($k = 4.0 \times 10^{-7}\ s^{-1}$, $r^2 = 0.966$). The presence of a small amount of a radical scavenger, 1,1-diphenyl-2-picryl hydrazyl (DPPH), led to substantial retardation of the isomerization ($k = 0.81 \times 10^{-7}\ s^{-1}$, $r^2 = 0.913$); after 1 month, the isomerization proceeded up to 57% without DPPH and down to 31% in the presence of DPPH, suggesting the isomerization is caused by a radical contaminant. We have observed a similar retardation of the epimerization between dithiirane 1-oxides **2** (R = Ph) and **2′** (R = Ph) by DPPH (Eq. 3).[32]

cis-**1** $\xrightarrow[\text{3 months}]{CDCl_3,\ rt}$ *trans*-**1** (71%) + *Z*-**13** (29%) (2)

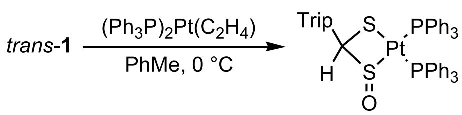


2 (R = Ph) **2′** (R = Ph) (3)

The divalent sulfur atom in a dithiirane 1-oxide is readily removed by treatment with tripheylphosphine to give the corresponding sulfine with retention of stereochemistry.[16] Treatment of *cis*-**1** and *trans*-**1** with triphenylphosphine gave *Z*-**13** and *E*-**13**, respectively, in high yields (Eqs. 4 and 5). The reaction of *trans*-**1** with $(Ph_3P)_2Pt(C_2H_4)$ yielded (sulfenato-thiolato)Pt^{II} complex **14** in 88% isolated yield.[33] When *cis*-**1** was allowed to react with $(Ph_3P)_2Pt(C_2H_4)$, the same complex was formed as the major product. A much low-field shift of the four-membered ring proton of **14** [δ 6.75 (d, $J = 2.3$ Hz)] compared with the corresponding dithiirane protons of *cis*-**1** (δ 4.98) and *trans*-**1** (δ 5.49) implies the *cis* configuration of the hydrogen to the S=O oxygen.

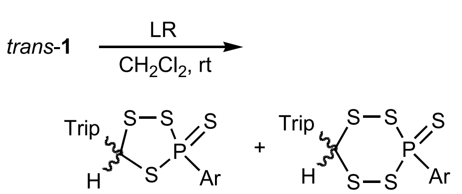
$$cis\text{-}\mathbf{1} \xrightarrow[CH_2Cl_2,\ 0\ °C]{PPh_3} Z\text{-}\mathbf{13}\ \ 72\% \quad (4)$$

$$trans\text{-}\mathbf{1} \xrightarrow[CH_2Cl_2,\ 0\ °C]{PPh_3} E\text{-}\mathbf{13}\ \ 88\% \quad (5)$$

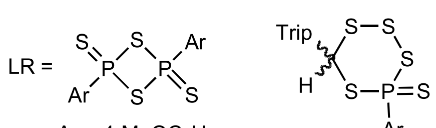


14 88% (6)

In the hope of obtaining the corresponding unoxidized dithiirane, *trans*-**1** was treated with LR in benzene at room temperature.[18] However, we obtained not the desired dithiirane but stereoisomers of 1,3,4,2-trithiaphospholanes **15a**,**b** and 1,2,4,5,3-tetrathiaphosphorinanes **16a**,**b**. The structures of **15a**,**b** and **16a**,**b** were elucidated by their ^{1}H, ^{13}C, and ^{31}P NMR data and mass spectroscopic data, though their stereochemistries were not determined. In the ^{1}H NMR of **15a**, the 1,3,4,2- trithiaphospholane ring proton appeared as a doublet with 2.7 Hz of the ^3J (^{1}H–^{31}P) coupling constant, and in the ^{13}C NMR, the ring carbon appeared as a doublet with 4.5 Hz of the ^2J (^{13}C–^{31}P) coupling constant. Similarly, the corresponding proton and carbon of **15b** resonated as a doublet. Such long-range couplings were not observed for **16a**,**b**, and their tetrathiaphosphorinane ring protons and the carbons appeared as a broad singlet. These observations would rule out 1,2,3,5,4-tetrathiaphosphorinane structures **17** for the six-membered compounds. Compounds **15a**,**b** formally correspond to adducts of $TripCHS_2$ with $ArPS_2$ (Ar=4-$MeOC_6H_4$), and **16a**,**b** correspond to those of $TripCHS_3$ with $ArPS_2$. Incidentally, we have recently, obtained adducts of thioketones with $ArPS_2$, which are 1,3,2-dithiaphosphetane derivatives.[34] Noteworthy is the formation of trithiaphospholanes **15a** and **15b** by the reaction of sulfine *Z*-**13** with LR in 31 and 17% yields, respectively. It has been reported that the reaction of a sulfine with LR gave the dithiirane.[19] At present, however, we do not have direct evidence of intervention of $TripCHS_2$ in these reactions.



15a: δ_p 101.8 (22%) **16a**: δ_p 91.2 (41%)
15b: δ_p 108.0 (6%) **16b**: δ_p 94.1 (13%) (7)



Ar = 4-$MeOC_6H_4$ **17**

3. Conclusion

3-Monosubstituted dithiirane 1-oxides *trans*-**1** and *cis*-**1** were successfully synthesized, for the first time, by taking advantage of a 9-triptycyl group as the steric-demanding group. The dithiirane 1-oxides **1** presented reactivities similar to those of 3,3-disubstituted dithiirane 1-oxides but the reaction with LR gave sulfur–phosphorus-containing heterocycles.

4. Experimental

4.1. General

The melting points were determined on a Mel-Temp capillary tube apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were determined on Bruker AM400 or DRX400 (400 and 100.6 MHz, respectively), AC300P (300 MHz for ^{1}H), or AC200 (200 and 50 MHz, respectively), spectrometers using $CDCl_3$ as the solvent at 25 °C, unless otherwise noted. ^{31}P NMR spectra were determined on Bruker AM400 or DRX400 (162 MHz) spectrometers using 85% H_3PO_4 as the external standard in $CDCl_3$ at 25 °C. IR spectra were taken on a Hitachi 270-50 spectrometer. Mass spectra were determined on a JEOL JMS-DX303 or a JEOL JMS-700AM spectrometers operating at 70 eV in the EI mode. FAB MS was measured with *m*-nitrobenzyl alcohol as the matrix. Elemental analysis was performed by the Chemical Analysis Center of Saitama University. Column chromatography was performed with silica gel (70–230 mesh), high-pressure liquid chromatography (HPLC) with a packed SiO_2 column (INERTSIL PREP-SIL: 10 mm i.d. or 20 mm i.d., GL Science Inc.), and gel permeation chromatography (GPC) on a Japan Analytical Industry LC-908; the eluent is shown in parentheses.

4.2. Preparation of (9-triptycyl)diazomethane (10)

4.2.1. Preparation of triptycene-9-carbaldehyde. Butyllithium (1.56 M in hexane, 5.6 mL, 8.74 mmol) was added to a solution of 9-bromotriptycene[35] (1.42 g, 4.25 mmol) in benzene (60 mL) and ether (95 mL) at −15 °C under argon, and the solution was stirred for 1 h at −15 °C. To the solution was added ethyl formate (5.6 mL, 69 mmol), and the mixture was warmed to room temperature. After stirring for 15 min, aqueous ammonium chloride and then ether were added to the mixture. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (CH_2Cl_2/hexane 1:1) to give the aldehyde (825 mg, 69%).

Triptycene-9-carbaldehyde.[36] Colorless crystals. ^{1}H NMR (300 MHz) δ 5.40 (s, 1H), 6.98–7.05 (m, 6H), 7.40–7.44 (m, 3H), 7.59–7.63 (m, 3H), 11.22 (s, 1H).

4.2.2. Preparation of triptycene-9-carbaldehyde hydrazone. A solution of triptycene-9-carbaldehyde (1.40 g, 4.96 mmol) and hydrazine monohydrate (22 mL, 0.41 mol) in diethylene glycohol (50 mL) was refluxed for 0.5 h. The mixture was cooled to room temperature, diluted with water, and then extracted with dichloromethane. The extract was washed with water and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (CH_2Cl_2) to give the hydrazone (1.438 g, 98%).

Triptycene-9-carbaldehyde hydrazone. Colorless powder, mp >352 °C decomp. (EtOH–water). ^{1}H NMR (400 MHz) δ 5.39 (s, 1H), 5.93 (br s, 2H), 6.95–7.05 (m, 6H), 7.35–7.43 (m, 3H), 7.56–7.65 (m, 3H), 8.44 (s, 1H); ^{13}C NMR (100.6 MHz) δ 54.3 (CH), 54.6 (C), 123.0 (CH), 123.6 (CH), 124.9 (CH), 125.2 (CH), 141.1 (CH), 145.4 (C), 145.8 (C); IR (KBr) 3378 (NH_2), 1455, 754, 729 cm^{-1}. Anal. Found: C, 84.09; H, 5.53; N, 9.23. Calcd for $C_{21}H_{16}N_2\cdot 0.112C_2H_6O\cdot 0.213H_2O$: C, 83.48; H, 5.64; N, 9.17 (the ^{1}H NMR spectrum of the sample subjected to the elemental analysis showed that it contained 11.2 mol% of ethanol and 21.3 mol% of H_2O).

4.2.3. Preparation of (9-triptycyl)diazomethane (10). To a solution of triptycene-9-carbaldehyde hydrazone (221 mg, 0.745 mmol) in benzene was added 378 mg (1.54 g-atom of oxygen) of nickel peroxide (4.08×10^{-3} g-atom of oxygen/g).[37,38] The mixture was stirred for 1 h at room temperature. After filtration, the solvent was removed under reduced pressure to give (9-triptycyl)diazomethane (**10**). The diazomethane was used without further purification.

9-Triptycyl)diazomethane (**10**).[39] Orange oil. ^{1}H NMR (300 MHz) δ 5.07 (s, 1H), 5.42 (s, 1H), 7.01–7.09 (m, 6H), 7.38–7.43 (m, 6H); IR (neat) 2063, 1456, 748 cm^{-1}.

4.3. Reaction of (9-triptycyl)diazomethane (10) with S_8O

A mixture of S_8O[40] (415 mg, 1.53 mmol) and **10**, prepared above, in dichloromethane (45 mL) under argon was stirred for 1.5 h at room temperature. The solvent was evaporated to dryness, and the residue was passed through a short column of silica gel (dichloromethane). The fraction containing products was further subjected to HPLC (dichloromethane/hexane 60:40 and then 80:20 for *E*-**5**) to give a mixture of thiadiazoline **11** and azine **12**, *cis*-dithiirane 1-oxide *cis*-**1** (21.7 mg, 8%), *trans*-dithiirane 1-oxide *trans*-**1** (26.2 mg, 10%), *Z*-sulfine *Z*-**5** (16 mg, 7%), and *E*-sulfine *E*-**5** (11.8 mg, 5%) in this order. The mixture of **11** and **12** was subjected to GPC ($CHCl_3$) and again HPLC (dichloromethane/hexane 40:60) to give thiadiazoline **11** (36.5 mg, 16%) and azine **12** (4 mg, 2%).

4.3.1. *t*-3-(9-Triptycyl)dithiirane *r*-1-oxide (*trans*-1). Mp 186–187 °C (Et_2O–CH_2Cl_2). ^{1}H NMR (400 MHz): 300 K: δ 5.40 (s, 1H), 5.49 (s, 1H), 6.90 (br s, 1H), 7.09 (br s, 6H), 7.43 (br s, 3H), 7.83 (br s, 2H); 323 K: δ 5.36 (s, 1H), 5.47 (s, 1H), 6.80–8.06 (br s, 3H), 7.03 (br s, 6H), 7.38–7.41 (m, 3H); ^{13}C NMR (100.6 MHz, 323 K) δ 54.5 [CH, ^1J (^{13}C–^{1}H) = 138 Hz], 55.0 (C), 66.9 [CH, ^1J (^{13}C–^{1}H) = 173 Hz], 122.6 (br, CH), 124.0 (CH), 125.4 (CH), 126.0 (CH), 143.9 (br, C), 146.2 (C); IR (KBr) 1460, 1128 (S=O), 742 cm^{-1}. Anal. Calcd for $C_{21}H_{14}OS_2$: C, 72.80; H, 4.07. Found: C, 72.43; H, 3.93.

Crystallographic data for trans-**1**. $C_{21}H_{14}OS_2$, M_w = 346.470, colorless plate, $0.20\times 0.12\times 0.06$ mm^3, monoclinic, $P2_1/c$, a = 15.761(2) Å, b = 8.1384(13) Å, c = 13.756(2) Å, b = 112.596(12)°, V = 1629.0(5) Å^3, ρ_{calcd} = 1.413 g cm^{-3}, Z = 4, μ(Cu Kα) = 2.981 cm^{-1}. Mac Science MXC3KHF diffractometer with graphite-monochromated Cu Kα radiation (λ = 1.54178 Å), $\theta/2\theta$ scans method in the range $3° < 2\theta < 140°$ ($-19 < h < 17$, $0 < k < 9$, $0 < l < 16$), 2740 independent reflections. Absorption correction was done by the psi-can method.[41] The structure was solved with a direct method (SIR97[42]) and refined with full-matrix least-squares (SHELXL-97[43]) using all independent reflections, where nonhydrogen atoms were refined anisotropically and hydrogen atoms isotropically without the AFIX code except C(1)–*H*. $R1$ = 0.0894 ($I > 2\sigma I$, 2485 reflections), w$R2$ = 0.2674 (for all), GOF = 1.070, 271 parameters; max/min residual electron density = 1.021/−0.542 e Å^{-3}. CCDC-268216 contains the supplementary crystallographic data. 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: (internat.) +44-1223 336-033; E-mail: deposit@ccdc.cam.ac.uk].

4.3.2. *c*-3-(9-Triptycyl)dithiirane *r*-1-oxide (*cis*-1). ^{1}H NMR (400 MHz) δ 4.98 (s, 1H), 5.42 (s, 1H), 6.86 (td, J = 7.7, 1.3 Hz, 1H), 6.94 (td, J = 7.4, 0.9 Hz, 1H), 7.03–7.21 (m, 4H), 7.34 (dd, J = 7.2, 1.1 Hz, 1H), 7.43–7.48 (m, 3H), 7.92 (d, J = 8.6 Hz, 1H), 7.94 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 54.5 [two carbons: CH with ^1J (^{13}C–^{1}H) = 141 Hz and C], 59.9 [CH, ^1J (^{13}C–^{1}H) = 169 Hz], 121.6 (CH), 121.9 (CH), 123.2 (CH), 123.78 (CH), 123.82 (CH), 124.0 (CH), 125.1 (CH), 125.3 (CH), 125.5 (CH), 126.0 (CH), 126.1 (CH), 128.0 (CH), 141.4 (C), 143.3 (C), 145.4 (C), 146.1 (C), 146.2 (C), 146.8 (C); IR (KBr) 1462, 1130, 1122 (S=O), 752 cm^{-1}.

4.3.3. 2,5-Di-(9-triptycyl)-1,3,4-thiadiazoline (11). Colorless crystals, mp 207–210 °C decomp. (hexane–CH_2Cl_2). ^{1}H NMR (300 MHz) δ 5.49 (s, 2H), 6.85 (d, J = 7.7 Hz, 2H), 6.98–7.12 (m, 10H), 7.19 (td, J = 7.7, 1.4 Hz, 2H), 7.45–7.53 (m, 6H), 7.59 (d, J = 7.4 Hz, 2H), 8.10 (s, 2H), 8.54 (d, J = 7.7 Hz, 2H); ^{13}C NMR (100.6 MHz) δ 54.8 (CH), 59.0 (C), 102.6 (CH), 121.8 (CH), 122.7 (CH), 123.5 (CH), 123.8 (CH), 124.2 (CH), 124.6 (CH), 124.8 (CH), 125.1 (CH), 125.2 (CH), 125.5 (CH), 125.7 (CH), 126.0 (CH), 141.1 (C), 145.0 (C), 145.1 (C), 146.0 (C), 146.4 (C), 147.2 (C); IR (KBr) 1458, 744 cm^{-1}. Anal. Found: C, 81.31; H, 4.98; N, 4.27. Calcd for $C_{42}H_{28}N_2S\cdot 0.354CH_2Cl_2\cdot 0.261C_6H_{14}$: C, 81.74; H, 5.06; N, 4.34 (the ^{1}H NMR spectrum of the sample subjected to the elemental analysis showed that it contained 35.4 mol% of CH_2Cl_2 and 26.1 mol% of hexane).

4.3.4. Triptycene-9-carbaldehyde azine (12).[39] Colorless crystals, mp >352 °C decomp. ($CHCl_3$). ^{1}H NMR (400 MHz) δ 5.50 (s, 2H), 7.06–7.14 (m, 12H), 7.47–7.49 (m, 6H), 7.85–7.88 (m, 6H), 9.72 (s, 2H); ^{13}C NMR (100.6 MHz) δ 54.5 (CH), 55.4 (C), 123.1 (CH), 123.9 (CH), 125.2 (CH), 125.7 (CH), 144.5 (C), 145.9 (C), 164.4 (CH); IR (KBr) 1661, 1456, 758 cm^{-1}. Anal. Found: C, 88.79; H, 4.87; N, 4.92. Calcd for $C_{42}H_{28}N_2\cdot 0.0457CHCl_3$: C, 89.20; H, 4.99; N, 4.95 (the ^{1}H NMR spectrum, measured in CD_2Cl_2, of the sample subjected to the elemental analysis showed that it contained at least 4.57 mol% of $CHCl_3$).

4.3.5. (9-Triptycyl)methanethial (*E*)-*S*-oxide (*E*-13). Colorless crystals, mp 239–241 °C (CH_2Cl_2–hexane). ^{1}H NMR (400 MHz) δ 5.45 (s, 1H), 7.02–7.09 (m, 6H), 7.40–7.46 (m, 6H), 10.15 (s, 1H); ^{13}C NMR (100.6 MHz) δ 54.1 (CH), 58.2 (C), 122.1 (CH), 124.1 (CH), 125.3 (CH), 126.1 (CH), 143.9 (C), 145.1 (C), 180.1 (CH); IR (KBr) 1457, 1103 (S=O), 743 cm^{-1}. MS (EI) *m/z* 314 (M$^+$). HRMS (EI): Calcd for $C_{21}H_{14}OS$: *M* 314.0765. Found: *m/z* 314.0792. Anal. Calcd for $C_{21}H_{14}OS$: C, 80.22; H, 4.49. Found: C, 79.53; H, 4.40.

4.3.6. (9-Triptycyl)methanethial (*Z*)-*S*-oxide (*Z*-13). Colorless crystals, mp 245–246 °C (CH_2Cl_2–hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 (s, 1H), 7.03–7.08 (m, 6H), 7.37–7.42 (m, 3H), 7.42–7.47 (m, 3H), 9.01 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 54.1 (CH), 60.5 (C), 121.8 (CH), 124.2 (CH), 125.1 (CH), 126.0 (CH), 141.0 (C), 144.7 (C), 165.5 (CH); IR (KBr) 1457, 1120 (S=O), 753 cm^{-1}; MS (EI) *m/z* 314 (M$^+$). HRMS (EI): Calcd for $C_{21}H_{14}OS$: *M* 314.0765. Found: *m/z* 314.0774. Anal. Calcd for $C_{21}H_{14}OS$: C, 80.22; H, 4.49. Found: C, 80.04; H, 4.41%.

4.4. Reaction of dithiirane 1-oxides *cis*-1 and *trans*-1 with triphenylphosphine

Dithiirane 1-oxide *cis*-**1** (7.0 mg, 0.02 mmol) and triphenylphosphine (5.6 mg, 0.021 mmol) were dissolved in dichloromethane (4 mL) under argon, and the solution was stirred at 0 °C for 5 min. The solvent was removed under reduced pressure, and the residue was subjected to HPLC (dichloromethane/hexane 65:35) to give sulfine *Z*-**13** (4.5 mg, 72%).

In a similar manner, *trans*-**1** (11 mg, 0.032 mmol) was treated with triphenylphosphine (8.6 mg, 0.033 mmol) in dichloromethane (3 mL) to yield *E*-**13** (8.9 mg, 88%).

4.5. Reaction of dithiirane 1-oxides *trans*-1 with $(Ph_3P)_2Pt(C_2H_4)$

To a solution of *trans*-**1** (15.8 mg, 0.456 mmol) in toluene (5 mL) under argon at 0 °C was added a solution of $(Ph_3P)_2Pt(C_2H_4)$ (34.1 mg, 0.456 mmol) in toluene (4 mL). The mixture was stirred for 1 h at 0 °C, and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (dichloromethane/ether 3:1) to give (sulfenato-thiolato)Pt^{II} complex **14** (42.5 mg, 88%).

4.5.1. [(9-Triptycyl)methanedithiolato(2-)-κ*S*,κ*S*′]bis(triphenylphosphine)platinum *S*-oxide (14). Yellow crystals, mp 192–193 °C decomp. (hexane–$CHCl_3$). ^{1}H NMR (400 MHz) δ 5.23 (s, 1H), 6.75 (d, J=2.3 Hz, 1H), 6.81–6.89 (m, 3H), 6.92 (td, J=7.5, 1.3 Hz, 1H), 7.05 (td, J=7.4, 0.7 Hz, 1H), 7.13 (td, J=7.5, 1.2 Hz, 1H), 7.17–7.21 (m, 13H), 7.23–7.32 (m, 6H), 7.36 (dd, J=7.3, 0.7 Hz, 1H), 7.44–7.53 (m, 13H), 7.82 (d, J=7.5 Hz, 1H), 8.14 (d, J=7.5 Hz, 1H), 8.55 (d, J=7.6 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 54.9 (CH), 64.4 (C), 75.4 (CH), 122.7 (CH), 123.0 (CH), 123.2 (CH), 123.3 (CH), 124.2 (CH), 124.36 (CH), 124.44 (CH), 124.5 (CH), 124.6 (2CH), 125.5 (CH), 127.0 (CH), 127.9 (CH, L), 128.0 (CH, L), 128.1 (CH, L), 128.2 (CH, L), 129.4 (C, L), 129.7 (C, L), 129.8 (C, L), 130.3 (C, L), 130.4 (*p*-CH, L), 134.2 (CH, L), 134.3 (CH, L), 134.5 (CH, L), 134.6 (CH, L), 143.4 (C), 144.1 (C), 144.8 (C), 146.6 (C), 146.7 (C), 147.0 (C) [L in the parentheses means that the signal is due to the Ph_3P ligand. Their J (^{13}C–^{31}P) coupling constants are not determined, and signals due to the Ph_3P ligands are listed as appeared]; ^{31}P NMR (162 MHz) δ 16.2 [d, ^2J (^{31}P–^{31}P)= 25 Hz, ^1J (^{31}P–^{195}Pt)=2418 Hz], 17.7 [d, ^2J (^{31}P–^{31}P)= 25 Hz, ^1J (^{31}P–^{195}Pt)=3189 Hz]; IR (KBr) 1484, 1460, 1438, 1096 (S=O), 1000, 982, 746, 692 cm^{-1}. Calcd for: $C_{57}H_{44}OP_2PtS_2\cdot CHCl_3$: C, 58.76; H, 3.83. Found: C, 58.28; H, 3.74.

4.6. Reaction of dithiirane 1-oxide *trans*-1 with Lawesson's reagent (LR)

A solution of dithiirane 1-oxide *trans*-**1** (31.4 mg, 0.091 mmol) and LR (76.2 mg, 0.188 mmol, Sigma-Aldrich Co.) in dichloromethane (15 mL) under argon was stirred for 4 h at room temperature. The solvent was removed under reduced pressure. Polar decomposition products of LR were removed by passing the residue through a short column of silica gel (dichloromethane), and a mixture containing the products thus obtained was subjected to HPLC (dichloromethane/hexane 45:55) to give tetrathiaphosphorinane **16a** (the major isomer) (20.8 mg, 41%), a 37:63 mixture of tetrathiaphosphorinane **16b** (the minor isomer) (13%) and trithiaphospholane **15a** (the major isomer) (22%), and trithiaphospholane **15b** (the minor isomer) (3.1 mg, 6%) in this order. A mixture of **16b** and **15a** could be separated with HPLC (dichloromethane/hexane 40:60) to give pure **16a** and **15a** in this order.

4.6.1. 1,2,4,5,3-Tetrathiaphosphorinane (16a). White powder, mp 219–221 °C decomp. (CH_2Cl_2–hexane). ^{1}H NMR (400 MHz) δ 3.94 (s, 3H), 5.34 (s, 1H), 6.19 (br s, 1H), 6.97–7.10 (m, 4H), 7.10–7.21 (m, 4H), 7.21–7.45 (m, 3H), 7.47 (dd, J=7.0, 1.0 Hz, 1H), 8.03 (br s, 1H), 8.31 (br s, 1H), 8.44 (dd, J=13.1, 8.8 Hz, 2H); ^{13}C NMR (100.6 MHz) δ 54.6 (CH), 55.7 (CH_3), 59.5 (br s, CH), 61.6 (br s, C), 114.4 [d, J (^{13}C–^{31}P)=15 Hz, CH), 122.0 (br s, CH), 123.7 (br s, 2CH), 124.0 (br s, 2CH), 124.6 (2CH), 125.3 (CH), 125.6 (br s, 3CH), 126.3 (CH) 134.5 [d, J (^{13}C–^{31}P)=12 Hz, CH], 139.9 (C), 144.3 (2C), 145.0 (C), 146.4 (C), 147.3 (C), 164.4 [d, J (^{13}C–^{31}P)=3 Hz, C] (the quaternary carbon bonded to the P atom was not observed probably because of overlapping with signals due to CH carbons); ^{31}P NMR (162 MHz) δ 91.2; MS (FAB) *m/z* 565 (M$^+$+1). Anal. Calcd for $C_{28}H_{21}OPS_5$: C; 59.55%, H; 3.75%. Found: C; 59.53%, H; 3.63%.

4.6.2. 1,2,4,5,3-Tetrathiaphosphorinane (16b). Off-white powder, mp 172–177 °C decomp. (MeOH–MeCN). ^{1}H NMR (400 MHz) δ 3.93 (s, 3H), 5.34 (s, 1H), 6.32 (br s, 1H), 6.98–7.15 (m, 8H), 7.34–7.37 (m, 2H), 7.46–7.65 (m, 2H), 7.96 (br s, 1H), 8.09 (br s, 1H), 8.29 (dd, J=13.6, 8.8 Hz, 2H); ^{13}C NMR (100.6 MHz) δ 54.5 (CH), 55.7 (CH_3), 61.3 (br s, CH and C), 114.5 [CH, J (^{13}C–^{31}P)= 15 Hz], 122.5 (br s, CH), 123.8 (br s, 3CH), 124.1 (CH), 124.8 (3CH), 125.2 (br s, CH), 125.6 (br s, 2CH), 126.2 (CH), 133.5 [d, J (^{13}C–^{31}P)=13 Hz, CH), 140.1 (br s, C), 144.2 (2C), 145.3 (C), 145.4–147.3 (2C), 164.1 (C) (the quaternary carbon bonded to the P atom was not observed probably because of overlapping with signals due to CH carbons); ^{31}P NMR (162 MHz) δ 94.1; MS (EI) *m/z* (rel. intensity) 564 (M^+, 3), 298 (100), 265 (74), 253 (67), 252 (65). The intensity ratio of *m/z* 564 (M^+)/565 ($M^+ + 1$)/566 ($M^+ + 2$) was 100/34.1/28.8, which is consistent with the calculated value of 100/35.8/28.6 for $C_{28}H_{21}OPS_5$.

4.6.3. 1,3,4,2-Trithiaphospholane (15a). White powder, mp 199–200 °C decomp. (MeOH–MeCN). ^{1}H NMR (400 MHz) δ 3.90 (s, 3H), 5.36 (s, 1H), 6.75 [d, *J* (^{1}H-^{31}P) = 2.7 Hz, 1H], 6.95–7.13 (m, 7H), 7.19 (td, *J* = 7.5, 1.1 Hz, 1H), 7.33–7.40 (m, 2H), 7.46 (d, *J* = 7.0 Hz, 1H), 7.52–7.56 (m, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 8.35 (dd, *J* = 14.2, 8.8 Hz, 2H), 8.83 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 54.5 (CH), 55.7 (CH_3), 57.5 [d, *J* (^{13}C–^{31}P) = 5 Hz, C), 74.4 [d, *J* (^{13}C–^{31}P) = 6 Hz, CH], 114.5 [d, *J* (^{13}C–^{31}P) = 15 Hz, CH], 122.2 [d, *J* (^{13}C–^{31}P) = 11 Hz, CH], 122.7 [d, *J* (^{13}C–^{31}P) = 85 Hz, C], 123.4 (CH), 123.6 (CH), 123.7 (CH), 123.8 (CH), 124.76 (CH), 124.80 (CH), 125.0 (CH), 125.7 (CH), 125.8 (CH), 126.0 (CH), 126.9 (CH), 134.9 [d, *J* (^{13}C–^{31}P) = 14 Hz, CH], 139.5 (C), 144.0 (C), 145.0 (C), 145.5 (C), 146.3 (C), 147.2 (C), 163.9 [d, *J* (^{13}C–^{31}P) = 3 Hz, C); ^{31}P NMR (162 MHz) δ 101.8; MS (EI) *m/z* (rel. intensity) 532 (M^+, 5), 298 (100), 265 (72), 252 (63). The intensity ratio of *m/z* 532 (M^+)/533 ($M^+ + 1$)/534 ($M^+ + 2$) was 100/33.8/25.4, which is consistent with the calculated value of 100/35.0/23.9 for $C_{28}H_{21}OPS_4$.

4.6.4. 1,3,4,2-Trithiaphospholane (15b). Off-white powder, mp 198–200 °C (MeOH–MeCN). ^{1}H NMR (400 MHz) δ 3.93 (s, 3H), 5.34 (s, 1H), 6.84–6.90 (m, 2H δ 6.86 [d, *J* (^{1}H-^{31}P) = 5.9 Hz]), 6.98–7.10 (m, 7H), 7.34–7.38 (m, 2H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.81 (d, *J* = 7.5 Hz, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 8.18 (dd, *J* = 15.0, 8.6 Hz, 2H); ^{13}C NMR (100.6 MHz) δ 54.5 (CH), 55.6 (CH_3), 57.8 [d, *J* (^{13}C–^{31}P) = 5 Hz, C], 73.9 [d, *J* (^{13}C–^{31}P) = 6 Hz, CH), 114.4 [d, *J* (^{13}C–^{31}P) = 16 Hz, CH], 123.2 (CH), 123.3 (CH), 123.6 (CH), 123.8 (CH), 124.0 (CH), 124.3 (CH), 124.9 (CH), 125.1 (CH), 125.4 (CH), 125.7 (CH), 125.8 (CH), 126.2 (CH), 129.0 [d, *J* (^{13}C–^{31}P) = 83 Hz, C], 133.1 [d, *J* (^{13}C–^{31}P) = 14 Hz, CH], 139.9 (C), 143.8 (C), 145.0 (C), 145.5 (C), 146.1 (C), 147.0 (C), 163.3 [d, *J* (^{13}C–^{31}P) = 4 Hz, C); ^{31}P NMR (162 MHz) δ 108.0; MS (EI) *m/z* (rel. intensity) 532 (M^+, 4), 298 (100), 265 (73), 252 (62). The intensity ratio of *m/z* 532 (M^+)/533 ($M^+ + 1$)/534 ($M^+ + 2$) was 100/35.4/24.0, which is consistent with the calculated value of 100/35.0/23.9 for $C_{28}H_{21}OPS_4$.

4.7. Reaction of sulfine *Z*-13 with LR

A mixture of *Z*-**13** (29 mg, 0.091 mmol) and LR (74.7 mg, 0.185 mmol) in dichloromethane was stirred under argon at room temperature for 7 h. The solvent was removed under reduced pressure, and the residue was subjected to a short column of silica gel (dichloromethane) to remove derivatives of LR. A mixture of **15a** and **15b** thus obtained was separated with HPLC (CH_2Cl_2/hexane 45:50) to give **15a** (15 mg, 31%) and **15b** (8.0 mg, 17%).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.05.017

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Cytotoxic dimeric sesquiterpenoids from *Curcuma parviflora*: isolation of three new parviflorenes and absolute stereochemistry of parviflorenes A, B, D, F, and G

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Abstract—Three novel dimeric sesquiterpenoids, named parviflorenes G–I (**1–3**), have been isolated from *Curcuma parviflora* (Zingiberaceae), and their structures were elucidated by means of spectroscopic studies. Absolute stereochemistry of parviflorene G (**1**) as well as previously isolated related compounds, parviflorenes A (**4**), B (**5**), D (**6**), and F (**7**), was revealed by CD spectral data and chemical means. Parviflorenes G (**1**) and I (**3**) were cytotoxic against HeLa cells, while parviflorenes A (**4**) and F (**7**) were cytotoxic against all tested tumor cell lines in the human cancer cell line panel assay.
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1. Introduction

During our search for bioactive natural products from tropical plants,[1] we investigated the chemical constituents of *Curcuma parviflora* Wall. (Zingiberaceae) collected in Thailand. This plant is a perennial herb widely distributed over a forest area of the northern part of Thailand, and is used as an ornamental plant, and is edible, and also it has been said to be used for detoxification of scorpion bites in certain areas. We recently isolated cytotoxic sesquiterpene-dimers, parviflorenes A–F from this plant, and their structures were elucidated by spectroscopic studies including X-ray crystal analysis.[2,3] Further investigation of extracts of the underground part of this plant led to the isolation of three more new dimeric sesquiterpenoids, parviflorenes G–I (**1–3**). Here we describe isolation and structure elucidation of **1–3** and studies on determination of absolute stereochemistry of parviflorenes A (**4**), B (**5**), D (**6**), F (**7**), and G (**1**). Parviflorenes A (**4**) and F (**7**) were cytotoxic against all tested tumor cell lines in the human cancer cell line panel assay.

Keywords: Zingiberaceae; *Curcuma parviflora*; Dimeric sesquiterpene; Absolute stereochemistry; Cytotoxicity.
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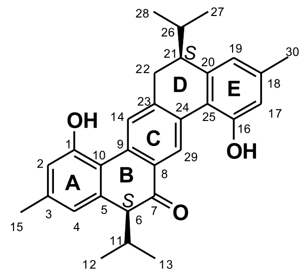
2. Results and discussions

We have isolated parviflorenes A–F from the EtOAc-soluble fraction of the MeOH extracts, combined with previously obtained EtOAc and *n*-BuOH-soluble fractions of the underground part of *C. parviflora*.[2,3] Further fractionations of this extract using repeated chromatography on silica gel and Sephadex LH-20 as well as purification with HPLC on ODS afforded three new compounds, parviflorenes G–I (**1–3**).

Parviflorene G (**1**) was obtained as yellow amorphous solids, $[\alpha]_D^{24}+200$ (*c* 0.27, MeOH), and the molecular formula was established to be $C_{30}H_{32}O_3$ by its HRFABMS data (*m*/*z* 440.2367, M^+, Δ +1.6 mmu). The ^{1}H NMR spectrum of **1** (Table 1) showed signals of two tertiary methyls attached on sp^2 carbons [δ_H 2.28 (3H, s) and 2.29 (3H, s)] and six aromatic ring protons. The ^{13}C NMR spectrum of **1** (Table 1) showed the presence of 18 aromatic carbons, one carbonyl, and 11 sp^3 carbons. Since 10 out of 15 unsaturation degrees were thus accounted for, **1** was implied to be a pentacyclic compound. The ^{1}H NMR also showed signals due to four secondary methyl groups, which were assigned to two isopropyl groups from the analysis of the ^{1}H–^{1}H COSY spectrum (H_3-12/H-11/H_3-13 and H_3-27/H-26/H_3-28). These spectral features were almost similar



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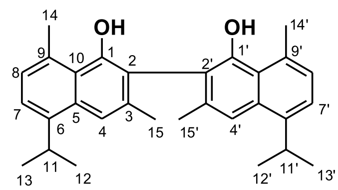

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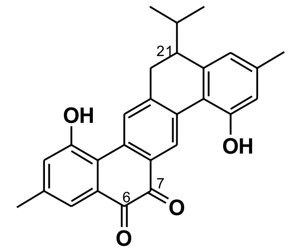

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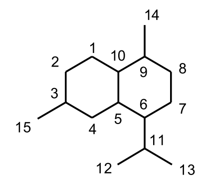

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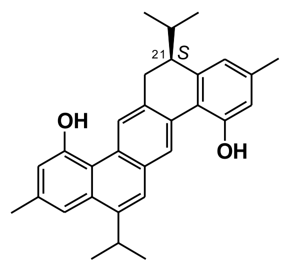

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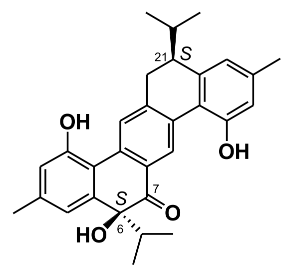

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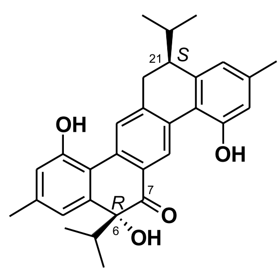

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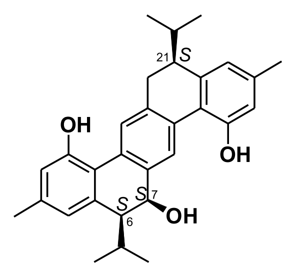

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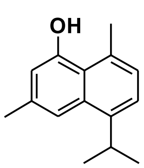
to those of parviflorene B (**5**) or D (**6**),[3] although compound **1** possessed one less oxygen atom than **5** or **6**. The HMBC spectrum of **1** afforded long-range ^{1}H–^{13}C correlations as shown in Figure 1, which suggested that **1** possessed the same pentacyclic carbon framework as **5** or **6**, and the positions of two methyls, two phenols, one carbonyl, and two isopropyl groups were also the same. The ^{1}H–^{1}H COSY correlations of **1** observed for H-6/H-11 and H-21/26 revealed that both isopropyl groups were attached to sp^3 methines, while one of two isopropyl groups of **5** or **6** was attached to a quaternary carbon bearing tertiary hydroxyl group (C-6). The ^{13}C NMR chemical shifts of C-6 (δ_C 61.6 for **1**; δ_C 82.1 for **5**; δ_C 82.1 for **6**) were also consistent with this observation. From these results, the planar structure of parviflorene G (**1**) was revealed as a 6-deoxy derivative of parviflorene B (**5**) or D (**6**). The stereochemistry of two chiral center of **1** was elucidated as 6*S* and 21*S* on the basis of CD spectral data (vide infra).

Parviflorene H (**2**) was obtained as pale yellow amorphous solids, and its ^{1}H and ^{13}C NMR data of **2** closely resembled those of a sesquiterpene monomer, 8-hydroxycadalene (**8**),[4] which was previously isolated from this plant.[2] However, the molecular formula of **2** was suggested as $C_{30}H_{34}O_2$ by its HRFABMS data (*m*/*z* 426.2523, M$^+$, Δ −3.6 mmu), corresponding to a sesquiterpene dimer. Since the ^{13}C NMR spectrum of **2** exhibit only 15 signals and its ^{1}H NMR spectrum also showed signals corresponding to a monomer (Table 1), compound **2** was inferred to be a symmetric dimer. Comparison of the ^{1}H NMR data of **2** and **8** revealed that **2** did not have the aromatic ring proton on C-2, which resonated at δ_H 6.60 for compound **8**.[2] A quaternary sp^2 carbon resonated at δ_C 114.1 in the ^{13}C NMR of **2** was assignable to C-2, while the C-2 of **8** was observed at δ_C 111.8 as an sp^2 methine carbon.[2] Thus, parviflorene H (**2**) was deduced to be a symmetric dimer of **8** connected at C-2 positions with each other. Although it was conceivable that parviflorene H (**2**) might be optically active due to atropisomerism around the C-2/C-2′ bond, the optical rotation of **2** was zero and its CD spectrum showed no curve. A natural product, gossypol (**9**), possessing the same bis-cadinane skeleton as **2** was previously isolated from cotton seed.[5]

Table 1. ^{1}H and ^{13}C NMR spectral data of compounds **1–3**

Position	**1**[a]		**2**[a]		**3**[b]	
	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C	δ_H (J in Hz)	δ_C
1		153.3		153.1		156.2[c]
2	6.57 s	116.6	7.69 s	114.1	7.11 s	124.8
3		138.3		134.9		139.1
4	6.60 s	123.8		117.0	7.38 s	121.9
5		139.4		134.3		132.5[c]
6	3.27 d (7.6)	61.6		141.5		180.9
7		203.3	7.31 d (7.8)	122.8		180.2
8		130.7	7.16 d (7.8)	127.6		128.8
9		135.1		133.7		133.8
10		116.4		122.5		118.9
11	1.92 m	35.3	3.67 m	28.6		–
12	0.88 d (6.7)	20.8	1.39 d (6.7)	23.7		–
13	0.79 d (6.7)	20.3	1.41 d (6.7)	23.4		–
14	8.30 s	127.8	2.86 s	25.0	8.87 s	128.6
15	2.29 s	21.2	2.14 s	20.7	2.29 s	20.4
16		153.3				155.1[c]
17	6.65 s	115.9			6.67 s	115.4
18		138.0				137.6
19	6.57 s	122.8			6.52 s	121.3
20		143.1				142.4
21	2.37 m	46.6			2.38 m	45.4
22	3.02 (2H) d (3.6)	33.7			2.97dd (15.4, 2.5) 2.93dd (15.4, 5.0)	33.5
23		142.8				143.7
24		131.8				132.4[c]
25		117.5				115.7
26	1.38 m	28.8			1.32 m	28.5
27	0.75 d (6.7)	21.8			0.71 d (6.6)	21.4
28	0.83 d (6.4)	20.8			0.84 d (6.6)	20.4
29	8.62 s	124.6			8.97 s	128.5
30	2.28 s	21.0			2.24 s	20.9
1-OH	5.32 br s				9.87 br s	
16-OH	5.83 br s				10.76 br s	

[a] In $CDCl_3$.
[b] In DMSO.
[c] Signals may be reversed.



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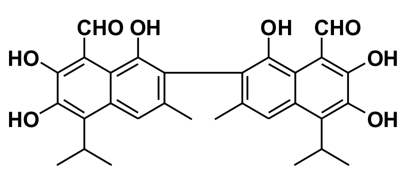

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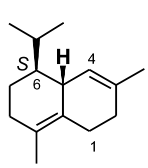

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Parviflorene I (**3**) was obtained as red-purple amorphous solids, and its molecular formula was determined as $C_{27}H_{24}O_4$ by its HRFABMS data (m/z 412.1742, M^+, Δ -1.1 mmu), possessing three less carbon atoms than other parviflorenes. The ^{1}H NMR spectrum of **3** showed signals for only one isopropyl group [δ_H 0.71 (3H, d, $J=6.6$ Hz), 0.84 (3H, d, $J=6.6$ Hz), and 1.32 (1H, m)], and in the ^{13}C NMR spectrum of **3** two carbonyl carbons were observed at δ_C 180.2 and 180.9. The HMBC spectrum of **3** showed correlations from the H-4 aromatic proton (δ_H 7.38, 1H, s) to one carbony carbon (δ_C 180.9) and from the H-29 aromatic proton (δ_H 8.97) to the other carbonyl carbon (δ_C 180.2). These observations implied that compound **3** possessed two ketone groups vicinally at C-6 and C-7. Other parts of the molecule (A, C, D, and E rings) of compound **3** was revealed as the same as those of previously isolated parviflorenes such as compounds **1** and **4–7** by comparison of the ^{1}H and ^{13}C NMR data (Table 1). Thus, the structure of parviflorene I was concluded as **3**.

The absolute configurations of C-6, C-7, and C-21 positions of parviflorenes A (**4**), B (**5**), D (**6**), F (**7**), and G (**1**) were elucidated as follows. In our previous report,[3] the absolute

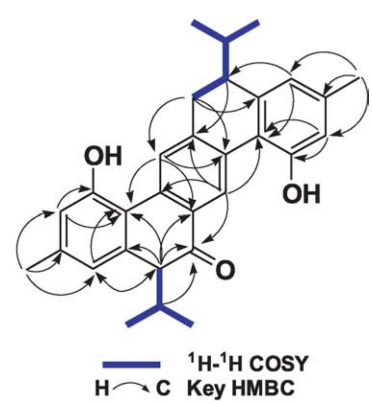
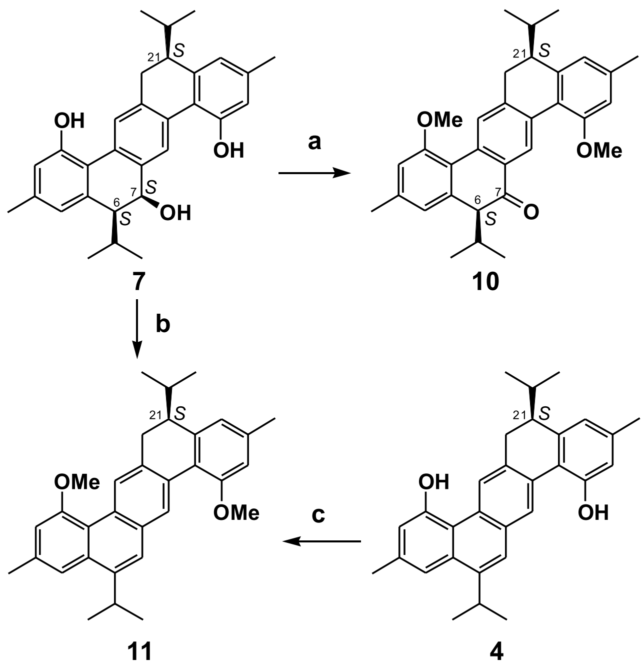


Figure 1. Key ^{1}H–^{1}H COSY and HMBC data of parviflorene G (**1**).



Scheme 1. (a) (i) $TMSCHN_2$, MeOH, rt, 14 h; (ii) Dess–Martin periodinane, CH_2Cl_2, rt, 2 h. (b) (i) $TMSCHN_2$, MeOH, rt, 14 h; (ii) (*S*)- or (*R*)-MTPACl, pyridine, rt, 14 h. (c) $TMSCHN_2$, MeOH, rt, 24 h.

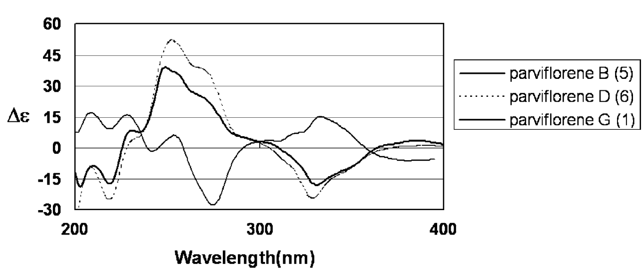


Figure 2. CD spectra of parviflorenes B (**5**), D (**6**), and G (**1**).

configurations of C-6 and C-7 positions of parviflorene F (**7**) were determined as 6*S* and 7*S* on the basis of modified Mosher's method, and the relative stereochemistry of parviflorene B (**5**) was unambiguously established by X-ray analysis.[3] Parviflorene F (**7**) was converted into the 1,16-di-*O*-methyl-7-keto derivative (**10**) by methylation of two phenol groups with $TMSCHN_2$,[6] followed by oxidation with Dess-Martin periodinane (Scheme 1). Since **7** had 6*S*-configuration, this 7-keto derivative (**10**) possessed 6*S*-configuration, and **10** also corresponded to 1,16-di-*O*-methyl derivative of parviflorene G (**1**). Since the CD spectra of compounds **10** and **1** were superimposable, the conformations and absolute stereochemistries of the whole molecules of **10** and **1** containing C-6 and C-21 chiral centers were implied to be the same, thus suggesting that **1** possessed 6*S*-configuration. The CD spectrum of parviflorene G (**1**) was also superimposable to that of parviflorene D (**6**), which had a hydroxyl group on C-6 (Fig. 2 and Table 2); this result suggested that the conformations of the whole molecules of **1** and **6** were parallel and the two isopropyl groups of **1** and **6** had the same configurations on C-6 and C-21. Thus, parviflorene D (**6**) was inferred to have 6*R*-configuration.[7,8] Parviflorenes D (**6**) and B (**5**) had been assigned as the diastereoisomers at the C-6 position in our previous report[3] since they showed almost opposite CD curves (Fig. 2 and Table 2); thus, parviflorenes B (**5**) was revealed to have 6*S*-configuration.[7,8] Since the relative stereochemistry of parviflorenes B (**5**) was established by X-ray analysis and the C-6 of **5** was assigned as *S* as above, the absolute configuration of C-21 of **5** was revealed as *S*. Since **5** was revealed to have 21*S*-configuration, compounds **6**, **1**, **10**, and **7**, in turn, were also revealed to have 21*S*-configurations on the basis of comparison of their CD spectral data and discussions described above. On the other hand, when the MTPA esters were prepared from 1,16-dimethyl ether of parviflorene F (**7**),[3] a dehydration product (**11**) was obtained concomitantly as a side product, and the compound (**11**) was also prepared by methylation of parviflorene A (**4**) by $TMSCHN_2$ (Scheme 1). The spectral data of compound **11** derived from **7** and **4** were found to be identical including CD spectral data. Since compound **7** was shown to have 21*S*-configuration (vide supra), parviflorene A (**4**) was also deduced to have 21*S*-configuration. Thus, all these five compounds, parviflorenes A (**4**), B (**5**), D (**6**), F (**7**), and G (**1**) were concluded to have 21*S*-configuration, and this conclusion was consistent with the fact that cadinane sesquiterpenes such as (+)-δ-cadinene (**12**) generally have 6*S*-configuration.[9,10]

Parviflorenes G (**1**) and I (**3**), possessing unsymmetrical biscadinane-type skeleton, exhibited cytotoxicity against HeLa cells with IC_{50} values of 11.8 and 3.6 μM, respectively, while parviflorenes H (**2**) with symmetrical biscadinane skeleton was almost inactive with the IC_{50} value of >100 μM. Parviflorenes A (**4**) and F (**7**), most abundantly obtained dimeric sesquiterpenoids from this plant, were evaluated in the Japanese Foundation for Cancer Research 39 human cancer cell line panel assay.[11] Although compounds **4** and **7** showed low differential cellular sensitivities, both compounds were cytotoxic against all these cell lines tested at considerably low concentrations (mean values of log GI_{50} (log concentration of compound for inhibition of cell growth at 50% compared to control) over all cell lines tested: −5.53 for **4**; −5.59 for **7** (Table 3)). Further investigations to elucidate which genes are differentially expressed in relation of cytotoxic effect of parviflorenes and the signaling mechanisms caused by parviflorenes are currently in progress in our laboratories.

Table 2. CD Spectral data of parviflorenes B (**5**), D (**6**), and G (**1**)

Parviflorene B (**5**)	λ_{ext} (nm)	380	358	333	291	275	254	239	228	219
	Δε	−6.4	0	15.2	0	−28.0	5.9	0	16.0	9.0
Parviflorene D (**6**)	λ_{ext} (nm)	391	371	329	306	271	253	232	228	219
	Δε	1.2	0	−24.2	0	37.9	52.5	4.5	0	−25.0
Parviflorene G (**1**)	λ_{ext} (nm)	386	364	331	310	270	249	231	226	219
	Δε	3.6	0	−18.1	0	24.2	39.3	8.3	0	−17.6

Table 3. Results of human cancer cell line panel assay of parviflorenes A (**4**) and F (**7**)

Origin of cancer	Cell line	Parviflorene A (**4**)		Parviflorene F (**7**)	
		log GI_{50} (M)[a]	(log GI_{50})-(MG-MIG)	log GI_{50} (M)[a]	(log GI_{50})-(MG-MIG)
Breast	HBC-4	−5.30	−0.23	−5.40	−0.19
	BSY-1	−5.58	0.05	−5.66	0.07
	HBC-5	−5.51	−0.02	−5.58	−0.01
	MCF-7	−5.59	0.06	−5.61	0.02
	MDA-MB-231	−5.52	−0.01	−5.81	0.22
Central nervous system	U251	−5.63	0.10	−5.55	−0.04
	SF-268	−5.54	0.01	−5.54	−0.05
	SF-295	−5.67	0.14	−5.57	−0.02
	SF-539	−5.74	0.21	−5.71	0.12
	SNB-75	−5.63	0.10	−5.56	−0.03
	SNB-78	−5.50	−0.03	−5.48	−0.11
Colon	HCC2998	−5.49	−0.04	−5.58	−0.01
	KM-12	−5.55	0.02	−5.57	−0.02
	HT-29	−5.46	−0.07	−5.60	0.01
	HCT-15	−5.52	−0.01	−5.47	−0.12
	HCT-116	−5.55	0.02	−5.65	0.06
Lung	NCI-H23	−5.46	−0.07	−5.54	−0.05
	NCI-H226	−5.60	0.07	−5.56	−0.03
	NCI-H522	−5.59	0.06	−5.59	0.00
	NCI-H460	−5.58	0.05	−5.67	0.08
	A549	−5.57	0.04	−5.53	−0.06
	DMS273	−5.66	0.13	−5.64	0.05
	DMS114	−5.65	0.12	−5.61	0.02
Melanoma	LOX-IMVI	−5.64	0.11	−5.81	0.22
Ovary	OVCAR-3	−5.63	0.10	−5.65	0.06
	OVCAR-4	−5.45	−0.08	−5.59	0.00
	OVCAR-5	−5.55	0.02	−5.40	−0.19
	OVCAR-8	−5.32	−0.21	−5.51	−0.08
	SK-OV-3	−5.27	−0.26	−5.52	−0.07
Kidney	RXF-631L	−5.43	−0.10	−5.72	0.13
	ACHN	−5.56	0.03	−5.56	−0.03
Stomach	St-4	−5.41	−0.12	−5.69	0.10
	MKN1	−5.35	−0.18	−5.58	−0.01
	MKN7	−5.58	0.05	−5.59	0.00
	MKN28	−5.47	−0.06	−5.62	0.03
	MKN45	−5.44	−0.09	−5.59	0.00
	MKN74	−5.67	0.14	−5.64	0.05
Prostate	DU-145	−5.38	−0.15	−5.56	−0.03
	PC-3	−5.56	0.03	−5.56	−0.03
MG-MID[b]		−5.53		−5.59	
Delta[c]		0.21		0.22	
Range[d]		0.47		0.41	

[a] Log concentration of compound for inhibition of cell growth at 50% compared to control.
[b] Mean value of log GI_{50} over all cell lines tested.
[c] The difference in log GI_{50} value of the most sensitive cell and MG-MID value.
[d] The difference in log GI_{50} value of the most sensitive cell and the least sensitive cell.

3. Experimental

3.1. Extraction and isolation

The plant *Curcuma parviflora* was collected at Khon Kaen, Thailand. A voucher specimen is maintained at the Department of Horticulture, Faculty of Agriculture, Khon Kaen University. The air-dried underground part (280 g) was extracted with MeOH and acetone. The combined extract (12.6 g) suspended in water (200 mL) was partitioned against EtOAc (400 mL×2 and 200 mL) and *n*-BuOH (200 mL×2). The EtOAc-soluble fraction (8.0 g) and previously obtained EtOAc and *n*-BuOH-soluble fractions (2.9 g) from the whole plant were combined, and then were subjected to silica gel column chromatography (column A; 4.5×57 cm) eluted with 0–100% EtOAc in hexane. The fraction (0.9 g) eluted with 33–50% EtOAc in hexane was again subjected to silica gel column chromatography (3.5×21 cm) eluted with 20–50% EtOAc in hexane, followed by gel filtration with Sephadex LH-20 (column B; 1.5×53 cm) eluted with MeOH. The fraction of column B (60 mg) in the 97–125 mL elution was purified by HPLC on ODS (Develosil ODS-HG-5, 20×250 mm; eluent, 80% MeOH, flow rate, 8.0 mL/min; detection UV at 380 nm and RI) to give parviflorene G (**1**, 5.3 mg, t_R = 53 min). The fraction (2.53 g) of column A eluted with 10% EtOAc in hexane was separated again by silica gel column chromatography (5×40 cm) eluted with 1% EtOAc in hexane, followed by gel filtration with Sephadex LH-20 (1.5×55 cm) eluted with MeOH to give parviflorene H (**2**, 4.9 mg) in the 105–120 mL elution. The fraction (283 mg) of column A eluted with 50–100% EtOAc in hexane was subjected again to silica gel column chromatography (2.5×20 cm) eluted with 33% EtOAc in hexane, followed by separation with Sephadex LH-20 (1.5×50 cm) eluted with MeOH to afford parviflorene I (**3**, 8.6 mg) in the 534–555 mL elution.

3.1.1. Parviflorene G (1). Yellow amorphous; $[\alpha]_D^{24}+200$ (*c* 1.0, MeOH); IR (ATR) ν_{max} 3320, 2950, 2920, 2870, 1660, and 1620 cm^{-1}; UV (MeOH) λ_{max} nm (log ε) 374 (3.8), 325 (4.3), 313 (4.3), 274 (4.5), 237 (4.3), and 220 (4.4); CD (0.061 mM, MeOH, 24 °C) $\Delta\varepsilon$ (λ_{ext} nm) 0 (450), 3.6 (386), 0 (364), −18.1 (331), 0 (310), 24.2 (270), 39.3 (249), 8.3 (231), 0 (226), −17.6 (219), −8.5 (210), and −19.1 (203); ^1H and ^{13}C NMR (Table 1); EIMS *m/z* (%) 440 (M^+, 100), 398 (M-$(CH_3)_2$CH, 12), 369 (25), 355 (43), and 327 (10); HRFABMS calcd for $C_{30}H_{32}O_3$ (M^+) 440.2351, found *m/z* 440.2367.

3.1.2. Parviflorene H (2). Yellow amorphous; $[\alpha]_D^{24}$ 0 (*c* 0.13, hexane); IR (ATR) ν_{max} 3500, 2960, 2930, 2870, 1650, and 1430 cm^{-1}; UV (MeOH) λ_{max} nm (log ε) 337 (3.2), 333 (3.8), 303 (4.0), and 242 (4.8); CD (0.059 mM, hexane, 24 °C) $\Delta\varepsilon$ (λ_{ext} nm) 0 (600–200); ^1H and ^{13}C NMR (Table 1); EIMS *m/z* (%) 426 (M^+, 34) and 362 (12); HRFABMS calcd for $C_{30}H_{34}O_2$ (M^+) 426.2559, found *m/z* 426.2523.

3.1.3. Parviflorene I (3). Red purple amorphous; $[\alpha]_D^{24}+$ 107 (*c* 0.32, MeOH);IR (ATR) ν_{max} 3390, 2960, 2920, 2860, 1700, 1610, 1580, and 1300 cm^{-1}; UV (MeOH) λ_{max} nm (log ε) 530.5 (3.40), 312.5 (4.60), and 222.5 (4.55); CD (0.027 mM, MeOH, 24 °C) $\Delta\varepsilon$ (λ_{ext} nm) 0 (362), −7.7 (301), 15.2 (283), 2.1 (257), 22.8 (242), 0 (221), and −21.7 (208); ^1H and ^{13}C NMR in $CDCl_3$ (Table 1); EIMS *m/z* (%) 412 (M^+, 98), 369 (33), 341 (100), and 256 (39); HRFABMS calcd for $C_{27}H_{25}O_4$ $(M+H)^+$413.1753, found *m/z* 413.1742.

3.1.4. Conversion of parviflorenen F (7) into 1,16-di-*O*-methylparviflorene G (10). A soluion of **7** (17 mg) in MeOH (1 mL) was treated with 10% TMS-CHN_2 in hexane (0.5 mL) at room temperature for 14 hr. The reaction mixture was evaporated and purified over a silica gel column chromatography eluted with hexane/EtOAc to afford dimethyl ether (14 mg), part of which (0.4 mg) was then dissolved in dichloromethane (40 μL), and treated with Dess-Martin periodinane (2.1 mg) at rt for 2 h. The reaction mixture was evaporated and purified over a silica gel column chromatography eluted with hexane/EtOAc (4:1) to give 1,16-di-*O*-methylparviflorene G (**10**): ^1H NMR ($CDCl_3$) δ_H 6.72 (1H, s, H-2[a]), 6.70 (1H, s, H-4[a]), 3.22 (1H, d, $J=7.6$ Hz, H-6), 1.89 (1H, m, H-11), 0.87 (3H, d, $J=6.6$ Hz, H_3-12[b]), 0.76 (3H, d, $J=6.6$ Hz, H_3-13[b]), 8.30 (1H, s, H-14), 2.35 (6H, s, H_3-15, H_3-30), 6.62 (2H, s, H-17[a], H-19[a]), 2.38 (1H, m, H-21), 3.01 (2H, m, H_2-22), 1.40 (1H, m, H-26), 0.75 (3H, d, $J=6.6$ Hz, H_3-27[b]), 0.83 (3H, d, $J=6.6$ Hz, H_3-28[b]), 8.65 (1H, s, H-29), and 3.90 (6H, s, 1-OMe, 16-OMe). ([a,b]signals may be reversed); EIMS *m/z* (%) 468 (M^+100), 425 (7), 397 (22), and 383 (20); CD (0.020 mM, MeOH, 24 °C) $\Delta\varepsilon$ (λ_{ext} nm) 9.6 (383), 0 (361), −43.4 (331), 0 (309), 50.7 (270), 113.4 (248), 0 (228), −43.4 (217), and −30.4 (209); UV (MeOH) λ_{max} nm (log ε) 370 (4.1), 325 (4.6), 313 (4.6), 276 (4.8), 237 (4.6), and 219 (4.7).

3.1.5. 1,16-Di-*O*-methylparviflorene A (11). The dimethyl ether of parviflorene F (2.1 mg) obtained as above was then dissolved in dry pyridine (20 μL), and treated with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(*S*)-MTPA-Cl] (5 μL) at rt for 14 h. After addition of 3-[(dimethylamino)propyl]amine (3 μL), the reaction mixture was evaporated and purified over a silica gel column chromatography eluted with hexane/EtOAc (100:1) to give the (*R*)-MTPA ester (1.3 mg) and 1,16-di-*O*-methylparviflorene A (**11**, 0.4 mg). By the same procedure, treatment of the dimethyl ether (2.2 mg) with (*R*)-MTPA-Cl afforded (*S*)-MTPA ester (1.7 mg) and **11** (0.3 mg). **11**: amorphus solids; ^1H NMR ($CDCl_3$) δ_H 6.95 (1H, s, H-2), 7.59 (1H, s, H-4), 7.64 (1H, s, H-7), 3.67 (1H, s, H-11), 1.42 (3H, d, $J=$ 6.8 Hz, H_3-12), 1.46 (3H, d, $J=6.8$ Hz, H_3-13), 9.31 (1H, s, H-14), 2.56 (3H, s, H_3-15), 6.75 (1H, s, H-17), 6.68 (1H, s, H-19), 3.16 (2H, m, H_2-22), 1.36 (1H, m, H-26)0.73 (3H, d, $J=6.8$ Hz, H_3-27), 0.87 (3H, d, $J=6.8$ Hz, H_3-28), 8.66 (1H, s, H-29), 2.38 (3H, s, H_3-30), 4.10 (1H, s, 1-OMe[a]), 3.95 (1H, s, 16-OMe[a]). ([a]signals may be reversed); EIMS *m/z* (%) 452 (M^+, 100), 409 (34), 367 (94), and 352 (20); CD (MeOH) $\Delta\varepsilon$ (λ_{ext} nm) −7.9 (326), 3.5 (297), 13.9 (283), 15.1 (275), −10.3 (250), 5.6 (241), 17.7 (231), and −8.1 (215).

1,16-Di-*O*-methylparviflorene A (**11**) was also prepared from parviflorene A (**4**) as follows. Parviflorene A (**4**, 2.3 mg) dissolved in MeOH (100 μL) was treated with 10% TMS-CHN_2 in hexane (50 μL) at room temperature for 24 h. The reaction mixture was purified with silica gel column chromatography eluted with hexane/EtOAc (100:0 to 50:1) to give **11** (0.3 mg), whose spectral data (^1H NMR, EIMS, and CD) were all identical with those of **11** prepared from parviflorene F (**7**).

Acknowledgements

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7. The hydrogen on C-6 of **1** was replaced with a hydroxyl group with retention of configuration for **6**, and with inversion of configuration for **5**. Since the priority order in nomenclature was changed, **1** had 6*S*-, **6** had 6*R*-, and **5** had 6*S*-configurations.
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Investigation of the scope of a [3+2] cycloaddition approach to isoxazole boronic esters

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Abstract—The [3+2] cycloaddition reaction of nitrile oxides and alkynylboronates provides direct access to a wide variety of isoxazole boronic esters. Specifically, this technique has been employed to generate trisubstituted isoxazole 4-boronates and disubstituted isoxazoles where the boronic ester moiety can be installed at C-4 or C-5 with high levels of regiocontrol. The application of this methodology in the synthesis of non-steroidal antiinflammatory agents is also described.
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1. Introduction

The versatility of organoboron reagents renders them one of the most popular classes of synthetic intermediates in modern organic chemistry.[1] Among the many transformations that these compounds will undergo, the Pd-catalysed cross-coupling reaction has found widespread use in academia and industry because of the relatively mild conditions used in this carbon–carbon bond forming process and the relative non-toxicity of the reagents employed.[2] In the context of aromatic boronic acids and esters, these compounds are typically prepared from the appropriate Grignard or organolithium species,[1] or more recently, via Pd-catalysed C–B bond forming processes.[3] An alternative strategy that is of significant potential in the synthesis of these substrates is the use of transition metal catalysts that promote C–H activation processes.[4] Both of these approaches constitute C–X to C–B bond transformations and therefore require an appropriately functionalised starting aromatic compound. Recent work in our laboratories has focused on an alternative strategy whereby aromatic boronic esters are prepared by benzannulation processes of readily available alkynylboronates.[5] In this case, incorporation of the boronic ester and any additional functionality is carried out in a convergent sense via the cycloaddition of simple starting materials. These three strategies are outlined in Figure 1. We report herein, the scope and limitations of this strategy in the synthesis of heteroaromatic boronic esters based on the isoxazole ring via a [3+2] cycloaddition reaction of nitrile oxides with alkynylboronates.[6]

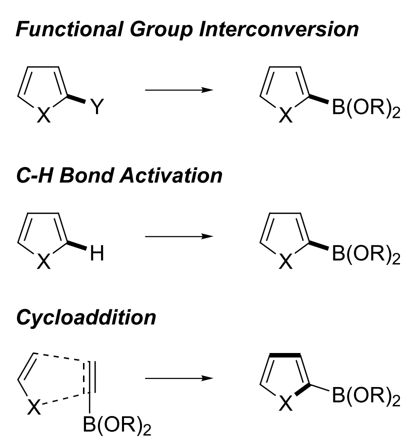

Figure 1.

2. Results and discussion

At the outset of our studies, we were aware of only a single report describing the [3+2] cycloaddition of some benzonitrile oxides with dibutyl ethynylboronate.[7] Notably,

Keywords: Cycloadditions; Boronic esters; Isoxazoles; Regioselective.
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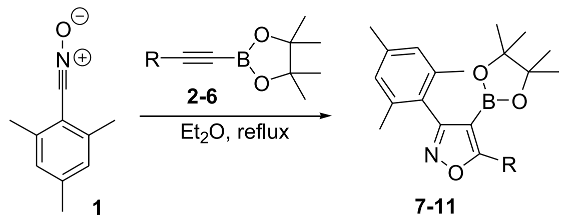
Table 1.



Entry	R	Yield
1	Bu; **2**	**7**; 73%
2	Ph; **3**	**8**; 64%
3	Me_3Si; **4**	**9**; 65%
4	$BnOCH_2$; **5**	**10**; 61%
5	$PhSCH_2$; **6**	**11**; 60%

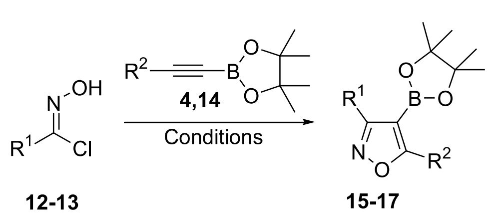
the boronic acid products obtained were unstable and not readily isolated. Additionally, the authors did not extend their study to more heavily substituted alkyne substrates. Accordingly, in an effort to assess the effectiveness of this strategy in the synthesis of these potentially useful organoboron intermediates, we decided to undertake a study of the scope of this process. We began by examining the cycloaddition reaction of mesitylenecarbonitrile oxide **1**—a stable and easily accessible dipole substrate, our results are outlined in Table 1. Upon warming an ether solution of **1** and various alkynylboronates we were pleased to find that the corresponding isoxazole boronic esters were isolated in high yield. Moreover, we were only able to detect a single regioisomer in each case (as judged by 250 MHz ^{1}H NMR spectroscopy of the crude reaction mixture) where the boronate unit was incorporated in the 4-position.[8]

These preliminary experiments confirmed that the [3+2] cycloaddition process could be employed for the synthesis of 3,4,5-trisubstituted isoxazoles with incorporation of the boronate at C-4 with excellent levels of regiocontrol. Furthermore, this technique allowed a reasonable variety of substituents to be installed at C-5. We therefore next addressed the issue of substituent scope at C-3, in this regard, various nitrile oxides would be needed to achieve good flexibility. Generally speaking, nitrile oxides are prone to dimerisation to furoxans and the rate of this process is dependent on the steric demands of the dipole.[9] Accordingly, these compounds are typically generated in situ from the corresponding hydroximic acid chlorides in low concentrations in an effort to promote dipolarophile cycloaddition over competing dimerisation. We decided to employ two protocols for the in situ formation of nitrile oxides; the slow addition of triethylamine to an ethereal solution of hydroximic acid chlorides and the use of a potassium bicarbonate/DME suspension. In the latter case, the sparing solubility of the bicarbonate in DME ensures that nitrile oxide formation proceeds relatively slowly.[10] The utilisation of these procedures in isoxazole boronic ester synthesis is outlined in Table 2. The formation of benzonitrile oxide under either set of conditions permitted a smooth cycloaddition reaction to take place with trimethylsilylethynylboronate **4** to furnish the corresponding isoxazole 4-boronate **15**, again as a single regioisomer (entires 1 and 2). The inorganic base conditions were readily extended to include *t*-Bu-substituted dipole (from **13**), however, attempts to carry out a similar cycloaddition using triethylamine with **13** resulted in a low yield of isoxazole **17** (entries 3 and 4).

In an effort to broaden the scope of substituents available at C-3 yet further, we decided to investigate the cycloaddition reaction of halonitrile oxides. These dipoles are also highly prone to dimerisation and are prepared in situ from the corresponding dihaloformaldoximes. We attempted the cycloaddition of representative alkynylboronates with these species and our results are outlined in Table 3. We began by comparing the efficiency of isoxazole formation in the presence of triethylamine versus potassium bicarbonate. As shown in entries 1 and 2, the latter base was considerably more efficient and we therefore employed these conditions for the remainder of the study. Indeed, we were pleased to find that this technique allowed us to access a wide range of 3-bromoisoxazoles in good yield, again a single regioisomer was detected in each case.[11] Finally, as outlined in entry 8, this process was also viable for the preparation of 3-chloroisoxazoles.

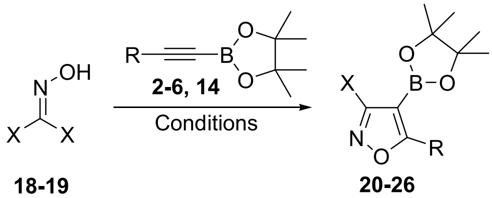
During the course of this work, we became aware of a study by Itoh et al. that outlined the formation of acetylnitrile oxide from acetone and ammonium cerium (IV) nitrate in the presence of formic acid.[12] Given that our investigations up to this point had demonstrated that the alkynylboronates were compatible with mild bases, it seemed that this process would provide the opportunity to demonstrate the acid stability of these reagents. As outlined in Eq. 1, subjecting

Table 2.



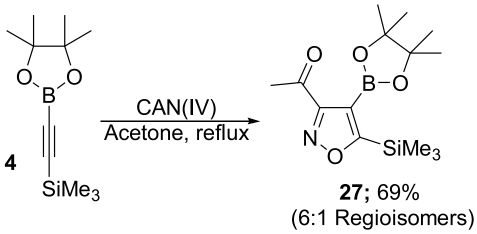
Entry	R^1	R^2	Conditions	Yield
1	Ph; **12**	Me_3Si; **4**	Et_3N, Et_2O, reflux	**15**; 72%
2	Ph; **12**	Me_3Si; **4**	$KHCO_3$, DME, 50 °C	**15**; 69%
3	Bu^t; **13**	Me_3Si; **4**	$KHCO_3$, DME, 50 °C	**16**; 58%
4	Bu^t; **13**	Me; **14**	Et_3N, Et_2O, reflux	**17**; 27%

Table 3.



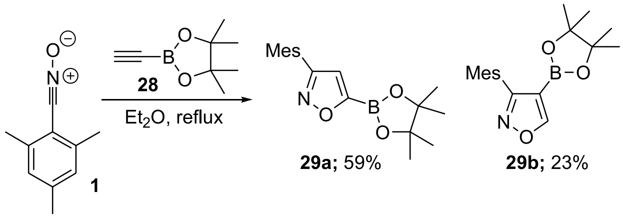
Entry	X	R	Conditions	Yield
1	Br; **18**	Ph; **3**	Et_3N, Et_2O, reflux	**20**; 14%
2	Br; **18**	Ph; **3**	$KHCO_3$, DME, 50 °C	**20**; 69%
3	Br; **18**	Bu; **2**	$KHCO_3$, DME, 50 °C	**21**; 44%
4	Br; **18**	Me; **14**	$KHCO_3$, DME, 50 °C	**22**; 43%
5	Br; **18**	Me_3Si; **4**	$KHCO_3$, DME, 50 °C	**23**; 58%
6	Br; **18**	$BnOCH_2$; **5**	$KHCO_3$, DME, 50 °C	**24**; 40%
7	Br; **18**	$PhSCH_2$; **6**	$KHCO_3$, DME, 50 °C	**25**; 48%
8	Cl; **19**	Bu; **2**	$KHCO_3$, DME, 50 °C	**26**; 44%

the TMS-substituted alkyne **4** to these conditions provided the corresponding 3-acetylisoxazole **27** in good yield. Interestingly, this cycloaddition furnished a 6:1 mixture of regioisomers with the major product incorporating the boronate in the 4-position as before.[13] Unfortunately, however, this chemistry was not easily expanded to include other alkynes suggesting that alkyne **4** is unusually stable under these conditions.



(1)

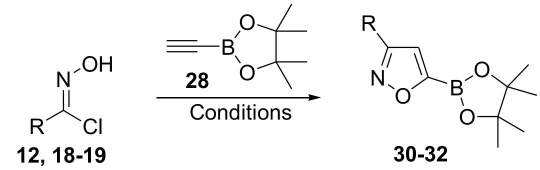
Having explored the scope of the cycloaddition process for the synthesis of trisubstituted isoxazoles, we next turned our attention to the synthesis of the corresponding disubstituted heterocycles. We anticipated that these compounds would be prepared directly by the [3+2] cycloaddition reaction of nitrile oxides and a terminal alkynylboronate. Once again, our preliminary studies focused on the use of mesitylene-carbonitrile oxide **1**. As outlined in Eq. 2, the cycloaddition reaction proceeded in excellent yield to provide a 2.6:1 mixture of isoxazole regioisomers **29a/b**, favouring the 5-boronate.[14]



(2)

Attempts to use this approach in a more general sense met with mixed success (Table 4). We found that the cycloaddition of benzonitrile oxide with **28** using triethylamine proceeded with reasonable efficiency and with high levels of regioselectivity of the 3,5-isomer of **30**. In contrast, the yields for the corresponding halonitrile oxide

Table 4.



Entry	R	Conditions	Yield
1	Ph; **12**	Et_3N, Et_2O, reflux	**30**; 59% (9:1)
2	Br; **18**	$KHCO_3$, DME, 50 °C	**31**; 37% (9:1)[a]
3	Cl; **19**	$KHCO_3$, DME, 50 °C	**32**; 29% (15:1)[a]

[a] Yield and regiochemistry estimated from the ^1H NMR spectrum of the crude cycloadducts.

cycloadditions were significantly less efficient. These reactions were further hampered by the significant sensitivity of **31** and **32** to protodeboronation on chromatographic purification.

Whilst the natural regioselectivity of the cycloaddition reaction provides isoxazoles with the 3,5-substitution pattern, we anticipated that protodesilylation of trisubstituted isoxazoles would provide an indirect route for accessing 3,4-disubstituted isoxazole 4-boronates. Indeed, as outlined in Figure 2, subjection of isoxazole **15** to CsF provided the corresponding disubstituted heteroaromatic boronic ester **33** in good yield. Therefore, it appears that the cycloaddition can be employed to access complementary 3,4- and 3,5-disubstituted isoxazole boronic ester products.

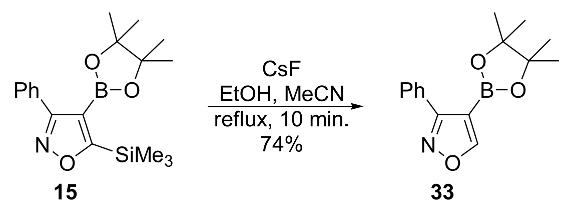


Figure 2.

Having explored the scope of the isoxazole forming process, we turned our attention to the employment of the methodology in target synthesis. Specifically, we were intrigued by the potential for this methodology to permit the synthesis of the non-steroidal antiinflammatory drug (NSAID) valdecoxib **34**.[15] As well as preparing this specific target, we envisaged that our strategy would be sufficiently flexible so as to allow analogues to be prepared also (Fig. 3).

The therapeutic effect of NSAIDs originates from their selective inhibition of the COX-2 enzyme, indeed, inhibition of related isoform COX-1 leads to unwanted side-effects such as gastrointestinal irritation. In the context of valdecoxib, it is notable that the sulfonamide unit plays a key role in COX-2 inhibition selectivity. Our synthetic route to valdecoxib **34** and mesityl-substituted analogue **37** are shown in Figure 4. We chose **37** specifically, because attempts to prepare this particular analogue by sulfonation of the 4-aryl group has been shown to be thwarted by addition to the more electron rich mesityl unit.[15] The [3+2] cycloaddition of alkyne **14** with benzonitrile oxide (prepared using $KHCO_3$ under conditions outlined in Table 2)

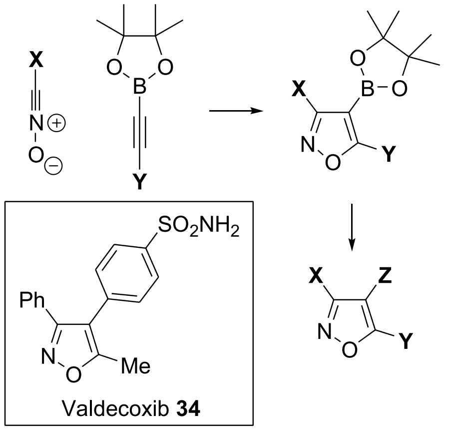


Figure 3.

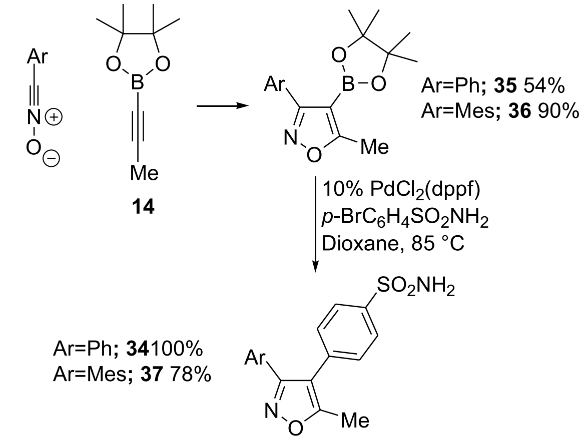


Figure 4.

and mesitylenecarbonitrile oxide proceeded smoothly to provide the isoxazole 4-boronates as single regioisomers in high yield. These intermediates were smoothly transformed to valdecoxib and analogue **37** after Suzuki coupling reactions with *p*-bromobenzene sulfonamide (Fig. 4).

3. Conclusion

The [3+2] cycloaddition reaction of nitrile oxides with alkynylboronates provides a direct route to 3,4,5-trisubstituted isoxazoles and 3,5-disubstituted isoxazoles with good to excellent levels of regiocontrol. Additionally, the desilylation of 5-trimethylsilyl isoxazoles takes place in the presence of the boronic ester moiety when CsF is employed to furnish the 3,4-disubstituted isoxazole isomer. We believe that this strategy provides a potentially facile route to a wide range of isoxazole based targets as illustrated by the synthesis of NSAID valdecoxib **34** and analogue **37**.

4. Experimental

Our general experimental procedures have been reported elsewhere.[16] Alkynylboronates were prepared from the corresponding terminal alkynes by the method of Brown.[17] Nitrile oxides **1**,[18] **12**,[19] **13**,[20] **18**,[21] **19**[22] were prepared according to literature procedures.

4.1. General procedure for the [3+2] cycloaddition reaction of mesitylnitrile oxide with alkynylboronates

4.1.1. 5-Benzyloxymethyl-4-(4,4,5,5-tetramethyl[1,3]-dioxolan-2-yl)-3-(2,4,6-trimethylphenyl)-isoxazole (10). A solution of 2-(3-benzyloxy-prop-1-ynyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**5**) (0.10 g, 0.37 mmol) and mesitylnitrile oxide (**1**) (0.06 g, 0.37 mmol) in diethyl ether (0.5 ml) was stirred for 16 h under reflux. The reaction was stopped and the solvent removed in vacuo. The product was purified by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 20:1 ratio) to give the title compound (**10**) as a colourless oil, 0.097 g, 61% yield. (250 MHz, $CDCl_3$): δ 1.04 (12H, s, 4×C*H*$_3$), 1.98 (6H, s, 2×Ar-C*H*$_3$), 2.23 (3H, s, Ar-C*H*$_3$), 4.62 (2H, s, OC*H*$_2$Ph), 4.78 (2H, s, C*H*$_2$OCH$_2$Ph), 6.80 (2H, s, Ar-*H*), 7.19–7.38 (5H, m, Ar-*H*); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 20.1, 21.2, 24.5, 62.6, 73.0, 83.5, 126.6, 127.7, 127.9, 128.0, 128.1, 137.0, 137.6, 138.0, 165.6, 175.9; FTIR ν_{max}/CHCl$_3$, 2976 (m), 2925 (m), 2860 (w), 1726 (w), 1601 (s), 1455 (s), 1413 (s), 1373 (s), 1359 (s), 1317 (w) cm^{-1}; HRMS calcd for $C_{27}H_{32}BNO_4$: 433.2424, found: 433.2425.

4.1.2. 4-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)-3-(2,4,6-trimethylphenyl)-5-butyl-isoxazole (7). The same general procedure was carried out with (**1**) (0.75 g, 4.63 mmol), 2-hexy-1-nyl-4,4,5,5-tetramethyl-[1,3,2]dioxaboralane (**2**) (1.90 g, 9.26 mmol), purification by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 10:1 ratio) gave the title compound (**7**) as a colourless solid, 1.23 g, 73% yield. Mp 58–60 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.94 (3H, t, J=7.0 Hz, C*H*$_3$), 1.11 (12H, s, 4×C*H*$_3$), 1.36 (2H, m, C*H*$_2$), 1.75 (2H, pent, J=7.5 Hz, C*H*$_2$), 2.04 (6H, s, 2×C*H*$_3$), 2.28 (3H, s, C*H*$_3$), 3.00 (2H, t, J=7.5 Hz, C*H*$_2$), 6.84 (2H, s, Ar-*H*); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.7, 19.9, 21.2, 22.1, 24.5, 26.8, 30.3, 83.0, 127.2, 127.6, 136.8, 137.6, 165.8, 181.6; FTIR ν_{max}/CHCl$_3$, 2976 (m), 2864 (w), 1592 (m), 1417 (s), 1351 (m) cm^{-1}. Anal. Calcd for $C_{22}H_{32}BNO_3$: C, 71.55; H, 8.73; N, 3.79. Found: C, 71.30; H, 8.84; N, 3.71.

4.1.3. 4-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)-3-(2,4,6-trimethylphenyl)-5-phenyl-isoxazole (8). The same general procedure was carried out with (**1**) (0.50 g, 3.10 mmol), 2-phenylethynyl-4,4,5,5-tetramethyl-[1,3,2]-dioxaboralane (**3**) (1.40 g, 6.20 mmol), purification by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 10:1 ratio) gave the title compound (**8**) as a colourless solid, 0.78 g, 64% yield. Mp 87–88 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.11 (12H, s, 4×C*H*$_3$), 2.13 (6H, s, 2×C*H*$_3$), 2.32 (3H, s, C*H*$_3$), 6.89 (2H, s, Ar-*H*), 7.43–7.48 (3H, m, Ar-*H*), 8.05–8.13 (2H, m, Ar-*H*); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 20.1, 21.2, 24.3, 83.8, 127.1, 127.5, 127.6, 128.5, 128.6, 130.3, 137.2, 138.1, 166.9, 174.4; FTIR ν_{max}/CHCl$_3$, 2981 (m), 1570 (m), 1417 (s), 1144 (m) cm^{-1}. Anal. Calcd for $C_{24}H_{28}BNO_3$: C, 74.05; H, 7.25; N, 3.60. Found: C, 73.94; H, 7.23; N, 3.45.

4.1.4. 4-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)-3-(2,4,6-trimethylphenyl)-5-trimethylsilanyl-isoxazole (9). The same general procedure was carried out with (**1**) (0.20 g, 1.24 mmol), 4,4,5,5-tetramethyl-2-trimethylsilanyl-ethynyl-[1,3,2]dioxaborolane (**4**) (0.28 g, 1.24 mmol), purification by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 50:1 ratio) gave the title compound (**9**) as a colourless solid, 0.31 g, 65% yield. Mp 104–106 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.25 (9H, s, Si(CH_3)$_3$), 0.92 (12H, s, 4×CH_3), 1.83 (6H, s, 2×CH_3), 2.11 (3H, s, CH_3), 6.68 (2H, s, Ar-*H*); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −1.45, 20.1, 21.2, 24.5, 83.3, 127.1, 127.5, 137.0, 137.6, 164.5, 185.8; FTIR ν_{max}/$CHCl_3$, 2978 (m), 2923 (m), 1614 (w), 1532 (s), 1508 (w), 1375 (s), 850 (s) cm^{-1}; HRMS (EI$^+$) calcd for $C_{21}H_{32}BNO_3Si$: 385.2245, found: 385.2240. Anal. Calcd for $C_{21}H_{32}BNO_3Si$: C, 65.45; H, 8.37; N, 3.63. Found: C, 65.20; H, 8.49; N, 3.63.

4.1.5. 5-Phenylsulfanylmethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3-(2,4,6-trimethylphenyl)-isoxazole (11). The same general procedure was carried out with (**1**) (0.05 g, 0.31 mmol), 4,4,5,5-tetramethyl-2-(3-phenylsulfanyl-prop-1-ynyl)-[1,3,2]dioxa-borolane (**6**) (0.10 g, 0.37 mmol), purification by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 20:1 ratio) gave the title compound (**11**) as a colourless oil, 0.08 g, 60% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.98 (12H, s, 4×CH_3), 1.90 (6H, s, 2×Ar-CH_3), 2.21 (3H, s, Ar-CH_3), 4.30 (2H, s, CH_2SPh), 7.11–7.22 (3H, m, Ar-*H*), 7.29–7.39 (2H, m, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.0, 21.2, 24.5, 30.2, 83.3, 127.6, 127.7, 128.3, 128.8, 132.8, 133.8, 136.9, 137.9, 165.6, 176.6; FTIR ν_{max}/$CHCl_3$, 2979 (m), 2926 (w), 1589 (s), 1460 (w), 1413 (s), 1374 (s), 1346 (s), 1319 (w) cm^{-1}; HRMS calcd for $C_{25}H_{30}BNO_3S$: 435.2031, found: 435.2039.

4.2. General procedure for the [3+2] cycloaddition reaction of in situ generated nitrile oxides with alkynylboronates

4.2.1. 3-Phenyl-4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-5-trimethylsilanyl-isoxazole (15). *Potassium bicarbonate*. A solution of 4,4,5,5-tetramethyl-2-trimethylsilanylethynyl-[1,3,2] dioxaborolane (**4**) (0.51 g, 2.28 mmol), benzaldehyde chloro oxime (**12**) (0.36 g, 2.31 mmol) and $KHCO_3$ (0.46 g, 4.60 mmol) in DME (20 ml) was heated at 50 °C for 16 h and then cooled to room temperature. The solid was removed by vacuum filtration and then conc. in vacuo purified by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 5:1 ratio) to give the title compound (**15**) as a colourless solid, 0.54 g, 69% yield. Mp 87–89 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.43 (9H, s, Si(CH_3)$_3$, 1.30 (12H, s, 4×CCH_3), 7.37–7.45 (3H, m, Ar-*H*), 7.73–7.81 (2H, m, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −1.4, 24.8, 83.9, 128.3, 129.2, 129.3, 130.1, 165.1, 187.1; FTIR ν_{max}/$CHCl_3$, 2978 (m), 2361 (w), 1534 (m), 1441 (m), 1373 (m), 1340 (s), 1250 (m) cm^{-1}; HRMS (ES$^+$) calcd for $C_{18}H_{27}BNO_3Si$: 344.1853, found: 344.1858. Anal. Calcd for $C_{18}H_{26}NO_3$-BSi: C 62.97; H 7.63; N 4.08. Found: C 63.08; H 7.39; N 4.28.

Triethylamine. A solution of 4,4,5,5-tetramethyl-2-trimethylsilanylethynyl-[1,3,2] dioxaborolane (**4**) (0.23 g, 1.03 mmol) and benzaldehyde chloro oxime (**12**) (0.16 g, 1.03 mmol) in diethyl ether (15 ml) was stirred and a solution of triethylamine (4.11 ml, of a 0.5 M solution in diethyl ether) was added via syringe pump as the mixture was heated under reflux for 12 h. The solid was removed by vacuum filtration and the solvent conc. in vacuo. Purification by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 5:1 ratio) gave the title compound (**15**) as a colourless solid, 0.25 g, 72% yield.

4.2.2. 3-*tert*-Butyl-4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-5-trimethylsilanyl-isoxazole (16). A solution of chloro oxime (**13**) (0.30 g, 2.21 mmol), 4,4,5,5-tetramethyl-2-trimethylsilanylethynyl-[1,3,2] dioxaborolane (**4**) (0.36 g, 2.21 mmol) and $KHCO_3$ (0.44 g, 4.42 mmol) in DME (2.7 ml) were heated at 50 °C for 40 h. The mixture was cooled to room temperature and filtered through celite. The filtrate was conc. in vacuo to give a yellow oil, which was purified by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 40:1 ratio) to give the title compound as a colourless solid, 0.41 g, 58% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.24 (9H, s, Si(CH_3)$_3$, 1.20 (12H, s, 4×CH_3), 1.28 (9H, s, 3×CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ−1.31, 25.1, 29.3, 32.7, 83.7, 172.9, 187.0; FTIR ν_{max}/$CHCl_3$, 2966 (m), 1556 (w), 1534 (m), 1453 (m), 1374 (m) cm^{-1}; HRMS (EI$^+$) calcd for $C_{16}H_{30}NO_3BSi$: 323.2088, found: 323.2101.

4.2.3. 3-*tert*-Butyl-4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-5-methyl-isoxazole (17). The general procedure described with triethylamine base was carried out with 2-propy-1-nyl-4,4,5,5-tetramethyl-[1,3,2]dioxaboralane (**14**) (0.62 g, 3.70 mmol, 2.0 equiv), purification by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 40:1 ratio) to give the title compound as a colourless solid, 0.14 g, 27% yield. Mp 126–127 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.30 (12H, s, 4×CH_3), 1.36 (9H, s, 3×CH_3), 2.49 (3H, s, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.0, 24.8, 28.9, 32.9, 83.5, 174.3, 178.6; FTIR ν_{max}/$CHCl_3$, 2978 (m), 1586 (s), 1420 (m), 1147 (m) cm^{-1}. Anal. Calcd for $C_{14}H_{24}BNO_3$: C, 63.42; H, 9.12; N 5.28. Found: C, 63.29; H, 9.38; N, 5.15.

4.3. General procedure for the [3+2] cycloaddition reaction of bromonitrile oxide with alkynylboronates

4.3.1. 3-Bromo-5-butyl-4-(4,4,5,5-tetramethyl[1,3,2]-dioxaborolan-2-yl)-isoxazole (21). A solution of 2-hexy-1-nyl-4,4,5,5-tetramethyl-[1,3,2]dioxaboralane (**2**) (0.90 g, 4.32 mmol), dibromoformaldoxime (**18**) (0.88 g, 4.32 mmol) and $KHCO_3$ (0.87 g, 8.65 mmol) in DME (5 ml) was stirred for 16 h at 50 °C. The residual solid was removed by vacuum filtration and solvent removed in vacuo. The product was purified by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 50:1 ratio then petroleum ether/ethyl acetate 5:1 ratio) followed by Kugelrohr distillation 110 °C/0.4 mmHg, to give the title compound (**21**) as a colourless oil, 0.63 g, 44% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.91 (3H, t, J=7.0 Hz, CH_3), 1.22–1.41 (2H, m, CH_2C$H_2$$CH_3$), 1.31 (12H, s, 4×C$H_3$), 1.58–1.73 (2H, m, C$H_2$$CH_2CH_3$), 2.94 (2H, t, J=7.0 Hz, CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.5, 22.0, 24.8, 26.8, 30.1, 83.8, 144.5, 183.6; FTIR ν_{max}/$CHCl_3$, 2978 (s), 2934 (s), 2874 (s), 1741 (m), 1589 (s) cm^{-1}; HRMS calcd. for $C_{13}H_{22}BNO_3Br$: 330.0871, found: 330.0876. Anal. Calcd for $C_{13}H_{22}BNO_3Br$: C, 47.31; H, 6.41; N, 4.24; Br, 24.21. Found: C, 47.33; H, 6.58; N, 4.23; Br, 24.18.

4.3.2. 3-Bromo-5-phenyl-4-(4,4,5,5-tetramethyl[1,3,2]-dioxa-borolan-2-yl)-isoxazole (20). The same general procedure was carried out with 2-phenylethynyl-4,4,5,5-tetramethyl-[1,3,2]dioxaboralane (**3**) (0.25 g, 1.08 mmol, 1.0 equiv), purification by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 10:1 ratio) gave the title compound (**20**) as a colourless solid, 0.26 g, 69% yield. Mp: 76–79 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.30 (12H, s, 4×CH_3), 7.33–7.47 (3H, m, Ar-*H*), 7.84–7.93 (2H, m, Ar-*H*); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 24.7, 84.5, 127.3, 128.0, 128.5, 131.0, 145.2, 176.5; FTIR ν_{max}/$CHCl_3$, 2195 (m), 2360 (m), 2932 (s), 2979 (s) 1725 (m) cm^{-1}; HRMS calcd for $C_{15}H_{17}BBrNO_3$: 349.0485, found: 349.0490.

4.3.3. 3-Bromo-5-methyl-4-(4,4,5,5-tetramethyl[1,3,2]-dioxa-borolan-2-yl)-isoxazole (22). The same general procedure was carried out with 2-propy-1-nyl-4,4,5,5-tetramethyl-[1,3,2]dioxaboralane (**14**) (0.20 g, 1.18 mmol, 1.0 equiv), purification by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 10:1 ratio) gave the title compound (**22**) as a colourless solid, 0.15 g, 43% yield. Mp 86–87 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.26 (12H, s, 4×CH_3), 2.50 (3H, s, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 13.1, 24.8, 83.9, 144.6, 179.7; FTIR ν_{max}/$CHCl_3$, 2982 (s), 1593 (s) cm^{-1}; HRMS calcd for $C_{10}H_{15}NO_3Br$ 287.0328, found: 287.0332. Anal. Calcd for $C_{10}H_{15}BNO_3Br$: C, 41.71; H, 5.25; N 4.86; Br, 27.75. Found: C, 41.99; H, 5.06; N, 4.86; Br, 27.87.

4.3.4. 3-Bromo-4-(4,4,5,5-tetramethyl[1,3,2]-dioxaborolan-2-yl)-5-trimethylsilanyl-isoxazole (23). The same general procedure was carried out with 2-trimethylsilyl-4,4,5,5-tetramethyl-[1,3,2]dioxaboralane (**4**) (0.20 g, 0.89 mmol, 1.0 equiv), purification by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 20:1 ratio) gave the title compound (**23**) as a colourless solid, 0.18 g, 58% yield. Mp 108–110 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.32 (12H, s, 4×CH_3), 1.27 (9H, s, Si(CH_3)$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −1.82, 24.8, 84.2, 143.9, 189.1; FTIR ν_{max}/$CHCl_3$, 3392 (w), 2979 (s), 1541 (s), 1480 (m), 1374 (s), 1328 (s) cm^{-1}; HRMS calcd for $C_{12}H_{21}BNO_3SiBr$: 345.0567, found: 345.0569. Anal. Calcd for $C_{12}H_{21}BNO_3BrSi$: C, 41.64; H, 6.12; N, 4.05; Br, 23.09. Found: C, 41.48; H, 5.85; N, 4.13; Br, 23.31.

4.3.5. 5-Benzyloxymethyl-3-bromo-4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-isoxazole (24). The same general procedure was carried out with 2-(3-benzyloxy-prop-1-ynyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane (**5**) (0.20 g, 0.74 mmol, 2.5 equiv), purification by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 10:1 ratio) gave the title compound (**24**) as a colourless oil, 0.046 g, 40% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.29 (12H, s, 4×CH_3), 4.60 (2H, s, CH_2), 4.77 (2H, s, CH_2), 7.31–7.38 (5H, m, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.8, 65.4, 73.1, 84.3, 127.7, 128.2, 128.6, 137.3, 144.5, 177.8; FTIR ν_{max}/$CHCl_3$, 3419 (br), 2977 (m), 2926 (w), 2867 (w), 1596 (s) cm^{-1}; HRMS calcd for $C_{17}H_{21}BNO_4Br$: 393.0747, found: 393.0741.

4.3.6. 3-Bromo-5-phenylsulfanylmethyl-4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-isoxazole (25). The same general procedure was carried out with 4,4,5,5-tetramethyl-2-(3-phenylsulfanyl-prop-1-ynyl)-[1,3,2]dioxaborolane (**6**) (0.25 g, 0.91 mmol, 5.0 equiv), purification by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 10:1 ratio) gave the title compound (**25**) as a colourless oil, 0.035 g, 48% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.27 (12H, s, 4×CH_3), 4.31 (2H, s, CH_2SPh), 7.22–7.40 (5H, m, Ar-*H*); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 24.8, 29.9, 84.2, 127.7, 129.4, 131.1, 132.9, 144.5, 178.9; FTIR ν_{max}/$CHCl_3$, 3060 (w), 2980 (m), 2931 (w), 1589 (s), 1481 (m), 1440 (m), 1407 (m) cm^{-1}; HRMS (EI$^+$) calcd for $C_{16}H_{19}BNO_3BrS$: 395.0362, found: 395.0379.

4.4. General procedure for the [3+2] cycloaddition reaction of chloronitrile oxide with alkynylboronates

4.4.1. 3-Chloro-5-butyl-4-(4,4,5,5-tetramethyl[1,3,2]-dioxa-borolan-2-yl)-isoxazole (26). A solution of *N*-chlorosuccinimide (1.34 g, 3.86 mmol) and glyoxylic acid aldoxime (0.46 g, 3.86 mmol) in DME (5 ml) were heated under reflux for 10 min (gas evolved). The mixture was then cooled to room temperature and stirred until gas evolution had stopped, at which point chlorination was assumed complete. The resulting solution was used directly for further reaction. A solution of 2-hexy-1-nyl-4,4,5,5-tetramethyl-[1,3,2]dioxaboralane (**2**) (1.73 g, 7.72 mmol) in DME (0.5 ml) was added via cannula to the chloronitrile oxide solution, followed by the addition of $KHCO_3$ (1.54 g, 15.4 mmol) and the mixture stirred for 16 h at 50 °C, then the residual solid was removed by vacuum filtration and solvent was removed in vacuo followed by extraction into ethyl acetate (3×20 ml) and conc. in vacuo. Purification by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 20:1 ratio) gave the title compound (**26**) as a yellow oil, 0.48 g, 44% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.91 (3H, t, J=7.0 Hz, CH_2CH_3), 1.27–1.41 (2H, m, CH_2C$H_2$$CH_3$), 1.31 (12H, s, 4×C$H_3$), 1.59–1.73 (2H, m, C$H_2$$CH_2CH_3$), 2.92 (2H, t, J=7.5 Hz, OCCH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 13.6, 22.0, 24.8, 27.0, 30.0, 83.8, 156.9, 184.0; FTIR ν_{max}/$CHCl_3$, 2979 (m), 2934 (m), 2874 (w), 1595 (s), 1455 (s), 1436 (m), 1414 (s), 1345 (s) cm^{-1}; HRMS calcd for $C_{13}H_{21}BNOCl$: 285.1303, found: 285.1296.

4.4.2. 1-[4-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolan-2-yl)-5-trimethylsilanyl-isoxazol-3-yl]-ethanone (27). A solution of 4,4,5,5-tetramethyl-2-trimethylsilanylethynyl-[1,3,2]-dioxaborolane (**4**) (0.10 g, 0.45 mmol), ammonium cerium (IV) nitrate (0.24 g, 0.45 mmol), formic acid (0.21 g, 4.50 mmol) in acetone (3 ml) were stirred under reflux for 10 h. The mixture was cooled to room temperature then extracted with diethyl ether (5 ml) and washed with sodium hydrogen carbonate {(2×2 ml) CARE: effervescence was observed!}, brine (2×2 ml) and distilled water (2×2 ml). The organics were dried (Na_2SO_4), filtered and conc. in vacuo, then purified by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 5:1 ratio) to give the title compound (**27**) and its regioisomer as a yellow oil, 0.097 g, 69% yield as a 5:1 mixture of regioisomers. (**27**) (minor): ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.23 (9H, s, Si(CH_3)$_3$), 1.31 (12H, s, 4×CH_3), 2.61 (3H, s, COCH_3); (**27**) (major): ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.32 (9H, s, Si(CH_3)$_3$), 1.34 (12H, s, 4×CH_3), 2.59 (3H, s, COCH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) Major regioisomer only δ −1.8, 25.0, 28.4, 84.5, 163.6, 184.5, 193.1; FTIR ν_{max}/$CHCl_3$, 2995 (m), 2979 (m), 2953 (m), 1705 (s), 1555 (m) cm^{-1}; HRMS (ES^+) calcd for $C_{14}H_{25}BNO_4Si$: 310.1646, found: 310.1633.

4.4.3. 3-(2,4,6-Trimethylphenyl)-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-isoxazole (29). The same general procedure as described for the synthesis of (**10**) was carried out with (**1**) (0.50 g, 3.08 mmol), 2-ethynyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**28**) (1.03 g, 6.06 mmol). Purification by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 20:1 ratio) gave the title compound (**29a**) as a yellow oil, 0.57 g, 59% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.33 (12H, s, 4×C*H*$_3$), 2.02 (6H, s, 2×C*H*$_3$), 2.24 (3H, s, C*H*$_3$), 6.68 (1H, s, C*H*), 6.85 (2H, s, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.2, 21.1, 24.7, 85.3, 116.5, 125.8, 128.3, 137.1, 138.6, 160.8; FTIR ν_{max}/$CHCl_3$, 2978 (s), 2926 (m), 1454 (s), 1140 (m) cm^{-1}; HRMS calcd for $C_{18}H_{24}BNO_3$: 313.1849, found: 313.1847. Minor regioisomer (**29b**) was isolated as a yellow oil, 0.22 g, 23% yield; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.15 (12H, s, 4×C*H*$_3$), 2.01 (6H, s, 2×C*H*$_3$), 2.26 (3H, s, C*H*$_3$), 6.80 (2H, s, Ar-*H*), 8.75 (1H, s, C*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.0, 21.2, 24.5, 83.5, 127.8, 128.4, 137.4, 138.5, 165.8, 168.2; HRMS calcd for $C_{18}H_{24}BNO_3$: 313.1849, found: 313.1838.

4.4.4. 3-Phenyl-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-isoxazole (30). The same general procedure as described for the synthesis of (**15**) using triethylamine was carried out with 2-ethynyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**28**) (1.50 g, 10.30 mmol, 2.0 equiv). Purification by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 20:1 ratio) gave the title compound (**30**) as a colourless solid, 0.82 g, 59% yield. Mp 90–91 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.36 (12H, s, 4×C*H*$_3$), 7.13 (1H, s, C*H*), 7.36–7.50 (3H, m, Ar-*H*), 7.74–7.87 (2H, m, Ar-*H*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.8, 85.3, 113.2, 126.9, 128.9, 129.0, 129.9, 161.4; FTIR ν_{max}/$CHCl_3$, 3067 (w), 2980 (m), 1441 (s), 1141 (s) cm^{-1}; HRMS calcd for $C_{15}H_{18}BNO_3$: 271.1379, found: 271.1387. Anal. Calcd for $C_{15}H_{18}BNO_3$: C, 66.45; H, 6.69; N, 5.17. Found: C, 66.37; H, 6.64; N, 5.18.

4.4.5. 3-Bromo-5-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-isoxazole (31). The same general procedure was carried out with 2-ethynyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**28**). Purification by flash column chromatography resulted in product decomposition, therefore the products were tentatively characterized by ^{1}H NMR spectroscopy (supplementary material) and mass spectrometry. HRMS calcd for $C_9H_{13}NO_3Br$: 273.0172, found: 273.0167.

4.4.6. 3-Chloro-4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-isoxazole (32). The same general procedure was carried out with 2-ethynyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (**28**). Purification by flash column chromatography resulted in product decomposition, therefore the products were tentatively characterized by ^{1}H NMR spectroscopy (supplementary material).

4.4.7. 3-Phenyl-4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-isoxazole (33). 3-Phenyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5-trimethylsilanyl-isoxazole (**15**) (0.50 g, 1.46 mmol) was added to a stirred suspension of cesium fluoride (0.44 g, 2.91 mmol) in acetonitrile (5 ml) and ethanol (0.5 ml). The mixture was heated at reflux under N_2 for 10 min then cooled to room temperature. The reaction was quenched by the addition of distilled water (10 ml) and extracted into ethyl acetate (3×10 ml). The combined organics were dried ($MgSO_4$), filtered and conc. in vacuo. Purification by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 10:1 ratio) to give the title compound as a colourless solid, 0.29 g, 74% yield. Mp 100–103 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.30 (12H, s, 4×C*H*$_3$), 7.37–7.45 (3H, m, Ar-*H*), 7.90–7.96 (2H, m, Ar-*H*), 8.65 (1H, s, C*H*); ^{13}C NMR (62.9 MHz,) δ 24.8, 84.1, 128.3,, 128.9, 129.7, 130.6, 158.9, 167.4; FTIR ν_{max}/$CHCl_3$, 3067 (w), 2974 (w), 2940 (w), 1659 (w), 1617 (w), 1587 (w), 1587 (w) 1562 (m) cm^{-1}; HRMS (EI^+) calcd for $C_{15}H_{18}BNO_3$: 271.1380, found: 271.1393.

4.4.8. Synthesis of 5-methyl-3-phenyl-4-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-isoxazole (35). A solution of starting chloroxime (**12**) (0.12 g, 0.80 mmol), 4,4,5,5-tetramethyl-2-prop-1-ynyl-[1,3,2]dioxa-borolane (**14**) (0.13 g, 0.80 mmol) and $KHCO_3$ (0.16 g, 1.60 mmol) in DME (0.5 ml) was heated at 50 °C for 48 h. The reaction mixture was cooled to room temperature and filtered to remove solids. The filtrate was conc. in vacuo to give a yellow oil purification by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 20:1 ratio) gave the title compound (**35**) as a colourless solid, 0.12 g, 54% yield. Mp 84–86 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.30 (12H, s, 4×C*H*$_3$), 2.61 (3H, s, C*H*$_3$), 7.37–7.56 (4H, m, Ar-*H*), 7.76–7.84 (2H, m, Ar-*H*); ^{13}C NMR (125.76 MHz, $CDCl_3$) δ 13.1, 24.8, 83.7, 128.0, 128.9, 129.4, 130.1, 166.2, 178.9; FTIR ν_{max}/$CHCl_3$, 2978 (m), 2932 (w), 1597 (m), 1443 (s) cm^{-1}; HRMS (ES^+) calcd for $C_{16}H_{20}BNO_3$: 285.1536, found: 285.1535. Anal. Calcd for $C_{16}H_{20}BNO_3$: C, 67.39; H, 7.07; N, 4.91. Found: C, 67.23; H, 6.99; N, 4.90.

4.4.9. Synthesis of 4-(5-methyl-3-phenyl-isoxazol-4-yl) benzenesulfonamide (Valdecoxib®)[15] (34) A solution of 5-methyl-3-phenyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-isoxazole (0.053 g, 0.186 mmol), $PdCl_2$(dppf)·DCM (0.015 g, 0.0186 mmol), *p*-bromobenzenesulfonamide (0.090 g, 0.372 mmol) and K_3PO_4 (0.118 g, 0.558 mmol) in dioxane (1 ml) was heated at 85 °C for 21 h under N_2. The reaction was cooled to room temperature and quenched by the addition of distilled water (10 ml) and extracted into dichloromethane (3×20 ml), the organics were washed with brine (20 ml) and dried ($MgSO_4$), filtered and conc. in vacuo to give a brown oil, which was purified by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 3:2 ratio) to give the title compound (**34**) as a colourless powder, 0.058 g, 100% yield. Mp 172–173 °C; ^{1}H NMR (250 MHz, CD_3OD): δ 2.48 (3H, s, C*H*$_3$), 4.89 (2H, s, N*H*$_2$), 7.26–7.47 (7H, m, Ar-*H*), 7.90 (2H, d, J=9.0 Hz, Ar-*H*); ^{13}C NMR (62.9 MHz, CD_3OD) δ 11.6, 108.9, 116.0, 127.7, 129.6, 129.8, 130.9, 131.4, 135.6, 144.4, 162.6, 169.1.

4.4.10. Synthesis of 5-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)-3-(2,4,6-trimethyl-phenyl)-isoxazole (36). A solution of 4,4,5,5-tetramethyl-2-prop-1-ynyl-[1,3,2]dioxaborolane (**14**) (0.200 g, 1.21 mmol), and mesitylnitrile oxide (**15**) (0.195 g, 1.21 mmol) in diethyl ether (3 ml) was heated under reflux for 64 h and cooled to room temperature and conc. in vacuo to give a colourless solid, which was purified by flash column chromatography (eluting solvent petroleum ether/ethyl acetate 40:1 ratio) to give the title compound (**36**) as a colourless solid, 0.356 g, 90% yield. Mp 111–113 °C; ^{1}H NMR (250 MHz,): δ 1.12 (12H, s, 4×CH_3), 2.05 (6H, s, 2×Ar-CH_3), 2.30 (3H, s, Ar-CH_3), 2.61 (3H, s, CH_3), 6.84 (2H, s, 2×Ar-*H*); ^{13}C NMR (62.9 MHz,) δ 13.0, 20.0, 21.2, 24.5, 83.0, 127.0, 127.6, 136.8, 137.7, 165.9, 177.8; FTIR ν_{max}/CHCl$_3$, 2995 (w), 1591 (m), 1432 (m), 1112 (s) cm^{-1}. Anal. Calcd for $C_{19}H_{26}BNO_3$: C, 69.74; H, 8.01; N, 4.28. Found: C, 69.69; H, 8.15; N, 4.12.

4.4.11. Synthesis of 4-[5-methyl-3-(2,4,6-trimethyl-phenyl)-isoxazol-4-yl]-benzenesulfonamide (37). A solution of 5-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3-(2,4,6-trimethyl-phenyl)-isoxazole (**36**) (0.05 g, 0.15 mmol), $PdCl_2$(dppf)·DCM (0.012 g, 0.015 mmol), *p*-bromobenzenesulfonamide (0.072 g, 0.3 mmol) and K_3PO_4 (0.097 g, 0.46 mmol) in dioxane (1 ml) was heated at 85 °C for 64 h under N_2. The reaction was cooled to room temperature and quenched by the addition of distilled water (10 ml) and extracted into dichloromethane (3×20 ml), the organics were washed with brine (20 ml) and dried ($MgSO_4$), filtered and conc. in vacuo to give a brown oil. The product was purified by flash column chromatography (eluting solvent petroleum ether/ ethyl acetate 3:2 ratio) gave the title compound (**37**) as a colourless oil, 0.043 g, 78% yield; ^{1}H NMR (250 MHz, CDCl$_3$): δ 1.94 (6H, s, 2×Ar-CH_3), 2.23 (3H, s, Ar-CH_3), 2.55 (3H, s, CH_3), 4.72 (2H, br, NH_2), 6.81 (2H, s, 2×Ar-*H*), 7.09 (2H, d, J=8.5 Hz, Ar-*H*), 7.72 (2H, d, J=8.5 Hz, Ar-*H*); ^{13}C NMR (125.76 MHz,) δ 11.4, 19.1, 20.2, 108.9, 114.3, 126.2, 127.4, 127.5, 134.3, 136.1, 138.1, 139.3, 160.1, 165.6; FTIR ν_{max}/CHCl$_3$,3177 (w), 3084 (w), 2923 (w), 16.15 (m) cm^{-1}; HRMS (EI^{+}) calcd for $C_{19}H_{20}N_2O_3S$: 356.1195, found: 396.1204.

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Supplementary data

^{1}H NMR Spectra of compounds **31** and **32**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.05.015.

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Bi(III) Catalysed *O*-acylative cleavage of 2,5-dimethyltetrahydrofuran: a substrate dependent borderline mechanism

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Abstract—The Bi(III) catalysed *O*-acylative cleavage of *cis*- and *trans*-2,5-dimethyltetrahydrofuran **4** with AcCl, BzCl or *i*-PrCOCl is stereochemically consistent with the operation of a concerted process (A_ND_N), which proceeds via a stabilised carbocation or 'loose' S_N2 transition state. However, the *O*-acylative cleavage of *cis*-2,5-dimethyltetrahydrofuran **4** with sterically demanding electrophiles such as *t*-BuCOCl, appears to be stereochemically consistent with the alternative S_N1 (D_N+A_N) pathway. The apparent merging of mechanistic pathways is rationalised by the participation of a strained acyloxy cation.
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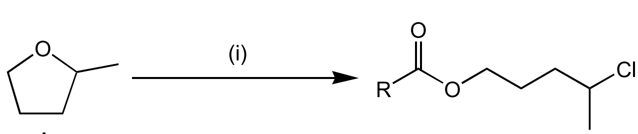
1. Introduction

It has been known for some time that the cleavage of cyclic ethers to afford 4-halobutanes may be achieved using Lewis acids.[1] This procedure has failed to attain any prominence in organic synthesis, possibly because both stoichiometric amounts of Lewis acid and extended periods of heating are often required for cleavage to occur (i.e., $ZnCl_2$,[2] $FeCl_3$,[3] $MgBr_2$,[4a] $AlCl_3$[5]). In addition, the majority of procedures reported to date fail to afford regioselective cleavage (i.e., 1° vs 2°). Our interest in the unique stereoelectronic and mechanistic characteristics associated with main group organometallic complexes[6] encouraged us to investigate Bi(III) salts as versatile, cheap non-toxic catalysts for organic synthesis.[7] We recently reported a mild (DCM/20 °C), high yielding Bi(III) catalysed (5%) *O*-acylative cleavage procedure using a variety of acid chlorides RCOCl **2**, which in the case of 2-methyltetrahydorfuran **1**, affords haloesters **3** with excellent regioselectivity (Scheme 1).[8]



Scheme 1. (i) RCOCl **2**, $BiCl_3$ (5%), DCM, r/t.[8]

As the Bi(III) catalysed *O*-acylative cleavage of tetrahydrofuran fails to afford products consistent with the operation of a unimolecular process, that is, 3-chlorobutylbenzoate, we assumed that this reaction must proceed via a concerted mechanism. The regioselectivity observed for the Bi(III) catalysed *O*-acylative cleavage of **1** is however, inconsistent with the classical perception of a bimolecular process. Insight into the mechanism of such reactions may be gained by examining the stereochemical outcome accompanying the *O*-acylative cleavage of enantiomerically pure 2-alkyltetrahydrofurans. However, we have chosen an alternative approach which examines the *O*-acylative cleavage of *cis*- and *trans*-2,5-dimethyltetrahydrofuran **4**; the loss of configurational integrity during *O*-acylative cleavage will afford mixtures of diastereoisomers as opposed to enantiomers. We describe here studies which reveal the possible origin of the regioselectivity accompanying the Bi(III) catalysed *O*-acylative cleavage of 2-methyltetrahydrofuran **1**. In addition, we describe how the *cis* and *trans* isomers of 2,5-dimethyltetrahydrofuran **4** appear to undergo *O*-acylative cleavage via alternative mechanisms, depending upon the structure of the electrophile.

2. Results and discussion

2.1. *O*-Acylative cleavage using acid chlorides 2a–c

2,5-Dimethyltetrahydrofuran **4**, used here as the commercially available mixture of *cis* and *trans*-isomers,[9a]

Keywords: Bi(III) Catalysis; Cyclic ethers; *O*-Acylative cleavage; Borderline mechanism.
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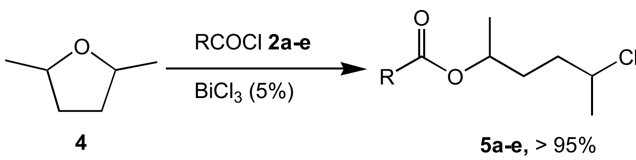
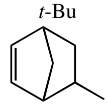
undergoes smooth $BiCl_3$ (5%) catalysed *O*-acylative cleavage with acid chlorides RCOCl **2a–c** to afford the corresponding 1-methyl-4-chloropentyl esters **5a–c** in isolated yields of >95% (Table 1). As anticipated, both the *syn*- (i.e., 1*SR*,4*SR*) and *anti*- (i.e., 1*SR*,5*RS*) diastereoisomers of **5a–c** are formed in approximately equal amounts, as established by $^1H/^{13}C$ NMR, GC and GC–MS analyses.

Table 1. Chloroesters **5a–e**



	R	Isomeric ratio
5a	Me	1:1
5b	Ph	1:1
5c	*i*-Pr	1:1
5d	*t*-Bu	5:3 (*anti*:*syn*)
5e		1:1 (*exo*- *anti*:*syn*) 4:2 (*endo*- *anti* and *syn*)

The *cis* isomer of **4** employed for these studies was obtained by the stereospecific catalytic hydrogenation of 2,5-dimethylfuran using Raney nickel.[9] ^1H NMR spectroscopy was used to establish that the hydrogenation of 2,5-dimethylfuran is accompanied by a small quantity (ca. 5%) of the epimeric *trans* isomer. The Bi(III) catalysed *O*-acylative cleavage of *cis*-**4** with acid chlorides **2a–c** affords a single diastereoisomer (GC ca. 95%) of the corresponding 1-methyl-4-chloropentyl esters **5a–c** (see Section 4).

The relative configuration of the product chloroesters **5a–c** was established unambiguously by an in situ hydrolysis and re-cyclisation procedure to afford the corresponding 2,5-dimethyltetrahydrofuran **4**.[4b] Thus, a single diastereoisomer of **5a–c** was gently heated in the presence of potassium hydroxide and ethylene glycol for 6 h to afford **4**, which was distilled (bp = 91–92 °C) directly from the crude reaction mixture (yield = 50%). ^1H NMR spectroscopy was used to establish that in each case, re-cyclised **4** was in fact the *cis* isomer.[10] Heating the 1:1 diastereoisomeric mixtures of **5a–c** in potassium hydroxide/ethylene glycol afforded the corresponding 1:1 mixtures of *cis*/*trans* **4**. It may be concluded then, that the re-cyclisation of esters **5** to ether **4** (step **B**) proceeds via a concerted S_N2 (A_ND_N)[11] mechanism (Fig. 1). From this, it follows that the original $BiCl_3$ catalysed *O*-acylative cleavage of *cis*-**4** with **2a–c** must afford *syn*-**5a–c** (Fig. 1).

If *cis*-**4** had undergone a stepwise Bi(III) catalysed *O*-acylative cleavage process to afford a liberated intermediate, appreciable amounts of both diastereoisomers of **5a–c** should have been observed, and as a consequence, a mixture of *cis*- and *trans*-**4** would be obtained upon re-cyclisation. This is not the case. Furthermore, if *O*-acylative cleavage with retention of configuration had occurred, *trans*-**4** would be the ultimate product of the ring opening and subsequent re-cyclisation of *cis*-**4**. It would appear then, that the ethereal C–O bond of the intermediate acyloxy:$BiCl_4^-$ ion pair becomes significantly polarised without actual cleavage prior to attack by the chloride anion (step **A**; Fig. 1). The result may be viewed as either an unusually 'loose' transition-state for an S_N2 reaction, or a carbocation that is stabilised by the interaction of both attacking and leaving groups.[12] This would appear to account for the observed regioselectivity attending the Bi(III) catalysed *O*-acylative cleavage of **1**. A search of the literature reveals just one other example of a 'loose' S_N2 transition-state being invoked to rationalise the unexpected regioselectivity attending ring cleavage.[13] Here also, an acylated heteroatom serves to stabilise a developing carbocation during the cleavage of a 2,2-dimethyl *N*-acylaziridine with thiolate as nucleophile.

2.2. *O*-Acylative cleavage using acid chlorides 2d–e

Surprisingly, the Bi(III) catalysed *O*-acylative cleavage of **4** with *t*-BuCOCl **2d** affords **5d**, not as a 1:1 mixture but as a 3:5 mixture of diastereoisomers (retention times = 17.4 and 17.9 min, respectively; Scheme 2). The relative configuration of the major diastereoisomer in this mixture was deduced by the in situ hydrolysis/re-cyclisation procedure described earlier. Thus, heating a 5:3 mixture of **5d** in potassium hydroxide/ethylene glycol affords a 5:3 mixture of *trans*-**4** and *cis*-**4**, respectively. As the re-cyclisation procedure proceeds via a concerted mechanism, the initial $BiCl_3$ *O*-acylative cleavage of **4** with **2d** must generate *anti*-**5d** (retention time = 17.9 min) as the major diastereoisomer.

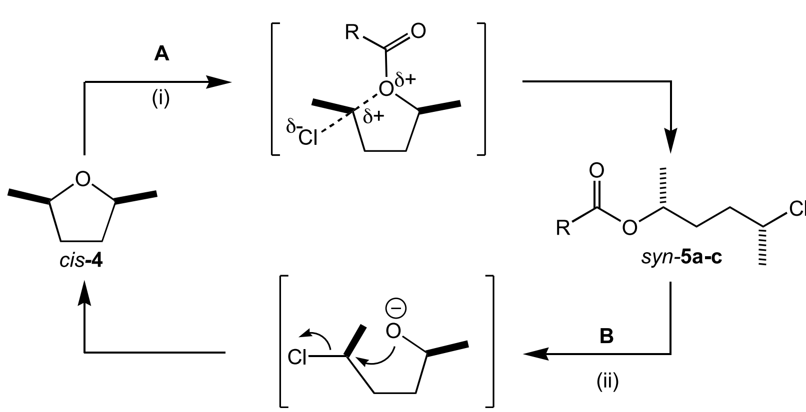
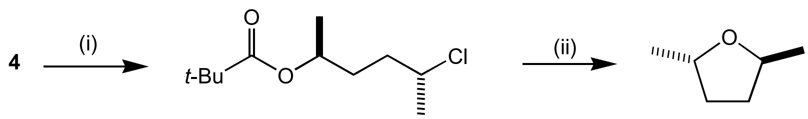


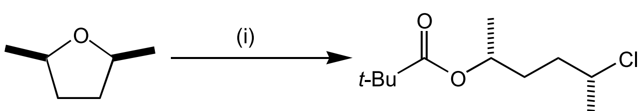
Figure 1. (i) RCOCl 2a–c, $BiCl_3$ (5%), DCM, r/t, 4 h; (ii) KOH, $HO(CH_2)_2OH$, 60 °C, 6 h.



Scheme 2. (i) *t*-BuCOCl **2d**, $BiCl_3$ (5%), DCM, r/t, 4 h; (ii) KOH, $HO(CH_2)_2OH$, 60 °C.

In short, *O*-acylative cleavage of **4** with **2d** contrasts with the corresponding reactions of **2a–c**; the former generates a mixture of diasteroisomers consistent with the operation of a S_N1 (D_N+A_N) process.

The partitioning of concerted and stepwise reaction pathways for *cis*- and *trans*-**4** was examined further by considering the reaction of *cis*-**4** with *t*-BuCOCl. Here, *O*-acylative cleavage affords a 3:1 mixture of diastereoisomeric esters **5d** [retention times = 17.4 (*syn*) and 17.9 (*anti*) min, respectively]. As the $^1H/^{13}C$ NMR, GC and GC–MS characteristics of *anti*-**5d** were established previously by the re-cyclisation protocol, we deduced that the diastereoisomer distribution generated by the cleavage of *cis*-**4** with **2d** is approximately 75% *syn*-**5d** and 25% *anti*-**5d** (Scheme 3).



Scheme 3. (i) *t*-BuCOCl **2d**, $BiCl_3$ (5%), DCM, r/t, 4 h.

Overall then, *O*-acylative cleavage of *cis*-**4** → 3:1 mixture of *syn*:*anti*-**5d**. Having established earlier that the cleavage of **4** → 3:5 *syn*:*anti*-**5d**, it is necessary to conclude that *cis*-**4** alone undergoes some degree of non-concerted *O*-acylative cleavage to afford an additional 25% *anti*-**5d**. To examine the reproducibility of this product partitioning, we prepared a 73:27 mixture of *cis*- and *trans*-**4** and exposed it to the effects of $BiCl_3$ (5%) with **2d**. As the *anti* stereoisomer of **5d** is expected to afford merely 75% of the product, consistent with a concerted process, an overall distribution of 55:45 *syn*:*anti*-**5d** was predicted. The experimentally determined ratio of **5d** was found to be 56:44, thereby confirming that *cis*-**4** affords ca. 25% *anti*-**5d**.

The cleavage of **4** with another sterically demanding electrophile, namely norborn-2-ene-5-carboxylic acid chloride (**2e**, Table 1), was examined.[14] The Bi(III) catalysed *O*-acylative cleavage of **4** with a 1:1 mixture (*endo*/*exo*) of **2e** generates all four possible diastereoisomers of **5e** in the ratio 1:1 (*exo*: *syn*/*anti*) and 4:2 (*endo*: *syn* and *anti*).[15] An overall preference for the *endo* isomer is noted (i.e., 1:3). Importantly, the reaction of *cis*-**4** affords all four possible diastereoisomers of **5e** in the ratio 1:1 (*exo*: *syn*/*anti*) and 2:1 (*endo*: *syn* and *anti*). Although we have not characterised all of the diastereoisomers in this mixture, it is safe to conclude that at least ca. 40% *cis*-**4** cleaves to afford the products consistent with an S_N1 pathway.

Our observations are summarised in Figure 2. The Bi(III) catalysed *O*-acylative cleavage of *trans*-**4** with acid chlorides **2a–e** affords *anti*-**5a–e** by a concerted process, presumably via the acyloxy cation *trans*-**6a–e**. Similarly, cleavage of *cis*-**4** with **2a–c** affords the corresponding esters *syn*-**5a–c**, also by a concerted process, presumably via *cis*-**6a–c**. However, the sterically demanding acid chlorides **2d–e** appear to interfere with the concerted C–O bond cleavage and Cl–C bond formation processes associated with the collapse of *cis*-**6d–e**.

A clearer distinction between mechanistic options is assisted by considering the lifetime of an intermediate, rather than the character of a transition state.[12] A merging of mechanisms may arise then, when the lifetime of an intermediate increases with respect to that of a concerted process. We have demonstrated that the Bi(III) catalysed *O*-acylative cleavage of *trans*-**4** and **1** with **2d** is

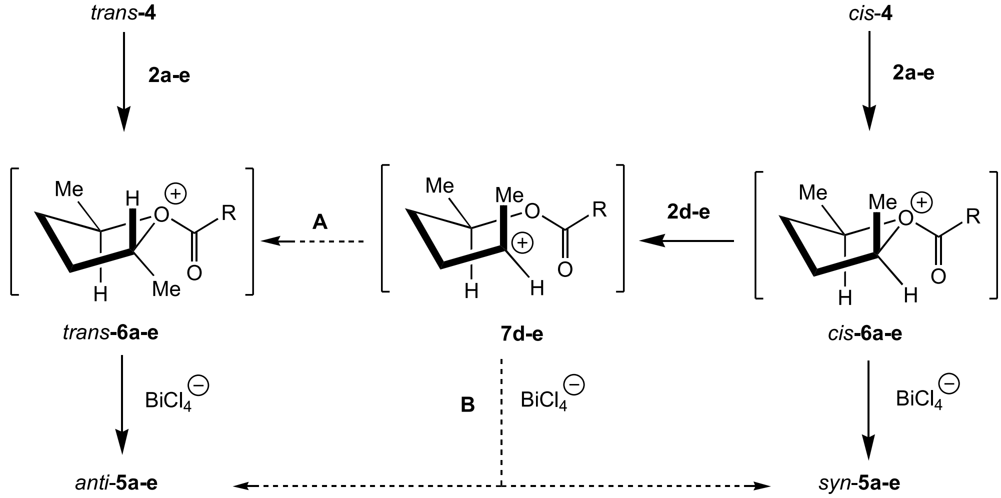


Figure 2. Reaction summary.

stereochemically consistent with a concerted process.[8] The *cis* 2,5-substituents clearly effect the synchronicity of bond cleavage/formation during the Bi(III) catalysed *O*-acylative cleavage of *cis*-**4**. It is reasonable to suggest that steric compression attending the pseudo-axial 2,5-dimethyl groups and the bulky acyloxy substituent R (i.e., **2d–e**) destabilise cationic *cis*-**6d–e**, leading to premature cleavage of the polarised C–O bond to afford an intermediate ion pair **7d**–**e**, prior to chloride attack.[16] Calculations[17] upon *trans*-**6d** and *cis*-**6d** indicate that the latter is strained by an additional 2.5 kcal/mol with respect to the former; an effect presumably derived from the compression associated with the *t*-butyl moiety and the axial dimethyl groups of the *O*-acylated heterocycle (Fig. 3a–b). This modest level of intramolecular strain would appear sufficient to perturb the synchronicity of bond formation/cleavage of *cis*-**6d**.

(a) *trans*-**6d** (E = 0) (b) *cis*-**6d** (E = 2.49)

Figure 3. The calculated equilibrium geometries, and relative DFT energies (kcal/mol) of acyloxycations (a) *trans*, and (b) *cis*-**6d**.

As we have demonstrated, it is not easy to predict the circumstances which favour S_N2 versus the alternative S_N1 process in diastereoisomeric systems. However, an appreciation of these factors can ultimately lead to complete diastereoselectivity.[18] For now, we and others can only speculate upon the fate of species **7d–e**. Internal ion-pair return to afford the less strained *trans*-**6d–e** (step **A**, Fig. 2) is not unreasonable given the estimated rate constant for conformational change (1×10^{11} s^{-1}).[19] Alternatively, stereochemical scrambling may proceed via an 'uncoupled concerted'[12] process that avoids the formation of a formal carbocation. Here, the distribution of products reflects shielding by the leaving group against 'frontside' attack by the nucleophile (step **B**, Fig. 2).[20]

3. Conclusions

To summarise, the synthetically useful Bi(III) catalysed *O*-acylative cleavage of tetrahydrofurans proceeds via a concerted mechanism with inversion of configuration. In the case of 2-alkyl tetrahydrofurans, excellent regioselectivity is rationalised by an unusually 'loose' transition-state for an S_N2 (A_ND_N) process, which may be likened to a carbocation stabilised by the interaction of both attacking and leaving groups. We now assume that the Bi(III) catalysed *O*-acylative cleavage of *cis* substituted 2,5-dialkyltetrahydrofurans with bulky electrophiles may afford products consistent with a stepwise S_N1 (D_N+A_N) process. This is a limiting consideration for those who may wish to exploit the stereospecific nature of this methodology in the future.

4. Experimental

4.1. General

Reactions were performed under an atmosphere of dry nitrogen. Dichloromethane (DCM) was distilled under an atmosphere of nitrogen from calcium hydride. Unless otherwise stated, all other materials were purchased from Aldrich or Avocado and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL Eclipse +300 (300 MHz) spectrometer, using $CDCl_3$ as solvent and referenced to residual $CHCl_3$, with chemical shifts being reported as δ (ppm) from tetramethylsilane, and J values measured in Hz. GC–MS analyses were performed upon either a HP 5989 MS engine or an Agilent Technologies 5973 MSD instrument using a HP5 capilliary column with He as the carrier gas, at a programmed temperature rate increase of 4 °C/min. from an initial temperature of 50 °C. GC analyses were performed using a Carbowax 20M column at a programmed temperature rate increase of 5 °C/min, initial temperature 50→160 °C. HR-ESI-MS were performed by the University of Bristol mass spectrometry service.

4.1.1. Representative procedure for 1(*SR*)-methyl-4(*SR*)-chloropentylacetate (*syn*)-(5a). *trans*-(**4**) (570 mg, 5.7 mmol) was added to a rapidly stirred suspension of $BiCl_3$ (90 mg, 0.3 mmol) in DCM (30 mL). Acetyl chloride (440 mg, 5.6 mmol) in DCM (20 mL) was added dropwise, and the resulting solution was stirred at room temperature for 4 h. The dark red solution was filtered through a plug of SiO_2 and concentrated in vacuo to afford a clear colourless oil characterised as *syn*-(**5a**) (965 mg, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.87–4.71 (1H, m), 4.00–3.84 (1H, m), 1.90 (3H, s), 1.74–1.48 (4H, m), 1.37, (3H, d $J=6.0$ Hz), 1.07 (3H, d $J=7.0$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 69.9, 58.1, 35.9, 32.9, 25.3, 20.8, 20.0; ν_{max}(liquid film) 2976, 17376, 1448, 1372, 1244 cm^{-1}; HRMS Calcd for $C_{18}H_{15}O_2ClNa$ (M+Na$^+$) 201.0658, found 201.0664. GC retention times *syn*/*anti*-**5a**=10.9 and 11.2 min, respectively.

4.1.2. 1(*SR*)-Methyl-4(*SR*)-chloropentylbenzoate (*syn*)-(5b). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (2H, d, $J=7.0$ Hz), 7.51 (1H, t, $J=7.0$ Hz), 7.51–7.42 (2H, m), 5.28–7.11 (1H, m), 4.12–3.95 (1H, m), 1.95–1.70 (4H, m), 1.47, (3H, d $J=6.0$ Hz), 1.35 (3H, d $J=7.0$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 133.0, 130.3, 129.6, 128.4, 70.8, 58.3, 36.0, 33.1, 29.3, 26.24, 25.5, 20.3; ν_{max}(liquid film) 2975, 2565, 1716, 1451, 1276, 1130, 712 cm^{-1}; HRMS Calcd for $C_{13}H_{17}O_2ClNa$ (M+Na$^+$) 263.0810, found 263.0814. GC retention times *syn*/*anti*-**5b**=22.9 and 23.1 min, respectively.

4.1.3. 1(*SR*)-Methyl-4(*SR*)-chloropentyl-*i*-propionoate (*syn*)-(5c). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98–4.79 (1H, m), 4.15–3.88 (1H, m), 2.62–2.44 (1H, m), 1.81–1.61 (4H, m), 1.47 (3H, d $J=6.0$ Hz), 1.19 (3H, d $J=7.0$ Hz), 1.15, 1.13 (6H, 2×d $J=6.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 69.7, 58.2, 36.0, 34.2, 32.9, 25.4, 20.1, 19.1, 19.0; ν_{max}(liquid film) 2975, 2935, 1731, 1469, 1196, 1161 cm^{-1}; HRMS Calcd for $C_{10}H_{19}O_2ClNa$ (M+Na$^+$) 229.0966, found 229.0971. GC retention times for *syn*/*anti*-**5c** = 17.0 and 17.4 min, respectively.

4.1.4. 1(*SR*,*SR*)-Methyl-4(*SR*,*RS*)-chloropentyl-*t*-butanoate (*syn*/*anti* 3:1)-(5d). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.97–4.88 (1H, m), 4.09–3.91 (1H, m), 1.83–1.62 (4H, m), 1.50 (major)/1.49 (minor) (3H, 2×d J = 6.0 Hz), 1.19/1.18 (3H, 2×d J = 7.0 Hz), 1.18, 1.17 (6H, 2×s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 70.2, 69.6, 58.7, 36.3, 36.0, 33.2, 32.9, 27.2, 25.5, 25.4, 20.1, 20.0; ν_{max}(liquid film) 2976, 2934, 1726, 1703, 1482, 1284, 1166 cm^{-1}; HRMS Calcd for $C_{11}H_{21}O_2ClNa$ ($M+Na^+$) 243.1122, found 243.1127. GC retention times for *syn*/*anti*-**5d** = 17.4 and 17.9 min, respectively.

4.1.5. 1(*SR*,*SR*)-Methyl-4(*SR*,*RS*)-chloropentyl-[(*endo*/*exo*)-norborn-2-ene-5-] carboxylate-(5e). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20–6.05 (3H, m), 5.94–5.86 (1H, m), 4.90–4.76 (1H, m), 4.10–3.90 (1H, m), 3.18 (1H, br s), 3.00 (1H, br s), 2.97–2.84 (2H, m), 2.22–2.14 (1H, m), 1.91–1.55 (4H, m), 1.52 (3H, 2×d J = 6.0 Hz), 1.40–1.20 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 174.3, 138.3, 137.8, 135.2, 133.1, 133.0, 70.2, 70.1, 69.6, 69.5, 58.8, 58.7, 47.8, 47.6, 46.0, 44.0, 43.8, 36.3, 36.0, 33.2, 32.9, 31.0, 27.2, 25.3, 20.1; ν_{max}(liquid film) 2975, 2873, 1727, 1177 cm^{-1}; HRMS Calcd for $C_{14}H_{21}O_2ClNa$ ($M+Na^+$) 279.1122, found 279.1127. GC-retention times = 30.6/30.7 (*exo*) and 31.0/31.4 (*endo*) min.

Acknowledgements

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Stereoselective formation of dicondensed spiropyran product obtained from the reaction of excess Fischer base with salicylaldehydes: first full characterization by X-ray crystal structure analysis of a DC·acetone crystal

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Abstract—The structure and stereochemistry of the dicondensed spiropyran product (**DC**-**1**, X=COOH) obtained from reaction of excess Fischer base with substituted salicylaldehydes has been fully assigned as **C** with (8*R*, 10*R*) configuration on the basis of single crystal X-ray diffraction analysis. The stereoselective formation of DC molecules indicates that the most plausible mechanism for DC formation involves dehydration of the cyclic carbinol intermediate with the aid of intramolecular H-bonding via transition structure $TS^{\ddagger}_{1}$.
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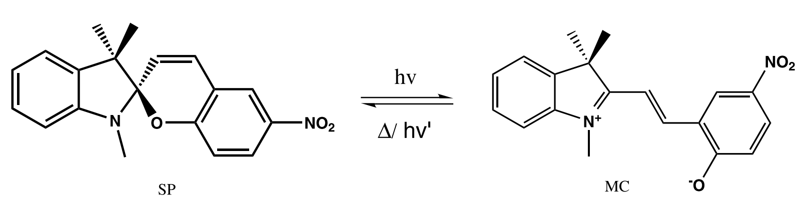
1. Introduction

The thermochromism and photochromism of spiropyrans has received wide attention because of the potential practical applications of these materials to a variety of optoelectronic and molecular information devices.[1] The indolinobenzospiropyran structure, **3**, that is 1,3,3-trimethyl-6′-nitrospiro(indoline-2,2′-benzopyran) derivatives, typifies this class of compounds. These materials exemplify some of the typical organic photochromic compounds having high extinction coefficients in the near-infra region and have thus been featured in a number of recent studies.[1,2] Their photochromic behavior is normally based on the UV irradiation-promoted opening of the spiro ring system (SP) to produce the colored merocyanine species (MC) and their photo and/or thermal relaxation to regenerate the spiropyrans (Scheme 1).

In contrast to the many available reports[1–4] on the synthesis and structural and mechanistic aspects of spiropyran species, little is known about the structural chemistry of dicondensed (DC) products, although a few authors have speculated on the most likely structure of DC through ^{1}H NMR spectroscopy. Interest in these dicondensed heterocycles as additives in silver halide emulsions[5,6] and as components of thermal paper[7,8] provides further motivation for the unequivocal structure assignment of these compounds. An ongoing research focus in our laboratories has been the development of new optoelectronic materials. Thus of special interest pertaining to these dicondensed adducts,



Scheme 1. Photochromism of indolinobenzospiropyrans.

Keywords: Dicondensed spiropyran; Single crystal X-ray diffraction analysis; Stereoselective formation; Cyclic carbinol intermediate; Intramolecular H-bonding.
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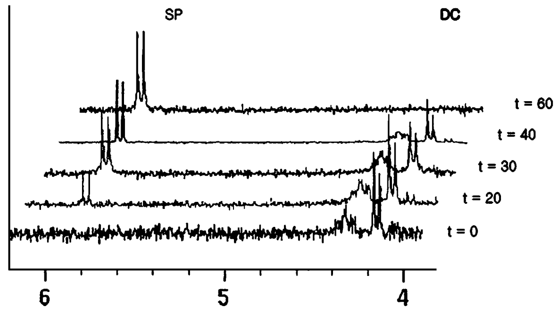


Figure 1. ^{1}H NMR spectra of **DC-1** in the range of 4–6 ppm at 140 °C, T= (a) 0; (b) 20; (c) 30; (d) 40; (e) 60 min.

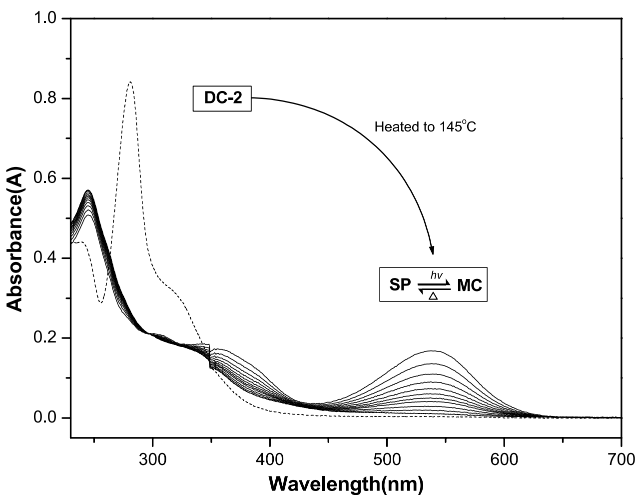


Figure 2. Thermal transformation of **DC-2** in diglyme, showing formation of the corresponding SP; **DC-2** (dotted line) and SP/MC photochromic behavior (solid line) after irradiation in EtOH (2.19×10^{-5} M).

containing two indoline units, is the possibility that these structures could function as optical switches.

In particular, the DC stereochemical aspects have not been reported due to the lack of a convenient method for the formation of DC crystals. This aspect is described in detail in the following section, but the main conclusion can be drawn here. Structure analysis was effected for one representative compound, **DC-1**, which was obtained in satisfactory crystalline form as a 1:1 complex with one mole of solvent (acetone). We report here the first X-ray structural determination of this class of compound.

2. Results

2.1. Synthesis

The reaction of Fischer base **1** and salicylaldehyde **2** in 1:1 molar ratio yields both the monocondensed product **3** and the dicondensed product **4**. The product ratios **3**:**4** are ∼1:1–2:1 depending upon solvent used, the substituents (X,Y) in the salicylaldehydes and reaction conditions. Predominance of the dicondensed product could be achieved by using a 2- to 3-fold excess of Fischer base over the salicylaldehyde.

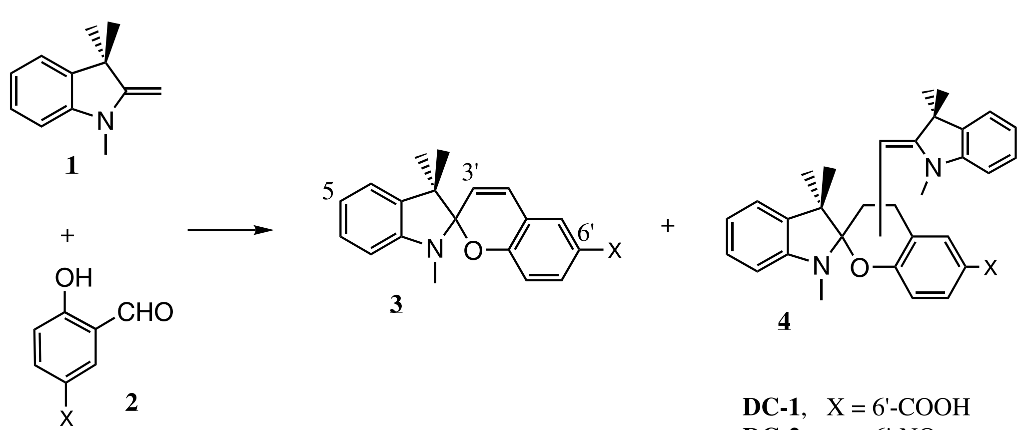
From the reaction of **1** and **2** in 1:1 molar ratio, the monocondensed spiropyran compounds (SP) are generally formed as the major product when an electron-withdrawing substituents is present in the salicylaldehyhyde.

DC materials melted around 170 °C but decomposed over temperature ranges of 141–149 °C, with changes of colour before melting. NMR monitoring showed that **DC-1** survived heating up to 140 °C for 50 min in the solid state, thereafter forming Fischer base and spiropyran.

$$DC \rightarrow SP + FB$$

Resonances at 4.15 and 4.32 ppm are characteristic of DC and 5.86 ppm for SP.[3] In the presence of excess acid decomposition to Fischer base and MCH+ (protonated open-form spiropyrans) occurs in about 50 min.[9] A ^{1}H NMR temperature study of the decomposition of **DC-1** in DMF is shown in Figure 1.

The DC molecules are thus shown to be precursors of SP molecules. The thermal transformation of DC molecules to the corresponding SP molecules is confirmed further via UV–vis spectral behavior of **DC-2**. SP–NO_2, which exhibits typical photochromic behavior shown in Figure 2.



DC-1, X = 6'-COOH
DC-2; = 6'-NO_2
DC-3; = 6'-N=N-Ph

Scheme 2. Synthetic scheme of SP and DC compounds.

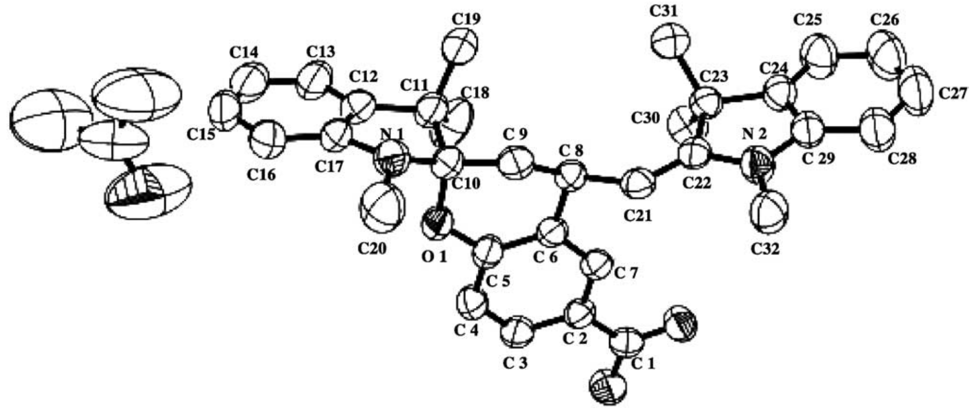


Figure 3. ORTEP diagram with an atomic labeling system in the **DC-1**.

2.2. Structural analysis of DC-1 by X-ray diffraction

Structure analysis was effected for one representative compound, **DC-1** (X=COOH), which was obtained in satisfactory crystalline form, as an 1:1 complex with one molecule of solvent (acetone). This is the first isolation of 'dicondenced product' from the reaction of Fischer base with salicylaldehydes. Attempts to grow crystals of other DC molecules such as **DC-2** or **DC-3** (Scheme 2) from various solvents were unsuccessful for X-ray crystal analysis. An ORTEP diagram with atomic labeling in the **DC-1** molecule is shown in Figure 3.

The crystal data, structure refinement, atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **DC-1** are briefly given in the Section 9.

Table 1. Selected geometrical parameters (bond lengths in Å, angles in degrees)

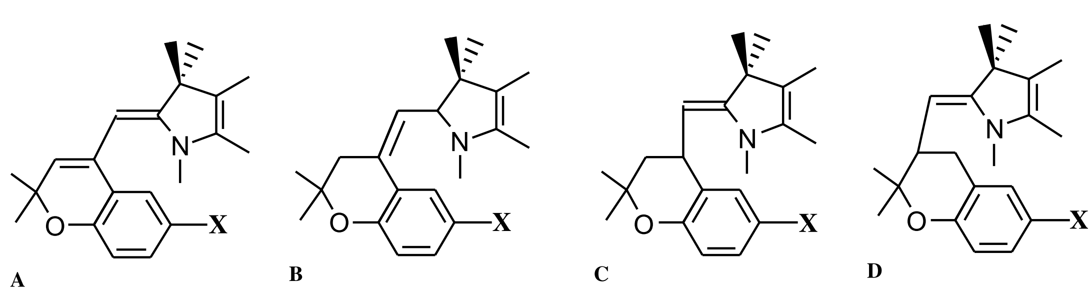
Bonds	Length	Bonds	Angle
O(1)–C(5)	1.347(4)	C(5)–O(1)–C(10)	120.9(3)
O(1)–C(10)	1.475(4)	O(1)–C(5)–C(6)	123.4(3)
N(1)–C(10)	1.444(4)	C(5)–C(6)–C(8)	120.0(3)
N(1)–C(17)	1.395(5)	C(21)–C(8)–C(6)	111.5(3)
N(1)–C(20)	1.446(5)	C(21)–C(8)–C(9)	111.6(3)
N(2)–C(22)	1.406(4)	C(6)–C(8)–C(9)	108.8(3)
N(2)–C(29)	1.378(4)	C(10)–C(9)–C(8)	113.8(3)
N(2)–C(32)	1.443(4)	C(22)–C(21)–C(8)	128.7(3)
C(6)–C(8)	1.521(5)	C(21)–C(22)–N(2)	123.2(3)
C(8)–C(9)	1.534(5)	C(21)–C(22)–C(23)	129.8(4)
C(8)–C(21)	1.510(5)	N(1)–C(10)–O(1)	104.9(3)
C(9)–C(10)	1.511(5)	N(1)–C(10)–C(9)	113.6(3)
C(21)–C(22)	1.325(5)	N(2)–C(22)–C(23)	107.0(3)
C(22)–C(23)	1.532(5)	O(1)–C(10)–C(9)	108.7(3)
C(23)–C(24)	1.515(5)	O(1)–C(10)–C(11)	108.0(3)

Selected bond lengths and bond angles are collected in Table 1.

The main conclusion of the X-ray crystal structure study is that the second molecule of Fischer base is attached to C(8), as proposed previously from the ^{1}H NMR study,[15] that is structure C in Scheme 3. The C(8)–C(9) and C(8)–C(21) distances are 1.534 and 1.510 Å, respectively, typical of C–C single bond. The enamine C(21)–C(22) bond length of the second Fischer base unit is 1.325 Å which is typical of the C=C bond. The O(1)–C(5) and O(1)–C(10) distances are 1.347 and 1.475 Å, respectively. The most interesting aspect is the conformational structure of the benzopyran ring of **DC-1**. The four hydrogens (Ha, Ha′ Hb and Hc) are located adjacent to each other, as depicted in Figure 4.

Dihedral angles of **DC-1** are 53.0, 170.4 and 172.16° for Hb–C(8)–C(9)–Ha (θ_1), Hb–C(8)–C(9)–Ha′ (θ_2), and Hb–C(8)–C(21)–Hc (θ_3), respectively. The double bond C(21)=C(22) of the second Fischer base moiety has an E configuration. From the ^{1}H NMR vicinal coupling constant values of **DC-1**, dihedral angles are calculated using the modified Karplus equation.[14] The dihedral angles (50.1, 170.4 and 172.1° for θ_1, θ_2 and θ_3, respectively) are in complete agreement with calculated values.[15]

The stereochemical relationship of the two centers can now be established. The absolute configuration of the product is (8*R*, 10*R*). The geometry about the olefinic bond is also determined. The enamine proton H(21) is located close to the N-methyl group of the second Fischer base unit. The stereoselective formation of (8*R*, 10*R*) isomer of DC molecules from the reaction of Fischer base and salicylaldehydes requires further consideration (see Section 3). ^{1}H



Scheme 3. Proposed structures of DC molecules.

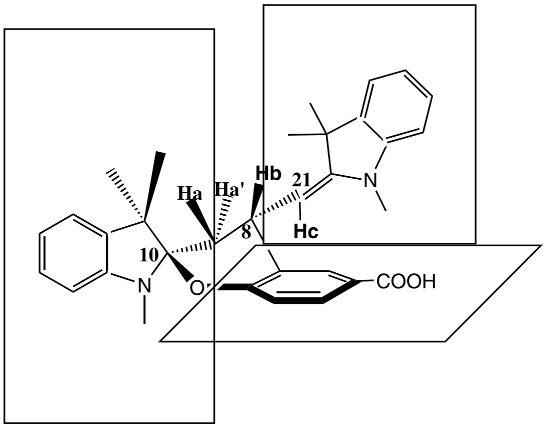


Figure 4. Structure of **DC-1** showing the (8*R*, 10*R*, 21*E*) configuration.

NMR data of **DC-2**, before recrystallization, showed formation of (8*R*/10*S*, 8*S*/10*R*) isomer in less than 1%.

The **DC-1** molecules are stacked in linear chains in the crystal. All molecules are juxtaposed alternatively. The indole unit stays parallel to the plane of the second molecule of Fischer base unit. The crystal **DC-1** is monoclinic. All molecules pack in the crystal with their long axes almost parallel.

3. Discussion

3.1. Structure and stereochemistry of the DC molecules

Four isomeric structures (A–D) shown in Scheme 3 have been proposed for the dicondensed product. Koelsch and Workman[10] assumed the structure of the product was A. This conjecture was supported by the infrared studies of Schiele and Arnold.[11] Bertelson[12] then pointed out that structure B must also be considered as a possibility. Hinnen et al.[13] later preferred C or D based on ^{1}H NMR considerations.

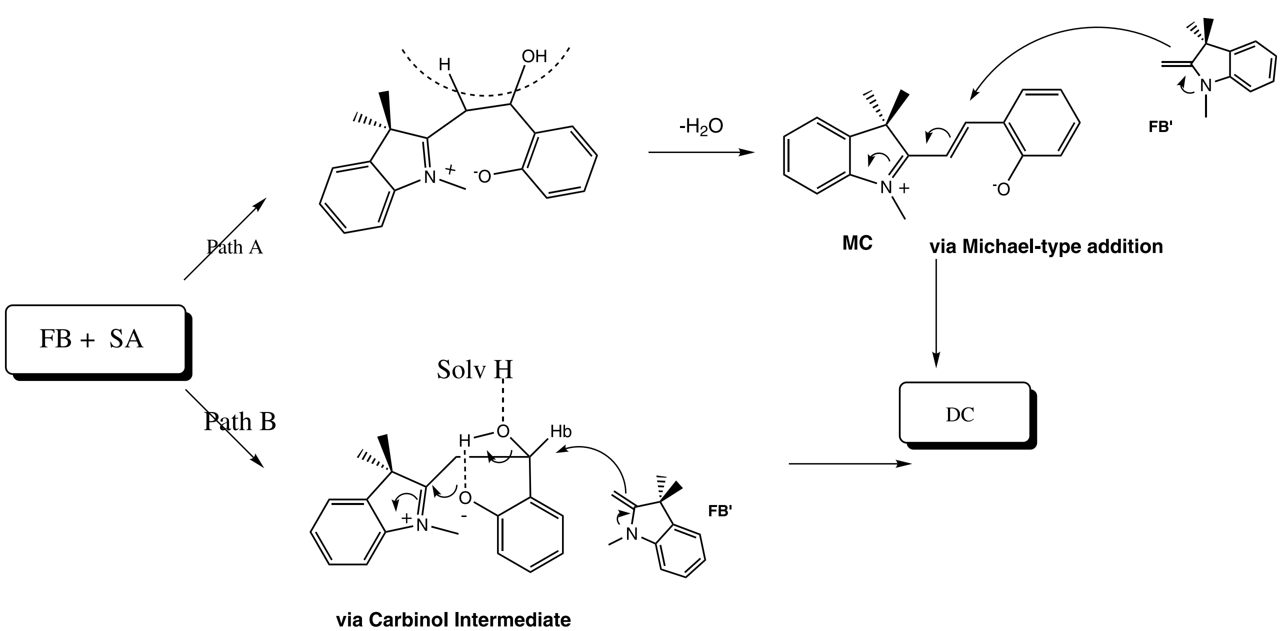
Unequivocal structure assignment of the dicondensed product requires the following three segments. First, the four isomeric structures A–D (Scheme 3) must be considered. Second, since the dicondensed compound contains two chiral centers, the stereochemical relationship of these centers must be established. Finally, in the case of structures B, C and D, the geometry about the olefinic bond must be ascertained.

The unequivocal structure and stereochemistry of the DC system is hereby established by X-ray single crystal analysis as C in Scheme 3. Due to the lack of a convenient method for the formation of DC crystals until now, no papers have reported the detailed structure and the stereochemical identification of the DC molecules. The X-ray single crystal structure of the dicondensed product is important, not only because of the molecular conformation including stereochemistry at three stereogenic centers, C(8), C(10) and C(21) (Fig. 3), but because this may give a clue to the mechanism of DC formation in the reaction.

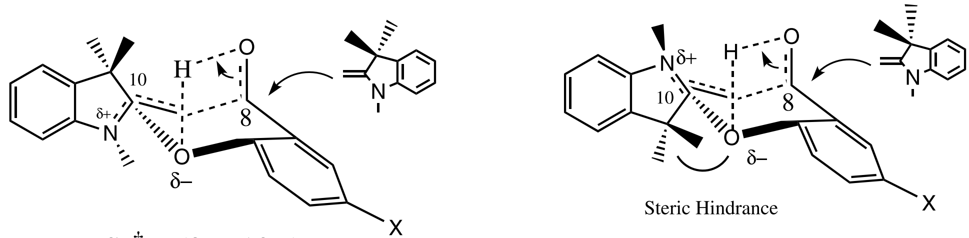
3.2. Mechanism of DC formation

Having established the structure of the dicondensed product it is possible to rationalize the mechanism of its formation. Dicondensed products can be formed from the reaction of Fischer base and salicylaldehydes by either of two variations of a reasonable pathway, as in Scheme 4. The salicylaldehydes may condense with two molecules of Fischer base via the intermediate carbinol (Path B) or the Fischer base may undergo a Michael addition to the open MC form of the spiropyran (Path A).

The most plausible mechanism for its formation is Path B, which involves dehydration of the carbinol intermediate. Dehydration of this carbinol intermediate might occur via a



Scheme 4. Formation processes of DC molecules via Path A and Path B.



$TS_1^‡$ (8R, 10R) $TS_2^‡$ (8R, 10S)

Scheme 5. Cyclic TS‡ in DC formation via Path A.

cyclic transition state, $TS_1^‡$, with the aid of intramolecular H-bonding, as in Scheme 5. $TS_1^‡$ would lead to (8*R*, 10*R*) or (8*S*, 10*S*) configuration, whereas $TS_2^‡$ leads to (8*S*, 10*R*) or (8*R*, 10*S*) configuration. A steric effect may be involved between the dimethyl groups of indoline and the forthcoming phenolic oxygen moiety.

This hypothesis is supported by the observation from the X-ray data of **DC-1**, that the stereogenic centers C-8 and C-10 have the RR or SS configuration. Thus the proton locates at the same side of the pyranose ring oxygen in $TS_1^‡$. Without this type of H-bonding, the epimeric proton on C-8 would not be steroselective. In addition, the fact that the (8*R*, 10*R*) or (8*S*, 10*S*) DC isomer was formed stereoselectively may rule out the Path A formation mechanism involving capture of the open merocyanine intermediate prior to ring closure to the spiropyran, since stereoselectivity at C-10 could not be expected from the Michael addition to the open merocyanine intermediate.

4. Conclusions

The results of X-ray structure determination for **DC-1** as **C** with (8*R*, 10*R*) or (8*S*, 10*S*) configuration are in complete agreement with our earlier structural assignments based solely on ^{1}H NMR results for the series of DC compounds.[15] The most plausible mechanism of DC formation involves dehydration of the carbinol intermediate via the cyclic $TS_1^‡$ with the aid of intramolecular H-bonding (Path B in Scheme 4), rather than capture of the open merocyanine intermediate prior to ring closure to the spiropyran (Path A, Scheme 4).

5. Experimental

5.1. Materials

Fischer base (2-ethylene-1,3,3-trimethylindoline) and salicylaldehyde were available from Aldrich Chemical Co. and were used without further purification.

The azoarylated salicylaldehydes were obtained from the reaction of 1:1 molar ratio of commercially available salicylaldehydes and the corresponding substituted benzene diazonium salts, which were prepared from diazotization of substituted anilines with nitrous acid.

For preparation of DC's, a mixture of 5-substituted salicylaldehyde and excess (2–3-fold) Fischer base in ethanol was refluxed for 8 h. The yellow precipitate was filtered from the hot solution and washed thoroughly with cold diethyl ether. Purification was carried out either by recrystallization from acetone or by precipitation from chloroform/diethyl ether. The product was identified by ^{1}H NMR and mass spectroscopy and gave satisfactory elemental analysis.

5.1.1. 4-(2-Methylene-1,3,3-trimethylindoline-2′-yl)-6-carboxylic-1′,3′,3′-trimethyl-spiro[3,4-dihydro-2*H*-1-benzopyran-2,2′-indoline], DC-1. Yellow, yield 75%, mp 167 (dec 133) °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25(s, 3H), 1.26 (s, 3H), 1.55 (s, 6H), 2.19 (dd, J=14.2, 12.0 Hz, 1H), 2.43 (dd, J=14.2, 4.20 Hz, 1H), 2.85 (s, 3H), 3.04 (s, 3H), 4.16 (d, J=9.90 Hz, 1H), 4.27 (m, J=12.4, 9.90, 4.20 Hz, 1H), 6.78 (t, 1H), 6.56 (d, 1H), 6.59 (d, J=7.50 Hz, 1H), 6.75 (d, J=8.70 Hz, 1H), 6.86 (t, 1H), 7.10 (t, 1H), 7.18 (d, 1H), 7.15 (t, J=7.50 Hz, 1H), 7.19 (d, 1H), 7.81 (d, J=8.70 Hz, 1H), 8.06 (s, 1H); ES-Mass for $C_{32}H_{34}N_2O_3$, M_w: 494; 105 (23.5), 158 (11.0), 174 (100), 494 (1.2) *m*/*z* (%); C, 77.7; H, 6.93; N, 5.66; O, 9.70 obtained C, 77.2; H, 7.10; N, 5.78, O, 9.92.

5.1.2. 4-(2-Methylene-1,3,3-trimethylindoline-2′-yl)-6-nitro-1′,3′,3′-trimethylspiro[3,4-dihydro-2*H*-1-benzopyran-2,2′-indoline], DC-2. Yellow, yield 82%, mp 176 (dec 137) °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.31(s, 3H), 1.33 (s, 3H), 1.62 (s, 6H), 2.23 (dd, J=14.3, 13.0 Hz, 1H), 2.85 (s, 3H), 3.00 (dd, J=14.3, 4.87 Hz, 1H), 3.05 (s, 3H), 4.15 (d, J=10.1 Hz, 1H), 4.32 (m, J=13.0, 10.1, 4.87 Hz, 1H), 6.83 (t, 1H), 6.59 (d, 1H), 6.60 (d, J=7.43 Hz, 1H), 6.75 (d, 1H), 6.86 (t, 1H), 7.06 (t, 1H), 7.07 (d, 1H), 7.09 (t, J=7.43 Hz, 1H), 7.11 (d, 1H), 7.96 (d, 1H), 8.23 (s, 1H); ES-Mass for $C_{31}H_{33}N_3O_3$, M_w: 496; 118 (16.1), 132 (22.7), 174 (100) 323 (33.2), 496 (4.1) *m*/*z* (%); C, 75.13; H, 6.71; N, 8.48; O, 9.68; found C, 74.9; H, 6.80; N, 8.57; O, 9.73.

5.1.3. 4-(2-Methylene-1,3,3-trimethylindoline-2′-yl)-6-phenylazo-1′,3′,3′-trimethyl spiro[3,4-dihydro-2*H*−1-benzopyran-2,2′-indoline], DC-3. Yellow, yield 73%, mp 170 (dec 142) °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 1H), 1.38 (s, 1H), 1.65 (s, 3H), 1.69 (s, 3H), 2.24 (dd, J=14.2, 12.0 Hz, 1H), 2.87 (s, 3H), 2.45 (dd, J=14.2, 4.89 Hz, 1H), 3.06 (s, 3H), 4.26 (d, J=10.0 Hz, 1H), 4.37 (m, J=12.0, 10.0, 4.89 Hz, 1H), 6.75 (t, 1H), 6.57 (d, 1H), 6.57 (d, 1H), 6.82 (d, J=8.55 Hz, 1H), 6.85 (t, 1H), 7.08 (t, 1H), 7.19 (d, 1H), 7.09 (t, 1H), 7.22 (d, 1H), 7.79 (d, J=8.55 Hz, 1H); ES-Mass for $C_{37}H_{38}O$, M_w: 554; 105 (35.4), 158 (16.4), 174 (100) 382 (22.9), 555 (0.5) *m*/*z* (%); C, 80.11; H, 6.90; N, 10.10; O, 2.88 obtained C, 80.6; H, 6.88; N, 10.2; O, 2.32.

5.2. Measurements

Melting points were determined on a Fischer–Johns bloc and are uncorrected. The ^1H NMR spectra were taken with a Bruker CXP-400 FT NMR spectrophotometer. Electrospray (ES) mass spectra were recorded on a VG Quattro mass spectrometer at Queen's University.

5.3. X-ray crystallography

Crystal data for $C_{35}H_{40}N_2O_4$, $M=552.69$, monoclinic, $a=17.689(7)$ Å, $b=11.770(4)$ Å, $c=16.112(6)$ Å, $U=3150.3(19)$ Å^3, $T=298(2)$ K, space group $P2(1)/c$, $Z=4$, μ(Mo K_α)$=0.076$ mm^{-1}, 6487 reflections measured, 3926 unique ($R_{int}=0.0423$) which were used in all calculations. The final $wR(F^2)$ was 0.1696 (all data). Intensity data for **DC-1** was collected using a Siemens SMART ccd area detector mounted on a Siemen P4 diffractometer equipped with graphite-monochromated Mo K_α radiation ($\lambda=0.71073$ Å) radiation source and a CCD detector. A total of multi frames of two-dimensional diffraction images were collected. The frames data were processed to give structure factors using the program SAINT.[16] The structure was solved by direct methods and refined by full matrix least-squares on F^2 for all data using SHELXTL software.[17] Hydrogen atom position were initially determined by geometry and refined by a dreiding model. Non-hydrogen atoms were refined using anisotropic displacement parameters.

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 216486. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

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Chemo- and stereoselectivity in titanium-mediated regioselective ring-opening reaction of epoxides at the more substituted carbon

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Abstract—Chemo- and stereoselectivity in the ring-opening reaction of epoxides with a reagent prepared from allylmagnesium halide and chlorotitanium triphenoxide is described. It has been proven that the allylating reagent can also be used for the reaction of epoxides bearing a *tert*-butyl ester, amide, or acetal moiety, and that the epoxide cleavage regioselectively takes place at the more substituted carbon in all cases. Interestingly, while the reaction of acyclic 2,2,3-trialkyl epoxides or 3,3-disubstituted 2,3-epoxy alcohol derivatives with the allyltitanium reagent yielded the allylated products as an almost 1:1 diastereomixture, the ring-opening reaction of 2-substituted 2,3-epoxy alcohol derivatives stereospecifically proceeded through the *anti* pathway. The latter reaction is extremely useful for asymmetric construction of quaternary carbon centers.
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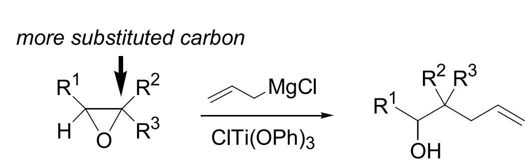
1. Introduction

Ring-opening reaction of epoxides is a powerful method for the stereoselective carbon–carbon bond formation,[1] due to the availability of various chiral epoxides in an enantiomerically pure form.[2] Although the ring-opening reaction of epoxides at the less hindered position or at the activated carbon having a vinyl or aryl group is extensively studied,[3,4] considerably less success has been realized in the regioselective ring-opening at the more substituted unactivated carbon, except for intramolecular reactions[5] including rearrangement.[6] If the ring opening at the more substituted carbon of a wide variety of epoxides proceeds in a regioselective manner, it can serve as a synthetically useful method for construction of tertiary and quaternary carbon centers. However, as far as we are aware, only a few examples of such reaction were reported to date, most of which are based on organoaluminium chemistry.[7,8]

In 1990, we reported that an allyltitanium reagent prepared from chlorotitanium triphenoxide and allylmagnesium chloride selectively cleaves the carbon–oxygen bond of epoxides **1** at the more substituted carbon atom to give an allylated product **2** (Scheme 1).[9] When the ring-opening reaction of simple epoxides (not activated by a vinyl or an aryl group) was conducted with an allyltitanium reagent derived from chlorotitanium triisopropoxide,[10] a considerable amount of the undesired reduction product as well as the allylated product at the less hindered carbon were obtained. Formation of the reduction product was attributed to the Meerwein–Ponndorf–Verley reaction with isopropoxide derived from chlorotitanium triisopropoxide. In contrast, our titanium reagent prepared from chlorotitanium triphenoxide prevents the formation of the reduction product. Since our previous study was limited to the reaction of unfunctionalized alkyl epoxides, the chemoselectivity of the ring-opening reaction remains to be seen. Furthermore, although we have already shown that the reaction of cyclic epoxides stereoselectively proceeds through the *anti* pathway (>10:1), the stereochemical course of the reaction with acyclic epoxides has not been investigated. In this paper, we present the chemo- and stereoselectivity in the regioselective ring-opening reaction of epoxides with the allyltitanium reagent. Construction of chiral quaternary carbons from 2-substituted 2,3-epoxy alcohols is also presented.[11]



1 2

Scheme 1. Regioselective ring cleavage of epoxides at the more hindered carbon

Keywords: Epoxides; Titanium; Allylation; Quaternary carbon.
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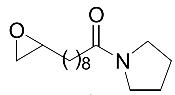
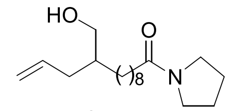
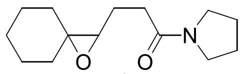
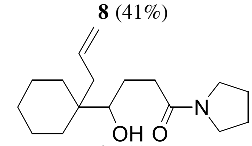
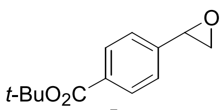
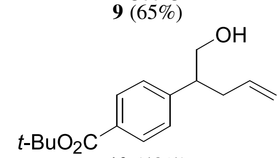
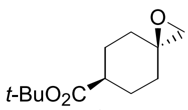
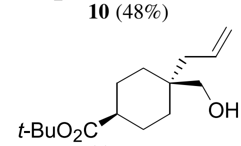
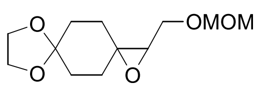
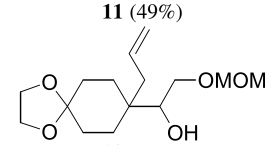
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.05.006

Table 1. Chemoselective epoxide cleavage with the allyltitanium reagent[a]

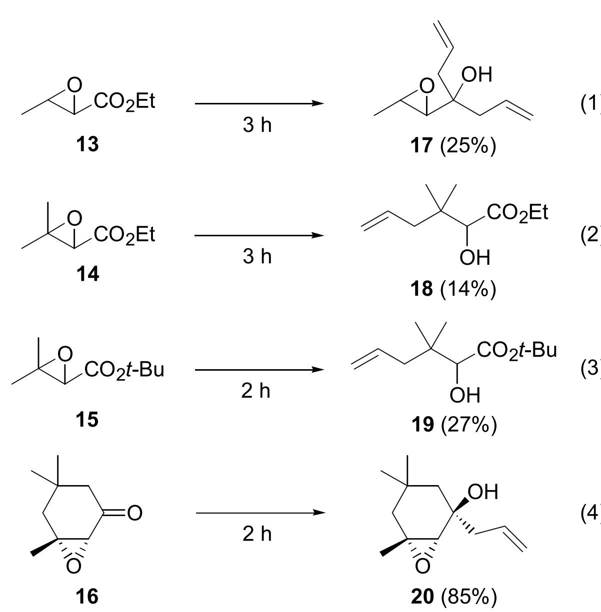
Entry	Epoxides	Reagent (equiv)	Conditions	Product (yield)[b]
1	 **3**	7	−78 °C to rt, 96 h	 **8** (41%)
2	 **4**	5	−78 °C to rt, 24 h	 **9** (65%)
3	 **5**	2	−78 to 0 °C, 1 h	 **10** (48%)
4	 **6**	3	−78 to 0 °C, 3 h	 **11** (49%)
5	 **7**	3	−78 to 0 °C, 4 h	 **12** (84%)

[a] Reagents: allylmagnesium bromide, $ClTi(OPh)_3$, THF.
[b] Isolated yields.

2. Results and discussion

2.1. Reaction of epoxides bearing an electrophilic functionality

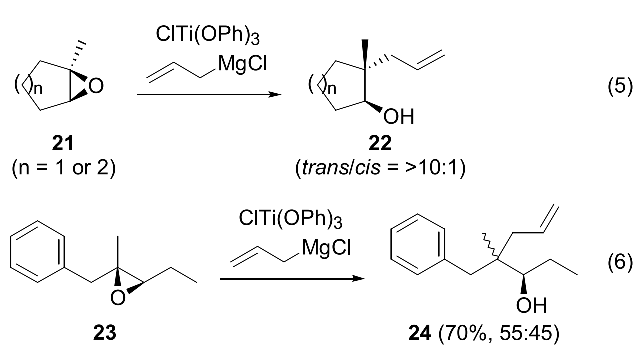
First, we prepared epoxides **3–7** bearing an electrophilic functionality through the standard protocol (see the Section 4) and investigated the chemoselectivity of the ring-opening reaction with the allyltitanium reagents (Table 1). Treatment of epoxy amide **3** with allylmagnesium bromide[12] in the presence of chlorotitanium triphenoxide (1 equiv to the Grignard reagent) afforded allylated product **8** in 41% yields (entry 1), as well as the recovered starting material (15%). This is presumably due to the lower reactivity of the mono-substituted epoxides with the titanium reagent. More reactive trisubstituted epoxy amide **4** gave the desired product **9** in a better yield (65%, entry 2). In contrast, the allyltitanium reagent reacted with the carbonyl group of ethyl ester **13** (Eq. 1 in Scheme 2) to give diallylated epoxide **17** in 25% yield. Furthermore, the reaction of β,β-disubstituted-α,β-epoxy esters **14** and **15** afforded low yields of the desired alcohols **18** and **19** (14 and 27% yield, Eqs. 2 and 3). These results clearly show the limitation of the chemoselectivity of the ring-opening reaction of epoxides having an ester moiety. In contrast, the ring-opening reaction of epoxides **5** and **6** (entries 3 and 4) bearing a *tert*-butyl ester apart from the reaction site selectively proceeded in moderate yields (48 and 49%). Allylation of the carbonyl group of epoxy ketone **16** (Eq. 4) with the allyltitanium reagent predominated over the epoxide cleavage, yielding the epoxy alcohol **20**.[13] However, the undesired allylation of the ketone can be readily suppressed by acetalization of the ketone: reaction of epoxide **7** (entry 5) having an ethylene acetal moiety gave the desired alcohol **12** in 84% yield. From these observations, epoxides having an amide, *tert*-butyl ester, and appropriately-protected ketone can be used in the allylative epoxide cleavage at the more hindered carbon with the titanium reagent.



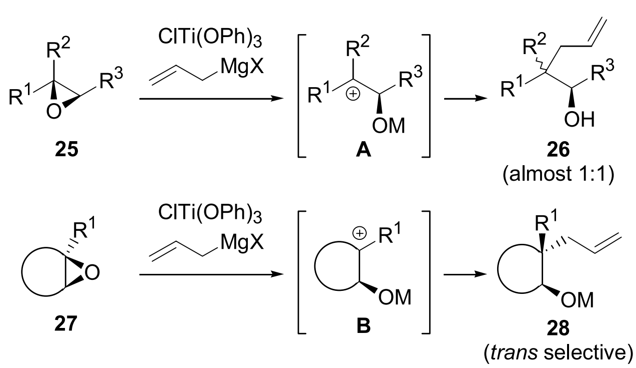
Scheme 2. Reagents and conditions: allylmagnesium bromide, $ClTi(OPh)_3$, THF, −78 to 0 °C.

2.2. Stereoselectivity of the ring-opening of epoxides

In the previous study,[9] we have demonstrated that the allyltitanium-mediated ring-opening reaction of cyclic epoxides **21** stereoselectively proceeds through the *anti* pathway to give the cyclic alcohols **22** (Eq. 5 in Scheme 3).[14] However, the stereochemical course of the reaction of acyclic epoxides was not understood.[15] Thus, we next investigated the reaction of acyclic chiral trisubstituted epoxides **23** (Eq. 6). Unfortunately, the reaction of trialkylepoxide **23** gave the allylated product **24** as a mixture of diastereomers (55:45).

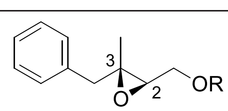
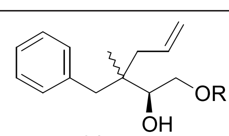
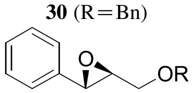
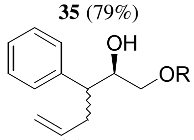


Scheme 3. Stereoselectivity of the epoxide cleavage.



Scheme 4. Stereoselectivity of the reaction of epoxides with the titanium reagent.

Table 2. Stereoselectivity of the reaction of acyclic epoxides

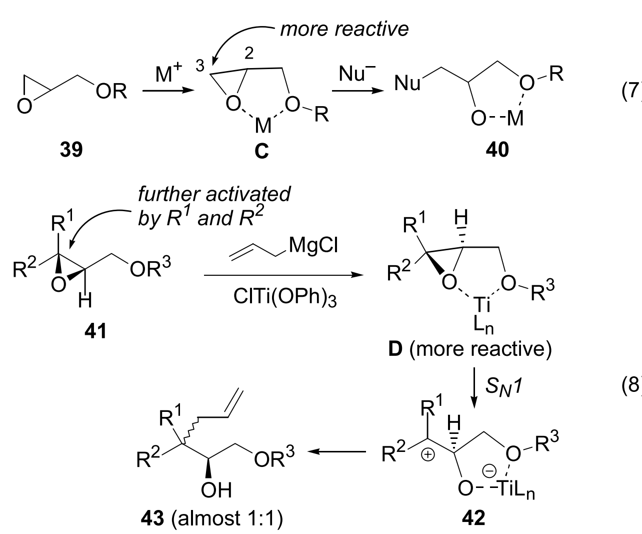
Entry	Epoxy alcohol	Product (yield)[a]	Ratio[b] (*syn*/*anti*)
			
1	**29** (R = MOM)	**34** (70%)	50:50
2	**30** (R = Bn)	**35** (79%)	54:46
			
3	**31** (R = MOM)	**36** (83%)	48:52
4	**32** (R = Bn)	**37** (72%)	43:57
5	**33** (R = TBS)	**38** (53%)	48:52

Reagents: allylmagnesium halide, $ClTi(OPh)_3$, THF.
[a] Isolated yields.
[b] Determined by ^{1}H NMR.

From these results, it is apparent that the titanium-mediated epoxide cleavage proceeds through the S_N1-like pathway including the cationic intermediate **A** (Scheme 4), affording the allylated products **26** as a mixture of diastereomers without stereoselectivity. The good stereoselectivities observed in the reaction of the cyclic epoxides will be attributed to the nucleophilic attack of the allylating reagent from the less hindered side of the cyclic cationic intermediate **B**.

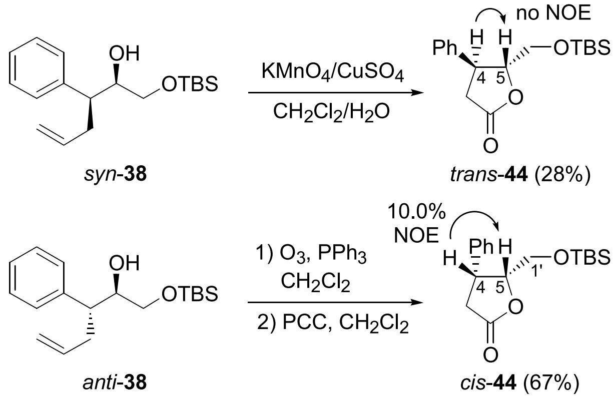
We next investigated the reaction of 2,3-epoxy alcohol derivatives **29–33** (Table 2). Treatment of protected 3,3-disubstituted 2,3-epoxy alcohols **29** and **30** with allylmagnesium bromide and chlorotitanium triphenoxide proceeded in good yields (70 and 79%, respectively) but without stereoselectivity. Similarly, 3-substituted 2,3-epoxy alcohol derivatives **31–33** also gave almost 1:1 diastereomixtures **36–38** (entries 3–5).

It is well known that ring-opening reaction of 2,3-epoxy alcohol derivatives **39** with a nucleophilic metal reagent such as titanium,[16] aluminum,[17] and other nucleophiles[18] regioselectively proceeds at the 3-position to form 1,2-diols such as **40** (Eq. 7 in Scheme 5).[19] Also in the reaction of 2,3-epoxy alcohol derivatives **29–33** (Table 2), the ring-opening reaction regioselectively took place at the 3-position. In these cases, two alkyl substituents (entries 1 and 2) or a phenyl group (entries 3–5) at the 3-position further facilitates the S_N1-type ring-opening reaction of **41** at this position to form the cationic intermediate **42** through the intermediate **D** (Eq. 8). Accordingly, the low stereoselectivity of the ring-opening reaction is understandable. In order to realize the stereoselective ring-opening reaction of acyclic epoxides, it is essential to suppress the S_N1-type reaction. This difficulty has been overcome by accelerating the ring-opening reaction at the 2-position of the epoxy alcohols as described later (Section 2.3).



Scheme 5. Ring-opening reaction at the 3-position of protected 2,3-epoxy alcohol.

Stereochemical assignments for the synthesized alcohols were readily made by their transformation into the lactone derivatives as shown in Scheme 6. The allylated diol derivative *syn*-**38**, formed by the reaction of the protected

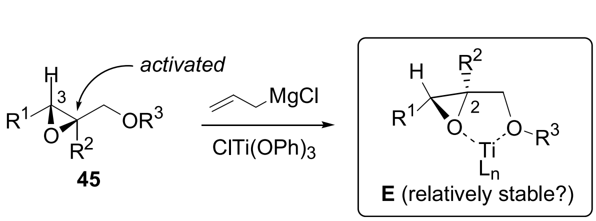


Scheme 6. Determination of stereochemistries of *syn*-**38** and *anti*-**38**.

epoxy alcohol **33** with titanium reagent, was treated with $KMnO_4$ and $CuSO_4$ in CH_2Cl_2 to give the corresponding lactone *trans*-**44** in a one-pot manner. Irradiation of the signal of 4-H led to no NOE enhancement of the signals of 5-H.[20] In contrast, 10% of NOE was observed between 4-H and 5-H of the lactone *cis*-**44** derived from *anti*-**38** as shown in Scheme 6. Stereochemistries of other allylated products including those described later were also confirmed in a similar manner.

2.3. Asymmetric construction of quaternary carbon centers by stereospecific ring-opening reaction

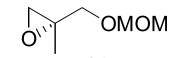
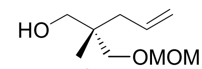
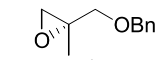
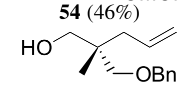
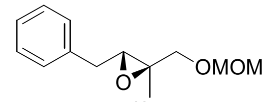
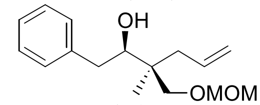
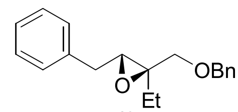
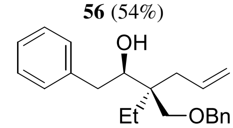
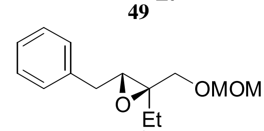
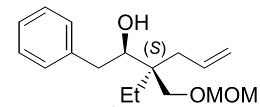
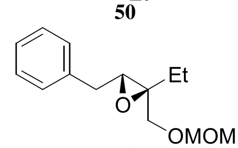
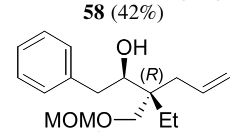
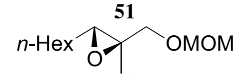
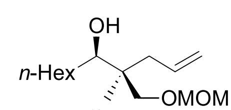
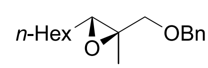
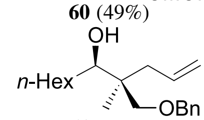
As described in Section 2.2, it was extremely difficult to realize the stereospecific ring-opening reaction of the protected 2,3-epoxy alcohols at the 3-position, due to the high reactivity at this position to form the carbocation intermediate. In contrast, if the relatively unreactive 2-position of the protected 2,3-epoxy alcohols **45** can be appropriately activated (Scheme 7), the intermediate **E** may be more stable than the intermediate **D** (Scheme 5) and unreactive toward the unfavorable S_N1-like ring-opening reaction. Furthermore, if the allylating reagent approaches from the back side of the C_2–O bond of the intermediate **E**, the ring-opening reaction would proceed through the stereospecific *anti* pathway. Therefore, we next turned our attention to the ring-opening reaction of 2-substituted 2,3-epoxy alcohols.



Scheme 7. Ring-opening reaction at the 2-position of protected 2,3-epoxy alcohol.

The results with the protected 2-substituted 2,3-epoxy alcohols **46–53** are summarized in Table 3. As we expected, the reaction of **46** with the allylmagnesium chloride[12] and chlorotitanium triphenoxide yielded 1,3-diol derivative **54** bearing a quaternary carbon center as a single isomer (entry 1). The corresponding benzyl ether **47** also afforded **55** under the identical reaction conditions (entry 2). Reaction of 2,3-disubstituted 2,3-epoxy alcohols **48–53** yielded the allylated product **56–61** bearing two contiguous stereocenters including a chiral quaternary carbon (entries 3–8).[21] Although the yields are moderate, all the reactions proceeded in a stereospecific manner. The ring-opening reaction of epoxide **50** derived from (*E*)-allylic alcohol afforded the desired product **58** with (*S*)-configuration, which is opposite to that obtained with the corresponding (*Z*)-allylic alcohol derivative **51**, both via the *anti* pathway. Stereochemistries of the products were readily confirmed by the NOE analysis of the corresponding lactone derivatives.[22] These results clearly demonstrate that the allylation proceeds through the S_N2-type stereospecific reaction, not through the stereoselective S_N1 reaction, the latter of which would produce the same diastereomer from both of the (*E*)- and (*Z*)-allylic alcohol derivatives **50** and **51**.

Table 3. Construction of chiral quaternary carbon centers from 2-substituted 2,3-epoxy alcohols[a]

Entry	Epoxy alcohol	Product (yield)[b]
1	 **46**	 **54** (46%)
2	 **47**	 **55** (41%)
3	 **48**	 **56** (54%)
4	 **49**	 **57** (34%)
5	 **50**	 **58** (42%)
6	 **51**	 **59** (37%)
7	 **52**	 **60** (49%)
8	 **53**	 **61** (33%)

[a] Reagents: allylmagnesium chloride, $ClTi(OPh)_3$, THF, −78 to 0 °C.
[b] Isolated yields.

3. Conclusion

In conclusion, we have demostrated the chemo- and stereoselectivity in the ring-opening reaction of epoxides with allylmagnesium halide[23] and chlorotitanium triphenoxide. The ring cleavage of the functionalized epoxides chemoselectively proceeded in the presence of a *tert*-butyl ester, amide, or acetal moiety, and the more substituted carbon of the epoxides regioselectively reacted to give the allylated product. Although the ring-opening reaction proceeds through the S_N1 pathway in most cases, it has been proven that *anti*-selective ring-opening reaction of epoxides is possible when using 2-substituted 2,3-epoxy alcohol derivatives, presumably due to the relatively low reactivity of the epoxy alcohol at the 2-position. This is the first example of the asymmetric construction of quaternary carbon centers by a stereospecific ring-opening reaction of readily available chiral acyclic epoxides using a titanium reagent. Since the products obtained have three distinguishable functional groups around the chiral quaternary stereocenter, this reaction would serve as an extremely useful method for the synthesis of complex molecules having a chiral quaternary carbon.

4. Experimental

4.1. General methods

All reactions were carried out under a positive pressure of argon, and glassware and syringes were dried in an electric oven at 100 °C prior to use. THF was distilled from sodium benzophenone ketyl under N_2. Other solvents and reagents were used without further purification. Melting points are uncorrected. ^{1}H NMR spectra (270, 300 or 500 MHz) were recorded in $CDCl_3$. Chemical shifts are reported in parts per million downfield from internal Me_4Si (s = singlet, d = doublet, dd = double doublet, ddd = doublet of double doublet, t = triplet, m = multiplet). For flash chromatography, silica gel 60 (230–400 mesh, Merck) was employed. Known epoxides **13**,[24] **14**,[24] and **47**[25] were prepared according to the literature. Compound **16** was purchased from Aldrich and used without purification.

4.2. Allyltitanium-mediated ring-opening reaction of epoxides

4.2.1. General procedure: synthesis of (±)-10-(hydroxymethyl)-1-pyrrolidinyltridec-12-en-1-one (8) (Table 1, entry 1). A solution of chlorotitanium triphenoxide (0.5 M in THF; 7.0 mL, 3.5 mmol) was added dropwise to a solution of allylmagnesium bromide (1.0 M in Et_2O; 3.5 mL, 3.5 mmol) at −78 °C, and the mixture was stirred for 30 min at −50 °C. To the stirred mixture was slowly added a solution of epoxide **3** (127 mg, 0.50 mmol) in THF (1 mL) at −78 °C, and the mixture was stirred for 96 h with warming to room temperature. After the mixture was diluted with Et_2O (30 mL), saturated aqueous KF (5 mL) was added under stirring, and precipitate was filtered off. The filtrate was washed with 2 N NaOH, water, and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to leave an oily residue, which was purified by column chromatography over silica gel with $CHCl_3$–MeOH (200:1; hexane–EtOAc was used in other cases) to give **8** (61 mg, 41% yield) as a colorless oil; IR (KBr) cm^{-1} 3415 (OH), 1626 (C═O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21–1.66 (m, 23H), 3.39–3.59 (m, 6H, 2′-CH_2, 5′-CH_2 and OCH_2), 4.99–5.09 (m, 2H, 13-CH_2), 5.75–5.89 (m, 1H, 12-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 24.9, 26.1, 26.8, 29.3 (2C), 29.4, 29.8, 30.5, 34.8, 35.8, 40.3, 45.6, 46.6, 65.5, 116.0, 137.2, 171.9; MS (FAB) *m/z* (%): 296 (MH^+, 100); HRMS (FAB) calcd for $C_{18}H_{34}NO_2$ (MH^+): 296.2590; found: 296.2573.

4.2.2. (±)-4-Hydroxy-4-[1-(prop-2-enyl)cyclohexyl]-1-pyrrolidinylbutan-1-one (9) (Table 1, entry 2). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **4** (119 mg, 0.50 mmol) was converted into **9** (91 mg, 65% yield) by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 2.5 mL, 2.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 5.0 mL, 2.5 mmol) at −78 to 0 °C for 24 h. In this reaction, allylmagnesium bromide was added dropwise to a solution of chlorotitanium triphenoxide: colorless oil; IR (KBr) cm^{-1} 3470 (OH), 1643 (C═O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46–1.66 (m, 6H), 1.77–2.46 (m, 14H), 3.41–3.53 (m, 5H, 2′-CH_2, 5′-CH_2 and 4-H), 5.01–5.13 (m, 2H, CH═C*H*$_2$), 5.78–5.92 (m, 1H, C*H*═CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4 (2C), 26.1 (2C), 27.9, 28.5 (2C), 30.7, 35.3, 37.0, 40.2, 46.2, 46.5, 70.2, 116.8, 136.9, 176.3; MS (FAB) *m/z* (%): 280 (MH^+, 100); HRMS (FAB) calcd for $C_{17}H_{30}NO_2$ (MH^+): 280.2277; found: 280.2280.

4.2.3. *tert*-Butyl (±)-4-[1-(hydroxymethyl)but-3-enyl]-benzoate (10) (Table 1, entry 3). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **5** (55 mg, 0.25 mmol) was converted into **10** (32 mg, 48% yield) by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 0.5 mL, 0.50 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 1.0 mL, 0.50 mmol) at −78 to 0 °C for 1 h: colorless oil; IR (KBr) cm^{-1} 3452 (OH), 1714 (C═O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (br s, 1H, OH), 1.59 (s, 9H, CMe_3), 2.37–2.43 (m, 1H, 2′-C*H*H), 2.48–2.54 (m, 1H, 2′-CH*H*), 2.93–2.99 (m, 1H, 1′-H), 3.75–3.84 (m, 2H, OCH_2), 4.96–5.04 (m, 2H, 4′-CH_2), 5.65–5.73 (m, 1H, 3′-H), 7.27 (d, *J* = 7.9 Hz, 2H, Ph), 7.95 (d, *J* = 7.9 Hz, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2 (3C), 36.4, 48.2, 66.6, 80.9, 116.7, 127.9 (2C), 129.7 (2C), 130.6, 135.8, 146.9, 165.6; MS (FAB) *m/z* (%): 285 (MNa^+, 40.5), 207 (100); HRMS (FAB) calcd for $C_{16}H_{22}NaO_3$ (MNa^+): 285.1467; found: 285.1446.

4.2.4. *tert*-Butyl (±)-(1*R,4*R**)-4-allyl-4-(hydroxymethyl)cyclohexanecarboxylate (11)** (Table 1, entry 4). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **6** (106 mg, 0.50 mmol) was converted into **11** (62 mg, 49% yield) by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 1.5 mL, 1.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 3.0 mL, 1.5 mmol) at −78 to 0 °C for 3 h: colorless oil; IR (KBr) cm^{-1} 3446 (OH), 1728 (C═O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.13–1.23 (m, 2H, 2-C*H*H and 6-C*H*H), 1.44 (s, 9H, CMe_3), 1.52–1.66 (m, 4H, 3-CH_2 and 5-CH_2), 1.72–1.81 (m, 2H, 2-CH*H* and 6-CH*H*), 2.09–2.16 (m, 1H, 1-H), 2.19 (d, *J* = 8.5 Hz, 2H, C*H*$_2$CH═CH_2), 3.34 (s, 2H, C*H*$_2$OH), 5.05 (m, 2H, CH═C*H*$_2$), 5.75–5.89 (m, 1H, C*H*═CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7 (2C), 28.1 (3C), 30.9 (2C), 36.2, 37.3, 43.9, 70.9, 79.9, 117.4, 134.8, 175.4; MS (FAB) *m/z* (%): 255 (MH^+, 50), 181 (100); HRMS (FAB) calcd for $C_{15}H_{27}O_3$ (MH^+): 255.1960; found: 255.1965.

4.2.5. (±)-4-(1-Hydroxy-2-methoxymethoxy)ethyl-4-(prop-2-enyl)cyclohexan-1-one 1,1-ethylene acetal (12) (Table 1, entry 5). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **7** (122 mg, 0.50 mmol) was converted into **12** (120 mg, 84% yield) by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 1.5 mL, 1.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 3.0 mL, 1.5 mmol) at −78 to 0 °C for 4 h: colorless oil; IR (KBr) cm^{-1} 3504 (OH); ^1H NMR (300 MHz, $CDCl_3$) δ 1.46–1.76 (m, 8H), 2.14 (dd, J=13.9, 7.5 Hz, 1H, C*H*HCH=CH_2), 2.34 (dd, J=13.9, 7.0 Hz, 1H, CH*H*CH=CH_2), 2.52 (br s, 1H, OH), 3.37 (s, 3H, OMe), 3.46–3.52 (m, 1H, 1′-H), 3.71–3.79 (m, 2H, 2′-CH_2), 3.93 (s, 4H, OC_2H_4O), 4.66 (s, 2H, OCH_2O), 5.05–5.10 (m, 2H, CH=C*H*$_2$), 5.81–5.94 (m, 1H, C*H*=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 28.6, 30.1, 30.3, 36.3, 38.1, 55.3, 64.1 (2C), 69.2, 74.0, 96.9, 108.7, 117.4, 134.9; MS (EI) *m/z*: 286 (M^+). Anal. Calcd for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 63.06; H, 9.02.

4.2.6. (±)-4-[(2*R,3*S**)-3-Methyloxiran-2-yl]-1,6-heptadien-4-ol (17).** By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **13** (130 mg, 1.0 mmol) was converted into **17** (43 mg, 25% yield) by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 1.2 mL, 1.2 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 2.6 mL, 1.3 mmol) at −78 to 0 °C for 3 h: colorless oil; IR (KBr) cm^{-1} 3477 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 1.30 (d, J=5.5 Hz, 3H, CMe), 1.91 (s, 1H, OH), 2.25–2.42 (m, 4H, 3-CH_2 and 5-CH_2), 2.68 (d, J=2.4 Hz, 1H, 2′-H), 3.05 (qd, J=5.5, 2.4 Hz, 1H, 3′-H), 5.09–5.18 (m, 4H, 1-CH_2 and 7-CH_2), 5.82–5.95 (m, 2H, 2-H and 6-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.9, 41.5, 44.4, 51.0, 63.7, 70.6, 118.3, 119.2, 132.7, 133.0; MS (FAB) *m/z* (%): 175 (MLi^+, 25), 160 (100); HRMS (FAB) calcd $C_{10}H_{16}LiO_2$ (MLi^+): 175.1310; found: 175.1311.

4.2.7. Ethyl (±)-2-hydroxy-3,3-dimethyl-5-hexenoate (18). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **14** (144 mg, 1.0 mmol) was converted into **18** (26 mg, 14% yield) by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 1.5 mL, 1.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 3.0 mL, 1.5 mmol) at −78 to 0 °C for 3 h: colorless oil; IR (KBr) cm^{-1} 3469 (OH); ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, J=6.9 Hz, 3H, CMe), 1.38 (s, 3H, CMe), 1.43 (s, 3H, CMe), 2.24 (d, J=2.4 Hz, 2H, 4-CH_2), 3.33 (s, 1H, 2-H), 4.20–4.34 (m, 2H, OCH_2), 5.09–5.17 (m, 2H, 6-CH_2), 5.80–5.94 (m, 1H, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 18.2, 24.2, 43.6, 59.4, 60.1, 61.3, 118.7, 133.5, 168.5; MS (FAB) *m/z* (%): 193 (MLi^+, 100); HRMS (FAB) calcd for $C_{10}H_{18}LiO_3$ (MLi^+): 193.1416; found: 193.1425.

4.2.8. *tert*-Butyl (±)-2-hydroxy-3,3-dimethyl-5-hexenoate (19). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **15** (86 mg, 0.50 mmol) was converted into **19** (29 mg, 27% yield) by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 1.5 mL, 1.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 3.0 mL, 1.5 mmol) at −78 to 0 °C for 2 h: colorless oil; IR (KBr) cm^{-1} 3516 (OH), 1716 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (s, 3H, CMe), 0.95 (s, 3H, CMe), 1.51 (s, 9H, CMe_3), 2.03 (dd, J=13.4, 7.3 Hz, 1H, 4-C*H*H), 2.20 (dd, J=13.4, 7.9 Hz, 1H, 4-CH*H*), 2.86 (d, J=6.7 Hz, 1H, OH), 3.76 (d, J=6.7 Hz, 1H, 2-H), 5.06–5.90 (m, 2H, 6-CH_2), 5.81–5.89 (m, 1H, 5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 23.3, 28.1 (3C), 38.1, 43.4, 76.8, 82.7, 117.8, 134.7, 173.8; MS (FAB), *m/z* (%): 215 (MH^+, 100). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 66.86; H, 10.30.

4.2.9. (±)-(1*R,2*S**,6*S**)-4,4,6-Trimethyl-2-(prop-2-enyl)-7-oxabicyclo[4.1.0]heptan-2-ol (20).** By the general procedure for the allyltitanium-mediated ring-opening reaction, isophorone oxide **16** (154 mg, 1.0 mmol) was converted into **20** (167 mg, 85% yield) by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 2.0 mL, 2.0 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 4.0 mL, 2.0 mmol) at −78 to 0 °C for 2 h: colorless oil; IR (KBr) cm^{-1} 3498 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (s, 3H, CMe), 1.03 (s, 3H, CMe), 1.22 (d, J= 14.6 Hz, 1H), 1.30 (d, J=14.6 Hz, 1H), 1.36 (s, 3H, CMe), 1.57 (dd, J=14.6, 1.8 Hz, 1H), 1.62 (d, J=14.6 Hz, 1H), 1.82 (s, 1H, OH), 2.27 (dd, J=13.4, 7.9 Hz, 1H, 1′-C*H*H), 2.42 (dd, J=13.4, 7.3 Hz, 1H, 1′-CH*H*), 2.77 (s, 1H, 1-H), 5.20–5.26 (m, 2H, CH=C*H*$_2$), 5.92–6.00 (m, 1H, C*H*=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 28.4, 29.5, 31.7, 43.3, 44.7, 45.8, 59.5, 63.8, 70.7, 120.2, 132.5; MS (FAB) *m/z* (%): 219 (MNa^+, 13.3), 176 (100); HRMS (FAB) calcd for $C_{12}H_{20}NaO_2$ (MNa^+): 219.1361; found: 219.1381.

4.2.10. (3*R*,4*R*)- and (3*R*,4*S*)-4-Benzyl-4-methylhept-6-en-3-ol (24). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **23** (176 mg, 1.0 mmol) was converted into an inseparable mixture of *syn*-**24** and *anti*-**24** (55:45 by ^1H NMR; 153 mg, 70% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 1.5 mL, 3.0 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 6.0 mL, 3.0 mmol) at −78 to 0 °C for 4 h: colorless oil; IR (KBr) cm^{-1} 3500 (OH); ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 1.5H, 4-Me), 0.88 (s, 1.5H, 4-Me), 1.01 (dd, J=14.8, 7.3 Hz, 3H, CMe), 1.25–1.76 (m, 2H, 2-CH_2), 1.81–2.26 (m, 2H, 5-CH_2), 2.52 (d, J=13.0 Hz, 0.5H, PhC*H*H), 2.61 (d, J=13.2 Hz, 0.5H, PhC*H*H), 2.73 (d, J=13.2 Hz, 0.5H, PhCH*H*), 2.82 (d, J=13.0 Hz, 0.5H, PhCH*H*), 3.26 (t, J=11.8 Hz, 1H, 3-H), 5.06–5.13 (m, 2H, 7-CH_2), 5.84–6.05 (m, 1H, 6-H), 7.16–7.29 (m, 5H, Ph); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 12.32 (0.5C), 12.35 (0.5C), 21.4 (0.5C), 22.0 (0.5C), 24.7 (0.5C), 24.8 (0.5C), 41.4 (0.5C), 41.5 (0.5C), 42.3 (0.5C), 42.4 (0.5C), 42.5 (0.5C), 42.7 (0.5C), 79.1 (0.5C), 79.2 (0.5C), 118.0 (1C), 126.5 (1C), 128.4 (2C), 131.3 (2C), 136.1 (0.5C), 136.3 (0.5C), 139.26 (0.5C), 139.29 (0.5C); MS (FAB) *m/z* (%): 241 (MNa^+, 18), 142 (100); HRMS (FAB) calcd for $C_{15}H_{22}NaO$ (MNa^+): 241.1568; found: 241.1572.

4.2.11. (2*S*,3*R*)- and (2*S*,3*S*)-3-Benzyl-1-(methoxymethoxy)-3-methylhex-5-en-2-ol (34) (Table 2, entry 1). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **29** (111 mg, 0.50 mmol) was converted into an inseparable mixture of *syn*-**34** and *anti*-**34** (50:50 by ^1H NMR; 92 mg, 70% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 0.75 mL, 1.5 mmol) and chlorotitanium triphenoxide (0.5 M in

THF; 3.0 mL, 1.5 mmol) at −78 to 0 °C for 2 h: colorless oil; IR (KBr) cm^{-1} 3560 (OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 1.5H, CMe), 0.91 (s, 1.5H, CMe), 1.79–1.86 (m, 0.5H, 4-C*H*H), 2.03–2.10 (m, 0.5H, 4-C*H*H), 2.18–2.31 (m, 1H, 4-CH*H*), 2.46–2.62 (m, 2H, PhC*H*H and OH), 2.82–2.93 (m, 1H, PhCH*H*), 3.37 (d, *J*=0.4 Hz, 1.5H, OMe), 3.39 (d, *J*=0.4 Hz, 1.5H, OMe), 3.46–3.66 (m, 2H, 1-C*H*H and 2-H), 3.72–3.83 (m, 1H, 1-CH*H*), 4.65 (s, 1H, OCH_2O), 4.68 (s, 1H, OCH_2O), 5.05–5.13 (m, 2H, 6-CH_2), 5.82–6.02 (m, 1H, 5-H), 7.18–7.33 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6 (0.5C), 21.1 (0.5C), 40.62 (0.5C), 40.64 (0.5C), 41.1 (0.5C), 41.3 (0.5C), 42.3 (0.5C), 42.5 (0.5C), 50.58 (0.5C), 50.63 (0.5C), 71.36 (0.5C), 71.39 (0.5C), 72.7 (1C), 98.9 (0.5C), 99.0 (0.5C), 117.3 (0.5C), 117.5 (0.5C), 126.3 (1C), 128.0 (1C), 128.3 (1C), 128.6 (1C), 128.8 (1C), 136.6, (1C), 140.2 (0.5C), 140.4 (0.5C); MS (FAB) *m*/*z* (%): 265 (MH^+, 18), 151 (100); HRMS (FAB) calcd for $C_{16}H_{25}O_3$ (MH^+): 265.1804; found: 265.1810.

4.2.12. (2*S*,3*R*)- and (2*S*,3*S*)-3-Benzyl-1-benzyloxy-3-methylhex-5-en-2-ol (35) (Table 2, entry 2). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **30** (134 mg, 0.5 mmol) was converted into an inseparable mixture of *syn*-**35** and *anti*-**35** (54:46 by ^{1}H NMR; 123 mg, 79% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 0.75 mL, 1.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 3.0 mL, 1.5 mmol) at −78 to 0 °C for 2 h: colorless oil; IR (KBr) cm^{-1} 3528 (OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 1.5H, CMe), 0.88 (s, 1.5H, CMe), 1.75–1.83 (m, 0.5H, 4-C*H*H), 1.99–2.07 (m, 0.5H, 4-C*H*H), 2.15–2.31 (m, 1H, 4-CH*H*), 2.44–2.60 (m, 1.5H, PhC*H*$_2$), 2.81–2.91 (m, 0.5H, PhC*H*$_2$), 3.45–3.69 (m, 3H, 1-CH_2 and 2-H), 4.53 (d, *J*=1.5 Hz, 1H, OC*H*$_2$Ph), 4.56 (d, *J*=2.4 Hz, 0.5H, OC*H*$_2$Ph), 5.00–5.10 (m, 2H, 6-CH_2), 5.80–6.00 (m, 1H, 5-H), 7.15–7.39 (m, 10H, Ph); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 20.6 (0.5C), 21.1 (0.5C), 39.9 (0.5C), 40.1 (0.5C), 40.4 (0.5C), 40.6 (0.5C), 41.6 (0.5C), 42.1 (0.5C), 71.0 (1C), 73.39 (0.5C), 73.41 (0.5C), 73.8 (0.5C), 73.9 (0.5C), 117.5 (0.5C), 117.7 (0.5C), 125.8 (1C), 127.6 (3C), 127.7 (1C), 128.4 (2C), 130.78 (1C), 130.83 (1C), 134.6 (1C), 135.0 (1C), 137.75 (0.5C), 137.80 (0.5C), 138.2 (1C); MS (FAB) *m*/*z* (%): 333 (MNa^+, 33), 174 (100); HRMS (FAB) calcd for $C_{21}H_{26}NaO_2$ (MNa^+): 333.1830; found: 333.1836.

4.2.13. (2*R*,3*S*)- and (2*R*,3*R*)-1-(Methoxymethoxy)-3-phenylhex-5-en-2-ol (36) (Table 2, entry 3). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **31** (146 mg, 0.75 mmol) was converted into an inseparable mixture of *syn*-**36** and *anti*-**36** (48:52 by ^{1}H NMR; 147 mg, 83% yield) by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 2.25 mL, 2.25 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 4.5 mL, 2.25 mmol) at −78 to −20 °C for 120 h: colorless oil; IR (KBr) cm^{-1} 3474 (OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27–2.89 (m, 4H, 3-H, 4-CH_2 and OH), 3.23–3.64 (m, 5H, OMe and 1-CH_2), 3.86–3.92 (m, 0.5H, 2-H), 4.00–4.05 (m, 0.5H, 2-H), 4.54–4.63 (m, 2H, OCH_2O), 4.85–5.06 (m, 2H, 6-CH_2), 5.54–5.73 (m, 1H, 5-H), 7.13–7.39 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.4 (0.5C), 36.5 (0.5C), 48.2 (0.5C), 49.2 (0.5C), 55.41 (0.5C), 55.43 (0.5C), 71.4 (1C), 72.5 (0.5C), 74.0 (0.5C), 96.95 (0.5C), 97.04 (0.5C), 116.1 (0.5C), 116.4 (0.5C), 126.67 (0.5C), 126.74 (0.5C), 128.27 (1C), 128.30 (1C), 128.5 (1C), 128.9 (1C), 136.4 (0.5C), 136.6 (0.5C), 140.4 (0.5C), 141.2 (0.5C); MS (FAB) *m*/*z* (%): 237 (MH^+, 13.3), 126 (100); HRMS (FAB) calcd for $C_{14}H_{21}O_3$ (MH^+): 237.1491; found: 237.1490.

4.2.14. (2*R*,3*S*)- and (2*R*,3*R*)-1-Benzyloxy-3-phenylhex-5-en-2-ol (37) (Table 2, entry 4). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **32** (120 mg, 0.50 mmol) was converted into an inseparable mixture of *syn*-**37** and *anti*-**37** (43:57 by ^{1}H NMR; 102 mg, 72% yield) by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 1.5 mL, 1.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 3.0 mL, 1.5 mmol) at −78 to −20 °C for 3 h: colorless oil; IR (KBr) cm^{-1} 3477 (OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 (br s, 0.4H, OH), 2.36–2.88 (m, 3.6H, 3-H, 4-H and OH), 3.15–3.48 (m, 2H, 1-CH_2), 3.88–3.93 (m, 0.4H, 2-H), 4.05–4.06 (m, 0.6H, 2-H), 4.35–4.51 (m, 2H, OC*H*$_2$Ph), 4.84–5.03 (m, 2H, 6-CH_2), 5.52–5.72 (m, 1H, 5-H), 7.11–7.36 (m, 10H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.3 (0.5C), 36.4 (0.5C), 48.0 (0.5C), 49.2 (0.5C), 72.2 (0.5C), 72.7 (0.5C), 72.8 (0.5C), 73.2 (0.5C), 73.3 (0.5C), 73.8 (0.5C), 116.0 (0.5C), 116.4 (0.5C), 126.6 (0.5C), 126.7 (0.5C), 127.67 (1.5C), 127.72 (1.5C), 128.2 (1.5C), 128.3 (1.5C), 128.4 (1.5C), 128.9 (1.5C), 136.5 (0.5C), 136.6 (0.5C), 137.8 (0.5C), 137.9 (0.5C), 140.4 (0.5C), 141.2 (0.5C); MS (FAB) *m*/*z* (%): 283 (MH^+, 21), 150 (100); HRMS (FAB) calcd for $C_{19}H_{23}O_2$ (MH^+): 283.1698; found: 283.1690.

4.2.15. (2*R*,3*S*)-1-(*tert*-Butyldimethylsiloxy)-3-phenylhex-5-en-2-ol (*syn*-38) and Its (2*R*,3*R*)-isomer (*anti*−38) (Table 2, entry 5). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **33** (264 mg, 1.0 mmol) was converted into a diastereomixture of *syn*-**38** and *anti*-**38** by the reaction with allylmagnesium bromide (1.0 M in Et_2O; 2.0 mL, 2.0 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 4.0 mL, 2.0 mmol) at −78 to 0 °C for 1 h. The diastereomixture was purified by column chromatography over silica gel with hexane–Et_2O (20:1) to give, in the order of elution, *syn*-**38** (78 g, 25% yield) and *anti*-**38** (86 mg, 28% yield).

Compound syn-**38**. Colorless oil; $[\alpha]_D^{27}$ −18.8 (*c* 0.43, $CHCl_3$); IR (KBr) cm^{-1} 3469 (OH); ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.03 (s, 6H, $SiMe_2$), 0.87 (s, 9H, CMe_3), 2.36–2.47 (m, 1H, OH), 2.63–2.74 (m, 2H, 4-CH_2), 2.81–2.90 (m, 1H, 3-H), 3.24 (dd, *J*=9.9, 6.6 Hz, 1H, 1-C*H*H), 3.37 (dd, *J*=9.9, 3.1 Hz, 1H, 1-CH*H*), 3.71–3.79 (m, 1H, 2-H), 4.84–4.97 (m, 2H, 6-CH_2), 5.54–5.67 (m, 1H, 5-H), 7.12–7.31 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5 (2C), 18.2, 25.8 (3C), 36.6, 49.1, 65.2, 75.0, 115.9, 126.6, 128.3 (2C), 128.4 (2C), 136.8, 141.4; MS (FAB) *m*/*z* (%): 329 (MNa^+, 100); HRMS (FAB) calcd for $C_{18}H_{30}NaO_2Si$ (MNa^+): 329.1913; found: 329.1911.

Compound anti-**38**. Colorless oil; $[\alpha]_D^{27}$ −39.1 (*c* 0.55, $CHCl_3$); IR (KBr) cm^{-1} 3466 (OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 3H, SiMe), 0.04 (s, 3H, SiMe), 0.88 (s, 9H, CMe_3), 2.20 (br s, 1H, OH), 2.43–2.63 (m, 2H, 4-CH_2), 2.78–2.85 (m, 1H, 3-H), 3.39 (dd, *J*=10.1, 7.3 Hz, 1H, 1-C*H*H), 3.57 (dd, $J=10.1$, 4.2 Hz, 1H, 1-CH*H*), 3.86–3.88 (m, 1H, 2-H), 4.91–5.05 (m, 2H, 6-CH_2), 5.59–5.72 (m, 1H, 5-H), 7.18–7.33 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.43, −5.38, 18.2, 25.8 (3C), 36.4, 47.9, 65.3, 73.8, 116.2, 126.6, 128.2 (2C), 128.9 (2C), 136.6, 140.8; MS (FAB) *m*/*z* (%): 329 (MNa^+, 100); HRMS (FAB) calcd for $C_{18}H_{30}NaO_2Si$ (MNa^+): 329.1913; found: 329.1913.

4.2.16. (4*S*,5*R*)-5-(*tert*-Butyldimethylsiloxy)methyl-4-phenyloxolan-2-one (*trans*-44). To a mixture of powdered $KMnO_4$ (800 mg) and $CuSO_4$ (400 mg) were added H_2O (40 μL) and CH_2Cl_2 (2.0 mL) under stirring. A solution of *syn*-**38** (61 mg, 0.2 mmol) in CH_2Cl_2 (0.5 mL) was added to the mixture and the mixture was stirred under reflux for 5 days. The mixture was filtered through Celite with CH_2Cl_2, and the filtrate was concentrated under reduced pressure to leave an oily residue, which was purified by column chromatography over silica gel with hexane–EtOAc (10:1) to give *trans*-**44** (17 mg, 28% yield) as a colorless oil; $[\alpha]_D^{28}$ −16.7 (*c* 0.59, $CHCl_3$); IR (KBr) cm^{-1} 1770 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 3H, SiMe), 0.09 (s, 3H, SiMe), 0.85 (s, 9H, CMe_3), 2.67 (dd, $J=17.7$, 7.3 Hz, 1H, 3-C*H*H), 3.04 (dd, $J=17.7$, 9.2 Hz, 1H, 3-CH*H*), 3.66–3.71 (m, 1H, 4-H), 3.73 (dd, $J=11.6$, 2.4 Hz, 1H, 1′-C*H*H), 3.92 (dd, $J=11.6$, 2.4 Hz, 1H, 1′-CH*H*), 4.49–4.51 (m, 1H, 5-H), 7.23–7.38 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.5, −5.4, 18.3, 25.8 (3C), 37.3, 42.1, 63.1, 86.8, 126.9 (2C), 127.5, 129.1 (2C), 140.9, 176.2; MS (FAB) *m*/*z* (%): 307 (MH^+, 36), 181 (100); HRMS (FAB) calcd for $C_{17}H_{27}O_3Si$ (MH^+): 307.1729; found: 307.1725.

4.2.17. (4*R*,5*R*)-5-(*tert*-Butyldimethylsiloxy)methyl-4-phenyloxolan-2-one (*cis*-44). Ozone was bubbled through a solution of *anti*-**38** (45 mg, 0.15 mmol) in CH_2Cl_2 (3 mL) at −78 °C until a blue color persisted (30 min). To this mixture was added PPh_3 (115 mg, 0.44 mmol) at −78 °C and the mixture was stirred for 2 h at 0 °C. Concentration under reduced pressure gave an oily residue, which was purified by short column chromatography over silica gel with hexane–EtOAc (3:1) to give the corresponding lactol. Pyridinium chlorochromate (39 mg, 0.18 mmol) in CH_2Cl_2 (3 mL) was added to a solution of the lactol in CH_2Cl_2 (1 mL) at 0 °C, and the mixture was stirred for 5 days at room temperature. The mixture was filtered through Celite with CH_2Cl_2, and the filtrate was concentrated under reduced pressure to leave an oily residue, which was purified by column chromatography over silica gel with hexane–EtOAc (5:1) to give *cis*-**44** (31 mg, 67% yield) as a colorless oil; $[\alpha]_D^{28}$ −95.9 (*c* 0.78, $CHCl_3$); IR (KBr) cm^{-1} 1774 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ −0.09 (s, 3H, SiMe), −0.05 (s, 3H, SiMe), 0.85 (s, 9H, CMe_3), 2.73 (dd, $J=17.1$, 9.2 Hz, 1H, 3-C*H*H), 3.13 (dd, $J=17.1$, 10.4 Hz, 1H, 3-CH*H*), 3.41 (dd, $J=11.6$, 2.4 Hz, 1H, 1′-C*H*H), 3.64 (dd, $J=11.6$, 3.7 Hz, 1H, 1′-CH*H*), 3.90–3.96 (m, 1H, 4-H), 4.70–4.73 (m, 1H, 5-H), 7.27–7.36 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.91, −5.89, 18.1, 25.7 (3C), 34.1, 43.8, 62.0, 82.7, 127.5, 127.9 (2C), 128.6 (2C), 136.4, 176.7; MS (FAB) *m*/*z* (%): 307 (MH^+, 25), 181 (100); HRMS (FAB) calcd for $C_{17}H_{27}O_3Si$ (MH^+): 307.1729; found: 307.1734.

4.2.18. (2*S*)-2-(Methoxymethoxymethyl)-2-methylpent-4-en-1-ol (54) (Table 3, entry 1). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **46** (106 mg, 0.80 mmol) was converted into **54** (64 mg, 46% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 2.8 mL, 5.6 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 11.2 mL, 5.6 mmol) at −78 to 0 °C for 2 h: colorless oil; $[\alpha]_D^{28}+8.6$ (*c* 0.96, $CHCl_3$); IR (KBr) cm^{-1} 3524 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 1.09 (s, 3H, CMe), 2.18 (dd, $J=14.0$, 7.9 Hz, 1H, 3-C*H*H), 2.20–2.28 (m, 1H, 3-CH*H*), 2.54 (br s, 1H, OH), 3.38 (s, 3H, OMe), 3.46 (s, 2H, 1-CH_2), 3.52 (s, 2H, 1′-CH_2), 4.80 (s, 2H, OCH_2O), 5.11–5.16 (m, 2H, 5-CH_2), 5.83–5.92 (m, 1H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 38.0, 39.2, 50.5, 70.4, 72.2, 99.4, 117.6, 128.4; MS (FAB) *m*/*z* (%): 175 (MH^+, 35), 90 (100); HRMS (FAB) calcd for $C_9H_{19}O_3$ (MH^+): 175.1334; found: 175.1329.

4.2.19. (2*S*)-2-(Benzyloxymethyl)-2-methylpent-4-en-1-ol (55) (Table 3, entry 2). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **47** (89 mg, 0.50 mmol) was converted into **55** (45 mg, 41% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 1.75 mL, 3.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 7.0 mL, 3.5 mmol) at −78 to 0 °C for 4 h: colorless oil; $[\alpha]_D^{24}+18.0$ (*c* 0.80, $CHCl_3$); IR (KBr) cm^{-1} 3507 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.96 (s, 3H, CMe), 2.24 (dd, $J=14.0$, 7.9 Hz, 1H, 3-C*H*H), 2.29–2.33 (m, 1H, 3-CH*H*), 2.45 (d, $J=4.9$ Hz, 1H, OH), 3.27–3.63 (m, 4H, 1-CH_2 and 1′-CH_2), 4.42 (s, 2H, PhC*H*$_2$), 5.02–5.08 (m, 2H, 6-CH_2), 5.83–5.90 (m, 1H, 5-H), 7.30–7.38 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 38.2, 38.8, 70.0, 73.4, 77.4, 117.7, 127.3, 128.8 (2C), 132.2 (2C), 135.5, 137.0; MS (FAB) *m*/*z* (%): 221 (MH^+, 45), 90 (100); HRMS (FAB) calcd for $C_{14}H_{21}O_2$ (MH^+): 221.1542; found: 221.1550.

4.2.20. (2*R*,3*S*)-3-(Methoxymethoxymethyl)-3-methyl-1-phenylhex-5-en-2-ol (56) (Table 3, entry 3). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **48** (111 mg, 0.50 mmol) was converted into **56** (71 mg, 54% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 1.75 mL, 3.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 7.0 mL, 3.5 mmol) at −78 to 0 °C for 2 h: colorless oil; $[\alpha]_D^{24}+10.6$ (*c* 1.02, $CHCl_3$); IR (KBr) cm^{-1} 3492 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.96 (s, 3H, CMe), 2.24 (dd, $J=14.0$, 7.9 Hz, 1H, 4-C*H*H), 2.29–2.33 (m, 1H, 4-CH*H*), 2.45 (d, $J=4.9$ Hz, 1H, OH), 2.57 (dd, $J=13.4$, 10.4 Hz, 1H, 1-C*H*H), 2.93 (dd, $J=13.4$, 1.2 Hz, 1H, 1-CH*H*), 3.38 (s, 3H, OMe), 3.46–3.58 (m, 2H, 1′-CH_2), 3.71–3.73 (m, 1H, 2-H), 4.61 (s, 2H, OCH_2O), 5.10–5.13 (m, 2H, 6-CH_2), 5.85–5.93 (m, 1H, 5-H), 7.20–7.32 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8, 38.1, 39.9, 41.1, 55.5, 73.4, 77.4, 96.8, 117.9, 126.2, 128.4 (2C), 129.3 (2C), 134.3, 140.0; MS (FAB) *m*/*z* (%): 265 (MH^+, 15), 172 (100); HRMS (FAB) calcd for $C_{16}H_{25}O_3$ (MH^+): 265.1804; found: 265.1812.

4.2.21. (2*R*,3*S*)-3-(Benzyloxymethyl)-3-ethyl-1-phenylhex-5-en-2-ol (57) (Table 3, entry 4). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **49** (141 mg, 0.50 mmol) was converted into **57** (55 mg, 34% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 1.75 mL, 3.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 7.0 mL, 3.5 mmol) at −78 to 0 °C for 6 h: colorless oil; $[\alpha]_D^{26}+45.5$ (c 1.00, $CHCl_3$); IR (KBr) cm^{-1} 3483 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, J=6.4 Hz, 3H, CMe), 1.13 (q, J=6.4 Hz, 2H, CH_2Me), 2.18 (dd, J=14.0, 7.9 Hz, 1H, 4-C*H*H), 2.20–2.32 (m, 1H, 4-CH*H*), 2.52 (d, J=4.9 Hz, 1H, OH), 2.64 (dd, J=13.4, 10.4 Hz, 1H, 1-C*H*H), 2.82 (dd, J=13.4, 1.2 Hz, 1H, 1-CH*H*), 3.40–3.56 (m, 2H, 1′-CH_2), 3.64–3.68 (m, 1H, 2-H), 4.47 (s, 2H, PhCH_2), 5.12–5.16 (m, 2H, 6-CH_2), 5.84–5.93 (m, 1H, 5-H), 7.12–7.40 (m, 10H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.3, 22.5, 37.1, 39.0, 41.9, 70.7, 75.9, 78.4, 117.1, 125.9, 127.7 (2C), 127.9 (2C), 130.7 (2C), 131.0 (2C), 138.3, 138.4, 138.6 (2C); MS (FAB) m/z (%): 347 (MNa^+, 48), 126 (100); HRMS (FAB) calcd for $C_{22}H_{28}NaO_2$ (MNa^+): 347.1987; found: 347.1990.

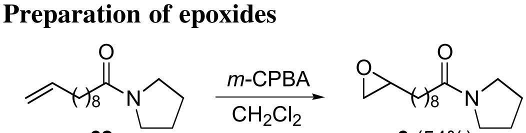
4.2.22. (2*R*,3*S*)-3-Ethyl-3-(methoxymethoxymethyl)-1-phenylhex-5-en-2-ol (58) (Table 3, entry 5). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **50** (118 mg, 0.50 mmol) was converted into **58** (58 mg, 42% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 1.75 mL, 3.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 7.0 mL, 3.5 mmol) at −78 to 0 °C for 3 h: colorless oil; $[\alpha]_D^{24}+12.6$ (c 0.96, $CHCl_3$); IR (KBr) cm^{-1} 3546 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J=6.4 Hz, 3H, CMe), 1.05 (q, J=6.4 Hz, 2H, 3-CH_2Me), 2.14 (dd, J=14.0, 7.9 Hz, 1H, 4-C*H*H), 2.20–2.29 (m, 1H, 4-CH*H*), 2.43 (d, J=4.9 Hz, 1H, OH), 2.50 (dd, J=13.4, 10.4 Hz, 1H, 1-C*H*H), 2.90 (dd, J=13.4, 1.2 Hz, 1H, 1-CH*H*), 3.28 (s, 3H, OMe), 3.43–3.51 (m, 2H, 1′-CH_2), 3.69–3.76 (m, 1H, 2-H), 4.61 (s, 2H, OCH_2O), 5.10–5.14 (m, 2H, 6-CH_2), 5.80–5.93 (m, 1H, 5-H), 7.25–7.34 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.5, 37.6, 38.9, 41.6, 56.3, 72.0, 78.4, 96.0, 117.4, 126.6, 129.3 (2C), 128.9 (2C), 136.1, 138.6; MS (FAB) m/z (%): 279 (MH^+, 30), 184 (100); HRMS (FAB) calcd for $C_{17}H_{27}O_3$ (MH^+): 279.1960; found: 279.1952.

4.2.23. (2*R*,3*R*)-3-Ethyl-3-(methoxymethoxymethyl)-1-phenylhex-5-en-2-ol (59) (Table 3, entry 6). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **51** (118 mg, 0.50 mmol) was converted into **59** (52 mg, 37% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 1.75 mL, 3.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 7.0 mL, 3.5 mmol) at −78 to 0 °C for 3 h: colorless oil; $[\alpha]_D^{28}+34.4$ (c 0.90, $CHCl_3$); IR (KBr) cm^{-1} 3560 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, J=6.4 Hz, 3H, CMe), 1.08 (q, J=6.4 Hz, 2H, 3-CH_2Me), 2.20 (dd, J=14.0, 7.9 Hz, 1H, 4-C*H*H), 2.29–2.33 (m, 1H, 4-CH*H*), 2.45 (d, J=4.9 Hz, 1H, OH), 2.57 (dd, J=13.4, 10.4 Hz, 1H, 1-C*H*H), 2.93 (dd, J=13.4, 1.2 Hz, 1H, 1-CH*H*), 3.38 (s, 3H, OMe), 3.46–3.58 (m, 2H, 1′-CH_2), 3.71–3.77 (m, 1H, 2-H), 4.61 (s, 2H, OCH_2O), 5.10–5.13 (m, 2H, 6-CH_2), 5.86–5.92 (m, 1H, 5-H), 7.23–7.30 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 22.7, 37.8, 38.9, 41.0, 56.1, 72.3, 77.9, 95.9, 117.3, 126.6, 129.0 (2C), 129.1 (2C), 136.1, 138.7; MS (FAB) m/z (%): 279 (MH^+, 26), 184 (100); HRMS (FAB) calcd for $C_{17}H_{27}O_3$ (MH^+): 279.1960; found: 279.1971.

4.2.24. (4*S*,5*R*)-4-(Methoxymethoxymethyl)-4-methylundec-1-en-5-ol (60) (Table 3, entry 7). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **52** (108 mg, 0.50 mmol) was converted into **60** (63 mg, 49% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 1.75 mL, 3.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 7.0 mL, 3.5 mmol) at −78 to 0 °C for 6 h: colorless oil; $[\alpha]_D^{26}+18.4$ (c 1.02, $CHCl_3$); IR (KBr) cm^{-1} 3486 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, J=6.9 Hz, 3H, CMe), 0.97 (s, 3H, CMe), 1.16–1.46 (m, 10H), 2.22–2.36 (m, 2H, 3-CH_2), 3.38 (s, 3H, OMe), 3.46–3.58 (m, 3H, 5-H and 1′-CH_2), 4.63 (s, 2H, OCH_2O), 5.10–5.13 (m, 2H, 1-CH_2), 5.85–5.93 (m, 1H, 2-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 15.8, 22.9, 24.2, 30.4, 31.0, 34.1, 35.9, 41.1, 55.5, 72.7, 76.7, 98.8, 120.2, 130.6; MS (FAB) m/z (%): 259 (MH^+, 34), 183 (100); HRMS (FAB) calcd for $C_{15}H_{31}O_3$ (MH^+): 259.2273; found: 259.2286.

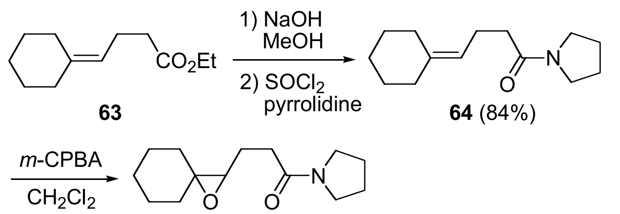
4.2.25. (4*S*,5*R*)-4-(Benzyloxymethyl)-4-methylundec-1-en-5-ol (61) (Table 3, entry 8). By the general procedure for the allyltitanium-mediated ring-opening reaction, epoxide **53** (131 mg, 0.50 mmol) was converted into **61** (50 mg, 33% yield) by the reaction with allylmagnesium chloride (2.0 M in THF; 1.75 mL, 3.5 mmol) and chlorotitanium triphenoxide (0.5 M in THF; 7.0 mL, 3.5 mmol) at −78 to 0 °C for 8 h: colorless oil; $[\alpha]_D^{24}+29.0$ (c 0.90, $CHCl_3$); IR (KBr) cm^{-1} 3523 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J=6.9 Hz, 3H, CMe), 0.95 (s, 3H, CMe), 1.12–1.34 (m, 10H), 2.18–2.26 (m, 2H, 3-CH_2), 2.40 (d, J=5.4 Hz, 1H, OH), 3.20 (dd, J=13.4, 5.4 Hz, 1H, 5-H), 3.46 (s, 2H, 1′-CH_2), 4.50 (s, 2H, PhCH_2), 5.06–5.12 (m, 2H, 1-CH_2), 5.78–5.83 (m, 1H, 2-H), 7.22–7.36 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 15.3, 22.2, 24.8, 30.2, 30.4, 34.7, 36.0, 40.6, 68.6, 74.2, 77.4, 117.9, 127.04, 127.07, 130.1 (2C), 132.6 (2C), 136.4; MS (FAB) m/z (%): 305 (MH^+, 40), 91 (100); HRMS (FAB) calcd for $C_{20}H_{33}O_2$ (MH^+): 305.2481; found: 305.2476.

4.3. Preparation of epoxides



62 **3** (54%)

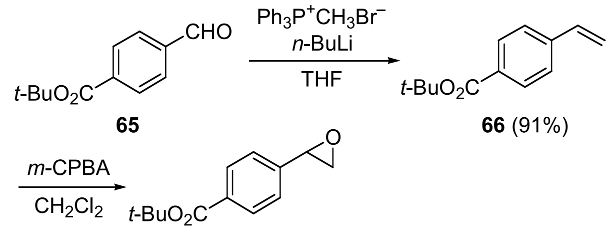
4.3.1. (±)-9-(Oxiran-2-yl)-1-pyrrolidinylnonan-1-one (3). To a stirred solution of 1-pyrrolidinylundec-10-en-1-one **62**[26] (2.50 g, 10.5 mmol) in CH_2Cl_2 (20 mL) was added dropwise a solution of 75% *m*-CPBA (3.08 g, 13.4 mmol) in CH_2Cl_2 (30 mL) at 0 °C, and the mixture was stirred for 4 h at room temperature. Saturated $Na_2S_2O_3$ was added to the mixture and stirring was continued for 30 min. Organic layer was separated and washed with saturated $NaHCO_3$ (×2), water, and brine, and dried over $MgSO_4$. Concentration of the filtrate under reduced pressure gave an oily residue, which was purified by column chromatography over silica gel with hexane–EtOAc (3:2) to give **3** (1.43 g, 54% yield) as a colorless oil; IR (KBr) cm^{-1} 1643 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.25–1.66 (m, 14H, 7× CH_2), 1.80–2.00 (m, 4H, 3′-CH_2 and 4′-CH_2), 2.22–2.28 (m, 2H, 2-CH_2), 2.45–2.48 (m, 1H, OC*H*H), 2.73–2.76 (m, 1H, OCH*H*), 2.88–2.93 (m, 1H, OCH), 3.39–3.48 (m, 4H, 2′-CH_2 and 5′-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4, 24.9, 25.9, 26.1, 29.31 (2C), 29.35, 29.4, 32.4, 34.8, 45.5, 46.6, 47.1, 52.4, 171.8; MS (FAB) m/z (%): 254 (MH^+, 100); HRMS (FAB) calcd for $C_{15}H_{28}NO_2$ (MH^+): 254.2120; found: 254.2101.



63 → **64** (84%) → **4** (54%)

4.3.2. 4-Cyclohexylidene-1-pyrrolidinylbutan-1-one (64). To a stirred solution of ethyl 4-cyclohexylidenebutyrate **63**[27] (5.00 g, 25.5 mmol) in MeOH (60 mL) was added 5 N NaOH (20 mL), and the mixture was stirred under reflux for 3 h. The mixture was concentrated under reduced pressure and diluted with Et_2O. The mixture was made acidic with 10% HCl and extracted with Et_2O (×3). The extract was washed with brine and dried over $MgSO_4$. Concentration of the filtrate under reduced pressure gave a crude carboxylic acid, which was used in the next reaction without further purification. To a mixture of this crude carboxylic acid and DMF (1 mL) in CH_2Cl_2 (60 mL) was added dropwise thionyl chloride (2.23 mL, 30.6 mmol) at −78 °C. The mixture was stirred under reflux for 30 min and, after cooling, pyrrolidine (5.11 mL, 61.2 mmol) was added dropwise to the mixture at 0 °C. The mixture was stirred overnight at room temperature and concentrated under reduced pressure. The residue was diluted with Et_2O and made acidic with 5% HCl. The whole was extracted with Et_2O (×2) and the extract was washed with saturated $NaHCO_3$ and brine, dried and evaporated. The residue was purified by column chromatography over silica gel with $CHCl_3$–Et_2O (10:1) to give **64** (4.74 g, 84% yield) as a colorless oil; IR (KBr) cm^{-1} 1642 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.51 (m, 6H), 1.74–2.00 (m, 4H, 3′-CH_2 and 4′-CH_2), 2.05–2.16 (m, 4H, 2×CH_2), 2.24–2.39 (m, 4H, 2×CH_2), 3.39–3.48 (m, 4H, 2′-CH_2 and 5′-CH_2), 5.10 (t, J=7.2 Hz, 1H, 4-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 24.4, 26.1, 26.9, 27.8, 28.6 (2C), 35.3, 37.1, 45.6, 46.6, 119.8, 140.7, 171.4; MS (FAB) m/z (%): 222 (MH^+, 36), 182 (100); HRMS (FAB) calcd for $C_{14}H_{24}NO$ (MH^+): 222.1858; found: 222.1852.

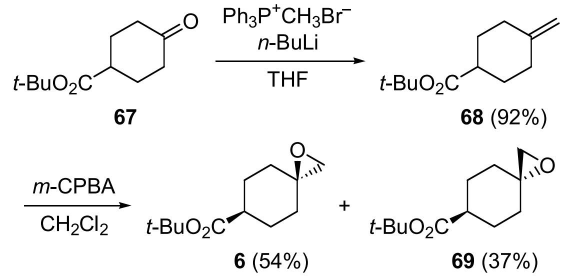
4.3.3. (±)-3-(1-Oxaspiro[2.5]oct-2-yl)-1-pyrrolidinyl-propan-1-one (4). By a procedure identical with that described for the synthesis of the epoxide **3**, the alkene **64** (2.50 g, 11.3 mmol) was converted into **4** (1.45 g, 54% yield) by the reaction with 75% *m*-CPBA (3.13 g, 13.6 mmol) at room temperature for 1 h: colorless oil; IR (KBr) cm^{-1} 1640 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.48–1.64 (m, 6H), 1.73–2.01 (m, 4H, 3′-CH_2 and 4′-CH_2), 2.07–2.38 (m, 8H, 4×CH_2), 2.90–2.93 (m, 1H, OCH), 3.40–3.48 (m, 4H, 2′-CH_2 and 5′-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 24.4, 26.2, 27.0, 27.9, 28.6 (2C), 35.2, 37.0, 45.5, 46.5, 47.7, 52.9, 172.0; MS (FAB) m/z (%): 238 (MH^+, 46), 90 (100); HRMS (FAB) calcd for $C_{14}H_{24}NO_2$ (MH^+): 238.1807; found: 238.1810.



65 → **66** (91%) → **5** (45%)

4.3.4. *tert*-Butyl 4-vinylbenzoate (66). To a stirred solution of methyltriphenylphosphonium bromide ($Ph_3P^+CH_3Br^-$; 1.90 g, 5.32 mmol) in THF (8 mL) was added dropwise *n*-BuLi (1.55 M solution in hexane; 3.43 mL, 5.32 mmol) at −78 °C. The mixture was gradually warmed until a red color persisted. After the mixture was cooled to −78 °C, a solution of aldehyde **65**[28] (1.02 g, 4.94 mmol) in THF (8 mL) was added dropwise to the mixture under stirring. After the mixture was stirred for 2 h at 0 °C, saturated NH_4Cl was added to the mixture. Organic layer was separated and washed with saturated NH_4Cl and brine, dried, and evaporated. The residue was purified by column chromatography over silica gel with hexane–EtOAc (20:1) to give **66** (914 mg, 91% yield) as a colorless oil; IR (KBr) cm^{-1} 1709 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.60 (s, 9H, CMe_3), 5.36 (d, J=11.0 Hz, 1H, CH=C*H*H), 5.84 (d, J=17.7 Hz, 1H, CH=CH*H*), 6.75 (dd, J=17.7, 11.0 Hz, 1H, C*H*=CH_2), 7.44 (d, J=8.5 Hz, 2H, Ph), 7.94 (d, J=8.5 Hz, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2 (3C), 80.9, 116.1, 125.9 (2C), 129.7 (2C), 131.2, 136.1, 141.4, 165.5; MS (FAB) m/z (%): 205 (MH^+, 68), 154 (100); HRMS (FAB) calcd for $C_{13}H_{17}O_2$ (MH^+): 205.1229; found: 205.1227.

4.3.5. *tert*-Butyl (±)-4-(oxiran-2-yl)benzoate (5). By a procedure identical with that described for the synthesis of the epoxide **3**, the alkene **66** (905 mg, 4.43 mmol) was converted into **5** (443 mg, 45% yield) by the reaction with 75% *m*-CPBA (1.22 g, 5.32 mmol) in the presence of 0.5 M $NaHCO_3$ (20 mL) at room temperature overnight: colorless oil; IR (KBr) cm^{-1} 1710 (C=O); ^1H NMR (300 MHz, $CDCl_3$) δ 1.59 (s, 9H, CMe_3), 2.76–2.79 (m, 1H, C*H*H), 3.16–3.20 (m, 1H, CH*H*), 3.89–3.91 (m, 1H, CH), 7.32 (d, J=8.4 Hz, 2H, Ph), 7.96 (d, J=8.4 Hz, 2H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2 (3C), 51.4, 52.0, 81.1, 125.2 (2C), 129.6 (2C), 131.8, 142.3, 165.4; MS (FAB) m/z (%): 221 (MH^+, 100); HRMS (FAB) calcd for $C_{13}H_{17}O_3$ (MH^+): 221.1178; found: 221.1182.



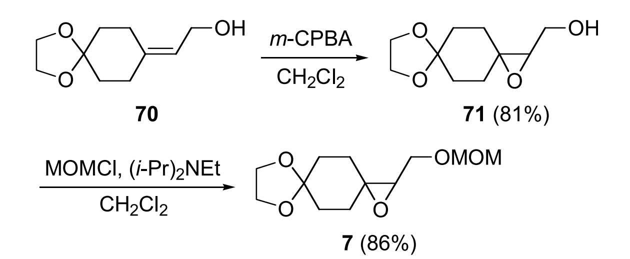
67 → **68** (92%) → **6** (54%) + **69** (37%)

4.3.6. *tert*-Butyl (±)-4-methylenecyclohexanecarboxylate (68). By a procedure identical with that described for the synthesis of the alkene **66**, the ketone **67**[29] (2.00 g, 10.1 mmol) was converted into **68** (1.83 g, 92% yield) by the reaction with $Ph_3P^+CH_3Br^-$ (4.32 g, 12.1 mmol) and *n*-BuLi (1.55 M solution in hexane; 7.81 mL, 12.1 mmol) at 0 °C for 1 h: colorless oil; IR (KBr) cm^{-1} 1725 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H, CMe_3), 1.50–1.58 (m, 2H), 1.93–1.98 (m, 2H), 2.01–2.07 (m, 2H), 2.03–2.37 (m, 3H, 1-H and 2×CH), 4.63 (s, 2H, $C{=}CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.1 (3C), 30.2 (2C), 33.7 (2C), 43.5, 79.9, 107.7, 148.0, 174.9; MS (FAB) *m/z* (%): 219 (MNa^+, 10.5), 55 (100).

4.3.7. *tert*-Butyl (±)-(3*R,6*R**)-1-oxaspiro[2.5]octane-6-carboxylate (6) and its (3*R**,6*S**)-Isomer (69).** By a procedure identical with that described for the synthesis of the epoxide **3**, the alkene **68** (1.75 g, 8.92 mmol) was converted into, in the order of elution, **69** (707 mg, 37% yield) and **6** (1.03 g, 54% yield) by the reaction with 75% *m*-CPBA (2.67 g, 11.6 mmol) in the presence of 0.5 M $NaHCO_3$ (40 mL) at room temperature for 2 h.

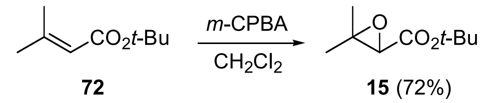
Compound **6**. Colorless needles; mp 32–35 °C; IR (KBr) cm^{-1} 1724 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.39–1.41 (m, 2H), 1.45 (s, 9H, CMe_3), 1.78–1.87 (m, 4H), 1.89–1.97 (m, 2H), 2.26–2.32 (m, 1H, 6-H), 2.64 (s, 2H, 2-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.5 (2C), 28.0 (3C), 31.9 (2C), 42.7, 53.8, 57.6, 80.1, 174.4; MS (FAB) *m/z* (%): 235 (MNa^+, 7.3), 176 (100); HRMS (FAB) calcd for $C_{12}H_{21}O_3$ (MH^+): 213.1491; found: 213.1467.

Compound **69**. Colorless needles; mp 35–38 °C; IR (KBr) cm^{-1} 1726 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 9H, CMe_3), 1.49–1.52 (m, 2H), 1.67–1.76 (m, 4H), 2.02–2.05 (m, 2H), 2.30–2.36 (m, 1H, 6-H), 2.60 (s, 2H, 2-CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.7 (2C), 28.0 (3C), 32.1 (2C), 42.3, 54.6, 58.6, 80.2, 174.5; MS (FAB) *m/z* (%): 235 (MNa^+, 9.3), 176 (100); HRMS (FAB) calcd for $C_{12}H_{21}O_3$ (MH^+): 213.1491; found: 213.1493.

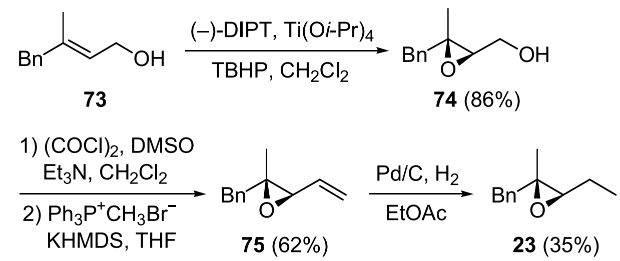


4.3.8. (±)-2-(Hydroxymethyl)-1-oxaspiro[2.5]octan-6-one 6,6-ethylene acetal (71). By a procedure identical with that described for the synthesis of the epoxide **3**, the allyl alcohol **70**[30] (3.20 g 17.4 mmol) was converted into **71** (2.83 g, 81% yield) by the reaction with 75% *m*-CPBA (4.80 g, 20.8 mmol) at room temperature overnight: colorless oil; IR ($CHCl_3$) cm^{-1} 3421 (OH); ^1H NMR (300 MHz, $CDCl_3$) δ 1.54–1.95 (m, 8H), 3.05 (dd, $J{=}6.7$, 4.3 Hz, 1H, 2-H), 3.72 (dd, $J{=}12.0$, 7.0 Hz, 1H, OC*H*H), 3.86 (dd, $J{=}12.0$, 4.0 Hz, 1H, OCH*H*), 3.98 (t, $J{=}2.7$ Hz, 4H, OCH_2CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 32.0, 32.8 (2C), 61.0, 62.0, 63.6, 64.38, 64.40, 108.1; MS (EI) *m/z*: 200 (M^+). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.04; H, 7.94.

4.3.9. (±)-2-(Methoxymethoxymethyl)-1-oxaspiro-[2.5]octan-6-one 6,6-ethylene acetal (7). To a stirred mixture of the alcohol **71** (1.50 g, 7.49 mmol) and $(i\text{-}Pr)_2NEt$ (2.61 mL, 15.0 mmol) in CH_2Cl_2 (40 mL) was added MOMCl (0.85 mL, 11.2 mmol) at room temperature and the stirring was continued overnight. 5% HCl was added to the mixture and the whole was extracted with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$ (×2) and brine, dried and evaporated. The residue was purified by column chromatography over silica gel with hexane–EtOAc (3:1) to give **7** (1.58 g, 86% yield) as a colorless oil; $[\alpha]_D^{25}+0.36$ (*c* 1.27, $CHCl_3$); IR ($CHCl_3$) cm^{-1} 1265, 1099; ^1H NMR (300 MHz, $CDCl_3$) δ 1.55–1.95 (m, 8H), 3.06 (dd, $J{=}6.0$, 5.1 Hz, 1H, 2-H), 3.38 (s, 3H, OMe), 3.65 (dd, $J{=}11.4$, 6.0 Hz, 1H, OC*H*H), 3.73 (dd, $J{=}11.4$, 5.1 Hz, 1H, OCH*H*), 3.97 (t, $J{=}2.5$ Hz, 4H, OCH_2CH_2O), 4.65 (d, $J{=}6.6$ Hz, 1H, OC*H*HO), 4.68 (d, $J{=}6.6$ Hz, 1H, OCH*H*O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.2, 32.0, 32.7, 32.8, 55.3, 61.1, 61.8, 64.37, 64.40, 66.0, 96.6, 108.2; MS (EI) *m/z*: 244 (M^+). Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 58.91; H, 8.08.



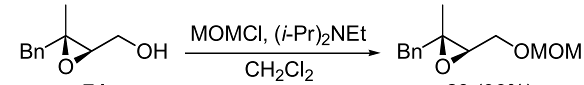
4.3.10. *tert*-Butyl (±)-2,3-epoxy-3-methylbutyrate (15). By a procedure identical with that described for the synthesis of the epoxide **3**, the enoate **72**[31] (1.27 g, 8.13 mmol) was converted into **15** (1.01 g, 72% yield) by the reaction with 75% *m*-CPBA (2.39 g, 10.4 mmol) under reflux overnight: colorless oil; IR (KBr) cm^{-1} 1710 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 3H, CMe), 1.41 (s, 3H, CMe), 1.50 (s, 9H, CMe_3), 3.22 (s, 1H, 2-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1, 24.3, 28.1 (3C), 59.7, 59.9, 82.2, 167.6; MS (FAB) *m/z* (%): 173 (MH^+, 5), 154 (100); HRMS (FAB) calcd for $C_9H_{17}O_3$ (MH^+): 173.1178; found: 173.1188.



4.3.11. (2*R*,3*R*)-2,3-Epoxy-3-methyl-4-phenylbutan-1-ol (74). To a stirred mixture of molecular sieves 4A (2.50 g) in CH_2Cl_2 (150 mL) were added dropwise D-(−)-diisopropyl tartrate [D-(−)-DIPT; 1.50 mL, 7.05 mmol] and $Ti(Oi\text{-}Pr)_4$ (1.39 mL, 4.70 mmol) at −20 °C. After stirring for 30 min, *tert*-butylhydroperoxide (TBHP; 2.6 M solution in toluene, 36.2 mL, 94.1 mmol) was added dropwise to the mixture. After the mixture was stirred for 1 h, a solution of **73**[32] (7.63 g, 47.0 mmol) in CH_2Cl_2 (50 mL) was slowly added to the mixture over 1 h at −30 °C. After 5 h, 10% NaOH saturated with sodium chloride were added to the mixture, and the mixture was vigorously stirred at 10 °C for 30 min. Anhydrous $MgSO_4$ (6.5 g) and Celite (1.0 g) were added to the mixture, and vigorous stirring was continued for additional 30 min. The mixture was filtered through Celite, and the filtrate was dried and evaporated. The residue was purified by column chromatography over silica gel with hexane–EtOAc (2:1) to give **74** (7.21 g, 86% yield) as a colorless oil; $[\alpha]_D^{24}+21.4$ (*c* 0.96, $CHCl_3$); IR (KBr) cm^{-1} 3462 (OH); ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H, CMe), 2.60 (br s, 1H, OH), 2.74 (d, $J=14.6$ Hz, 1H, 4-C*H*H), 2.80 (d, $J=14.6$ Hz, 1H, 4-CH*H*), 3.23 (d, $J=4.2$ Hz, 1H, 2-H), 4.10–4.18 (m, 2H, 1-CH_2), 7.21–7.33 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 34.1, 58.0, 63.3, 66.6, 126.3, 128.3 (2C), 128.6 (2C), 136.8; MS (FAB) *m/z* (%): 201 (MNa^+, 100); HRMS (FAB) calcd for $C_{11}H_{14}NaO_2$ (MNa^+): 201.0891; found: 201.0889.

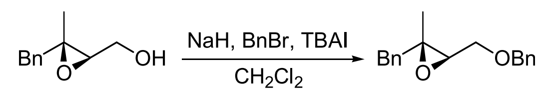
4.3.12. (2*R*,3*R*)-2,3-Epoxy-2-methyl-1-phenylpent-4-ene (75). To a stirred solution of oxalyl chloride (2.9 mL, 33.7 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added dropwise a solution of DMSO (4.78 mL, 67.3 mmol) in CH_2Cl_2 (15 mL). After stirring for 30 min, a solution of the alcohol **74** (3.00 g, 16.8 mmol) in CH_2Cl_2 (25 mL) was added to the above reagent at −78 °C, and the mixture was stirred for 1 h at this temperature. Triethylamine (18.8 mL, 134.7 mmol) was added to the above solution at −78 °C, and the mixture was stirred for 2 h at −30 °C. Saturated NH_4Cl was added to the mixture, and the whole was extracted with CH_2Cl_2. The extract was washed successively with NH_4Cl, $NaHCO_3$, and brine and dried over $MgSO_4$. Concentration under reduced pressure followed by short column chromatography over silica gel with hexane–EtOAc (7:1) gave a crude aldehyde as an oil, which was used in the next reaction without further purification. By a procedure identical with that described for the synthesis of the alkene **66**, this aldehyde was converted into **75** (1.70 g, 62% yield) by the reaction with $Ph_3P^+CH_3Br^-$ (8.27 g, 23.1 mmol) and KHMDS (0.50 M solution in toluene, 46.3 mL, 23.1 mmol) at 0 °C for 15 min: colorless oil; $[\alpha]_D^{26}+35.2$ (*c* 1.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (s, 3H, CMe), 2.72 (d, $J=14.2$ Hz, 1H, 1-C*H*H), 2.84 (d, $J=14.2$ Hz, 1H, 1-CH*H*), 3.56 (s, 1H, 3-H), 5.21–5.32 (m, 2H, 5-CH_2), 5.90–5.98 (m, 1H, 4-H), 7.22–7.30 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 33.8, 61.9, 68.7, 113.8, 126.3, 128.3 (2C), 128.6 (2C), 136.8, 140.0; MS (FAB) *m/z* (%): 175 (MH^+, 42), 96 (100); HRMS (FAB) calcd for $C_{12}H_{15}O$ (MH^+): 175.1123; found: 175.1140.

4.3.13. (2*R*,3*R*)-2,3-Epoxy-2-methyl-1-phenylpentane (23). To a mixture of **75** (1.00 g, 5.76 mmol) and 5% Pd/C (100 mg) in EtOAc (35 mL) was stirred for 9 h under hydrogen atmosphere. The mixture was filtered through Celite, and the filtrate was concentrated and purified by column chromatography over silica gel with hexane–EtOAc (20:1) to give **23** (355 mg, 35% yield) as a colorless oil; $[\alpha]_D^{24}+8.6$ (*c* 0.82, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (t, $J=7.5$ Hz, 3H, CH_2CH_3), 1.20 (s, 3H, CMe), 1.51–1.64 (m, 2H, C*H*$_2$Me), 2.74–2.92 (m, 2H, PhC*H*$_2$), 7.20–7.33 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 16.2, 21.5, 42.5, 60.7, 61.1, 125.8, 127.6 (2C), 128.3 (2C), 134.1; MS (FAB) *m/z* (%): 183 (MLi^+, 100); HRMS (FAB) calcd for $C_{12}H_{16}LiO$ (MLi^+): 183.1361; found: 183.1358.



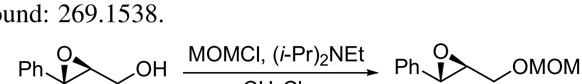
74 **29** (96%)

4.3.14. (2*R*,3*R*)-2,3-Epoxy-*O*-methoxymethyl-3-methyl-4-phenylbutan-1-ol (29). By a procedure identical with that described for the synthesis of **7**, the alcohol **74** (650 mg, 3.65 mmol) was converted into **29** (776 mg, 96% yield) by the reaction with MOMCl (1.12 mL, 13.1 mmol) and (i-Pr)$_2$NEt (2.86 mL, 16.4 mmol) at room temperature for 24 h: colorless oil; $[\alpha]_D^{24}+23.6$ (*c* 0.96, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 3H, CMe), 2.83 (d, $J=14.1$ Hz, 1H, 4-C*H*H), 2.91 (d, $J=14.1$ Hz, 1H, 4-CH*H*), 3.04 (t, $J=5.5$ Hz, 1H, 2-H), 3.37 (s, 3H, OMe), 3.60–3.75 (m, 2H, 1-CH_2), 4.62–4.68 (m, 2H, OCH_2O), 7.21–7.32 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 44.4, 55.3, 60.4, 60.5, 66.3, 96.5, 126.6, 128.4 (2C), 129.6 (2C), 136.8; MS (FAB) *m/z* (%): 223 (MH^+, 12), 132 (100); HRMS (FAB) calcd for $C_{13}H_{19}O_3$ (MH^+): 223.1334; found: 223.1340.



74 **30** (89%)

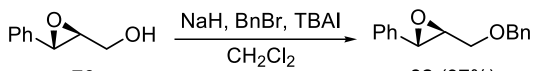
4.3.15. (2*R*,3*R*)-*O*-Benzyl-2,3-epoxy-3-methyl-4-phenylbutan-1-ol (30). 60% NaH (297 mg, 7.43 mmol) was washed with dry hexane and suspended in THF (10 mL). To this suspension were successively added tetrabutylammonium iodide [(n-Bu)$_4$NI; 250 mg, 0.68 mmol], BnBr (0.88 mL, 7.43 mmol), and a solution of the alcohol **74** (1.20 g, 6.76 mmol) in THF (10 mL) at room temperature. After stirring for 4 h, H_2O was added to the mixture at 0 °C. The whole was extracted with EtOAc and the extract was washed with brine, dried and evaporated. The residue was purified by column chromatography over silica gel with hexane–EtOAc (30:1) to give **30** (1.62 g, 89% yield) as a colorless oil; $[\alpha]_D^{24}+10.6$ (*c* 1.02, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.23 (s, 3H, CMe), 2.80 (d, $J=14.0$ Hz, 1H, 4-C*H*H), 2.87 (d, $J=14.0$ Hz, 1H, 4-CH*H*), 3.03 (m, 1H, 2-H), 3.58–3.71 (m, 2H, 1-CH_2), 4.56–4.64 (m, 2H, OC*H*$_2$Ph), 7.25–7.34 (m, 10H, 2×Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.0, 44.6, 59.4, 60.0, 67.1, 78.7, 125.3 (2C), 126.8 (2C), 127.4 (2C), 128.4, 128.7 (3C), 136.8, 137.8; MS (FAB) *m/z* (%): 223 (MH^+, 26), 90 (100); HRMS (FAB) calcd for $C_{18}H_{21}O_2$ (MH^+): 269.1542; found: 269.1538.



76 **31** (83%)

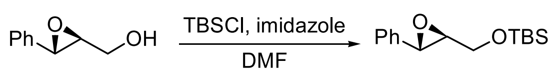
4.3.16. (2*S*,3*S*)-2,3-Epoxy-*O*-methoxymethyl-3-phenylpropan-1-ol (31). By a procedure identical with that described for the synthesis of **7**, the alcohol **76**[26] (1.50 g, 10.0 mmol) was converted into **31** (1.61 g, 83% yield) by the reaction with MOMCl (1.14 mL, 15.0 mmol) and (i-Pr)$_2$NEt (3.48 mL, 20.0 mmol) at room temperature for 12 h: colorless oil; $[\alpha]_D^{26}$ −39.9 (*c* 1.00, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 3.23–3.25 (m, 1H, 2-H), 3.39 (s, 3H, OMe), 3.71 (dd, $J=11.6$, 5.5 Hz, 1H, 1-C*H*H), 3.81 (d, $J=$

3.1 Hz, 1H, 3-H), 3.88 (dd, *J*=11.6, 3.1 Hz, 1H, 1-CH*H*), 4.69 (d, *J*=6.7 Hz, 1H, OC*H*HO), 4.71 (d, *J*=6.7 Hz, 1H, OCH*H*O), 7.27–7.36 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4, 56.1, 60.9, 67.3, 96.7, 125.7 (2C), 128.3, 128.5 (2C), 136.8; MS (FAB) *m/z* (%): 217 (MNa^+, 10.2), 176 (100); HRMS (FAB) calcd for $C_{11}H_{14}NaO_3$ (MNa^+): 217.0841; found: 217.0861.



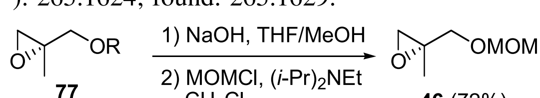
76 **32** (97%)

4.3.17. (2*S*,3*S*)-*O*-Benzyl-2,3-epoxy-3-phenylpropan-1-ol (32). By a procedure identical with that described for the synthesis of **30**, the alcohol **76**[26] (1.20 g, 8.00 mmol) was converted into **32** (1.86 g, 97% yield) by the reaction with 60% NaH (352 mg, 8.80 mmol), (n-Bu)$_4$NI (29.6 mg, 0.08 mmol), and BnBr (1.05 mL, 8.83 mmol) at room temperature for 3 h: colorless oil; $[\alpha]_D^{28}$ −38.9 (*c* 0.82, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.23–3.27 (m, 1H, 2-H), 3.59–3.65 (m, 1H, 3-H), 3.79–3.86 (m, 2H, 1-CH_2), 4.58–4.67 (m, 2H, PhC*H*$_2$), 7.24–7.37 (m, 10H, 2×Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.9, 61.2, 69.8, 73.4, 125.7 (2C), 127.8 (2C), 128.2, 128.4 (2C), 128.5 (3C), 136.8, 137.8; MS (FAB) *m/z* (%): 263 (MNa^+, 41), 176 (100); HRMS (FAB) calcd for $C_{16}H_{16}NaO_2$ (MNa^+): 263.1048; found: 263.1048.



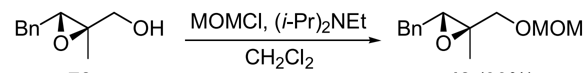
76 **33** (91%)

4.3.18. (2*S*,3*S*)-*O*-(*tert*-Butyldimethylsilyl)-2,3-epoxy-3-phenylpropan-1-ol (33). To a stirred solution of the alcohol **76**[26] (2.00 g, 13.3 mmol) in DMF (50 mL) were successively added imidazole (2.26 g, 33.2 mmol) and TBSCl (2.41 g, 16.0 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. Saturated NH_4Cl was added to the mixture, and the whole was extracted with EtOAc. The extract was washed with saturated $NaHCO_3$ and brine, dried and evaporated. The residue was purified by column chromatography over silica gel with hexane–Et_2O (40:1) to give **33** (3.22 g, 91% yield) as a colorless oil; $[\alpha]_D^{28}$ −28.8 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.105 (s, 3H, SiMe), 0.113 (s, 3H, SiMe), 0.92 (s, 9H, CMe_3), 3.14–3.15 (m, 1H, 2-H), 3.80 (d, *J*=1.8 Hz, 1H, 3-H), 3.83 (dd, *J*=12.2, 4.3 Hz, 1H, 1-C*H*H), 3.96 (dd, *J*=12.2, 3.1 Hz, 1H, 1-CH*H*), 7.27–7.36 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.3 (2C), 18.4, 25.9 (3C), 55.8, 62.7, 63.0, 125.7 (2C), 128.1, 128.4 (2C), 137.2; MS (FAB) *m/z* (%): 265 (MH^+, 32), 207 (100); HRMS (FAB) calcd for $C_{15}H_{25}O_2Si$ (MH^+): 265.1624; found: 265.1629.



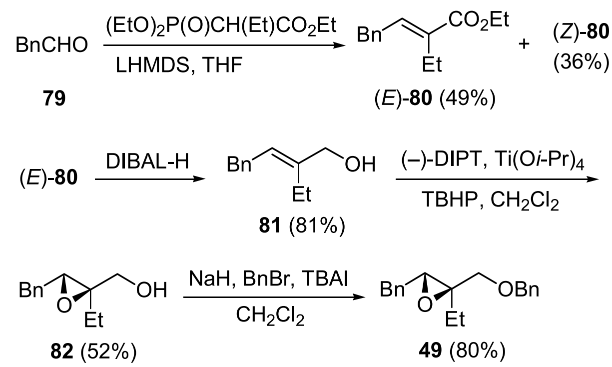
77 (R = 4-NO_2PhCO) **46** (72%)

4.3.19. (*R*)-2,3-Epoxy-*O*-methoxymethyl-2-methylpropan-1-ol (46). To a stirred solution of **77**[26] (3.52 g, 14.8 mmol) in THF/MeOH (4:1, 30 mL) was added 10% NaOH (10 mL), and the mixture was stirred at 0 °C for 3 h. The whole was extracted with EtOAc, and the extract was washed with saturated $NaHCO_3$ and brine, dried and evaporated to give a crude alcohol, which was used in the next reaction without further purification. By a procedure identical with that described for the synthesis of **7**, this alcohol was converted into **46** (1.41 g, 72% yield) by the reaction with MOMCl (3.37 mL, 44.4 mmol) and (i-Pr)$_2$NEt (12.9 mL, 74.0 mmol) at room temperature overnight: colorless oil; $[\alpha]_D^{26}$ −5.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3H, CMe), 2.53 (s, 2H, 3-CH_2), 3.34 (s, 3H, OMe), 3.40 (s, 2H, 1-CH_2), 5.13 (s, 2H, OCH_2O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 51.3, 51.5, 67.2, 77.0, 98.9; MS (FAB) *m/z* (%): 133 (MH^+, 100); HRMS (FAB) calcd for $C_6H_{13}O_3$ (MH^+): 133.0865; found: 133.0859.



78 **48** (93%)

4.3.20. (2*R*,3*R*)-2,3-Epoxy-*O*-methoxymethyl-2-methyl-4-phenylbutan-1-ol (48). By a procedure identical with that described for the synthesis of **7**, the alcohol **78**[33] (1.50 g, 8.42 mmol) was converted into **48** (1.74 g, 93% yield) by the reaction with MOMCl (0.96 mL, 12.6 mmol) and (i-Pr)$_2$NEt (2.92 mL, 16.8 mmol) at room temperature overnight: colorless oil; $[\alpha]_D^{23}$ +1.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 3H, CMe), 2.86 (dd, *J*=14.6, 6.1 Hz, 1H, 4-C*H*H), 2.90–3.02 (m, 1H, 4-CH*H*), 3.10–3.20 (m, 1H, 3-H), 3.33 (s, 3H, OMe), 3.53 (d, *J*=11.0 Hz, 1H, 1-C*H*H), 3.56 (d, *J*=11.0 Hz, 1H, 1-CH*H*), 4.61 (s, 2H, OCH_2O), 7.22–7.33 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 34.7, 55.3, 59.8, 61.2, 71.7, 96.5, 126.6, 128.6 (2C), 128.7 (2C), 137.7; MS (FAB) *m/z* (%): 223 (MH^+, 13.4), 45 (100); HRMS (FAB) calcd for $C_{13}H_{19}O_3$ (MH^+): 223.1334; found: 223.1330.



4.3.21. Ethyl (*E*)-2-ethyl-4-phenylbut-2-enoate [(*E*)-80] and its (*Z*)-isomer [(*Z*)-80]. To a stirred solution of triethyl phosphonobutyrate (28.4 mL, 120 mmol) in THF (120 mL) was added dropwise LHMDS (1.02 M solution in toluene; 118 mL, 120 mmol) at −78 °C. After the mixture was stirred for 30 min at 0 °C, a solution of 60% phenylacetaldehyde (19.5 mL, 100 mmol) in THF (30 mL) was added dropwise to the mixture at −78 °C. The mixture was stirred for 5 h at 0 °C, and saturated NH_4Cl was added to the mixture. The organic layer was separated and washed with saturated NH_4Cl and brine, dried and evaporated. The residue was purified by column chromatography over silica gel with hexane–EtOAc (30:1) to give, in the order of elution, (*Z*)-**80** (7.95 g, 36% yield) and (*E*)-**80** (10.8 g, 49% yield).

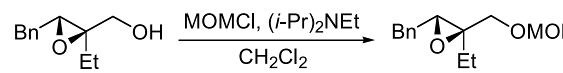
Compound (*E*)-**80**. Colorless oil; IR (KBr) cm^{-1} 1709 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.07 (t, J=7.3 Hz, 3H, CMe), 1.28 (t, J=7.3 Hz, 3H, CMe), 2.44 (q, J=7.3 Hz, 2H, CH_2Me), 3.54 (d, J=7.9 Hz, 2H, 4-CH_2), 4.19 (q, J=7.3 Hz, 2H, OCH_2), 6.86 (t, J=7.9 Hz, 1H, 3-H), 7.19–7.32 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 14.2, 20.1, 34.5, 60.4, 126.4, 128.5 (2C), 128.6 (2C), 134.6, 139.1, 139.5, 167.7; MS (FAB) *m*/*z* (%): 219 (MH^+, 100); HRMS (FAB) calcd for $C_{14}H_{19}O_2$ (MH^+): 219.1385; found: 219.1380.

Compound (*Z*)-**80**. Colorless oil; IR (KBr) cm^{-1} 1712 (C=O); ^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, J=7.3 Hz, 3H, CMe), 1.33 (t, J=7.3 Hz, 3H, CMe), 2.32 (q, J=7.3 Hz, 2H, CH_2Me), 3.77 (d, J=7.3 Hz, 2H, 4-CH_2), 4.26 (q, J=7.3 Hz, 2H, OCH_2), 5.97 (t, J=7.3 Hz, 1H, 3-H), 7.19–7.31 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 14.3, 27.5, 35.8, 60.2, 126.1, 128.5 (2C), 128.6 (2C), 134.3, 137.9, 140.4, 168.2; MS (FAB) *m*/*z* (%): 219 (MH^+, 100); HRMS (FAB) calcd for $C_{14}H_{19}O_2$ (MH^+): 219.1385; found: 219.1393.

4.3.22. (*E*)-2-Ethyl-4-phenylbut-2-en-1-ol (81). To a stirred solution of (*E*)-**80** (9.00 g, 41.2 mmol) in THF (150 mL) was added dropwise DIBAL-H (0.93 M solution in hexane; 133 mL, 124 mmol) at −78 °C, and the mixture was stirred for 1 h at this temperature. Saturated NH_4Cl was added to the mixture, and the precipitate was filtered off. The filtrate was dried and concentrated to leave an oily residue, which was purified by column chromatography over silica gel with hexane–EtOAc (5:1) to give **81** (5.89 g, 81% yield) as a colorless oil; IR (KBr) cm^{-1} 3323 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (t, J=7.6 Hz, 3H, CMe), 1.31 (br, 1H, OH), 2.24 (q, J=7.6 Hz, 2H, CH_2Me), 3.42 (d, J=7.3 Hz, 2H, 4-CH_2), 4.10 (s, 2H, 1-CH_2), 5.58 (t, J=7.3 Hz, 1H, 3-H), 7.18–7.30 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2, 21.0, 33.5, 66.5, 124.3, 125.9, 128.3 (2C), 128.4 (2C), 141.0, 141.4; MS (FAB) *m*/*z* (%): 183 (MLi^+, 100); HRMS (FAB) calcd for $C_{12}H_{16}LiO$ (MLi^+): 183.1361; found: 183.1367.

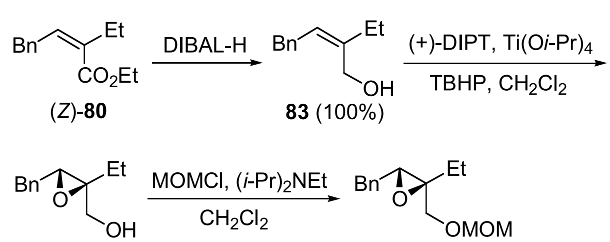
4.3.23. (2*R*,3*R*)-2,3-Epoxy-2-ethyl-4-phenylbutan-1-ol (82). By a procedure identical with that described for the synthesis of **74**, the alcohol **81** (4.41 g, 25.0 mmol) was converted into **82** (2.50 g, 52% yield) by the reaction with TBHP (2.6 M solution in toluene; 19.2 mL, 50.0 mmol), D-(−)-DIPT (0.80 mL, 3.75 mmol), Ti(O*i*-Pr)$_4$ (0.74 mL, 2.50 mmol), and molecular sieves 4A (1.5 g) at −30 °C for 5 h: colorless oil; $[\alpha]_D^{24}$ +12.3 (*c* 0.96, $CHCl_3$); IR (KBr) cm^{-1} 3434 (OH); ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, J=6.4 Hz, 3H, CMe), 1.42 (q, J=6.4 Hz, 2H, CH_2Me), 2.43 (br s, 1H, OH), 2.83 (dd, J=14.2, 6.4 Hz, 1H, 4-C*H*H), 2.90 (dd, J=14.2, 6.1 Hz, 1H, 4-CH*H*), 2.93–3.05 (m, 1H, 3-H), 3.74 (s, 2H, 1-CH_2), 7.22–7.34 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.2, 25.0, 36.1, 59.3, 69.0, 71.4, 124.9, 128.3 (2C), 128.8 (2C), 137.5; MS (FAB) *m*/*z* (%): 199 (MLi^+, 100); HRMS (FAB) calcd for $C_{12}H_{16}LiO_2$ (MLi^+): 199.1310; found: 199.1321.

4.3.24. (2*R*,3*R*)-*O*-Benzyl-2,3-epoxy-2-ethyl-4-phenylbutan-1-ol (49). By a procedure identical with that described for the synthesis of **30**, the alcohol **82** (0.76 g, 3.95 mmol) was converted into **49** (0.89 g, 80% yield) by the reaction with 60% NaH (174 mg, 4.35 mmol), (*n*-Bu)$_4$NI (148 mg, 0.40 mmol), and BnBr (0.52 mL, 4.37 mmol) at room temperature for 6 h: colorless oil; $[\alpha]_D^{24}$ +12.6 (*c* 0.98, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J=6.2 Hz, 3H, CMe), 1.32 (q, J=6.2 Hz, 2H, CH_2Me), 2.81 (dd, J=14.2, 6.4 Hz, 1H, 4-C*H*H), 2.92–3.04 (m, 1H, 4-CH*H*), 3.13–3.25 (m, 1H, 3-H), 3.48–3.59 (m, 2H, 1-CH_2), 4.54–4.62 (m, 2H, PhCH_2), 7.20–7.37 (m, 10H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.4, 24.5, 34.7, 59.8, 61.4, 69.9, 73.2, 126.0 (2C), 127.4 (2C), 128.5 (4C), 128.8 (2C), 136.9, 137.9; MS (FAB) *m*/*z* (%): 283 (MH^+, 13.3), 90 (100); HRMS (FAB) calcd for $C_{19}H_{23}O_2$ (MH^+): 283.1698; found: 283.1688.



82 **50** (82%)

4.3.25. (2*R*,3*R*)-2,3-Epoxy-2-ethyl-*O*-methoxymethyl-4-phenylbutan-1-ol (50). By a procedure identical with that described for the synthesis of **7**, the alcohol **82** (0.82 g, 4.27 mmol) was converted into **50** (0.83 g, 82% yield) by the reaction with MOMCl (0.97 mL, 12.8 mmol) and (*i*-Pr)$_2$NEt (3.73 mL, 21.4 mmol) at room temperature overnight: colorless oil; $[\alpha]_D^{26}$ +7.3 (*c* 1.02, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J=5.9 Hz, 3H, CMe), 1.36 (q, J=5.9 Hz, 2H, CH_2Me), 2.82 (dd, J=14.2, 6.4 Hz, 1H, 4-C*H*H), 2.93–3.05 (m, 1H, 4-CH*H*), 3.15–3.27 (m, 1H, 3-H), 3.36 (s, 3H, OMe), 3.50 (d, J=11.0 Hz, 1H, 1-C*H*H), 3.53 (d, J=11.0 Hz, 1H, 1-CH*H*), 4.59 (s, 2H, OCH_2O), 7.20–7.34 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.7, 24.8, 34.9, 56.1, 59.6, 61.7, 71.3, 96.8, 126.8, 128.5 (2C), 128.8 (2C), 137.7; MS (FAB) *m*/*z* (%): 237 (MH^+, 23), 151 (100); HRMS (FAB) calcd for $C_{14}H_{21}O_3$ (MH^+): 237.1491; found: 237.1487.

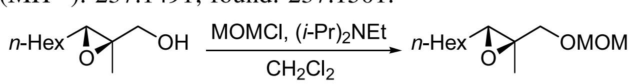


(*Z*)-**80** **83** (100%) **84** (52%) **51** (78%)

4.3.26. (*Z*)-2-Ethyl-4-phenylbut-2-en-1-ol (83). By a procedure identical with that described for the synthesis of **81**, the ester (*Z*)-**80** (7.10 g, 32.5 mmol) was converted into **83** (5.73 g, 100% yield) by the reaction with DIBAL-H (0.93 M solution in hexane; 105 mL, 97.6 mmol) at −78 °C for 1 h: colorless oil; IR (KBr) cm^{-1} 3319 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 1.07 (t, J=7.3 Hz, 3H, CMe), 1.28 (br s, 1H, OH), 2.21 (q, J=7.3 Hz, 2H, CH_2Me), 3.46 (d, J=7.9 Hz, 2H, 4-CH_2), 4.26 (s, 2H, 1-CH_2), 5.52 (t, J=7.9 Hz, 1H, 3-H), 7.17–7.30 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7, 27.8, 33.6, 60.3, 125.5, 125.9, 128.2 (2C), 128.4 (2C), 140.96, 141.02; MS (FAB) *m*/*z* (%): 183 (MLi^+, 100); HRMS (FAB) calcd for $C_{12}H_{16}LiO$ (MLi^+): 183.1361; found: 183.1360.

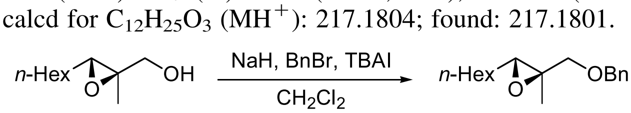
4.3.27. (2*S*,3*R*)-2,3-Epoxy-2-ethyl-4-phenylbutan-1-ol (84). By a procedure identical with that described for the synthesis of **74**, the alcohol **83** (3.52 g, 20.0 mmol) was converted into **84** (2.01 g, 52% yield) by the reaction with TBHP (2.6 M solution in toluene; 23.1 mL, 60.0 mmol), L-(+)-DIPT (0.64 mL, 3.00 mmol), Ti(O*i*-Pr)$_4$ (0.59 mL, 2.00 mmol), and molecular sieves 4A (1.3 g) at −20 °C for 12 h: colorless oil; $[\alpha]_D^{24}$ −21.6 (*c* 0.92, $CHCl_3$); IR (KBr) cm^{-1} 3440 (OH); ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, *J*=6.4 Hz, 3H, CMe), 1.44 (q, *J*=6.4 Hz, 2H, C*H*$_2$Me), 2.50 (br s, 1H, OH), 2.83 (dd, *J*=14.2, 6.1 Hz, 1H, 4-C*H*H), 2.91 (dd, *J*=14.2, 6.4 Hz, 1H, 4-CH*H*), 2.90–3.01 (m, 1H, 3-H), 3.80 (s, 2H, 1-CH_2), 7.21–7.34 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.2, 25.1, 36.1, 59.6, 69.4, 71.2, 124.9, 127.2 (2C), 128.0 (2C), 135.5; MS (FAB) *m/z* (%): 199 (MLi^+, 100); HRMS (FAB) calcd for $C_{12}H_{16}LiO_2$ (MLi^+): 199.1310; found: 199.1301.

4.3.28. (2*S*,3*R*)-2,3-Epoxy-2-ethyl-*O*-methoxymethyl-4-phenylbutan-1-ol (51). By a procedure identical with that described for the synthesis of **7**, the alcohol **84** (0.91 g, 4.73 mmol) was converted into **51** (0.87 g, 78% yield) by the reaction with MOMCl (1.08 mL, 14.2 mmol) and (*i*-Pr)$_2$NEt (4.13 mL, 23.7 mmol) at room temperature overnight: colorless oil; $[\alpha]_D^{24}$ −11.1 (*c* 1.06, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, *J*=5.9 Hz, 3H, CMe), 1.38 (q, *J*=5.9 Hz, 2H, C*H*$_2$Me), 2.83–2.96 (m, 1H, 4-C*H*H), 3.03 (dd, *J*=14.2, 6.1 Hz, 1H, 4-CH*H*), 3.17–3.29 (m, 1H, 3-H), 3.36 (s, 3H, OMe), 3.54 (d, *J*=11.0 Hz, 1H, 1-C*H*H), 3.58 (d, *J*=11.0 Hz, 1H, 1-CH*H*), 4.57 (s, 2H, OCH_2O), 7.21–7.33 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.7, 24.9, 35.2, 56.1, 59.4, 61.6, 71.0, 96.6, 126.9, 128.5 (2C), 128.8 (2C), 137.7; MS (FAB) *m/z* (%): 237 (MH^+, 15), 151 (100); HRMS (FAB) calcd for $C_{14}H_{21}O_3$ (MH^+): 237.1491; found: 237.1501.



85 **52** (89%)

4.3.29. (2*R*,3*R*)-2,3-Epoxy-*O*-methoxymethyl-2-methylnonan-1-ol (52). By a procedure identical with that described for the synthesis of **7**, the alcohol **85**[34] (1.50 g, 8.71 mmol) was converted into **52** (1.68 g, 89% yield) by the reaction with MOMCl (0.99 mL, 13.1 mmol) and (*i*-Pr)$_2$NEt (3.03 mL, 17.4 mmol) at room temperature overnight: colorless oil; $[\alpha]_D^{26}$ +14.4 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, *J*=6.9 Hz, 3H, CMe), 1.30–1.60 (m, 10H), 1.32 (s, 3H, CMe), 2.89 (t, *J*=6.0 Hz, 1H, 3-H), 3.37 (s, 3H, OMe), 3.52 (s, 2H, 1-CH_2), 4.64 (s, 2H, OCH_2O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 14.5, 22.5, 26.4, 28.2, 29.1, 31.7, 55.3, 59.4, 61.2, 72.0, 96.5; MS (FAB) *m/z* (%): 217 (MH^+, 100); HRMS (FAB) calcd for $C_{12}H_{25}O_3$ (MH^+): 217.1804; found: 217.1801.



85 **53** (95%)

4.3.30. (2*R*,3*R*)-*O*-Benzyl-2,3-epoxy-2-methylnonan-1-ol (53). By a procedure identical with that described for the synthesis of **30**, the alcohol **85**[34] (1.30 g, 7.55 mmol) was converted into **53** (1.88 g, 95% yield) by the reaction with 60% NaH (330 mg, 8.30 mmol), (*n*-Bu)$_4$NI (27.9 mg, 0.076 mmol), and BnBr (0.99 mL, 8.30 mmol) at room temperature for 4 h: colorless oil; $[\alpha]_D^{24}$ +18.2 (*c* 0.96, $CHCl_3$); IR (KBr) cm^{-1} 1603 (Ph); ^1H NMR (270 MHz, $CDCl_3$) δ 0.89 (t, *J*=6.9 Hz, 3H, CMe), 1.30–1.60 (m, 10H), 1.33 (s, 3H, CMe), 2.85 (t, *J*=6.0 Hz, 1H, 3-H), 3.43 (d, *J*=10.9 Hz, 1H, 1-C*H*H), 3.50 (d, *J*=10.9 Hz, 1H, 1-CH*H*), 4.52 (d, *J*=12.0 Hz, 1H, PhC*H*H), 4.58 (d, *J*=12.0 Hz, 1H, PhCH*H*), 7.24–7.38 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 14.5, 22.5, 26.4, 28.2, 29.1, 31.7, 59.6, 61.0, 73.0, 74.7, 127.4 (3C), 128.1 (2C), 137.9; MS (FAB) *m/z* (%): 263 (MH^+, 100); HRMS (FAB) calcd for $C_{17}H_{27}O_2$ (MH^+): 263.2011; found: 263.2020.

4.3.31. (±)-(1*R,2*R**,6*S**)-4,4,6-Trimethyl-2-(prop-2-enyl)-7-oxabicyclo[4.1.0]heptan-2-ol (86).** To a stirred mixture of isophorone oxide **16** (154 mg, 1.0 mmol) in THF (5 mL) was added dropwise allylmagnesium bromide (1.0 M in Et_2O; 1.5 mL, 1.5 mmol) at −78 °C, and the mixture was stirred for 4 h at room temperature. 5% HCl was added to the mixture, and diluted organic layer was separated and washed with $NaHCO_3$ and brine, and dried over $MgSO_4$. Concentration of the filtrate under reduced pressure gave an oily residue, which was purified by flash column chromatography over silica gel with hexane–EtOAc (5:1) to give, in the order of elution, **20** (33 mg, 17% yield) and **86** (109 mg, 56% yield). Compound **86**: colorless oil; IR (KBr) cm^{-1} 3477 (OH); ^1H NMR (500 MHz, $CDCl_3$) δ 0.87 (s, 3H, CMe), 1.02 (s, 3H, CMe), 1.24–1.27 (m, 1H, C*H*H), 1.33 (s, 3H, CMe), 1.36 (d, *J*=14.0 Hz, 1H, C*H*H), 1.53 (d, *J*=14.6 Hz, 1H, CH*H*), 1.64 (dd, *J*=14.6, 1.8 Hz, 1H, CH*H*), 1.66 (s, 1H, OH), 2.28 (dd, *J*=14.0, 6.7 Hz, 1H, 1′-C*H*H), 2.33–2.37 (m, 1H, 1′-CH*H*), 2.82 (s, 1H, 1-H), 5.12–5.17 (m, 2H, CH=C*H*$_2$), 5.75–5.83 (m, 1H, C*H*=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4, 28.9, 29.4, 31.8, 41.0, 42.8, 46.0, 61.5, 63.5, 69.9, 118.4, 132.8; MS (FAB) *m/z* (%): 219 (MNa^+, 18.7), 176 (100); HRMS (FAB) calcd for $C_{12}H_{21}O_2$ (MH^+): 197.1542; found: 197.1559.

Acknowledgements

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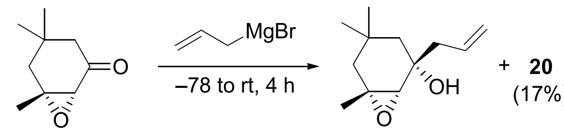
13. The stereochemistry of **20** is opposite to that of **86** which was obtained by the reaction with allylmagnesium bromide. This stereochemical outcome can be explained by the chelating ability of the titanium reagent to the oxygen atom of the epoxide, which allows the allylation of the ketone from the side of the epoxide oxygen.



16 **86** (56%)

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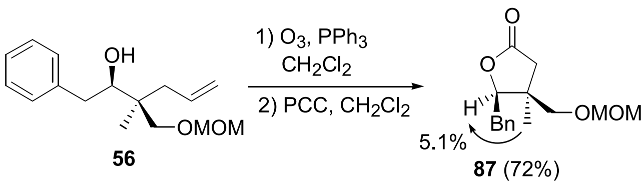
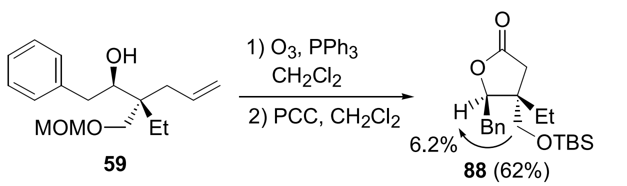
20. Only a relatively small NOE enhancement was observed between 4-H and the siloxymethyl group.
21. Halohydrin is one of the representative side products irrespective of the Grignard reagent used, the stereochemistry

of which is not determined. No stereo- or regioisomer of the allylated product was detected in the reaction mixture.

22. Relative stereochemistries of the quaternary carbons were determined by NOE experiment of the corresponding lactones. Typical examples are shown below.





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The reactivity of 1,1-diamino-2,2-dinitroethene (FOX-7)

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Abstract—The reactivity of 1,1-diamino-2,2-dinitroethene (DADNE) or FOX-7 was studied. Various reactions like cycloadditions, nitration, halogenation and acylation were performed in order to evaluate the reactivity of the C–C double bond and the amino moieties. Several products were isolated and two of them were characterised by X-ray analysis. Two reactive sites were identified. The chemical behaviour of DADNE is also discussed.
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1. Background

Latypov et al. was the first team to report the synthesis of DADNE;[1] an interesting energetic molecule with a density of 1.885 g/cm^3 and a heat of formation of 32 kcal/mol. DADNE was prepared by nitration of 2-methyl-imidazole with concentrated nitric and sulphuric acid to give a mixture of parabanic acid and 2-(dinitromethylene)-4,5-imidazolidinedione. This latter compound was further treated with aqueous ammonia solution to produce DADNE.

Based on the X-ray data[2] and acid–base properties[3] of DADNE, the molecule can be seen as a resonance hybrid between the mesomers **3** and **4** in equilibrium with the tautomers **1** and **2** (Scheme 1).

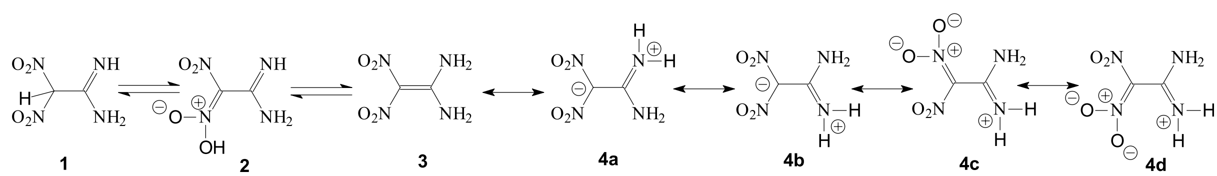
Consequently, it would be reasonable to imagine three types of reactions: nucleophilic substitution on the amine substituted carbon, addition to double-bonds and electrophilic attacks on either amino groups or the negatively charged carbon.

The first type of reaction has been thoroughly studied by Bellamy et al. by the treatment of DADNE with various different amines leading to mono and disubstituted derivatives.[4] Primary amines reacted with DADNE to afford *N*-substituted and *N*,*N*′-disubstituted-1,1-diamino-2,2-dinitroethene via transamination reactions. Treatment of DADNE with hydrazine led only to the monosubstituted product 1-amino-1-hydrazino-2,2-dinitro-ethene. Bellamy and co-workers highlighted the ability of DADNE to react by a so called push-pull mechanism.

2. Results and discussion

In this work, reactions between DADNE and various dipolar reactants and electrophiles have been explored (Scheme 2).

First, many attempts were carried out to test the DADNE's double bond character in presence of various dipolar reactants, which are known to react on ethylenic systems. Dipolar reactants like sodium azide,[5] substituted azide,



Scheme 1. Resonance hybrid of DADNE.

Keywords: Nitro compounds; Electrophilic reactions; Ethelenic compounds; Nitration.
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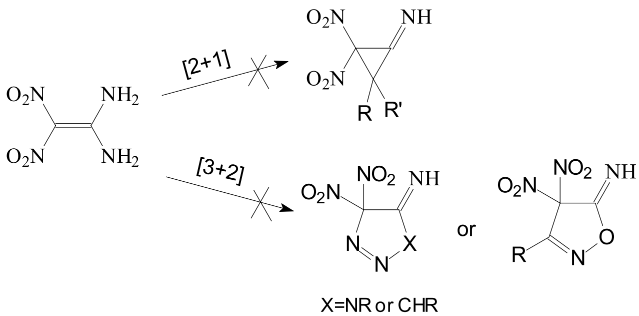


Scheme 2. Cycloaddition reactions on DADNE.

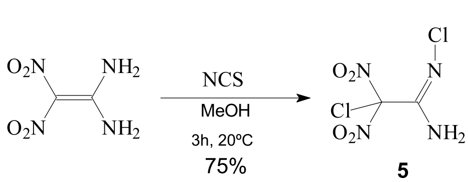
nitrile oxide[7] and diazomethane derivatives are known to undergo [3+2] cycloadditions on ethylene compounds.[8] Sodium azide either in acidic or neutral conditions did not react with DADNE. Grassivaro et al. showed that cycloaddition of substituted azides on polarized ethylenic compounds like 1,1-dialkylamino-2-nitro- ethenes were effective to afford 5-dialkylamino-1-substituted-1,2,3-triazoles.[6] However attempts to prepare the expected 1,2,3-triazole from benzyl azide and DADNE were unsuccessful. DADNE was recovered unchanged.

Benzyl nitrile oxide and ethyl diazoacetate did not either react with DADNE. After two days at ambient temperature in DMF DADNE and ethyl diazoacetate were recovered unchanged. Consequently no [3+2] cycloaddition on DADNE was observed despite various attempts.

[2+1] cycloadditions on DADNE were also studied (Scheme 2). Dichlorocarbenes generated in situ by different methods did not react with DADNE, even under ultrasound irradiation.[9] 'Pseudo' carbenes bearing both nucleophilic and electrophilic sites on the same carbon were tested. Chloroacetone and ethyl chloromalonate were expected to react with DADNE[10] but they did not afford cycloaddition products. Once again DADNE was recovered unchanged.

The reactivity towards electrophiles was implied by the work of Latypov et al.[1] who reacted oxalyl chloride with DADNE to afford 4,5-imidazolidinedione. As a poor nucleophile, DADNE was able to react with alkyl bromide only after a preliminary treatment by 2 equiv of strong base to deprotonate and enhance its nucleophilicity. Indeed it was shown that DADNE nucleophilicity was limited. We here report an extended study of DADNE reactivity towards electrophiles.

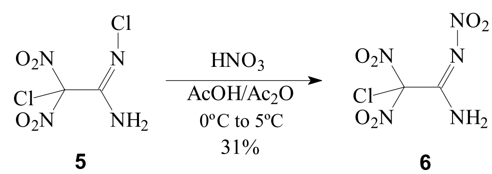
When DADNE reacted with *N*-chlorosuccinimide in methanol, a chlorinated product was obtained with a 75% yield (Scheme 3). The product was analysed by NMR and MS, which confirmed the addition of two chlorine atoms to the DADNE molecule.



Scheme 3. Chlorination of DADNE.

According to ^{15}N NMR data showing three different nitrogen signals, the structure **5** was suggested to be the correct one.

Attempts to grow a suitable single crystal for X-ray analysis failed. It was thus decided to prepare derivatives of this compound in order to definitely assess its structure. The nitrolysis of the dichloride compound **5** in nitric acid and in acetic acid led to the mono nitrated product **6** (Scheme 4).



Scheme 4. Preparation of a derivative of the chlorinated compound **5** by nitrolysis.

The compound **6** was characterised by X-ray analysis which clearly showed that the chlorine atom was linked to the C(1) dinitro-carbon (Fig. 1).

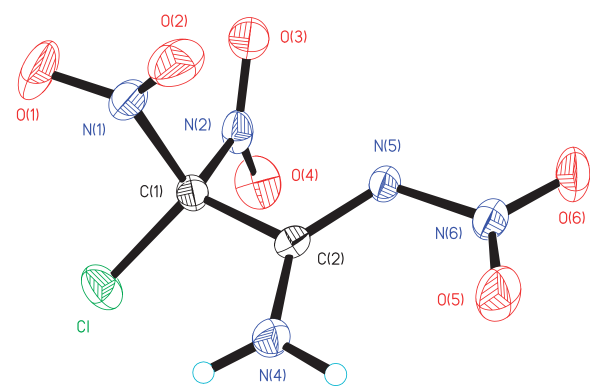
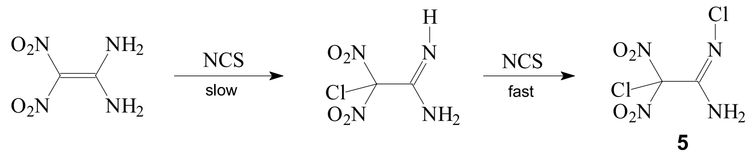


Figure 1. ORTEP plot of compound **6**.

X-ray data also showed an exact single C(1)–C(2) bond (1.53 Å) and a normal sp^3 hybridisation of C(1) with for instance a C(2)–C(1)–N(1) angle of 109°.

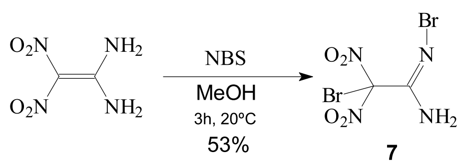
The C(2)–N(4) and C(2)–N(5) were shown to have the same bond length (1.31 Å), in-between a single and double bond. This means that the C(2)–N(4) bond had double character and also that the C(2)–N(5) bond was longer than an ordinary one (1.31 Å instead of 1.28 Å). The shortened bond lengths indicate delocalisation. We could notice a quite short C(1)–Cl bond (1.72 Å) and an unusual C(2)–C(1)–Cl angle (114° instead of 109°), possibly due to the electrostatic interaction between H(4B) and the chlorine atom or the repulsion between the chlorine atom and the nitro groups.

If the same chlorination reaction was carried out with only one equivalent of *N*-chlorosuccinimide, the resulting product was still the double substituted compound **5** and unreacted DADNE. This indicates that the second step of the chlorination is faster than the first one. A plausible mechanism for this reaction is shown in Scheme 5. Though, the order of the chlorination on the two sites was not checked by kinetic measurements.



Scheme 5. Probable DADNE chlorination mechanism.

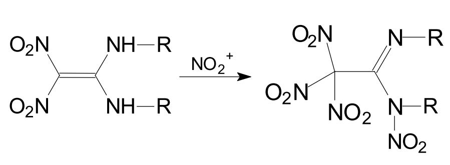
The bromination of DADNE was also attempted. The same conditions were applied with two equivalents of NBS. In analogy with the chlorination, the reaction yielded the dibrominated product **7** (Scheme 6). The reaction was complete in 3 h at ambient temperature.



Scheme 6. Bromination of DADNE.

The compound was analysed by MS, NMR spectroscopy and confirmed the expected structure. Its IR analysis showed a spectrum remarkably close to the respective dichloro compound **5** one. Both of the NH_2 signals (shape and assignments) coincided perfectly indicating that the amino group had the same environment and the same interactions. All the other main bands around 1600, 1300, 1000, and 800 cm^{-1} were also very close to the compound **5** with only slight frequency shifts indicating the same kind of bonds. Only two very weak bands at 676 and 573 cm^{-1} appeared in the brominated compound **7** spectrum, probably due to the bromine bonds vibrations, which are known to occur in this range. The analyses proved the formation of the dibrominated compound **7**, as previously shown for the dichloride compound **5**.

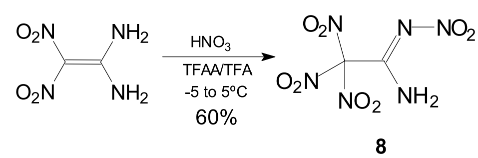
The previous results confirmed that DADNE is susceptible to react with electrophiles, vide supra. To extend this work the direct nitration of DADNE was studied. Relevant studies by Baum and Nguyen on the nitration of 1,1-diamino-alkylated-2,2-dinitroethenes[11] showed the formation of *N*,*N*′-dialkyl-*N*-nitro-2,2,2-trinitro-acetamidine derivatives (Scheme 7), but the nitration of DADNE itself has not been reported yet.



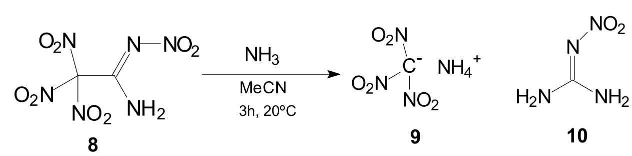
Scheme 7. Nitration of 1,1-diaminoalkylated-2,2-dinitroethenes.

The nitration of DADNE was studied in mixtures of nitric acid and acetic anhydride or trifluoroacetic anhydride, respectively. Both reactions yielded the same nitrated product (confirmed by IR and tlc). The reaction was much faster in trifluoroacetic anhydride media (60% yield within 1 h between −5 and 5 °C) than in acetic anhydride (2–3 h at 20 °C) (Scheme 8).

Analyses of the nitrated product **8** were difficult to perform due to its instability. The compound was analysed by DSC after purification on silica gel and found to decompose at 50 °C. Its decomposition was even observed at 20 °C, clearly seen as an evolution of nitrogen oxides, as a result of either impurities or inherent properties of the product. The purified product could be stored at −20 °C for a week. The structure of the nitrated compound was deduced from its reaction with ammonia in acetonitrile (Scheme 9). After work up this reaction afforded two stable products namely ammonium nitroformate **9** and mononitroguanidine (MNG) **10** in good yield (70% yield).



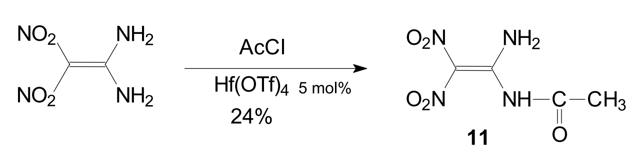
Scheme 8. Nitration of DADNE in trifluoroacetic anhydride.



Scheme 9. Ammoniac treatment of the nitrated DADNE derivative **8**.

Both compounds were identified by comparison with authentic samples (IR, UV and NMR). It is very probable that the halogenation and nitration occur by the same electrophilic mechanism.

Acylation attempts of DADNE were also performed and led to somewhat different results. DADNE was refluxed in acetyl chloride for 18 h, but unchanged DADNE was recovered. Kobayashi and co-workers showed the effectiveness of lanthanide triflates, as a Lewis acid catalyst in acylation reactions.[12,13] By adding 5 mol% of hafnium triflate in refluxing acetyl chloride, DADNE produced 23% of the monoacylated product **11** and several other unidentified compounds after 2–3 h (Scheme 10).



Scheme 10. Acetylation of DADNE.

The position of the acetyl group was checked by X-ray analysis (Fig. 2). The C(1)–C(2) bond length in the acylated compound was found to be 1.43 Å, which is close to the corresponding to the C–C bond in the starting material.

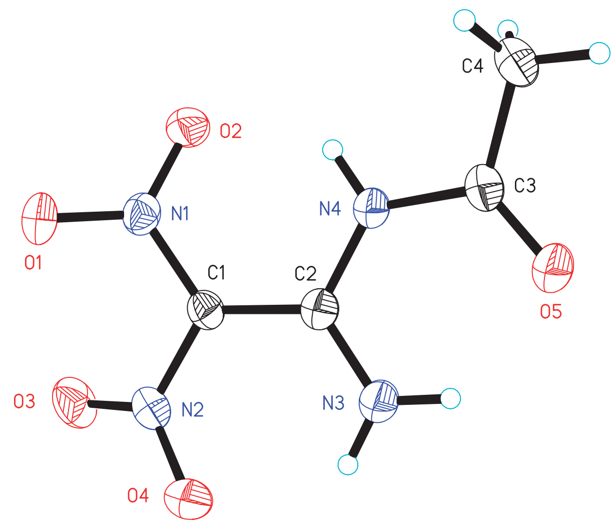


Figure 2. ORTEP plot of acetylated DADNE **11**.

C(2)–N(4) bond (1.37 Å) was longer than C(2)–N(3) bond (1.30 Å). The C(3)–O(5) bond seemed a normal carbonyl bond (1.21 Å) and the N(4)–C(3) bond was very close to a Csp^2–N formamide bond (1.39 Å instead of 1.38 Å). C(2)–N(4) in this molecule and the C–$NHNO_2$ in 1,2-dinitroguanidine (DNG) have the same lengths.[14] The same is true for the shortened C(2)–N(3) bond in the structure above, which is exactly the same as the corresponding C–NH_2 bond in DNG, thus indicating that the N(3)H_2 amino contrary to N(4)-Ac acetamide moiety still participates in the π-delocalisation on DADNE structure. The N(3)H_2 amino group had also two hydrogen bonds with nitro O(4) and with acetyl O(5). Hydrogen bonds may thus have limited the free amino rotation; ^{1}H NMR spectrum showed actually three different NH broad signals as a result of a differentiation of blocked N(3)–H protons.

3. Conclusions

Cycloadditions at the double bond with several reagents were unsuccessful. However, di-substituted derivatives of DADNE were formed by attacks of electrophiles on the dinitro-carbon and amidine nitrogen. The same behaviour towards electrophiles was observed by Baum et al. in their studies of 1,1-dialkylamino-2,2-dinitro-ethenes.[11] In our studies of nitrations we did observe the same phenomenon on the dinitro-carbon. The nitration of amidines is also known to give *N*-nitro substituted derivatives.[15] Thus these reactions of DADNE can be represented as consecutive electrophilic substitutions on the *gem*-dinitro-carbon and amidine moiety. The observed chemical behaviour might be explained by an imine structure of DADNE similar to the illustrated structure **2** (Fig. 1). This directs potential electrophile attacks on the *gem*-dinitro-carbon. This arrangement of the structure probably inhibits cycloadditions around the C–C double bond.

Nevertheless, this chemical behaviour towards electrophiles does not seem to be the only one. Acylated DADNE was a novel example and actually proved that amino moieties were able to react with very potent electrophiles induced for instance by powerful catalysts. We must add that the phenomenon may occur in severe experimental conditions and prove once again that the amino nucleophilicity is very limited.

These results together with X-ray data of DADNE prove that the real structure of the product is far from the assumption of enamines (resonance structure **3**). Probably tautomers **1**, **2** and resonance structure **4** are the main contributors to the reactivity of the molecule.

4. Experimental

Reagents were commercial grades from Aldrich and Acros Organics used as received. IR spectra were recorded on a Nicolet Avatar 320 FTIR instrument in dry KBr pellets. NMR spectra were recorded with a Bruker Avance 400 MHz machine fitted with a 10 mm broadband ATM probe. Chemical shifts were referred to TMS for ^{13}C and ^{1}H and to nitromethane for ^{14}N and ^{15}N. For compounds **6**, **7** and **8** ^{15}N NMR analyses, which require long time of acquisition, were not performed due to their respective thermal instability. Mass spectrometer is a Nermag R10-10H. Elemental analyses were performed with a NA2500 ThermoElectron Corporation apparatus. Thermal analysis equipment was a DSC 822 Mettler Toledo apparatus.

4.1. X-ray crystallography

Crystals of dimensions, 0.28×0.16×0.10 (**6**) and 0.70×0.10×0.04 (**11**) mm^3, were glued to a glass fibre. Intensity data were collected at room temperature with a Siemens SMART diffractometer equipped with a CCD two-dimensional detector [λ Mo Kα=0.71073 Å].

Slightly more than one hemisphere of data was collected in 1271 frames with ω scans (width of 0.30° and exposure time of 10 s per frame). Data reduction was performed with SAINT software. Data were corrected for Lorentz and polarization effects, and a semi-empirical absorption correction based on symmetry equivalent reflections was applied by using the SADABS program.[16] Lattice parameters were obtained from least-squares analysis of all reflections. The structure was solved by direct method and refined by full matrix least-squares, based on F^2, using the SHELX-TL software package.[17] All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were located with geometrical restraints in the riding mode.

4.1.1. Compound 6. Crystal structure analysis: orthorhombic, space group *Pbca*; dimensions $a=6.0843(2)$ Å, $b=10.6128(5)$ Å, $c=24.2030(8)$ Å, $V=1562.8(1)$ Å^3; $Z=8$; total reflections collected: 9888; independent reflections: 2097 (1349 $F_o>4\sigma(F_o)$); a hemisphere of data was collected up to a $2\Theta_{max}$ value of 59.46° (94.0% coverage). Number of variables: 135; $R_1=0.0608$, $wR_2=0.1192$, $S=1.065$; highest residual electron density 0.342 e Å^{-3}.

4.1.2. Compound 11. Crystal structure analysis: monoclinic, space group *P*2(1)/*c*; dimensions $a=9.7808(6)$ Å, $b=4.6112(2)$ Å, $c=18.9990(9)$ Å, $\beta=117.412(2)°$, $V=$

760.67(7) Å^3; $Z=4$; total reflections collected: 3814; independent reflections: 1341 ($947F_o>4\sigma(F_o)$); a hemisphere of data was collected up to a $2\Theta_{max}$ value of 49.96° (100% coverage). Number of variables: 124; $R_1=0.0549$, $wR_2=0.1391$, $S=1.046$; highest residual electron density 0.328 e Å^{-3}.

Crystallographic data for the structural analysis have been deposited at the Crystallographic Data Centre, CCDC 264136–264137 for compounds **6** and **11**. Copies of this information may be obtained free of charge from the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

4.2. Caution

All polynitro compounds described in this paper are explosive and sensitive to shocks, frictions and sparkles. Certain compounds are unstable and may decompose at ambient temperature. Proper shielding is strongly recommended.

4.2.1. 1-Chloro-1,1-dinitro-2-(*N*-chloroamidino)-ethane 5. DADNE (0.50 g, 3.4 mmol) was placed in methanol (30 mL). The yellow suspension was stirred at 20 °C and then *N*-chlorosuccinimide was quickly added (0.90 g, 6.8 mmol). The mixture was stirred 3 h until it was colourless and limpid. Dichloromethane was added (120 mL) and the organic layer was washed six times with 30 mL, 0.4 M sodium hydrogenocarbonate solution. 0.46 g of white solid (75% yield) was yielded. Mp 90 °C; ^{1}H NMR ($CDCl_3$) $\delta=5.87$ (s, broad). ^{13}C NMR ($CDCl_3$) $\delta=118.1$, 153.7 ppm. ^{14}N NMR ($CDCl_3$) $\delta=-27$ (NO_2). ^{15}N NMR ($CDCl_3$) $\delta=-304$ (NH_2), -158 (C=N), -27 (NO_2) ppm. IR (KBr) 3435, 3327, 1647, 1605, 1384, 1348, 1300, 1055, 957, 834, 792, 776, 623, 452 cm^{-1}. MS (EI): $m/z=216$ (3), 170 (8); MS (CI$^+$, NH_3): $m/z=217$ (5), 171 (100); elemental analysis calcd (%): C 11.1, H 0.9, N 25.8, O 29.5, Cl 32.7; found: C 12.0, H 1.0, N 25.5, O 27.7, Cl 33.8.

4.2.2. 1-Bromo-1,1-dinitro-2-(*N*-bromooamidino)-ethane 7. The same procedure as above was used. 53% yield. Mp 71 °C; ^{1}H NMR (acetone) $\delta=7.59$ (s, broad). ^{13}C NMR (acetone) $\delta=113.0$, 157.6 ppm. ^{14}N NMR (acetone) $\delta=-24$ (NO_2). IR (KBr) 3430, 3328, 1634, 1595, 1384, 1325, 1296, 1025, 925, 829, 786, 753, 676, 623, 444 cm^{-1}. MS (CI$^+$, NH_3): $m/z=343$ (6), 341 (12), 339 (6), 326 (11), 324 (21), 322 (11); MS (CI$^-$, NH_3): $m/z=307$ (12) 305 (23), 303 (12), 225 (62).

4.2.3. 1-Chloro-1,1-dinitro-2-(*N*-nitramidino)-ethane 6. In a 50 mL round stirred flask containing nitric acid (1.50 g), acetic acid (1.34 g) was added drop wise at 0–5 °C. Acetic anhydride (2.08 g) was then slowly added drop wise at 0–5 °C. 1-Chloro-1,1-dinitro-2-(*N*-chloroamidino)-ethane (0.400 g) was introduced by small portions within 15 min at 0 °C. The mixture was stirred, maintained between 0 and 5 °C for 1 h and finally poured into ice (60 g). When the mixture reached 20 °C, it was filtered. The filtrate was evaporated to dryness under vacuum. The residual solid was dried over P_2O_5, washed several times with dichloromethane. A white solid product was yielded (31%). Mp 129 °C; ^{1}H NMR (acetone) $\delta=9.67$ (s, broad). ^{13}C NMR (acetone) $\delta=121.0$, 155.9 ppm. ^{14}N NMR (acetone) $\delta=-279$ (broad, NH_2), -27 (C–NO_2), -23 (N–NO_2). IR (KBr) 3388, 3253, 1637, 1623, 1599, 1578, 1509, 1384, 1264, 1103, 791 cm^{-1}. MS (CI$^+$, NH_3): $m/z=245$ (7), 170 (8); MS (CI$^-$, NH_3): $m/z=226$ (100).

4.2.4. 1-Amino-1-*N*-acetylamino-2,2-dinitroethene 11. DADNE (0.74 g, 5 mmol) was introduced in refluxing acetyl chloride. Hafnium trifluoro-methanesulfonate (0.19 g, 0.25 mmol) was added. The mixture was stirred 3 h and became dark red, filtrated and evaporated to dryness under vacuum. The crude product was purified by chromatography on silica gel (Et_2O). The product was then crystallised with acetone/hexane (10:80, v/v) to afford a yellow solid product (0.170 g, 24% yield). Mp 132–133 °C; ^{1}H NMR (acetone) $\delta=2.44$ (s, 3H) 9.45 (s, 1H), 10.40 (s, 1H), 11.28 (s, 1H). ^{13}C NMR (acetone) $\delta=132.6$, 152.6, 175.1, 25.8 ppm. ^{14}N NMR (acetone) $\delta=-24$ (NO_2). IR (KBr) 3365, 3237, 1764, 1713, 1632, 1570, 1527, 1463, 1371, 1239, 1201, 1167, 1046, 787, 750, 660, 568 cm^{-1}. MS (EI): $m/z=190$ (6), 147 (8), 144 (10), 43 (100); MS (CI$^+$, NH_3): $m/z=191$ (12), 208 (100), 225 (5).

4.2.5. 1,1,1-Trinitro-2-*N*-nitramidinoethene 8. Trifluoroacetic acid (16 mL) was introduced drop wise in nitric acid (8.88 g) at 0 °C. Trifluoroacetic anhydride (24 mL) was added drop wise at 0 °C. The mixture was stirred 10 min and reached -5 °C. DADNE (1.600 g, 10.8 mmol) was added in one portion. The mixture was stirred until the temperature reached 5 °C. The mixture was cool (-5 °C) and filtrated. The solid product was washed twice with very small amounts of cold dichloromethane (-20 °C). The product was poured into 100 mL of cold ethyl acetate (-20 °C). The organic layer was washed with 30 mL of cold water (0 °C), dried over sodium sulphate and concentrated under vacuum ($T=20$ °C). A yellow oil (2.63 g) was yielded. The product was purified by chromatography on silica gel ($CHCl_3$/MeCN, 20:12). 1.53 g of pale brown oil was yielded (60% yield). Acetonitrile traces remained even after evaporation under good vacuum. Decomposition temp. 50 °C (8 °C/min DSC); ^{13}C NMR (acetone) $\delta=125.3$, 151.0 ppm. ^{14}N NMR (acetone) $\delta=-34$ (C–NO_2), -22 (N–NO_2). IR (KBr) 1628, 1586, 1577, 1508, 1459, 1326, 1285, 1252, 846, 804 cm^{-1}.

4.2.6. Reaction of 1,1,1-triamino-2-*N*-nitramidinoethene 8 with ammonia. 1,1,1-Triamino-2-*N*-nitramidinoethene (0.36 g, 1.5 mmol) was dissolved in acetonitrile (6 mL). A low stream of ammonia slowly bubbled into the mixture. It was stirred for 3 h at ambient temperature. It became deep yellow and a white solid (110 mg, 70% yield) was filtered and washed four times with acetone (3 mL). Mp 210 °C; ^{1}H NMR (DMSO) $\delta=7.64$ (s, broad), 11.54 (s, 1H). ^{13}C NMR (DMSO) $\delta=160.8$ ppm. ^{14}N NMR (DMSO) $\delta=-12$ (NO_2). IR (KBr) 3452, 3397, 3345, 3279, 3201, 1665, 1637, 1527, 1407, 1302, 1151, 1044, 743, 724, 644, 568, 476 cm^{-1}; UV λ_{max} 265 nm.

The yellow filtrate was concentrated and ammonium nitroformate **9** was purified by chromatography on silica gel ($CHCl_3$/MeCN, 2:1). A yellow solid was yielded (70%).

^{1}H NMR (DMSO) $\delta=7.45$ (s, broad); ^{13}C NMR (DMSO) $\delta=151.1$ ppm. ^{14}N NMR (DMSO) $\delta=-31$ (NO_2), -363 (NH_4^+). IR (KBr) 3231, 1534, 1481, 1411, 1277, 1172, 792, 736 cm^{-1}; UV λ_{max} 350 nm; MS (CI^-, NH_3): $m/z=167$ (52).

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[1,2] Boc migration during pyroglutamate alkylations

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Abstract—Treatment of *N*-Boc protected pyroglutamates with strong bases lead to a Boc migration from the N-atom to the C2 position when no or poor electrophiles are being used.
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1. Introduction

Pyroglutamates and their syntheses have received a lot of attention over the years because of their importance in several domains. Pyroglutamic acid is a very useful and versatile starting material for the synthesis of both natural and unnatural products. Intensive study of glutamate analogues resulted in specific inhibitors of different receptor types of the mammalian central nervous system.[1] It has also been used for the synthesis of pyrrolidine alkaloids,[2] kainoids,[3] (−)-bulgecinine,[4] (−)-domoic acid,[5] enantiomerically pure glycine and proline derivatives,[6] a wide variety of non-proteinogenic amino acids,[7] etc.

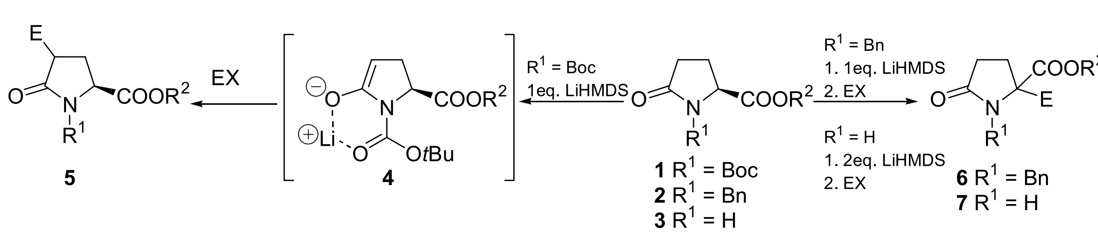
Alkylation of pyroglutamates has therefore been essential in order to expand the range of glutamate analogues and to study their biological properties. The attractiveness of pyroglutamates as a building block lies in the fact that the site of alkylation can be directed by changing the protecting group on *N* (Scheme 1). Alkylation of *N*-Boc protected pyroglutamates **1** results in C4 functionalized derivatives **5** whereas alkylation of *N*-benzyl **2** or N-unprotected **3** pyroglutamates occurs at the 2-position, resulting in **6** and **7**.[8]

The regioselectivity of the alkylation of *N*-Boc protected pyroglutamates was explained by the formation of a stabilized Li-salt **4** which directs the alkylation to the 4-position. This stabilized intermediate cannot be formed in *N*-benzyl or N-unprotected derivatives, thus resulting in alkylation at the 2-position.

This proves that the Boc protecting group plays a crucial role in pyroglutamate chemistry. The reactivity of this carbamate group, however, is often an underestimated feature. There are numerous reports of cases where the Boc group reacts as an electrophile or a nucleophile, resulting in unexpected and often undesired side reactions.[9]

2. Results and discussion

During an ongoing project on the synthesis of 2,4-methanoproline **9**,[10] pyroglutamate derivative **8** was



Scheme 1.

Keywords: Boc migration; Pyroglutamate; Alkylation; Carbamates.
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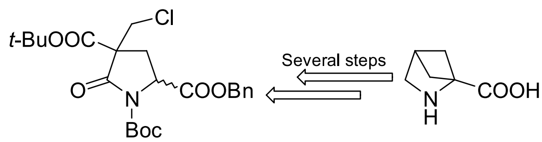


8 9

Scheme 2.

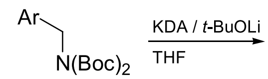
synthesized,[11] as a possible precursor for this interesting amino acid (Scheme 2).

It was observed however, that treating **8** with 1.5 equiv of LiHMDS did not lead to the envisaged 2-azabicyclo[2.1.1]-hexane skeleton, although the starting material was completely converted to a new product. In the ^{1}H-spectrum, the CH proton at the C2-position had disappeared and the remaining CH_2 of the ring was reduced from a ABX-system to a AB-system. Furthermore a broad singlet appeared around 6.41 ppm, which is typical for a NH proton of an amide. In the ^{13}C-spectrum the carbonyl of the Boc group, which is normally around 150 ppm was missing, but two *t*-Butyl groups were still present. Taking all this information into account, structure **10** was deduced, proving that the Boc-group migrated from the N-atom to the C2 position.

The proposed mechanism is depicted in Scheme 3. The formed anion at the 2-position is unreactive towards the chloromethyl group, probably because of the high ring strain involved in the formation of a four-membered ring within a five-membered ring, combined with the planar character of the lactam functionality. However, at room temperature the anion is reactive enough to attack the adjacent *N*-Boc group. The formed bicyclic intermediate **11** is not stable and opens again to form **10** upon work up.

Although there are reports of the Boc moiety reacting as an electrophile, these reactions are usually limited to intramolecular attacks by oxygen or nitrogen nucleophiles.[9] In the literature, only two cases of intramolecular attack on a Boc group by a carbon nucleophile followed by Boc migration were reported. Snieckus mentioned the migration of the Boc group from N to the *ortho* carbon atom of aniline derivatives after directed *ortho* metallation leading to anthranilate esters.[12] Kise et al. described that the reaction of *N*,*N*-di-Boc-protected benzylamines **12** with KDA/*t*-BuOLi at −78 °C gave *N*-Boc protected *t*-Butyl phenylglycines **13** (Scheme 4).[13]

These examples show the Boc migration under quite extreme reaction conditions, whereas in the case of pyroglutamate alkylation, the Boc migration can really compete with the alkylation reaction. In order to investigate the generality of this reaction, a number of pyroglutamate



12 13

Scheme 4.

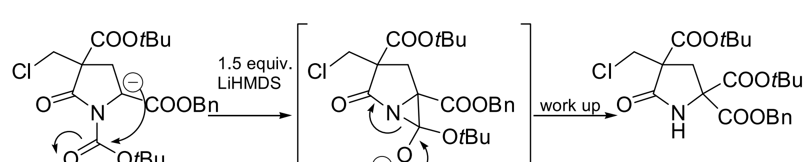
derivatives were synthesized and subjected to the same reaction conditions (Table 1). In this way, we found that esters with a varying substitution pattern underwent the same reaction. Although deprotonation of the pyroglutamates in entries b and h could result in theory in intramolecular substitution of the chloride with formation of a six-membered ring, only the [1,2] Boc migrated product was observed. When there is no or only one substituent present on the C4 position, a double amount of base is needed since the first equivalent is consumed in deprotonating this position. In this case, the Boc migration occurs via a dianion. Some of the Boc migrated products proved to be quite unstable on silica gel during purification (e.g., entries g and h), leading to a substantial loss of material.

When no substituent is present on the C4 position (entries i and j), no Boc migration was observed. Instead, the ring-opened products were isolated. Apparently, in these cases, the formed dianions are unstable and the esters fragment with formation of alkoxide anions. These anions in turn attack another pyroglutamate molecule and induce ring-opening with formation of racemic glutamate derivatives **15i**, **j** (no optical rotation). In this fashion, the yield is limited to 50% and explains the low yield of the isolated products.

In summary, we have shown that deprotonation of *N*-Boc protected pyroglutamates at the C2 position can result in the [1,2] Boc migration in the absence of good electrophiles resulting in the formation of functionalized γ-lactam *gem* dicarboxylates. This is the first example of an intramolecular nucleophilic attack of an ester enolate onto a Boc-protecting group. Not only should this side reaction be taken into account when working with pyroglutamates, γ-lactam *gem* dicarboxylates are useful intermediates in organic synthesis.[14]

3. Experimental

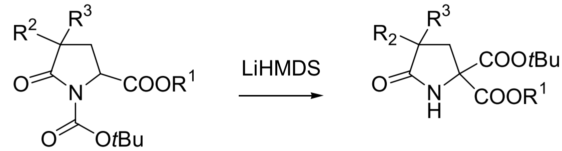
High-resolution ^{1}H NMR (270 MHz) and ^{13}C NMR (68 MHz) spectra were run with a Jeol JNM-EX 270 NMR spectrometer or on a Jeol JNM-EX 300 NMR. Peak assignments were obtained with the aid of DEPT, 2D-HETCOR, 2D-COSY spectra. The compounds were diluted in deuterated solvents and the used solvent is indicated for each compound. Mass spectra were recorded on a Varian



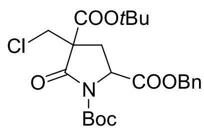
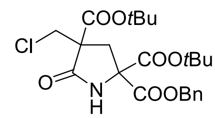
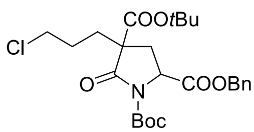
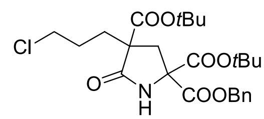
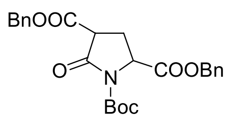
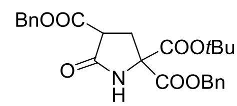
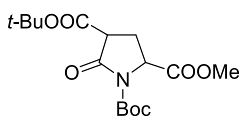
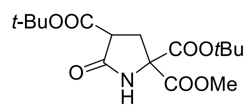
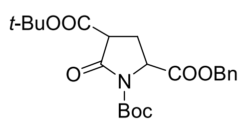
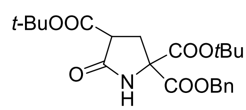
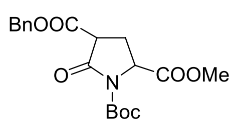
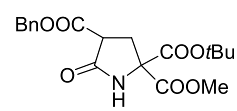
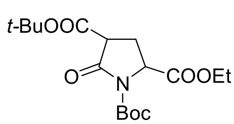
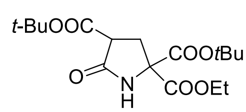
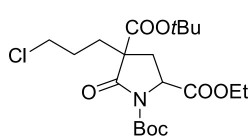
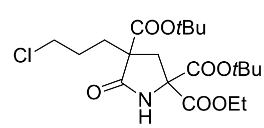
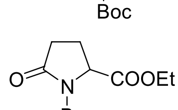
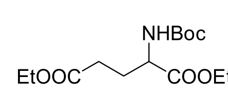
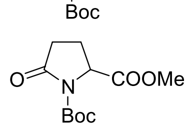
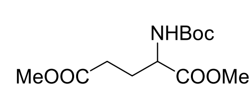
8 11 10

Scheme 3.

Table 1. [1,2] Boc migration observed for different *N*-Boc protected pyroglutamates upon treatment with LiHMDS in THF



14 **15**

Entry	Substrate	LiHMDS (equiv)	Product	Conversion[a]	Yield[b]
a		1.5		100%	61%
b		1.5		91%	64%
c		3		90%	72%
d		3		82%	56%
e		3		86%	62%
f		3		81%	69%
g		3		79%	[c]
h		1.5		91%	[c]
i		3		77%	36%
j		3		71%	32%

[a] Conversion determined by ^{1}H NMR on the crude reaction mixture.
[b] Yield after purification by flash chromatography.
[c] The product could not be obtained in sufficient purity.

MAT 112 spectrometer (70 eV), using either GC–MS coupling or a direct inlet system. Some volatile samples were recorded on an HP 6890 GC coupled with a HP 5973 MSD (Mass selective detector; quadrupole). Mass spectra of molecules with a high molecular weight were recorded on an Agilent 1100 Series VS (ES, 4000 V) mass spectrometer. IR-spectra were obtained from a Perkin–Elmer Spectrum One infrared spectrometer. For liquid samples, the spectra were collected by preparing a thin film of compound between two sodium chloride plates. The crystalline compounds were mixed with potassium bromide and pressed until a transparent potassium bromide plate was obtained. Melting points of crystalline compounds were measured with a Büchi 540 apparatus and are uncorrected. The elemental analysis was performed on a Perkin–Elmer 2400 Elemental Analyzer. The purification of reaction mixtures was performed by flash chromatography using a glass column with silica gel (Across, particle size 0.035–0.070 mm, Pore diameter ca. 6 nm).

4-Alkoxycarbonyl-2-alkyl-1-*t*-butyl 5-oxo-1,2,4-pyrrolidinetricarboxylates (**14c**, **14d**, **14e**, **14f**, **14g**) were prepared following the literature procedure.[11]

3.1. General procedure for the alkylation of 2,4-dialkyl 1-*t*-butyl 5-oxo-1,2,4-pyrrolidinetricarboxylate at the 4-position

In a classical experiment, 1 g of 2-benzyl 1,4-di-*t*-butyl 5-oxo-1,2,4-pyrrolidinetricarboxylate (2.3 mmol) was dissolved in 10 ml of dry THF and kept under a positive N_2-pressure. 0.29 g of KO*t*Bu (1.1 equiv) was added and the mixture was stirred for 30 min after which the electrophile (2 equiv) was added. The reaction mixture was subsequently refluxed overnight. After cooling, the solution was poured in water and extracted with diethyl ether. The organic layers were combined and dried with $MgSO_4$. Filtering off the drying agent and evaporating the solvent led to a mixture which was purified by chromatography to remove the excess of electrophile.

3.1.1. 2-Benzyl 1,4-di-*t*-butyl 4-(chloromethyl)-5-oxo-1,2,4-pyrrolidinetricarboxylate (14a). The reaction was performed on 2.3 mmol of starting material. Chloroiodomethane was used as electrophile (yield=58%, major/minor 53/47). The product was obtained as a white powder.

^{1}H NMR (270 MHz, $CDCl_3$) δ: *major*: 1.41 (9H, s, *t*-Bu), 1.42 (9H, s, *t*-Bu), 2.54 (1H, dd, J=13.9, 10.2 Hz, CH_aH$_b$ ring), 2.81 (1H, dd, J=13.9, 2.6 Hz, CH$_a$$H_b$ ring), 3.83 (1H, d, J=11.2 Hz, CH_aH$_b$Cl), 3.96 (1H, d, J=11.2 Hz, CH$_a$-H_bCl), 4.69 (1H, dd, J=10.2, 2.6 Hz, CH ring), 5.15 (1H, d, J=12.2 Hz, CH_aH$_b$Ph), 5.26 (1H, d, J=12.2 Hz, CH$_a$$H_b$-Ph), 7.35−7.38 (5H, m, CH, Ph). *Minor*: 1.43 (9H, s, *t*-Bu), 1.47 (9H, s, *t*-Bu), 2.22 (1H, dd, J=13.3, 6.9 Hz, CH_aH$_b$ ring), 2.87 (1H, dd, J=13.9, 8.9 Hz, CH$_a$$H_b$ ring), 3.80 (1H, d, J=11.3 Hz, CH_aH$_b$Cl), 3.99 (1H, d, J=11.3 Hz, CH$_a$-H_bCl), 4.69 (1H, dd, J=9.0, 6.9 Hz, CH ring), 5.21 (1H, d, J=12.5 Hz, CH_aH$_b$Ph), 5.23 (1H, d, J=12.5 Hz, CH$_a$$H_b$-Ph), 7.35–7.38 (5H, m, CH, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 27.64 (*t*-Bu), 27.73 (*t*-Bu), 28.77 (CH_2 ring), 29.29 (CH_2 ring), 45.30 (CH_2Cl), 47.08 (CH_2Cl), 56.39 (CH, ring), 56.78 (CH, ring), 59.19 (C$_{quat.}$, C4), 59.55 (C$_{quat.}$, C4), 67.46 (CH_2Ph), 67.55 (CH_2Ph), 84.06 (C$_{quat.}$, *t*-Bu), 84.15 (C$_{quat.}$, *t*-Bu), 84.47 (C$_{quat.}$, *t*-Bu), 128.50 (CH), 128.53 (CH), 128.61 (CH), 128.71 (CH), 134.82 (C$_{quat.}$, Ph), 135.09 (C$_{quat.}$, Ph), 148.80 (C=O, Boc), 165.87 (C=O), 166.50 (C=O), 167.92 (C=O), 169.93 (C=O), 170.71 (C=O). IR (cm^{-1}) ν_{max}: (KBr) 1782, 1742. MS: *m*/*z* (%): (ES, Pos) no M$^+$, 314 (12), 312 (28), 91 (100). Chromatography: Hex/EtOAc 80/20 R_f=0.22 and 0.19. Mp 89.2–90.3 °C. Anal. Calcd $C_{23}H_{30}ClNO_7$: C 59.03%, H 6.46%, N 2.99%; found: C 58.89%, H 6.56%, N 3.10%.

3.1.2. 2-Benzyl 1,4-di-*t*-Butyl 4-(3-chloropropyl)-5-oxo-1,2,4-pyrrolidinetricarboxylate (14b). The reaction was performed on 2.3 mmol of starting material. 3-Bromo-1-chloro-propane was used as electrophile (yield =82%, major/minor 54/46). The product was obtained as a white powder.

Major. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.44 (9H, s *t*-Bu), 1.45 (9H, s, *t*-Bu), 1.37–1.5 (2H, m, CH_2CH$_2$CH$_2$Cl), 1.79–1.88 (2H, m, CH$_2$CH_aH$_b$CH$_2$Cl+CH_aH$_b$ ring), 2.05–2.14 (1H, m, CH$_2$CH$_a$$H_bCH_2$Cl), 2.76 (1H, dd, J=13.5, 8.9 Hz, CH$_a$$H_b$ ring), 3.46 (2H, t, J=5.9 Hz, CH$_2$Cl), 4.64 (1H, dd, J=8.9, 7.3 Hz, CH ring), 5.19 (1H, d, J=12.0 Hz, CH_aH$_b$-Ph), 5.22 (1H, d, J=12.0 Hz, CH$_a$$H_b$Ph), 7.37 (5H, s, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 27.60 ($CH_2CH_2CH_2$), 27.78 (*t*-Bu), 30.67 ($CH_2CH_2CH_2$), 31.18 (CH_2 ring), 44.64 (CH_2Cl), 56.85 (CH, C2), 56.99 (C$_{quat.}$, C4), 67.51 (CH_2Ph), 83.22 (C$_{quat.}$, *t*-Bu), 84.15 (C$_{quat.}$, *t*-Bu), 128.71 (CH), 128.77 (CH), 134.86 (C$_{quat.}$, Ph), 149.09 (C=O, Boc), 168.68 (C=O), 170.58 (C=O), 170.92 (C=O). IR (cm^{-1}) ν_{max}: 1793, 1724. MS: *m*/*z* (%): (ES, Pos) no M$^+$, 342 (17), 340 (50), 91 (100). Chromatography: Hex/EtOAc 80/20 R_f=0.27. Mp 79.2–83.1 °C. Anal. Calcd $C_{25}H_{34}ClNO_7$: C 60.54%, H 6.91%, N 2.82%; found: C 60.40%, H 6.99%, N 2.89%.

Minor. ^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.36–1.50 (1H, m, CH_aH$_b$CH$_2$CH$_2$Cl), 1.41 (9H, s, *t*-Bu), 1.42 (9H, s, *t*-Bu), 1.64–1.87 (2H, m, CH$_a$$H_bCH_2CH_2$Cl+CH$_2CH_aH_bCH_2$Cl), 2.13–2.25 (1H, m, CH$_2$CH$_a$$H_bCH_2$Cl), 2.17 (1H, dd, J=13.5, 9.9 Hz, CH_aH$_b$ ring), 2.82 (1H, dd, J=13.5, 2.0 Hz, CH$_a$$H_b$ ring), 3.52 (2H, t, J=5.8 Hz, CH$_2$Cl), 4.61 (1H, dd, J=9.9, 2.0 Hz, CH ring), 5.12 (1H, d, J=12.0 Hz, CH_aH$_b$-Ph), 5.24 (1H, d, J=12.0 Hz, CH$_a$$H_b$Ph), 7.34–7.38 (5H, m, CH, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 27.69 (*t*-Bu), 27.74 (*t*-Bu), 27.92 ($CH_2CH_2CH_2$), 30.98 (CH_2 ring), 33.24 ($CH_2CH_2CH_2$), 44.47 (CH_2Cl), 56.24 (CH, C2), 56.73 (C$_{quat.}$, C4), 67.42 (CH_2Ph), 83.16 (C$_{quat.}$, *t*-Bu), 83.83 (C$_{quat.}$, *t*-Bu), 128.48 (CH), 128.54 (CH), 128.61 (CH), 135.09 (C$_{quat.}$, Ph), 149.09 (C=O, Boc), 167.94 (C=O), 170.19 (C=O), 170.22 (C=O). IR (cm^{-1}) ν_{max}: 1792, 1725. MS: *m*/*z* (%): (ES, Pos) no M$^+$, 342 (15), 340 (45), 91 (100). Chromatography: Hex/EtOAc 80/20 R_f=0.19. Mp 91.5–93.0 °C. Anal. Calcd $C_{25}H_{34}ClNO_7$: C 60.54%, H 6.91%, N 2.82%; found: C 60.42%, H 7.11%, N 2.88%.

3.1.3. 1,4-Di-*t*-Butyl 4-(3-chloropropyl) 2-ethyl 5-oxo-1,2,4-pyrrolidinetricarboxylate (14h). The reaction was performed on the diastereoisomeric mixture of **14g**. 3-Bromo-1-chloro-propane was used as electrophile (yield=80%, major/minor 52/48). The product was obtained as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 1.41–1.55 (1H, m, CH_AH$_B$CH$_2$CH$_2$Cl); 1.45 (9H, s, *t*-Bu); 1.46 (9H, s, *t*-Bu); 1.50 (9H, s, *t*-Bu); 1.71–1.80 (2H, m, CH$_A$$H_BCH_2CH_2$Cl+CH$_2CH_AH_BCH_2$Cl); 1.82–1.91 (2H, m, CH$_2$CH_AH$_B$CH$_2$Cl+CH-$_A$H$_B$ ring); 2.11–2.25 (1H, m, CH$_2$CH$_A$$H_BCH_2$Cl); 2.11–2.25 (2H, m, CH$_2$CH$_A$$H_BCH_2$-Cl+C$H$-$_AH_B$ ring); 2.78 (1H, dd, J=13.5, 8.5 Hz, CH$_A$$H_B$

ring); 2.80 (1H, dd, $J=14.1$, 2.5 Hz, CH-$_A$$H_B$ ring); 3.53 (2H, t, $J=6.1$ Hz, CH_2Cl); 3.53 (2H, t, $J=6.0$ Hz, CH_2Cl); 4.13–4.29 (2H, m, CH_2CH_3); 4.13–4.29 (2H, m, CH_2CH_3); 4.55 (1H, dd, $J=10.0$, 2.1 Hz, CH ring); 4.59 (1H, dd, $J=8.6$ Hz, $J=7.7$ Hz, CH ring). ^{13}C NMR (75 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 14.13 (CH_2CH_3–); 14.13 (CH_2CH_3–); 27.72 (*t*-Bu); 27.84 (*t*-Bu); 27.95 (CH_2CH_2-CH_2); 28.29 (CH-$_2CH_2CH_2$); 30.97 ($CH_2CH_2CH_2$); 31.16 (CH_2 ring, C3); 31.29 (CH_2 ring, C3); 33.32 ($CH_2CH_2CH_2$); 44.47 (CH-$_2$Cl); 44.70 (CH_2Cl); 56.21 (CH ring, C2); 56.71 (C_{quat}, C4); 56.96 (CH ring, C2); 57.04 (C_{quat}, C4); 61.69 (CH_2CH_3); 61.81 (CH_2CH_3); 83.02 (C_{quat}, *t*-Bu); 83.19 (C_{quat}, *t*-Bu); 83.68 (C_{quat}, *t*-Bu); 84.03 (C_{quat}, *t*-Bu); 149.15 (C=O, *N*-Boc); 149.15 (C=O, *N*-Boc); 167.94 (C=O); 168.74 (C=O); 170.25 (C=O); 170.32 (C=O); 170.65 (C=O); 171.12 (C=O). IR (cm^{-1}) ν_{max}: 1725 (C=O); 1794 (C=O). MS: *m*/*z* (%): (ES, pos) no M$^+$; 366 (13); 325 (7); 280 (41); 279 (14); 278 (100); 234 (6); 232 (11); 202 (16); 158 (9). Anal. Calcd $C_{20}H_{32}ClNO_7$: C 55.36%, H 7.43%, N 3.23%; found: C 55.18%, H 7.62%, N 3.46%.

3.1.4. 2-Benzyl 2,4-di-*t*-butyl 4-(chloromethyl)-5-oxo-2,2,4-pyrrolidinetricarboxylate (15a). To a solution of 0.1 g (0.2 mmol) of the major diastereoisomer of **14a** in 2 ml of dry THF, 0.32 ml (1.5 equiv) of a LiHMDS solution (1 M in hexanes) was added at −78 °C and under a N_2-atmosphere. The mixture was stirred for 30 min at this temperature. After allowing the reaction to warm up overnight to room temperature, it was quenched with a saturated NH_4Cl/NH_4OH solution and extracted with EtOAc. The organic phase was washed with water and dried with $MgSO_4$. Filtering off the $MgSO_4$ and evaporating the filtrate gave the crude product that was purified by column chromatography which led to 0.061 g of **15a** as a clear oil (yield =61%).

^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.34 (9H, s, *t*-Bu), 1.42 (9H, s, *t*-Bu), 2.90 (1H, d, $J=14.5$ Hz, CH_aH_b ring), 3.23 (1H, d, $J=14.5$ Hz, CH_aH_b ring), 3.86 (1H, d, $J=11.4$ Hz, CH_a-H_bCl), 3.90 (1H, d, $J=11.4$ Hz, CH_aH_bCl), 5.22 (1H, d, $J=11.9$ Hz, CH_aH_bPh), 5.26 (1H, d, $J=11.9$ Hz, CH_aH_bPh), 6.41 (1H, br. s, NHCO), 7.36 (5H, s, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 27.53 (*t*-Bu), 27.66 (*t*-Bu), 34.44 (CH_2 ring), 45.48 (CH_2Cl), 57.68 ($C_{quat.}$, C4), 66.31 ($C_{quat.}$, C2), 68.18 (CHC=O_2Ph), 83.74 ($C_{quat.}$, Ph), 84.46 ($C_{quat.}$, *t*-Bu), 128.70 (CH), 128.79 (CH), 128.88 (CH), 134.72 ($C_{quat.}$, Ph), 167.33 (C=O), 167.96 (C=O), 170.83 (C=O). IR (cm^{-1}) ν_{max}: 1739. MS: *m*/*z* (%): (ES, Pos) no M$^+$, 358 (10), 356 (20), 91 (100). Chromatography: 80/20 Hex/EtOAc $R_f=0.30$. Anal. Calcd $C_{23}H_{30}ClNO_7$: C 59.03%, H 6.46%, N 2.99%; found: C 59.10%, H 6.39%, N 3.08%.

3.1.5. 2-Benzyl 2,4-di-*t*-butyl 4-(3-chloropropyl)-5-oxo-2,2,4-pyrrolidinetricarboxylate (15b). The reaction is similar to that of the conversion of **14a–15a**. The reaction was performed on the major diastereoisomer of **14b**. The product was obtained as a clear oil.

^{1}H NMR (270 MHz, $CDCl_3$) δ: 1.33 (9H, s, *t*-Bu), 1.42 (9H, s, *t*-Bu), 1.39–1.47 (2H, m, $CH_2CH_2CH_2Cl$), 1.78–1.87 (1H, m, $CH_2CH_aH_bCH_2Cl$), 2.05–2.12 (1H, m, $CH_2CH_aH_bCH_2$-Cl), 2.53 (1H, d, $J=14.3$ Hz, CH_aH_b ring), 3.16 (1H, d, $J=14.3$ Hz, CH_aH_b ring), 3.53–3.55 (2H, m, CH_2Cl), 5.22 (2H, br. s, CH_2Ph), 6.39 (1H, br. s, N*H*C=O), 7.36 (5H, m, CH, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: 27.61 (*t*-Bu), 27.78 (*t*-Bu), 27.78 ($CH_2CH_2CH_2Cl$), 31.75 ($CH_2CH_2CH_2Cl$), 36.39 (CH_2 ring), 44.80 (CH_2Cl), 55.20 ($C_{quat.}$, C4), 66.39 ($C_{quat.}$, C2), 68.11 ($COOCH_2Ph$), 82.79 ($C_{quat.}$, *t*-Bu), 84.44 ($C_{quat.}$, *t*-Bu), 128.77 (CH), 129.22 (CH), 134.86 ($C_{quat.}$, Ph), 166.97 (C=O), 168.35 (C=O), 169.36 (C=O), 173.70 (C=O). IR (cm^{-1}) ν_{max}: 1742, 2978. MS: *m*/*z* (%): (ES, Pos) no M$^+$, 386 (20), 384 (57), 91 (100). Chromatography: Hex/EtOAc 70/30 $R_f=0.21$. Anal. Calcd $C_{25}H_{34}ClNO_7$: C 60.54%, H 6.91%, N 2.82%; found: C 60.38%, H 7.09%, N 3.02%.

3.1.6. 2,4-Dibenzyl 1-*t*-butyl-5-oxo-1,2,4-pyrrolidinetricarboxylate (14c). Yield 83% (major/minor 80/20), the product is obtained as a brown oil.

^{1}H NMR (270 MHz, $CDCl_3$) δ: *major*: 1.43 (9H, s, *t*-Bu), 2.23 (1H, dd, $J=13.4$, 2.3 Hz), 2.71 (1H, ddd, $J=13.5$, 9.1, 10.2 Hz, CH_aH_b ring), 3.71 (1H, dd, $J=10.7$ Hz, $J=9.1$ Hz, CH, C4), 4.70 (1H, dd, $J=9.6$, 2.3 Hz, NCH). *Minor*: 1.41 (9H, s, *t*-Bu), 2.52–2.59 (2H, m, CH_aH_b ring), 3.58 (1H, dd, $J=8.9$, 5.6 Hz, CH, C4) 4.64 (1H, dd, $J=8.6$, 5.0 Hz, NCH), *not assigned* 5.07–5.26 (4H, m, CH_2Ph), 7.33–7.39 (10H, m, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 24.65 (CH_2), 25.3 (CH_2), 27.31 (*t*Bu), 27.71 (*t*Bu), 48.44 (CH, C4), 48.75 (CH, C4), 57.19 (NCH), 57.63 (NCH), 67.35 (CH_2Ph), 67.49 (CH_2Ph), 67.62 (CH_2Ph), 83.99 (C_{quat}), 84.15 (C_{quat}), 128.15 (CH), 128.3 (CH), 128.37 (CH), 128.49 (CH), 128.57 (CH), 128.67 (CH), 134.89 (C_{quat}, Ph), 135.11 (C_{quat}, Ph), 148.85 (C=O, Boc), 148.94 (C=O, Boc), 167.74 (C=O), 167.81 (C=O), 170.17 (C=O, Boc), 170.65 (C=O, Boc). IR (cm^{-1}) ν_{max}: 1795, 1733. MS: *m*/*z* (%): no M$^+$, 353 (23), 219 (19), 200 (32), 180 (18), 107 (38), 92 (38), 91 (100), 65 (22), 57 (93). Chromatography: Hex/EtOAc 80/20 $R_f=0.12$. Anal. Calcd $C_{25}H_{27}NO_7$: C 66.21%, H 6.00%, N 3.09%; found: C 65.92%, H 6.12%, N 3.25%.

3.1.7. 2,4-Dibenzyl 2-*t*-butyl 5-oxo-2,2,4-pyrrolidinetricarboxylate (15c). The reaction is similar to that of the conversion of **14a–15a**.The reaction was performed on the diastereoisomeric mixture of **14c** and gave **15c** as a clear oil. (Major/minor 54/46).

^{1}H NMR (270 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 1.32 (9H, s, *t*-Bu), 1.34 (9H, s, *t*-Bu), 2.82–2.94 (2H, m, CH_2), 3.57–3.64 (1H, m, $CHCH_2$), 5.13–5.26 (4H, m, $COOCH_2Ph$), 6.54 (1H, NH), 7.26–7.37 (10H, m, CH, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: MAJOR, MINOR, not assigned: 27.51 (*t*-Bu), 27.55 (*t*-Bu), 31.21 (CH_2 ring), 31.32 (CH_2 ring), 47.12 (CH, C4), 47.19 (CH, C4), 66.88 ($C_{quat.}$, C2), 67.21 ($C_{quat.}$, C2), 67.49 ($COOCH_2Ph$), 67.53 ($COOCH_2Ph$), 68.03 ($COOCH_2Ph$), 68.21 ($COOCH_2Ph$), 84.17 ($C_{quat.}$, *t*-Bu), 84.31 ($C_{quat.}$, *t*-Bu), 128.30 (CH), 128.34 (CH), 128.43 (CH), 128.55 (CH), 128.66 (CH), 128.69 (CH), 134.55 ($C_{quat.}$, Ph), 134.70 ($C_{quat.}$, Ph), 135.27 ($C_{quat.}$, Ph), 135.33 ($C_{quat.}$, Ph), 166.41 (C=O), 166.75 (C=O), 167.98 (C=O), 168.35 (C=O), 170.83 (C=O). ^{1}H NMR (270 MHz, C_6D_6) δ: 1.18 (9H, s, *t*-Bu), 1.21 (9H, s, *t*-Bu), 2.62 (1H, dd, $J=13.9$, 9.2 Hz, CH_aH_b), 2.68 (1H, dd, $J=13.7$, 9.6 Hz, CH_aH_b), 3.04 (1H, dd, $J=13.7$, 10.6 Hz, CH_aH_b), 3.06 (1H, dd, $J=13.9$, 11.2 Hz, CH_aH_b), 3.39–3.46

(1H, m, CH), 4.86–4.99 (4H, m, CH_2Ph), 7.04–7.24 (10H, m, CH, Ph), 8.07(1H, br. s, NH), 8.10 (1H, br. s, NH). ^{13}C NMR (68 MHz, C_6D_6) δ: 27.39 (*t*-Bu), 27.46 (*t*-Bu), 31.59 (CH_2 ring), 31.46 (CH_2 ring), 47.69 (CH, C4), 47.76 (CH, C4), 67.24 (CH_2Ph), 67.31 (CH_2Ph), 67.67 (CH_2Ph), 67.74 (CH_2Ph), 67.82 ($C_{quat.}$, C2), 68.00 ($C_{quat.}$, C2), 83.36 ($C_{quat.}$, *t*-Bu), 83.49 ($C_{quat.}$, *t*-Bu), 128.21 (CH), 128.25 (CH), 128.39 (CH), 128.66 (CH), 128.75 (CH), 135.56 ($C_{quat.}$, Ph), 135.70 ($C_{quat.}$, Ph), 136.15 ($C_{quat.}$, Ph), 136.21 ($C_{quat.}$, Ph), 167.04 (C=O), 167.36 (C=O), 168.51 (C=O), 168.75 (C=O), 168.78 (C=O), 168.87 (C=O), 171.79 (C=O), 171.86 (C=O). IR (cm^{-1}) ν_{max}: 3032, 1610, 1495, 1454, 1741, 1714. MS: *m/z* (%): (ES, Pos) 454 ($M+H^+$, 25), 398 (100), 181 (34), 91 (35). Chromatography: Hex/EtOAc 70/30 $R_f=0.19$. Anal. Calcd $C_{25}H_{27}NO_7$: C 66.21%, H 6.00%, N 3.09%; found: C 65.99%, H 6.10%, N 3.18%.

3.1.8. 1,4-Di-*t*-butyl 2-methyl 5-oxo-1,2,4-pyrrolidinetricarboxylate (14d). ^1H NMR (300 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 1.47 (9H, s, *t*-Bu); 1.49 (9H, s, *t*-Bu); 1.50 (9H, s, *t*-Bu); 2.18 (1H, ddd, $J=13.4$, 9.0, 2.5 Hz, CH_AH_B); 2.43–2.59 (2H, m, CH_2 ring); 2.68 (1H, ddd, $J=13.4$, 10.2, 9.4 Hz, CH_AH_B); 3.47 (1H, dd, $J=9.4$, 5.8 Hz, CH, C4); 3.56 (1H, dd, $J=10.2$, 9.0 Hz, CH, C4); 3.78 (3H, s, OCH_3); 3.79 (3H, s, CH_3); 4.61 (1H, dd, $J=9.1$, 5.0 Hz, CH, C2); 4.67 (1H, dd, $J=9.4$, 2.5 Hz, CH, C2). ^{13}C NMR (75 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 24.81 (CH_2 ring); 25.33 (CH_2 ring); 27.82 (*t*-Bu); 27.91 (*t*-Bu); 49.36 (CH, C4); 49.68 (CH, C4); 52.49 (CH_3); 52.67 (OCH_3); 57.12 (CH, C2); 57.50 (CH, C2); 82.66 (C_{quat}, *t*-Bu); 83.71 (C_{quat}, *t*-Bu); 83.93 (C_{quat}, *t*-Bu); 149.03 (C=O, *N*-Boc); 149.03 (C=O, *N*-Boc); 166.38 (C=O); 167.14 (C=O); 168.10 (C=O); 168.41 (C=O); 171.03 (C=O); 171.49 (C=O). IR (cm^{-1}) ν_{max}: 1729 (C=O); 1753 (C=O); 1797 (C=O). MS: *m/z* (%): (ES, neg) 342 ($M-H^+$, 100). Anal. Calcd $C_{16}H_{25}NO_7$: C 55.97%, H 7.34%, N 4.08%; found: C 56.30%, H 7.52%, N 4.29%.

3.1.9. 2,4-Di-*t*-butyl 2-methyl 5-oxo-2,2,4-pyrrolidinetricarboxylate (15d). The reaction is similar to that of the conversion of **14a–15a**. The reaction was performed on the diastereoisomeric mixture of **14d** and gave **15d** as a clear oil (major/minor 53/47).

^1H NMR (300 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 1.46 (9H, s, *t*-Bu); 1.48 (9H, s, *t*-Bu); 1.49 (9H, s, *t*-Bu); 2.82–2.88 (2H, m, CH_2 ring, C3); 3.43 (1H, dd, $J=8.9$, 5.9 Hz, CH ring, C4); 3.45 (1H, dd, $J=9.1$, 7.2 Hz, CH ring, C4); 3.80 (3H, s, CH_3); 3.82 (3H, s, CH_3); 6.51 (1H, br. s, NH); 6.53 (1H, br. s, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 27.71 (*t*-Bu); 27.74 (*t*-Bu); 27.91 (*t*-Bu); 27.94 (*t*-Bu); 31.38 (CH_2 ring, C3); 31.50 (CH_2 ring, C3); 48.03 (CH ring, C4); 48.13 (CH ring, C4); 53.32 (CH_3); 53.44 (CH_3); 66.77 (C_{quat}, C2); 67.15 (C_{quat}, C2); 82.48 (C_{quat}, *t*-Bu); 82.54 (C_{quat}, *t*-Bu); 84.11 (C_{quat}, *t*-Bu); 84.30 (C_{quat}, *t*-Bu); 166.68 (C=O); 167.14 (C=O); 167.64 (C=O); 168.88 (C=O); 169.31 (C=O); 171.48 (C=O); 171.51 (C=O). IR (cm^{-1}) ν_{max}:1717 (C=O); 1739 (C=O, br.). MS: *m/z* (%): (ES, neg) 342 ($M-H^+$, 100). Chromatography: Hex/EtOAc (70/30) $R_f=0.34$. Anal. Calcd $C_{16}H_{25}NO_7$: C 55.97%, H 7.34%, N 4.08%; found: C 55.85%, H 7.46%, N 4.19%.

3.1.10. 2-Benzyl 1,4-di-*t*-butyl 5-oxo-1,2,4-pyrrolidinetricarboxylate (14e). Di-*t*-butyldicarbonate (1.5 equiv) was used as electrophile and once it was added the reaction was allowed to warm to room temperature. The product crystallizes as a white powder (major/minor 78/22).

^1H NMR (270 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 1.40 (9H, s, *t*-Bu), 1.42 (9H, s, *t*-Bu), 1.45 (9H, s, *t*-Bu), 1.47 (9H, s, *t*-Bu), 2.18 (1H, ddd, $J=13.4$, $J=9.0$, 2.3 Hz, CH_aH_b), 2.47–2.53 (2H, m, CH_2 ring), 2.67 (1H, ddd, $J=13.5$, 10.1, 9.9 Hz, CH_aH_b), 3.42 (1H, dd, $J=6.4$, 8.4 Hz, CH), 3.53 (1H, dd, $J=10.4$, 9.1 Hz, CH), 4.61 (1H, dd, $J=5.9$, 7.9 Hz, NCH), 4.68 (1H, dd, $J=9.6$, 2.3 Hz, NCH), 5.13–5.28 (2H, m, $COOCH_2Ph$), 7.26–7.45 (5H, m, CH, Ph). ^{13}C NMR (68 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 24.71 (CH_2 ring), 25.23 (CH_2 ring), 27.67 (*t*-Bu), 27.76 (*t*-Bu), 27.85 (*t*-Bu), 28.23 (*t*-Bu), 49.29 (CH, C4), 49.67 (CH, C4), 57.18 (NCH), 57.56 (NCH), 67.24 ($COOCH_2Ph$), 67.38 ($COOCH_2Ph$), 82.59 ($C_{quat.}$, *t*-Bu), 83.63 ($C_{quat.}$, *t*-Bu), 83.84 ($C_{quat.}$, *t*-Bu), 128.44 (CH), 128.50 (CH), 128.55 (CH), 128.66 (CH), 135.02 ($C_{quat.}$, Ph), 135.16 ($C_{quat.}$, *t*-Bu), 148.93 (C=O, Boc), 148.98 (C=O, Boc), 156.6 (C=O), 166.45 (C=O), 167.09 (C=O), 168.14 (C=O), 168.43 (C=O), 170.42 (C=O), 170.83 (C=O). IR (cm^{-1}) ν_{max}: 1703, 1726. MS: *m/z* (%): (direct inlet) no M^+, 308 (7), 264 (25), 129 (19), 128 (98), 110 (37), 91 (87), 57 (100). Chromatography: Hex/EtOAc 70/30 $R_f=0.31$ Mp 84–86.5 °C (yield =77%). Anal. Calcd $C_{22}H_{29}NO_7$: C 62.99%, H 6.97%, N 3.34%; found: C 62.71%, H 7.25%, N 3.25%.

3.1.11. 2-Benzyl 2,4-di-*t*-butyl 5-oxo-2,2,4-pyrrolidinetricarboxylate (15e). The reaction is similar to that of the conversion of **14a–15a**. The reaction was performed on the diastereoisomeric mixture of **14e** and gave **15e** as a clear oil. (Major/minor 52/48).

^1H NMR (300 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 1.33 (9H, s, *t*-Bu); 1.36 (9H, s, *t*-Bu); 1.47 (9H, s, *t*-Bu); 1.47 (9H, s, *t*-Bu); 2.82–2.87 (2H, m, CH_2 ring, C3); 3.41 (1H, dd, $J=9.4$, 2.5 Hz, CH ring, C4); 3.44 (1H, dd, $J=9.1$, 3.0 Hz, CH ring, C4); 5.14–5.28 (2H, m, CH_2Ph); 6.56 (1H, br. s, NH); 6.58 (1H, br. s, NH); 7.31–7.36 (5H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 27.54 (*t*-Bu); 27.59 (*t*-Bu); 27.93 (*t*-Bu); 31.27 (CH_2 ring, C3); 31.41 (CH_2 ring, C3); 48.00 (CH ring, C4); 48.14 (CH ring, C4); 66.83 (C_{quat}, C2); 67.15 (C_{quat}, C2); 68.03 (CH_2Ph); 68.16 (CH_2Ph); 82.45 (C_{quat}, *t*-Bu); 82.49 (C_{quat}, *t*-Bu); 84.04 (C_{quat}, *t*-Bu); 84.20 (C_{quat}, *t*-Bu); 126.97 (CH, Ph); 128.60 (CH, Ph); 128.66 (CH, Ph); 128.71 (CH, Ph); 128.74 (CH, Ph); 128.82 (CH, Ph); 134.62 (C_{quat}, Ph); 134.77 (C_{quat}, Ph); 166.53 (C=O); 166.94 (C=O); 167.63 (C=O); 167.67 (C=O); 168.12 (C=O); 168.54 (C=O); 171.51 (C=O). IR (cm^{-1}) ν_{max}:1732 (C=O, br.). MS: *m/z* (%): (ES, neg) 418 ($M-H^+$, 100). Chromatography: Hex/EtOAc (70/30) $R_f=0.40$. Anal. Calcd $C_{22}H_{29}NO_7$: C 62.99%, H 6.97%, N 3.34%; found: C 62.78%, H 7.26%, N 3.42%.

3.1.12. 4-Benzyl 1-*t*-butyl 2-methyl 5-oxo-1,2,4-pyrrolidinetricarboxylate (14f). Yield 80% (major/minor 77/23), the product is obtained as a white powder.

^{1}H NMR (300 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 1.50 (9H, s, *t*-Bu); 2.25 (1H, ddd, $J=13.5$, 8.8, 2.5 Hz, CH_AH_B ring, C3); 2.52–2.57 (2H, m, CH_2 ring, C3); 2.74 (1H, ddd, $J=13.5$, 10.4, 9.4 Hz, CH_AH_B ring, C3); 3.59 (1H, dd, $J=8.3$, 6.6 Hz, CH ring, C4); 3.69 (3H, s, CH_3); 3.74 (1H, dd, $J=10.4$. 8.8 Hz, CH ring, C4); 3.78 (3H, s, CH_3); 4.61 (1H, dd, $J=7.8$, 5.9 Hz, CH ring, C2); 4.68 (1H, dd, $J=9.4$, 2.5 Hz, CH ring, C2); 5.11 (2H, s, CH_2Ph); 5.22 (2H, s, CH_2Ph); 7.30–7.40 (5H, m, Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 24.69 (CH_2 ring, C3); 25.37 (CH_2 ring, C3); 27.85 (*t*-Bu); 27.85 (*t*-Bu); 48.53 (CH ring, C4); 48.82 (CH ring, C4); 52.57 (CH_3); 52.77 (CH_3); 57.12 (CH ring, C2); 57.57 (CH ring, C2); 66.86 (CH_2Ph); 67.75 (CH_2Ph); 84.18 (C_{quat}, Ph); 84.32 (C_{quat}, Ph); 128.13 (CH, Ph); 128.24 (CH, Ph); 128.41 (CH, Ph); 128.47 (CH, Ph); 128.55 (CH, Ph); 128.58 (CH, Ph); 128.62 (CH, Ph); 135.08 (C_{quat}, Ph); 135.14 (C_{quat}, Ph); 148.99 (C=O, *N*-Boc); 148.99 (C=O, *N*-Boc); 167.76 (C=O); 167.91 (C=O); 170.79 (C=O); 171.37 (C=O). IR (cm^{-1}) ν_{max}:1737 (C=O); 1777 (C=O, br.). MS: *m/z* (%): (ES, neg) 376 ($M-H^+$, 100). Chromatography: Hex/EtOAc (70/30) $R_f=0.19$. Mp 94–97 °C. Anal. Calcd $C_{19}H_{23}NO_7$: C 60.47%, H 6.14%, N 3.71%; found: C 60.58%, H 6.24%, N 3.88%.

3.1.13. 4-Benzyl 2-*t*-butyl 2-methyl 5-oxo-2,2,4-pyrrolidinetricarboxylate (15f). The reaction is similar to that of the conversion of **14a–15a**. The reaction was performed on the diastereoisomeric mixture of **14f** and gave **15f** as a clear oil. (Major/minor 51/49).

^{1}H NMR (300 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 1.45 (9H, s, *t*-Bu); 1.47 (9H, s, *t*-Bu); 2.89 (2H, m, CH_2 ring, C3); 3.58–3.66 (1H, m, CH ring, C4); 3.76 (3H, s, CH_3); 3.79 (3H, s, CH_3); 5.16–5.27 (2H, m, CH_2Ph); 6.62 (1H, br. s, NH); 7.28–7.40 (5H, m, Ph). ^{13}C^{13}C NMR (75 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 27.70 (*t*-Bu); 31.31 (CH_2 ring, C3); 31.42 (CH_2 ring, C3); 47.13 (CH ring, C4); 47.19 (CH ring, C4); 53.35 (CH_3); 53.51 (CH_3); 66.80 (C_{quat}, C2); 67.18 (C_{quat}, C2); 67.56 (CH_2Ph); 67.61 (CH_2Ph); 84.29 (C_{quat}, *t*-Bu); 84.45 (C_{quat}, *t*-Bu); 128.16 (CH, Ph); 128.27 (CH, Ph); 128.34 (CH, Ph); 128.39 (CH, Ph); 128.57 (CH, Ph); 128.66 (CH, Ph); 128.72 (CH, Ph); 128.86 (CH, Ph); 135.24 (C_{quat}, Ph); 135.31 (C_{quat}, Ph); 166.57 (C=O); 166.96 (C=O); 168.36 (C=O); 168.71 (C=O); 169.11 (C=O); 170.80 (C=O); 170.83 (C=O). IR (cm^{-1}) ν_{max}:1740 (C=O, br.). MS: *m/z* (%): (ES, Pos) 378 ($M+H^+$, 43); 323(17); 322 (100). Chromatography: Hex/EtOAc (70/30) $R_f=0.09$ and 0.17. Anal. Calcd $C_{19}H_{23}NO_7$: C 60.47%, H 6.14%, N 3.71%; found: C 60.35%, H 6.53%, N 3.86%.

3.1.14. 1,4-Di-*t*-butyl 2-ethyl 5-oxo-1,2,4-pyrrolidinetricarboxylate (14g). Di-*t*-butyldicarbonate (1.5 equiv) was used as electrophile and once it was added the reaction was allowed to warm to room temperature. **14g** is obtained (yield 80% major/minor 70/30) as a brown oil.

H NMR (300 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 1.30 (3H, t, $J=7.2$ Hz, CH_2CH_3); 1.45 (9H, s, *t*-Bu); 1.47 (9H, s, *t*-Bu); 1.49 (9H, s, *t*-Bu); 1.50 (9H, s, *t*-Bu); .2.20 (1H, ddd, $J=13.5$, 8.8, 2.5 Hz, CH_AH_B ring); 2.48–2.53 (2H, m, CH_2 ring); 2.68 (1H, ddd, $J=13.5$, 10.5, 9.6 Hz, CH_AH_B ring); 3.44 (1H, dd, $J=7.7$, 7.4 Hz, CH ring, C4); 3.56 (1H, dd, $J=10.5$, 8.8 Hz, CH ring, C4); 4.19–4.27 (2H, m, CH_2CH_3); 4.19–4.27 (2H, m, CH_2CH_3); 4.56 (1H, dd, $J=7.2$, 6.6 Hz, CH ring, C2); 4.64 (1H, dd, $J=9.6$, 2.5 Hz, CH ring, C2). ^{13}C NMR (75 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 14.24 (CH_2CH_3–); 14.24 (CH_2CH_3–); 24.88 (CH_2 ring, C3); 25.46 (CH-$_2$ ring, C3); 27.75 (*t*-Bu); 27.93 (*t*-Bu); 28.03 (*t*-Bu); 28.30 (*t*-Bu); 49.45 (CH, C4); 49.77 (CH, C4); 57.28 (CH ring, C2); 57.63 (CH ring, C2); 61.81 (CH_2CH_3); 61.92 (CH_2CH_3); 82.90 (C_{quat}, *t*-Bu); 82.98 (C_{quat}, *t*-Bu); 83.95 (C_{quat}, *t*-Bu); 84.11 (C_{quat}, *t*-Bu); 149.22 (C=O, *N*-Boc); 149.22 (C=O, *N*-Boc); 166.40 (C=O); 167.26 (C=O); 168.13 (C=O); 168.46 (C=O); 170.55 (C=O); 172.09 (C=O). IR (cm^{-1}) ν_{max}:1729 (br., C=O); 1796 (C=O). MS: *m/z* (%): (ES, pos) No M^+; 297 (8); 254 (12); 203 (8); 202 (100). Anal. Calcd $C_{17}H_{27}NO_7$: C 57.13%, H 7.61%, N 3.92%; found: C 57.00%, H 7.89%, N 3.88%.

3.1.15. 2,4-Di-*t*-butyl 2-ethyl 5-oxo-2,2,4-pyrrolidinetricarboxylate (15g). The reaction is similar to that of the conversion of **14a–15a**. The reaction was performed on the diastereoisomeric mixture of **14g** and gave **15g** as a brown oil. (Major/minor 51/49, purity 85%).

^{1}H NMR (300 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 1.29 (3H, t, $J=7.2$ Hz, CH-$_2CH_3$); 1.31 (3H, t, $J=7.0$ Hz, CH_2CH_3); 1.46 (9H, s, *t*-Bu); 1.48 (9H, s, *t*-Bu); 1.48 (9H, s, *t*-Bu); 1.49 (9H, s, *t*-Bu); 2.82–2.85 (2H, m, CH-$_2$ ring); 3.41–3.48 (1H, m, CH ring); 4.23–4.30 (2H, m, CH_2CH_3); 4.23–4.30 (2H, m, CH_2CH_3); 6.30 (1H, br. s, NH); 6.32 (1H, br. s, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: *major*, *minor*, not assigned: 13.97 (CH_2CH_3); 14.01 (CH_2CH_3); 27.66 (*t*-Bu); 27.71 (*t*-Bu); 27.87 (*t*-Bu); 28.01 (*t*-Bu); 31.23 (CH-$_2$ ring, C3); 31.35 (CH-$_2$ ring, C3); 48.12 (CH ring, C4); 48.20 (CH ring, C4); 62.41 (CH_2CH_3); 62.59 (CH_2CH_3); 66.93 (C_{quat}, C2); 67.23 (C_{quat}, C2); 82.27 (C_{quat}, *t*-Bu); 82.32 (C_{quat}, *t*-Bu); 83.77 (C_{quat}, *t*-Bu); 83.98 (C_{quat}, *t*-Bu); 166.80 (C=O); 167.27 (C=O); 167.74 (C=O); 167.74 (C=O); 168.32 (C=O); 168.80 (C=O); 171.82 (C=O); 171.82 (C=O). IR (cm^{-1}) ν_{max}: 1736 (br.); 1793 (C=O). MS: *m/z* (%): (ES, pos) No M^+; 247 (15); 246 (100); 202 (11).

3.1.16. 1,5-Diethyl-2-[(*t*-butoxycarbonyl)amino]pentanedioate (15i). The reaction is similar to that of the conversion of **14a–15a**.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.26 (3H, t, $J=7.2$ Hz, CH_2CH_3); 1.28 (3H, t, $J=7.2$ Hz, CH_2CH_3); 1.44 (9H, s, *t*-Bu); 1.88–2.01 (1H, m, $COCH_2CH_AH_B$); 2.12–2.24 (1H, m, $COCH_2CH_AH_B$); 2.36–2.43 (2H, m, $COCH_2$); 4.14 (2H, q, $J=7.2$ Hz, CH_2CH_3); 4.20 (2H, q, $J=7.2$ Hz, CH_2CH_3); 4.31 (1H, dd, $J=13.1$ Hz, $J=8.4$ Hz, COCH); 5.19 (1H, br. s, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.16 (CH_2CH_3); 14.19 (CH_2CH_3); 27.84 ($COCH_2CH_2$); 28.29 (*t*-Bu); 30.37 ($COCH_2$); 52.98 (CH); 60.65 (CH_2CH_3); 61.52 (CH_2CH_3); 79.96 (C_{quat}, *t*-Bu); 155.39 (C=O, NH-Boc); 172.26 (C=O); 172.79 (C=O). IR (cm^{-1}) ν_{max}:1719 (C=O); 1737 (C=O). MS: *m/z* (%): (ES, pos) no M^+; 204 ($M-Boc+H^+$, 100). Chromatography: Hex/EtOAc (70/30) $R_f=0.43$.

3.1.17. 1,5-Dimethyl-2-[(*t*-butoxycarbonyl)amino]pentanedioate (15j). The reaction is similar to that of the conversion of **14a–15a**.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.44 (9H, s, *t*-Bu); 1.99–2.02 (1H, m, $COCH_2CH_AH_B$); 2.13–2.25 (1H, m, $COCH_2CH_AH_B$); 2.39–2.45 (2H, m, $COCH_2$); 3.68 (3H, s, CH_3); 3.75 (3H, s, CH_3); 4.30–4.37 (1H, m, COCH); 5.19 (1H, br. s, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.78 ($COCH_2CH_2$); 28.32 (*t*-Bu); 30.09 ($COCH_2$); 51.81 (CH_3); 52.44 (CH_3); 52.91 (CH); 80.04 (C_{quat}, *t*-Bu); 155.42 (C=O, NH-Boc); 172.72 (C=O); 173.21 (C=O). IR (cm^{-1}) ν_{max}: 1714 (C=O); 1736 (C=O); 1793 (C=O). MS: *m/z* (%): (ES, pos) no M^+; 176 ($M-Boc+H^+$, 100); 144 (24). Chromatography: Hex/EtOAc (70/30) $R_f=0.31$.

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Lanthanide complexes of new polyaminocarboxylate complexes with two chromophores derived from bispyrazolylpyridine and aceto or benzophenone: synthesis, characterization and photophysical properties

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Abstract—New ionophores derived from 2,6-bis(*N*-pyrazolyl)pyridine and aceto/benzophenone have been synthesized and fully characterized. The lanthanide complexes of these new ligands were studied from their UV–vis and fluorescence data. Eu^{3+} and Tb^{3+} complexes were easily formed and their photophysical properties measured. In all cases, lanthanide emission lifetimes were in the range of ms albeit quantum yields were relatively low. Possible flaws in the energy-transfer mechanisms are discussed.
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1. Introduction

Lanthanide trivalent cations have excellent photoluminescent properties usable in a high range of different applications. But the ions' poor ability to absorb light makes it necessary to dress them up with an organic skin in the form of a complex. The design of the organic part of such complexes is thus paramount in achieving the required circumstances for the complex to be efficiently luminescent. The usual conditions to be fulfilled are good yields for intersystem crossing and reasonable matching between the chromophore first triplet state and the resonance level of the metal. The organic ligand must also provide good isolation of the metal from water vibronic O–H deactivators. The achievement of all these requirements is not an easy task and research in this area is very active.[1]

Suitable building blocks for designing photoactive probes are heteroaromatic rings like pyridine, pyrazine or pyrazole. We have already prepared a number of useful complexes based on these motifs.[2] From all chromophores synthesized, 2,6-bis(*N*-pyrazolyl)pyridine (**1**; Fig. 1) was the most successful and its Eu^{3+} and Tb^{3+} complexes displayed excellent luminescent properties.[3] More recently, we have also shown that complexes based on the relatively simple acetophenone chromophore (**2**; Fig. 1) possessed excellent quantum yields for triplet sensitization of lanthanide luminescence.[4] Also Beeby and Williams have described recently the photosensitization of lanthanides by means of acetophenone and benzophenone in polyazamacrocyclic

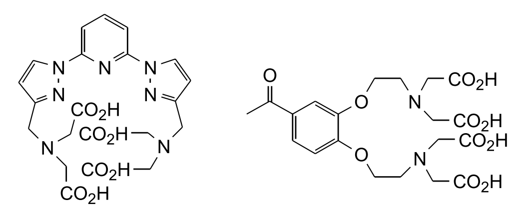

Figure 1. 2,6-Bis(*N*-pyrazolyl)pyridine and acetophenone derivatives used as reference in this work.

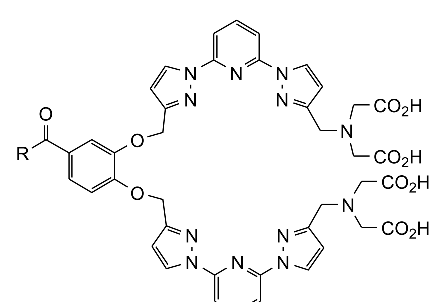

Figure 2. Ligands prepared in this work.

Keywords: Lanthanides; Luminescence.

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structures.[5] Both the outstanding properties of these two chromophores and our previous studies on photoactive macrocycles,[6] cryptates[7] and polyaminocarboxylates[8] led us to design two new ligands based on a combination of these chromophores. Therefore, this paper deals with the synthesis and photophysical study of Eu^{3+} and Tb^{3+} complexes of ligands **3** (Fig. 2), based on 2,6-bis(*N*-pyrazolyl)pyridine and aceto/benzophenone subunits. All compounds were studied from their UV–vis and emission data.

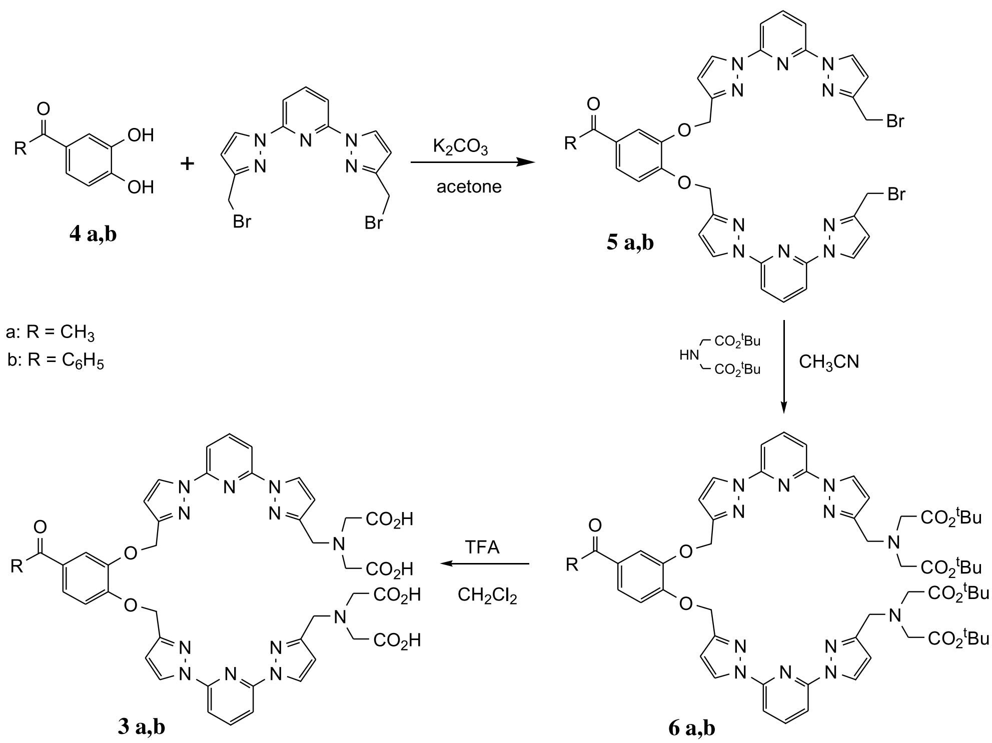
2. Results and discussion

2.1. Synthesis of the ligands

Compounds **3a**,**b** were synthesized as depicted in Scheme 1, starting from 3,4-dihydroxyacetophenone (**4a**) and 3,4-dihydroxybenzophenone (**4b**), obtained respectively from acetylation or benzoylation of hydroxyl groups of pyrocatechol, followed by Fries rearrangement, as previously reported.[9] Reaction of **4a**,**b** with an excess of dibromoderivative of 2,6-bis(*N*-pyrazolyl)pyridine, in the presence of potassium carbonate in acetone, afforded compounds **5a**,**b**. The introduction of the aminocarboxylate moieties was performed by treatment of the dibromo derivative with di-*tert*-butyliminodiacetate. The resulting *tert*-butyl esters **6a**,**b** were cleaved to the acids **3a**,**b** with trifluoroacetic acid in dichloromethane with good yields.

2.2. Lanthanide complexes

The Eu^{3+} and Tb^{3+} complexes of ligands **3a**,**b** were prepared by the addition of the stoichiometric amount of the corresponding lanthanide chloride (aqueous solution) to the ligand in water. The 1:1 stoichiometry was confirmed in



Scheme 1. Compounds synthesized in this work.

Table 1. Wavelength maxima and molar absorption coefficients of Eu^{3+} and Tb^{3+} complexes of compounds **1**,**2**, and **3a**,**b** (buffer pH 8.6; rt)

	Ligand		Complex			
			Eu^{3+}		Tb^{3+}	
1						
λ abs (nm)	245	300	270	313	270	313
ε (10^3 M^{-1} cm^{-1})	17.6	12.2	12.3	8.1	11.2	7.8
2						
λ abs (nm)	272	301	260	287	260	287
ε (10^3 M^{-1} cm^{-1})	10.7	8.0	12.2	5.0	11.8	5.0
3a						
λ abs (nm)	246	303	245	306	245	306
ε (10^3 M^{-1} cm^{-1})	45.5	33.0	40.1	28.0	38.4	26.6
3b						
λ abs (nm)	249	309	250	310	250	310
ε (10^3 M^{-1} cm^{-1})	43.5	30.5	39.2	27.6	35.4	25.4

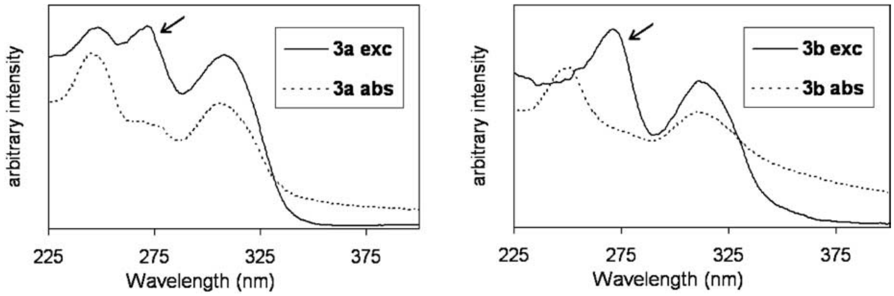


Figure 3. Absorption and excitation spectra of Eu^{3+} complex of **3a** and **3b** respectively.

both ligands by titration experiments performed in the emission spectra. The photophysical study was performed in borate buffer (pH 8.6) at a concentration 10^{-5} M for absorption and 10^{-7} M for emission spectroscopy. No changes in absorption and luminescence spectra were observed in aerated water after several days at room temperature, indicating that these complexes are kinetically inert in water solution.

2.3. Electronic spectra

The UV–vis spectra of the ligands showed the characteristic bands for the bis-pyrazolylpyridine chromophore, (245 and 300 nm), with minor variations (Table 1). The bands of aceto/benzophenone chromophore (270 and 290 nm) should be obscured under the first, owing to the higher molar absorption coefficients of the double bispyrazolylpyridine system.

The first feature that should be remarked is that compounds **1** and **2** showed substantial changes in wavelength maxima upon complexation (ca. 13 and −12 nm, respectively). Due to the excellent quantum yields measured for these ligands (vide infra), these sizable variations were attributed to conformational rearrangements leading to enhanced cooperativity between the different coordinating atoms with the lanthanide. In contrast, ligands **3a**,**b** displayed much smaller changes, if any, suggesting that the conformational changes, which undoubtedly should take place upon complexation, might not involve such alterations in the electronic states of the chromophore.

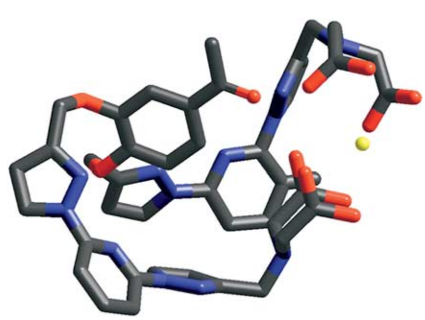


Figure 4. Calculated energy minimum (AM1/MM+) for complex **3a**/Eu^{3+}.

Table 2. Triplet state energy of gadolinium complexes and differences between this state and others indicated in cm^{-1}

Compound	$^{3}E_{00}$	$^{1}E_{00}-^{3}E_{00}$	$^{3}E_{00}-^{5}D_{0}$ (Eu)	$^{3}E_{00}-^{5}D_{4}$ (Tb)
1	25150	6798	7900	4650
2	24000	10843	6750	3500
3a	24572	8107	7322	4072
3b	24572	7686	7322	4072

2.4. Luminescence studies

The emission spectra of the Eu^{3+} and Tb^{3+} complexes, excited into the lowest energy (ligand-centered) absorption band, showed the well-known, structured luminescence of the lanthanide ions, with the highest intensity band at 615 nm for Eu^{3+}($^{5}D_{0}$–$^{7}F_{2}$ transition) and 545 nm for Tb^{3+}($^{5}D_{4}$–$^{7}F_{5}$ transition).

The global accordance between absorption and excitation spectra (Fig. 3) clearly shows that in the two complexes lanthanide ions are efficiently excited by ligand-to-metal intersystem energy transfer from sensitized bis-(*N*-pyrazolyl)pyridine and aceto or benzophenone chromophores. It is noteworthy that the excitation spectra of **3a**,**b** showed important maxima at ca. 270 nm, very similar to that displayed by compound **2** (depicted in Fig. 1). This is a qualitative proof of the higher importance of the phenone chromophore in transferring energy to the metal, despite its apparent long distance to the iminodiacetate groups where the metal is assumed to be coordinated. Unfortunately, we were unable to obtain good crystals of the complexes to carry out x ray studies. However, simple conformational analysis of the complexes suggested that the phenone moiety may lay in reasonable proximity to the metal. In this situation lanthanide ion could be surrounded by up to nine oxygen atoms saturating the first lanthanide coordinating sphere, see below. Nitrogen heterocyclic atoms are not directly involved in this coordination. Figure 4 displays the calculated energy minimum.

The cascade of photophysical processes that occurs in these lanthanide complexes is well known. Light is absorbed into the first excited singlet state ($^{1}E_{00}$) of the ligand that is followed by intersystem crossing (ISC) to its triplet state ($^{3}E_{00}$) which finally populates the lanthanide emissive levels. Table 2 shows the energy values of $^{3}E_{00}$ levels measured in the gadolinium complexes for the compounds **3a**,**b** studied in this work and **1** and **2** (depicted in Fig. 1) as a reference.

It may be seen that **3a**,**b** $^{3}E_{00}$ levels are comprised between the $^{3}E_{00}$ levels of **1** and **2** complexes, suggesting that ligands **3a**,**b** may be, a priori, as good lanthanide sensitizers as **1** and

Table 3. Lifetime data in H_2O and D_2O at rt and 77 K (ms), quantum yields, (ϕ) of the metal-centered emission of the complexes with ligands **1**, **2** and **3a**,**b** and number of water molecules estimated with the Horrocks method

	$\tau_{H_2O}^{300\ K\,a}$	$\tau_{D_2O}^{300\ K\,a}$	$\tau_{D_2O}^{77\ K\,a}$	ϕ^{b}	q_{H2O}^{c}
1 Eu^{3+}	1.3	2.5	3.4	0.1	0.4
Tb^{3+}	2.8	3.3	3.1	0.6	0.3
2·Eu^{3+}	0.6	1.9	3.1	0.2	1.1
Tb^{3+}	1.6	2.7	3.0	0.9	1.0
3a·Eu^{3+}	0.3–1.7[d]	2.2	3.0	0.002	0.3
Tb^{3+}	1.5	1.9	2.9	0.03	0.6
3b Eu^{3+}	1.5	2.2	2.7	0.001	0.3
Tb^{3+}	1.8	2.0	3.0	0.02	0.2

[a] Estimated standard error $<10\%$.
[b] Measured in borate buffer pH = 8.6. Estimated standard error of 30%.
[c] Uncertainty ± 0.5 water molecules.
[d] Bi-exponential decay.

2, and in fact, they are. However Table 3 shows that complexes **3a**,**b** displayed much lower emission quantum yields (ϕ) than those obtained with ligands **1** and **2** containing each chromophore separately[†],[2] Therefore, there should be some flaws in the energy transfer mechanism of complexes **3a**,**b** that are absent with ligands **1** and **2**.

The lanthanide quantum yield of luminescence (ϕ) is a balance between the ligand-to-metal energy transfer efficiency and the radiative and non-radiative rate constants of the luminescent Ln(III) levels. An important non-radiative, deactivation mechanism of sensitized lanthanides comprises their coupling with O–H oscillators that effectively quenches metal luminescence. In Table 3 it can be seen that the number of water molecules in the first coordination sphere of complexes **3a**,**b** is very low (0.3–0.6) and similar to **1** and inferior to **2**, as calculated by Horrocks equation,[10] and other different methods.[11,12] This result confirmed the disposition of the lanthanide discussed from the calculated structure.

It is thus clear that the lanthanides in complexes of **3a**,**b** are as well protected from surrounding water molecules as they are within ligand **1** or even better than in **2** and therefore, the low quantum yields cannot be explained only by the quenching due to coupling with first coordination sphere water molecules.

The lifetimes gathered in Table 3, were calculated from the decay curves of the excited states of the Eu^{3+} and Tb^{3+} complexes, excited in the lowest energy ligand-centred absorption band. In each case, monoexponential decay curves were observed, except in the case of complex **3a** Eu^{3+}. In H_2O solution and at room temperature, the luminescence lifetimes were in the 1.5–1.8 ms range, with **3b** Tb^{3+} complex having the longest lifetime and **3a** Eu^{3+} the shortest. The lifetime values are higher in D_2O than in H_2O (1.4 and 1.1 factors for Eu^{3+} and Tb^{3+} respectively) indicating that nonradiative deactivation of the $^5D_0$ or $^5D_4$ metal excited states thought the O–H vibration occurs, even with a low number of water molecules in the first coordination sphere. The higher values of the lifetime at 77 K, may be indicative of other deactivation pathways, caused by excited states which can be thermally populated from the emitting state, or the existence of potencial LMCT states for the case of Eu^{3+}.

In relation with other factors involved in the lanthanide energy-transfer process, (LET), it is imperative a good match between $^3E_{00}$ and ^5D_i levels, as Mukkala and coworkers have stated.[13] Had the $^3E_{00}$–^5D_i energy gap been too small, non-radiative deactivation by metal-to-ligand back-energy transfer is a serious competing process to metal luminescence. On the contrary, if the gap is too large, ligand-to-metal energy transfer is produced to high vibronic levels of the metal which partially relaxes by thermal, non-radiative pathways, thus reducing energy-transfer efficiency. The best match between $^3E_{00}$ and ^5D_i levels is achieved when their differences are above 6500 cm^{-1} for Eu^{3+} complexes and 3500 cm^{-1}, for Tb^{3+}. Compounds **3a**,**b** ample fulfil this condition, see their increments in Table 2. Concerning ISC efficiency, it is known[14] that the energy gap between the singlet and triplet states of the ligand ($^1E_{00} - {}^3E_{00}$) should be at least 5000 cm^{-1}. It can be seen in Table 2 that complexes **3a**,**b** also satisfy this condition.

Therefore, the low quantum yields with Eu^{3+} complexes and in minor extent with Tb^{3+}, cannot be explained only with the concourse of the points mentioned above, specially when all the photophysical parameters fulfil the optimal values, estimated by comparison with complexes with the close related ligands **1** and **2** which showed excellent quantum yields.

It is widely known that the distance chromophore lanthanide plays an important role in the energy transfer process, and two mechanisms have been proposed in the literature.[15] The so-called Dexter mechanism implies two simultaneous, concerted electron transfers which requires good orbital overlapping. The batho- or hypsochromic shifts upon complexation not exhibited by ligands **3a**,**b** (vide supra) suggests that their heteroatoms do not modify their positions as a result of the required orbital overlapping. The alternative Förster mechanism does not entail electron

[†] The quantum yield were measured only by excitation at the lowest energy band (306 nm for **3a** and 310 nm for **3b**). In fact, although the 245 nm band is characteristic from the bispyrazolyl moiety whereas that of 270 nm comes from the phenone, measurements by excitation on these bands are ambiguous as the maximum at 245 nm shifts to 270 nm and that of 270 nm to 260 nm by complexation.

transfer but coulombic coupling of the appropriate orbitals. This interaction is strongly dependent upon orientation and distance ($k\alpha$ r-6). The low experimental ϕ values indicate that a good coulombic coupling cannot be attained either in ligands **3a**,**b**. Although molecular modelling suggests that the phenone chromophore may lay much closer to the metal than anticipated, the only explanation to the low quantum yields measured for **3a**,**b** is that the probable, preferential chelation of the metal with the iminodiacetates unfortunately makes its relative arrangement to the chromophores to be inappropriate for efficient energy transfer.

3. Conclusion

Two new ionophores derived from 2,6-bis(*N*-pyrazol-1-yl)pyridine motif attached to aceto/benzophenone and iminodiacetic subunits have been synthesized. Eu^{3+} and Tb^{3+} complexes were prepared and their luminescence properties were studied in borate buffer. Lanthanide emission lifetimes were long enough (well in the range of ms) to make these complexes highly valuable for applications in time-resolved luminescence measurements. However, quantum yields were much lower than those observed for simpler complexes prepared by us in the recent past. Probably, the arrangement of the chelating iminodiacetate subunits relative to the chromophores hampers an efficient path for energy transfer.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR: *Bruker* AC-200 (200 and 50 MHz), AMX-300 (300 and 75 MHz), (Departamento de Química Orgánica, DQO) and DRX-500 (500 and 125 MHz), (Servicio Interdepartamental de Invesigación, SIdI). M.S.: VG Autospec spectrometer (SIdI) in FAB mode (L-SIMS$^+$) or EI+. Absorption spectra: Lambda 6 Perkin-Elmer spectrophotometer (DQO). Excitation and emission spectra: LS50 Perkin-Elmer spectrofluorometer (DQO). The excitation spectra were automatically corrected and the emission spectra were corrected according to the instrument guidebook. Elemental analyses of compounds (Perkin-Elmer CHN 2400 automatic analyzers, SIdI) were correct within experimental error. All solvents were purified prior to their use. Lanthanide chlorides were purchased from Aldrich and used as received. Structure of Figure 4 was calculated using the HyperChem 7.0 package.

4.2. General methods

Synthesis of lanthanide complexes. Absorption and emission measurements. The complexes were formed by addition of equimolecular amounts of the corresponding lanthanide chloride to the ligand solutions in borate buffer pH = 8.6. (Europium complexes: 10^{-5} M for absorption and emission. Terbium complexes: 10^{-5} M for absorption and 10^{-7} M for emission). The resulting solutions were kept closed at rt for 18 h. The emission quantum yields were measured complying with reported procedures by Rhys-Williams[16] and referenced to four standards, two fluorescent (quinine sulfate and 9,10-diphenylanthracene) and two phosphorescent (Ru(bipy)$_3$Cl$_2$ and Tb Terbipy complex) delivered by Wallac Oy. Despite this, the expected errors of this measurement are within 30%. Triplet state energy levels were measured from the highest energy band in the 77 K phosphorescence spectrum of the gadolinium complexes.

4.2.1. 3,4-Bis-{[6-(3-bromomethyl-1-pyrazolyl)-pyridin-2-yl]-1*H*-pyrazol-3-yl-methoxy} acetophenone (5a) and 3,4-bis-{[6-(3-bromomethyl-1-pyrazolyl)-pyridin-2-yl]-1*H*-pyrazol-3-yl-methoxy}benzophenone (5b). To a suspension of 2,6-bis-(3-bromomethyl-1-pyrazolyl)pyridine (1.6 g, 4.03 mmol) and potassium carbonate (2.7 g, 20.15 mmol) in refluxed acetone, was added slowly an acetone solution of 3,4-dihydroxyacetophenone or benzophenone (0.39 mmol in 10 mL). The mixture was refluxed and stirred for 7 h. The salts were filtered off and the filtrate was evaporated to dryness. The solid residue was flash chromatographed. The first elution with dichloromethane yields the unreacted dibromo derivative. Further elution with dichloromethane/methanol 97:3 yields the derivatives **5a** (168 mg, 55%) or **5b** (220 mg 62%).

Compound **5a** data. Mp: 206–208 °C. MS:(L-SIMS+):783 (M^+, 9), 785 ((M+2)+H^+, 19), 787 ((M+4)+H^+, 9). ^{1}H NMR: (CDCl$_3$) δ (ppm) (500 MHz): 8.46 (2H, d, J=2.5 Hz, Pz(H5)); 8.44 (2H, 2d, J=2.6 Hz, Pz(H5)); 7.91 (2H, t, J= 8.0 Hz Py (H4)); 7.81–7.74 (5H, m, Py (H3,5) and Ar(H2)); 7.55 (1H, dd, J=2.1, 8.3 Hz, Ar(H6)); 7.08 (1H, d, J= 8.4 Hz, Ar(H5)); 6.59 (1H, d, J=2.6 Hz, Pz(H4)); 6.57 (1H, d, J=2.6 Hz, Pz(H4)); 6.52 (2H, t, J=2.4 Hz, Pz(H4)); 5.31 (2H, s, *p*-OCH$_2$Pz); 5.29 (2H, s, *m*-OCH$_2$Pz); 4.53 (4H, s, PzCH$_2$Br); 2.51 (3H, s, CH$_3$CO). ^{13}C NMR: (CDCl$_3$) δ (ppm) (75 MHz):197.5 (CO); 153.2 (Ar4); 152.1;152.0 (Pz3); 150.4 (Py 2–6); 148.5 (Ar3); 141.7 (Py4); 130.9 (Ar1); 128.7;128.4 (Pz5); 124.0 (Ar6); 114.4 (Ar2); 113.2 (Ar5); 109.9; 109.7 (Py 3,5); 108.4; 108.1 (Pz4); 65.5 (*m*-OCH$_2$Pz); 65.3 (*p*-OCH$_2$Pz); 26.5 (CH$_3$CO); 24.9 (PzCH$_2$Br).

Compound **5b** data. Mp: 110–111 °C. MS:(L-SIMS+):845 (M+H^+, 22), 847 ((M+2)+H^+, 44,), 849 ((M+4)+H^+, 24). ^{1}H NMR: (CDCl$_3$) δ (ppm) (300 MHz):8.42 (4H, m, Pz(H5)); 7.81–7.28 (13H, m, Py(H) and Ar(H)); 7.09 (1H, d, J=8.4 Hz, Ar(H5)); 6.53 (2H, m, Pz(H4)); 6.47 (2H, d, J= 2,6 Hz, Pz(H4)); 5.28 (2H, s, *p*-OCH$_2$Pz); 5.23 (2H, s, *m*-OCH$_2$Pz); 4.48 (4H, s, PzCH$_2$Br).^{13}C NMR: (CDCl$_3$) δ (ppm) (75 MHz): 195.3 (CO); 152.5; 151.9; 151.5; 151.3; 149.7; 148.0; 141.4; 138.0; 131.8; 130.6; 129.6; 128.3; 128.1; 125.6; 115.9; 112.8; 109.4; 108.1; 107.7; 107.4 (ArC); 65.3 (*m*-OCH$_2$Pz); 65.1 (*p*-OCH$_2$Pz); 24.7 (PzCH$_2$Br).

4.2.2. *N*,*N*,*N'*,*N'*-3,4-Bis-{[6-(3-aminomethyl-1-pyrazolyl)-pyridin-2-yl]-1*H*-pyrazol-3-yl-methoxy} acetophenone tetra(*tert*-butil acetate) (6a) and *N*,*N*,*N'*,*N'*-3,4-bis-{[6-(3-aminomethyl-1-pyrazolyl)-pyridin-2-yl]-1*H*-pyrazol-3-yl-methoxy}benzophen-one tetra(*tert*-butyl acetate) (6b). A mixture of the dibromo derivative (**5a** or **5b**) (0.1 mmol), *tert*-butyl iminodiacetate (0.2 mmol) and sodium carbonate (0.5 mmol) in 90 mL of acetonitrile were stirred at rt for 24 h. The solvent was then removed and the resulting residue was washed with water and extracted with dichloromethane. The tetra ester was obtained as a yellow oil and used without further purification. Yield 70–75%.

Compound **6a** data. MS: (L-SIMS+):1135 (M+Na^+, 70). ^{1}H NMR: ($CDCl_3$) δ (ppm) (300 MHz):8.51 (4H, m, Pz(H5)); 8.10–7.53 (6H, m, Py(H) and Ar(H)); 7.44 (2H, t, J=7.6 Hz, Py(H4)); 7.11 (1H, d, J=8.7 Hz, Ar(H5)); 6.55 (4H, m, Pz(H4)); 5.36 (2H, s, p-OCH_2Pz); 5.32 (2H, s, m-OCH_2Pz); 4.03 (4H, s, PzCH_2N); 3.50 (8H, s, NCH_2-CO_2^tBu); 2.53 (3H, s, CH_3CO); 1.47 (36H, s, CO_2^tBu). ^{13}C NMR: ($CDCl_3$) δ (ppm) (75 MHz): 196.6 (CO); 170.4 (CO_2^tBu); 153.5; 152.9; 151.4; 151.2; 150.0; 149.8; 148.3; 141.4; 141.2; 133.1; 130.9; 129.7; 128.3; 128.2; 128.0; 127.7; 123.5; 114.1; 113.0; 109.4; 108.9; 108.8; 108.4; 108.1; 107.7; 107.5 (ArC); 80.9 ($C(CH_3)_3$); 65.4 (OCH_2Pz); 65.2 (OCH_2Pz); 55.3 (NCH_2CO); 51.1(NCH_2Pz); 28.1 ($C(CH_3)_3$).

Compound **6b** data. ^{1}H NMR: ($CDCl_3$) δ (ppm) (200 MHz): 8.50 (4H, m, Pz(H5)); 7.97–7.36 (13H, m, Py(H) and Ar(H)); 7.15 (1H, d, J=8.3 Hz, Ar(H5)); 6.60 (4H, m, Pz(H4)); 5.40 (2H, s, p-OCH_2Pz); 5.35 (2H, s, m-OCH_2Pz); 4.05 (4H, s, PzCH_2N); 3.51 (8H, s, $NCH_2CO_2^t$Bu); 1.48 (36H, s, CO_2^tBu). ^{13}C NMR ($CDCl_3$) δ (ppm) (75 MHz): 195.3 (CO); 170.3 (CO_2H); 153.3; 152.5; 151.4; 151.2; 149.9; 149.6; 148.0; 141.3; 141.2; 138.0; 131.8; 130.6; 129.6; 128.0; 127.9; 128.5; 116.1; 112.9; 109.4; 109.3; 107.6; 107.5 (ArC); 80.9 ($C(CH_3)_3$); 65.4 (OCH_2Pz); 65.2 (OCH_2Pz); 59.9; 55.3 (NCH_2CO); 55.1 (NCH_2Pz); 28.1 ($C(CH_3)_3$.

4.2.3. *N*,*N*,*N*′,*N*′-3,4-Bis-{[6-(3-aminomethyl-1-pyrazolyl)-pyridin-2-yl]-1*H*-pyrazol-3-yl-methoxy} acetophenone tetracetic acid (3a) and *N*,*N*,*N*′,*N*′-3,4-bis-{[6-(3-aminomethyl-1-pyrazolyl)-pyridin-2-yl]-1*H*-pyrazol-3-yl-methoxy}benzophenone tetracetic acid (3b). A solution of tetraester (**6a** or **6b**), (0.07 mmol), trifluoroacetic acid (TFA) (1 mL) in dichloromethane (2 mL) was stirred at rt for 18 h. The solvent is then removed in vacuo and the residue was crushed in diethyl ether. The resulting white solid **3a** or **3b** was filtered. Yield 65–70%.

Compound **3a** data. Mp: 190–192 °C. MS: (L-SIMS+): 889 (M+H^+, 79), 911 (M+Na^+, 100). Anal. calc. for: $C_{13}H_{13}N_5O_2 2CF_3CO_2H$ Calc(%): C 49.47; H 3.79; N 15.05. Found(%): C 49.16; H 3.83; N 15.73. ^{1}H NMR: (DMSO-d_6) δ (ppm) (300 MHz): 8.89 (2H, m, Pz(H5)); 8.84 (2H, m, Pz(H5)); 8.09 (2H, t, J=7.8 Hz, Py(H4)); 7.76–7.63 (6H, m, Py(H3,5) and Ar(H2,6)); 7.30 (1H, d, J=8.5 Hz, Ar(H5)); 6.70 (1H, m, Pz(H4)); 6.67 (1H, m, Pz(H4)); 6.53 (2H, m, Pz(H4)); 5.30 (2H, s, p-OCH_2Pz); 5.26 (2H, s, m-OCH_2Pz); 3.92 (4H, s, PzCH_2N); 3.45 (8H, s, NCH_2-CO_2H); 2.51 (3H, s, CH_3CO). ^{13}C NMR: (DMSO-d_6) δ (ppm) (75 MHz): 196.5 (CO); 172.5 (CO_2H); 152.5; 151.5; 151.2; 149.6; 149.4; 147.8; 142.8; 130.5; 129.4; 129.1; 123.7; 113.6; 113.2; 109.2; 108.8; 108.6 (ArC); 64.6 (OCH_2Pz); 64.4 (OCH_2Pz); 55.7 (NCH_2CO_2H); 51.9 (PzCH_2N); 26.6 (CH_3).

Compound **3b** data. Mp: 184–185 °C. MS: (L-SIMS+): 951 (M+H^+, 13); 973 (M+Na^+, 7). ^{1}H NMR: (DMSO-d_6) δ (ppm) (300 MHz): 8.92 (2H, m, Pz(H5)); 8.85 (2H, m, Pz(H5)); 8.10 (2H, m, Py(H4)); 7.78–7.36 (12H, m, Py(H3,5) and Ar(H)); 6.74 (1H, d, J=2.6 Hz, Pz(H4)); 6.66 (1H, d, J=2,1 Hz, Pz(H4)); 6.54 (2H, m, Pz(H4)); 5.32 (2H, s, p-OCH_2Pz); 5.26 (2H, s, m-OCH_2Pz); 3.93 (4H, s, PzCH_2N); 3.46 (8H, s, NCH_2CO_2H). ^{13}C NMR: (DMSO-d_6) δ (ppm) (75 MHz): 194.8 (CO); 172.5 (CO_2H); 152.1; 150.5; 148.7; 138.3; 131.2; 130.0; 128.2; 125.1; 114.5; 108.0 (ArC); 65.0 (OCH_2Pz); 54.1 (NCH_2CO_2H); 50.5 (PzCH_2N).

Acknowledgements

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Wittig reactions of moderate ylides with heteroaryl substituents at the phosphorus atom

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Abstract—The influence of various heteroaryl substituents at the phosphorus atom to the stereoselectivity of Wittig reactions of allylic and benzylic ylides has been studied. In the case of nitrogen bearing heteroaromatic ligands at the phosphorous atom of benzylidenephosphoranes high *E*-alkene selectivity's of up to 90:10 could be observed. NMR spectroscopic investigations revealed that substituents at the phosphorus have influences on the reactivity of ylides as well as the stability of reaction intermediates. Indications for chelation of lithium ions with ylides could also be detected and will be discussed in this article.
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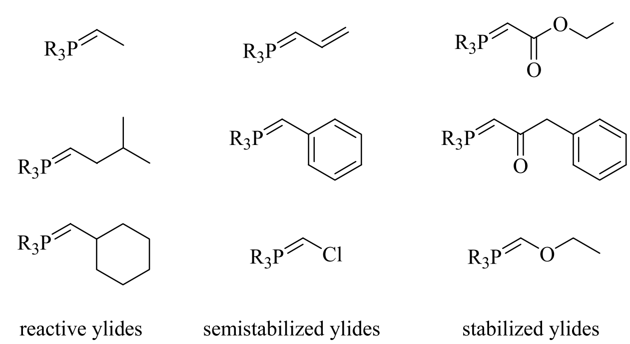
1. Introduction

The Wittig reaction (Scheme 1) is known for more than 50 years and belongs to the most important carbon–carbon double bond forming reactions in organic chemistry[1] and is also used in large scale in industry.[2]

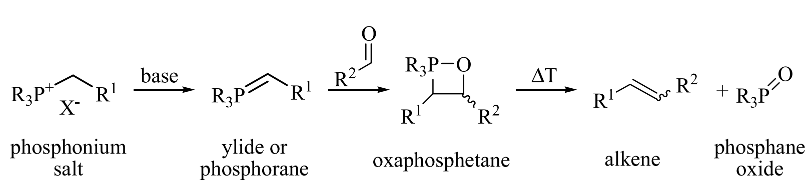
The popularity of the Wittig reaction is mainly due to the regioselective formation of the double bond at the position of the former carbonyl group and the possibility to control the stereoselectivity by applying special reaction conditions.[3] The reaction conditions needed for maximum *Z*- or *E*-alkene selectivity's are strongly dependent on the nature of the ylide used (Scheme 2).

For unstabilized, so called 'reactive ylides', the selective formation of *Z*-alkenes is possible by applying 'salt free' reaction conditions.[4,5] Salt free means performing the reactions in the absence of lithium ions, although other cations (e.g., Na^+ or K^+) can be present. In the presence of lithium ions most often reduced alkene selectivity's are



Scheme 2. Examples for different classes of phosphorus ylides.

observed. The negative influence of lithium ions on the stereochemistry of Wittig reactions is concentration dependent[6] and is attributed to the fact, that lithium salts are at least partially soluble in many organic solvents. Solvated Li^+ is able to complex the carbonyl compound, which then reacts faster with the ylide. This catalysed pathway of the Wittig reaction is rather unspecific, explaining the reduced selectivity's in the presence of Li^+.



Scheme 1. General overview of the Wittig reaction.

Keywords: Wittig reactions; NMR spectroscopy; Ylides; Configuration; Low-temperature chemistry.
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The selective formation of *E*-alkenes in the case of reactive ylides is possible using the Schlosser methodology.[7] For stabilized ylides the selective formation of *E*-alkenes is achieved using phosphorus ylides[8] or PO-ylides within the Horner–Wadsworth–Emmons reaction.[9] *Z*-Alkene selective variants of the Horner–Wadsworth–Emmons reaction with stabilized ylides are also known, for example, the Ando-methodology[10] or the Still–Gennari-variant.[11] Despite these traditional and well established methods for the selective formation of alkenes using reactive and stabilized ylides, there is still a considerable lack of efficient methods for the selective formation of alkenes in the case of moderate or semistabilized ylides. Schlosser reported a *Z*-alkene selective variant of the Wittig reaction for moderate ylides using 'methoxymethoxy-armed' ylides.[3,12] However, the yields are below 50% in many cases due to the steric demand of the 2-methoxymethoxyphenyl groups. The *E*-alkene selective formation of alkenes in the case of moderate ylides has been reported in some cases.[13,14,15]

We were interested in the influence of heteroaromatic substituents at the phosphorus center on stereochemistry and reaction mechanism of Wittig reactions. Previously we reported that reactive ylides bearing 2-furyl substituents at the phosphorus atom react with greatly enhanced *Z*-alkene selectivity's.[16] 2-Pyridyl substituents also increase the *Z*-alkene ratio.[17]

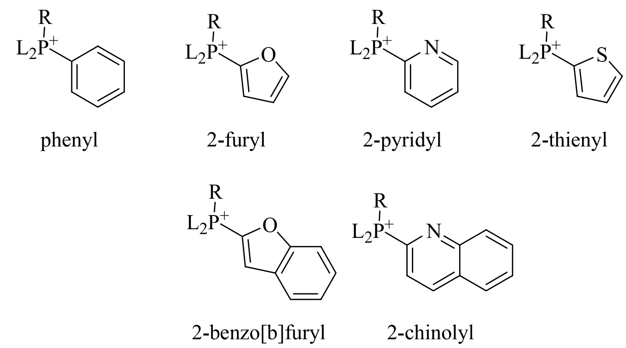
Encouraged by this observation we wanted to test, if those and other heteroaromatic substituents have similar effects of increased alkene selectivity in Wittig reactions of moderate ylides.

Here we want to report our investigations of the influence of a number of different heteroaromatic substituents at the phosphorus to selectivity and yield of Wittig reactions with moderate ylides. The preparative results will be analysed by means of NMR spectroscopy.

2. Results and discussion

For our studies we chose the well investigated Wittig reaction of benzaldehyde with allylidenetriphenylphosphorane or benzylidenetriphenylphosphorane in THF. For deprotonation of the corresponding phosphonium salts either NaHMDS or *n*-BuLi was used. We investigated the influence of the heteroaromatic systems at phosphorus by replacing one or all three standard phenyl substituents by different heteroaromatic systems. The phosphonium salts bearing heteroaromatic substituents at phosphorus are accessible in two to three steps with an overall yield in the range of 50%.

The following heteroaromatic systems have been implemented in phosphonium salts (Scheme 3).



Scheme 3. Overview over the heteroaromatic substituents tested. R denotes allyl or benzyl groups, L represents either a phenyl substituent or a heteroaryl system.

The Wittig reactions with these heteroaromatic systems were repeated two to three times to get reliable results. In the following sections the experimental results of our investigations will be presented, divided in two parts, for the allylic and benzylic Wittig reaction, respectively.

2.1. Results of allylic Wittig reactions

The Wittig reaction of allylidenetriphenylphosphorane with benzaldehyde is well investigated and results were published by a number of different authors.[18,19,20,21] The reported yields vary from 58 to 95% and the stereochemical outcome spread from 44:56 *Z*:*E* to 75:25 *Z*:*E*. The results of our investigations concerning Wittig reactions between allylic ylides bearing heteroaromatic systems and benzaldehyde are presented in Table 1.

The standard reaction with three phenyl substituents at the phosphorus atom is indeed rather unspecific yielding *Z*:*E*-alkene ratios of 55:45 and 73:27 with *n*-BuLi and NaHMDS as base, respectively. The introduction of different heteroaromatic substituents has only minor influences of the stereochemical outcome of allylic Wittig reactions. Interestingly, Wittig reactions with one 2-pyridyl ring at

Table 1. Yield and stereochemical results of Wittig reactions in THF using allylideneheteroaryl-phenylphosphoranes and benzaldehyde with either NaHMDS or *n*-BuLi as base

Compound	*n*-BuLi		NaHMDS	
	Z:*E*[a]	Yield (%)[b]	*Z*:*E*	Yield (%)
AllylideneP$^+$Ph$_3$	55:45	63	73:27	68
AllylideneP$^+$(2-thienyl)Ph$_2$	66:34	68	74:26	46
AllylideneP$^+$(2-furyl)Ph$_2$	70:30	59	75:25	50
AllylideneP$^+$(2-furyl)$_3$	66:34	63	67:33	68
AllylideneP$^+$(benzo[*b*]furyl)Ph$_2$	61:39	33	63:37	62
AllylideneP$^+$(2-pyridyl)Ph$_2$	37:63	32	44:56	12
AllylideneP$^+$(2-pyridyl)$_3$	66:34	19	54:46	20

[a] *Z*:*E* ratios were determined on isolated products using NMR-spectroscopy and GC.
[b] All yields were determined on isolated products.

Table 2. Yield and stereochemical results of Wittig reactions in THF using benzylideneheteroaryl-phenylphosphoranes and benzaldehyde with either NaHMDS or *n*-BuLi as base

Compound	*n*-BuLi		NaHMDS	
	Z:*E*[a]	Yield (%)[b]	*Z*:*E*	Yield (%)
BenzylideneP^+Ph_3	65:35	66	61:39	81
BenzylideneP^+(2-thienyl)Ph_2	79:21	89	53:47	91
BenzylideneP^+(2-furyl)Ph_2	67:33	82	42:58	65
BenzylideneP^+(2-furyl)$_3$	69:31	92	51:49	92
BenzylideneP^+(benzo[*b*]furyl)Ph_2	55:45	85	30:70	81
BenzylideneP^+(benzo[*b*]furyl)$_3$	46:54	87	32:68	86
BenzylideneP^+(2-pyridyl)Ph_2	40:60	79	14:86	85
BenzylideneP^+(2-pyridyl)$_3$	49:51	65	51:49	69
BenzylideneP^+(2-chinolyl)Ph_2	24:76	58	11:89	84

[a] *Z*:*E* ratios were determined on isolated product using NMR-spectroscopy and GC.
[b] All yields were determined on isolated products.

phosphorus yield a slight excess of the *E*-alkene in contrast to the standard reaction. The yield of this Wittig reaction drops from above 60% to less than 20% with nitrogen bearing ligands present in the phosphonium salt. In these cases a side product could be isolated, which is formed via γ-substitution of the allylic ylides.[19]

It has to be summarized that the introduced heteroaromatic substituents at phosphorus had not the anticipated influences on Wittig reactions of allylic ylides. Instead of increased stereoselectivity only minor influences on the stereochemistry of Wittig reactions could be observed. The decreased yield in some cases could be attributed to a concurrence reaction of allylic ylides.

2.2. Results of benzylic Wittig reactions

The Wittig reaction of benzylidenetriphenylphosphorane with benzaldehyde is extraordinary well investigated and many results have been published in literature.[19,22,23,24,25,26] The *Z*:*E* alkene ratios reported vary from of 68:32 to 47:53 with a yield typically above 90%. Our results for Wittig reactions between different benzylidenephosphoranes and benzaldehyde are shown in Table 2.

Our results for the standard reaction with three phenyl groups at phosphorus are in accordance with reported values in literature and proof that this reaction is unspecific. Only a slight preference for the *Z*-alkene could be observed. Introduction of heteroaromatic systems changes the stereochemical results of this Wittig reaction fundamentally. In most cases with NaHMDS as base the *E*-alkene gets the preferred product. With one 2-pyridyl or one 2-chinolyl group present, the *E*-alkene is even formed in ratios of almost 90:10. With *n*-BuLi as base the tendency to form the *E*-alkene is also present, although to a lesser extent. The yield remains in the order of 80% in most cases.

Heteroaromatic substituents at the phosphorus atom have at least in benzylic Wittig reactions significant influences on the stereoselectivity. Often an inversion of the stereoselectivity is obtained, leading to high *E*-alkene selectivity's in two cases. The origin of these influences was unknown at this point and numerous NMR experiments where initiated to clarify the role of those heteroaryl groups at phosphorus.

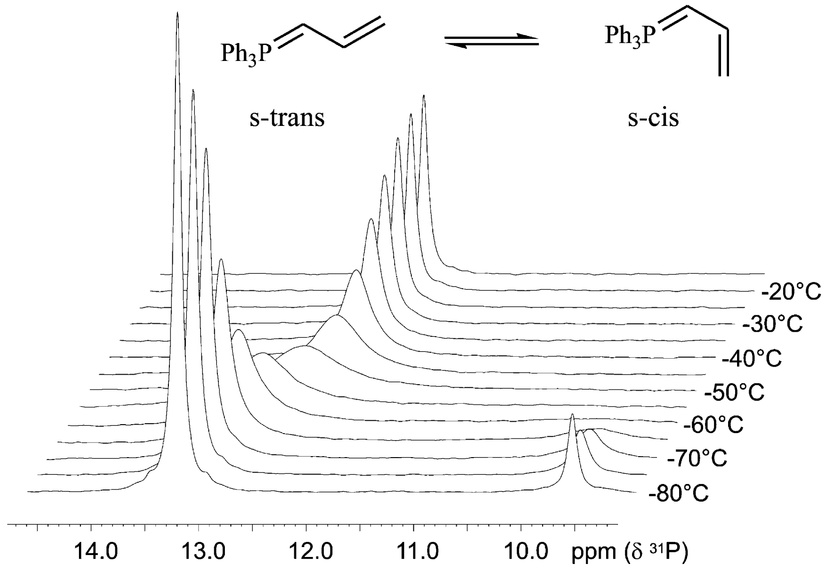
2.3. NMR investigations

We rationalized three kinds of possible influences of the different heteroaryl groups at phosphorus on the stereochemistry of the investigated Wittig reactions.

(a) Steric influences
(b) Chelation of metal ions with ylides
(c) Electronic influences on ylide reactivity

The stereoselectivity of benzylic Wittig reactions was changed the most, when one 2-chinolyl group was present in the ylide. The question arose, if this influence is due to the increased steric demand of the 2-chinolyl group in comparison to the phenyl substituent. We therefore prepared a 2-naphthyl group bearing ylide. The 2-naphthyl group has almost the same steric demand as the 2-chinolyl group, but lacks the heteraoatom. The Wittig reaction of benzylidene(2-naphthyl)diphenylphosphorane with benzaldehyde yielded *Z*:*E*-alkene ratios of 73:27 with *n*-BuLi as base and 67:33 with NaHMDS. These values are almost identical to the results of the similar Wittig reaction with three phenyl groups at phosphorus presented in Table 2 (entry 1). Furthermore, the stereochemistry of benzylic Wittig reactions is similar with one or three benzo[*b*]furyl groups at phosphorus (Table 2, entries 5 and 6). We therefore rule out any significant steric influence of the investigated heteroaromatic systems on the stereo selectivity of the presented Wittig reactions with benzylic ylides.

Another possible influence on stereochemistry of Wittig reactions might be the chelation of solvated metal ions between the carbanion site and the heteroatom of the heteroarylsubstituent. Such chelated species might possess a preferred conformation in the transition state of the Wittig reaction, which could be an explanation for the selective formation of one alkene.[17] To investigate the possible presence of such species we switched our attention to allylic ylides. Although the stereo selectivity of Wittig reactions with allylic ylides was rather unaffected by heteroaromatic systems, these species in contrast to benzylic ylides showed dynamic behaviour at different temperatures. This circumstance allowed NMR studies concerning chelation. In Scheme 4 ^{31}P NMR spectra of allylidenetriphenylphosphorane in THF are shown, which were recorded at



Scheme 4. ^{31}P NMR spectra of allylidenetriphenylphosphorane at different temperatures.

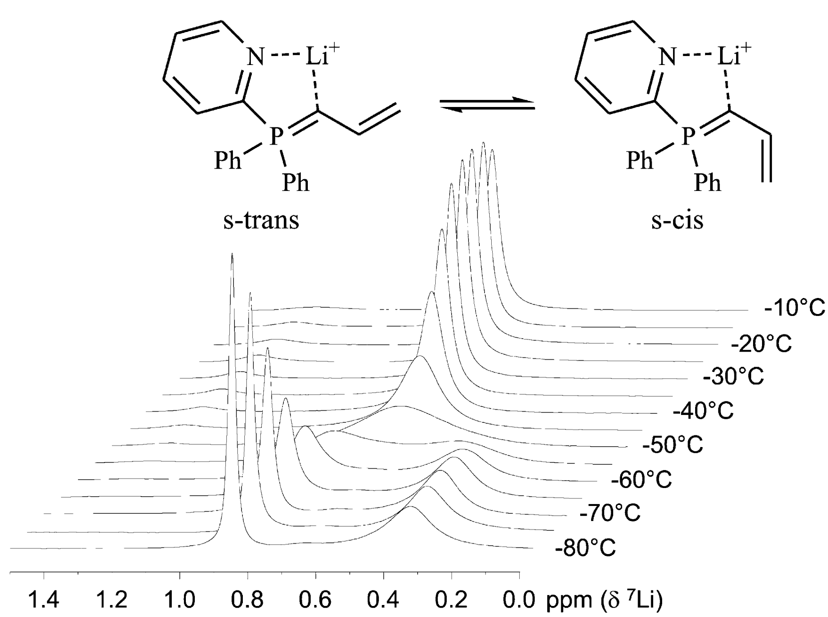
different temperatures between −80 and −15 °C. The ylide has been prepared using NaHMDS as base.

At higher temperatures one sharp signal represents the phosphorus ylide. At temperatures below −50 °C two different conformers are present in the solution. The coalescence temperature for this dynamic and reversible process is at −50 °C. The calculated free activation enthalpy is 40.8 kJ/mol.[27] To the best of our knowledge such dynamic behaviour of allylidenephosphoranes has so far not been described in literature.

In Scheme 5 ^{7}Li NMR spectra of allylidene(2-pyridyl)-diphenylphosphorane are shown, which were recorded at temperatures between −80 and −10 °C. This ylide was prepared using *n*-BuLi as base.

Again a dynamic interconversion of the two conformers could be detected, the coalescence temperature lies also at −50 °C. It has to be stressed, that here the dynamic process has been detected via ^{7}Li NMR spectra, although the lithium ions are not covalently bound to the phosphorus ylide. This result therefore is a strong indication for the presence of lithium–ylide complexes, which have been postulated above. The two different ^{7}Li NMR-signals at lower temperatures do not represent different lithiated species, since the same splitting can be observed in Scheme 4, were no ^{7}Li-ions were present. Unfortunately, numerous other methods, including several HOESY experiments[28,29,30] and the detection of ^{15}N-chemical shifts in possibly chelated structures, failed to provide any further evidence for the existence of such lithium–ylide complexes.

Nevertheless it has to be concluded, that these investigations give a clear indication for the presence of lithium ion–ylide chelate complexes, since the conformational changes in the



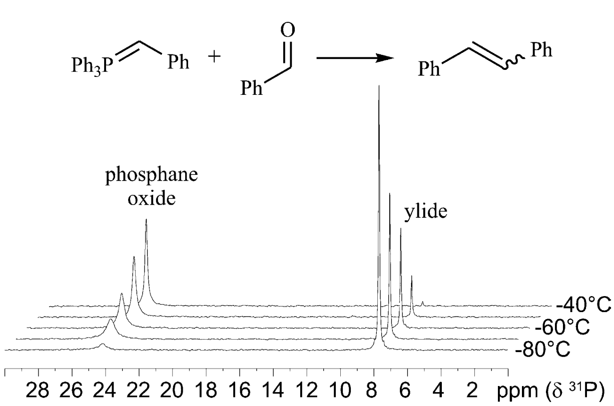
Scheme 5. ^{7}Li NMR spectra of allylidene(2-pyridyl)diphenylphosphorane at different temperatures.

ylide structure can be detected via ^{31}P NMR spectroscopy as well as ^{7}Li NMR.

Finally, we wanted to investigate the possible influence of heteroaryl groups at phosphorus on ylide reactivity. Again NMR is the most valuable tool for this purpose. Different phosphorus ylides bearing heteroaromatic substituents were prepared in NMR tubes. All ylides were prepared using the base NaHMDS, since the highest stereoselectivity's could be observed in this case. Furthermore, with the base *n*-BuLi often several peaks are observed for one species, which are broadened at lower temperatures, most likely due to the formation of different lithiated species. The Wittig reaction was started by adding 1.5 equiv of benzaldehyde at low temperatures. The reaction was then monitored with ^{31}P NMR spectra at temperatures between −80 °C and room temperature. For these experiments we switched our attention back to benzylic ylides, since they were generally more influenced by heteroaryl substituents than allylic ylides.

First of all we investigated the standard reaction with benzylidenetriphenylphosphorane and benzaldehyde in THF. The reaction was started by addition of the benzaldehyde at −80 °C and after that the NMR tube was put into the NMR spectrometer, which was precooled to −80 °C. The first ^{31}P NMR spectrum could be recorded ca. 1 min after addition of the benzaldehyde. In the first spectrum a sharp signal at 8 ppm was detected representing the phosphorus ylide. At 24 ppm a signal slowly arose, corresponding to the phosphane oxide. Since, here moderate ylides are under investigation, the reaction from the ylide to the phosphane oxide is rather slow at low temperatures of −80 °C. No oxaphosphetane species could be detected in the expected chemical shift range, in accordance with earlier investigations concerning benzylic Wittig reactions.[31] As expected, the reaction was slow at −80 °C. After 20 min ca. 45% of the ylide had reacted to phosphane oxide and alkene. After that point the reaction rate dramatically decreased, so that no further decay of the ylide signal could be detected at −80 °C. The reaction mixture had to be warmed to −70 °C in order to let the reaction proceed any further. The progress of the reaction at temperatures between −80 and −40 °C is shown in Scheme 6.

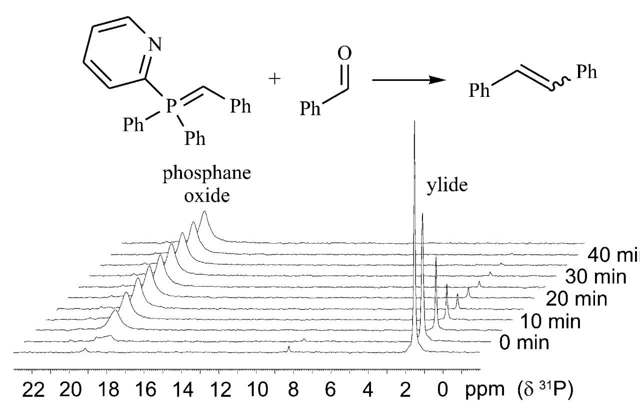
Each spectrum was recorded after 5 min at the temperature denoted in Scheme 6. The temperature was kept for 20 min and then warmed further. At a temperature of −40 °C the reaction was finished. All the ylide had been reacted into alkene and phosphane oxide.



Scheme 6. Progress of the Wittig reaction between benzylidenetriphenylphosphorane and benzaldehyde.

In conclusion, the standard benzylic Wittig reaction with three phenyl rings at the phosphorus atom proceeds at temperatures between −80 and −40 °C. At very low temperatures of −80 °C the reaction gets very slow, after 50% of the starting material is consumed. The mixture had to be warmed, to let the reaction proceed further. This might be an explanation, why Wittig reactions of moderate ylides are rather unspecific, since the reaction takes place over a temperature span of 40 °C. Different thermal influences act to the transition state of the reaction, yielding different alkene ratios at each temperature. These different alkene ratios add to a rather unspecific overall reaction.

The highest *E*-alkene selectivity for benzylic Wittig reactions could be observed, when one 2-pyridyl substituent was bound to the phosphorus atom. This reaction was also monitored by ^{31}P NMR spectroscopy. The result of this experiment is shown in Scheme 7.

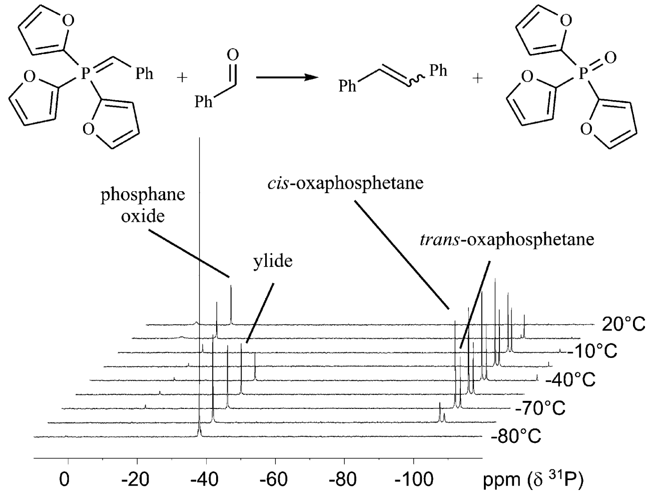


Scheme 7. Progress of the Wittig reaction between benzylidene(2-pyridyl)diphenylphosphorane and benzaldehyde.

All shown spectra were recorded at a temperature of −80 °C. Again no oxaphosphetane species could be detected. More importantly, the reaction is finished after 40 min at −80 °C. The introduction of one 2-pyridyl substituent thus greatly increases the ylide reactivity. This might explain the high alkene selectivity in this reaction. The reaction proceeds completely at low temperatures, therefore a change of temperature does not lower the alkene selectivity. However, unexplained remains the fact, that the *E*-alkene is the preferred product, which is formed with an excess of almost 90:10 in this reaction.

Finally, we want to present the effect, which 2-furyl substituents have in this benzylic Wittig reaction. In Scheme 8 ^{31}P NMR spectra of the Wittig reaction between benzylidenetris-(2-furyl)phosphorane with benzaldehyde are shown.

Like in the standard case with three phenyl rings at phosphorus, the reaction mixture has to be warmed to let the reaction proceed. But in contrast to the case above, here



Scheme 8. Progress of the Wittig reaction between benzylidenetris(2-furyl)phosphorane and benzaldehyde at −80 °C.

we were able to detect oxaphosphetane intermediates. They are formed by the reaction of benzaldehyde with the ylide and remain stable until ca. −20 °C. This is the first time well characterized oxaphosphetane signals can be observed in the case of benzylic Wittig reactions. Furthermore, the two isomers *cis* and *trans* could be resolved in the chemical shift region of −100 ppm. The two peaks were assigned to the *cis*- and *trans*-oxaphosphetane taking into account, that the *cis*-oxaphosphetane is less stable then the *trans*-isomer.[31] This explains why at 5 °C the signal for the *cis*-isomer is almost gone, whereas still significant amounts of the *trans*-oxaphosphetane are present. In the Wittig reaction of benzylidene-(2-furyl)diphenylphosphorane, where only one 2-furyl ring is present, also oxaphosphetanes could be observed. However, in this case, only one signal was resolved for the two oxaphosphetane species. Furthermore, the oxaphosphetanes were only semistable in this case. They were formed up to a maximum concentration, which remained constant until the beginning of decomposition at −10 °C. We can conclude that 2-furyl substituents stabilize oxaphosphetane intermediates and the amount of stabilisation is higher the more 2-furyl rings are present within the phosphorane. Additionally 2-furyl systems have a dramatic shielding effect on the phosphorus nucleus. These two effects have been observed previously for reactive ylides.[16] In the case of reactive ylides the stabilization of oxaphosphetanes was strong enough that these intermediates could be isolated at ambient temperatures allowing the recording of a crystal structure.

In summary we could show, that heteroarylsubstituents at the phosphorus nucleus change the reactivity of phosphorus ylides, which has consequences for the reaction intermediates and most important for the observed alkene ratio. 2-Pyridyl substituents increase the ylide reactivity so, that the Wittig reaction is finished in less than 1 h at −80 °C. This results in a high *E*-alkene selectivity. In contrast 2-furyl substituents increase the stability of reaction intermediates, allowing for the first time the detection of oxaphosphetanes in the case of moderate ylides, which are stable until −20 °C.

3. Conclusion

This work investigated the influence of heteroaryl substituents at phosphorus on the stereochemistry of Wittig reactions of moderate ylides. With standard phenyl ligands at phosphorus Wittig reactions of allylic and benzylic ylides are rather unspecific. While the introduction of heteroaryl substituents does not significantly change the stereochemistry of allylic Wittig reactions, the situation is different with benzylic Wittig reactions. With the introduction of heteroaryl substituents the *E*-alkene gets the predominant product in most reactions. With one nitrogen containing heteroaromatic substituent the *E*-alkene selectivity almost reaches 90:10.

The reasons for these influences have been investigated by three different approaches. First, steric interactions of the heteroaromatic systems can be ruled out, since the stereochemistry of benzylic Wittig reactions is not changed if one phenyl or one bigger naphthyl ligand is present. Second, we investigated the possibility of a metal ion chelation with ylides. We observed a conformational equilibrium for allylic ylides in ^{31}P NMR as well as ^{7}Li NMR spectra, indicating some kind of contact between both nuclei. The third investigation concerned the influence of heteroaryl substituents on ylide reactivity. We could show, that one 2-pyridyl substituent greatly increases the reactivity of benzylic ylides, so that the Wittig reaction proceeds completely at very low temperatures. This circumstance favours high alkene selectivity's. We could show, that 2-furyl substituents greatly increase the stability of oxaphosphetane intermediates. The reasons for this stabilization and the unusual values of ^{31}P NMR chemical shift will be discussed elsewhere.

4. Experimental

4.1. General remarks

All reactions were carried out with exclusion of air and moisture. THF was dried over sodium/benzophenone and freshly distilled prior to use. Benzaldehyde was also distilled. All other reagents were bought from commercial sources and were used without further purification.

NMR spectra were recorded with a Bruker DRX 400 spectrometer in $CDCl_3$, with TMS as internal shift reference. ^{31}P- and ^{7}Li NMR spectra were calibrated according to the Ξ-scale, in which nitromethane is at 0 ppm.[32] NMR investigations of Wittig reactions were performed in [D_8]THF, shifts being referred to traces of undeuterated solvent. High resolution mass spectra were recorded with a Bruker FT-ICR-MS apex II with ESI technique.

4.2. Synthesis of phosphanes

Phosphanes with 2-furyl, 2-thienyl or 2-benzo[*b*]furyl substituents were prepared according to a procedure described by Allen et al.[33] 2-Pyridyl bearing phosphanes were prepared by a procedure starting from 2-bromopyridine.[34] Phosphanes with 2-chinolyl substituents were prepared by the same procedure, however 2-bromochinolin is not commercially available and had to be synthesised.[35]

4.3. Synthesis of phosphonium salts

One equivalent phosphane was dissolved in toluene and stirred with 2 equiv allyl bromide or benzyl bromide at temperatures of 80 °C until a white precipitate had formed. If this method was unsuccessful, the reaction was performed in neat allyl bromide or benzyl bromide. The precipitate was filtered off, washed and dried. If necessary recrystallisation was performed in ethanol/ethyl acetate.

4.4. Wittig reactions

Wittig reactions were performed as described previously.[16]

4.4.1. Allyl(2-thienyl)diphenylphosphonium bromide. Yield 78%; mp 178–182 °C. ^{31}P NMR ($CDCl_3$): $\delta=16.7$. MS (FAB): $m/z=389.0$ and 387.0 (1:1).

4.4.2. Allyl(2-furyl)diphenylphosphonium bromide. Yield 88%; mp 180–185 °C. ^{31}P NMR ($CDCl_3$): $\delta=11.4$. HR-MS: $m/z=293.10874$ [$C_{19}H_{18}OP^+$], Calcd 293.10898.

4.4.3. Allyltris(2-furyl)phosphonium bromide. Yield 45%; mp 153–157 °C. ^{31}P NMR ($CDCl_3$): $\delta=-14.3$. HR-MS: $m/z=273.06735$ [$C_{15}H_{14}O_3P^+$], Calcd 273.06751.

4.4.4. Allyl(2-benzo[*b*]furyl)diphenylphosphonium bromide. Yield 76%; mp 152–156 °C. ^{31}P NMR ($CDCl_3$): $\delta=12.8$. HR-MS: $m/z=343.12465$ [$C_{23}H_{20}OP^+$], Calcd 343.12463.

4.4.5. Allyl(2-pyridyl)diphenylphosphonium bromide. Yield 78%; mp 187–190 °C. ^{31}P NMR ($CDCl_3$): $\delta=17.0$. HR-MS: $m/z=304.12452$ [$C_{20}H_{19}NP^+$], Calcd 304.12496.

4.4.6. Allyltris(2-pyridyl)phosphonium bromide. Yield 83%; mp 106–110 °C. ^{31}P NMR ($CDCl_3$): $\delta=9.8$. HR-MS: $m/z=306.11548$ [$C_{18}H_{17}N_3P^+$], Calcd 306.11546.

4.4.7. Benzyl(2-thienyl)diphenylphosphonium bromide. Yield 89%; mp >260°C. ^{31}P NMR ($CDCl_3$): $\delta=18.4$.MS (FAB): $m/z=439.3$.

4.4.8. Benzyl(2-furyl)diphenylphosphonium bromide. Yield 84%; mp 260–263 °C. ^{31}P NMR ($CDCl_3$): $\delta=13.2$. HR-MS: $m/z=343.12403$ [$C_{23}H_{20}OP^+$], Calcd 343.12463.

4.4.9. Benzyltris(2-furyl)phosphonium bromide. Yield 90%; mp 218–220 °C. ^{31}P NMR ($CDCl_3$): $\delta=-12.7$. HR-MS: $m/z=323.08282$ [$C_{19}H_{16}O_3P^+$], Calcd 323.08316.

4.4.10. Benzyl(benzo[*b*]furyl)diphenylphosphonium bromide. Yield 98%; mp 165–168 °C. ^{31}P NMR ($CDCl_3$): $\delta=14.5$. HR-MS: $m/z=393.140347$ [$C_{27}H_{22}OP^+$], Calcd 393.14028.

4.4.11. Benzyltris(benzo[*b*]furyl)phosphonium bromide. Yield 83%; mp 180–185 °C. ^{31}P NMR ($CDCl_3$): $\delta=-6.8$. HR-MS: $m/z=473.1303$ [$C_{31}H_{22}O_3P^+$], Calcd 473.13011.

4.4.12. Benzyl(2-chinolyl)diphenylphosphonium bromide. Yield 61%; mp ca. 265 °C. ^{31}P NMR ($CDCl_3$): $\delta=19.5$. HR-MS: $m/z=404.15630$ [$C_{28}H_{23}NP^+$], Calcd 404.15626.

4.4.13. Benzyl(2-pyridyl)diphenylphosphonium bromide. Yield 89%; mp 217–220 °C. ^{31}P NMR ($CDCl_3$): $\delta=19.6$. HR-MS: $m/z=354.14010$ [$C_{24}H_{21}NP^+$], Calcd 354.14061.

4.4.14. Benzyltris(2-pyridyl)phosphonium bromide. Yield 54%; ^{31}P NMR ($CDCl_3$): $\delta=9.8$. HR-MS: $m/z=356.13122$ [$C_{22}H_{19}N_3P^+$], Calcd 356.13111.

4.4.15. Benzyl(2-naphthyl)diphenylphosphonium bromide. Yield 71%; mp 253–255 °C. ^{31}P NMR ($CDCl_3$): $\delta=23.4$. HR-MS: $m/z=403.16108$ [$C_{29}H_{24}P^+$], Calcd 403.16101.

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Short synthesis of hydroxylated thiolane and selenolane rings from mono-benzylated pentitols and aldoses dithioacetals bis-thionocarbonates as bis-electrophilic substrates

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Abstract—1-*O*-Benzylpentitols (with D-*arabino*, D-*lyxo*, D,L-*xylo* and D,L-*ribo* configurations) and aldoses dibenzyldithioacetals (with L-*arabino*, D-*lyxo*, D-*xylo*, D-*ribo*, D-*galacto*, D-*gluco* and D-*manno* configurations) were directly and efficiently transformed into their cyclic bis-thionocarbonate derivatives (61–73%) by reaction with diimidazolyl thione (Im_2CS) in 1,4-dioxane. These bis-electrophilic adducts react regioselectively with $Na_2S\cdot 9H_2O$ or Se/$NaBH_4$ to lead regioselectively to the corresponding thiolane and selenolane rings in good yields for a short synthesis (47–65%).
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1. Introduction

It is currently well known that the thiaheterocycles analogues of sugars are weak or not at all inhibitors of glycosidases[1] in contrast with aza-sugars analogues. In the later field, considerable development was realised since the first discovery of glycosidase inhibition effect of deoxynojirimicine.[2] However, since the first structural elucidation of salacinol (**A**) (Fig. 1),[3] potent α-glycosidases inhibitor used in treatment of type-II non-insulinodependant diabetes,[4] a renewal of interest has demonstrated for thioanhydro sugars. Indeed, this zwitterionic compound involves a thiolane subunit with D-*arabino* configuration where the trivalent sulfide cation mimics the oxonium ion in transition state of the enzymatic hydrolysis process.[5] We and other groups had developed some synthetic strategy to obtain a wide library of thiaheterosugars during the last years.[6] For instance, we had published the first short synthesis of the racemic mixture of arabinothiolane subunit of salacinol (**B**) from S-heterocyclisation of bis-cyclic sulfate of monobenzyl-D,L-xylitol.[6a] The latter was obtained from regioselective benzylation of xylitol stannylether complex[7] and subsequent two steps bis-cyclic sulfates synthesis. Using α,ω-dibromoalditol intermediates synthesised regioselectively from bidirectional transformation of free alditols we have provided one of the most versatile synthesis of thia and selenaanhydroalditols (Scheme 1).[8]

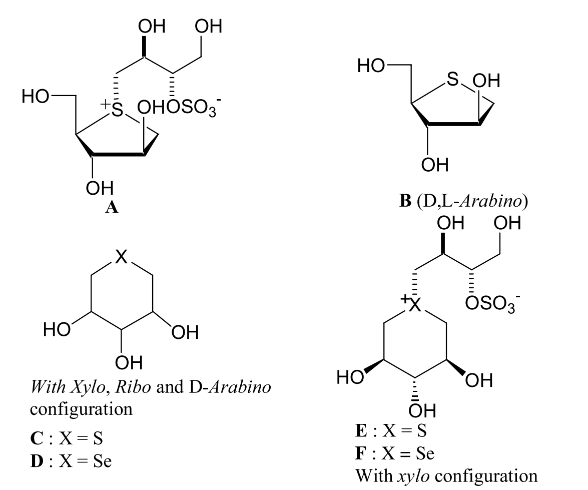
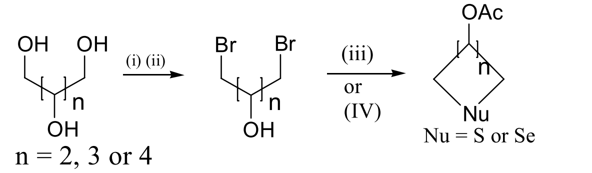


Figure 1.

Some of them were recently used by Pinto and co-workers in the synthesis of tetrathiopyrane and selenopyrane analogues of salacinol **E** and **F**.[9]



Scheme 1. (i) AcBr, 1,4-dioxane, rt, 16 h; (ii) Ac_2O, pyridine; (iii) Na_2S, DMSO; (iv) Se, $NaBH_4$, H_2O, DMSO, rt, <10 min.

Keywords: Alditols; Aldoses; Cyclic-thionocarbonate; Thiolane; Selenolane.
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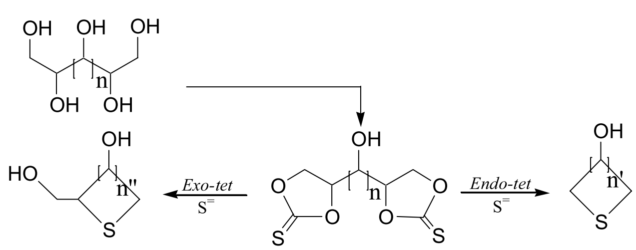
This bis-electrophilic heterocyclisation strategy was also developed with other intermediate such as bis-epoxides,[10] bis-sulfonates,[11] and more recently by us with bis-cyclic thionocarbonates[12] in the presence of sodium sulfide nonahydrate. Some six- and seven-membered rings obtained following this approach could subsequently be converted to tetrahydrothiophenes by transannular processes by reaction with trimethylsilyl halides,[13] with PPh_3/CBr_4 and when undergoing the Mitsunobu reaction[1] or by intramolecular S_N2 substitution with appropriately mesylated thiepane.[14]

The lack of general strategies to thiolane ring with differing configurations led us to explore the heterocyclisation of bis-cyclicsulfates of linear polyols. If the use of this kind of bis-electrophilic intermediate obtained by oxidation of the corresponding cyclic sulfite gave good results in the partially protected alditols series,[6a] substrates like pentose dithioacetals met a serious limitation because of the oxidation induced α,β-unsaturated monosulfoxide formation.[15] Owing to this undesirable dithioacetal oxidation, the use of cyclic-thionocarbonates as electrophilic intermediates appears to be an alternative because of their easy formation from diols and polyols. For instance, the 1,2:4,5- and 1,2:5,6-bis-thionocarbonates were formed regioselectively by reaction of the corresponding alditols stannylene acetal complexes and PhOCSCl (Scheme 2). We carried out, on this bis-electrophilic system, for the first time, the thiaheterocyclisation using a $S^{=}$ bi-anion as a soft binucleophilic reagent. Unfortunately this original heterocyclisation often led to inseparable mixtures of *endo-tet* and *exo-tet* thiaheterocycles.[12]



Scheme 2. $n=0$ (Tetritols) or 1 (pentitols): $n'=2$, 3 or 4; $n''=2$ or 3.

However the heterocyclisation involving primary–secondary electrophilic sites in an *exo-tet* process is of interest and could be exploited in the synthesis of a wide range of thiolane rings. Herein, we describe a short and versatile synthesis of hydroxylated thiolane derivatives from monobenzylpentitols with D-*arabino*, D-*lyxo*, D,L-*xylo* and D,L-*ribo* configurations, and from the dibenzyldithioacetal of aldoses with L-*arabino*, D-*lyxo*, D-*xylo*, D-*ribo*, D-*galacto*, D-*gluco* and D-*manno* configurations. Both pentitols and aldose dibenzyldithioacetal substrates react smoothly with diimidazolyle thione in dry 1,4-dioxane to give the corresponding bis-thionocarbonates in good yields. The subsequent thiaheterocyclisation and on other hand selenaheterocyclisation gave thiolane and selenolane rings with various configurations.

2. Results and discussion

The first synthesis of the bis-thionocarbonate derivatives was carried out with a mixture of 1-*O*-benzyl-D-arabinitol (**1**) and 1-*O*-benzyl-D-lyxitol (**5**) (Table 1, entry 1) obtained regioselectively from the D-arabinitol stannylether complex and BnBr in a 52% overall yield (in a 1:1 ratio).[7] This inseparable mixture was transformed to the corresponding bis-cyclic thionocarbonate derivatives **2** (D-*arabino*) and **6** (D-*lyxo*) separated by chromatography on silica gel in 32 and 40% yields, respectively (yields evaluated from the starting mixture of **1** and **5**). The identification of these two regioisomers was achieved by NMR spectroscopy of their anhydro derivatives D-*arabino* **2c** (from 2,3-deprotection, path 1, Scheme 3a) or L-*ribo* **2f** (from 4,5-deprotection, path 2) and D-*lyxo* **6c** (from 2,3-deprotection, path 1, Scheme 3b) or L-*xylo* **6f** (from 4,5-deprotection, path 2) obtained in 31 and 47% yields, respectively, by reaction of **2** and **6** with a catalytic amount of MeONa in MeOH. Compounds **2c** (or **2f**) and **6c** (or **6f**) were characterised by coupling constants for the H-3,4 *syn*-methine configuration $J_{3,4}=5.01$ Hz and for the *trans*-methine configuration of H-2,3, $J_{2,3}=3.01$ Hz respectively. Consequently, by TLC performed on silica gel, the most polar is the bis-thionocarbonate derivative of D-lyxose **6** ($R_f=0.08$, 7/3 hexane–EtOAc) and the less polar is the D-*arabino* derivative **2** ($R_f=0.17$). The possible regioselective deprotection of cyclic thionocarbonates in compounds **2** and **5** had not been elucidated until now.

With the rest of the pentitol and pentose derivatives the vicinal bis-cyclic thionocarbonates were formed similarly in good isolated yields (from pentitols: **10** (D,L-*xylo*) (61%), **14** (D,L-*ribo*) (72%) (entries 2 and 3); from pentoses: **18** (D-*xylo*) (73%), **22** (D-*ribo*) (76%), **26** (L-*arabino*) (68%) and **30** (D-*lyxo*) (73%) (entries 4 to 7). With hexoses bearing five free hydroxyl groups, the configurations of the hexoses studied appeared to control the regioselectivity of the bis-cyclic thionocarbonate formation. Thus the D-*galacto* and the D-*gluco* isomers **33** and **37** showed 2,3:5,6-bis-cyclic thionocarbonate formation with the hydroxyl in the 4-position left free (entries 8 and 9). In contrast, the *manno* configuration **41** led to the bis-cyclic thionocarbonate derivative **42** with the free 2-OH in 23% yield and **43** with the imidazolyl thionocarbonate group in the 2-position in 34% yield.

The 2,3:5,6 positions in **34** (*galacto*) and **38** (*gluco*) and 3,4:5,6 position of the cyclic thionocarbonate groups in **42** (*manno*) were easily confirmed by ^{13}C NMR spectroscopy. In fact, while **34** and **38** showed 2-C and 4-C chemical shifts at approximately 84.8 and 69.6 ppm, respectively, the *manno* compound **42** showed 2-C at 72.5 and 4-C at 82.6 ppm. The 2-C signals in **34** and **38**, and 4-C signal in **42** were shifted upfield due to the cyclic thionocarbonate group. The unexpected formation of the *trans* 2,3:5,6-bis-thionocarbonate **38** is probably due to the bent conformation involved by the stereoelectronic 1,3-parallel interaction between 2-OH and 4-OH in zig-zag form of the *gluco* configuration.

The first thiaheterocyclisation attempted with **2** by reaction with $Na_2S\cdot 9H_2O$ in DMSO at room temperature led to a complex mixture with no formation of the expected thioanhydro derivative. When the temperature was

Table 1. Isolated yields of bis-thionocarbonates and thia[a] and selenaheterocycles[b] obtained from monobenzyl pentitols and aldose dithioacetal derivatives[c] as substrates

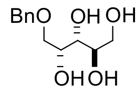
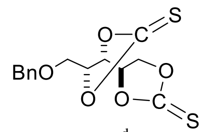
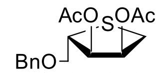
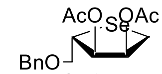
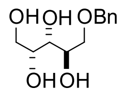
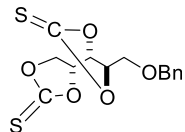
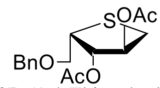
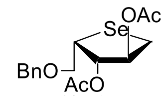
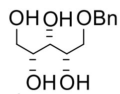
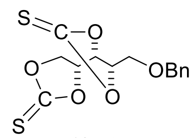
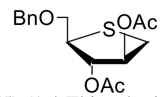
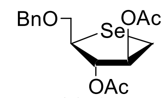
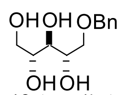
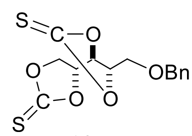
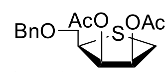
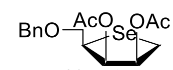
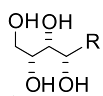
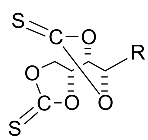
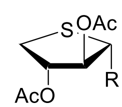
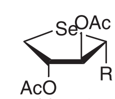
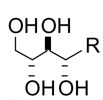
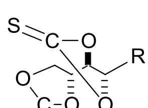
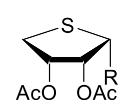
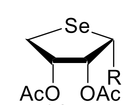
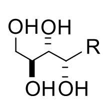
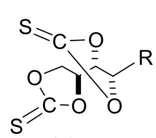
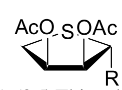
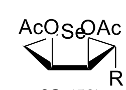
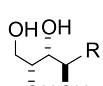
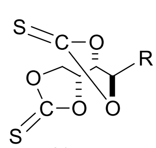
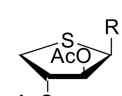
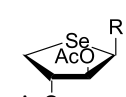
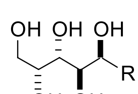
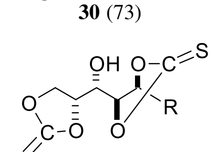
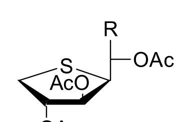
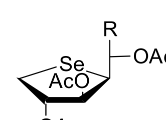
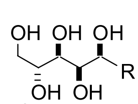
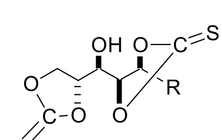
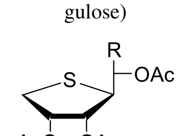
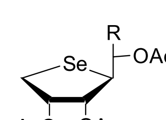
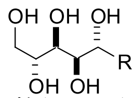
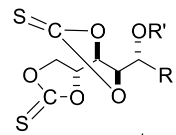
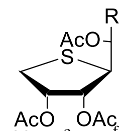
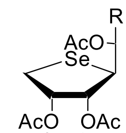
Entry	Substrate	Bis-thionocarbonate (yield (%))	Solated thiolane yield (%)	Isolated selenolane yield (%)
1	 **1** (1-*O*-Bn-D-*arabino*) +	 **2** (32[d])	 **3** (47) (2,5-thioanhydro-D-*ribo* or 1,4-L-*ribo*)	 **8** (50)
	 **5** (5-*O*-Bn-D-*arabino* or 1-*O*-Bn-D-*lyxo*)	 **6** (40[d])	 **7** (65) (1,4-Thioanhydro-L-*xylo* or 2,5-D-*xylo*)	 **12** (50)
2	 **9** (D,L-*xylo*)	 **10** (61)	 **11** (55) (1,4-Thioanhydro-D,L-arabino)	 **16** (50)
3	 **13** (D,L-ribo)	 **14** (72)	 **15** (45) (2,5-Thioanhydro-D,L-arabino)	 **20** (45)
4	 **17** (D-*xylo*)	 **18** (73)	 **19** (60) (2,5-Thioanhydro-D-lyxose)	 **20** (45)
5	 **21** (D-*ribo*)	 **22** (76) **22** (76)	 **23** (0) (2,5-Thioanhydro-D-*arabino*)	 **24** (0)
6	 **25** (L-*arabino*)	 **26** (68)	 **27** (50) (2,5-Thioanhydro-L-ribose)	 **28** (50)
7	 **29** (D-*lyxo*)	 **30** (73)	 **31** (60) (2,5-Thioanhydro-D-xylose)	 **32** (55)
8	 **33** (D-*galacto*)	 **34** (65)	 **35** (3,6-Thioanhydro-D-gulose)	 **36** (55)
9	 **37** (D-*gluco*)	 **38** (60)	 **39** (3,6-Thioanhydro-D-allose)	 **40** (53)

Table 1 (*continued*)

Entry	Substrate	Bis-thionocarbonate (yield (%))	Solated thiolane yield (%)	Isolated selenolane yield (%)
10	 **41** (D-*manno*)	 **42** R=H (23) **43** R′=CSIm (34)	 **44** (36[e]) (16[f])	 **45** (50)

[a] 1.5 equiv of $Na_2S \cdot 9H_2O$, 80 °C, 1 h, DMSO.
[b] Se, $NaBH_4$, H_2O, DMSO, 80 °C, 45 mn.
[c] HCl (12 N), BnSH (2.2 equiv).
[d] From starting mixture of **2** and **5**.
[e] From isolated **42**.
[f] From isolated **43**. R=CH(SBn).

increased to 80 °C for 1 h, 2,3-di-*O*-acetyl-5-*O*-benzyl-1,4-thioanhydro-L-ribitol (**3**) was isolated after acetylation in 47% yield (entry 1). The same conditions, when applied to **6** with the D-*lyxo* configuration, led to the L-*xylo* thioanhydro derivative **7** in a better yield (65%) (entry 1). This is probably due to the steric hindrance caused by the *cis*-configuration of the 3-OH/4-OH groups in the transition state which limits the thiaheterocyclisation of **2**. Steric hindrance could also be invoked in the cases of **15** (entry 3, 45%) and in a large part with **23** (entry 5) for which the formation was excluded due to the interaction between 3-OH, 4-OH and the bulky dibenzyldithioacetal group in the *syn*-position.

A very interesting result was obtained with hexose dithioacetals where the 1,4-thiolane rings were formed regioselectively from both 2,3:5,6 and 3,4:5,6-bis-cyclic thionocarbonate derivatives. Thus the 2,4,5-tri-*O*-acetyl-3,6-thioanhydro-D-gulose (**35**), D-allose (**39**) and D-altrose (**44**) (Entries 8 to 10) were obtained in 60, 51 and 36% yields, respectively. With the D-*manno* configuration, the 2-imidazolylthionocarbonate **43** was also submitted to the thiaheterocyclisation reaction. Only a 16% yield was extracted from a complex mixture.

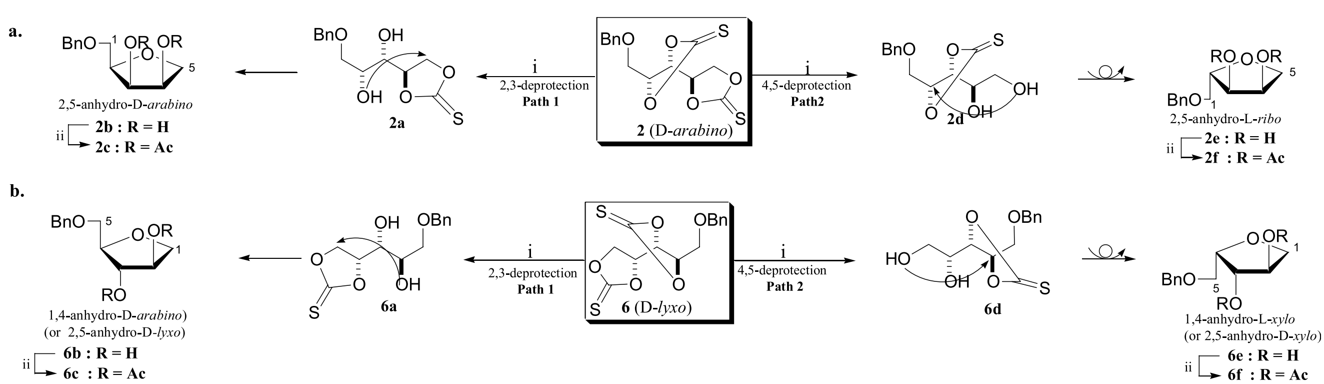
The 3,6-thiaheterocyclisation leading to **35**, **39** and **44** is justified by ^{13}C NMR spectroscopy which shows 3-C signals at 50.6, 49.2 and 49.6 ppm, and 6-C signals at 36.1, 31.0 and 31.1 ppm, respectively.

On other hand, it is well recognised that some diseases such cancer,[16] aids and the neurodegenerative diseases (e.g., Parkinson and Alzheimer)[17] emerging from abnormally high production of free radicals (oxidative stress).[18] This is attributed to antioxidants deficiency like vitamins[19] or enzymes such selenodependent glutathione peroxidase.[20] This enzymatic antioxidant catalysed the hydroperoxyde reduction (reduced metabolite precursor of deleterious $HO^{\cdot}$ free radical) with concomitant oxidation of a biologically important thiol, the glutathione.[21]

It was reported that small organic molecules like Ebselen **G**[22] or the diphenyldiselenide **H**[23] play an important part as glutathione peroxidase mimics (Fig. 2). Schiesser and co-workers reported the ten steps synthesis of **D** (described in its perbenzylated *xylo*, *ribo* and D-*arabino* configurations) (Fig. 1) which is an hydrosoluble possible antioxidant.[24] More recently we had described the expedious synthesis of the later and other configurations in two steps including direct alditols bromination and subsequent selenaheterocyclisation at room temperature in DMSO by reaction

G **H**

Figure 2.



Scheme 3. (i) MeONa in MeOH, rt, 16 h; (ii) Ac_2O, pyridine.

with $Se^{=}$ prepared from Se/$NaBH_4$ mixture in water (Scheme 1).[8]

In the present work, we increased the library of selenasugars using the selenaheterocyclisation of bis-thionocarbonates of pentitols and aldoses. The selenolane ring was obtained by addition of the bis-cyclic thionocarbonates **2** to **42** solutions in DMSO as solvent, respectively (entries 1 to 10) to the mixture of Se and $NaBH_4$ in water and heating for 1 h. The selenolane compounds **4**, **8**, **12**, **16**, **20**, **28**, **32**, **36**, **40** and **45** obtained after acetylation were isolated in 45 to 55% yields (Table 1). Despite the higher nucleophilicity of $Se^{=}$ as binucleophile, similar results were obtained as in the case of sulfur.

In conclusion, herein we report a short and versatile use of bis-cyclic thionocarbonates as intermediates for a wide range of polyhydroxylated 1,4-, 2,5- and 3,6-thio and selenolanes from both pentitols and linear aldose substrates. It is of interest to point out that the major part of thia and selenaheterosugar analogues described are enantiopure.

3. Experimental

3.1. General methods

Melting points were determined with a Buchi 535 apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker 300 WB spectrometer; chemical shifts are reported in δ (ppm) relative to Me_4Si. Coupling constants, assigned by double irradiation, are in Hz. All ^{13}C NMR signals were assigned through C,H-correlated spectra with hsqc.grad experiment. TLC was performed on silica Gel 60 F_{254} 230 mesh (E. Merck) with hexane–EtOAc as eluant, and zones were detected by vanillin–H_2SO_4 reagent. The silica gel used in column chromatography was 35–70 m (Amicon). Optical rotations were determined with Perkin–Elmer instruments, model 343 polarimeter (1 mL cell). Elemental analyses were performed by the 'Service de Microanalyse du CNRS (Laboratoire de Bioorganique, Université de Reims Champagne Ardenne'). Low resolution electrospray mass spectra (ESI-MS) in the positive ion mode were obtained on Waters-Micromass ZQ quadripole instrument, equiped with an electrospray (Z-spray) ion source (Waters-Micromass, Manchester, UK).

3.2. Synthesis of bis-cyclicthionocarbonate derivatives 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42 and 43

General procedure. To a suspension monobenzyl alditols or aldosedibenzyldithioacetals (1 mmol) in 1,4-dioxane (0.05 g ml^{-1}), was added Im_2CS (2.2 mmol) and the mixture was stirred at room temperature overnight. The crude product obtained after concentration was purified by chromatography on silica gel and mixture of hexane–EtOAc as eluant.

3.2.1. 1-*O*-Benzyl-2,3:4,5-di-*O*-thiocarbonyl-D-arabinitol (2). 32% Yield; colorless syrup; $[\alpha]_D$ +24.1 (*c* 1.4, CH_2Cl_2); R_f 0.36 (5:5, hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 3.70 (dd, 1H, $J_{1a,1b}=11.3$ Hz, $J_{1a,2}=2.4$ Hz, H_{1a}), 3.85 (dd, 1H, $J_{1b,2}=3.5$ Hz, H_{1b}), 4.90 (m, 1H, $J_{2,3}=5.6$ Hz, H_2), 5.00 (t, 1H, $J_{3,4}=5.6$ Hz, H_3), 5.15 (m, 1H, $J_{4,5b}=J_{5a,5b}=9.5$ Hz, $J_{4,5a}=6.2$ Hz, H_4), 4.55 (m, 1H, H_{5a}), 4.80 (t, 1H, H_{5b}), 7.20–7.30 (m, 5H, Ph), 4.60 (m, 2H, CH_2); ^{13}C NMR: δ 68.4 (C_1), 82.2 (C_2), 80.7 (C_3), 79.2 (C_4), 71.0 (C_5), 74.2 (CH_2), 128.3–137.7 (Ph), 190.1–190.3 (CS). Anal. Calcd for $C_{14}H_{14}O_5S_2$: C, 51.52; H, 4.32; O, 24.51; S, 19.65. Found: C, 51.86; H, 4.34. ESMS *m/z* calcd (M^+ + Na) 349.01. Found 349.10.

3.2.2. 1-*O*-Benzyl-2,3:4,5-di-*O*-thiocarbonyl-D-lyxitol (6). 40% Yield; colorless syrup; $[\alpha]_D$ −18.7 (*c* 2, CH_2Cl_2); R_f 0.19 (5:5, hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 3.90 (m, 2H, $H_{1a,1b}$), 5.10 (m, 1H, $J_{2,3}=J_{3,4}=3.1$ Hz, H_2), 5.19 (t, 1H, H_3), 5.30 (ddd, 1H, $J_{4,5b}=J_{5a,5b}=9.1$ Hz, $J_{4,5a}=6.5$ Hz, H_4), 4.60 (dd, 1H, H_{5a}), 4.70 (t, 1H, H_{5b}), 7.30–7.45 (m, 5H, Ph), 4.55 (m, 2H, CH_2); ^{13}C NMR: δ 66.2 (C_1), 81.7 (C_2), 80.6 (C_3), δ 78.4 (C_4), 71.2 (C_5), 74.6 (CH_2), 128.7–136.9 (Ph), 189.8–190.6 (CS). Anal. Calcd for $C_{14}H_{14}O_5S_2$: C, 51.52; H, 4.32; O, 24.51; S, 19.65. Found: C, 51.81; H, 4.54. ESMS *m/z* calcd (M^+ + Na) 349.01. Found 349.10.

3.2.3. 1-*O*-Benzyl-2,3:4,5-di-*O*-thiocarbonyl-D,L-xylitol (10). 61% Yield; white solid: mp 115–117 °C; R_f 0.60 (EtOAc); ^1H NMR ($CDCl_3$): 3.75 (q, 1H, $J_{1a,1b}=11.8$ Hz, H_{1a}), 3.75 (dd, 1H, $J_{1a,2}=J_{1b,2}=2.4$ Hz, H_{1b}), 5.30 (t, 1H, $J_{2,3}=4.6$ Hz, H_2), 5.35 (dd, 1H, $J_{3,4}=1.7$ Hz, H_3), δ 5.50 (dq, 1H, $J_{4,5a}=J_{5a,5b}=9.1$ Hz, $J_{4,5b}=5.9$ Hz, H_4), 4.80 (t, 1H, H_{5a}), 4.90 (q, 1H, H_{5b}), 7.25–7.40 (m, 5H, Ph), δ 4.60 (m, 2H, CH_2); ^{13}C NMR: δ 69.1 (C_1), 83.3 (C_2), 82.0 (C_3), 81.3 (C_4), 71.8 (C_5), 73.4 (CH_2), 128.3–138.5 (Ph), 191.4–191.8 (CS). Anal. Calcd for $C_{14}H_{14}O_5S_2$: C, 51.52; H, 4.32; O, 24.51; S, 19.65. Found: C, 51.91; H, 4.17. ESMS *m/z* calcd (M^+ + Na) 349.01. Found 349.30.

3.2.4. 1-*O*-Benzyl-2,3:4,5-di-*O*-thiocarbonyl-D,L-ribitol (14). 72% Yield; white solid: mp 118–120 °C; R_f 0.51 (5:5, hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 3.85 (s, 2H, $H_{1a,1b}$), 5.20 (m, 2H, $H_{2,3}$), 5.40 (m, 1H, H_4), 4.70 (m, 2H, $H_{5a,5b}$), 7.20–7.30 (m, 5H, Ph), 4.60 (m, 2H, CH_2); ^{13}C NMR: δ 66.2 (C_1), δ 81.9 (C_2), 80.5 (C_3), 78.4 (C_4), 71.6 (C_5), 74.8 (CH_2), 128.5–136.4 (Ph), 189.8–190.6 (CS). Anal. Calcd for $C_{14}H_{14}O_5S_2$: C, 51.52; H, 4.32; O, 24.51; S, 19.65. Found: C, 51.86; H, 4.42. ESMS *m/z* calcd (M^+ + Na) 349.01. Found 349.13.

3.2.5. 2,3:4,5-Di-*O*-thiocarbonyl-D-xylose dibenzyl dithioacetal (18). 73% Yield; white solid: mp 85–87 °C; $[\alpha]_D$ −100.1 (*c* 0.3; CH_2Cl_2); R_f 0.31 (7:3, hexane–EtOAc); ^1H NMR ($CDCl_3$): 3.80 (d, 1H, $J_{1,2}=4.8$ Hz, H_1), 5.04 (q, 1H, $J_{2,3}=5.7$ Hz, H_2), 4.70 (dd, 1H, $J_{3,4}=1.5$ Hz, H_3), 4.88 (dq, 1H, H_4), 4.60–4.75 (m, 2H, $H_{5a,b}$), 7.10–7.30 (m, 10H, Ph), 3.73–3.92 (m, 4H, CH_2); ^{13}C NMR: δ 49.8 (C_1), 84.2 (C_2), 81.7 (C_3), 79.9 (C_4), 70.3 (C_5), 36.7–37.0 (CH_2), 128.3–136.9 (Ph), 188.9–190.0 (CS). Anal. Calcd for $C_{21}H_{20}O_4S_4$: C, 54.28; H, 4.34; O, 13.77; S, 27.60. Found: C, 54.61; H, 4.34. ESMS *m/z* calcd (M^+ + Na) 487.01. Found 487.24.

3.2.6. 2,3:4,5-Di-*O*-thiocarbonyl-D-ribose dibenzyl dithio acetal (22). 76% Yield; white solid: mp 71–73 °C; $[\alpha]_D$ + 22.5 (*c* 1.0; CH_2Cl_2); R_f 0.42 (8:2, hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 3.48 (d, 1H, $J_{1,2}=5.0$ Hz, H_1), 5.25 (dd, 1H, $J_{2,3}=8.2$ Hz, H_2), 4.87 (dd, 1H, $J_{3,4}=J_{4,5a}=6.8$ Hz, H_3), 4.88 (dq, 1H, $J_{4,5b}=14.8$ Hz, H_4), 3.99 (m, 1H, $J_{5a,5b}=9.3$ Hz, H_{5a}), 4.25 (dd, 1H, H_{5b}), 6.95–7.40 (m, 10H, Ph), 3.82 (m, 4H, CH_2); ^{13}C NMR: 46.2 (C_1), 85.6 (C_2), 80.9 (C_3), 75.7 (C_4), 70.4 (C_5), 36.6–36.7 (CH_2), 128.4–137.4 (Ph), 188.5–189.5 (CS). Anal. Calcd for $C_{21}H_{20}O_4S_4$: C, 54.28; H, 4.34; O, 13.77; S, 27.60. Found: C, 55.26; H, 4.42. ESMS *m/z* calcd (M^+ + Na) 487.01. Found 487.54.

3.2.7. 2,3:4,5-Di-*O*-thiocarbonyl-L-arabinose dibenzyl dithioacetal (26). 68% Yield; white solid: mp 118–120 °C; $[\alpha]_D$ −123.1 (*c* 1.2; CH_2Cl_2); R_f 0.57 (6:4, hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 3.70 (d, 1H, $J_{1,2}=J_{2,3}=4.5$ Hz, H_1), 4.80 (t, 1H, H_2), 4.60 (dd, 1H, $J_{3,4}=J_{,5a}=6.0$ Hz, H_3), 5.00 (dt, 1H, $J_{4,5b}=8.3$ Hz, H_4), 4.50 (dd, 1H, $J_{5a,5b}=9.6$ Hz, H_{5a}), 4.70 (dd, 1H, H_{5b}), 7.10–7.60 (m, 10H, Ph), 3.70–3.90 (m, 4H, CH_2); ^{13}C NMR: δ 49.9 (C_1), δ 84.3 (C_2), 81.5 (C_3), 78.9 (C_4), 70.6 (C_5), 36.8–37.0 (CH_2), 128.3–137.0 (Ph), 189.0–189.7 (CS). Anal. calcd for $C_{21}H_{20}O_4S_4$: C, 54.28; H, 4.34; O, 13.77; S, 27.60. Found: C, 54.41; H, 4.33. ESMS *m/z* calcd (M^+ + Na) 487.01, found 487.12.

3.2.8. 2,3:4,5-Di-*O*-thiocarbonyl-D-lyxose dibenzyl dithioacetal (30). 73% Yield; white solid: mp 158–160 °C; $[\alpha]_D$ +32.6 (*c* 0.9; CH_2Cl_2); R_f 0.21 (7:3, hexane–EtOAc); ^1H NMR (DMSO-d_6): δ 3.75 (d, 1H, $J_{1,2}=10.7$ Hz, H_1), 5.48 (q, 1H, $J_{2,3}=7.8$ Hz, H_2), 5.40 (m, 1H, $J_{3,4}=11.7$ Hz, H_3), 4.50 (m, 3H, $H_{4,5a,5b}$), 6.75–7.50 (m, 10H, Ph), 3.53–4.10 (m, 4H, CH_2); ^{13}C NMR: δ 45.4 (C_1), 85.8 (C_2), 82.1 (C_3), 78.1 (C_4), 71.8 (C_5), 34.9–37.3 (CH_2), 128.1–138.5 (Ph), 190.0–190.9 (CS). Anal. Calcd for $C_{21}H_{20}O_4S_4$: C, 54.28; H, 4.34; O, 13.77; S, 27.60. Found: C, 54.40; H, 4.04. ESMS *m/z* calcd (M^+ + Na) 487.01. Found 487.09.

3.2.9. 2,3:5,6-Di-*O*-thiocarbonyl-D-galactose dibenzyl dithioacetal (34). 65% Yield; white solid: mp 148–150 °C; R_f 0.28 (7:3, hexane–EtOAc); ^1H NMR (DMSO-d_6): δ 4.05 (d, 1H, $J_{1,2}=J_{2,3}=J_{3,4}=3.9$ Hz, H_1), 5.35 (t, 1H, H_2), 4.87 (t, 1H, H_3), 4.10 (m, 1H, H_4), 5.18 (dq, 1H, $J_{5,6a}=J_{6a,6b}=8.6$ Hz, $J_{5,6b}=5.6$ Hz, H_5), 4.51 (t, 1H, H_{6a}), 4.82 (q, 1H, H_{6b}), 7.25–7.40 (m, 10H, Ph), 3.80–4.00 (m, 4H, CH_2); ^{13}C NMR: δ 52.2 (C_1), 84.9 (C_2), 85.2 (C_3), δ 69.5 (C_4), δ 82.4 (C_5), 72.4 (C_6), δ 36.0–36.3 (CH_2), 128.1–137.9 (Ph), 191.2–192.6 (CS). Anal. Calcd for $C_{22}H_{22}O_5S_4$: C, 53.42; H, 4.48; O, 16.17; S, 25.93. Found: C, 53.48; H, 4.42. ESMS *m/z* calcd (M^+ + Na) 517.02. Found 517.22.

3.2.10. 2,3:5,6-Di-*O*-thiocarbonyl-D-glucose dibenzyl dithioacetal (38). 60% Yield; white solid: mp 129–131 °C; $[\alpha]_D$ −115.3 (*c* 0.5; CH_2Cl_2); R_f 0.24 (5:5, hexane–EtOAc); ^1H NMR ($CDCl_3$): 3.75 (d, 1H, $J_{1,2}=J_{2,3}=5.3$ Hz, H_1), 5.03 (t, 1H, H_2), 4.68 (dd, 1H, $J_{3,4}=1.5$ Hz, H_3), 4.00 (m, 1H, $J_{4,5}=3.8$ Hz, H_4), 4.90 (ddd, 1H, $J_{5,6a}=1.1$ Hz, $J_{5,6b}=7.4$ Hz, H_5), 4.75 (m, 2H, $J_{6a,6b}=9.1$ Hz, $H_{6a,6b}$), 7.12–7.37 (m, 10H, Ph), 3.70–3.90 (m, 4H, CH_2); ^{13}C NMR: δ 50.0 (C_1), 84.7 (C_2),83.7 (C_3), 69.7 (C_4), 81.7 (C_5), 70.7 (C_6), 36.6–36.7 (CH_2), 128.2–137.1 (Ph), 190.3–191.8 (CS). Anal. Calcd for $C_{22}H_{22}O_5S_4$: C, 53.42; H, 4.48; O, 16.17; S, 25.93. Found: C, 54.79; H, 4.50. ESMS *m/z* calcd (M^+ + Na) 517.02. Found 517.30.

3.2.11. 3,4:5,6-Di-*O*-thiocarbonyl-D-mannose dibenzyl dithioacetal (42). 23% Yield; colorless syrup; $[\alpha]_D$ +6.5 (*c* 1.1; CH_2Cl_2); R_f 0.45 (5:5, hexane–EtOAc); ^1H NMR (DMSO-d_6): δ 3.82 (d, 1H, $J_{1,2}=10.0$ Hz, H_1), 4.18 (q, 1H, $J_{2,3}=J_{3,4}=5.3$ Hz, H_2), 5.01 (t, 1H, H_3), 5.36 (dd, 1H, $J_{4,5}=2.7$ Hz, H_4), 5.13 (ddd, 1H, $J_{5,6a}=6.1$ Hz, $J_{5,6b}=J_{6a,6b}=9.0$ Hz, H_5), 4.25 (dd, 1H, H_{6a}), 4.60 (t, 1H, H_{6b}), 7.18–7.36 (m, 10H, Ph), 3.75–3.90 (m, 4H, CH_2); ^{13}C NMR: δ 53.5 (C_1), 72.8 (C_2), 82.6 (C_3,C_4), 75.6 (C_5), 65.5 (C_6), 35.6–35.8 (CH_2), 127.9–138.6 (Ph), 191.0–191.8 (CS). ESMS *m/z* calcd (M^+ + Na) 517.02, found 517.05.

3.2.12. 2-*O*-Imidazolylthiocarbonyl-3,4:5,6-di-*O*-thio carbonyl-D-mannose dibenzyl dithioacetal (43). 34% Yield; green solid: mp 85–87 °C; R_f 0.24 (5:5, hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 3.98 (d, 1H, $J_{1,2}=J_{2,3}=J_{3,4}=4.5$ Hz, H_1), 6.00 (t, 1H, H_2), 5.32 (t, 1H, H_3), 5.22 (dt, 1H, $J_{4,5}=J_{5,6a}=2.7$ Hz, H_4), 5.13 (q, 1H, $J_{5,6b}=J_{6a,6b}=10.0$ Hz, H_5), 4.25 (dd, 1H, H_{6a}), 4.60 (t, 1H, H_{6b}), 7.00–8.25 (m, 12H, Ph), 4.60–4.90 (m, 4H, CH_2); ^{13}C NMR: δ 48.4 (C_1), 80.2 (C_2), 81.1 (C_3), 80.1 (C_4), 78.6 (C_5), 70.6 (C_6), 36.8–37.1 (CH_2), 118.6–137.6 (Ph), 182.5–189.4 (CS). Anal. Calcd for $C_{26}H_{24}N_2O_5S_5$: C, 51.63; H, 4.00; N, 4.63; O, 13.23; S, 26.51. Found: C, 53.18; H, 4.25; N, 4.13.

3.3. Synthesis of anhydroalditols 2c (or 2f) and 6c (or 6f)

To a solution of bis-cyclic thionocarbonate **2** (D-*arabino*) or **6** (D-*lyxo*) was added Na (10 mg). The mixture was stirred overnight and neutralised with Amberlite IRN-120 (H^+). The filtrate was concentrated and acetylated following the standard procedure (Ac_2O, pyridine). The crude product obtained after concentration was separated by chromatography on silica gel and mixture of hexane–EtOAc as an eluant.

3.3.1. 3,4-Di-*O*-acetyl-1-*O*-benzyl-2,5-anhydro-D-arabinitol (2c) (or 3,4-di-*O*-acetyl-1-*O*-benzyl-2,5-anhydro-L-ribitol (2f)). 31% Yield; syrup; R_f 0.17 (7:3, hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 3.65 (d, 2H, $H_{1a,1b}$), 5.39 (m, 1H, H_2), 5.50 (t, 1H, $J_{2,3}=J_{3,4}=5.0$ Hz, H_3), 4.25 (m, 1H, H_4), 3.87 (dd, 2H, $J_{4,5a}=J_{4,5b}=6.0$ Hz, $J_{5a,5b}=9.60$ Hz, H_{5a}), 4.08 (dd, 2H, H_{5b}), 4.50 (d, 1H, $J_{a,b}=12.1$, Ha (CH_2Ph)), 4.50 (d, 1H, H_b (CH_2Ph)), 2.05 (s, 3H, CH_3); ^{13}C NMR: δ 69.8 (C_1), 78.5 (C_2), 71.9 (C_3), 72.3 (C_4), 68.6 (C_5), 73.9 (CH_2Ph), 20.9, 21.0 (2×CH_3), 128.2–138.2 (Ph), 170.2 (CO). Anal Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54; O, 31.13. Found C, 62.45; H, 6.73.

3.3.2. 2,3-Di-*O*-acetyl-5-*O*-benzyl-1,4-anhydro-D-arabinitol (6c) (or 2,3-di-*O*-acetyl-5-*O*-benzyl-1,4-anhydro-D-xylitol 6f). 47% Yield; syrup; R_f 0.08 (7:3, hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 4.00 (m, 2H, $H_{1a,1b,4}$), 5.20 (d, 2H, $J_{2,3}=3.0$ Hz, $J_{3,4}=0$ Hz, $H_{2,3}$), 3.68 (dd, 1H, $J_{4,5a}=4.1$ Hz, $J_{5a,5b}=10.3$ Hz, H_{5a}), 3.69 (dd, 1H, $J_{4,5b}=6$ Hz, H_{5b}), 4.61 (s, 2H, CH_2Ph)), 4.50 (d, 1H, H_b (CH_2Ph)), 2.05 (s, 3H, CH_3); ^{13}C NMR: δ 72.4 (C_1), 78.5 (C_2), 78.8 (C_3), 83.4 (C_4), 70.2 (C_5), 73.9 (CH_2Ph), 21.2 (2×CH_3), 128.1–138.4 (Ph), 170.3, 170.6 (CO). Anal calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54; O, 31.13. Found C, 62.63; H, 6. 58.

3.4. Synthesis of thiaheterocycles 3, 7, 11, 15, 19, 27, 31, 35, 39 and 44

General procedure. To a solution of bis-cyclicthionocarbonates (1 mmol) in DMSO (5 mL), was added Na_2S, $9H_2O$ (1.5 mmol) and the mixture was stirred at 80 °C during 1 h. After concentration and acetylation of crude product with Ac_2O in pyridine, the desired compounds were extracted by chromatography on silica gel and mixture of hexane–EtOAc as eluant.

3.4.1. 2,3-Di-*O*-acetyl-5-*O*-benzyl-1,4-thioanhydro-L-ribitol (3). 47% Yield; yellow syrup; $[\alpha]_D$ −59.4 (*c* 0.4; CH_2Cl_2); R_f 0.33 (8:2, hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 2.96 (dd, 1H, $J_{1a,1b}=11.3$ Hz, H_{1a}), 3.17 (dd, 1H, $J_{1a,2}=J_{1b,2}=5.6$ Hz, H_{1b}), 5.47 (m, 1H, $J_{2,3}=3.6$ Hz, H_2), 5.32 (dd, 1H, $J_{3,4}=J_{4,5a}=4.8$ Hz, H_3), 3.65 (m, 1H, $J_{5a,5b}=J_{4,5b}=7.9$ Hz, H_4), 3.55–3.62 (m, 2H, $H_{5a,5b}$), 7.25–7.40 (m, 5H, Ph), 4.56 (m, 2H, CH_2), 2.05–2.10 (2s, $2CH_3$); ^{13}C NMR: δ 31.2 (C_1), 74.1 (C_2), 76.0 (C_3), 47.3 (C_4), 71.8 (C_5), δ 73.7 (CH_2), 21.3 (2 CH_3), 128.1–138.2 (Ph), 170.4–170.5 (CO). ESMS *m/z* calcd for $C_{16}H_{20}O_5S$ (M^+ + Na) 347.09. Found 347.29.

3.4.2. 2,3-Di-*O*-acetyl-5-*O*-benzyl-1,4-thioanhydro-L-xylitol (7). 65% Yield; yellow syrup; $[\alpha]_D$ −65.1 (*c* 0.7; CH_2Cl_2); R_f 0.13 (9:1, hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 2.85 (dd, 1H, $J_{1a,1b}=12.0$ Hz, $J_{1a,2}=2.8$ Hz, H_{1a}), 3.25 (dd, 1H, $J_{1b,2}=5.1$ Hz, H_{1b}), 5.36 (m, 1H, $J_{2,3}=J_{3,4}=4.3$ Hz, H_2), 5.42 (t, 1H, H_3), 3.92 (q, 1H, $J_{4,5a}=7.4$ Hz, $J_{4,5b}=6.1$ Hz, H_4), 3.52 (dd, 1H, $J_{5a,5b}=9.3$ Hz, H_{5a}), 3.70 (dd, 1H, H_{5b}), 7.25–7.40 (m, 5H, Ph), 4.51 (m, 2H, CH_2), 2.00–2.10 (2s, $2CH_3$); ^{13}C NMR: 33.3 (C_1), 77.7 (C_2), 77.0 (C_3), 46.8 (C_4), 69.2 (C_5), δ 73.7 (CH_2), 21.1–21.4 ($2CH_3$), 128.2–138.2 (Ph), 170.1–170.2 (CO). ESMS *m/z* calcd for $C_{16}H_{20}O_5S$ (M^+ + Na) 347.09. Found 347.29.

3.4.3. 2,3-Di-*O*-acetyl 5-*O*-benzyl-1,4-thioanhydro-D,L-arabinitol (11). 50% Yield; yellow syrup; R_f 0.14 (9:1, hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 2.91 (dd, 1H, $J_{1a,1b}=11.9$ Hz, $J_{1a,2}=J_{1b,2}=4.8$ Hz, H_{1a}), 3.23 (dd, 1H, H_{1b}), 5.31 (q, 1H, $J_{2,3}=J_{3,4}=4.8$ Hz, H_2), 5.39 (t, 1H, H_3), 3.50 (m, 1H, H_4), 3.52 (m, 1H, H_{5a}), 3.73 (m, 1H, H_{5b}), 7.25–7.40 (m, 5H, Ph), 4.60 (m, 2H, CH_2), 1.90–2.10 (2s, $2CH_3$); ^{13}C NMR: δ 33.4 (C_1), 78.5 (C_2), 79.2 (C_3), 49.4 (C_4), δ 72.3 (C_5), 73.6 (CH_2), 21.3–21.4 ($2CH_3$), 128.2–138.3 (Ph), 170.1–170.2 (CO). ESMS *m/z* calcd for $C_{16}H_{20}O_5S$ (M^+ + Na) 347.09. Found 347.29.

3.4.4. 3,4-Di-*O*-acetyl-1-*O*-benzyl-2,5-thioanhydro-D,L-arabinitol (15). 40% Yield; yellow syrup; R_f 0.27 (8:2, hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 3.47–3.77 (2 dd, 2H, $J_{1a,1b}=7.9$ Hz, $J_{1a,2}=8.9$ Hz, $J_{1b,2}=6.4$ Hz, $H_{1a,1b}$), 3.85 (m, 1H, $J_{2,3}=4.3$ Hz, H_2), 5.70 (dd, 1H, $J_{3,4}=3.3$ Hz, H_3), 5.30 (m, 1H, $J_{4,5a}=6.9$ Hz, $J_{4,5b}=9.4$ Hz, H_4), 3.00 (m, 2H, $J_{5a,5b}=10.0$ Hz), 7.25–7.40 (m, 5H, Ph), 4.52 (m, 2H, CH_2), 2.02–2.04 (2s, $2CH_3$); ^{13}C NMR: δ 69.7 (C_1), 45.0 (C_2), 72.9 (C_3), 75.4 (C_4), 30.4 (C_5), 73.2 (CH_2), 21.1 (CH_3), 128.2–138.2 (Ph), 170.2–170.4 (CO). ESMS *m/z* calcd for $C_{16}H_{20}O_5S$ (M^+ + Na) 347.09 Found 347.20.

3.4.5. 3,4-Di-*O*-acetyl-2,5-thioanhydro-D-lyxose dibenzyl dithioacetal (19). 60% Yield; yellow syrup; $[\alpha]_D$ +36 (*c* 0.4; CH_2Cl_2); R_f 0.17 (7:1, hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 3.76 (d, 1H, $J_{1,2}=7.5$ Hz, H_1), 3.62 (dd, 1H, $J_{2,3}=J_{3,4}=5.1$ Hz, H_2), 5.60 (t, 1H, H_3), 5,22 (q, 1H, $J_{4,5a}=J_{4,5b}=11.4$ Hz, H_4), 2.90 (dd, 1H, $J_{5a,5b}=5.8$ Hz, H_{5a}), 3.15 (dd, 1H, H_{5b}), 7.20–7.30 (m, 10H, Ph), 3.83 (m,4H, CH_2), 1.88–1.99 (2s, CH_3); ^{13}C NMR: δ 54.5 (C_1), 54.3 (C_2), 78.9 (C_3), δ 77.8 (C_4), δ 32.6 (C_5), 35.5–35.7 (CH_2), 127.5–138.0 (Ph), 21.3–21.5 (CH_3), 169.8–170.3 (CO). ESMS *m/z* calcd for $C_{23}H_{26}O_4S_3$ (M^+ + Na) 485.09. Found 485.20.

3.4.6. 3,4-Di-*O*-acetyl-2,5-thioanhydro-L-ribose dibenzyl dithioacetal (27). 50% Yield; yellow syrup; $[\alpha]_D$ +108.3 (*c* 0.3; CH_2Cl_2) R_f 0.48 (7:3, hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 3.61 (d, 1H, $J_{1,2}=4.2$ Hz, H_1), 3.95 (dd, 1H, $J_{2,3}=7.7$ Hz, H_2), 5.12 (dd, 1H, $J_{3,4}=3.6$ Hz, H_3), 5.53 (q, 1H, $J_{4,5a}=3.6$ Hz, $J_{4,5b}=7.9$ Hz, H_4), 2.86 (dd, 1H, $J_{5a,5b}=12.0$ Hz, H_{5a}), 3.16 (dd, 1H, H_{5b}), 7.00–7.40 (m, 10H, Ph), 3.80 (s, 4H, CH_2), 1.87–2.13 (2s, CH_3); ^{13}C NMR: δ 51.6 (C_1), 52.9 (C_2), 76.6 (C_3), 74.1 (C_4), δ 31.9 (C_5), 35.6–36.5 ($2CH_2$), 21.0–21.4 (2 CH_3), 127.4–138.1 (Ph), 169.8-170.4 (CO). ESMS *m/z* calcd for $C_{23}H_{26}O_4S_3$ (M^+ + Na) 485.09. Found 485.20.

3.4.7. 3,4-Di-*O*-acetyl-2,5-thioanhydro-D-xylose-dibenzyl dithioacetal (31). 60% Yield; yellow syrup; R_f 0.18 (7:1, hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 3.80 (d, 1H, $J_{1,2}=4.8$ Hz, H_1), 3.90 (m, 1H, $J_{2,3}=3.7$ Hz, H_2), 5.18 (dd, 1H, $J_{3,4}=2.6$ Hz, H_3), 5.30 (m, 1H, $J_{4,5a}=4.6$ Hz, $J_{4,5b}=1.8$ Hz, H_4), 2.80 (dd, 1H, $J_{5a,5b}=12.5$ Hz, H_{5a}), 3.20 (dd, 1H, H_{5b}), 7.20–7.45 (m, 10H, Ph), 3.75–3.90 (m, 4H, CH_2), 1.70–2.10 (2s, CH_3); ^{13}C NMR: δ 51.4 (C_1), 54.7 (C_2), 76.8 (C_3), 78.9 (C_4), 34.9 (C_5), 34.4–34.9 ($2CH_2$), 20.9–21.5 (2 CH_3), 127.3–138.1 (Ph), 169.8–169.9 (CO). ESMS *m/z* calcd for $C_{23}H_{26}O_4S_3$ (M^+ + Na) 485.09. Found 485.24.

3.4.8. 2,4,5-Tri-*O*-acetyl-3,6-thioanhydro-D-gulose dibenzyl dithioacetal (35). 60% Yield; yellow syrup; $[\alpha]_D$ −140.4 (*c* 0.5; CH_2Cl_2); R_f 0.32 (8:2, hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 3.60 (d, 1H, $J_{1,2}=2.1$ Hz, H_1), 5.55 (dd, 1H, $J_{2,3}=10.4$ Hz, H_2), 4.15 (dd, 1H, $J_{3,4}=3.9$ Hz, H_3), 5.40 (dd, 1H, $J_{4,5}=1.4$ Hz, H_4), 5.20 (m, 1H, $J_{5,6a}=0$ Hz, $J_{5,6b}=4.2$ Hz, H_5), 2.80 (d, 1H, $J_{6a,6b}=12.4$ Hz, H_{6a}), 3.25 (dd, 1H, H_{6b}), 7.10–7.30 (m, 10H, Ph), 3.70–3.80 (m, 4H, CH_2), 2.05–2.15 (3s, CH_3); ^{13}C NMR: δ 53.6 (C_1), 72.2 (C_2), 50.6 (C_3), 76.3 (C_4), 78.0 (C_5), 36.1 (C_6), 36.0–36.8 ($2CH_2$), 21.1–21.5 ($3CH_3$), 127.6–137.8 (Ph), 170.0–170.2 (CO). ESMS *m/z* calcd for $C_{26}H_{30}O_6S_3$ (M^+ + Na) 557.11. Found 557.28.

3.4.9. 2,4,5-Tri-*O*-acetyl-3,6-thioanhydro-D-allose dibenzyl dithioacetal (39). 60% Yield; yellow syrup; $[\alpha]_D$ −57.6 (*c* 0.4; CH_2Cl_2); R_f 0.16 (8:2, hexane–EtOAc); ^1H NMR ($CDCl_3$): 3.90 (d, 1H, $J_{1,2}=3.2$ Hz, H_1), 5.25 (dd, 1H, $J_{2,3}=9.1$ Hz, H_2), 3.70 (dd, 1H, $J_{3,4}=J_{4,5}=3.9$ Hz, H_3), 5.21 (t, 1H, H_4), 5.30 (m, 1H, $J_{5,6a}=5.6$ Hz, $J_{5,6b}=6.5$ Hz, H_5), 2.80 (dd, 1H, $J_{6a,6b}=10.9$ Hz, H_{6a}), 3.20 (dd, 1H, H_{6b}), 7.10–7.45 (m, 10H, Ph), 3.75–3.85 (m, 4H, CH_2), 1.90–2.10 (m, CH_3); ^{13}C NMR: δ 52.8 (C_1), 72.2, 76.3 (C_2, C_4),, 49.2 (C_3), 74.0 (C_5), 31.0 (C_6), 35.5–36.2 ($2CH_2$), 20.3 ($3CH_3$), 127.5–138.2 (Ph), 169.5–170.0 (CO). ESMS *m/z* calcd for $C_{26}H_{30}O_6S_3$ (M^+ + Na) 557.11. Found 557.19.

3.4.10. 2,4,5-Tri-*O*-acetyl-3,6-thioanhydro-D-altrose

dibenzyl dithioacetal (44). 52% Yield; yellow syrup; $[\alpha]_D$ −36.2 (*c* 0.5; CH_2Cl_2); R_f 0.15 (8:2, hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 3.68 (d, 1H, $J_{1,2}=7.7$ Hz, H_1), 5.35 (dd, 1H, $J_{2,3}=4.1$ Hz, H_2), 4.00 (dd, 1H, $J_{3,4}=6.1$ Hz, H_3), 5.00 (t, 1H, $J_{4,5}=3.6$ Hz, H_4), δ 5.40 (q, 1H, $J_{5,6a}=J_{5,6b}=$ 5.4 Hz, H_5), 2.83 (dd, 1H, $J_{6a,6b}=11.3$ Hz, H_{6a}), 3.02 (dd, 1H, H_{6b}), 7.20–7.40 (m, 10H, Ph), 3.75–3.95 (m, 4H, CH_2), 2.00–2.20 (m, CH_3); ^{13}C NMR: 54.0 (C_1), 71.9, 73.5, 75.5 (C_2,C_4,C_5), 49.6 (C_3), 31.1 (C_6), 35.4–35.7 (2CH_2), 21.2, 21.3 (3CH_3), 127.6–137.6 (Ph), 170.5 (CO). ESMS *m/z* calcd for $C_{26}H_{30}O_6S_3$ (M^+ + Na) 557.11. Found 557.40.

3.5. Synthesis of selenaheterocycles 4, 8, 12, 16, 20, 28, 32, 36, 40 and 45

General procedure. To a suspension freshly prepared from Se powder (3 mmol) and $NaBH_4$ (6 mmol) in H_2O (1 mL) was added a solution of bis-cyclicthionocarbonates of alditols or aldoses dibenzyldithioacetal (1 mmol) in DMSO (1 mL). The mixture was stirred at 80 °C during 1 h. After concentration and acetylation of crude product with Ac_2O in pyridine, the desired compounds were extracted by chromatography on silica gel and mixture of hexane–EtOAc as eluant.

3.5.1. 2,3-Di-*O*-acetyl-5-*O*-benzyl-1,4-selenoanhydro-L-ribitol (4). 53% Yield; colorless syrup; R_f 0.29 (7:3, hexane–EtOAc); $[\alpha]_D$ +64.7 (*c* 1.4; CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 2.92 (dd, 1H, H_1, $J_{1a1b}=11.21$ Hz, $J_{12}=5.43$), 3.17 (dd, 1H, H_{1b}, $J_{1b1a}=10.52$ Hz; J_{1b2} =5.32 Hz), 5.53 (dd, 1H, H_2, $J_{23}=3.29$ Hz, $J_{21}=5.49$ Hz), 5.35 (dd, 1H, H_3, $J_{32}=3.3$ Hz, $J_{34}=5.81$ Hz), 3.58 (m, 1H, H_4), 3.79 (dd, 2H, H_5, $J_{5a,5b}=11$ Hz, $J_{5b,4}$ =6.6 Hz); 4.56 (s, 2H, H_6), 2.05 (s, 3H), 2.09 (s, 3H), 7.35 (m, 5H, H_{Ar}). ^{13}C NMR: δ 22.08 (C_1), 77.36 (C_2), 75.64 (C_3); 40.85 (C_4), 72.50 (C_5), 73.64 (C_6); 21.27 (CH_3), 21.33 (CH_3), 128.09–128.82 (Ph); 138.19 C_{ipso}, 170.47, 170.57 (CO). ESMS calcd for $C_{23}H_{26}O_4S_2Se$ (M^+ + Na) 395.04. Found 395.15.

3.5.2. 2,3-Di-*O*-acetyl-5-*O*-benzyl-1,4-selenoanhydro-L-xylitol (8). 50% Yield; colorless syrup; R_f 0.28 (8:2, hexane–EtOAc); $[\alpha]_D$ +76 (*c* 2.1; CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 2.80 (dd, 1H, $J_{1a,1b}=11.4$ Hz, $J_{1a,2}=3$ Hz, H_{1a}), 3.28 (dd, 1H, J_{1b2} =3 Hz, H_{1b}), 5.42 (m, 2H, $H_{2,3}$), 4.08 (m, 1H, H_4), 3.54 (dd, 1H, $J_{5a,5b}=9.5$ Hz, $J_{5a,4}=5.9$ Hz, H_{5a}), 3.82 (dd, 1H, $J_{5b,4}=7.3$ Hz, H_{5b}), 4.53 (d, 2H, CH_2, $J_{6a,6b}=$ 6.7 Hz), 2.01 (s, 3H), 2.09 (s, 3H), 7.35 (m, 5H, Ph). ^{13}C NMR: δ 24.54 (C_1), 78.28 (C_2), 77.68 (C_3), 40.8 (C_4), 69.9 (C_5), 73.7 (CH_2), 21.1 (CH_3), 21.4 (CH_3), 128.1–128.8 C(Ph), 138.2 C_{ipso}, 170.1 (CO), ESMS calcd for $C_{23}H_{26}O_4S_2Se$ (M^+ + Na) 395.04. Found 395.22.

3.5.3. 2,3-Di-*O*-acetyl-5-*O*-benzyl-1,4-selenoanhydro-D,L-arabinitol (12). 50% Yield; colorless syrup; R_f 0.32 (8:3, hexane–EtOAc); ^1H NMR ($CDCl_3$): δ 2.94 (dd, 1H, $J_{1a,1b}=$ 11.1 Hz, $J_{1,2}=5.4$, H_1), 3.30 (dd, 1H, $J_{1b,2}=5.5$ Hz, H_{1b}), 5.60 (m, 2H, H_2, H_3), 3.68 (m, 1H, H_4), 3.82 (dd, 2H, $J_{5a,5b}=10.0$ Hz, $J_{5b,4}=5.6$ Hz, H_5), 4.50 (s, 2H, CH_2Ph), 2.07 (s, 3H), 2.1 (s, 3H), 7.4 (m, 5H, Ph). ^{13}C NMR: δ 22.0 (C_1), 77.4 (C_2), 75.7 (C_3), 40.9 (C_4), 72.7 (C_5), 73.8 (CH_2), 21.3 (CH_3), 21.4 (CH_3), 127.1–127.8 (Ph), 134.2 C_{ipso}, 170.4, 170.5 (CO), ESMS calcd for $C_{23}H_{26}O_4S_2Se$ (M^+ + Na) 395.04. Found 395.12.

3.5.4. 3,4-Di-*O*-acetyl-1-*O*-benzyl-2,5-selenoanhydro-D,L-arabinitol (16). 50% Yield; colorless syrup; R_f 0.27 (8:2, hexane–EtOAc); ^1H NMR ($CDCl_3$):δ 3.07 (dd, 2H, $J_{5a,5b}=$ 9.6 Hz, $J_{5,4}=6.5$ Hz, H_5), 5.26 (m, 1H, H_4), 5.77 (m, 1H, H_3), 3.97 (m, 1H, H_2), 3.15 (dd, 1H, $J_{1a,1b}=9.3$ Hz, $J_{1a,2}=$ 7.4 Hz, H_{1a}), 3.85 (dd, 1H, H_{1b}, $J_{1b,2}=7.5$ Hz), 4.48 (d, H_6, 2H, $J_{6a6b}=12.01$ Hz), 2.03, 2.06 (2s, 3H), 7.27–7.35 (m, 5H, Ph). ^{13}C NMR: δ 70.06 (C_1), 38.31 (C_2), 77.42 (C_3), 77.00 (C_4), 21.97 (C_5), 71.47 (C_6), 21.1, 21.2 (2 CH_3), 128.13, 128.83 C(Ph), 138.20 (C_{ipso}), 170.26 and 170.42 (CO). ESMS calcd for $C_{23}H_{26}O_4S_2Se$ (M^+ + Na) 395.03. Found 395.16.

3.5.5. 3,4-Di-*O*-acetyl-2,5-selenoanhydro-D-lyxose dibenzyl dithioacetal (20). 45% Yield; colorless syrup; R_f 0.28 (6:4, hexane–EtOAc); $[\alpha]_D$ +72.1 (*c* 0.6; CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 3.80 (m, 6H, $H_{1,2}+CH_2Ph$), 5.60 (dd, 1H, $J_{3,2}=J_{3,4}=6.3$ Hz, H_3), 5.30 (dt, 1H, H_4, $J_{4,5a}=7$ Hz,), 2.90 (dd, 1H, $J_{5a,5b}=10.2$ Hz, $J_{5a,4}=7$ Hz, H_{5a}), 3.10 (dd, 1H, $J_{5,4}=6$ Hz, H_{5b}), 1.89 (s, 3H), 1.95 (s, 3H), 7.20–7.33 (m, Ph). ^{13}C NMR: δ 46.70 (C_1), 54.56 (C_2), 78.38 (C_3), 78.67 (C_4), 21.57 (C_5), 21.20, 21.33 (CH_3), 35.35, 35.74 (CH_2Ph), 127–137 (Ph), 169.68, 170.25 (CO). ESMS calcd for $C_{23}H_{26}O_4S_2Se$ (M^+ + Na) 533.034. Found 533.10.

3.5.6. 3,4-Di-*O*-acetyl-2,5-selenoanhydro-L-ribose dibenzyl dithioacetal (28). 50% Yield; colorless syrup; R_f 0.35 (8:2, hexane–EtOAc); $[\alpha]_D$ +128 (*c* 0.75; CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 3.65 (d, 1H, $J_{1,2}=4$ Hz, H_1), 4.1 (dd, 1H, $J_{2,3}=9.81$ Hz, H_2), 5.2 (dd, 1H, $J_{34}=3.5$ Hz, H_3), 5.63 (dt, 1H, $J_{4,5}=8$ Hz, H_4), 2.84 (dd, 1H, $J_{5a5b}=11.13$ Hz, J_{5a4} = 3.73 Hz, H_{5a}), 3.16 (dd, 1H, J_{5b4} =4.56 Hz, H_{5b}), 3.69 (s, 2H, CH_2Ph), 3.81 (s, 2H, CH_2Ph), 1.8 (s, 3H), 2.1 (s, 3H), 7.03–7.33 (m, Ph). ^{13}C NMR: δ 47.23 (C_1), 52.11 (C_2), 77.79 (C_3), 75.53 (C_4), 22.69 (C_5), 35.53 (CH_2), 36.49 (CH_2), 21.01 (CH_3), 21.4 (CH_3), 127–138 C(Ph), 169.89 and 170.4 (CO). ESMS calcd for $C_{23}H_{26}O_4S_2Se$ (M^+ + Na) 533.032. Found 533.11.

3.5.7. 3,4-Di-*O*-acetyl-2,5-selenoanhydro-D-xylose dibenzyl dithioacetal (32). 55% Yield; colorless syrup; R_f 0.23 (6:4, hexane–EtOAc); $[\alpha]_D$ −9.4 (*c* 2.1; CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 3.96 (d, 1H, $J_{12}=11.4$ Hz, H_1), 4.13 (dd, 1H, $J_{23}=4$ Hz, H_2), 5.2 (dd, 1H, $J_{34}=2.3$ Hz, H_3), 5.4 (m, 1H, H_4), 2.86 (dd, 1H, $J_{5a,5b}=11.7$ Hz, $J_{5a,4}=4.3$ Hz, H_{5a}), 3.16 (dd, 1H, $J_{5b,4}=4.3$ Hz, H_{5b}), 3.85 (s, 2H, CH_2 Ph), 3.89 (s, 2H, CH_2 Ph), 1.75 (s, 3H), 2.06 (s, 3H), 7.27–7.36 (m, Ph). ^{13}C NMR: δ 49.53 (C_1), 52.21 (C_2), 77.29 (C_3), 79.31 (C_4), 25.57 (C_5), 34.31 (CH_2), 35.06 (CH_2), 20.88 (CH_3); 21.51 (CH_3); 125.5–138.64 C(Ph); 169.7 and 169.77 (CO), ESMS calcd for $C_{23}H_{26}O_4S_2Se$ (M^+ + Na) 533.03. Found 533.11.

3.5.8. 2,4,5-Tri-*O*-acetyl-3,6-selenoanhydro-D-gulose dibenzyl dithioacetal (36). 55% Yield; colorless syrup; R_f 0.42 (6:4, hexane–EtOAc); $[\alpha]_D$ −136.9 (*c* 2.15; CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 3.49 (d, 1H, $J_{1,2}=2.6$ Hz, H_1), 5.63 (dd, 1H, $J_{2,3}=10.7$ Hz, H_2), 4.24 (dd, 1H, $J_{3,4}=3.9$ Hz, H_3), 5.54 (m, 1H, H_4), 5.29 (m, 1H, H_5), 2.95 (dd, 1H, $J_{6a,6b}=$ 11.7 Hz, H_{6a}), 3.29 (dd, 1H, $J_{6b,5}=4.13$ Hz, H_{6b}), 3.72 (s, 2H, CH_2Ph), 3.75 (s, 2H, CH_2 Ph), 2.02 (s, 3H), 2.95 (s, 3H), 2.11 (s, 3H), 7.12–7.33 (m, Ph). ^{13}C NMR: δ 53.69 (C_1), 72.59 (C_2), 44.62 (C_3), 77.46 (C_4), 78.38 (C_5), 28.82 (C_6), 36.10 (CH_2), 36.70 (CH_2), 21.09 (CH_3), 21.37 (CH_3), 21.49 (CH_3), 127.62–137.81 C(Ph), 169.96, 170.09 and 170.21 (CO). ESMS calcd for $C_{26}H_{30}O_6S_2Se$ (M^+ + Na) 605.05. Found 605.11.

3.5.9. 2,4,5-Tri-*O*-acetyl-3,6-selenoanhydro-D-allose dibenzyl dithioacetal (40). 53% Yield; colorless syrup; R_f 0.45 (7:3, hexane–EtOAc); $[\alpha]_D$ −124.1 (*c* 1; CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 3.75 (m, 5H, H_{1+2} CH_2Ph), 5.24–5.3 (m, 3H, $H_{2,4,5}$), 3.68 (dd, 1H, $J_{3,2}=6.8$ Hz, $J_{3,4}=6.1$ Hz, H_3), 2.83 (dd, 1H, $J_{5,6a}=5.6$ Hz, $J_{6a,6b}=9.4$ Hz, H_{6a}), 3.09 (dd, 1H, $J_{5,6b}=5.9$ Hz, H_{6b}), 2.05 (s, 3H), 2.06 (s, 3H), 2.17 (s, 3H), 7.07–7.33 (m, 10H, Ph). ^{13}C NMR: δ 52.55 (C_1), 75.56, 76.27, 77.65 (C2, C4, C5), 42.72 (C_3), 22.85 (C_6), 21.1; 21.25; 21.29 (CH_3), 35.57 (CH_2), 36.69 (CH_2), 127.64–129.58 (Ph), 170.01, 170.38, 170.85 (CO). ESMS calcd for $C_{26}H_{30}O_6S_2Se$ (M^+ + Na) 605.08. Found 605.05.

3.5.10. 2,4,5-Tri-*O*-acetyl-3,6-selenoanhydro-D-altrose dibenzyl dithioacetal (45). 50% Yield; colorless syrup; R_f 0.29 (7:3, hexane–EtOAc); $[\alpha]_D$ −90.3 (*c* 1.25; CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 3.61 (d, 1H, $J_{1,2}=6.93$ Hz, H_1), 5.00 (dd, 1H, $J_{2,3}=3.58$ Hz, H_2), 4.02 (dd, 1H, $J_{3,4}=6.94$ Hz, H_3), 5.38 (dd, 1H, $J_{4,5}=3.3$ Hz, H_4), 5.49 (dt, H, J_{6a5} = 5.42 Hz, $J_{5,6b}=5.13$ Hz, H_5), 2.86 (dd, 1H, $J_{6a,6b}=10.6$ Hz, H_{6a}), 3.04 (dd, 1H, H_{6b}), 3.84 (s, 4H, CH_2Ph), 1.95 (s, 3H), 2 (s, 3H), 2.08 (s, 3H), 7.2–7.3 (m, 10H, Ph). ^{13}C NMR: δ 54.85 (C_1), 71.83 (C_2), 43.60 (C_3), 77 (C_4), 74.57 (C_5), 22.48 (C_6), 35.44 (CH_2); 35.86 (CH_2), 21.19, 21.20, 21.36 (CH_3), 127–137 C(Ph), 170 (CO). ESMS calcd for $C_{26}H_{30}O_6S_2Se$ (M^+ + Na) 605.05. Found 605.02.

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Structure and conformational processes of bis(*o*-cumyl)sulfide, sulfoxide and sulfone

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Abstract—The NMR solution spectra of the title sulfide and sulfone show decoalescence of the geminal methyl signals of the isopropyl groups at low temperature (−178 °C for the ^{13}C signal of sulfide at 150.8 MHz and −147 °C for the ^{1}H signal of sulfone at 600 MHz). The barriers for the related dynamic processes were measured (4.3 and 7.0 kcal mol^{-1} for the sulfide and sulfone, respectively). The preferred conformer of sulfide has a propeller shape with a C_1 symmetry, as suggested by Molecular Mechanics (MM) calculations. In the case of sulfone the preferred conformer has a propeller shape with a C_2-anti symmetry, as indicated by calculations and supported by X-ray crystallographic determination. The computed contour map of the potential energy shows that in both cases the dynamic processes take place via correlated rotations (cogwheel mechanism) of the two aromatic substituents about the Ar–S bonds. Dynamic processes could not be observed by NMR in the title sulfoxide, which was also found to adopt a propeller shaped conformation, as indicated by MM calculations and X-ray diffraction.
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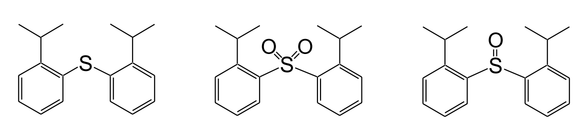
1. Introduction

It has been shown that dimesitylsulfide[2] and sulfone[3] adopt a propeller-like conformation which entails the existence of two stereolabile enantiomers that interconvert with a quite rapid exchange rate. NMR spectra at very low temperatures allowed the barriers involved in these processes to be determined (4.25 and 5.0 kcal mol^{-1}, respectively).[2,3] Molecular Mechanics calculations indicated that the process occurred via a correlated cogwheel mechanism, according to a one-ring flip pathway.[4,5] If the two mesityl groups are replaced by two less symmetric aromatic groups bearing solely one substituent in the *ortho* position of the phenyl ring, a number of conformers with different energy can be generated in principle. Each of these conformational types comprises a pair of enantiomers. In the present paper we investigated the *ortho*-cumyl derivatives **1**–**3** (Chart 1), where the isopropyl group was selected as the *ortho* substituent because it is a convenient NMR probe (both at ^{13}C and ^{1}H frequencies) for detecting the molecular dissymmetry.[6]

2. Results and discussion

In the general case of Ar–X–Ar derivatives (Ar being the same *ortho* substituted phenyl moiety) three propeller conformers can be populated in principle. One such conformer does not have any element of symmetry (C_1 point group), whereas the other two possess a two-fold symmetry axis (C_2 point group). The latter differ for the relative disposition of the two aryl rings that can have the *ortho* substituent either close to (C_2-syn), or remote from (C_2-anti), the X atom. These three conformers exist as pairs of enantiomers, as illustrated in Scheme 1.

In the case of sulfide **1** molecular mechanics calculations[7] and ab initio computations (see Section 4) identify three energy minima, corresponding to the conformers of Scheme 1 (X=S),[8] and indicate that the asymmetric C_1 is more stable than the other two (Table 1). In particular ab initio computations suggest that the asymmetric conformer C_1 might be, in practice, the only appreciably populated form experimentally detectable at very low temperature.



1 **2** **3**

Chart 1.

Keywords: Dynamic NMR spectroscopy; MM calculations; X-ray diffraction.
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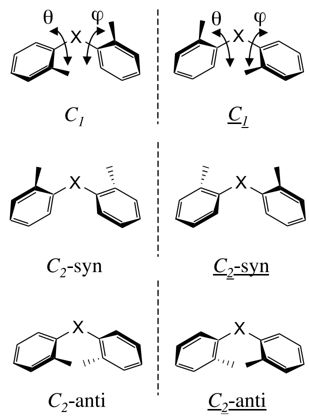


Scheme 1.

an internal motion has been made slow in the NMR timescale, with molecules in a conformation where the geminal methyl groups are diastereotopic.[9] From a complete line shape simulation (Fig. 1) the rate constants for the dynamic process were obtained and the free energy of activation[10] ($\Delta G^{\neq} = 4.3 \pm 0.15$ kcal mol^{-1}) derived. No evidence was found of significant presence of minor signals due to a second conformer, hence the single conformer observed at −178 °C should conceivably correspond to the C_1 structure which has the lowest computed global energy (Table 1).

In the asymmetric conformer C_1, however, the two aryl substituents bonded to sulfur are not equivalent, so that different NMR signals should have been detected for all the pairs of atoms, including the CH isopropyl carbons. To understand why this was not the case and why only the geminal methyl signals are split, the whole rotation pathway of **1** has to be analyzed.

Table 1. Computed relative energy values (kcal mol^{-1}) for the ground and transition states of sulfide **1**

	C_1	C_2-syn	C_2-anti	TS-A	TS-B	TS-C	TS-D
MMFF-94 Force field	0.0	0.26	1.35	2.5	11.0	2.2	1.6
Ab-initio	0.0	0.70	0.98				

See Scheme 2 for the meaning of TS-A, TS-B, TS-C, TS-D.

The aliphatic region of the 150.8 MHz ^{13}C NMR spectrum of **1** displays a single sharp line for the methine and for the methyl carbons from ambient temperature down to −150 °C. On further cooling, the isopropyl methyl line broadens considerably more than that of the corresponding methine carbon (Fig. 1) and eventually decoalesces into a pair of equally intense signals at −178 °C. This proves that

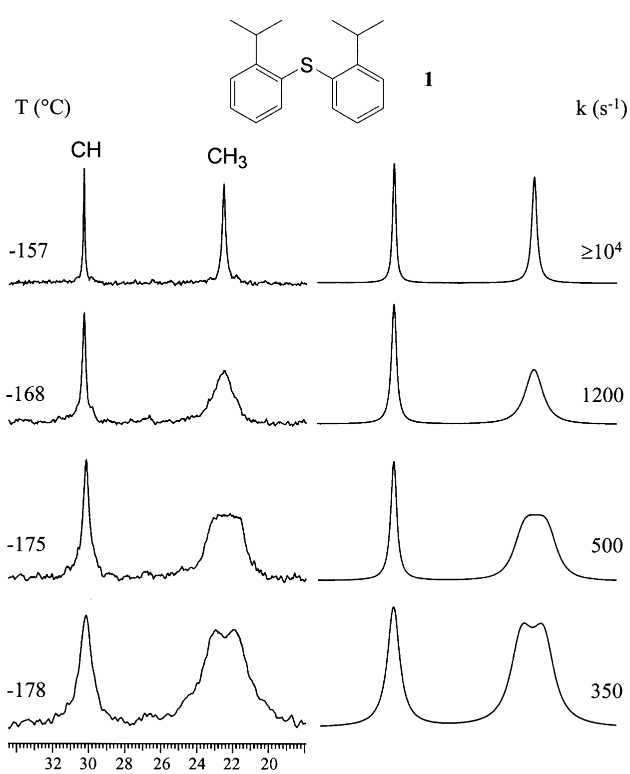


Figure 1. Experimental (left) and simulated (right) ^{13}C NMR spectra (150.8 MHz) of the aliphatic region of sulfide **1** in $CHF_2Cl/CHFCl_2$ as function of temperature.

Figure 2 shows the contour map of the potential energy as function of the Ar–S dihedral angles θ and ϕ, computed using the MMFF 94 force field,[7] with the three energy minima[8] corresponding to the conformers of Scheme 1.

In Scheme 2 are sketched the expected transition states, and in Scheme 3 are also displayed the possible connections between the various ground states described according to the terminology proposed by Mislow[4] and followed by other authors:[5] the reader is referred to these papers for the meaning of the terms employed.

In the case of sulfide **1** (X=S) calculations suggest that the two-ring flip pathway interconverting the asymmetric conformer C_1 with its enantiomer $\underline{C_1}$ (Scheme 3) through the transition state TS-C is a motion too fast to be frozen in a dynamic NMR experiment, as indicated by the computed barrier of only 2.2 kcal mol^{-1} (Table 1). Such a fast process (described by the blue lines of Fig. 2 and of Scheme 3) exchanges the positions of the two rings and creates, in practice, a dynamic plane of symmetry perpendicular to the C–S–C plane, which makes the signals of all the pairs of carbons isochronous, with the exception of those of the geminal methyl groups. This is because the local symmetry plane of the isopropyl substituent is not coincident with the dynamic plane of the whole molecule, thus making the geminal methyl groups diastereotopic:[6,11] such an interpretation accounts for the NMR spectrum at −178 °C. From the NMR experimental point of view the pairs of rapidly interconverting C_1, $\underline{C_1}$ enantiomers can be thus considered as an average conformer having a dynamic plane of symmetry perpendicular to the C–S–C plane. Support for this model is offered by the observation that in the

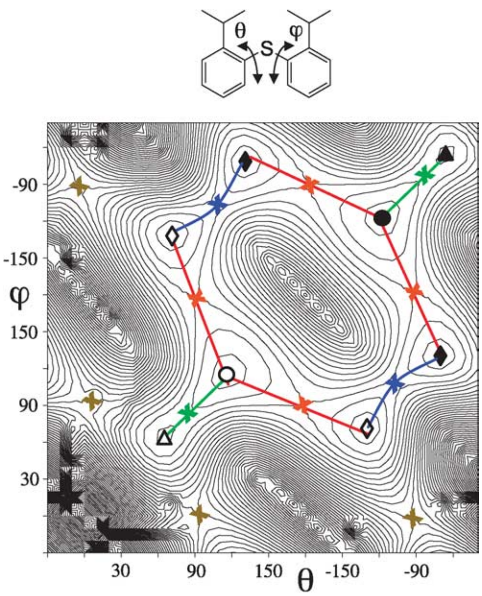
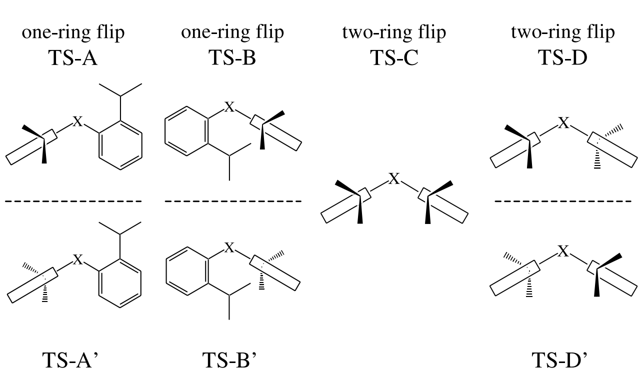


Figure 2. Contour energy map of **1**, as function of the dihedral angles indicated (the contour lines are separated by 1 kcal mol^{-1}). The ground states are identified by circles (hollow for C_2-syn and full for $\underline{C_2}$-syn), triangles (hollow for C_2-anti and full for $\underline{C_2}$-anti), hollow diamonds (C_1) and full diamonds ($\underline{C_1}$). The allowed rotation pathways are indicated by the red lines (one-ring flip via TS-A/TS-A′), by the blue lines (two-ring flip via TS-C) and by green lines (two-ring flip via TS-D/TS-D′). The crosses represent the transition states (the brown crosses identifies the TS-B/TS-B′ transition states).

hydrocarbon of similar structure $Ar_2C{=}CH_2$ (Ar = *ortho*-isopropylphenyl) it was possible to detect, as in **1**, the decoalescence of the methyl signals and, on further lowering the temperature, also the predicted decoalescence of the isopropyl methine signals,[12] which is invisible in **1**. Due to the greater steric hindrance, in fact, the barrier for the interconversion of the enantiomers C_1 and $\underline{C_1}$ is higher in this hydrocarbon than in sulfide **1**. Although experimental evidence for the existence of the mentioned enantiomerization process could not be obtained in **1**, it was at least detected in an analogous case.

The C_1 conformer (identified by the hollow diamond in Fig. 2) can undergo a mutual exchange with its homomeric form by passing twice through the transition state TS-A and visiting the C_2-syn conformer: these pathways are represented by the red lines of Figure 2. This motion exchanges the environments of the two diastereotopic geminal methyl groups (see Scheme 3), thus accounting for the single ^{13}C line observed above −175 °C in Figure 1.[13] In other words, this interconversion creates a dynamic plane of symmetry coincident with the C–S–C plane, thus also coincident with the local plane of symmetry of the isopropyl substituents: a condition[6] which renders equivalent (enantiotopic) the geminal methyl groups.[14] It is the passage through TS-A/TS-A′ which corresponds therefore to the experimental barrier of 4.3 kcal mol^{-1}.



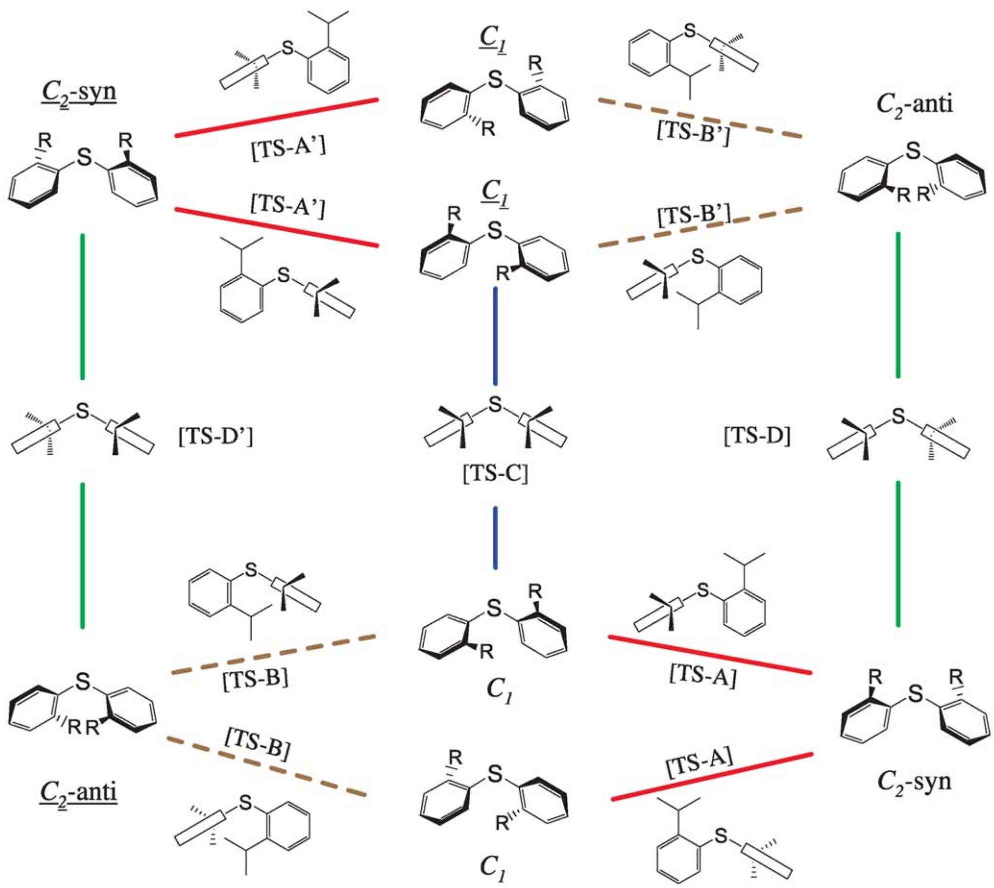
Scheme 2. Representation of the possible transition states for Ar–X–Ar, (Ar = *ortho*-isopropylphenyl).

Although the C_2-syn conformer must be visited in the course of this pathway in order to account for the exchange of the geminal methyl groups, the corresponding NMR signal is invisible since, as mentioned, its higher energy makes the corresponding population too low to be experimentally detected. For the same reason it is also invisible the spectrum of C_2-anti (Scheme 2) which is expected to exchange with C_2-syn with an even lower barrier (Table 1) via the TS-D/TS-D′ transition states (the corresponding pathways have been represented by the green lines of Fig. 2).

From the saddle points of the map of Figure 2 the theoretical energies of the four possible transition states could be estimated and the values are collected in Table 1. As mentioned, the interconversion barrier (2.2 kcal mol^{-1}) between the enantiomers C_1 and $\underline{C_1}$ via TS-C, described by the blue lines of Figure 2 and of Scheme 3, is calculated to be lower than that (2.5 kcal mol^{-1}) for the passage of C_1 through C_2-syn via TS-A (and of C_1 through $\underline{C_2}$-syn via TS-A′), described by the red lines of Figure 2 and of Scheme 3: this result is in agreement with the above interpretation of the experimental findings. The difference between these two values (0.3 kcal mol^{-1}) is very small, but in this type of approximate calculation, it is the relative trend, rather than the absolute value, that should be considered. Furthermore, the measured barrier of 4.3 kcal mol^{-1} corresponds to the lowest possible value that can be determined by a dynamic NMR experiment in solution, so that an exchange process having a barrier lower by even a few tenth of kcal mol^{-1} would be undetectable. On the basis of symmetry considerations and calculations, we conclude that the direct exchange between the C_1 and $\underline{C_1}$ enantiomers via TS-C is too fast to be detected by NMR in solution, whereas that involving the intermediacy of C_2-syn (via TS-A/TS-A′) is measured experimentally to be 4.3 kcal mol^{-1}. The correspondence with the magnitude of the computed barrier (2.5 kcal mol^{-1}) is quite acceptable given the intrinsic approximations of the theoretical approach and the complexity of the dynamic process investigated.[15]

It should be also pointed out that the lines connecting the energy minima of Figure 2 run diagonally with respect to the θ and ϕ axes. This indicates that the rotation processes about the two Ar–S bonds are correlated motions, as in a cogwheel mechanism,[4,5] where the rotation of one ring drives the concomitant rotation of the second one (molecular gear). If these processes had occurred independently of each other, the mentioned connections would have appeared as lines parallel to the Cartesian axes.[2,3,16–18]

Although sulfone **2** ($X{=}SO_2$) has the same overall symmetry as sulfide **1**, the corresponding conformational preferences are quite different. MM computations[7] indicate



Scheme 3. Possible pathways connecting the ground states of sulfide **1** (R = isopropyl). The dashed lines represent processes having too high an energy (see text).

that there are only two minima of energy, corresponding to a C_1 and to a C_2-anti conformer: the C_2-syn conformation does not correspond here to a minimum, most likely owing to the steric hindrance exerted by the oxygen atoms upon the isopropyl groups. Computations also predict that the C_2-anti is substantially more stable than the C_1 conformer (Fig. 3). This result is supported by the X-ray structure showing that solely the C_2-anti structure is present in the crystalline state. In Figure 3 the computed and experimental structures of **2** are reported: the structure that theory predicts to be the most stable is indeed essentially equal to the experimental one. It has also to be pointed out that the state TS-A of Scheme 2 is not a transition state in the case of sulfone **2** (as it was in the case of sulfide **1**): inspection of Figure 3 shows, in fact, that the conformer C_1, which is an energy minimum, corresponds to TS-A of Scheme 2.

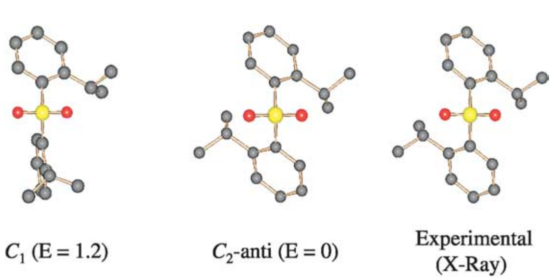


Figure 3. MM computed energy minima and experimental crystal structure for sulfone **2** (the unit cell in the crystal also contains the enantiomer of the structure shown). The energy values are in kcal mol^{-1}.

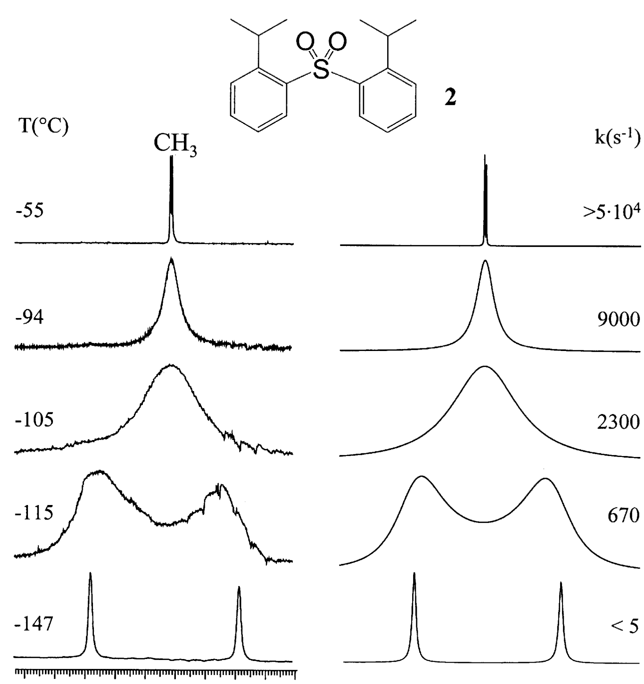


Figure 4. Temperature dependence of the 600 MHz ^1H NMR methyl signal of **2** (left) in $CHF_2Cl/CHFCl_2$ with the simulations (right) obtained using the rate constants indicated.

In Fig. 4, the methyl doublet of the 600 MHz ^{1}H NMR spectrum is reported as a function of temperature. The signal broadens on cooling and, below -110 °C, decoalesces into a pair of lines separated by 590 Hz at -147 °C (at this temperature the splitting due to the coupling with CH is invisible due to the viscosity broadened lines). An analogous behavior is observed in the corresponding 150.8 MHz ^{13}C NMR spectrum where the methyl signal decoalesces into a pair of lines separated by 50 Hz at -147 °C, whereas the CH signal remains a single line at all temperatures. Simulations of the ^{1}H and of ^{13}C spectra provide a $\Delta G^{\neq}$ value of 7.0 ± 0.15 kcal mol^{-1} for this dynamic process. No evidence was observed of signals due to a second minor conformer, in agreement with the theoretical prediction indicating a negligible population of the C_1 conformer.

The symmetry of the C_2-anti conformer requires that every pair of atoms yields isochronous NMR signals, with the exception of the geminal isopropyl methyl groups that are diastereotopic because the conformer does not possess a molecular plane of symmetry:[6] this agrees with the observed ^{1}H and ^{13}C NMR spectra at -147 °C. When the temperature is increased above -110 °C the exchange rate of the C_2-anti conformer with its enantiomer C_2-anti becomes fast on the NMR time scale. Such a process creates a dynamic plane of symmetry coincident with the C–S–C plane, thus coincident also with the local plane of symmetry of the isopropyl groups. This makes the methyl groups become equivalent (enantiotopic),[6] yielding a single NMR line: the measured barrier thus corresponds to the energy required for this enantiomerisation process.

The details of this pathway can be understood by examining the contour map of the potential energy reported in Fig. 5.

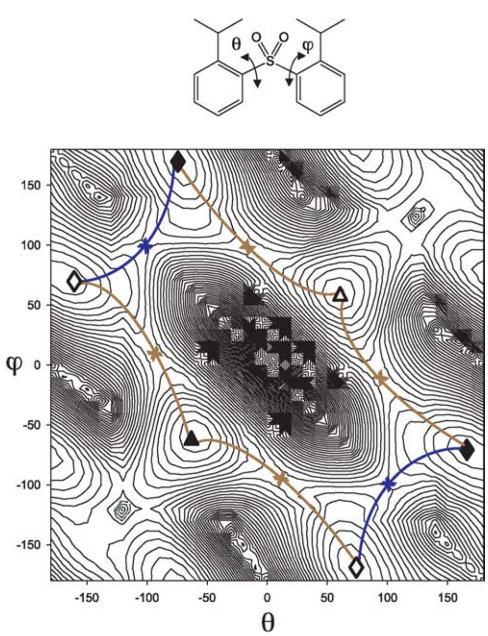


Figure 5. Contour energy map (MMFF force field) for compound **2**, as function of the dihedral angles indicated. The ground states are identified by a hollow triangle (C_2-anti), a full triangle ($\underline{C_2\text{-anti}}$), hollow diamonds ($C_1$) and full diamonds ($\underline{C_1}$). The allowed rotation pathways are indicated by the brown lines (one-ring flip via TS-B/TS-B′) and by the blue lines (two-ring flip via TS-C). The crosses represent the corresponding transition states.

The ground state conformer C_2-anti interconverts into the $\underline{C_1}$ conformer via the transition state TS-B′ (X = SO_2 in Scheme 2), as indicated by the brown line. According to MM calculations the energy of the latter transition state is 7.1 kcal mol^{-1} higher than that of the ground state. Although C_1 is visited in the course of this pathway, its computed energy, as mentioned, is too high to yield an appreciable population, so the corresponding NMR signals were not detected. Subsequently $\underline{C_1}$ interconverts (blue line) into its enantiomer C_1 via a TS-C transition state (the energy of the latter is computed to be 5.8 kcal mol^{-1} higher with respect to C_1) which finally interconverts into the enantiomeric $\underline{C_2\text{-anti}}$ via TS-B. Thus computations indicate that the barrier to be overcome in order to accomplish the stereomutation of C_2-anti with its enantiomer $\underline{C_2\text{-anti}}$ is 7.1 kcal mol^{-1}, a value in good agreement with that experimentally measured (7.0 kcal mol^{-1}).

As in the case of sulfide **1** also in sulfone **2** the lines corresponding to the allowed pathways between the ground states run diagonally to the axes in the contour map of Figure 5, thus indicating that here too we are in the presence of a correlated cogwheel process.[2–5,16–18]

With SO being a prochiral moiety, the geminal methyl groups of sulfoxide **3** are diastereotopic since, contrary to the cases of **1** and **2**, there is not a molecular plane of symmetry coincident with the local plane bisecting the isopropyl substituent.[6,11] As a consequence, two anisochronous ^{1}H and ^{13}C signals are observed for these methyl groups, even at ambient temperature. For this reason the isopropyl moiety cannot be used as a probe for monitoring the dynamic processes due to restricted motions, as in the previous cases of **1** and **2**. The only way of observing a dynamic process in **3** would be the existence of an exchange between conformers having a different population: such a feature, however, was not observed at any attainable temperature, not even below -175 °C. This suggests that only one conformer is essentially populated, although it is impossible to identify its structure solely on the basis of the NMR spectrum.

MM calculations[7] predict that the two lowest energy minima of **3** differ by as much as 3.1 kcal mol^{-1} (Fig. 6), a result in agreement with the low temperature NMR experiment indicating that only one conformer is populated in solution. In addition, X-ray diffraction shows that the crystal structure of **3** (Fig. 6) corresponds to that of the conformer predicted by calculations to have the lowest global energy. It seems thus conceivable to conclude that

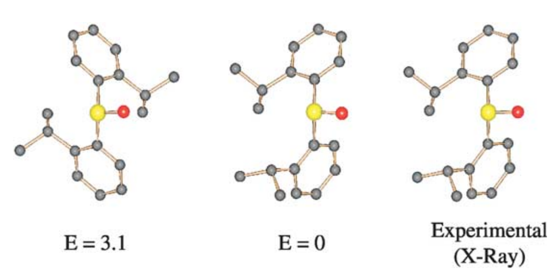


Figure 6. MM computed energy minima and experimental crystal structure for sulfoxide **3** (the unit cell in the crystal also contains the enantiomer of the structure shown). The energy values are in kcal mol.$^{-1}$.

the only conformation populated by sulfoxide **3** in solution is the same propeller shaped structure observed in the solid state.

3. Conclusions

The observation of anisochronous NMR geminal methyl signals in the solution spectrum of sulfide **1** at −178 °C is due to the presence of a pair of rapidly interconverting enantiomers (C_1 point group symmetry) having a propeller-like structure. This rapid motion, occurring via a two-ring flip correlated pathway, creates a dynamic plane of symmetry orthogonal to the C–S–C plane which renders equivalent the two aromatic rings, but leaves diastereotopic the methyl groups of the isopropyl substituents. The methyl signals coalesce above −175 °C allowing the measurement of an interconversion barrier of 4.3 kcal mol^{-1}. This process corresponds to the exchange between the two homomeric forms of conformer C_1 according to a one-ring flip correlated pathway involving the intermediacy of the C_2-syn conformer (the same occurs for $\underline{C_1}$ via $\underline{C_2\text{-syn}}$). The MM computed barrier for this process (2.5 kcal mol^{-1}) is compatible with the experimental value. The anisochronicity of the isopropyl methyl signals of sulfone **2**, observed at −147 °C, is due, on the other hand, to the presence of the C_2-anti conformer, as also confirmed by single crystal X-ray diffraction. The coalescence of these signals, occurring above −110 °C, allowed the determination of a 7.0 kcal mol^{-1} interconversion barrier. This process corresponds to the exchange between the C_2-anti and its $\underline{C_2\text{-anti}}$ enantiomeric form, and takes place according to a one-ring flip pathway involving the intermediacy of the C_1 conformer. The MM computed value for this process (7.1 kcal mol^{-1}) agrees well with the experimental observation.

4. Experimental

4.1. Synthesis

4.1.1. Bis(*ortho*-cumyl)sulfide or bis(2-isopropylphenyl)-sulfide, (1). To a suspension of $LiAlH_4$ (2.2 mmol in 12 ml of Et_2O) were added 233 mg (0.74 mmol) of bis(2-isopropylphenyl)sulfoxide **3** in 10 ml of THF at ambient temperature. When the addition was terminated the reaction was refluxed for 2 h and then cautiously quenched with aqueous NH_4Cl. The product was extracted with Et_2O, dried (Na_2SO_4) and the solvent removed at reduced pressure. The crude (189 mg 0.7 mmol) was purified by chromatography on silica gel (Pet. ether/Et_2O 10/1) colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$, 22 °C, TMS): δ=1.46 (d, 12H, Me, J=8.2 Hz), 3.65 (septet, 2H, CH, J=8.2 Hz), 7.05–7.07 (m, 4H, Ph), 7.21–7.24 (m, 2H, Ph), 7.32 (d, 2H, Ph, J=8.2 Hz); ^{13}C NMR (150.8 MHz, $CDCl_3$, 22 °C, TMS): δ=22.8 (CH_3), 30.6 (CH), 126.0 (CH), 126.7 (CH), 127.6 (CH), 131.8 (CH), 134.0 (q), 149.5 (q). Anal. Calcd for $C_{18}H_{22}S$: C, 80.02; H, 8.20; S, 11.78. Found: C, 79.88; H, 8.16; S, 11.74.

4.1.2. Bis(*ortho*-cumyl)sulfone or bis(2-isopropylphenyl)-sulfone, (2). To a cooled (0 °C) solution of 286 mg (1 mmol) of bis(2-isopropylphenyl)sulfoxide **3** in 10 ml of CH_2Cl_2 was added *meta*-chloroperbenzoic acid (MCPBA, 690 mg 2 mmol 77% w/w). After 4 h at room temperature the reaction was quenched with aqueous Na_2SO_3, extracted with Et_2O, washed with NaCl, dried (Na_2SO_4) and the solvent removed at reduced pressure. The crude (271 mg 0.9 mmol) was purified by chromatography on silica gel (Pet. ether/Et_2O 3/2). Single crystal suitable for X-ray diffraction were obtained by slow crystallisation from hexane. White solid, Mp=148.5–149.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$, 22 °C, TMS): δ=1.06 (d, 12H, Me, J=6.9 Hz), 3.77 (septet, 2H, CH, J=6.9 Hz), 7.35–7.41 (m, 4H, Ph), 7.53–7.58 (t, 2H, Ph, J=8.2 Hz), 8.2 (d, 2H, Ph, J=7.7 Hz); ^{13}C NMR (150.8 MHz, $CDCl_3$, 22 °C, TMS): δ=22.6 (CH_3), 29.2 (CH), 126.4 (CH), 128.3 (CH), 128.7 (CH), 134.0 (CH), 139.3 (q), 149.2 (q). Anal. Calcd for $C_{18}H_{22}SO_2$: C, 71.48; H, 7.33; S, 10.60; O, 10.58 Found: C, 71.52; H, 7.38; S, 10.56; O, 10.50.

4.1.3. Bis(*ortho*-cumyl)sulfoxide or bis(2-isopropyl-phenyl)sulfoxide (3). Thionyl chloride 1.5 (12.5 mmol) was added dropwise, under stirring, to an ice-cooled solution of imidazole 3.5 g (51.0 mmol) in 40 ml of anhydrous tetrahydrofuran. A white precipitate formed immediately. After cooling for several minutes, the reaction mixture was rapidly filtered by suction under a nitrogen atmosphere. The resulting solution, containing *N*,*N*′-thionyldiimidazole, was added at −78 °C to a solution of 1-bromo-2-isopropylbenzene–lithium, obtained by addition of *n*-butyl-lithium (30 mmol, 1.6 M in hexane) to 1-bromo-2-isopropylbenzene (5 g, 25 mmol in 20 ml of THF). After 3 h the mixture was allowed to warm and quenched with cooled aqueous HCl. The product was extracted with Et_2O, washed with Na_2CO_3, dried (Na_2SO_4) and the solvent removed at reduced pressure. The crude (4.65 g, 16.2 mmol) was purified by chromatography on silica gel (Pet. ether/Et_2O 1/1). Crystal suitable for X-ray diffraction was obtained by slow crystallisation in hexane. White solid, Mp 78.5–79.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$, 22 °C, TMS): δ=1.15 (d, 12H, Me, J=6.9 Hz), 3.65 (septet, 2H, CH, J=6.9 Hz), 7.32–7.36 (m, 4H, Ph), 7.42–7.46 (ddd, 2H, Ph, J=7.5, 7.4, 1.2 Hz), 7.65–7.67 (dd, 2H, Ph, J=7.8, 1.4 Hz); ^{13}C NMR (600 MHz, $CDCl_3$, 22 °C, TMS): δ=22.1 (CH_3), 23.9 (CH_3), 29.6 (CH), 126.0 (CH), 126.5 (CH), 127.3 (CH), 131.8 (CH), 141.6 (q), 147.7 (q).

4.2. Computations

A conformational search, using a Molecular Mechanics (MMFF 94 Force Field[7]) approach, was performed to locate the potential minima of **1** and **2**. For each of the mentioned structures C_1, C_2-syn and C_2-anti, other local minima can be also reached by rotation of the isopropyl groups. The latter minima, however, have energies quite higher than that corresponding to the ground states appearing in Table 1 and in Figure 3, so that their populations can be considered negligible. An analogous conformational search, using the same approach, was performed to locate the potential minima of sulfoxide **3**. The potential energy maps of **1** and **2** were obtained using the dihedral drive option of the software.[7] The two dihedral angles were simultaneously driven by 10° steps, leading to a matrix composed by 1296 optimised structures. The transition states were located by identifying the saddle points of the energy map, as in Figures 2 and 5. To better localize the transition states, the dihedral drive was then restricted to a 10°×10° range around the saddle region, using a step angle of 1°. Ab initio computations on compound **1** were carried out at the RHF/6-31G* level by means of the Gaussian 03 series of programs.[19] Harmonic vibrational frequency were calculated in order to ascertain the nature of the stationary points: for each optimised ground state the frequency analysis showed the absence of imaginary frequencies. The search and the computations of the transition states by the same ab initio approach exceeded the capabilities of our computing facilities. For this reason in Table 1 only the barriers computed by MM are indicated.

4.3. NMR measurements

The samples for the low temperature measurements were prepared by connecting to a vacuum line the NMR tubes containing the compound and some C_6D_6 for locking purpose and condensing therein the gaseous CHF_2Cl and $CHFCl_2$ (4:1 v/v) under cooling with liquid nitrogen. The tubes were subsequently sealed in vacuo and introduced into the precooled probe of a spectrometer (Varian Inova, equipped with a variable temperature device where the nitrogen gas was precooled to −40 °C before entering in the liquid nitrogen heat exchanger) operating at 600 MHz for ^1H and 150.8 MHz for ^{13}C. The temperatures were calibrated by substituting the sample with a precision Cu/Ni thermocouple before the measurements. Complete fitting of dynamic NMR line shapes was carried out using a PC version of the DNMR-6 program.[20] Since the isopropyl methine ^{13}C signal of **1** does not undergo exchange broadening, its width at any temperature was assumed as intrinsic line width also for the methyl ^{13}C signals. The separation of the latter, obtained by spectral simulation (Fig. 1), was estimated as 250±20 Hz (at 150.8 MHz). The signals of the aromatic region of **1–3** were not clearly detectable being overlapped by the much more intense signals of the non deuteriated solvents needed to reach such low temperatures.

4.4. X-ray diffraction

4.4.1. Crystal data of bis(2-isopropylphenyl)sulfone, (2). Molecular formula: $C_{18}H_{22}O_2S$, M_r =302.42, orthorhombic, space group P_{bca} (No. 61), a=11.4062(17), b=13.43(2), c=21.909(3) Å, V=3356.2(9) Å^3, T=295(2) K, Z=8, ρ_c=1.197 g cm^{-3}, $F(000)$=1296, graphite-monochromated Mo K_α radiation (λ=0.71073 Å), μ (Mo K_α)=0.195 mm^{-1}, colourless block (0.40×0.40×0.40 mm^3), empirical absorption correction with SADABS (transmission factors: 0.9261–0.9263), 1800 frames, exposure time 20 s, $1.86\leq\theta\leq30.02$, $-16\leq h\leq15$, $-18\leq k\leq18$, $-30\leq l\leq30$, 41,300 reflections collected, 4906 independent reflections (R_{int} =0.0700), 3022 reflections with $I>2\sigma(I)$ (R_σ=0.0482), solution by direct methods (SHELXS) and subsequent Fourier syntheses, full-matrix least-squares on F_o^2 (SHELXTL), hydrogen atoms refined with a riding model, data/parameters=4906/185, $S(F^2)$=1.009, $R(F)$=0.0932 and $wR(F^2)$=0.1599 on all data, $R(F)$=0.07519 and $wR(F^2)$=0.1236 for reflections with $I>2\sigma(I)$, weighting scheme $w=1/[\sigma^2(F_o^2)+(0.0695P)^2+1.2582P]$ where $P=(F_o^2+2F_c^2)/3$, largest difference peak and hole 0.372 and −0.502 e Å^{-3}. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-264520. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

4.4.2. Crystal data of bis(2-isopropylphenyl)sulfoxide, (3). Molecular formula: $C_{18}H_{22}OS$, M_r =286.42, monoclinic, space group $P2_1/c$ (No. 14), a=13.994(4), b=8.031(2), c=15.948(4) Å, β=114.958°; V=1625.0(7) Å^3, T=295(2) K, Z=4, ρ_c=1.171 g cm^{-3}, $F(000)$=616, graphite-monochromated Mo K_α radiation (λ=0.71073 Å), μ (Mo K_α)=0.193 mm^{-1}, colourless plate (0.60 ×0.60×0.20 mm^3), empirical absorption correction with SADABS (transmission factors: 0.8928–0.9624), 1800 frames, exposure time 10 s, $1.61\leq\theta\leq30.12$, $-19\leq h\leq19$, $-11\leq k\leq11$, $-22\leq l\leq22$, 19,743 reflections collected, 4769 independent reflections (R_{int}=0.0497), 4066 reflections with $I>2\sigma(I)$, solution by direct methods (SHELXS) and subsequent Fourier syntheses, full-matrix least-squares on F_o^2 (SHELXTL), hydrogen atoms refined with a riding model, data/parameters=4769/181, $S(F^2)$=1.045, $R(F)$ = 0.0462 and $wR(F^2)$=0.1140 on all data, $R(F)$=0.0384 and $wR(F^2)$=0.1067 for reflections with $I>2\sigma(I)$, weighting scheme $w=1/[\sigma^2(F_o^2)+(0.0607P)^2+0.4870P])$ where $P=(F_o^2+2F_c^2)/3$, largest difference peak and hole 0.510 and −0.299 e Å^{-3}. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-264698. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

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7. MMFF-94 force field as implemented in the computer package PC Model v 7.5, Serena Software, Bloomington, IN.
8. These conformers can be also classified on the basis of the value and of the sign of dihedral angles C2–C1–S–C1′ (θ) and C2′–C1′S–C1 (ϕ) indicated in Scheme 1. In the case of the sulfide **1** the values of these angles (MM computed) are: $\theta = +70°$, $\phi = -130°$ for conformer C_1 and $\theta = -130°$, $\phi = +70°$ for its identical (homomeric) form: in Figure 2 they are identified by hollow diamonds. The angles $\theta = +130°$, $\phi = -70°$ correspond to the enantiomer $\underline{C_1}$ and $\theta = -70°$, $\phi = +130°$ to its homomeric form: in Figure 2 they are identified by full diamonds. The angles for C_2-syn, identified by a hollow circle in Figure 2, are $\theta = \phi = +115°$ (the enantiomer $\underline{C_2\text{-syn}}$ has $\theta = \phi = -115°$ and is identified by a full circle). The angles for C_2-anti, identified by a hollow triangle in Figure 2, are $\theta = \phi = +65°$ (the enantiomer $\underline{C_2\text{-anti}}$ has $\theta = \phi = -65°$ and is identified by a full triangle).
9. This motion cannot be due to a slow Ph–Pr^i rotation since the corresponding barrier is too low to yield separate signals at any accessible temperature in a liquid phase NMR experiment: examples of such an occurrence, in fact, have never been reported. The observed anisochronicity of the methyl signals must be therefore a consequence of the molecular dissymmetry (see, for instance: Kessler, H.; Rieker, A.; Rundel, W. *Chem. Commun.* **1968**, 475–476.
10. As often observed in conformational processes, the $\Delta G^{\neq}$ values are essentially independent of temperature (indicating negligible $\Delta S^{\neq}$ values) since the corresponding variations lie within the experimental error (about ± 0.15 kcal mol^{-1}) which is a consequence of the uncertainties on the measurement of the temperature, of the shift separation and of the T_2 values, see: (a) Hoogosian, S.; Bushweller, C. H.; Anderson, W. G.; Kigsley, G. *J. Phys. Chem.* **1976**, *80*, 643. (b) Lunazzi, L.; Cerioni, G.; Ingold, K. U. *J. Am. Chem. Soc.* **1976**, *98*, 7484–7488. (c) Bernardi, F.; Lunazzi, L.; Zanirato, P.; Cerioni, G. *Tetrahedron* **1977**, *33*, 1337–1343. (d) Lunazzi, L.; Magagnoli, C.; Guerra, M.; Macciantelli, D. *Tetrahedron Lett.* **1979**, 3031–3032. (e) Cremonini, M. A.; Lunazzi, L.; Placucci, G.; Okazaki, R.; Yamamoto, G. *J. Am. Chem. Soc.* **1990**, *112*, 2915–2921. (f) Anderson, J. E.; Tocher, D. A.; Casarini, D.; Lunazzi, L. *J. Org. Chem.* **1991**, *56*, 1731–1739. (g) Borghi, R.; Lunazzi, L.; Placucci, G.; Cerioni, G.; Foresti, E.; Plumitallo, A. *J. Org. Chem.* **1997**, *62*, 4924–4927.
11. A situation analogous to that of **1** at −178 °C is, for instance, that of $(Me_2CH)_2PPh$ at ambient temperature, where the methyl groups are diastereotopic whereas the methine hydrogens are equivalent (enantiotopic) because the molecular plane of symmetry is not coincident with the local plane of symmetry of the isopropyl substituents, see: McFarlane, W. *Chem. Commun.* **1968**, 229–230.
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13. The same type of interconversion might occur through the transition state TS-B of Scheme 2, but calculations show that the corresponding energy (Table 1) is much higher than that of TS-A, so that this rotation process can be considered as not allowed. For this reason this pathway has not been indicated in Figure 2 and only the positions corresponding to TS-B/TS-B′ (brown crosses) are displayed.
14. Above −174 °C the situation of **1** becomes analogous, for instance, to that of $(Me_2CH)_2CO$, where the methyl groups are enantiotopic and exhibit, therefore, a single line in the ^{13}C NMR spectrum because the molecular plane of symmetry is coincident with the local plane of symmetry of the isopropyl substituents.
15. It cannot be excluded, in principle, that the chemical shift difference of the methine isopropyl carbons of sulfide **1** might be smaller than the line width (about 110 Hz) at −178 °C, so that the observed spectrum might actually correspond to that of the static asymmetric C_1 conformer. This hypothesis would also require that four lines be observed for the methyl groups: again the corresponding shift difference should be assumed to be lower than 110 Hz in order to explain why only two methyl signals are resolved. Also the aromatic lines should be split in this case but, unfortunately, they are overlapped by the intense signals of the solvents needed to reach such extremely low temperatures and cannot be used to check whether the aromatic rings are different, as expected for the static C_1 conformer. If all these assumptions are accepted, the two mentioned interconversion processes would be, in practice, undistinguishable: in other words, the interconversion through the TS-C and the TS-A transition states should be considered as having essentially the same barrier. In view of the similarity between these two computed barriers (2.2 and 2.5 kcal mol^{-1}, respectively) we feel that this alternative explanation cannot be unambiguously rejected.
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Stereoselective synthesis of dienylamines: from amino acids to *E*-alkene dipeptide isosters

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Abstract—A stereoselective approach to dienylamines is described, starting from enantiomerically enriched stannylated allylamines, which are in turn derived from amino acids. Conveniently the procedure allows to introduce diversity at 1-,2- and 4- positions of the final compounds. Conversion to vinylstannane has been extended to dipeptido aldehydes. The possible elaboration of 4-methyl substituted dienylamines to Boc-Gly-Ψ[(*E*)-CH=CH]-(L,D)-Ala and Boc-Phe -Ψ[(*E*)-CH=CH]-(L,D)-Ala dipeptide isosters is also shown.
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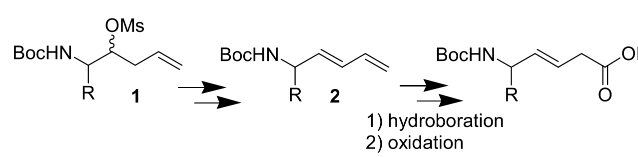
1. Introduction

Dienylamines are a very interesting moiety, frequently, used in organic synthesis, as for instance in Diels Alder reactions.[1,2] They are versatile building blocks which can be transformed to a range of products by functionalization, reduction or oxidation of double bonds. In addition this unit is found in many bioactive molecules like streptogramine antibiotics,[3] and has been shown as key intermediate to *E*-alkene dipeptide isosters.[4]

trans-Disubsbtituted alkene units have been introduced for the first time by Hann[5,6] as an ideal isosteric replacement for the backbone amide group of peptides as the C=C bond is inert to peptidases and the *trans* configuration mimics the conformational preference of a secondary amide. In addition this substitution does not diminish the conformational flexibility that is characteristics of a peptide.[7] The use of this isosteric replacement in peptides is thus, a very important tool in the development of new bioactive compounds and, affecting physical properties like folding and conformation,[8] can also serve as model for biological studies.

Basically, the synthesis of an *E*-alkene dipeptide isostere requires the preparation of a 5-amino-3-pentenoic acid bearing either one or two asymmetric centers in the α- and δ- position. Several methods have been reported to generate this class of compounds,[9–21] and especially Kessler and Kranz[4] showed how dienylamines **2**, which are generated by β-elimination of the corresponding mesyloxy derivative **1**, can be transformed into Phe-Gly *E*-alkene dipeptide isostere by regioselective hydroboration and subsequent oxidation (Scheme 1).



Scheme 1.

For all these reasons chiral pentadienylamines are an important synthetic goal, as it is addressed by several stereoselective approaches reported which include asymmetric nucleophillic additions to carbon–nitrogen double bond,[22] Julia[23] or Wittig-type chemistry,[1,24] cross coupling reactions between the C_3–C_4[25,26] or the C_5–C_6[27]atoms, indium mediated convertion of iodomethyl aziridine.[28] However, there is still a need for developing new convenient and practical approaches which are, if possible, designed to generate molecular diversity, compatible with the presence of sensitive functionalities and stereocenters on the substrates, and able to deliver the final compounds with total control of the geometry of the double bond.

We have already shown how chiral stannylated allylamines **3** can be efficiently obtained through the addition of stannylcuprate **4** on propargylamines **5** and coupled with

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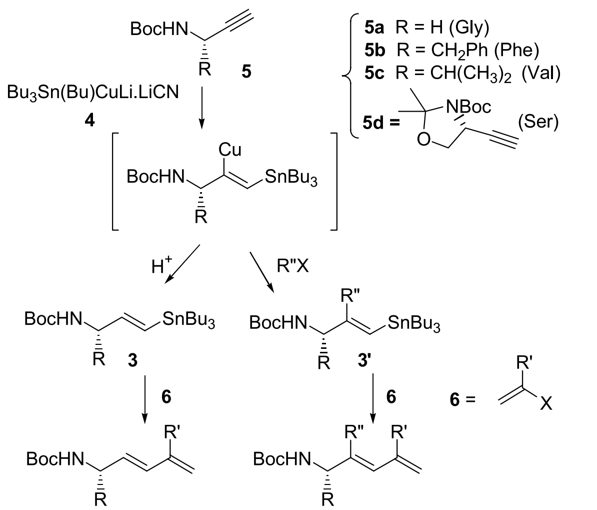
several electrophiles under Pd catalysis to afford a wide range of γ-substituted allylamines.[29] This protocol is mild, chemoselective and has worked remarkably well with chiral substrates, derived from naturally occurring amino acids.[30–32] Taking advantage of this approach, dienylamines could be simply obtained by coupling stannylallylamines **3** with vinylbromides **6** (see Scheme 2).

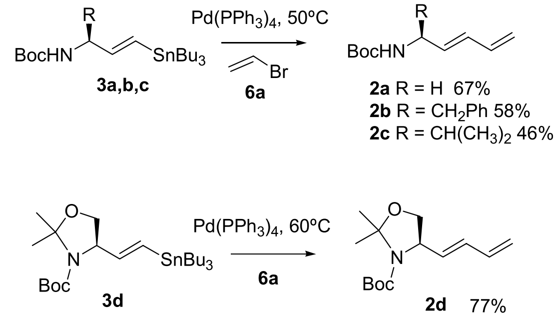


Scheme 2.

Although trivial, the value of this reaction scheme resides, in our opinion, in its flexibility since it allows to introduce three points of molecular diversification onto the dienylamine backbone. Substitution and configuration of the α-carbon can be determined, in fact, by choosing the appropriate starting amino acid, β-substitution can be achieved by quenching the intermediate vinylcuprates with different electrophiles and δ-substitution can be obtained through the coupling with α-branched vinylbromides **6** ($R' \neq H$). Thus, 1,2- or 1,4-disubstituted or 1,2,4-trisubstituted dienamines can be designed and possibly used as precursors for differently substituted *E*-alkene-dipeptide isosters.

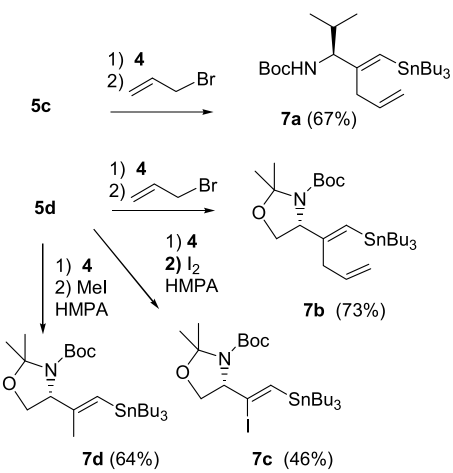
2. Results and discussion

In order to prove the feasibility of this approach, the reactivity of vinylstannanes **3a**,**b**,**c**,**d** with vinylbromide was studied. The required substrates were prepared from propargylamine **5a** and naturally occurring amino acids (phenylalanine **5b**, valine **5c** and serine **5d**) via standard methods.[33,29,30] According with the well known Stille procedure,[34] compounds **3a**,**b**,**c**,**d** were reacted with an excess of vinyl bromide **6a** in the presence of $Pd(PPh_3)_4$ as catalyst. Complete conversion of substrates into the coupled compounds **2a**,**b**,**c**,**d** was obtained performing the reaction in a sealed tube, at 50–60 °C, with excess of the electrophile and without solvent. ^{1}H NMR analysis of the crude mixture confirmed, as expected, that the coupling occurred with retention of configuration of the vinyl-tin bond, highlighting the method as a mild and efficient way for the preparation of α-branched dienylamines with an (*E*)-geometry. After work-up and chromatography, the final compounds were obtained in good yields (see Scheme 3).



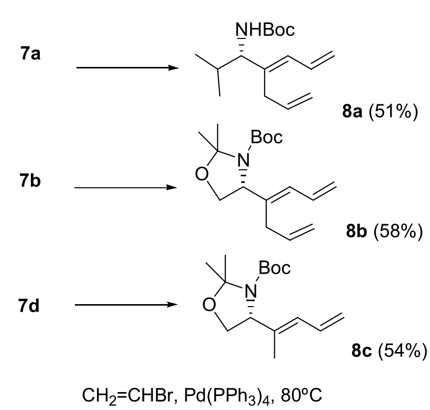
Scheme 3.

In the addition of stannylcuprate to triple bonds an intermediate vinylcuprate is generated which can be trapped with different electrophiles. This reactivity has been exploited in the past to obtain a range of β-substituted stannyl allylamines,[33] or enantiomerically enriched β-amino acrylates.[35] Certainly it can be also extended to prepare 1,2-disubstituted dienylamines. Aimed to show this, three different electrophiles have been used following addition of **4** onto amine **5c** or oxazolidine **5d**, as shown in Scheme 4.



Scheme 4.

Allylbromide gave excellent results affording more than 80% convertion to dienamine **7a** and **7b** in 95/5 regioisomeric mixture, as recovered by ^{1}H NMR analysis of the crude. Using a less powerful electrophilic partner, like MeI, addition of HMPA was required in order to obtain a good



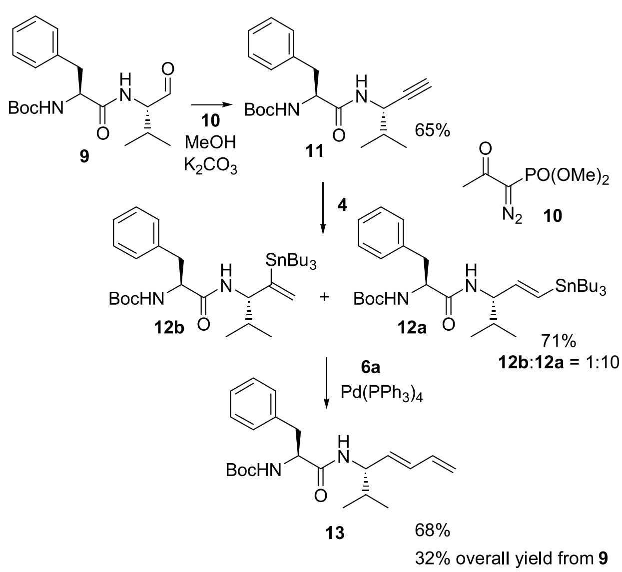
Scheme 5.

conversion into **7d**.[33] Trapping with I_2 in the presence of HMPA afforded **7c**, but in a 80/20 regiosomeric mixture and this was responsible for the lower yield observed. Final compounds **7a–d** were purified by flash chromatography and fully characterized.

2-Functionalized stannanes **7a**, **7b** and **7d** were also reacted with vinylbromide and transformed into the corresponding 1,2-disubstituted dienylmine **8a**,**b**,**c** as shown in Scheme 5.

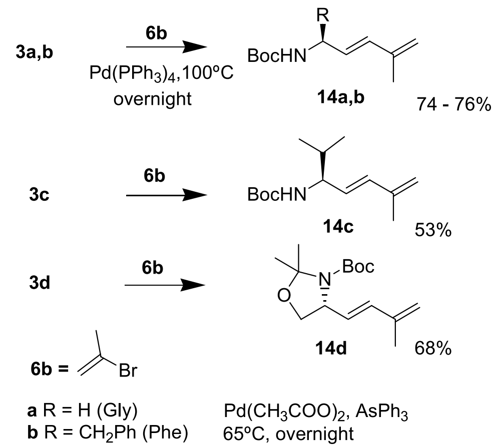
As we have already mentioned, the whole procedure, starting from amino aldehydes to give the target dienylamines, is very selective and requires mild conditions, which are compatible with functionalized substrates. It is known that the synthetic elaboration of dipeptides might be troublesome[36] because of their sensitivity, thus we thought to verify if our route could be extended to a dipeptido aldehyde like **9**,[36,37] aiming to obtain alkyne **11** and vinylstannane **12a**. Both these compounds can be regarded as very useful chiral building blocks to make selective transformations on a dipeptide structure.

When aldehyde **9** was reacted with oxopropyldiazophosphonate **10**,[38] alkyne **11** was obtained in 65% yield after purification on column chromatography (Scheme 6). No α-epimerization at the stereogenic center next to the carbonyl was observed, as confirmed by ^1H and ^{13}C NMR spectra of the crude mixture, where only one diastereoisomer was present. Reaction with stannylcuprate **4** gave a mixture of stannylated dipeptide **12a** and its regioisomer **12b** in a 10:1 ratio. Although the two regioisomer were not separated by flash chromatography, the mixture could be used in coupling reactions, due to the higher reactivity of isomer **12a**.[33] Reaction with vinylbromide, for instance, gave, after purification, dienylamine **13** in good yield (see Scheme 6) as a single diastereoisomer.



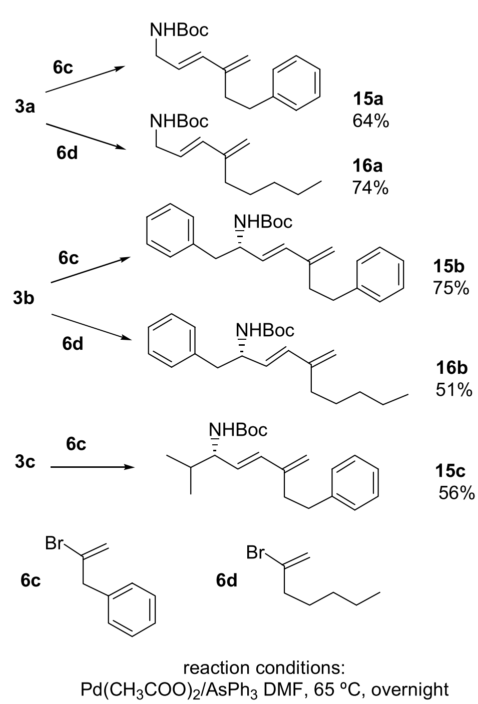
Scheme 6.

In view of accessing a wider molecular diversification, we finally examined the coupling with 2-branched vinylbromides: this would result in δ-substituted dienyl amines. Commercially available 2-bromopropene **6b** was selected to test the reactivity of our substrates (Scheme 7). Although an higher reaction temperature (100 °C), a longer reaction time and excess of electrophile were required, the corresponding 4-methyl dienes, **14a–b**, were recovered and isolated in good yields.



Scheme 7.

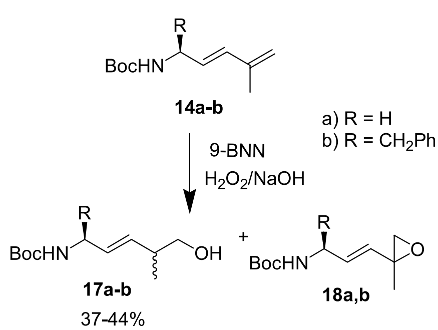
On the contrary, amine **3c** and oxazolidine **3d** reacted sluggishly and the corresponding coupling products could be isolated only in poor yield. Hence, we decided to look for milder conditions. It is known that ligands of reduced donicity usually lead to much faster coupling,[39] consequently when tri(2-furyl)phosphine or $AsPh_3$ are used together with $Pd(CH_3COO)_2$, the reaction can be performed at a lower temperature. Indeed, both these catalysts when reacted with **3c**,**d** promoted the coupling and the best results were finally found using $AsPh_3/Pd(CH_3COO)_2$ in DMF at 65 °C. Using these reaction conditions, compounds **14c**,**d** were obtained in good yields after purification.



Scheme 8.

Stannanes **3a**,**b**,**c** were also reacted with 2-bromo,4-phenyl-but-1-ene **6c** and with 2-bromo,4-methyl-hept-1-ene **6d**, in turn prepared by reaction of 1,2-dibromopropene with benzyl magnesium chloride or with $Bu_2CuLi \cdot LiCN$. Five new amines, **15a**,**b**,**c** and **16a**,**b** were consequently obtained and isolated after column chromatography, as shown in Scheme 8.

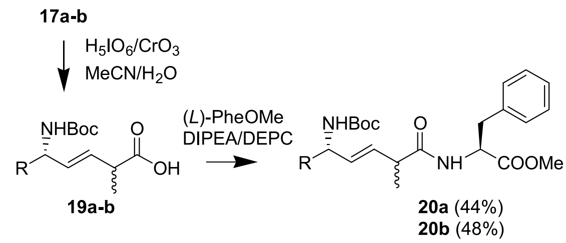
As we previously pointed out, dienamines have been shown to be key intermediates for the synthesis of *E*-alkene dipeptide isosters. In particular, dienamine **2b** was used for the synthesis of Phe-Ψ[(*E*)-CH=CH]-Gly type isoster.[4] The same procedure, if applied to 4-substituted dienamines, can usefully widen the field of target compounds. For instance, if dienamines **14a–b** are used as starting material, the corresponding Gly-Ψ[(*E*)-CH=CH]-Ala and Phe-Ψ[(E)-CH=CH]-Ala isosteres can be obtained. To verify this hypothesis we converted compounds **14a–b** into the corresponding primary alcohols **17a–b** in the reported conditions.[4] Regioselective hydroboration with 9-borabicyclo[3.3.1]-nonane (9-BBN) followed by treatment with $NaOH/H_2O_2$ (see Scheme 9) gave the target alcohols, although in poor yield. Unfortunately in both cases, variable amounts of a by-product were recovered in the ^{1}H NMR of crude mixture. These were finally identified as the corresponding epoxides **18a**,**b**. Nevertheless, alcohols **17a**,**b** were isolated and fully characterized. Concerning **17b**, it was obtained as a 1/1 mixture of diastereoisomers as shown by some diagnostic signals in the 400 MHz ^{1}H NMR spectrum. In particular, the more shielded of the two vinylic protons was splitted into two double doublets of the same intensity and two separated doublets ($\delta=0.93$, $\delta=0.90$) were observed for the methyl too. This was also split into two separate signals at $\delta=16.04$ and $\delta=16.15$ pmm in the ^{13}C NMR spectrum.



Scheme 9.

The two diastereoisomers **17b** were not separated and, after flash chromatography, were used for an oxidative step. Rapid and clean oxidation to Boc-Gly-Ψ[(E)-CH=CH]-(*rac*)-Ala **18a**, and Boc-(L)-Phe-Ψ[(E)-CH=CH]-(*rac*)-Ala **18b** occurred using periodic acid (H_5IO_6) as stoichiometric oxidant together with a catalytic amount of CrO_3.[40]

For characterization purposes, these were coupled with (L)-phenylalanine methyl ester to give tripeptide isosters Boc-Gly-Ψ[(E)-CH=CH]-(*rac*)-Ala-(L)-Phe-OMe **19a** and Boc-(L)-Phe-Ψ[(E)-CH=CH]-(*rac*)-Ala-(L)-Phe-OMe **19b** (see Scheme 10).



Scheme 10.

3. Conclusions

In conclusion stannylated allylamines have been confirmed as valuable chiral building blocks which can be elaborated into dienylamines. Due to the mild and selective procedure employed, the method has been proved to be appropriate also when applied to sensitive substrates like dipeptido aldehydes. We had then access to stannylated dipeptido derivatives which can be very useful building blocks. Transformation of dienamines into *E*-dipeptide isosters was estabilished in two cases and isoster of kind AA-Ψ[(E)-CH=CH]-(*rac*)-Ala were obtained by hydroboration/oxidation of the precursors 4-methyl pentadienylamines. Further improvement of the whole process using selective hydroboration methods is currently under investigation.

4. Experimental

4.1. General methods

Ethereal extracts were dried with Na_2SO_4. Reactions were monitored by TLC on SiO_2; detection was made using a $KMnO_4$ basic solution. Flash column chromatography[41] was performed using glass columns (10–50 mm wide) and SiO_2 (230–400 mesh). ^{1}H NMR were recorded at 200, 300 or 400 MHz. For those compounds which are present as slowly interconverting rotamers, ^{1}H NMR experiments were performed at 50 °C and signals of the averaged spectrum are reported when possible. ^{13}C NMR spectra were recorded at 50.3 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$, δ 7.26 ppm for ^{1}H NMR; $CHCl_3$, δ 77.0 ppm for ^{13}C NMR). FTIR spectra were registered in CH_2Cl_2 solution (CaF_2). Mass spectra were obtained at a 70 eV ionization potential and are reported in the form *m*/*z* (intensity relative to base = 100). Polarimetric measurements were performed at $\lambda=589$ nm, and the temperature is specified case by case.

Amines **3a–c**,[33,29,30] oxazolidine **3d**,[30] and dipeptide aldehyde **9**[36] were prepared according to the literature. $Pd[P(Ph_3)_4]$ was freshly prepared and stored under nitrogen. Starting materials are commercially available unless otherwise stated. All commercial reagents were used without further purification. THF was dried by distillation over sodium benzophenone ketyl. CH_2Cl_2 was dried over $CaCl_2$, and stored over 4 Å molecular sieves. DMF was distilled over $CaCl_2$, and stored over 4 Å molecular sieves. Petroleum ether, unless specified, is the 40–70 °C boiling fraction.

4.2. Coupling with vinyl bromide 6a: general procedure

A catalytic amount (0.01 equiv) of freshly prepared $Pd[P(Ph_3)]_4$ was poured into a sealed flask under nitrogen atmosphere, together with excess of vinyl bromide **6a**. Amine **3a–d** (1 equiv) was then added and the reaction mixture heated and reacted for a variable time, depending on the substrate. After the starting material was completely consumed the excess of electrophile was evaporated and the recovered material diluted with ether and treated with a aqueous KF saturated solution. After filtration and extraction with ether the organic phase was washed with brine and dried. The crude obtained after evaporation of the solvent was purified by flash chromatography.

4.2.1. (2*E*)-Penta-2,4-dienyl-carbamic acid *tert*-butyl ester 2a. Vinylbromide (0.5 mL) was reacted with **3a** (90 mg, 0.2 mmol) at 55 °C for 10 h. Purification [petroleum ether/ethyl acetate = 7:1] gave 26 mg of pure **2a** (67%) as a colorless oil.

Compound (**2a**): ^{1}H NMR (200 MHz) δ: 1.44 [s, 9H]; 3.72–3.78 [br m, 3H]; 4.53 [br s, 1H]; 5.04 [br d, 1H, $J=10.4$ Hz]; 5.16 [br d, 1H, $J=16.8$ Hz]; 5.64–5.71 [m, 1H]; 6.11–6.17 [m, 1H, $J_{AB}=15.8$ Hz]; 6.25–6.34 [m, 1H, $J_{AB}=15.8$ Hz]. ^{13}C NMR (50.3 MHz) δ: 28.25; 42.12; 79.33; 117.13; 130.20; 132.00; 136.10; 155.66. MS *m/z* (%): 127 (9); 57 (100). Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.37; H, 9.31; N, 7.73.

4.2.2. (2*E*),(1*S*)-(1-Benzyl-penta-2,4-dienyl)-carbamic acid *t*-butyl ester 2b. Vinylbromide (0.5 mL) was reacted with **3b** (110 mg, 0.2 mmol) at 50 °C for 20 h. Purification [petroleum ether/ethyl acetate = 6:1] gave 30 mg of pure **2b** (58%) as a pale yellow oil. ^{1}H NMR was in agreement with those previously reported.[4]

Compound (**2b**). ^{13}C NMR (50.3 MHz) 28.40; 33.21; 62.07; 79.12; 111.58; 115.82; 117.33; 127.67; 132.56; 135.96; 139.11; 147.20; 155.45. $[\alpha]_D^{24}$ +4.5 (*c* 1.0, $CHCl_3$).

4.2.3. (2*E*),(1*S*)-(Isopropyl-penta-2,4-dienyl)-carbamic acid *t*-butyl ester 2c. Vinylbromide (0.5 mL) was reacted with **3c** (100 mg, 0.2 mmol) at 50 °C for 20 h. After Purification [petroleum ether/ethyl acetate = 10:1] gave 21 mg of pure **2c** (46%) as a colorless oil.

Compound (**2c**): ^{1}H NMR (200 MHz) δ: 0.88 [d, $J=5.8$ Hz, 3H]; 0.90 [d, $J=5.8$ Hz, 3H]; 1.44 [s, 9H]; 1.58–1.88 [m, 1H]; 3.97 [br s, 1H]; 4.37–4.58 [m, 1H]; 5.05 [br d, $J=8.8$ Hz, 1H]; 5.18 [dd, $J=14.0$, $J=2.0$ Hz, 1H]; 5.58 [dd, $J=14.6$, $J=6.2$ Hz, 1H]; 6.08–6.41 [m, 2H]. ^{13}C NMR (50.3 MHz) δ: 18.04; 18.74; 28.46; 32.70; 58.15; 79.28; 116.75; 131.49; 133.13; 136.41; 155.44. MS *m/z* (%): 225 (4); 57 (100). $[\alpha]_D^{28}$ +5.2 (*c* 0.35, $CHCl_3$). Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.29; H, 10.29; N, 6.22. Found: C, 69.42; H, 10.32; N, 6.26.

4.2.4. (4*R*)-2,2-Dimethyl-4-[(*E*)-buta-1,3-dienyl)]-oxazolidine-3-carboxylic acid tert-butyl ester 2d. Vinylbromide (0.5 mL) was reacted with **3d** (135 mg, 0.2 mmol) at 60 °C for 20 h. Purification [petroleum ether/ethyl acetate = 5:1] gave 51 mg of pure **2d** (77%) as an oil. Spectroscopic data were in agreement with those previously reported.[42] $[\alpha]_D^{20}$ +20.2 (*c* 1.85, $CHCl_3$) {lit. $[\alpha]_D^{21}$ +21.2 (*c* 1.93, $CHCl_3$)}.

4.3. Trapping with electrophiles: general procedure

Stannylcuprate was prepared as reported[43] using CuCN (1 equiv), BuLi (1.6 M in hexane, 2 equiv) and *n*-Bu_3SnH (1.0 equiv). Substrate **5** (1 equiv) was then added and, after warming at −30 °C, reacted with the electrophile. After usual workup the corresponding 2-substituted stannylated amines were recovered and purified by flash chromatography.

4.3.1. (1*S*)-(1-Isopropyl-2-tributylstannanylmethylene-pent-4-enyl)-carbamic acid *t*-butyl ester 7a. CuCN (38 mg, 0.4 mmol), BuLi (0.50 mL, 0.8 mmol) and *n*-Bu_3SnH (116 mg, 0.4 mmol) were reacted with **5c** (92 mg, 0.4 mmol) and, after warming at −30 °C, with allylbromide (72 mg, 0.6 mmol) for 12 h. Purification [petroleum ether/ethyl acetate (20:1)], gave **7a** as a colorless oil (139 mg, 67%).

Compound (**7a**): ^{1}H NMR (200 MHz) δ: 0.79–0.94 [m, 15H+6H]; 1.43 [s, 9H]; 1.20–1.51 [m, 12H]; 1.78–1.96 [m, 1H]; 2.82 [d, $J=6.6$ Hz]; 3.86–4.00 [m, 1H]; 4.48–4.62 [br. d, $J=10.8$ Hz, 1H]; 4.98–5.20 [m, $J_{AB}=16.4$, $J_{AX}=9.9$, $J_{BX}=1.6$ Hz]; 5.68 [d, $J=0.8$ Hz, 1H]; 5.69–5.86 [m, $J_{AB}=16.4$, $J_{AX}=9.9$ Hz, 1H]. ^{13}C NMR (50.3 MHz) δ: 10.24; 13.64; 17.21; 20.21; 27.24; 28.37; 29.14; 30.04; 42.13; 61.43; 78.80; 116.34; 124.36; 136.90; 155.18; 155.51. MS *m/z* (%): 416 (10); 57 (100). FTIR ν_{max}: 3434, 1712. $[\alpha]_D^{21}$ −4.7 (*c* 1.18, $CHCl_3$).

4.3.2. (4*R*)-2,2-Dimethyl-4-{1-[(*E*)-1-tributyl-stannanyl-methylidene]-but-3-enyl}-oxazolidine-3-carboxylic acid *tert*-butyl ester 7b. CuCN (88 mg, 1.0 mmol), BuLi (1.25 mL, 2.0 mmol) and *n*-Bu_3SnH (290 mgl, 1.0 mmol) were reacted with oxazolidine **5d** (218 mg, 0.97 mmol) and, after warming at −30 °C, with allylbromide (180 mg, 1.5 mmol) for 12 h. Purification [petroleum ether/ethyl acetate (gradient)], gave **7b** as a colorless oil (392 mg, 73%).

Compound (**7b**): ^{1}H NMR (400 MHz, 50 °C) δ: 0.89 [t, $J=7.6$ Hz, 9H]; 0.89–0.94 [m, 6H]; 1.26–1.36 [m, 12H]; 1.38–1.58 [m, 15H]; 2.80–2.85 [m, $J_{AB}=8.0$, $J_{AX}=14.8$, 1H]; 2.91–2.96 [m, $J_{AX}=14.8$, $J_{BX}=6.4$ Hz, 1H]; 3.70–3.73 [m, $J_{AX}=2.8$, $J_{AB}=8.8$ Hz]; 4.06–4.02 [m, $J_{BX}=6.8$, $J_{AB}=8.8$ Hz, 1H]; 4.26–4.42 [br m, 1H]; 5.02–5.05 [dd, $J_{cis}=10.0$, $J_{gem}=1.6$ Hz, 1H]; 5.13–5.09 [br d, $J_{trans}=17.2$ Hz, 1H]; 5.69–5.78 [m, 1H]; 5.81 [s, $J_{Sn\text{-}H}=36.2$ Hz, 1H). ^{13}C NMR (50.3 MHz) δ: 10.30; 13.67; 23.34; 25.59; 27.29; 28.40; 29.20; 41.82; 62.34; 68.51; 79.38; 94.32; 116.40; 122.68; 136.50; 151.98; 153.51. MS *m/z* (%): 500 (2); 57 (100). FTIR ν_{max}: 1692, 1388. $[\alpha]_D^{21}$ −25.2 (*c* 0.98, $CHCl_3$).

4.3.3. (4*R*)-2,2-Dimethyl-4-{1-[(*Z*)-1-iodo-2-tributyl-stannyl]-vinyl}-oxazolidine-3-carboxylic acid *tert*-butyl ester 7c. CuCN (45 mg, 0.5 mmol), BuLi (0.65 mL, 1.0 mmol) and *n*-Bu_3SnH (148 mg, 0.5 mmol) were reacted with oxazolidine **5d** (113 mg, 0.5 mmol) and then with HMPA (0.2 mL) and a solution of I_2 (122 mg, 0.5 mmol) in THF (2 mL). Temperature was raised at −30 °C and the reaction mixture stirred overnight. Purification [petroleum ether/ethyl acetate=30:1] gave 143 mg of **7c** (46%) as an yellow oil.

Compound (**7c**): ^{1}H NMR (400 MHz, 50 °C) δ: 0.90 [t, J=7.2 Hz, 9H]; 1.30–1.57 [m, 6H+9H+18H]; 3.91–3.94 [m, J_{AB}=8.8, J_{AX}=3.2 Hz,, 1H]; 4.02–4.05 [m, J_{AB}=8.8, J_{BX}=7.2 Hz, 1H]; 4.39–4.45 [br m, 1H]; 7.13 [s, J_{Sn-H}=45.2 Hz, 1H]. ^{13}C NMR (50.3 MHz) δ: 10.65; 13.66; 23.55; 25.88; 27.25; 28.29; 29.06; 68.37; 69.96; 80.04; 95.42; 124.77; 139.45; 151.77. MS *m/z* (%): 587 (2); 57 (100). ν_{max}: 1712. $[\alpha]_D^{21}$ 0.00 (c 0.62, $CHCl_3$).

4.3.4. (4*R*)-2,2-Dimethyl-4-{1-[(*E*)-1-methyl-2-tributyl-stannyl]-vinyl}-oxazolidine-3-carboxylic acid *tert*-butyl ester 7d. CuCN (45 mg, 0.5 mmol), BuLi (0.65 mL, 1.0 mmol) and n-Bu_3SnH (146 mg, 0.5 mmol) were reacted with oxazolidine **5d** (108 mg, 0.5 mmol) together with HMPA (0.2 mL). Temperature was raised at −25 °C, methyliodide (112 mg, 0.8 mmol) was added and stirred overnight. Purification [petroleum ether/ethyl acetate (gradient)] gave **7d** as a pale yellow oil (167 mg, 64%).

Compound (**7d**): ^{1}H NMR (400 MHz, 55 °C) δ: 0.86–0.91 [t, J=7.2 Hz, 15H]; 1.26–1.35 [m, 6H]; 1.41–1.52 [m, 21H]; 1.75 [s, 3H]; 3.67–3.70 [m, J_{AB}=8.8, J_{AX}=1.6 Hz, 1H]; 4.03–4.09 [m, J_{AB}=8.8, J_{BX}=7.2 Hz, 1H]; 4.21–4.37 [br m, 1H]; 5.67 [s, J_{Sn-H}=65.6 Hz, 1H]. ^{13}C NMR (50.3 MHz) δ: 13.62; 20.76; 23.37; 25.73; 27.22; 28.25; 28.35; 29.01; 65.26; 68.38; 79.33; 94.29; 11.28; 122.74; 152.212. MS *m/z* (%): 474 (4); 57 (100). ν_{max}: 1708. $[\alpha]_D^{26}$ −30.3 (c 1.0, $CHCl_3$).

4.3.5. (1*S*)-(2-Allyl-1-isopropyl-penta-2,4-dienyl)-carbamic acid *t*-butyl ester 8a. Vinylbromide (0.5 mL) was reacted with 85 mg (0.2 mmol) of **7a** at 80 °C for 20 h. Purification [petroleum ether/ethyl acetate=5:1] gave pure **8a** as a colorless oil (28 mg, 51%).

Compound (**8a**): ^{1}H NMR (200 MHz) δ: 0.84–0.95 [m, 6H, CH_3 (*i*-Pr)]; 1.42 [s, 9H, *t*-Boc]; 1.56–1.68 [m, 1H, CH (*i*-Pr)]; 2.73–2.93 [m, 2H, CH_2C=]; 3.72–3.92 [m, 1H, (C1)–H]; 4.53 [br s, 1H, NH]; 4.90–5.24 [m, 2H+2H, C(5)–H+ CH_2=]; 5.70–5.84 [m, 1H, CH=]; 5.97 [d, J=11.0 Hz, 1H, C(3)–H]; 6.46–6.65 [m, 1H, C(4)–H]. ^{13}C NMR (50.3 MHz) δ: 17.28; 20.27; 28.40; 33.21; 37.78; 62.07; 79.12; 115.83; 127.68; 132.57; 135.97; 147.21; 155.45. MS *m/z* (%): 209 (7); 57 (100). $[\alpha]_D^{24}$ −9.7 (c 1.0, $CHCl_3$). Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.25; N, 5.28. Found: C, 72.54; H, 10.48; N, 5.22.

4.3.6. (4*R*)-2,2-dimethyl-4-[(*E*)-1-allyl-buta-1,3-dienyl]-oxazolidine-3-carboxylic acid *tert*-butyl ester 8b. Vinylbromide (0.5 mL) was reacted with 110 mg (0.2 mmol) of **7b** at 80 °C for 20 h. Purification [petroleum ether/ethyl acetate=5:1] gave **8b** as a colorless oil (34 mg, 58%).

Compound (**8b**): ^{1}H NMR (400 MHz, 50 °C) 1.52 [s, 9H]; 1.68 [br s, 6H]; 2.85–2.93 [br m, J_{AB}=15.6 Hz, 1H]; 2.99–3.05 [m, J_{AB}=15.6, J_{BX}=3.0 Hz, 1H]; 3.75–3.78 [m, J_{AB}=9.1, J_{AX}=3.1 Hz, 1H]; 4.04–4.08 [m, J_{AB}=9.1, J_{BX}=7.0 Hz, 1H]; 5.05–4.96[br m,1H]; 5.00–5.03 [m, 1H]; 5.05–5.11 [m, 2H]; 5.18 [dd, J=16.8, 1.8 Hz, 1H]; 5.72–5.83 [m, 1H]; 6.03 [br d, J=10.8 Hz, 1H]; 6.52–6.61 [m, 1H]. ^{13}C NMR (50.3 MHz) δ: 23.21; 25.19; 28.36; 37.01; 62.51; 67.87; 79.71; 94.36; 115.90; 116.77; 117.51; 127.28 132.40; 135.66; 152.22. MS *m/z* (%): 237 (5); 57 (100). $[\alpha]_D^{21}$ −25.2 (c 0.98, $CHCl_3$). Anal. Calcd for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.28; N, 4.77. Found: C, 69.46; H, 9.41; N, 4.63.

4.3.7. (4*R*)-2,2-Dimethyl-4-[(*E*)-1-methyl-buta-1,3-dienyl)-oxazolidine-3-carboxylic acid *tert*-butyl ester 8c. Vinylbromide (0.5 mL) was reacted with 104 mg (0.2 mmol) of **7d** at 80 °C for 20 h. Purification [petroleum ether/ethyl acetate=5:1] gave **8c** as a pale yellow oil (27 mg, 54%).

Compound (**8c**): 1.52 [s, 9H]; 1.69 [br s, 6H]; 1.75 [s, 3H]; 3.75–3.78 [m, J_{AB}=8.8, J_{AX}=2.8 Hz, 1H]; 4.08–4.13 [m, J_{AB}=8.8, J_{BX}=3.9 Hz, 1H]; 4.32–4.37 [br m,1H]; 4.87–4.90 [m, 1H]; 4.93–4.96 [m, 2H]; 5.97 [br d, J=10.8 Hz, 1H]; 6.68 [dt, J=10.8, 16.8 Hz, 1H]. ^{13}C NMR (50.3 MHz) δ: 17.9; 23.21; 25.19; 28.26; 32.41; 62.82; 65.43; 79.64; 94.36; 116.53; 131.22; 132.81; 136.10; 152.34. MS *m/z* (%): 211 (8); 57 (100). Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42; N, 5.24. Found: C, 67.25; H, 9.34; N, 5.36.

4.4. Synthetic elaboration of dipeptido aldehydes

4.4.1. {(*S*)-1-[(*S*)-1-Isopropyl-prop-2-ynylcarbamoyl]-2-phenyl-ethyl}-carbamic acid *tert*-butyl ester 11. Aldehyde **9** (606 mg, 1.7 mmol) was dissolved into MeOH (12 mL) together with diazophosphonate**10**,[38] (535 mg, 2.8 mmol). After cooling at 0 °C, K_2CO_3 (490 mg) was added and the reaction left at this temperature for 1 h, then at RT for 3 h. After hydrolysis (NH_4Cl saturated solution), MeOH was evaporated and the aqueous residue extracted with ethyl acetate (3×15 mL). The organic phase was washed with water and brine, then dried and evaporated. Purification [petroleum ether/ethyl acetate=3:1] gave **11** (386 mg, 1.1 mmol, 65%) as a white solid.

Compound (**11**): mp 125–127 °C. ^{1}H NMR (200 MHz) δ: 0.80 [d, J=6.5 Hz, 3H]; 0.89 [d, J=6.5 Hz, 3H]; 1.41 [s, 9H]; 1.66–1.86 [m, 1H]; 2.20 [d, J=2.2 Hz, 1H]; 3.04–3.10 [m, 2H]; 4.26–4.36 [m, 1H]; 4.56–4.64 [m, 1H]; 4.85–5.05 [m, 1H]; 6.08 [br d, J=8.4 Hz, 1H]; 7.34–7.19 [m, 5H]. ^{13}C NMR (50.3 MHz) δ: 17.16; 18.56; 28.15; 32.30; 38.37; 46.89; 55.72; 71.96; 80.11; 81.10; 126.83; 128.58; 129.24; 136.55; 155.38; 170.42. MS *m/z* (%): 271 (5); 120 (100). ν_{max}: 3420, 3302, 1712, 1675. $[\alpha]_D^{24}$ +0.96 (c 1.1, $CHCl_3$). Anal. Calcd for $C_{20}H_{28}N_2O_3$: C, 69.74; H, 8.19; N, 8.13. Found: C, 69.92; H, 8.32; N, 8.03.

4.4.2. {(*S*)-1-[(*E*)-(*S*)-1-Isopropyl-3-tributylstannanyl-allylcarbamoyl)-2-phenyl-ethyl}-carbamic acid *tert*-butyl ester 12a. Stannylcuprate was prepared using CuCN (55 mg, 0.6 mmol), BuLi (1.6 M, 0.75 mL, 1.2 mmol) and n-Bu_3SnH (178 mg, 0.6 mmol). Compound **11** (199 mg, 0.6 mmol) was added and reacted under stirring for 15 min. Usual workup afforded 435 mg of crude which, after purification [petroleum ether/ethyl acetate, gradient], gave 262 mg of a of **12a**+**12b** (95:5 mixture) as a pale yellow oil (71%).

Compound (**12a**): ^{1}H NMR (200 MHz) δ: 0.62–1.00 [m, 15H+6H]; 1.20–1.74 [m, 1H+12H]; 1.42 [s, 9H]; 3.00–3.14 [m, 2H]; 4.22–4.41 [m, 1H+1H]; 4.90–5.10 [br m, 1H]; 5.66–5.84 [m, $J_{AB}=19.2$, $J_{BC}=4.4$ Hz, 1H+1H]; 5.93 [d, $J_{AB}=19.2$ Hz, 1H]; 7.17–7.30 [m, 5H]. ^{13}C NMR (50.3 MHz) δ: 9.34; 13.57; 17.57; 18.34; 27.13; 28.15; 28.95; 31.88; 38.26; 56.23; 58.63; 80.04; 126.83; 128.63; 129.29; 136.55; 136.72; 145.46; 155.32; 170.38. MS *m/z*: 580 (4); 505 (100). ν_{max}: 3422, 1712, 1675.

4.4.3. {(*S*)-1-[(*E*)-(*S*)-1-Isopropyl-penta-2,4-dienyl-carbamoyl]-2-phenyl-ethyl}-carbamic acid *tert*-butyl ester 13. Vinylbromide (0.5 mL) was reacted with **12a**+**12b** (96 mg, 0.15 mmol) at 80 °C for 72 h. Purification [petroleum ether/ethyl acetate=5:1] gave **13** (38 mg, 68%) as a colorless oil.

Compound (**13**): ^{1}H NMR (200 MHz) δ: 0.80–0.89 [m, 6H]; 1.42 [s, 9H]; 1.50–1.86 [m, 1H]; 2.96–3.20 [m, 2H]; 4.20–4.39 [m, 1H+1H]; 4.90–5.19 [m, 2H+1H]; 5.48 [dd, J= 15.2, 6.1 Hz, 1H]; 5.92 [br d, J=9.2 Hz, 1H]; 6.04 [dd, J= 14.6, 10.2 Hz, 1H]; 6.15–6.36 [m, 1H]; 7.11–7.28 [m, 5H]. ^{13}C NMR (50.3 MHz) δ: 17.28; 18.45; 28.24; 32.23; 38.13; 55.80; 56.48; 80.29; 117.11; 126.91; 128.71; 129.30; 129.34; 132.00; 136.28; 136.60; 155.39; 170.58. MS *m/z*: 315 (2); 57 (100). $[\alpha]_D^{24}$ −26.4 (*c* 1.5). Anal. Calcd for $C_{22}H_{32}N_2O_3$: C, 70.94; H, 8.66; N, 7.52. Found: C, 71.12; H, 8.42; N, 7.22.

4.5. Coupling with 2-substituited-vinylbromides 6b,c,d

4.5.1. Synthesis of electrophiles.

4.5.1.1. (3-Bromo-but-3-enyl)-benzene 6c. 2,3-Dibromopropene (400 mg, 2 mmol) was dissolved in ether (5 mL) and reacted with benzyl magnesium chloride (1.0 M in ether, 2.5 mL, 2.5 mmol) at RT, overnight. Workup gave 360 mg of crude which were used without further, purification.

Compound (**6c**): ^{1}H NMR (200 MHz) δ: 2.72–2.76 [m, 2H]; 2.85–2.89 [m, 2H]; 5.39 [d, J=1.8 Hz, 1H]; 5.51 [d, J= 1.8 Hz, 1H]; 7.18–7.30 [m, 5H]. ^{13}C NMR (50.3 MHz) δ: 34.23; 43.13; 116.91; 125.72; 128.13; 128.27; 133.35; 140.09. MS *m/z*: 209/211 (2/2); 91 (100).

4.5.1.2. 2-Bromo-hept-1-ene 6d. A slurry of CuCN (180 mg, 2 mmol) in THF (5 mL) was cooled at −78 °C and reacted with BuLi (1.6 M, 2.5 mL, 4 mmol) for 1 h. 2,3-dibromopropene (400 mg, 2 mmol) was added at −30 °C and reacted overnight. After workup 286 mg of crude were obtained and used without further, purification.

Compound (**6d**): ^{1}H NMR (200 MHz) δ: 0.90 [t, J=6.6 Hz, 3H]; 1.18–1.41 [m, 4H]; 1.44–1.62 [m, 2H]; 2.41 [t, J= 7.0 Hz, 2H]; 5.37 [d, J=1.6 Hz, 1H]; 5.45–5.56 [m, 1H]. ^{13}C NMR (50.3 MHz) δ: 14.22; 22.62; 27.33; 31.40; 41.43; 112.81; 131.82. MS *m/z*: 178/176 (6/5); 122/120 (44/43).

4.5.2. Coupling: general procedure. $Pd(CH_3COO)_2$ (0.03 equiv) and $AsPh_3$ (0.12 equiv) were mixed in DMF at 65 °C for 1 h. Electrophile **6** (2 equiv) was added and the mixture degassed, then reacted with amine **3** (1 equiv) for 20 h. After DMF was evaporated, the recovered material was diluted with ether and treated with a KF saturated solution. The mixture was filtered, extracted with ether and the organic phase washed with brine and dried. The crude obtained after evaporation was purified by flash chromatography.

4.5.2.1. [(*E*)-4-Methyl-penta-2,4-dienyl]-carbamic acid tert-butyl ester 14a. 2-Bromo-propene **6b** (2.0 mmol, 0.25 mL) was reacted with **3a** (430 mg, 1.0 mmol) in DMF (2.0 mL). Purification [petroleum ether/ethyl acetate=10:1] gave **14a** (153 mg, 76%) as a pale yellow oil.

Compound (**14a**): ^{1}H NMR (200 MHz) δ: 1.44 [s, 9H]; 1.82 [s, 3H]; 3.77–3.83 [m, 2H]; 4.61 [br s, 1H]; 4.92–4.99 [m, 2H]; 5.62 [dt, $J_{AB}=15.6$, J=5.8 Hz, 1H]; 6.23 [d, $J_{AB}=$ 15.6 Hz, 1H]. ^{13}C NMR (50.3 MHz) δ: 18.53; 28.35; 42.45; 79.38; 116.40; 126.15; 134.20; 143.41; 155.93. MS *m/z*: 141 (8); 57 (100). Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.85; H, 9.56; N, 7.11.

4.5.2.2. [(*E*)-(*S*)-1-Benzyl-4-methyl-penta-2,4-dienyl]-carbamic acid *tert*-butyl ester 14b. 2-Bromo-propene **6b** (0.5 mmol, 0.1 mL) was reacted with **3b** (100 mg, 0.2 mmol) in DMF (1.0 mL). Purification [petroleum ether/ethyl acetate=10:1] gave **14b** (43 mg, 74%) as a thick oil.

Compound (**14b**): ^{1}H NMR (200 MHz) δ: 1.40 [s, 9H]; 1.80 [s, 3H]; 2.83–2.89 [m, 2H]; 4.37–4.52 [m, 1H]; 4.82–4.97 [m, 2H]; 5.52–5.63 [m, $J_{AB}=15.6$ Hz, 1H]; 6.19 [d, $J_{AB}=$ 15.6 Hz, 1H]. 7.38–7.12 [m, 5H]. ^{13}C NMR (50.3 MHz) δ: 18.59; 28.33; 41.97; 53.07; 79.41; 116.52; 126.43; 128.30 (×2); 129.54; 132.89; 137.43; 141.22; 155.12. MS *m/z* (%): 231 (10); 140 (100); 96 (100). $[\alpha]_D^{24}$ 3.3 (*c* 1.5, $CHCl_3$). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.37; H, 8.68; N, 4.96.

4.5.2.3. [(*E*)-(*S*)-1-Isopropyl-4-methyl-penta-2,4-dienyl]-carbamic acid *tert*-butyl ester 14c. 2-Bromo-propene **6b** (0.5 mmol, 0.1 mL) was reacted with **3c** (100 mg, 0.2 mmol) in DMF (1.0 mL). Purification [petroleum ether/ethyl acetate=10:1] gave **14c** (25 mg, 53%) as a colorless oil.

Compound (**14c**): ^{1}H NMR (200 MHz) δ: 0.83 [d, J= 5.2 Hz, 3H]; 0.87 0.83 [d, J=5.2 Hz, 3H]; 1.45 [s, 9H]; 1.72–1.84 [m, 1H]; 1.83 [s, 3H]; 3.94–4.09 [m, 1H]; 4.41–4.57 [m, 1H]; 4.95 [br s, 2H]; 5.51 [dd, J=6.6, 15.8 Hz, 1H]; 6.23 [d, J=15.8 Hz, 1H]. MS *m/z* (%): 182 (10); 57 (100). $[\alpha]_D^{23}$ −4.4 (*c* 0.9, $CHCl_3$). Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.34; H, 10.19; N, 5.92

4.5.2.4. 2,2-Dimethyl-4-[(*R*)-(*E*)-3-methyl-buta-1,3-dienyl]-oxazolidine-3-carboxylic acid *tert*-butyl ester 14d. 2-Bromo-propene **6b** (0.5 mmol, 0.15 mL) was reacted with **3d** (104 mg, 0.2 mmol). Purification [petroleum ether/ethyl acetate=10:1] gave **14d** (34 mg, 68%) as a colorless oil.

Compound (**14d**): ^{1}H NMR (400 MHz, 50 °C) δ: 1.47 [s, 9H]; 1.56 [s, 3H]; 1.64 [s, 3H]; 1.84 [s, 3H]; 3.79 [dd, J=

2.4, 8.8 Hz 1H]; 4.11 [dd, $J=6.4$, 8.8 Hz 1H]; 4.23–4.31 [m, 1H]; 5.00 [br s, 2H]; 5.64 [dd, $J=7.6$, 15.6 Hz, 1H]; 6.28 [d, $J=15.6$ Hz, 1H]. ^{13}C NMR (50.3 MHz) δ: 22.97; 23.69; 28.89; 30.31; 59.37; 68.41; 80.04; 95.23; 116.38; 128.77; 130.87; 141.19; 155.56. MS *m/z* (%): 211 (8); 57 (100). Anal. Calcd for $C_{15}H_{25}NO_3$: C, 67.38; H, 9.42; N, 5.24. Found: C, 67.48; H, 9.63; N, 5.33.

4.5.2.5. [(*E*)-4-Methylene-6-phenyl-hex-2-enyl]-carbamic acid *tert*-butyl ester 15a. Vinylbromide **6c** (93 mg, 0.4 mmol) was reacted with **3a** (100 mg, 0.2 mmol). Purification [petroleum ether/ethyl acetate = 15:1] gave **15a** (41 mg, 64%) as a pale yellow oil.

Compound (**15a**): ^{1}H NMR (200 MHz) δ: 1.45 [s, 9H]; 2.45–2.53 [m, 2H]; 2.76–2.84 [m, 2H]; 3.77–3.83 [m, 2H]; 4.53 [br s, 1H]; 4.88–5.10 [m, 2H]; 5.69 [dt, $J=16.1$, 6.0 Hz, 1H]; 6.19 [dt, $J=16.1$ Hz]; 7.16–7.33m, 5H]. ^{13}C NMR (50.3 MHz) δ: 28.46; 33.99; 34.67; 42.70; 79.46; 115.71; 125.60; 128.27; 128.33; 130.81; 133.50; 137.41; 144.71; 155.62. MS *m/z* (%): 230 (7); 91 (100). Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.16; H, 8.68; N, 4.74.

4.5.2.6. [(*E*)-(*R*)-1-Benzyl-4-methylene-6-phenyl-hex-2-enyl]-carbamic acid *tert*-butyl ester 15b. Vinylbromide **6c** (91 mg, 0.4 mmol) was reacted with **3b** (123 mg, 0.2 mmol). Purification [petroleum ether/ethyl acetate = 20:1] gave **15b** (65 mg, 75%) as a pale yellow oil.

Compound (**15b**): ^{1}H NMR (200 MHz) δ: 1.43 [s, 9H]; 2.42–2.50 [m, 2H]; 2.73–2.89 [m, 2H + 2H]; 4.39–4.66 [m, 1H + 1H]; 4.79–5.08 [m, 2H]; 5.66 [dd, $J=5.8$, 16.2 Hz, 1H]; 6.15 [d, $J=16.2$ Hz, 1H]; 7.15–7.34 [m, 10H]. ^{13}C NMR (50.3 MHz) δ: 28.29; 34.08; 34.60; 41.90; 52.12; 79.41; 115.88; 125.80; 126.41; 128.25; 128.31; 128.89; 129.49; 129.51; 132.08; 133.16; 137.38; 144.60; 155.07. MS *m/z* (%): 321 (5); 91 (100). ν_{max}: 3434, 1710. $[\alpha]_D^{26}$ −40.4 (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{25}H_{31}NO_2$: C, 79.54; H, 8.28; N, 3.71. Found: C, 79.58; H,8.19; N, 3.76.

4.5.2.7. [(*E*)-(*R*)-1-Isopropyl-4-methylene-6-phenyl-hex-2-enyl]-carbamic acid *tert*-butyl-ester 15c. Vinylbromide **6c** (68 mg, 0.3 mmol) was reacted with **3c** (70 mg, 0.15 mmol). Purification [petroleum ether/ethyl acetate = 15:1] gave **15c** (27 mg, 58%) as a colorless oil.

Compound (**15c**): ^{1}H NMR (200 MHz) δ: 0.89 [d, $J=6.6$ Hz, 3H]; 0.91 [d, $J=6.6$ Hz, 3H]; 1.45 [s, 9H]; 1.64–1.84 [m, 1H]; 2.45–2.52 [m, 2H]; 2.76–2.83 [m, 2H]; 4.01 [br s, 1H]; 4.47 [br s, 1H]; 4.96–5.01 [m, 1H]; 5.58 [dd, $J=6.6$, 16.2 Hz, 1H]; 6.18 [d, $J=16.2$ Hz, 1H]. ^{13}C NMR (50.3 MHz) δ: 18.35; 18.81; 28.46; 29.73; 32.85; 34.69; 38.78; 57.93; 79.31; 115.42; 125.83; 128.29 (x2); 130.80; 132.64; 144.79; 155.12. MS *m/z* (%): 287 (4); 91 (100). $[\alpha]_D^{23}$ −5.3 = 1.3 $CHCl_3$). Anal. Calcd for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.71; H, 9.53; N, 4.33.

4.5.2.8. [(*E*)-4-methylene-non-2-enyl]-carbamic acid *tert*-butyl-ester 16a. Vinyl-bromide **6d** (76 mg, 0.4 mmol) was reacted with **3a** (100 mg, 0.2 mmol). Purification [petroleum ether/ethyl acetate = 15:1] gave **16a** (42 mg, 74%) as a colorless oil.

Compound (**16a**): ^{1}H NMR (400 MHz) δ: 0.89 [t, $J=5.6$ Hz, 3H]; 1.21–1.42 [m, 6H]; 1.45 [s, 9H]; 2.16 [t, $J=7.6$ Hz, 3H]; 3.85–3.76 [br m, 1H]; 4.56 [br s, 1H]; 4.90–5.00 [m, 2H]; 5.67 [dt, $J=15.4$, 6.0 Hz, 1H]; 6.16 [d, $J=15.4$ Hz, 1H]. ^{13}C NMR (50.3 MHz) δ: 14.04; 22.52; 27.83; 28.39; 31.79; 32.05; 42.75; 79.33; 115.15; 125.33; 133.84; 145.68; 155.18. MS *m/z* (%): 197 (2); 57 (100). Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.53. Found: C, 70.83; H,10.66; N, 5.59.

4.5.2.9. [(*E*)-(*R*)-1-benzyl-4-methylene-non-2-enyl]-carbamic acid *tert*-butyl-ester 16b. Vinyl-bromide **6d** (78 mg, 0.4 mmol) was reacted with **3b** (116 mg, 0.2 mmol). Purification [petroleum ether/ethyl acetate = 15:1] gave **16b** (38 mg, 51%) as a colorless oil.

Compound (**16b**): ^{1}H NMR (400 MHz) δ: 0.98 [t, $J=6.6$ Hz, 3H]; 1.33–1.55 [m, 6H]; 1.48 [s, 9H]; 2.21 [t, $J=7.8$ Hz, 2H]; 2.90–2.99 [m, 2H]; 4.56 [br s, 1H]; 4.88–5.12 [m,2H]; 5.68 [dd, $J=6.0$, 15.6 Hz, 1H]; 6.17 [d, $J=15.6$ Hz, 1H]; 7.22–7.38 [m, 5H]. ^{13}C NMR (50.3 MHz) δ: 14.05; 22.52; 27.88; 28.30; 31.75; 31.10; 41.99; 52.98; 79.20; 115.27; 126.42; 128.69; 128.90; 129.58; 132.36; 137.43; 145.60; 155.11. MS *m/z* (%): 287 (6); 57 (100). ν_{max}: 3432, 1706. $[\alpha]_D^{28}$ −0.6 (*c* 1.0, $CHCl_3$). Anal. Calcd for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.68; N, 4.08. Found: C, 76.87; H, 9.63; N, 4.04.

4.6. Synthesis of Boc-Gly-ψ[(*E*)-CH=CH]-(*rac*)-Ala-(L)-Phe-OMe 19a and Boc-(L)-Phe-ψ[(*E*)-CH=CH]-(*rac*)-Ala-(L)-Phe-OMe 19b

4.6.1. Reduction: general procedure. Dienamines **14a**,**b** (1 equiv) were dissolved in THF and stirred overnight with 9-BBN (0.5M in THF, 1 equiv), then treated with NaOH (0.1 M) and H_2O_2 (35%, 0.1 mL), heated at 50°C and reacted for 1 h. After dilution with ethyl acetate and washing with K_2CO_3 saturated solution, the organic phase was dried, evaporated and purified by flash chromatography.

4.6.1.1. [(*E*)-(*R,S*)-(4-methyl-5-hydroxy-pent-2-enyl)-carbamic acid tert-butyl ester (17a). Dienamine **14a** (180 mg, 0.9 mmol) in THF (1.5 mL) was reacted with 9-BBN (0.9 mmol), then with NaOH and H_2O_2 (35%, 0.1 mL). Purification [petroleum ether/ethyl acetate = 10:1] gave **17a** (86 mg, 44%) as an oil.

Compound (**17a**): ^{1}H NMR (200 MHz) δ: 0.97 [d, $J=7.0$ Hz, 3H]; 1.43 [s, 9H]; 1.89 [br s, 1H]; 2.30 [sept, $J=7.0$ Hz, 1H]; 3.34-3.56 [m, 2H]; 3.61-3.84 [m, 2H]; 4.75 [br s, 1H]; 5.30-5.71 [m, 2H]. ^{13}C NMR (50.3 MHz) δ: 16.23; 28.35; 39.28; 42.57; 67.11; 79.40; 127.68; 134.78; 155.81. MS *m/z* (%): 127 (57); 56 (100). Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N. 6.51. Found: C, 61.55; H, 9.79; N, 6.53.

4.6.1.2. [(*E*)-(*1S*)-(*4R,S*)(1-Benzyl-4-methyl-5-hydroxy-pent-2-enyl)-carbamic acid tert-butyl ester (17b). Dienamine **14b** (202 mg, 0.7 mmol) in THF (1.5 mL) was reacted with 9-BBN (0.7 mmol), then with NaOH and H_2O_2 (35%, 0.1 mL). Workup and purification [petroleum ether/ethyl acetate = 10:1] gave **17b** as a 1:1 diastereomeric mixture (79 mg, 37%).

Compound (**17b**): ^{1}H NMR (400 MHz) δ: 0.90 (0.93) [d, J=6.8 Hz, 3H]; 1.40 (1.41) [s, 9H]; 2.19–2.40 [m, 1H]; 2.66–2.97 [m, 2H]; 3.16–3.32 [m, 1H]; 3.33–3.48 [m, 1H]; 4.27–4.33 [br Fm, 1H]; 4.57 [br d, 1H]; 5.33–5.24 (5.31–5.21) [m, J_{AB}=15.4, J_{BX}=7.4 Hz, 1H]; 5.34–5.49 [m, J_{AB}=15.4, J_{AX}=6.2 Hz, 1H]; 7.40–7.10 [m, 5H]. ^{13}C NMR (50.3 MHz) δ: 16.04 (16.15); 24.57; 28.32; 39.44; 41.60 (41.67); 53.78; 66.94; 79.50; 126.50; 128.34; 129.49; 131.01 (131.22); 137.61 (137.86); 155.18 (155.27). MS *m/z* (%): 158 (43); 91 (92); 56 (100). Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N. 4.59. Found: C, 70.64; H, 8.77; N, 4.63.

4.6.2. Oxidation: general procedure. A stock solution of H_5IO_6 (0.4 M, 2.5 equiv) and CrO_3 (0.5% mol) in wet acetonitrile was added dropwise to a cooled solution of amino alcohols **17a**,**b** in wet acetonitrile. The reaction mixture was stirred for 30 min. then quenched with phosphate buffer. After dilution with ethyl acetate the organic layer was separated, washed with brine/aqueous $NaHSO_3$ (0.4 M)/brine and then dried. Crude acids **19a**,**b** were dissolved in CH_2Cl_2, cooled at 0 °C and reacted with (L)-phenylalanine methyl ester (1.5 equiv), DIPEA (3 equiv) and diethylcyanophosphonate at room temperature overnight. Dilution with ethyl acetate, washing with water and evaporation afforded crude **20a**,**b** which were purified by flash chromatography.

4.6.2.1. Boc-Gly-ψ-[(*E*)-CH=CH]-(*rac*)-Ala-(*S*)-Phe-OMe (19a). Oxidation of **17a** (67 mg, 0.3 mmol) and coupling with (L)-phenylalanine methyl ester (94 mg, 0.45 mmol) gave, after purification [petroleum ether/ethyl acetate=1:3], **19a** (53 mg, 44%) as a white solid.

Compound (**19a**): ^{1}H NMR (200 MHz) δ: 1.22 (1.23) [d, J=7.0 Hz, 3H]; 1.45 (1.46) [s, 9H]; 2.83–3.00 [m, 1H]; 3.04–3.19 [m, 2H]; 3.64–3.75 [m, 2H]; 3.73 [s, 3H]; 4.53 [br s, 1H]; 4.76–5.89 [m, 1H]; 5.51–5.60 [m, 2H]; 6.01 [br s, 1H]; 7.03–7.19 [m, 5H]. ^{13}C NMR (50.3 MHz) δ: 17.57; 28.42; 32.54; 42.31; 43.90; 52.87 (52.34); 55.97; 79.28; 127.11; 128.47; 129.22; 129.49; 131.53; 136.22; 156.12; 171.89; 173.34.

4.6.2.2. Boc-(L)Phe-ψ-[(*E*)-CH=CH]-(*rac*)-Ala-(*S*)-Phe-OMe (19b). Oxidation of **17b** (63 mg, 0.20 mmol) and coupling with (L)-phenylalanine methyl ester (83 mg, 0.43 mmol) gave, after purification [petroleum ether/ethyl acetate=1:3], **19b** (46 mg, 48%) as a white solid.

Compound (**19b**): ^{1}H NMR (200 MHz) δ: 1.16 [d, J=6.8 Hz, 3H]; 1.40 (1.39) [s, 9H]; 2.76–3.19 [m, 2H+1H+2H]; 3.72 [s, 3H]; 4.22–4.47 [m+ br s, 1H+1H]; 4.67–4.76 [m, 1H]; 5.46–5.12 [m, 2H]; 6.03 [br s, 1H]; 7.03–7.29 [m, 10H]. ^{13}C NMR (50.3 MHz) δ: 173.32; 171.92; 155.04; 137.25; 135.99; 132.53; 130.13; 129.47; 129.24; 128.45; 128.34; 127.03; 126.47; 79.49; 53.11; 52.98; 52.29; 43.93 (43.86); 41.51; 37.73; 28.39; 17.13 (16.97).

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Concise syntheses of 2-aminoindans via indan-2-ol

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Abstract—2-Amino-5,6-dimethoxyindan hydrochloride was synthesized in seven steps and with an overall yield of 48%. Indan-2-ol was converted to 5,6-dibromo-indan-2-ol in three steps by acetylation, electrophilic bromination and deacetylation. Dimethoxylation of 5,6-dibromoindan-2-ol with $NaOCH_3$ in the presence of CuI gave 5,6-dimethoxy-indan-2-ol, which was converted to 2-amino-5,6-dimethoxyindan hydrochloride by azidation, followed by Pd–C catalyzed hydrogenation. Similarly, 2-amino-5-bromoindan was synthesized in five steps and with an overall yield of 50%. Indan-2-ol was converted to 2-aminoindan by azidation followed by Pd–C catalyzed hydrogenation. The reaction of 2-aminoindan with 2.5 equiv Br_2 afforded 2-amino-5,6-dibromoindan.
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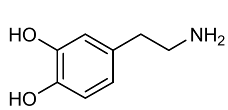
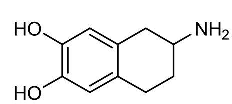
1. Introduction

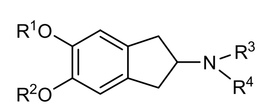
The neurotransmitter dopamine (**1**) plays a central role in central nervous system (CNS)-related disorders such as schizophrenia and Parkinson's disease.[1] In recent years many chemical compounds have been found to possess dopamine-like actions. It has been suggested that 6,7-ADTN (**2**), a dopamine-like compound, interacts with the dopamine receptor with slightly greater affinity than dopamine itself.[2] Cannon et al.[3] have synthesized a series of 2-amino-4,5-dihydroxyindans, including compounds **3–6**, and reported that certain *N*-alkylated 4,5-dihydroxyindanes were violent emetics in the dog, and were potent in blockade of the effect of stimulation of the cardioaccelarator nerve in the cat. Aminoindan **3** has been reported to have α-adrenergic effects[4] and covalent binding[5] to Src family SH2 domains. The hydrochloride salt of **4** has been reported to be useful as an analgesic.[6] 5,6-Dimethoxy-2-(*N*-dipropyl)-aminoindan (**5**), PNU-99194A, has been reported to be a selective dopamine D_3 receptor antagonist with potential



1 Dopamin



2 6,7-ADTN

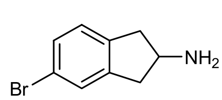


3 R^1=R^2=R^3=R^4=H

4 R^1=R^2=Me; R^3=R^4=H

5 R^1=R^2=Me; R^3=R^4=n-propyl (PNU-99194 A)

6 R^1=R^2=H; R^3=R^4=n-propyl



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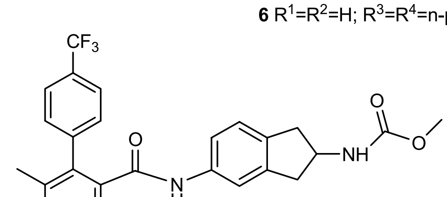

8 LAB687

Keywords: 2-Aminoindans; Synthesis; 2-Azidoindans; 2-Indanols; Mitsunobu reaction; Dopamine.
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antipsychotic properties in animal models.[7] Some valuable papers have recently appeared on the pharmacological actions of compound **5**.[8]

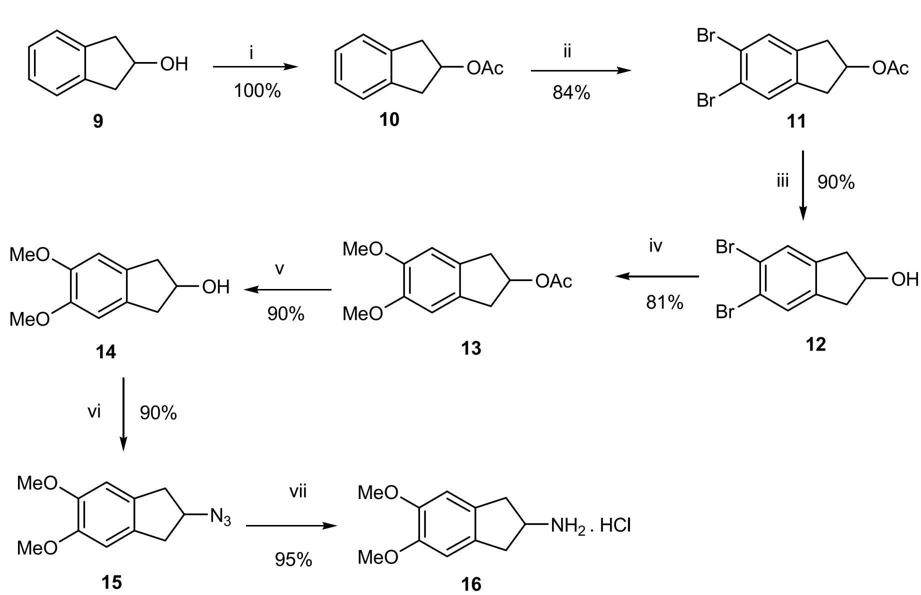
The synthesis of 5,6-dimethoxy-2-aminoindan (**4**) from 3-(3,4-dimethoxyphenyl)-propionic acid has been described[3,7] in six steps with an overall yield of 38%. In our ongoing project on the synthesis of biologically active dopamine-like compounds, we reported a concise synthesis of 6,7-ADTN (**2**).[9] In the present study we performed an alternative and concise synthesis of 2-amino-5,6-dimethoxyindan (**4**) from indan-2-ol, a commercially available reagent much cheaper than 3-(3,4-dimethoxyphenyl)-propionic acid, in seven steps and with a 48% total yield. On the other hand, 2-amino-5-bromoindan (**7**) is an important precursor of LAB687 (**8**), which is an inhibitor of microsomal triglyceride transfer protein (MTP).[10] In the present study we also performed an alternative preparation of **7**, starting from indan-2-ol in five steps and with a 50% total yield.

2. Results and discussion

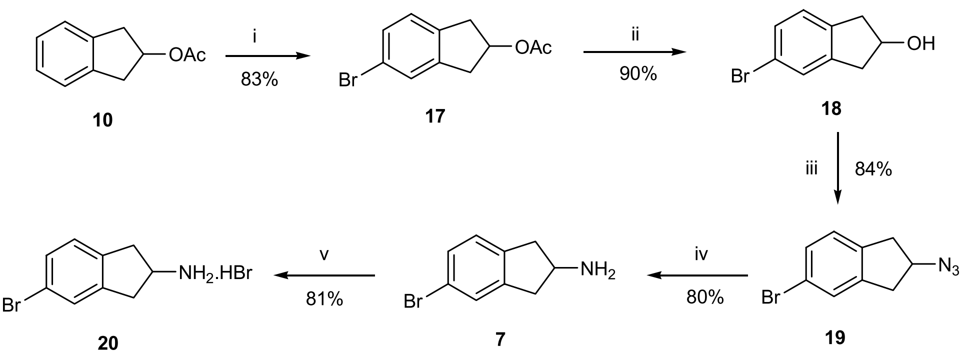
The reaction of indan-2-ol (**9**) with AcCl gave indan-2-ol acetate (**10**). The bromination of **10** with NBS–Br_2 in acetonitrile in the dark gave dibromoacetate **11** and the hydrolysis of **11** with NaOH in H_2O/MeOH gave 5,6-dibromoindan-2-ol (**12**). The most critical step of our synthesis was the substitution of the bromines in compound **12** with NaOMe. Copper-assisted nucleophilic substitutions of aryl halogens are described in the literature.[11] Considering the applicability of the reaction, we assumed that the methoxylation of **12** would proceed with the substitution of bromide with methoxide. Indeed, the reaction of **12** with NaOMe in the presence of CuI in a mixture of MeOH and DMF gave the expected dimethoxide **14** which was converted to its acetate derivative **13** by acetylation with AcCl for further purification. Then, acetate **13** was hydrolyzed to alcohol **14** with NaOH in H_2O–MeOH. Esterification of alcohol **14** with $MeSO_2Cl$ and substitution of the corresponding mesylate with NaN_3 in DMF afforded 2-azido-5,6-dimethoxyindan (**15**). The reduction of azide **15** with Pd–C catalyzed hydrogenation in the presence of $CHCl_3$[12] in MeOH gave 2-amino-5,6-dimethoxyindan hydrochloride (**16**) (Scheme 1). The preparation of *N*,*N*-dialkyl derivatives from the free base of 5,6-dimethoxy-2-aminoindan (**16**), including PNU-99194A (**5**), was previously well defined.[3,7]

Our next purpose in this study was to develop an alternative synthesis of 2-amino-5-bromoindan (**7**), starting from indan-2-ol (**9**). To our knowledge, different syntheses of **7** have been reported in the literature. One of these procedures uses 1-bromo-4-(bromomethyl)benzene as the starting material and includes a many-step reaction.[13] The other procedure uses the bromination of commercially available 2-aminoindan in one step and with 65% yield.[10b] However, 2-aminoindan is 25 times more expensive than indan-2-ol (**9**). Therefore, we developed an alternative method for the synthesis of 2-amino-5-bromoindan (**7**).

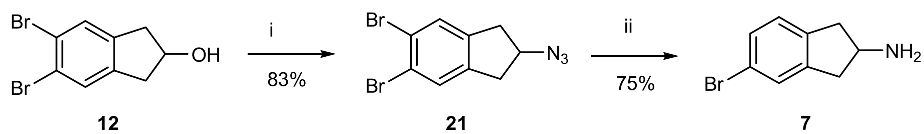
The first step of the synthesis was the bromination of indan-2-ol acetate **10** with NBS in acetonitrile and in the dark to give monobromide **17**. Hydrolysis of **17** with NaOH in MeOH–H_2O gave 5-bromo-indan-2-ol (**18**). In our previous studies we reported[14] the conversion of some epoxides, *trans*-1,2-diols, and azidoalcohols to the corresponding azide compounds via the Mitsunobu reaction with DEAD, PPh_3 and HN_3. A similar procedure applied to alcohol **18** gave bromoazide **19**. Prashad et al.[10b] have reported that Pd–C catalyzed hydrogenolysis of 2-amino-5-bromoindan gave 2-aminoindan. Therefore, we had to choose a reagent that would reduce only the azide functional group. Although the reduction of azides with $LiAlH_4$ to give the corresponding amines has been well defined,[15] this method resulted in a product mixture including debrominated **19**, which was not characterized. The reduction of bromoazide **19** with



Scheme 1. (i) AcCl, 0–25 °C. (ii) NBS (2 equiv), Br_2 (1.1 equiv), CH_3CN, 0–25 °C, in darkness. (iii) 10% aq NaOH, MeOH, 0–25 °C. (iv) NaOMe, CuI (cat.), DMF, MeOH, reflux, 90 °C, then AcCl, 0–25 °C. (v) 10% aq NaOH, MeOH, 0–25 °C. (vi) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 25 °C, then NaN_3, DMF, reflux. (vii) Pd–C (cat.), H_2, $CHCl_3$, MeOH.



Scheme 2. (i) NBS, CH_3CN, 25 °C. (ii) 10% aq NaOH, MeOH, 0–25 °C. (iii) DEAD, PPh_3, HN_3, 0–25 °C. (iv) $NaBH_4$, $CuSO_4$ (cat.), MeOH, 0–25 °C. (v) 36% HBr, MeOH, 0 °C.



Scheme 3. (i) DEAD, PPh_3, HN_3, THF, 0–25 °C. (ii) $NaBH_4$ (2.1 equiv), $CuSO_4$ (cat.), MeOH, 0–25 °C.

$CuSO_4 \cdot 5H_2O$–$NaBH_4$ as described by Rao and Siva[16] gave the corresponding 2-amino-5-bromoindan (**7**) with a good yield, which was converted to its HBr salt **20**[10b] for further characterization (Scheme 2).

We supposed that 5,6-dibromoindan-2-ol (**12**) could be used as an important precursor for LAB687 (**8**) type compounds. Therefore, we converted alcohol **12** to the corresponding azide **21** under Mitsunobu conditions as before. Our attempts to reduce azide **21** with hydride reagents to yield 2-amino-5,6-dibromoindan failed. While the reduction of **21** with 1 equiv $LiAlH_4$ gave 2-aminoindan, the reduction of **21** with 1 equiv of $NaBH_4$ gave an inseparable mixture containing 2-amino-5,6-dibromoindan, 2-amino-5-bromoindan and unreacted **21**. However, following a literature procedure,[16] the reduction of **21** with 2 equiv $NaBH_4$ in the presence of $CuSO_4$ within 3 h gave 2-amino-5-bromoindan (**7**) as the sole product (Scheme 3). If we use 2 equiv $NaBH_4$ in the presence of $CuSO_4$ and extend the reaction time, we observed that azide group and two bromide group may be reduced.

For the synthesis of 2-amino-5,6-dibromoindan, we changed our strategy. In the second strategy, the reaction of indan-2-ol (**9**) with the Mitsunobu reagents (DEAD, PPh_3, HN_3) gave 2-azidoindan (**22**). The reduction of azide **22** with Pd–C catalyzed hydrogenation in MeOH in the presence of $CHCl_3$ afforded 2-aminoindan hydrochloride (**23**). The bromination of **23** with 2.5 equiv of Br_2 in H_2O gave 2-amino-5,6-dibromoindan hydrobromide (**24**) (Scheme 4).

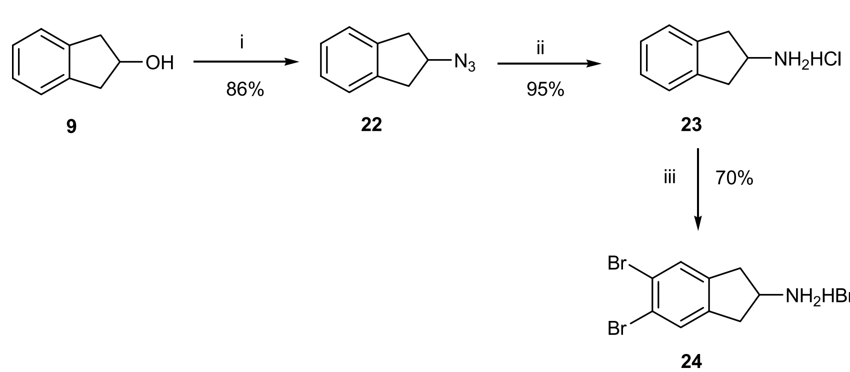
3. Conclusion

Starting from indan-2-ol, we describe a concise synthesis of 2-amino-5,6-dimethoxyindan, an important precursor for selective dopamine D_3 receptor antagonist drugs, and an alternative synthesis of 2-amino-5-bromoindan, an important precursor of LAB687 (**8**) type compounds. We also describe the first synthesis of 2-amino-5,6-dibromo-indan, which can be used for the synthesis of biologically active compounds.

4. Experimental

4.1. General information

Solvents were purified and dried by standard procedures



Scheme 4. (i) DEAD, PPh_3, HN_3, THF, 0–25 °C. (ii) Pd–C (cat), H_2, $CHCl_3$, MeOH. (iii) Br_2, H_2O, 50–60 °C.

before use. Melting points were determined on a Büchi 539 capillary melting apparatus and are uncorrected. Infrared spectra were obtained from KBr or film on a Mattson 1000 FT-IR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on 400 (100) or 200 (50) MHz Varian spectrometers. Elemental analyses were carried out with a Leco CHNS-932 instrument. EI-MS spectra were recorded on a Thermo-Finnigan mass analyzer. Column chromatography was performed on silica gel 60 (70–230 mesh ASTM). Thin layer chromatography was carried out on Merck 0.2 mm silica gel, and 60 F254 analytical aluminum plates.

4.1.1. Indan-2-ol acetate (10). AcCl (30 mL) was added dropwise to indan-2-ol (**9**) (10.00 g, 74.6 mmol) at 0 °C. After the addition was completed the mixture was stirred at rt for 16 h. The evaporation of the excess AcCl gave indan-2-ol acetate (**10**)[17] as a clear oil (13.13 g, 100%). ^{1}H NMR is in agreement with the literature.[17] ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.6, 140.3, 126.5, 124.5, 75.2, 23.5, 21.0.

4.1.2. 5,6-Dibromoindan-2-ol acetate (11). To a stirred solution of indan-2-ol acetate (**10**) (10.00 g, 56.8 mmol) in freshly distilled acetonitrile (300 mL) from P_2O_5 was added NBS (20.23 g, 113.6 mmol) and Br_2 (10.00 g, 62.5 mmol) at 25 °C in darkness. The mixture was stirred at rt in darkness for 5 days. The solvent and excess Br_2 were evaporated. The residue was dissolved in 150 mL of CH_2Cl_2 and the organic layer was washed with 3×100 mL of saturated Na_2CO_3 solution. The organic layer was dried from Na_2SO_4 and the solvent was evaporated. Chromatography of the crude product on a short silica gel column (20 g), eluting with hexane–EtOAc (4:1), gave 5,6-dibromoindan-2-ol acetate (**11**) (16.00 g, 84%). Clear oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.47 (bs, 2H, H-4 and H-7), 5.49 (tt, 1H, H-2, J=6.3, 2.8 Hz), 3.24 (A part of AB system, ddd, 2H, J=17.4, 6.3, 1.0 Hz), 2.93 (B part of AB system, dd, 2H, J=17.4, 2.8 Hz), 2.01 (s, 3H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.6, 141.8, 129.6, 122.6, 75.0, 39.1, 21.1. IR (CH_2Cl_2) 3056, 2968, 2910, 2852, 1739, 1466, 1428, 1374, 1247, 1100. Anal. Calcd for $C_{11}H_{10}Br_2O_2$ (334): C, 39.56; H, 3.02; Found: C, 39.88; H, 2.84.

4.1.3. 5,6-Dibromoindan-2-ol (12). To a stirred solution of 5,6-dibromoindan-2-ol acetate (**11**) (10.00 g, 29.9 mmol) in MeOH (80 mL) was added 10% aqueous NaOH (20 mL) and the mixture was stirred at rt for 15 h. After the evaporation of the MeOH, 50 mL of H_2O was added and the organic layer was extracted with CH_2Cl_2 (3×50 mL). The organic layer was dried (Na_2SO_4) and evaporation of the solvent gave 5,6-dibromoindan-2-ol (**12**) (7.87 g, 90%). Colorless crystal. Mp 130–132 °C (from CH_2Cl_2–Hexane). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.51 (bs, 2H, H-4 and H-7), 4.72 (tt, 1H, H-2, J=5.9, 3.0 Hz), 3.16 (A part of AB system, dd, 2H, J=16.8, 5.9 Hz), 2.86 (B part of AB system, dd, 2H, J=16.8, 3.0 Hz), 1.86 (s, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.2, 129.9, 122.4, 73.1, 42.1. IR (KBr) 3287, 2933, 2825, 1458, 1420, 1351, 1285, 1254, 1200, 1100. Anal. Calcd for $C_9H_8Br_2O$ (292.0): C, 37.02; H, 2.76; Found: C, 36.86; H, 2.74. EIMS *m/e* (%): 293.9 (M^+, 16), 291.8 (M^+, 36), 289.9 (M^+, 18), 264.8 (50), 262.8 (100), 260.8 (56), 192.9 (20), 183.0 (24), 181.9 (20), 132.0 (16), 131.0 (28), 114.0 (18), 104.0 (32), 103.0 (64), 102.0 (54), 78.0 (18), 77.0 (46).

4.1.4. 5,6-Dimethoxyindan-2-ol acetate (13). To refluxing MeOH (70 mL) was added Na (3.15 g, 137.0 mmol) in small pieces over 1 h under N_2. To the solution was added 5,6-dibromoindan-2-ol (**12**) (10.00 g, 34.2 mmol) in freshly distilled DMF (40 mL). While the reaction mixture was being heated at reflux, CuI (approximately 100–150 mg) was added. After heating for 20 h, the reaction mixture was cooled to rt. After the removal of MeOH under reduced pressure H_2O (50 mL) and CH_2Cl_2 (100 mL) were added and the organic layer was separated. The organic layer was washed with H_2O (3×50 mL) and dried (Na_2SO_4). After evaporation of the solvent, the residue was reacted with AcCl at rt for 16 h. After evaporation of the excess AcCl, the residue was filtered on a short silica gel column (10 g), eluting with CH_2Cl_2. Evaporation of the solvent gave 5,6-dimethoxyindan-2-ol acetate (**13**) (6.55 g, 81%) Colorless crystals. Mp 71–73 °C (CH_2Cl_2–hexane). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.76 (s, 2H, H-4 and H-7), 5.50 (tt, 1H, H-2, J=6.6, 3.0 Hz), 3.84 (s, 6H, 2×OCH_3), 3.25 (A part of AB system, dd, 2H, J=16.6, 6.6 Hz), 2.92 (B part of AB system, dd, 2H, J=16.6, 3.0 Hz), 2.01 (s, 3H, C(O)CH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.8, 148.5, 131.9, 108.0, 75.6, 56.0, 39.5, 21.1. IR (KBr) 3068, 2996, 2940, 2834, 1735, 1611, 1507, 1466, 1455, 1443, 1374, 1315, 1240, 1190, 1090, 1025. Anal. Calcd for $C_{13}H_{16}O_4$ (236.3): C, 66.09; H, 6.83; Found: C, 65.77; H, 6.95.

4.1.5. 5,6-Dimethoxyindan-2-ol (14). The hydrolysis procedure above described for 5,6-dibromo-indan-2-ol acetate (**11**) in 4.1.3 was applied to 5,6-dimethoxyindan-2-ol acetate (**13**) to give 5,6-dimethoxyindan-2-ol (**14**) (90%). Colorless crystals. Mp 68–70 °C (from CH_2Cl_2–hexane). ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.74 (s, 2H, H-4 and H-7), 4.61 (tt, 1H, H-2, J=5.9, 3.3 Hz), 3.81 (s, 6H, 2×OMe), 3.10 (A part of AB system, dd, 2H, J=15.9, 5.9 Hz), 2.78 (B part of AB system, dd, 2H, J=15.9, 3.3 Hz), 2.60 (bs, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.1, 132.3, 108.2, 73.2, 55.9, 42.4. IR (KBr) 3393, 2996, 2937, 2833, 1610, 1465, 1454, 1311, 1244, 1186, 1088. Anal. Calcd for $C_{11}H_{14}O_3$ (194.1): C, 68.02; H, 7.27; Found: C, 67.85; H, 7.19. EIMS *m/e* (%): 194.9 (M^+, 8), 193.8 (M^+, 78), 175.8 (28), 164.8 (100), 160.7 (22), 150.7 (18), 132.7 (12), 122.7 (10).

4.1.6. 2-Azido-5,6-dimethoxyindan (15). To a stirred solution of 5,6-dimethoxyindan-2-ol (**14**) (1.40 g, 7.2 mmol) and NEt_3 (0.88 g, 8.7 mmol) in CH_2Cl_2 (30 mL) was added a solution of $MeSO_2Cl$ (1.83 g, 15.9 mmol) in CH_2Cl_2 dropwise at 0 °C over 15 min. The mixture was stirred at rt for 3.5 h. After the filtration of the reaction mixture and removal of the solvent of the filtrate, freshly distilled DMF (30 mL) and NaN_3 (1.41 g, 21.7 mmol) were added. The reaction mixture was stirred at 120 °C for 18 h. The reaction mixture was cooled to rt and H_2O (50 mL) and CH_2Cl_2 (60 mL) were added. The organic layer was separated and washed with H_2O (3×50 mL). The organic layer was dried over Na_2SO_4 and CH_2Cl_2 was evaporated. Chromatography of the crude product on a short silica gel column (15 g), eluting with CH_2Cl_2, gave 2-azido-5,6-dimethoxyindan (**15**) (1.42 g, 90%). Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.77 (s, 2H, H-4 and H-7), 4.34

(tt, 1H, H-2, J=6.6, 4.2 Hz), 3.85 (s, 6H, 2×OCH_3), 3.18 (A part of AB system, dd, 2H, J=15.8, 6.6 Hz), 2.93 (B part of AB system, dd, 2H, J=15.8, 4.2 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.5, 131.6, 107.8, 62.0, 56.0, 38.9. IR ($CDCl_3$) 3070, 2997, 2937, 2833, 2110, 1610, 1504, 1465, 1454, 1313, 1265, 1230, 1189, 1089.

4.1.7. 2-Amino-5,6-dimethoxyindan hydrochloride (16). Into a 100-mL flask were placed Pd–C (50 mg) and 2-azido-5,6-dimethoxyindan (**15**) (1.00 g, 4.6 mmol) in MeOH (35 mL) and $CHCl_3$ (2 mL). A balloon filled with H_2 gas (3 L) was fitted to the flask. The mixture was deoxygenated by flushing with H_2 and then hydrogenated at rt for 20 h. The catalyst was removed by filtration. Recrystallization of the residue from MeOH–Et_2O gave 2-amino-5,6-dimethoxyindan hydrochloride (**16**) (1.00 g, 95%). Colorless crystal. Mp 287–289 °C (from MeOH–Et_2O), lit.[3] Mp 288–290 °C (from 2-PrOH–Et_2O). ^1H NMR (200 MHz, D_2O) δ 6.97 (s, 2H, H-4 and H-7). 4.23 (tt, 1H, H-2, J=7.3, 3.7 Hz), 3.83 (s, 6H, 2×OCH_3), 3.35 (A part of AB system, dd, 2H, J=16.9, 7.3 Hz), 2.98 (B part of AB system, dd, 2H, J=16.9, 3.7 Hz). ^{13}C NMR (50 MHz, D_2O) δ 152.2, 135.7, 112.8, 60.2, 56.4, 41.6. Anal. Calcd for $C_{11}H_{16}NO_2Cl$ (229.7): C, 67.52; H, 7.02; N, 6.10 Found: C, 57.85; H, 7.12; N, 5.91.

4.1.8. 5-Bromoindan-2-ol acetate (17). To a stirred solution of indan-2-ol acetate (**10**) (10.00 g, 56.8 mmol) in freshly distilled acetonitrile (300 mL) from P_2O_5 was added *N*-bromo-succinimide (30.34 g, 170.4 mmol) at rt in darkness. The mixture was stirred at rt in darkness for 7 days. The solvent was evaporated and the mixture was dissolved in 150 mL of CH_2Cl_2. The organic layer was washed with saturated aqueous Na_2CO_3 solution (3×100 mL). The organic layer was dried over Na_2SO_4 and the solvent was evaporated. Chromatography of the crude product on a short silica gel column (15 g), eluting with hexane–EtOAc (4:1), gave 5-bromoindan-2-ol acetate (**17**). (12.00 g, 83%). Colorless crystal. Mp 75–77 °C (from CH_2Cl_2–hexane). ^1H NMR (200 MHz, $CDCl_3$) δ 7.30 (bs, 1H, H-4), 7.32 (A part of AB system, dd, 1H, H-6, $J_{6,7}$=8.0 Hz, $J_{4,6}$=1.6 Hz), 7.11 (B part of AB system, 1H, H-7, d, $J_{6,7}$=8.0 Hz), 5.53 (m, 1H, H-2), 3.29 (A part of AB system, dd, 1H, J=17.2, 6.4 Hz), 3.26 (A part of AB system, dd, 1H, J=17.2, 6.6 Hz), 3.01 (B part of AB system, dd, 1H, J=17.2, 3.0 Hz), 2.97 (B part of AB system, dd, 1H, J=17.2, 3.0 Hz), 2.04 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.7, 142.0, 139.4, 129.0, 127.8, 126.0, 120.5, 75.1, 39.5, 39.1, 22.1. IR (CH_2Cl_2) 2968, 2921, 1736, 1470, 1420, 1370, 1254, 1197 cm^{-1}. Anal. Calcd for $C_{11}H_{11}BrO_2$ (254.0): C, 51.79; H, 4.35; Found: C, 51.51; H, 4.32. EI-MS: 195.9 (M^+ − CH_3COOH, 38%), 193.9 (M^+ − CH_3COOH, 40%), 115.0 (100%).

4.1.9. 5-Bromoindan-2-ol (18). The hydrolysis procedure above described for 5,6-dibromo-indan-2-ol acetate (**11**) was applied to 5-bromoindan-2-ol acetate (**17**) to give 5-bromoindan-2-ol (**18**) (90%). Colorless crystal. Mp 115–117 °C (from CH_2Cl_2–hexane). ^1H NMR (200 MHz, $CDCl_3$) δ 7.38 (bs, 1H, H-4), 7.31 (A part of AB system, dd, 1H, H-6, $J_{6,7}$=8.1 Hz, $J_{4,6}$=2.1 Hz), 7.12 (B part of AB system, d, 1H, H-7, $J_{6,7}$=8.1 Hz), 4.68 (m, 1H, H-2), 3.19 (A part of AB system, dd, 1H, J=16.6, 5.8 Hz), 3.14 (A part of AB system, dd, 1H, J=16.5, 5.9 Hz), 2.88 (B part of AB system, dd, 1H, J=16.5, 3.1 Hz), 2.84 (B part of AB system, dd, 1H, J=16.6, 3.2 Hz), 2.05 (bs, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.3, 139.8, 129.7, 128.1, 126.4, 120.3, 73.1, 42.6, 42.2. IR (KBr) 3295, 3064, 2948, 2894, 2817, 1601, 1574, 1474, 1420, 1412, 1343, 1293, 1258, 1197, 1162. Anal. Calcd for C_9H_9BrO (213.1): C, 50.73; H, 4.26; Found: C, 50.52; H, 4.11. EI-MS: 214.0 (M^+, 40%), 212.0 (M^+, 42%), 185.0 (M^+, 98%), 183.0 (100%), 115.0 (30%), 105.1 (32%), 104.1 (22%), 77.0 (24%).

4.1.10. Mitsunobu reaction of 5-bromo-indan-2-ol (18): 2-azido-5-bromoindan (19). The literature procedure[14a] described for the conversion of *trans*-diols to the corresponding diazides was applied to 5-bromo-indan-2-ol (**18**). To a stirred solution of PPh_3 (3.2 g, 12.2 mmol) in THF (20 mL) was added a solution of DEAD (1.97 g, 11.3 mmol) in THF (10 mL) dropwise under N_2 atm at 0 °C. To this mixture was added a solution of HN_3[18] (12.6 mmol, 7 mL, 1.8 M) and a solution of 5-bromoindan-2-ol (**18**) (2.00 g, 9.4 mmol) in THF (15 mL). The reaction mixture was stirred at 0 °C for 30 min and then stirred at rt for 12 h. The solvent of the reaction mixture was evaporated at 30 °C. The residue was dissolved in 100 mL of Et_2O and left in a refrigerator overnight. After the filtration of the precipitate, the solvent was evaporated. Chromatography of the residue on a silica gel column (15 g) eluting with hexane–Et_2O–$CHCl_3$ (100:7:7) gave 2-azido-5-bromoindan (**19**) (1.88 g, 84%). Colorless oil. ^1H NMR (200 MHz, $CDCl_3$) δ 7.40 (bs, 1H, H-4), 7.35 (A part of AB system, dd, 1H, H-6, $J_{6,7}$=8.1 Hz, $J_{4,6}$=1.9 Hz), 7.14 (B part of AB system, d, 1H, H-7, $J_{6,7}$=8.1 Hz), 4.38 (m, 1H, H-2), 3.24 (A part of AB system, dd, 1H, J=16.5, 7.5 Hz), 3.20 (A part of AB system, dd, 1H, J=16.5, 6.9 Hz), 3.01 (B part of AB system, dd, 1H, J=16.5, 4.1 Hz), 2.98 (B part of AB system, dd, 1H, J=16.5, 4.1 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.3, 139.0, 129.8, 127.6, 125.9, 120.4, 61.5, 38.7, 38.6. IR (film) 3068, 2941, 2837, 2110, 1601, 1470, 1431, 1316, 1266, 1208, 1170 cm^{-1}.

4.1.11. 2-Amino-5-bromoindan (7).[13] (a) *From 2-azido-5-bromoindan* (**19**). To a stirred solution of $CuSO_4 \cdot 5H_2O$ (0.11 g, 0.042 mmol) in 12 mL of MeOH was added $NaBH_4$ (0.046 g, 1.24 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 15 min. To this mixture was added a solution of 2-azido-5-bromoindan (**19**) (1.00 g, 4.2 mmol) in 10 mL of MeOH and then $NaBH_4$ (0.114 g, 3.00 mmol) in four portions over 1.5 h. After the addition of $NaBH_4$ was completed, the stirring was continued and monitored by TLC at rt for 3 h. After the precipitate was filtered off, MeOH was evaporated and the mixture was made sufficiently alkaline (pH=12) with 3 M NaOH. The organic phase was extracted with EtOAc (3×25 mL). The drying of the organic layer over Na_2SO_4 and evaporation of EtOAc gave oily 2-amino-5-bromoindan (**7**) (0.71 g, 80%).

(b) *From 2-azido-5,6-dibromoindan* (**21**). The procedure above was applied to 2-azido-5,6-dibromoindan (**21**) using 2 equiv $NaBH_4$ to give 2-amino-5-bromoindan (**7**) in a yield of 75%.

For **7**: ^1H NMR (200 MHz, DMSO-d_6) δ 7.48 (bs, 1H, H-4), 7.37 (A part of AB system, d, 1H, H-6, $J_{6,7}$=8.1 Hz), 7.23

(B part of AB system, d, 1H, H-7, $J_{6,7}=8.1$ Hz), 6.23 (bs, 2H, NH_2), 3.97 (quasi quintet, 1H, H-2, $J=6.8$ Hz), 3.28 (A part of AB system, dd, 1H, $J=16.8$, 8.1 Hz), 3.23 (A part of AB system, dd, 1H, $J=16.8$, 7.7 Hz), 3.04 (B part of AB system, dd, 1H, $J=16.8$, 5.9 Hz), 2.98 (B part of AB system, dd, 1H, $J=16.8$, 5.6 Hz). ^{13}C NMR (50 MHz, DMSO-d_6) δ 144.8, 141.3, 131.4, 129.3, 128.4, 121.5, 52.4, 39.1, 38.8. IR (film): 3352, 3274, 3048, 3021, 2939, 2901, 2835, 1597, 1571, 1468, 1431, 1407, 1385, 1314, 1247, 1206, 1166 cm^{-1}.

4.1.12. 2-Amino-5-bromoindan hydrobromide (20). To a stirred solution of 2-amino-5-bromoindan (**7**) (0.50 g, 2.4 mmol) in MeOH (10 mL) was added HBr solution (47%, 10 mL) at 0 °C. MeOH and excess HBr were evaporated. The residue was recrystallized from MeOH–ether to give 2-amino-5-bromoindan hydrobromide (**20**) (0.56 g, 81%).Yellowish crystal. Mp > 290 °C (lit.[10b] Mp > 300 °C). The ^{1}H NMR is in agreement with the literature.[10b] ^{13}C NMR (50 MHz, DMSO-d_6) δ 144.6, 141.1, 131.5, 129.4, 128.5, 121.6, 52.3, 38.9, 38.6.

4.1.13. 2-Azido-5,6-dibromoindan (21). The procedure above described for the synthesis of 2-azido-5-bromoindan (**19**) applied to 5,6-dibromoindan-2-ol (**12**) to give 2-azido-5,6-dibromoindan (**21**) in a yield of 83%. Colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48 (s, 2H, H-4 and H-7), 4.37 (tt, 1H, H-2, $J=6.6$, 4.1 Hz), 3.18 (A part of AB system, ddd, 2H, $J=16.7$, 6.6, 0.9 Hz), 2.93 (B part of AB system, dd, 2H, $J=16.7$, 4.1 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.4, 129.6, 122.7, 51.7, 38.5. IR (film) 3068, 2941, 2844, 2113, 1466, 1431, 1266, 1104 cm^{-1}.

4.1.14. 2-Azidoindan (22). The procedure above described for the synthesis of 2-azido-5-bromoindan (**19**) applied to indan-2-ol (**9**) to give 2-azidoindan (**22**) in a yield of 86%. Colorless oil. The ^{1}H NMR is in agreement with the literature.[17] ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.0, 126.9, 124.5, 61.6, 38.9. IR (film) 2112 cm^{-1} (for N_3).

4.1.15. 2-Aminoindan hydrochloride (23). The hydrogenation procedure described above for 2-azido-5,6-dimethoxyindan (**15**) was applied to 2-azidoindan (**22**) to give 2-aminoindan hydrochloride (**23**) in a yield of 95%. Colorless crystal. Mp > 237 °C (from MeOH–Et_2O, lit.[19] decomp. at 220 °C). ^{1}H NMR (200 MHz, D_2O) δ 7.34–7.22 (AA′BB′ system, m, 4H, Aryl-H), 4.13 (tt, 1H, H-2, $J=7.2$, 3.9 Hz), 3.37 (A part of AB system, dd, 2H, $J=16.9$, 7.2 Hz), 3.01 (B part of AB system, dd, 2H, $J=16.9$, 3.9 Hz). ^{13}C NMR (50 MHz, D_2O) δ 143.7, 131.9, 129.4, 56.0, 41.7.

4.1.16. 2-Amino-5,6-dibromoindan hydrobromide (24). The literature procedure for the synthesis of 2-amino-5-bromoindan hydrobromide (**20**)[10b] was applied to 2-aminoindan hydrochloride (**23**) using 2.5 equiv Br_2 to give 2-amino-5,6-dibromoindan hydrobromide (**24**) in a yield of 70%. Yellowish crystal. Mp > 290 °C (from MeOH–Et_2O). ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.25 (bs, 3H, NH_3Br), 7.71 (bs, 2H, H-4 and H-7), 4.10–4.00 (m, 1H, H-2), 3.28 (A part of AB system, dd, 2H, $J=17.0$, 7.3 Hz), 2.98 (B part of AB system, dd, 2H, $J=17.0$, 4.9 Hz). ^{13}C NMR (50 MHz, DMSO-d_6) δ 143.8, 131.5, 123.6, 52.4, 38.5. Anal. Calcd for $C_9H_{10}Br_3N$ (371.9): C, 29.07; H, 2.71; N, 3.77; Found: C, 29.11; H, 2.68; N, 3.79.

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Synthesis, structure, and biological aspects of cyclopeptides related to marine phakellistatins 7–9

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Abstract—Phakellistatins 7, 8 and 9, three cyclic decapeptides naturally occurring in marine sponges of the genus *Phakellia* and characterized by the distinctive presence of Pro–Pro tracts, pose a non-trivial synthetic challenge, despite only containing coded amino acid residues. Their chemical synthesis was approached using a combination of solid and solution-phase techniques. As expected, our synthetic efforts yielded, for each cyclopeptide, a mixture of geometric isomers, owing to their *cis–trans* isomerism at Pro peptide linkages. A further complication arose because their synthesis yielded, together with the desired monomeric cyclopeptides, cyclodimeric species. In the case of phakellistatin 7 (originally determined as *cis*-Pro^2, *cis*-Pro^8) our synthetic product was chemically and spectrally identical to the natural one, whereas none of the different isomeric products obtained for both phakellistatins 8 and 9 resulted to be fully equivalent (with respect to Pro geometries) to their natural counterparts. Finally, all synthetic cyclopeptides were submitted to biological assays and, as noted before for other members of the 'proline rich' family, synthetic compounds did not fully reproduce the biological properties (in terms of in vitro cytotoxicity against a panel of cancer cell lines) originally found for the natural products.
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1. Introduction

Homodetic cyclopeptides of 'proline rich' class, so named for their unusual high content of proline residues, are mainly distributed in marine environments,[1] but were found also in higher plants.[2] They have attracted great interest owing to their remarkable pharmacological activities, such as anti-proliferative and cytotoxic effects, and also due to their peculiar structural aspects that make more challenging the spectral analysis as well as their chemical synthesis.

In the course of our on-going studies on bioactive marine metabolites as potential candidates for the development of novel and more effective pharmaceuticals, we have recently focused our attention on several members belonging to the proline-rich cyclopeptides family;[3] we already reported the synthesis and the biological evaluation of yunnanins A and C, two cyclic heptapeptides isolated from the roots of *Stellaria yunnanensis*, and phakellistatins 1 and 10, a hepta- and octacyclopeptide, respectively, first isolated from marine sponges of genus *Phakellia*.[4] Also, in this case, in accordance with the typical behavior associated to such products, already observed by our own as well as by other research groups,[5] we found that the biological properties of the synthesized cyclopeptides significantly differed from those found for their natural counterparts. There seems to be a growing consensus on the fact that these products are endowed with a quite remarkable conformational profile, which likely results from combined effects due to several simultaneous *cis–trans* isomerisms (at Pro linkages) in a constrained macrocyclic ring. Intrigued by this puzzle, we decided to further explore the structural and the biological aspects of other members of this singular class of marine natural products,[6] in the hope to shed more light on the topic of their chemical and yet not biological equivalence. Herein, we describe our work towards the total synthesis of phakellistatins 7–9 (**1–3**, Fig. 1)[7] and our subsequent efforts aimed at a thorough exploration of their conformational and biological properties. In terms of synthetic challenge, phakellistatins 7–9, by virtue of their unusual sequences comprising two Pro–Pro tracts in somewhat constrained

Abbreviations: AcOH, acetic acid; AA, amino acid; DCM, dichloromethane; DIEA, diisopropylethylamine; DKP, diketopiperazine; DMEM, Dulbecco's modified Eagle's medium; DMF, *N*,*N*-dimethylformamide; ESIMS, electrospray ionization mass spectrometry; Fmoc, 9-fluorenylmethoxycarbonyl; HATU, *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium; HBTU, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium; HEPES, 4-(2-hydroxyethyl)-1-piperazine ethanesulfonic acid; HOBt, 1-hydroxy-1,2,3-benzotriazole; MeOH, methanol; 6-MP, 6-mercaptopurine; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-phenyl-2*H*-tetrazolium bromide; NMM, *N*-methyl morpholine; ROESY, rotating-frame Overhauser effect spectroscopy; rt, room temperature; SDS, sodium dodecyl sulfate; SPG, side-chain protecting group; TFA, trifluoroacetic acid; TFE, 2,2,2-trifluoroethanol; TIS, triisopropylsilane.
Keywords: Cyclopeptides; Solid phase synthesis; Marine natural products; Cytotoxic.
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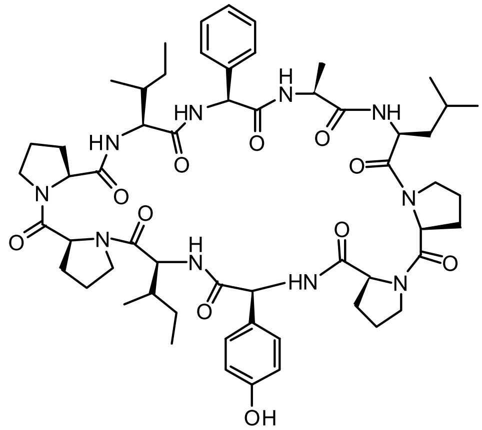
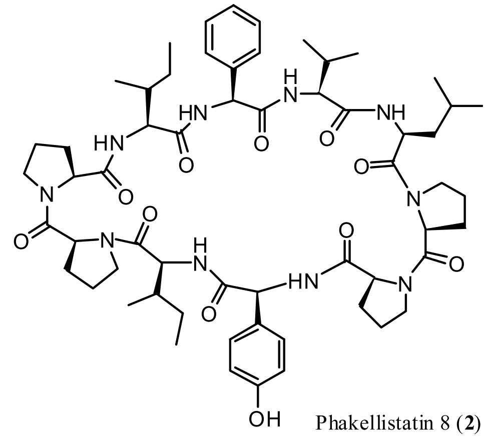
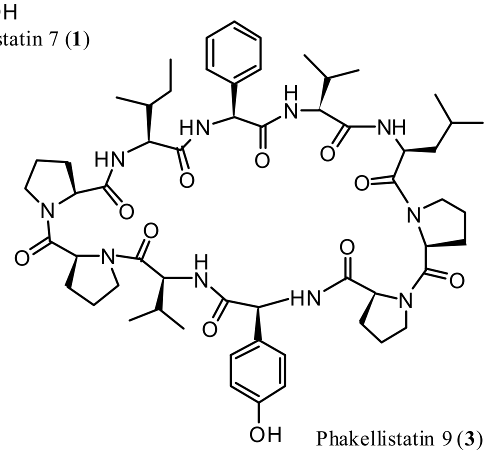


Phakellistatin 7 (**1**)



Phakellistatin 8 (**2**)



Phakellistatin 9 (**3**)

Figure 1. Chemical structures of natural cyclopeptides **1**–**3**.

decapeptidic macrocyclic frameworks, have to be considered relatively demanding targets, even though their structures just encompass proteinogenic amino acids. Not surprisingly, difficulties in obtaining the desired geometric isomers for all the target phakellistatins, have in fact emerged, preventing us from obtaining substantial amounts of compounds identical in all structural respects to the naturally occurring phakellistatins 8 (**2**) and 9 (**3**). Remarkably, in the case of phakellistatin 7, the compound with correct Pro–Pro geometry was obtained as unique product. We wish to point out that rather subtle (and fully conservative) amino acidic substitutions in the sequence of these related compounds, have translated into quite dramatic differences in the final outcome of our synthesis.

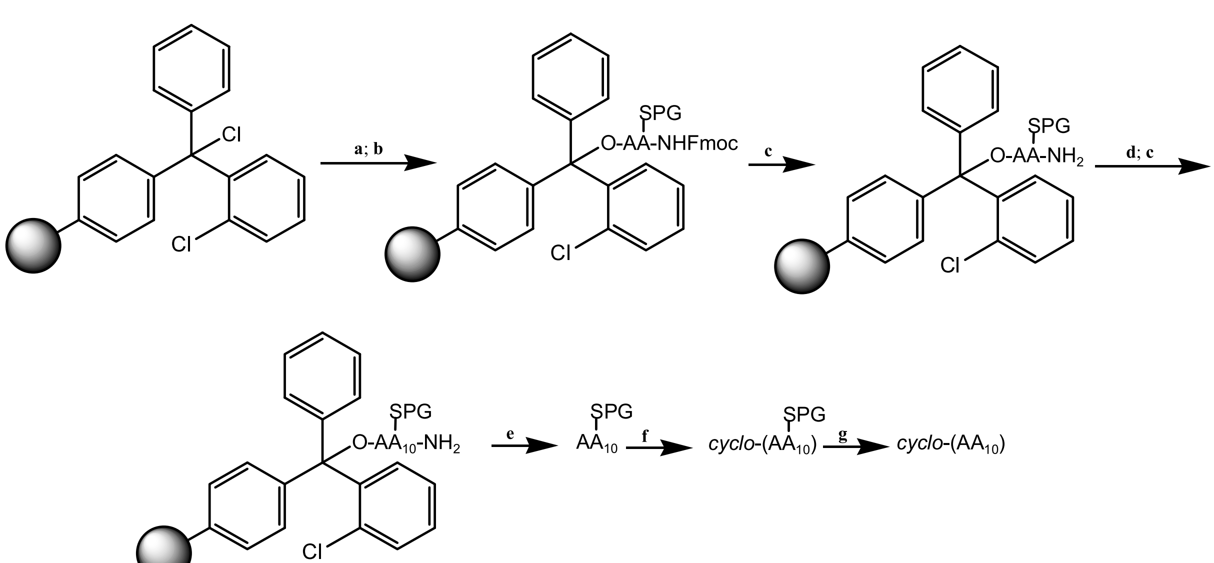


Figure 2. Synthetic scheme: (a) loading with C-terminal amino acid: Fmoc-AA, DIEA, DCM, 2 h; (b) capping: DCM/MeOH/DIEA; (c) N^{α}-deprotection: 20% piperidine in DMF; (d) cycles of nine amino acid couplings: HOBt, HBTU, NMM, DMF, 2 h; (e) cleavage: AcOH/TFE/DCM (2:2:6), 2 h; (f) cyclization: HATU, DIEA, DCM; (g) side-chain deprotection: TFA/TIS/H_2O (95.2.5:2.5).

Indeed, phakellistatin 7 (**1**) differs from the two remaining because in its sequence Ala-5 is replaced by a Val residue, whereas phakellistatin 8 (**2**) and phakellistatin 9 (**3**) for a substitution of Ile-10 in the former by a Val residue in the latter.

2. Results and discussion

Phakellistatins 7–9 (**1–3**) are cyclo-(P^1P^2IFALP^{7}P^{8}YI), cyclo-(P^1P^2IFVLP^{7}P^{8}YI), cyclo-(P^1P^2IFVLP^{7}P^{8}YV), respectively. Their synthesis was approached by solid-phase chemistry, using a Fmoc/*t*Bu protecting scheme and a 2-chlorotritylchloride resin as solid support, in a VAC MASTER system (Fig. 2), followed in the end by a cyclization step, in solution, of the linear precursors. The first Fmoc-protected amino acid was anchored to the linker by diisopropylethlyamine (DIEA) treatment under anydrous conditions, followed by capping of unreacted trityl groups with methanol. The resulting loading degree was determined by UV spectrophotometric analysis according to general procedure described in Section 3. The resin was then submitted to nine coupling–deprotection cycles to build the linear decapeptides as precursors of the cyclic phakellistatin 7 (**1**), phakellistatin 8 (**2**) and phakellistatin 9 (**3**). All the Fmoc-protected amino acids were activated by hydroxybenzotriazole/*O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HOBt/HBTU) in presence of *N*-methylmorpholine (NMM); the progress of the amino acid coupling was checked through the Kaiser test (the ninidrine colorimetric test). Fmoc deprotection before each coupling step was achieved by treatment of the resin-anchored peptide with a 20% solution of piperidine in *N*,*N*-dimethylformamide (DMF). After each linear peptide was obtained, the Fmoc protecting group was removed from the N-terminal residue and the peptide was cleaved from the resin by using a 2:2:6 acetic acid/2,2,2-trifluoroethanol/dichloromethane (AcOH/TFE/DCM) solvent mixture. The linear protected precursors were then submitted to the cyclization reaction in solution using *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) and DIEA in DCM following general procedure described in Section 3; side-chain deprotection was obtained by treatment with TFA/TIS/H_2O 95:2,5:2,5 for 1 h under stirring; finally purification on semi-preparative reversed-phase HPLC (RP-HPLC) yielded the pure cyclopeptides. The chemical features of these natural products, notably the two consecutive proline residues in their sequences, were surely influential in inducing peculiar conformational motifs and secondary structures of the peptide backbone. As stated before, we believe that the synthetic problems we faced are likely attributable to their complex conformational profile.

HPLC monitoring of the cyclization step showed that, upon conditions of relatively high dilution (10^{-4} M), each product yielded two main cyclic peptide sequences: a major one, corresponding to the dimeric cyclopeptide, and a minor one identified as the desired monomeric species. In facts, while the analysis of ESIMS spectral data for each minor product confirmed the presence of a cyclic monomeric species, the MS investigation on the major ones showed in all cases the presence of two ion peaks, corresponding to the singly and doubly charged species, both accounting for a dimeric cyclopeptide structure. This hypothesis was also validated by its pattern of fragmentation as determined by MS^2 spectra. On the basis of these results, we set to seek the right experimental conditions to avoid the formation of the dimeric by-product during the cyclization step.[8] To this end, we used progressively higher dilution conditions up to the point where the monomeric cyclopeptide was obtained as a unique compound. Following there is a more detailed account on our synthetic results. Furthermore, an in depth analysis of the results of our synthetic efforts had to account for the well-known phenomenon that each X-Pro peptide linkage in a peptide sequence can adopt a *cis* or *trans* geometry. Once the cyclization conditions were optimized, HPLC analysis of the crude macrolactamization product showed, in the case of phakellistatin 7, one main peak, identified on the basis of ESIMS data, ^{1}H NMR spectrum and ROESY cross-peaks' pattern, as the cyclodecapeptide **1**. NMR dipolar couplings established that peptide linkages had the usual *trans* geometry, except for the Pro^1-Pro^2 and Pro^7-Pro^8 bonds that showed a *cis* geometry (ROESY cross-peak Hα-Pro^1/Hα-Pro^2, Hα-Pro^7/Hα-Pro^8; Table 1). Overall, the synthetic product resulted, chemically and spectrally, to be identical to the natural substance.

Table 1. ^{1}H and ^{13}C NMR data for phakellistatin 7 (600 MHz, CD_3OD, δ in ppm)

Position	^{1}H	^{13}C	Position	^{1}H	^{13}C
Pro^1			Leu		
α	3.68	60.35	α	4.69	49.56
β	1.84	29.38	β	1.25	
	2.26			1.45	42.61
γ	2.14	26.09	γ	1.58	25.36
	1.86		CH_3	0.89	23.69
δ	3.67	49.03	CH_3	1.01	21.50
	3.97		NH	7.04	
Pro^2			Pro^7		
α	4.35	62.62	α	3.26	58.27
β	2.25	32.37	β	2.08	29.73
	2.47			1.62	
γ	1.71	22.78	γ	1.80	25.97
	2.01			1.12	
δ	3.54	47.80	δ	3.45	49.04
				3.66	
Ile^3			Pro^8		
α	4.29	57.82	α	4.24	62.31
β	2.15	33.63	β	2.05	31.45
CH_3	0.94	17.07		2.50	
γ	1.17	25.94	γ	1.64	22.87
	1.50			1.94	
CH_3	0.87	9.91	δ	3.45	47.52
Phe			Tyr		
α	4.23	57.79	α	4.48	57.34
β	2.86	38.83	β	3.15	33.16
	3.07			3.43	
2,6	7.27	130.47	2,6	7.01	131.98
3,5	7.39	129.58	3,5	6.56	115.24
4	7.33	127.77			
NH	7.13				
Ala			Ile^{10}		
α	4.58	59.87	α	4.57	55.66
CH_3	1.36	17.65	β	1.68	
NH	8.12		CH_3	1.01	14.69
			γ	1.68	25.25
				1.08	
			CH_3	0.89	10.83

Table 2. ^{1}H and ^{13}C NMR data for *trans*-Pro^2, *trans*-Pro^8 phakellistatin 8 (600 MHz, CD_3OD, δ in ppm)

Position	^{1}H	^{13}C	Position	^{1}H	^{13}C
Pro^1			Leu		
α	4.57	59.22	α	4.70	50.52
β	1.99	29.25	β	1.62	40.87
	2.31		γ	1.79	25.44
γ	2.04	25.45	CH_3	0.99	21.43
	2.09		CH_3	1.00	23.39
δ	3.66	48.48	NH	8.16	
	3.76				
Pro^2			Pro^7		
α	4.49	61.13	α	4.68	59.49
β	2.10	29.74	β	2.28	29.32
	1.95			1.95	
γ	2.05	25.59	γ	2.12	25.55
	2.09			2.01	
δ	3.69	48.49	δ	3.65	48.32
	3.86			3.92	
Ile			Pro^8		
α	4.18	59.70	α	4.47	61.08
β	1.78	37.83	β	1.96	29.66
CH_3	0.89	15.25		2.15	
γ	1.15	25.25	γ	1.99	25.45
	1.48			2.04	
CH_3	0.83	10.99	δ	3.67	48.31
NH	7.81			3.80	
Phe			Tyr		
α	4.73	54.75	α	4.55	55.82
β	2.95	38.492	β	2.94	37.74
	3.18		2,6	7.01	131.22
2,6	7.22	129.79	3,5	6.68	115.82
3,5	7.27	129.44	NH	7.79	
4	7.26	127.06			
			Ile^{10}		
NH	7.99		α	4.42	55.82
			β	1.79	37.83
Val			CH_3	0.93	15.43
α	4.20	59.62	γ	1.15	25.18
β	2.07	31.47		1.56	
CH_3	0.94	18.81	CH_3	0.88	10.64
NH	7.93		NH	7.89	

Table 3. ^{1}H and ^{13}C NMR data for *cis*-Pro^2, *cis*-Pro^7, *trans*-Pro^8 phakellistatin 8 (600 MHz, CD_3OD, δ in ppm)

Position	^{1}H	^{13}C	Position	^{1}H	^{13}C
Pro^1			Leu		
α	4.12	60.54	α	3.91	52.91
β	1.84	29.26	β	1.41	40.13
	2.31			1.71	
γ	2.00	25.75	γ	1.86	25.47
	2.15		CH_3	1.03	23.53
δ	3.70	48.37	CH_3	1.04	21.50
	3.88		NH	8.81	
Pro^2			Pro^7		
α	4.62	59.70	α	4.75	58.74
β	1.36	33.10	β	1.42	32.11
	2.20			2.34	
γ	1.62	23.14	γ	1.50	22.79
	1.76			1.84	
δ	3.40	47.77	δ	3.52	47.75
	3.58				
Ile^3			Pro^8		
α	4.19	59.59	α	4.55	63.50
β	1.86	37.38	β	1.95	30.21
CH_3	0.92	14.93		2.45	
γ	1.20	25.60	γ	2.05	25.89
	1.62			2.15	
CH_3	0.91	10.38	δ	3.73	48.44
				3.79	
Phe			Tyr		
α	4.61	54.79	α	4.48	54.81
β	3.09	36.47	β	2.91	35.18
	3.43			3.41	
2,6	7.26	130.25	2,6	7.05	131.27
3,5	7.39	130.11	3,5	6.83	116.80
4	7.33	128.35	NH		
NH					
Val			Ile^{10}		
α	4.33	58.74	α	4.66	55.68
β	1.71	33.06	β	1.60	39.12
CH_3	0.87	19.80	CH_3	1.07	14.64
CH_3	1.10	19.34	γ	1.12	25.51
NH	7.02			1.46	
			CH_3	0.91	11.96
			NH	6.84	

Concerning phakellistatin 8 (**2**), the HPLC chromatogram contained two main peaks, corresponding to a pair of isomeric products, among which the major possessed a *trans* geometry at all peptide linkages (Table 2), with the minor differing from the former only for the *cis* geometries observed at Pro^1-Pro^2 and Leu-Pro^7 connectivities (ROESY cross-peak Hα-Pro^1/Hα-Pro^2, Hα-Leu/Hα-Pro^7; Table 3). Unfortunately, in this case, none of the synthetic products resulted chemically to be equivalent to the natural counterpart. They were characterized, instead, by a *cis* geometry at both Pro^1-Pro^2 and Pro^7-Pro^8 levels. It remains to be clarified, why the naturally occurring compound is one that appears to be kinetically disfavored in its formation, even though, generally speaking, X-Pro tracts with *cis* geometry are usually more compatible with constrained ring closures and therefore can be easily accommodated in a cyclopeptidic structure. Conversely, it is also true that most of the other ‘proline rich’ peptides display a somewhat smaller size of the macrocylic ring (typically 7–8 residues); compounds **1–3** may have reached a critical size of the macrolactame that allows a more comfortable arrangement of *trans* peptide geometries, which, in turn, are less sterically demanding.

Our synthetic route to phakellistatin 9 also produced two geometric isomers: the all-*trans* cyclopeptide (Table 4) and another one showing a *cis* geometry at Pro^1-Pro^2 and Leu-Pro^7 levels (ROESY cross-peak Hα-Pro^1/Hα-Pro^2, Hα-Leu/Hα-Pro^7; Table 5). Also, in this case, none of the two kinetically favored synthetic products resulted to be spectrally superimposable with the natural compound.

Biological evaluation of the synthetic phakellistatins against a minipanel of three cancer cell lines showed cell growth inhibitory activity lower than their natural counterparts (Table 6).

These results were not unexpected, especially in the case of phakellistatins 8 and 9 in which the synthetic isomers were not chemically identical to the natural products. On the contrary, the results concerning phakellistatin 7 are more difficult to explain, owing to the full chemical equivalence between the synthetic and the natural product. Even admitting that biological data relative to in vitro cellular assays are never fully comparable, unless measured in the same experimental conditions (ideally in the same laboratory), the extent of the observed differences in IC_{50} values appears hard to justify entirely on such grounds. Presently, we believe that a conceivable hypothesis is to look at this

Table 4. ^{1}H and ^{13}C NMR data for *trans*-Pro^{2}, *trans*-Pro^{8} phakellistatin 9 (600 MHz, CD_3OD, δ in ppm)

Position	^{1}H	^{13}C	Position	^{1}H	^{13}C
Pro^{1}			Leu		
α	4.59	59.39	α	4.70	54.54
β	1.99	29.33	β	1.60	40.97
	2.30		γ	1.76	25.44
γ	2.06	25.65	CH_3	0.98	21.74
	2.09		CH_3	1.01	23.53
δ	3.65	48.65	NH	8.12	
	3.74				
Pro^{2}			Pro^{7}		
α	4.48	60.97	α	4.68	59.44
β	2.11	29.93	β	2.27	29.17
	1.96			1.96	
γ	2.04	25.63	γ	2.11	25.79
	1.97			1.98	
δ	3.67	48.43	δ	3.65	48.42
	3.83			3.92	
Ile			Pro^{8}		
α	4.18	58.93	α	4.47	61.17
β	1.78	38.22	β	2.15	30.07
CH_3	0.91	15.51		/	
γ	1.14	25.51	γ	1.99	25.65
	1.49			/	
CH_3	0.86	11.24	δ	3.63	48.18
				3.79	
Phe			Tyr		
α	4.73	55.48	α	4.55	55.84
β	2.97	38.41	β	2.94	37.75
	3.19		2,6	7.02	131.22
2,6	7.18	127.45	3,5	6.68	115.82
3,5	7.27	129.19	NH	7.97	
4	7.26	130.08			
NH					
Val^{5}			Val^{10}		
α	4.20	59.93	α	4.36	57.25
β	2.06	31.76	β	1.99	31.81
CH_3	0.94	19.51	CH_3	0.93	18.70
NH	7.93		NH	7.82	

Table 5. ^{1}H and ^{13}C NMR data for *cis*-Pro^{2}, *cis*-Pro^{7}, *trans*-Pro^{8} phakellistatin 9 (600 MHz, CD_3OD, δ in ppm)

Position	^{1}H	^{13}C	Position	^{1}H	^{13}C
Pro^{1}			Leu		
α	4.12	60.38	α	3.89	52.76
β	1.83	29.01	β	1.41	40.08
	2.29			1.69	
γ	1.99	25.56	γ	1.83	25.53
	2.15		CH_3	1.03	23.47
δ	3.70	48.26	CH_3	1.04	21.55
	3.88		NH	8.81	
Pro^{2}			Pro^{7}		
α	4.61	59.58	α	4.74	58.87
β	1.37	33.14	β	1.41	33.24
	2.19			2.33	
γ	1.62	23.32	γ	1.56	23.60
	1.77			1.84	
δ	3.42	47.57	δ	3.50	47.53
	3.58				
Ile			Pro^{8}		
α	4.18	59.45	α	4.54	62.11
β	1.86	36.98	β	1.92	29.32
CH_3	0.91	15.57		2.42	
γ	1.18	25.45	γ	2.02	25.55
	1.58			2.13	
CH_3	0.88	11.23	δ	3.70	48.65
				3.78	
Phe			Tyr		
α	4.61	54.81	α	4.46	54.83
β	3.09	36.52	β	2.94	35.23
	3.42			3.39	
2,6	7.25	130.27	2,6	7.04	131.34
3,5	7.40	130.09	3,5	6.80	116.69
4	7.32	128.30	NH		
NH					
Val^{5}			Val^{10}		
α	4.33	58.65	α	4.59	58.34
β	1.72	32.97	β	1.82	31.77
CH_3	0.86	18.44	CH_3	0.90	19.71
CH_3	1.09	19.48	CH_3	1.07	19.57
NH	7.03		NH	6.91	

biological variability in terms of subtle conformational changes stemming from slightly diverse arrangements at the level of proline units, conformational differences hardly detectable by simple inspection of the pattern of ROESY correlations. Such diversity in the three-dimensional arrangement may be in turn related to the asymmetric environment operated by the enzymatic machinery upon biosynthesis of a naturally occurring substance, as opposed to the case of the end-product of a cyclization step which is intrinsically endowed with more degrees of freedom.

3. Experimental

3.1. General procedures

Unless specified, solvents were reagent grade. They were purchased from Aldrich or Fluka or Carlo Erba and were used without further purification. DCM and DMF used for solid-phase reactions were synthesis grade (dried over 4 Å molecular sieves), CH_3CN was HPLC grade.

2-Chlorotritylchloride resin was purchased from Novabiochem (loading capacity 1.04 mmol/g). The Fmoc-L-amino acids and the coupling reagents (HOBt, HBTU, HATU) were supplied by Novabiochem or Fluka and used without further purification.

Solid-phase reactions were carried out on a polypropylene ISOLUTE SPE column on a VAC MASTER system (a manual parallel synthesis device purchased from Stepbio, Bologna, Italy) and using the Fmoc/*t*-Bu protocol.

The spectrophotometric analysis of the fluorene–piperidine adduct chromophore was performed on duplicate samples as described below. 0.4 ml of piperidine and 0.4 ml of DCM were added each of two dried samples of the resin-bound peptide (∼6 mg) in two 10 ml volumetric flasks. The reaction was allowed to proceed for 30 min at rt in the sealed flasks. 1.6 ml of MeOH was added and the solutions were diluted to 10 ml volume with DCM. A reference solution was prepared in a 10 ml volumetric flask using 0.4 ml of piperidine, 1.6 ml of MeOH and DCM to volume. The solutions were shook and the absorbance of the samples versus the reference solution was measured at 301 nm. The substitution degree (in mmol of amino acid/g of resin) was calculated from the equation: $\text{mmol/g} = (A_{301}/7800) \times (10\ \text{ml/g of resin})$. For quantification of the Fmoc amino acids on the resin, the absorbance at 301 nm was measured employing a Shimadzu UV 2101 PC spectrophotometer. The ^{1}H and ^{13}C (^{1}H–^{1}H and ^{1}H–^{13}C) spectra were recorded using a Bruker Avance 600 MHz spectrometer with a deuterated solvent (CD_3OD). The LCQ Thermoquest mass spectrometer was used to record the ESIMS spectra.

Table 6. In vitro anti-proliferative activity of proline rich cyclopeptides **1–3** on a minipanel of three cancer cell lines

Cyclopeptides	$[IC_{50}$ M][a]		
	J774.A1[b]	WEHI-164[c]	HEK-293[d]
Phakellistatin 7	5.6×10^{-4}	5.4×10^{-4}	5.8×10^{-4}
Phakellistatin 8 major product	6.7×10^{-4}	5.8×10^{-4}	6.22×10^{-4}
Phakellistatin 8 minor product	5.9×10^{-4}	5.7×10^{-4}	6.11×10^{-4}
Phakellistatin 9 major product	6.1×10^{-4}	5.5×10^{-4}	5.88×10^{-4}
Phakellistatin 9 minor product	7.8×10^{-4}	5.1×10^{-4}	5.1×10^{-4}

[a] The IC_{50} value is the concentration of compound that affords 50% reduction in cell growth (after 3 days incubation).
[b] J774.A1, murine monocyte/macrophage cell line.
[c] WEHI-164, murine fibrosarcoma cell line.
[d] HEK-293, human epithelial kidney cell line.

3.1.1. Synthesis of the linear side chain protected peptides of phakellistatin 7, 8 and 9. 2-Chlorotrityl-chloride resin was placed into a 25 ml polypropylene ISOLUTE column on a VAC MASTER system, swelled for 1 h with 3 ml of DMF by a N_2 stream and then washed with 2×3 ml of DCM. In order to obtain a lower substitution level, a solution of corresponding C-terminal Fmoc-AA-OH (0.5 equiv) and DIEA (2 equiv) in DCM (10 ml/g of resin) was added. The reaction mixture was stirred for 2 h under a N_2 stream. The reaction was terminated by capping with methanol unreacted trityl groups (20 ml of DCM–MeOH–DIEA = 17:2:1). The Fmoc-AA-O-2ClTrt-resin was subjected to the following washings: DCM (3×3 ml×1.5 min), DMF (2×3 ml×1.5 min), DCM (3×3 ml×1.5 min) and then dried under vacuum over KOH. The resulting substitution level was determined according to the spectrophotometric assay previously described. After Fmoc-AA-*O*-2ClTrt-resin swelling (1 h with 3 ml of DMF), removal of the Fmoc protecting group was carried out by a general procedure, using 20% piperidine in DMF (1×3 ml×1.5 min; 1×3 ml×10 min); washings after deprotection were carried out with DMF (2×3 ml×1.5 min), DCM (3×3 ml×1.5 min) and DMF (2×3 ml×1.5 min). The resin was subsequently submitted to a series of nine coupling–deprotection cycles. The first peptide coupling was carried out with the appropriate amino acid (4 or 5 equiv), HOBt (4 or 5 equiv), HBTU (4 or 5 equiv) and NMM (5 or 6 equiv) in DMF (500 μl/100 mg of resin) for 2 h, followed by washings with DMF (3×3 ml×1.5 min) and DCM (3×3 ml×1.5 min). At this step, to avoid the formation of DKPs, Fmoc deprotection was obtained using 20% piperidine in DMF for 5 min (3 ml), followed by washings with DMF (2×3 ml×1.5 min), DCM (3×3 ml×1.5 min) and DMF (2×3 ml×1.5 min). The result of the Fmoc removal was monitored according to the spectrophotometric assay described above. The following peptide couplings and Fmoc deprotections were carried out according to general procedures previously described, up to obtain the expected linear protected peptide. After the second peptide coupling, the spectrophotometric assay was performed to define the degree of substitution of the resin bound peptide in the case of DKPs formation. The ninhydrin test was performed after each amino acid coupling step and the coupling repeated if necessary.

The resin was washed with methanol and dried under vacuum over KOH for 1 h. The overall resin-bound peptide was cleaved from the solid support by treatment with an AcOH/TFE/DCM (2:2:6) solution (10 μl×mg of resin) for 2 h under stirring. The cleavage mixture was filtered off and the resin was washed 2 times with the same solution. Hexane was added (15 times volume) and the solution was evaporated, adding further hexane if necessary. The crude peptide product was lyophilized and analyzed by RP-HPLC on a Jupiter C-18 analytical column (250×4.60 mm, 5 μm, 300 Å), using a 31 min gradient from 5% to 100% of CH_3CN in H_2O (each containing 0.1% TFA) at a flow rate of 1.0 ml/min and UV detection at 220 nm. The HPLC analysis showed one peak that was identified as the linear side-chain protected peptide on the basis of ESIMS data (Tables 7 and 8).

Table 7. Most significant data of the linear protected peptides

		HPLC t_R (min)	Mass data[a]
1	Phakellistatin 7	20.53	1183
2	Phakellistatin 8	19.76	1211
3	Phakellistatin 9	19.48	1197

[a] ESIMS, *m/z* for $[M+H]^+$.

3.1.2. Cyclization of the linear side-chain protected phakellistatin 7. The crude linear peptide (31.9 mg, 0.027 mmol) was dissolved in DCM (2.4×10^{-4} M) with HATU (20.1 mg, 0.053 mmol, 2 equiv) and DIEA (11.6 μl, 0.067 mmol, 2.5 equiv). The solution was stirred for 1 h on an ice bath and then allowed to warm at rt and kept at this temperature for 7 h. During this time DCM was gradually added until to 1.3×10^{-4} M to avoid side reactions such as oligodimerization.

The cyclization reaction was monitored via HPLC and ESIMS spectra of selected fractions. After 7 h the solvent was removed. Side-chain deprotection was obtained by treatment with TFA/TIS/H_2O (95:2.5:2.5, 100 μl×1 mg of resin) for 1 h under stirring. The cleavage mixture was evaporated and lyophilised, yielding 52.1 mg of crude cyclopeptide. The crude cyclopeptide was analyzed by RP-HPLC on a Jupiter C-18 analytical column (250×4.60 mm, 5 μm, 300 Å), using a 31 min gradient from 5% to 100% of CH_3CN in H_2O (each containing 0.1% TFA) at a flow rate of 1.0 ml/min and UV detection at 220 nm. The HPLC analysis showed one main peak (R_t = 21.72 min; ESIMS, *m/z* 1109 for $[M+H]^+$) identified as the *cis*-Pro[2], *cis*-Pro[8] cyclopeptide phakellistatin 7 on the basis of ESIMS and ^{1}H NMR experiments. The crude cyclopeptide was then purified by semi-preparative RP-HPLC on a Jupiter C-18 column (250×10.00 mm, 10 μm, 300 Å), using a 48 min gradient from 35:65 to 65:35 of CH_3CN/H_2O (each containing 0.1% TFA) at a flow rate of 5.0 ml/min and UV detection at 220 nm. The HPLC purification yielded, as white solid, 6.8 mg (yield = 22.7%) of *cis*-Pro[2], *cis*-Pro[8]

Table 8. Most significant data of the linear protected peptides

	Phakellistatin 7	Phakellistatin 8	Phakellistatin 9
Resin amount	0.400 g	0.800 g	0.800 g
Initial loading level	1.04 mmol/g	1.04 mmol/g	1.04 mmol/g
AA, C-terminal	Fmoc-Phe-OH, 80.5 mg, 0.21 mmol	Fmoc-Phe-OH, 161.1 mg, 0.41 mmol	Fmoc-Phe-OH, 161.1 mg, 0.41 mmol
Loading level	0.35 mmol/g	0.27 mmol/g	0.24 mmol/g
1° coupling	Fmoc-Ile-OH, 197.9 mg, 0.56 mmol	Fmoc-Ile-OH, 380 mg, 1.07 mmol	Fmoc-Ile-OH, 333.9 mg, 0.94 mmol
2° coupling	Fmoc-Pro-OH, 188.9 mg, 0.56 mmol	Fmoc-Pro-OH, 362.7 mg, 1.07 mmol	Fmoc-Pro-OH, 318.8 mg, 0.94 mmol
Loading level	0.13 mmol/g	0.27 mmol/g	0.24 mmol/g
3° coupling	Fmoc-Pro-OH, 188.9 mg, 0.56 mmol	Fmoc-Pro-OH, 362.7 mg, 1.07 mmol	Fmoc-Pro-OH, 318.8 mg, 0.94 mmol
4° coupling	Fmoc-Ile-OH, 197.9 mg, 0.56 mmol	Fmoc-Ile-OH, 380 mg, 1.07 mmol	Fmoc-Val-OH, 364.8 mg, 0.94 mmol
5° coupling	Fmoc-Tyr(OtBu)-OH, 257.3 mg, 0. 56 mmol	Fmoc-Tyr(OtBu)-OH, 494.1 mg, 1. 07 mmol	Fmoc-Tyr(OtBu)-OH, 434.3 mg, 0. 94 mmol
6° coupling	Fmoc-Pro-OH, 188.9 mg, 0.56 mmol	Fmoc-Pro-OH, 362.7 mg, 1.07 mmol	Fmoc-Pro-OH, 318.8 mg, 0.94 mmol
7° coupling	Fmoc-Pro-OH, 188.9 mg, 0.56 mmol	Fmoc-Pro-OH, 362.7 mg, 1.07 mmol	Fmoc-Pro-OH, 318.8 mg, 0.94 mmol
8° coupling	Fmoc-Leu-OH, 197.9 mg, 0.56 mmol	Fmoc-Leu-OH, 380 mg, 1.07 mmol	Fmoc-Leu-OH, 333.9 mg, 0.94 mmol
9° coupling	Fmoc-Ala-OH, 87.1 mg, 0.56 mmol	Fmoc-Val-OH, 366.5 mg, 1.07 mmol	Fmoc-Val-OH, 364.8 mg, 0.94 mmol

cyclopeptide phakellistatin 7 (R_t=17.53 min; ESIMS, *m/z* 1109 for $[M+H]^+$).

3.1.3. Cyclization of the linear side-chain protected phakellistatin 8. A portion of the crude linear peptide (50 mg, 0.041 mmol) was dissolved in DCM (8×10^{-5} M) with HATU (30.4 mg, 0.08 mmol, 2 equiv) and DIEA (17.4 μl, 0.1 mmol, 2.5 equiv). The solution was stirred for 1 h on an ice bath and then allowed to warm at rt and kept at this temperature for 7 h. During this time DCM was gradually added until to 6.1×10^{-5} M to avoid side reactions such as oligodimerization.

The cyclization reaction was monitored via HPLC and ESIMS spectra. After 7 h the solvent was removed. Side-chain deprotection was obtained by treatment with TFA/TIS/H_2O (95:2.5:2.5, 100 μl×1 mg of resin) for 1 h under stirring. The cleavage mixture was evaporated and lyophilised, yielding 65.3 mg of crude cyclopeptide. The crude cyclopeptide was analyzed by RP-HPLC on a Jupiter C-18 analytical column (250×4.60 mm, 5 μm, 300 Å), using a 31 min gradient from 5 to 100% of CH_3CN in H_2O (each containing 0.1% TFA) at a flow rate of 1.0 ml/min and UV detection at 220 nm. The HPLC analysis showed two main peaks; the major one was identified as the *trans*-Pro^2, *trans*-Pro^8 cyclopeptide phakellistatin 8 (R_t=22.41 min; ESIMS, *m/z* 1137 for $[M+H]^+$) on the basis of ESIMS and ^{1}H NMR experiments, while the minor one was the geometric isomer *cis*-Pro^2, *trans*-Pro^8 of cyclopeptide phakellistatin 8 (R_t=21 min; ESIMS, *m/z* 1137 for $[M+H]^+$). The crude cyclopeptides were then purified by semi-preparative RP-HPLC on a Jupiter C-18 column (250×10.00 mm, 10 μm, 300 Å), using a 62 min gradient from 30:70 to 55:45 of CH_3CN/H_2O (each containing 0.1% TFA) at a flow rate of 5.0 ml/min and UV detection at 220 nm. The HPLC purification yielded, as white solid, 8 mg (yield=17.1%) of *trans*-Pro^2, *trans*-Pro^8 cyclopeptide phakellistatin 8 (R_t=43.4 min; ESIMS, *m/z* 1137 for $[M+H]^+$) and 2.9 mg (yield=6.2%) of *cis*-Pro^2, *cis*-Pro^7, *trans*-Pro^8 cyclopeptide phakellistatin 8 (R_t=39.83 min; ESIMS, *m/z* 1137 for $[M+H]^+$).

3.1.4. Cyclization of the linear side-chain protected phakellistatin 9. A portion of the crude linear peptide (50 mg, 0.042 mmol) was dissolved in DCM (8×10^{-5} M) with HATU (31.5 mg, 0.083 mmol, 2 equiv) and DIEA (18.3 μl, 0.105 mmol, 2.5 equiv). The solution was stirred for 1 h on an ice bath and then allowed to warm at rt and kept at this temperature for 7 h. During this time DCM was gradually added until to 6.1×10^{-5} M to avoid side reactions such as oligodimerization.

The cyclization reaction was monitored via HPLC and ESIMS spectra. After 7 h the solvent was removed. Side-chain deprotection was obtained by treatment with TFA/TIS/H_2O=95:2.5:2.5 (100 μl×1 mg of resin) for 1 h under stirring. The cleavage mixture was evaporated and lyophilised, yielding 74.1 mg of crude cyclopeptide. The crude cyclopeptide was analyzed by RP-HPLC on a Jupiter C-18 analytical column (250×4.60 mm, 5 μm, 300 Å), using a 31 min gradient from 5 to 100% of CH_3CN in H_2O (each containing 0.1% TFA) at a flow rate of 1.0 ml/min and UV detection at 220 nm. The HPLC analysis showed two main peaks; the major one was identified as the *trans*-Pro^2, *trans*-Pro^8 cyclopeptide phakellistatin 9 (R_t=21.73 min; ESIMS, *m/z* 1123 for $[M+H]^+$) on the basis of ESIMS and ^{1}H NMR experiments, while the minor one was the geometric isomer *cis*-Pro^2, *trans*-Pro^8 of cyclopeptide phakellistatin 9 (R_t=22.04 min; ESIMS, *m/z* 1123 for $[M+H]^+$). The crude cyclopeptides were then purified by semi-preparative RP-HPLC on a Jupiter C-18 column (250×10.00 mm, 10 μm, 300 Å), using a 56 min gradient from 25:75 to 60:40 of CH_3CN/H_2O (each containing 0.1% TFA) at a flow rate of 5.0 ml/min and UV detection at 220 nm. The HPLC purification yielded, as white solid, 5.6 mg (yield=11.8%) of *trans*-Pro^2, *trans*-Pro^8 cyclopeptide phakellistatin 9 (R_t=36.89 min; ESIMS, *m/z* 1123 for $[M+H]^+$) and 1.7 mg (yield =3.6%) of *cis*-Pro^2, *cis*-Pro^7, *trans*-Pro^8 cyclopeptide phakellistatin 9 (R_t=38.52 min; ESIMS, *m/z* 1123 for $[M+H]^+$).

3.1.5. Preparation of cells. J774.A1, murine monocyte/macrophage cells were grown in adhesion on Petri dishes and maintained with DMEM at 37 °C in DMEM supplemented with 10% foetal calf serum (FCS), 25 mM HEPES, 2 mM glutamine, 100 u/ml penicillin and 100 μg/mL streptomycin. WEHI-164, murine fibrosarcoma cells were maintained in adhesion on Petri dishes with DMEM supplemented with 10% heat-inactivated FCS, 25 mM HEPES, 100 u/ml penicillin and 100 μg/mL streptomycin. HEK-293, human epithelial kidney cells were maintained and grown in adhesion on Petri dishes with DMEM supplemented with 10% FCS, 25 mM HEPES, 100 u/ml penicillin and 100 μg/mL streptomycin. All reagents for cell culture were from Hy-Clone (Euroclone, Paignton Devon, U.K.); MTT and 6-MP were from Sigma Chemicals (Milan, Italy).

3.1.6. Antiproliferative assay. J774.A1, WEHI-164 and HEK-293 (3.5×10^4 cells) were plated on 96-well microtiter plates and allowed to adhere at 37 °C in 5% CO_2 and 95% air for 2 h.

Thereafter, the medium was replaced with 50 μL of fresh medium and a 75 μL aliquot of 1:4 serial dilution of each test compound was added and then the cells incubated for 72 h. In some experiments, serial dilutions of 6-MP were added. The cell viability was assessed through an MTT conversion assay.[9,10] Briefly, 25 μl of MTT (5 mg/ml) were added and the cells were incubated for an additional 3 h. Thereafter, cells were lysed and the dark blue crystals solubilised with 100 μl of a solution containing 50% (v:v) *N*, *N*-dimethylformamide, 20% (w:v) SDS with an adjusted pH of 4.5.[11] The optical density (OD) of each well was measured with a microplate spectrophotometer (Titertek Multiskan MCC/340) equipped with a 620 nm filter. The viability of each cell line in response to treatment with tested compounds and 6-MP was calculated as: % dead cells = 100 − (OD treated/OD control) × 100. Table 6 shows the results obtained expressed as IC_{50} values (μM), that is the concentration that inhibited cell growth by 50% as compared to the control.

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Intramolecular 1,3-dipolar cycloaddition of unsaturated nitrones derived from methyl α-D-glucopyranoside

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Abstract—The intramolecular 1,3-dipolar cycloaddition of unsaturated nitrones derived from methyl α-D-glucopyranoside with 2-furaldehyde has been studied. This cycloaddition was found to afford three 9-oxa-1-azabicyclo[4.2.1]nonane diastereomers in a 3:1:1 ratio [with the principal isomer possessing a (3*S*,4*R*,5*S*,6*S*,8*S*) configuration, determined by NMR spectroscopy]. The effects of different Lewis acid catalysts ($MgCl_2$, $ZnCl_2$ and $BF_3 \cdot OEt_2$) on yields and diastereomeric ratios have been examined in detail. The best result (90% yield) was achieved when $MgCl_2$ was present (in toluene, 120 °C bath temperature, 12 h). The stereoselectivity of the 1,3-dipolar cycloaddition was not significantly altered under the conditions investigated.

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1. Introduction

Peptide nucleic acids (PNAs) are nucleic acid mimics bearing a pseudopeptide backbone (Fig. 1).[1,2] They possess very favourable hybridisation properties with nucleic acid targets, display high chemical and biological stabilities and have the potential to be used as both antisense and antigene therapeutic agents. Unfortunately, PNA has low lipid penetration and, consequently, poor cellular uptake. In an attempt to overcome these undesirable attributes, we have designed a conformationally restricted oligonucleotide analogue whose backbone should be positively charged under physiological conditions. These new chiral nucleoside analogues are termed azetidine nucleic acids (ANAs, Fig. 1). The pivotal step in the synthesis of the ANA monomers, needed for construction of the oligomers, is a diastereoselective intramolecular 1,3-dipolar cycloaddition involving unsaturated nitrones derived from carbohydrate precursors. Subsequent transformations on the corresponding isoxazolidines obtained should then afford the desired azetidine derivatives (Fig. 2).

We envisage that it will be possible to control the stereochemical outcome of the intramolecular 1,3-dipolar cycloaddition by virtue of steric constraint so that the actual number of isoxazolidine isomers produced would be reduced compared to the theoretical. The use of different Lewis acid catalysts is anticipated to improve both the stereoselectivity and reactivity of the nitrone. The mechanism of such 1,3-dipolar cycloadditions has been extensively studied by several authors.[3] Nitrones are nucleophiles which

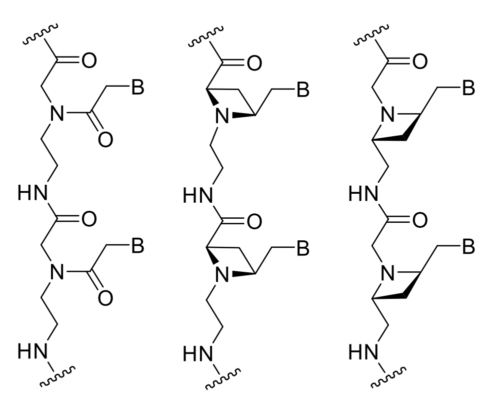

Figure 1. The structure of PNA and ANA oligomers (B, nucleobase). Only one diastereoisomer is shown for each ANA structure.

Keywords: 1,3-Dipolar cycloaddition; Isoxazolidines; Bicyclic 1,2-oxazepanes; 9-Oxa-1-azabicyclo[4.2.1]nonanes; Asymmetric synthesis.

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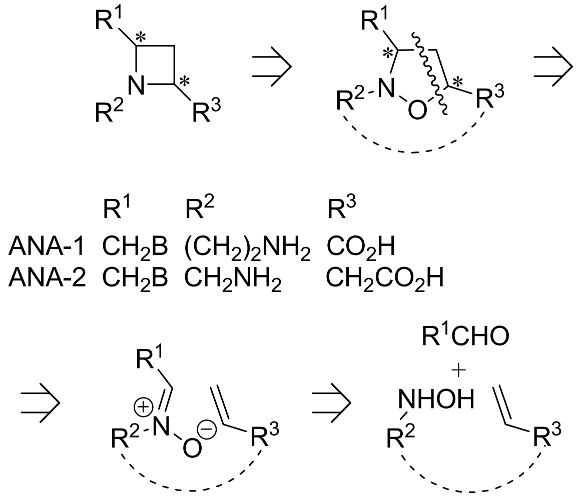

Figure 2. Retrosynthetic analysis of ANA monomers.

co-ordinate strongly to Lewis acids to form nitrone/Lewis acid complexes. These complexes are generated easily and they serve to assist in 1,3-dipolar cycloadditions through stabilization of the corresponding transition state and decreasing the energy gap between the LUMO and HOMO of one of the substrates.[4,5] Thus, a series of catalysts (metals and their complexes) has been developed for use in either normal or inverse electron demand 1,3-dipolar cycloadditions, for example, Mg^{2+}, Ti^{2+}, Zn^{2+}, Ni^{2+}, Pd^{2+}, Yb^{3+}, B(III), Al^{3+}, Cu^{2+}.[3] The 1,3-dipolar cycloaddition of nitrones bearing heteroaryl rings with electron-deficient alkenes has been investigated in detail by Merino et al.[6–8]

Our interest in the development of an efficient route for the synthesis of chiral isoxazolidines and, ultimately, azetidines led us to therefore consider using a similar strategy, utilizing unsaturated nitrones derived from carbohydrates, for their preparation. The starting material employed for the work reported herein was methyl α-D-glucopyranoside (**1**) (Fig. 3). In this case, the 1,3-dipolar cycloaddition investigated was a model reaction in order that suitable reaction procedures for performing such cycloadditions could be identified. It is envisaged that future employment of appropriate carbohydrate derivatives from the D-*manno* and D-*galacto* series in place of **1** will permit formation of isoxazolidines in which the hydroxyl groups in the carbohydrate portion are differentiated. The preparation of such compounds is an integral part of our synthetic approach to the desired ANA monomers.

2. Results and discussion

The starting material, methyl α-D-glucopyranoside **1**, was successfully converted into the benzoylated (**2**) and benzylated (**9**) 6-deoxy-6-iodo derivatives according to the methods described by Garegg[9] and Vasella,[10] respectively (Fig. 3). The subsequent Boord reaction on the halo derivatives [**2**→**3**, **9**→**10** (Fig. 3)] was accomplished upon treatment with zinc followed by sonication.[11] However, it was discovered that acceptable yields of the products **3** and **10** were only obtained for small scale

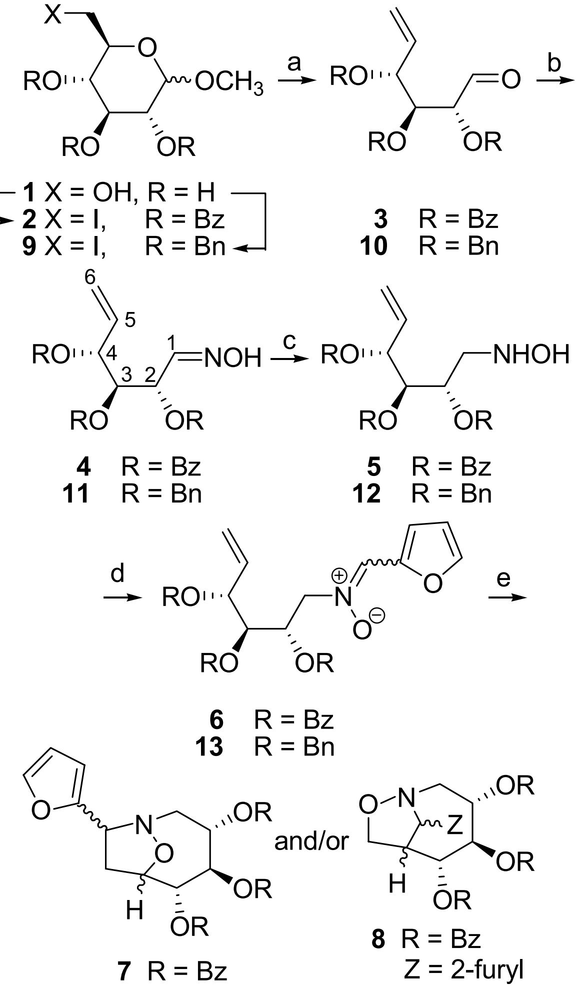

Figure 3. a: (**2**→**3**, **9**→**10**): Zn, sonication (1.6 g scale: 90%, 5 g scale: 30%) or Zn and Co(II)phthalocyanine (5 g scale: 70%), b: $NH_2OH \cdot HCl$, $NaHCO_3$ (70%), c: $NaBH_3CN$, HCl/dioxane, d: 2-furaldehyde, toluene (c + d: 30–40%), 4 Å MS, 50 °C, 18 h, e: toluene, 120 °C, 4 Å MS, Lewis acid catalyst, **7**: 9-oxa-1-azabicyclo-[4.2.1]nonane, **8**: 8-oxa-1-azabicyclo-[4.2.1]nonane skeletons.

reactions (up to 1.6 g of **2** or **9** afforded **3** or **10** in ca. 90% yields). Thus, several attempts were made to increase the scale of this reaction by employing activated zinc instead. This was prepared according to established methods,[13] for example, zinc–copper alloy[14] or the reduction of anhydrous zinc chloride with various alkali metals in the presence of naphthalene.[15,16] Heating solutions of **2** or **9** in ethanol at reflux in the presence of activated zinc produced by either method, afforded the same result, with respect to scale and yield (1 g scale ca. 70%, 5 g scale ca. 30% yield). When more than 5 g of the starting 6-deoxy-6-iodo derivative (**2** or **9**, respectively) was used and the activated zinc was prepared in situ from zinc chloride and lithium, the reaction also failed to go to completion. In this case, though, the remaining lithium in the reaction mixture caused decomposition of the unsaturated aldehyde and, also, prevented addition of water to the reaction mixture, which is necessary to dissolve zinc salts from the surface of zinc. Thus, all these procedures gave optimum product yields up to a maximum 1 g scale. Upon conducting further investigations into this Boord reaction, we found that, for large scale reactions, reasonable yields of the products **3** and **10** could be obtained when zinc and cobalt(II) phthalocyanine was utilised (Kleban et al.[12] employed zinc and vitamin B_{12} for the same purpose) rather than zinc and sonication (5 g scale, ca. 70% yield).

Having prepared unsaturated aldehydes **3** and **10**, the next step in our synthetic pathway involved treatment with hydroxylamine at room temperature[17] to give oximes **4** and **11**, respectively (*E*/*Z* isomers in 1:1 ratio) (Fig. 3). Subsequently, **4** or **11**[18] were reduced with sodium cyanoborohydride and HCl/1,4-dioxane at the appropriate pH, depending on the protecting groups present, to afford **5** or **12**, respectively (Fig. 3). These hydroxylamines were used in the next step without further purification in order to avoid their decomposition. The mixture of HCl/1,4-dioxane had to be added slowly due to the acid sensitive nature of the benzoyl protecting groups and because further reduction of the hydroxylamine could easily occur at low pH which would result in formation of the amine instead. It was envisaged that this amine by-product would hinder the subsequent condensation step as it could react with 2-furaldehyde to give a Schiff's base, drastically reducing the yield of the cycloaddition reaction. Therefore, in an attempt to overcome this limitation, we have investigated performing the reduction of **4** and **11** in phosphate buffer solutions at various pHs, ranging from 4 to 8. Unfortunately, to date, all attempts have proved unsuccessful and so our original approach for preparing hydroxylamines **5** and **12** has been retained for the present work. Finally, crude hydroxylamines **5** and **12** were condensed with 2-furaldehyde to furnish the desired nitrones, **6** and **13**, required for investigation of the 1,3-dipolar intramolecular cycloaddition reaction (Fig. 3). These were afforded in overall yields of 30–40% for the two steps, after purification.

With nitrones **6** and **13** to hand, it was now possible to investigate the intramolecular 1,3-dipolar cycloaddition. This was simply accomplished by heating a solution of the appropriate nitrone in toluene at reflux in the presence of 4 Å molecular sieves (Fig. 3). Unfortunately, for the benzyl protected nitrone **13**, this reaction proved to be sluggish (toluene, reflux, 1 week) and very low yielding (<10%); therefore it was abandoned. For the benzoyl nitrone **6**, this reaction was found to be more successful and gave isoxazolidine **7** (Fig. 3) as a mixture of diastereoisomers in 17–90% yield as expected. These isomers were subsequently separated by column chromatography and characterised by NMR spectroscopy as the 9-oxa-1-azabicyclo[4.2.1]nonane diastereoisomers **7b–7d** (Fig. 4).

We were unable to isolate the fourth diastereisomer from the 9-oxa series (**7a**) (Fig. 4) as its yield was negligible. We assume that the other alternative product from this cycloaddition, 8-oxa-1-azabicyclo[4.2.1]nonane **8** (Fig. 3), did not form because of steric hindrance between the furyl side chain and the oxazepane ring.

Tables 1 and 2 show selected proton and carbon chemical shifts recorded in the ^{1}H and ^{13}C NMR spectra of compounds **7b–7d**. Upon assignment of the individual resonances by means of ^{1}H, ^{13}C, HSQC and HMBC NMR measurements, it was shown that protons H-6 and H-8 adopt a relative *trans* arrangement in the principal isomer **7b** whereas the equivalent protons in isomers **7c** and **7d** assume a *cis* arrangement. The NOESY spectrum of **7b** (Fig. 5) indicates the spatial proximity of protons H-2a, H-4, and H-8 and that of H-7b, H-4, H-8. Protons H-7b and H-2a reside on the bottom face of the structure relative to the oxazepane ring. In addition, it appears that proton H-7b is located far from its neighbours, H-2a, H-4 and H-8, as no coupling between H-7b and H-2a was detected (Table 4).

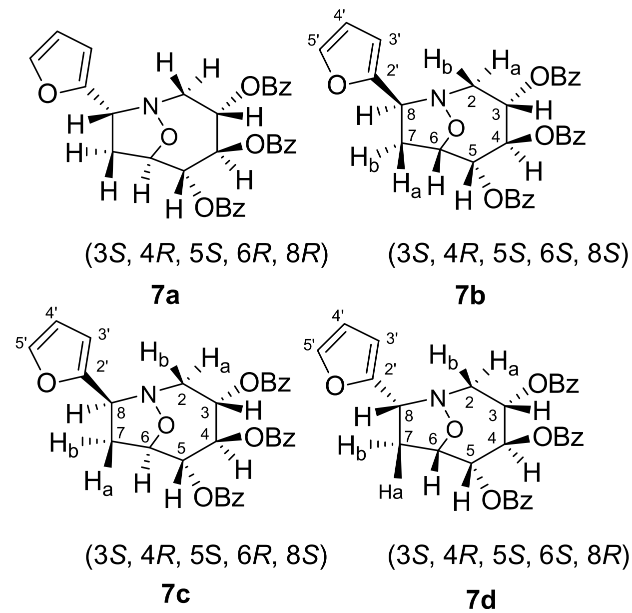

Figure 4. The structures of 9-oxa-1-azabicyclo[4.2.1]nonanes **7a–7d**.

Table 1. Selected ^{1}H NMR chemical shifts of compounds **7b–7d**

Compound/atom	7b	7c	7d
H-2a (dd)[a]	3.22	3.60	3.02
H-2b (dd)	4.22	2.89	3.53
H-3	5.85 (m)	5.96 (ddd)	5.89 (ddd)
H-4 (dd)	6.00	6.21	5.98
H-5	5.68 (dd)	5.51 (d)	5.69 (dd)
H-6	5.02 (m)	4.82 (dd)	4.96 (ddd)
H-7a (ddd)	2.75	2.83	2.67
H-7b (ddd)	3.18	3.14	2.86
H-8 (dd)	4.63	4.74	4.71
H-3′ (d)	6.28	6.60	6.51
H-4′(dd)	6.32	6.44	6.42

[a] Multiplicities in parenthesis.

Table 2. Selected ^{13}C NMR chemical shifts of compounds **7b–7d**

Compound/atom	7b	7c	7d
C-2	58.7	54.7	52.2
C-3	68.8	68.1	66.8
C-4	73.1	74.7	74.6
C-5	73.1	79.2	73.2
C-6	77.7	81.8	77.6
C-7	34.2	38.1	31.2
C-8	65.4	60.9	64.1
C-2′	154.3	147.1	148.1
C-3′	106.2	111.2	111.1
C-4′	110.3	110.8	110.7
C-5′	142.3	143.6	143.4

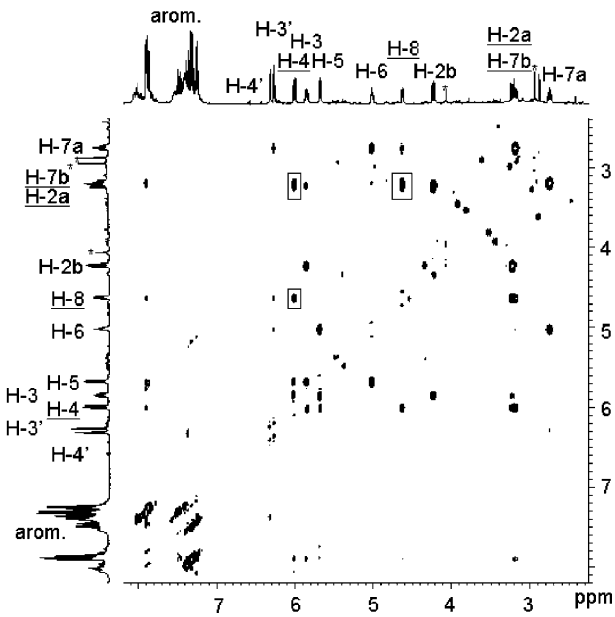

Figure 5. NOESY spectrum of compound **7b**. Crucial correlations between underlined protons are shown in boxes.

Table 3. Coupling constants for compounds **7b–7d** (Hz)

Compd/coupling constant	**7b**	**7c**	**7d**
$J_{2a,2b}$	13.8	15.0	12.5
$J_{2a,3}$	7.9	10.9	10.3
$J_{2b,3}$	4.9	4.0	4.0
$J_{3,4}$	9.2	10.9	10.1
$J_{4,5}$	7.9	7.6	8.7
$J_{5,6}$	6.0	—	5.8
$J_{6,7a}$	8.8	6.1	8.7
$J_{6,7b}$	3.8	10.0	6.2
$J_{7a,7b}$	13.1	13.5	13.2
$J_{7a,8}$	3.6	11.0	7.2
$J_{7b,8}$	8.5	9.5	11.2
$J_{3',4'}$	3.2	3.2	3.1
$J_{4',5'}$	1.9	2.0	1.9

Table 4 reveals that compounds **7b** and **7d** adopt similar structures. Naturally, though, the position of protons H-8 and H-3′ in the furyl ring are reversed for isomer **7d** compared to isomer **7b** [**7b**: (8*S*), **7d**: (8*R*)]. This was confirmed by the coupling constants measured between protons H-6, H-7 and H-8 (Table 3). The only real difference between their structures is that proton H-7b is located closer to protons H-2a and H-4 in isomer **7d** (evaluated from the dihedral angles). Thus, for isomer **7d**, a cross-correlation peak was visible in the NOESY spectrum (H-7b/H-2a/H-4). In the case of isomer **7c**, protons H-3′/H-3/H-7a and H-5/H-3/H-7a on the top face of the oxazepane ring are found to be in close proximity to each other, according to the NOESY spectrum recorded. By taking into account the coupling constants for all the isoxazolidine and 1,2-oxazepane ring protons in all three isomers, we have been able to determine the configuration of each of the newly formed chiral centres [**7b**: (6*S*,8*S*); **7c**: (6*R*,8*S*); and **7d**: (6*S*,8*R*) (Fig. 4)]. The stereochemistry of the remaining chiral centres have been deduced from D-glucose and the conformation of the 1,2-oxazepane ring.

The effects of different Lewis acid catalysts ($BF_3 \cdot OEt_2$, $ZnCl_2$, $MgCl_2$), solvents, absence or presence of 4 Å molecular sieves and reflux time on yields and diastereomeric ratios for this intramolecular 1,3-dipolar cycloaddition with nitrone **6** (Fig. 3) have been examined in detail (Table 5). The diastereomeric ratios of **7b–7d** obtained from each reaction were initially determined by the combined use of TLC and RP-HPLC. However, as this method proved cumbersome and inaccurate, alternatives were sought. The fortunate finding that, in the ^{1}H NMR spectra, the peaks assigned to protons H-3′ and H-4′ of the furyl ring were located in unique positions for each of the three isomers, that is, **7b–7d**, led us to investigate using ^{1}H NMR spectroscopy instead for these measurements. This afforded ratios which were in good agreement with those obtained previously from RP-HPLC experiments and so, due to its convenience and accuracy, it became the method of choice.

From Table 5, it can be seen that when the intramolecular 1,3-dipolar cycloaddtion was performed in toluene, the reflux time (24 or 48 h) had no effect on yield or diastereomeric ratio. However, since nitrone **6** decomposed quickly at temperatures above 100 °C, even under an argon atmosphere, it was not advantageous to heat the reaction in toluene at reflux for more than 24 h. 1,4-Dioxane was found to be an unsuitable solvent for this reaction; the mixture of isomers **7b–7d** was afforded in only 17% yield.

We have established that the main diastereoisomer obtained from these cycloaddition reactions (except when 1,4-dioxane and $ZnCl_2$ was used) was **7b**, bearing the (6*S*,8*S*) configuration at the newly formed chiral centres (Table 5). The maximum yield for this intramolecular 1,3-dipolar cycloaddition was achieved when $MgCl_2$ was added [90%, toluene, 120 °C (bath temperature), 12 h, Table 5]. Unexpectedly, in the presence of the harder Lewis acid catalyst, $BF_3 \cdot OEt_2$, most of the starting nitrone **6** decomposed after only a few hours to give an undesired product which contained one less benzoyl group (as determined from MS data). As a result of this finding, we propose that this also attributed to the reduced yield observed for the reaction performed in the presence of $ZnCl_2$, although here decomposition of the nitrone was slower.

In conclusion, we have ascertained that the optimum conditions for performing this 1,3-dipolar cycloaddition

Table 4. NOESY data of compounds **7b–7d**

Compd	Connected protons (upside positions)[a]	Connected protons (downside positions)[a]	Connected protons (peripheral positions)[a]
7b	H-3···H-2b; H-5···H-6	H-7b···H-8···H-4; H-8···H-2a···H-4	H-6···H-7a; H-7a···H-3′
7c	H-3′···H-3···H-7a H-3···H-5···H-7a H-3···H-2b	H-2a···H-4	H-7b···H-8; H-7b···H-6
7d	H-3···H-2b; H-5···H-6	H-7b···H-2a···H-4···H-3′	H-7a···H-6; H-7a···H-8

[a] Relative to the 9-oxa-1-azabicyclo[4.2.1]nonane skeleton as shown in Figure 6.

Table 5. The effect of Lewis acids and solvents on yields and diastereomeric ratios

Solvent, mol sieves	Catalyst	Time (h)	Temperature (°C)[a]	Yield (%)	Diastereomeric ratios (HPLC)[b]	Diastereomeric ratios (NMR)[b,c]
Toluene, 4 Å	—	24	120	70	2.8:1:1	3:1:1
Toluene	—	48	120	75	2.8:1:1.2	3:1:1
Benzene, 4 Å	—	24	80	32	2.1:1:1	2:1:1
1,4-Dioxane, 4 Å	—	24	100	17	1:1.1:1.2	—[d]
Toluene, 4 Å	$ZnCl_2$	24	120	50	4:1:1[e]	0.5:1:1
Toluene, 4 Å	$MgCl_2$	12	120	90	2:1:1	2:1:1
Toluene, 4 Å	$BF_3 \cdot OEt_2$	24	120	—[f]	—	—

[a] Bath temperature.
[b] Ratio of isomers **7b**:**7c**:**7d** isolated from the reaction mixture.
[c] Determined from the integral of protons H-3′ and H-4′.
[d] Not determined due to the presence of impurities.
[e] Diastereomer **7b** could not be separated from an impurity.
[f] The starting material decomposed and a by-product was formed (see text).

reaction with nitrone **6** (Fig. 3) involve using toluene as the solvent and $MgCl_2$ as the Lewis acid catalyst. It appears that if the Lewis acid catalyst added is hard, a side reaction involving elimination of a benzoyl protecting group from the starting nitrone becomes significant and this may be accompanied by decomposition and conversion of the furyl group, too. The stereoselectivity of the cycloaddition was found not to alter much under the conditions investigated here.

3. Theoretical investigations

In order to analyse the geometry of all four diastereoisomers of the isozaxolidine derivative (i.e., **7a–7d** (Fig. 4)) produced from the intramolecular 1,3-dipolar cycloaddition with nitrone **6** (Fig. 3), we have conducted a systematic computational investigation. This involved performing molecular dynamics simulations followed by high-level ab initio calculations. For the molecular dynamics studies, the ‘simulated annealing’ protocol described in the SYBYL program package[19] was employed to obtain the required starting geometries for isomers **7a–7d** for the subsequent higher level investigations. The Merck’s force field parameter set (MMFF94) was applied with its own charge distribution. The molecules were equilibrated for 2000 fs at 1200 K and then cooled to 50 K exponentially over 10,000 fs. In this way, 1000 conformations were provided for each isomer. Next a semi-empirical optimization using the PM3 method was performed and the results afforded were grouped according to their energies. Finally, ab initio

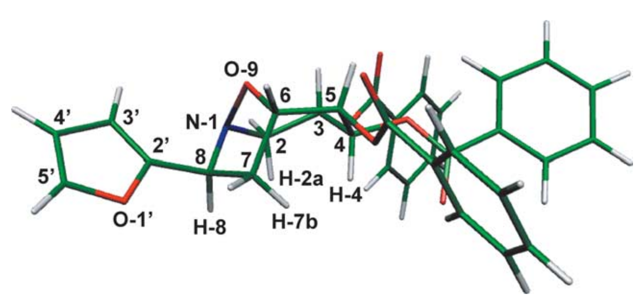

Figure 6. The lowest-energy conformation of compound **7b** calculated by HF/3-21 method. Proximal hydrogen atoms of 9-oxa-1-azabicyclo[4.2.1]-nonane skeleton, supporting the configuration and conformation of the above compound (NMR evidence), are shown with the H prefix. Carbon atoms of the above skeleton and those of the furan skeleton (primed numbers) are labelled without the C prefix for clarity.

calculations were conducted on a representative for each of the different energy clusters. These utilised the Hartree–Fock method with 3-21 Gaussian basis set and applied the Gaussian03 code.[20] Although this is one of the simplest methods, it was reasoned that this was sufficient for our purposes. The conformations of the oxazepane rings for isomers **7b–7d** derived from the computational studies were found to be in very good agreement with the structures obtained previously from NMR studies. In Figure 6, the optimized geometry of isomer **7b** is presented. The spatial proximity of protons H-7b, H-8, H-4 and H-2a on the bottom face can be clearly seen. In addition to the theoretical calculations providing information about the geometry of isomers **7a–7d**, we had hoped that they could also be used to predict the diastereomeric ratio afforded by the cycloaddition reaction (**7a**:**7b**:**7c**:**7d** ≈ 0:3:1:1) based on the total energy of each of the isomers.

However, it appeared that, at this level of theory, significant differences could not be observed with the total energies for diastereoisomers **7a–7d** being approximately the same. In Table 6, the HF/3-21G total energies of the minimized geometries for each of the different isozaxolidine isomers are presented.

Table 6. Calculated total energies of compounds **7a–7d**[a]

Compound	Total energy (hartree)
7a	−1870.388634
7b	−1870.389014
7c	−1870.389014
7d	−1870.389272

[a] Ab initio (HF/3-21G method).

4. Conclusion

We have successfully synthesized a variety of isoxazolidine derivatives of chiral moieties employing a Lewis acid-catalyzed 1,3-dipolar cycloaddition. In our preliminary studies, the exclusive formation of 9-oxa-1-azabicyclo-[4.2.1]nonane diastereomers **7b–7d** (Fig. 4) from nitrone **6** (Fig. 3) has been observed. The maximum yield for the 1,3-dipolar cycloaddition reaction was achieved with $MgCl_2$ as the Lewis acid catalyst [toluene, 120 °C (bath temperature), 12 h]. The ratio of the diastereoisomers of **7b–7d** was 3:1:1 and this did not alter significantly under the different reaction conditions investigated here. The theoretical total energies of the minimized geometries for **7a**–**7d** obtained computationally failed to rationalise the experimentally determined diastereomeric ratios of these cycloadducts produced from the intramolecular 1,3-dipolar cycloaddition. Further studies are in progress to obtain chiral 1,2,4-substituted azetidines from the cycloadducts afforded and new cycloaddition reactions are envisaged.

5. Experimental

5.1. General procedures

The following abbreviations are employed: ACN (acetonitrile); ANA (azetidine nucleic acid(s)); anh. (anhydrous); Bn (benzyl); Bz (benzoyl); $CDCl_3$ (deuterochloroform); CH_2Cl_2 (dichloromethane); ESI (electrospray ionization); EtOAc (ethyl acetate); FAB (fast atom bombardment); HRMS (high resolution mass spectrometry); LRMS (low resolution mass spectrometry); MeOD (deuteromethanol); MeOH (methanol); PNA [peptide nucleic acid(s)]; rt (room temperature); THF (tetrahydrofuran).

Chemicals were purchased from Aldrich, Fluka, Merck or Reanal (Budapest, Hungary). 2-Furaldehyde and $BF_3\cdot OEt_2$ were freshly distilled prior to use. Anhydrous solvents and anhydrous Lewis acid catalysts were prepared as described.[21] Organic solutions were dried using anhydrous $MgSO_4$ and evaporated in Büchi rotary evaporators. TLC: Kieselgel 60 F_{254} (Merck), solvent systems: CH_2Cl_2/MeOH, hexane/EtOAc, visualization: UV light, H_2SO_4/ethanol. Mp: Electrothermal IA 8103 apparatus. IR spectra: Bio-Rad FTS-60A (KBr pellets unless otherwise stated, ν_{max}/cm^{-1}, s, strong; m, medium; w, weak). NMR: Bruker Avance DRX 400 and 500 spectrometers (^{1}H: 400.13, 500.13 MHz; ^{13}C: 125.76 MHz, respectively), MeOD, $CDCl_3$ solutions, δ (ppm), J (Hz). Spectral patterns: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; br, broad; deut, deuterable. The superscripts *, # denote interchangeable assignments. For the 2D experiments (HSQC, HMBC, NOESY) the standard Bruker software packages (INV4GSSW, INV4GSLRNDSW) were applied. LRMS: Finnigan MAT TSQ 7000, ESI technique. HRMS: VG ZAB SEQ high resolution mass spectrometer using FAB ion source. Samples were dissolved in glycerol, the resolution of the instrument was 10,000. TLC/MS; TLC/HPLC: the analyte solution has been applied onto a 5 cm wide silica gel TLC plate as a band to obtain sufficient material. After developing in a solvent system the appropriate band was removed, the silica gel was suspended in MeOH (100 μL for MS, 1000 μL for HPLC), sonicated, centrifuged and the supernatant was used for MS analysis and HPLC (for HPLC 10 μL was injected). HPLC: SHIMADZU UV/VIS detector: SPD-10A VP, pump: LC-10AC VP, column: LiChrospher 6.1, RP select B (5 μm). Eluent system: gradient: 70–90% ACN within 25 min, flow rate: 1 mL/min.

5.1.1. (2*S*,3*S*,4*R*)-1-(Hydroxyimino)hex-5-ene-2,3,4-triyl tribenzoate (4). The unsaturated aldehyde **3**[11] (5.00 g, 10.92 mmol, 1 equiv) was dissolved in ethanol (100 mL) and distilled water (30 mL). The solution was treated with hydroxylamine hydrochloride (3.41 g, 41.19 mmol, 4.5 equiv) and sodium hydrogen carbonate (3.41 g, 49.80 mmol, 4.6 equiv). After 2 h stirring at room temperature, the ethanol was removed under reduced pressure, and the residue was dissolved in dichloromethane (100 mL). The solution was washed with water (3×50 mL), dried ($MgSO_4$) and evaporated in vacuo. Further purification was accomplished by column chromatography [10%–50% (v/v) EtOAc in hexane] to give oxime **4** as a light yellow oil (5.16 g, 70%, 1:1 mixture of *E* and *Z* isomers). R_f: 0.60; 0.53 (*E*/*Z* isomer), (1:1, hexane/EtOAc); IR (film, ν_{max}/cm^{-1}): 3426m, 3069w, 2984w, 1726s, 1601m, 1450m, 1315m, 1260s, 1246s, 1177m, 1105s, 1094s, 1069s, 1026m, 942w, 710s; δ_H (500 MHz, CH_3OD): 5.36 (m, 2H, H-6a, H-6b), 6.02 (m, 4H, H-2, H-3, H-4, H-5), 6.60 (m, 1H, H-1, *E*) 6.80 (d, 1H, $J_{1,2}$ = 5.4 Hz, H-1, *Z*), 7.34–7.56 (m, 9H, arom. H), 7.96–8.04 (m, 6H, arom. H), 8.63 (s, 1H, OH). δ_c (125 MHz, CH_3OD): 68.1 (C-2, *Z*), 71.8 (C-2, *E*), 73.8 (C-3, *Z*), 74.5 (C-3, *E*), 74.6 (C-4, *E*), 74.8 (C-4, *Z*), 120.4 (C-6, *E*), 121.0 (C-6, *Z*), 129.6–129.7 (6×arom. CH), 130.7 (3×arom. C_q), 130.8 (6×arom. CH), 132.7 (C-5, *Z*), 134.6 (C-5, *E*), 134.7 (3×arom. CH), 145.9 (C-1, *E*) 147.0 (C-1, *Z*), 166.6 (C=O), 166.7 (C=O), 167.1 (C=O); LRMS (ESI): *m*/*z* 474 (57%, $[M+H]^+$), 491 (100%, $[M+NH_4]^+$), 496 (75%, $[M+Na]^+$); HRMS (FAB, glycerol): Calcd for $C_{27}H_{24}NO_7$ $[M+H]^+$ *m*/*z* 474.15473, found *m*/*z* 474.15418.

5.1.2. (2*S*,3*S*,4*R*)-2,3,4-Tris(benzoyloxy)-*N*-(furan-2-ylmethylene)hex-5-en-1-amine oxide (6). To a stirred solution of oxime **4** (0.50 g, 1.06 mmol, 1 equiv) in dioxane (5 mL) was added sodium cyanoborohydride (0.22 g, 3.20 mmol, 3 equiv) in small portions, while the solution was carefully treated with HCl/dioxane (1.7 M, ~1 mL), to maintain the pH between 3 and 5. After completion of reaction (TLC), the solution was evaporated in vacuo, the residue was dissolved in EtOAc (50 mL), the organic layer was washed with aqueous sodium carbonate (40 mL), water (40 mL) and brine (40 mL), dried ($MgSO_4$) and evaporated in vacuo. The resulting hydroxylamine **5** was used without any further purification.

Compound **5** was dissolved in toluene (20 mL) and treated with freshly distilled 2-furaldehyde (176 μL, 2.12 mmol) in the presence of 4 Å molecular sieves. After stirring at 50 °C for 18 h, the solution was filtered, evaporated under reduced pressure and co-evaporated with ACN (3×50 mL). The crude residue was purified by column chromatography (10–30% (v/v) EtOAc in hexane) to give nitrone isomers **6** as a pale yellow foam (0.23 g, 40%). R_f: 0.17; 0.23 (*E*/*Z* isomer, 7:3, hexane/EtOAc); IR (KBr, ν_{max}/cm^{-1}): 3429w, 3065w, 2980w, 1728s, 1612m, 1601w, 1450w, 1315m, 1261s, 1240s, 1179w, 1107s, 1096s, 1069m, 1026w, 948w, 863m, 708s; δ_H (500 MHz, $CDCl_3$): 4.31 (d, 1H, $J_{1,2}$ = 5.5 Hz, H-1), 5.35 (d, 1H, $J_{5,6b}$ = 10.1 Hz H-6b, *Z*), 5.45 (d, 1H, H-6a, $J_{5,6a}$ = 16.6 Hz, *E*), 5.95–6.07 (m, 4H, H-2, H-3, H-4, H-5), 6.16 (dd, 1H, $J_{3',4'}$ = 1.7 Hz, $J_{4',5'}$ = 3.4 Hz, H-4′), 6.52 (d, 1H, $J_{3',4'}$ = 1.7 Hz, H-3′), 7.26 (s, 1H, $^-O^+N$=CH), 7.34–7.42 (m, 9H, arom. H), 7.79 (d, 1H, $J_{4',5'}$ = 3.4 Hz, H-5′), 7.97–8.04 (m, 6H, arom. H). δ_C (125 MHz, $CDCl_3$): 65.3 (C-1), 69.5 (C-2), 73.0 (C-4*), 73.5 (C-3*), 112.4 (C-3′), 116.3 (C-4′), 120.7 (C-6), 127.3 (CH=N), 128.4 (3×arom. CH), 128.5 (3×arom. CH), 128.6 (arom. C_q), 129.7 (3×arom. CH), 129.9 (3×arom.

CH), 131.5 (C-5), 133.2 (arom. CH), 133.5 (2×arom. CH), 144.0 (C-5′), 146.3 (C-2′), 165.1 (C=O), 165.3 (C=O), 165.7 (C=O); LRMS (ESI): *m/z* 554 (100%, $[M+H]^+$), 576 (20%, $[M+Na]^+$); HRMS (FAB, glycerol): Calcd for $C_{32}H_{28}NO_8$ $[M+H]^+$ *m/z* 554.18094, found *m/z* 554.18324.

5.1.3. (3*S*,4*R*,5*S*,6*S*,8*S*)-8-(Furan-2-yl)-9-oxa-1-aza-bicyclo[4.2.1]nonane-3,4,5-triyl tribenzoate (7b); (3*S*,4*R*,5*S*,6*R*,8*S*)-8-(furan-2-yl)-9-oxa-1-azabicyclo-[4.2.1]-nonane-3,4,5-triyl tribenzoate (7c) and (3*S*,4*R*,5*S*,6*S*,8*R*)-8-(furan-2-yl)-9-oxa-1-azabicyclo[4.2.1]-nonane-3,4,5-triyl tribenzoate (7d). *General procedure*. The pure nitrone **6** (0.40 g, 0.72 mmol) was dissolved in dry toluene (20 mL) in the presence of 4 Å molecular sieves and the solution was heated at 80–100–120 °C (bath temperature) for 12–48 h under an argon atmosphere. The reaction mixture was cooled, filtered, evaporated in vacuo and co-evaporated with ACN (3×50 mL). Chromatographic purification [0–10% (v/v) EtOAc in hexane], yielded three isomers (**7b**,**7c**,**7d**) as an oil or foam, in different isomer ratios depending on the reaction conditions, in 17–90% yield (Table 6). The ratios of the three diastereisomers were determined by TLC, RP-HPLC and ^{1}H NMR (Table 6). The reactions were carried out under different conditions, for example, solvents, temperature, reflux time and with or without Lewis acid catalysts (see Table 5). The catalysts, anh. $ZnCl_2$, anh. $MgCl_2$ and freshly distilled $BF_3\cdot OEt_2$, were used in 0.1–0.2 mol equiv with respect to nitrone. R_f: 0.32 (7:3, hexane/EtOAc as a single spot; after 5× development in an 8:2, hexane/EtOAc eluent it could be separated into three isomers).

Compound **7b**: IR (KBr, ν_{max}/cm^{-1}): 3429w, 3065w, 2961w, 1726s, 1601w, 1450w, 1315m, 1281s, 1261s, 1179w, 1107s, 1096s, 1069m, 1026w, 708s; δ_H (500 MHz, $CDCl_3$): 2.75 (ddd, 1H, $J_{7a,7b}$=13.1 Hz, $J_{6,7a}$=8.8$^{\#}$ Hz, $J_{7a,8}$=3.6* Hz, H-7a), 3.18 (ddd, 1H, $J_{7a,7b}$=13.1 Hz, $J_{7b,8}$=8.5$^{\#}$ Hz, $J_{6,7b}$=3.8* Hz, H-7b), 3.22 (dd, 1H, $J_{2a,2b}$=13.8 Hz, $J_{2a,3}$=7.9 Hz, H-2a), 4.22 (dd, 1H, $J_{2a,2b}$=13.8 Hz, $J_{2b,3}$=4.9 Hz, H-2b), 4.63 (dd, 1H, $J_{7b,8}$=8.5$^{\#}$ Hz, $J_{7a,8}$=3.6* Hz, H-8), 5.02 (m, 1H, H-6), 5.68 (dd, 1H, $J_{4,5}$=7.9 Hz, $J_{5,6}$=6.0 Hz, H-5), 5.85 (m, 1H, H-3), 6.00 (dd, 1H, $J_{3,4}$=9.2 Hz $J_{4,5}$=7.9 Hz, H-4), 6.28 (d, 1H, $J_{3',4'}$=3.2 Hz, H-3′), 6.32 (dd, 1H, $J_{3',4'}$=3.2 Hz, $J_{4',5'}$=1.9 Hz, H-4′), 7.24–7.50 (m, 10H, arom. H, H-5′), 7.86–8.00 (m, 6H, arom. H); δ_C (125 MHz, $CDCl_3$): 34.2 (C-7), 58.7 (C-2), 65.4 (C-8), 68.8 (C-3), 73.1 (C-4, C-5), 77.7 (C-6), 106.2 (C-3′), 110.3 (C-4′), 128.3 (3×arom. CH), 128.4 (3×arom. C), 129.6 (3×arom. C_q, 3×arom. CH), 129.7 (3×arom. CH), 133.2 (3×arom. CH), 142.3 (C-5′), 154.3 (C-2′), 165.0 (C_q), 165.1 (C_q), 165.6 (C_q); LRMS (ESI): *m/z* 554 (100%, $[M+H]^+$), 576 (50%, $[M+Na]^+$); HRMS (FAB, glycerol): Calcd for $C_{32}H_{28}NO_8$ $[M+H]^+$ *m/z* 554.18094, found *m/z* 554.18213.

Compound **7c**: IR (KBr, ν_{max}/cm^{-1}): 3433w, 3063w, 2924w, 1726s, 1601w, 1450m, 1315m, 1281s, 1271s, 1179w, 1107s, 1069m, 1026m, 710s; δ_H (500 MHz, $CDCl_3$): 2.83 (ddd, 1H, $J_{7a,7b}$=13.5 Hz, $J_{7a,8}$=11.0 Hz, $J_{6,7a}$=6.1 Hz, H-7a), 2.89 (dd, 1H, $J_{2a,2b}$=15.0 Hz, $J_{2b,3}$=4.0 Hz, H-2b), 3.14 (ddd, 1H, $J_{7a,7b}$=13.5 Hz, $J_{6,7b}$=10.0 Hz, $J_{7b,8}$=9.5 Hz, H-7b), 3.60 (dd, 1H, $J_{2a,2b}$=15.0 Hz, $J_{2a,3}$=10.9 Hz, H-2a), 4.74 (dd, 1H, $J_{7a,8}$=11.0 Hz, $J_{7b,8}$=9.5 Hz, H-8), 4.82 (dd, 1H, $J_{6,7b}$=10.0 Hz, $J_{6,7a}$=6.1 Hz, H-6), 5.51 (d, 1H, $J_{4,5}$=7.6 Hz, H-5), 5.96 (ddd, 1H, $J_{3,4}$=10.9 Hz, $J_{2a,3}$=10.9 Hz, $J_{2b,3}$=4.0 Hz, H-3), 6.21 (dd, 1H, $J_{3,4}$=10.9 Hz, $J_{4,5}$=7.6 Hz, H-4), 6.44 (dd, 1H, $J_{3',4'}$=3.2 Hz, $J_{4',5'}$=2 Hz, H-4′), 6.60 (d, 1H, $J_{3',4'}$=3.2 Hz, H-3′), 7.19–7.54 (m, 9H, arom. H, 1H, H-5′), 7.75–8.00 (m, 6H, arom. H); δ_C (125.76 MHz, $CDCl_3$): 38.1 (C-7), 54.7 (C-2), 60.9 (C-8), 68.1 (C-3), 79.2 (C-5), 74.7 (C-4), 81.8 (C-6), 110.8 (C-4′) 111.2 (C-3′), 127.6 (3×arom. CH), 127.9 (3×arom. CH), 129.0 (3×arom. CH, 3×arom. C_q), 132.5 (3×arom. CH), 132.9 (3×arom. CH), 143.6 (C-5′), 147.1 (C-2′), 164.3 (C_q), 165.1 (C_q), 165.7 (C_q); LRMS (ESI): *m/z* 554 (100%, $[M+H]^+$), 576 (43%, $[M+Na]^+$); HRMS (FAB, glycerol): Calcd for $C_{32}H_{28}NO_8$ $[M+H]^+$ *m/z* 554.18094, found *m/z* 554.18268.

Compound **7d**: IR (KBr, ν_{max}/cm^{-1}): 3067w, 2928w, 1730s, 1601w, 1450w, 1315w, 1281s, 1260s, 1179w, 1109m, 1096m, 1070m, 1026w, 710m; δ_H (500 MHz, $CDCl_3$): 2.67 (ddd, 1H, $J_{7a,7b}$=13.2 Hz, $J_{6,7a}$=8.7 Hz, $J_{7a,8}$=7.2 Hz, H-7a), 2.86 (ddd, 1H, $J_{7a,7b}$=13.2 Hz, $J_{7b,8}$=11.2 Hz, $J_{6,7b}$=6.2 Hz, H-7b), 3.02 (dd, 1H, $J_{2a,2b}$=12.5 Hz, $J_{2a,3}$=10.3 Hz, H-2a), 3.53 (dd, 1H, $J_{2a,2b}$=12.5 Hz, $J_{2b,3}$=4.0 Hz, H-2b), 4.71 (dd, 1H, $J_{7a,8}$=7.2 Hz, $J_{7b,8}$=11.2 Hz, H-8), 4.96 (ddd, 1H, $J_{6,7a}$=8.7 Hz, $J_{6,7b}$=6.2 Hz, $J_{5,6}$=5.8 Hz, H-6), 5.89 (ddd, 1H, $J_{2a,3}$=10.3 Hz, $J_{3,4}$=10.1 Hz, $J_{2b,3}$=4.0 Hz, H-3), 5.69 (dd, 1H, $J_{4,5}$=8.7 Hz, $J_{5,6}$=5.8 Hz, H-5), 5.98 (dd, 1H, $J_{3,4}$=10.1 Hz, $J_{4,5}$=8.7 Hz, H-4), 6.42 (dd, 1H, $J_{3',4'}$=3.1 Hz, $J_{4',5'}$=1.9 Hz, H-4′), 6.51 (d, 1H, $J_{3',4'}$=3.1 Hz, H-3′), 7.20–7.25 (m, 3H, arom. H), 7.39–7.41 (m, 3H, arom. H), 7.49–7.52 (m, 4H, arom. H, H-5′), 7.78–7.82 (m, 3H, arom. H), 7.97–7.99 (m, 3H, arom. H); δ_C (125 MHz, $CDCl_3$): 31.2 (C-7), 52.2 (C-2), 64.1 (C-8), 66.8 (C-3), 73.2 (C-5), 74.6 (C-4), 77.6 (C-6), 111.1 (C-3′), 110.7 (C-4′), 128.1, 128.2 (3×arom. CH), 128.5 (3×arom. C_q,) 129.6 (3×arom. CH) 129.8 (3×arom. CH), 133.0 (3×arom. CH), 133.4 (3×arom. CH), 143.4 (C-5′), 148.1 (C-2′), 165.0 (C_q), 165.4 (C_q), 165.9 (C_q); LRMS (ESI): *m/z* 554 (100%, $[M+H]^+$), 576 (56%, $[M+Na]^+$); HRMS (FAB, glycerol): Calcd for $C_{32}H_{28}NO_8$ $[M+H]^+$ *m/z* 554.18094, found *m/z* 554.18379.

NOESY data: Table 4.

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Enhanced activity of α-chymotrypsin in organic media using designed molecular staples

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Abstract—We report the enhancement of α-chymotrypsin activity in organic solvents using modified peptides bearing two crown ethers. The transesterification of *N*-acetyl-L-phenylalanine ethyl ester with 1-propanol was used as model reaction. Co-lyophilization of crown ether modified peptides with α-chymotrypsin prior to use resulted in an increase of enzyme catalytic activity in non-aqueous media. The efficiency of enzyme activation is dependent on the amino acid sequence of peptidic additives and on the positions of the amino acids bearing the crown ligand.
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1. Introduction

Enzymes are continuously gaining importance as 'green' bio catalysts in organic processes and useful tools in organic synthesis due to their exquisite enantioselectivity and chemoselectivity.[1–4] Furthermore, enzymes often simplify the synthetic protocol by reducing the overall number of steps required. Thus, enzymes are competitive and economic alternatives for small and large scale production of enantiopure pharmaceutical intermediates and other useful chiral synthons.[5]

Unfortunately, activity of enzymes decreases in non-aqueous media, in which starting materials are soluble in. To overcome such problems, considerable developments have been made in the past to understand enzyme behavior and reactivity in non-aqueous media.[6,7] Several procedures involving additives have been devised to improve efficiency of enzymes in organic media.[8–12] Among these procedures, the use of additives such as crown ether,[13] sorbitol,[14] sugars,[14] polyethylene glycol,[15] cyclodextrins,[16] and salts,[17] represents an attractive method as it is both straightforward and economical.

However, all of these additives are non-specific and their efficiency is unpredictable. Tailor-made devices specifically designed to enhanced stability, activity and solubility of many different enzymes in non-aqueous media, are therefore highly desirable. Towards that goal, Reinhoudt et al. have studied the use of crown ethers.[13] They observed an improvement of chymotrypsin activity up to 500 fold in organic media by co-lyophilization of the biocatalyst with 250 equiv of 18-crown-6. Recent studies by this group, on the mechanism of crown-ether-induced activation of enzymes in non-aqueous media revealed the possibility of a conformational stabilization in organic solvent by crown ethers.[18] On the other hand, Griebenow et al.[20,21] have demonstrated by infrared spectroscopy that no relationship could be established between secondary structure and activity in various subtilisin-crown ether preparations. The crown ether enhancing effect has also been associated with a molecular imprinting effect. Indeed, it has been proposed that the crown ether is not able to stabilize the overall active 3D structure of the enzyme, but rather helps preserve the active site structure.[19]

Towards more efficient crown systems, Shinkai et al.[22] have developed multi-crown ether compounds, 'crowned' arborols. They have tested the efficiency of these arborols to solubilize myoglobin. Their results showed that smaller 'crowned' arborols gave better results for dissolution of myoglobin in DMF. The authors proposed that the larger multiple crown systems were less efficient probably due to their lower ability to cover the myoglobin surface accurately.

On the basis of our groundwork on functional peptidic devices,[23] we sought to exploit bis-crown ether modified peptides for the structural stabilization and solubilization of enzymes in organic media.

Keywords: Peptide nanostructure; Enzyme stabilization; Crown ether; Organic solvent.
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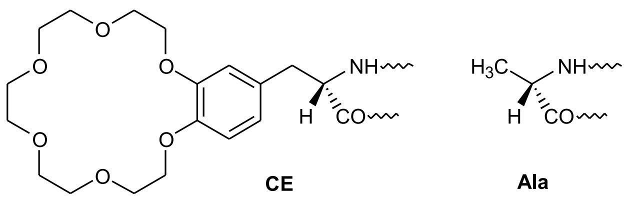
Herein, we report our results on the ability of bis-crown peptides **1**–**3** to act as ‘molecular staples’ for protein surfaces and their effect on the catalytic activity of α-chymotrypsin in an organic environment.

N-BOC-Ala-Ala-Ala-CE-Ala-CE-Ala-NH-CH_2-CH_2-CH_3 **1**

N-BOC-Ala-Ala-CE-Ala-Ala-CE-Ala-NH-CH_2-CH_2-CH_3 **2**

N-BOC-Ala-CE-Ala-Ala-Ala-CE-Ala-NH-CH_2-CH_2-CH_3 **3**

N-BOC-Ala-Phe-Ala-Ala-Ala-Phe-Ala-NH-CH_2-CH_2-CH_3 **4**



Macrocyclic ligands of the 18-crown-6 family are known to complex Na^+, K^+, and R-NH_3^+ ions. Hence, we envisioned that bis-crown peptides like **1**–**3** could potentially bind tightly at the surface of globular proteins through cooperative complexation of two adjacent charged groups from exposed Lys, Arg, Asp, and Glu residues (Fig. 1).

The hydrophobic nature of the peptidic framework and the neutralization of charged groups at the surface should enhanced solubility in low polarity solvents. Likewise, the ‘linkage’ of distant functional groups by bis-crown ether devices should also stabilize the active 3D structures of the enzyme. In other words, peptidic devices **1**–**3** could possibly acts as flexible but rigidifying ‘staples’ that allow stabilization of enzyme active conformation without significant lost of mobility. To demonstrate the proof of concept, we investigated the model reaction consisting of transesterification of *N*-Ac-L-Phe ethyl ester with *n*-propanol catalyzed by α-chymotrypsin in cyclohexane (Scheme 1). This transformation was used previously by several groups for enzyme activity studies.[13]

We have already described the synthesis, conformational

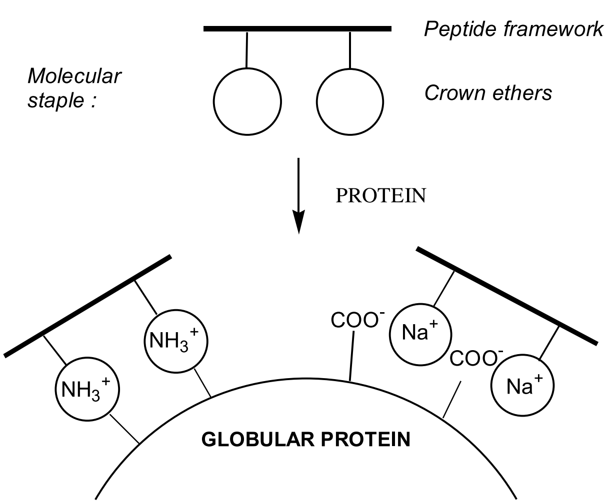
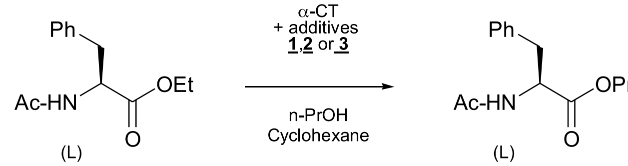


Figure 1. Proposed complexation mode of molecular staples on the surface of a globular protein.



Scheme 1. Transesterification reaction of *N*-acetyl-L-phenylalanine ethyl ester catalyzed by α-chymotrypsin used as model system in the present studies.

behavior, and ion binding ability of peptides **1**–**3**. These compounds were shown to complex Cs^+ ions selectively by forming ‘sandwich’ type complexes with one Cs^+ by the cooperative action of the two 18-crown-6 rings.[24] Furthermore, they were also shown to bind selectively and efficiently diammonium compounds.[25] The alanine based heptapeptide frameworks were chosen for their ability to adopt several different conformations, hence to facilitate the cooperative complexation of two charged groups at variable distances on the surface of α-chymotrypsin. The crown ether residue was synthesized from L-DOPA and the peptides were prepared by solid phase peptide synthesis using the oxime resin.[24]

2. Results and discussion

α-Chymotrypsin was coated with variable amount of **1**, **2** or **3** by adding the bis-crown additive to an aqueous solution (pH 7.8) of the biocatalyst, and then lyophilizing to dryness. As control, we also prepared the enzyme coated with twice as much of 18-crown-6 by the same procedure.

To affect the transesterification, coated enzymes were suspended at room temperature in cyclohexane in the presence of *N*-acetyl-L-phenylalanine ethyl ester and *n*-propanol. The rate of transesterification was followed by high performance liquid chromatography (HPLC) measuring the appearance of *N*-Ac-L-Phe-O-*n*-Pr. Initial rates (V_o) were calculated from conversion $<10\%$. In order to define the most efficient conditions, experiments with α-chymotrypsin coated with 5, 10, 25, and 50 equiv of bis-crown peptides **1**–**3**, as compared to enzyme, were performed. Results are shown in Table 1.

It has to be noted that almost no activity was observed with α-chymotrypsin alone under the reaction conditions used. For α-chymotrypsin coated with 5 equiv of each additive, an increase of enzymatic activity was observed. However, no differences could be noted between biocatalyst stabilized with bis-crown ether additives **1**, **2**, **3**, and 18-Crown-6.

When α-chymotrypsin coated with 10 equiv of peptide additives were used, the initial rate increased by 40 fold compared to α-chymotrypsin without additives, but only two-fold compared to 18-Crown-6. The conversion of the substrate after 30 min is more than 30% for the systems with peptide **1** and with 18-Crown-6, and 15% for both **2** and **3** (Table 1). Interestingly, in this case α-chymotrypsin coated with bis-crown peptide **1** is a little more active then α-chymotrypsin coated with peptide **2** and **3** and 18-Crown-6. This difference could be due to the better enzyme surface

Table 1. Effect of peptides **1–3** on the activity of α-chymotrypsin in the transesterification of *N*-acetyl-L-phenylalanine ethyl ester in cyclohexane/1 M 1-PrOH[a]

Additive	Mole additive / (mole α-chymotrypsin)	V_o (+additive) (10^{-5} M min^{-1})	V_o (+additive) / V_o	Conversion (%) 30 min	Conversion (%) 2 h
None	0	12	1	<5	<10
Peptide **1**	5	125	10	<10	20–25
Peptide **2**	5	95	7	<10	15–20
Peptide **3**	5	90	7	<10	15–20
18-Crown-6	10	65	5	<10	15–20
Peptide **1**	10	515	41	30–35	60–70
Peptide **2**	10	420	33	15–20	35–40
Peptide **3**	10	200	16	15–20	20–25
18-Crown-6	20	285	23	25–30	55–60
Peptide **1**	25	2600	208	80	>95
Peptide **2**	25	755	60	30–35	60
Peptide **3**	25	450	36	20–25	40–50
18-Crown-6	50	420	34	40	60–70
18-Crown-6	50	3.3[b]	41[b]		
Peptide **1**	50	3175	254	70–80	> 95
Peptide **2**	50	3695	295	70–80	>95
Peptide **3**	50	1255	100	60–70	70–80
18-Crown-6	100	10	<1	<5	<5

[a] Conditions: 2.5 mM substrate, 1 mg mL^{-1} enzyme powder (not corrected for buffer salts weight), 22 °C.
[b] Results obtained by Reinhoudt and co-workers under the same conditions.[13]

complexation of bis-crown peptide **1** that has the two crown ether residues separated by only one alanine.

The most pronounced effect was observed with 25 equiv of **1** (Table 1). In only 30 min, the conversion of the substrate reached 80% and completion after 1 h with α-chymotrypsin coated with this additive compared to 40% and even less when using 18-Crown-6, peptides **2** or **3**. An improvement of chymotrypsin activity up to 200 fold is observed with peptide **1**, compared to 30 fold for 18-Crown-6. So, the peptide chain allows a six-fold increase of enzyme activity.

Although, not optimized crown peptide additives compared favorably then with commonly used additives (Table 2). These new additives could eventually be used with other enzyme or mixed with other additives like KCl to increase enzyme activation.

Using α-chymotrypsin coated with 50 equiv of peptide **1** lead to a modest improvement of rate compared to reaction with 25 equiv of **1**. Improvement was more important with 50 equiv of peptide **2** and **3** but without a good reproducibility. This is probably due to difficulties of additive dissolution in phosphate buffer with a larger amount of peptide **2** or **3**. Indeed in all other cases, experiments were highly reproducible in duplicate runs. When 100 equiv of 18-Crown-6 were colyophilized with α-chymotrypsin, the rate enhancement of the biocatalyst thus obtained, decreased dramatically. This behavior has also been reported when using more then 250 equiv of 18-Crown-6 with α-chymotrypsin.[18] The important lost of activity is probably due to enzyme denaturation during co-lyophilization.

In order to make this procedure more convenient for synthetic chemists, reactions were performed using conventional glassware and magnetic stirring comparatively to mechanical stirring frequently used with biocatalytic processes. Interestingly, no significant changes were observed in the results between reactions carried out with magnetic or mechanical stirring for reaction times of 2 h or less. However, for reactions requiring longer period of time (>2 h) to attain a reasonable conversion level, it is preferable to use mechanical stirring. Along the same lines, it is important to note that very high conversion of the substrate can be achieved with only 10 equiv of peptidic additive **1** after 24 h (>95% with magnetic stirring and >99% with mechanical stirring).

These results show the efficiency of crown ether peptide to enhance the α-chymotrypsin activity in cyclohexane. However, more work is required to understand the mechanism of enzyme activation by peptide **1–3**. CD and IR studies could not be investigated due to the chiral nature of additives **1–3**. Hence, it is not possible to study their effect on structural stability of chymotrypsin as their own

Table 2. Rate enhancement α-chymotrypsin colyophilized with different additives

Entry	Additives	Enhancement	Reference
1	Crown peptide **1** (25 equiv)	208	
2	18-C-6 (50 equiv)	41	13
3	KCl 94% w/w[a]	51	17
4	Various cyclodextrins[b]	2–40	16
5	Substrate analog[c]	264	14
6	Sorbitol[c]	19	14

[a] For transesterification reaction of *N*-Ac-L-Phe-OEt in anhydrous hexane.
[b] For transesterification reaction of *N*-Ac-L-Tyr-OMe in various organic solvent/water (97:3).
[c] For transesterification reaction of *N*-Ac-L-Phe-OEtCl in anhydrous carbon tetrachloride.

spectrum interferes with the one of the enzyme. The different enhancing ability between **1–3** demonstrates that the peptidic framework plays a functional role in the stabilization of the enzyme structure. Therefore, it is fair to say that bis-crown peptides with other amino acid sequences could be engineered to stabilize numerous enzymes of industrial and synthetic interest.

To evaluate the influence of bis-crown peptide **1** on the enantioselectivity of α-chymotrypsin, the transesterification reaction was studied with *N*-Ac-D-Phe-OEt and *N*-Ac-D,L-Phe-OEt as substrates using α-chymotrypsin coated with 10 equiv of **1** as catalyst. After 2 h, almost no conversion was observed for the experiment with the D substrate, whereas around 40% conversion was measured when using the racemic substrate. With the latter reaction, we have determined the enantiomeric excess of product and remaining substrate (ee_p and ee_s) to calculate the enantiomeric ratio (E) of the bis-crown peptide enzyme system.[26] An E value >200 was obtained; no D-enantiomer could be detected by chiral HPLC even after four days. These results clearly demonstrate that the enantioselectivity of the enzyme is not altered significantly by the presence of crown peptide.

The activity of α-chymotrypsin stabilized with 25 equiv of bis-crown peptide **1** was also studied at different temperature in cyclohexane (Table 3). In comparison with room temperature (22 °C), the activity decreased slightly at 30 °C and significantly at 40 and 50 °C. Therefore, for practical purpose the actual synthetic procedure should be carried out at room temperature.

Table 3. Effect of increasing temperature on catalytic activity of α-chymotrypsin coated with 25 equiv of bis-crown device **1** in the transesterification of *N*-acetyl-L-phenylalanine ethyl ester in cyclohexane/1 M 1-PrOH[a]

T (°C)	V_o (+additive) (10^{-5}M min^{-1})	Conversion (%) 30 min	Conversion (%) 2 h
22	2600	80	>95
30	2210	50	65
40	770	25	30–35
50	45	<10	10–15

[a] Conditions: 2.5 mM substrate, 1 mg mL^{-1} enzyme powder.

Because peptides **1–3** incorporate derivatives of phenylalanine, their stability to degradation in presence of α-chymotrypsin was verified. Studies were done in phosphate buffer with bis-crown peptide **3** and compared to its phenylalanine analog **4** that gives no enhancement of catalytic activity in cyclohexane. HPLC analysis demonstrated a rapid degradation of peptide **4**, but complete stability of peptide **3** towards hydrolytic degradation by α-chymotrypsin. The crown ether ring attached to the phenyl group therefore prohibits the accessibility to the active site of α-chymotrypsin, leading to enzymatic degradation stability.

3. Conclusions

We have reported the use of peptides bearing two crown ethers as tailor-made additives for the stabilization of the structure and for increasing activity of α-chymotrypsin in organic solvents. Co-lyophilization of α-chymotrypsin with different amount of **1–3** lead to coated biocatalysts with enhanced activity that catalyzes efficiently a model transesterification reaction. The best results were obtained with α-chymotrypsin coated with 25 equiv of bis-crown peptide **1** in cyclohexane with complete conversion of the substrate after less than an hour, a tremendous improvement over the control reaction using uncoated α-chymotrypsin. Important differences of efficiency between additives **1–3** point out the functional role of the peptidic framework to allow the two binding groups (crown ether) to cooperatively complex and bridge charged groups at the biocatalyst surface. Therefore, it is possible to envision that this stabilization strategy could be applied to numerous enzymes of interest and that efficiency of peptidic devices could be improved rapidly by parallel solid phase synthesis. Although, ‘tailor-made’ nanoscale additives are presently more expensives then polyethylene glycol, their potential applicability to a wide variety of enzymes not responding to actual additives make them attractive and a valuable alternative. Improvement of **1–3** through parallel synthesis and their use with other biocatalysts are currently underway in our laboratories.

4. Experimental

Synthesis, purification, and characterization of bis-crown ether peptides **1–3** was done according to the reported procedures.[23] α-Chymotrypsin (E.C. 3.4.21.1), type II, from bovine pancreas and 18-Crown-6 were obtained from Aldrich (Milwaukee, WI, USA) and used without further purification. Distilled cyclohexane over molecular sieves was used. *n*-Propanol was purified by a benzene azeotropic distillation.

4.1. Coating of α-chymotrypsin

α-Chymotrypsin (10 mg, 4E-4 mmol) and the appropriate amount of bis-crown ether peptides or 18-Crown-6 were dissolved in 50 mM sodium phosphate buffer, pH 7.8 (2 mL). The solution was shaken manually (for the solution with 50 equiv of bis-crown ether peptide, a short sonication gave a better dissolution but it was still incomplete). The samples were lyophilized to a white powder after freezing in liquid nitrogen.

4.2. Catalytic activity

Reactions were performed on a 1.5 mL scale with magnetic stirring. In every reaction, 1.5 mg of α-chymotrypsin, free or coated, was used (quantities were adjusted to always have 1.5 mg of α-chymotrypsin content. For example, 3.5 mg of the solid obtained from co-lyophilization of 25 equiv of peptide **1** and α-chymotrypsin were used). The biocatalyst was added to a cyclohexane solution containing *N*-Ac-L-Phe-OEt (2.5 mM) and 1-propanol (1 M) at 22 °C. The transesterification reaction was immediately followed by high-performance liquid chromatography (HPLC) monitoring the appearance of the reaction product ($t_{ret}=5.2$ min). HPLC analyses were performed on an Agilent 1050 HPLC system using an analytical C_{18} reverse phase column (Vydac, Hesperia, CA, USA). Column was eluted isocratic at a flow rate of 1 mL/min with 45% acetonitrile in water (with 0.1% TFA). 10 μL of reaction mixtures were injected at regular intervals.

Chiral HPLC was performed with a Hypersil Phenylglycine column (250×4.6 mm, 5 μm) using hexane with 1% ethanol as eluent (1.5 mL min^{-1}).

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Synthesis of spirane-bridged rigidified oxalkyl cyclopentadienyl ligands

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Abstract—Methods for the preparation of constrained spirane-bridged oxalkyl indenyl ligands are described. The *cis*,*cis*-α,α′-spirane derivatives were synthesised in several steps from spiro[4.4]nonane-1,6-dione. Carbylation was achieved by Wittig methenylation. A subsequent stereoselective hydroboration by 9-BBN followed by peroxide treatment furnished the corresponding *cis*-methanol. Further manipulations provided the *cis*-carboxylic ester, which in a double Grignard reaction with α,α′-dichloro-*o*-xylene, furnished the corresponding indenyl derivative. The final products were *cis*,*cis*-α-(2-indenyl)-α′-(methoxy or methoxymethyl)spiro[4.4]nonanes.
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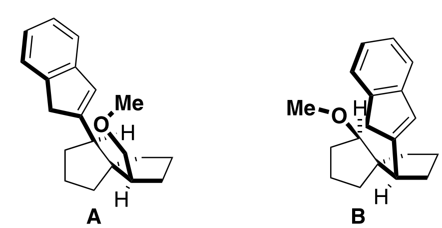
1. Introduction

Ligands for *ansa*-semimetallocenes may have a coordinating heteroatom in a side-chain tethered to a cyclopentadienyl unit. The heteroatom may be an oxygen in the form of an ether or a carbonyl group,[1,2] or a nitrogen in the form of an amino group.[3] We herein describe some oxa derivatives. The heteroatom in the bidentate ligand influences the electronic and steric properties of the metal center by intramolecular coordination. The reversible blocking of a vacant metal site in this manner will stabilise a highly reactive center in catalytic reactions with an increase in lifetime of the catalyst system. Preparation of chiral catalyst systems, however, is hampered by the fluctuation of the cyclopentadienyl unit, which makes it difficult to obtain the rigid chiral environment required for asymmetric transformations.[4] This report describes construction of some rigidified bidentate spirane-bridged ligands with an ether oxygen in the side-chain. The commonly used ethylene spacer between the cyclopentadienyl and the alkoxy units in *ansa* semimetallocenes has been replaced in the spiranes by a three- or four-atom bridge, but the spacing of the α,α′-functional groups in the rigid spirane scaffold is appropriate for metal coordination. Small ring spiranes are rigid structures with the two rings fixed in an orthogonal relationship through the common spiro atom. Substituents are rigidly fixed in corresponding configurational relationships. We describe synthesis of derivatives of the spiro[4.4]nonane system as an extension of earlier studies of spirane systems.[5–7] The target molecules have the cyclopentadienyl unit embedded in the indenyl system as shown for the *cis*,*cis*-disubstituted spiranes **A** and **B** in Scheme 1.



Scheme 1.

2. Results and discussion

The target compounds were to have a 2-indenyl and an ether function in the adjacent α,α′-positions in the spirane scaffold, structures **A** and **B** in Scheme 1. The indenyl function was to be introduced by a double Grignard reaction of the intermediate carboxylic ester derivatives **6** and **14** which were prepared as shown in Schemes 2 and 3. The spirane substrate **1** in Scheme 2 was available from spiro[4.4]nonane-1,6-dione essentially as described.[8] The silyl group at the secondary alcohol function in the substrate was removed with TBAF in THF. The alcohol **2** was subsequently *O*-methylated by MeI with NaH as base. Stereochemical control in the preparation of the *cis*-alcohol **4** was achieved by hydroboration with the bulky 9-BBN reagent. Adduct formation occurs at the less shielded face

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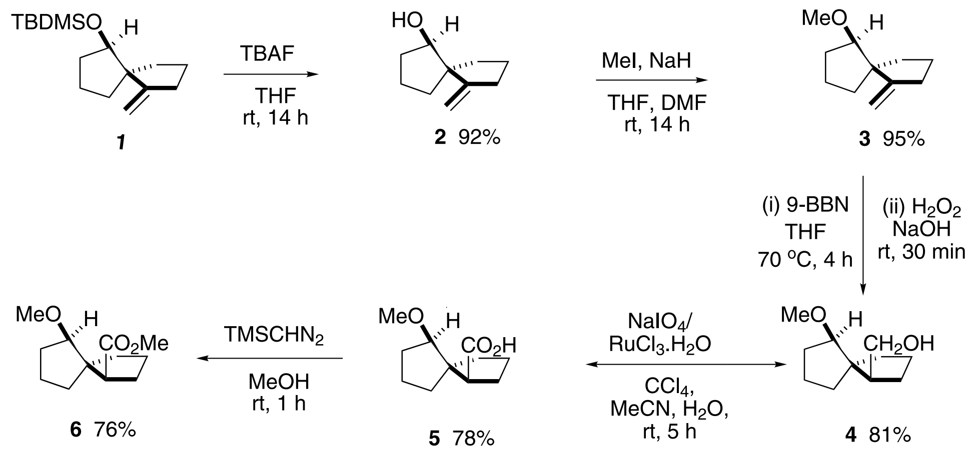
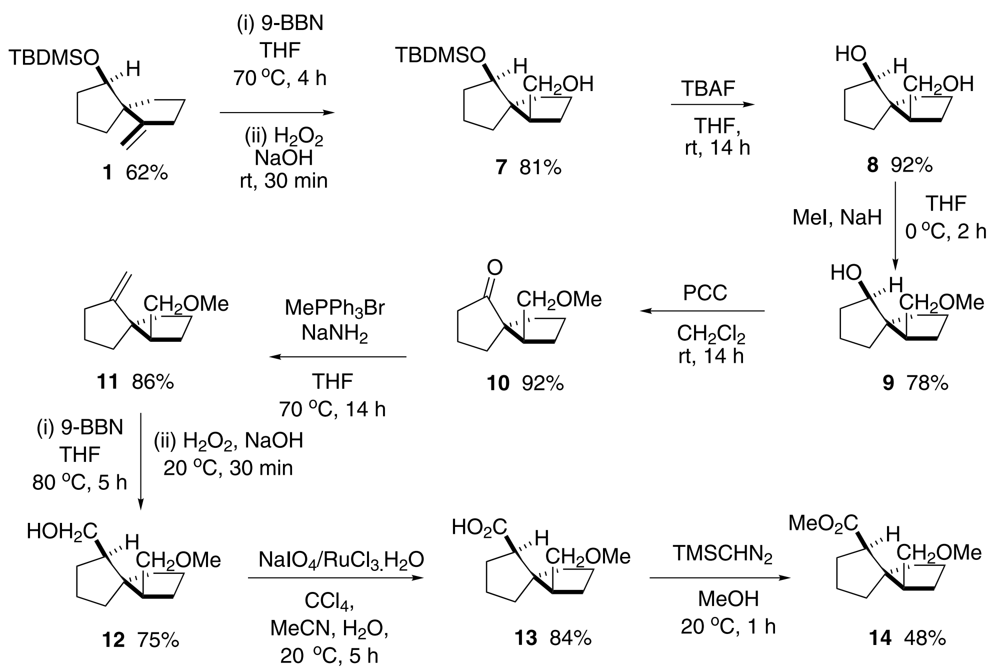


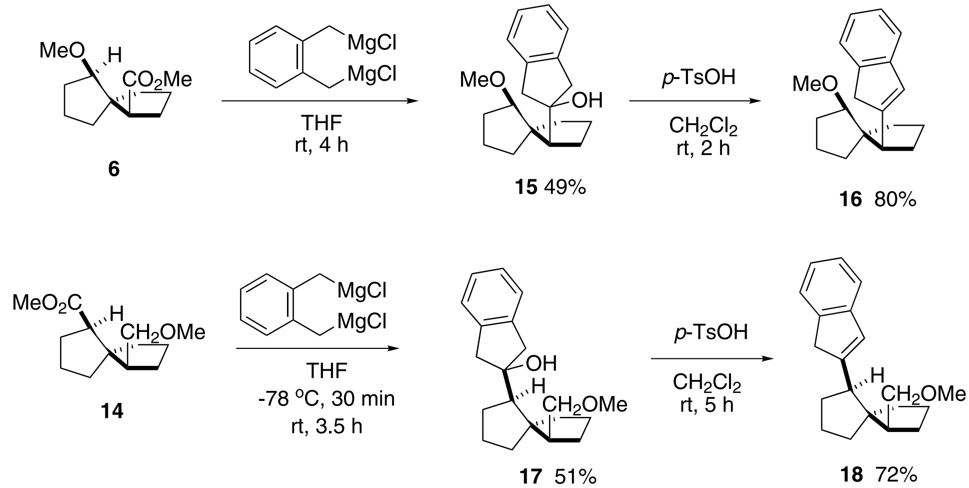
Scheme 2.



Scheme 3.

which forces the methylene side-chain carbon into a spirane *cis*-configuration despite the higher steric repulsion. Hydrogen peroxide treatment subsequently provided the alcohol **4** with the *cis*-configuration which is a requirement for coordination to a metal in a semi-metallocene arrangement. Only the *cis*,*cis*-isomer spirane **4** was detected and was isolated in 81% yield. A subsequent oxidation with sodium periodate–ruthenium trichloride gave the corresponding carboxylic acid **5** in good yield. The acid was converted into its methyl ester **6** with the silyl modified diazomethane reagent $TMSCHN_2$.

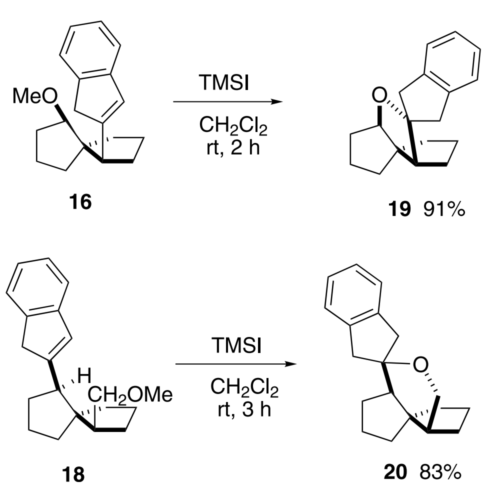
Synthesis of the second carboxylate substrate **14** for indenylation is shown in Scheme 3. The methylene substrate **1** was regio- and stereoselectively hydroborated by the bulky 9-BBN reagent, and hydroxylated by alkaline hydrogen peroxide to provide the *cis*-methanol **7**. Attempts to *O*-methylate the free hydroxyl group in the methanol **7** by a reaction with methyl iodide in the presence of a base resulted in extensive silyl group migration from the secondary alcohol to the primary alcohol group for steric reasons. The migration presumably proceeds by iodide effected desilylation followed by resilylation at the primary alcohol function under the applied reaction conditions. Removal of the silyl group protection by treatment with TBAF provided the diol **8** with a primary and a secondary alcohol function. Differentiation between these hydroxyl functions for preparation of the desired *O*-methylation was successful. In our best conditions for selective methylation of the primary alcohol function, methyl iodide together with sodium hydride in cold THF provided chemoselectively the desired methyl ether **9** in 78% yield. A subsequent PCC oxidation of the remaining hydroxyl function yielded the ketone **10** in 92% yield. A Wittig reaction was used to convert the ketone to the methylene derivative **11**. A commercially available dry mixture of methyl(triphenyl)-phosphonium bromide–sodamide in THF was used for the methenylation, yield 86%. For the hydroxylation, 9-BBN



Scheme 4.

was used to effect stereocontrolled hydroboration. A subsequent reaction with alkaline hydrogen peroxide furnished the *cis*-methanol **12**. Oxidation of the alcohol with the $NaIO_4$–$RuCl_3 \cdot H_2O$ reagent provided the carboxylic acid **13** in high yield. The latter was converted into its methyl ester **14** by treatment with the silyl modified diazomethane reagent TMS–diazomethane.

The preparation of the targeted half-sandwich ligands **16** and **18** is shown in Scheme 4. The cyclopentadiene unit in these structures is part of the indene ring system. The key reaction for construction of the indene ring was a double Grignard reaction with the bismagnesium derivative from α,α′-dichloro-*o*-xylene. In the preparation of the bis(Grignard) reagent from α,α′-dichloro-*o*-xylene and magnesium, the recommended powdered magnesium (50 mesh) was used.[9] The cyclic alcohol **15** was isolated in 49% yield. A subsequent treatment with *p*-toluenesulfonic acid led to water elimination and isolation of the 2-indenyl derivative **16** in 80% yield. In a similar series of reactions, the spirane ester **14** and the bis(Grignard) reagent provided the cyclised alcohol **17** in 51% yield. Water elimination effected by *p*-toluenesulfonic acid catalysis furnished the indenyl target **18** in 72% yield. The products **16** and **18** have the same *cis*,*cis*-configuration as was established in the formation of their precursors **4**, **7** and **12**. The assigned relative configuration is also in accord with the transformations shown in Scheme 5. The methyl ether **16** in its reaction with trimethylsilyl iodide suffered demethylation and a subsequent addition of the hydroxy function to the indenyl double bond. The product was the five-membered bridged spirane **19** in high yield, 91%. Assignment of the structure was supported by NMR data. In a similar manner the methyl ether **18** provided the six-membered bridged spirane **20** in 83% yield.



Scheme 5.

3. Conclusion

This report describes the preparation of *cis*,*cis*-α,α′-substituted and constrained spirane-bridged oxalkyl–indenyl ligands in several steps from spiro[4.4]nonane-1,6-dione. Carbylation was achieved by Wittig methenylation. A subsequent stereoselective hydroboration by 9-BBN followed by peroxide treatment furnished the corresponding *cis*-methanol which was transformed into the *cis*-carboxylic ester. A double Grignard reaction between the ester and α,α′-dichloro-*o*-xylene, furnished the corresponding indenyl derivative. The final products were *cis*,*cis*-α-(2-indenyl)-α′-(methoxy or methoxymethyl)-spiro[4.4]nonanes.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded in $CDCl_3$ at 300 or 200 MHz with a Bruker DPX 300 or DPX 200 spectrometer. The ^{13}C NMR spectra were recorded in $CDCl_3$ at 75 or 50 MHz. Chemical shifts are reported in ppm using residual $CHCl_3$ (7.24 ppm) and $CDCl_3$ (77 ppm) as references. *J*-Values are given in Hz. Mass spectra under electron-impact conditions (EI) were recorded at 70 eV ionising potential; methane was used for chemical ionisation (CI). The spectra are presented as *m*/*z* (% rel. int.). IR spectra were recorded on a Nicolet Magna 550 spectrometer using liquid film or ATR (attenuated total reflectance).

Dry THF was distilled from sodium and benzophenone under argon. Dry dichloromethane and NMP were distilled from calcium hydride. Dry DMF was distilled from BaO.

4.1.1. *cis*-Spiro[4.4]nonane-6-methylen-1-ol (2). A solution of *cis*-1-*tert*-butyldimethylsilyloxyspiro[4.4]-nonane-6-methylene (**1**)[8] (1.00 g, 3.76 mmol) and TBAF (1 M in THF, 7.52 mL, 7.52 mmol) in dry THF (20 mL) under argon was stirred at room temperature overnight. Water was added and the pH adjusted to 4.5 with acetic acid before the solution was extracted with EtOAc, washed with water and brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc 5:1; yield 526 mg (92%) of a colourless oil. HRMS: M 152.1209. Calcd for $C_{10}H_{16}O$: 152.1201. IR (film) ν cm^{-1} 3393 (br), 2955, 2926, 2872, 2856; ^1H NMR ($CDCl_3$): δ 1.4–2.4 (12H, m, CH_2), 3.51 (1H, d, $J=4.7$ Hz, CH), 4.89 (1H, s, C*H*H), 5.10 (1H, s, C*H*H); ^{13}C NMR ($CDCl_3$): δ 21.4 (CH_2), 22.7 (CH_2), 32.5 (CH_2), 34.0 (CH_2), 35.6 (CH_2), 38.8 (CH_2), 58.9 (C), 76.7 (CH), 107.4 (CH), 155.6 (C); MS (EI): 152 (M, 1%), 134 (41), 119 (30), 108 (86), 95 (47), 93 (60), 81 (42), 79 (47).

4.1.2. *cis*-1-Methoxyspiro[4.4]nonane-6-methylene (3). NaH (50% in oil, 316 mg, 6.58 mmol) was added to a solution of *cis*-spiro[4.4]nonane-6-methylen-1-ol (**2**) (500 mg, 3.29 mmol) in dry THF (30 mL) and dry DMF (10 mL) at 0 °C under argon. The solution was stirred at 0 °C for 2 h before MeI (1.401 g, 9.87 mmol) was added. The reaction mixture was stirred overnight at room temperature and evaporated. Diethyl ether was added and the solution was washed with water (4×) and brine, dried ($MgSO_4$) and the filtrate evaporated. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc 10:1; yield: 519 mg (95%) of a colourless oil. HRMS: M 166.2635. Calcd for $C_{11}H_{18}O$: 166.2633. IR (film) ν cm^{-1} 3079, 2953, 2873, 2819, 1118; ^1H NMR ($CDCl_3$): δ 1.43–1.87 (10H, m, CH_2), 2.34–2.38 (2H, m, CH_2), 3.20 (3H, s, OCH_3), 4.89 (1H, br s, C*H*H=), 4.95 (1H, br s, C*H*H=); ^{13}C NMR ($CDCl_3$): δ 20.8 (CH_2), 22.6 (CH_2), 30.3 (CH_2), 34.3 (CH_2), 36.9 (CH_2), 39.7 (CH_2), 56.7 (C), 57.4 (CH_3), 88.8 (CH), 106.8 (CH_2), 154.4 (C); MS (EI): *m*/*z* (%) 166 (M, 4%), 134 (100), 119 (60), 106 (36), 93 (30), 91 (48), 79 (43), 71 (67).

4.1.3. *cis*,*cis*-6-Methoxyspiro[4.4]nonane-1-methanol (4). 9-BBN (0.5 M in hexane) (7.23 mL, 3.61 mmol) was added with a syringe to a solution of *cis*-1-methoxyspiro[4.4]-nonane-6-methylene (**3**) (300 mg, 1.81 mmol) in dry THF (10 mL) under argon. The solution was stirred at 80 °C for 5 h and cooled to 0 °C. NaOH (4 mL, 2 M) and H_2O_2 (4 mL, 35%) were added, and the solution was stirred at room temperature for 30 min. Ethyl acetate was added, the solution washed with brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc 3:1; yield: 283 mg (85%) of a colourless oil. IR (film) ν cm^{-1} 3412 (br), 2954, 2874, 2820, 1110; ^1H NMR ($CDCl_3$): δ 1.2–2.1 (13H, m, CH_2 and CH), 3.24 (3H, s, OCH_3), 3.31–3.40 (1H, m, C*H*H), 3.50 (1H, br s, CHO), 3.57–3.67 (1H, m, C*H*H); ^{13}C NMR ($CDCl_3$): δ 20.0 (CH_2), 22.1 (CH_2), 28.1 (CH_2), 29.5 (CH_2), 36.0 (CH_2), 36.5 (CH_2), 48.7 (CH), 55.3 (OCH_3), 57.5 (C), 65.1 (CH_2O), 87.8 (CHO); MS (CI-CH_4): *m*/*z* (%) 185 (M+H, 2%), 165 (5), 151 (6), 136 (12), 135 (100), 134 (8), 133 (11), 121 (6).

4.1.4. *cis*,*cis*-6-Methoxyspiro[4.4]nonane-1-carboxylic acid (5). $RuCl_3\cdot H_2O$ (9 mg, 0.04 mmol) was added to a solution of *cis*,*cis*-6-methoxyspiro[4.4]nonane-1-methanol (**4**) (150 mg, 0.82 mmol) and $NaIO_4$ (567 mg, 2.65 mmol) in CCl_4 (1.5 mL), MeCN (1.5 mL) and H_2O (2.5 mL) at room temperature. The reaction mixture was stirred for 5 h at room temperature and CH_2Cl_2 added. The water layer was extracted with CH_2Cl_2 (3×). The combined organic solutions were dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using EtOAc; yield 125 mg (78%) of a colourless oil. HRMS: M 198.1256. Calcd for $C_{11}H_{18}O_3$: 198.1250; IR (film) ν cm^{-1} 3500–2500 (br), 2959, 2873, 1732, 1698; ^1H NMR ($CDCl_3$): δ 1.3–2.3 (13H, m, CH_2 and CH), 3.12 (3H, s, CH_3), 3.49 (1H, br s, CH), 10.6 (1H, br s, CO_2H); ^{13}C NMR ($CDCl_3$): δ 21.3 (CH_2), 24.1 (CH_2), 28.8 (CH_2), 30.4 (CH_2), 36.6 (CH_2), 37.4 (CH_2), 50.8 (CH), 55.8 (CH_3), 59.2 (C), 87.9 (CH), 181.2 (CO); MS (EI): *m*/*z* (%) 198 (M, 35%), 180 (23), 166 (32), 121 (57), 120 (64), 111 (65), 93 (36), 71 (100).

4.1.5. Methyl *cis*,*cis*-6-methoxyspiro[4.4]nonane-1-carboxylate (6). $TMSCHN_2$ (2 M in hexane, 0.6 mL, 1.2 mmol) was added to a solution of *cis*,*cis*-6-methoxy-spiro[4.4]nonane-1-carboxylic acid (**5**) (120 mg, 0.61 mmol) in hexane (3.5 mL) and MeOH (1 mL) at room temperature. The solution was stirred at room temperature for 1 h and evaporated. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc 8:1; yield 97 mg (76%) of a colourless oil. HRMS: M 212.1412. Calcd for $C_{12}H_{20}O_3$: 212.1419. IR (film) ν cm^{-1} 2956, 2873, 2819, 1732, 1154; ^1H NMR ($CDCl_3$): δ 1.2–2.0 (12H, m, CH_2), 2.62 (1H, dd, $J=5.0$, 7.9 Hz, CH), 3.10 (3H, s, CH_3), 3.42 (1H, br s, CH), 3.61 (3H, s, CH_3); ^{13}C NMR ($CDCl_3$): δ 21.3 (CH_2), 24.4 (CH_2), 28.7 (CH_2), 30.8 (CH_2), 37.1 (CH_2), 37.5 (CH_2), 50.3 (CH), 51.3 (CH_3), 56.1 (CH_3), 59.2 (C), 87.8 (CH), 176.1 (CO); MS (EI): *m*/*z* (%) 212 (M, 45%), 180 (37), 152 (25), 151 (13), 121 (100), 120 (83), 111 (81), 93 (37).

4.1.6. *cis*,*cis*-6-*tert*-Butyldimethylsilyloxyspiro[4.4]-nonane-1-methanol (7). 9-BBN (0.5 M in hexane) (13 mL, 6.54 mmol) was added with a syringe to a solution of *cis*-1-*tert*-butyldimethylsilyloxyspiro[4.4]nonane-6-methylene[9] (**1**) (870 mg, 3.27 mmol) in dry THF (50 mL) under argon. The solution was stirred at 70 °C for 4 h and cooled to 0 °C. NaOH (6 mL, 2 M) and H_2O_2 (6 mL, 35%) were added. The resultant solution was stirred at room temperature for 30 min. Ethyl acetate was added and the solution was washed with brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc 3:1; yield: 750 mg (81%) of a colourless oil. HRMS: M 227.1477. Calcd for $C_{12}H_{23}O_2Si$ (M−*t*Bu): 227.1467. IR (film) ν cm^{-1} 3381 (br), 2954, 2930, 2860, 1251; ^1H NMR ($CDCl_3$): δ 0.10 (3H, s, CH_{-3}), 0.11 (3H, s, CH_3), 0.90 (9H, s, CH_3), 1.2–2.0 (13H, m, CH_2 and CH), 3.33–3.44 (1H, m, C*H*H), 3.60–3.72 (1H, m, C*H*H), 3.97 (1H, t, $J=6.3$ Hz, CH); ^{13}C NMR ($CDCl_3$): δ −4.0 (CH_3), −3.4 (CH_3), 18.7 (C), 19.1 (CH_2), 22.1 (CH_2), 26.4 (CH_3), 28.5 (CH_2), 32.8

(CH_2), 35.1 (CH_2), 36.8 (CH_2), 47.8 (CH), 56.4 (C), 64.7 (CH_2), 79.0 (CH); MS (CI-CH_4) *m/z* (%): 285 (M + H, 7%), 153 (6), 151 (5), 136 (12), 135 (100), 133 (6), 93 (3), 75 (7).

4.1.7. *cis,cis*-6-Hydroxyspiro[4.4]nonane-1-methanol (8). A solution of *cis,cis*-6-*tert*-butyldimethylsilyloxyspiro[4.4]-nonane-1-methanol (**7**) (186 mg, 0.65 mmol) and TBAF (1 M in THF, 1.3 mL, 1.3 mmol) in dry THF (10 mL) under argon was stirred overnight at room temperature. Water was added to the solution and the pH adjusted to 4.5 with acetic acid. The solution was extracted with EtOAc, washed with water and brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc 1:4; yield 102 mg (92%) of a colourless oil. (Found C, 70.29; H, 10.37. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66%). HRMS: M 170.1302. Calcd for $C_{10}H_{18}O_2$: 170.1307; IR (film) ν cm^{-1} 3285 (br), 2953, 2874, 1443, 1049; ^{1}H NMR ($CDCl_3$): δ 1.2–2.1 (13H, m, CH_2 and CH), 3.46 (1H, dd, J = 3.2, 10.6 Hz, C*H*H), 3.66 (1 H, t, J = 10.6 Hz, C*H*H), 4.00 (1H, t, J = 3.5 Hz, CH), 4.5 (2 H, br s, OH); ^{13}C NMR ($CDCl_3$): δ 20.5 (CH_2), 22.0 (CH_2), 29.1 (CH_2), 33.3 (CH_2), 33.8 (CH_2), 35.6 (CH_2), 48.2 (CH), 59.1 (C), 65.4 (CH_2), 78.3 (CH); MS (EI) *m/z* (%): 170 (M, 1%), 134 (52), 122 (43), 108 (100), 95 (49), 93 (67), 81 (58), 79 (66).

4.1.8. *cis,cis*-6-Methoxymethylspiro[4.4]nonane-1-ol (9). NaH (60% in oil, 55 mg, 1.37 mmol) was added to a solution of *cis,cis*-6-hydroxyspiro[4.4]nonane-1-methanol (**8**) (233 mg, 1.37 mmol) in dry THF (10 mL) under argon at 0 °C. The suspension was stirred at 0 °C for 2 h before MeI (234 mg, 1.64 mmol) was added. The solution was stirred at 0 °C for 2 h, evaporated and the crude product was purified by flash chromatography on silica gel using hexane/EtOAc 5:1; yield 197 mg (78%) of a colourless oil. IR (film) ν cm^{-1} 3486 (br), 2954, 2876, 1117, 1099; ^{1}H NMR ($CDCl_3$): δ 1.2–2.0 (13H, m, CH_2 and CH), 3.15–3.38 (2H, m, CH_2), 3.30 (3H, s, CH_3), 3.80 (1H, br s, CHO), 4.15 (1H, s, OH); ^{13}C NMR ($CDCl_3$): δ 19.8 (CH_2), 21.1 (CH_2), 28.3 (CH_2), 32.1 (CH_2), 32.3 (CH_2), 34.7 (CH_2), 45.5 (CH), 58.7 (CH_3), 59.3 (C), 76.1 (CH_2), 78.0 (CH); MS (EI): *m/z* (%) 184 (M, 3%), 152 (30), 134 (100), 119 (26), 108 (95), 93 (58), 81 (62), 79 (69).

4.1.9. *cis*-6-Methoxymethylspiro[4.4]nonan-1-one (10). *cis,cis*-6-Methoxymethylspiro[4.4]nonane-1-ol (**9**) (197 mg, 1.07 mmol) and PCC (462 mg, 2.14 mmol) were stirred in dry CH_2Cl_2 (10 mL) under argon at room temperature overnight. A small amount of silica gel was added to the solution and the mixture was evaporated to dryness. The residue was added on top of a silica gel column and the product isolated after flash chromatography using hexane/EtOAc 10:1; yield: 180 mg (92%) of a colourless oil. HRMS: M 182.1313. Calcd for $C_{11}H_{18}O_2$: 182.1307; IR (film) ν cm^{-1} 2951, 2869, 1731, 1450, 1098; ^{1}H NMR ($CDCl_3$): δ 1.2–2.3 (13H, m, CH_2 and CH), 3.05–3.26 (2H, m, CH_2O), 3.12 (3H, s, CH_3O); ^{13}C NMR ($CDCl_3$): δ 20.3 (CH_2), 25.7 (CH_2), 30.3 (CH_2), 38.0 (CH_2), 39.4 (CH_2), 40.5 (CH_2), 50.3 (CH), 56.9 (C), 58.3 (CH_3), 73.5 (CH_2), 220.8 (CO); MS (EI): *m/z* (%) 182 (M, 8%), 150 (71), 122 (34), 121 (29), 94 (45), 93 (42), 84 (46), 45 (100).

4.1.10. *cis*-1-Methoxymethylspiro[4.4]nonane-6-methylene (11). A dry mixture of methyltriphenylphosphonium bromide and sodamide (2.25 g, 5.49 mmol) was dissolved in dry THF (10 mL) under argon and the medium stirred at room temperature for 15 min before *cis*-6-methoxymethyl-spiro[4.4]nonan-1-one (**10**) (500 mg, 2.75 mmol) in dry THF (10 mL) was added with a syringe. The solution was stirred at 70 °C overnight. A small amount of silica gel was added to the solution and the mixture evaporated to dryness. The residue was added on top of a silica gel column and the product isolated after flash chromatography using hexane/EtOAc 10:1; yield: 425 mg (86%) of a colourless oil. (Found: C, 80.11; H, 11.05. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18%). HRMS: M 180.1517. Calcd for $C_{12}H_{20}O$: 180.1514. IR (film) ν cm^{-1} 3071, 2950, 2871, 1646, 1101; ^{1}H NMR ($CDCl_3$): δ 1.5–1.9 (11H, m, CH_2 and CH), 2.32–2.34 (2H, m, CH_2), 3.06–3.24 (2H, m, CH_2), 3.26 (3H, s, CH_3), 4.67 (1H, br s, C*H*H=), 4.90 (1H, br s, C*H*H=); ^{13}C NMR ($CDCl_3$): δ 22.6 (CH_2), 23.5 (CH_2), 29.9 (CH_2), 34.4 (CH_2), 40.0 (CH_2), 42.4 (CH_2), 47.6 (CH), 54.9 (C), 58.6 (CH_3), 75.7 (CH_2), 105.0 (CH_2), 156.8 (C); MS (EI): *m/z* (%) 180 (M, 2%), 149 (37), 148 (25), 135 (100), 133 (20), 107 (14), 105 (20), 93 (27).

4.1.11. *cis,cis*-6-Methoxymethylspiro[4.4]nonane-1-methanol (12). 9-BBN (0.5 M in hexane) (10.22 mL, 5.11 mmol) was added with syringe to a solution of *cis*-1-methoxymethylspiro[4.4]nonane-6-methylene (**11**) (460 mg, 2.56 mmol) in dry THF (30 mL) under argon. The solution was stirred at 80 °C for 5 h and cooled to 0 °C. NaOH (5 mL, 2 M) and H_2O_2 (5 mL, 35%) were added and the solution was stirred at room temperature for 30 min. Diethyl ether was added and the solution was washed with brine, dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc 1:2; yield: 382 mg (75%) of a colourless oil. HRMS: (M -H_2O) 180.1522. Calcd for $C_{12}H_{20}O$: 180.1514; IR (film) ν cm^{-1} 3374 (br), 2952, 2876, 1452, 1105; ^{1}H NMR ($CDCl_3$): δ 1.2–1.8 (14H, m, CH_2 and CH), 2.83 (1H, br s, OH), 2.96–3.02 (1H, m, C*H*H), 3.15–3.24 (1H, m, CH*H*), 3.23 (3H, s, OCH_3), 3.38–3.41 (1H, m, C*H*H), 3.63–3.67 (1H, m, C*H*H); ^{13}C NMR ($CDCl_3$): δ 19.2 (2 × CH_2), 27.2 (CH_2), 27.6 (CH_2), 35.4 (CH_2), 35.5 (CH_2), 45.2 (CH), 48.1 (CH), 54.6 (C), 58.5 (CH_3), 62.9 (CH_2), 73.7 (CH_2); MS (CI-CH_4): *m/z* (%) 199 (M + H, 94%), 181 (15), 150 (12), 149 (100), 148 (24), 136 (18), 135 (30), 93 (10).

4.1.12. *cis,cis*-6-Methoxymethylspiro[4.4]nonane-1-carboxylic acid (13). A mixture of *cis*-6-methoxymethyl-spiro[4.4]nonane-1-methanol (**12**) (433 mg, 2.19 mmol) and $NaIO_4$ (1.521 g, 7.10 mmol) in CCl_4 (4 mL), MeCN (4 mL) and H_2O (6 mL) was stirred at room temperature for 5 h. CH_2Cl_2 was added, the layers separated and the water layer extracted with CH_2Cl_2 (3×). The combined organic solutions were dried ($MgSO_4$), evaporated and the crude product purified by filtration through a silica gel plug using EtOAc; yield 390 mg (84%) of a colourless oil. The crude acid product was used as such in the subsequent synthesis of its methyl ester. HRMS: M 212.1415: calcd for $C_{12}H_{20}O_3$: 212.1412. ^{1}H NMR ($CDCl_3$): δ 1.4–2.0 (12H, m, CH_2), 2.15–2.22 (1H, m, CH), 2.53–2.56 (1H, m, CH), 3.10–3.17 (1H, m, C*H*H), 3.25 (3H, s, CH_3), 3.33–3.38 (1H, m, C*H*H), 11.00 (1H, br s, CO_2H); ^{13}C NMR ($CDCl_3$): δ 20.2 (CH_2), 20.7 (CH_2), 27.5 (CH_2), 29.8 (CH_2), 35.8 (CH_2), 36.4 (CH_2), 45.2 (CH), 50.7 (CH), 56.0 (C), 58.3 (CH_3), 74.3 (CH_2), 181.6 (CO); MS (EI): *m/z* (%) 212 (M, 4%), 180 (41), 167 (23), 166 (42), 135 (37), 121 (100), 120 (28), 93 (31).

4.1.13. Methyl *cis,cis*-6-methoxymethylspiro[4.4]-nonane-1-carboxylate (14). TMSCHN$_2$ (2 M in hexane, 1.84 mL, 3.68 mmol) was added to a solution of the crude acid product from above *cis,cis*-6-methoxymethyl-spiro[4.4]nonane-1-carboxylic acid (**13**) (390 mg, 1.84 mmol) in hexane (14 mL) and MeOH (4 mL) at room temperature. The solution was stirred for 1 h at room temperature and evaporated. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc 5:1; yield 201 mg (48%) of a colourless oil. HRMS: M 226.1550: calcd for $C_{13}H_{22}O_3$: 226.1569; IR (film) ν cm^{-1} 2951, 2874, 1735, 1434, 1362; ^{1}H NMR (CDCl$_3$): δ 1.3–1.8 (12H, m, CH$_2$), 2.07–2.13 (1H, m, CH), 2.47–2.50 (1H, m, CH), 3.02 (1H, dd, J=7.7, 9.4 Hz, C*H*H), 3.17 (3H, s, CH$_3$), 3.17–3.23 (1H, m, C*H*H), 3.56 (3H, s, CH$_3$); ^{13}C NMR (CDCl$_3$): δ 20.3 (CH$_2$), 20.8 (CH$_2$), 27.6 (CH$_2$), 29.8 (CH$_2$), 36.2 (CH$_2$), 36.6 (CH$_2$), 45.4 (CH), 50.5 (CH), 50.9 (CH$_3$), 56.0 (C), 58.4 (CH$_3$), 74.3 (CH$_2$), 176.3 (CO); MS (EI): *m/z* (%) 226 (M, 4%), 209 (31), 208 (34), 180 (77), 148 (40), 135 (33), 121 (100), 120 (42).

4.1.14. *cis,cis*-1-Methoxy-6-(2-hydroxyindan-2-yl)spiro-[4.4]nonane (15). 1,2-Dibromoethane (one drop) was added to a suspension of Mg (124 mg, 5.10 mmol) in dry THF (2 mL) under argon and the mixture heated briefly to initiate a vigorous reaction. The THF was removed under vacuum after 15 min and fresh THF (3 mL) was added. A solution of α,α'-dichloro-*o*-xylene (226 mg, 1.29 mmol) in THF (20 mL) was added slowly to the Mg suspension at room temperature over 1 h. The reaction was stirred at room temperature for 12 h, cooled to −78 °C, and a solution of methyl *cis,cis*-6-methoxyspiro[4.4]nonane-1-carboxylate (**6**) (80 mg, 0.38 mmol) in THF (6 mL) added over 20 min. The mixture was allowed to warm to room temperature. After 4 h at room temperature, water (5 mL) was added slowly, the mixture filtered, and the THF was removed under vacuum. EtOAc and aqueous 1 M NH$_4$Cl were added to the residue and the two layers were separated. The organic solution was washed with water (2×) and brine, dried (MgSO$_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc 5:1; yield 53 mg (49%) of a colourless oil. HRMS: M 286.1943. Calcd for $C_{19}H_{26}O_2$: 286.1933. IR (film) (cm^{-1} 3387 (br), 3020, 2951, 2873, 1059; ^{1}H NMR (CDCl$_3$): δ 1.3–2.3 (13H, m, CH$_2$ and CH), 2.97–3.17 (4H, m, CH$_2$), 3.30 (3H, s, OCH$_3$), 3.60 (1H, d, J=3.6 Hz, CH), 5.55 (1H, s, OH), 7.10–7.23 (4H, m, Ph); ^{13}C NMR (CDCl$_3$): δ 19.3 (CH$_2$), 21.4 (CH$_2$), 27.7 (CH$_2$), 28.7 (CH$_2$), 36.8 (CH$_2$)ν, 39.4 (CH$_2$), 46.1 (CH$_2$), 48.1 (CH$_2$), 55.0 (CH), 55.4 (CH$_3$), 57.7 (C), 82.5 (CH), 86.6 (C), 124.46 (CH), 124.56 (CH), 126.02 (CH), 126.14 (CH), 142.0 (C), 142.2 (C); MS (EI): *m/z* (%) 286 (M, 10%), 181 (50), 149 (13), 132 (29), 122 (46), 121 (100), 105 (28), 104 (31).

4.1.15. *cis,cis*-1-Methoxy-6-(2-indenyl)spiro[4.4]nonane (16). *cis,cis*-1-Methoxy-6-(2-hydroxyindan-2-yl)spiro[4.4]-nonane (**15**) (53 mg, 0.19 mmol) and *p*-TsOH·H$_2$O (18 mg, 0.093 mmol) were dissolved in CH$_2$Cl$_2$ (3 mL) and the solution stirred at room temperature for 2 h. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel using hexane/EtOAc 15:1; yield 40 mg (80%) of a colourless oil. (Found C, 85.29; H, 9.22. Calcd for $C_{19}H_{24}O$: C, 85.03; H, 9.01%). HRMS: M 268.1838. Calcd for $C_{19}H_{24}O$: 268.1827. IR (film) ν cm^{-1} 3387 (br), 3054, 3017, 2956, 2873, 1461; ^{1}H NMR (CDCl$_3$): δ 1.4–2.0 (13H, m, CH$_2$ and CH), 3.00 (3H, s, CH$_3$), 3.17 (1H, d, J=3.8 Hz, CH), 3.32–3.57 (2H, m, CH$_2$), 6.51 (1H, s, CH), 7.09–7.39 (4H, m, Ph); ^{13}C NMR (CDCl$_3$): δ 20.4 (CH$_2$), 22.0 (CH$_2$), 28.0 (CH$_2$), 32.0 (CH$_2$), 34.2 (CH$_2$), 35.9 (CH$_2$), 42.5 (CH$_2$), 47.5 (CH), 55.6 (CH$_3$), 60.2 (C), 88.2 (CH), 119.7 (CH), 123.1 (CH), 123.2 (CH), 125.4 (CH), 126.0 (CH), 143.1 (C), 146.0 (C), 155.2 (C); MS (EI): *m/z* (%) 268 (M, 59%), 236 (100), 155 (81), 142 (76), 141 (36), 129 (30), 128 (33), 115 (33).

4.1.16. *cis,cis*-6-Methoxymethyl-1-(2-hydroxyindan-2-yl)spiro[4.4]nonane (17). 1,2-Dibromoethane (one drop) was added to a suspension of Mg (86 mg, 3.54 mmol) in dry THF (2 mL) under argon and the mixture heated briefly to initiate a vigorous reaction. The THF was removed under vacuum after 15 min and fresh THF (3 mL) was added. A solution of α,α'-dichloro-*o*-xylene (308 mg, 1.76 mmol) in THF (30 mL) was added slowly to the Mg suspension at ambient temperature over 1 h. The reaction was stirred for an additional 12 h, cooled to −78 °C, and a solution of methyl *cis,cis*-6-methoxymethylspiro[4.4]nona-1-carboxyl-ate (**14**) (200 mg, 0.88 mmol) in THF (15 mL) was added over 20 min. The mixture was allowed to warm to ambient temperature and kept at this temperature for 3.5 h before water (5 mL) was added slowly. The mixture was filtered, the THF removed at reduced pressure, EtOAc and aqueous 1 M NH$_4$Cl added, and the two layers separated. The organic solution was washed with water (2×) and brine, dried (MgSO$_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc 5:1; yield 135 mg (51%) of a colourless oil. (Found C, 80.13; H, 9.59. Calcd for $C_{20}H_{28}O_2$: C, 79.96; H, 9.39%). HRMS: M 300.2077. Calcd for $C_{20}H_{28}O_2$: 300.2089. IR (film) ν cm^{-1} 3408 (br), 2954, 2877, 1735, 1459; ^{1}H NMR (CDCl$_3$): δ 1.5–1.7 (12H, m, CH$_2$), 2.24–2.26 (1H, m, CH), 2.40–2.42 (1H, m, CH), 2.8–3.1 (4H, m, CH$_2$), 3.22–3.37 (2H, m, CH$_2$), 3.32 (3H, s, CH$_3$), 4.12 (1H, s, OH), 7.11–7.24 (4H, m, Ph); ^{13}C NMR (CDCl$_3$): δ 18.9 (CH$_2$), 20.1 (CH$_2$), 28.2 (CH$_2$), 28.8 (CH$_2$), 35.8 (2×CH$_2$), 44.9 (CH$_2$), 45.4 (CH$_2$), 49.3 (CH), 52.5 (CH), 56.5 (C), 58.5 (CH$_3$), 75.5 (CH$_2$), 84.8 (C), 124.8 (2×CH), 126.09 (CH), 126.11 (CH), 141.1 (C), 142.7 (C); MS (EI): *m/z* (%) 300 (M, 4%), 282 (32), 268 (10), 250 (21), 195 (57), 163 (23), 136 (31), 135 (100).

4.1.17. *cis,cis*-6-Methoxymethyl-1-(2-indenyl)spiro[4.4]-nonane (18). *cis,cis*-6-Methoxymethyl-1-(2-hydroxyindan-2-yl)spiro[4.4]nonane (**17**) (135 mg, 0.45 mmol) and *p*-TsOH·H$_2$O (43 mg, 0.22 mmol) were dissolved in CH$_2$Cl$_2$ (5 mL) and stirred at room temperature for 5 h. The solvent was evaporated and the crude product was purified by flash chromatography on silica gel using hexane/EtOAc 15:1; yield 91 mg (72%) of a colourless oil. (Found C, 85.31; H, 9.11. Calcd for $C_{20}H_{26}O$: C, 85.06; H, 9.28%). HRMS: M 282.1981. Calcd for $C_{20}H_{26}O$: 282.1984; IR (film) ν cm^{-1} 2951, 2922, 2873, 1461, 1110; ^{1}H NMR (CDCl$_3$): δ 1.4–2.1 (13H, m, CH$_2$ and CH), 2.82 (1H, d, J= 7.1 Hz, CH), 3.04 (1H, t, J=9.7 Hz, C*H*HO), 3.13 (3H, s,

CH_3), 3.30–3.41 (3H, m, CH_2 and C*H*HO), 6.55 (1H, s, CH), 7.11–7.40 (4H, m, Ph); ^{13}C NMR ($CDCl_3$): δ 20.3 (CH_2), 20.7 (CH_2), 27.4 (CH_2), 32.9 (CH_2), 37.2 (CH_2), 38.0 (CH_2), 41.4 (CH_2), 46.2 (CH), 48.5 (CH), 56.8 (C), 58.5 (CH_3), 73.2 (CH_2), 120.0 (CH), 123.2 (CH), 123.6 (CH), 126.2 (CH), 126.4 (CH), 142.8 (C), 145.5 (C), 153.4 (C); MS (EI): *m*/*z* (%) 282 (M, 17%), 250 (64), 169 (38), 168 (32), 155 (76), 142 (100), 141 (45), 129 (38).

4.1.18. *cis*,*cis*-1,6-[1-Oxaethano-2-spiro(2,3-dihydroinden-2-yl)]spiro[4.4]nonane (19). TMSI (52 mg, 0.26 mmol) was added with a syringe to a solution of *cis*,*cis*-1-methoxy-6-(2-indenyl)spiro[4.4]nonane (**16**) (35 mg, 0.13 mmol) in dry CH_2Cl_2 (5 mL) under argon at room temperature. The solution was stirred at this temperature for 2 h and evaporated. The crude product was purified by flash chromatography using hexane/EtOAc 15:1; yield 30 mg (91%) of a colourless oil. (Found C, 85.15; H, 8.58.Calcd for $C_{18}H_{22}O$: C, 84.99; H, 8.72%). HRMS: M 254.1664.Calcd for $C_{18}H_{22}O$: 254.1671; IR (film) ν cm^{-1} 3021, 2946, 2863, 1483, 1041; ^{1}H NMR ($CDCl_3$): δ 1.45–1.88 (12H, m, CH_2), 2.38–2.40 (1H, m, CH), 2.86–3.09 (4H, m, CH_2), 4.01 (1H, d, J=4.6 Hz, CH), 7.10–7.21 (4H, m, Ph); ^{13}C NMR ($CDCl_3$): δ 24.8 (CH_2), 27.3 (CH_2), 29.2 (CH_2), 33.6 (CH_2), 38.9 (CH_2), 39.4 (CH_2), 41.9 (CH_2), 46.6 (CH_2), 60.1 (CH), 63.1 (C), 89.4 (CH), 94.5 (C), 124.3 (CH), 124.7 (CH), 126.2 (CH), 126.3 (CH), 141.1 (C), 142.1 (C); MS (EI): *m*/*z* (%): 254 (M, 100%), 225 (25), 149 (20), 132 (45), 121 (19), 115 (12), 105 (19), 104 (25).

4.1.19. *cis*,*cis*-1,6-[2-Oxapropano-1-spiro(2,3-dihydroinden-2-yl)]spiro[4.4]nonane (20). TMSI (92 mg, 0.46 mmol) was added with a syringe to a solution of *cis*,*cis*-6-methoxymethyl-1-(2-indenyl)spiro[4.4]nonane (**18**) (65 mg, 0.23 mmol) in dry CH_2Cl_2 (5 mL) under argon at room temperature. The solution was stirred at this temperature for 3 h and evaporated. The crude product was purified by flash chromatography on silica gel using hexane/EtOAc 20:1; yield 51 mg (83%) of a colourless oil. HRMS: M 268.1830.Calcd for $C_{19}H_{24}O$: 268.1827. IR (film) ν cm^{-1} 3020, 2943, 2860, 1485, 1079; ^{1}H NMR ($CDCl_3$): δ 1.4–2.0 (12H, m, CH_2), 2.24–2.32 (1H, m, CH), 2.64–2.87 (2H, m, CH_2), 2.97–3.11 (3H, m, CH_2 and CH), 3.37 (1H, dd, J= 8.9, 6.5 Hz, C*H*H), 3.89 (1H, dd, J=8.8, 7.7 Hz, C*H*H), 6.89–7.19 (4H, m, Ph); ^{13}C NMR ($CDCl_3$): δ 22.9 (CH_2), 28.1 (CH_2), 31.1 (CH_2), 34.3 (CH_2), 34.8 (CH_2), 35.2 (CH_2), 36.1 (CH_2), 42.1 (CH_2), 43.9 (CH), 54.7 (CH), 64.0 (C), 71.7 (CH_2), 96.7 (C), 124.2 (CH), 124.4 (CH), 126.0 (CH), 126.1 (CH), 142.7 (C), 143.7 (C); MS (EI): *m*/*z* (%): 268 (M, 100%), 155 (22), 152 (30), 151 (88), 145 (20), 142 (30), 116 (39), 115 (31).

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A convenient, large-scale synthesis of 4′-carboxamido *N*-Boc-2′,6′-dimethyl-L-phenylalanines

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Abstract—A large-scale synthesis of a series of 4′-carboxamido *N*-Boc-2′,6′-dimethyl-L-phenylalanines is described. This method features mild reaction conditions and high chemical yields from commercially available *N*-Boc-2′,6′-dimethyl-L-tyrosine methyl ester.
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1. Introduction

Dimethyl-L-tyrosine (Dmt) is an unnatural amino acid that has been widely used in the development of highly selective and potent opioid receptor (OR) agonists and antagonists.[1] The substitution of Dmt for the N-terminal tyrosine (Tyr) in opioid peptides generally increases δ/μ receptor binding affinities, and also enhances δ antagonist potencies.[2] However, a liability of the phenolic moiety of Tyr related compounds is their propensity for metabolism.[3] Recent studies demonstrated that the bioisosteric $CONH_2$ replacement of the phenolic OH in non-peptide cyclazocine opiate analogues displayed comparable OR binding affinities and bioactivities.[4] We envisioned such a bioisosteric replacement could be applied for the phenol moiety of both Tyr and Dmt in peptide related OR ligands. Although the carboxamido analog of Tyr has been made, we first disclosed the synthesis of 4′-carboxamido *N*-Boc-2′,6′-dimethyl-L-phenylalanines, and their derivatives as opioid receptor modulators, in a PCT patent application with biological activities disclosed.[5] For example, the Ki's for compound **A** (Fig. 1) are 0.06 and 1.44 nM for delta and mu opioid receptors, respectively. During the preparation of this article, the carboxamido for phenol replacement of the Tyr residue has been successfully applied to surrogates for Tyr in opioid peptide ligands.[6] In this paper, we report a convenient, detailed method for scalable preparation of 4′-carboxamido *N*-Boc-2′,6′-dimethyl-L-phenylalanines from commercially available *N*-Boc-2′,6′-dimethyl-L-tyrosine methyl ester. This general methodology has also enabled us to prepare many substituted 4′-carboxamides from primary to tertiary amines.

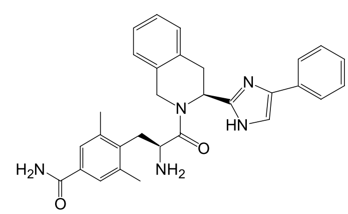

Figure 1. Compound A.

2. Results and discussion

The synthesis of 4-carboxamido *N*-Boc-2′,6′-dimethyl-L-phenylalanines was straightforward and is outlined in Scheme 1. Treatment of *N*-Boc-2′,6′-dimethyl-L-tyrosine methyl ester (*N*-Boc-Dmt-OMe) **1** with phenyltriflimide[7] and triethylamine afforded the triflate **2** (99%). The resulting aryl triflate **2** was converted to the aryl carboxylic acid **3** by a palladium-catalyzed carbonylation[8] in the presence of palladium acetate and DPPF (1,1′-bis(diphenylphosphino)-ferrocene) under an ambient CO atmosphere. By monitoring the reaction with LC/MS, we found that the best yield (94%) could be achieved after 8 h at 60 °C.

To selectively convert the aryl acid to the carboxamido intermediates and to avoid the formation of the undesired amide from the methyl ester moiety, Wang and McMurray's method[9] was used. Thus, the primary amide **4a** was successfully prepared by using ammonium chloride

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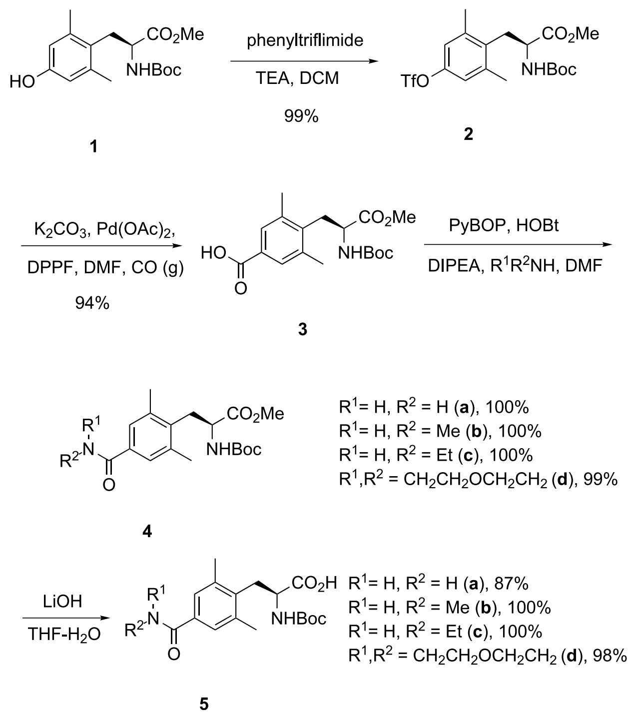

Scheme 1.

as a nitrogen source and (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP) as a coupling agent. In similar methodology, the secondary and tertiary amides **4b–c** were prepared in nearly quantitative yields wherein the corresponding amines were used instead of ammonium chloride. Finally, the resulting amino acid methyl esters **4a–d** were selectively hydrolyzed with lithium hydroxide in a mixture of THF and water at 0 °C and gave the target 4′-carboxamido *N*-Boc-2′,6′-dimethyl-L-phenylalanines **5a–d**.

In summary, we have described a convenient, scalable synthesis of several unnatural amino acid derivatives that have been subsequently converted into novel opioid receptor modulators. The potent binding affinities have been disclosed previously.[5] Additional biological activities will be published elsewhere in due course.

3. Experimental

3.1. General

N-Boc-2′,6′-dimethyl-L-tyrosine methyl ester was purchased from RSP Amino Acid, Shirley, MA, USA. PyBOP was purchased from Novabiochem. All other reagents were purchased from Aldrich and used as received. For column chromatography, EMD silica gel 60 (230–400 mesh) was used. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker ACS-60.

3.1.1. 4′-Trifluoromethanesulfonyl *N*-Boc-2′,6′-dimethyl-L-phenylalanine methyl ester (2). Into a cool solution of *N*-Boc-Dmt-OMe **1** (7.0 g, 21.6 mmol) and *N*-phenyltrifluoromethanesulfonimide (7.9 g, 22.0 mmol) in DCM (60 mL) was added triethylamine (3.25 mL, 23.3 mmol). The resulting solution was stirred at 0 °C for 1 h and slowly warmed to rt. Upon disappearance of starting materials (monitored by TLC), the reaction was quenched by addition of water. The separated organic phase was washed with 1 N NaOH aqueous solution, water and dried over Na_2SO_4 overnight. After filtration and evaporation, the residue was purified by flash column chromatography (eluent: EtOAc-hexane: 3:7, v/v) to give triflate **2** as colorless gel. 9.74 g, 99%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (9H, s), 2.39 (6H, s), 3.06 (2H, d, $J=7.7$ Hz), 3.64 (3H, s), 4.51–4.59 (1H, m), 5.12 (1H, d, $J=8.5$ Hz), 6.92 (2H, s); ^{13}C NMR (300 MHz, $CDCl_3$): δ 20.3, 28.1, 33.1, 52.2, 53.4, 79.9, 118.7 (q, $J=320.5$ Hz, CF_3), 120.3, 134.2, 139.8, 147.7, 154.8, 172.7; HRMS(ES$^+$) $[M+H]^+$ calcd. For $C_{18}H_{25}F_3NO_7S$: 456.1304, found, 456.1264; MS(ES$^+$) (relative intensity): 355.8 (100) (M-Boc)$^+$.

3.1.2. 4′-Carboxyl *N*-Boc-2′,6′-dimethyl-L-phenylalanine methyl ester (3). To a suspension of triflate **2** (9.68 g, 21.3 mmol), K_2CO_3 (14.1 g, 0.102 mol), $Pd(OAc)_2$ (0.48 g, 2.13 mmol) and 1,1′-bis(diphenylphosphino)ferrocene (DPPF, 2.56 g, 4.47 mmol) in DMF (48 mL) was bubbled in gaseous CO for 15 min. The mixture was heated to 60 °C for 8 h with CO balloon. The cool mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc, and filtered. The aqueous layer was separated, acidified with 10% citric acid aqueous solution, extracted with EtOAc, and finally dried over Na_2SO_4. Recrystallization from EtOAc–hexane afforded the acid **3** as a white solid. 7.05 g, 94%; mp 188.0–189.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (9H, s), 2.42 (6H, s), 3.14 (2H, $J=7.4$ Hz), 3.65 (3H, s), 4.57–4.59 (1H, m), 5.14 (1H, d, $J=8.6$ Hz), 7.75 (2H, s); ^{13}C NMR (300 MHz, DMSO-d_6): δ 19.6, 28.0, 31.1, 51.7, 52.8, 78.2, 128.4, 128.7, 137.1, 139.7, 155.1, 167.3, 172.2; HRMS(ES$^+$) $[M+H]^+$ calcd. For $C_{18}H_{26}NO_6$: 352.1760, found, 352.1742; MS(ES$^+$) (relative intensity): 251.9 (100) $(M-Boc)^+$.

3.1.3. 4′-Carbamoyl *N*-Boc-2′,6′-dimethyl-L-phenylalanine methyl ester (4a). Into a stirring solution of benzoic acid **3** (3.00 g, 8.54 mmol), PyBOP (6.68 g, 12.8 mmol) and HOBt (1.74 g, 12.8 mmol) in DMF (36 mL) was added DIPEA (5.96 mL, 34.2 mmol) and NH_4Cl (0.92 g, 17.1 mmol). The resulting mixture was stirred at rt for 40 min before being partitioned between saturated aqueous NH_4Cl solution and EtOAc. The separated organic phase was washed with 2 N citric acid aqueous solution, saturated aqueous $NaHCO_3$ solution and brine, and dried over Na_2SO_4 overnight. After concentration, the residue was purified by flash column chromatography (eluent: EtOAc) to give the amide **4a** as a white solid. 3.00 g, 100%; mp 95.5–96.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (9H, s), 2.39 (6H, s), 3.11 (2H, $J=7.2$ Hz), 3.65 (3H, s), 4.53–4.56 (1H, m), 5.12 (1H, d, $J=8.7$ Hz), 5.65 (1H, br s), 6.09 (1H, br s), 7.46 (2H, s); ^{13}C NMR (300 MHz, DMSO-d_6): δ 19.6, 28.0, 31.1, 51.7, 52.8, 78.2, 128.4, 128.7, 137.1, 139.7, 155.1, 167.3, 172.2; HRMS(ES$^+$) $[M+H]^+$ calcd. For $C_{18}H_{27}N_2O_5$: 351.1920, found, 351.1869; MS(ES$^+$) (relative intensity): 250.9 (100) $(M-Boc)^+$.

3.1.4. 4′-Methylcarbamoyl *N*-Boc-2′,6′-dimethyl-L-phenylalanine methyl ester (4b). Similar method to preparation of **4a** while methylamine hydrochloride was used instead of NH_4Cl. 100%; white solid; mp 200.5–201.5 °C; ^1H NMR (300 MHz, CD_3CN): δ 1.34 (9H, s), 2.38 (6H, s), 2.85 (3H, d, $J=4.7$ Hz), 3.06 (1H, dd, $J=9.4$, 14.0 Hz), 3.16 (1H, dd, $J=7.9$, 14.2 Hz), 3.63 (3H, s), 4.38 (1H, m), 5.69 (1H, d, $J=8.3$ Hz), 6.88 (1H, s), 7.43 (2H, s); ^{13}C NMR (300 MHz, DMSO-d_6): δ 19.7, 26.1, 28.0, 30.9, 51.7, 52.9, 78.2, 126.5, 132.2, 136.7, 137.5, 155.1, 166.5, 172.3; HRMS(ES^+) $[M+H]^+$ calcd. For $C_{19}H_{29}N_2O_5$: 365.2076, found, 365.2101; MS(ES^+) (relative intensity): 365.0 (15) $(M+H)^+$.

3.1.5. 4′-Ethylcarbamoyl *N*-Boc-2′,6′-dimethyl-L-phenylalanine methyl ester (4c). Similar method to preparation of **4a** while ethylamine hydrochloride was used instead of NH_4Cl. 100%; white solid; mp 176.0–177.0 °C; ^1H NMR (300 MHz, CD_3CN): δ 1.20 (3H, t, $J=7.2$ Hz), 1.34 (9H, s), 2.38 (6H, s), 3.05 (1H, dd, $J=7.2$, 14.8 Hz), 3.18 (1H, dd, $J=6.4$, 14.0 Hz), 3.36 (2H, m), 3.63 (3H, s), 4.38 (1H, m), 5.96 (1H, d, $J=8.3$ Hz), 6.94 (1H, s), 7.44 (2H, s); ^{13}C NMR (300 MHz, DMSO-d_6): δ 14.8, 19.8, 28.1, 31.0, 33.9, 51.7, 53.0, 78.3, 126.6, 132.4, 136.7, 137.5, 155.2, 165.8, 172.4; HRMS(ES^+) $[M+H]^+$ calcd. For $C_{20}H_{31}N_2O_5$: 379.2233, found, 379.2190; MS(ES^+) (relative intensity): 379.0 (15) $(M+H)^+$.

3.1.6. 4′-Morpholinylcarbonyl *N*-Boc-2′,6′-dimethyl-L-phenylalanine methyl ester (4d). Similar method to preparation of **4a** while morpholine was used instead of NH_4Cl. 99%; white solid; mp 97.0–98.0 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 1.34 (9H, s), 2.37 (6H, s), 3.09 (2H, m), 3.35–3.90 (8H, m), 3.68 (3H, s), 4.54 (1H, m), 5.09 (1H, d, $J=8.4$ Hz), 7.02 (2H, s); ^{13}C NMR (300 MHz, CD_3OD): δ 20.3, 28.7, 33.1, 43.9, 52.7, 54.6, 67.8, 80.6, 127.7, 134.6, 137.9, 139.1, 157.2, 172.7, 174.1; HRMS(ES^+) $[M+H]^+$ calcd. For $C_{22}H_{33}N_2O_6$: 421.2339, found, 421,2373; MS(ES^+) (relative intensity): 421.0 (40) $(M+H)^+$.

3.2. General procedure for hydrolysis of amino acid methyl esters 4a–d

Into an ice-cooled solution of methyl ester **4** (8.54 mmol) in THF (50 mL) was added an aqueous LiOH solution (1 N, 50 mL) and stirred at 0 °C. Upon disappearance of starting materials (monitored by TLC), the organic solvents were removed and the aqueous phase was neutralized with cooled 1 N HCl at 0 °C, and extracted with EtOAc, finally dried over Na_2SO_4 overnight. Filtration and evaporation to dryness led to the acid **5**.

3.2.1. 4′-Carbamoyl *N*-Boc-2′,6′-dimethyl-L-phenylalanine (5a). White solid; mp > 210 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 1.30 (9H, s), 2.32 (6H, s), 2.95 (1H, dd, $J=8.8$, 13.9 Hz), 3.10 (1H, dd, $J=6.2$, 14.0 Hz), 4.02–4.12 (1H, m), 7.18–7.23 (2H, m), 7.48 (2H, s), 7.80 (1H, s); ^{13}C NMR (300 MHz, DMSO-d_6): δ 19.8, 28.0, 31.2, 53.1, 78.0, 126.9, 131.7, 136.6, 138.3, 155.2, 167.8, 173.4; HRMS(ES^+) $[M+H]^+$ calcd. For $C_{17}H_{25}N_2O_5$: 337.1763, found, 337.1780; MS(ES^+) (relative intensity): 236.9 (6) $(M-Boc)^+$.

3.2.2. 4′-Methylcarbamoyl *N*-Boc-2′,6′-dimethyl-L-phenylalanine (5b). 100%; white foam; mp > 210 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 1.30 (9H, s), 2.32 (6H, s), 2.74 (3H, d, $J=4.5$ Hz), 2.94 (1H, dd, $J=6.0$, 14.4 Hz), 3.10 (1H, dd, $J=6.5$, 14.1 Hz), 4.02–4.12 (1H, m), 7.21 (1H, d, $J=8.4$ Hz), 7.44 (2H, s), 8.27 (1H, d, $J=4.5$ Hz); ^{13}C NMR (300 MHz, DMSO-d_6): δ 19.1, 26.1, 28.0, 31.2, 53.1, 78.0, 126.5, 132.0, 136.7, 138.1, 155.2, 166.6, 173.4; HRMS(ES^+) $[M+H]^+$ calcd. For $C_{18}H_{27}N_2O_5$: 351.1920, found, 351.1909; MS(ES^+) (relative intensity): 351.0 (15) $(M+H)^+$.

3.2.3. 4′-Ethylcarbamoyl *N*-Boc-2′,6′-dimethyl-L-phenylalanine (5c). 100%; white foam; mp > 210 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 1.10 (3H, t, $J=7.2$ Hz), 1.31 (9H, s), 2.33 (6H, s), 2.94 (1H, dd, $J=6.0$, 14.4 Hz), 3.10 (1H, dd, $J=6.0$, 14.1 Hz), 3.30–3.23 (2H, m), 4.04–4.11 (1H, m), 7.17 (1H, d, $J=8.4$ Hz), 7.45 (2H, s), 8.30 (1H, t, $J=5.4$ Hz); ^{13}C NMR (300 MHz, DMSO-d_6): δ 14.8, 20.0, 28.1, 31.3, 33.7, 53.3, 78.0, 126.6, 132.2, 136.9, 138.2, 155.2, 165.9, 173.5; HRMS(ES^+) $[M+H]^+$ calcd. For $C_{19}H_{29}N_2O_5$: 365.2076, found, 365.2099; MS(ES^+) (relative intensity): 365.0 (16) $(M+H)^+$.

3.2.4. 4′-Morpholinylcarbamoyl *N*-Boc-2′,6′-dimethyl-L-phenylalanine (5d). White foam; mp > 210 °C; ^1H NMR (300 MHz, DMSO-d_6): δ 1.29 (9H, s), 2.31 (6H, s), 2.93 (1H, dd, $J=9.0$, 14.1 Hz), 3.10 (1H, dd, $J=5.8$, 14.0 Hz), 3.30–3.85 (8H, m), 4.11 (1H, m), 6.99 (2H, s), 7.19 (1H, d, $J=8.7$ Hz); ^{13}C NMR (300 MHz, CD_3OD): δ 18.8, 27.1, 32.0, 42.3, 53.1, 66.3, 78.9, 126.5, 133.6, 136.8, 137.7, 156.1, 171.3, 173.9; HRMS(ES^+) $[M+H]^+$ calcd. For $C_{21}H_{31}N_2O_6$: 407.2182, found, 407.2180; MS(ES^+) (relative intensity): 407.1 (38) $(M+H)^+$.

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Directing-protecting groups for carbohydrates. Design, conformational study, synthesis and application to regioselective functionalization

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Abstract—A novel concept of regioselective transformation of secondary hydroxyl groups in carbohydrates is presented. First, the relative reactivity of the free hydroxyl groups of onoprotected D-glucose derivatives was assessed using acetylation as a model reaction. As a result, acylation of these polyols gave a mixture of monosubstituted products in which the 3-*O* functionalized derivatives predominated. Novel hydrogen bond acceptor protecting groups were next designed to modulate the 4-OH and 3-OH reactivity in the hope to mediate higher regioselective transformations. A molecular modeling study later validated by spectroscopic analysis predicted additional intramolecular hydrogen bonds between the hydroxyl groups and pyridyl-containing protecting groups. Taking advantage of this induced hydrogen bond network, we achieved regioselective acetylation of the hydroxyl group at position 3 without protecting any secondary hydroxyl groups of the carbohydrate moiety. This designed protecting/directing group increased the nucleophilicity and the steric hindrance of position 3. As a result, optimization of the reaction conditions enabled the monoacetylation (not affected by steric hindrance) of 6-*O*-protected glucopyranosides at position 3 and selective silylation (affected by steric hindrance) of position 2 in high isolated yields and regioselectivities. This result certainly opens doors to the regioselective open glycosylation of carbohydrates.
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1. Introduction

Carbohydrates are biologically relevant molecules whose potential in medicinal chemistry is still under-evaluated. This partly stems from the lack of universal synthetic approaches for the synthesis of oligosaccharides in a stereo- and regiocontrolled manner. Regioselective functionalization of the secondary hydroxyl groups has been achieved using metals (tin,[1] copper[2]), Lewis acids,[3] or designed bases.[4] However, these efficient methods have been restricted to specific transformations. More recently, innovative approaches exploiting the hydrogen bond network of the carbohydrate alcohols have appeared.[5] In all these approaches, the regioselective transformations rely on the modulation of the relative reactivity of the many hydroxyl groups of the carbohydrates. The relative reactivity of the secondary hydroxyl groups depends strongly on both their acidity and their nucleophilicity, which are modulated by intramolecular H-bonds (Fig. 1).[6] One of the

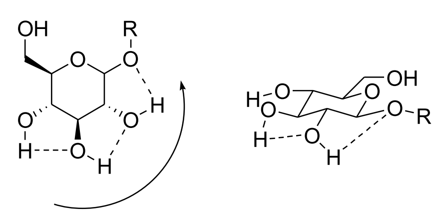

Figure 1. Intramolecular H-bond network as proposed by Yoshida and co-workers.[4,7]

first reports on the evaluation of the relative reactivity of secondary hydroxyl groups in monosaccharides appeared recently.[7] In this report, Yoshida and co-workers shed light on intramolecular H-bonds, which control the relative reactivity of the four hydroxyl groups (Fig. 1) and relate the enhanced reactivity of the 3-hydroxyl group to the hydrogen bond network.[8] More recently, ab initio calculations questioned whether these hydrogen bonds exist.[9]

An efficient and convenient regioselective strategy would allow regiocontrolled manipulation of the hydroxyl groups without extensive recourse to protection/deprotection steps. Such an approach implies the control of the relative reactivity of the secondary hydroxyl groups of the

Keywords: Carbohydrate; Relative reactivity; Regioselectivity; Open glycosylation; Hydrogen bond; Pyridyl ring; Acetylation.
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carbohydrate unit. We reasoned that a protecting group at position 6—the easiest to install—could modulate the reactivity of the secondary hydroxyl groups. Thus, we first focused on the effect of 6-hydroxyl protecting groups on the relative reactivity of the free secondary hydroxyls.[5a] Herein, we wish to provide a full report on the design, preparation, solution conformation study and use of original pyridyl-containing protecting groups, which served as a basis for regiocontrolled transformation of monoprotected glycosyl acceptors. Even though the regioselective glycosylation is our primary concern, acetylation was found to be a more convenient model reaction. Thus a variety of acceptors were monoacetylated under kinetic conditions and the regioselectivity was evaluated.

2. Results and discussion

2.1. Preparation of 6-*O*-monoprotected glucopyranosides

Monosaccharides are molecules with limited conformational freedom. Thus the shape of the substrates should not be affected much by the functionalization of the 6-OH. In contrast, the influence of the 6-*O* protecting group on the electrostatic potential of the molecule or on the cooperative network of intramolecular hydrogen bonds should influence the relative reactivity of the three secondary hydroxyl groups.

A variety of protecting groups were installed at the position 6 of methyl-α-D-glucopyranoside **1a**. The protecting groups (aromatic or aliphatic, silyl ether or ester) depicted in Figure 2 were chosen due to their common use in carbohydrate chemistry. In addition, these protecting groups can be quantitatively removed by hydrogenation or under acidic conditions. Although the removal of the protecting group is not greatly important in the present study, it will be crucial when glycosylation will be studied. The influence of the hydroxymethyl group in the reactivity of the secondary hydroxyl groups was also evaluated by means of the xylopyranoside derivative **1k**. Other protecting groups were investigated including TMS, $PhSi(Me_2)$, and $CF_3C(O)$. However, they were found to be prone to migration or cleavage under the acetylation conditions employed during the course of this study.

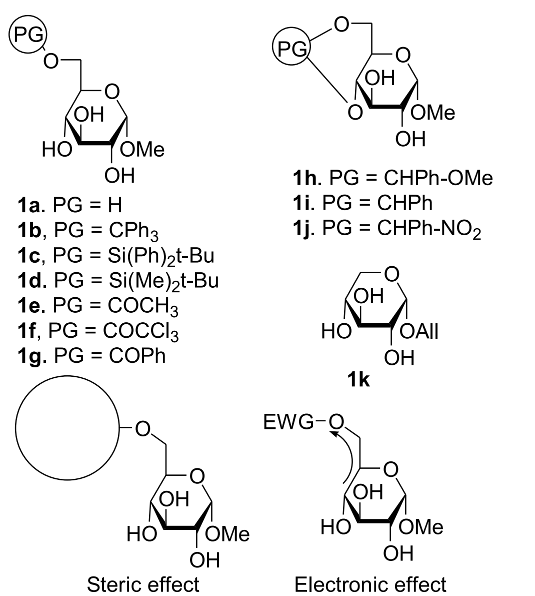
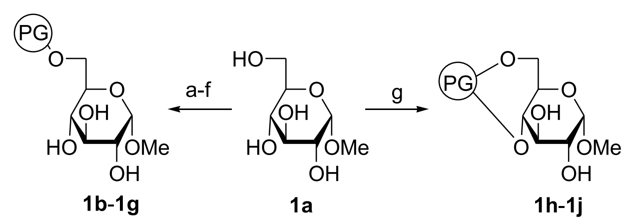


Figure 2. **1a**,[10] **1b**,[11] **1c**,[12] **1d**,[13] **1e**,[14] **1f**, **1g**,[15] **1h**,[16] **1i**,[17] **1j**,[18] **1k**.[19]

Thus, compound **1a** was subjected to regioselective protection by standard methods including reaction with the suitable chloride reagent either in DMF in presence of imidazole at room temperature, in pyridine at 0 °C or in collidine at −40 °C as reported by Yamamoto and co-workers (Scheme 1).[20] Benzylidene derivatives were regioselectively prepared on treatment with the appropriate aryl dimethylacetal reagents in presence of a catalytic amount of PTSA.



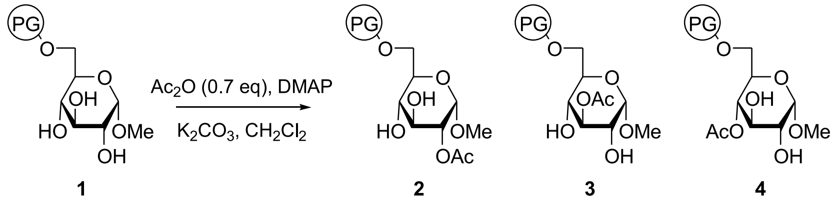
Scheme 1. (a) TrCl, pyridine, 81% (**1b**); (b) TBDPSCl, imidazole, DMF, 82% (**1c**); (c) TBSCl, pyridine, 78% (**1d**); (d) AcCl, collidine, −40 °C, 55% (**1e**); (e) $(CCl_3CO)_2O$, collidine, −20 °C, 13% (**1f**); (f) PhCOCl, collidine, −10 °C, 49% (**1g**); (g) $ArCH(OMe)_2$, PTSA, 81% (**1h**), 90% (**1i**), 82% (**1j**).

2.2. Acetylation as a model reaction

Although we were concerned by the glycosylation reaction, analysis of the steric and electronic contributions by direct study of the six possible isomers (regio- and stereoisomers) would be tedious. Thus, our efforts, directed at evaluating the relative nucleophilicity of the secondary hydroxyl group, focused on regioselectivity of acetylation as a model study.[21] Application to the glycosylation reaction will follow and will be reported in due course. The choice of this reaction was dictated by the ease of evaluation of the regioselectivity using routine ^{1}H NMR on crude mixtures. After usual work-up, the ratios of regioisomers were conveniently and reliably estimated by integration of methyl signals around 2 ppm and of either H-2, H-3 or H-4 peak that shifted downfield due to acetylation of the adjacent hydroxyl groups.

Among the parameters that can affect the regioselectivity of the reaction are the reaction conditions and the chemical nature of the protecting group at position 6. The reaction conditions (K_2CO_3, Ac_2O, DMAP) optimized by Yoshida and co-workers led to a kinetic control of the reaction.[4,7] Dichloromethane and THF, two solvents widely used for the glycosylation reaction that we wish to model, were chosen[22] and DMAP (5 mol%) and acetic anhydride (0.7 equiv) were added as freshly prepared dichloromethane solutions. Low concentrations of carbohydrate (0.5 mmol L^{-1}) precluded any aggregation or intermolecular interactions. However, although the reaction proceeded smoothly in dichloromethane, the reaction rate was too low in THF and higher concentrations were needed (2 mmol L^{-1}) with 10 mol% DMAP. No concentration effect was noticed since the ratio

Table 1. Regioselectivity of the acetylation of the secondary hydroxyl groups



Entry	Compd	Protecting group	Solvent	**2** (%)[a]	**3** (%)[a]	**4** (%)[a]	Ratio
1	**1b**	Ph_3C	THF	14	68	18	1: 4.8: 1.2
2			CH_2Cl_2	**13**	**74**	**13**	1: 5.5: 1.0
3			$CHCl_3$	**7**	**80**	**13**	1: 11.8: 1.0
4	**1c**	t-Bu(Ph)$_2$Si	THF	15	67	18	1: 4.4: 1.2
5			CH_2Cl_2	**12**	**74**	**14**	1: 6.0: 1.1[23]
6	**1d**	t-Bu(Me)$_2$Si	THF	19	66	15	1: 3.5: 0.8
7			CH_2Cl_2	16	68	16	1: 4.3: 1.0
8	**1e**	MeC(O)	THF	17	62	20	1: 3.6: 1.2
9			CH_2Cl_2	19	69	12	1: 3.8: 0.6
10	**1f**	$Cl_3CC(O)$[b]	THF	18	57	25	1: 3.6: 2.0
11	**1g**	PhC(O)	THF	17	56	27	1: 3.1: 1.6
12			CH_2Cl_2	11	66	23	1: 5.9: 2.0
13	**1h**	MeOPhCH	THF[c]	**38**	**62**	—	1: 1.6: –
14			CH_2Cl_2[c]	47	53	—	1: 1.1: –
15	**1i**	PhCH	THF[c]	45	55	—	1: 1.3: –
16			CH_2Cl_2[c]	49	51	—	1: 1.0: –
17	**1j**	NO_2PhCH	THF[c]	45	55	—	1: 1.3: –
18			CH_2Cl_2[c]	**57**	**43**	—	1: 0.75: –
19	**1k**	—	THF	8	75	17	1: 11.6: 2.0
20	**1k**	—	CH_2Cl_2	9	74	17	1: 8.5: 2.0

[a] Based on reacted material, 40–65% conversion.
[b] Insoluble in dichloromethane.
[c] Reacted for 2 h.

remained the same at concentrations of carbohydrate ranging from 0.5 to 2 mmol L^{-1}. Thus, the series of pyranosides were subjected to acetylation and the results are summarized in Table 1 with an accuracy of about 3%. All the triols were allowed to react for one hour and conversion rates of 40–65% were observed. Benzylidene derivatives were found to be less reactive, requiring longer reaction times to give similar conversions. Although this was a purely qualitative observation, it revealed the lowest intrinsic reactivity of this class of compounds.

The data summarized in Table 1 clearly indicates that the steric effects were negligible since **1b** and **1k** (entries 2 and 20) led to similar regioselectivities. Thus, the following study will primarily focus on the differences of reactivity between each hydroxyl group. The data also reveals that the electronic effects, although weak, affected the regioselectivity. Indeed, the 3-*O*Ac/2-*O*Ac ratios in either dichloromethane or THF correlate well with the electron-donating/withdrawing properties of the protecting groups (**1h**, **1i** and **1j**, entries 13–18). These benzylidene derivatives (**1h**–**1j**) exhibited a different reactivity pattern with a higher preference for position 2 relative to the 6-*O* monoprotected compounds (**1b**–**1g**).

A difference between silyl ethers (**1c**, **1d**, entries 4–7), ether (**1b**, entries 1–3) and esters (**1e**, **1f**, **1g**, entries 8–12) is discernible, ethers and silyl ethers leading to the highest regioselectivities. In the four examples shown in entries 8, 9, 11 and 12, the amount of 4-*O*Ac was slightly enhanced in THF compared to dichloromethane. Similarly, going from THF to dichloromethane led to an increase in the amount of 3-*O*Ac isomers when triols were reacted but to a decrease in the 3-*O*Ac in the benzylidene series (**1h**, **1i**, **1j**, entries 13–18). The higher regioselectivity in dichloromethane compared to THF may stem from the postulated intramolecular hydrogen bonds, which are believed to be stronger in dichloromethane. These preliminary data prompted us to further explore the influence of the intramolecular hydrogen bonds.

2.3. Design and synthesis of second generation protecting groups

Although this data indicates clear electronic and solvent effects in the regioselectivity, they are not useful from a practical viewpoint. In addition, these monoprotected pyranosides were reacted with 0.7 equiv of acetic anhydride and a maximum conversion of 70% is to be expected. Reaction with a stoichiometric amount of acetic anhydride led to mixtures of mono-, di- and tri-acetylated products along with unreacted material. The overacetylation can be explained by the small difference in reactivity of the hydroxyl groups and the low hindrance around the monoacetylated products. Hence, the next stage of our research program involved the development of original protecting/directing groups that would mediate regioselective functionalization of the polyols. We postulated that hydrogen bond acceptor moieties would perturb the hydrogen bond network and modulate the relative reactivity of the free OH groups. During the course of our work, a similar approach was used with glucosamine derivatives and led to enhancement of reactivity of the 6-*O*H.[24] The authors used a picolinyl protecting group which experienced an intramolecular hydrogen bond.

The design of such groups calls for complementary spatial positions of the H-bond acceptor and donor. Molecular modeling was therefore instrumental at this stage. Our previous work have demonstrated the predictive power of molecular mechanics methods which was herein exploited in the design of novel protecting/directing groups.[25] Thus, a series of protecting groups were virtually screened (molecular mechanics studies) and the ones which were found to interact with OH-4 were selected for synthesis. As a result, 2-pyridyl counterparts of the trityl (the most regioselective so far, see Table 1) and benzoyl groups were prepared (Fig. 3) and installed onto **1a** leading to **1l** and **1m**, respectively. Although one can expect a role of this pyridyl rings in the acetylation reaction, the hydrogen bond (if strong enough) should shut down the nucleophilicity of the nitrogen. This concern will be addressed further in this report. To improve the effect of these selected protecting groups (**1l** and **1m**), other polyaromatic moieties were prepared (**1n** and **1p**). Finally, to assess the computational study predictions, the thiophene derivative **1o** which was predicted to behave as compound **1b**, was also prepared.

The appropriate chloride reagents were synthesized according to literature procedures.[26] For example, **1n** was prepared from 4-dimethylaminopyridine, which was regioselectively metallated according to Fort's procedure[26c,d] and reacted with benzophenone. The tertiary alcohol was subsequently chlorinated and reacted with the free carbohydrate **1a**.

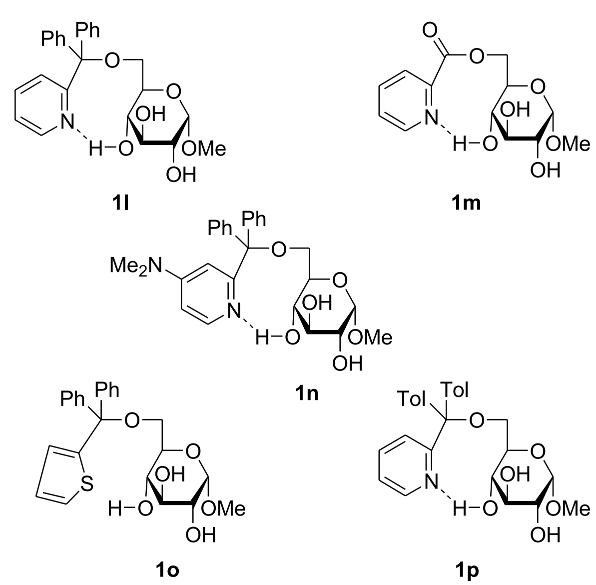


Figure 3. 1l–**1p**. Tol: *p*-tolyl, Th: 2-thiophenyl.

2.4. Solution conformation analysis

The molecular modeling study suggested that the most energetically favored conformations of **1l** would exhibit the postulated H-bond (Fig. 4). After synthesis, the amorphous solid was unfortunately not suitable for X-ray diffraction analysis.

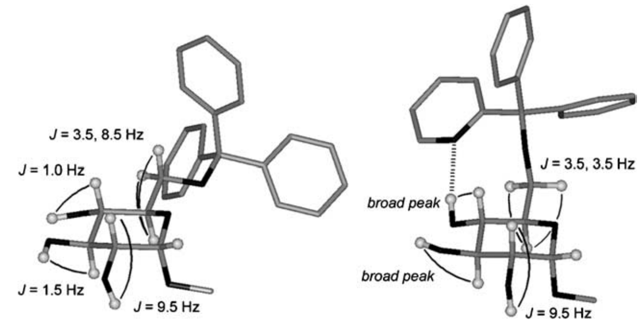


Figure 4. Proposed solution conformations of **1b** and **1l** and observed coupling constants.

1D and 2D ^{1}H NMR spectroscopic analysis in deuterated chloroform and DMSO confirmed this hypothesis (Figs. 4 and 5). The OH peaks were first unambiguously assigned

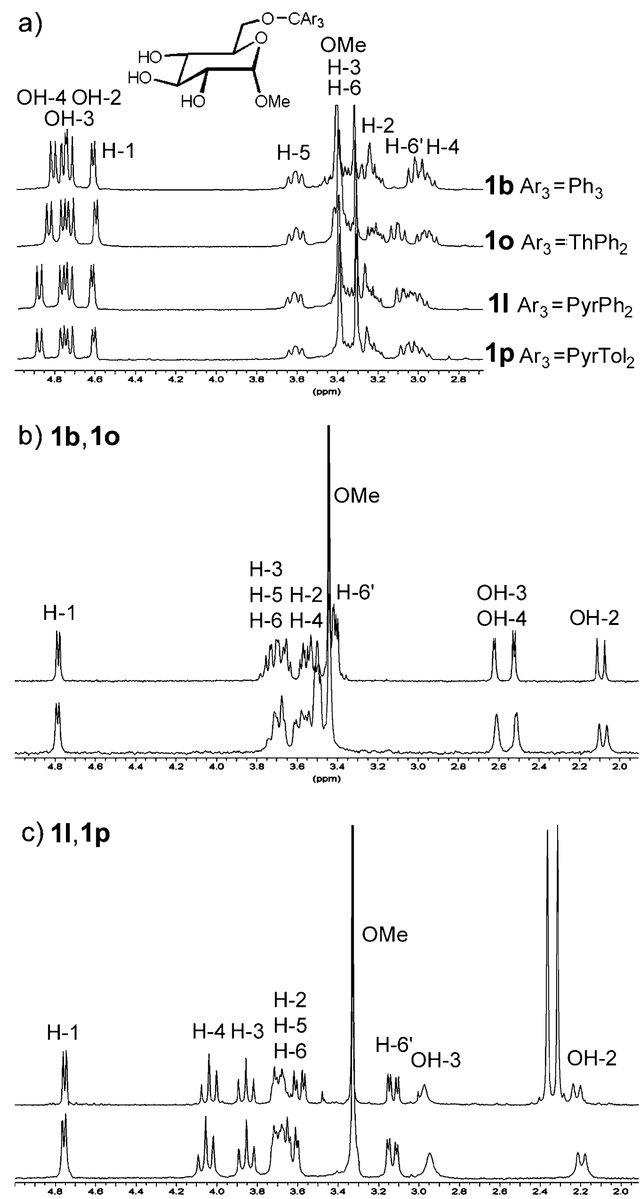


Figure 5. ^{1}H NMR spectra of (a) **1b**, **1o**, **1l**, **1p** in DMSO-d^6, (b) **1b**, **1o** in $CDCl_3$ and (b) **1l**, **1p** in $CDCl_3$ (4 mg/mL). OH-4's are missing on the bottom spectra (7–8 ppm).

using COSY experiments. As expected, the spectra of **1b** and **1l** were similar in DMSO-d^6 (Fig. 5a), a solvent known to disrupt the hydrogen bonding. Going from **1b** to **1l**, characteristic shifts of the OH-4 peak ($\Delta\delta$ (OH-4) = 4.73 ppm) and of the H-4 signal ($\Delta\delta$ (H-4) = 0.55 ppm) were observed in $CDCl_3$ (Fig. 5b and c, $\Delta\delta$ represents the chemical shift difference between **1b** and **1l** spectra). More in-depth NMR spectra analysis also brought some information about both the solution conformation and the H bond network (Figs. 4 and 5).[27] For instance, H-3 shifted downfield ($\Delta\delta$ (H-3) = 0.15 ppm). This shift was attributed to a new hydrogen bond between the activated oxygen O-4 and OH-3 thus leading to the proposed structures shown in Figure 4. More interestingly, the characteristic change in the H-6 peak pattern was observed. The values for $J_{5,6a}$ and $J_{5,6b}$ (3.5 and 8.5 Hz) measured for **1b** correspond to a *gt* conformation of the C-5–C-6 bond.[28] The values measured for **1l** ($J_{5,6a}$,$J_{5,6b}$ = 3.5 and 3.5 Hz) confirmed the computationally predicted conformational change and a *gg* conformation. These NMR experiments indicate that the observed solution conformations match well with the predicted models.

Careful examination of the ^{1}H NMR spectra also suggested that substituting the phenyl ring in **1g** (R = PhCO) for a pyridyl (**1m**, R = PyrCO) led to a weak intramolecular H-bond. The small shift of the H-4 peak and the broadness of the OH peaks were presumably the result of a perturbation of the H-bond network by the pyridyl group or the formation of aggregates.

In an attempt to further increase the hydrogen bond strength, the pyridine nitrogen was electron-enriched by a dimethylamino group (**1n**). The recorded spectra in DMSO and $CDCl_3$ were similar to those of **1l**. For the sake of quantitative comparison, NMR solvent titration was next carried out (Fig. 6). As can be observed in Figure 6, the hydrogen bond observed for **1l** is strong and a substantial amount of DMSO is required to disrupt it. It appears even stronger for **1n** which features the more basic *para*-substituted protecting group. The OH-4 peak for **1l** is well resolved for any concentration of DMSO whereas it is spread over the spectrum for **1n** and even not observed in neat $CDCl_3$. This broadness was attributed to the pyridinium character of this proton. Extrapolation of the curve predicts a chemical shift of around 9 ppm for the 4-OH, a value that is rarely observed for a secondary alcohol. Again the role of the DMAP ring in the acetylation will have to be assessed.

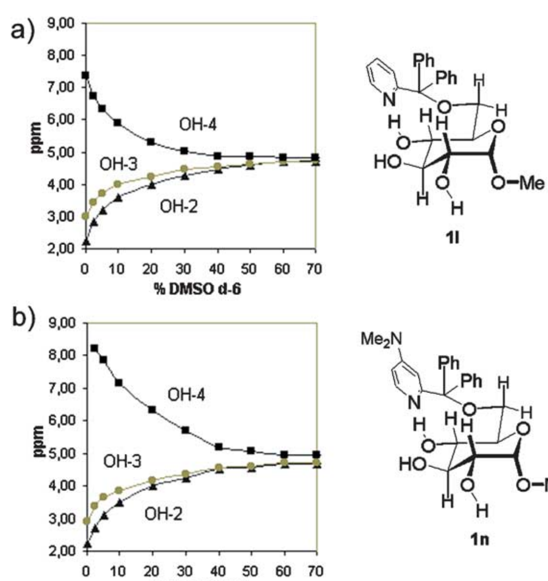
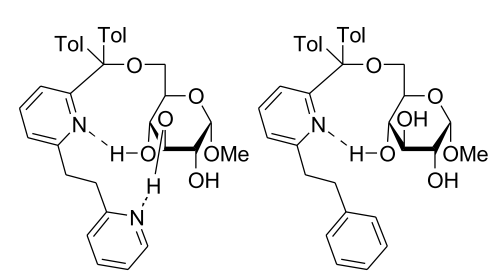


Figure 6. Chemical shift dependence of OH protons as a function of solvent composition for **1l** (a) and **1n** (b).

Although we succeeded in inducing an hydrogen bond in **1l**, any attempt to remove the protecting group either by standard methods (TFA, formic acid) or more recent procedures such as acetyl chloride,[29] cerium chloride/sodium iodide[30] failed. Only hydrogenolysis (H_2, 30 bar, 10% Pd/C) slowly removed this trityl-like group. The low yielding introduction of the DMAP-containing group in **1n** was also a limitation to its practical use. These observations called for other protecting groups, which maintain hydrogen bond acceptor properties while being easy to prepare, introduce and remove. The deprotection issue could be addressed by substituting the protonatable pyridyl ring for a non-basic thiophene or furan ring, which would also act as a hydrogen bond acceptor, though weaker. However, the computational study predicted no hydrogen between these heterocycles and the carbohydrate OH's. To validate these predictions, **1o** was selected as a negative reference and prepared following the same strategy as for **1l**. As expected, the similarity of the ^{1}H NMR spectra of **1b** and **1o** indicated that the desired H bond did not occur (Fig. 5b). The preparation of the corresponding furan analog appeared to be low yielding. Keeping the nitrogen was therefore essential for the success of our approach. The problematic stability was tackled by adding electron-donating groups on the phenyl rings. Two methoxy groups were introduced however providing a fairly unstable dimethoxytrityl-like moiety. Introducing two methyl groups was a more successful strategy affording an appropriately stable ether bond (**1p**, Fig. 3). Gratifyingly, the hydrogen bond was observed (Fig. 5c) and this protecting group was easily removed by a solution of TFA in dichloromethane.

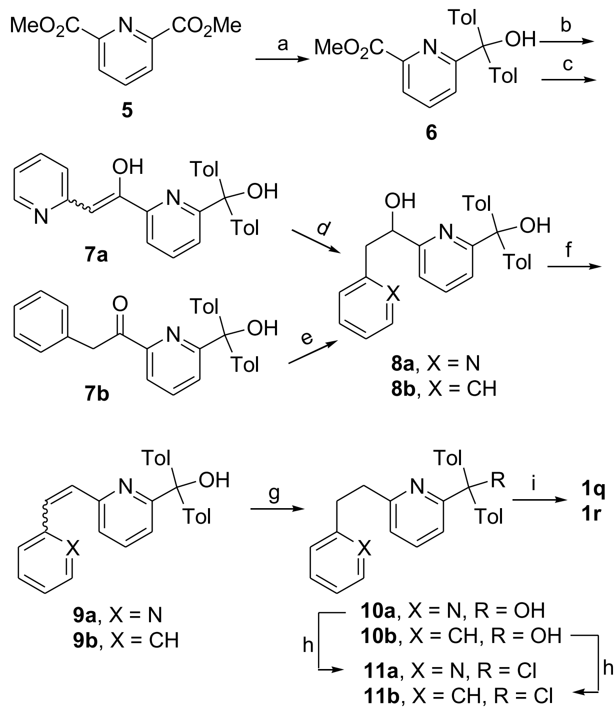
2.5. Design, synthesis and solution conformation analysis of third generation protecting groups

An additional protecting group (**1q**, Fig. 7) was further designed that would participate in two intramolecular hydrogen bonds. In order to differentiate between hydrogen bond and steric effect, **1r** was also prepared.



1q **1r**

Figure 7. Compounds **1q** and 1r.



Scheme 2. (a) TolMgBr, THF, rt then TolMgBr, −78 °C, 45%; (b) 2-picoline, *n*-BuLi, THF, −78 °C then 6, HMPT, 83% (**7a**); (c) toluene, *t*-BuLi, THF, −78 °C then 6, HMPT, 35% (**7b**, along with 30% 6); (d) H_2, 10% Pd/C, EtOH/THF, 60% (**8a**); (e) $LiAlH_4$, THF, 0 °C, 70% (**8b**); (f) NaHMDS, THF, −78 °C, then $PhNTf_2$, −50 °C, 76% (**9a**), 83% (**9b**); (g) H_2, 10% Pd/C, EtOH/THF, 72% (**10a**), 94% (**10b**); (h) HCl, H_2O, reflux then $SOCl_2$, AcCl; (i) pyridine, **1a**, 63% (**1q**, two steps along with 23% of **10a**), 50% (**1r**, two steps, along with 29% of **10b**). Tol: *p*-tolyl.

The synthesis of **1q** and **1r** is illustrated in Scheme 2. It began with two regioselective Grignard addition to the pyridine derivative **5** followed by a third addition of picolinyl lithium or *p*-tolyl lithium to the second carbonyl group. These successive additions led to the enol **7a** and the ketone **7b**, which were subsequently reduced into **10a** and **10b**. For this purpose, catalytic hydrogenation of **7a** and hydride reduction of **7b** afforded compounds **8a** and **8b** along with over-reduced products resulting from concomitant cleavage of the tertiary alcohol group. Triflation followed by in situ elimination was achieved using $PhN(Tf)_2$ as a mild triflating reagent, yielding olefins **9a** and **9b**. Finally, catalytic hydrogenation and subsequent chlorination of the tertiary alcohols **10a** and **10b** led to **11a** and **11b**, respectively. Prior protonation of both pyridyl rings was necessary to avoid hydrolysis of these reagents. The trityl chloride-like compounds **11a** and **11b** were finally reacted with **1a** in pyridine yielding the intended target compounds **1q** and **1r**.

To further validate the presence of the postulated hydrogen bonds, the dependence of the solvent composition on the chemical shift was studied. From comparison of Figure 8c with Figure 6a, we hypothesized that the hydrogen bond with OH-4 still exists in **1q** and seems to be approximately as strong as in **1l**. The NMR titration curve for OH-3 reveals the presence of the expected additional hydrogen bond, although weaker than the hydrogen bond with OH-4.

2.6. Role of the pyridyl ring in the acetylation reaction

Prior to the use of these protecting groups, we confirmed the existence of the hydrogen bond in dichloromethane used as a solvent for the acetylation reaction. The similarity between the ^1H NMR spectra in deuterated dichloromethane and chloroform confirmed the strong hydrogen bond between OH-4 and the pyridyl ring of **1l** (Fig. 9). Thus, the data obtained through extensive NMR studies carried out in deuterated chloroform can be transferred to the reactions in dichloromethane.

In order to rule out any catalytic role of the pyridyl-containing protecting groups, reactions were carried out in absence of DMAP (Table 2, entries 3, 9 and 18). The lack of reaction demonstrates that the hydrogen bond is strong enough to prevent the pyridyl ring from reacting with acetic anhydride or that the pyridyl rings are poor nucleophiles. Indeed, the pyridyl ring is known to be a much weaker catalyst than dimethylaminopyridine (DMAP) and is unlikely competing with DMAP.[31] Reactions in CD_2Cl_2 monitored by ^1H NMR confirmed the lack in reactivity of **1l** with acetic anhydride as well as the poor catalytic properties of 2-picoline used as a model for the pyridyl-containing groups. Even with 2 equiv of 2-picoline, compound **1l** in CD_2Cl_2 in presence of acetic anhydride remained unchanged after 2 h. As a comparison, addition of a

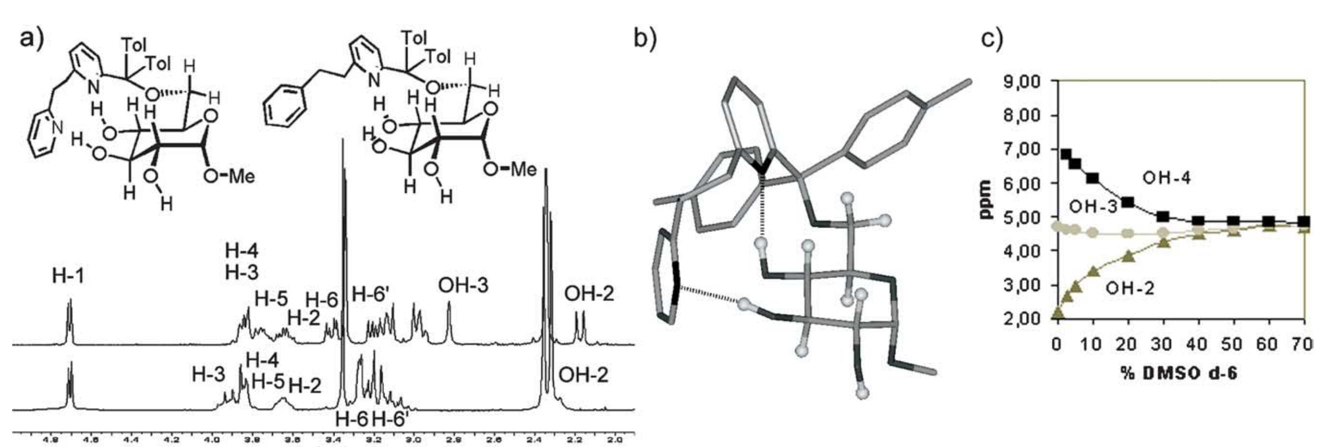


Figure 8. (a) NMR spectra of **1q** (bottom) and **1r** (top) in $CDCl_3$ (dilution: 4 mg/mL), (b) Proposed modeled structure and (c) OH proton chemical shift vs. DMSO/$CDCl_3$ composition for **1r**.

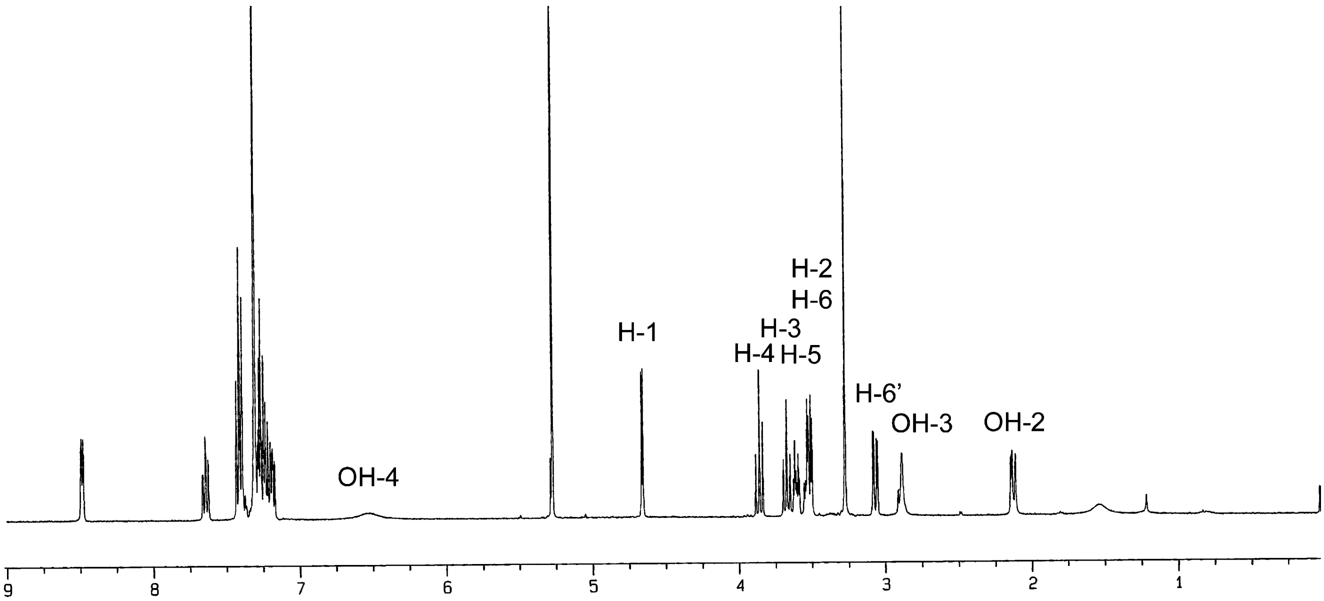


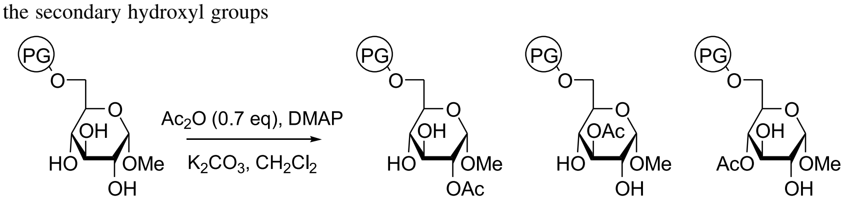
Figure 9. ^{1}H NMR spectra of **1l** in CD_2Cl_2 (dilution: 4 mg/mL).

catalytic amount of DMAP led to completion within an hour.

2.7. Regioselectivity of the acetylation reaction

The prepared monoprotected substrates were subjected to acetylation conditions (Table 2) and the ratios were compared to the data obtained with the trityl and benzoyl derivatives **1b** and **1g** (Table 1, entries 1–3, 11 and 12). From the proposed structural models, we can expect that O-3 would be the most reactive. O-4 is both activated by the pyridyl ring (O*H*-4···*N* bond) and deactivated by the hydrogen bond with OH-3 (*O*-4···*H*O-3). O-3 does not interact with any hydrogen while O*H*-3 interacts with O-4

Table 2. Nucleophilicity of the secondary hydroxyl groups



1 **2** **3** **4**

Entry	Compd	Protecting group	Conditions	**2** (%)[a]	**3**(%)[a]	**4**(%)[a]	Ratio
1	**1l**	Pyr(Ph)$_2$C	THF	15	69	16	1: 4.6: 1.1
2			CH_2Cl_2	16	79	5	1: 5.0: 0.34
3			CH_2Cl_2, no DMAP		NR		
4			CH_2Cl_2, no DMAP, 2-picoline		NR		
5			$CHCl_3$[b]	19[b]	74[b]	7[b]	1: 3.9: 0.40
6	**1m**	PyrC(O)	THF	12	66	22	1: 5.4: 1.8
7			CH_2Cl_2	6	80	14	1: 14.3: 2.5
8	**1n**	DMAP(Ph)$_2$C	THF	12	77	(11)[c]	1: 4.6: 1.1
9			CH_2Cl_2	15	76	(9)[c]	1: 5.0: 0.34
10			CH_2Cl_2, no DMAP		NR		
11	**1o**	Th(Ph)$_2$C	THF	13	70	17	1: 5.3: 1.3
12			CH_2Cl_2	10	75	15	1: 7.4: 1.4
13	**1p**	Pyr(Tol)$_2$C	THF	15	73	12	1: 4.8: 0.8
14			CH_2Cl_2	11	83	6	1: 7.2: 0.5
15			$CHCl_3$[b]	22[b]	71[b]	7[b]	1: 3.2: 0.35
16	**1q**	Pyr-(CH$_2$)$_2$-Pyr(Tol)$_2$C	THF	13	76	11	1: 5.8: 0.84
17			CH_2Cl_2	11	83	6	1: 7.2: 0.66
18			CH_2Cl_2, no DMAP		NR		
19			$CHCl_3$		NR		—
20	**1r**	Ph-(CH$_2$)$_2$-Pyr(Tol)$_2$C	THF	17	78	5	1: 4.5: 0.30
21			CH_2Cl_2	14	81	5	1: 5.8: 0.38
22			$CHCl_3$[b]	7[b]	93[b]	<3[b]	1: 13.2: <0.1

[a] Based on recovered starting material, 40–65% conversion, measured on crude ^{1}H NMR, NR: no reaction.
[b] Conversions of 10%; ratios are given but are not highly accurate.
[c] Amount of 3,4-di-*O*-Ac derivative (see text).

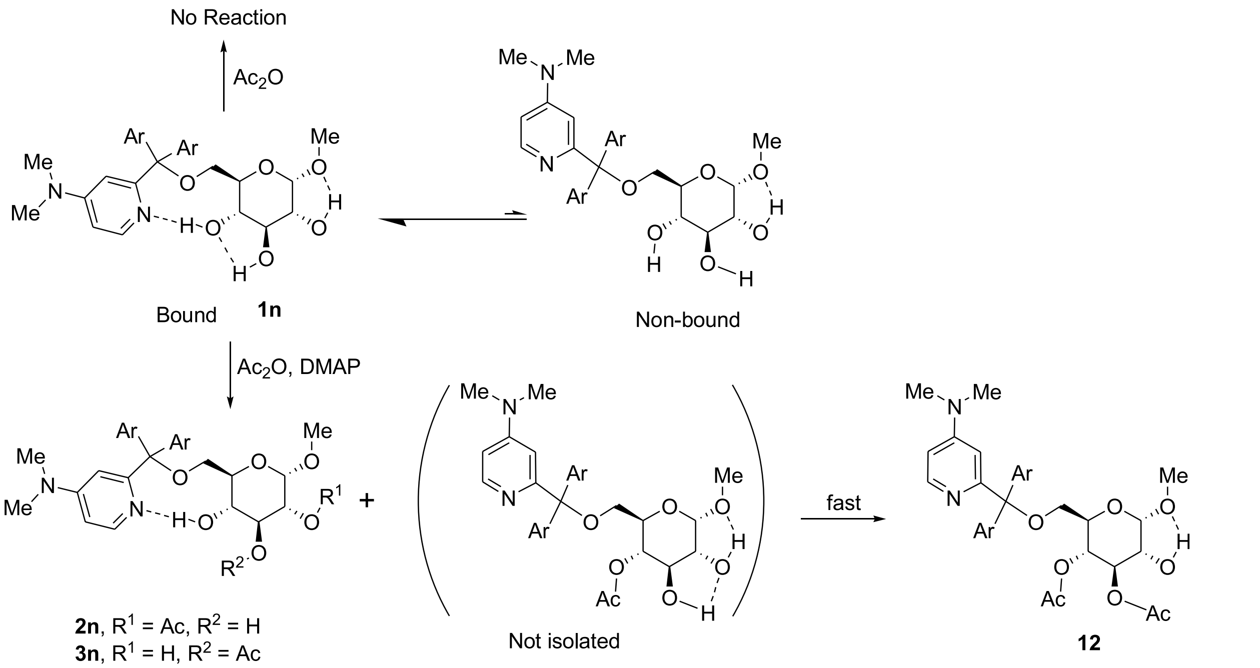


Figure 10. Intramolecular catalysis.

(*O*-4···*H*O-3). In fact, the observed 3-*O*Ac/4-*O*Ac ratio increased remarkably by substituting a phenyl of the trityl group for a pyridyl ring (**1b**: 5.5:1, Table 1, entry 2, **1l**: 14:1, Table 2, entry 2). This significant loss of reactivity of the 4-hydroxyl group presumably arose from the observed intramolecular hydrogen bond formed between the 4-OH and the pyridyl ring. More surprisingly, even the DMAP-based protecting group of **1n** did not catalyze the reaction (entry 10). In addition, when **1n** was reacted in presence of a catalytic amount of DMAP, the 3,4-di-*O*-acetylated compound was isolated instead of the 4-*O*Ac derivative. This unexpected behavior was rationalized as shown in Figure 10. The strong hydrogen bond between the pyridyl ring and 4-OH prevents any catalytic action of the protecting group. However, when 4-OH is converted into the 4-*O*Ac, this bond no longer exists and the protecting group acts as a catalyst resulting in acetylation of 3-OH. This is an additional evidence of the strength of the hydrogen bond experienced by this designed protecting group. Similar behaviors were not observed with the other pyridyl-containing protecting groups which do not compete with DMAP.

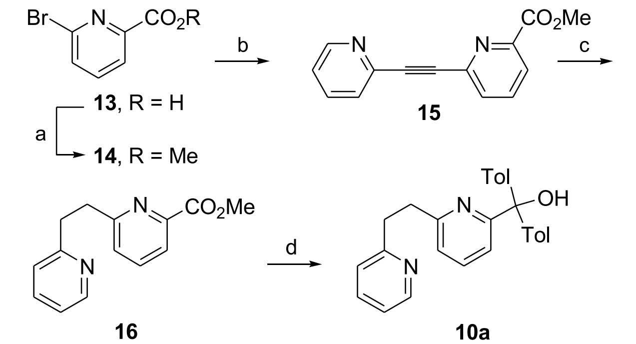
The solvent effect previously observed for **1g** (Table 1, entries 11 and 12) became more pronounced for **1m** (Table 2, entries 6 and 7). The two electron donating methyl groups of **1p** presumably increased the pyridyl nitrogen partial charge resulting in a stronger hydrogen bond hence the observed enhanced regioselectivities (entries 13 and 14 vs. 1 and 2). More surprising was the discernible loss of reactivity of the carbohydrate hydroxyl groups in chloroform. One hydrogen bond reduced dramatically the conversion rate (around 10% after 1 h, entries 5, 15 and 22) while the additional pyridyl ring in **1q** completely inhibited the reaction (entry 19). The formation of the hydrogen bonds might result in a significant decrease of the oxygen partial charges, hence a decrease of their nucleophilicity.

Fortunately, the reactivity was good enough in dichloromethane to allow for the estimation of the second pyridyl ring effect. As can be seen in Table 2 (entries 16 and 17 vs. 13 and 14) the additional aromatic ring does not significantly modify the regioselectivity neither in THF nor in dichloromethane.

2.8. Regioselective acetylation, silylation and pivaloylation on preparative scale

At this stage, we thought to check the practical usefulness of the proposed strategy based on directing/protecting groups. The previously proposed preparation of the protecting group was judged to be lengthy and hazardous on a large scale. The original synthesis of **10a** was initially achieved in five steps and only 12% overall yield. We sought alternative reaction sequences to the synthetic pathway previously envisaged which would provide the expected tertiary alcohol in higher yields. Exploratory experiments were thus conducted and other strategies were envisaged including the use of 2,6-dibromopyridine as a starting material. Ultimately, the Sonogashira coupling[32] was advantageously employed and afforded the intermediate **10a** in a much higher overall yield (76% in four steps, Scheme 3). Readily available dissymmetric pyridine derivative **14**[33] (prepared by high yielding methylation of commercially available bromopicolinic acid **13**) was coupled with 2-ethynylpyridine to afford dipyridine compound **15** in excellent yield. Reduction under standard conditions followed by condensation of 2 equiv of a Grignard reagent on the ester group completed the synthesis of **10a**.

With a scalable synthesis of the protecting group in hand, the preparative use of this protecting group could now be evaluated. For this purpose, a slight excess of acetic anhydride was reacted with **1q** in presence of DMAP (Scheme 4). For the comparison purpose, **1p** was reacted

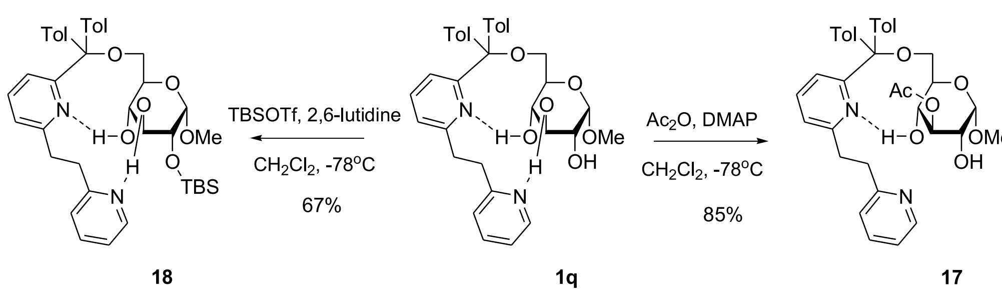


Scheme 3. a) Ref 33, quant.; (b) 2-ethynylpyridine, $PdCl_2(PPh_3)_2$, CuI, Et_3N/THF 1:1, 60 °C, 96%; (c) H_2, 10% Pd/C, EtOH/THF, 90%; (d) TolMgBr, THF, 0 °C, 88%. Tol: *p*-tolyl.

under the same conditions (Table 3, entries 1–4). In a hope to introduce a single acetyl group by increasing the hydrogen bond strength, the temperature was lowered. Under the conditions used previously, no reaction occurred. Increasing the amount of DMAP restored a reasonable rate. Eventually, regioisomer **3q** was isolated in 70% yield along with the regioisomer **2q** (13%) and overacetylated products (17%) (entry 1). When the reaction was carried out at −60 °C, the preference for O-3 was further enhanced (entry 2). Upon cooling further, the reaction was even more selective and led to the isolation of **3q** in 85% yield. It is notable that the second major compound is the 2,3-*O*-diacetylated product presumably arising from overacetylation of **3q**. In order to attribute this high regioselectivity to the protecting group, the same reaction was performed with **1p** (entry 4). The observed ratios confirmed the role played by the terminal pyridyl ring in **1q**. Indeed, when the reaction was carried out at −78 °C, the amount of isolated **3p** (**3p**/other isomers, 2.0:1) is much lower than when **1q** was acetylated (**3q**/other isomers, 5.7:1).

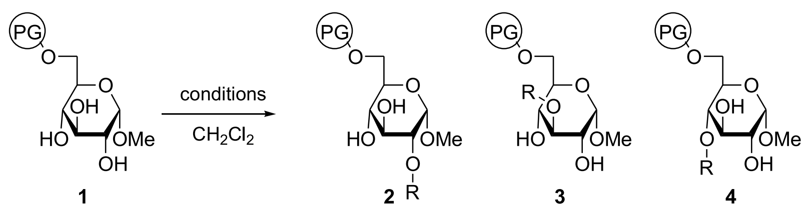
1b was previously found to provide the 3-*O* isomer as the major compound (Table 1) with 0.7 equiv of acetic anhydride. However, when **1b** was reacted with 1 or more equivalent of acetic anhydride, a complex mixture of the 3-*O* isomer along with unreacted material, diacetylated and triacetylated products was obtained. This low selectivity precludes the use of the trityl group to achieve regioselective acetylation.

The successful application of this methodology to the regioselective acetylation of the hydroxyl at position 3 led us to consider the regioselective protection of the position 2. Although the reactivity of the hydroxyl group on position 3 has been increased by the designed protecting group, the steric hindrance at this position has also been increased. The acetylation was found to be unaffected by the steric hindrance of the protecting group (Table 1, entries 2 and 20). We reasoned that a bulky reagent would be more sensitive to the steric effects. Thus the pivaloylation and silylation reactions were selected. Table 3 entries 5 and 6 summarize the data for these two reactions. Optimal conditions for pivaloylation have been developed and shown in Table 3. Although the increase of the steric effects has been observed, the reversal of regioselectivity between positions 2 and 3 has not been reached. Moreover,



Scheme 4. Regioselective protection of **1q**.

Table 3. Preparative scale application



Entry	Compd	Protecting group	Conditions	**2** (%)[a]	**3** (%)[a]	**4** (%)[a]	Diprotected[b]
1	**1q**	Pyr-$(CH_2)_2$-Pyr$(Tol)_2$C	Ac_2O, DMAP, −30 °C	13	70	—[c]	17 (13)
2			Ac_2O, DMAP, −60 °C	10	81	—[c]	9 (6)
3			Ac_2O, DMAP, −78 °C	8	85	—[c]	7 (5)
4	**1p**	Pyr$(Tol)_2$C	Ac_2O, DMAP, −78 °C	14	67	—[c]	19 (9)
5	**1q**	Pyr-$(CH_2)_2$-Pyr$(Tol)_2$C	PivCl, DMAP, Et_3N, −78 °C	31	32	—[c]	0
6			TBSOTf, 2,6-lutidine, −78 °C	67	23	—[c]	7

[a] Measured on crude ^1H NMR, accuracy ±2%.
[b] Amount of 2,3-di-*O*-acetyl derivative in brackets.
[c] Not detected.

the conversion rate is low and the use of different nucleophilic bases did not improve neither the conversion nor the ratio. We next investigated the silylation reaction. Again a series of nucleophilic bases including DMAP, 2,6-lutidine and imidazole were tried with either TBSCl or TBSOTf. A single combination shown in Table 3 did provide complete conversion. Gratifyingly, the expected reversal of selectivity was observed and further validated the concept of protecting/directing group. This last result demonstrated that the steric effects can balance the higher reactivity of position 3. Thus a small reagent would react with position 3 (most nucleophilic) and a bulky reagent would react with position 2 (least hindered). This is a good indication for the coming studies on regioselective glycosylation (Scheme 4).

3. Conclusion

For the last 20 years or so, regioselective manipulation of carbohydrate hydroxyl groups has been addressed with challenging strategies. In this context, we carried out exploratory experiments directed toward the evaluation of the effect of the 6-*O* protecting group on the relative reactivity of the secondary alcohols. With a designed protecting group installed at position 6, we have observed the expected decrease in reactivity of the 4-OH and a concomitant increase in reactivity of the adjacent 3-OH. The designed H-bond acceptor protecting groups operate by partly modifying the intramolecular H-bond network. Thus, we have established a plausible strategy for modulation of the relative reactivity of the 2-, 3- and 4-OH's consistent with the experimentally observed hydrogen bonds. The preparative applicability has been demonstrated and a high yielding synthesis of the protecting group was proposed. Furthermore, we have shown that the designed protecting/directing group can be used to regioselectively react the positions 2 or 3, the selectivity being tuned by the size of the reagent.

Further design and synthesis of more synthetically accessible protecting groups and their application to regioselective glycosylation and alkylation of glucose, mannose and galactose is underway and will be reported in due course. This concept might also be extended to acyclic polyols.

4. Experimental

4.1. General methods

Solvents were distilled and dried by standard methods; THF and ether, from Na/benzophenone; and CH_2Cl_2 from P_2O_5. All commercially available reagents were used without further purification. 4 Å molecular sieves were dried at 100 °C prior to use. Melting points are uncorrected and recorded with a Büchi capillary tube melting-point apparatus. Optical rotations were measured on a Perkin Elmer 141 polarimeter in a 1 dm cell at 20 °C. FTIR spectra were recorded on Perkin Elmer Spectrum 1000 on NaCl windows or KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC 250 or DRX 400 spectrometers (250 and 400 MHz, respectively), or Varian Mercury 300 (300 MHz). Chemical shifts are reported in ppm using the residual of chloroform as internal standard (7.27 ppm for ^{1}H and 77.0 ppm for ^{13}C, respectively). Mass spectra were recorded on a Trio 1000 Thermo Quest spectrometer in the electron impact mode or a Platform Micromass in the electrospray mode. Elemental analyses were obtained on a Perkin Elmer 240C microanalyser. Analytical thin-layer chromatography was performed on Merck 60 F_{254} pre-coated silica gel plates. Visualization was performed by UV or by development using $KMnO_4$, H_2SO_4/MeOH or Mo/Ce solutions. Preparative chromatography was performed on silica gel 60 (230–40 mesh ASTM) at increased pressure.

4.1.1. Methyl 6-*O*-(diphenyl-(2-pyridyl)methyl) α-D-glucopyranoside (1l). To a solution of methyl α-D-glucopyranoside **1a** (5.0 g, 25.7 mmol) in pyridine (100 mL) was added diphenyl-(2-pyridyl)methyl chloride (5.6 g, 20 mmol, prepared from benzophenone and 2-pyridyl lithium as described in the litterature[26]). The mixture was stirred for 48 h then concentrated. The residue was extracted with CH_2Cl_2, washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. Purification by chromatography (CH_2Cl_2/MeOH, 1:0 then 19:1) afforded compound **1l**, which was recrystallized (CH_2Cl_2/hexanes) (4.8 g, 55%, white powder); $R_f = 0.37$ (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D$ −3.5 (*c* 1.2, $CHCl_3$); mp 132 °C; IR (neat/NaCl) 3400, 1587 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.57 (d, 1H, J=4.5 Hz), 7.63 (dd, 1H, J=7.5, 8.0 Hz), 7.50–7.22 (m, 11H), 7.16 (dd, 1H, J=4.5, 7.5 Hz), 4.78 (d, 1H, J=3.5 Hz), 4.11 (dd, 1H, J=9.0, 9.5 Hz), 3.85 (dd, 1H, J=9.5, 9.5 Hz), 3.75–3.65 (m, 2H), 3.58 (dd, 1H, J=3.5, 9.5 Hz), (3.34 (s, 3H), 3.13 (dd, 1H, J=3.5, 9.5 Hz), 2.95 (bs, 1H), 2.20 (d, 1H, J=9.5 Hz); ^{13}C NMR (65 MHz, $CDCl_3$) δ 161.8, 147.8, 143.6, 142.2, 136.3, 129.2, 128.4, 127.6, 127.3, 127.0, 123.7, 121.6, 99.4, 86.5, 73.5, 71.9, 71.0, 70.4, 64.7, 54.7; LRMS (EI+, *m/z*, %): 438 (11) $(M+H^+)$, 437 (13) (M^+), 260 (100) $(Pyr(Ph)_2CO^+)$, 244 (92) $(Pyr(Ph)_2C^+)$; HRMS (*m/z*): $[M+H]^+$ calcd for $C_{25}H_{27}NO_6$ 437.18384, found 437.18463; Anal. calcd for $C_{25}H_{27}NO_6$: C, 68.63; H, 6.22; N, 3.20; found: C, 68.57; H, 6.24; N, 3.18.

4.1.2. Methyl 6-*O*-picolinyl α-D-glucopyranoside (1m). To a solution of methyl α-D-glucopyranoside **1a** (5.0 g, 25.7 mmol) in collidine (40 mL) was added picolinyl chloride (3.5 g, 25 mmol) at −20 °C. The resulting mixture was stirred for 3 h at −20 °C and for 6 h at room temperature. After evaporation, the residue was extracted with EtOH/CH_2Cl_2 1:1, filtrated and concentrated in vacuo. The residue was purified three times by chromatography (MeOH/CH_2Cl_2, 9:1) to afford compound **1m** (1.9 g, 26%, yellowish gum); $R_f = 0.31$ (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D$ +90.4 (*c* 1.1, $CHCl_3$); IR (neat/NaCl) 3418, 1731 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.76 (d, 1H, J=4.5 Hz), 8.13 (d, 1H, J=8.0 Hz), 7.86 (ddd, 1H, J=1.5, 8.0, 8.0 Hz), 7.50 (ddd, 1H, J=1.5, 4.5, 8.0 Hz), 4.88 (d, 1H, J=3.5 Hz), 4.83 (dd, 1H, J=4.5, 12.0 Hz), 4.60 (dd, 1H, J=2.0, 12.0 Hz), 4,25 (m, 1H), 3.90 (m, 1H), 3.88 (m, 1H), 3.82 (dd, 1H, J=9.5, 9.5 Hz), 3.60 (m, 2H), 3.45 (s, 3H), 1.98 (m, 2H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 164.9, 147.5 (2), 137.3, 127.1, 125.3, 99.6, 73.9, 71.9, 70.1, 69.6, 64.7, 55.2; LRMS (EI+, *m/z*, %): 300 (21) $(M+H^+)$, 124

(100) ($PyCOOH+H^+$), 106 (90) ($PyrCO^+$); HRMS (*m/z*): $[M+H]^+$ calcd for $C_{13}H_{18}NO_7$ 300.1083, found 300.1093.

4.1.3. Methyl 6-*O*-diphenyl-(2-(4-dimethylaminopyridyl)methyl α-D-glucopyranoside (1n). A suspension of diphenyl-(2-(4-dimethylaminopyridyl)methanol (4.4 g, 14.5 mmol, prepared from 4-dimethylaminopyridine and benzophenone as described by Fort)[26] in water (50 mL) and conc. HCl (5 mL) was refluxed for 1 h. The resulting mixture was concentrated and the residue precipitated in ether. A solution of this white powder in AcCl (12 mL) and $SOCl_2$ (18 mL) was stirred for 72 h then concentrated at rt and co-evaporated twice with toluene. To this crude mixture was added a solution of pyranoside **1a** (10 g, 51.4 mmol) in pyridine (200 mL). The resulting mixture was stirred for a further 48 h, concentrated, extracted with CH_2Cl_2, filtrated, washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography (CH_2Cl_2/MeOH, from 19:1 to 9:1) to afford compound **1n** (1.2 g, 17%, white powder); $R_f=0.21$ (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D+16.1$ (*c* 1.0, $CHCl_3$); IR (neat/NaCl) 3403, 1586 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, 1H, *J*=4.0 Hz), 7.52–7.44 (m, 4H), 7.36–7.24 (m, 4H), 6.47 (s, 1H), 6.41 (m, 1H), 4.75 (br s, 1H), 4.06 (dd, 1H, *J*=7.5, 9.0 Hz), 3.86 (dd, 1H, *J*=8.5, 9.0 Hz), 3.73–3.63 (m, 3H), 3.32 (s, 3H), 3.09 (d, 1H, *J*=9.5 Hz), 2.91 (s, 7H), 2.30 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 154.3, 147.3, 144.9, 142.4, 130.1, 129.9, 128.3, 128.1, 127.8, 127.7, 127.6, 127.2, 121.6, 107.6, 105.5, 99.6, 86.9, 74.1, 72.5, 71.1, 70.8, 65.3, 55.1, 39.0; LRMS (EI+, *m/z*, %): 481 (29) ($M+H^+$), 287 (100) ($DMAP(Ph)_2CO^+$); Anal. calcd for $C_{27}H_{32}N_2O_6$: C, 67.48; H, 6.71; N, 5.83; found: C, 67.55; H, 6.70; N, 5.80.

4.1.4. Methyl 6-*O*-diphenyl-(thiophenyl)methyl α-D-glucopyranoside (1o). Using the procedure as for compound **1m**, a solution of methyl α-D-glucopyranoside **1a** (4.56 g, 23.5 mmol) in pyridine (100 mL) and diphenylthiophenylmethyl chloride (2.55 g, 8.97 mmol, prepared from 4,4′-dimethyl benzophenone and bromopyridine as described in the litterature[1]) afforded, after chromatography (CH_2Cl_2/MeOH, 1:0 then 19:1), compound **1o**, which was precipitated (CH_2Cl_2/hexanes) (2.05 g, 52%, white powder); $R_f=0.49$ (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D+64.2$ (*c* 1.0, $CHCl_3$); mp 150 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 7.52 (m, 3H), 7.39–7.22 (m, 9H), 7.00 (m, 1H), 4.79 (d, 1H, *J*=3.5 Hz), 3.75–3.62 (m, 2H), 3.62–3.45 (m, 4H), 3.45 (s, 3H), 2.61 (s, 1H), 2.51 (d, 1H, *J*=1.0 Hz), 2.08 (d, 1H, *J*=9.5 Hz); ^{13}C NMR (65 MHz, $CDCl_3$) δ 144.0, 143.8, 128.3, 127.9, 127.5, 126.4, 126.1, 99.0, 84.8, 74.6, 72.1, 71.6, 70.0, 64.0, 55.2; LRMS (EI+, *m/z*, %): 443 (3) ($M+H^+$), 442 (8) (M^+), 265 (10) ($Th(Ph)_2CO^+$), 249 (100) ($Th(Ph)_2C^+$); Anal. calcd for $C_{24}H_{26}O_6S$: C, 65.14; H, 5.92; found: C, 64.89; H, 5.85.

4.1.5. Methyl 6-*O*-ditolyl-(2-pyridyl)methyl α-D-glucopyranoside (1p). To a suspension of NaH (730 mg, 18.2 mmol) in THF (20 mL) was added a solution of ditolyl-(2-pyridyl)methanol (3.5 g, 12.1 mmol, prepared from 4,4′-dimethyl benzophenone and bromopyridine as described in the literature[26]) in THF (100 mL) at 0 °C. After stirring for 1 h, $SOCl_2$ (1.15 mL, 15.7 mmol) was added and the mixture was stirred for a further 5 h. The mixture was diluted with chloroform and washed with satd $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated in vacuo. To the obtained residue was added a solution of methyl α-D-glucopyranoside **1a** (7.0 g, 36.3 mmol) in pyridine (150 mL). The mixture was stirred for 48 h then concentrated and purified twice by chromatography (CH_2Cl_2/MeOH, 1:0 then 19:1) to afford compound **1p**, which was recrystallized (CH_2Cl_2/hexanes) into highly pure compound (2.85 g, 50%, yellow powder); $R_f=0.38$ (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D+0.6$ (*c* 1.1, $CHCl_3$); mp 112 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 8.54 (d, 1H, *J*=5.0 Hz), 7.63 (ddd, *J*=1.5, 7.5, 7.5 Hz), 7.40–7.05 (m, 10H), 4.76 (d, 1H, *J*=3.5 Hz), 4.05 (dd, 1H, *J*=9.0, 9.0 Hz), 3.85 (dd, 1H, *J*=9.0, 9.0 Hz), 3.70 (m, 2H), 3.60 (dd, 1H, *J*=3.5, 9.5 Hz), 3.34 (s, 3H), 3.22 (dd, 1H, *J*=3.5, 9.5 Hz), 2.97 (bs, 1H), 2.38 (s, 3H), 2.32 (s, 3H), 2.22 (d, 1H, *J*=9.5 Hz); ^{13}C NMR (65 MHz, $CDCl_3$) δ 161.9, 147.8, 141.1, 139.2, 137.2, 136.8, 136.4, 129.4, 128.5, 128.4, 128.3, 124.4, 121.8, 99.6, 86.5, 73.7, 72.2, 71.3, 70.5, 64.9, 55.0, 20.9, 20.8; LRMS (EI+, *m/z*, %): 466 (10) ($M+H^+$), 465 (28) (M^+), 288 (100) ($Pyr(Tol)_2CO^+$), 273 (75) ($Pyr(Tol)_2C+H^+$), 272 (70) ($Pyr(Tol)_2C^+$); Anal. calcd for $C_{27}H_{31}NO_6$: C, 69.66; H, 6.71; N, 3.01; found: C, 69.48; H, 6.77; N, 3.00.

4.2. Preparation of compounds 1q and 1r

4.2.1. 6-(Hydroxy-di-*p*-tolyl-methyl)-pyridine-2-carboxylic acid methyl ester (6). To a solution of dimethyl-2,6-pyridinedicarboxylate **5** (5.0 g, 25.6 mmol) in THF (200 mL) was added *p*-tolylmagnesium bromide (1 M solution in ether, 25 mL, 25 mmol) at rt. After stirring for 30 min, another portion of *p*-tolylmagnesium bromide (20 mL, 20 mmol) was added at −78 °C. The mixture was stirred at −78 °C for 1 h then allowed to warm up to rt over 2 h and quenched with satd NH_4Cl. The mixture was diluted with $CHCl_3$ then washed with satd $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by chromatography (H/EA, 4:1 then 7:3) to afford the alcohol **6** (4.04 g, 45%, brownish oil); $R_f=0.45$ (H/EA, 7:3); IR (neat/NaCl) 3427, 1728, 1587 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.07 (d, 1H, *J*=7.3 Hz), 7.78 (dd, 1H, *J*=7.3, 7.3 Hz), 7.33 (d, 1H, *J*=7.3 Hz), 7.17 (d, 4H, *J*=8.0 Hz), 7.12 (d, 4H, *J*=8.0 Hz), 6.29 (s, 1H), 3.98 (s, 3H), 2.35 (s, 6H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 164.8, 163.5, 145.6, 142.7, 137.0, 136.7, 128.3, 127.7, 125.8, 123.3, 80.3, 52.2, 20.6; LRMS (EI+, *m/z*, %): 348 (4) ($M+H^+$), 346 (11) (M^+), 119 (100), 91 (63) (Tol^+); HRMS (*m/z*): $[M+H]^+$ calcd for $C_{22}H_{22}NO_3$ 348.1599, found 348.1592.

4.2.2. 1-[6-(Hydroxy-di-*p*-tolyl-methyl)-pyridin-2-yl]-2-pyridin-2-yl-ethanol (7a). To a solution of 2-picoline (4.7 mL, 47.3 mmol) in THF (100 mL) at −78 °C was added BuLi (1.6 M solution in hexanes, 27.3 mL, 44.5 mmol) dropwise. After stirring for 30 min, this solution was cannulated to a solution of alcohol **6** (4.7 g, 13.5 mmol) in THF (200 mL) at −78 °C. The resulting mixture was stirred for a further 1.5 h at −40 °C then quenched with satd NH_4Cl. The mixture was diluted with $CHCl_3$ then washed with satd $NaHCO_3$, water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was filtrated on a silica gel pad then precipitated in hexanes to afford the enol **7a**

(4.6 g, 83%, yellow powder); $R_f = 0.40$ (H/EA, 1:1); ^{1}H NMR (250 MHz, $CDCl_3$, 4:1 mixture of isomers) δ 8.52 (d, 0.2H, $J = 4.5$ Hz), 8.35 (d, 0.8H, $J = 4.5$ Hz), 8.01 (d, 0.2H, $J = 4.5$ Hz), 7.92 (d, 0.8H, $J = 4.5$ Hz), 7.82–7.55 (m, 2H), 7.33–7.01 (m, 12.2H), 6.83 (s, 0.8H), 6.52 (s, 0.8H), 5.83 (s, 0.2H), 2.35 (s, 6H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 162.2, 161.1, 158.1, 151.5, 149.6, 144.4, 143.5, 142.9, 137.4, 137.3, 137.0, 136.9, 136.5, 128.6, 128.5, 128.1, 127.9, 126.3, 124.1, 123.0, 122.5, 121.6, 120.8, 119.2, 118.6, 96.2, 80.4, 21.0; LRMS (EI+, *m/z*, %): 409 (19) ($M+H^+$), 408 (48) (M^+), 91 (Tol^+); HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{25}N_2O_2$ 409.1916, found 409.1915.

4.2.3. 1-[6-(Hydroxy-di-*p*-tolyl-methyl)-pyridin-2-yl]-2-phenyl-ethanone (7b). To a solution of toluene (12.8 mL, 120 mmol) in THF (125 mL) at −78 °C was added *t*-BuLi (1.7 M solution in pentane, 25 mL, 42.3 mmol) dropwise. After stirring for 1 h, this solution was cannulated onto a solution of alcohol **6** (4.2 g, 12.1 mmol) in THF (125 mL) at −78 °C. The resulting mixture was stirred for a further 1.5 h at −50 °C then was quenched with satd NH_4Cl, diluted with $CHCl_3$, washed with satd $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography (H/EA, 4:1) to afford ketone **7b** (1.70 g, 35%, colorless oil) along with starting material **6** (1.25 g, 30%); $R_f = 0.57$ (H/EA, 4:1); IR (neat/NaCl) 3452, 1697, 1583 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.99 (d, 1H, $J = 7.5$ Hz), 7.78 (d, 1H, $J = 7.5$, 7.5 Hz), 7.35 (d, 1H, $J = 7.5$ Hz), 7.32–7.10 (m, 13H), 5.68 (s, 1H), 4.49 (s, 2H), 2.36 (s, 6H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 163.2, 150.8, 142.7, 137.4, 137.0, 134.2, 130.4, 129.6, 128.6, 128.4, 128.0, 127.9, 127.7, 126.6, 126.2, 120.9, 80.7, 44.5, 20.9; LRMS (EI+, *m/z*, %): 408 (12) ($M+H^+$), 407 (32) (M^+), 389 (50), 119 (90), 91 (100) (Tol^+); HRMS (*m/z*): $[M-OH]^+$ calcd for $C_{28}H_{24}NO$ 390.1858, found 390.1866.

4.2.4. 1-[6-(Hydroxy-di-*p*-tolyl-methyl)-pyridin-2-yl]-2-pyridin-2-yl-ethanol (8a). A solution of enol **7a** (3.5 g, 8.55 mmol) in EtOH/THF (1:2, 250 mL) was stirred under hydrogen (1 atm) in presence of 10% Pd/C (3.3 g) for 24 h. The catalyst was filtered off and the solution concentrated in vacuo. The residue was purified by chromatography (H/EA, 2:1 then 1:1 then 1:4) to afford diol **8a** (2.11 g, 60%, yellowish powder); $R_f = 0.38$ (H/EA, 1:1); IR (neat/NaCl) 3383, 1593, 1572 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.49 (d, 1H, $J = 4.5$ Hz), 7.62 (dd, 1H, 7.5, 7.5 Hz), 7.56 (dd, 1H, $J = 8.0$, 9.5 Hz), 7.52 (d, 1H, $J = 7.3$ Hz), 7.21–7.08 (m, 9H), 7.06 (d, 1H, $J = 8.0$ Hz), 6.97 (d, 1H, $J = 7.3$ Hz), 6.25 (s, 1H), 6.15 (bs, 1H), 5.26 (dd, 1H, $J = 3.0$, 8.5 Hz), 3.42 (dd, 1H, $J = 3.0$, 14.5 Hz), 3.22 (dd, 1H, $J = 8.5$, 14.5 Hz), 2.36 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 161.8, 160.9, 159.1, 148.1, 143.4, 143.3, 136.8, 136.5, 128.3, 127.8, 123.8, 121.4, 120.9, 118.7, 80.2, 73.3, 43.2, 20.8; LRMS (EI+, *m/z*, %): 411 (19) ($M+H^+$), 410 (63) (M^+), 300 (52), 299 (47), 119 (93), 93 (100), 91 (78) (Tol^+); HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{27}N_2O_2$ 411.2072, found 411.2083.

4.2.5. 1-[6-(Hydroxy-di-*p*-tolyl-methyl)-pyridin-2-yl]-2-phenyl-ethanol (8b). To a suspension of $LiAlH_4$ (225 mg, 5.9 mmol) in THF (75 mL) at 0 °C was added a solution of ketone **7b** (801 mg, 1.97 mmol) in THF (25 mL) dropwise. After stirring for 1 h, water was added followed by 3 N NaOH then water. The resulting mixture was extracted with CH_2Cl_2. The aqueous layers were mixed then washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography (H/EA, 1:1) to afford diol **8b** (560 mg, 70%, colorless oil); $R_f = 0.32$ (H/EA, 4:1); IR (neat/NaCl) 3411, 1591, 1575 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.60 (dd, 1H, $J = 7.5$, 7.5 Hz), 7.30–7.07 (m, 15H), 7.02 (d, 1H, $J = 7.5$ Hz), 5.71 (bs, 1H), 5.04 (dd, 1H, $J = 5.0$, 7.5 Hz), 3.20 (dd, 1H, $J = 5.0$, 14.0 Hz), 3.05 (dd, 1H, $J = 7.5$, 14.0 Hz), 3.30–2.80 (bs, 1H), 2.37 (s, 6H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 162.6, 159.9, 143.3, 143.2, 137.0, 136.9, 129.6, 128.5, 128.3, 128.0, 126.5, 121.6, 119.1, 80.6, 74.4, 44.6, 21.0; LRMS (EI+, *m/z*, %): 410 (15) ($M+H^+$), 409 (56) (M^+), 300 (74), 119 (80), 91 (100) (Tol^+); HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{28}NO_2$ 410.2120, found 410.2137.

4.2.6. [6-(2-Pyridin-2-yl-vinyl)-pyridin-2-yl]-di-*p*-tolyl-methanol (9a). To a solution of diol **8a** (1.85 g, 4.50 mmol) in THF (130 mL) at −78 °C was added NaHMDS (2 M solution in THF, 5.6 mL, 11.2 mmol) followed by a solution of $PhNTf_2$ (1.93 g, 5.41 mmol) in THF (20 mL). The resulting mixture was stirred for 2 h then quenched with satd NH_4Cl, diluted with $CHCl_3$, washed with water and brine, dried over Na_2SO_4 then concentrated in vacuo. The residue was purified by chromatography (H/EA, 9:1 then 3:2) to afford olefin **9a** (1.33 g, 76%, colorless oil); $R_f = 0.33$ (H/EA, 1:1); IR (neat/NaCl) 3370, 1586, 1567 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.64 (d, 1H, $J = 4.5$ Hz), 7.72 (m, 3H), 7.64 (dd, 1H, $J = 7.5$, 7.5 Hz), 7.44 (d, 1H, $J = 8.0$ Hz), 7.44 (d, 1H, $J = 7.5$ Hz), 7.21 (m, 5H), 7.11 (d, 4H, $J = 9.0$ Hz), 7.03 (d, 1H, $J = 8.0$ Hz), 6.65 (bs, 1H), 2.36 (s, 6H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 162.9, 154.7, 152.6, 149.6, 143.4, 137.0, 136.8, 136.6, 132.2, 130.8, 128.5, 128.0, 123.2, 122.7, 121.9, 121.6, 80.4, 20.9; LRMS (EI+, *m/z*, %): 393 (18) ($M+H^+$), 392 (88) (M^+), 301 (78), 182 (63), 181 (94), 119 (100), 91 (98) (Tol^+).

4.2.7. (6-Styryl-pyridin-2-yl)-di-*p*-tolyl-methanol (9b). Using the same procedure as for olefin **9a**, a solution of diol **8b** (540 mg, 1.32 mmol) in THF (40 mL) at −78 °C, NaHMDS (2 M solution in THF, 1.65 mL, 3.30 mmol) and a solution of $PhNTf_2$ (565 mg, 1.58 mmol) in THF (10 mL) afforded, after chromatography (H/EA, 1:0 then 9:1), olefin **9b** (430 mg, 83%, colorless oil); $R_f = 0.60$ (H/EA, 4:1); IR (neat/NaCl) 3368, 1584, 1566 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.73–7.56 (m, 3H), 7.45–7.26 (m, 4H), 7.24 (d, 2H, $J = 7.5$ Hz), 7.14 (d, 2H, $J = 7.5$ Hz), 7.01 (d, 1H, $J = 8.0$ Hz), 6.71 (bs, 1H), 2.37 (s, 6H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 162.8, 153.3, 143.5, 136.9, 136.8, 136.4, 133.3, 128.7, 128.5, 128.4, 128.1, 127.1, 121.3, 120.5, 80.4, 21.0; LRMS (EI+, *m/z*, %): 392 (14) ($M+H^+$), 391 (54) (M^+), 300 (61), 180 (82), 119 (100), 91 (81) (Tol^+); HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{26}NO$ 392.2014, found 392.2031.

4.2.8. [6-(2-Pyridin-2-yl-ethyl)-pyridin-2-yl]-di-*p*-tolyl-methanol (10a). A solution of olefin **9a** (1.31 g, 3.34 mmol) in EtOH/THF (1:1, 100 mL) in presence of 10% Pd/C (700 mg) was stirred under H_2 (1 atm) for 1.5 h. The suspension was filtered and the filtrate concentrated in vacuo. The residue was purified by chromatography (H/EA, 4:1 then 1:2) to afford alcohol **10a** (941 mg, 72%, colorless oil); $R_f = 0.45$ (H/EA, 1:1); IR (neat/NaCl) 3350, 1590, 1574 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.42 (d, 1H, $J=$ 3.5 Hz), 7.38 (2dd, 2H, $J=8.0$, 8.0 Hz), 7.08–6.90 (m, 11H), 6.81 (d, 1H, $J=7.5$ Hz), 6.40 (bs, 1H), 3.15 (m, 4H), 2.35 (s, 6H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 162.2, 160.5, 158.6, 148.9, 143.4, 136.4, 136.3, 135.9, 128.2, 127.7, 122.8, 121.1, 120.8, 119.9, 80.0, 37.1, 37.0, 20.7; LRMS (EI+, *m/z*, %): 395 (18) ($M+H^+$), 394 (72) (M^+), 303 (88), 156 (88), 119 (90), 91 (100) (Tol^+); HRMS (*m/z*): $[M+H]^+$ calcd for $C_{27}H_{27}N_2O$ 395.2123, found 395.2131.

4.2.9. (6-Phenethyl-pyridin-2-yl)-di-*p*-tolyl-methanol (10b). Using the same procedure as for alcohol **10a**, a solution of olefin **9b** (480 mg, 1.09 mmol) in EtOH (25 mL) afforded, after chromatography (H/EA, 1:0 then 9:1) alcohol **10b** (403 mg, 94%, colorless oil); $R_f=0.68$ (H/EA, 4:1); IR (neat/NaCl) 3378, 1591, 1574 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.50 (dd, 1H, $J=7.5$, 8.0 Hz), 7.28–7.16 (m, 5H), 7.18 (d, 2H, $J=7.5$ Hz), 7.12 (d, 2H, $J=7.5$ Hz), 6.99 (d, 1H, $J=7.5$ Hz), 6.93 (d, 1H, $J=8.0$ Hz), 6.61 (s, 1H), 3.18–3.03 (m, 4H), 2.35 (s, 6H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 162.4, 158.9, 143.6, 141.2, 136.6, 136.5, 128.4, 128.2, 128.0, 125.8, 121.4, 120.2, 80.2, 39.4, 35.2, 20.9; LRMS (EI+, *m/z*, %): 394 (11) ($M+H^+$), 393 (49) (M^+), 302 (45), 156 (48), 119 (76), 91 (100) (Tol^+); HRMS (*m/z*): $[M+H]^+$ calcd for $C_{28}H_{28}NO$ 394.2171, found 394.2445.

4.2.10. Methyl 6-*O*-[6-(2-Pyridin-2-yl-ethyl)-pyridin-2-yl]-di-*p*-tolyl-methyl-α-D-glucopyranoside (1q). A suspension of alcohol **10a** (910 mg, 2.3 mmol) in water (18 mL) and conc. HCl (2 mL) was refluxed for 1 h. The resulting mixture was concentrated and the residue precipitated in ether. A solution of this white powder in AcCl (4 mL) and $SOCl_2$ (6 mL) both freshly distilled was stirred for 48 h then concentrated at rt and co-evaporated twice with toluene. To the crude alkyl chloride **11a** was added a solution of pyranoside **1a** (1.8 g, 9.2 mmol) in pyridine (40 mL) and the mixture was stirred for 48 h, concentrated, extracted with CH_2Cl_2, filtrated, washed with water and brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography (CH_2Cl_2/MeOH, from 49:1 to 9:1) to afford protected compound **1q** (820 mg, 63%, white powder) along with recovered alcohol **10a** (205 mg, 23%); $R_f=0.39$ (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D+56.0$ (*c* 0.3, $CHCl_3$); mp 92 °C; IR (neat/NaCl) 3400, 1589, 1573 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.59 (dd, 1H, $J=1.5$, 5.5 Hz), 7.55 (ddd, 1H, $J=$ 1.5, 8.0, 8.0 Hz), 7.53 (dd, 1H, $J=8.0$, 8.0 Hz), 7.38 (d, 2H, $J=8.0$ Hz), 7.28 (d, 2H, $J=8.0$ Hz), 7.26 (dd, 1H, $J=5.5$, 8.0 Hz), 7.17–7.09 (m, 6H), 7.05 (d, 1H, $J=7.5$ Hz), 4.71 (d, 1H, $J=3.5$ Hz), 4.70 (bs, 1H), 3.94 (m, 1H), 3.85 (m, 2H), 3.65 (m, 1H), 3.35 (s, 3H), 3.33–3.05 (m, 6H), 2.37 (s, 3H), 2.33 (s, 3H), 2.29 (d, 1H, $J=9.5$ Hz); ^{13}C NMR (65 MHz, $CDCl_3$) δ 161.7, 160.6, 160.3, 149.2, 141.1, 139.3, 137.3, 136.8, 136.5, 129.5, 128.4, 128.3, 123.1, 122.2, 121.3, 121.2, 99.5, 86.9, 73.7, 73.5, 72.6, 69.7, 66.7, 55.2, 38.9, 38.0, 20.9; LRMS (EI+, *m/z*, %): 571 (2) ($M+H^+$), 570 (5) (M^+), 394 (21), 393 (76), 378 (69) ($PG+H^+$), 377 (56) (PG^+), 376 (100) ($PG-H^+$), 284 (75), 119 (50), 91 (36) (Tol^+); HRMS (*m/z*): $[M+H]^+$ calcd for $C_{34}H_{39}N_2O_6$ 571.2808, found 571.2796.

4.2.11. Methyl 6-*O*-[6-phenethyl-pyridin-2-yl]-di-*p*-tolyl-methyl-α-D-glucopyranoside (1r). Following the same procedure as for compound **1p**, alcohol **10b** (401 mg, 1.02 mmol) in water (10 mL) and conc. HCl (1 mL) led to a white powder that was reacted with AcCl (4 mL) and $SOCl_2$ (6 mL) then with pyranoside **1a** (1.1 g, 5.7 mmol) in pyridine (20 mL) to afford, after chromatography (CH_2Cl_2/MeOH, 49:1 then 19:1), compound **1r** (265 mg, 50%) along with recovered alcohol **10b** (115 mg, 29%); $R_f=0.48$ (CH_2Cl_2/MeOH, 9:1); $[\alpha]_D+0.5$ (*c* 0.8, $CHCl_3$); mp 72 °C; IR (neat/NaCl) 3401, 1586, 1574 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.47 (dd, 1H, $J=7.5$, 8.0 Hz), 7.31 (d, 1H, $J=8.0$ Hz), 7.29–7.08 (m, 13H), 6.91 (d, 1H, $J=$ 7.5 Hz), 6.75 (s, 1H), 4.71 (d, 1H, $J=3.5$ Hz), 3.88–3.80 (m, 2H), 3.76 (m, 1H), 3.64 (ddd, 1H, $J=3.5$, 9.0, 9.0 Hz), 3.41 (ddd, 1H, $J=3.5$, 9.0 Hz), 3.34 (s, 3H), 3.20 (ddd, 1H, $J=$ 5.0, 9.0 Hz), 3.13 (dd, 2H, $J=6.5$, 8.0 Hz), 2.98 (dd, 2H, $J=6.5$, 8.0 Hz), 2.82 (s, 1H), 2.35 (s, 6H), 2.28 (d, 1H, $J=$ 9.0 Hz); ^{13}C NMR (65 MHz, $CDCl_3$) δ 161.5, 160.6, 141.1, 140.3, 140.1, 137.2, 137.1, 136.6, 129.1, 128.9, 128.6, 128.5, 128.2, 125.8, 122.2, 121.3, 99.5, 86.8, 74.0, 72.9, 72.3, 69.8, 65.9, 55.3, 39.3, 36.5, 21.0; LRMS (EI+, *m/z*, %): 570 (14) ($M+H^+$), 569 (27) (M^+), 393 (25), 392 (88), 377 (100) ($PG+H^+$), 376 (60) (PG^+), 376 (100) ($PG-H^+$), 284 (72), 119 (83), 91 (63) (Tol^+); HRMS (*m/z*): $[M+H]^+$ calcd for $C_{35}H_{40}NO_6$ 570.2855, found 570.2903.

4.3. Optimized synthesis of compound 10a

4.3.1. 6-Pyridin-2-ylethynyl-pyridine-2-carboxylic acid methyl ester (15). To a solution of bromopicolinic acid methyl ester **14** (1.88 g, 8.7 mmol.) and 2-ethynylpyridine in a mixture of triethylamine and THF (80 mL, 1:1) were added copper iodide (33 mg, 0.17 mmol) and $PdCl_2(PPh_3)_2$ (244 mg, 0.35 mmol). The resulting mixture was heated to 60 °C and stirred for 2 h. The solid suspension was filtered, concentrated in vacuo and the residue was purified by flash chromatography (H/A/CH_2Cl_2, 4:1:1 then 1:4:1) to afford compound **15** (1.99 g, 96%, light yellow solid); $R_f=0.40$ (EA); IR (neat/NaCl) 1718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, 1H, $J=4.5$ Hz), 8.08 (dd, 1H, $J=1.5$, 7.0 Hz), 7.84 (dd, 1H, $J=8.0$, 8.0 Hz), 7.80–7.58 (m, 3H), 7.26 (m, 1H), 3.97 (s, 3H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 164.2, 149.5, 147.6, 142.0, 141.5, 136.9, 135.6, 130.1, 127.1, 123.9, 123.0, 88.1, 86.4, 52.3; LRMS (EI+, *m/z*, %): 261.5 (100) ($M+Na^+$), 239.5 (66) ($M+H^+$); Anal. calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76; found: C, 70.47; H, 4.22. N, 11.54.

4.3.2. 6-(2-Pyridin-2-yl-ethyl)-pyridine-2-carboxylic acid methyl ester (16). A suspension of ester **15** (1.94 g, 8.15 mmol) and 10% Pd/C (1.9 g) was stirred for 24 h under hydrogen, filtered and concentrated in vacuo. The residue was next purified by chromatography (CH_2/Cl_2/MeOH, 99:1 then 94:6) to afford compound **16** (1.78 g, 90%, light yellow solid); $R_f=0.48$ (CH_2Cl_2/MeOH); IR (neat/NaCl) 1740, 1723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, 1H, $J=$ 4.5 Hz), 7.96 (d, 1H, $J=8.0$ Hz), 7.70 (dd, 1H, $J=8.0$, 8.0 Hz), 7.56 (ddd, 1H, $J=2.0$, 8.0, 8.0 Hz), 7.30 (d, 1H, $J=8.0$ Hz), 7.12 (m, 2H), 4.01 (s, 3H), 3.38 (m, 2H), 3.26 (m, 2H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 165.8, 161.6, 160.5, 149.1, 147.4, 137.0, 136.1, 126.3, 122.9, 122.6, 121.1, 52.7, 37.8, 37.7; LRMS (EI+, *m/z*, %): 265.5 (32) ($M+Na^+$), 243.5 (100) (M+H$^+$); Anal. calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56; found: C, 69.40; H, 5.85. N, 11.50.

4.4. Acetylation reaction

Acetylation—general procedure. To a solution of **1b–1r** (0.25 mmol) in CH_2Cl_2 (50 mL) or THF (25 mL) was added K_2CO_3 (350 mg) then DMAP (0.25 mL of a 0.05 M solution in CH_2Cl_2) and Ac_2O (0.35 mL of a 0.5 M solution in CH_2Cl_2). After stirring for 1 h at rt, the solution was filtrated on a silica gel pad and concentrated in vacuo. Integration on ^{1}H NMR spectra of the mixture permitted accurate measure of the regioselectivity. COSY experimental were done to assign the peaks.

Table 4. Representative chemical shifts of monoacetylated compounds

	2, H-1/H-2	3, H-1/H-3	4, H-1/H-4
1b	4.92/4.73	4.78/5.05	4.86/4.86
1c	4.89/4.70	4.74/5.10	4.82/4.84
1d	4.88/4.69	4.75/5.10	4.79/4.82
1e	4.91/4.72	4.80/5.08	4.83/4.88
1f	4.94/4.70	4.78/5.05	4.80/4.84
1g	5.04/–	4.82/5.12	4.99/4.94
1h	4.96/4.82	4.77/5.33	—
1i	4.96/4.82	4.80/5.32	—
1j	4.97/4.79	4.81/5.32	—
1k	4.91/4.50	4.77/5.05	4.88/4.62
1l	5.02/4.70	4.79/5.26	4.85/5.00
1m	4.92/–	4.78/5.13	— /5.01
1n	4.90/4.87	4.65/5.23	
1o	4.93/4.74	4.80/5.08	4.87/4.88
1p	4.90/4.85	4.75/5.24	4.90/4.97
1q	4.88/4.73	4.76/5.28	4.85/4.94
1r	4.86/4.81	4.71/5.26	4.88/4.95

4.4.1. Methyl 3-*O*-acetyl-6-*O*-[6-(2-Pyridin-2-yl-ethyl)-pyridin-2-yl]-di-*p*-tolyl-methyl-α-D-glucopyranoside (17). To a solution of pyranoside **1q** (143 mg, 0.25 mmol) in CH_2Cl_2 (25 mL) was added K_2CO_3 (350 mg) then DMAP (2.0 mL of a 0.05 M solution in CH_2Cl_2, 0.4 equiv) and Ac_2O (0.60 mL of a 0.5 M solution in CH_2Cl_2, 1.2 equiv) at −78 °C. After stirring for 5 h, the solution was filtrated on a silica gel pad and concentrated in vacuo. Chromatography (H/EA, 2:3 then 1:4) afforded monoacetylated compound **17** (130 mg, 85%) along with other isomers; R_f=0.46 (EA); $[\alpha]_D$+32.9 (*c* 2.0, $CHCl_3$); IR (neat/NaCl) 3378, 3215, 1739 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.50 (d, 1H, *J*=4.5 Hz), 7.54 (ddd, 1H, *J*=1.5, 7.5, 7.5 Hz), 7.48 (dd, 1H, *J*=7.5, 7.5 Hz), 7.30 (m, 4H), 7.22 (d, 1H, *J*=7.5 Hz), 7.14 (m, 7H), 7.00 (d, 1H, *J*=7.5 Hz), 6.50–6.10 (bs, 1H), 5.26 (dd, 1H, *J*=9.5, 9.5 Hz), 4.72 (d, 1H, *J*=3.5 Hz), 3.99 (dd, 1, *J*=9.5, 9.5 Hz), 3.83 (m, 1H), 3.64 (m, 1H), 3.52 (dd, *J*=3.5, 9.5 Hz), 3.37 (s, 3H), 3.30–3.10 (m, 5H), 2.36 (s, 3H), 2.35 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (65 MHz, $CDCl_3$) δ 171.5, 161.6, 161.0, 160.3, 148.8, 140.4, 140.1, 137.1, 136.6, 136.4, 129.0, 128.9, 128.5, 128.4, 123.3, 122.0, 121.2, 121.0, 99.6, 86.8, 75.4, 71.3, 70.5, 70.4, 65.7, 55.2, 38.6, 37.8, 21.0; HRMS (*m*/*z*): [M+H]$^+$ calcd for $C_{36}H_{41}N_2O_7$ 613.2914, found 613.2894.

4.4.2. Methyl 2-*O*-*tert*-butyl dimethyl silyl-6-*O*-[6-(2-pyridin-2-yl-ethyl)-pyridin-2-yl]-di-*p*-tolyl-methyl-α-D-glucopyranoside (18). To a solution of pyranoside **1q** (209 mg, 0.367 mmol) in CH_2Cl_2 (35 mL) was added 2,6-lutidine (1.45 mL of a 0.5 M solution in CH_2Cl_2, 2 equiv) then TBSOTf (345 mg, 1.308 mmol, portionwise as a 100 mg/mL CH_2Cl_2 solution, 3.5 equiv) at −78 °C. After stirring for 3 h, 3 mL of methanol were added at −78 °C, and after warming up to room temperature the solution was filtrated on a silica gel pad and concentrated in vacuo. Chromatography (DCM/MeOH, 99:1, then 95:5) afforded monosilylated compound **18** along with the 3-*O*-TBS isomer as a minor product and recovered starting material **1q** (26 mg); R_f=0.29 (CH_2Cl_2/MeOH, 19:1); IR (neat/NaCl) 3500–3000 (broad), 3054, 2930, 1451, 1265 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (dd, 1H, *J*=8.0, 2.5 Hz), 7.48 (dd, 1H, *J*=8.0, 8.0 Hz), 7.47 (dd, 1H, *J*=8.0, 8.0 Hz), 7.30 (m, 4H), 7.23 (d, 1H, *J*=8.0 Hz), 7.09 (m, 7H), 6.97 (d, 1H, *J*=1.0 Hz), 4.56 (d, 1H, *J*=5.4 Hz), 3.98–3.78 (m, 3H), 3.73–3.60 (m, 2H), 3.42 (d, 1H, *J*=5.0 Hz), 3.36 (m, 1H), 3.33 (s, 3H), 3.27 (d, 1H, *J*=5.0 Hz), 3.19 (m, 5H), 2.46 (t, 1H, *J*=8.0 Hz), 2.34 (s, 3H), 0.93 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 160.7, 160.2, 149.7, 148.9, 140.5, 139.9, 137.1, 136.9, 136.6, 136.4, 129.5, 129.2, 128.7, 128.5, 128.4, 123.2, 122.1, 121.1, 100.4, 86.9, 74.0, 73.4, 73.1, 69.8, 66.4, 55.4, 38.9, 38.0, 26.0, 21.1, 18.4, −4.2, −4.5; HRMS (*m*/*z*): [M+H]$^+$ calcd for $C_{40}H_{53}N_2O_6Si$ 685.3673, found 685.3682.

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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.2005.04.060

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Electrolytic partial fluorination of organic compounds. Part 78: Regioselective anodic fluorination of 2-oxazolidinones

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Abstract—Various 2-oxazolidinones were galvanostatically electrooxidized in the presence of various fluoride salts. It was found that a fluorine atom was introduced to the α-position of the nitrogen atom of *N*-acyl- and *N*-alkoxycarbonyl-2-oxazolidinones to provide the corresponding α-fluorinated products in moderate to good yields. In the case of *N*-phenoxycarbonyl derivative, fluorination took place on the phenyl group selectively.

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1. Introduction

2-Oxazolidinone derivatives have attracted a great deal of interest owing to their wide application in various fields such as material science and medicinal chemistry.[1] For example, oxazolidinones are biologically active compounds use of which has been found as anticonvulsants. Particularly interesting therapeutic properties were found in trimethadione® (3,5,5-trimethyloxazolidine-2,4-dione), paramethadione® (5-ethyl-3,5-dimethyloxazolidine-2,4-dione), and malidone® (3-allyl-5-methyloxazolidine-2,4-dione).[2] Several compounds belonging to this class were shown to display remarkable herbicidal activity, specially in preemergent testing on broadleaf weeds.[3] Recently, it was also reported that oxazolidinones are a new class of synthetic antimicrobial agents active mainly against Gram-positive organisms, including Gram-positive anaerobes.[4] On the other hand, it is well known that the introduction of fluorine atom(s) into organic molecules sometimes enhances or greatly changes their biological activities. 3-Trifluoromethyl-2-oxazolidinone is useful as a synthetic building block for the preparation of organophosphorus compounds, which have insecticidal, miticidal or nematicidal effects.[5] It was also reported that anodic perfluorination of 3-methyl-2-oxazolidinone increased its thermic and electrochemical stability and, on the other hand, decreased its melting and boiling points as well as the viscosity.[6]

Electrochemical partial fluorination methods have been shown to be highly efficient and consequently, they serve as a new tool in fluoro-organic synthesis because the reactions can be carried out under mild conditions using relatively simple equipment with the advantage of avoiding hazardous and toxic reagents.[7] However, the regioselective anodic direct introduction of a fluorine atom into the α-position of nitrogen-containing heterocycles such as β-lactam is generally difficult, and activation by the substituents such as sulfur[8] or silyl groups[9] is necessary. Recently, the anodic fluorination at the α-position of an oxygen atom of cyclic carbonate was successfully carried out in ionic liquids like Et_4NF–5HF under solvent-free conditions.[10] Moreover, anodic fluorination of oxazolidine derivatives[11a] and *N*-protected lactams such as *N*-acyl and *N*-ethoxycarbonyl[11b] was also achieved.

With these facts in mind, in this paper, we attempted the regioselective anodic fluorination of *N*-substituted-2-oxazolidinones under various electrolysis conditions.

2. Results and discussion

2.1. Oxidation potentials of *N*-substituted oxazolidinones 1–3

The substrates **1a** and **1b** were commercial available and other substrates **1c**,[14] **1b**[15], **2a–b**[12] and **3a–c**[13] were prepared according to the literatures.

The oxidation potentials (anodic peak potentials) of oxazolidinones **1–3** were determined by cyclic voltammetry using a platinum disc electrode in 0.1 M Bu_4NClO_4/MeCN

Keywords: 2-Oxazolidinone; Electrochemical fluorination; Partial fluorination; Fluorinated 2-oxazolidinone.

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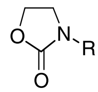
Table 1. Oxidation potentials (peak potentials, E_p^{ox}) of 2-oxazolidinones[a]



1~3

Substrate	R	E_p^{ox} V vs SCE
1a	H	2.52
1b	CH_3	2.37
1c	Ph	1.67
1d	CH_2Ph	2.30
2b	COPh	2.72
3a	$COOCH_3$	2.69
3b	COOPh	2.44

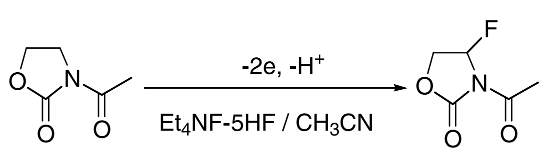
[a] Pt electrodes, 0.1 M Bu_4NClO_4/MeCN, Sweep rate 100 mV/s.

and an SCE reference electrode. These oxazolidinones exhibited irreversible oxidation waves. The first oxidation peak potentials (E_p^{ox}) are shown in Table 1.

It was found that substituents on the nitrogen atom of 2-oxazolidinones affected the oxidation potentials significantly. *N*-Methyl-2-oxazolidinone (**1b**) exhibited a lower oxidation potential than non-substituted oxazolidinone **1a** owing to the electron-donating effect of a methyl group. In addition, on comparison of *N*-phenyl-2-oxazolidinone (**1c**) with **1a**, it was shown that the conjugated effect of the phenyl group caused a considerable decrease in the oxidation potential. On the other hand, the *N*-benzoyl derivative **2b** and *N*-methoxy- and *N*-phenoxycarbonyl derivatives **3a** and **3b** were oxidized at more positive potentials than oxazolidinones with and without alkyl groups, **1a** and **1b**, owing to the electron-withdrawing effect of the benzoyl and ester groups.

2.2. Anodic fluorination of *N*-acyl- and *N*-alkoxycarbonyl-2-oxazolidinones 2 and 3

Initially, anodic monofluorination was investigated in detail using *N*-acetyl-2-oxazolidinone (**2a**) as a model compound.



2a **4a**

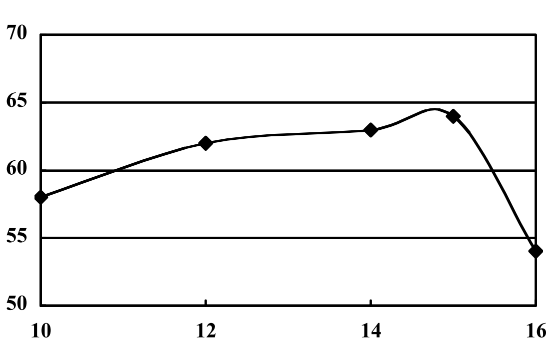


Figure 1. Relationship between the yield of **4a** and electricity. Current density: 15 mA/cm^2.

The fluorination was carried out at a constant current under variation of the current density and electricity by using an undivided cell and platinum electrodes in anhydrous acetonitrile. In consideration of the relatively high oxidation potentials of the substrates, a stable quaternary ammonium salt, Et_4NF–5HF was used as a supporting electrolyte and a fluoride ion source. Fluorination proceeded regardless of the electrolytic conditions to provide the corresponding α-monofluorinated product **4a**. A fluorine atom was regioselectively introduced into the position α to the nitrogen. Fluorination at the α-position of the oxygen did not take place at all. The relationship between the yields of the product **4a** and the electricity passed or the current density is shown in Figures 1 and 2, respectively.

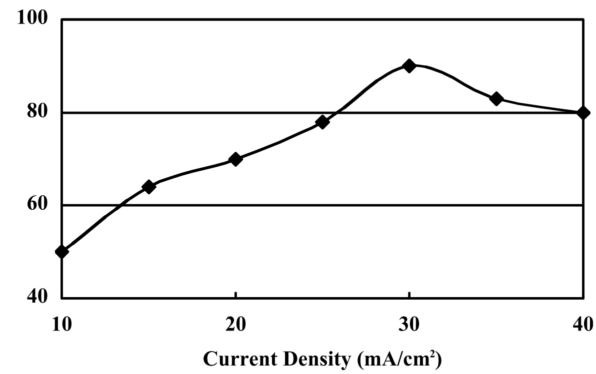
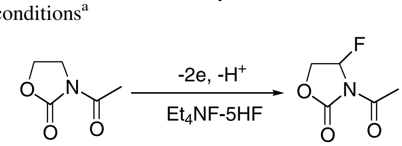


Figure 2. Relationship between the yield of **4a** and current density. Electricity: 15 F/mol.

As shown in Figure 1, the yield of α-monofluorinated 2-oxazolidinone **4a** increased with an increase of the electricity and the maximum yield (64%) was obtained at 15 F/mol of electricity, and then the yield decreased owing to the overoxidation of **4a**. On the other hand, at 15 F/mol of electricity, the yield of **4a** also increased with an increase of current density and the maximum yield (90%) was obtained at 30 mA/cm^2 of current density, and then the yield decreased probably because of simultaneous competitive oxidation of the solvent and the supporting electrolyte as well as the monofluorinated product **4a**. Thus, 30 mA/cm^2 of current density and 15 F/mol of electricity were found to be the most suitable electrolysis conditions for the anodic fluorination of **2a**. The achievement of 90% yield encouraged us to attempt to obtain a quantitative yield by using other electrolysis conditions as shown in Table 2.

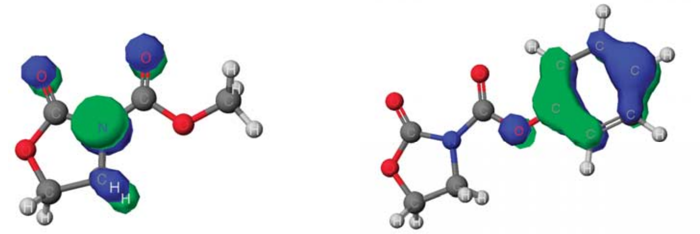
Table 2. Anodic fluorination of 3-acetyl-2-oxazolidinone **2a** under various electrolytic conditions[a]



2a **4a**

Run	Electrode	Solvent	Yield (%)[b]
1	Pt–Pt	CH_3CN	90 (76)[c]
2	GC–Pt	CH_3CN	25
3	Pt–Pt	—	20

[a] Constant current, 30 mA/cm^2; Electricity, 15 F/mol.
[b] Determined by ^{19}F NMR.
[c] Isolated yield.



3a **3b**

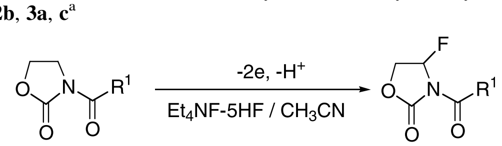
Figure 3. HOMO calculation of **3a** and **3b**.

The use of a glassy carbon anode (GC) instead of a platinum anode resulted in much lower yield (Table 2, Run 2). The electrolysis in an ionic liquid, Et_4NF–5HF, without any solvents was not efficient either (Table 2, Run 3).

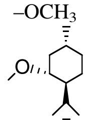
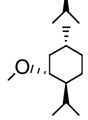
Next, as shown in Table 3, we extended this anodic fluorination to *N*-benzoyl-2-oxazolidinone (**2b**). However, the starting material **2b** was mostly recovered. This is possibly owing to its high oxidation potential (2.72 V vs SCE). On the other hand, anodic fluorination of alkoxycarbonyl derivatives **3a** and **3c** proceeded smoothly in Et_4NF–5HF/CH_3CN to give monofluorinated products **5a** and **5c** in good to moderate yields (Table 3, Runs 2–4). Anodic fluorination of *N*-menthoxycarbonyl-2-oxazolidinone (**3c**) was significantly affected by the current density. Although α-monofluorinated product **5c** was obtained in low yield at 30 mA/cm^2, the yield of **5c** was increased to 56% at a higher current density like 50 mA/cm^2 (Table 3, Run 4). The diastereoselectivity of monofluorinated product **5c** in the both reactions was not observed. In consideration of our highly diastereoselective anodic fluorination through 1,2-asymmetric induction,[16] no diastereoselectivity in this case seems to be attributable to the long distance between the chiral center of the chiral auxiliary and the reaction site.

In sharp contrast, in the anodic fluorination of *N*-phenoxycarbonyl derivative **3b** under the same electrolytic conditions as **3a**, the fluorination took place on the benzene ring instead of the α-position of the nitrogen atom to provide monofluorinated product **5b** in moderate yield as shown in Table 4, Run 1. The yield of **5b** was increased to 55% at a higher current density like 100 mA/cm^2 (Table 4, Run 2). Furthermore, much higher yield of **5b** was obtained at a lower concentration of the substrate **3b** (Table 4, Run 3). In both cases, the applied anode potential should be higher than that in Run 1. These results indicated that a higher anode potential is more effective for the formation of **5b**.

Table 3. Anodic fluorination of *N*-acyl and *N*-alkoxycarbonyl oxazolidinones **2b**, **3a**, **c**[a]

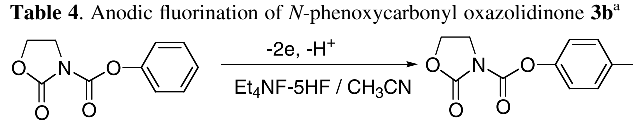


2, 3 **4, 5**

Run	Substrate R[1]	Substrate No.	Current density mA/cm^2	Yield (%)[b]	
1	–Ph	**2b**	30	0	**4b**
2	–OCH_3	**3a**	30	75 (68)	**5a**
3		**3c**	30	27[c]	**5c**
4		**3c**	50	56 (44)[c]	**5c**

[a] Electricity, 15 F/mol.
[b] Determined by ^{19}F NMR. Figures in parentheses are isolated yields.
[c] Diastereomeric ratio: (1:1).

Table 4. Anodic fluorination of *N*-phenoxycarbonyl oxazolidinone **3b**[a]



3b **5b**

Run	Concentration of substrate	Yield (%)[b]
1	0.1 M	48 (35)[c]
2[d]	0.1 M	55
3	0.01 M	70

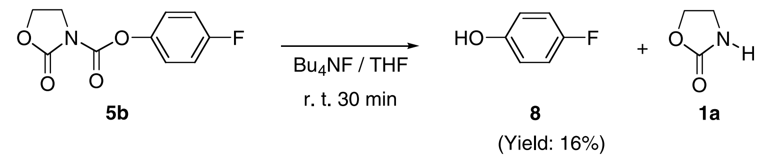
[a] Current density, 30 mA/cm^2; Electricity, 15 F/mol.
[b] Determined by ^{19}F NMR.
[c] Isolated yield.
[d] Current density, 100 mA/cm^2; Electricity, 15 F/mol.

In order to identify the structure of this monofluorinated product, hydrolysis of **5b** was carried out in THF containing Bu_4NF according to the literature.[17] After being stirred at room temperature for 30 min, the *para*-fluorophenol **8** was obtained in 16% yield, which was estimated by ^{19}F NMR. Besides, **8**, 2-oxazolidinone **1a** was also obtained as shown in Scheme 1.

In order to disclose which moiety of **3b** was initially oxidized, the HOMO of **3b** as well as that of methoxycarbonyl derivative **3a** were calculated as shown in Figure 3. The calculations were carried out with the MOPAC 2000 program using PM3. Interestingly, it was found that the HOMO of **3b** was located at the benzene ring, while that of **3a** was located at the nitrogen atom. Therefore, the initial electron transfer should take place at the benzene ring in the case of **3b**. Thus, the fluorination on the benzene ring is reasonably explained.

2.3. Anodic fluorination of 2-oxazolidinone and its *N*-alkyl and *N*-aryl derivatives 1

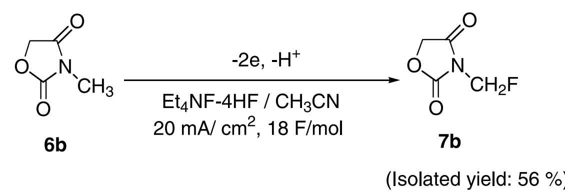
We also attempted the anodic fluorination of 2-oxazolidinone



Scheme 1.

(**1a**) and its various *N*-substituted 2-oxazolidinone derivatives **1b–1d** as shown in Table 5. The reaction of 3-methyl-2-oxazolidinone **1b** was initially carried out using Et_4NF–5HF as a supporting electrolyte. Oxygenation instead of the desired fluorination occurred mainly at the α-position of the nitrogen atom to give the product **6b**. In addition, the monofluorinated product **7b** was also obtained in very low yield (Table 5, Run 2). Considering the high acidity of Et_4NF–5HF, we altered the supporting electrolyte to Et_4NF–4HF to attempt the fluorination of **1b**. The yields of both products **6a** and **7b** increased; however, the desired ring-fluorinated product was not obtained (Table 5, Run 3). The anodic fluorination of other oxazolidinones gave the ring-oxygenated products solely (Table 5, Runs 1, 4 and 5). It is noted that **6a** was obtained from **1c** and the corresponding oxygenated product **6c** was not formed (Table 5, Run 4). Carbonyl derivatives **6** seem to be formed by the hydrolysis of the once-formed monofluorinated **A** followed by further anodic oxidation or the hydrolysis of *gem*-difluorinated products **B** as shown in Scheme 2. However, we have no evidence at the present time.

Furthermore, the resulting product **6** would be further oxidized and the fluorination would take place at the *N*-methyl group to give the monofluorinated product **7**. In support of this hypothesis, we carried out anodic fluorination of 3-methyloxazolidine-2,4-dione **6b** in CH_3CN containing Et_4NF–4HF similarly to the case of **1b**. As expected, the monofluorinated product **7b** was obtained in moderate yield as shown in Scheme 3.

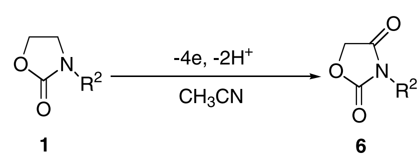


Scheme 3.

2.4. Possible reaction mechanism

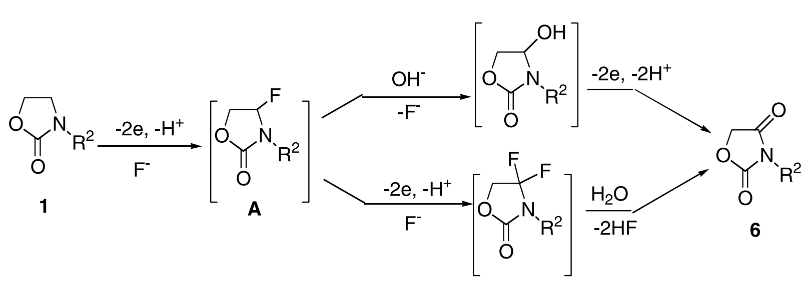
In consideration of the results of the calculation of HOMO of **3a** as a model compound, initial electron transfer should take place at the nitrogen atom of the heterocyclic ring except for **3b** to generate the corresponding radical cation **C**. The deprotonation of **C** and the subsequent oxidation generates the cationic intermediate **D**. This can be explained

Table 5. Anodic fluorination of *N*-alkyl- and *N*-aryl-2-oxazolidinone **1**

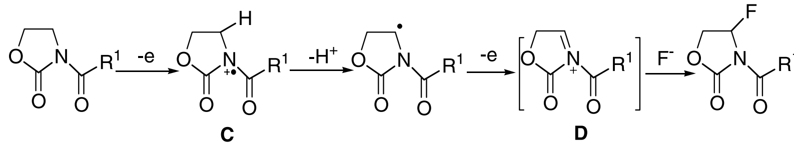


Run	Substrate		Supporting electrolyte	Current density mA/cm^2	Electricity F/mol	Yield (%)[a]	
	R^2	No.					
1	H	**1a**	Et_4NF–4HF	20	18	**6a**	26
2	CH_3	**1b**	Et_4NF–5HF	20	18	**6b**	36[b]
3	CH_3	**1b**	Et_4NF–4HF	20	18	**6b**	42[b]
4	Ph	**1c**	Et_4NF–4HF	20	18	**6a**	22
5	$PhCH_3$	**1d**	Et_4NF–4HF	5	5	**6d**	38

[a] Isolated yield.
[b] 3-Fluoromethyloxazolidine-2,4-dione (**7b**) was also formed in 6–21% yield.



Scheme 2.

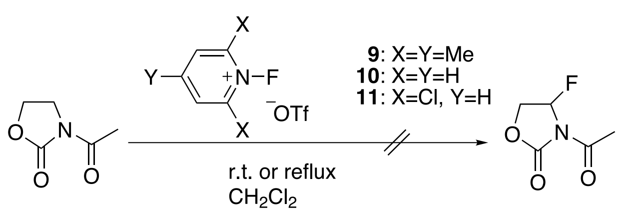


Scheme 4.

in terms of the facilitation of deprotonation of **C** by the electron-withdrawing group on the nitrogen atom.[18] The resulting intermediate **D** followed by attack with a fluoride ion forms α-fluorinated products as shown in Scheme 4.

2.5. Chemical fluorination

N-Fluoropyrindinium salts are known to be good fluorinating reagents. [19] The chemical fluorination of 3-acetyl-2-oxazolidinone **2a** as a model compound was also attempted. However, treatment of **2a** with various *N*-fluoropyridinium triflates in dichloromethane at either room temperature or under reflux resulted in no formation of fluorinated products as shown in Scheme 5. In the case of weakly fluorinating reagent **9**, the starting material was mostly recovered, while the use of strongly fluorinating reagents **10** and **11** caused the decomposition of **2a**.



Scheme 5.

2.6. Conclusion

We have successfully carried out the anodic fluorination of *N*-acyl- and *N*-alkoxycarbonyl-2-oxazolidinones to give the corresponding α-monofluorinated products in good to moderate yields. However, in the case of *N*-phenoxycarbonyl oxazolidinone **3b** the fluorination took place at the benzene ring instead of the α-position of the nitrogen. In sharp contrast, in the case of *N*-alkyl- and *N*-aryl-2-oxazolidinone derivatives as well as unsubstituted 2-oxazolidinone, the ring methylene group at the α-position of the nitrogen atom was converted to a carbonyl group via an unstable mono- and *gem*-difluoromethylene group. Thus, the product selectivity was found to be controlled mainly by the electron-withdrawing ability of the substituents at the nitrogen atom.

3. Experimental

3.1. General

^{1}H NMR (270 MHz), ^{13}C NMR (68 MHz) and ^{19}F NMR (254 MHz) spectra were determined using $CDCl_3$ as a solvent. The chemical shift for ^{19}F NMR is given in δ (ppm) upfield from the peak for external trifluoroacetic acid. The product yields were determined by ^{19}F NMR using monofluorobenzene as an internal standard material. Mass spectra were obtained with SHIMADZU GC–MS QP5050A spectrometer. Cyclic voltammetry was performed using a BAS ALS/HCH Instruments Model 600A, and preparative electrolysis experiments were carried out using a METRONIX constant current power supply 5944 and Coulomb/Amperehour meter HF-201.

3.2. Materials

The starting materials **1a** and **1b** were purchased from TCI Co. Ltd, and used without purification. Other starting materials **1c**[14], **1b**[15], **2a**[12], **2b**[12], **3a**[13], **3b**[13] and **3c**[13] were prepared according to the literatures.

3.2.1. 3-(+)-Menthoxy-carbonyl-2-oxazolidinone (3c). white solid, mp 88–89 °C; yield 56%; ^{1}H NMR ($CDCl_3$) δ 0.79 (d, =7.0 Hz, 3H), 0.91 (d, J=7.0 Hz, 3H), 0.92 (d, J= 6.2 Hz, 3H), 1.01–2.13 (m, 9H), 4.01 (t, J=7.7 Hz, 2H), 4.37 (t, J=8.0 Hz, 2H), 4.75 (td, J=10.8, 4.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.34, 20.88, 22.06, 23.34, 26.23, 31.47, 34.09, 40.79, 43.44, 46.90, 61.45, 77.97, 150.54 (2C); MS m/z 155 ($M^+-C(O)OCH_2CH_2NC(O)$), 138 ($M^+-C(O)OCH_2CH_2NC(O)OH$); Anal. Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.70; H, 8.45; N, 5.15.

Fluoride salts were obtained from Morita Chemical Industries Co. Ltd, (Japan).

3.3. Electrolytic procedures for fluorination

A typical procedure is as follows. Electrolysis was carried out at a platinum anode and cathode (2×2 cm^2, each) in a solvent (10 ml) containing a fluoride salt (1 M) and 1 mmol of **2a** using an undivided glass cell. Constant current (20 mA/cm^2) was passed until the starting material was consumed. After the electrolysis, the resulting electrolytic solution was passed through a short column chromatography on silica gel using ethyl acetate to remove the fluoride salt. The eluent was evaporated under vacuum, and the residue was purified by column chromatography on silica gel using ethyl acetate/hexane (2:1) as an eluent.

3.4. Chemical fluorination using *N*-fluoropyridinium salts

A typical procedure is as follows. To a solution of **2a** (64.5 mg, 0.5 mmol) in dry CH_2Cl_2 (5 ml) was added *N*-fluoropyridinium salt **9–11** and stirred at room temperature overnight or under reflux for 12 h in a nitrogen atmosphere.

3.4.1. 3-Acetyl-4-fluoro-2-oxazolidinone (4a). Yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.58 (s, 3H), 4.49 (dd, J=28.1, 2.7 Hz, 2H), 6.56 (dd, J=63.7, 2.7 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ −59.83 (ddd, J=64.3, 34.3, 24.1 Hz); ^{13}C NMR ($CDCl_3$) δ

23.48, 68.25 (d, $J=28.5$ Hz), 91.03 (d, $J=213.2$ Hz), 152.03, 168.92 (d, $J=2.2$ Hz); MS *m/z* 147 (M^+), 127 (M^+-HF), 119 (M^+-CO), 106 (M^+-COCH); HRMS (*m/z*) calcd for $C_5H_6FNO_3$ 147.0332, found 147.0332.

3.4.2. 3-Methoxycarbonyl-4-fluoro-2-oxazolidinone (5a). Yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 4.50 (m, 2H), 6.44 (dd, $J=65.6$, 4.3 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ -58.27 (ddd, $J=65.8$, 35.1, 22.1 Hz); ^{13}C NMR ($CDCl_3$) δ 54.57, 68.02 (d, $J=27.9$ Hz), 92.69 (d, $J=215.2$ Hz), 149.56 (d, $J=3.3$ Hz), 150.13 (d, $J=2.2$ Hz); MS *m/z* 163 (M^+), 143 (M^+-HF), 133 (M^+-OCH_2), 105 ($M^+-COOCH_2$); HRMS (*m/z*) calcd for $C_5H_6FNO_4$ 163.0281, found 163.0269.

3.4.3. 3-(4-Fluorophenoxycarbonyl)-2-oxazolidinone (5b). Yellow oil; ^{1}H NMR ($CDCl_3$) δ 4.04 (t, $J=8.1$ Hz, 2H), 4.41 (t, $J=8.1$ Hz, 2H), 6.32 (m, 2H), 6.68 (m, 2H); ^{19}F NMR ($CDCl_3$) δ -18.55 (dm, $J=63.8$ Hz); ^{13}C NMR ($CDCl_3$) δ 43.30, 61.69, 128.40–130.04 (6c, arom, m), 146.88, 151.04; MS *m/z* 225 (M^+), 181 (M^+-CO_2); HRMS (*m/z*) calcd for $C_{10}H_8FNO_4$ 225.0437, found 225.0438.

3.4.4. 3-(+)-Menthoxycarbonyl-4-fluoro-2-oxazolidinone (5c). White solid, mp 119–120 °C; ^{1}H NMR ($CDCl_3$) δ 0.79 (d, $J=7.0$ Hz, 3H), 0.91 (d, $J=7.0$ Hz, 3H), 0.92 (d, $J=6.2$ Hz, 3H), 1.01–2.13 (m, 9H), 4.44 (dd, $J=25.4$, 3.0 Hz, 2H), 4.83 (m, 1H), 6.39 (dd, $J=66.2$, 4.1 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ -57.46 (ddd, $J=65.8$, 33.3, 22.1 Hz, 0.5F), -57.78 (ddd, $J=65.8$, 33.3, 22.1 Hz, 0.5F); ^{13}C NMR ($CDCl_3$) δ 16.31, 20.85, 22.01, 23.32, 26.33, 31.47, 34.02, 40.40, 46.87, 67.49, 79.18, 90.94, 94.12 (2C); MS *m/z* 138 ($M^+-C(O)OCH_2CHFNC(O)OH$); Anal. Calcd for $C_{14}H_{22}FNO_4$: C, 58.52; H, 7.72; N, 4.87. Found: C, 58.37; H, 7.31; N, 4.80.

3.4.5. 3-Fluoromethyloxazolidine-2,4-dione (7b). Yellow oil; ^{1}H NMR ($CDCl_3$) δ 4.82 (s, 2H), 5.61 (d, $J=50.8$ Hz, 2H); ^{19}F NMR ($CDCl_3$) δ -102.07 (t, $J=50.8$ Hz); ^{13}C NMR ($CDCl_3$) δ 67.99 (d, $J=12.3$ Hz), 88.65 (d, $J=214.8$ Hz), 158.40, 168.54, MS *m/z* 133 (M^+), 114 (M^+-F), 105 (M^+-CO); HRMS (*m/z*) calcd for $C_4H_4FNO_3$ 133.0175, found 133.0163.

3.4.6. Oxazolidine-2,4-dione (6a),[20a] 3-methyloxazolidine-2,4-dione (6b)[20b], 3-benzyloxazolidine-2,4-dione (6d)[20c], and 4-fluorophenol (8). The compounds were indentified by their ^{1}H NMR and MS spectroscopy.

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Inter- and intramolecular Mitsunobu reaction based approaches to 2-substituted chromans and chroman-4-ones

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Abstract—Two approaches to optically active 2-substituted chromans and chroman-4-ones are described. The first utilized an intermolecular Mitsunobu reaction of a homochiral halopropanol and 2-bromophenol followed by cyclization to the 2-substituted chroman. In addition, a double lithiation procedure was developed to introduce additional functionality to the chroman. The second approach utilized an intramolecular Mitsunobu cyclization to give the 2-substituted chroman-4-one nucleus. The methodologies were applied to the syntheses of several biologically active natural and synthetic products.
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1. Introduction

2-Substituted chromans (benzopyrans) are widely distributed in nature and many show significant biological activity.[1] Examples include α-tocopherol (vitamin E) (**1**),[2] the antibiotic LLD253α (**2**)[3] and the aromatase inhibitor pinostrobin (**3**).[4] In addition, chromans are valued as targets in their own right and several biologically active synthetic chromans have been reported. For example, racemic 4′,6-dichloroflavan (BW683C) (**4**) is a potent in vitro inhibitor of rhinovirus replication (Fig. 1).[5]

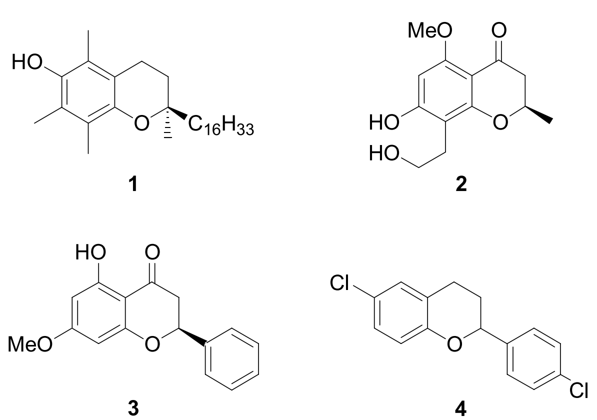
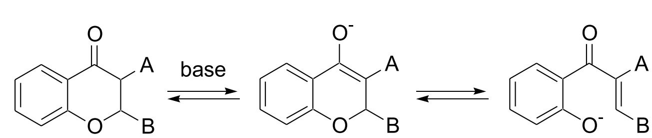


Figure 1.

While there is extensive literature precedent for the synthesis of chromans and chroman-4-ones, few are amenable to the synthesis of single enantiomers. Knight[6a] has reported an approach to 2-substituted chromans based on the intramolecular trapping by alcohols of benzynes generated from 7-substituted-1-aminobenzotriazoles and Sames has developed a method based on a Ruthenium catalyzed cyclization of an arene–alkene substrate.[6b] Routes to 2-substituted chroman-4-ones include the diastereoselective conjugate addition of cuprates to homochiral 3-(*p*-tolylsulfinyl)chromanones described by Wallace[7] and an approach based on the Houben–Hoesch reaction.[8] The synthesis of related 2-substituted chromenes[9] and chromanols[10] has also been reported. Notwithstanding these examples, the preparation and manipulation of substituted chroman-4-ones can be problematic, due in part to the ease with which they undergo racemization via the ring-opening equilibrium shown in Scheme 1.[11]



Scheme 1.

With this in mind, we have evaluated two approaches to 2-substituted chromans and chromanones in which inter- and intramolecular Mitsunobu reactions are key steps (Scheme 2).[12] In the first, halogen–metal exchange of the aryl bromide **6** and subsequent cyclization, should give the chroman **5**.[13] The stereocenter to be located at the 2-position could be installed by a Mitsunobu[14] inversion reaction

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Keywords: Mitsunobu; Cyclization; Chroman; Chromanone.
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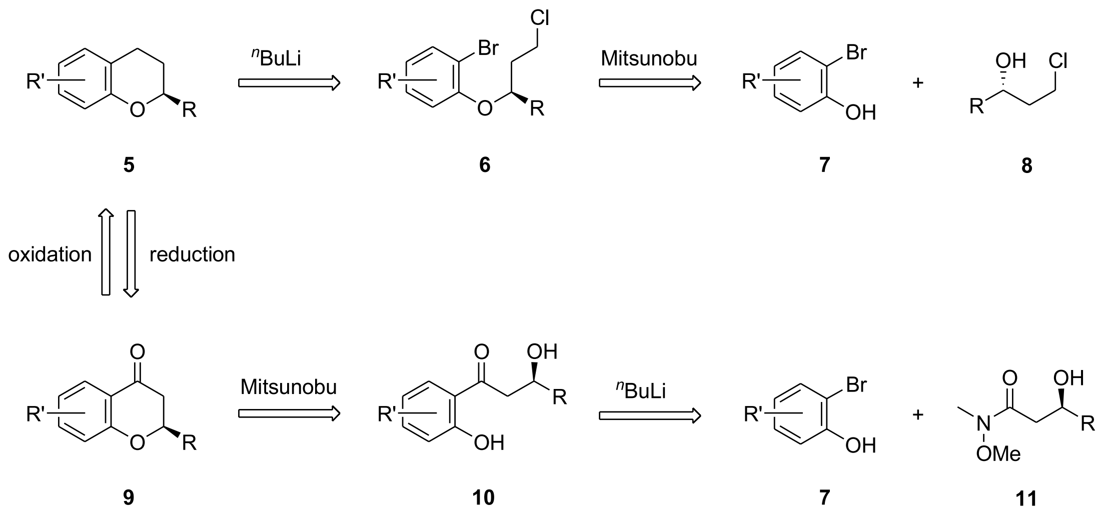
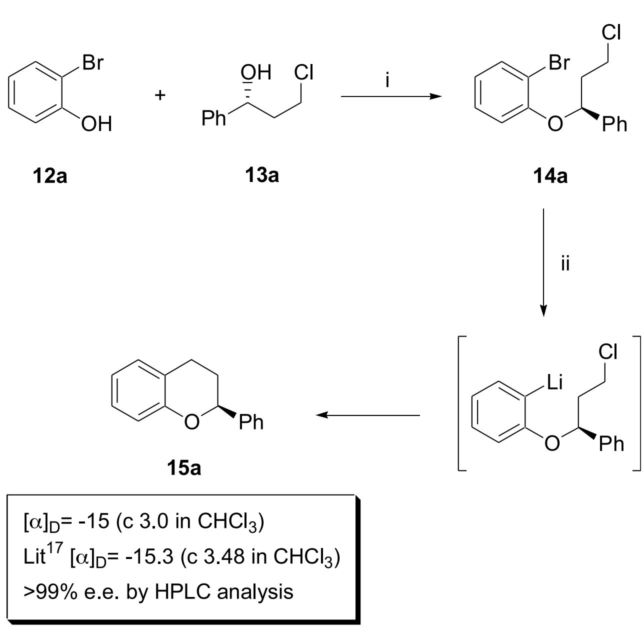


Scheme 2.

between the 2-bromophenol **7** and the appropriately substituted chiral halopropanol **8**. Alternatively, intermolecular Mitsunobu cyclization of the chiral hydroxyphenol **10** should give the chromanone **9**. The hydroxyphenol **10** should be accessible from the 2-bromophenol **7** and the appropriately substituted Weinreb amide **11**. In this paper, we report our results in full detail.[12]

Commercially available (*R*)-3-chloro-1-phenyl-1-propanol (**13a**)[15] was treated with 2-bromophenol (**12**) under standard Mitsunobu[14] inversion conditions and gave, following chromatography, the (*S*)-phenyl ether **14a** in 78% yield (Scheme 3). Initially **14a** was subjected to the cyclization conditions originally described by Parham, but these lead to only moderate yields of the 2-phenylchroman (**15a**). Optimal conditions for the Parham cyclization were found to be a modified version of those recently described by Spoors[16] for the cyclization of 2-(*o*-bromophenoxy)ethyl bromides to benzodihydrofurans; addition of **14a** to 1 equiv of *n*-butyllithium in THF at −50 °C and allowing the reaction to warm to room temperature. Under these conditions, (2*S*)-phenylchroman (**15a**), $[\alpha]_D = -15$ (*c* 3.0 in $CHCl_3$) [lit[17] $[\alpha]_D = -15.3$ (*c* 3.48 in $CHCl_3$)] was obtained in 83% yield. The sign and magnitude of rotation confirmed that the Mitsunobu reaction occurred with inversion and the cyclization without significant racemization. A single recrystallization from methanol gave enantiomerically pure material by HPLC analysis.[18]

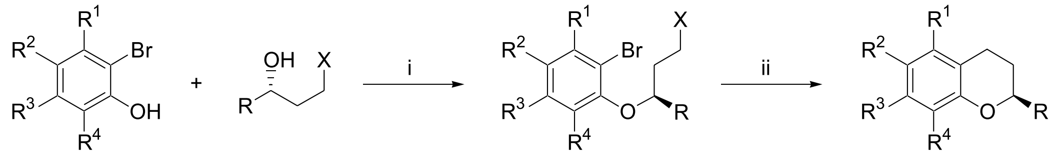


Scheme 3. Reaction conditions: (i) PPh_3, DEAD, THF, RT, 18 h, (78%) (ii) ⁿBuLi, THF, −50 °C to RT (83%).

In order to investigate the utility of the methodology, a variety of commercially available substituted bromophenols **12a–f** were studied in the reaction with (*R*)-3-chloro-1-phenyl-1-propanol (**13a**) (Table 1). The Mitsunobu reaction and cyclization all proceeded in good yields to furnish the (2*S*)-phenyl chromans **15b**, **15c**, **15d**, and **15f**, respectively. Tephrowatsin E (**15f**) was previously isolated from the aerial parts of *Tephrosia watsoniana*.[19] The spectral properties of the synthetic sample were in close agreement with the reported spectral data.[19] The phenyl substituent at the 2-position could be replaced by an alkyl group. For example, repeating the sequence with 2-bromophenol (**12**) and (*S*)-4-bromobutane-2-ol (**13e**)[20] gave (2*R*)-methylchroman (**15e**) in 54% yield and 97% e.e.[18] over the two steps (entry e).

To extend the synthetic utility of the methodology a one-pot cyclization and in situ functionalization of the chroman ring was investigated.[21] The 2,4-dibromo ether **16** was prepared by Mitsunobu reaction as described previously. Halogen–metal exchange was expected to be selective for the bromide adjacent to the ether and this proved to be the case. Addition of **16** to 1 equiv of *n*-butyllithium, in THF at −50 °C and allowing the reaction to warm to room temperature gave the cyclized product, 6-bromo-2-phenylchroman (**17a**) in 84% yield, thereby confirming the selectivity for the *ortho*-bromide. The reaction was repeated, but when the cyclization was judged to be complete, the reaction mixture was re-cooled to −50 °C and the second bromide was exchanged by further addition of *n*-butyllithium. The resultant chromanyl lithium was then quenched by the addition of an excess of an electrophile. A range of electrophiles were screened in the process (entries b, c, d,

Table 1. Reaction conditions: (i) PPh_3, DEAD, THF, RT, 8–36 h; (ii) ^{n}BuLi, THF, −50 °C to RT



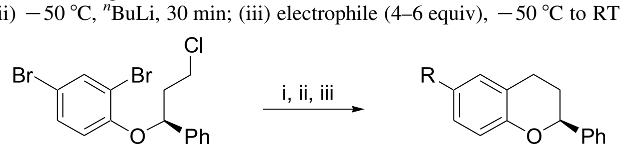
12 **13** **14 a-f** **15 a-f**

Entry	R^1	R^2	R^3	R^4	R	X	Yield **14** (%)	Yield **15** (%)
a	H	H	H	H	Ph	Cl	78	83
b	H	Me	H	H	Ph	Cl	82	77
c	H	Cl	H	H	Ph	Cl	81	78
d	$–(CH)_4–$		H	H	Ph	Cl	64	74
e	H	H	H	H	Me	Br	67	81
f	MeO	H	MeO	H	Ph	Cl	76	78

and e, Table 2) and gave moderated to good yields of the corresponding 6-carbaldehyde **17b**, 6-carboxylic acid **17c**, 6-hydroxymethyl **17d**, and 6-methyl **15b** analogues.

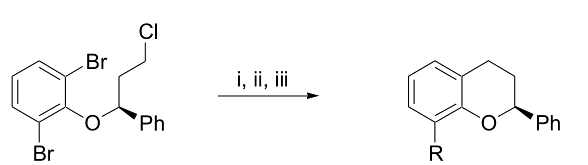
The sequence outlined in Table 2 was repeated with the 2,6-dibromoether **18**. Treatment of the dibromide **18** with 1 equiv of *n*-butyllithium followed by aqueous work-up gave the expected 8-bromo-2-phenylchroman (**19**) in 79% yield. Repeating the reaction, but when the cyclization was judged to be complete, the reaction mixture was re-cooled to −50 °C and *n*-butyllithium was added followed by an excess of DMF. This time 8-carbaldehyde-2-phenylchroman (**20**) was isolated in 76% yield (Scheme 4). The double lithiation procedure allows the introduction of a variety of functional groups to the chroman that would not normally be compatible with the conditions of the original cyclization.

Table 2. Reagents and conditions: (i) ^{n}BuLi, THF, −50 °C to RT, 2 h; (ii) −50 °C, ^{n}BuLi, 30 min; (iii) electrophile (4–6 equiv), −50 °C to RT



16 **17a-d, 15b**

Entry	Electrophile	Product	R	Yield (%)
a	None	**17a**	Br	84
b	DMF	**17b**	CHO	81
c	CO_2 (g)	**17c**	CO_2H	78
d	$(CH_2O)n$	**17d**	CH_2OH	57
e	MeI	**15b**	Me	80



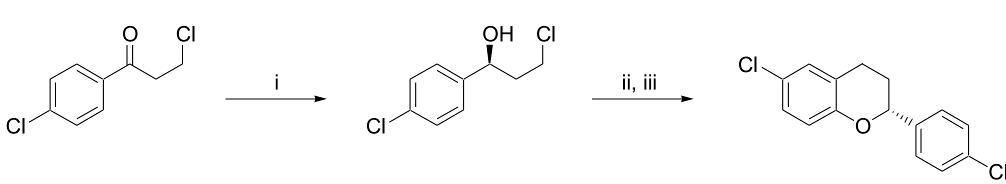
18

19 R = Br (79%)
20 R = CHO (76%)

Scheme 4. Reagents and conditions: (i) ^{n}BuLi, THF, −50 °C to RT, 2 h; (ii) −50 °C, ^{n}BuLi, 30 min; (iii) electrophile (4–6 equiv), −50 °C to RT.

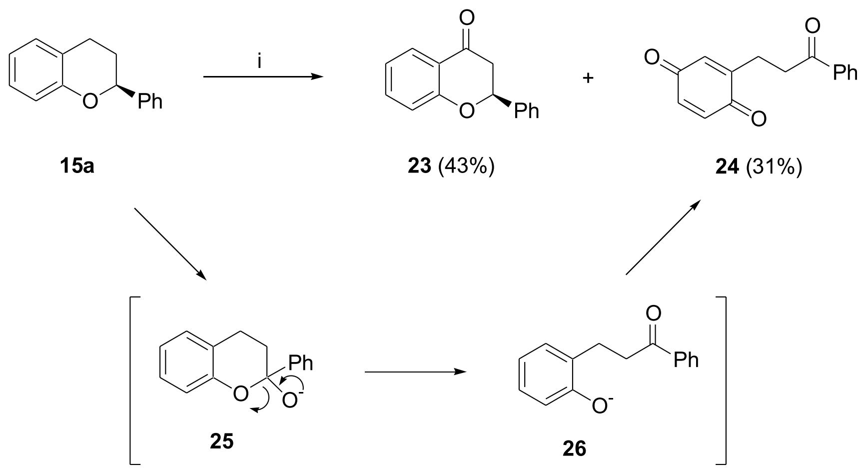
The range of potential substituents located at the chroman 2-position can be extended by taking advantage of the asymmetric reduction of suitable prochiral ketones,[22] as exemplified by the synthesis of enantiomerically pure (*R*)-4′,6-dichloroflavan (**4**) (Scheme 5). Catalytic asymmetric reduction of 3,4′-dichloropropiophenone (**21**) with (*R*)-oxazaborolidine and borane, under the conditions described by Corey,[23] gave (*S*)-3-chloro-1-(4-chlorophenyl)-1-propanol (**22**) in 91% yield and 94% ee as judged by ^{1}H NMR analysis of the MTPA (Mosher) ester.[24] Mitsunobu reaction of **22** with 2-bromo-4-chlorophenol followed by treatment with 1 equiv of *n*-butyllithium under the standard cyclization conditions gave, following recrystallization from methanol, enantiomerically pure BW683C (**4**).[18] Racemic BW683C (**4**) is a potent in vitro inhibitor of rhinovirus replication and was previously isolated in enantiomerically pure form following preparative HPLC using the chiral stationary phase cellulose tris(3,5-dimethylphenylcarba-mate).[25]

2-Substituted chroman-4-ones such as LLD253α (**2**)[3] and pinostrobin (**3**)[4] were also targets for our work. The most direct route appeared to be the oxidation of a chiral 2-substituted chroman to the corresponding chroman-4-one. Several methods for benzylic oxidation are known in the



21 **22** **4**

Scheme 5. Reaction conditions: (i) BH_3, (*R*)-oxazaborolidine, THF, 0 °C, 91%; (ii) 2-bromo-4-chlorophenol, PPh_3, DEAD, THF, RT, 16 h (85%); (iii) ^{n}BuLi, THF, −50 °C to RT (78%).



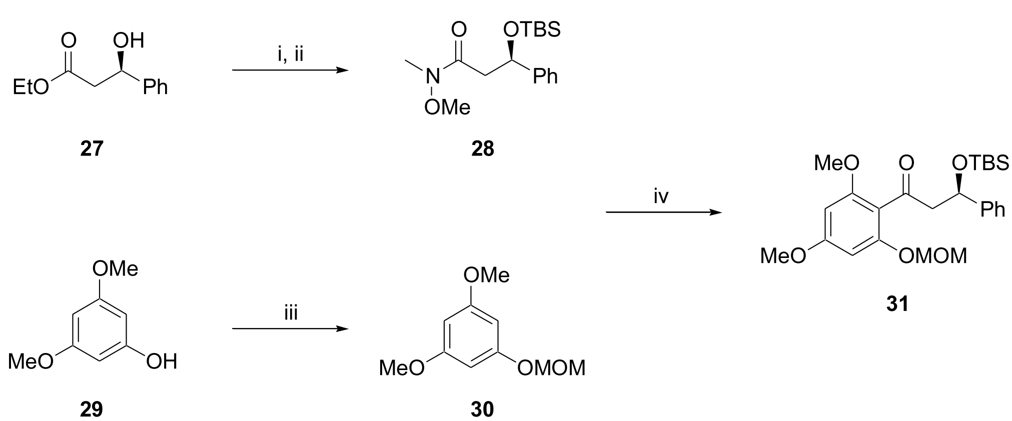
Scheme 6. Reaction conditions: (i) H_5IO_6, CrO_3 (cat), CH_3CN, RT.

literature, these include (i) catalytic chromium(VI) oxide in the presence of periodic acid,[26] (ii) copper sulfate and peroxydisulfate,[27] and (iii) cerium ammonium nitrate in acetic acid.[28] (2*S*)-Phenyl chroman (**15a**)[29] was subjected to the above sets of conditions, but unfortunately yields of the desired 2-phenyl chroman-4-one (**23**)[30] were low and complicated by competing processes. For example, treatment of **15a** with 2 equiv of periodic acid and 5 mol% chromium(VI) oxide in acetonitrile at room temperature gave the desired (2*S*)-phenyl chroman-4-one (**23**) in a moderate 43% yield accompanied by a significant amount of the quinone **24**. The magnitude of rotation of **23** indicated that the oxidation had proceeded without significant racemization. The quinone **24** was presumably formed by competing oxidation at the benzylic chroman-2-position, ring-opening to the phenol **26**, and finally oxidation to the quinone **24** (Scheme 6). The moderate isolated yields in the oxidation step prompted the investigation of an alternative route to 2-substituted chroman-4-ones.

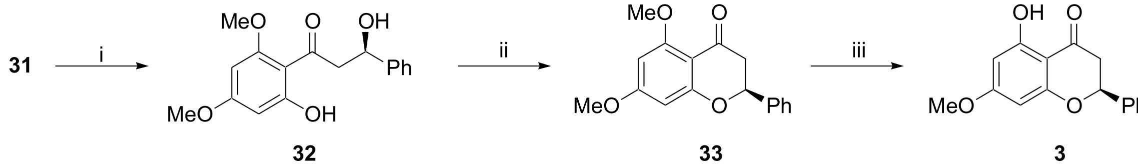
We next investigated an approach to 2-substituted chroman-4-ones based on an intermolecular Mitsunobu cyclization[31] (Scheme 2) and pinostrobin (**3**) was chosen as the target. Pinostrobin (**3**) has been isolated from several natural sources[4] and has also been shown to inhibit aromatase, a cytochrome P450 enzyme converting C19 androgens such as androstenedione and testosterone to estrone and estradiol, respectively.[32] This mode of action could prevent the development of estrogen related tumors such as breast and prostate cancer.[33] In addition, pinostrobin (**3**) has been isolated from *T. graveolens*, a plant used in traditional Mexican medicine for the treatment of gastrointestinal ailments such as diarrhea and stomach pain.[34] It was recently demonstrated that pinostrobrin (**3**) was an active ingredient in *T. graveolens* and inhibited intestinal smooth muscle contractions by a calcium-mediated mechanism.[35] The interesting biological activity made pinostrobin (**3**) an attractive target for synthesis.

The key fragments, Weinreb amide **28** and the methoxymethyl (MOM) protected phenol **30**, were readily prepared from commercially available starting materials. Ethyl (*R*)-3-hydroxy-3-phenylpropanoate (**27**)[36] was protected as the *tert*-butyldimethylsilyl (TBS) ether and then converted into the Weinreb amide **28** (Scheme 7).[37] 3,5-Dimethoxyphenol (**29**) was protected as the MOM ether **30** using standard conditions. The MOM ether **30** was *ortho*-lithiated by treatment with *tert*-butyllithium[31c] in toluene at −78 °C and the Weinreb amide **28** then added to produce the ketone **31** in 72% yield (based on the amide **28**).

The protecting groups on **31** were conveniently cleaved by treatment with 10% *p*=*via*-TsOH in aqueous THF, which gave the hydroxyphenol **32** (Scheme 8). Intramolecular



Scheme 7. Reaction conditions: (i) TBSCl, imidazole, CH_2Cl_2 (94%); (ii) MeONHMe·HCl, Me_3Al, CH_2Cl_2 (82%); (iii) CH_3OCH_2Cl, K_2CO_3, DMF (94%); (iv) ^{t}BuLi, PhMe, −78 °C then **28** (0.5 equiv) (72%).



Scheme 8. Reaction conditions (i) *p*-TsOH (10%), THF/H_2O (9:1), 55 °C (86%); (ii) PPh_3, DEAD, THF, 0 °C (88%); (iii) $AlCl_3$, CH_3CN, reflux (79%).

Mitsunobu cyclization of **32** gave an 88% yield of dimethylpinocembrin **33**.[38] The intramolecular Mitsunobu reaction has been used by several groups to prepare 6- and 7-membered cyclic ethers, but we believe this to be the first example of the formation of an optically active 2-substituted chroman-4-one via such an approach.[31] Regioselective demethylation of **33** with aluminum chloride gave, following chromatography, (−)-pinostrobin (**3**) $[\alpha]_D = -48$ ($c = 1$ in $CHCl_3$) [lit.[4a] $[\alpha]_D = -52.7$ ($c = 1$ in $CHCl_3$)].

In conclusion, we have developed a two-step synthesis of 2-substituted chromans utilizing an intermolecular Mitsunobu reaction and an aryl lithium cyclization as key steps. In addition, a double lithiation procedure was developed to introduce additional functionality into the chroman. Oxidation of 2-phenyl chroman to the corresponding chroman-4-one was possible, but complicated by competing reactions at the benzylic 2-positon. A route to 2-substituted chroman-4-ones was also developed that featured an intramolecular Mitsunobu reaction as the key step. The methodologies were applied to the synthesis of the natural products tephrowatsin E (**15f**) and pinostrobin (**3**) and a biologically active synthetic compound BW683 (**4**).

2. Experimental

2.1. General methods

Melting points were determined using a Thomas–Hoover capillary melting apparatus and are uncorrected. Elemental analyses were performed at Robertson Microlabs, Madison, NJ, USA, and are within 0.4% of theoretical C, H, and N. ^1H and ^{13}C NMR spectra were recorded in deuteriochloroform (unless otherwise noted) with tetramethylsilane as the internal standard on a Varian Unity 400 MHz spectrometer. Coupling constants (*J* values) are quoted to the nearest 0.5 Hz. Mass spectra were recorded on a VG 70SE magnetic sector mass spectrometer. Chiral HPLC analyses were recorded on a CHIRALCEL®OJ-R (4.6 mm×150 mm) column with methanol as the mobile phase and a flow rate of 0.6 mL/min.

Starting materials and solvents were routinely purified by conventional techniques[39] and most reactions were carried out under a nitrogen atmosphere. Organic solutions were dried using anhydrous magnesium sulfate and concentrated by rotary evaporation. Analytical thin layer chromatography (TLC) was carried out on Camlab Polygram SIL G/UV_{254} plates. The chromatograms were visualized by UV light or suitable developing agent. Unless otherwise stated, preparative column chromatography was carried out on 60H silica gel (Merck 9385) using the flash technique.[40] Compositions of solvent mixtures are quoted as ratios of volume.

2.1.1. (*S*)-1-Bromo-2-(3-chloro-1-phenylpropoxy)-benzene (14a). To a stirred solution of triphenylphosphine (1.52 g, 5.8 mmol) and diethyl azodicarboxylate (1.02 g, 5.8 mmol) in THF (10 mL) at 0 °C was added a solution of 2-bromophenol (**12**) (1.0 g, 5.8 mmol) and (*R*)-3-chloro-1-phenyl-1-propanol (**13**) (1.0 g, 5.8 mmol) in THF (5 mL). The mixture was allowed to return to room temperature and stirred overnight or until the reaction was complete by TLC. The THF was removed by evaporation, the residue triturated with hexane (3×50 mL) and the combined hexane fractions concentrated. Flash chromatography of the residue, eluting with hexane, gave the title compound (1.48 g, 78%) as a colorless oil: $[\alpha]_D^{22} + 73$ (*c* 3.0, $CHCl_3$); δ_H (400 MHz) 2.25–2.33 (1H, m), 2.54–2.62 (1H, m), 3.70 (1H, quintet, $J = 5.5$ Hz), 3.92–3.99 (1H, m), 5.48 (1H, dd, $J = 4.5$, 9.0 Hz), 6.74–6.81 (2H, m), 7.09 (1H, t, $J = 8$ Hz), 7.32–7.45 (5H, m), 7.55 (1H, d, $J = 7.5$ Hz); δ_C (100 MHz) 41.27, 41.31, 77.79, 112.63, 115.01, 122.01, 125.80, 128.02, 128.19, 128.79, 133.25, 140.15, 154.08; EI-LRMS *m/z* (relative intensity) 326 and 324 (5%), 153 (95), 117 (48), 91 (100); EI-HRMS calcd. for $C_{15}H_{14}^{81}BrClO$ 325.9896, found 325.9893.

2.1.2. (*S*)-2-Bromo-1-(3-chloro-1-phenylpropoxy)-4-methyl-benzene (14b). The ether **14b** was prepared using the same procedure and scale as described for **14a** but using 2-bromo-4-methylphenol. Flash chromatography of the residue, eluting with hexane, gave the title compound (82%) as a colorless oil: $[\alpha]_D^{22} + 22$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.23 (3H, s), 2.25–2.32 (1H, m), 2.52–2.61 (1H, m), 3.69 (1H, quintet, $J = 5.5$ Hz), 3.92–3.98 (1H, m), 5.43 (1H, dd, $J = 4.0$, 8.5 Hz), 6.64 (1H, d, $J = 8.5$ Hz), 6.88 (1H, d, $J = 8.5$ Hz), 7.30–7.44 (6H, m); δ_C (100 MHz) 20.05, 41.29, 77.92, 112.92, 114.95, 125.87, 127.95, 128.60, 128.73, 131.71, 133.61, 140.33, 151.92 (one signal obscured, 41.29); Anal. $C_{16}H_{16}BrClO$ requires: C, 56.58; H, 4.75. Found: C, 56.79; H, 4.90%.

2.1.3. (*S*)-2-Bromo-4-chloro-1-(3-chloro-1-phenylpropoxy)-benzene (14c). The ether **14c** was prepared using the same procedure and scale as described for **14a** but using 2-bromo-4-chlorophenol. Flash chromatography of the residue, eluting with hexane, gave the title compound (81%) as a colorless oil: $[\alpha]_D^{22}$ −34 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.22–2.30 (1H, m), 2.51–2.60 (1H, m), 3.66 (1H, quintet, $J = 5.5$ Hz), 3.88–3.94 (1H, m), 5.41 (1H, dd, $J = 4.0$, 8.5 Hz), 6.64 (1H, d, $J = 9.0$ Hz), 7.03 (1H, dd, $J = 2.5$, 9.5 Hz), 7.31–7.33 (1H, m), 7.37–7.38 (4H, M), 7.52 (1H, d, $J = 2.5$ Hz); δ_C (100 MHz) 41.17, 78.23, 113.12, 115.63, 125.82, 126.25, 128.05, 128.25, 128.91, 132.74, 139.65, 152.93 (one signal obscured, 41.17); Anal. $C_{15}H_{13}BrCl_2O$ requires: C, 50.03; H, 3.64. Found: C, 49.81; H, 3.79%.

2.1.4. 2-((1*S*)-3-Chloro-1-phenylpropoxyl)-1-bromonaphthalene (14d). The ether **14d** was prepared using the same procedure and scale as described for **14a** but using 2-bromo-1-naphthol. Flash chromatography of the residue, eluting with hexane, gave the title compound (64%) as a white solid, mp 101 °C: $[\alpha]_D^{22}$ −120 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.29–2.37 (1H, m), 2.59–2.68 (1H, m), 3.71 (1H, quintet, *J*=5.5 Hz), 3.96–4.02 (1H, m), 5.60 (1H, dd, *J*=4.0, 8.5 Hz), 7.06 (1H, d, *J*=9.0 Hz), 7.29 (1H, d, *J*=8.0 Hz), 7.34–7.39 (3H, m), 7.44–7.46 (2H, M), 7.55 (1H, t, *J*=8.0 Hz), 7.61 (1H, d, *J*=9 Hz), 7.70 (1H, d, *J*=8 Hz), 8.23 (1H, d, *J*=8.5 Hz); δ_C (100 MHz) 41.33, 41.39, 78.59, 109.91, 116.07, 124.46, 126.08, 126.19, 127.62, 127.96, 128.16, 128.60, 128.85, 129.89, 133.12, 140.26, 152.14; EI-LRMS 376 and 374 (4%), 222 (86), 193 (10), 153 (22), 117 (20), 91 (100); EI-HRMS calcd. for $C_{19}H_{16}^{79}BrClO$ 374.0072, found 374.0069; Anal. $C_{19}H_{16}BrClO$ requires: C, 60.74; H, 4.29. Found: C, 60.70; H, 4.10%.

2.1.5. (*R*)-1-Bromo-2-(3-bromo-1-methylpropoxy)-benzene (14e). The ether **14e** was prepared using the same procedure and scale as described for **14a** but using 2-bromophenol and (*S*)-4-bromobutane-2-ol. Flash chromatography of the residue, eluting with hexane, gave the title compound (67%) as a colorless oil: $[\alpha]_D^{22}$ −102 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 1.37 (3H, d, *J*=6 Hz), 2.10–2.18 (1H, m), 2.34–2.43 (1H, m), 3.56–3.69 (2H, m), 4.61–4.66 (1H, m), 6.84 (1H, d, *J*=8 Hz), 6.98 (1H, d, *J*=8 Hz), 7.26 (1H, t, *J*=8 Hz), 7.54 (1H, *d*, *J*=8 Hz); δ_C (100 MHz) 19.45, 29.81, 39.60, 73.68, 113.57, 115.52, 122.21, 128.41, 133.50, 154.35; EI-LRMS 310, 308 and 306 (48%), 174 (100), 55 (50); EI-HRMS calcd. for $C_{10}H_{12}^{79}Br_2O$ 305.9255, found 305.9252.

2.1.6. (*S*)-2-Bromo-1-(3-chloro-1-phenylpropoxy)-3,5-dimethoxy-benzene (14f). The ether **14f** was prepared using the same procedure and scale as described for **14a** but using 2-bromo-3,5-dimethoxyphenol. Flash chromatography, eluting with hexane–ether (4:1), gave the title compound (76%) as a white solid, mp 66–67 °C: $[\alpha]_D^{22}$ +56 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.21–2.27 (1H, m), 2.51–2.57 (1H, m), 3.62 (3H, s), 3.63–3.69 (1H, m), 3.84 (3H, s), 3.87–3.95 (1H, m), 5.40 (1H, dd, *J*=4.5, 8.5 Hz), 5.99 (1H, d, *J*=2.5 Hz), 6.10 (1H, d, *J*=2.5 Hz), 7.26–7.30 (1H, m), 7.33–7.40 (4H, m); δ_C (100 MHz) 41.19, 41.30, 55.24, 56.23, 78.00, 92.09, 93.11, 94.33, 125.80, 128.01, 128.78, 140.26, 155.62, 157.34, 159.98; EI-LRMS 386 and 384 (10%), 234 (75), 153 (20), 117 (15), 91 (100); EI-HRMS calcd. for $C_{17}H_{18}^{79}BrClO_3$ 384.0127, found 384.0130; Anal. $C_{17}H_{18}BrClO_3$ requires: C, 52.94; H, 4.70. Found: C, 53.11; H, 4.55%.

2.1.7. (*S*)-3,4-Dihydro-2-phenyl-2*H*-1-benzopyran (15a). To a stirred solution of *n*-butyllithium in hexane (2.5 M, 4.0 mL, 10.0 mmol) in THF (30 mL) at −50 °C was added dropwise a solution of (*S*)-1-bromo-2-(3-chloro-1-phenylpropoxy)-benzene (**14a**) (3.0 g, 9.2 mmol) in THF (8 mL). The mixture was stirred at −50 °C for 2 h and allowed to warm to room temperature over 2 h. The reaction was quenched by pouring into saturated aqueous ammonium chloride (40 mL). The mixture was extracted with ethyl acetate (3×75 mL), and the combined extracts washed with water (50 mL), brine (50 mL), dried and evaporated. Flash chromatography of the residue, eluting with hexane, gave the title compound (1.6 g, 83%) as a white solid, mp 52 °C (MeOH): $[\alpha]_D^{22}$ −15 (*c* 3.0, $CHCl_3$); δ_H (400 MHz) 2.10–2.20 (1H, m), 2.24–2.30 (1H, m), 2.85 (1H, dt, *J*=2.5, 16.5 Hz), 3.01–3.09 (1H, m), 5.12 (1H, dd, *J*=2.5, 10.0 Hz), 6.92–7.00 (2H, m), 7.14–7.21 (2H, m), 7.38–7.40 (1H, m), 7.43–7.50 (4H, m); δ_C (100 MHz) 25.09, 29.90, 77.68, 116.88, 120.27, 121.77, 125.94, 127.29, 127.76, 128.46, 129.48, 141.70, 155.08; FAB-LRMS 210 (100%), 117 (30); FAB-HRMS calcd. for $C_{15}H_{14}O$ 210.1044, found 210.1042; Anal. $C_{15}H_{14}O$ requires: C, 85.68; H, 6.71. Found: C, 85.41; H, 6.66%.

2.1.8. (*S*)-3,4-Dihydro-6-methyl-2-phenyl-2*H*-1-benzopyran (15b). The benzopyran **15b** was prepared using the same procedure and scale as described for **15a** but using (*S*)-2-bromo-1-(3-chloro-1-phenylpropoxy)-4-methyl-benzene (**14b**) and gave the title compound as a colorless oil (77%), $[\alpha]_D^{22}$ −18 (*c* 3.0, $CHCl_3$); δ_H (400 MHz) 2.07–2.16 (1H, m), 2.20–2.26 (1H, m), 2.31 (3H, s), 2.76 (1H, dt, *J*=4.5, 16.5 Hz), 2.95–3.04 (1H, m), 5.12 (1H, dd, *J*=2.0, 10.0 Hz), 6.86 (1H, d, *J*=8.0 Hz), 6.94–6.98 (2H, m), 7.35–7.37 (1H, m), 7.40–7.47 (4H, m); δ_C (100 MHz) 20.47, 25.02, 30.03, 77.65, 116.63, 121.43, 125.96, 127.72, 127.92, 128.46, 129.41, 129.83, 141.86, 152.90; FAB-LRMS 224 (100%), 117 (24); FAB-HRMS calcd. for $C_{16}H_{16}O$ 224.1201, found 224.1197.

2.1.9. (*S*)-6-Chloro-3,4-dihydro-2-phenyl-2*H*-1-benzopyran (15c). The benzopyran **15c** was prepared using the same procedure and scale as described for **15a** but using (*S*)-2-bromo-4-chloro-1-(3-chloro-1-phenylpropoxy)-benzene (**14c**) and gave the title compound as white crystals (78%), mp 54 °C; $[\alpha]_D^{22}$ −12 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.03–2.13 (1H, m), 2.19–2.26 (1H, m), 2.77 (1H, dt, *J*=4.5, 16.5 Hz), 2.93–3.01 (1H, m), 5.06 (1H, d, *J*=10.0 Hz), 6.85 (1H, d, *J*=8.0 Hz), 7.08–7.10 (2H, m), 7.34–7.39 (1H, m), 7.40–7.42 (4H, m); δ_C (100 MHz) 24.90, 29.44, 77.83, 118.22, 123.38, 124.97, 125.91, 127.30, 127.94, 128.55, 129.03, 141.25, 153.72; FAB-LRMS 244 (100%), 209 (20), 117 (26); FAB-HRMS calcd. for $C_{15}H_{13}ClO$ 244.0655, found 244.6419; Anal. $C_{15}H_{13}ClO$ requires: C, 73.62; H, 5.35. Found: C, 73.75; H, 5.39%.

2.1.10. (*S*)-3,4-Dihydro-2-phenyl-2*H*-naphtho[1,2-*b*]-pyran (15d). The benzopyran **15d** was prepared using the same procedure and scale as described for **15a** but using 2-((1*S*)-3-chloro-1-phenylpropoxyl)-1-bromonaphthalene (**14d**) and gave the title compound as a white solid (74%), mp 73 °C; $[\alpha]_D^{22}$ +34 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.26–2.34 (1H, m), 2.41–2.47 (1H, m), 3.19–3.23 (2H, m), 5.18 (1H, d, *J*=10.0 Hz), 7.26 (1H, d, *J*=9 Hz), 7.42–7.51 (4H, m), 7.55–7.60 (3H, m), 7.73 (1H, d, *J*=9 Hz), 7.88 (2H, t, *J*=9.5 Hz); δ_C (100 MHz) 21.62, 29.62, 77.38, 113.52, 119.14, 121.90, 123.22, 126.00, 126.28, 127.72, 127.80, 128.38, 128.47, 128.95, 132.97, 141.49, 152.62; FAB-LRMS 260 (100%), 157 (26), 117 (85), 91 (26); FAB-HRMS calcd. for $C_{19}H_{16}O$ 260.1201, found 260.1204; Anal. $C_{19}H_{16}O$ requires: C, 87.66; H, 6.19. Found C, 87.34; H, 5.94%.

2.1.11. (*R*)-3,4-Dihydro-2-methyl-2*H*-1-benzopyran (15e). The benzopyran **15e** was prepared using the same procedure and scale as described for **15a** but using (*R*)-1-bromo-2-(3-bromo-1-methylpropoxy)-benzene (**14e**) and gave the title compound as a colorless oil (81%), $[\alpha]_D^{22}+89$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 1.42 (3H, d, $J=6.5$ Hz), 1.69–1.79 (1H, m), 1.98–2.04 (1H, m), 2.73–2.79 (1H, m), 2.84–2.93 (1H, m), 4.14–4.18 (1H, m), 6.81–6.87 (2H, m), 7.06–7.12 (2H, m); δ_C (100 MHz) 21.32, 24.81, 29.20, 72.08, 116.63, 119.91, 121.75, 127.10, 129.48, 154.99; FAB-LRMS 121 (20%), 107 (55), 89 (66), 77 (75); Anal. $C_{10}H_{12}O$ requires: C, 81.04; H, 8.16. Found: C, 81.31; H, 8.86%.

2.1.12. (*S*)-3,4-Dihydro-5,7-dimethoxy-2-phenyl-2*H*-1-benzopyran (15f). The benzopyran **15f** was prepared using the same procedure and scale as described for **15a** but using (*S*)-2-bromo-1-(3-chloro-1-phenylpropoxy)-3,5-dimethoxy-benzene (**14f**) and flash chromatography, eluting with hexane–ether (4:1), gave the title compound as a colorless oil (78%), $[\alpha]_D^{22}-9$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.05–2.14 (1H, m), 2.23–2.29 (1H, m), 2.69–2.77 (1H, m), 2.81–2.87 (1H, m), 3.83 (3H, s), 3.86 (3H s), 5.05 (1H, dd, $J=2.5$, 10.0 Hz), 6.18 (1H, d, $J=2.5$ Hz), 6.24 (1H, d, $J=2.5$ Hz), 7.39–7.52 (5H, m); δ_C (100 MHz) 19.14, 29.46, 55.12, 55.23, 77.64, 91.27, 93.36, 103.26, 125.92, 127.65, 128.35, 141.62, 156.22, 158.46, 159.30; FAB-LRMS 270 (100%), 167 (50), 91 (24); FAB-HRMS calcd. for $C_{17}H_{18}O_3$ 270.1256, found 270.1273.

2.1.13. (*S*)-2,4-Dibromo-1-(3-chloro-1-phenylpropoxy)-benzene (16). The ether **16** was prepared using the same procedure and scale as described for **14a** but using 2,4-dibromophenol. Flash chromatography of the residue, eluting with hexane, gave the title compound (79%) as a colorless oil: $[\alpha]_D^{22}+45$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.22–2.30 (1H, m), 2.51–2.59 (1H, m), 3.67 (1H, quintet, $J=5.5$ Hz), 3.88–3.95 (1H, m), 5.42 (1H, dd, $J=4.5$, 10.0 Hz), 6.59 (1H, d, $J=9.0$ Hz), 7.17 (1H, dd, $J=2.5$, 9.0 Hz), 7.31–7.33 (1H, m), 7.37–7.39 (4H, m), 7.66 (1H, d, $J=2.5$ Hz); δ_C (100 MHz) 41.15, 41.18, 78.11, 113.23, 113.51, 116.14, 125.79, 128.26, 128.92, 130.98, 135.41, 139.58, 153.37; FAB-LRMS 154 (100%), 136 (35), 91 (24); Anal. $C_{15}H_{13}Br_2ClO$ requires: C, 44.54; H, 3.24. Found: C, 44.36; H, 3.36%.

2.1.14. (*S*)-6-Bromo-3,4-dihydro-2-phenyl-2*H*-1-benzopyran (17a). The benzopyran **17a** was prepared using the same procedure and scale as described for **15a** but using (*S*)-2,4-dibromo-1-(3-chloro-1-phenylpropoxy)-benzene (**16**) and gave the title compound as a white solid (84%), mp 67 °C: $[\alpha]_D^{22}+3$ (*c* 3.0, $CHCl_3$); δ_H (400 MHz) 2.06–2.13 (1H, m), 2.19–2.26 (1H, m), 2.77 (1H, dt, $J=4.5$, 16.5 Hz), 2.93–3.02 (1H, m), 5.06 (1H, dd, $J=2.5$, 10.0 Hz), 6.82 (1H, d, $J=9.0$ Hz), 7.24 (2H, brs), 7.35–7.43 (5H, m); δ_C (100 MHz) 24.80, 29.36, 77.77, 112.26, 118.66, 123.95, 125.87, 127.97, 128.51, 130.15, 131.94, 141.16, 154.19; FAB-LRMS 290 and 288 (92%), 209 (34), 149 (40), 117 (90), 91 (100); FAB-HRMS calcd. for $C_{15}H_{13}^{79}BrO$ 288.0150, found 288.0161; Anal. $C_{15}H_{13}BrO$ requires: C, 62.30; H, 4.53. Found: C, 62.57; H, 4.71%.

2.1.15. (*S*)-3,4-Dihydro-2-phenyl-2*H*-1-benzopyran-6-carboxaldehyde (17b). To a stirred solution of *n*-butyllithium in hexane (2.5 M, 0.24 mL, 0.6 mmol) in THF (3 mL) at −50 °C was added dropwise a solution of (*S*)-2,4-dibromo-1-(3-chloro-1-phenylpropoxy)-benzene (**16**) (202 mg, 0.5 mmol) in THF (2 mL). After 1 h at −50 °C, the cooling bath was removed and the solution stirred at room temperature for 1 h. The solution was re-cooled to −50 °C and *n*-butyllithium in hexane (2.5 M, 0.3 mL, 0.75 mmol) added dropwise. After 30 min, DMF (365 mg, 5 mmol) was added and, following stirring for 30 min, the solution was allowed to return to room temperature. The reaction was quenched by pouring into saturated aqueous ammonium chloride (5 mL). The mixture was extracted with ethyl acetate (3×10 mL), and the combined extracts washed with water (10 mL), brine (10 mL), dried and evaporated. Flash chromatography of the residue, eluting with hexane, gave the title compound (1.6 g, 81%) as a white solid (81%), mp 82–83 °C: $[\alpha]_D^{22}+109$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.07–2.17 (1H, m), 2.25–2.32 (1H, m), 2.87 (1H, dt, $J=4.5$, 16.0 Hz), 2.99–3.08 (1H, m), 5.17 (1H, dd, $J=2.5$, 10.0 Hz), 7.01 (1H, d, $J=8.0$ Hz), 7.34–7.38 (1H, m), 7.40–7.42 (4H, m), 7.66–7.68 (2H, m), 9.86 (1H, s); δ_C (100 MHz) 24.74, 29.31, 78.52, 117.59, 122.40, 125.86, 128.14, 128.61, 129.59, 129.73, 131.84, 140.65, 160.53, 190.96; FAB-LRMS 239 (100%), 117 (24), 91 (10); FAB-HRMS calcd. for $C_{16}H_{14}O_2$ 239.1072, found 239.1071; Anal. $C_{16}H_{14}O_2$ requires: C, 80.65; H, 5.92. Found: C, 81.01; H, 5.87%.

2.1.16. (*S*)-3,4-Dihydro-2-phenyl-2*H*-1-benzopyran-6-carboxylic acid (17c). The benzopyran **17c** was prepared using the same procedure and scale as described for **17b** but using an excess of carbon dioxide gas as the electrophile and gave the title compound as a white solid (78%), mp 208–209 °C: $[\alpha]_D^{22}+37$ (*c* 1.0, $CHCl_3$); δ_H (acetone 400 MHz) 2.02–2.12 (1H, m), 2.26–2.32 (1H, m), 2.86 (1H, dt, $J=4.5$, 16.5 Hz), 3.02–3.10 (1H, m), 5.22 (1H, dd, $J=2.5$, 10.0 Hz), 6.92 (1H, d, $J=9.0$ Hz), 7.32–7.36 (1H, m), 7.38–7.43 (2H, m), 7.47–7.49 (2H, m), 7.81–7.49 (2H, m); δ_C (100 MHz) 25.47, 30.34, 79.10, 117.55, 123.04, 123.36, 126.91, 128.75, 129.37, 130.13, 132.70, 142.48, 160.14, 167.64; FAB-LRMS 255 (100%), 237 (30), 209 (12), 151 (12), 117 (36), 91 (12); FAB-HRMS calcd. for $C_{16}H_{14}O_3$ 255.1021, found 255.1017; Anal. $C_{16}H_{14}O_3$ requires: C, 75.57; H, 5.55. Found: C, 75.50; H, 5.45%.

2.1.17. (*S*)-3,4-Dihydro-2-phenyl-2*H*-1-benzopyran-6-methanol (17d). The benzopyran **17d** was prepared using the same procedure and scale as described for **17b** but using an excess of paraformaldehyde powder as the electrophile and gave the title compound as a colorless oil (57%): $[\alpha]_D^{22}+2$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.04–2.14 (1H, m), 2.20–2.26 (1H, m), 2.79 (1H, dt, $J=4.0$, 16.5 Hz), 2.95–3.03 (1H, m), 4.59 (2H, s), 5.07 (1H, dd, $J=2.0$, 10.0 Hz), 6.91 (1H, d, $J=8.0$ Hz), 7.11 (1H, s), 7.33–7.44 (6H, m); δ_C (100 MHz) 25.24, 30.06, 51.81, 65.39, 78.05, 117.27, 122.13, 126.19, 126.83, 128.09, 128.76, 133.04, 141.82, 154.99; FAB-LRMS 240 (92%), 223 (100), 209 (25), 117 (38), 91 (52); FAB-HRMS calcd. for $C_{16}H_{14}O_2$ 240.1155, found 240.1155.

2.1.18. (*S*)-1,3-Dibromo-2-(3-chloro-1-phenylpropoxy)-benzene (18). The ether **18** was prepared using the same procedure and scale as described for **14a** but using 2,6-dibromophenol. Flash chromatography of the residue, eluting with hexane, gave the title compound (77%) as a colorless oil: $[\alpha]_D^{22}$ −78 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.45–2.53 (1H, m), 2.70–2.79 (1H, m), 3.39–3.45 (1H, m), 3.68–3.74 (1H, m), 5.77 (1H, t, *J*=7.0 Hz), 6.78 (1H, t, *J*=8.0 Hz), 7.33–7.35 (3H, m), 7.44–7.48 (4H, m); δ_C (100 MHz) 38.51, 41.16, 82.30, 118.61, 125.76, 128.06, 128.27, 128.75, 132.93, 137.90, 151.59; EI-LRMS 252 (18%), 153 (78), 117 (50), 91 (100); Anal. $C_{15}H_{13}Br_2ClO$ requires: C, 44.54; H, 3.24. Found: C, 44.78; H, 3.59%.

2.1.19. (*S*)-8-Bromo-3,4-dihydro-2-phenyl-2*H*-1-benzopyran (19). The benzopyran **19** was prepared using the same procedure described for **15a** but using (*S*)-1,3-dibromo-2-(3-chloro-1-phenylpropoxy)-benzene (**18**) and gave the title compound as a colorless oil (79%): $[\alpha]_D^{22}$ −143 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.02–2.12 (1H, m), 2.28–2.34 (1H, m), 2.79 (1H, dt, *J*=5.0, 16.5 Hz), 2.96–3.04 (1H, m), 5.23 (1H, d, *J*=9.0 Hz), 6.77 (1H, dt, *J*=1.0, 8.0 Hz), 7.04 (1H, d, *J*=8.0 Hz), 7.35 (1H, d, *J*=8.0 Hz), 7.40–7.44 (3H, m), 7.47–7.49 (2H, m); δ_C (100 MHz) 24.92, 29.54, 77.99, 111.08, 120.89, 123.63, 125.51, 127.62, 128.44, 128.53, 131.02, 141.10, 151.35; FAB-LRMS 288 (58%), 185 (26), 117 (100), 91 (56); FAB-HRMS calcd. for $C_{15}H_{13}^{79}BrO$ 288.0150, found 288.0188.

2.1.20. (*S*)-3,4-Dihydro-2-phenyl-2*H*-1-benzopyran-8-carboxaldehyde (20). The benzopyran **20** was prepared using the same procedure described for **17b** but using (*S*)-1,3-dibromo-2-(3-chloro-1-phenylpropoxy)-benzene (**18**) and gave the title compound as colorless needles following recrystallization from ethanol (76%), mp 94–95 °C (EtOH): $[\alpha]_D^{22}$ −287 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.08–2.17 (1H, m), 2.28–2.34 (1H, m), 2.85 (1H, dt, *J*=4.5, 16.5 Hz), 2.99–3.07 (1H, m), 5.20 (1H, dd, *J*=2.5, 10.0 Hz), 6.94 (1H, t, *J*=7.5 Hz), 7.31 (1H, d, *J*=8.0 Hz), 7.35–7.43 (5H, m), 7.70 (1H, d, *J*=8.0 Hz), 10.52 (1H, s); δ_C (100 MHz) 24.76, 29.31, 78.18, 120.10, 123.15, 124.28, 125.65, 126.19, 128.01, 128.58, 135.77, 140.79, 157.71, 189.83; FAB-LRMS 239 (100%), 135 (62), 117 (15), 91 (24); FAB-HRMS calcd. for $C_{16}H_{14}O_2$ 239.1072, found 239.1071; Anal. $C_{16}H_{14}O_2$ requires: C, 80.65; H, 5.92. Found: C, 81.05; H, 6.02%.

2.1.21. (*S*)-3-Chloro-1-(4-chlorophenyl)-1-propanol (22). To (*R*)-oxazaborolidine (1.0 M in toluene, 1.0 mL, 1.0 mmol) in THF (2 mL) at 0 °C was added dropwise borane–THF complex (1.0 M, 6 mL, 6 mmol). After 5 min a solution of 3,4′-dichloropropiophenone (**21**) (2.03 g, 10 mmol) in THF (10 mL) was added dropwise and the reaction mixture stirred for an additional 1 h. Methanol (3 mL) was added and after 10 min hydrogen chloride in ether (1.0 M, 2.0 mL, 2.0 mmol) was added. After 30 min, the volatiles were removed by evaporation and the residue triturated with ether and filtered to remove any insoluble material. The ether solution was washed with brine (10 mL), saturated aqueous sodium bicarbonate (10 mL), dried and evaporated to give the title compound as a colorless oil (1.86 g, 91%); $[\alpha]_D^{22}$ −17 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 1.98–2.06 (1H, m), 2.12–2.19 (1H, m), 2.43 (1H, brs), 3.48–3.54 (1H, m), 3.66–3.73 (1H, m), 4.89 (1H, dd, *J*=4.5, 8.5 Hz), 7.25–7.33 (4H, m); δ_C (100 MHz) 41.28, 41.43, 70.54, 127.09, 128.72, 133.47, 142.08; FAB-LRMS 208, 206 and 204 (12%), 187 (100), 141 (70), 125 (60); FAB-HRMS calcd. for $C_9H_{10}^{35}Cl_2O$ 204.0105, found 204.0106.

2.1.22. (*R*)-6-Chloro-3,4-dihydro-2-(4-chlorophenyl)-2*H*-1-benzopyran (4). Following the same procedure and scale as described for the preparation of **14a** but using (*S*)-3-chloro-1-(4-chlorophenyl)-1-propanol (**22**) and 2-bromo-4-chlorophenol (**12c**) gave (*R*)-2-bromo-4-chloro-1-[3-chloro-1-(4-chlorophenyl)propoxy]-benzene (85%) as a colorless oil: $[\alpha]_D^{22}$ +85 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.17–2.25 (1H, m), 2.47–2.56 (1H, m), 3.63 (1H, quintet, *J*=5.5 Hz), 3.85–3.91 (1H, m), 5.38 (1H, dd, *J*=4.5, 9.0 Hz), 6.60 (1H, d, *J*=9.0 Hz), 7.05 (1H, dd, *J*=2.5, 9.0 Hz), 7.29–7.35 (4H, m), 7.51 (1H, d, *J*=2.5 Hz); δ_C (100 MHz) 40.96, 41.00, 77.67, 113.25, 115.68, 126.65, 127.29, 128.12, 129.18, 132.90, 134.13, 138.20, 152.73 which was used in the next step: using the same procedure and scale as described for **15a** but using (*R*)-2-bromo-4-chloro-1-[3-chloro-1-(4-chlorophenyl)propoxy]-benzene gave the title compound (78%) as a white solid, mp 107 °C; δ_H (400 MHz) 1.98–2.06 (1H, m), 2.15–2.22 (1H, m), 2.72–2.99 (1H, m), 2.75 (1H, dt, *J*=4.5, 16.0 Hz), 5.01 (1H, dd, *J*=2.5, 10.0 Hz), 6.83 (1H, d, *J*=8.5 Hz), 7.07–7.09 (2H, m), 7.33–7.35 (4H, m); δ_C (100 MHz) 24.72, 29.39, 77.31, 118.15, 123.18, 125.12, 127.26, 127.33, 128.66, 129.01, 133.62, 139.72, 153.39; FAB-LRMS 282, 280 and 278 (100%), 243 (20), 217 (85), 176 (55); FAB-HRMS calcd. for $C_{15}H_{12}^{35}Cl_2O$ 278.0265, found 278.0264; Anal. $C_{15}H_{12}Cl_2O$ requires: C, 64.54; H, 4.33. Found: C, 64.67; H, 4.60%.

2.2. Oxidation of (*S*)-3,4-dihydro-2-phenyl-2*H*-1-benzopyran (15) with periodic acid and chromium(VI) oxide

Periodic acid (455 mg, 2.0 mmol) was dissolved in acetonitrile by vigorous stirring followed by the addition of chromium(VI) oxide (5 mg, 0.05 mmol). (*S*)-3,4-Dihydro-2-phenyl-2*H*-1-benzopyran (**15**) (210 mg, 1.0 mmol) was added and an exotherm and white precipitate were immediately observed. The mixture was stirred for 1 h, filtered through Celite®, and the volatiles evaporated. The residue was dissolved in dichloromethane (10 mL), washed with saturated aqueous sodium bicarbonate (10 mL), brine (10 mL), dried and evaporated. Flash chromatography of the residue, eluting with hexane–ether (3:1 then 1:1), gave first (*S*)-2,3-dihydro-2-phenyl-4*H*-1-benzopyran-4-one (**23**) (96 mg, 43%) as a white solid: $[\alpha]_D^{22}$ −63 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.90 (1H, dd, *J*=3.0, 1.0 Hz), 3.10 (1H, dd, *J*=3.5, 17.0 Hz), 5.49 (1H, dd, *J*=3.0, 13.5 Hz), 7.05–7.08 (2H, m), 7.39–7.54 (6H, m), 7.94 (1H, dd, *J*=2.0, 8.0 Hz); IR 1684 cm^{-1}. Later fractions contained 2-(3-oxo-3-phenylpropyl)cyclohexa-2,5-diene-1,4-dione (**24**) (74 mg, 31%). Recrystallization from hexane/ethyl acetate gave yellow needles mp 127 °C: δ_H (400 MHz) 2.87 (2H, t, *J*=7.0 Hz), 3.25 (2H, d, *J*=7.0 Hz), 6.64 (1H, s), 6.70–6.78 (2H, m), 7.46 (2H, t, *J*=8.0 Hz), 7.57 (1H, t, *J*=8.0 Hz), 7.94 (2H, *J*=8.0 Hz); δ_C (100 MHz) 23.95, 36.39, 127.98, 128.68, 133.25, 133.35, 136.38, 136.76, 148.17, 187.37, 187.47, 197.78 (one signal obscured); FAB-LRMS 241 (40%), 223 (20), 105 (100); Anal. $C_{15}H_{12}O_3$ requires: C, 74.99; H, 5.03%. Found: C, 74.82; H, 4.93%.

2.2.1. (*R*)-3-(*tert*-Butyldimethylsily)oxy-*N*-methoxy-*N*-methyl-benzenepropanamide (28). To a stirred solution of ethyl-(*R*)-3-hydroxy-3-phenyl propionate (**27**) (1.94 g, 10 mmol) and imidazole (1.36 g, 20 mmol) in dichloromethane (50 mL) was added *tert*-butyldimethylsilyl chloride (1.65 g, 11 mmol). The mixture was stirred at room temperature overnight and the resulting white precipitate was poured into saturated aqueous ammonium chloride (150 mL). The mixture was extracted with dichloromethane (3×50 mL) and the combined extracts washed with water (50 mL), brine (50 mL), dried and evaporated. Flash chromatography of the residue, eluting with hexane–ether (19:1), gave (*R*)-3-phenyl-3-(*tert*-butyldimethylsily)oxypropanoate[41] as a colorless oil (2.89, 94%); δ_H (400 MHz) −0.18 (3H, s), 0.01 (3H, s), 0.87 (9H, s), 1.25 (3H, t, *J*=6 Hz), 2.53 (1H, dd, *J*=4.0, 14.5 Hz), 2.72 (1H, dd, *J*=9.5, 14.5 Hz), 4.13 (2H, q, *J*=6 Hz), 5.14 (1H, dd, *J*=4.0, 9.5 Hz), 7.24–7.36 (5H, m).

To a stirred suspension of *N*, *O*-dimethylhydroxylamine hydrochloride (1.75 g, 18 mmol) in dichloromethane (45 mL) at 0 °C under nitrogen was added dropwise trimethylaluminum (2.0 M in toluene, 9 mL, 18 mmol). The reaction mixture was stirred for 20 min and then treated with a solution of (*R*)-3-phenyl-3-(*tert*-butyldimethylsily)oxypropanoate[41] (2.77 g, 9 mmol) in dichloromethane (15 mL). The mixture was stirred at room temperature overnight and poured into saturated aqueous ammonium chloride (150 mL). The resulting precipitate was filtered through Celite®, the filtrate extracted with dichloromethane (3×75 mL) and the combined extracts washed with water (50 mL), brine (50 mL), dried and evaporated. Flash chromatography of the residue, eluting with hexane–ether (1:1), gave the title compound as a colorless oil (2.38 g, 82%); $[\alpha]_D^{22}+138$ (*c* 1.0, $CHCl_3$); δ_H (400 MHz) −0.14 (3H, s), 0.08 (3H, s), 0.84 (9H, s), 2.47 (1H, dd, *J*=3.5, 14.5 Hz), 3.02–3.07 (1H, brm), 3.17 (3H, s), 3.63 (3H, s), 5.26 (1H, dd, *J*=3.5, 9.0 Hz), 7.21–7.26 (1H, m), 7.29–7.32 (2H, m), 7.36–7.38 (2H, m); δ_C (100 MHz) −4.57, 18.34, 25.99, 32.17, 43.46, 61.53, 72.34, 76.96, 126.07, 127.49, 128.42, 145.05, 171.87; FAB-LRMS 346 (M+23, 100%), 266 (38), 221 (16), 150 (15), 73 (98).

2.3. 1,5-Dimethoxy-3-(methoxymethoxy)benzene (30)

To a vigorously stirred solution of 3,5-dimethoxyphenol (10 g, 65 mmol) and potassium bicarbonate (17.94 g, 130 mmol) in DMF (250 mL) was added chloromethyl methyl ether (6.44 g, 80 mmol). The mixture was stirred overnight, poured into saturated ammonium chloride (250 mL) and extracted with ethyl acetate (3×150 mL). The combined extracts were washed with water (5×200 mL), 2.0 M sodium hydroxide (200 mL), brine, dried and evaporated to give the title compound as a colorless oil (9.9 g, 94%); δ_H (400 MHz) 3.47 (3H, s), 3.76 (6H, s), 5.14 (2H, s), 6.14 (1H, s), 6.23 (2H, s); δ_C (100 MHz) 55.31, 56.02, 94.18, 94.45, 94.96, 159.09, 161.43.

2.3.1. (*R*)-1-[2,4-Dimethoxy-6-(methoxymethoxy)-phenyl]-3-phenyl-3-(*tert*-butyldimethylsily)oxy-propan-1-one (31). To a stirred solution of 1,5-dimethoxy-3-(methoxymethoxy)benzene (**30**) (297 mg, 1.5 mmol) in toluene (5 mL) at −78 °C under nitrogen was added dropwise *tert*-butyllithium in pentane (1.7 M, 0.88 mL, 1.5 mmol). The reaction mixture was stirred at −78 °C for 15 min, allowed to warm to 0 °C over 1 h, re-cooled to −78 °C and (*R*)-3-(*tert*-butyldimethylsily)oxy-*N*-methoxy-*N*-methyl-benzenepropanamide (**28**) (154 mg, 0.5 mmol) in toluene (2 mL) added dropwise. The solution was allowed to return to room temperature over 2 h and quenched by the dropwise addition of saturated aqueous ammonium chloride (10 mL). The phases were separated and the aqueous layer extracted with ether (3×10 mL), combined and washed with water (10 mL), brine (10 mL), dried and evaporated. Flash chromatography of the residue, eluting with hexane–ether (3:1), gave the title compound as a colorless oil (165 mg, 72%): $[\alpha]_D^{22}+71$ (*c* 1.0, $CHCl_3$) δ_H (400 MHz) −0.13 (3H, s), 0.08 (3H, s), 0.85 (9H, s), 3.02 (1H, dd, *J*=4.5, 17.5 Hz), 3.30 (1H, dd, *J*=7.5, 17.5 Hz), 3.39 (3H, s), 3.69 (3H, s), 3.77 (3H, s), 5.03 (2H, s), 5.38 (1H, dd, *J*=4.5, 7.5 Hz), 6.09 (1H, s), 6.29 (1H, s), 7.20 (1H, t, *J*=8.0 Hz), 7.27 (2H, t, *J*=7.5 Hz), 7.35 (2H, d, *J*=8.0 Hz); δ_C (100 MHz) −5.15, −4.73, 18.08, 25.76, 55.29, 55.39, 55.58, 55.89, 56.16, 70.47, 92.11, 93.16, 94.59, 114.42, 126.11, 126.90, 127.94, 145.31, 155.99, 158.16, 162.14, 200.65; FAB-LRMS 483 (M+23, 100%), 221 (26), 73 (100).

2.3.2. (*R*)-3-Hydroxy-1-(2-hydroxy-4,6-dimethoxy-phenyl)-3-phenylpropan-1-one (32). To a stirred solution of (*R*)-1-[2,4-dimethoxy-6-(methoxymethoxy)phenyl]-3-phenyl-3-(*tert*-butyldimethylsily)oxy-propan-1-one (**31**) (230 mg, 0.5 mmol) in THF (9 mL) and water (1 mL) was added *p*-toluene sulfonic acid (19 mg, 0.1 mmol). The solution was heated to 55 °C for 12 h, cooled and poured onto saturated aqueous sodium bicarbonate (15 mL). The mixture was extracted with ethyl acetate (3×15 mL) and the combined extracts washed with brine (25 mL), dried and evaporated. Flash chromatography of the residue, eluting with hexane–ether (1:1), gave the title compound (130 mg, 86%) as a white solid, mp 91 °C: $[\alpha]_D^{22}+49.5$ (*c* 2.0, $CHCl_3$); δ_H (400 MHz) 3.33–3.51 (3H, m, ^1H exchanges with D_2O), 3.77 (3H, s), 3.81 (3H, s), 5.27 (1H, dd, *J*=4.0, 9.0 Hz), 5.90 (1H, s), 6.07 (1H, s), 7.28 (1H, t, *J*=8.0 Hz), 7.27 (2H, t, *J*=8.0 Hz), 7.35 (2H, d, *J*=7.5 Hz); δ_C (100 MHz) 52.58, 55.51, 55.55, 70.07, 90.92, 93.66, 105.81, 125.84, 127.34, 128.37, 143.33, 162.83, 166.43, 167.71, 204.05; FAB-LRMS 303 (15%), 284 (10), 181 (100); FAB-HRMS calcd. for $C_{17}H_{19}O_5$ 303.1232, found 303.1232; Anal. $C_{17}H_{18}O_5$ requires: C, 67.54; H, 6.00. Found: C, 67.31; H, 6.23%.

2.3.3. (*S*)-5,7-Dimethoxy-2-phenylchroman-4-one (33). A solution of triphenylphosphine (131 mg, 0.5 mmol) and diethyl azodicarboxylate (88 mg, 0.5 mmol) in THF (3 mL) at 0 °C was stirred for 15 min and then added dropwise to a solution of (*R*)-3-hydroxy-1-(2-hydroxy-4,6-dimethoxy-phenyl)-3-phenylpropan-1-one (**32**) (130 mg, 0.43 mmol) in THF (3 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and the volatiles removed by evaporation. Flash chromatography of the residue, eluting with hexane–ether (1:1 and then 1:2), gave the title compound (120 mg, 88%) as a white solid, mp 159–160 °C; $[\alpha]_D^{22}$ −28 (*c* 2.0, MeOH–$CHCl_3$, 1:1); δ_H (400 MHz) 2.79 (1H, dd, *J*=3.0, 16.5 Hz), 3.01 (1H, dd, *J*=13.0, 16.5 Hz), 3.81 (3H, s), 3.88 (3H, s), 5.40 (1H, dd, *J*=3.0, 13.0 Hz), 6.09 (1H, d, *J*=2.0 Hz), 6.15 (1H, d, $J=2.0$ Hz), 7.38–7.46 (5H, m); δ_C (100 MHz) 45.56, 55.56, 56.13, 79.18, 93.14, 93.52, 105.97, 126.08, 128.63, 128.75, 138.74, 162.26, 164.94, 165.94, 189.13; Anal. $C_{17}H_{16}O_4$ requires: C, 71.82%; H, 5.67%. Found: C, 71.70%; H, 5.67%.

2.3.4. (*S*)-5-Hydroxy-7-methoxy-2-phenylchroman-4-one (pinostrobin) (3). To a solution of (*S*)-5,7-dimethoxy-2-phenylchroman-4-one (**33**) (140 mg, 0.5 mmol) in acetonitrile (10 mL) at room temperature was added aluminum chloride (265 mg, 2.0 mmol). The mixture was heated to reflux for 3 h, cooled and the volume reduced by evaporation. 2.0 M hydrochloric acid (5 mL) was added and the solution extracted with ethyl acetate (3×10 mL). The combined organics were washed with water (10 mL), brine (10 mL), dried and evaporated. Flash chromatography of the residue, eluting with hexane–ether (3:1), gave the title compound (106 mg, 79%) as a white solid, mp 89–90 °C (MeOH); $[\alpha]_D^{22}$ −48 (*c* 1.0, $CHCl_3$); δ_H (400 MHz) 2.82 (1H, dd, $J=3.0$, 17.0 Hz), 3.09 (1H, dd, $J=13.0$, 17.0 Hz), 3.81 (3H, s), 5.43 (1H, dd, $J=3.0$, 13.0 Hz), 6.06–6.09 (2H, m), 7.41–7.46 (5H, m), 12.03 (1H, s); δ_C (100 MHz) 43.36, 53.41, 55.67, 79.20, 94.24, 95.12, 103.12, 126.11, 128.85, 138.34, 162.76, 164.16, 167.96, 195.73; Anal. $C_{16}H_{14}O_4$ requires: C, 71.10%; H, 5.22%. Found: C, 71.07%; H, 5.21%.

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Diels–Alder reactivity of 4-aryl-1-phthalimido-2-siloxy-1,3-butadienes

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Abstract—The reaction of (1*Z*,3*E*) and (1*E*,3*E*) 4-aryl-1-phthalimido-2-trialkylsiloxy-1,3-butadienes with maleimides and quinones has been studied. The observed *exo*-stereospecifity can be attributed to the simultaneous presence of the phthalimido and aryl groups, which produce strong hindrance during the *endo* approach.
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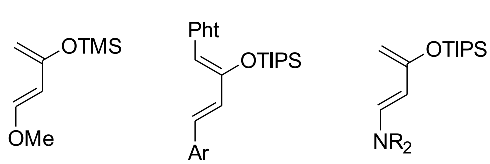
1. Introduction

Trialkylsiloxy-1,3-butadienes have been used as versatile reagents for the synthesis of functionalized ring systems via the Diels–Alder cycloaddition reaction. The most well known is 1-methoxy-3-trimethylsiloxy-1,3-butadiene, Danishefsky's diene (**I**)[1] (Fig. 1), which shows high reactivity towards a large number of dienophiles. Some time ago we began a line of research aimed at the synthesis of new siloxydienes, analogues of Danishefsky's diene, that contain at position C-1 an aromatic ring (the siloxy moiety lying at position C-3) and are useful for the synthesis, via Diels–Alder reaction, of 3-arylcyclohexenone derivatives as intermediates for the synthesis of more complex polycyclic systems related to marine alkaloids. As aryl groups we used phenyl, carrying electron donor or withdrawing groups (OMe, NO_2),[2] or heterocyclic moieties[3] such as indole, pyrrole or thiophene, these dienes showing high reactivity with dienophiles such as maleimides or quinones. In all the Diels–Alder reactions carried out with this family of 1-(aryl or heteroaryl)-3-trialkylsiloxy-1,3-butadienes, the *endo* cycloadducts were obtained.



I **II** **III**

Figure 1.

Due to the presence of amino groups and derivatives in a large number of natural and synthetic products, we were interested in the development of new dienes that, in addition to these functional groups, would contain nitrogen groupings able to be transformed into the amino derivatives by simple transformations. To this end, 1-phthalimido-4-(aryl or heteroaryl)-2-trialkylsiloxy-1,3-butadienes (**II**) (Fig. 1) were designed. The incorporation of both siloxy and amino substituents into the diene structure has received little attention, although in recent years Rawal's group has been actively studying the chemistry of 1-amino-3-siloxy-1,3-butadienes (**III**) (Fig. 1).[4] These authors have shown that these dienes are highly reactive and that they undergo Diels–Alder reaction with complete regiocontrol and in some cases with exceptional diastereoselectivity. In our case, we are interested in the development of similar dienes, but changing the position between both groups. This change should lead to 1-amino-4-aryl-2-trialkylsiloxy-2-cyclohexenes that might be useful in the synthesis of different types of alkaloids.[5] The literature contains some references to studies on trialkylsilyl enol ethers aimed at introducing α-amino functionalization. Treatment with CAN/NaN_3 accompanied by hydrolysis of the siloxy group gives α-azidoketones,[6] whereas treatment with $(TsN)_2Se$ allows the enol function to be preserved and α-*N*-tosylamino-siloxyderivatives[7] to be obtained.

In our case, we are currently attempting to obtain 1-amino-

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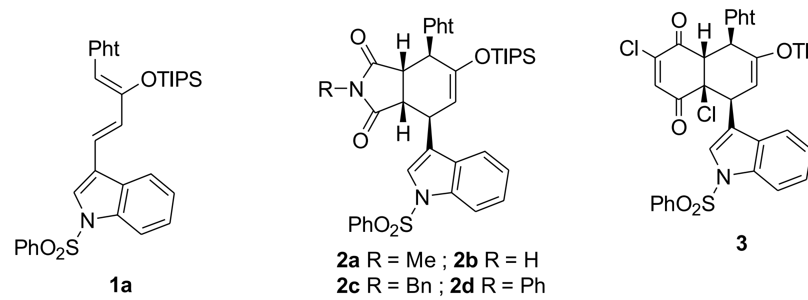
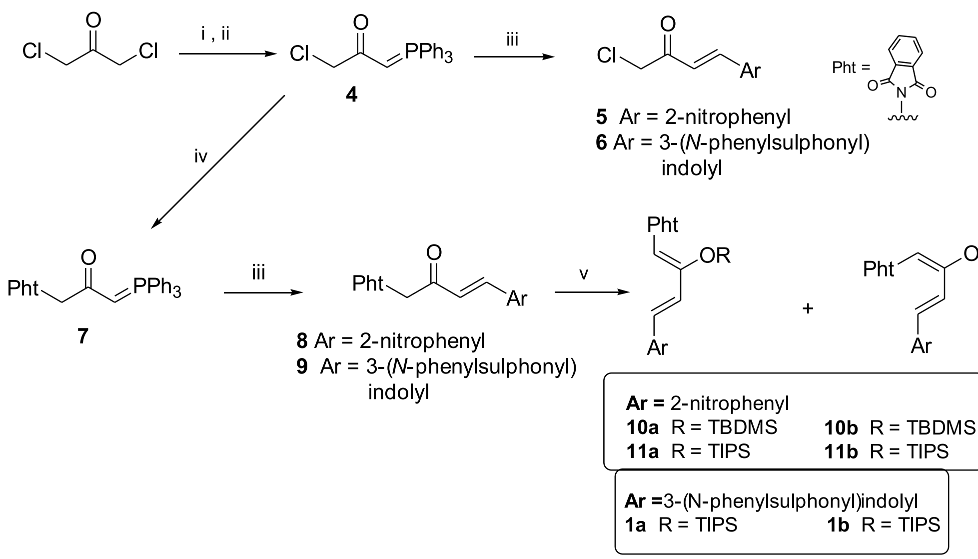


Figure 2.



Scheme 1. Reagents and conditions: (i) PPh_3/THF/reflux; (ii) Na_2CO_3/MeOH–H_2O, rt; (iii) Ar-CHO (1 equiv), C_6H_6, reflux; (iv) Potassium phthalimide, DMF, 100 °C; (v) TIPSOTf, or TBDMSOTf, Et_3N, CH_2Cl_2, 50 °C.

4-aryl-2-trialkylsiloxy-2-cyclohexenes through the Diels–Alder reaction by the use of conveniently functionalized dienes. First, we chose the phthalimido group as a precursor of the amino group. In this sense some preliminary studies have recently been published.[8] 1*Z*,3*E*-1-Phthalimido-4-(3-indolyl)-2-siloxy-1,3-butadiene (**1a**), prepared from 1,3-dichloroacetone, was assayed in the Diels–Alder reaction with maleimides and quinones as dienophiles. The reaction products **2** and **3** displayed the *exo* stereochemistry (Fig. 2), as deduced from NMR spectroscopy and X-ray diffraction studies, unlike the results obtained with related disubstituted dienes lacking the phthalimido substituent at C-1.[2a]

In this full paper we present further information from studies carried out with diene **1a**, its 1*E*,3*E* stereoisomer **1b** and related dienes carrying a 2-nitrophenyl group at C-4.

2. Results and discussion

Following a similar methodology to that previously described[8] (Scheme 1), intermediate **4** was prepared from 1,3-dichloroacetone and converted into the chloroenones **5** and **6**; very low yields were obtained. However, the nucleophilic substitution on **4** with potassium phthalimide took place conveniently to produce phosphorane **7**, which was coupled with 2-nitrobenzaldehyde, yielding the 2-nitroderivative **8**. From this synthetic intermediate, both stereoisomers **10a/10b** and **11a/11b** were obtained in a 3:1 ratio, by means of silylenolization in 2 h whereas from the 3-indole derivative **9** only **1a** was produced. In the latter case, longer reaction times (3 h or more) led to a mixture of **1a** and its stereoisomer **1b** in a 3:2 ratio.

The 3*E* configuration was established for all of these compounds by analysis of their ^{1}H NMR data, which showed a large coupling constant (15.6 Hz) between H-3 and H-4. The 1*Z* configuration in **10a** was deduced from the correlations observed between H-1 and H-4 protons in ROESY experiments (Fig. 3). Other correlations observed between the H-1 and H-3, H-4 and TBDMS could be explained in terms of the existence of an equilibrium between the *cisoid* and the *transoid* conformers of **10a**. Diene **10b** was more unstable than **10a**, as observed after

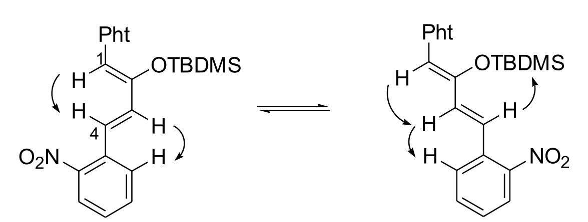
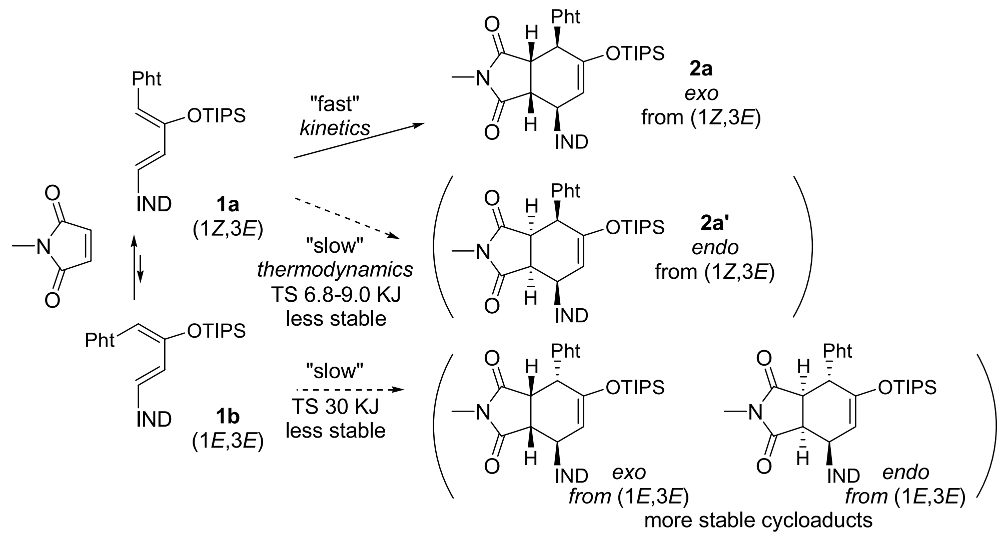


Figure 3. Selected ROESY correlations for **10a**.



Scheme 2. *endo*/*exo* Selectivity between **1a** + **1b** and *N*-methylmaleimide.

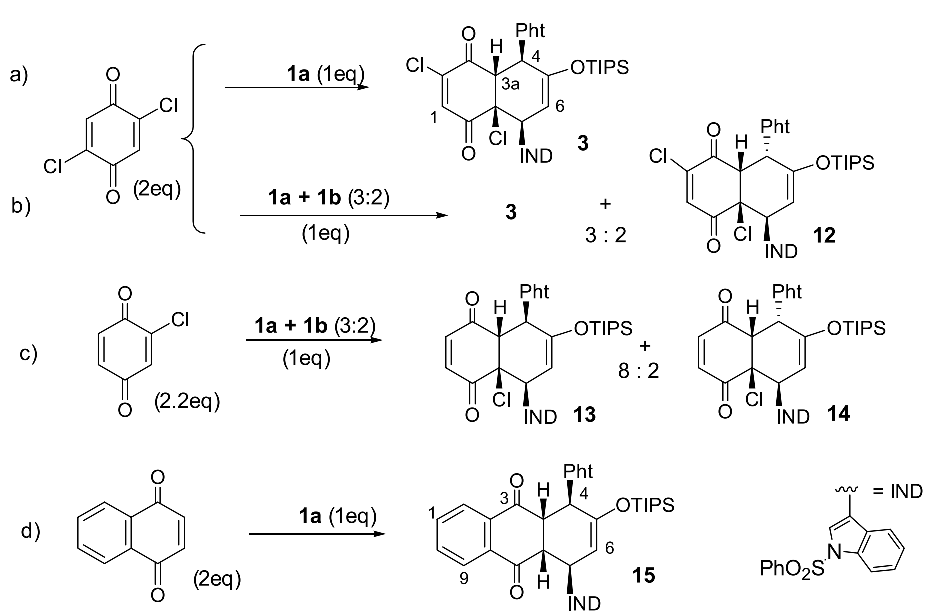
20 h in $CDCl_3$ solution, in which it isomerized to **10a**, accompanied by its transformation into enone **8**.

As reported, the different reaction time conditions allowed us to prepare **1a** (1*Z*,3*E*) or the **1a** + **1b** (1*Z*/*E*,3*E*) mixture, and hence we were able to use either the single stereoisomer or the mixture to study Diels–Alder reactivity.

In the first instance, we carried out the reaction between **1a** and maleimides (*N*-H, *N*-methyl, *N*-benzyl) and 2,5-dichloroquinone, which gave exclusively the *exo* adducts **2a–d** and **3**.

Following the same methodology, we performed the reaction between *N*-methylmaleimide and the mixture **1a** + **1b** (in 3:2 ratio), but only the *exo* cycloadduct **2a** was obtained with no reaction product derived from the *E*,*E* stereoisomer **1b** (Scheme 2). This implies a fast (as compared to the Diels–Alder reaction) equilibration of the dienes in solution, and either a higher reactivity of diene **1a** (kinetic control) or a higher stability of its adduct(s) (thermodynamic control). Molecular mechanics calculations (as implemented in the MM2 forcefield of Macromodel v.5.5) were carried out for representative *endo* and *exo* Diels–Alder transition states of the reaction between **1a** or **1b** and *N*-methylmaleimide and for the resulting cycloadducts. The stabilities of *exo* (**2a**) and *endo* (**2a′**) cycloadducts from **1a** (1*Z*,3*E*) were similar, but lower than those of cycloadducts that could be produced from **1b** (1*E*,3*E*).

Additionally, the *exo* transition state from **1a** was calculated to be 6.8–9.0 kJ/mol more stable than the *endo* one, and more than 30 kJ/mol more stable than those from **1b**. These observations suggest that the reaction would be controlled kinetically, yielding the less stable cycloadduct from the more reactive diene 1*Z*,3*E* through the more stable *exo* transition state. The interconversion of **1a** and **1b** under the



Scheme 3. Diels–Alder reactivity of **1a**, **1b** with quinones.

reaction conditions accounts for the formation of the cycloadducts derived only from the more reactive **1a** without the appearance of products derived from the less reactive **1b**. This interconversion was confirmed by refluxing pure **1a** in toluene, resulting in the formation of the equilibrium mixture **1a** + **1b** in a 3:2 ratio.

Next, we carried out several experiments with **1a** and differently substituted quinones (Scheme 3, entries a and d), and they gave the same stereochemical results as those observed with the maleimides. Thus, *exo* cycloadducts **3** and **15** were obtained. The structure of compound **3**, previously described, has now been confirmed by X-ray diffraction studies.[9] Figure 4 shows an ORTEP diagram in which the phthalimido and the chloro substituents occupy a pseudo-equatorial disposition and the indolyl an pseudo-axial disposition.

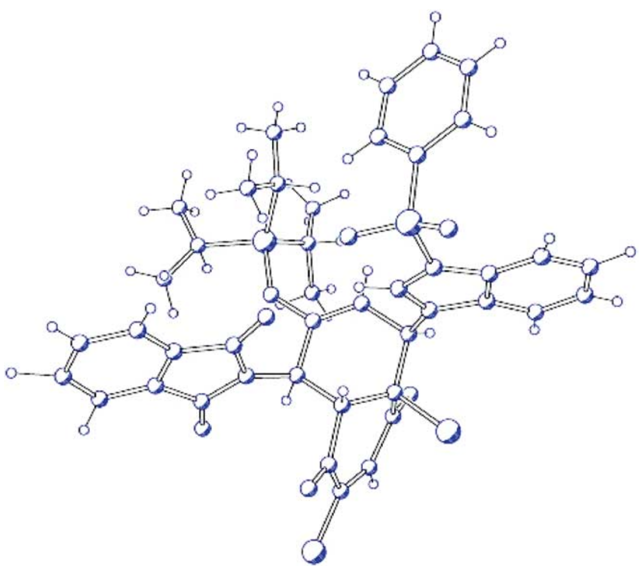


Figure 4. X-ray crystallographic analysis of **3**.

However, when mixtures of dienes **1a** and **1b** were reacted with an excess of quinones, mixtures of **3** + **12** and **13** + **14** were observed in the NMR spectra (Scheme 3, entries b and c). The main differences between them correspond to the H-2 of the indole (8.56 and 8.54 ppm) and H-3a (4.27 and 4.24 ppm) (values for **3/12**). In these cases, both dienes (1*Z*,3*E* and 1*E*,3*E*) afforded the corresponding adducts, contrary to the case of maleimides, where only adducts from diene **1a** were observed. The observed ratio between **3** and **12** was the same as that of the starting dienes, implying that both dienes have similar reactivities against the dichloroquinone and, since the reaction time (7 h) was similar to those of maleimides, that diene **1b** would be more reactive in this case than in the former one. When the reaction time required for the complete disappearance of diene was longer (20 h), as in the case of 2-chloroquinone, a higher ratio of the reaction product **13** derived from the 1*Z*,3*E* stereoisomer (**1a**) was observed. This indicates that in the equilibrium mixture diene **1a** is still more reactive than **1b**.

The dienes containing the 2-nitrophenyl moiety **10** and **11** were obtained as mixtures 1*Z*/1*E* (3:1) that were difficult to separate. We decided to use these mixtures in the Diels–Alder reaction with *N*-methylmaleimide and compare the results with those obtained from the **1a** + **1b** mixture. The reaction was carried out at a diene/dienophile 1:2 molar ratio in refluxing toluene, but no reaction was observed after 2 days. No evolution of the reaction was detected, even when $EtAlCl_2$ (20%) was added as catalyst and the reaction was heated to reflux. This lower reactivity could be explained in terms of the presence of two electron-withdrawing groups, the 2-nitrophenyl and the phthalimido moieties. We have previously shown that when only one of these electron-withdrawing groups is present, as is the case of 4-(2-nitrophenyl)-2-trialkylsiloxy-1,3-butadiene,[2b] the Diels–Alder reaction proceeds adequately.

In view of the good results obtained in the previous Diels–Alder reaction using the crude of the reaction produced in the synthesis of dienes (carrying the excess of triflate reagent), we decided to check the reactivity of dienes **10** and **11** again. The mixture **11a** and **11b** (3:1 ratio), without removing the excess of the triisopropyltriflate, was reacted with *N*-methylmaleimide and naphthoquinone, yielding **16** and **17** (Fig. 5) as the only reaction products after purification by chromatography and crystallization. In these products the *exo* stereochemistry was also proposed based on the ^{1}H NMR studies and it was confirmed by X-ray studies of **17**.[9] The formation of other stereoisomers from **11** was not detected by ^{1}H NMR of the reaction product.

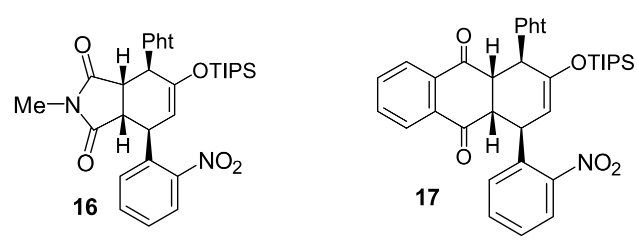
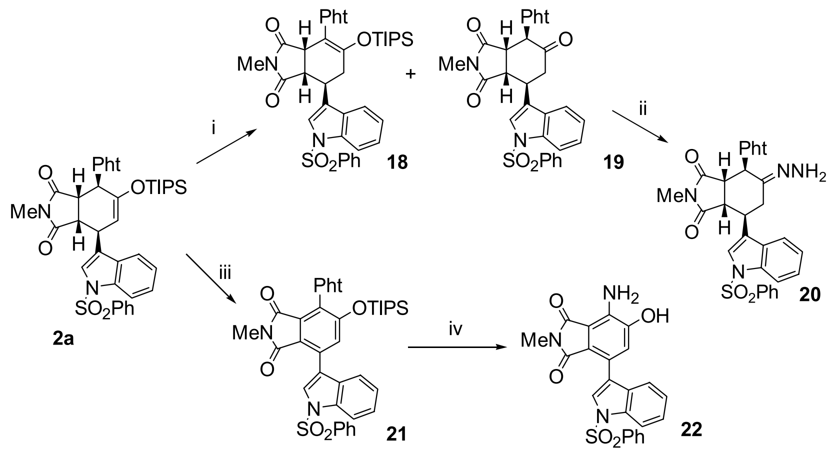


Figure 5.

From the above results, a noteworthy preference for the *exo* stereochemistry in the Diels–Alder reaction between the title dienes and maleimides or quinones can be deduced. Regardless of the nature of the C-4 aryl group, the presence of the phthalimido moiety on the C-1 of the diene produced a complete change of the preferred *endo*-stereochemistry of 4-aryl-2-siloxy-1,3-butadienes to the *exo*-stereochemistry now observed. This change would be due to the presence of a bulky *N*-substituent in the C-1 position of the diene and also to secondary interactions between the phthalimido and the aromatic ring with the dienophiles during the *exo* approach. In the case of 1-amino-3-siloxybutadienes, *endo*/*exo* mixtures, depending on the substituents of amino group have been observed. A combination of steric and electronic effects of dienes and dienophiles has been proposed to explain the factors influencing the stereoselectivity of these cycloadditions.[10] In any case, the high *exo*-stereoselectivity now observed by us has not been previously described.

After optimizing the Diels–Alder reaction, some transformations on the cycloadducts **2** were carried out to replace the



Scheme 4. Reagents and conditions: (i) HCl, CH_2Cl_2, rt; (ii) $NH_2NH_2 \cdot H_2O$, EtOH, reflux; (iii) DDQ, C_6H_6, reflux; (iv) $NH_2NH_2 \cdot H_2O$, THF, rt.

phthalimido by an amino group. These transformations are of interest in the application of this methodology to the synthesis of more elaborated polycyclic systems with fused heterocycles in their structures. Unfortunately, the usual deprotection of the phthalimido to the amino group by treatment with hydrazine[11] failed to produce any observable change. Other deprotection reactions such as treatment with methylamine,[12] also failed and thus we decided to check other transformations prior to the use of deprotecting agents.

When cycloadduct **2a** was treated with hydrochloric acid, two reaction products were isolated: compound **18** resulting from the double-bond migration, and the expected ketone **19** (Scheme 4). This migration has been observed for related cycloadducts carrying the double bond and the trialkylsiloxy substituent at the same position, producing compounds with the unsaturation closer to the ring system junction.[13] The preferred conformation of ketone **19** was similar to that of compound **2a**, as revealed by the large coupling constants between H-3a and H-4 or H-7 and H-7a in the ^{1}H NMR spectrum, in agreement with the pseudo-equatorial disposition of the phthalimido and indol-3-yl moieties. Ketone **19** gave hydrazone **20** by treatment with hydrazine but no product containing the amino function at the C-4 position was detected.

Another key step in the synthesis of fused polycyclic systems is the aromatization of the central cyclohexene ring to the corresponding benzene ring. In the present case, it is of interest to know whether this process takes place with or without elimination of the phthalimido moiety. Maintenance of the nitrogenated function is necessary for the construction of fused heterocycles, such as oxazoles. The aromatization of **2a** to **21** under DDQ standard conditions occurred in high yield, preserving the phthalimido moiety. Treatment of **21** with hydrazine afforded the expected deprotection of the amino group, thus obtaining the aminophenol derivative **22**.

3. Conclusions

We have efficiently prepared new trisubstituted dienes and studied their reactivity against different dienophiles. 1-Phthalimido-2-trialkylsiloxy-4-aryl-1,3-butadienes were highly reactive when the crude of the silylation enone reaction was used. The stereochemistry of the cycloadducts, regardless of the structure of the aromatic moiety, changed from the usually preferred *endo* when position C-4 was not substituted to the *exo*, when the bulky *N*-phthalimido was present in this position. The present methodology offers a way to obtain fused cyclohexene rings containing amino (under the protected phthalimido moiety) and an aromatic (heteroaromatic) groups as substituents. The resulting cycloadducts are versatile synthetic intermediates for the preparation of diverse heterocyclic systems.

4. Experimental

Melting points were determined on a Büchi 510 instrument and are uncorrected. NMR spectra were recorded on Bruker 400 MHz DRX spectrometer in $CDCl_3$ as solvent with TMS as internal standard. Mass spectra were obtained by EI or FAB methods on a VGTS-250 mass spectrometer. Microanalyses were carried out on Perkin-Elmer 2400 CHN. Flash chromatography was performed with Merck 60 silica gel (0.063–0.2 or 0.040–0.063 mm).

4.1. Preparation of (*E*)-*N*-[4-(aryl or 3-indolyl)-2-oxo-3-butenyl]phthalimide 8 and 9

To 1,3-dicholoroacetone (7.0 g, 55 mmol), a solution of triphenylphosphine (13.1 g, 50 mmol) in THF (33 mL) was added and the mixture was refluxed for 4 h. The monophosphonium chloride thus formed was isolated by filtration (15.6 g, 73%) and then treated with a solution of Na_2CO_3/MeOH–H_2O (1:1) at rt. After 30 min a precipitate appeared, **4**, and was filtered from the solution (12.2 g, 89%). To a suspension of **4** (3 mmol) in dry benzene, a solution of the 2-nitrobenzaldehyde (1 mmol) or *N*-(phenylsulphonyl)-3-indolylcarbaldehyde (1 mmol) was added. Compound **5** (54%) was obtained after reflux for 24 h, purification by chromatography and crystallization. In the case of **6**, the reaction was much slower and after 4 days at reflux it was isolated in 15% yield.

A solution of **4** (1.5 g, 4.25 mmol) in DMF (5 mL) was added dropwise to a stirred suspension of potassium phthalimide (2.4 g, 12.7 mmol) in DMF (35 mL) and left to reflux for 45 min. After extraction with EtOAc, it was washed with water and brine, dried and evaporated in vacuo, and the residue was crystallized (ether/MeOH) to obtain **7** (1.1 g, 62%). To phosphorane **7** (1.5 mmol), under the same conditions described previously, the corresponding aldehyde (1 mmol) was added to give, after 2 h of reaction, **8** (78%). Phosphorane **7** (1 mmol) and *N*-(phenylsulphonyl)-3-indolylcarbaldehyde (2 mmol), under the conditions described previously, yielded **9** (79%) after 72 h of reaction.

4.1.1. Data for 4. White solid. Mp 180 °C (MeOH/H_2O); ^{1}H NMR (δ ppm) 7.8–7.2 (15H, m), 4.28 (1H, d, $J=23.8$ Hz), 4.02 (2H, s).

4.1.2. Data for 5. Yellow solid. ^{1}H NMR (δ ppm) 8.10 (1H, d, $J=16.0$ Hz), 8.06 (1H, d, $J=8.4$ Hz), 8.1–7.5 (3H, m), 6.82 (1H, d, $J=16.0$ Hz), 4.34 (2H, s).

4.1.3. Data for 6. Yellow solid. ^{1}H NMR (δ ppm) 8.0–7.3 (9H, m), 7.94 (1H, s), 7.84 (1H, d, $J=15.8$ Hz), 7.09 (1H, d, $J=15.8$ Hz), 4.28 (2H, s).

4.1.4. Data for 7. White solid. Mp 222 °C (ether/MeOH); ^{1}H NMR (δ ppm) 7.81 (2H, dd, $J=5.0$, 3.3 Hz), 7.7–7.5 (15H, m), 7.39 (2H, dd, $J=5.3$, 3.3 Hz), 4.46 (2H, s), 3.68 (1H, d, $J=23.0$ Hz).

4.1.5. Data for 8. Yellow solid. Mp 180 °C (ether); ^{1}H NMR (δ ppm) 8.18 (1H, d, $J=16.4$ Hz), 8.10 (1H, d, $J=8.2$ Hz), 7.90 (2H, dd, $J=5.2$, 3.2 Hz), 7.7–7.5 (3H, m), 7.76 (2H, dd, $J=5.2$, 3.2 Hz), 6.70 (1H, d, $J=16.4$ Hz), 4.85 (2H, s). Anal. Calcd for $C_{18}H_{12}N_2O_5$: C, 64.29; H, 3.60; N, 8.33. Found: C, 64.46; H, 3.83; N, 8.15. HRMS *m*/*z* calcd for $C_{18}H_{12}N_2O_5$ 336.0746, found 336.0792.

4.1.6. Data for 9. Yellow solid. Mp 184 °C (ether); ^{1}H NMR (δ ppm) 8.02 (1H, dd, $J=7.2$, 2.0 Hz), 7.94 (1H, s), 7.9–7.3 (12H, m), 7.83 (1H, d, $J=16.4$ Hz), 6.93 (1H, d, $J=16.4$ Hz), 4.78 (2H, s). Anal. Calcd for $C_{26}H_{18}N_2O_5S$: C, 66.37; H, 3.86; N, 5.95; S, 6.82. Found: C, 66.08; H, 4.12; N, 6.03; S, 6.66. HRMS *m*/*z* calcd for $C_{26}H_{18}N_2O_5S$ 470.0936, found 470.0951.

4.2. General procedure for the preparation of 2-trialkylsiloxy-4-(2-nitrophenyl)-1-phthalimido-1,3-butadienes (10 and 11)

To a solution of enone **8** (1 mmol) in CH_2Cl_2 (20 mL) under Ar, Et_3N (5.4 mmol) and *tert*-butyldimethyl- or triisopropylsilyltriflate (4 mmol) were added dropwise. The reaction mixture was allowed to react at 50 °C for 2 h, and then Et_3N (1 mmol) was added. The mixture was diluted in CH_2Cl_2, washed with aqueous saturated $NaHCO_3$ and brine, dried (Na_2SO_4) and the solvent evaporated.

The corresponding reaction product was purified by flash chromatography on SiO_2 eluting with hexane/ether (1:1) to give **10a** (63%) and **10b** (21%).

4.2.1. Data for 10a. Yellow oil. ^{1}H NMR (δ ppm) 7.93 (1H, dd, $J=8.4$, 1.2 Hz, H-3Ar), 7.89 (2H, dd, $J=5.2$, 3.2 Hz, H-3, 6Pht), 7.75 (2H, dd, $J=5.2$, 3.2 Hz, H-4, 5Pht), 7.68 (1H, dd, $J=7.6$, 0.8 Hz, H-6Ar), 7.59 (1H, td, $J=8.0$, 0.8 Hz, H-5Ar), 7.45 (1H, d, $J=15.6$ Hz, H-4), 7.40 (1H, td, $J=8.4$, 0.8 Hz, H-4Ar), 6.73 (1H, d, $J=15.6$ Hz, H-3), 5.95 (1H, s, H-1), 0.90 (9H, TBDMS), 0.00 (6H, TBDMS). ^{13}C NMR (δ ppm) 166.3 (2-C), 149.8 (C), 148.2 (C), 134.4 (2-CH), 133.0 (CH), 132.3 (2-C), 131.7 (C), 129.3 (CH), 128.5 (CH), 128.1 (CH), 125.6 (CH), 124.8 (CH), 123.6 (2-CH), 105.2 (CH), 25.6 (3-CH_3), 18.2 (C), −4.2 (2-CH_3).

4.2.2. *Characteristic signals for* 10b. ^{1}H NMR (δ ppm) 7.34 (1H, d, $J=15.3$ Hz, H-4), 6.53 (1H, d, $J=15.3$ Hz, H-3), 5.80 (1H, s, H-1).

4.3. Diels–Alder reaction. General procedure

The corresponding diene (obtained without removing the excess of triisopropylsilyltriflate) (1 equiv) and dienophile (maleimides or quinones) (2–2.2 equiv) were dissolved in dry toluene and allowed to react at reflux for several hours under Ar atmosphere. The reaction products were purified by chromatography and crystallization to give compounds **3**, **13–17**.

4.3.1. (±)(1*R*,4*S*,4a*R*,8a*S*)-2-[4-(1-Benzenesulfonyl-1*H*-indol-3-yl)-4a,7-dichloro-5,8-dioxo-2-triisopropylsiloxy-1,4,4a,5,8,8a-hexahydro-1-naphthyl]isoindole-1,3-dione (3). After 7 h reflux, **3** was isolated in 85% yield as a brown solid. Mp 242 °C (hexane/AcOEt). ^{1}H NMR (δ ppm) 8.56 (1H, s, H-2 Ind), 8.2–7.2 (13H, Ar), 7.17 (1H, s, H-1), 5.12 (1H, dd, $J=6.0$, 1.2 Hz, H-6), 5.04 (1H, dt, $J=10.8$, 1.2 Hz, H-4), 4.77 (1H, dd, $J=6.0$, 1.2 Hz, H-7), 4.27 (1H, d, $J=10.8$ Hz, H-3a), 1.0–0.9 (TIPS). ^{13}C NMR (δ ppm) 186.6 (C), 186.5 (C), 167.6 (C), 166.8 (C), 145.7 (C), 144.3 (C), 137.4 (C), 135.4 (C), 134.6 (2-CH), 133.9 (CH), 133.6 (CH), 131.8 (C), 131.4 (C), 131.1 (C), 129.1 (2-CH), 126.8 (2-CH), 124.7 (CH), 123.9 (CH), 123.8 (2-CH), 123.2 (CH), 121.8 (C), 120.1 (CH), 114.0 (CH), 104.7 (CH), 69.4 (C), 54.2 (CH), 49.1 (CH), 34.4 (CH), 17.6 (6-CH_3), 12.7 (3-CH). HRMS *m*/*z* Calcd for $C_{41}H_{40}Cl_2N_2O_7SSi$ 802.1703, found 802.1780.

Characteristic signals for **12**. ^{1}H NMR (δ ppm) 8.54 (1H, s, H-2 Ind), 4.24 (1H, d, $J=10.8$ Hz, H-3a).

4.3.2. (±)(1*R*,4*S*,4a*R*,8a*S*)-2-[4-(1-Benzenesulfonyl-1*H*-indol-3-yl)-4a-chloro-5,8-dioxo-2-triisopropylsiloxy-1,4,4a,5,8,8a-hexahydro-1-naphthyl]isoindole-1,3-dione (13). After 20 h reflux, a mixture 8:2 ratio (in ^{1}H NMR) of **13** and **14** was isolated in 79% yield as a brown solid. Data for **13**: ^{1}H NMR (δ ppm) 8.58 (1H, s, H-2 Ind), 8.1–7.2 (13H, Ar), 6.91 (1H, d, $J=10.4$ Hz, H1), 6.67 (1H, dd, $J=10.4$, 2.0 Hz, H-2), 5.13 (1H, dd, $J=6.0$, 1.2 Hz, H-6), 5.06 (1H, dt, $J=10.8$, 1.2 Hz, H-4), 4.76 (1H, dd, $J=6.0$, 1.2 Hz, H-7), 4.13 (1H, dd, $J=10.8$, 2.0 Hz, H-3a), 1.0–0.9 (TIPS). ^{13}C NMR (δ ppm) 193.8 (C), 189.0 (C), 127.0 (2-C), 144.4 (C), 138.1 (C), 137.6 (C), 137.1 (C), 137.0 (CH), 134.5 (2-CH), 133.6 (CH), 131.9 (C), 131.5 (C), 131.2 (C), 129.0 (2-CH), 127.0 (2-CH), 124.6 (CH), 123.9 (2-CH), 123.6 (CH), 123.1 (CH), 122.1 (C), 120.2 (CH), 114.0 (CH), 104.5 (CH), 69.1 (C), 54.4 (CH), 49.3 (CH), 34.4 (CH), 16.6 (6-CH_3), 13.7 (3-CH). HRMS *m*/*z* calcd for $C_{41}H_{41}ClN_2O_7SSi$ 768.2092, found 768.2105.

Characteristic signals for **14**. ^{1}H NMR 8.53 (δ ppm) (1H, s, H-2 Ind), 4.11 (1H, dd, $J=10.8$, 2.0 Hz, H-3a).

4.3.3. (±)(1*R*,4*R*,4a*S*,9a*S*)-2-[4-(1-Benzenesulfonyl-1*H*-indol-3-yl-9,10-dioxo-2-triisopropylsiloxy-1,4,4a,9,9a,10-hexahydro-1-anthryl]isoindole-1,3-dione (15). After 13 h reflux, **15** was isolated in 90% as a white solid. Mp 225 °C (hexane/AcOEt). ^{1}H NMR (δ ppm) 8.11 (1H, s, H-2 Ind), 8.3–7.2 (17H, Ar), 5.25 (1H, dd, $J=5.2$, 1.6 Hz, H-6), 4.89 (1H, dd, $J=11.2$, 1.6 Hz, H-4), 4.80 (1H, d, $J=5.2$ Hz, H-7), 3.89 (1H, dd, $J=11.2$, 4.8 Hz, H-3a), 3.40 (1H, d, $J=4.8$ Hz, H-7a), 1.0–0.9 (TIPS). ^{13}C NMR (δ ppm) 195.1 (C), 194.7 (C), 167.8 (C), 167.6 (C), 145.7 (C), 137.9 (C), 135.8 (C), 134.8 (CH), 134.6 (2-CH), 134.3 (CH), 134.1 (CH), 134.1 (C), 133.6 (CH), 133.1 (C), 131.9 (2-C), 129.3 (C), 129.0 (2-CH), 127.4 (CH), 127.2 (2-CH), 127.0 (CH), 126.7 (CH), 124.8 (CH), 124.1 (C), 123.3 (2-CH), 118.5 (CH), 114.2 (CH), 103.5 (CH), 50.7 (CH), 48.3 (CH), 47.3 (CH), 28.7 (CH), 17.7 (6-CH_3), 12.4 (3-CH). HRMS *m/z* calcd for $C_{45}H_{44}N_2O_7SSi$ 784.2716, found 784.2726.

4.3.4. (±)(3a*S*,4*R*,7*R*,7a*S*)-2-Methyl-7-(2-nitrophenyl)-4-phthalimido-5-triisopropylsiloxy-3a,4,7,7a-tetrahydro isoindole-1,3-dione (16). After 7 h reflux, **16** was isolated in 87% yield as a yellow solid. ^{1}H NMR (δ ppm) 7.90 (1H, dd, $J=7.8$, 1.5 Hz, H-3Ar), 7.79 (1H, dd, $J=7.8$, 1.5 Hz, H-6Ar), 7.71 (1H, td, $J=7.8$, 1.5 Hz, 1H, H-5Ar), 7.45 (1H, dt, $J=7.8$, 1.5 Hz, H-4Ar), 7.7–8.0 (4H, m, Pht), 5.10 (1H, dt, $J=8.0$, 2.4 Hz, H-4), 4.91 (1H, t, $J=2.4$ Hz, H-6), 4.50 (1H, dt, $J=8.0$, 2.4 Hz, H-7), 3.82 (1H, t, $J=8.0$ Hz, H-3a), 3.27 (1H, t, $J=8.0$ Hz, H-7a), 2.99 (3H, s, N-Me), 1.1–0.8 (TIPS). ^{13}C NMR (δ ppm) 176.3 (2-C), 167.7 (2-C), 149.4 (C), 147.4 (C), 138.1 (C), 134.1 (2-CH), 133.5 (CH), 131.9 (2-C), 130.6 (CH), 128.0 (CH), 124.6 (CH), 123.4 (2-CH), 103.8 (CH), 46.1 (CH), 45.4 (CH), 42.8 (CH), 35.1 (CH), 24.8 (CH_3), 17.7 (6-CH_3), 12.4 (3-CH). HRMS *m/z* calcd for $C_{32}H_{37}N_3O_7Si$ 603.2401 found, 603.2479.

4.3.5. (±)(1*R*,4*R*,4a*S*,9a*S*)-2-[4-(2-Nitrophenyl-9,10-dioxo-2-triisopropylsiloxy-1,4,4a,9,9a,10-hexahydro-1-anthryl]isoindole-1,3-dione (17). After 7 h reflux, **17** was isolated in 84% yield as a brown solid. ^{1}H NMR (δ ppm) 8.41 (1H, dd, $J=8.1$, 1.2 Hz, H-6Ar), 8.17 (1H, dd, $J=7.5$, 1.2 Hz, H-9), 7.96 (1H, dd, $J=7.5$, 1.2 Hz, H-2), 7.92 (1H, dd, $J=8.1$, 1.2 Hz, H-3Ar), 7.76 (1H, td, $J=8.0$, 1.2 Hz, 1H, H-5Ar), 7.7–7.9 (6H, m, H-1, H-10, Pht), 7.46 (1H, dt, $J=8.1$, 1.2 Hz, H-4Ar), 5.08 (1H, d, $J=5.2$ Hz, H-7), 5.05 (1H, dd, $J=5.2$, 1.2 Hz, H-6), 4.95 (1H, dd, $J=10.8$, 1.2 Hz, H-4), 4.00 (1H, dd, $J=10.8$, 4.8 Hz, H-3a), 3.82 (1H, d, $J=4.8$ Hz, H-7a), 1.1–0.8 (TIPS). ^{13}C NMR (δ ppm) 195.2 (C), 193.6 (C), 167.6 (2C), 148.9 (C), 146.9 (C), 137.3 (C), 134.8 (CH), 134.6 (CH), 133.5 (C), 133.4 (CH), 132.8 (CH), 131.8 (2-CH), 131.7 (2-C), 130.3 (C), 128.0 (CH), 127.4 (CH), 127.3 (CH), 127.0 (CH), 123.3 (2-CH), 104.2 (CH), 51.9 (CH), 48.3 (CH), 47.5 (CH), 33.8 (CH), 17.3 (6-CH_3), 12.7 (3-CH). HRMS *m/z* calcd for $C_{37}H_{38}N_2O_7Si$ 650.2448, found 650.2526.

4.4. Hydrolysis of cycloadduct 2a (18 and 19)

Compound **2a** (75 mg, 0.10 mmol) dissolved in 4 mL of CH_2Cl_2 was treated with concentrated HCl (360 μl) and then stirred for 24 h. The reaction mixture was washed with saturated $NaHCO_3$ dried and evaporated. The reaction product was chromatographed on silica (hexane/EtOAc 7:3) to give **18** (38 mg, 50%) and **19** (22 mg, 36%).

4.4.1. (±)(3a*S*,4*R*,7a*S*)-4-(1-Benzenesulfonyl-1*H*-indol-3-yl)-2-methyl-7-phthalimido-6-triisopropylsiloxy-3a,4,5,7a-tetrahydroisoindole-1,3-dione (18). White solid. Mp 252 °C (ether/MeOH). ^{1}H NMR (δ ppm) 8.04 (1H, d, $J=8.2$ Hz, H-7 Ind), 7.93 (1H, s, H-2 Ind), 7.56 (1H, d, $J=7.2$ Hz, H-4 Ind), 7.35 (1H, t, $J=8.2$ Hz, H-6 Ind), 7.3–8.2 (10H, m, Ar), 4.20 (1H, m, H-7), 4.04 (1H, dd, $J=8.0$, 2.4 Hz, H-3a), 3.42 (1H, t, $J=8.0$ Hz, H-7a), 3.02 (3H, s, N-Me), 2.86 (1H, ddd, $J=16.8$, 2.8, 1.2 Hz, H-6), 2.38 (1H, d, $J=16.8$ Hz, H-6), 1.0–0.8 (TIPS). ^{13}C NMR (δ ppm) 177.2 (C), 175.2 (C), 167.8 (C), 166.0 (C), 149.7 (C), 133.9 (CH), 133.8 (CH), 138.2 (C), 134.7 (C), 133.5 (CH), 132.5 (C), 132.2 (C), 129.5 (C), 129.1 (2-CH), 127.4 (2-CH), 124.9 (CH), 123.6 (CH), 123.5 (CH), 123.3 (CH), 123.1 (CH), 122.3 (C), 118.6 (CH), 113.7 (CH), 102.1 (C), 44.2 (CH), 41.3 (CH), 32.3 (CH_2), 28.1 (CH), 25.1 (CH_3), 16.9 (6-CH_3), 12.8 (3-CH). Anal. Calcd for $C_{40}H_{43}N_3O_7SSi$: C, 65.10; H, 5.87; N, 5.69; S, 4.35. Found: C, 65.34; H, 6.00; N, 5.91; S, 4.19.

4.4.2. (±)(3a*S*,4*R*,7*R*,7a*S*)-7-(1-Benzenesulfonyl-1*H*-indol-3-yl)-2-methyl-4-phthalimidotetrahydro iso-indole-1,3,5-trione (19). White solid. Mp 196 °C (ether/MeOH). ^{1}H NMR (δ ppm) 7.98 (1H, d, $J=8.2$ Hz, H-7 Ind), 7.70 (1H, s, H-2 Ind), 7.55 (1H, d, $J=7.3$ Hz, H-4 Ind), 7.35 (1H, t, $J=7.2$ Hz, H-6 Ind), 7.2–8.0 (10H, m, Ar), 5.09 (1H, d, $J=12.1$ Hz, H-4), 4.17 (1H, dd, $J=12.0$, 9.4 Hz, H-3a), 3.93 (1H, td, $J=11.0$, 4.8 Hz, H-7), 3.73 (1H, dd, $J=11.0$, 9.4 Hz, H-7a), 2.98 (3H, s, N-Me), 2.93 (2H, m, H-6). ^{13}C NMR (δ ppm) 199.1 (C), 175.3 (2-C), 167.4 (2-C), 138.0 (C), 135.3 (C), 134.3 (2-CH), 133.8 (CH), 131.7 (2-C), 129.2 (2-CH), 126.9 (2-CH), 125.2 (CH), 124.1 (CH), 123.8 (2-CH), 123.4 (CH), 121.3 (C), 119.0 (CH), 117.4 (C), 114.1 (CH), 54.1 (CH), 43.9 (CH), 43.7 (CH_2), 39.0 (CH), 30.4 (CH), 25.1 (CH_3). Anal. Calcd for $C_{31}H_{23}N_3O_7S$: C, 64.02; H, 3.99; N, 7.22; S, 5.51. Found: C, 64.34; H, 4.020; N, 7.51; S, 5.19.

4.4.3. (±)(3a*S*,4*R*,7*R*,7a*S*)-7-(1-Benzenesulfonyl-1*H*-indol-3-yl)-5-hydrazono-2-methyl-4-phthalimido hexa-hydroisoindole-1,3-dione (20). One millimole of **19** in EtOH was treated with 3 mmol of hydrazine hydrate for 24 h at reflux. By crystallization, **20** was isolated in 90% yield as a yellow solid. Mp 239 °C (ether/MeOH). ^{1}H NMR (δ ppm) 7.96 (1H, d, $J=8.2$ Hz, H-7 Ind), 7.72 (1H, s, H-2 Ind), 7.52 (1H, d, $J=7.3$ Hz, H-4 Ind), 7.33 (1H, t, $J=7.2$ Hz, H-6 Ind), 7.2–8.0 (10H, m, Ar), 5.26 (1H, d, $J=12.0$ Hz, H-4), 4.38 (1H, dd, $J=12.0$, 9.2 Hz, H-3a), 3.68 (1H, td, $J=9.0$, 4.0 Hz, H-7), 3.59 (1H, t, $J=9.2$ Hz, H-7a), 2.94 (3H, s, N-Me), 2.93 (2H, m, H-6). ^{13}C NMR (δ ppm) 175.8 (2-C), 167.9 (2-C), 141.1 (C), 138.1 (C), 134.0 (2-CH), 135.3 (C), 132.0 (2-C), 133.7 (CH), 129.2 (2-CH), 126.9 (2-CH), 126.0 (CH), 125.8 (C), 124.1 (CH), 123.8 (2-CH), 123.5 (CH), 121.9 (C), 119.1 (CH), 114.1 (CH), 49.3 (CH), 43.5 (CH), 39.2 (CH), 31.7 (CH_2), 30.4 (CH), 24.9 (CH_3). Anal. Calcd for $C_{31}H_{24}N_4O_6$: C, 64.10; H, 4.17; N, 9.85; S, 5.52. Found: C, 63.90; H, 4.46; N, 9.88; S, 5.49.

4.4.4. 7-(1-Benzenesulfonyl-1*H*-indol-3-yl)-2-methyl-4-phthalimido-5-triisopropylsiloxyisoindole-1,3-dione

(21). To **2a** (50 mg, 0.07 mmol) dissolved in benzene (4 mL) was added DDQ (22 mg, 0.09 mmol), and the mixture was refluxed for 24 h. The crude reaction was diluted in AcOEt, washed with $NaHCO_3$ and brine, dried and evaporated to yield **21** (38 mg, 75%). Red solid. ^{1}H NMR (δ ppm) 8.20 (1H, s, H-2 Ind), 8.01 (1H, d, $J=7.0$ Hz, H-7 Ind), 7.3–8.1 (12H, m, Ar), 7.38 (1H, s, H-6), 3.07 (3H, s, N-Me), 1.1–0.9 (TIPS). ^{13}C NMR (δ ppm) 173.1 (C), 172.6 (C), 166.5 (C), 165.8 (C), 158.1 (C), 138.0 (C), 134.9 (C), 134.4 (2-CH), 134.0 (CH), 132.7 (2-C), 129.2 (2-CH), 128.0 (CH), 127.3 (2-CH), 126.5 (C), 125.0 (CH), 124.5 (C), 124.4 (CH), 123.6 (CH), 123.9 (2-CH), 121.0 (C), 120.1 (C), 119.6 (CH), 118.3 (C), 116.0 (C), 114.0 (CH), 24.0 (CH_3), 17.3 (6-CH_3), 12.7 (3-CH).

4.4.5. 4-Amino-7-(1-benzenesulfonyl-1*H*-indol-3-yl)-5-hydroxy-2-methylisoindole-1,3-dione (22). One millimole of **21** in THF was treated with an excess of hydrazine hydrate for 20 h at rt. The reaction product was submitted to chromatography to give **22** in 41% yield as a red solid. ^{1}H NMR (δ ppm) 8.02 (1H, dd, $J=7.2$, 1.6 Hz, H-7 Ind), 7.98 (1H, s, H-2 Ind), 7.4–8.0 (5H, m, Ar), 7.38 (1H, s, H-6), 7.28 (1H, t, $J=7.2$ Hz, H-6 Ind), 7.19 (1H, t, $J=7.2$ Hz, H-5 Ind), 6.98 (1H, s, H-6), 3.08 (3H, s, N-Me). ^{13}C NMR (δ ppm) 169.6 (C), 168.7 (C), 167.6 (C), 147.9 (C), 143.0 (C), 140.3 (C), 138.0 (C), 135.1 (C), 134.7 (C), 133.8 (CH), 129.2 (2-CH), 127.1 (2-CH), 126.6 (CH), 124.6 (CH), 123.3 (CH), 120.0 (CH), 118.9 (CH), 117.3 (C), 113.6 (CH), 102.6 (C), 23.5 (CH_3). HRMS *m/z* calcd for $C_{23}H_{17}N_3O_5S$ 447.0889, found 447.0892.

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Microwave-assisted one-pot regioselective synthesis of 2-alkyl-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines☆

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Abstract—A protocol for regioselective one-pot synthesis of 2-alkyl-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines under controlled microwave heating has been developed. Starting from commercially available 2-aminophenols, a base-mediated regioselective *O*-alkylation took place with 2-bromoalkanoates to give the acyclic intermediates, which underwent spontaneously an intramolecular amidation reaction to furnish 2-alkyl-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines in 44–82% yields. For the acyclic intermediate possessing an electron-withdrawing group, microwave heating was necessary for the annulation reaction.
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1. Introduction

The 2*H*-1,4-benzoxazine scalfold[1a] is a structural subunit of many naturally occurring and synthetic bioactive compounds. For example, the chromophore of enediyne antibiotic C-1027[2] possesses a 2-methylene-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine skeleton (Fig. 1). Derivatives of 2*H*-1,4-benzoxazine have been reported to exhibit diverse biological activities. These include plant resistance factors against microbial disease and insects,[3] serotonin-3 (5-HT_3) receptor antagonists,[4] potassium channel modulators,[5] antirheumatic agents,[6] and antihypertensive agents.[7] 2-Aminophenols and 2-nitrophenols have been widely used as the starting materials in the synthesis of 3,4-dihydro-2*H*-1,4-benzoxazines via stepwise sequences.[1b] In the cases of 2-nitrophenols, the initial *O*-alkylation was followed by nitro reduction and subsequent intramolecular *N*-substitution.[6,8] In contrast, differentiation among the two nucleophilic groups in 2-aminophenols is required normally through protection/deprotection manipulations.[9a,b] For synthesis of 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines, 2-aminophenols were usually treated with 2-haloalkanoyl chlorides or bromides in the first place to form 2-amidophenols, which then underwent an intramolecular *O*-alkylation on heating in the presence of a base.[4,5a,b,8a,9c] In connection with our previous studies on synthesis of heterocycles such as indoles[10,11] and benzofuranes[12] from 2-aminophenols, we report here a regioselective synthesis of 2-alkyl-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines via a one-pot protocol under controlled microwave heating.[13]

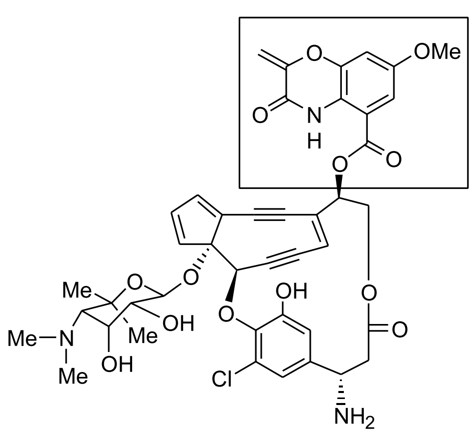

Figure 1. Molecular structure of C-1027 chromophore.

2. Results and discussion

Coudert and co-workers reported a synthesis of *N*-Boc-2,3-dihydrobenzoxazine via the reaction of *N*-Boc-2-aminophenol with a symmetrical alkylating agent, 1,2-dibromoethane in refluxing pentan-3-one (bp 102 °C) by using a domestic microwave oven.[9d] In order to establish the reaction conditions for one-pot regioselective annulation,

☆ Part 5 of Chemistry of Aminophenols. For Part 4, see Ref. 10c.

Keywords: 1,4-Benzoxazines; 2-Aminophenols; Microwave; Regioselectivity; Annulation.

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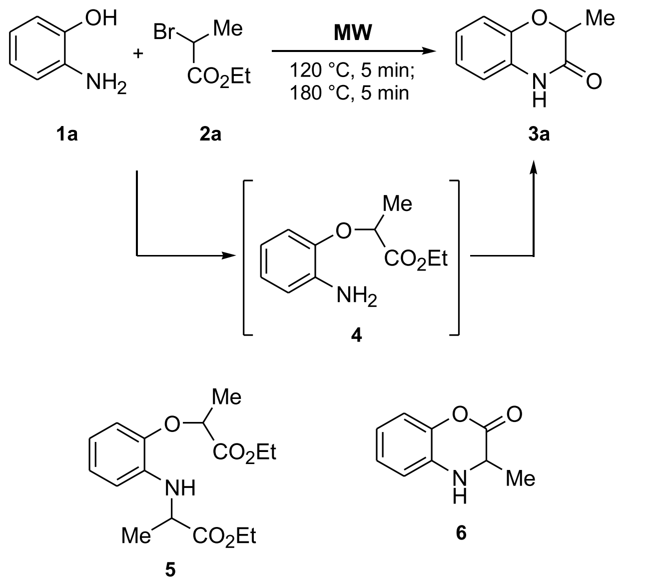


Scheme 1. Microwave-assisted one-pot synthesis of **3a**.

we first examined the reaction of 2-aminophenol (**1a**) with ethyl 2-bromopropionate (**2a**) as shown in Scheme 1 and the results are summarized in Table 1. We heated the reaction at 120 °C for 5 min to allow a selective alkylation followed by at 180 °C for another 5 min for completing the ring closure although we found later that it was not necessary to heat at two different temperatures (Table 1, entries 10–12). As expected, in the absence of a base, the amino group of **1a** reacted preferentially to give the *N*-alkylation–lactonization product **6** and the desired 3,4-dihydro-2-methyl-3-oxo-2*H*-1,4-benzoxazine (**3a**) was not detected (Table 1, entry 1). We considered that a base might help to remove the phenolic proton and reverse the reactivity of 2-aminophenol. Indeed, **3a** was obtained in 45% yield in the presence of 1.1 equiv of Et_3N together with the bis-alkylation by-product **5** (Table 1, entry 2). By using *i*-Pr_2NEt, pyridine, and K_2CO_3, **3a** was obtained in 23–51% yields along with **5**, and the acyclic intermediate **4** was observed when the reactions were carried out in DMF (Table 1, entries 4 and 5). A much more clean reaction resulted by using 1.1 equiv of DBU as the base in DMF to afford the product **3a** in 61% yield and no further improvement was observed by increasing the amount of DBU to 3.0 equiv (Table 1, entry 6 vs entry 7). Moreover, increase of **2a** to 1.2–2.0 equiv brought the yield of **3a** up to 70–71% in DMF and to 76–77% in NMP (Table 1, entries 8–11). However, use of a catalytic amount of DBU as the base resulted in a complex reaction mixture and only 12% of **3a** was isolated (Table 1, entry 12). Therefore, we selected the reaction conditions used in entry 10 of Table 1 (**1a**:**2a**:DBU = 1.2:1.0:1.1, NMP, 180 °C, 3 min) for further investigation. For the purpose of comparison, we carried out the same reaction with conventional oil bath heating at 180 °C for 3 min. The desired product **3a** was isolated in 65% yield (Table 1, entry 10), which is slightly lower than that obtained with microwave irradiation. It may be explained by the differences among rapid and volumetric microwave heating and slow and superficial conventional heating.[13c]

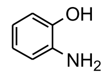
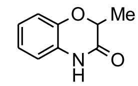
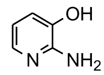
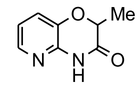
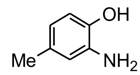
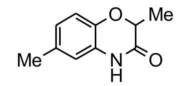
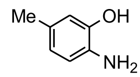
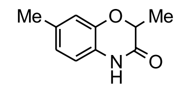
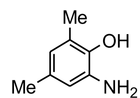
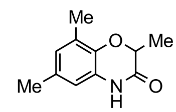
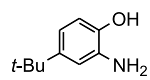
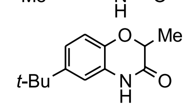
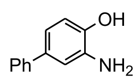
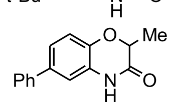
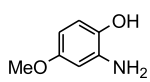
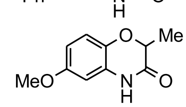
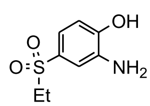
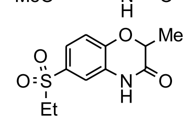
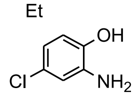
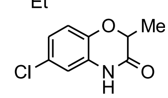
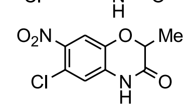
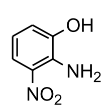
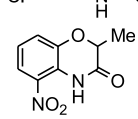
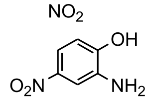
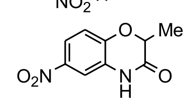
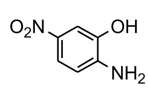
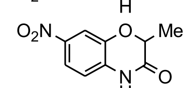
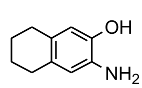
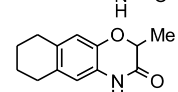
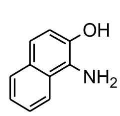
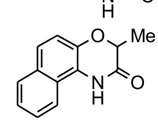
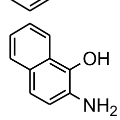
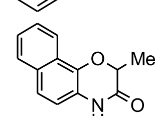
We explored the scope of the one-pot synthesis of 3,4-dihydro-2-methyl-3-oxo-2*H*-1,4-benzoxazines **3** under controlled microwave heating at 180 °C for 3 min by using a variety of commercially available substituted 2-aminophenols **1** with **2a**. The results are summarized in Table 2. The aza analog **3b** of **3a** was formed in a similar yield of 78% from the reaction of 2-amino-3-hydroxypyridine (Table 2, entry 2). In general, substituted 2-aminophenols possessing alkyl or moderately electron-withdrawing group(s) afforded the products **3c–g**,**i**,**j** in 57–80% yields (Table 2, entries 3–7, 9, and 10). However, a significant reduction in the yield of **3h** (44%) was noted presumably due to diminished acidity of the 4-methoxy-substituted phenol **1h**, allowing the competing *N*-alkylation taking place. The electronic effect was observed for the nitro-substituted substrates. A *meta*-nitro group in 2-aminophenols **1k**,**l**,**n** generally decreased the product yields as compared to the *para*-nitro analog **1m** (Table 2, entries 11, 12 and 14 vs entry 13). An enhanced acidity of the phenolic proton should be accounted for the higher yield of **3m**. Moreover, a steric effect was observed for the *O*-alkylation–cyclization of 2-amino-1-naphthol (**1q**) (Table 2, entry 17) as compared to the reactions of 3-amino-5,6,7,8-tetrahydro-2-naphthol (**1o**) and 1-amino-2-naphthol (**1p**) (Table 2, entries 15 and 16).

Table 1. Optimization of conditions for one-pot synthesis of **3a**[a]

Entry	Conditions	Yield (%)[b]
1	Without base, NMP	**1a**: 30; **5**: 7; **6**: 46
2	Et_3N (1.1 equiv), NMP	**3a**: 45; **5**: <10
3	*i*-Pr_2NEt (1.1 equiv), NMP	**3a**: 43; **5**: <10
4	Pyridine (1.1 equiv), DMF	**3a**: 23; **4**: 10; **5**: <10
5	K_2CO_3 (1.1 equiv), DMF	**3a**: 51; **4**: 5; **5**: <10
6	DBU (1.1 equiv), DMF	**3a**: 61; **5**: trace
7	DBU (3.0 equiv), DMF	**3a**: 60
8	**2a** (1.5 equiv), DBU (1.1 equiv), DMF	**3a**: 71
9	**2a** (1.5 equiv), DBU (3.0 equiv), DMF	**3a**: 70
10	**1a** (1.2 equiv), DBU (1.1 equiv), NMP[c]	**3a**: 76 (65)[d]
11	**1a** (2.0 equiv), DBU (1.1 equiv), NMP[c]	**3a**: 77
12	**1a** (1.5 equiv), DBU (0.2 equiv), NMP[c]	**3a**: 12[e]

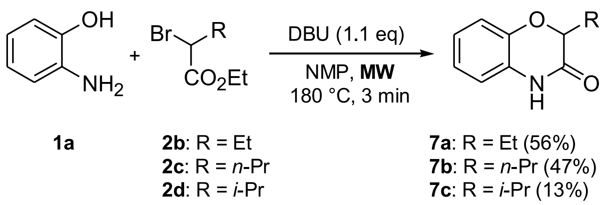
[a] One equivalent each of **1a** and **2a** were used. All reactions were carried out on a commercial technical microwave reactor with temperature and pressure controlling capacity.
[b] The substrate **1a** was detected in all reactions.
[c] Heating at 180 °C for 3 min.
[d] Yield obtained with oil bath heating for 3 min at 180 °C.
[e] A very complex reaction mixture.

Table 2. Microwave-assisted one-pot synthesis of **3**[a]

Entry	**1**: 2-Aminophenol	**3**: Product	Yield (%)[b]
1			**3a**: 76
2			**3b**: 78
3			**3c**: 63
4			**3d**: 64
5			**3e**: 61
6			**3f**: 76
7			**3g**: 58
8			**3h**: 44
9			**3i**: 57
10			**3j**: 80
11			**3k**: 72
12			**3l**: 60
13			**3m**: 82
14			**3n**: 62
15			**3o**: 62
16			**3p**: 65
17			**3q**: 44

[a] All reactions were carried out with **1**:**2a**:DBU = 1.2:1.0:1.1 in NMP at 180 °C for 3 min on a commercial technical microwave reactor with temperature and pressure controlling capacity.
[b] Isolated yields.

We also carried out the one-pot synthesis of 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines **7a–c** by using ethyl 2-bromobutyrate (**2b**), ethyl 2-bromovalerate (**2c**) and ethyl 2-bromoisobutyrate (**2d**) with 2-aminophenol (**1a**) (Scheme 2). The desired products **7a–c** were isolated in 56, 47, and 13% yields, respectively, suggesting that a steric effect of the bulky R group came into play in the *O*-alkylation of the 2-aminophenol.



Scheme 2. Microwave-assisted one-pot synthesis of **7a–c**.

3. Conclusion

In summary, we have established a regioselective one-pot synthesis of 2-alkyl-3,4-dihydro-3-oxo-2*H*-1,4-benzoxazines from commercially available substituted 2-aminophenols under controlled microwave heating. Use of a base such as DBU is critical for achieving the regioselectivity. The desired products **3** possessing alkyl, aryl, halogen, nitro, and sulfonyl group(s), and ring structures can be conveniently and efficiently prepared in synthetically useful chemical yields, typically in the range of 60–80%.

4. Experimental

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, acetone-d_6, DMSO-d_6, or CD_3OD (300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively) with $CHCl_3$, acetone, DMSO, or MeOH as the internal reference. IR spectra were taken on a FT-IR spectrophotometer. Mass spectra (MS) were measured by the +CI or +ESI method. Elemental analyses were performed by Zhejiang University, Hangzhou, China. Melting points are uncorrected. All reactions were carried out on a technical microwave reactor (Emrys™ creator from Personal Chemistry AB, Uppsala, Sweden) with temperature and pressure controlling capacity. E. Merck silica gel plates (0.25-mm, 60 F-254) was used for thin-layer chromatography using UV light, or 7% ethanolic phosphomolybdic acid and heating as the visualizing methods. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. Reagents were obtained commercially and used as received.

4.1. Microwave-assisted one-pot reaction of 2-aminophenol with ethyl 2-bromopropionate in the absence of a base

4.1.1. 3,4-Dihydro-3-methyl-2-oxo-2*H*-1,4-benzoxazine (6). A 10 mL process vial was charged with a mixture of ethyl 2-bromopropionate (**2a**, 0.50 mmol) and 2-aminophenol (**1a**, 0.50 mmol) in distilled NMP (2 mL) and sealed with a cap containing a septum. The loaded vial was then placed into the cavity of the microwave reactor and heated at 120 °C for 5 min and at 180 °C for another 5 min in the fixed mode. The reaction mixture was diluted with EtOAc (10 mL) and washed with brine (3×5 mL). The combined organic layer was dried over $MgSO_4$ and condensed under reduced pressure. The residue was purified by flash column chromatography over silica gel with EtOAc–hexane as eluent. The compounds **5** and **6** were obtained in 7 and 46% yields along with recovery of **1a** in 30% yield (Table 1, entry 1). *Compound* **5**. R_f=0.58 (25% EtOAc in hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90–6.50 (m, 4H), 4.71 (q, J=6.8 Hz, 1H), 4.26–4.07 (m, 5H), 1.65 (d, J=6.8 Hz, 3H), 1.51 (d, J=6.8 Hz, 3H), 1.29–1.20 (m, 6H) (N–H not observed); MS (+ESI) m/z 310 (M+H$^+$, 100). *Compound* **6**. A white crystalline solid; mp 102.0–103.0 °C (EtOAc–hexane); R_f=0.46 (25% EtOAc in hexane); IR (film) 3319, 1749, 1504, 1205 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02–6.76 (m, 4H), 4.06–3.85 (br s, 1H), 3.97 (q, J=6.6 Hz, 1H), 1.53 (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 142.0, 133.7, 125.5, 121.0, 117.4, 115.7, 51.2, 17.8; MS (+CI) m/z 164 (M+H$^+$, 100). Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.25; H, 5.51; N, 8.98%.

4.2. Representative procedure for microwave-assisted one-pot reactions of substituted 2-aminophenols with ethyl 2-bromoalkanoates in the presence of DBU

4.2.1. 3,4-Dihydro-2-methyl-3-oxo-2*H*-1,4-benzoxazine (3a). A 10 mL process vial was charged with a mixture of ethyl 2-bromopropionate (**2a**, 0.50 mmol), 2-aminophenol (**1a**, 0.60 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.55 mmol) in distilled NMP (2 mL) and sealed with a cap containing a septum. The loaded vial was then placed into the cavity of the microwave reactor and heated at 180 °C for 3 min in the fixed mode. The reaction mixture was diluted with EtOAc (10 mL) and washed with brine (3×5 mL). The combined organic layer was dried over $MgSO_4$ and condensed under reduced pressure. The residue was purified by flash column chromatography over silica gel with EtOAc–hexane as eluent. The product **3a** was obtained in 76% yield (Table 2, entry 1). *Compound* **3a**. A light brown crystalline solid; mp 143.2–144.0 °C (EtOAc–hexane); R_f=0.29 (25% EtOAc in hexane); IR (film) 1676, 1500, 1108 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.87 (br s, 1H), 7.00–6.85 (m, 4H), 4.68 (q, J=6.8 Hz, 1H), 1.59 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 143.8, 127.2, 124.8, 123.2, 117.6, 116.6, 73.9, 16.9; MS (+ESI) m/z 164 (M+H$^+$, 100). Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.57; H, 5.59; N, 9.07%.

4.2.2. 3,4-Dihydro-2-methyl-3-oxo-2*H*-pyrido[3,2-*b*]-[1,4]oxazine (3b). Prepared in 78% yield. *Compound* **3b**. A white crystalline solid; mp 170.0–170.2 °C (EtOAc–hexane); R_f=0.33 (33% EtOAc in hexane); IR (film) 1695, 1607, 1489 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 10.40 (br s, 1H), 8.08 (d, J=4.9 Hz, 1H), 7.47 (d, J=7.7 Hz, 1H), 7.14 (dd, J=7.6, 4.9 Hz, 1H), 4.90 (q, J=6.3 Hz, 1H), 1.67 (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.9, 142.1, 141.0, 138.8, 123.3, 119.0, 72.9, 16.2; MS (+ESI) m/z 165 (M+H$^+$, 100); Anal. Calcd for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.51; H, 4.90; N, 17.07%.

4.2.3. 3,4-Dihydro-2,6-dimethyl-3-oxo-2*H*-1,4-benzoxazine (3c). Prepared in 63% yield. *Compound* **3c**. A light brown crystalline solid; mp 143.4–144.2 °C (EtOAc–hexane); R_f=0.38 (33% EtOAc in hexane); IR (film) 1683, 1608, 1496, 1399 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.00–6.88 (m, 3H), 4.72 (q, J=6.8 Hz, 1H), 2.43 (s, 3H), 1.65 (d, J=6.8 Hz, 3H); ^{13}C NMR (300 MHz, CD_3OD) δ 170.4, 142.7, 133.7, 128.4, 125.5, 117.8, 117.5, 74.5, 21.8, 16.8; MS (+ESI) *m/z* 178 (M+H$^+$, 100); Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.84; H, 6.36; N, 7.93%.

4.2.4. 3,4-Dihydro-2,7-dimethyl-3-oxo-2*H*-1,4-benzoxazine (3d). Prepared in 64% yield. *Compound* **3d**. A grey crystalline solid; mp 173.4–174.2 °C (EtOAc–hexane); R_f= 0.36 (33% EtOAc in hexane); IR (film) 2917, 1683, 1520 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.56 (br s, 1H), 6.85–6.74 (m, 3H), 4.56 (q, J=6.6 Hz, 1H), 2.24 (s, 3H), 1.45 (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.8, 142.7, 132.4, 125.1 122.8, 116.9, 115.3, 72.6, 20.4, 16.1; MS (+ESI) *m/z* 178 (M+H$^+$, 100); Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.70; H, 6.21; N, 8.28%.

4.2.5. 3,4-Dihydro-2,6,8-trimethyl-3-oxo-2*H*-1,4-benzoxazine (3e). Prepared in 61% yield. *Compound* **3e**. A light brown crystalline solid; mp 180.0–180.4 °C (EtOAc–hexane); R_f=0.38 (33% EtOAc in hexane); IR (film) 1687, 1612 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 6.82 (s, 1H), 6.72 (s, 1H), 4.73 (q, J=6.8 Hz, 1H), 2.39 (s, 3H), 2.34 (s, 3H), 1.65 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 170.5, 140.7, 133.0, 128.0, 127.5, 127.3, 115.2, 74.6, 21.1, 16.8, 15.7; MS (+ESI) *m/z* 192 (M+H$^+$, 100); Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.08; H, 6.80; N, 7.46%.

4.2.6. 6-*tert*-Butyl-3,4-dihydro-2-methyl-3-oxo-2*H*-1,4-benzoxazine (3f). Prepared in 76% yield. *Compound* **3f**. A white crystalline solid; mp 156.6–157.4 °C (EtOAc–hexane); R_f=0.30 (33% EtOAc in hexane); IR (film) 1713, 1563, 1458 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.61 (br s, 1H), 7.18 (d, J=2.1 Hz, 1H), 7.13 (dd, J=8.4, 2.1 Hz, 1H), 7.01 (d, J=8.4 Hz, 1H), 4.73 (q, J=6.8 Hz, 1H), 1.62 (d, J=6.7 Hz, 3H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, acetone-d_6) δ 168.3, 146.6, 142.4, 128.5, 121.2, 117.2, 113.8, 74.4, 35.2, 32.1 (×3), 16.9; MS (+CI) *m/z* 220 (M+H$^+$, 100); Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.17; H, 7.87; N, 6.38%.

4.2.7. 3,4-Dihydro-2-methyl-6-phenyl-3-oxo-2*H*-1,4-benzoxazine (3g). Prepared in 58% yield. *Compound* **3g**. A grey crystalline solid; mp 180.0–180.4 °C (EtOAc–hexane); R_f=0.37 (33% EtOAc in hexane); IR (film) 1689, 1602, 1488 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.87 (br s, 1H), 7.73 (d, J=7.5 Hz, 2H), 7.37–7.60 (m, 5H), 7.18 (d, J=8.2 Hz, 1H), 4.82 (q, J=6.8 Hz, 1H), 1.66 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 168.2, 144.2, 141.5, 136.8, 130.1 (×2), 129.4, 128.3 (×2), 127.7, 122.9, 118.2, 115.2, 74.6, 17.0; MS (+CI) *m/z* 240 (M+H$^+$, 100); Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.29; H, 5.44; N, 6.18%.

4.2.8. 3,4-Dihydro-6-methoxy-2-methyl-3-oxo-2*H*-1,4-benzoxazine (3h). Prepared in 44% yield. *Compound* **3h**. A dark brown crystalline solid; mp 140.8–141.8 °C (EtOAc–hexane); R_f=0.19 (33% EtOAc in hexane); IR (film) 1679, 1515, 1159 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.60 (br s, 1H), 7.05–7.01 (m, 1H), 6.71–6.67 (m, 2H), 4.73 (q, J=6.8 Hz, 1H), 3.89 (s, 3H), 1.61 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 167.5, 157.4, 143.4, 122.3, 117.1, 109.0, 104.0, 74.5, 56.2, 16.9; MS (+CI) *m/z* 194 (M+H$^+$, 100); Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.19; H, 5.71; N, 7.30%.

4.2.9. 3,4-Dihydro-6-ethylsulfonyl-2-methyl-3-oxo-2*H*-1,4-benzoxazine (3i). Prepared in 57% yield. *Compound* **3i**. A white crystalline solid; mp 156.6–157.4 °C (EtOAc–hexane); R_f=0.33 (33% EtOAc in hexane); IR (film) 3508, 3420, 1682, 1607, 1496, 1294, 1133 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.69 (dd, J=8.4, 1.6 Hz, 1H), 7.59 (d, J=1.6 Hz, 1H), 7.35 (d, J=8.4 Hz, 1H), 4.97 (q, J= 6.9 Hz, 1H), 3.37 (q, J=7.4 Hz, 2H), 1.74 (d, J=6.8 Hz, 3H), 1.41 (t, J=7.3 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 169.1, 149.3, 133.9, 129.6, 125.6, 118.8, 116.9, 75.2, 51.7, 17.1, 8.0; MS (+ESI) *m/z* 256 (M+H$^+$, 100); Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49. Found: C, 51.98; H, 5.13; N, 5.71%.

4.2.10. 6-Chloro-3,4-dihydro-2-methyl-3-oxo-2*H*-1,4-benzoxazine (3j). Prepared in 80% yield. *Compound* **3j**. A white crystalline solid; mp 171.6–172.2 °C (EtOAc–hexane); R_f=0.49 (33% EtOAc in hexane); IR (film) 1694, 1608, 1497 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.13–7.07 (m, 3H), 4.80 (q, J=6.8 Hz, 1H), 1.68 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, CD_3OD) δ 169.8, 143.7, 130.1, 128.6, 124.6, 119.3, 116.8, 74.8, 16.8; MS (+ESI) *m/z* 198 (M+H$^+$, 100), 200 (M+2+H$^+$, 20); Anal. Calcd for $C_9H_8ClNO_2$: C, 54.70; H, 4.08; N, 7.09. Found: C, 54.66; H, 4.13; N, 7.27%.

4.2.11. 6-Chloro-3,4-dihydro-2-methyl-7-nitro-3-oxo-2*H*-1,4-benzoxazine (3k). Prepared in 72% yield. *Compound* **3k**. A pale brown crystalline solid; mp 213.6–214.0 °C (EtOAc–hexane); R_f=0.28 (33% EtOAc in hexane); IR (film) 1708, 1535, 1305 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ 7.84 (s, 1H), 7.26 (s, 1H), 4.94 (q, J=6.8 Hz, 1H), 1.74 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.5, 141.4, 141.0, 133.1, 119.7, 116.7, 114.3, 73.1, 16.1; MS (+CI) *m/z* 243 (M+H$^+$, 100), 245 (M+2+H$^+$, 42); Anal. Calcd for $C_9H_7ClN_2O_4$: C, 44.55; H, 2.91; N, 11.55. Found: C, 44.70; H, 2.99; N, 11.64%.

4.2.12. 3,4-Dihydro-2-methyl-5-nitro-3-oxo-2*H*-1,4-benzoxazine (3l). Prepared in 60% yield. *Compound* **3l**. A light yellow crystalline solid; mp 141.6–142.4 °C (EtOAc–hexane); R_f=0.47 (33% EtOAc in hexane); IR (film) 3297, 1702, 1527, 1294 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.08 (d, J=8.4 Hz, 1H), 7.56 (d, J=7.9 Hz, 1H), 7.33 (dd, J=8.1, 8.1 Hz, 1H), 4.98 (q, J=6.6 Hz, 1H), 1.75 (d, J= 6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6+acetone-d_6) δ 167.1, 145.5, 135.7, 124.6, 123.1, 123.0, 119.4, 73.1, 16.0; MS (+ESI) *m/z* 209 (M+H$^+$, 100); Anal. Calcd for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 51.90; H, 3.81; N, 13.46%.

4.2.13. 3,4-Dihydro-2-methyl-6-nitro-3-oxo-2*H*-1,4-benzoxazine (3m). Prepared in 82% yield. *Compound* **3m**. A light yellow crystalline solid; mp 187.0–188.0 °C (EtOAc–hexane); R_f=0.37 (33% EtOAc in hexane); IR (film) 2919, 1697, 1526, 1343 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 10.11 (br s, 1H), 8.05–8.01 (m, 2H), 7.31–7.27 (m, 1H), 5.01 (q, J=6.6 Hz, 1H), 1.70 (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6+acetone-d_6) δ 167.1, 149.6, 143.4, 129.4, 119.8, 117.7, 111.8, 74.6, 17.1; MS (+CI) m/z 209 (M+H$^+$, 100); Anal. Calcd for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 51.63; H, 3.87; N, 13.46%.

4.2.14. 3,4-Dihydro-2-methyl-7-nitro-3-oxo-2*H*-1,4-benzoxazine (3n). Prepared in 62% yield. *Compound* **3n**. A light yellow crystalline solid; mp 215.0–215.6 °C (EtOAc–hexane); R_f=0.24 (33% EtOAc in hexane); IR (film) 1689, 1603, 1509 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 10.31 (br s, 1H), 8.07 (dd, J=8.7, 2.4 Hz, 1H), 7.93 (d, J=2.4 Hz, 1H), 7.34 (d, J=8.7 Hz, 1H), 4.97 (q, J=6.6 Hz, 1H), 1.69 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.9, 142.5, 142.3, 134.3, 118.9, 115.5, 111.8, 72.9, 16.1; MS (+CI) m/z 209 (M+H$^+$, 100); Anal. Calcd for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 51.80; H, 3.83; N, 13.39%.

4.2.15. 3,4,6,7,8,9-Hexahydro-2-methyl-3-oxo-2*H*-naphtho[2,3-*b*][1,4]oxazine (3o). Prepared in 62% yield. *Compound* **3o**. A grey crystalline solid; mp 117.4–118.6 °C (EtOAc–hexane); R_f=0.57 (33% EtOAc in hexane); IR (film) 3209, 2918, 1694, 1605 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.59 (br s, 1H), 6.71 (s, 1H), 6.64 (s, 1H), 4.63 (q, J=6.6 Hz, 1H), 2.69 (br s, 4H), 1.76 (br s, 4H), 1.47 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.1, 140.7, 131.2, 130.3, 125.2, 116.2, 115.3, 72.6, 28.4, 28.2, 22.8, 22.7, 16.1; MS (+CI) m/z 218 (M+H$^+$, 100); Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.65; H, 7.45; N, 6.37%.

4.2.16. 3,4-Dihydro-2-methyl-3-oxo-2*H*-naphtho[2,1-*b*][1,4]oxazine (3p). Prepared in 65% yield. *Compound* **3p**. A dark purple crystalline solid; mp 188.2–189.0 °C (EtOAc–hexane); R_f=0.27 (33% EtOAc in hexane); IR (film) 2917, 1679, 1641, 1410 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6+acetone-d_6) δ 10.43 (br s, 1H), 7.71 (d, J=8.3 Hz, 1H), 7.52 (d, J=8.1 Hz, 1H), 7.23 (d, J=8.7 Hz, 1H), 7.18 (t, J=7.4 Hz, 1H), 7.08 (t, J=7.4 Hz, 1H), 6.90 (d, J=8.6 Hz, 1H), 4.48 (q, J=6.8 Hz, 1H), 1.24 (d, J=6.8 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6+acetone-d_6) δ 167.8, 137.0, 131.1, 128.6, 126.9, 125.4, 125.4, 123.7, 122.8, 121.0, 117.2, 74.1, 16.7; MS (+ESI) m/z 214 (M+H$^+$, 100); Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 72.90; H, 5.25; N, 6.41%.

4.2.17. 3,4-Dihydro-2-methyl-3-oxo-2*H*-naphtho[1,2-*b*][1,4]oxazine (3q). Prepared in 44% yield. *Compound* **3q**. A dark red crystalline solid; mp 181.2–182.0 °C (EtOAc–hexane); R_f=0.35 (33% EtOAc in hexane); IR (film) 1685, 1477, 1399 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 10.07 (br s, 1H), 8.39 (d, J=8.5 Hz, 1H), 8.03 (d, J=8.2 Hz, 1H), 7.75–7.67 (m, 2H), 7.58 (t, J=7.3 Hz, 1H), 7.38 (d, J=8.8 Hz, 1H), 4.87 (q, J=6.9 Hz, 1H), 1.70 (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 168.5, 141.5, 131.3, 129.7, 127.6, 125.6, 124.8, 124.4, 121.8, 121.0, 118.9, 74.5, 16.6; MS (+CI) m/z 214 (M+H$^+$, 100); Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.19; H, 5.15; N, 6.75%.

4.2.18. 3,4-Dihydro-2-ethyl-3-oxo-2*H*-1,4-benzoxazine (7a). Prepared in 56% yield from 2-aminophenol (**1a**) and ethyl 2-bromobutyrate (**2b**). *Compound* **7a**. A white crystalline solid; mp 102.0–103.0 °C (EtOAc–hexane); R_f=0.44 (33% EtOAc in hexane); IR (film) 1678, 1610, 1503, 1408 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.74 (br s, 1H), 7.14–7.07 (m, 4H), 4.60 (dd, J=7.9, 4.7 Hz, 1H), 2.13–1.87 (m, 2H), 1.20 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 167.7, 144.3, 128.9, 124.4, 123.5, 117.8, 116.7, 79.1, 24.8, 10.0; MS (+ESI) m/z 178 (M+H$^+$, 100); Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.40; H, 6.29; N, 7.39%.

4.2.19. 3,4-Dihydro-2-propyl-3-oxo-2*H*-1,4-benzoxazine (7b). Prepared in 47% yield from 2-aminophenol (**1a**) and ethyl 2-bromovalerate (**2c**). *Compound* **7b**. A white crystalline solid; mp 86.2–87.0 °C (EtOAc–hexane); R_f=0.53 (33% EtOAc in hexane); IR (film) 1678, 1611, 1502 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.75 (br s, 1H), 7.10 (br s, 4H), 4.67 (dd, J=8.0, 4.9 Hz, 1H), 2.05–1.86 (m, 2H), 1.82–1.58 (m, 2H), 1.10 (t, J=7.4 Hz, 3H); ^{13}C NMR (75 MHz, acetone-d_6) δ 167.9, 144.2, 128.9, 124.4, 123.6, 117.9, 116.7, 77.8, 33.5, 19.2, 14.3; MS (+ESI) m/z 192 (M+H$^+$, 100); Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.99; H, 6.79; N, 7.40%.

4.2.20. 3,4-Dihydro-2-(*iso*-propyl)-3-oxo-2*H*-1,4-benzoxazine (7c). Prepared in 47% yield from 2-aminophenol (**1a**) and ethyl 2-bromoisobutyrate (**2d**). *Compound* **7c**. A white crystalline solid; mp 118.4–119.2 °C (EtOAc–hexane); R_f=0.56 (33% EtOAc in hexane); IR (film) 1688, 1610, 1504 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.73 (br s, 1H), 7.12–7.06 (m, 4H), 4.44 (d, J=5.7 Hz, 1H), 2.45–2.33 (m, 1H), 1.22 (d, J=6.9 Hz, 3H), 1.15 (d, J=6.9 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6+acetone-d_6) δ 166.8, 144.1, 128.5, 123.9, 123.0, 117.1, 116.5, 82.0, 19.1, 17.7; MS (+ESI) m/z 192 (M+H$^+$, 100); Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.18; H, 6.80; N, 7.50%.

4.3. One-pot reaction of 2-aminophenol with ethyl 2-bromopropionate in the presence of DBU using conventional oil bath heating

4.3.1. 3,4-Dihydro-2-methyl-3-oxo-2*H*-1,4-benzoxazine (3a). A 10 mL process vial was charged with a mixture of ethyl 2-bromopropionate (**2a**, 0.50 mmol), 2-aminophenol (**1a**, 0.60 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.55 mmol) in distilled NMP (2 mL) and sealed with a cap containing a septum. The loaded vial was then placed into a pre-heated oil bath (180 °C) and kept for 3 min. The reaction mixture was diluted with EtOAc (10 mL) and washed with brine (3×5 mL). The combined organic layer was dried over $MgSO_4$ and condensed under reduced pressure. The residue was purified by flash column chromatography over silica gel with EtOAc–hexane as eluent. The product **3a** was obtained in 65% yield (Table 1, entry 10).

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Tetrahedron

Synthesis of 3,4,5-trisubstituted indoles via iterative directed lithiation of 1-(triisopropylsilyl)gramines

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Abstract—Directed lithiation of 1-(triisopropylsilyl)gramines **1** with *tert*-butyllithium followed by reaction with trimethylsilylmethyl azide produced 4-amino-1-(triisopropylsilyl)gramines **7**. The *N*-*tert*-butoxycarbonyl derivatives **8** were lithiated selectively at C-5 with *tert*-butyllithium and the lithiated species were reacted with a variety of electrophiles to give 5-functionalized compounds, **9** and **10**. A facile method to produce 3,4,5-trisubstituted indoles from readily available gramine derivatives is thereby established.
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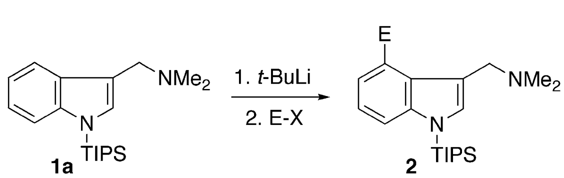
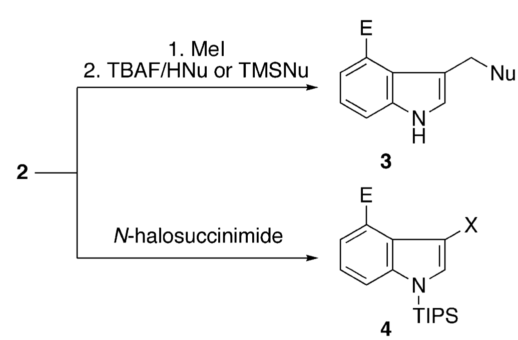
1. Introduction

Functionalization at the 1-, 2-, and 3-positions of the indole ring can be effected easily by conventional methods.[1] On the other hand, regioselective substitution at the benzenoid portion is rather problematic. Consequently, the development of procedures to achieve this objective has been a challenge for synthetic chemists for many years.[2] In 1993, we reported a facile method to produce 4-substituted indoles via directed lithiation of 1-(triisopropylsilyl)gramine (**1a**) (Scheme 1).[2g] The selective lithiation at the 4-position is achieved by both the *ortho*-directing effect of the *N*,*N*-dimethylaminomethyl group and the steric shielding of the proton at C-2 by a bulky *N*-triisopropylsilyl group. The synthetic utility of this reaction has been expanded by development of a procedure for further elaboration at the C-3 side chain via the fluoride-induced elimination–addition reaction of 1-(triisopropylsilyl)gramine methiodides (Scheme 2).[3] The combination of these reactions allows short-step synthesis of a wide range of 3,4-disubstituted indoles **3**, including biologically significant natural products and their analogues, such as clavicipitic acids,[4] pyrroloiminoquinone marine alkaloids,[5] indolactam- and teleocidin-class PKC regulators,[6] 4-fluoroserotonine and -melatonine,[7] and so on.[8] Halonium-induced retro-Mannich reaction, recently reported by Snieckus, allows the ring functionalization at C-3 of the gramines (Scheme 2).[9]

Iterative directed lithiation proposed by Snieckus is a potentially valuable method to produce multisubstituted aromatics in short steps.[10,2k] The process is a series of lithiation-electrophilic substitution in which a newly created directing group promotes the next lithiation. We intended to apply this methodology for the synthesis of 3,4,5-trisubstituted indoles starting from 1-(triisopropylsilyl)gramine (**1a**), because no general synthetic approach to such indoles has been reported. The concept is shown in Scheme 3. The initial C-4 lithiation of **1a** followed by quenching with an appropriate electrophile produces 4-substituted gramine **5** having a directing group (DG) at C-4, which can promote



Scheme 1. Directed lithiation of 1-(triisopropylsilyl)gramine (**1a**).



Scheme 2. Functionalization at C-3 (side chain or ring) of gramines **2**.

Keywords: 1-(Triisopropylsilyl)gramines; *tert*-Butyllithium; Lithiation.
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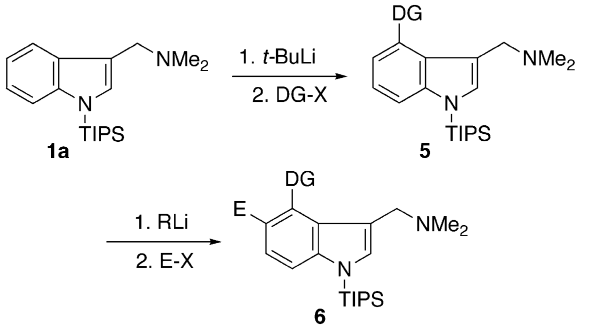


Scheme 3. Iterative directed lithiation of **1a** to produce 3,4,5-trisubstituted indoles **6**.

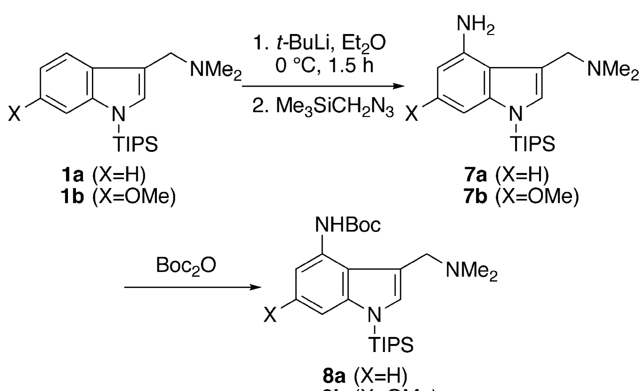
the next lithiation at C-5 to give a variety of 3,4,5-trisubstituted indoles **6**.

2. Results and discussion

In the synthetic transformation described above, the choice of the directing group at C-4 may be most important. From a practical point of view, we selected *tert*-butoxycarbonylamino (Boc-NH) group as a director, because (1) good directing ability of Boc-NH has been established in the *ortho*-lithiation of aniline derivatives,[11] (2) 4-amino-1-(triisopropylsilyl) gramine is readily available in high yield via directed lithiation of **1**,[2g,6] (3) the amino group at C-4 of the indoles could be readily transformed to a variety of functionalities via diazonium salt displacement reactions,[12] and finally, (4) some biologically significant natural products comprise a 4-aminoindole substructure in their molecular framework.[5,6]

The synthesis of 4-(*N*-*tert*-butoxycarbonyl)amino-1-(triisopropylsilyl)gramines **8** is shown in Scheme 4. Directed lithiation of **1** under the established conditions (*tert*-butyllithium, diethyl ether, −78 °C, 15 min, then 0 °C, 1.5 h)[2g] followed by reaction with trimethylsilylmethylazide[13] produced 4-aminogramines **7a** and **7b** in 79 and 86% yields, respectively. Treatment of **7** with di-*tert*-butyl dicarbonate in refluxing THF gave the corresponding *N*-*tert*-butoxycarbonyl derivatives **8**.

Ortho-lithiation of *N*-(*tert*-butoxycarbonyl)aniline was achieved for the first time by Muchowski in 1980.[11a] The



Scheme 4. Synthesis of 4-(*N*-*tert*-butoxycarbonyl)amino-1-(triisopropylsilyl)gramines **8**.

compound was lithiated with *tert*-butyllithium in THF at −20 °C. In 1992, Stanetty re-examined this reaction precisely and discovered that utilization of diethyl ether instead of THF as a solvent is essential for good and reproducible results.[11d] Thus, we employed the conditions similar to Stannety's for the lithiation of **8**. After some optimization studies using iodomethane as an electrophile, we found that the selective C-5 lithiation can be effected most satisfactorily by treatment of **8a** in diethyl ether with 3.0 equiv of *tert*-butyllithium at −78 °C for 15 min and then at 0 °C for 1 h. The lithiated species was reacted with a range of electrophiles at 0 °C for 1 h to give 5-substituted compounds **9a–g** in good isolated yields (Table 1, entries 1–7). Utilization of a slight excess of electrophile (1.5 equiv to the substrate) is enough to trap the lithiated species. This means excess *tert*-butyllithium was decomposed by the reaction with the solvent under the lithiation conditions.[11d] A substrate **8b** having a methoxy group at C-6 was also lithiated at C-5 selectively under similar conditions. However, the lithiated species was found to be somewhat unstable under the lithiation conditions and, after quenching with electrophiles, the C-5 substituted products **10a–g** were isolated in moderate yields (Table 1, entries 8–14).[14]

3. Conclusion

We have developed a general synthetic route to 3,4,5-trisubstituted indoles from readily available gramine derivatives via an iterative directed lithiation strategy. In view of the facile substitution at C-3 (side chain or ring) of the gramines and the C-4 functionalization of 4-aminoindoles via diazonium salts, the present procedure may open the way to diverse 3,4,5-trisubstituted indoles, which are not readily available by conventional synthetic methodology.

4. Experimental

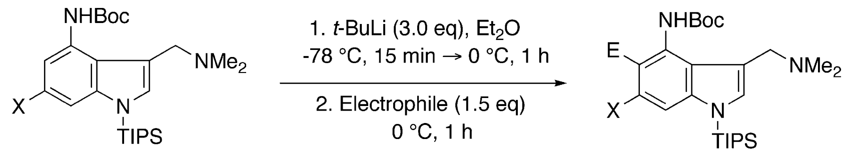
4.1. General

Melting points were determined with a Yanagimoto micro melting points apparatus and are uncorrected. IR spectra were obtained with a Perkin-Elmer System 2000 instrument. NMR spectra were recorded on a JEOL JNM-AL400 instrument (400 MHz for ^{1}H and 100 MHz for ^{13}C) using tetramethylsilane as an internal standard. Column chromatography was conducted on Aluminum oxide 90 standardized (Merck KGaA), or Silica Gel 60N, 63–210 μm (Kanto Chemical Co., Inc.). *tert*-Butyllithium was purchased from Aldrich Chemical Co., Inc. and used after titration with 2,5-dimethoxybenzyl alcohol. Diethyl ether and THF were dried over Na–benzophenone ketyl under Ar and distilled immediately before use. 1-(Triisopropylsilyl)-gramine (**1a**),[4a] 6-methoxy-1-(triisopropylsilyl)gramine (**1b**),[5a] and trimethylsilylmethyl azide[13] were prepared according to the reported procedures.

4.2. Procedure for the synthesis of 4-amino-1-(triisopropylsilyl)gramines 7

Under an argon atmosphere, a pentane solution of *tert*-butyllithium (12 mmol) was added dropwise to a solution of

Table 1. Directed lithiation-functionalization at C-5 of 4-(*N-tert*-butoxycarbonyl)amino-1-(triisopropylsilyl)gramines **8**



8a (X=H)
8b (X=OMe)

9 (X=H)
10 (X=OMe)

Entry	Substrate	Electrophile	E	Product	Yield (%)[a]
1	**8a**	MeI	Me	**9a**	91
2	**8a**	Cl_3CCCl_3	Cl	**9b**	83
3	**8a**	BrF_2CCBrF_2	Br	**9c**	81
4	**8a**	DMF	CHO	**9d**	82
5	**8a**	PhCHO	CH(OH)Ph	**9e**	81
6	**8a**	*t*-BuNCO	CONH(*t*-Bu)	**9f**	65
7	**8a**	Et_2NCOCl	$CONEt_2$	**9g**	71
8	**8b**	MeI	Me	**10a**	60
9	**8b**	Cl_3CCCl_3	Cl	**10b**	59
10	**8b**	BrF_2CCBrF_2	Br	**10c**	56
11	**8b**	DMF	CHO	**10d**	49
12	**8b**	PhCHO	CH(OH)Ph	**10e**	52
13	**8b**	*t*-BuNCO	CONH(*t*-Bu)	**10f**	41
14	**8b**	Et_2NCOCl	$CONEt_2$	**10g**	37

[a] Isolated yield.

1 (10 mmol) in diethyl ether (50 mL) at −78 °C. After being stirred for 15 min, the reaction mixture was allowed to warm to 0 °C and stirred for an additional 1.5 h at the same temperature. The reaction mixture was cooled to −78 °C, and a solution of trimethylsilylmethyl azide (1.94 g, 15 mmol) in diethyl ether (3 mL) was added dropwise. After being stirred for 1 h, the reaction mixture was allowed to warm to room temperature and quenched with saturated aqueous NH_4Cl. The products were extracted with diethyl ether and the extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Aluminum oxide 90 standardized (hexane–ethyl acetate = 10:1) to give **7**.

4.2.1. 4-Amino-1-(triisopropylsilyl)gramine (7a). According to the procedure described above, **1a** (3.31 g, 10 mmol) was reacted to give **7a** as pale yellow solid (2.75 g, 79%). Mp 97–97.5 °C (pentane); IR (KBr): 3415, 3283, 3165, 3052, 2942, 2866, 2824, 1619, 1585, 1560, 1491, 1459, 1438, 1375, 1315, 1284, 1245, 1130, 1073, 1035, 1017, 1001, 883, 724, 693, 658, 574, 512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, $J=7.6$ Hz, 18H), 1.59–1.71 (m, 3H), 2.25 (s, 6H), 3.54 (s, 2H), 5.43 (br s, 2H), 6.31 (d, $J=7.4$ Hz, 1H), 6.82 (d, $J=8.4$ Hz, 1H), 6.87–6.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.80, 18.15, 44.55, 56.57, 104.01, 104.32, 115.89, 119.61, 122.59, 128.11, 142.38, 143.32. Anal. Calcd for $C_{20}H_{35}N_3Si$: C, 69.51; H, 10.21; N, 12.16. Found: C, 69.48; H, 10.38; N, 12.04.

4.2.2. 4-Amino-6-methoxy-1-(triisopropylsilyl)gramine (7b). According to the procedure described above, **1b** (7.21 g, 20 mmol) was reacted to give **7b** as pale brown solid (6.47 g, 86%). This compound was somewhat unstable and used for the next reaction without further purification. Mp 78–80 °C; IR (KBr): 3398, 3135, 2946, 2867, 2821, 1616, 1589, 1561, 1464, 1200, 1161, 1128, 1012, 882, 692, 652, 515 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, $J=7.3$ Hz, 18H), 1.57–1.67 (m, 3H), 2.24 (s, 6H), 3.50 (s, 2H), 3.77 (s, 3H), 5.47 (br s, 2H), 6.01 (d, $J=2.0$ Hz, 1H), 6.36 (d, $J=2.0$ Hz, 1H), 6.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.78, 18.18, 44.52, 55.42, 56.55, 88.53, 93.52, 114.32, 115.88, 126.86, 142.63, 143.79, 157.02. Anal. Calcd for $C_{21}H_{37}N_3OSi$: C, 67.15; H, 9.93; N, 11.19. Found: C, 67.27; H, 10.27; N, 11.11.

4.3. Procedure for the synthesis of 4-(*N-tert*-butoxycarbonyl)amino-1-(triisopropylsilyl)gramines 8

Di-*tert*-butyl dicarbonate (1.40 g, 6.4 mmol) was added as a neat liquid to a solution of **7** (6.1 mmol) in THF (30 mL) at room temperature and the solution was refluxed for 2 h. The reaction mixture was then cooled to room temperature, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica Gel 60N (hexane–ethyl acetate = 10:1) to give **8**.

4.3.1. 4-(*N-tert*-Butoxycarbonyl)amino-1-(triisopropylsilyl)gramine (8a). According to the procedure described above, **7a** (2.11 g, 6.1 mmol) was reacted to give **8a** as colorless solid (2.46 g, 91%). Recrystallization from hexane gave colorless prisms. Mp 102.5–103.5 °C; IR (KBr): 3124, 2946, 2869, 2825, 2779, 1715, 1624, 1583, 1557, 1488, 1458, 1419, 1288, 1245, 1158, 1015, 1001, 882, 735, 663, 578, 513 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, $J=7.5$ Hz, 18H), 1.53 (s, 9H), 1.60–1.72 (m, 3H), 2.31 (s, 6H), 3.54 (s, 2H), 6.96 (s, 1H), 7.05–7.11 (m, 2H), 7.69 (br s, 1H), 11.61 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.78, 18.09, 28.55, 43.97, 55.95, 78.44, 108.25, 109.58, 114.83, 121.60, 122.43, 128.91, 133.25, 142.83, 154.04. Anal. Calcd for $C_{25}H_{43}N_3O_2Si$: C, 67.37; H, 9.72; N, 9.43. Found: C, 67.02; H, 9.76; N, 9.39.

4.3.2. 4-(*N-tert*-Butoxycarbonyl)amino-6-methoxy-1-(triisopropylsilyl)gramine (8b). According to the procedure described above, **7b** (5.63 g, 15 mmol) was reacted to give **8b** as colorless solid (5.70 g, 80%). Recrystallization from hexane gave colorless prisms. Mp 108.5–109.5 °C; IR (KBr): 3112, 2947, 2868, 1712, 1639, 1583, 1466, 1412, 1279, 1200, 1163, 1133, 1016, 884, 839, 683, 655, 593, 586, 517 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, $J=$ 7.6 Hz, 18H), 1.53 (s, 9H), 1.60–1.70 (m, 3H), 2.31 (s, 6H), 3.50 (s, 2H), 3.84 (s, 3H), 6.64 (d, $J=2.1$ Hz, 1H), 6.85 (s, 1H), 7.53 (br s, 1H), 11.78 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.76, 18.12, 28.54, 43.91, 55.88, 55.90, 78.52, 93.83, 97.84, 114.69, 116.11, 127.70, 133.57, 143.23, 153.91, 156.60. Anal. Calcd for $C_{26}H_{45}N_3O_3Si$: C, 65.64; H, 9.53; N, 8.83. Found: C, 65.59; H, 9.59; N, 8.84.

4.4. Selective C-5 lithiation-electrophilic substitution of 4-(*N*-*tert*-butoxycarbonyl)amino-1-(triisopropylsilyl)-gramines 8. General procedure

Under an argon atmosphere, a pentane solution of *tert*-butyllithium (1.4 mmol) was added dropwise to a solution of **8** (0.45 mmol) in diethyl ether (4.5 mL) at −78 °C. After being stirred for 15 min, the reaction mixture was allowed to warm to 0 °C and stirred for an additional 1 h at the same temperature. A solution of an appropriate electrophile (0.68 mmol) in diethyl ether (3 mL) was added and the solution was stirred for an additional 1 h at 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl at the same temperature and allowed to warm to room temperature. The products were extracted with diethyl ether and the extract was washed successively with water and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography over Silica gel 60N using the following eluents: hexane–ethyl acetate = 5:1 for **9a**, hexane–ethyl acetate = 3:1 for **9b**, **9c**, and **9d**, hexane–ethyl acetate = 5:1–3:1 for **9e**, hexane–ethyl acetate = 1:1 for **9f**, hexane–ethyl acetate = 1:2 for **9g**, hexane–ethyl acetate = 2:1 for **10a**, **10b**, **10c**, **10e**, and **10f**, hexane–ethyl acetate = 2:1–1:1 for **10d**, ethyl acetate for **10g**. The results are shown in Table 1.

4.4.1. 4-(*N*-*tert*-Butoxycarbonyl)amino-5-methyl-1-(triisopropylsilyl)gramine (9a). According to the general procedure, **8a** (201 mg, 0.45 mmol) and iodomethane (42 μL, 0.68 mmol) were reacted to give **9a** as colorless solid (188 mg, 91%). Recrystallization from hexane gave colorless prisms. Mp 128.5–129 °C; IR (KBr): 3096, 2948, 2869, 2827, 1718, 1518, 1492, 1459, 1419, 1364, 1306, 1269, 1244, 1160, 1129, 1045, 1009, 883, 786, 730, 647, 579 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, $J=$ 7.6 Hz, 18H), 1.53 (s, 9H), 1.59–1.71 (m, 3H), 2.27 (s, 6H), 2.35 (s, 3H), 3.48 (s, 2H), 6.95 (s, 1H), 6.98 (d, $J=8.4$ Hz, 1H), 7.17 (d, $J=8.4$ Hz, 1H), 10.36 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.71, 18.07, 28.53, 44.30, 56.13, 78.57, 110.76, 114.76, 124.31, 125.16, 125.27, 129.23, 129.85, 140.96, 154.18. Anal. Calcd for $C_{26}H_{45}N_3O_2Si$: C, 67.92; H, 9.87; N, 9.14. Found: C, 67.73; H, 10.18; N, 9.16.

4.4.2. 4-(*N*-*tert*-Butoxycarbonyl)amino-5-chloro-1-(triisopropylsilyl)gramine (9b). According to the general procedure, **8a** (201 mg, 0.45 mmol) and hexachloroethane (160 mg, 0.68 mmol) were reacted to give **9b** as colorless solid (179 mg, 83%). Recrystallization from diethyl ether–hexane gave colorless prisms. Mp 163–164 °C; IR (KBr): 3090, 2948, 2869, 2828, 1724, 1517, 1478, 1416, 1365, 1268, 1251, 1215, 1162, 1041, 1017, 882, 849, 786, 714, 674, 647, 593, 574 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.11 (d, $J=7.5$ Hz, 18H), 1.54 (s, 9H), 1.58–1.71 (m, 3H), 2.27 (s, 6H), 3.48 (br s, 2H), 7.01 (s, 1H), 7.15 (d, $J=$ 8.8 Hz, 1H), 7.18 (d, $J=8.8$ Hz, 1H), 10.51 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.67, 18.00, 28.45, 44.23, 55.72, 79.19, 111.62, 115.21, 121.45, 123.69, 126.42, 128.52, 130.83, 140.99, 153.77. Anal. Calcd for $C_{25}H_{42}ClN_3O_2Si$: C, 62.54; H, 8.82; N, 8.75. Found: C, 62.68; H, 9.09; N, 8.70.

4.4.3. 4-(*N*-*tert*-Butoxycarbonyl)amino-5-bromo-1-(triisopropylsilyl)gramine (9c). According to the general procedure, **8a** (201 mg, 0.45 mmol) and 1,2-dibromo-1,1,2,2-tetrafluoroethane (81 μL, 0.68 mmol) were reacted to give **9c** as colorless solid (191 mg, 81%). Recrystallization from diethyl ether–hexane gave colorless prisms. Mp 168.5–169.5 °C; IR (KBr): 3090, 2948, 2869, 2828, 1724, 1473, 1415, 1365, 1268, 1251, 1215, 1161, 1146, 1040, 1015, 882, 782, 586 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.11 (d, $J=$ 7.5 Hz, 18H), 1.55 (s, 9H), 1.60–1.70 (m, 3H), 2.26 (s, 6H), 3.47 (br s, 2H), 6.99 (s, 1H), 7.12 (d, $J=8.8$ Hz, 1H), 7.31 (d, $J=8.8$ Hz, 1H), 10.51 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.66, 17.99, 28.47, 44.25, 55.74, 79.20, 111.25, 112.13, 115.19, 126.47, 126.84, 130.17, 130.70, 141.54, 153.68. Anal. Calcd for $C_{25}H_{42}BrN_3O_2Si$: C, 57.24; H, 8.07; N, 8.01. Found: C, 56.91; H, 8.22; N, 7.90.

4.4.4. 4-(*N*-*tert*-Butoxycarbonyl)amino-5-formyl-1-(triisopropylsilyl)gramine (9d). According to the general procedure, **8a** (201 mg, 0.45 mmol) and *N*,*N*-dimethylformamide (52 μL, 0.68 mmol) were reacted to give **9d** as colorless solid (175 mg, 82%). Recrystallization from diethyl ether–hexane gave colorless prisms. Mp 158–159 °C; IR (KBr): 3074, 2948, 2868, 2777, 1723, 1681, 1613, 1575, 1474, 1422, 1314, 1253, 1160, 1045, 1015, 884, 797, 654, 580, 572 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, $J=7.6$ Hz, 18H), 1.53 (s, 9H), 1.61–1.73 (m, 3H), 2.33 (s, 6H), 3.55 (s, 2H), 7.07 (s, 1H), 7.27 (d, $J=8.8$ Hz, 1H), 7.73 (d, $J=8.8$ Hz, 1H), 10.12 (s, 1H), 11.38 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.71, 17.98, 28.37, 44.17, 55.71, 79.94, 110.84, 116.41, 121.59, 121.73, 123.91, 130.66, 136.14, 145.94, 155.77, 190.08. Anal. Calcd for $C_{26}H_{43}N_3O_3Si$: C, 65.92; H, 9.15; N, 8.87. Found: C, 65.83; H, 9.19; N, 8.77.

4.4.5. 4-(*N*-*tert*-Butoxycarbonyl)amino-5-[hydroxy(phenyl)methyl]-1-(triisopropylsilyl)gramine (9e). According to the general procedure, **8a** (201 mg, 0.45 mmol) and benzaldehyde (69 μL, 0.68 mmol) were reacted to give **9e** as colorless solid (201 mg, 81%). Recrystallization from diethyl ether–hexane gave colorless prisms. Mp 167–168 °C; IR (KBr): 3449, 3179, 3086, 2949, 2869, 2819, 2773, 1702, 1617, 1523, 1457, 1422, 1367, 1275, 1254, 1159, 1043, 1018, 882, 795, 709, 584 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.08 (d, $J=7.5$ Hz, 9H), 1.09 (d, $J=$ 7.5 Hz, 9H), 1.55 (s, 9H), 1.55–1.66 (m, 3H), 2.32 (s, 6H), 3.13 (d, $J=12.7$ Hz, 1H), 3.89 (d, $J=12.7$ Hz, 1H), 5.31 (br s, 1H), 6.20 (d, $J=2.2$ Hz, 1H), 6.82 (d, $J=8.8$ Hz, 1H), 7.00 (s, 1H), 7.14 (d, $J=8.8$ Hz, 1H), 7.21 (t, $J=7.5$ Hz, 1H), 7.31 (t, $J=7.5$ Hz, 2H), 7.47 (d, $J=7.5$ Hz, 2H), 10.69 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.68, 18.03, 18.05, 28.50, 44.39, 56.09, 70.03, 80.00, 112.05, 115.23, 123.85, 124.72, 125.97, 126.34, 127.53, 129.00, 130.30, 131.19, 141.80, 144.30, 157.48. Anal. Calcd for $C_{32}H_{49}N_3O_3Si$: C, 69.65; H, 8.95; N, 7.61. Found: C, 69.45; H, 9.09; N, 7.63.

4.4.6. 4-(*N-tert*-Butoxycarbonyl)amino-5-(*N-tert*-butylcarbamoyl)-1-(triisopropylsilyl)gramine (9f). According to the general procedure, **8a** (223 mg, 0.50 mmol) and *tert*-butyl isocyanate (86 μL, 0.75 mmol) were reacted to give **9f** as colorless solid (176 mg, 65%). Recrystallization from dichloromethane–pentane gave colorless powder. Mp 145–147 °C; IR (KBr): 3330, 3087, 2951, 2869, 2824, 2778, 1735, 1703, 1655, 1614, 1534, 1458, 1419, 1364, 1314, 1249, 1165, 1043, 1020, 883, 651, 585 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (d, $J=7.6$ Hz, 18H), 1.46 (s, 9H), 1.53 (s, 9H), 1.59–1.72 (m, 3H), 2.27 (s, 6H), 3.48 (br s, 2H), 6.86 (br s, 1H), 7.02 (s, 1H), 7.25 (d, $J=8.6$ Hz, 1H), 7.51 (d, $J=8.6$ Hz, 1H), 10.65 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.69, 18.01, 28.67, 28.87, 44.35, 50.80, 55.89, 79.48, 111.03, 115.67, 123.86, 124.90, 124.95, 128.49, 130.75, 143.43, 155.56, 168.01. Anal. Calcd for $C_{30}H_{52}N_4O_3Si$: C, 66.13; H, 9.62; N, 10.28. Found: C, 65.92; H, 9.38; N, 10.13.

4.4.7. 4-(*N-tert*-Butoxycarbonyl)amino-5-(*N*,*N*-diethylcarbamoyl)-1-(triisopropylsilyl)gramine (9g). According to the general procedure, **8a** (201 mg, 0.45 mmol) and diethylcarbamoyl chloride (86 μL, 0.68 mmol) were reacted to give **9g** as colorless solid (174 mg, 71%). Recrystallization from diethyl ether–hexane gave colorless powder. Mp 133–134 °C; IR (KBr): 3092, 2948, 2869, 2821, 2775, 1724, 1635, 1546, 1458, 1419, 1364, 1313, 1288, 1252, 1174, 1102, 1043, 1013, 882, 787, 655, 583 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (d, $J=7.5$ Hz, 18H), 1.18 (t, $J=7.1$ Hz, 3H), 1.24 (t, $J=7.1$ Hz, 3H), 1.48 (s, 9H), 1.59–1.71 (m, 3H), 2.26 (s, 6H), 3.14 (br d, $J=11.7$ Hz, 1H), 3.19–3.36 (m, 2H), 3.57–3.72 (m, 1H), 3.72–3.87 (m, 2H), 6.98 (s, 1H), 6.99 (d, $J=8.5$ Hz, 1H), 7.14 (d, $J=8.5$ Hz, 1H), 10.80 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.19, 12.71, 13.59, 18.03, 28.55, 38.09, 43.00, 44.31, 55.86, 78.48, 109.34, 115.76, 121.55, 122.78, 124.78, 129.51, 130.15, 142.72, 154.29, 171.43. Anal. Calcd for $C_{30}H_{52}N_4O_3Si$: C, 66.13; H, 9.62; N, 10.28. Found: C, 65.96; H, 9.96; N, 10.28.

4.4.8. 4-(*N-tert*-Butoxycarbonyl)amino-6-methoxy-5-methyl-1-(triisopropylsilyl)gramine (10a). According to the general procedure, **8b** (476 mg, 1.0 mmol) and iodomethane (93 μL, 1.5 mmol) were reacted to give **10a** as colorless solid (292 mg, 60%). Mp 96–98 °C; IR (KBr): 3134, 2949, 2868, 2820, 2776, 1728, 1626, 1558, 1456, 1427, 1365, 1249, 1216, 1171, 1130, 1115, 1048, 1016, 883, 691, 652, 585 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, $J=7.6$ Hz, 18H), 1.53 (s, 9H), 1.60–1.70 (m, 3H), 2.18 (s, 3H), 2.26 (s, 6H), 3.45 (br s, 2H), 3.81 (s, 3H), 6.78 (s, 1H), 6.85 (s, 1H), 10.42 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.74, 18.12, 28.52, 44.29, 56.05, 56.10, 78.60, 94.00, 114.86, 115.78, 119.26, 127.96, 129.80, 140.42, 154.28, 155.23. Anal. Calcd for $C_{27}H_{47}N_3O_3Si$: C, 66.21; H, 9.67; N, 8.58. Found: C, 66.40; H, 10.07; N, 8.61.

4.4.9. 4-(*N-tert*-Butoxycarbonyl)amino-5-chloro-6-methoxy-1-(triisopropylsilyl)gramine (10b). According to the general procedure, **8b** (476 mg, 1.0 mmol) and hexachloroethane (355 mg, 1.5 mmol) were reacted to give **10b** as colorless solid (299 mg, 59%). Recrystallization from diethyl ether–hexane gave colorless prisms. Mp 150–151 °C; IR (KBr): 3170, 2948, 2868, 2821, 2776, 1732, 1618, 1559, 1522, 1470, 1427, 1365, 1244, 1213, 1163, 1047, 1022, 884, 691, 651 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, $J=7.6$ Hz, 18H), 1.54 (s, 9H), 1.58–1.67 (m, 3H), 2.26 (s, 6H), 3.45 (br s, 2H), 3.87 (s, 3H), 6.89 (s, 1H), 6.91 (s, 1H), 10.56 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.70, 18.05, 28.45, 44.22, 55.70, 56.95, 79.21, 95.56, 113.09, 115.16, 120.30, 129.05, 129.56, 140.35, 152.09, 153.61. Anal. Calcd for $C_{26}H_{44}ClN_3O_3Si$: C, 61.21; H, 8.69; N, 8.24. Found: C, 61.25; H, 8.82; N, 8.14.

4.4.10. 4-(*N-tert*-Butoxycarbonyl)amino-5-bromo-6-methoxy-1-(triisopropylsilyl)gramine (10c). According to the general procedure, **8b** (476 mg, 1.0 mmol) and 1,2-dibromo-1,1,2,2-tetrafluoroethane (178 μL, 1.5 mmol) were reacted to give **10c** as colorless solid (311 mg, 56%). Recrystallization from diethyl ether–hexane gave colorless prisms. Mp 158.5–159.5 °C; IR (KBr): 3169, 2948, 2868, 2821, 2776, 1732, 1612, 1559, 1517, 1467, 1425, 1365, 1244, 1212, 1163, 1019, 883, 691, 650 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, $J=7.6$ Hz, 18H), 1.54 (s, 9H), 1.58–1.67 (m, 3H), 2.26 (s, 6H), 3.48 (br s, 2H), 3.87 (s, 3H), 6.84 (s, 1H), 6.90 (s, 1H), 10.58 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.69, 18.05, 28.47, 44.24, 55.72, 57.00, 79.19, 95.48, 104.12, 115.09, 120.88, 129.05, 131.16, 141.25, 152.78, 153.53. Anal. Calcd for $C_{26}H_{44}BrN_3O_3Si$: C, 56.30; H, 8.00; N, 7.58. Found: C, 56.23; H, 8.08; N, 7.40.

4.4.11. 4-(*N-tert*-Butoxycarbonyl)amino-5-formyl-6-methoxy-1-(triisopropylsilyl)gramine (10d). According to the general procedure, **8b** (476 mg, 1.0 mmol) and *N*,*N*-dimethylformamide (116 μL, 1.5 mmol) were reacted to give **10d** as colorless solid (247 mg, 49%). Mp 103–105 °C; IR (KBr): 3102, 2949, 2868, 2823, 2775, 1727, 1687, 1621, 1556, 1468, 1424, 1366, 1336, 1246, 1167, 1048, 1012, 884, 692, 650, 581 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (d, $J=7.6$ Hz, 18H), 1.52 (s, 9H), 1.58–1.67 (m, 3H), 2.30 (s, 6H), 3.48 (br s, 2H), 3.86 (s, 3H), 6.74 (s, 1H), 6.92 (s, 1H), 10.29 (s, 1H), 11.32 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.71, 18.03, 28.43, 44.12, 55.64, 56.38, 79.74, 93.61, 113.40, 116.48, 118.48, 129.25, 134.87, 145.82, 154.59, 157.76, 189.48. Anal. Calcd for $C_{27}H_{45}N_3O_4Si$: C, 64.38; H, 9.00; N, 8.34. Found: C, 64.44; H, 9.31; N, 8.33.

4.4.12. 4-(*N-tert*-Butoxycarbonyl)amino-5-[hydroxy(phenyl)methyl]-6-methoxy-1-(triisopropylsilyl)gramine (10e). According to the general procedure, **8b** (476 mg, 1.0 mmol) and benzaldehyde (152 μL, 1.5 mmol) were reacted to give **10e** as colorless solid (304 mg, 52%). Mp 111–113 °C; IR (KBr): 3386, 2949, 2868, 2821, 2776, 1702, 1622, 1557, 1467, 1426, 1367, 1277, 1253, 1169, 1048, 1016, 883, 694, 652, 593 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, $J=7.5$ Hz, 18H), 1.49 (s, 9H), 1.55–1.68 (m, 3H), 2.27 (s, 6H), 3.26 (d, $J=12.5$ Hz, 1H), 3.47 (s, 3H), 3.64 (d, $J=12.5$ Hz, 1H), 4.99 (br s, 1H), 6.21 (d, $J=6.5$ Hz, 1H), 6.78 (s, 1H), 6.89 (s, 1H), 7.10–7.16 (m, 1H), 7.20–7.26 (m, 2H), 7.32–7.37 (m, 2H), 10.58 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.71, 18.07, 28.47, 44.27, 55.96, 56.26, 69.22, 79.64, 96.41, 115.38, 119.45, 121.55, 125.06, 125.22, 126.98, 128.70, 130.01, 142.14, 145.46, 155.73, 156.60. Anal. Calcd for $C_{33}H_{51}N_3O_4Si$: C, 68.12; H, 8.83; N, 7.22. Found: C, 68.07; H, 9.07; N, 7.15.

4.4.13. 4-(*N-tert*-Butoxycarbonyl)amino-5-(*N-tert*-butylcarbamoyl)-6-methoxy-1-(triisopropylsilyl)gramine (10f). According to the general procedure, **8b** (476 mg, 1.0 mmol) and *tert*-butyl isocyanate (171 μL, 1.5 mmol) were reacted to give **10f** as colorless solid (235 mg, 41%). Recrystallization from diethyl ether–hexane gave colorless powder. Mp 156–158 °C; IR (KBr): 3360, 3187, 2952, 2868, 2821, 2774, 1715, 1649, 1624, 1543, 1459, 1365, 1310, 1251, 1207, 1161, 1049, 1027, 1015, 882, 689, 654, 571, 524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (d, $J=7.5$ Hz, 18H), 1.46 (s, 9H), 1.52 (s, 9H), 1.55–1.67 (m, 3H), 2.20 (s, 6H), 3.41 (s, 2H), 3.81 (s, 3H), 6.81 (s, 1H), 6.84 (br s, 1H), 6.88 (s, 1H), 10.11 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.69, 18.05, 28.66, 28.70, 44.40, 51.05, 56.66, 79.30, 95.39, 115.59, 119.84, 119.86, 128.34, 129.03, 137.80, 142.45, 153.85, 156.38, 166.21. Anal. Calcd for $C_{31}H_{54}N_4O_4Si$: C, 64.77; H, 9.47; N, 9.75. Found: C, 64.73; H, 9.57; N, 9.92.

4.4.14. 4-(*N-tert*-Butoxycarbonyl)amino-5-(*N,N*-diethylcarbamoyl)-6-methoxy-1-(triisopropylsilyl)gramine (10g). According to the general procedure, **8b** (476 mg, 1.0 mmol) and diethylcarbamoyl chloride (190 μL, 1.5 mmol) were reacted to give **10g** as colorless solid (213 mg, 37%). Recrystallization from hexane gave colorless powder. Mp 184–186 °C; IR (KBr): 3134, 2948, 2868, 2819, 2775, 1727, 1623, 1557, 1457, 1427, 1289, 1250, 1212, 1170, 1142, 1046, 1014, 883, 787, 692, 651, 610, 524 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (d, $J=7.5$ Hz, 9H), 1.13 (d, $J=7.5$ Hz, 9H), 1.17 (t, $J=7.3$ Hz, 3H), 1.22 (t, $J=7.1$ Hz, 3H), 1.47 (s, 9H), 1.57–1.68 (m, 3H), 2.21 (s, 6H), 3.02 (d, $J=12.5$ Hz, 1H), 3.23–3.39 (m, 2H), 3.49–3.59 (m, 1H), 3.75 (s, 3H), 3.80 (d, $J=12.5$ Hz, 1H), 3.81–3.90 (m, 1H), 6.71 (s, 1H), 6.86 (s, 1H), 10.28 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.55, 12.72, 12.97, 18.06, 18.09, 28.53, 37.53, 43.00, 44.42, 55.58, 55.80, 78.54, 93.09, 115.76, 116.66, 119.76, 128.65, 129.52, 142.51, 152.84, 154.60, 167.34. Anal. Calcd for $C_{31}H_{54}N_4O_4Si$: C, 64.77; H, 9.47; N, 9.75. Found: C, 64.63; H, 9.74; N, 9.80.

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Reactions of guaiazulene with methyl terephthalaldehydate and 2-hydroxy- and 4-hydroxybenzaldehydes in methanol in the presence of hexafluorophosphoric acid: comparative studies on molecular structures and spectroscopic, chemical and electrochemical properties of monocarbocations stabilized by 3-guaiazulenyl and phenyl groups

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Abstract—Reaction of guaiazulene (**1**) with methyl terephthalaldehydate (**2**) in methanol in the presence of hexafluorophosphoric acid at 25 °C for 2 h under aerobic conditions gives (3-guaiazulenyl)[4-(methoxycarbonyl)phenyl]methylium hexafluorophosphate (**5**) in 94% yield. Similarly, reactions of **1** with 2-hydroxybenzaldehyde (**3**) and 4-hydroxybenzaldehyde (**4**) under the same reaction conditions as **2** give (3-guaiazulenyl)(2-hydroxyphenyl)methylium hexafluorophosphate (**6**) and (3-guaiazulenyl)(4-hydroxyphenyl)methylium hexafluorophosphate (**7**) in 89 and 97% yields, respectively. Comparative studies on the molecular structures as well as the spectroscopic, chemical and electrochemical properties of the monocarbocation compounds **5**–**7** stabilized by 3-guaiazulenyl and 4-(methoxycarbonyl)phenyl (or 2-hydroxy- or 4-hydroxyphenyl) groups are reported.
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1. Introduction

In the previous papers,[1–8] we reported a facile preparation and the crystal structures as well as the spectroscopic, chemical and electrochemical properties of the mono- and dicarbocations stabilized by a 3-guaiazulenyl group. Along with the spectroscopic data and the chemical evidences for those carbocation derivatives in acetonitrile, a comparative study on the X-ray crystallographic analyses of those single crystals also led to the molecular structures with resonance forms of the 3-guaiazulenylmethylium- and 3-guaiazulenylium-ions. In relation to our basic studies, Ito et al. reported the synthesis, properties and redox behavior of a series of (1-azulenyl)methylium and [9-(azuleno[1,2-*b*]thienyl)]methylium hexafluorophosphates.[9,10] During the course of our investigations, we have quite recently found (i) that the reaction of naturally occurring guaiazulene (**1**) with methyl terephthalaldehydate (**2**) in methanol in the presence of hexafluorophosphoric acid gave the corresponding new monocarbocation compound, (3-guaiazulenyl)-[4-(methoxycarbonyl)phenyl]methylium hexafluorophosphate (**5**), in 94% yield, which upon reduction with zinc powder in dichloromethane afforded a chromatographically separable mixture of a *meso* form and two enantiomeric forms of the molecular structure, 1,2-bis[4-(methoxycarbonyl)phenyl]-1,2-di(3-guaiazulenyl)ethane (**10**), and (ii) that the reactions of **1** with 2-hydroxybenzaldehyde (**3**) and 4-hydroxybenzaldehyde (**4**) under the same reaction conditions as **2** gave (3-guaiazulenyl)(2-hydroxyphenyl)-methylium hexafluorophosphate (**6**) and (3-guaiazulenyl)(4-hydroxyphenyl)methylium hexafluorophosphate (**7**) in 89 and 97% yields. Similarly, as in the case of **5**, the reductions of **6** and **7** with zinc powder in acetonitrile afforded a chromatographically separable mixture of a *meso* form and two enantiomeric forms of the molecular

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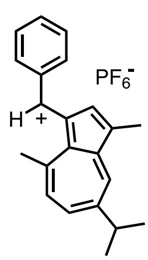
structures, 1,2-bis(2-hydroxyphenyl)-1,2-di(3-guaiazulenyl)-ethane (**11**) and 1,2-bis(4-hydroxyphenyl)-1,2-di(3-guaiazulenyl)ethane (**12**). Although (3-guaiazulenyl)(2-hydroxyphenyl)methylium perchlorate[11] and (3-guaiazulenyl)(4-hydroxyphenyl)methylium perchlorate[11] are known compounds, which were prepared by the reactions of **1** with **3** (and **4**) in tetrahydrofuran in the presence of perchloric acid, nothing has really been documented regarding the accurate spectral data and the detailed properties of those compounds. As a series of basic studies on the chemistry of the carbocations stabilized by 3-guaiazulenyl and phenyl groups, we now wish to report the detailed studies on an efficient preparation and the molecular structures as well as the spectroscopic, chemical and electrochemical properties of the monocarbocation products **5–7** compared with those of the previously-documented monocarbocation compounds, (3-guaiazulenyl)phenylmethylium hexafluorophosphate and tetrafluoroborate (**A** and **A′**),[4–7] (3-guaiazulenyl)(4-isopropylphenyl)methylium tetrafluoroborate and hexafluorophosphate (**B** and **B′**)[3,5] and [4-(dimethylamino)phenyl](3-guaiazulenyl)methylium tetrafluoroborate (**C**).[5]



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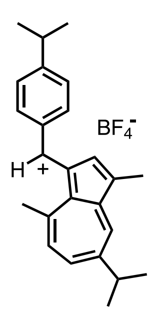

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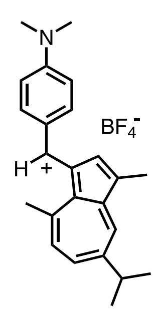

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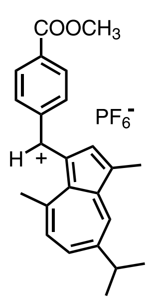

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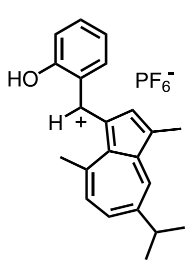

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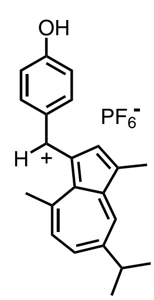

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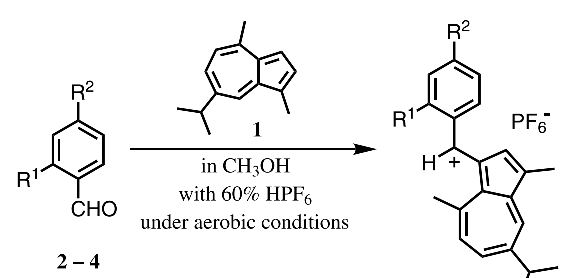
2. Results and discussion

2.1. Reaction of guaiazulene (1) with methyl terephthalaldehydate (2) in methanol in the presence of hexafluorophosphoric acid: preparation and spectroscopic properties of (3-guaiazulenyl)[4-(methoxycarbonyl)phenyl]methylium hexafluorophosphate (5)

Compound **5** was prepared using a methanol as a solvent as shown in Figure 1, Table 1 and Section 4.1.1, whose molecular structure was established on the basis of elemental analysis and spectroscopic data [UV–vis, IR, FAB-MS, ^{1}H and ^{13}C NMR including 2D NMR (H–H COSY, HMQC = ^{1}H detected heteronuclear multiple quantum coherence and HMBC = ^{1}H detected heteronuclear multiple bond connectivity)].

Compound **5** was yellow plates, mp > 148 °C [decomp., determined by thermal analysis (TGA and DTA)]. A comparative study on the UV–vis [λ_{max} (CH_3CN) nm] spectrum of **5** with those of guaiazulene (**1**)[8] and (3-guaiazulenyl)phenylmethylium hexafluorophosphate (**A**)[5] showed (i) that, similarly as in the case of **A**, no characteristic UV–vis absorption bands (λ_{max} 200–800 nm) based on **1** were observed, indicating the formation of the molecular structure **5** with a delocalized π-electron system between the 3-guaiazulenylmethylium substituent and the 4-(methoxycarbonyl)phenyl group, and (ii) that, although the spectral pattern of the characteristic UV–vis absorption bands for **5** resembled that of **A**, the longest absorption wavelength of **5** (λ_{max} 447 nm, log ε = 4.37) revealed a slight hypsochromic shift (Δ 9 nm) and a slight hyperchromic effect in comparison with that of **A** (λ_{max} 456 nm, log ε = 4.30). The IR (KBr) spectrum showed two specific bands based on the counter anion (PF_6^-) at ν_{max} 837 and 559 cm^{-1}. The molecular formula $C_{24}H_{25}O_2$ for the carbocation unit was determined by the exact FAB-MS (3-nitrobenzyl alcohol matrix) spectrum. The elemental



5 – 7

Figure 1. The reactions of **1** with **2–4** in CH_3OH with HPF_6 under aerobic conditions.

Table 1. The yield/% of the products **5–7** obtained from the reactions of **1** with **2–4** in CH_3OH with HPF_6 under aerobic conditions

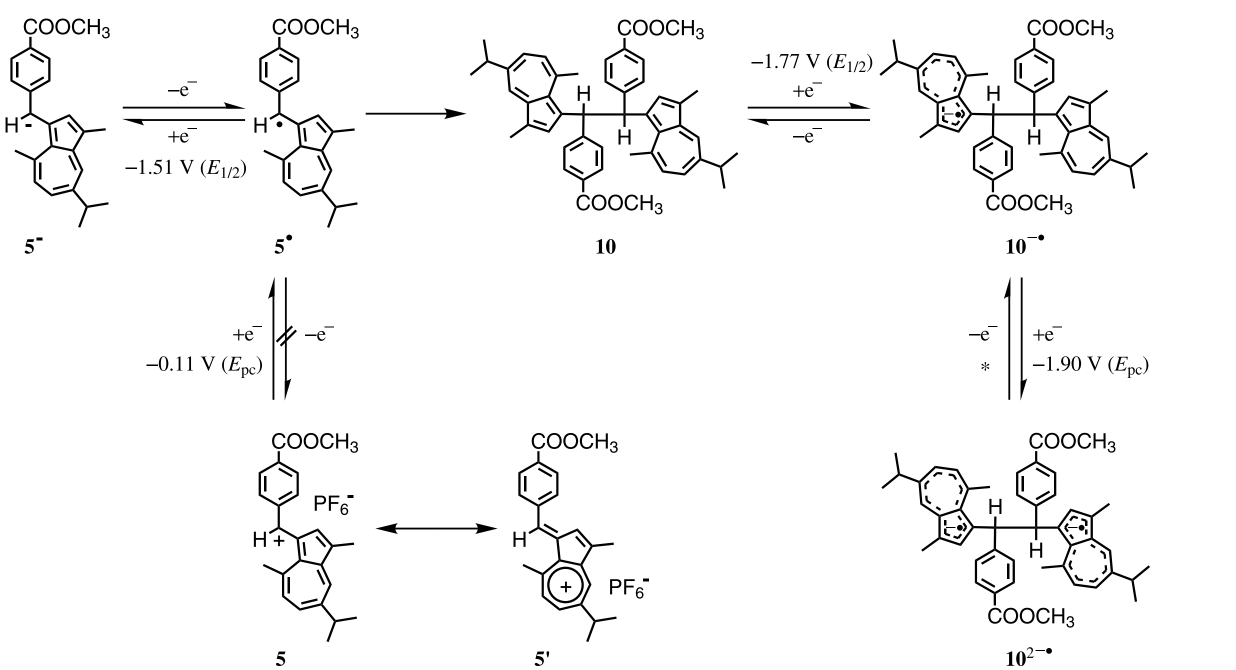
Entry	Substituent		Temp/°C	Time/h	Product	Yield/%[a]
	R^1	R^2				
1	H	$COOCH_3$	25	2	**5**	94
2	OH	H	25	2	**6**	89
3	H	OH	25	2	**7**	97

[a] Isolated yield.

analysis confirmed the molecular formula $C_{24}H_{25}F_6O_2P$. The 500 MHz ^{1}H NMR (CD_3CN) spectrum showed signals based on the 3-guaiazulenylmethylium substituent with a resonance form of the 3-guaiazulenylium structure **5′** (see Scheme 1), and revealed signals based on the 4-(methoxycarbonyl)phenyl group, whose signals were carefully assigned using the computer-assisted simulation analysis. The 125 MHz ^{13}C NMR (CD_3CN) spectrum exhibited 21 carbon signals assigned by HMQC and HMBC techniques. A comparative study of the chemical shifts (δ, ppm) for the proton and carbon signals of the HC^+-α carbenium-ion center of **5** with those of the HC^+-α carbenium-ion center of **A** showed that the proton signal of **5** (8.77) coincided with that of **A** (8.78);[5,6] however, the carbon signal of **5** (147.4) revealed an up-field shift in comparison with that of **A** (149.6).[5,6] The elemental analysis and these spectroscopic data for **5** led to the molecular structure, (3-guaiazulenyl)[4-(methoxycarbonyl)phenyl]methylium hexafluorophosphate, with a delocalized π-electron system.

2.2. X-ray crystal structure of (3-guaiazulenyl)[4-(methoxycarbonyl)pheny]methylium hexafluorophosphte (5) compared with those of (3-guaiazulenyl)phenylmethylium hexafluorophosphate (A), (3-guaiazulenyl)(4-isopropylphenyl)methylium tetrafluoroborate (B) and [4-(dimethylamino)phenyl](3-guaiazulenyl)methylium tetrafluoroborate (C)

The crystal structure of **5** was then determined by means of X-ray diffraction, producing accurate structural parameters (see Section 4.1.2). The ORTEP drawing of **5**, indicating the molecular structure, (3-guaiazulenyl)[4-(methoxycarbonyl)phenyl]methylium hexafluorophosphate, is shown in Figure 2. A comparative study on the selected C–C bond distances for the 3-guaiazulenylmethylium substituents and the phenyl groups of **5**, **A**, **B** and **C** is shown in Tables 2 and 3. The structural parameters of **5** revealed (i) that, from the dihedral angles between the least-squares planes, it was found that the plane of the 4-(methoxycarbonyl)phenyl group twisted by 33.4° from the plane of the 3-guaiazulenyl group owing to the influence of a slight steric hindrance between the hydrogen atoms of the C2 and C6 positions of the 4-(methoxycarbonyl)phenyl group and the hydrogen atom of the C2′ position of the 3-guaiazulenyl group, which was larger than the dihedral angles observed for those of **A** (21.3°)[4,5] and **C** (20.7°),[5] and which was smaller than that of **B** (40.1°),[5] (ii) that, similarly as in the cases of **A**–**C**, the 3-guaiazulenylmethylium substituent clearly underwent bond alternation between the single and double bonds in comparison with the bond distances of the 3-guaiazulenyl group of 1,4-bis[(3-guaiazulenyl)methyl]benzene (**D**) [see Fig. 9c and Ref. 13], (iii) that the 4-(methoxycarbonyl)phenyl group also clearly underwent bond alternation between the single and double bonds in comparison with the bond distances of the phenyl group of **A**, (iv) that the average C–C bond distance for the seven-membered ring of the 3-guaiazulenyl group (1.401 Å) coincided with the bond distances observed for those of **A** (1.401 Å), **B** (1.401 Å) and **C** (1.399 Å), (v) that the bond distances of the five-membered ring of the 3-guaiazulenyl group appreciably varied between 1.345 and 1.491 Å; in particular, the C1′–C2′ bond distance (1.345 Å) was characteristically shorter than the average C–C bond distance for the five-membered ring (1.437 Å), which coincided with the bond distances observed for the five-membered rings of **A**, **B** and **C**, and (vi) that the C3′–Cα bond distance (1.352 Å) was also characteristically shorter than the C1–Cα bond distance (1.468 Å), and, although the C3′–Cα bond distance was shorter than the bond distances observed for those of **A** (1.361 Å), **B** (1.364 Å) and **C** (1.396 Å), the C1–Cα bond distance was longer than the bond distances observed for those of **A** (1.461 Å), **B** (1.451 Å) and **C** (1.414 Å). Moreover, it can be inferred (i) that, from a comparative study on the bond distances of **5** with those of **A**, **B** and **C**,



Scheme 1. A plausible electron transfer mechanism based on the CV and DPV data of **5**. * The potential of the E_{pa} (V) is included in the half-wave potential of -1.77 ($E_{1/2}$) V.

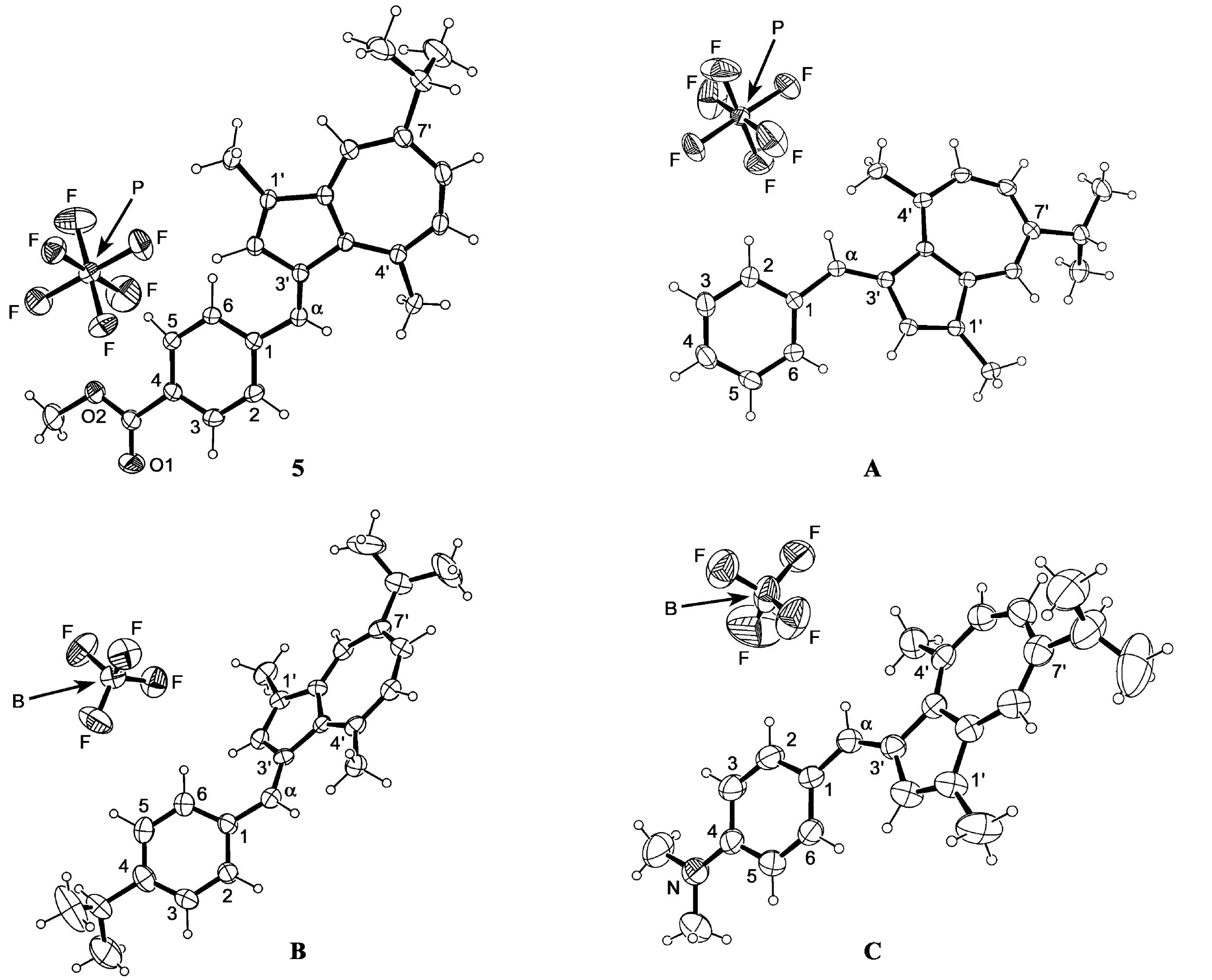


Figure 2. The ORTEP drawings with the numbering scheme (30% probability thermal ellipsoids) of **5** and **A**–**C**.

although the positive charge of **5** in the single crystal is mainly localized at the Cα carbon atom, forming a 3-guaiazulenylmethylium-ion, the positive charge apparently is slightly transferred to the seven-membered ring, forming a 3-guaiazulenylium structure, and (ii) that, from the result of the dihedral angle between the least-squares planes of the 3-guaiazulenyl group and the 4-(methoxycarbonyl)phenyl group, formation of a conjugated π-electron system between them, which combined with the Cα carbon atom, is possible. Thus, along with the spectroscopic data for **5** in acetonitrile, the X-ray crystallographic analysis for **5** also led to the crystal structure, (3-guaiazulenyl)[4-(methoxycarbonyl)phenyl]methylium hexafluorophosphate with a resonance form of the 3-guaiazulenylium structure **5′** (see Scheme 1).

Along with the crystal structure of **5**, the two different (top and side) views for the packing (molecular) structure of **5** revealed that this molecule formed a π-stacking structure in the single crystal, and that the average inter-plane distance between the over-lapping molecules [i.e. the 3-guaiazulenylmethylium plane of a molecule and the 4-(methoxycarbonyl)phenyl plane of another molecule], which were overlapped so that those dipole moments might be negated mutually, was 4.39 Å (see Fig. 3). Thus, the reason why the

Table 2. The selected C–C bond distances (Å) for the 3-guaiazulenylmethylium substituents of **5** and **A**–**C**

Atom	5	A	B	C
C1′–C2′	1.345	1.345	1.347	1.351
C2′–C3′	1.454	1.449	1.456	1.448
C3′–C3a′	1.491	1.481	1.470	1.457
C3a′–C4′	1.401	1.398	1.391	1.385
C4′–C5′	1.416	1.408	1.411	1.406
C5′–C6′	1.365	1.375	1.383	1.373
C6′–C7′	1.409	1.393	1.400	1.386
C7′–C8′	1.391	1.394	1.380	1.379
C8′–C8a′	1.386	1.389	1.373	1.392
C8a′–C1′	1.459	1.459	1.440	1.416
C3a′–C8a′	1.438	1.450	1.466	1.465
C3′–Cα	1.352	1.361	1.364	1.396

Table 3. The selected C–C bond distances (Å) for the phenyl groups of **5** and **A**–**C**

Atom	5	A	B	C
C1–C2	1.403	1.393	1.408	1.405
C2–C3	1.373	1.384	1.376	1.372
C3–C4	1.392	1.380	1.381	1.390
C4–C5	1.389	1.379	1.388	1.403
C5–C6	1.385	1.376	1.376	1.360
C6–C1	1.403	1.407	1.393	1.404
C1–Cα	1.468	1.461	1.451	1.414

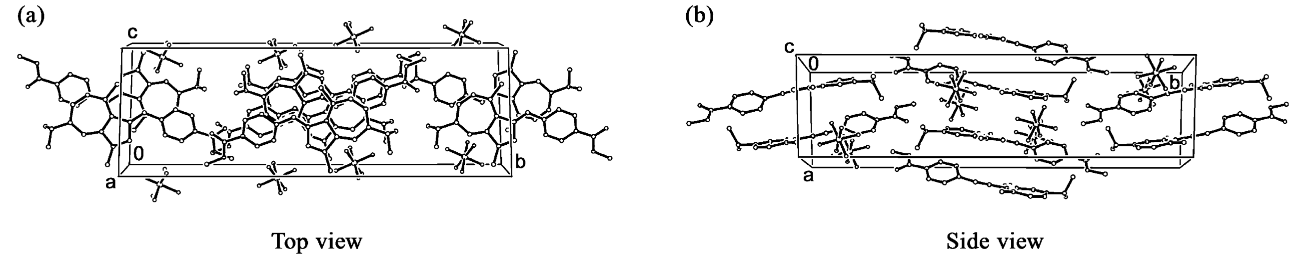
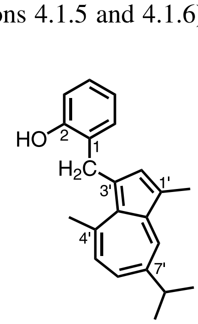


Figure 3. The two different [top (a) and side (b)] views for the packing (molecular) structure of **5**; hydrogen atoms are omitted for reasons of clarity.

yield of **5** as single crystals was high (94%) can be inferred to be that **5** readily forms an accumulation (i.e., an intermolecular π-stacking structure) in the recrystallization solvent, providing the single crystals of **5**, quantitatively.

2.3. A comparative study on the reactions of guaiazulene (1) with 2-hydroxybenzaldehyde (3) and 4-hydroxybenzaldehyde (4) under the same reaction conditions as the reaction of 1 with methyl terephthalaldehydate (2)

The reactions of guaiazulene (**1**) with 2-hydroxybenzaldehyde (**3**) and 4-hydroxybenzaldehyde (**4**) under the same reaction conditions as the reaction of **1** with methyl terephthalaldehydate (**2**) were investigated (see Fig. 1, Table 1 and Sections 4.1.3 and 4.1.4). As a result, the corresponding monocarbocation products, (3-guaizulenyl)(2-hydroxyphenyl)methylium hexafluorophosphate (**6**) and (3-guaiazulenyl)(4-hydroxyphenyl)methylium hexafluorophosphate (**7**), were isolated in 89 and 97% yields, respectively. The molecular structures of **6** and **7** were established on the basis of elemental analysis and spectroscopic data [UV–vis, IR, FAB-MS, ^{1}H and ^{13}C NMR including 2D NMR (i.e., H–H COSY, HMQC and HMBC)]. Along with the spectroscopic data of **6** and **7**, the reductions of **6** and **7** with $NaBH_4$ in a mixed solvent of ethanol and acetonitrile (1:1, v/v) at 25 °C for 30 min under aerobic conditions gave 1-(3-guaiazulenylmethyl)-2-hydroxybenzene (**8**) and 1-(3-guaiazulenylmethyl)-4-hydroxybenzene (**9**), in which a hydride-ion attached to the C-α positions of **6** and **7**, respectively, in 84 and 88% yields (see Sections 4.1.5 and 4.1.6).



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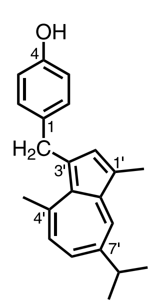


9

A comparative study on the UV–vis [λ_{max} (CH_3CN) nm] spectra of **6** and **7** with those of **8**, **9** and (3-guaiazulenyl)-phenylmethylium hexafluorophosphate (**A**)[5] showed (i) that the spectral patterns of the characteristic UV–vis absorption bands (λ_{max} 200–600 nm) based on the 3-guaiazulenyl groups of **6** and **7** changed in comparison with those of the molecules **8** and **9** without a conjugated π-electron system between the 3-guaiazulenyl group and the hydroxyphenyl group, which combined with the CH_2 carbon atom, and (ii) that the characteristic absorption bands based on the formation of the (3-guaiazulenyl)(2-hydroxyphenyl)methylium and (3-guaiazulenyl)(4-hydroxyphenyl)methylium moieties with a delocalized π-electron system appeared at the absorption maxima, λ_{max} 489 nm (log ε=4.50) for **6** and λ_{max} 510 nm (log ε=4.67) for **7**, as shown in Figure 4, which revealed larger bathochromic shifts and hyperchromic effects in comparison with that of **A** (λ_{max} 456 nm, log ε=4.30). The 500 MHz ^{1}H NMR (CD_3CN) spectra of **6** and **7** showed signals based on the 3-guaiazulenylmethylium substituents and the hydroxyphenyl groups, respectively, whose signals were carefully assigned using the computer-assisted simulation analysis. All the signals of **6** and **7** revealed larger down-field shifts in comparison with those of **8** and **9**, suggesting the formation of the (3-guaiazulenyl)(2-hydroxyphenyl)methylium and (3-guaiazulenyl)(4-hydroxyphenyl)methylium structures with a delocalized π-electron system. A comparative study on the chemical shifts (δ, ppm) for the 125 MHz ^{13}C NMR (CD_3CN) signals of the 3-guaiazulenylmethylium substituents (or 3-guaiazulenylmethyl groups) and the hydroxyphenyl groups of **6–9** is shown in Tables 4 and 5. The ^{13}C NMR spectra of **6** and **7** exhibited twenty and nineteen carbon signals, respectively, assigned by HMQC and HMBC techniques. The carbon signals of the C-2 (159.5) for **6** and the C-4 (163.3) for **7** showed apparent larger down-field shifts than those of the C-2 (154.8) for **8** and the C-4 (155.7) for **9**. From a comparative study on the chemical shifts for the proton and carbon signals of the HC^{+}-α carbenium-ion centers of **6** (9.01, 146.2) and **7** (8.72, 151.7) with that of **A** (8.78, 149.6),[5,6] it was found that, although the proton signal of **6** showed a down-field shift in comparison with that of **A**, the carbon signal of **6** revealed an up-field shift; however, although the proton signal of **7** coincided with that of **A**, the carbon signal of **7** showed a

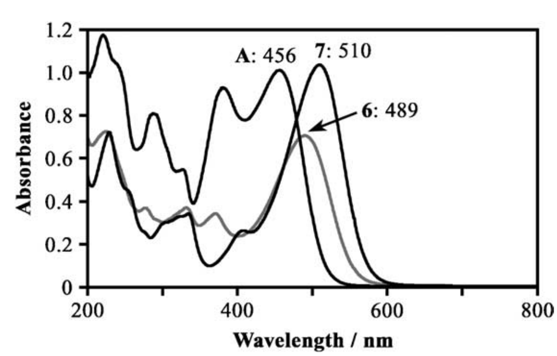


Figure 4. The UV–vis spectra of **6**, **7** and **A** in CH_3CN. Concentrations, **6**: 0.10 g/L (223 μmol/L), **7**: 0.10 g/L (223 μmol/L), **A**: 0.022 g/L (51 μmol/L). Length of the Cell, 0.1 cm for **6** and **7**, 1 cm for **A**.

Table 4. The selected ^{13}C NMR chemical shifts (δ, ppm) for the 3-guaiazulenylmethylium substituents (or the 3-guaiazulenylmethyl groups) of **6–9**

Compound	HC^{+}-α	C-1′	C-2′	C-3′	C-3a′	C-4′	C-5′	C-6′	C-7′	C-8′	C-8a′
6	146.2	145.4	141.8	139.2	153.6	157.5	150.3	144.8	170.9	139.8	161.1
7	151.7	144.6	141.8	137.3	153.3	157.1	149.1	144.3	169.3	139.6	159.6
8	31.7[a]	125.1	141.7	126.3	134.0	146.5	126.9	135.7	139.9	134.2	138.8
9	36.6[a]	125.1	142.0	127.4	133.7	146.3	126.9	135.7	139.9	134.2	138.8

[a] CH_2-3′.

Table 5. The ^{13}C NMR chemical shifts (δ, ppm) for the phenyl groups of **6–9**

Compound	C-1	C-2	C-3	C-4	C-5	C-6
6	124.0	159.5	117.2	135.7	122.2	134.7
7	128.6	137.6	118.3	163.3	118.3	137.6
8	130.7	154.8	115.6	127.8	120.9	130.8
9	135.67	130.2	116.0	155.7	116.0	130.2

down-field shift. The UV–vis, ^{1}H and ^{13}C NMR spectroscopic data and the chemical evidence (i.e., H^{-} reduction) led to the molecular structures, (3-guaiazulenyl)(2-hydroxyphenyl)methylium hexafluorophosphate for **6** and (3-guaiazulenyl)(4-hydroxyphenyl)methylium hexafluorophosphate for **7**, with the resonance forms of the 3-guaiazulenylium **6′**,**7′** and oxonium **6″**,**7″** structures, respectively, in acetonitrile as shown in Figure 5. Although an X-ray crystallographic analysis of **6** (and **7**) has not yet been achieved because of difficulty in obtaining a single crystal suitable for this purpose, the recrystallization conditions of these compounds are currently under intensive investigation.

2.4. Electrochemical behavior of (3-guaiazulenyl)[4-(methoxycarbonyl)phenyl]methylium hexafluorophosphate (5)

In the previous paper,[5] we reported the electrochemical behavior of [4-(dimethylamino)phenyl](3-guaiazulenyl)methylium tetrafluoroborate (**C**), and submitted a plausible electron transfer mechanism of **C** based on its CV and DPV data. We have been interested further in the electrochemical property of **5**. The electrochemical behavior of **5** was, therefore, measured by means of CV and DPV (Potential/V vs SCE) in CH_3CN containing 0.1 M [n-Bu_4N]PF_6 as a supporting electrolyte. Four reduction potentials observed by DPV were positioned at the E_p values of −0.02, −1.48, −1.73 and −1.89 V, while the corresponding four reduction potentials determined by CV were located at the values of −0.11 (E_{pc}), −1.51 ($E_{1/2}$), −1.77 ($E_{1/2}$) and −1.90 (E_{pc}) V as shown in Figure 6. From a comparative study on the reduction potentials of **5** with those of **C**,[5,12] a plausible electron transfer mechanism of **5** based on its CV and DPV data can be inferred as shown in Scheme 1; namely: (i) **5**, with a resonance form of the 3-guaiazulenylium structure **5′**, undergoes one-electron reduction at a potential of −0.11 (E_{pc}, irreversible) V by CV (−0.02 V by DPV), generating the corresponding (3-guaiazulenyl)[4-(methoxycarbonyl)phenyl]methyl radical species **5**˙. The radical **5**˙ generated is rapidly converted into the

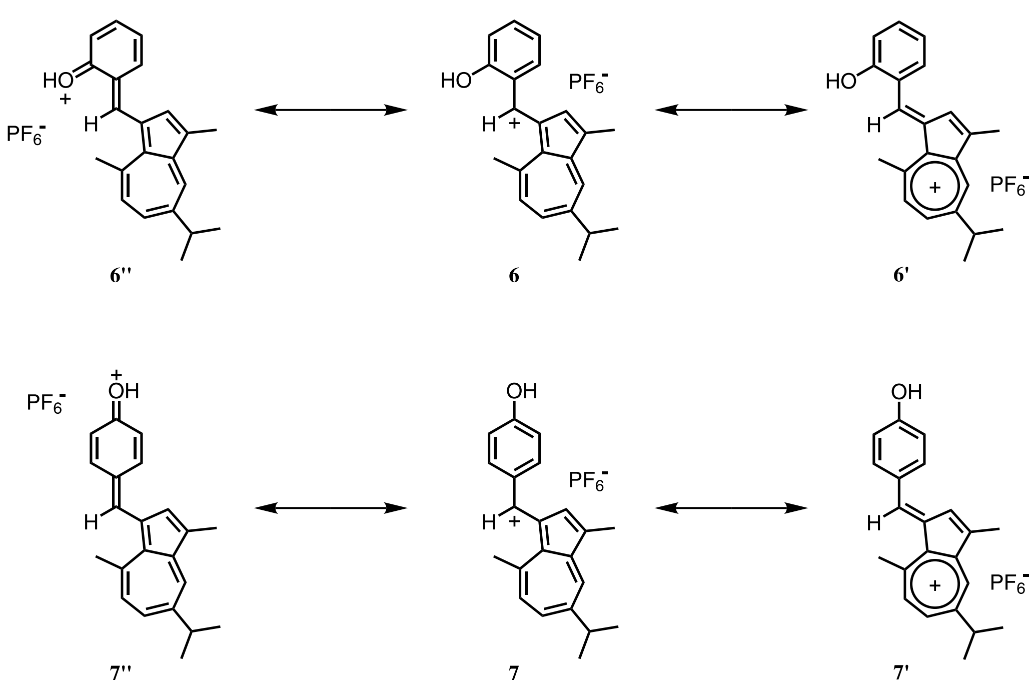


Figure 5. The molecular structures of **6** and **7** with the resonance forms of **6″**,**6″** and **7″**,**7″**.

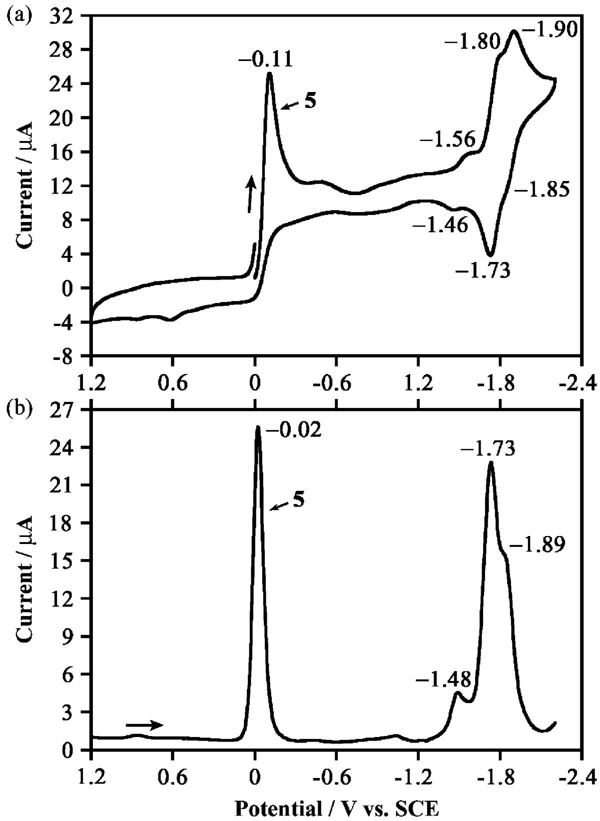


Figure 6. Cyclic (a) and differential pulse (b) voltammograms of **5** (3.0 mg, 6.1 μmol) in 0.1 M [n-Bu_4N]PF_6, CH_3CN (10 mL) at a glassy carbon (ID: 3 mm) and a platinum wire served as the working and auxiliary electrodes; scan rates 100 mV s^{-1} at 25 °C under argon, respectively. For comparative purposes, the oxidation potential using ferrocene as a standard material showed +0.42 (E_p) V by DPV and +0.40 ($E_{1/2}$) V by CV under the same electrochemical conditions as **5**.

radical homo-coupling product **10**, (ii) a small amount of the existing radical species $\mathbf{5}^{\cdot}$ without the radical homo-coupling is reduced to the corresponding (3-guaiazulenyl)[4-(methoxycarbonyl)phenyl]methylium-anion species $\mathbf{5}^{-}$ at a potential of −1.51 ($E_{1/2}$) V by CV (−1.48 V by DPV), and, further, (iii) the dimer **10** yielded on the surface of the working electrode is stepwise reduced to the anion radical species $\mathbf{10}^{-\cdot}$ at a potential of −1.77 ($E_{1/2}$) by CV (−1.73 V by DPV) and the di(anion radical) species $\mathbf{10}^{2-\cdot}$ at a potential of −1.90 (E_{pc}) V by CV (−1.89 V by DPV), whose stepwise reduction potentials were supported by those of the *meso* form, (1R,2S)-1,2-bis[4-(methoxycarbonyl)phenyl]-1,2-di(3-guaiazulenyl)ethane (**10a**) [−1.79 ($E_{1/2}$) V by CV (−1.77 V by DPV) and −1.87 ($E_{1/2}$) V by CV (−1.85 V by DPV)], and the enantiomeric forms, (1R,2R)- and (1S,2S)-1,2-bis[4-(methoxycarbonyl)phenyl]-1,2-di(3-guaiazulenyl)ethanes (**10b**) [−1.77 ($E_{1/2}$) V by CV (−1.74 V by DPV) and −1.90 ($E_{1/2}$) V by CV (−1.88 V by DPV)], isolated from the reduction of **5** with zinc powder (see Fig. 8, Tables 6 and 9 and Section 4.1.7).

2.5. A comparative study on the electrochemical behavior of (3-guaizulenyl)(2-hydroxyphenyl)-methylium hexafluorophosphate (6) and (3-guaiazulenyl)(4-hydroxyphenyl)methylium hexafluorophosphate (7) with those of (3-guaiazulenyl)phenyl-methylium hexafluorophosphate (A), (3-guaiazulenyl)(4-isopropylphenyl)methylium hexafluorophosphate (B′), [4-(dimethylamino)phenyl](3-guaiazulenyl)methylium tetrafluoroborate (C) and (3-guaiazulenyl)[4-(methoxy-carbonyl)phenyl]methylium hexafluorophosphate (5)

The electrochemical behavior of **6** and **7** was measured by means of CV and DPV (Potential/V vs SCE) in CH_3CN containing 0.1 M [n-Bu_4N]PF_6 as a supporting electrolyte. From a comparative study on the reduction potentials of **A**,[6] **B′**,[3] **C**,[5,12] **5**, **6** and **7**, it can be inferred that **6** and **7** undergo

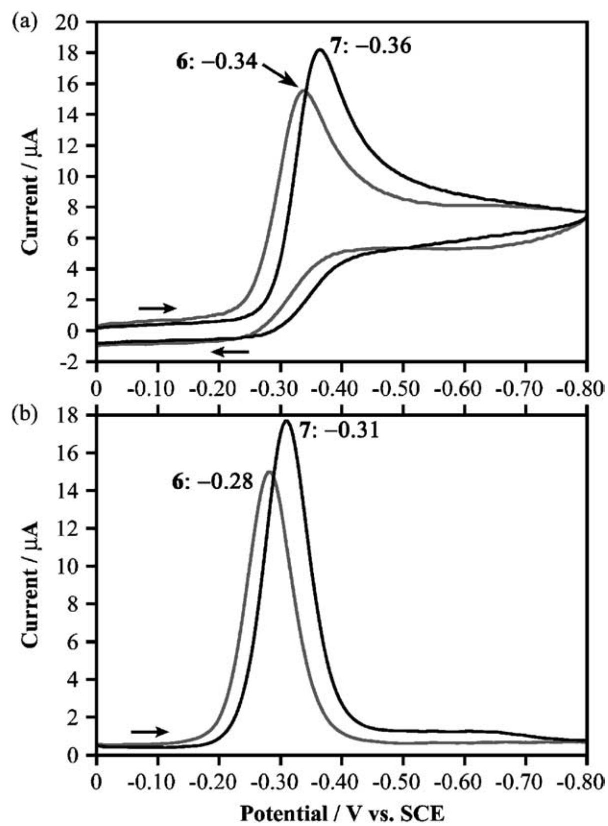


Figure 7. Cyclic (a) and differential pulse (b) voltammograms of **6** (3.0 mg, 6.7 μmol) and **7** (3.0 mg, 6.7 μmol) under the same electrochemical conditions as **5**.

Table 6. The yield/% of the products **10a**,**b**–**12a**,**b** obtained from the reductions of **5**–**7** with zinc powder in dichloromethane (or acetonitrile) under argon

Entry	Substituent		Temp/°C	Time	Product		Yield /%[a]	
	R^1	R^2			*meso*	Enantiomers	*meso*	Enantiomers
1	H	$COOCH_3$	25	20 min[b]	**10a**	**10b**	16	20
2	OH	H	25	2 h	**11a**	**11b**	15	17
3	H	OH	25	2 h	**12a**	**12b**	40	41

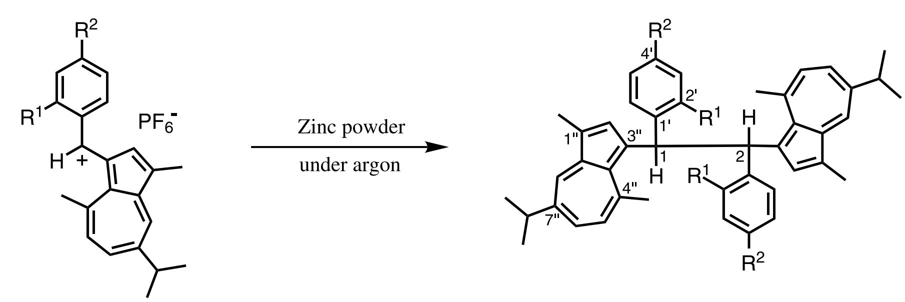
[a] Isolated yield.
[b] This reduction for 2 h gave about the same yield/% of the products **10a** and **10b** as in the case of the reaction time, 20 min.

one-electron reduction, respectively, at the potentials of −0.34 (E_{pc}, irreversible) V by CV (−0.28 V by DPV) for **6** and −0.36 (E_{pc}, irreversible) V by CV (−0.31 V by DPV) for **7** as shown in Figure 7, generating the corresponding (3-guaiazulenyl)(2-hydroxyphenyl)methyl and (3-guaiazulenyl)(4-hydroxyphenyl)methyl radical species, which are rapidly converted into the radical homo-coupling products, 1,2-bis(2-hydroxyphenyl)-1,2-di(3-guaiazulenyl)ethane (**11**) and 1,2-bis(4-hydroxyphenyl)-1,2-di(3-guaiazulenyl)ethane (**12**), respectively. Thus, **6** is slightly susceptible to reduction as compared with **7**, owing to the difference of the electron affinity (corresponding to LUMO) based on those molecular structures, and, further, although **6** and **7** are more susceptible to reduction than **C** [−0.47 (E_{pc}, irreversible) V by CV (−0.39 V by DPV)], they are less susceptible to reduction than **A** [−0.29 (E_{pc}, irreversible) V by CV (−0.20 V by DPV)], **B′** [−0.29 (E_{pc}, irreversible) V by CV (−0.22 V by DPV)] and **5** [−0.11 (E_{pc}, irreversible) V by CV (−0.02 V by DPV)]. The facility of one-electron reduction is in order of **5** > **A**, **B′** > **6** > **7** > **C**; namely, the order of higher stability based on their reduction potentials is **C** > **7** > **6** > **A**,**B′** > **5** and these different reduction potentials are obviously caused by the influence of a different functional group.

2.6. Reduction of (3-guaiazulenyl)[4-(methoxycarbonyl)-phenyl]methylium hexafluorophosphate (5) with zinc powder: preparation and properties of 1,2-bis[4-(methoxycarbonyl)phenyl]-1,2-di(3-guaiazulenyl)-ethane (10)

Although the reduction of (3-guaiazulenyl)phenylmethylium tetrafluoroborate (**A′**) with zinc powder in acetonitrile at 25 °C for 1 h under argon gave a ca. 10:9, chromatographically inseparable mixture of a *meso* form and two enantiomeric forms of the molecular structure, 1,2-di(3-guaiazulenyl)-1,2-diphenylethane, in 74% yield,[5] the reduction of **5** with zinc powder in dichloromethane at 25 °C for 20 min under argon afforded a chromatographically separable mixture of the *meso* form, (1*R*,2*S*)-1,2-bis[4-(methoxycarbonyl)phenyl]-1,2-di(3-guaiazulenyl)ethane (**10a**), in 16% yield, and the enantiomeric forms, (1*R*,2*R*)- and (1*S*,2*S*)-1,2-bis[4-(methoxycarbonyl)-phenyl]-1,2-di(3-guaiazulenyl)ethane (**10b**), in 20% yield (see Fig. 8, Table 6 and Section 4.1.7). The molecular structures of the products **10a**,**b** were established on the basis of elemental analysis and spectroscopic data [UV–vis, FAB-MS, ^{1}H and ^{13}C NMR including 2D NMR (i.e., H–H COSY, HMQC and HMBC)]. Furthermore, we clarified the crystal structure of the *meso* form **10a** by means of X-ray diffraction (see Sections 2.7 and 4.1.8).

The UV–vis [λ_{max} (CH_2Cl_2) nm] spectra of the *meso* form **10a** and the enantiomers **10b** showed that the characteristic UV–vis absorption bands (λ_{max} 200–800 nm) based on **1**[8] were observed for both of them, indicating the formation of the molecular structures **10a** and **10b**, respectively, without a conjugated π-electron system between the 3-guaiazulenyl group and the 4-(methoxycarbonyl)phenyl group, which combined with the HC-1 carbon atom of the ethane unit, and, further, that the characteristic UV–vis spectral pattern of **10a** coincided with that of **10b**. Similarly, as in the case of 1,2-di(3-guaiazulenyl)-1,2-diphenylethane,[5] a careful comparative study on the 500 MHz ^{1}H NMR signals for **10a** and **10b** led us to *meso* form **10a** and two enantiomeric forms **10b** of the molecular structure, 1,2-bis[4-(methoxy-carbonyl)phenyl]-1,2-di(3-guaiazulenyl)ethane (**10**). An inspection of the molecular models of the most favorable conformations suggested that in the *meso* form **10a** an anisotropic effect exerted by the (3-guaiazulenyl)phenyl-methyl region of the other moiety is likely to cause apparent up- and down-field shifts of the signals for the HC-1 (δ 6.12) of the ethane unit and the H-2′,6′ (7.10) of the 4-(methoxy-carbonyl)phenyl group and the Me-1″ (2.58), H-2″ (7.79), Me-4″ (2.95) of the 3-guaiazulenyl group in comparison with those [the HC-1 (δ 5.86) of the ethane unit and the H-2′,6′ (6.85) of the 4-(methoxycarbonyl)phenyl group and the Me-1″ (2.48), H-2″ (7.88), Me-4″ (3.10) of the 3-guaiazulenyl group] of the enantiomers **10b**; furthermore,



5 – 7 **10 – 12**

Figure 8. The reductions of **5–7** with zinc powder in dichloromethane (or acetonitrile) under argon.

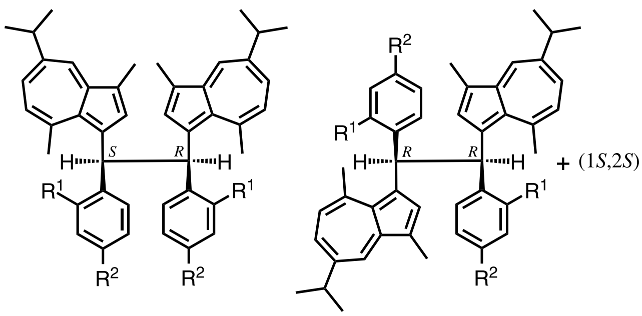
Table 7. The ^{1}H NMR chemical shifts (δ, ppm) for the ethane units and the 3-guaiazulenyl groups of **10a**,**b**–**12a**,**b**

Compound	HC-1	Me-1″	H-2″	Me-4″	H-5″	H-6″	Me_2CH-7″	$(CH_3)_2CH$-7″	H-8″
10a	6.12	2.58	7.79	2.95	6.74	7.20	2.98	1.30	8.01
10b	5.86	2.48	7.88	3.10	6.80	7.22	2.96	1.275, 1.283	7.97
11a	6.26	2.54	8.00	3.07	6.736	7.21	2.98	1.29	7.99
11b	6.32	2.45	7.96	3.10	6.70	7.14	2.91	1.24	7.87
12a	6.21	2.51	8.04	2.95	6.58	7.01	2.73	1.18	8.02
12b	5.94	2.23	8.12	3.13	6.60	6.98	2.67	1.13, 1.14	7.82

Table 8. The ^{1}H NMR chemical shifts (δ, ppm) for the phenyl groups of **10a**,**b**–**12a**,**b**

Compound	H-2′	H-3′	H-4′	H-5′	H-6′
10a	7.10	7.59	—	7.59	7.10
10b	6.85	7.65	—	7.65	6.85
11a	—	7.35	6.741	6.59	6.42
11b	—	7.27	6.87	6.68	6.52
12a	6.17	6.98	—	6.98	6.17
12b	6.35	6.81	—	6.81	6.35

in **10b** the same effect would cause division of the methyl protons of the isopropyl-7″ group into two signals (a ratio of almost 1:1). These findings enabled us to make the most plausible assignment of all the ^{1}H NMR signals of these two compounds (see Tables 7 and 8 and Section 4.1.7).



meso enantiomers

10a: R^{1} = H, R^{2} = $COOCH_3$ **10b**: R^{1} = H, R^{2} = $COOCH_3$
11a: R^{1} = OH, R^{2} = H **11b**: R^{1} = OH, R^{2} = H
12a: R^{1} = H, R^{2} = OH **12b**: R^{1} = H, R^{2} = OH

Moreover, the electrochemical behavior of the *meso* form **10a** and the enantiomers **10b** was measured under the same electrochemical conditions as **5** with a view to a comparative study. One oxidation and two reduction potentials observed by DPV were positioned at the E_p values of +0.56, −1.77 and −1.85 V for **10a** and +0.66, −1.74 and −1.88 V for **10b**, while the corresponding one oxidation and two reduction potentials determined by CV were located at the values of +0.56 (E_{pa}), −1.79 ($E_{1/2}$) and −1.87 ($E_{1/2}$) V for **10a** and +0.66 (E_{pa}), −1.77 ($E_{1/2}$) and −1.90 ($E_{1/2}$) V for **10b** (see Table 9). From a comparative study on the redox potentials of **10a** and **10b** with those of 1,2-di(3-guaiazulenyl)-1,2-diphenylethane,[5] it can be inferred (i) that **10a** undergoes one-electron oxidation at a potential of +0.56 (E_{pa}) V by CV (+0.56 V by DPV), which indicates **10a** is susceptible to oxidation in comparison with that of 1,2-di(3-guaiazulenyl)-1,2-diphenylethane [+0.64 (E_{pa}) V by CV (+0.64 V by DPV)];[5] however, (ii) that **10b** undergoes one-electron oxidation at a potential of +0.66 (E_{pa}) V by CV (+0.66 V by DPV), which coincided with that of 1,2-di(3-guaiazulenyl)-1,2-diphenylethane, and, further, (iii) that **10a** and **10b** are stepwise reduced to the di(anion-radical) at the potentials of −1.79 ($E_{1/2}$) and −1.87 ($E_{1/2}$) V by CV (−1.77 and −1.85 V by DPV) for **10a** and −1.77 ($E_{1/2}$) and −1.90 ($E_{1/2}$) V by CV (−1.74 and −1.88 V by DPV) for **10b**, respectively, which coincided with those of 1,2-di(3-guaiazulenyl)-1,2-diphenylethane [−1.80 ($E_{1/2}$) and −1.92 ($E_{1/2}$) V by CV (−1.76 and −1.88 V by DPV)].[5] The values of the two-electron reduction potentials for **10a** and **10b** coincided with the stepwise reduction potentials of **10** (see Scheme 1) generated from the electrochemical reduction of **5**, and, thus, supported a plausible electron transfer mechanism of **5** as shown in Scheme 1.

Table 9. The redox potentials of **10a** and **10b** measured by means of DPV

Compound	Redox potentials (*E*/V vs SCE)		
	E_1^{ox}	E_1^{red}	E_2^{red}
10a	+0.56	−1.77	−1.85
10b	+0.66	−1.74	−1.88

2.7. X-ray crystal structure of (1*R*,2*S*)-1,2-bis[4-(methoxycarbonyl)pheny]-1,2-di(3-guaiazulenyl)ethane (10a) compared with those of 1,4-bis(3-guaiazulenylmethyl)benzene (D) and hexestrol (E)

Although an X-ray crystallographic analysis of the enantiomers **10b** has not yet been achieved because of difficulty in obtaining a single crystal suitable for this purpose, the crystal structure of the *meso* form **10a** has been determined by means of X-ray diffraction, producing accurate structural parameters (see Section 4.1.8). The crystal structure of **10a**, indicating the molecular structure, (1*R*,2*S*)-1,2-bis[4-(methoxycarbonyl)pheny]-1,2-di(3-guaiazulenyl)ethane, is shown in Figure 9a together with the selected bond distances. Furthermore, we recently clarified the crystal structure of 1,4-bis(3-guaiazulenylmethyl)benzene (**D**) [see Fig. 9c and Ref. 13] yielded from the reduction of 1,4-phenylenebis(3-guaiazulenylmethylium) bis(tetrafluoroborate) with $NaBH_4$.[4] A comparative study on the structural parameters of **10a** with those of **D** and hexestrol (**E**)[14] revealed (i) that the C–C bond distance for the C1–C2 (1.529 Å) of the ethane unit was slightly shorter than that for the C1–C2 (1.553 Å) of the ethane unit of hexestrol (**E**), (ii) that the average C–C bond distance for the seven-membered ring of the 3″-guaiazulenyl group (1.406 Å) coincided with the bond distance observed for that of the 3′-guaiazulenyl group of **D** (1.407 Å), (iii) that the C–C bond distances for the five-membered ring of the 3″-guaiazulenyl group appreciably varied between 1.380 and 1.498 Å; in particular, the C1″–C2″ bond distance (1.380 Å) was characteristically shorter than the average C–C bond distance (1.424 Å) for the five-membered ring of the 3″-guaiazulenyl group, (iv) that the average C–C bond distance (1.424 Å) for the five-membered ring of the 3″-guaiazulenyl group coincided with that of the 3′-guaiazulenyl group of **D** (1.420 Å), and (v) that the average C–C bond distance for the benzene ring of the 4′-(methoxycarbonyl)phenyl group (1.385 Å) coincided with the bond distance observed for that of the 4-hydroxyphenyl group of **E** (1.386 Å). Along with the crystal structures of **10a** and **D**, the packing (molecular) structures of **10a** and **D** revealed that, although **10a** did not form a π-stacking structure in the single crystal (see Fig. 9b), **D** formed a π-stacking structure in the single

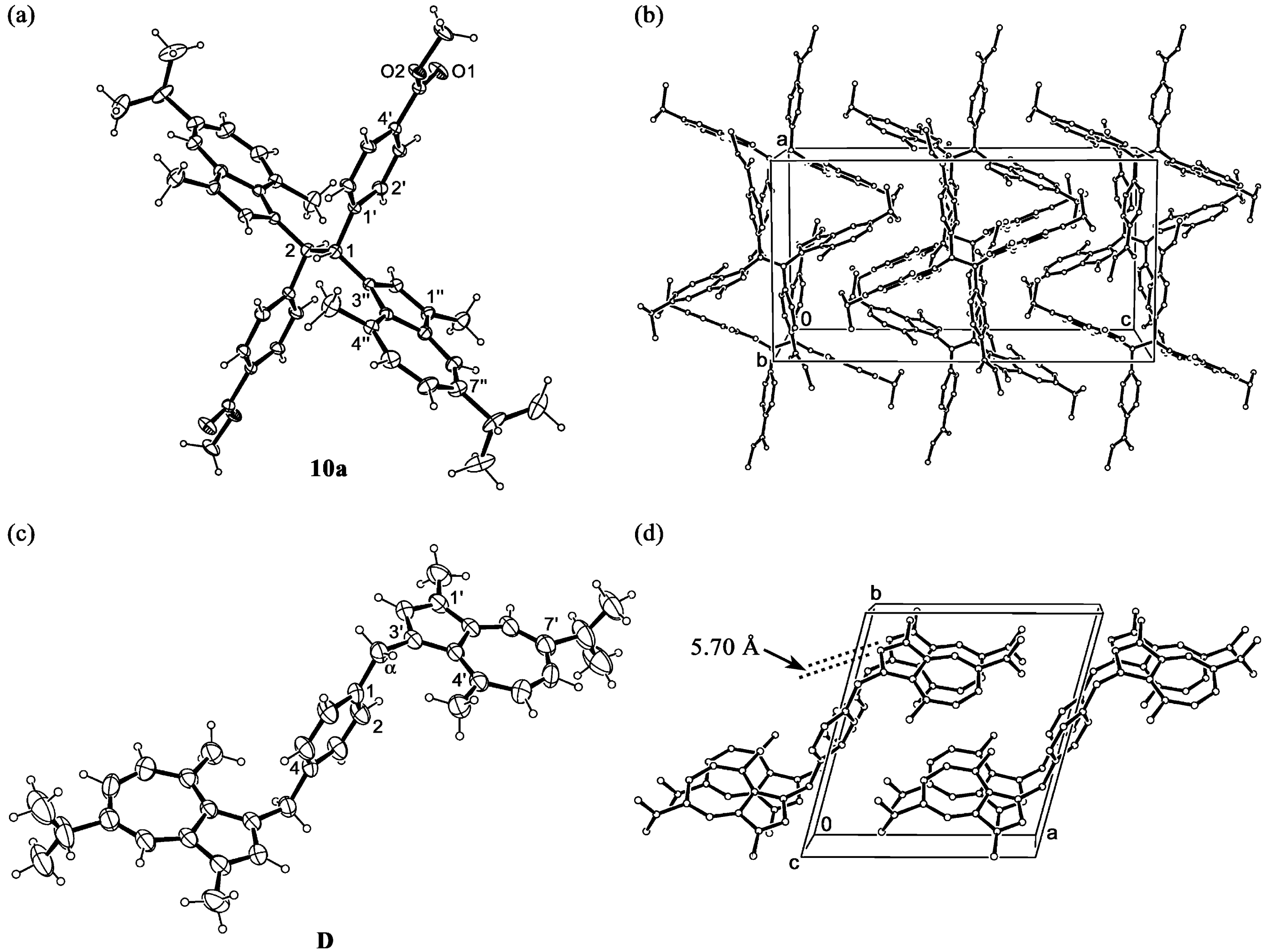


Figure 9. (a) The ORTEP drawing of **10a** with the numbering scheme (30% probability thermal ellipsoids). The selected bond distances (Å) are as follows: C1′–C2′; 1.385(4), C2′–C3′; 1.382(4), C3′–C4′; 1.389(4), C4′–C5′; 1.372(4), C5′–C6′; 1.382(4), C6′–C1′; 1.402(4), C1′–C1; 1.546(4), C1–C3″; 1.503(4), C1″–C2″; 1.380(4), C2″–C3″; 1.440(4), C3″–C3a″; 1.405(4), C3a″–C4″; 1.422(4), C4″–C5″; 1.393(5), C5″–C6″; 1.387(5), C6″–C7″; 1.374(5), C7″–C8″; 1.373(5), C8″–C8a″; 1.398(5), C8a″–C1″; 1.397(4), C8a″–C3a″; 1.498(4) and C1–C2; 1.529(6). (b) The ORTEP drawing of **D** with the numbering scheme (30% probability thermal ellipsoids). The selected bond distances (Å) are as follows: C1–C2; 1.372(5), C2–C3; 1.388(5), C6–C1; 1.368(5), C1–Cα; 1.533(5), Cα–C3′; 1.503(5), C1′–C2′; 1.391(5), C2′–C3′; 1.390(5), C3′–C3a′; 1.413(5), C3a′–C4′; 1.391(5), C4′–C5′; 1.401(6), C5′–C6′; 1.417(7), C6′–C7′; 1.394(7), C7′–C8′; 1.358(6), C8′–C8a′; 1.375(5), C8a′–C1′; 1.394(5) and C8a′–C3a′; 1.508(5). The packing (molecular) structures of **10a** (b) and **D** (d); hydrogen atoms are omitted for reasons of clarity, respectively.

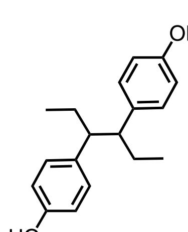
crystal, and that the average inter-plane distance between the overlapping molecules **D** was 5.70 Å (see Fig. 9d).

2.8. A comparative study on the reductions of (3-guaiazulenyl)(2-hydroxyphenyl)methylium hexafluorophosphate (6) and (3-guaiazulenyl)(4-hydroxyphenyl)methylium hexafluorophosphate (7) with zinc powder

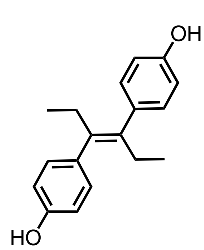
The reduction of **6** with zinc powder in acetonitrile at 25 °C for 2 h under argon gave a chromatographically separable mixture of the *meso* form, (1*R*,2*S*)-1,2-bis(2-hydroxyphenyl)-1,2-di(3-guaiazulenyl)ethane (**11a**), in 15% isolated yield and the enantiomerers, (1*R*,2*R*)- and (1*S*,2*S*)-1,2-bis(2-hydroxyphenyl)-1,2-di(3-guaiazulenyl)ethane (**11b**), in 17% isolated yield. Similarly, the reduction of **7** with zinc powder under the same reaction conditions as **6** afforded a chromatographically separable mixture of the *meso* form, (1*R*,2*S*)-1,2-bis(4-hydroxyphenyl)-1,2-di(3-guaiazulenyl)ethane (**12a**), in 40% isolated yield and the enantiomers, (1*R*,2*R*)- and (1*S*,2*S*)-1,2-bis(4-hydroxyphenyl)-1,2-di(3-guaiazulenyl)ethane (**12b**), in 41% isolated yield. The molecular structures of the products **11a**,**b** and **12a**,**b** were established on the basis of elemental analysis and spectroscopic data (UV–vis, IR, FAB-MS and ^{1}H NMR) (see Fig. 8, Table 6 and Sections 4.1.9 and 4.1.10).

A comparative study on the UV–vis spectra of the *meso* forms **11a**, **12a** and the enantiomers **11b**, **12b** showed that the characteristic UV–vis absorption bands (λ_{max} 200–800 nm) based on **1**[8] were observed for all of them, indicating the formation of the molecular structures **11a**,**b** and **12a**,**b**, respectively, without a conjugated π-electron system between the 3-guaiazulenyl group and the hydroxyphenyl group, which combined with the HC-1 carbon atom of the ethane unit, and, further, that the longest absorption wavelengths of **12a** (λ_{max} 626 nm, log ε = 3.03) and **12b** (λ_{max} 624 nm, log ε = 3.10) revealed slight bathochromic shifts and slight hyperchromic effects in comparison with those of **11a** (λ_{max} 619 nm, log ε=2.89) and **11b** (λ_{max} 619 nm, log ε=2.73). Similarly, as in the case of *meso* **10a** and two enantiomeric **10b** forms of the molecular structure, 1,2-bis[4-(methoxycarbonyl)phenyl]-1,2-di(3-guaiazulenyl)-ethane (**10**), a careful comparative study on the 500 MHz ^{1}H NMR signals for **11a**,**b** and **12a**,**b** led us to *meso* **11a**, **12a** and two enantiomeric **11b**, **12b** forms of the molecular structures, 1,2-bis(2-hydroxyphenyl)-1,2-di(3-guaiazulenyl)ethane (**11**) and 1,2-bis(4-hydroxyphenyl)-1,2-di(3-guaiazulenyl)ethane (**12**). An inspection of the molecular models of the most favorable conformations suggested that in the *meso* form **11a** an anisotropic effect exerted by the (3-guaiazulenyl)phenylmethyl region of the other moiety is likely to cause apparent up- and down-field shifts of the signals for the HC-1 (δ 6.26) of the ethane unit and the H-3′, 4′, 5′, 6′ (7.35, 6.741, 6.59, 6.42) of the 2-hydroxyphenyl group and the Me-1″ (2.54) and H-8″ (7.99) of the 3-guaiazulenyl group in comparison with those [the HC-1 (δ 6.32) of the ethane unit and the H-3′, 4′, 5′, 6′ (7.27, 6.87, 6.68, 6.52) of the 2-hydroxyphenyl group and the Me-1″ (2.45) and H-8″ (7.87) of the 3-guaiazulenyl group] of the enantiomers **11b**, and, similarly as in the cases of **10** and **11**, in the *meso* form **12a** an anisotropic effect exerted by the (3-guaiazulenyl)phenylmethyl region of the other moiety is likely to cause apparent up- and down-field shifts of the signals for the HC-1 (δ 6.21) of the ethane unit and the H-2′, 6′ (6.17) and H-3′, 5′ (6.98) of the 4-hydroxyphenyl group and the Me-1″ (2.51), Me-4″ (2.95) and H-8″ (8.02) of the 3-guaiazulenyl group in comparison with those [the HC-1 (δ 5.94) of the ethane unit and the H-2′, 6′ (6.35) and H-3′, 5′ (6.81) of the 4-hydroxyphenyl group and the Me-1″ (2.23), Me-4″ (3.13) and H-8″ (7.82) of the 3-guaiazulenyl group] of the enantiomers **12b**. Furthermore, similarly as in the case of **10b**, in **12b** the same effect would cause division of the methyl protons of the isopropyl-7″ group into two signals (a ratio of almost 1:1); however, in **11b** the same effect would not cause division of the methyl protons of the isopropyl-7″ group into two signals. These findings enabled us to make the most plausible assignment of all the ^{1}H NMR signals of these four products **11a**,**b** and **12a**,**b** (see Tables 7 and 8 and Sections 4.1.9 and 4.1.10).

It is well known that hexestrol (**E**)[14,16] and diethylstilbestrol (**F**)[15,16] exhibit significant estrogenic activity. On the other hand, naturally occurring guaiazulene (**1**) has been widely used clinically as anti-inflammatory and anti-ulcer agents. A comparative study on the estrogenic activity of **11a**,**b** and **12a**,**b**, possessing a similar-type structure as **E**, with that of **E** and **F** is noteworthy, and is currently under intensive investigation.



E



F

3. Conclusion

We have reported the following 11 points in this paper: (i) the reactions of guaiazulene (**1**) with methyl terephalaldehydate (**2**), 2-hydroxybenzaldehyde (**3**) and 4-hydroxybenzaldehyde (**4**) in methanol in the presence of hexafluorophosphoric acid at 25 °C for 2 h under aerobic conditions gave the corresponding monocarbocation compounds, (3-guaiazulenyl)[4-(methoxycarbonyl)phenyl]methylium hexafluorophosphate (**5**) (94% yield), (3-guaiazulenyl)(2-hydroxyphenyl)methylium hexafluorophosphate (**6**) (89% yield) and (3-guaiazulenyl)(4-hydroxyphenyl)methylium hexafluorophosphate (**7**) (97% yield); (ii) the recrystallization of **5** from a mixed solvent of acetonitrile and diethyl ether (1:5, v/v) (several times) provided pure **5** as stable single crystals suitable for X-ray crystallographic analysis; (iii) the spectroscopic data of the product **5** compared with those of (3-guaiazulenyl)phenylmethylium hexafluorophosphate (**A**) led to the molecular structure **5** with a resonance form of the 3-guaiazulenylium structure **5′** in acetonitrile; (iv) along with the spectroscopic data for **5** in acetonitrile, the X-ray crystallographic analysis for **5** compared with those of **A**, (3-guaiazulenyl)(4-isopropylphenyl)methylium tetrafluoroborate (**B**) and [4-(dimethylamino)phenyl](3-guaiazulenyl)methylium tetrafluoroborate (**C**) also led to the crystal structure **5** with a resonance form of the 3-guaiazulenylium structure **5′**; (v) the spectroscopic data of the products **6** and **7** compared with those of **A** and, further, the chemical evidence (i.e., the reductions of **6** and **7** with $NaBH_4$) led to the molecular structures **6** and **7** with the resonance forms of the 3-guaiazulenylium **6′**, **6″** and oxonium **7′**, **7″** structures in acetonitrile; (vi) the reduction of **5** with zinc powder in dichloromethane at 25 °C for 20 min under argon gave a chromatographically separable mixture of the *meso* form, (1*R*,2*S*)-1,2-bis[4-(methoxycarbonyl)phenyl]-1,2-di(3-guaiazulenyl)ethane (**10a**) (16% yield), and the enantiomers, (1*R*,2*R*)- and (1*S*,2*S*)-1,2-bis[4-(methoxycarbonyl)phenyl]-1,2-di(3-guaiazulenyl)ethane (**10b**) (20% yield); (vii) the recrystallization of **10a** from a mixed solvent of dichloromethane and hexane (1:4, v/v) (several times) provided pure **10a** as stable single crystals suitable for X-ray crystallographic analysis; (viii) along with the spectroscopic data for **10a** in dichloromethane, the crystal structure of **10a** compared with those of 1,4-bis(3-guaiazulenylmethyl)benzene (**D**) and hexestrol (**E**) was reported; (ix) the reduction of **6** with zinc powder in acetonitrile at 25 °C for 2 h under argon gave a chromatographically separable mixture of the *meso* form, (1*R*,2*S*)-1,2-bis(2-hydroxyphenyl)-1,2-di(3-guaiazulenyl)ethane (**11a**) (15% yield), and the enantiomers, (1*R*,2*R*)- and (1*S*,2*S*)-1,2-bis(2-hydroxyphenyl)-1,2-di(3-guaiazulenyl)-ethanes (**11b**) (17% yield); (x) the reduction of **7** with zinc powder under the same reaction conditions as **6** afforded a chromatographically separable mixture of the *meso* form, (1*R*,2*S*)-1,2-bis(4-hydroxyphenyl)-1,2-di(3-guaiazulenyl)-ethane (**12a**) (40% yield), and the enantiomers, (1*R*,2*R*)- and (1*S*,2*S*)-1,2-bis(4-hydroxyphenyl)-1,2-di(3-guaiazulenyl)-ethanes (**12b**) (41% yield); and, further, (xi) along with a comparative study on the reduction potentials of **5–7**, **A**, (3-guaiazulenyl)(4-isopropylphenyl)methylium hexafluorophosphate (**B′**) and **C**, a comparative study on the reduction potentials of **5** with those of **10a**, **10b** and **C** enabled us to submit a plausible electron transfer mechanism of **5** based on its CV and DPV data as shown in Scheme 1.

4. Experimental

4.1. General

Thermal (TGA/DTA) and elemental analyses were taken on a Shimadzu DTG-50H thermal analyzer and a Yanaco MT-3 CHN corder, respectively. MS spectra were taken on a JEOL The Tandem Mstation JMS-700 TKM data system. UV–vis and IR spectra were taken on a Beckman DU640 spectrophotometer and a Shimadzu FTIR-4200 Grating spectrometer, respectively. NMR spectra were recorded with a JEOL GX-500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) and JNM-ECA700 (700 MHz for ^{1}H and 176 MHz for ^{13}C) cryospectrometers at 25 °C. The ^{1}H NMR spectra were assigned using the computer-assisted simulation analysis (the software: gNMR developed by Adept Scientific plc) on a DELL Dimension XPS T500 personal-computer with a Pentium III processor. Cyclic and differential pulse voltammograms were measured by an ALS Model 600 electrochemical analyzer.

4.1.1. Preparation of (3-guaiazulenyl)[4-(methoxycarbonyl)phenyl]methylium hexafluorophosphate (5). To a solution of guaiazulene (**1**) (103 mg, 0.52 mmol) in methanol (1.3 mL) was added a solution of methyl terephalaldehydate (**2**) (113 mg, 0.69 mmol) in methanol (1.3 mL) containing hexafluorophosphoric acid (60% aqueous solution, 0.3 mL). The mixture was stirred at 25 °C for 2 h under aerobic conditions, giving a precipitation of a yellow solid of **5**, and then was centrifuged at 2.5 krpm for 1 min. The crude product **5** thus obtained was carefully washed with diethyl ether, and was recrystallized from acetonitrile–diethyl ether (1:5, v/v) (several times) to provide pure **5** as stable single crystals (241 mg, 0.49 mmol, 94% yield).

Compound **5**. Yellow plates, mp >148 °C [decomp., determined by thermal analysis (TGA and DTA)]. Found: C, 59.04; H, 5.02%. Calcd for $C_{24}H_{25}F_6O_2P$: C, 58.78; H, 5.14%; UV–vis λ_{max} (CH_3CN) nm (log ε), 219 (4.53), 272 (4.26), 281 (4.29), 325 (4.20), 373 (4.41) and 447 (4.37); IR ν_{max} (KBr) cm^{-1}, 1717, 1285 (C=O) and 837, 559 (PF_6^-); exact FAB-MS (3-nitrobenzyl alcohol matrix), found: *m/z* 345.1870; calcd for $C_{24}H_{25}O_2$: $[M-PF_6]^+$, *m/z* 345.1854; 500 MHz ^{1}H NMR (CD_3CN), signals based on the 3-guaiazulenylmethylium substituent: δ 1.48 (6H, d, J= 6.9 Hz, $(CH_3)_2$CH-7′), 2.52 (3H, s, Me-1′), 3.38 (3H, s, Me-4′), 3.53 (1H, sept, J=6.9 Hz, Me_2CH-7′), 7.92 (1H, br s, H-2′), 8.48 (1H, dd, J=11.4, 2.2 Hz, H-6′), 8.60 (1H, d, J= 11.4 Hz, H-5′), 8.61 (1H, d, J=2.2 Hz, H-8′) and 8.77 (1H, br s, HC^+-α); signals based on the 4-(methoxycarbonyl)-phenyl group: δ 3.94 (3H, s, 4-COOCH_3), 7.88 (2H, ddd, J=8.6, 2.5, 1.0 Hz, H-2,6) and 8.18 (2H, ddd, J=8.6, 2.5, 1.0 Hz, H-3,5); 125 MHz ^{13}C NMR (CD_3CN), δ 172.4 (C-7′), 161.6 (C-8a′), 166.1 (4-COOCH$_3$), 157.7 (C-4′), 152.9 (C-3a′), 150.8 (C-5′), 147.4 (HC^+-α), 146.5 (C-1′), 144.7 (C-6′), 141.2 (C-3′), 140.0 (C-2′), 139.7 (C-1), 139.3 (C-8′), 132.4 (C-2,6), 132.3 (C-4), 129.9 (C-3,5), 52.2 (4-COOCH_3), 39.5 (Me$_2$$C$H-7′), 28.8 (Me-4′), 22.8 ((CH$_3$)$_2$CH-7′) and 13.0 (Me-1′).

4.1.2. X-ray crystal structure of (3-guaiazulenyl)[4-(methoxycarbonyl)phenyl]methylium hexafuloro-phosphate (5). A total 5748 reflections with $2\theta_{max}=55.0°$ were collected on a Rigaku AFC-5R automated four-circle diffractometer with graphite monochromated Mo-Kα radiation (λ=0.71069 Å, rotating anode; 50 kV, 180 mA) at 296 K. The structure was solved by direct methods (SIR97) and expanded using Fourier techniques (DIRDIF94). The non-hydrogen 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. All calculations were performed using the teXsan crystallographic software package. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number CCDC 198714.

Crystallographic data for **5**: $C_{24}H_{25}F_6O_2P$ (FW=490.42), yellow plate (the crystal size, 0.30×0.30×0.70 mm^3), monoclinic, $P2_1/n$ (#14), a=7.912(3) Å, b=30.061(2) Å, c=10.185(2) Å, β=109.14(2)°, V=2288.4(9) Å^3, Z=4, D_{calcd}=1.423 g/cm^3, μ(Mo-Kα)=1.88 cm^{-1}, Scan width=(0.73+0.30 tanθ)°, Scan mode=ω, Scan rate= 8.0°/min, measured reflections=5748, observed reflections=3370, No. of parameters=298, $R1$=0.050, $wR2$= 0.163 and Goodness of Fit Indicator=1.70.

4.1.3. Preparation of (3-guaiazulenyl)(2-hydroxyphenyl)methylium hexafluorophosphate (6). To a solution of guaiazulene (**1**) (70 mg, 0.35 mmol) in methanol (1.0 mL) was added a solution of 2-hydroxybenzaldehyde (**3**) (40 μL, 0.40 mmol) in methanol (1.0 mL) containing hexafluorophosphoric acid (60% aqueous solution, 0.2 mL). The mixture was stirred at 25 °C for 2 h under aerobic conditions, giving a precipitation of a dark-red solid **6**, and then was centrifuged at 2.5 krpm for 1 min. The crude product **6** thus obtained was carefully washed with diethyl ether, and was recrystallized from acetnitrile–diethyl ether (1:5, v/v) (several times) to provide pure **6** as stable crystals (141 mg, 0.31 mmol, 89% yield).

Compound **6**. Dark-red needles, mp>141 °C [decomp., determined by thermal analysis (TGA and DTA)]. Found: C, 58.96; H, 5.02%. Calcd for $C_{22}H_{23}F_6OP$: C, 58.93; H, 5.17%; UV–vis λ_{max} (CH_3CN) nm (log ε), 224 (4.51), 276 (4.22), 331 (4.22), 370 (4.19) and 489 (4.50); IR ν_{max} (KBr) cm^{-1}, 3483 (O–H) and 845, 559 (PF_6^-); exact FAB-MS (3-nitrobenzyl alcohol matrix), found: *m/z* 303.1747; calcd for $C_{22}H_{23}O$: $[M-PF_6]^+$, *m/z* 303.1748; 700 MHz ^{1}H NMR (CD_3CN), signals based on the 3-guaiazulenylmethylium substituent: δ 1.45 (6H, d, J=6.8 Hz, $(CH_3)_2$CH-7′), 2.50 (3H, s, Me-1′), 3.32 (3H, s, Me-4′), 3.48 (1H, sept, J=6.8 Hz, Me_2CH-7′), 7.98 (1H, br s, H-2′), 8.39 (1H, dd, J=11.2, 2.4 Hz, H-6′), 8.48 (1H, d, J= 11.2 Hz, H-5′), 8.57 (1H, d, J=2.4 Hz, H-8′) and 9.01 (1H, br s, HC^+-α); signals based on the 2-hydroxyphenyl group: δ 7.01 (1H, dd, J=7.9, 1.0 Hz, H-3), 7.08 (1H, br ddd, J= 7.7, 7.6, 1.0 Hz, H-5), 7.46 (1H, br ddd, J=7.9, 7.7, 1.4 Hz, H-4) and 7.69 (1H, br dd, J=7.6, 1.4 Hz, H-6); 176 MHz

^{13}C NMR (CD_3CN), δ 170.9 (C-7′), 161.1 (C-8a′), 159.5 (C-2), 157.5 (C-4′), 153.6 (C-3a′), 150.3 (C-5′), 146.2 (HC^+-α), 145.4 (C-1′), 144.8 (C-6′), 141.8 (C-2′), 139.8 (C-8′), 139.2 (C-3′), 135.7 (C-4), 134.7 (C-6), 122.2 (C-5), 117.2 (C-3), 40.2 (Me_2CH-7′), 29.8 (Me-4′), 23.8 (($CH_3)_2$CH-7′) and 13.8 (Me-1′).

4.1.4. Preparation of (3-guaiazulenyl)(4-hydroxyphenyl)methylium hexafulorophosphate (7). To a solution of guaiazulene (**1**) (70 mg, 0.35 mmol) in methanol (1.0 mL) was added a solution of 4-hydroxybenzaldehyde (**4**) (49 mg, 0.40 mmol) in methanol (1.0 mL) containing hexafluorophosphoric acid (60% aqueous solution, 0.2 mL). The mixture was stirred at 25 °C for 2 h under aerobic conditions, giving a precipitation of a red solid of **7**, and then was centrifuged at 2.5 krpm for 1 min. The crude product **7** thus obtained was carefully washed with diethyl ether, and was recrystallized from acetnitrile–diethyl ether (1:4, v/v) (several times) to provide pure **7** as stable crystals (153 mg, 0.34 mmol, 97% yield).

Compound **7**. Metallic lustrous red plates, mp > 171 °C [decomp., determined by thermal analysis (TGA and DTA)]. Found: C, 59.16; H, 4.98%. Calcd for $C_{22}H_{23}F_6OP$: C, 58.93; H, 5.17%; UV–vis λ_{max} (CH_3-CN) nm (log ε), 229 (4.51), 334 (4.19), 409 (4.07) and 510 (4.67); IR ν_{max} (KBr) cm^{-1}, 3476 (O–H) and 837, 556 cm^{-1} (PF_6^-); exact FAB-MS (3-nitrobenzyl alcohol matrix), found: *m/z* 303.1747; calcd for $C_{22}H_{23}O$: $[M-PF_6]^+$, *m/z* 303.1748; 500 MHz ^{1}H NMR (CD_3CN), signals based on the 3-guaiazulenylmethylium substituent: δ 1.44 (6H, d, *J* = 7.0 Hz, ($CH_3)_2$CH-7′), 2.53 (3H, s, Me-1′), 3.33 (3H, s, Me-4′), 3.46 (1H, sept, *J* = 7.0 Hz, Me_2CH-7′), 8.08 (1H, br s, H-2′), 8.37 (1H, dd, *J* = 10.9, 1.8 Hz, H-6′), 8.43 (1H, d, *J* = 10.9 Hz, H-5′), 8.56 (1H, d, *J* = 1.8 Hz, H-8′) and 8.72 (1H, br s, HC^+-α); signals based on the 4-hydroxyphenyl group: δ 7.04 (2H, ddd, *J* = 8.6, 1.8, 1.0 Hz, H-3,5), 7.83 (2H, ddd, *J* = 8.6, 1.8, 1.0 Hz, H-2,6) and 8.22 (1H, br s, 4-OH); 125 MHz ^{13}C NMR (CD_3CN), δ 169.3 (C-7′), 163.3 (C-4), 159.6 (C-8a′), 157.1 (C-4′), 153.3 (C-3a′), 151.7 (HC^+-α), 149.1 (C-5′), 144.6 (C-1′), 144.3 (C-6′), 141.8 (C-2′), 139.6 (C-8′), 137.6 (C-2,6), 137.3 (C-3′), 128.6 (C-1), 118.3 (C-3,5), 40.1 (Me_2CH-7′), 30.0 (Me-4′), 23.8 (($CH_3)_2$CH-7′) and 13.8 (Me-1′).

4.1.5. Reduction of (3-guaiazulenyl)(2-hydroxyphenyl)methylium hexafluorophosphate (6) with $NaBH_4$. To a solution of $NaBH_4$ (11 mg, 291 μmol) in ethanol (2.0 mL) was added a solution of **6** (60 mg, 134 μmol) in acetonitrile (2.0 mL). The mixture was stirred at 25 °C for 30 min under aerobic conditions and then evaporated in vacuo. The residue thus obtained was dissolved in hexane and filtered. The hexane-filtrate was evaporated in vacuo, giving a blue paste residue, which was carefully separated by silica-gel column chromatography with hexane–ethyl acetate–benzene (70:20:10, v/v/v) as an eluant, giving pure 1-(3-guaiazulenylmethyl)-2-hydroxybenzene (**8**) as a blue paste (34 mg, 112 μmol, 84% yield).

Compound **8**. Blue paste, R_f = 0.40 on silica-gel TLC (hexane–AcOEt–benzene = 70:20:10, v/v/v); UV–vis λ_{max} (CH_3CN) nm (log ε), 216 (3.50), 247 (3.49), 289 (3.72), 306sh (3.34), 353 (2.87), 370 (2.78), 623 (2.43), 678sh (2.33) and 750sh (1.88); exact EI-MS (70 eV), found: *m/z* 304.1808; calcd for $C_{22}H_{24}O$: M^+, *m/z* 304.1827; 500 MHz ^{1}H NMR (CD_3CN), signals based on the 3-guaiazulenylmethyl group: δ 1.31 (6H, d, *J* = 6.9 Hz, ($CH_3)_2$CH-7′), 2.56 (3H, s, Me-1′), 2.76 (3H, s, Me-4′), 3.01 (1H, sept, *J* = 6.9 Hz, Me_2CH-7′), 4.47 (2H, s, CH_2-3′), 6.78 (1H, d, *J* = 10.7 Hz, H-5′), 7.27 (1H, dd, *J* = 10.7, 2.3 Hz, H-6′), 7.32 (1H, s, H-2′) and 8.10 (2H, d, *J* = 2.3 Hz, H-8′); signals based on the 2-hydroxyphenyl group: δ 6.50 (1H, dd, *J* = 7.6, 1.2 Hz, H-6), 6.66 (1H, ddd, *J* = 7.6, 7.6, 1.2 Hz, H-5), 6.83 (1H, dd, *J* = 7.8, 1.2 Hz, H-3), 6.89 (1H, br s, 2-OH) and 7.02 (1H, ddd, *J* = 7.8, 7.6, 1.2 Hz, H-4); 125 MHz ^{13}C NMR (CD_3CN), δ 154.8 (C-2), 146.5 (C-4′), 141.7 (C-2′), 139.9 (C-7′), 138.8 (C-8a′), 135.7 (C-6′), 134.2 (C-8′), 134.0 (C-3a′), 130.8 (C-6), 130.7 (C-1), 127.8 (C-4), 126.9 (C-5′), 126.3 (C-3′), 125.1 (C-1′), 120.9 (C-5), 115.6 (C-3), 38.3 (Me_2CH-7′), 31.7 (CH_2-3′), 26.4 (Me-4′), 24.8 (($CH_3)_2$CH-7′) and 12.9 (Me-1′).

4.1.6. Reduction of (3-guaiazulenyl)(4-hydroxyphenyl)methylium hexafluorophosphate (7) with $NaBH_4$. To a solution of $NaBH_4$ (11 mg, 291 μmol) in ethanol (2 mL) was added a solution of **7** (60 mg, 134 μmol) in acetonitrile (2.0 mL). The mixture was stirred at 25 °C for 30 min under aerobic conditions and then evaporated in vacuo. The residue thus obtained was dissolved in hexane and filtered. The hexane-filtrate was evaporated in vacuo, giving a blue paste residue, which was carefully separated by silica-gel column chromatography with hexane–ethyl acetate–benzene (70/20/10, v/v/v) as an eluant, giving pure 1-(3-guaiazulenylmethyl)-4-hydroxybenzene (**9**) as a blue paste (36 mg, 118 μmol, 88% yield).

Compound **9**. Blue paste, R_f = 0.35 on silica-gel TLC (hexane–AcOEt–benzene = 70:20:10, v/v/v); UV–vis λ_{max} (CH_3CN) nm (log ε), 219 (3.57), 247 (3.67), 289 (3.94), 306sh (3.56), 353 (3.07), 370 (2.99), 623 (3.35), 678sh (3.26) and 750sh (2.79); exact EI-MS (70 eV), found: *m/z* 304.1811; calcd for $C_{22}H_{24}O$: M^+, *m/z* 304.1827; 500 MHz ^{1}H NMR (CD_3CN), signals based on the 3-guaiazulenylmethyl group: δ 1.30 (6H, d, *J* = 6.9 Hz, ($CH_3)_2$CH-7′), 2.56 (3H, s, Me-1′), 2.78 (3H, s, Me-4′), 3.00 (1H, sept, *J* = 6.9 Hz, Me_2CH-7′), 4.45 (2H, s, CH_2-3′), 6 .77 (1H, d, *J* = 10.8 Hz, H-5′), 7.26 (1H, dd, *J* = 10.8, 2.3 Hz, H-6′), 7.35 (1H, s, H-2′) and 8.09 (2H, d, *J* = 2.3 Hz, H-8′); signals based on the 4-hydroxyphenyl group: δ 6.68 (2H, ddd, *J* = 8.5, 2.5, 1.0 Hz, H-3,5), 6.70 (1H, br s, 4-OH) and 6.81 (2H, ddd, *J* = 8.5, 2.5, 1.0 Hz, H-2,6); 125 MHz ^{13}C NMR (CD_3CN), δ 155.7 (C-4), 146.3 (C-4′), 142.0 (C-2′), 139.9 (C-7′), 138.8 (C-8a′), 135.70 (C-6′), 135.67 (C-1), 134.2 (C-8′), 133.7 (C-3a′), 130.2 (C-2,6), 127.4 (C-3′), 126.9 (C-5′), 125.1 (C-1′), 116.0 (C-3,5), 38.3 (Me_2CH-7′), 36.6 (CH_2-3′), 26.8 (Me-4′), 24.7 (($CH_3)_2$CH-7′) and 12.9 (Me-1′).

4.1.7. Reduction of (3-guaiazulenyl)[4-(methoxycarbonyl)phenyl]methylium hexafluorophosphate (5) with zinc powder. To a solution of **5** (98 mg, 0.20 mmol) in dichloromethane (4.0 mL) was added a zinc powder (1.0 g, 1.6 mmol) under argon. The mixture was stirred at 25 °C for 20 min. After the reaction, the zinc powder was removed by using a centrifugal separator. The reaction solution was evaporated in vacuo, giving a bluish-green paste. The residue thus obtained was carefully separated by silica-gel column chromatography with hexane–ethyl acetate–benzene (80:10:10, v/v/v) as an eluant, giving the *meso* form, (1*R*,2*S*)-1,2-bis[4-(methoxycarbonyl)phenyl]-1,2-di(3-guaiazulenyl)ethane (**10a**), as a blue solid and the enantiomers, (1*R*,2*R*)- and (1*S*,2*S*)-1,2-bis[4-(methoxycarbonyl)phenyl]-1,2-di(3-guaiazulenyl)ethane (**10b**), as a bluish-green solid. The *meso* form **10a** and the enantiomers **10b** thus obtained were recrystallized from dichloromethane–hexane (1:4, v/v) (several times), respectively, giving pure **10a** as stable single crystals (11 mg, 16 μmol, 16% yield), and giving pure **10b** as a bluish-green solid (14 mg, 20 μmol, 20% yield).

Compound **10a**. Blue blocks, mp = 255 °C [determined by thermal analysis (TGA and DTA)]. Found: C, 83.29; H, 7.24%. Calcd for $C_{48}H_{50}O_4$: C, 83.44; H, 7.29%; R_f = 0.19 on silica-gel TLC (hexane–AcOEt–benzene = 80:10:10, v/v/v); UV–vis λ_{max} (CH_2Cl_2) nm (log ε), 247 (4.87), 297 (4.88), 310 (4.81), 359 (4.22), 376 (4.28) and 620 (2.60); IR ν_{max} (KBr) cm^{-1}, 1713 and 1285 (C=O); exact FAB-MS (3-nitrobenzyl alcohol matrix), found: *m/z* 691.3794; calcd for $C_{48}H_{51}O_4$: $[M+H]^+$, *m/z* 691.3787; 500 MHz ^{1}H NMR (CD_2Cl_2), signals based on the 1,2-di(3-guaiazulenyl)ethane unit: δ 1.30 (12H, d, J = 7.1 Hz, $(CH_3)_2$CH-7″,7⁗), 2.58 (6H, s, Me-1″,1⁗), 2.95 (6H, s, Me-4″,4⁗), 2.98 (2H, sept, J = 7.1 Hz, Me_2CH−7″,7⁗), 6.12 (2H, s, HC-1,2), 6.74 (2H, d, J = 10.8 Hz, H-5″,5⁗), 7.20 (2H, dd, J = 10.8, 2.1 Hz, H-6″,6⁗), 7.79 (2H, br s, H-2″,2⁗) and 8.01 (2H, d, J = 2.1 Hz, H-8″,8⁗); signals based on the 1,2-bis[4-(methoxycarbonyl)phenyl] groups: δ 3.74 (6H, s, 4′,4‴-COOCH_3), 7.10 (4H, ddd, J = 8.6, 2.5, 1.0 Hz, H-2′,2‴,6′,6‴) and 7.59 (4H, ddd, J = 8.6, 2.5, 1.0 Hz, H-3′,3‴,5″,5‴); 125 MHz ^{13}C NMR (CD_2Cl_2), δ 166.7 (4′,4‴-*C*OOMe), 151.1 (C-4′,4‴), 144.6 (C-4″,4⁗), 140.0 (C-7″,7⁗), 138.4 (C-2″,2⁗), 138.3 (C-8a″,8a⁗), 134.5 (C-6″,6⁗), 133.7 (C-8″,8⁗), 132.2 (C-3a″,3a⁗), 129.3 (C-2′,6′,2‴,6‴), 128.9 (C-3′,5′,3‴,5‴), 128.1 (C-3″,3⁗), 127.1 (C-1′,1‴), 126.9 (C-5″,5⁗), 125.1 (C-1″,1⁗), 51.7 (4′,4‴-COOCH_3), 51.2 (C-1,2), 37.6 (Me_2CH-7″,7⁗), 28.2 (Me-4″,4⁗), 24.3 ((CH_3)CH-7″,7⁗) and 12.9 (Me-1″,1⁗).

Compound **10b**. Bluish-green solid, mp = 240 °C [determined by thermal analysis (TGA and DTA)]. Found: C, 83.13; H, 7.64%. Calcd for $C_{48}H_{50}O_4$: C, 83.44; H, 7.29%; R_f = 0.15 on silica-gel TLC (hexane–AcOEt–benzene = 80:10:10, v/v/v); UV–vis λ_{max} (CH_3CN) nm (log ε), 246 (4.82), 291 (4.80), 3.11sh (4.59), 361 (4.21), 372 (4.29), 622 (2.93), 684sh (2.80) and 750sh (2.32); IR ν_{max} (KBr) cm^{-1}, 1720 and 1277 (C=O); exact FAB-MS (3-nitrobenzyl alcohol matrix), found: *m/z* 691.3762; calcd for $C_{48}H_{51}O_4$: $[M+H]^+$, *m/z* 691.3788; 500 MHz ^{1}H NMR (CD_2Cl_2), signals based on the 1,2-di(3-guaiazulenyl)ethane unit: δ 1.275, 1.283 (6H each, d, J = 6.9 Hz, $(CH_3)_2$CH-7″,7⁗), 2.48 (6H, s, Me-1″,1⁗), 2.96 (2H, sept, J = 6.9 Hz, Me_2CH-7″,7⁗), 3.10 (6H, s, Me-4″,4⁗), 5.86 (2H, br s, HC-1,2), 6.80 (2H, d, J = 10.9 Hz, H-5″,5⁗), 7.22 (2H, dd, J = 10.9, 2.0 Hz, H-6″,6⁗), 7.88 (2H, br s, H-2″,2⁗) and 7.97 (2H, d, J = 2.0 Hz, H-8″,8⁗); signals based on the 1,2-bis[4-(methoxycarbonyl)phenyl] groups: δ 3.81 (6H, s, 4′,4‴-COOCH_3), 6.85 (4H, ddd, J = 8.6, 2.5, 1.0 Hz, H-2′,2‴,6′,6‴) and 7.65 (4H, ddd, J = 8.6, 2.5, 1.0 Hz, H-3′,3‴,5′,5‴); 125 MHz ^{13}C NMR (CD_2Cl_2), δ 166.8 (4′,4‴-*C*OOMe), 150.9 (C-4′,4‴), 145.0 (C-4″,4⁗), 139.7 (C-7″,7⁗), 138.6 (C-2″,2⁗), 137.7 (C-8a″,8a⁗), 134.8 (C-6″,6⁗), 133.5 (C-8″,8⁗), 133.3 (C-3a″,3a⁗), 129.8 (C-2′,6′,2‴,6‴), 129.0 (C-3′,5′,3‴,5‴), 128.1 (C-3″,3⁗), 127.5 (C-1′,1‴), 126.9 (C-5″,5⁗), 124.4 (C-1″,1⁗), 53.7 (C-1,2), 51.8 (4′,4‴-COOCH_3), 37.6 (Me_2CH-7″,7⁗), 27.9 (C-4″,4⁗), 24.3 (($CH_3)_2$CH-7″,7⁗) and 13.0 (Me-1″,1⁗).

4.1.8. X-ray crystal structure of (1*R*,2*S*)-1,2-bis[4-(methoxycarbonyl)phenyl]-1,2-di(3-guaiazulenyl)ethane (10a). A total 5070 reflections with $2\theta_{max}$ = 55.1° were collected on a Rigaku AFC-5R automated four-circle diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71069 Å, rotating anode; 50 kV, 180 mA) at 296 K. The structure was solved by direct methods (SIR97) and expanded using Fourier techniques (DIRDIF94). The non-hydrogen 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. All calculations were performed using the teXsan crystallographic software package. The deposition number CCDC: 203376.

Crystallographic data for **10a**. $C_{48}H_{50}O_4$ (FW = 690.92), blue block (the crystal size, 0.50×0.10×0.50 mm^3), monoclinic, *Pbcn* (#60), a = 12.340(3) Å, b = 13.698(3) Å, c = 23.400(4) Å, V = 3955(2) Å^3, Z = 4, D_{calcd} = 1.160 g/cm^3, μ(Mo-Kα) = 0.72 cm^{-1}, Scan width = (1.37 + 0.30 tanθ)°, Scan mode = $\omega - 2\theta$, Scan rate = 8.0°/min, measured reflections = 5070, observed reflections = 4546, No. of parameters = 235, $R1$ = 0.067, $wR2$ = 0.203 and Goodness of Fit Indicator = 1.40.

4.1.9. Reduction of (3-guaiazulenyl)(2-hydroxyphenyl)-methylium hexafluorophosphate (6) with zinc powder. To a solution of **6** (150 mg, 0.33 mmol) in acetonitrile (3.0 mL) was added a zinc powder (654 mg, 10 mmol) under argon. The mixture was stirred at 25 °C for 2 h. After the reaction, the zinc powder was removed by using a centrifugal separator. The reaction solution was evaporated in vacuo, giving a bluish-green paste. The residue thus obtained was carefully separated by silica-gel column chromatography with hexane–ethyl acetate–benzene (70:20:20, v/v/v) as an eluant, giving the *meso* form, (1*R*,2*S*)-1,2-bis(2-hydroxyphenyl)-1,2-di(3-guaiazulenyl)-ethane (**11a**), as a blue solid and the enantiomers, (1*R*,2*R*)- and (1*S*,2*S*)-1,2-bis(2-hydroxyphenyl)-1,2-di(3-guaiazulenyl)ethane (**11b**), as a bluish-green paste (17 mg, 28 μmol, 17% yield). The *meso* form **11a** thus obtained was recrystallized from ethanol (several times) to provide pure **11a** as stable crystals (15 mg, 25 μmol, 15% yield).

Compound **11a**. Blue blocks, mp > 156 °C [decomp., determined by thermal analysis (TGA and DTA)]; R_f = 0.51 on silica-gel TLC (hexane–AcOEt–benzene = 70:20:20, v/v/v); UV–vis λ_{max} (CH_2Cl_2) nm (log ε), 250 (4.59).298 (4.77).311 (4.70).357 (4.10).374 (4.07).619 (2.89), 670sh (2.78) and 738sh (2.27); IR ν_{max} (KBr) cm^{-1}, 3441 (O–H) and 2959 (C–H); FAB-MS (3-nitrobenzyl alcohol matrix), *m/z* 607 ($[M+H]^+$, 36%), 606 (M^+, 49%) and 605 ($[M-H]^+$, 100%); exact FAB-MS (3-nitrobenzyl alcohol matrix), found: *m/z* 606.3492; calcd for $C_{44}H_{46}O_2$: M^+, *m/z* 606.3498; 500 MHz ^{1}H NMR (CD_3CN), signals based on the 1,2-di(3-guaiazulenyl)ethane unit: δ 1.29 (12H, d, $J=6.9$ Hz, $(CH_3)_2$CH-7″,7⁗), 2.54 (6H, s, Me-1″,1⁗), 2.98 (2H, sept, $J=6.9$ Hz, Me_2CH-7″,7⁗), 3.07 (6H, s, Me-4″,4⁗), 6.26 (2H, br s, CH-1,2), 6.736 (2H, d, $J=10.9$ Hz, H-5″,5⁗), 7.21 (2H, dd, $J=10.9$, 2.3 Hz, H-6″,6⁗), 7.99 (2H, d, $J=2.3$ Hz, H-8″,8⁗) and 8.00 (2H, s, H-2″,2⁗); signals based on the 1,2-bis(2-hydroxyphenyl) groups: δ 6.42 (2H, dd, $J=8.0$, 1.5 Hz, H-6′,6‴), 6.59 (2H, br ddd, $J=8.0$, 7.5, 1.5 Hz, H-5′,5‴), 6.741 (2H, br ddd, $J=8.0$, 7.5, 1.5 Hz, H-4′,4‴) and 7.35 (2H, dd, $J=8.0$, 1.5 Hz, H-3′,3‴).

Compound **11b**. Bluish-green paste; $R_f=0.43$ on silica-gel TLC (hexane–AcOEt–benzene = 70:20:20, v/v/v); UV–vis λ_{max} (CH_3CN) nm (log ε), 247 (4.53), 291 (4.67), 310sh (4.43), 355 (3.96), 371 (3.95), 619 (2.73), 678sh (2.61) and 750sh (2.16); FAB-MS (3-nitrobenzyl alcohol matrix), *m/z* 607 ($[M+H]^+$, 37%), 606 (M^+, 49%) and 605 ($[M-H]^+$, 100%); exact FAB-MS (3-nitrobenzyl alcohol matrix), found: *m/z* 606.3464; calcd for $C_{44}H_{46}O_2$: M^+, *m/z* 606.3498; 500 MHz ^{1}H NMR (CD_3CN), signals based on the 1,2-di(3-guaiazulenyl)ethane unit: δ 1.24 (12H, d, $J=6.9$ Hz, $(CH_3)_2$CH-7″,7⁗), 2.45 (6H, br s, Me-1″,1⁗), 2.91 (2H, sept, $J=6.9$ Hz, Me_2CH-7'',7⁗), 3.10 (6H, s, Me-4″,4⁗), 6.32 (2H, br s, CH-1,2), 6.70 (2H, d, $J=10.9$ Hz, H-5″,5⁗), 7.14 (2H, dd, $J=10.9$, 2.0 Hz, H-6″,6⁗), 7.87 (2H, d, $J=2.0$ Hz, H-8″,8⁗) and 7.96 (2H, s, H-2″,2⁗); signals based on the 1,2-bis(2-hydroxyphenyl) groups: δ 6.52 (2H, dd, $J=8.0$, 1.5 Hz, H-6′,6‴), 6.68 (2H, br ddd, $J=8.0$, 7.5, 1.5 Hz, H-5′,5‴), 6.87 (2H, br ddd, $J=8.0$, 7.5, 1.5 Hz, H-4′,4‴) and 7.27 (2H, br dd, $J=8.0$, 1.5 Hz, H-3′,3‴).

4.1.10. Reduction of (3-guaiazulenyl)(4-hydroxyphenyl)-methylium hexafluorophosphate (7) with zinc powder. To a solution of **7** (150 mg, 0.33 mmol) in acetonitrile (3.0 mL) was added a zinc powder (654 mg, 10 mmol) under argon. The mixture was stirred at 25 °C for 2 h. After the reaction, the zinc powder was removed by using a centrifugal separator. The reaction solution was evaporated in vacuo, giving a bluish-green paste. The residue thus obtained was carefully separated by silica-gel column chromatography with hexane–ethyl acetate–benzene (70:20:20, v/v/v) as an eluant, giving the *meso* form, (1*R*,2*S*)-1,2-bis(4-hydroxyphenyl)-1,2-di(3-guaiazulenyl)-ethane (**12a**), as a blue solid and the enantiomers, (1*R*,2*R*)- and (1*S*,2*S*)-1,2-bis(4-hydroxyphenyl)-1,2-di(3-guaiazulenyl)ethane (**12b**), as a bluish-green solid. The *meso* form **12a** thus obtained was recrystallized from hexane–ethyl acetate–benzene (70:20:10, v/v/v) (several times), giving pure **12a** as stable crystals (40 mg, 66 μmol, 40% yield). The enantiomers **12b** thus obtained was recrystallized from ethanol (several times) to provide pure **12b** as a bluish-green solid (41 mg, 68 μmol, 41% yield).

Compound **12a**. Blue blocks, mp > 185 °C [decomp., determined by thermal analysis (TGA and DTA)]. Found: C, 83.00; H, 7.91%. Calcd for $C_{48}H_{54}O_4$ ($C_{44}H_{46}O_2$. $CH_3COOC_2H_5$): C, 82.96; H, 7.83%; $R_f=0.27$ on silica-gel TLC (hexane–AcOEt–benzene = 70:20:10, v/v/v); UV–vis λ_{max} (CH_2Cl_2) nm (log ε), 249 (4.72), 297 (4.89), 311 (4.85), 375 (4.25) and 626 (3.03); IR ν_{max} (KBr) cm^{-1}, 3433 (O–H) and 2954 (C–H); exact FAB-MS (3-nitrobenzyl alcohol matrix), found: *m/z* 607.3588; calcd for $C_{44}H_{47}O_2$: $[M+H]^+$, *m/z* 607.3576; 500 MHz ^{1}H NMR (CD_3CN), signals based on the 1,2-di(3-guaiazulenyl)ethane unit: δ 1.77 (12H, d, $J=7.0$ Hz, $(CH_3)_2$CH-7″,7⁗), 2.51 (6H, s, Me-1″,1⁗), 2.73 (2H, sept, $J=7.0$ Hz, Me_2CH-7″,7⁗), 2.95 (6H, s, Me-4″,4⁗), 6.21 (2H, br s, HC-1,2), 6.58 (2H, d, $J=11.0$ Hz, H-5″,5⁗), 7.01 (2H, dd, $J=10.5$ Hz, H-6″,6⁗), 8.02 (2H, d, $J=2.0$ Hz, H-8″,8⁗) and 8.04 (2H, br s, H-2″,2⁗); signals based on the 1,2-bis(4-hydroxyphenyl) groups: δ 6.17 (4H, ddd, $J=8.6$, 1.8, 1.0 Hz, H-2′,2‴,6′,6‴) and 6.98 (4H, ddd, $J=8.6$, 1.8, 1.0 Hz, H-3′,3‴,5′,5‴).

Compound **12b**. Bluish-green solid, mp > 159 °C [decomp., determined by thermal analysis (TGA and DTA)]. Found: C, 82.89; H, 7.69%. Calcd for $C_{48}H_{54}O_4$ ($C_{44}H_{46}O_2$. $CH_3COOC_2H_5$): C, 82.96; H, 7.83%; $R_f=0.12$ on silica-gel TLC (hexane–AcOEt–benzene = 70:20:10, v/v/v); UV–vis λ_{max} (CH_2Cl_2) nm (log ε), 248 (4.72), 292 (4.87), 312sh (4.58), 361 (4.21), 373 (4.32) and 624 (3.10); IR ν_{max} (KBr) cm^{-1}, 3275 (O–H) and 2959 (C–H); exact FAB-MS (3-nitrobenzyl alcohol matrix), found: *m/z* 607.3588; calcd for $C_{44}H_{47}O_2$: $[M+H]^+$, *m/z* 607.3576; 500 MHz ^{1}H NMR (CD_3CN), signals based on the 1,2-di(3-guaiazulenyl)-ethane unit: δ 1.14 (12H, d, $J=7.0$ Hz, $(CH_3)_2$CH-7″,7⁗), 2.23 (6H, s, Me-1″,1⁗), 2.67 (2H, sept, $J=7.0$ Hz. Me_2CH-7″,7⁗), 3.13 (6H, s, Me-4″,4⁗), 5.94 (2H, br s, HC-1,2), 6.60 (2H, d, $J=11.0$ Hz, H-5″,5⁗), 6.98 (2H, dd, $J=11.0$, 2.0 Hz, H-6″,6⁗), 7.82 (2H, d, $J=2.0$ Hz, H-8″,8⁗) and 8.12 (2H, br s, H-2″,2⁗); signals based on the 1,2-bis(4-hydroxyphenyl) groups: δ 6.35 (4H, ddd, $J=8.6$, 1.8, 1.0 Hz, H-2′,2‴,6′,6‴) and 6.81 (4H, ddd, $J=8.6$, 1.8, 1.0 Hz, H-3′,3‴,5′,5‴).

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12. For comparative purposes, the oxidation potential using ferrocene as a standard material showed +0.45 (E_p) V by DPV and +0.42 ($E_{1/2}$) V by CV in 0.1 M [n-Bu_4N]BF_4, CH_3CN under the same electrochemical conditions as **C**,[5] indicating that these values slightly shift +0.03 (E_p) V by DPV and +0.02 ($E_{1/2}$) V by CV from those in 0.1 M [n-Bu_4N]PF_6, CH_3CN (see Fig. 6).
13. Crystallographic data for **D**: $C_{38}H_{42}$ (FW = 498.75), blue prism (the crystal size, 0.30×0.10×0.50 mm^3, from CH_2Cl_2–hexane = 1:5, v/v), triclinic, *P*-1 (#2), $a = 11.185(1)$ Å, $b = 12.028(2)$ Å, $c = 5.7025(9)$ Å, $\alpha = 93.51(1)°$, $\beta = 91.19(1)°$, $\gamma = 74.86(1)°$, $V = 739.2(2)$ Å^3, $Z = 1$, $D_{calcd} = 1.120$ g/cm^3, μ(Mo-Kα) = 0.63 cm^{-1}, Scan width = (1.10 + 0.30 tanθ)°, Scan mode = $\omega - 2\theta$, Scan rate = 8.0°/min, measured reflections = 3587, observed reflections = 1785, No. of parameters = 172, $R1 = 0.069$, $wR2 = 0.204$, Goodness of Fit Indicator = 1.99. A total 3587 reflections with $2\theta_{max} = 55.1°$ were collected on a Rigaku AFC-5R automated four-circle diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71069 Å, rotating anode: 50 kV, 180 mA) at 296 K. The structure was solved by direct methods (SIR97) and expanded using Fourier techniques (DIRDIF94). The non-hydrogen 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. All calculations were performed using the teXsan crystallographic software package. The deposition number CCDC: 192756.
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Desilylation procedure via a naphthalene-catalysed lithiation reaction

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Abstract—The reaction of silyl protected alcohols, amines and thiols with lithium powder and a catalytic amount of naphthalene, in THF, at 0 °C led, after hydrolysis, to the recovery of the free alcohols, amines and thiols in very good yields. At least a phenyl group was required in the silyl protecting group for the success of the reaction. Some polyfunctionalised starting materials have successfully been deprotected. The stereochemical outcome of the deprotection of a silylated chiral secondary alcohol has also been studied and no racemization was observed. The process has shown to be a good alternative to the acid-catalysed desilylation procedures, the latter being not useful for the deprotection of some silylated tertiary alcohols.
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1. Introduction

The silyl group is one of the most popular protecting groups for alcohols[1] and, to a lesser extent, for amines[1b,2] and thiols.[3] This is due to the fact that its introduction and subsequent removal can be modulated by the proper choice of the substituents on the silicon atom.[1,4] The deprotection of the silyl group can be carried out under mild acidic conditions or by treatment with fluoride anion, although some other desilylation procedures have been published which involve basic reaction conditions or redox processes.[1] Some of these processes gave some incompatibility problems[5] with other functional groups present in poly-functionalised molecules or showed lack of chemo-selectivity when the selective deprotection[4] of molecules with several silyl groups was tested.[5b,6] Palladium catalysts have also been applied to the removal of several silyl protecting groups under hydrogenolysis conditions.[7]

In the last few years, we have been using an arene-catalysed lithiation[8,9] to prepare organolithium compounds under very mild reaction conditions. The use of an excess of lithium powder and a catalytic amount of an arene [mainly naphthalene or 4,4′-di-*tert*-butylbiphenyl (DTBB)] allowed us to generate simple organolithium compounds starting from non-halogenated materials,[10] and functionalised organolithium compounds[11] by chlorine–lithium exchange or by ring opening of heterocycles.[12] The reductive cleavage of several allylic and benzylic carbon-heteroatom bonds has led to a method for removal of some protecting groups for alcohols, amines and thioethers.[13] We have recently described the reductive detritylation of trityl ethers[14] and *N*-tritylamines[15] by a naphthalene-catalysed lithiation process. In a previous study, we described one example in which the dimethylphenylsilyl group could be removed from a protected aliphatic alcohol in a naphthalene-catalysed lithiation reaction.[13] We decided to investigate in more detail the scope of this process and in this paper we report the application of this lithiation methodology to the removal of different silyl groups from several protected alcohols, amines and thiols under mild reaction conditions.

2. Results and discussion

All silylated substrates **1–3** were prepared from commercially available alcohols (for **1**), amines (for **2**) or thiols (for **3**) and the corresponding silyl chlorides under basic reaction conditions, except for compound **3b** for which the general procedure was unsuccessful, but it could be prepared under Lewis acid catalysis. Some starting materials, especially the ones bearing a dimethyl(phenyl)-silyl group, were found to be relatively unstable, decomposing upon storage for some months at room temperature. The stability of the silylated substrates increased with the number of phenyl groups on the silicon atom. No

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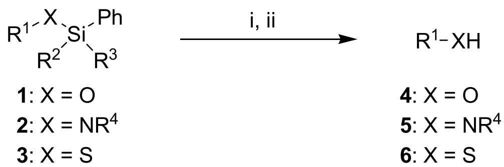

Scheme 1. *Reagents and conditions*: (i) Li, $C_{10}H_8$ (8 mol%), THF, 0 °C; (ii) H_2O.

decomposition was observed in the triphenylsilyl derivatives after storing them for one year at room temperature.

1-Decanol was used as a model starting material and it was converted into silyl ethers **1aa–1ad** (Scheme 1, Table 1, entries 1–4) possessing different substituents on the silicon atom. The reaction of compounds **1aa–1ac** with an excess of lithium powder (1:9 molar ratio) and a catalytic amount of naphthalene (1:0.16 molar ratio; 8 mol%) in THF at 0 °C gave, after hydrolysis with water, the expected primary alcohol **4a** in quantitative yield (Scheme 1 and Table 1, entries 1–3). Compound **1ad**, bearing a bulky *tert*-butyl and two phenyl groups as substituents at the silicon atom, did not react under the same reaction conditions, the unaltered starting material **1ad** being recovered after 8 h at 0 °C. However, the desilylation of **1ad** took place when the reaction was stirred at room temperature for 3 days, giving a 58% yield of 1-decanol **4a** and some unreacted starting material.[16] The yield of **4a** could be improved to 85% by running the reaction for 4 days at room temperature using DTBB as an electron carrier instead of naphthalene (Table 1, entry 4, footnote b). We assume that the reduction in the reaction rate is due to the steric hindrance caused by the bulky *tert*-butyl group. It was found that at least one phenyl group on the silicon atom was necessary for the success of the desilylation process. The reaction failed when trimethylsilyl-protected 1-decanol was used as substrate, the starting material being quantitatively recovered after 3 days at room temperature.

Next, the versatility of our method concerning the silylated substrate was studied. Compounds **1b** and **1c**, derived from secondary alcohols, gave the corresponding desilylated products in very good yields (Scheme 1 and Table 1, entries 5–7). Optically pure (*R*)-2-octanol was also protected with the dimethyl(phenyl)silyl group [(*R*)-**1c** (Table 1, entry 7)] and submitted to our lithiation reaction in order to check if there was any racemization during the process. Product (*R*)-**4c** was esterified with optically pure (*R*)-α-methoxyphenylacetic acid and no loss of enantiomeric purity was observed by comparison of the ^{13}C NMR spectra of the obtained ester and the esters that were prepared from the same acid and commercially available racemic 2-octanol and (*R*)-2-octanol. Thus, the stereochemistry of the chiral alcohol was preserved during the whole process. The triphenylsilyl group of the protected tertiary alcohol **1d** could also be removed in almost quantitative yield (Table 1, entry 8). It is worth noting that the attempted deprotection of compound **1d** by conventional methods was not satisfactory: whereas substrate **1d** was recovered unchanged after treatment with 1 M hydrochloric acid for 24 h at room temperature, the

Table 1. Desilylation of compounds **1–3** via a naphthalene-catalysed lithiation: preparation of compounds **4–6**

Entry	Substrate						Product	
	No.	X	R^1	R^2	R^3	Time (h)	No.	Yield (%)[a]
1	**1aa**	O	$Me(CH_2)_9$	Me	Me	3.5	**4a**	>99
2	**1ab**	O	$Me(CH_2)_9$	Me	Ph	2.0	**4a**	>99
3	**1ac**	O	$Me(CH_2)_9$	Ph	Ph	4.5	**4a**	>99
4	**1ad**	O	$Me(CH_2)_9$	Bu^t	Ph	96.0	**4a**	85[b]
5	**1b**	O	*c*-C_6H_{11}	Me	Me	5.0	**4b**	>99
6	**1c**	O	$Me(CH_2)_5CH(Me)$	Me	Me	4.0	**4c**	81[c]
7	(*R*)-**1c**	O	$Me(CH_2)_5CH(Me)$	Me	Me	3.5	(*R*)-**1c**	77[c]
8	**1d**	O	$Pr^i(CH_2)_3C(Me)(Et)$	Ph	Ph	5.0	**4d**	98
9	**1e**	O	$2,4,6\text{-}Me_3C_6H_2$	Ph	Ph	1.0	**4e**	94
10	**1f**	O	$HO(CH_2)_9$	Ph	Ph	1.0	**4f**	98[d]
11	**1ga**	O	$Ph_3SiO(CH_2)_9$	Me	Me	3.0	**4f**	79
12	**1gb**	O	$Ph_3SiO(CH_2)_9$	Bu^t	Ph	3.0	**4g**[e]	63[c]
13	**1h**	O	$Ph_3SiN(Me)(CH_2)_6$	Ph	Ph	6.0	**4h**[f]	63[g]
14	**2a**	$Me(CH_2)_7N$	$Me(CH_2)_7$	Me	Me	3.0	**5a**	97
15	**2b**	—[h]	—[h]	—[h]	—[h]	5.0	**5b**[i]	89
16	**2c**	MeN	Ph	Ph	Ph	3.0	**5c**	82
17	**2d**	$MeO(CH_2)_2N$	$MeO(CH_2)_2$	Ph	Ph	5.0	**5d**	97
18	**3a**	S	$Me(CH_2)_9$	Ph	Ph	5.0	**6a**	84
19	**3b**	S	*c*-C_6H_{11}	Ph	Ph	1.5	**6b**	51
20	**3c**	S	Ph	Ph	Ph	5.0	**6c**	48

[a] Yield determined by quantitative GLC, using commercially available compound **4–6** and *n*-dodecane (internal standard) in the determination of response factors.
[b] DTBB was used as an electron carrier instead of naphthalene and the reaction was run at 20 °C.
[c] Isolated yield after column chromatography (silica gel, hexane/ethyl acetate) based on the starting material **1**. All isolated compounds **4** were ≥95% pure (GLC and/or 300 MHz ^1H NMR).
[d] Compound **1f** was deprotonated with *n*-BuLi before performing the naphthalene-catalysed lithiation step.
[e] **4g** = 9-[*tert*-butyl(diphenyl)silyloxy]-1-nonanol.
[f] **4h** = 6-(methylamino)-1-hexanol.
[g] Yield determined by quantitative GLC, using commercially available compound **4h** and *n*-hexadecane (internal standard) in the determination of response factors.
[h] **2b** = 4-benzyl-*N*-(triphenylsilyl)piperidine.
[i] **5b** = 4-benzylpiperidine.

reaction between **1d** and tetrabutylammonium fluoride gave only a 34% yield of alcohol **4d** after 6 h at room temperature (compare with entry 8 in Table 1). Triphenylsilyl-protected phenol **1e** was also effectively desilylated, affording phenol **4e** in very good yield (Table 1, entry 9). Hydroxy-functionalised silylated alcohol **1f** gave the expected 1,9-nonanediol **4f** in almost quantitative yield after submitting its lithium alkoxide to the naphthalene-catalysed lithiation reaction for 1 h (Table 1, entry 10).

Our methodology was successfully applied to the desilylation of protected secondary amines and thiols (Scheme 1 and Table 1, entries 14–20). The dimethyl(phenyl)silyl and the triphenylsilyl groups could easily be removed from an acyclic and a cyclic protected secondary amine, respectively, in excellent yields (Table 1, entries 14 and 15). *N*-Methylaniline **5c** was obtained in a very good yield in the lithiation of substrate **2c** (Table 1, entry 16). Dimethoxy functionalised silylated amine **2d** afforded the free amine **5d** in almost quantitative yield (Table 1, entry 17). We also tried the desilylation of protected primary amines but it failed. Octylamine and cyclooctylamine were protected with dimethyl(phenyl)silyl and triphenylsilyl groups and the removal of these groups was attempted following the same procedure previously used by us in the deprotection of tritylated primary amines,[15] consisting in deprotonation with *n*-butyllithium and treatment with trimethylsilyl chloride before performing the lithiation step. Unfortunately, the reactions did not work as desired, the unchanged starting materials being quantitatively recovered. Concerning sulfur-containing substrates, silyl thioethers **3a**–**3c**, derived from primary, secondary and aromatic thiols, could also be desilylated in moderate to good yields (Table 1, entries 18–20). The moderate yields obtained with cyclohexanethiol **3b** and thiophenol **3c** could be attributed to some oxidation of the obtained thiols to the corresponding disulfides during the work-up, since, the latter were detected in the crude reaction mixtures (GC–MS).

We also studied the possible chemoselectivity of our methodology by performing the lithiation of the disilylated starting materials **1g** and **1h** (Scheme 1 and Table 1, entries 11–13). No selectivity was observed when unsymmetrically protected 1,9-nonanediol **1ga**, bearing a dimethyl(phenyl)-silyl and a triphenylsilyl group, was used as substrate: the diol **4f** was obtained in good yield (Table 1, entry 11). The result was the same when the reaction was repeated at −78 °C. The same lack of selectivity was found when two different functional groups were protected with the same silyl group. 6-Methylamino-1-hexanol was protected both at nitrogen and at oxygen with the triphenylsilyl group. When the obtained compound **1h** was submitted to the naphthalene-catalysed lithiation reaction, the free amino alcohol **4h** was recovered in good yield (Table 1, entry 13). However, when compound **1gb** bearing *tert*-butyl(diphenyl)silyloxy and triphenylsilyloxy groups was tested, only monodesilylation took place, the triphenylsilyl group being the only one that was removed when the reaction was performed at 0 °C (Table 1, entry 12). We were expecting this last result, according to the different reaction rates shown by compounds **1aa** and **1ad** (compare entries 1 and 4 in Table 1).

In all cases, the corresponding silanes were obtained (>90%) as by-products which could easily be separated from the desired products by column chromatography. The formation of these silanes suggests that a possible reaction mechanism would involve reductive cleavage of the silicon–heteroatom bond to generate lithium alkoxides (from **1**), amides (from **2**) or thiolates (from **3**) and the corresponding silyl radicals, which would be further, reduced to the silyllithium derivatives by reaction with lithium. Protonation of the silyllithium species in the hydrolysis step would afford the obtained silanes.

Allylic and benzylic substrates were tested too, but with unsatisfactory results. Benzyl alcohol was converted into the corresponding dimethyl(phenyl)silyl and triphenylsilyl ethers and the latter were treated with lithium and a catalytic amount of naphthalene at 0 °C. Toluene and the corresponding silanol were the only reaction products detected (GC–MS), indicating that cleavage of the carbon–oxygen bond instead of the silicon–oxygen bond had taken place. The same selectivity for the cleavage of the carbon–oxygen bond was observed in the lithiation of the geranyl triphenylsilyl ether. A similar carbon–oxygen bond cleavage had been found by us with trimethylsilyl protected allylic and benzylic alcohols.[17] Toluene was also obtained in the lithiation of *N*-methyl-*N*-(triphenylsilyl)benzylamine and benzyl triphenylsilyl sulfide.

3. Conclusion

In conclusion, we have reported here, a very efficient procedure to remove several silyl protecting groups from silylated alcohols, amines and thiols under mild reaction conditions. The methodology is applicable to aliphatic and aromatic derivatives, but not to allylic or benzylic ones. This desilylation procedure works very well even for branched alcohols and thiols, being superior to the conventional methods for the deprotection of tertiary alcohols. No racemization was observed when the deprotection of a silylated optically pure alcohol was performed. Concerning amines, the process is limited to secondary ones, being not useful for the deprotection of silylated primary amines. This method represents a good alternative to the common desilylation procedures, which require acidic reaction conditions or treatment with fluoride anion.

4. Experimental

4.1. General

For general information, see Ref. 15. All reagents used for the synthesis of silylated substrates **1–3** and naphthalene were commercially available (Acros, Aldrich) and were used without further, purification, except for triethylamine, which was refluxed for 1 h with phosphorus pentoxide and distilled under Ar before use. Lithium powder was prepared according to the procedure described in Ref. 18. Commercially available *n*-butyllithium was titrated with a 1 M solution of *sec*-butanol in xylene using 1,10-phenanthroline as indicator.[19] Commercially available anhydrous THF (99.9%, water content ≤0.006%, Acros) and CH_2Cl_2

(>99.5%, water content ≤0.005%, Fluka) were used as solvents in the reactions. All glassware was dried in an oven at 100 °C and cooled to room temperature under vacuum before use.

4.2. Synthesis of the silylated alcohols 1a–1g, amines 2 and thiols 3a and 3c. General procedure

Alcohol **1**, amine **2** or thiol **3** (5.0 mmol) was added to a stirred solution of the corresponding silylating agent [dimethyl(phenyl)silyl chloride, methyl(diphenyl)silyl chloride, *tert*-butyl(diphenyl)silyl chloride or triphenylsilyl chloride (see Scheme 1 and Table 1); 5.0 mmol], triethylamine (1.3 mL, 8.8 mmol) and 4-(dimethylamino)pyridine (92 mg, 0.4 mmol) in CH_2Cl_2 (10 mL) under Ar at 20 °C and the resulting mixture was stirred overnight. The crude reaction mixture was then adsorbed on basic aluminium oxide, transferred to a short column of basic aluminium oxide and eluted with hexane. Evaporation of the solvent (15 Torr) afforded the expected silylated compounds **1a–1g**, **2**, **3a** and **3c** in pure form. The synthesis of compounds **1g** was performed in a two step sequence: after stirring overnight the mixture of 1,9-nonanediol, triphenylsilyl chloride, triethylamine and 4-(dimethylamino)pyridine in the proportions indicated above, the same amount of dimethyl(phenyl)silyl chloride (for **1ga**) or *tert*-butyl-(diphenyl)silyl chloride (for **1gb**) were added and the reaction was stirred overnight again. The corresponding physical, spectroscopic and analytical data for compounds **1a–1g**, **2**, **3a** and **3c** follow.

4.2.1. 1-[Dimethyl(phenyl)silyloxy]decane (1aa). Colourless oil; yield: >99%; R_f 0.86 (hexane/ethyl acetate: 9:1) ν (film) 3082, 3057, 3029, 1596 (HC═C), 1115 (SiO), 1093 cm^{-1} (CO); δ_H 0.33 (6H, s, 2×MeSi), 0.88 (3H, t, J=6.7 Hz, *Me*CH$_2$), 1.17–1.65 [16H, m, Me(C*H*$_2$)$_8$], 3.64 (2H, t, J=6.6 Hz, CH$_2$O), 7.29–7.43, 7.48–7.61 (3H and 2H, respectively, 2m, ArH); δ_C 0.8 (2C, 2×MeSi), 14.1 (*Me*CH$_2$), 22.7, 25.7, 29.3, 29.4, 29.5, 29.6, 31.9, 32.8 [Me(*C*H$_2$)$_8$], 63.1 (CO), 127.7 (2C), 129.2, 133.0 (2C), 139.8 (ArC); *m/z* 277 (M$^+$−Me, 100), 214 (16), 137 (62), 135 (34), 121 (12); HRMS: M$^+$, found 292.2230. $C_{18}H_{32}OSi$ requires 292.2220.

4.2.2. 1-[Methyl(diphenyl)silyloxy]decane (1ab).[20] Colourless oil; yield: 99%; R_f 0.88 (hexane/ethyl acetate: 9:1); ν (film) 3069, 3049, 1590 (HC═C), 1118 (SiO), 1094 cm^{-1} (CO); δ_H 0.63 (3H, s, MeSi), 0.88 (3H, t, J=6.7 Hz, *Me*CH$_2$), 1.15–1.39 [14H, m, Me(C*H*$_2$)$_7$], 1.47–1.63 (2H, m, CH$_2$CO), 3.68 (2H, t, J=6.6 Hz, CH$_2$O), 7.26–7.45, 7.51–7.69 (6H and 4H, respectively, 2m, ArH); δ_C −3.0 (MeSi), 14.1 (*Me*CH$_2$), 22.7, 25.8, 29.3, 29.4, 29.55, 29.6, 31.9, 32.6 [Me(*C*H$_2$)$_8$], 63.6 (CO), 127.8 (4C), 129.7 (2C), 134.3 (4C), 136.5 (2C) (ArC); *m/z* 339 (M$^+$−Me, <1%), 244 (22), 243 (100), 166 (13), 165 (81).

4.2.3. 1-(Triphenylsilyloxy)decane (1ac).[21] Yellow solid; yield: >99%; R_f 0.70 (hexane/ethyl acetate: 9:1); mp 28 °C (hexane); ν (KBr) 3067, 3038, 1588 (HC═C), 1117 (SiO), 1088 cm^{-1} (CO); δ_H 0.88 (3H, t, J=6.9 Hz, Me), 1.19–1.40 [14H, m, Me(C*H*$_2$)$_7$], 1.50–1.65 (2H, m, CH$_2$CO), 3.78 (2H, t, J=6.2 Hz, CH$_2$O), 7.30–7.49, 7.61–7.63 (9H and 6H, respectively, 2m, ArH); δ_C 14.1 (Me), 22.7, 25.7, 29.3 (2C), 29.55, 29.6, 31.9, 32.5 [Me(*C*H$_2$)$_8$], 64.0 (CO), 127.8 (6C), 129.9 (3C), 134.5 (3C), 135.4 (6C) (ArC); *m/z* 416 (M$^+$, <1%), 340 (13), 339 (46), 338 (16), 261 (18), 260 (67), 253 (11), 200 (19), 199 (100), 190 (13), 184 (13), 183 (46), 182 (29), 181 (29), 176 (23), 155 (11), 123 (14).

4.2.4. 1-[*tert*-Butyl(diphenyl)silyloxy]decane (1ad).[22] Colourless oil; yield: 40%; R_f 0.92 (hexane/ethyl acetate: 9:1); ν (film) 3070, 3049, 1603 (HC═C), 1110 (SiO), 1088 cm^{-1} (CO); δ_H 0.88 (3H, t, J=6.9 Hz, *Me*CH$_2$), 1.04 (9H, s, 3×MeC), 1.16–1.40 [14H, m, Me(C*H*$_2$)$_7$], 1.49–1.62 (2H, m, CH$_2$CO), 3.65 (2H, t, J=6.6 Hz, CH$_2$O), 7.30–7.47, 7.59–7.73 (6H and 4H, respectively, 2m, ArH); δ_C 14.1 (*Me*CH$_2$), 19.2 (*C*Me$_3$), 26.9 (3C, 3×*Me*C), 22.7, 29.3, 29.4 (2C), 29.55, 29.6, 31.9, 32.6 [Me(*C*H$_2$)$_8$], 64.0 (CO), 127.5 (4C), 129.5 (2C), 134.3 (2C), 135.6 (4C) (ArC); *m/z* 396 (M$^+$, <1%), 340 (33), 339 (100), 199 (21), 183 (11).

4.2.5. [Dimethyl(phenyl)silyloxy]cyclohexane (1b).[23] Colourless oil; yield: 62%; R_f 0.92 (hexane/ethyl acetate: 9:1); ν (film) 3069, 3050, 1590 (HC═C), 1118 (SiO), 1088 cm^{-1} (CO); δ_H 0.38 (6H, s, 2×Me), 1.49–2.32 (10H, m, 5×CH$_2$), 3.99–4.13 (1H, m, CHO), 7.27–7.42, 7.51–7.65 (3H and 2H, respectively, 2m, ArH); δ_C −1.0 (2C, 2×Me), 24.3 (2C), 25.5, 35.8 (2C) (5×CH$_2$), 71.3 (CO), 127.7 (2C), 129.4, 133.4 (2C), 138.7 (ArC); *m/z* (DIP) 219 (M$^+$−Me, 60%), 191 (16), 156 (30), 146 (26), 137 (100), 135 (40), 111 (14), 97 (20), 85 (16), 83 (24), 82 (12), 71 (25), 70 (18), 69 (23), 57 (34), 56 (13), 55 (24), 43 (49), 41 (17).

4.2.6. 2-[Dimethyl(phenyl)silyloxy]octane (1c).[24] Colourless oil; yield: 97%; R_f 0.93 (hexane/ethyl acetate: 9:1); ν (film) 3069, 3050, 1591 (HC═C), 1118 (SiO), 1094 cm^{-1} (CO); δ_H 0.38 (6H, s, 2×MeSi), 0.87 (3H, t, J=6.9 Hz, *Me*CH$_2$), 1.09 (3H, d, J=6.9 Hz, MeCO), 1.10–1.52 [10H, m, Me(C*H*$_2$)$_5$], 3.72–3.84 (1H, m, CHO), 7.31–7.43, 7.51–7.64 (3H and 2H, respectively, 2m, ArH); δ_C −1.2, −1.1 (2×MeSi), 14.1 (*Me*CH$_2$), 23.7 (*Me*CO), 22.6, 25.7, 29.3, 31.8, 39.5 (5×CH$_2$), 69.0 (CO), 127.7 (2C), 129.4, 133.5 (2C), 138.5 (ArC); *m/z* 264 (M$^+$, <1%), 249 (21), 168 (13), 179 (56), 138 (11), 137 (88), 136 (14), 135 (100), 75 (34).

4.2.7. (2*R*)-2-[Dimethyl(phenyl)silyloxy]octane [(*R*)-1c]. Colourless oil; yield: 96%; R_f 0.93 (hexane/ethyl acetate: 9:1); $[\alpha]_D^{20}$ −1.5±0.2 (*c* 1, CHCl$_3$); ν (film) 3069, 3050, 1591 (HC═C), 1118 (SiO), 1071 cm^{-1} (CO); δ_H 0.38 (6H, s, 2×MeSi), 0.87 (3H, t, J=6.9 Hz, *Me*CH$_2$), 1.09 (3H, d, J=6.9 Hz, MeCO), 1.10–1.56 [10H, m, Me(C*H*$_2$)$_5$], 3.72–3.85 (1H, m, CHO), 7.28–7.42, 7.50–7.66 (3H and 2H, respectively, 2m, ArH); δ_C −1.2, −1.1 (2×MeSi), 14.1 (*Me*CH$_2$), 23.7 (*Me*CO), 22.6, 25.7, 29.3, 31.8, 39.5 [Me(*C*H$_2$)$_5$], 69.0 (CO), 127.7 (2C), 129.4, 133.5 (2C), 138.5 (ArC); *m/z* 264 (M$^+$, <1%), 249 (21), 168 (13), 179 (56), 138 (11), 137 (88), 136 (14), 135 (100), 75 (34); HRMS: M$^+$, found 264.1889. $C_{16}H_{28}OSi$ requires 264.1909.

4.2.8. 2,6-Dimethyl-6-(triphenylsilyloxy)octane (1d). Colourless oil; yield: >99%; R_f 0.64 (hexane/ethyl acetate: 9:1); ν (film) 3068, 3049, 1602 (HC═C), 1113 (SiO), 1064 cm^{-1} (CO); δ_H 0.76–0.93 (9H, m, 2×*Me*CH and *Me*CH$_2$), 1.15 (3H, s, MeC), 1.22–1.59 (9H, m, MeC*H* and 4×CH$_2$), 7.29–7.44, 7.60–7.72 (9H and 6H, respectively, 2m, ArH); δ_C 8.8 (*Me*CH$_2$), 21.9, 34.5, 39.4, 41.5 (4×CH$_2$), 22.5, 22.6 (2×*Me*CH), 27.8 (*Me*C), 78.7 (CO), 127.5 (6C), 129.4 (3C), 135.5 (6C), 136.8 (3C) (ArC); *m/z* 401 (M$^+$ −Me, <1%), 387 (25), 332 (12), 331 (43), 260 (25), 259 (100), 299 (15), 181 (12); HRMS: M$^+$−Me, found 401.2298. $C_{27}H_{33}OSi$ requires 401.2301.

4.2.9. 1,3,5-Trimethyl-2-(triphenylsilyloxy)benzene (1e).[21] Yellow solid; yield: 98%; R_f 0.63 (hexane/ethyl acetate: 9:1); mp 98 °C (hexane); ν (KBr) 3066, 3045, 1604 (HC=C), 1162 (CO), 1115 cm^{-1} (SiO); δ_H 2.17, 2.22 (3H and 6H, respectively, 2s, 3×Me), 6.78 (2H, s, 2×ArH), 7.27–7.48, 7.56–7.66 (9H and 6H, respectively, 2m, 15× ArH); δ_C 18.3 (2C), 20.4 (3×Me), 123.3 (2C), 127.7 (6C), 128.3 (2C), 129.0 (3C), 130.0 (3C), 130.7, 135.5 (6C), 149.9 (ArC); *m/z* 395 (M$^+$+1, 27%), 394 (M$^+$, 75), 260 (25), 259 (100), 181 (19), 105 (11).

4.2.10. 9-(Triphenylsilyloxy)-1-nonanol (1f).[25] Colourless oil; yield: 25%; R_f 0.85 (hexane/ethyl acetate: 9:1); ν (film) 3555 (OH), 3068, 3048, 3023, 1589 (HC=C), 1116 (SiO), 1094, 1061 cm^{-1} (CO); δ_H 1.12–1.69 [14H, m, (CH$_2$)$_7$CO], 3.57–3.69 (3H, m, CH$_2$OSi and OH), 3.78 (2H, t, J=6.6 Hz, C*H$_2$*OH), 7.32–7.50, 7.54–7.72 (9H and 6H, respectively, 2m, ArH); δ_C 25.7 (2C), 25.9, 29.2, 29.3, 32.5, 32.8 [(*C*H$_2$)$_7$CO], 63.1, 64.0 (2×CO), 127.8 (6C), 129.9 (3C), 135.0 (3C), 135.4 (6C) (ArC); *m/z* (DIP) 341 (M$^+$−Ph, 48%), 263 (11), 260 (19), 259 (88), 200 (18), 199 (100), 184 (16), 183 (14), 182 (10), 181 (23), 154 (10), 139 (28), 83 (12), 69 (22), 55 (10).

4.2.11. 1-[Dimethyl(phenyl)silyloxy]-9-(triphenylsilyloxy)nonane (1ga). White solid; yield: 56%; R_f 0.73 (hexane/ethyl acetate: 9:1); mp 42 °C (hexane); ν (KBr) 3069, 3050, 3023, 1589 (HC=C), 1117 (SiO), 1094 cm^{-1} (CO); δ_H 0.37 (6H, s, 2×Me), 1.11–1.38, 1.43–1.65 [10H and 4H, respectively, 2m, (C*H$_2$*)$_7$CO], 3.57, 3.77 (2H each, 2t, J=6.6 Hz each, 2×CH$_2$O), 7.30–7.47, 7.51–7.68 (12H and 8H, respectively, 2m, ArH); δ_C −1.8 (2C, 2×Me), 25.7, 25.75, 29.2, 29.3, 32.5 (2C), 32.6 [(*C*H$_2$)$_7$CO], 63.2, 64.0 (2×CO), 127.8 (6C), 129.5 (2C), 129.9 (4C), 133.4 (3C), 134.4 (2C), 135.4 (6C), 138.0 (ArC); *m/z* (DIP) 552 (M$^+$, <1%), 397 (12), 336 (24), 335 (82), 319 (14), 317 (16), 253 (11), 274 (15), 273 (59), 272 (11), 260 (24), 259 (100), 255 (22), 230 (15), 199 (49), 197 (20), 195 (25), 183 (20), 182 (11), 181 (24), 154 (12), 137 (28), 135 (32), 104 (11), 91 (19), 83 (16), 69 (27), 55 (13). Anal. Calcd for $C_{35}H_{44}O_2Si_2$: C, 76.03; H, 8.02. Found: C, 76.93; H, 8.18.

4.2.12. 1-[*tert*-Butyl(diphenyl)silyloxy]-9-(triphenylsilyloxy)nonane (1gb). Colourless oil; yield: 73%; R_f 0.86 (hexane/ethyl acetate: 9:1); ν (film) 3068, 3048, 1589 (HC=C), 1115 (SiO), 1064 cm^{-1} (CO); δ_H 1.04 (9H, s, 3× Me), 1.12–1.39, 1.47–1.64 [10H and 4H, respectively, 2m, (C*H$_2$*)$_7$CO], 3.65, 3.77 (2H each, 2t, J=6.5, 6.6 Hz, respectively, 2×CH$_2$O), 7.33–7.55, 7.58–7.72 (15H and 10H, respectively, 2m, ArH); δ_C 19.2 (*C*Me$_3$), 26.9 (3C, 3× Me), 22.6, 22.7, 25.7, 29.25, 29.35, 31.6, 32.5 [(*C*H$_2$)$_7$CO], 64.0, 64.05 (2×CO), 127.5 (3C), 127.8 (6C), 129.5 (2C), 129.9 (4C), 134.2 (2C), 134.5 (3C), 135.4 (6C), 135.6 (4C) (ArC); *m/z* (DIP) 656 (M$^+$, 6%), 655 (11), 501 (20), 500 (45), 499 (83), 422 (10), 216 (18), 259 (68), 257 (20), 250 (26), 211 (100), 199 (17), 188 (16), 181 (16); HRMS: M$^+$− Bu^t, found 599.2798. $C_{39}H_{43}O_2Si_2$ requires 599.2800.

4.2.13. *N*-[Dimethyl(phenyl)silyl]-*N*-octyl-1-octanamine (2a). Colourless oil; yield: >99%; R_f 0.92 (hexane/ethyl acetate: 9:1); ν (film) 3069, 3055, 1590 (HC=C), 1255 (CN), 1119 cm^{-1} (SiN); δ_H 0.46 (6H, s, 2×MeSi), 0.88 (6H, t, J=6.7 Hz, 2×*Me*CH$_2$), 0.84–1.03, 1.06–1.11 [20H and 4H, respectively, 2m, 2×Me(C*H$_2$*)$_6$], 2.53 (4H, t, J= 7.4 Hz, 2×CH$_2$N), 7.29–7.42, 7.50–7.65 (3H and 2H, respectively, 2m, ArH); δ_C 0.1 (2C, 2×MeSi), 14.1 (2C, 2×*Me*CH$_2$), 22.6 (2C), 27.3 (2C), 29.2 (2C), 29.5 (2C), 29.8 (2C), 31.8 (2C) [2×Me(*C*H$_2$)$_6$], 49.8 (2C, 2×CN), 127.7 (2C), 129.3, 133.0 (2C), 139.0 (ArC); *m/z* (DIP) 346 (M$^+$−Et, 2%), 272 (16), 271 (63), 193 (38), 143 (17), 142 (100), 44 (32), 43 (31); HRMS: M$^+$−C_7H_{15}, found 276.2187. $C_{17}H_{30}NSi$ requires 276.2150.

4.2.14. 4-Benzyl-*N*-(triphenylsilyl)piperidine (2b). White solid; yield: 58%; R_f 0.87 (hexane/ethyl acetate: 9:1); mp 82 °C (hexane); ν (KBr) 3065, 3055, 3023, 1600 (HC=C), 1228 (CN), 1111 cm^{-1} (SiN); δ_H 0.92–1.23 (2H, m, 2× C*H*HCN), 1.49–1.71 (3H, m, 2×C*H*HCN and C*H*CH$_2$Ph), 2.32–2.57 (4H, m, C*H$_2$*Ph and 2×C*H*HN), 2.84–3.00 (2H, m, 2×C*H*HN), 7.05–7.54 (20H, ArH); δ_C 32.7 (2C, 2× *C*H$_2$CN), 38.0 (*C*HCH$_2$), 43.5 (*C*H$_2$Ph), 46.0 (2C, 2×CN), 125.8, 127.6 (6C), 127.7 (5C), 129.7 (2C), 135.1 (6C), 135.4 (3C), 140.3 (ArC); *m/z* (DIP) 433 (M$^+$, <1%), 260 (17), 259 (72), 257 (19), 250 (27), 211 (100), 190 (14), 188 (17), 181 (15); HRMS: M$^+$, found 433.2256. $C_{30}H_{31}NSi$ requires 433.2226.

4.2.15. *N*-Methyl-*N*-(triphenylsilyl)aniline (2c). White solid; yield: 95%; R_f 0.89 (hexane/ethyl acetate: 9:1); mp 112 °C (hexane); ν (KBr) 3067, 3047, 3024, 1589 (HC=C), 1274 (CN), 1117 cm^{-1} (SiN); δ_H 3.00 (3H, s, Me), 6.68–6.77, 6.84–6.92, 6.98–7.10, 7.30–7.44, 7.56–7.68 (1H, 2H, 2H, 9H and 6H, respectively, 5m, ArH); δ_C 37.1 (Me), 118.7 (2C), 118.8, 127.9 (6C), 128.2 (2C), 129.7 (3C), 134.3 (3C), 135.9 (6C), 150.3 (ArC); *m/z* 366 (M$^+$+1, 25%), 365 (M$^+$, 79), 260 (24), 259 (100), 181 (23), 105 (15); HRMS: M$^+$, found 365.1606. $C_{25}H_{23}NSi$ requires 365.1600.

4.2.16. Bis(2-methoxyethyl)(triphenylsilyl)amine (2d). Colourless oil; yield: 95%; R_f 0.80 (hexane/ethyl acetate: 9:1); ν (film) 3068, 3048, 1589 (HC=C), 1259 (CN), 1111 cm^{-1} (SiN); δ_H 3.10–3.22 (10H, m, 2×Me and 2× CH$_2$N), 3.33 (4H, t, J=6.9 Hz, 2×CH$_2$O), 7.31–7.46, 7.58–7.69 (9H and 6H, respectively, 2m, ArH); δ_C 47.6 (2C, 2×CN), 58.5 (2C, 2×Me), 72.7 (2C, 2×CH$_2$O), 127.7 (6C), 129.5 (3C), 135.1 (3C), 136.1 (6C) (ArC); *m/z* 391 (M$^+$, <1%), 347 (27), 346 (90), 260 (25), 259 (100), 181 (17); HRMS: M$^+$, found 391.1963. $C_{24}H_{29}NO_2Si$ requires 391.1968.

4.2.17. 1-(Triphenylsilylthio)decane (3a). White solid; yield: 69%; R_f 0.88 (hexane/ethyl acetate: 9:1); mp 41 °C (hexane); ν (KBr) 3065, 3051, 3022, 1587 cm^{-1} (HC=C); δ_H 0.74 (3H, t, J=6.9 Hz, Me), 1.05–1.56 [16H, m, Me(C*H$_2$*)$_8$], 2.43 (3H, t, J=6.3 Hz, CH$_2$S), 7.31–7.51, 7.59–7.75 (9H and 6H, respectively, 2m, ArH); δ_C 14.1 (Me), 22.7, 27.6, 28.5, 29.0, 29.3, 29.4, 29.5, 31.9, 32.3 (9× CH$_2$), 128.0 (6C), 130.0 (3C), 133.4 (3C), 135.7 (6C) (ArC);

m/z (DIP) 432 (M^+, 26%), 346 (12), 276 (17), 261 (14), 260 (62), 259 (100), 199 (35), 181 (17); HRMS: M^+, found 432.2304. $C_{28}H_{36}SSi$ requires 432.2307.

4.2.18. (Triphenylsilylthio)benzene (3c).[26] white solid; yield: 41%; R_f 0.82 (hexane/ethyl acetate: 9:1); mp 110 °C (hexane); ν (KBr) 3066, 3049, 3016, 1580 cm^{-1} (HC=C); δ_H 7.15–7.74 (20H, m, ArH); δ_C 126.8, 127.1 (2C), 127.4 (2C), 127.9 (6C), 128.5 (3C), 130.1 (3C), 135.1, 135.9 (6C) (ArC); *m/z* 368 (M^+, 25%), 260 (27), 259 (100), 181 (13).

4.3. Preparation of disilylated amino alcohol 1h

n-BuLi (6.3 mL of a 1.6 M solution of *n*-BuLi in hexane, 10.0 mmol) was dropwise added to a stirred solution of 6-(methylamino)-1-hexanol (656 mg, 5.0 mmol) in anhydrous THF (7 mL) at 0 °C. 5 min after the addition had been completed, a solution of triphenylsilyl chloride (2.832 g, 10.0 mmol) in the same solvent (7 mL) was added during ca. 5 min. After stirring for 1 h at the same temperature, the crude reaction mixture was adsorbed on basic aluminium oxide, transferred to a short column of basic aluminium oxide and eluted with hexane. Evaporation of the solvent (15 Torr) gave the pure disilylated amino alcohol **1h** in 53% yield. The corresponding physical, spectroscopic and analytical data follow.

4.3.1. *N*-Methyl-*N*-(triphenylsilyl)-6-(triphenylsilyloxy)-1-hexanamine (1h). White solid; yield: 53%; R_f 0.84 (hexane/ethyl acetate: 9:1); mp 74 °C (hexane); ν (KBr) 3064, 3044, 3022, 1587 (HC=C), 1259 (CN), 1182 (SiN), 1109 (SiO), 1027 cm^{-1} (CO); δ_H 0.81–0.92, 1.32–1.54 [6H and 2H, respectively, 2m, $(CH_2)_4CO$], 2.65 (3H, s, Me), 2.79 (2H, t, $J=7.4$ Hz, CH_2N), 3.70 (2H, t, $J=6.6$ Hz, CH_2O), 7.28–7.67 (30H, m, ArH); δ_C 26.1, 26.8, 28.9, 32.5 [$(CH_2)_4CO$], 36.2 (Me), 50.9 (CN), 63.9 (CO), 127.6 (6C), 127.8 (6C), 129.3 (3C), 129.9 (3C), 135.4 (6C), 135.6 (3C), 135.9 (6C), 136.4 (3C) (ArC); *m/z* 388 ($M^+ - Ph_3Si$, <1%), 277 (24), 276 (98), 261 (15), 260 (64), 259 (100), 257 (10), 238 (15), 199 (100), 198 (16), 197 (19), 183 (15), 182 (26), 181 (57), 180 (19), 155 (15), 152 (11), 122 (33), 105 (16), 77 (19), 42 (22); HRMS: $M^+ - Ph_3Si$, found 388.2096. $C_{25}H_{30}NOSi$ requires 388.2100.

4.4. Synthesis of silylated thiol 3b

$B(C_6F_5)_3$ (25 mg, 0.05 mmol) was added to a solution of cyclohexanethiol (0.63 mL, 5.0 mmol) and triphenylsilyl chloride (1.342 g, 5.0 mmol) in CH_2Cl_2 (10 mL) under Ar at 20 °C and the reaction was stirred for four days at the same temperature.[27] The crude reaction mixture was adsorbed on basic aluminium oxide, transferred to a short column of basic aluminium oxide and eluted with hexane. Evaporation of the solvent (15 Torr) gave the pure silylated thiol **3b** in 52% yield. The corresponding physical, spectroscopic and analytical data follow.

4.4.1. (Triphenylsilylthio)cyclohexane (3b). White solid; yield: 52%; R_f 0.88 (hexane/ethyl acetate: 9:1); mp 103 °C (hexane); ν (KBr) 3066, 3048, 3011, 1588 cm^{-1} (HC=C); δ_H 0.96–1.85 (10H, m, $5\times CH_2$), 2.59–2.74 (1H, m, CH), 7.31–7.53, 7.59–7.76 (9H and 6H, respectively, 2m, ArH); δ_C 25.3, 26.1 (2C), 37.1 (2C) ($5\times CH_2$), 41.6 (CS), 127.9 (6C), 130.0 (3C), 135.2 (3C), 135.7 (6C) (ArC); *m/z* 375 ($M^+ + 1$, 18%), 374 (M^+, 60), 261 (18), 260 (81), 259 (100), 261 (18), 215 (19), 214 (10), 181 (24), 152 (12), 137 (15), 77 (12); HRMS: M^+, found 374.1516. $C_{24}H_{26}SSi$ requires 374.1524.

4.5. Naphthalene-catalysed lithiation of silylated compounds 1–3. Preparation of products 4–6. General procedure

A solution of the silylated substrate **1–3** (1.0 mmol) in THF (2 mL) was dropwise added to a green suspension of lithium powder (63 mg, 9.0 mmol) and naphthalene (20 mg, 0.16 mmol) in THF (5 mL), under Ar, at 0 °C. After stirring at the same temperature for the time indicated in Table 1, methanol (5 mL) was carefully added the cooling bath was removed and the reaction was stirred till it reached room temperature. The yields of the desilylated compounds were determined by quantitative GLC using commercially available alcohols **4**, amines **5**, thiols **6**, *n*-dodecane (internal standard) and *n*-hexadecane (internal standard for **1h**) in the determination of response factors. Compounds **4a**, **4b**, **4d–4f** and **4h–6** (commercially available) were characterised by comparison of their physical and spectroscopic data with authentic samples.

Compound **1f** was deprotonated with *n*-BuLi (0.69 mL of a 1.6 M solution in hexane, 1.1 mmol) at 0 °C before submitting it to the reductive cleavage step.

All reactions whose products were isolated (see Table 1) were hydrolysed with water (5 mL) instead of methanol. The mixture was extracted with ethyl acetate (3×15 mL) and the combined organic phases were washed with brine (5 mL), being then dried over sodium sulfate. After evaporation of the solvents (15 Torr), the resulting residue was purified by column chromatography (silica gel, hexane/ethyl acetate), affording the expected products in the yields indicated in Table 1. Compound **4c** (commercially available) was characterised by comparison of its physical and spectroscopic data with an authentic sample. The corresponding physical, spectroscopic and analytical data for compound **4g** follow.

4.5.1. 9-[*tert*-Butyl(diphenyl)silyloxy]-1-nonanol (4g). Colourless oil; yield: 63%; R_f 0.30 (hexane/ethyl acetate: 8:2); ν (film) 3316 (OH), 3069, 3049, 1596 (HC=C), 1113 (SiO), 1094 cm^{-1} (CO); δ_H 1.04 (9H, s, $3\times$Me), 1.12–1.40, 1.46–1.78 [10H and 5H, respectively, 2m, $(CH_2)_7CO$ and OH], 3.59–3.69 (4H, m, $2\times CH_2O$), 7.29–7.49, 7.57–7.72 (6H and 4H, respectively, 2m, ArH); δ_C 19.2 (CMe$_3$), 26.8 (3C, $3\times$Me), 25.7, 25.75, 29.3, 29.35, 29.5, 32.5, 32.8 [$(CH_2)_7CO$], 63.1, 64.0 ($2\times$CO), 127.5 (4C), 127.9 (2C), 135.0 (2C), 135.6 (4C) (ArC); *m/z* (DIP) 383 ($M^+ - Me$, 24%), 241 (43), 227 (31), 200 (19), 199 (100), 197 (11), 183 (19), 181 (32), 139 (23), 135 (12), 83 (13), 69 (20), 55(11); HRMS: $M^+ - Bu^t$, found 341.1919. $C_{21}H_{29}O_2Si$ requires 341.1940.

4.6. Determination of the optical purity of product (*R*)-4c

To determine the optical purity of product (*R*)-**4c**, it was reacted with optically pure (*R*)-α-methoxyphenylacetic acid following a previously described experimental procedure.[28] The ^{13}C NMR spectrum of the crude product obtained after work-up showed the same signals as the ester prepared from the same acid and commercially available (*R*)-2-octanol. No racemization was observed in any case by comparison of the ^{13}C NMR spectra of those esters with the spectrum of the ester that was prepared by the same method from racemic 2-octanol.[29] The absolute configuration of (*R*)-**4c** was determined by comparison of the sign of its optical rotation {$[\alpha]_D^{20}$ -8.8 ± 0.3 (*c* 1, $CHCl_3$) for the crude product} with the one of commercially available (*R*)-2-octanol {$[\alpha]_D^{20}$ -9.7 ± 0.3 (*c* 1, $CHCl_3$)}. The corresponding physical, spectroscopic and analytical data for the *O*-methylmandelate obtained from (*R*)-**4c**, as well as the ^{13}C NMR data for the *O*-methylmandelate prepared from racemic 2-octanol, follow.

4.6.1. (1*R*)-1-Methylheptyl (2*R*)-2-methoxy-2-phenylacetate. Colourless oil; yield: 95%; R_f 0.40 (hexane); $[\alpha]_D^{20}$ -21.5 ± 0.5 (*c* 1, $CHCl_3$); ν (film) 3071, 3032, 1494 (HC=C), 1747 (C=O), 1116 cm^{-1} (CO); δ_H 0.83 (3H, t, J=7.1 Hz, *Me*CH_2), 0.85–1.52 (10H, m, 5×CH_2), 1.22 (3H, d, J=6.2 Hz, *Me*CH), 3.41 (3H, s, MeO), 4.72 (1H, s, CHCO), 4.86–5.00 (1H, m, CHO), 7.22–7.63 (5H, m, ArH); δ_C 13.9 (*Me*CH_2), 20.0 (*Me*CO), 22.3, 24.8, 28.7, 31.5, 35.6 (5×CH_2), 57.1 (MeO), 71.9 (Me*C*O), 82.6 (*C*HPh), 127.1 (2C), 128.4 (2C), 128.5, 136.4 (ArH), 170.3 (C=O); *m/z* 278 (M^+, <1%), 121 (100); HRMS: M^+, found 278.1928. $C_{17}H_{26}O_3$ requires 278.1882.

4.6.2. (1*R)-1-Methylheptyl (2*R*)-2-methoxy-2-phenylacetate.** δ_C 13.9, 14.05 (2×*Me*CH_2), 19.6, 20.0 (2×*Me*CO), 22.3, 22.5, 24.8, 25.2, 28.7, 28.9, 31.5, 31.6, 35.6, 35.7 (10×CH_2), 57.1, 57.2 (2×MeO), 71.9, 72.1 (2×Me*C*O), 82.6, 82.7 (2×*C*HPh), 127.0 (2C), 127.1 (2C), 128.4 (4C), 128.5, 128.6, 136.4, 136.5 (ArH), 170.3 (2×C=O).

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