ELSEVIER

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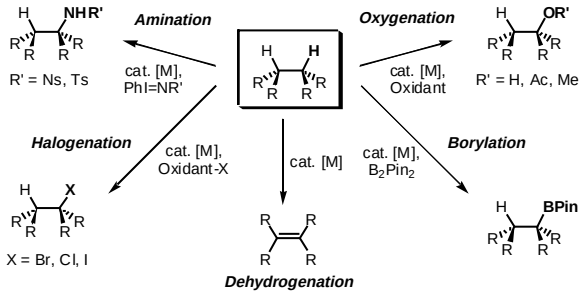
Contents

REPORT



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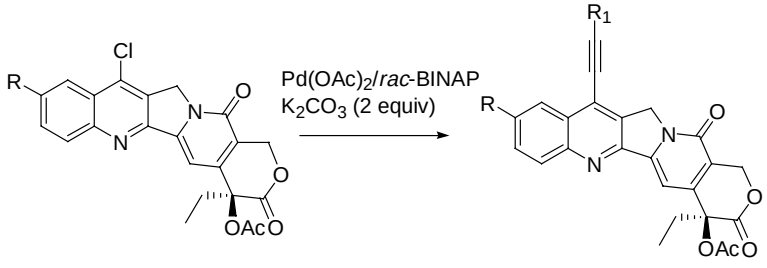
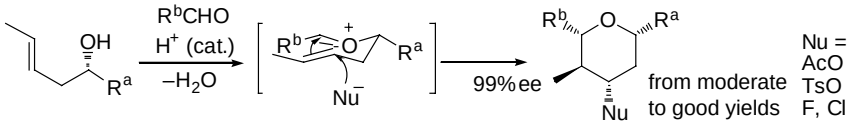
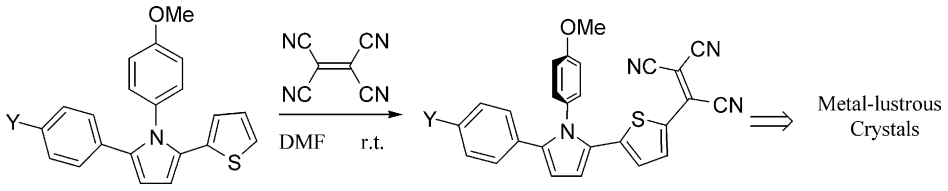
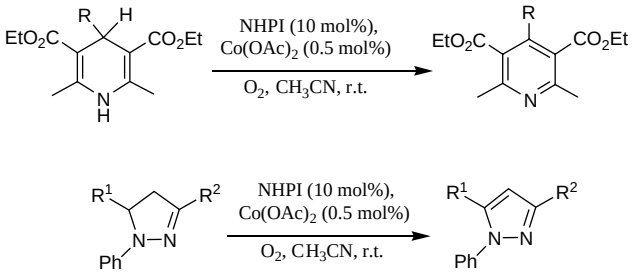
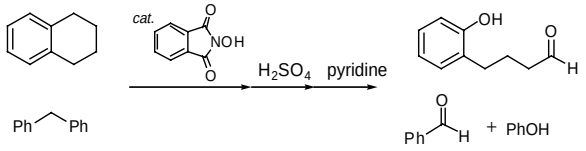
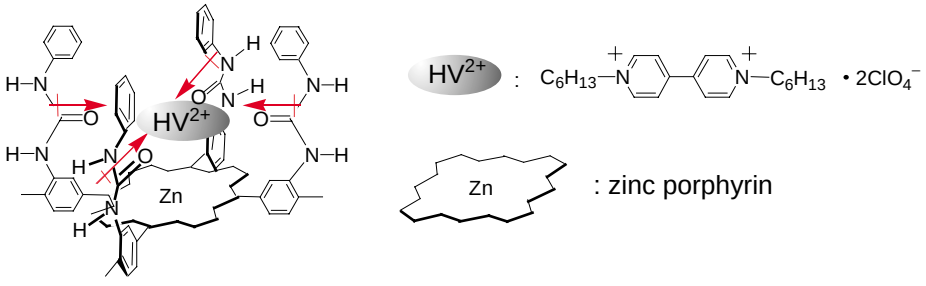


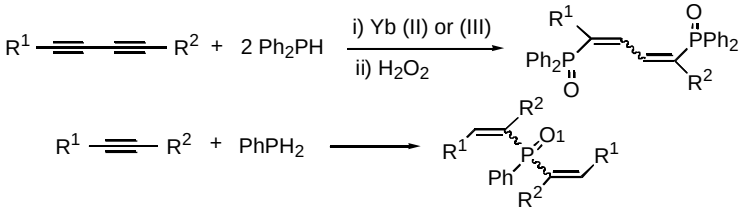


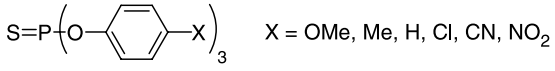




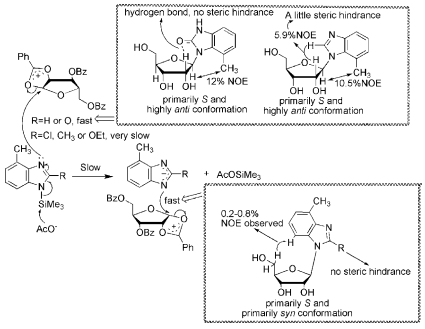


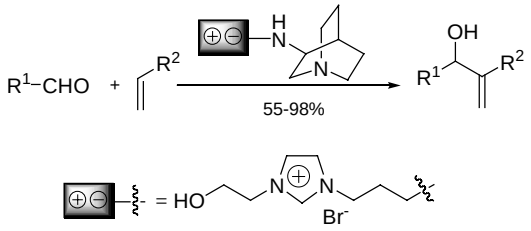


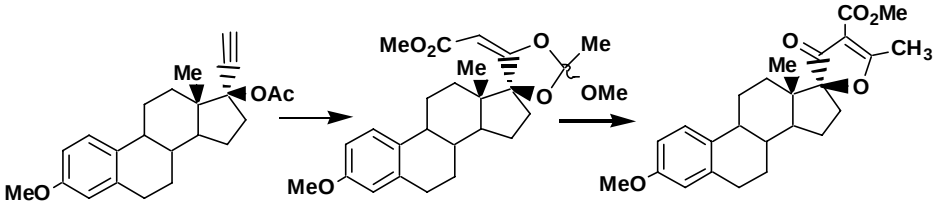


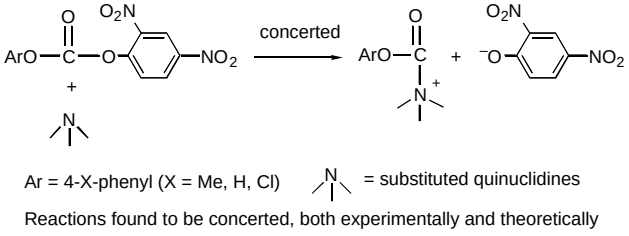


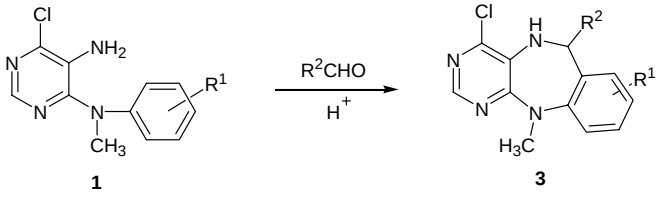
The substituent effects on the ^{31}P NMR chemical shifts of a series of six arylphosphorothionates [S=P(OAr)$_3$] are analyzed in terms of the changes observed in the geometries of the compounds by experimental and theoretical methods.











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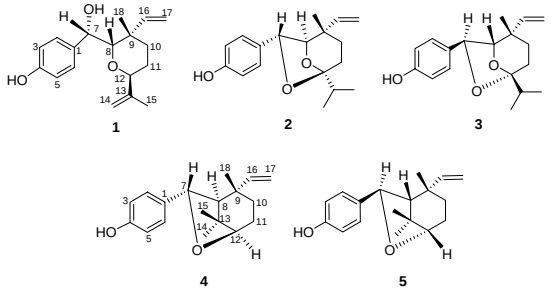

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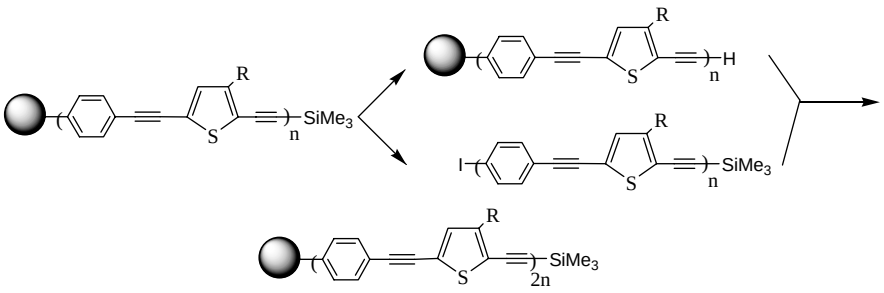
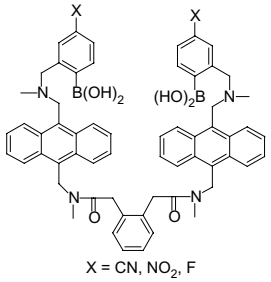
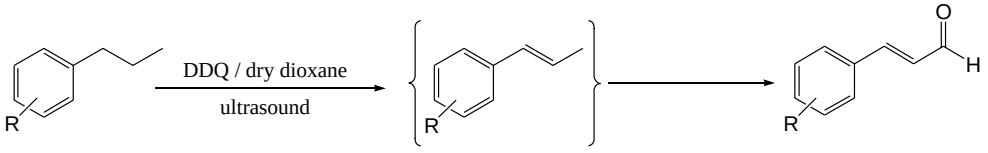
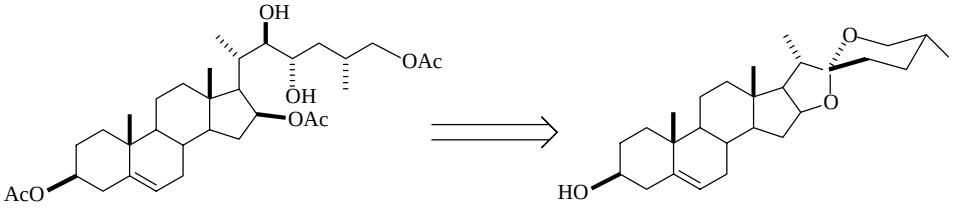
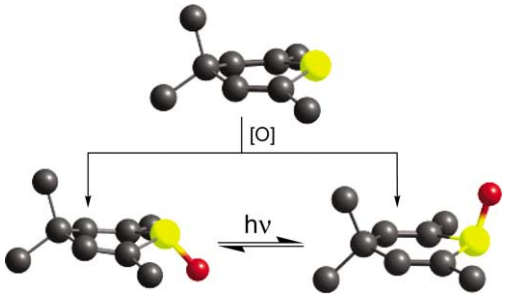


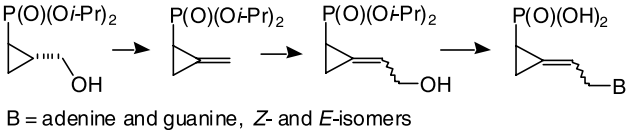


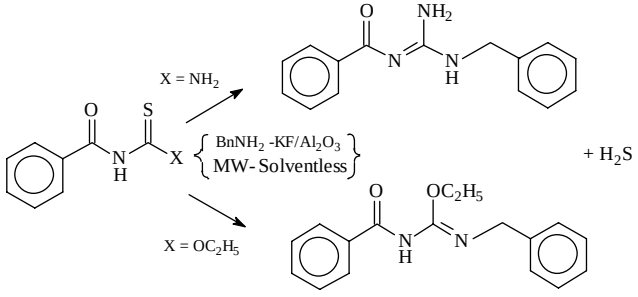


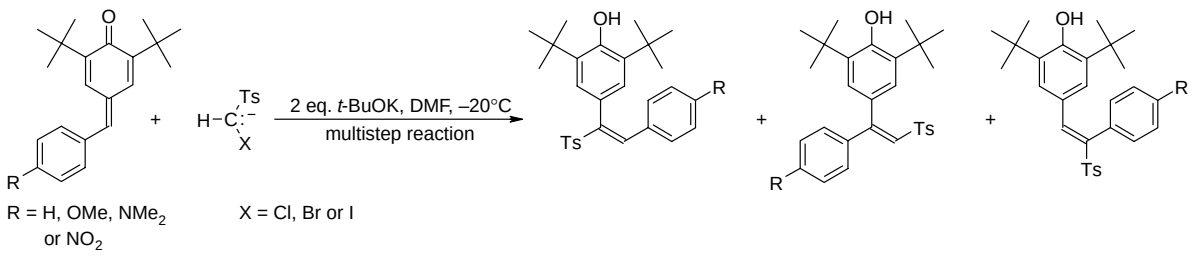
Where
R = OMe, OEt, -OCH_2O-, OH etc.

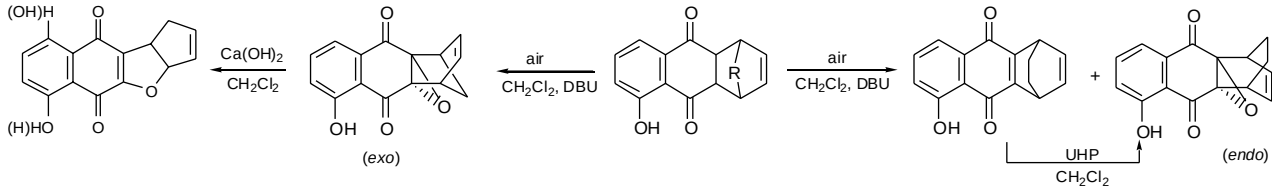




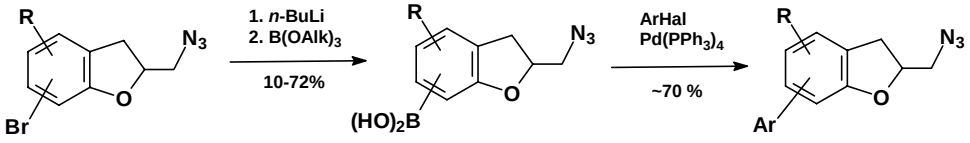


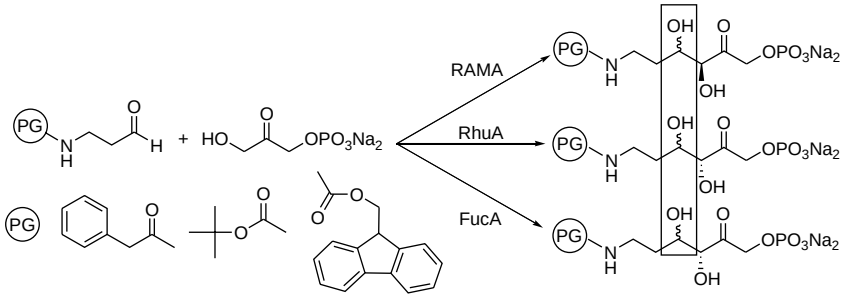


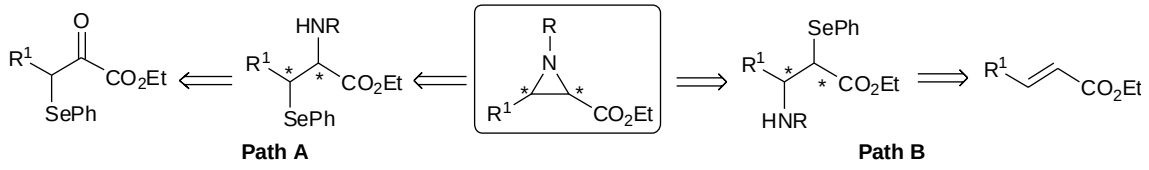


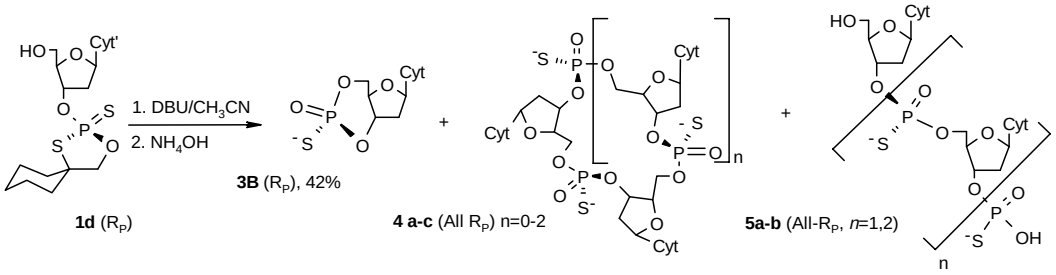


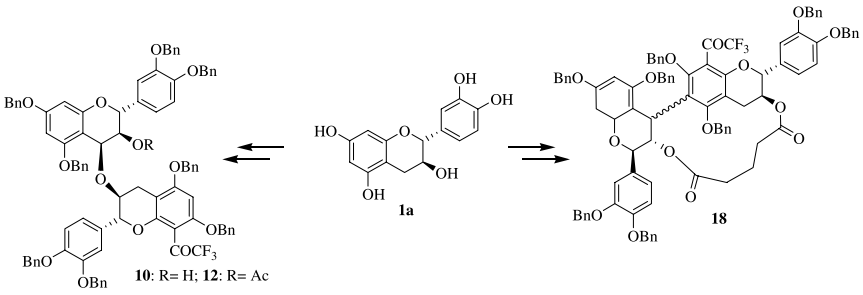
Aerobic oxidation of Diels–Alder adducts of naphthoquinones and thiophene-analogues in dichloromethane–DBU provides access to quinone epoxides. Isomerization of anthraquinone epoxides with calcium hydroxide yielded cytotoxic angular quinones.

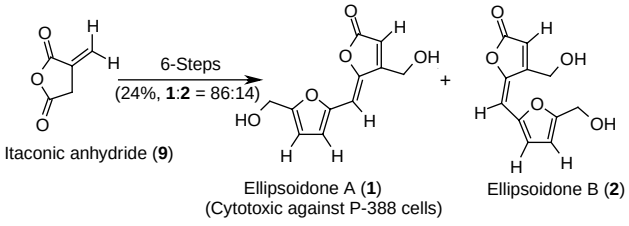


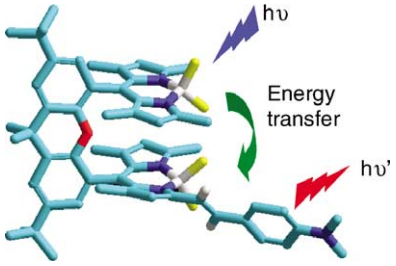












*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

COVER

Recent advances in the transition metal-catalyzed oxidation of alkane and arene C–H bonds are reviewed, with an emphasis on applications in organic synthesis. An elegant application of this chemistry involved Du Bois' total synthesis of tetrodotoxin, which is pictured in the background of this graphic. *Tetrahedron* **2005**, *62*, 2439–2463.

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Transition metal catalyzed oxidative functionalization of carbon–hydrogen bonds

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1. Introduction

The development of mild, general, and selective transition metal catalyzed methods for the functionalization of carbon–hydrogen bonds represents a significant current challenge in organic chemistry. Although this field is currently in its infancy, such transformations have the potential to fundamentally change retrosynthetic approaches to complex molecule synthesis. In addition, they could serve as powerful tools for the rapid and direct synthesis of diverse functionalized products for structure–activity relationship (SAR) studies in medicinal and materials chemistry.

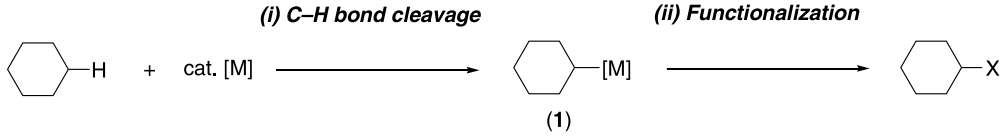
The vast majority of transition metal catalyzed C–H activation/functionalization reactions of complex organic molecules have focused on the transformation of C–H bonds into C–C bonds. These powerful methods have found recent application in the elegant syntheses of a variety of biologically active molecules[1–9] and have been the subject of numerous review articles.[10–18] In contrast, metal catalyzed C–H activation/oxidation reactions—which allow the selective installation of valuable functional groups such as carbon–oxygen, carbon–halogen, carbon–nitrogen, or carbon–boron bonds—have been less thoroughly reviewed in the literature. The latter transformations are the subject of the current article, which will focus on the background, recent exciting progress, and the potential for future developments in this area.

2. General mechanisms for transition metal catalyzed C–H bond functionalization

A variety of transition metal catalysts have been developed for the oxidative functionalization of carbon–hydrogen bonds to produce alcohol, amine, alkyl/aryl halide, and alkyl/aryl borane products. Although all of these catalysts promote the same general transformations (C–H→C–X), they can operate within two very different mechanistic manifolds. These two mechanisms, which are referred to as 'inner-sphere' and 'outer-sphere' throughout this review, are described in detail below. Notably, alternative terminology, introduced by Crabtree, labels these mechanisms 'organometallic' and 'coordination,' respectively.[19]

2.1. Inner-sphere mechanism

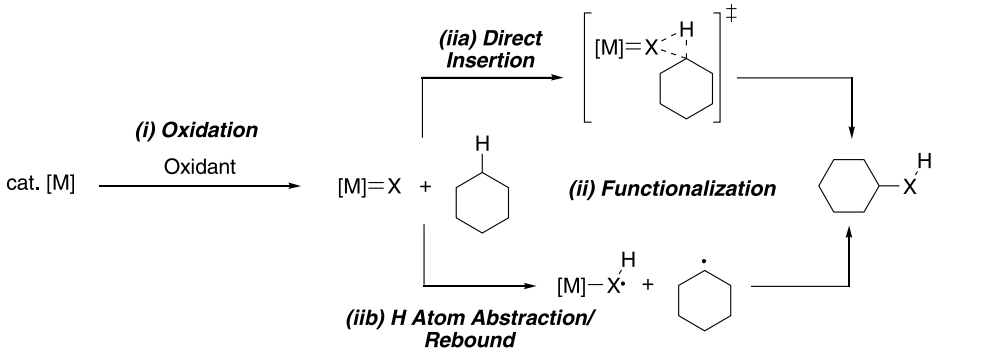
The 'inner-sphere' C–H bond functionalization mechanism involves two discrete steps: (i) cleavage of a carbon–hydrogen bond to afford a transition metal alkyl/aryl species (**1**) and (ii) functionalization of **1** by reaction with either an external reagent or at the metal center (Eq. 1). The key distinguishing feature of this mechanism is the formation of a discrete organometallic intermediate (**1**), and the structural and electronic requirements of this intermediate dictate the regio- and stereoselectivity of functionalization. These transformations often proceed with high selectivity for the less sterically hindered C–H bonds of a molecule; however, other factors, including the ligand environment at the metal center and the mechanism of the C–H bond cleavage step, can also influence selectivity in these systems.



(1)

2.2. Outer-sphere mechanism

The 'outer-sphere' mechanism for C–H bond functionalization mimics biological oxidation reactions catalyzed by enzymes such as cytochrome P450 and methane monooxygenase (MMO). These processes proceed via (i) formation of a high oxidation state metal complex containing an activated ligand X (typically a metal oxo-, imido- or carbene species) followed by (ii) reaction of ligand X with a C–H bond (Eq. 2). This latter step can proceed by either direct insertion (Eq. 2, iia) or H-atom abstraction/radical rebound (Eq. 2, iib). The key distinguishing feature of the outer-sphere mechanism is that the alkane/arene substrate does not interact directly with the transition metal center but instead reacts with a coordinated ligand. As shown in Eq. 2, these transformations involve build up of radical and/or cationic character at carbon, and therefore typically show high selectivity for weaker C–H bonds (e.g., those that are benzylic, allylic, 3°, or α to heteroatoms).



(2)

It is also important to note that there are a number of non-transition metal catalyzed reactions for the oxidative functionalization of carbon–hydrogen bonds.[20–22] These include electrophilic aromatic substitution, directed *ortho*-lithiation/electrophilic addition,[23] reactions of dioxiranes,[24–26] and free radical halogenation, hydroxylation, and/or amination.[20,21] Many of these reactions are widely used in synthetic organic chemistry, and often exhibit complementary levels of reactivity, functional group tolerance, and selectivity to the transition metal catalyzed reactions discussed throughout this review.

3. General challenges for transition metal catalyzed C–H bond functionalization

The four major challenges associated with the catalytic oxidative functionalization of C–H bonds within the context of complex organic molecules are (a) reactivity, (b) chemoselectivity, (c) regioselectivity, and (d) stereoselectivity. A short description of each challenge along with general strategies that have been used to address it is detailed below.

3.1. Reactivity

The strength of typical carbon–hydrogen bonds (which have bond dissociation energies between 85 and 105 kcal/mol) presents a first and very significant challenge in this area. While most oxidation reactions are thermodynamically downhill, there is generally a large kinetic barrier associated with the C–H bond cleavage event required prior to/during functionalization. As described throughout this review, transition metal catalysts serve to increase the rates of reactions of C–H bonds by many orders of magnitude.

3.2. Chemoselectivity

The ability to stop functionalization at the required oxidation state represents a second major challenge, as the over-oxidation of functionalized products is often highly thermodynamically downhill. A number of strategies have been used to address this important issue, including: (i) running reactions to low conversion, (ii) utilizing large excesses of substrate relative to oxidant, (iii) carrying out intra- rather than intermolecular functionalization reactions, (iv) kinetically blocking over-oxidation through the installation of deactivating functional groups, and (v) catalyst design and selection.

3.3. Regioselectivity

Most organic molecules contain many different types of carbon–hydrogen bonds; therefore, developing transformations that regioselectively functionalize a single C–H bond within a complex structure remains a third critical challenge in this field. A number of approaches have been used to address this problem, including: (i) the use of substrates containing weaker or activated C–H bonds (e.g., 3° or benzylic/allylic systems), (ii) the use of coordinating ligands within a substrate as directing groups, (iii) carrying out intramolecular functionalization reactions via favorable five- or six-membered transition states, (iv) the use of supramolecular chemistry to position a specific C–H bond near the catalyst active site, and (v) the use of the transition metal catalysts/ligands to control selectivity.

3.4. Stereoselectivity

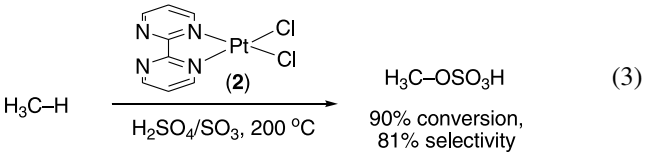
The functionalization of carbon–hydrogen bonds to generate new stereogenic centers in a highly diastereoselective and/or enantioselective fashion represents a fourth challenge in this field. While this issue has been the least well explored to date, both substrate-based approaches (involving the use of substrates containing pre-installed stereocenters or chiral auxiliaries) as well as catalyst-based approaches (involving the use of chiral transition metal complexes to control the enantioselectivity of functionalization) have been developed. Notably, the stereospecific oxidative functionalization of C–H bonds at existing stereocenters represents another attractive method for the construction of chiral molecules, and has also found a number of applications.

4. C–H bond oxygenation

The direct oxygenation of carbon–hydrogen bonds represents a powerful approach to alcohol products, which find widespread application as synthetic intermediates and as products in the commodity chemical, fine chemical, and pharmaceutical industries. As outlined below, efforts to develop methods for metal catalyzed C–H bond oxygenation have focused on both the inner-sphere and outer-sphere mechanisms.

4.1. Inner-sphere catalysts

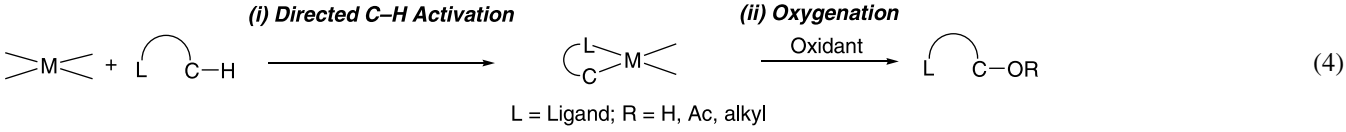
Applications of inner-sphere catalysts in C–H bond oxygenation have primarily focused on the transformation of methane to methanol, a process of great potential utility for the conversion of natural gas into a more readily transportable liquid fuel. A variety of catalysts (including Pt,[27] Pd,[28,29] and Au[30] complexes) and terminal oxidants (such as K_2PtCl_6,[27] $K_2S_2O_8$,[29] $CuCl_2$,[28] and O_2[31]) have been used, and the area has been extensively reviewed.[19,32–37] Platinum complex **2** is the most efficient and selective homogeneous catalyst reported to date, and converts CH_4 to CH_3OSO_3H in 90% conversion with 81% selectivity, with SO_3 as the terminal oxidant (Eq. 3).[38] The excellent chemoselectivity is due to the installation of an electron-withdrawing sulfonic acid group, which deactivates the product toward further oxidation. However, the high temperature (200 °C) and acidic medium (concentrated H_2SO_4) render this system untenable for the selective oxygenation of more complex organic molecules. Efforts to apply related Pt catalysts to the oxygenation of *n*-alkanes and simple substituted hydrocarbons have resulted in low TON's and only modest levels of regio- and chemoselectivity.[39–42]



(3)

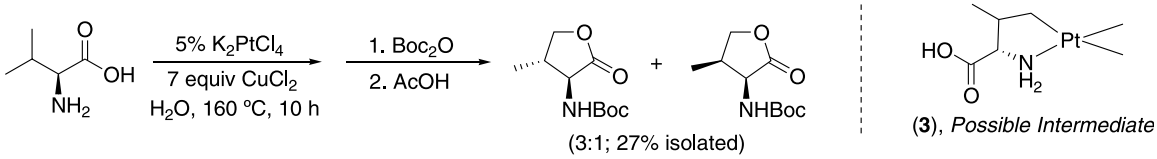
Homogeneous catalysts that operate under far milder conditions have been developed for the oxygenation of benzene C–H bonds.[43,44] In particular, palladium-based catalysts (typically $Pd(OAc)_2$) in conjunction with a variety of oxidants (for example, O_2/polyoxometallates,[45,46] dichromate,[47] peroxydisulfate,[48] and $PhI(OAc)_2$[49]) have been utilized for the transformation of benzene to phenol or an ester derivative at moderate temperatures (~100 °C) in acetic acid. However, the application of these transformations to substituted aromatic compounds (e.g., toluene, anisole, or naphthalene) generally results in the formation of undesirable mixtures of regioisomeric products.[49]

Several strategies have been successfully used to achieve regioselective C–H bond oxygenation via the inner-sphere mechanism. One approach involves the use of substrates containing coordinating functional groups, which can bind to the catalyst and direct C–H activation and subsequent functionalization to a specific C–H bond within the molecule (Eq. 4).[10,50–52]



(4)

Early work demonstrated the viability of this strategy in the K_2PtCl_4-catalyzed oxygenation of propionic acid with Pt^{IV} as a stoichiometric oxidant. While this transformation proceeded with <3 turnovers, it showed good regioselectivity for the β-position, which was rationalized based the formation of a chelated intermediate.[53,54] A related Pt-catalyzed method (using 5 mol% K_2PtCl_4 and 7 equiv $CuCl_2$ as a stoichiometric oxidant at 160 °C) has been used for the β-oxygenation of several amino acid derivatives (Eq. 5).[55] For example, valine underwent β-oxygenation with excellent regioselectivity and moderate diastereoselectivity (*anti*/*syn*=3:1), presumably due to the formation of metalacyclic intermediate **3**.[55]



(5)

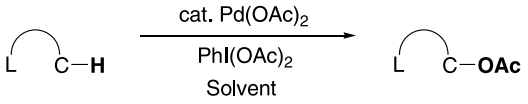
More recently, $Pd(OAc)_2$ has been used as the catalyst for ligand-directed C–H bond acetoxylation using $PhI(OAc)_2$ as a stoichiometric oxidant.[56–58] These Pd-catalyzed reactions typically proceed under significantly milder conditions (≤100 °C), with higher TON (often ≥50), and with broader substrate scope than those with Pt catalysts. As summarized in Table 1, a wide variety of directing groups, including pyridine, azo, amide, imine, oxime ether, and pyrazole derivatives, can be utilized, and this methodology is efficient for the regioselective oxygenation of both arene (sp^2) and alkane (sp^3) C–H bonds. Significantly, the oxidation of 3-methyl-2-pentanone *O*-methyl oxime (entry 8), which contains six different types of C–H bonds, selectively affords a single product in good (76%) yield. The observed selectivity for C–H activation/oxygenation at the less sterically encumbered 1° C–H bond relative to the 2° C–H bond in this substrate is a hallmark of the inner-sphere mechanism. Interestingly, C–H bonds can also be replaced with ether functionality (OR) through the use of alcohol-based solvents in these transformations (e.g., see entry 7).[58a,b] Notably, these reactions are believed to proceed via a $Pd^{II/IV}$ mechanism in which the key bond-forming step involves C–O reductive elimination from unusual Pd^{IV} intermediates.[49,58c]

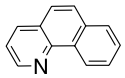
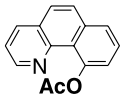
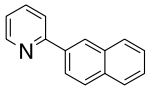
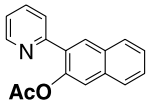
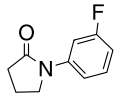
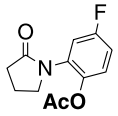
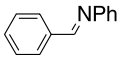
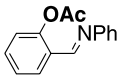
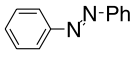
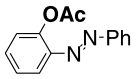
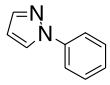
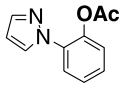
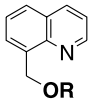
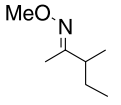
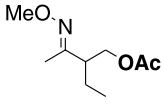
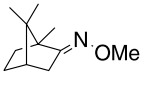
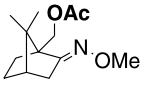
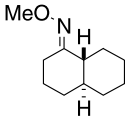
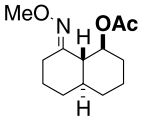
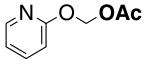
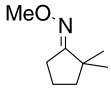
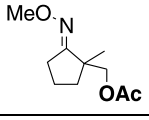
A second successful approach to regioselective C–H bond oxygenation with inner-sphere catalysts has involved the use of activated allylic substrates. Palladium trifluoroacetate has been shown to stoichiometrically cleave weak allylic C–H bonds to produce Pd-allyl intermediates,[59] and catalytic oxygenation of these species can be achieved in acetic acid using benzoquinone (BQ), duroquinone (DQ), or MnO_2 as a terminal oxidant.[60,61] Pd-catalyzed allylic acetoxylation has been applied to a variety of cyclic and acyclic substrates; furthermore, subtle modification of reaction conditions can be used to control the regioselectivity of oxygenation, providing efficient routes to both linear and branched allylic acetate products (Table 2, entries 3 and 4).[62,63] This methodology has been applied to the efficient construction of early intermediates in the syntheses of isoretronecanol and miyakolide (Table 2, entries 5 and 6, respectively).[64] Interestingly, when *tert*-butylhydroperoxide is used as a stoichiometric oxidant in related reactions, a peroxy moiety can be incorporated at the allylic position.[65]

4.2. Outer-sphere catalysts

The outer-sphere approach to C–H bond hydroxylation has been the subject of numerous reviews;[19,66–71] therefore, this section aims to summarize general features and the synthetic scope of these reactions, rather than providing a comprehensive treatment. The most active and most widely used outer-sphere catalysts are Mn, Fe, or Ru porphyrins of general structure **4** containing electron-withdrawing

Table 1. $Pd(OAc)_2$-catalyzed oxygenation of C–H bonds with $PhI(OAc)_2$



Entry	Starting material	Major product	Yield (%)
1[a]			86
2[a]			72
3[b]			88
4[a]			47
5[a]			62
6[a]			54
7[a]			R=Ac; 88, R=Me; 77[c]
8[d]			78
9[d]			75
10[d]			81
11[d]			66
12[d]			61

[a] Ref.58a.
[b] Ref.56.
[c] Reaction conducted in MeOH.
[d] Ref.57.

substituents (e.g., Ar=C_6F_5, C_6Cl_5, or 2,6-$C_6H_3Cl_2$; X=H, F, Cl, Br; Fig. 1).[72] These catalysts are utilized in conjunction with a stoichiometric oxidant (most commonly PhI=O, pyridine *N*-oxide, or peroxides), and their activity is often enhanced by the addition of an axial ligand such as imidazole.[73] Hydroxylation reactions catalyzed by **4** have been applied to a variety of substrates (Fig. 1) and typically show high selectivity for weak benzylic or 3° C–H bonds. The current limitations of this methodology from the perspective of a synthetic chemist are (i) the general requirement for large excesses of substrate relative to oxidant, (ii) modest levels of chemoselectivity (over-oxidation to ketones is a common side reaction), (iii) the general requirement for an 'activated' C–H bond within the molecule, (iv) modest levels of regioselectivity in substrates containing multiple weak C–H bonds, and (v) the inherent difficulties associated with synthesis and modification of porphyrin ligands.

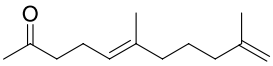
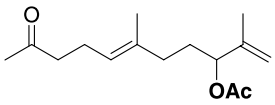
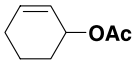
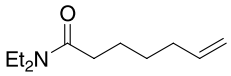
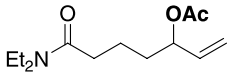
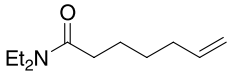
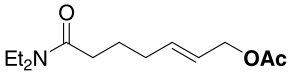
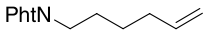
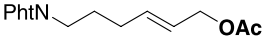
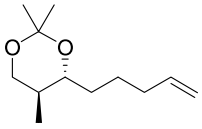
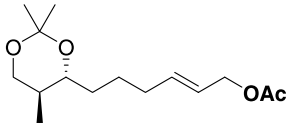
Recent work has made progress toward addressing a number of these limitations; for example, **4** (with M=Ru(CO), Ar = C_6F_5 or C_6H_5; X=H) has been shown to be a highly active catalyst for alkane hydroxylation without the requirement for large excesses of substrate relative to oxidant.[74,75] In these systems, a 1:1 ratio of alkane substrate (which can include adamantane, cyclohexane, methylcyclohexane, or decalin) to stoichiometric oxidant (2,6-dichloropyridine *N*-oxide) provides hydroxylated products in good yield (generally 70–90%) at low temperature (25–60 °C) with TON up to 120,000.

Significant recent efforts have also aimed to control the regioselectivity of oxygenation in substrates containing multiple C–H bonds of similar strengths. These methods typically rely on either substrate shape[76] or supramolecular interactions between catalyst and substrate[77–80] to geometrically bias oxygenation to a specific C–H bond. For example, cyclodextrin-substituted porphyrin **5** was used to orient steroid substrate **6**, facilitating highly regioselective hydroxylation at C_6, even in the presence of more activated 3° and benzylic C–H bonds (Fig. 2).[77] Interestingly, this transformation also proceeds with high levels of chemoselectivity (no ketone products were observed) and diastereoselectivity (only the equatorial C_6–H bond was hydroxylated) due to the strict geometric requirements of the catalyst active site (Fig. 2).

The enantioselective hydroxylation of alkanes using chiral metalloporphyrins and related outer-sphere catalysts has also been explored. Pioneering work by Groves demonstrated the asymmetric oxygenation of ethylbenzene and indan derivatives in 40–72% ee using a vaulted binaphthyl linked Fe porphyrin catalyst (**7**) (Fig. 3).[81,82] More recently, chiral Mn salen catalyst **8**[83] and chiral Ru porphyrin **9**[84] have been used to achieve slightly higher %ee values (generally ranging from 65–90%) for benzylic oxidations of a series of similar substrates (Table 3). The yields and substrate scope of all of these transformations remain modest, but they represent important precedent for the asymmetric oxygenation of hydrocarbon substrates.

Non-heme outer-sphere catalysts for alkane hydroxylation have also been developed, with Cr-[85,86] and Fe-based[87–91] complexes being the most common. These typically show comparable substrate scope and regioselectivity to the porphyrin systems (Fig. 1), but are often less robust.[92] Notably, the mechanism of hydroxylation reactions catalyzed by non-heme outer-sphere catalysts remains the subject of debate,[87,88,90,91,93–95] and some are likely to

Table 2. Palladium-catalyzed allylic oxygenation reactions

Entry	Conditions	Starting material	Major product	Yield (%) (linear: branched)
1[a]	5% $Pd(TFA)_2$, 20% PPh_3 1 equiv DQ, AcOH			31 (1:22)
2[b]	0.5% $Pd(OAc)_2$ 10% BQ, 1 equiv MnO_2, AcOH			77
3[c]	20% $Pd(OAc)_2$, 20% VS 2 equiv BQ, 4 equiv AcOH in dioxane			56 (1:18)
4[d]	10% $Pd(OAc)_2$, 10% VS 2 equiv BQ, 4 Å MS, 1:1 DMSO:AcOH			62 (23:1)
5[e]	10% $Pd(OAc)_2$, 2 equiv BQ, 4 Å MS 1:1.4 DMSO:AcOH			71 (17:1)
6[e]	10% $Pd(OAc)_2$, 2 equiv BQ, 4 Å MS 1:1.4 DMSO:AcOH			53 (19:1)

Abbreviations: DQ=duroquinone; BQ=benzoquinone; VS=vinylsulfoxide.
[a] Ref.61.
[b] Ref.60.
[c] Ref.62.
[d] Ref.63.
[e] Ref.64.

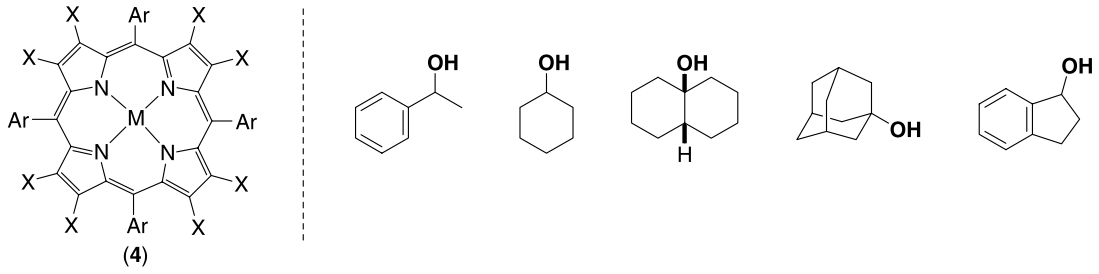


Figure 1. Porphyrin-based coordination catalyst **4** and representative alcohol products from C–H bond oxygenation reactions.

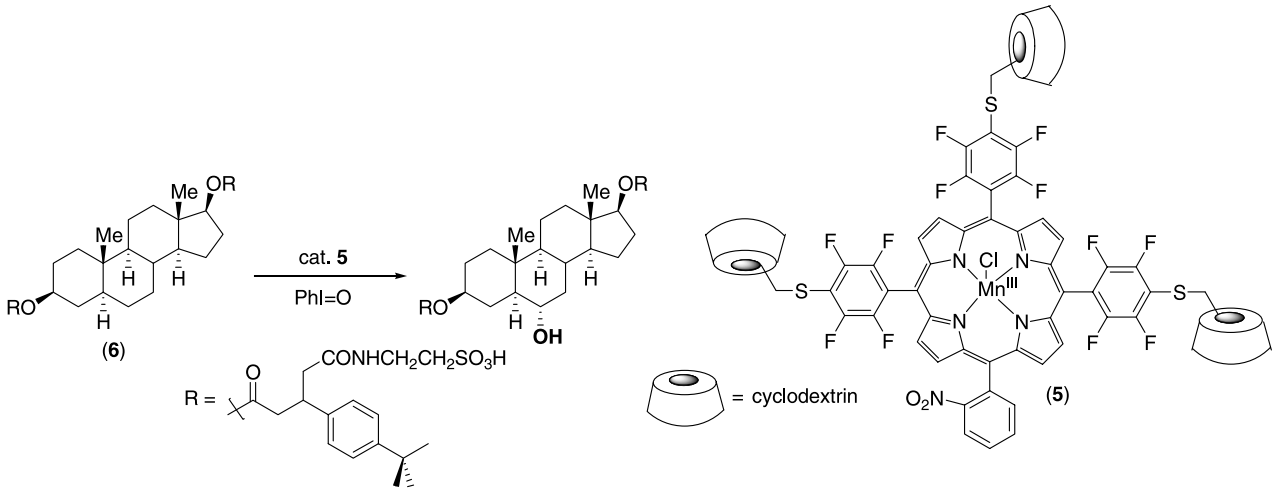


Figure 2. Regioselective oxidation with cyclodextrin substituted porphyrin **5**.

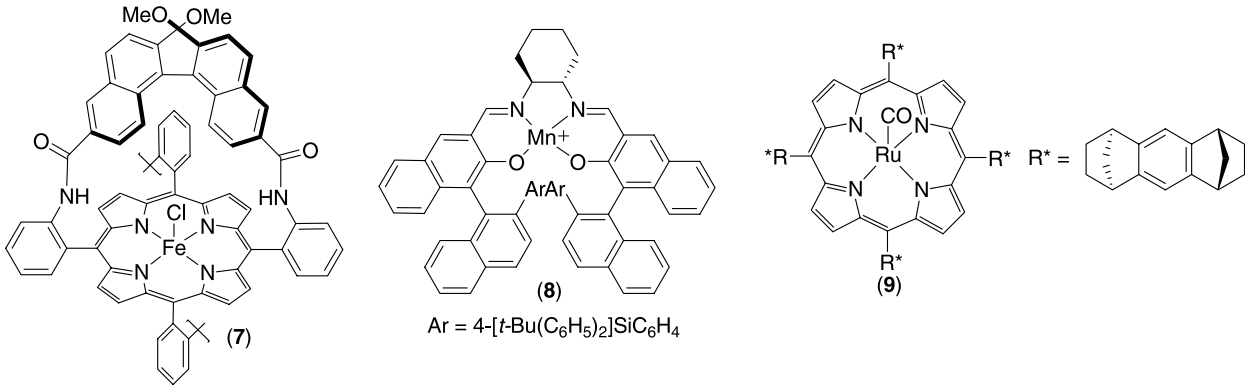
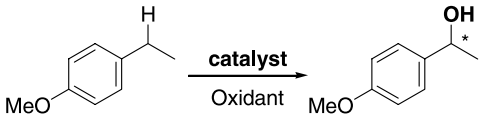


Figure 3. Chiral catalysts for asymmetric C–H bond hydroxylation.

Table 3. Asymmetric hydroxylation of *p*-methoxyethylbenzene



Catalyst	Oxidant	Yield (%)	ee (%)
7[a]	Ph-I=O	20	66 (*R*)
8[b]	Ph-I=O	13	87 (*R*)
9[c]	Cl_2pyNO	65[d]	62 (*S*)

[a] Ref. 81.
[b] Ref. 83.
[c] Ref. 84.
[d] Yield at 15% conversion.

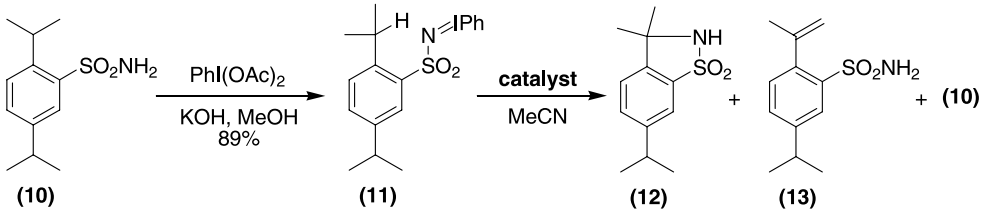
involve transition metal catalyzed generation of HO· followed by H-atom abstraction/propagation rather than a true outer-sphere mechanism.

In summary, significant progress has been made in the development of both inner-sphere and outer-sphere catalysts for the selective oxygenation of alkane and arene C–H bonds. In many cases, these two classes of catalysts exhibit highly complementary selectivities, and both have been used in a variety of synthetic applications. Future work in this area will likely include the application of these methods in the context of biologically active targets, the development and refinement of asymmetric catalysts for these transformations, and the continued pursuit of active transition metal catalysts for non-directed oxygenation of unactivated C–H bonds.

5. C–H bond amination

Amines are ubiquitous functional groups in organic synthesis and serve as critical components of a large number of biologically active molecules. Typical methods for the introduction of amino groups involve nucleophilic displacement, catalytic amination of aryl or vinyl halides,[96] nitration of an aromatic group followed by reduction, or addition of a nucleophile to an imine. These methods offer the disadvantages that they require pre-installation of reactive functional groups and often proceed under relatively harsh conditions. As such, methodology that allowed the regioselective formation of C–N bonds directly from carbon–hydrogen bonds would be of great potential synthetic utility.

In a seminal experiment in 1982, Breslow and Gellman reported the use of Mn or Fe porphyrin catalysts for the amination of cyclohexane using PhI=NTs as a stoichiometric oxidant.[97] While this reaction proceeded in low (~7%) yield, subsequent work demonstrated that intramolecular variants of this transformation are far more efficient.[98] For example, treatment of tosylamine **10** with $PhI(OAc)_2$/KOH in MeOH (which forms iodonium ylide **11** in situ) followed by the addition of a catalyst results in clean intramolecular C–H bond amination to afford **12** (Eq. 6). A survey of metal catalysts revealed that $Rh_2(OAc)_4$ is particularly effective, producing **12** in 86% yield. This key transformation demonstrated the first uses of both the oxidant ($PhI(OAc)_2$) and catalyst system (rhodium carboxylates) that have subsequently been widely applied in C–H bond amination reactions. Importantly, these transformations (and the related reactions described herein) are generally believed to proceed via the outer-sphere mechanism,[99] involving reactive metal–nitrene or metal–imido intermediates.[100–110]



(6)

Subsequent to this important work, a number of groups have recognized the potential synthetic utility of this transformation and have begun to develop its scope. In addition, such oxidative amination products have been observed as major side-products in catalytic aziridination reactions.[111–113] Due to heightened interest in this methodology, several reviews have recently appeared,[114–116] often in conjunction with their aziridination counterparts.[117,118]

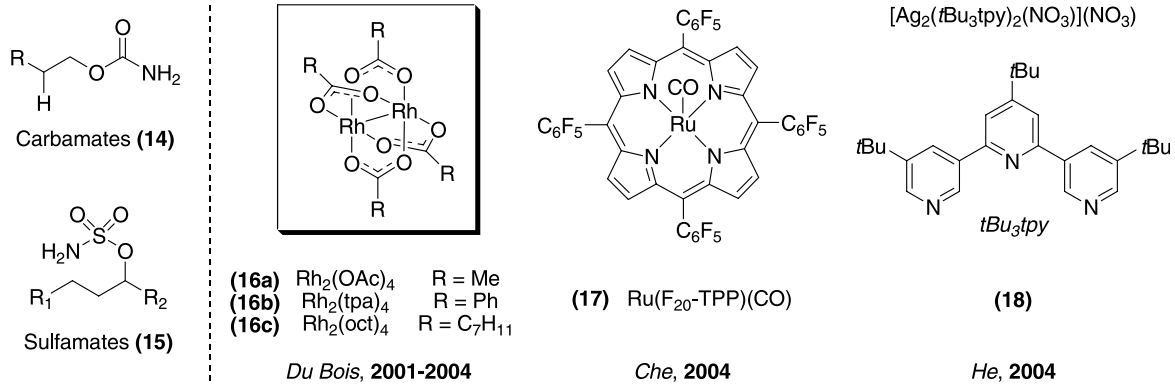


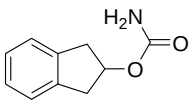
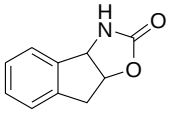
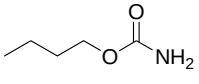
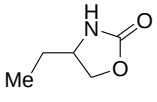
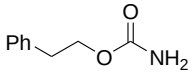
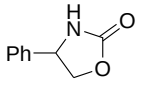
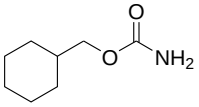
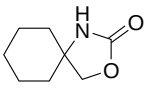
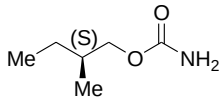
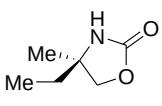
Figure 4. Common substrate classes and catalysts for intramolecular C–H amination.

5.1. Intramolecular C–H amination

The most synthetically useful recent developments in this field have involved intramolecular C–H insertion reactions. Early studies by Espino and Du Bois focused on carbamate-based substrates of general structure **14** (Fig. 4), which are readily synthesized from primary alcohols by treatment with $Cl_3CC(O)NCO$ followed by K_2CO_3/MeOH.[119] These substrates undergo facile $Rh_2(OAc)_4$-catalyzed intramolecular C–H bond amination to produce oxazolidinones in a mild one-pot procedure (5 mol% catalyst, 1.4 equiv $PhI(OAc)_2$, 2.3 equiv MgO, 40 °C, 12 h).

As summarized in Table 4, this methodology allows the intramolecular amination of a wide variety of 2°, 3° and benzylic C–H bonds to afford diverse 1,2 aminooxygenated products. Importantly, reactions of the chiral substrate shown in entry 5 proceed with complete retention of stereochemistry at the asymmetric carbon center, thereby providing a potential route to synthetically valuable α,α-disubstituted alkyl amines and quaternary α-amino acids. More recent work has demonstrated that other catalysts, including **16b**[119] and **18**[120] (Fig. 4) are also very effective for these transformations under only slightly more vigorous conditions (Table 4).

Table 4. Synthesis of oxazolidinones via intramolecular C–H amination

Entry	Substrate	Product	Catalyst	Yield (%)
1			**16a**	86
			18	89
2			**16b**	44
			18	58
3			**16b**	74
			18	81
4			**16a**	77
			16b	79
			18	85
5			**16**	nd
			18	73

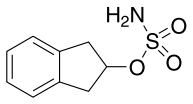
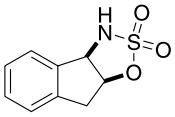
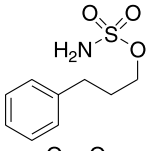
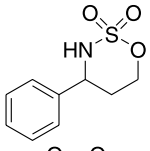
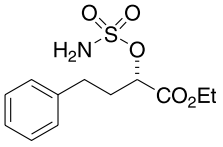
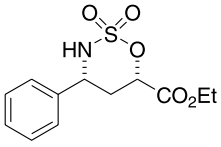
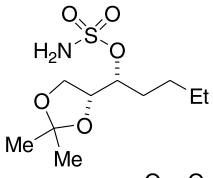
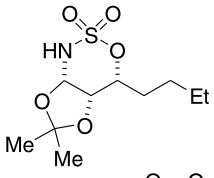
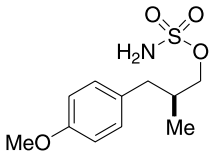
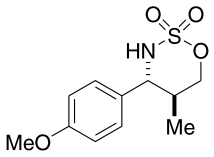
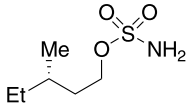
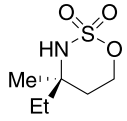
Reaction conditions: for catalysts **16a** and **16b**: 5% catalyst, 1.4 equiv $PhI(OAc)_2$, 2.3 equiv MgO, CH_2Cl_2, 40 °C, 12 h. (Ref. 119); for catalyst **18**: 4% $AgNO_3$, 4% tBu$_3$tpy, 2.0 equiv $PhI(OAc)_2$, MeCN, 82 °C (Ref. 120).

Sulfamate esters, which are readily available via condensation of $ClSO_2NH_2$ with primary and secondary alcohols, are also useful precursors for intramolecular C–H bond amination reactions.[120–125] Seminal early work by Du Bois and co-workers demonstrated that these substrates undergo intramolecular nitrogen insertion into 2°, 3° and benzylic C–H bonds[125] as well as α to oxygen substituents[121,123] under mild conditions (2–5% catalyst **16a** or **16c**, 1.1 equiv $PhI(OAc)_2$, 2.3 equiv MgO, CH_2Cl_2). Interestingly, the sulfamates show a strong preference for cyclization to form six-membered rings, in striking contrast to their carbamate counterparts. This allows access to synthetically useful 1,3-aminooxygenated products (Table 5). Notably, more recent work has demonstrated that **17**[122] and **18**[120] are also effective catalysts for cyclizations to afford these oxathiazinane products (Table 5, entries 1 and 2).

Like the carbamate cyclization reactions, sulfamate C–H insertion reactions proceed stereospecifically; for example, the $Rh_2(OAc)_4$-catalyzed cyclization of the chiral substrate shown in Table 5, entry 6 affords the product as a single enantiomer. In addition, these transformations proceed with high levels of diastereocontrol (typically >10:1) in substrates with both α-branching (Table 5, entries 1, 3 and 4) and β-branching (Table 5, entries 4 and 5). The diastereoselectivity of cyclization has been rationalized based on a chair-like transition state in which the metallonitrene inserts into an equatorial C–H bond.[124]

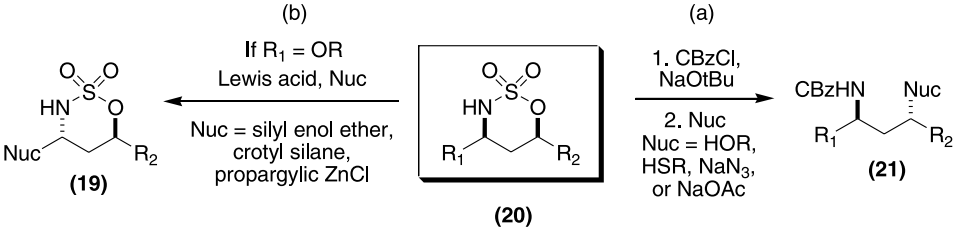
These cyclic oxathiazinane products are extremely synthetically useful intermediates, and a simple sequence of (a) *N*-CBz protection followed by (b) addition of an N-, O-, or S-based nucleophile (e.g., amines, thiols, alcohols, H_2O, N_3^-, AcO^-) results in nucleophilic ring opening to afford diverse 1,3-amino functionalized products (Eq. 7, a).[125] In addition, the N,O acetal products generated from C–N insertion α to oxygen serve as valuable precursors to iminium ions (via treatment with Lewis acids), which can then undergo highly

Table 5. Intramolecular amination of sulfamate esters

Entry	Substrate	Product	Catalyst	Yield (%)
1			**16a**[a] **17**[b] **18**[c]	60 66 65
2			**17**[b] **18**[c]	77 87
3			**16c**[d]	91 (dr=15:1)
4			**16b**[e]	91
5			**16c**[d]	85 (dr=20:1)
6			**16a**[a]	91

[a] Ref.125.
[b] Ref.126.
[c] Ref.120.
[d] Ref.124.
[e] Ref.123.

diastereoselective couplings with alkynyl zinc reagents,[123] allyl silanes,[121] and silyl enol ethers[121] (Eq. 7, b).



(7)

Very recent efforts have focused on the development of asymmetric catalysts for both carbamate and sulfamate cyclization reactions, and chiral Ru porphyrin **22**,[126] Rh dimer **23**,[127] and Mn salen complex **24**[128] have all been examined for these transformations (Fig. 5). The results obtained with these catalysts are typified by the reactions of substrate **25** shown in Table 6. In general, the Ru catalyst is the most selective, affording cyclized products in 70–86% ee, while the more readily accessible **24** provides moderate 23–71% ee for similar cyclizations. The Rh catalyst **23** gave poor results for sulfamate ester **25** (with a maximum of 30% ee); however, up to 66% ee was obtained with **23** using aliphatic sulfonamide-based substrates. In general, this problem is far from solved, and future work will aim to prepare more readily accessible catalysts that display increasing selectivity, higher reactivity, and greater substrate scope for these asymmetric transformations.

5.2. Intermolecular C–H amination

Intermolecular transition metal catalyzed C–H amination reactions are inherently more challenging, and they have been investigated far more extensively than their intramolecular analogues. A wide variety of catalysts have been developed for these transformations, including rhodium,[106–108,129,130] copper,[104,131–133] manganese,[100,103,109,110,134–136] and ruthenium[100–103,105,136–138] complexes (Fig. 6).

Despite significant work in this area, the scope of intermolecular C–H amination reactions generally remains limited to the functionalization of highly activated 2° benzylic or allylic C–H bonds to form

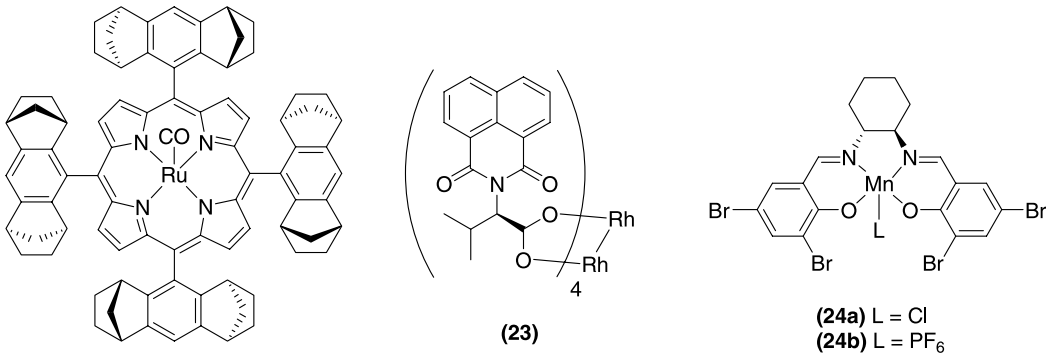
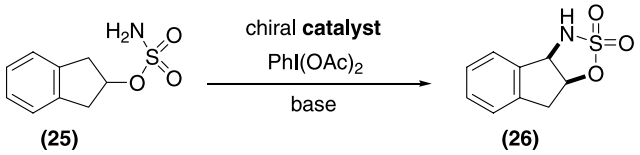


Figure 5. Chiral catalysts for intramolecular C–H amination.

Table 6. Asymmetric intramolecular C–H amination



Catalyst	Yield (%)	ee (%)
22[a]	53	81
23[b]	52	30
24a[c]	48	52

[a] Ref.126.
[b] Ref.127.
[c] Ref.128.

products such as those shown in Figure 7. In addition, the majority of current intermolecular amination reactions require large excesses of substrate (typically 5- to 5000-fold) relative to oxidant to achieve reasonable yields. These features clearly limit the broad utility of this methodology, and, as such, recent efforts in the area have focused on addressing these challenges.

An important recent advance was made by Che and co-workers, who reported that porphyrin catalyst **29** (with M=Mn and R=C_6F_5) is highly active for intermolecular alkane amination with PhI=NTs as a stoichiometric oxidant.[136] With this catalyst system, the amination of indan proceeds with TON's up to 2600; furthermore, a diverse set of activated substrates, including adamantane, tetrahydrofuran, *trans*-3-hexene, ethylbenzene and cyclohexene, are aminated efficiently without the requirement for an excess of organic substrate relative to oxidant.

Peréz and co-workers have developed a copper based catalyst **27** (Fig. 6) that has significantly expanded the substrate scope of C–H bond amination reactions. For example, **27** efficiently catalyzes the amination of 1° benzylic C–H bonds of toluene and mesitylene, unactivated 2° C–H bonds of cyclohexane,

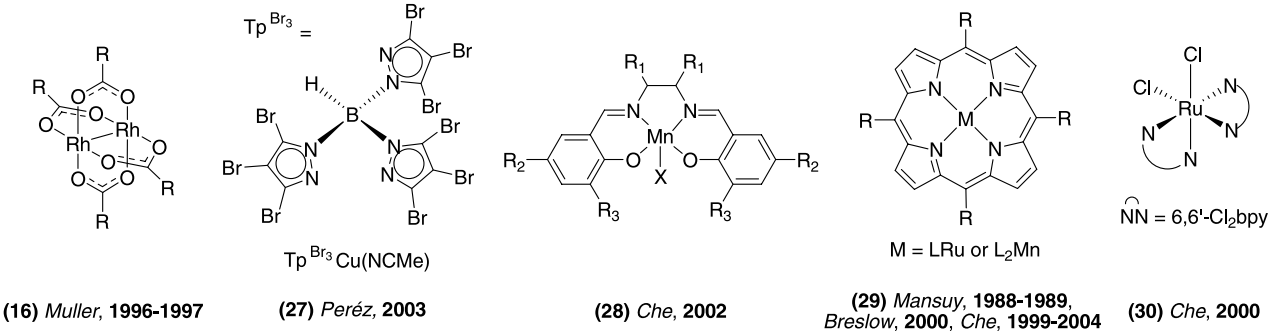


Figure 6. Catalysts for intermolecular C–H amination.

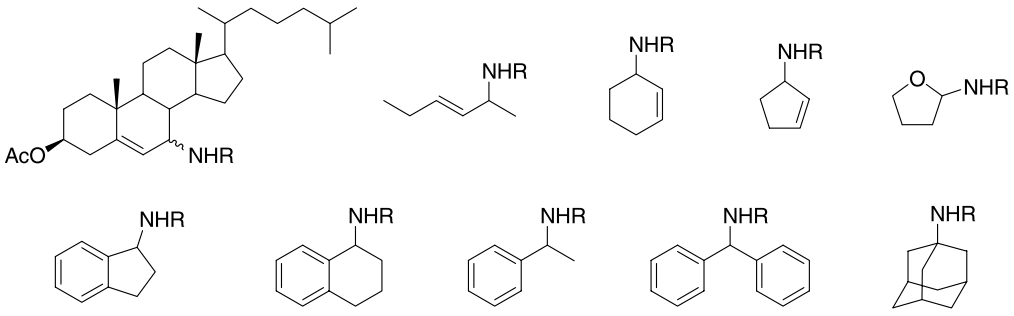


Figure 7. Typical products of intermolecular C–H amination (R=Ns or Ts).

and aromatic C–H bonds of benzene (Fig. 8).[132] The notable limitation of this system is that large excesses of substrate relative to stoichiometric oxidant (PhI=NTs) are required in order to achieve good yields.

Another class of substrates that has been recently explored for intermolecular C–H bond amination is aromatic heterocycles (Fig. 8). Che and co-workers have demonstrated that the amination of furan, pyrrole, and thiophene derivatives can occur in good yields at 40 °C with catalyst **29** (M=Ru-CO, R=*p*-$C_6H_4CH_3$, Fig. 6).[137] Again, however, a 10-fold excess of substrate relative to oxidant is required for optimal conversions. Notably, these transformations could proceed via either direct nitrene insertion into the activated C–H bond, or by initial aziridination followed by rearomatization, and further studies are required to distinguish these two mechanistic pathways.

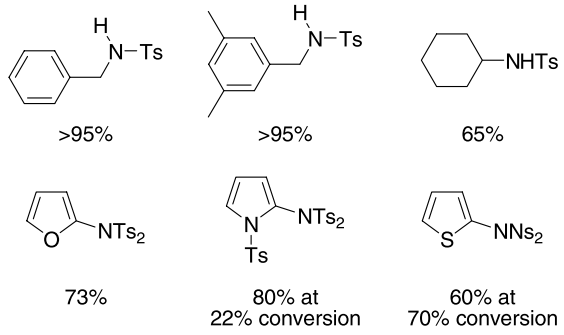
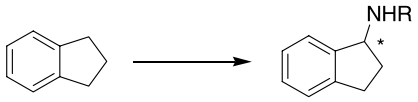


Figure 8. Expansion of substrate scope by Peréz and Che.

Very recent efforts by Du Bois and co-workers have made progress in addressing both the challenges of substrate scope and stoichiometry through the systematic design of a new Rh catalyst–$Rh_2(esp)_2$[139] (Fig. 9). The high stability of the catalyst incorporating the esp ligand (**31**) allows the intermolecular amination of *p*-methoxyethylbezene and cyclooctane with $H_2NSO_3CH_2CCl_3$/$PhI(OAc)_2$ to afford good yields (71 and 84% respectively) of **32** and **33** using ≤5-fold excess of substrate relative to oxidant.

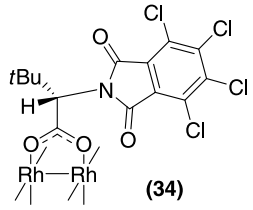
Significant efforts have also focused on the development of asymmetric catalysts for intermolecular C–H amination reactions, and Table 7 highlights the best results obtained

Table 7. Asymmetric intermolecular C–H amination



Entry	Catalyst	R	Yield (%)	ee (%)
1[a]	**22**	Ts	47	31 (*S*)
2[b]	**24b**	Ts	63	66 (*S*)
3[c]	**34**	Ns	82	70 (*R*)

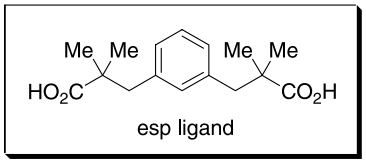
[a] Ref.103.
[b] Ref.134.
[c] Ref.130.



with catalysts **22**, **24b** (Fig. 5), and **34** in the amination of indan.[100,103,134] The chiral Rh dimer **34** is generally the best catalyst developed thus far for these transformations (providing 19–84% ee for a variety of substrates); however, further advancements will be necessary to render this methodology competitive with more mature asymmetric transformations.

5.3. Intramolecular C–H amination in natural product synthesis

Perhaps the greatest test of any synthetic methodology is its ability to be applied to the construction of highly complex molecules—in particular natural products. Although general methods for intramolecular C–H bond amination are relatively new, they have already found application in the preparation of a variety of natural product targets. The simplest example involves the synthesis of the glycon of L-vancosamine derivatives.[140] In the key transformation, carbamate **35** was converted to oxazolidinone **36** in 86% yield with $PhI(OAc)_2$ and 10% $Rh_2(OAc)_4$ (Eq. 8). This fragment can then be elaborated to many derivatives of vancosamine, which is a key component of the potent antibiotic vancomycin.



(31)

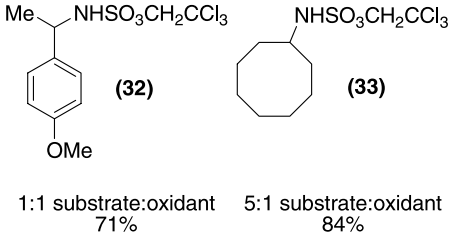
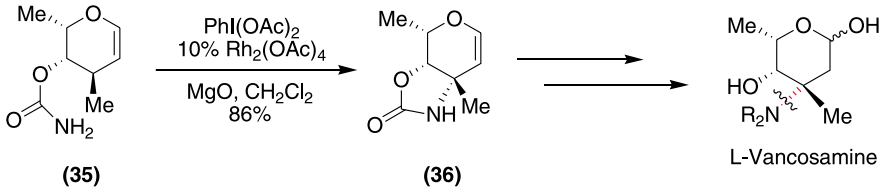


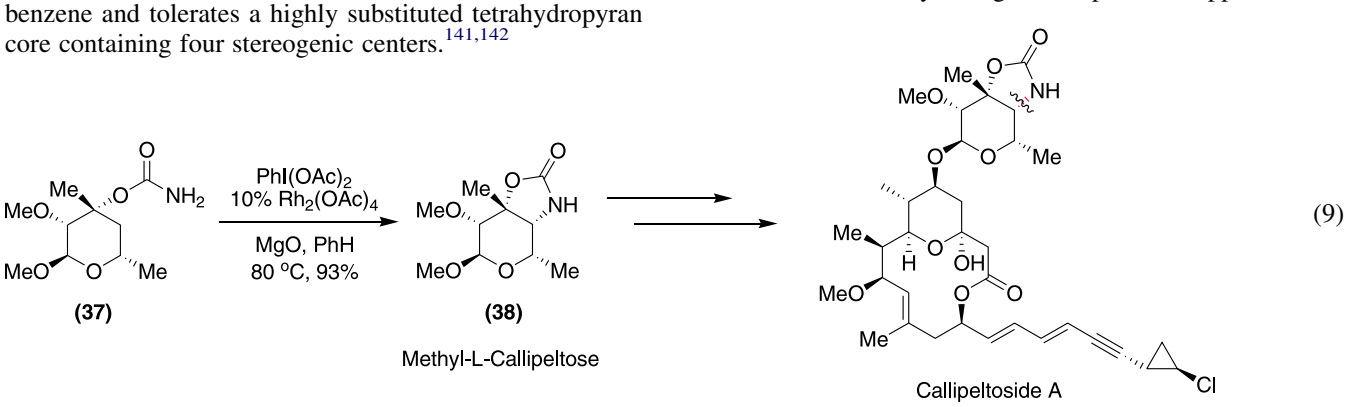
Figure 9. Expansion of substrate scope with $Rh_2(esp)_2$.



(35) (36)

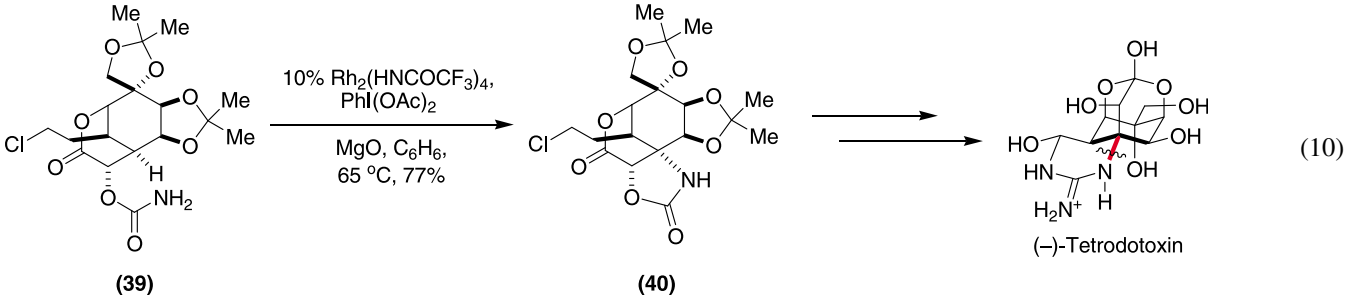
(8)

A carbamate C–H bond amination reaction has also been applied to the synthesis of methyl-L-callipeltose, a fragment of the antitumor natural product callipeltoside A. As summarized in Eq. 9, this transformation proceeds in good yield with $PhI(OAc)_2$ and 10% $Rh_2(OAc)_2$ in refluxing benzene and tolerates a highly substituted tetrahydropyran core containing four stereogenic centers.[141,142]



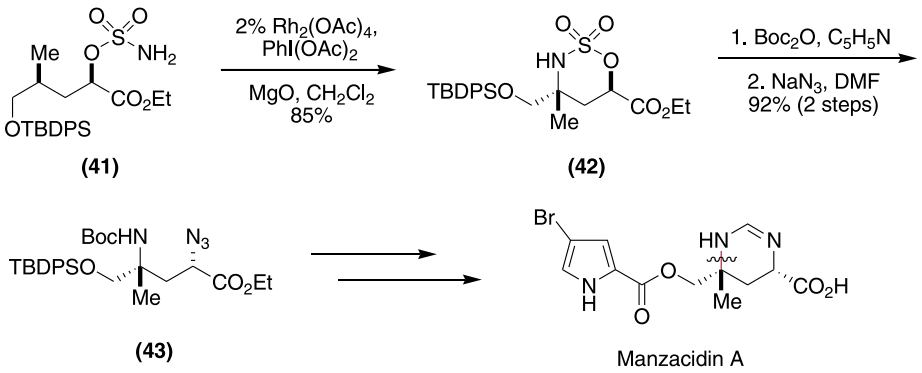
(9)

Intramolecular oxazolidinone formation was also utilized at a late stage in the synthesis of the guanidinium poison (−)-tetrodotoxin.[143] In the key step, Hinman and DuBois converted intermediate **39** to **40** in 77% yield using $PhI(OAc)_2$ and 10% $Rh_2(HNCOCF_3)_4$ in benzene (Eq. 10). This transformation is particularly remarkable because of the structural complexity of the substrate.



(10)

Finally, sulfamate esters were used for intramolecular amination in the synthesis of the bromopyrrole alkaloids manzacidins A and C.[144] Intermediate **41** was smoothly converted to **42** in 85% yield with $PhI(OAc)_2$ and only 2% $Rh_2(OAc)_4$ (Eq. 11), ultimately leading to manzacidin A. Manzacidin C was prepared in an identical manner from a different stereoisomer of the starting material. This is an elegant example of the versatility of oxathiazinane rings for elaboration to 1,3-difunctionalized products via a simple nucleophilic ring-opening event.

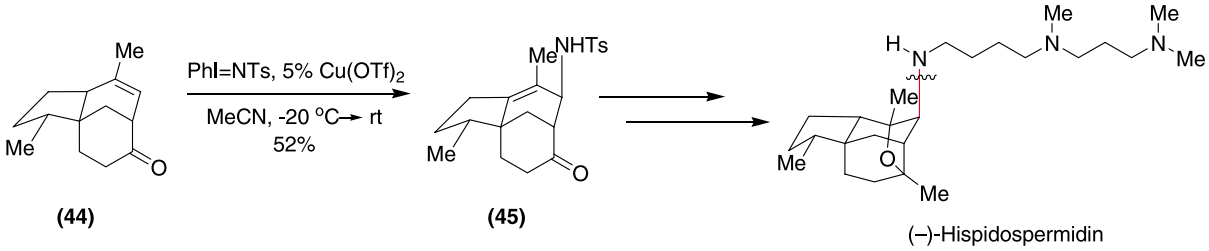


(11)

5.4. Intermolecular C–H amination in natural product synthesis

Due to the greater challenges inherent in intermolecular C–H amination, only a single example of its application in total synthesis has been reported: the construction of tetracyclic spermidine alkaloid hispidospermidin.[145] In what amounts to a formal 'ene' process, amination of intermediate **44** to produce **45** was accomplished in 52% yield using PhI=NTs and 5 mol% $Cu(OTf)_2$ in MeCN (Eq. 12). This is a remarkable example of allylic amination occurring without significant formation of aziridine byproduct. Additionally, this transformation involves a novel

double-bond migration that cleanly yields a single regioisomeric product.



(44) (45) (−)-Hispidospermidin (12)

In summary, catalytic C–H bond amination is a synthetically useful transformation that often proceeds with high levels of regio- and diastereoselectivity. As such, it has found application in the synthesis of a variety of different organic structures with increasing degrees of complexity. Future investigations should focus on expanding the substrate scope, especially of the intermolecular reactions, and developing more highly enantioselective catalysts for these transformations. The development of inner sphere catalysts for C–H bond amination represents another important future direction in this area, and a very recent report by Buchwald has demonstrated the potential viability of this approach.[99]

6. C–H bond halogenation

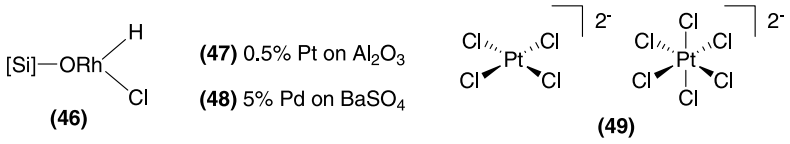
Halogenated hydrocarbons are incredibly versatile synthons for organic chemists. Classically, they have found use as substrates for nucleophilic substitution reactions,[146] benzyne formation,[147] and as precursors to a variety of main group organometallic reagents, including organolithium[148] and Grignard reagents.[149] Since the advent of transition metal cross coupling reactions, they have also become the substrates of choice for the formation of new carbon–carbon bonds.[150,151] Additionally, many natural products and pharmaceuticals contain halogen atoms in positions that are critical for their biological activity.

The construction of carbon–halogen (C–X) bonds from C–H bonds has been largely limited to classical organic reactions involving either electrophilic (X^+) or free radical ($X\cdot$) halogenating reagents.[20,21,23] Significant work has also aimed to develop transition metal catalysts that mimic the haloperoxidase enzymes;[152–156] however, the role of the metal in these systems is merely to generate X^+, which then acts as a classical electrophilic halogenating reagent. In contrast, metal-based catalyst systems that directly transform C–H to C–X bonds via inner-sphere mechanisms remain rare.

6.1. Chlorination of methane

Early studies of inner-sphere C–H bond halogenation focused on the reaction of methane with Cl_2.[157–159] A variety of heterogeneous and homogeneous complexes, including silica-supported Rh complexes,[159] Pt on Al_2O_3,[158] Pd on $BaSO_4$,[158] and aqueous mixtures of Na_2PtCl_4 and Na_2PtCl_6,[157] have been developed as catalysts for this transformation (Fig. 10).

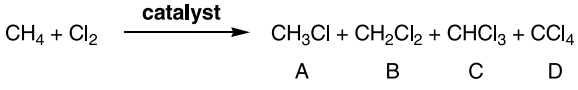
As summarized in Table 8, these reactions all proceed with high selectivity for the formation of monochlorinated CH_3Cl, and are proposed to proceed via metal-alkyl



Schwartz, **1984** *Olah*, **1985** *Horváth*, **1993**

Figure 10. Catalysts for the chlorination of methane.

Table 8. Transition metal catalyzed chlorination of methane



Entry	Catalyst	Conditions	Ratio A:B:C:D	Notes
1[a]	**46**	2% catalyst, 1:3.3 CH_4:Cl_2, 100 °C	92:8:trace:trace	13.7% conversion based on CH_4
2[b]	**47**	3:1 CH_4:Cl_2, 250 °C	99:1:0:0	36% conversion based on Cl_2
3[b]	**48**	2:1 CH_4:Cl_2, 200 °C	99:1:0:0	30% conversion based on Cl_2
4[c]	**49**	Pt^{IV}:Pt^{II}=7.5:1, w/Cl_2, 100 °C	Not reported, but A dominates	CH_3OH is major byproduct

[a] Ref.159.
[b] Ref.158.
[c] Ref.157.

intermediates. However, they remain limited by (i) moderate TON and/or high reaction temperatures, (ii) the requirement for corrosive Cl_2 (and in some cases super-stoichiometric Pt^{IV}) as the terminal oxidant, and (iii) limited applicability to the selective halogenation of more complex hydrocarbon substrates.[160,161]

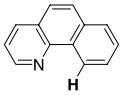
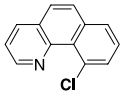
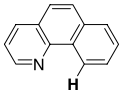
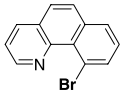
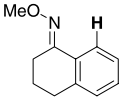
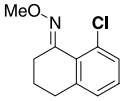
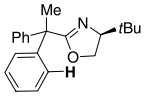
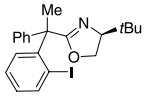
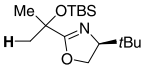
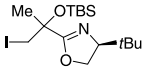
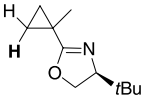
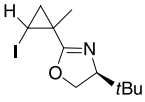
6.2. Selective halogenation of organic substrates

More recent work has revealed that highly regioselective palladium(II)-catalyzed C–H bond halogenation can be accomplished in complex organic substrates that contain appropriate chelate directing groups. For example, $Pd(OAc)_2$ serves as an efficient catalyst for the nitrogen-directed chlorination or bromination of benzo-[*h*]quinoline using *N*-chloro or *N*-bromosuccinimide as mild stoichiometric oxidants (Table 9, entries 1 and 2).[58a] These transformations proceed in excellent (>90%) yield with catalyst loadings as low as 1 mol% and show extremely high levels of regioselectivity for functionalization at C_{10}. Interestingly, directed Pd-catalyzed C–H bond halogenation proceeds rapidly and can effectively out-compete uncatalyzed reactions between the substrate and oxidant. For example, α-tetralone *O*-methyl oxime undergoes exclusive aromatic chlorination with *N*-chlorosuccinimide/catalytic $Pd(OAc)_2$ (Table 9, entry 3), while only benzylic oxidation is observed in the absence of palladium.[162] These reactions, like the related $Pd(OAc)_2$-catalyzed oxygenations, are also believed to proceed via a $Pd^{II/IV}$ mechanism, and the key product release step presumably involves C–X bond-forming reductive elimination from Pd^{IV} intermediates.[58c]

Palladium(II)-catalyzed directed C–H activation/halogenation reactions have also been expanded to the introduction of iodine substituents through the use of I_2 as a terminal oxidant in conjunction with $PhI(OAc)_2$ as an acetate source (which serves to regenerate the $Pd(OAc)_2$ catalyst after each turnover).[163] This system is effective for the regioselective oxazoline-directed iodination of both aromatic and aliphatic C–H bonds (Table 9, entries 4–6). The use of chiral oxazoline directing groups results in modest to excellent levels of diastereoselectivity in substrates containing diastereotopic phenyl groups, methyl groups, or C–H bonds (Table 9, entries 4, 5 and 6, respectively). Notably, the oxazoline auxiliary is readily removed by hydrolysis; therefore this transformation provides an unusual and potentially useful route to chiral carboxylic acid derivatives.

In general, transition metal catalyzed halogenation reactions are the least studied of all of the topics covered in this review. This leaves the door open for further advances in catalyst design, selectivity, functional group compatibility, and asymmetric transformations.

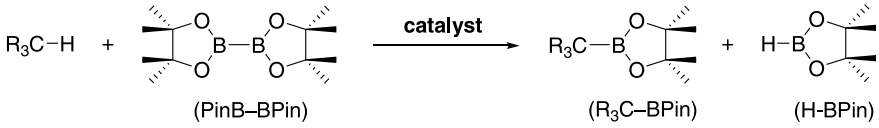
Table 9. Selective C–H activation/halogenation catalyzed by $Pd(OAc)_2$

Entry	Substrate	Product	Yield (%)
1[a,b]			95
2[a,b]			93
3[a,c]			86
4[d]			98 (dr=99:1)
5[d]			62 (dr=93:7)
6[d]			65 (dr=99:1)

[a] $Pd(OAc)_2$ (1%), 1.1 equiv *N*-halosuccinimide, MeCN, 100°.
[b] Ref.58a.
[c] Ref.162.

7. C–H bond borylation

Organoboron compounds are synthetically valuable intermediates that are readily transformed into alcohols and also find widespread application in cross-coupling reactions.[164,165] The direct transition metal catalyzed borylation of alkane or arene C–H bonds represents an attractive and atom economical approach to access these important compounds (Eq. 13). Experimental and computational studies have established that alkane/arene borylation is thermoneutral or thermodynamically downhill depending on the organic substrate, making this an ideal target for catalysis.[166,167]



(13)

A variety of transition metal catalysts have been developed for C–H activation/borylation (e.g., see **50**–**56** in Fig. 11), and these reactions generally proceed via inner-sphere mechanisms involving metal–aryl or metal–alkyl intermediates.[168–174] This section aims to summarize synthetically useful aspects of these reactions, including reactivity, regioselectivity, substrate scope, and functional group tolerance.

7.1. Aromatic C–H bond borylation

Iverson and Smith reported the first example of catalytic C–H activation/borylation using **50** as a catalyst for the borylation of benzene.[175] While this reaction was slow, required benzene as the solvent, and proceeded with only ~3 turnovers, it provided critical early precedent for the feasibility of this catalytic transformation. Based on prior work in C–H activation/silylation of arenes using similar

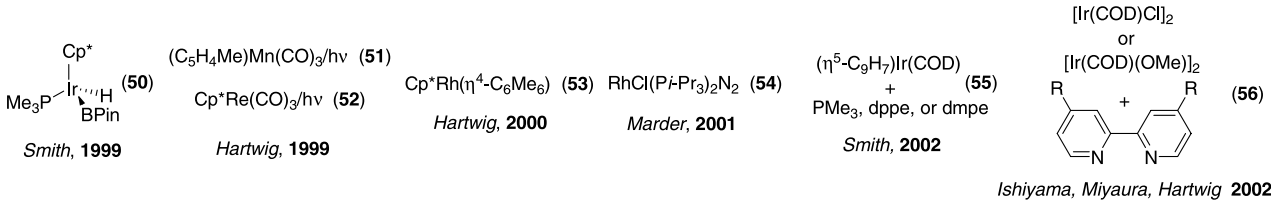
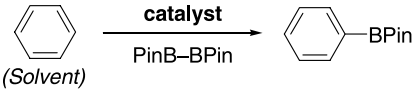


Figure 11. Precatalysts for C–H activation/borylation reactions.

catalysts,[176] Hartwig subsequently demonstrated that **51** and **53** are efficient catalysts for the photochemical (**51**)[177] and thermal (**53**)[178] borylation of benzene (Table 10). The activity of **53** (TON=328) was particularly remarkable at the time, as it was an order of magnitude greater than previously reported catalysts.[178] Later studies showed that catalysts **54**–**56** exhibit comparable (TON=222 for **54**) or significantly higher (TON=4500 for **55**; TON=8000 for **56**) activity for benzene borylation.[179–181]

Table 10. Catalytic borylation of benzene



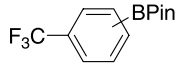
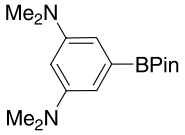
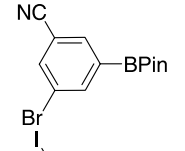
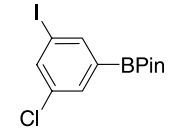
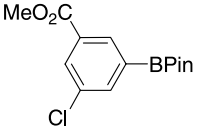
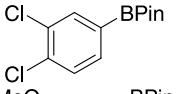
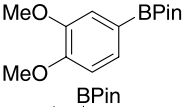
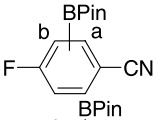
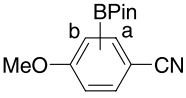
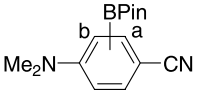
Catalyst	Conditions	TON
50[a]	150 °C, 120 h	3.1
51[b]	2 atm CO, 25 °C, 36 h	7.6
53[c]	150 °C, 45 h	328
54[d]	H–BPin, 140 °C, 104 h	222
55[e]	L=dmpe, 150 °C, 61 h	4500
56[f]	100 °C, 16 h	8000

[a] Ref.175.
[b] Ref.177.
[c] Ref.178.
[d] Ref.181.
[e] Ref.179.
[f] Ref.180.

More recent work has demonstrated the application of C–H activation/borylation to a wide variety of substituted aromatic substrates (Table 11).[179,182–185] In general, **53**, **55** and **56** are the most active, versatile, and general catalysts for these transformations, with overall activity following the trend **56**>**55**>**53**≫**50**. Remarkably, many reactions using catalyst **56** take place at room temperature![180,183,186] As a result of these highly active catalysts, most arene borylation reactions can now be carried out with only minimal (typically 1.1–4-fold) excess of arene substrate (Table 11, entries 2–10). This advance has dramatically expanded the synthetic utility of these transformations, and they can now be applied to valuable advanced intermediates.

As summarized in Table 11, C–H activation/borylation reactions catalyzed by **55** and **56** tolerate a wide variety of functionalities, including CN, CF_3, F, Cl, Br, I, OMe, NMe_2, and CO_2Me groups.[175,179,184,185] (Notably, **53** is somewhat less functional group tolerant and leads to partial reduction of nitriles and aryl halide derivatives.)[184] Catalyst **56** also generally shows low reactivity toward benzylic C–H bonds;[183,187] however, facile and selective benzylic C–H activation/borylation can be achieved using **54**[181] or Pd/C[187]

Table 11. Catalytic borylation of aromatic substrates

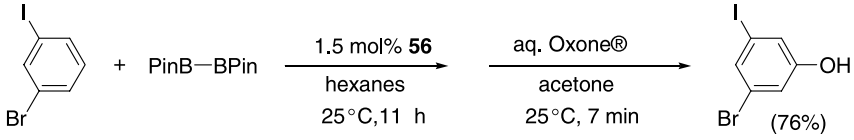
Entry	Product	Catalyst	Yield (%)
1		**53** **56**	84 (*m*:*p*=2:1)[a] 80 (*m*:*p*=2.3:1)[b]
2		**53**	69[c]
3		**56**	83[d]
4		**56**	82[d]
5		**55** **56**	95[e] 80[d]
6		**56**	82[d]
7		**55**	62[e]
8		**56**	71 (*a*:*b*=1:12)[f]
9		**56**	65 (*a*:*b*=2:1)[f]
10		**56**	58 (*a*:*b*=99:1)[f]

[a] Ref.185.
[b] Ref.180.
[c] Ref.184.
[d] Ref.183.
[e] Ref.179.
[f] Ref.182.

as catalysts. Although the origin of this selectivity is not well understood, these catalysts serve as useful complements to **56** in this context.

Arene borylation catalyzed by **53**, **55** and **56** proceeds with very high selectivity for functionalization of the least sterically hindered C–H bond of the substrate.[179,182–185] This remarkable selectivity (which is

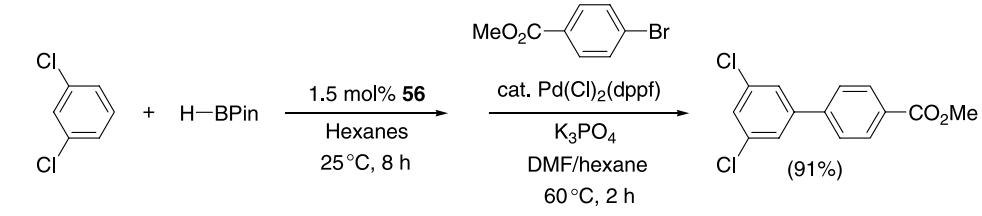
characteristic of inner-sphere catalysis) is typically independent of the electronic nature of the aromatic ring substituents, and often leads to substituted products that would not be accessible by either classical electrophilic aromatic substitution or directed *ortho*-lithiation reactions. For example, the borylation of 1,3 disubstituted substrates occurs exclusively at the sterically accessible *meta*-position regardless of the electronic nature of the substituents (Table 11, entries 2–5). High selectivity for functionalization at the 4-position is observed in diverse 1,2 disubstituted derivatives (entries 6 and 7). Furthermore, in 1,4 disubstituted systems containing a CN group, the regioselectivity of borylation



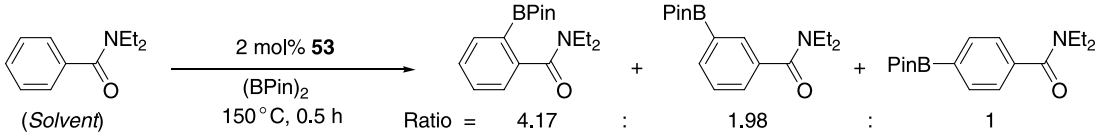
(15)

is exquisitely sensitive to the size of the second arene substituent. With small substituents such as F, substitution adjacent to the F is preferred (entry 8), while when the size increases to NMe_2 (entry 10), borylation occurs exclusively next to CN.[182]

In most mono-substituted arene substrates (Table 11, entry 1), a statistical (~2:1) mixture of *meta* and *para* substituted products is formed, and this ratio is largely independent of the transition metal catalyst.[180,185] When a good chelating group (e.g., an amide derivative) is placed on the arene ring, a significant amount of the *ortho*-borylated product is obtained (Eq. 14). This is believed to be due to competing coordination of the amide to the catalyst, resulting in ligand-directed *ortho*-functionalization.[185]



(16)



(14)

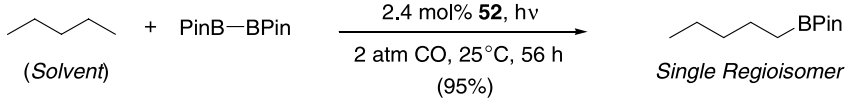
As summarized in Table 12, aromatic heterocycles are also excellent substrates for C–H activation/borylation catalyzed by **55** and **56**.[179,188–190] In general, high selectivity is observed for borylation at the 2-position of furans, thiophenes, pyrroles, and indoles (entries 1–3, 5, and 6). However, the regioselectivity of pyrrole or indole borylation can be shifted exclusively to the 3-position by protecting the nitrogen with a sterically bulky TIPS group (entry 4).[184,190] Again, this change in selectivity reflects a preference for reaction at the least sterically hindered C–H bonds.

Arylboronic esters are valuable precursors to phenol derivatives, and a convenient one pot synthesis of phenols via (i) catalytic arene C–H activation/borylation followed by (ii) oxidation with Oxone® has recently been reported (Eq. 15).[191] These reactions generally proceed in good to excellent yields, and a wide range of arene substituents (Cl, Br, F, NMe_2, CO_2Me, CH_3, CF_3) are tolerated without over-oxidation to quinones, *N*-oxides or benzylic oxidation products.

Several one-pot routes to biaryl compounds via catalytic C–H activation/borylation followed by Pd-catalyzed Suzuki–Miyaura cross-coupling have also been reported (Eq. 16),[179,186] and C–C coupled products are typically obtained in excellent (80–90%) yield over the two steps. Notably, the reaction shown in Eq. 16 offers the added advantages that C–H activation/borylation can be conducted at room temperature and that inexpensive and more readily available H–BPin rather than $(BPin)_2$ can be used as the boron source.

7.2. Alkane C–H bond borylation

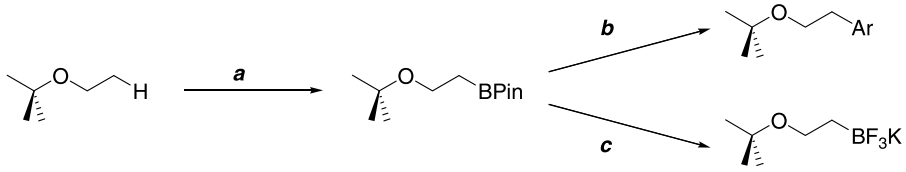
Chen and Hartwig reported the first example of catalytic alkane borylation using **52** as a catalyst for the borylation of *n*-pentane (Eq. 17).[177] This photochemical reaction proceeded at room temperature in neat *n*-pentane to afford 95% of the mono-borylated product. Importantly, functionalization occurs exclusively at the least sterically hindered terminal position. Control experiments (using an independently synthesized sample of the 2-borylated product) showed no isomerization under the catalytic conditions, indicating that the observed selectivity is kinetic in nature.



(17)

A key advance in this area involved the development of catalyst **53**, which promotes alkane borylation under convenient thermal conditions, and, to date, **53** remains the catalyst of choice for this transformation.[178] Simple hydrocarbons such as *n*-octane and methylcyclohexane undergo facile borylation catalyzed by **53**, and a variety of functional groups including ethers, acetals, 3° amines, and alkyl fluorides are well-tolerated.[178,192] As summarized in Figure 12, borylation proceeds with extremely high levels of regioselectively at the least sterically hindered 1° C–H bonds of most substrates. Notably, high selectivity (typically >20:1) for the 1° position is observed even in molecules containing relatively weak or acidic C–H bonds. Furthermore, comparable yields and selectivities are obtained when these reactions are conducted with alkane as the limiting reagent (albeit with approximately double catalyst loading). These features suggest that alkane borylation has significant potential for the selective functionalization of many more complex organic substrates.

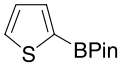
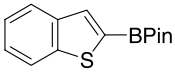
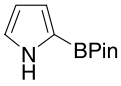
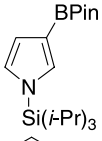
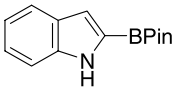
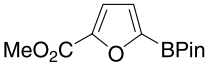
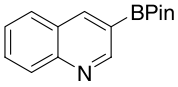
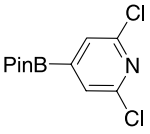
As shown in Eq. 18, Hartwig and co-workers also demonstrated the one pot conversion of alkanes to alcohols (using H_2O_2/KOH), alkyl arenes (using catalytic Pd^0 and an aryl bromide), and to alkyl trifluoroborates (using KHF_2).[192]



(18)

a. 5 mol% **53**, B_2Pin_2; ***b***. 10 mol% Pd_2dba_3, 10% $Fc(P\textit{i}\text{-}Pr_2)_2$, 2 equiv Ar–Br, 4 equiv CsOH; ***c***. KHF_2 in MeOH

Table 12. Catalytic borylation of heterocyclic substrates

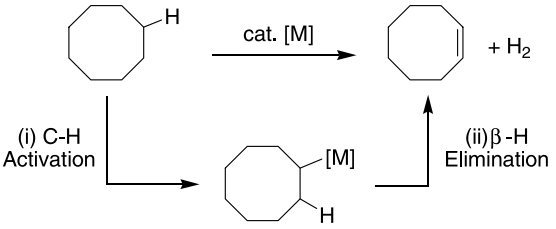
Entry	Product	Catalyst	Yield (%)
1		**56**	83[a]
2		**56**	89[a]
3		**56**	67[a]
4		**56**	79[a]
5		**56**	92[a]
6		**56**	80[b]
7		**56**	84[a]
8		**55**	69[c]

[a] Ref.190.
[b] Ref.189.
[c] Ref.179.

In conclusion, the past decade has seen impressive progress in the development of transition metal catalysts for the borylation of unactivated arene and alkane C–H bonds. Future investigations in this area will likely focus on further explorations of substrate scope and, in particular, the application of this methodology to complex biologically active target structures.

8. C–H bond dehydrogenation

The dehydrogenation of saturated carbon–hydrogen bonds (Eq. 19) represents an attractive approach to oxidatively transform alkanes into valuable alkene functionality. Unlike the other transformations discussed in this review, dehydrogenation involves a net removal of two C–H bonds rather than replacement of a C–H bond with a C–X bond. Typically, inner-sphere catalysts are used to effect this transformation via a general mechanism involving (i) C–H activation to generate a metal alkyl intermediate followed by (ii) β-hydride elimination to afford the alkene product (Eq. 19).[193]



(19)

A variety of Rh,[194–209] Ir,[194,195,210–226] Re,[220,227] and Pt[228–231] catalyst systems have been developed for this reaction (Fig. 13), with the most widely used being Rh complex **60**[199,200,203–209] and Ir complex **62**.[195,211,213–219]

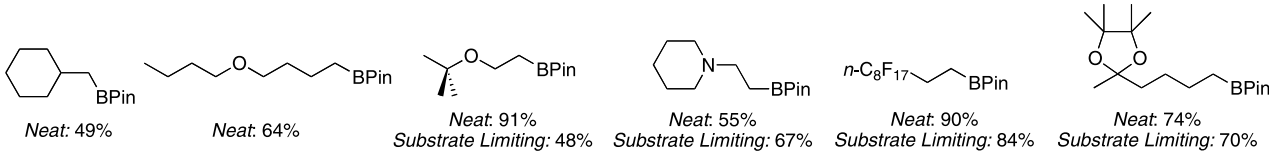


Figure 12. Scope of products obtained from alkane borylations catalyzed by **53**.

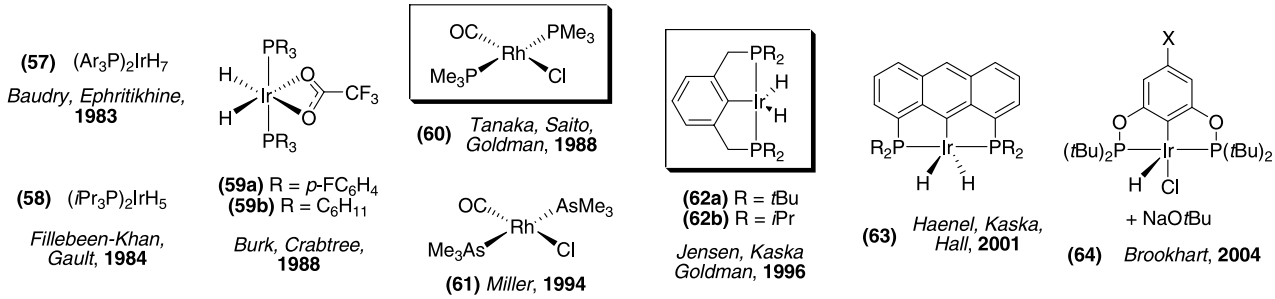
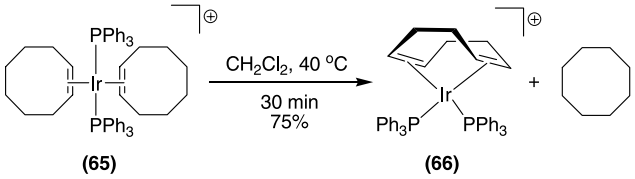


Figure 13. Commonly used organometallic catalysts for alkane dehydrogenation.

While catalysts can lower the kinetic barrier to the two C–H bond cleavage events, they cannot alter the thermodynamics of these transformations. Dehydrogenation reactions are typically endothermic (e.g., $\Delta H = +33$ kcal/mol for the conversion of ethane to ethylene and hydrogen), but are entropically favorable, as they release 1 equiv of H_2 gas.[232] High reaction temperatures (>500 °C) can be utilized to render dehydrogenative processes thermodynamically downhill;[232] however, such extreme conditions are generally not amenable to selective functionalization of more complex organic molecules. As such, recent work has focused on strategies to render these reactions thermodynamically favorable at lower temperatures. These include: (i) coupling the desired dehydrogenation reaction to the hydrogenation of a sacrificial olefin, (ii) utilizing photochemical rather than thermal energy to supply the necessary driving force, or (iii) removal of H_2 from the reaction mixture (via reflux or an inert gas purge) to drive the equilibrium to the right.

8.1. Transfer dehydrogenation

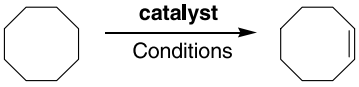
The most widely used approach to low temperature catalytic alkane dehydrogenation involves net hydrogen transfer from an alkane to a reactive sacrificial olefin (SO). This transformation was initially discovered by Crabtree, who reported that thermolysis of Ir complex **65** leads to clean stoichiometric transfer dehydrogenation to afford Ir cyclooctadiene product **66** along with free cyclooctane (Eq. 20).[233]



(65) (66) (20)

Subsequent to this initial discovery, a wide variety of catalysts, including **57**–**64** (Fig. 13), have been developed for transfer dehydrogenation processes, typically in conjunction with *tert*-butylethylene (tbe), norbornene, cyclohexene, or ethylene as sacrificial olefins. The conversion of cyclooctane to cyclooctene is commonly used as a test reaction because of the unusually low enthalpy of dehydrogenation of this reaction (23.3 kcal/mol, nearly 5 kcal/mol lower than cyclohexane).[204] The results of cyclooctane transfer dehydrogenation with a variety of different catalysts are summarized in Table 13, entries 1–5. In general, Rh-based catalysts are more efficient than their Ir counterparts, although iridium complexes containing terdentate P–C–P phosphine or phosphinite ligands have proven particularly active and robust. Interestingly, in some cases it was found that conducting the reaction under an atmosphere of H_2 actually promoted the reaction (Table 13, entries 2 and 5).[194,197,199,200]

Table 13. Catalytic dehydrogenation of cyclooctane



Entry	Catalyst	TON	Conditions
1[a]	**58**	70	150 °C, w/tbe, 5 days
2[b]	**60**	106	60 °C, w/cyclohexene, 1000 psi H_2, 100 min
3[c]	**62a**	>1000	150 °C, w/tbe added incrementally
4[d]	**64**	806–2210	200 °C, w/tbe, 8 min–2 weeks
5[e]	**61**	2460	100 °C, w/ethylene, 500 psi H_2, 4 h
6[f]	**60**	667	96 °C, *hν*, 6 h
7[g]	**60**	930	rt, *hν*, 68.5 h
8[h]	**60**	up to 5000	50 °C, *hν*, time not specified

[a] Ref.226.
[b] Ref.200.
[c] Ref.195.
[d] Ref.210.
[e] Ref.197.
[f] Ref.206.
[g] Ref.209.
[h] Ref.204.

8.2. 'Acceptorless' dehydrogenation

The synthetic utility of transfer dehydrogenation is limited by the requirement for a sacrificial olefin; as such, significant efforts have aimed to develop alternative driving forces for these transformations. Early work revealed that the dehydrogenation of cyclooctane catalyzed by **59b** can take place in the absence of an H_2 acceptor when conducted under photochemical conditions.[222] The efficacy of this process is attributed to the ability of photochemical energy to provide a thermodynamic driving force for these reactions.[222] These photochemical processes can be extremely efficient; for example, the photochemical dehydrogenation of cyclooctane with **60** proceeds with up to 5000 turnovers (Table 13, entry 8).[204]

Pioneering work by Fujii and Saito revealed that derivatives of **60** with varying phosphine ligands catalyze the

acceptorless dehydrogenation of cyclooctane under thermal conditions when the H_2 by-product is removed under reflux.[202] More recently, similar H_2-removal procedures have been successfully developed for the dehydrogenation of cycloalkanes with catalysts **59**, **62**, and others[198,211,214,219,220] with TON up to 987 for cyclodecane.[215] Importantly, these transformations proceed at comparable temperatures to the transfer dehydrogenation reactions described above (~150 °C).

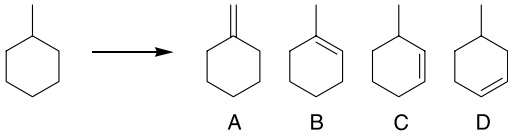
8.3. Substrate scope and selectivity

Because cyclooctane and other cyclic alkanes are symmetrical substrates, they yield no information about the regioselectivity of the dehydrogenation process. To address this, the dehydrogenation of methylcyclohexane[214,217,221,224,227] (Table 14) and *n*-hexane[203,206,208,209,221] (Table 15) have been studied.

Although the selectivity is somewhat catalyst dependent, the results in Tables 14 and 15 illustrate the general trend—under irreversible photochemical conditions at low conversions (kinetic control), these transformations proceed with modest selectivity for the functionalization of 1° C–H bonds to afford terminal olefins. In the case of catalyst **60**, this selectivity is further enhanced by addition of excess phosphine ligand (but at the expense of catalyst activity) (Table 15, entries 3–5). At longer reaction times or higher temperatures, however, equilibration to thermodynamically favored internal olefins is observed, presumably due to isomerization reactions unrelated to the inherent selectivity of the C–H activation event.

Dehydrogenations of isopropylcyclohexane,[199,204] ethylcyclohexane,[218] decalin,[214,217] and other *n*-alkanes[205,216,221] have also been examined for selectivity, producing similar

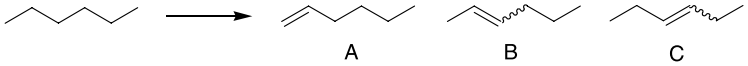
Table 14. Selectivity of dehydrogenation of methylcyclohexane



Entry	Catalyst	Cond	Ratio A:B:C:D (%)	TON
1[a]	**62b**	100 °C, 5 min	71:6:9:15	2.2
2[a]	**62b**	100 °C, 1 h	55:15:12:18	3.6
3[a]	**62b**	150 °C, 65 h	1:62:13:24	10
4[b]	**59a**	Δ	10:58:14:18	4.5
5[b]	**59a**	*hν*	39:31:12:18	7.1

[a] Ref.224.
[b] Ref.221.

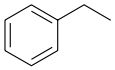
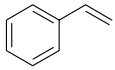
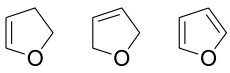
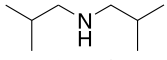
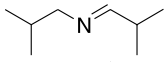
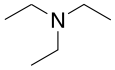
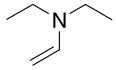
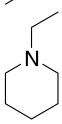
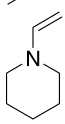
Table 15. Selectivity of dehydrogenation of *n*-hexane



Entry	Catalyst	Cond	Ratio A:B:C (%)	TON
1[a]	**59a**	Δ	4:74:22	5.1
2[a]	**59a**	*hν*	24:61:15	4.9
3[b]	**60**	*hν*, PMe_3:Rh=2:1	7:77:15	5.4
4[b]	**60**	*hν*, PMe_3:Rh=5:1	70:24:6	4.0
5[b]	**60**	*hν*, PMe_3:Rh=10:1	86:12:3	0.6

[a] Ref.221.
[b] Ref.208.

Table 16. Selected substrates for dehydrogenation reactions

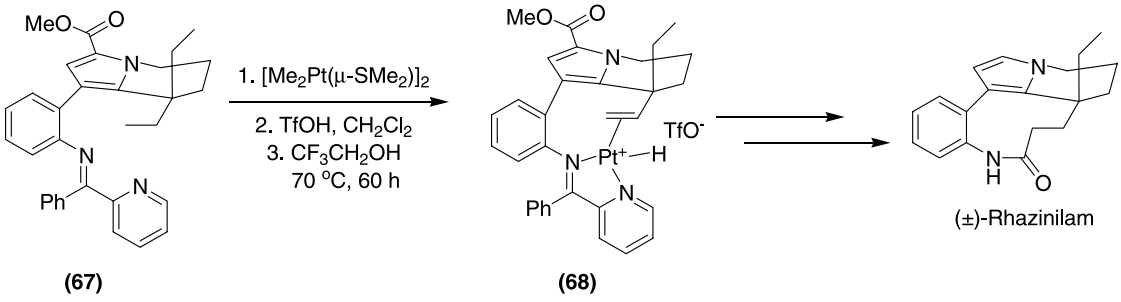
Entry	Substrate	Product(s)	Catalyst(s)
1			**62a**[a,b]
2			**60**[c,d] **62a**[a,b]
3			**62a**[e]
4			**62a**[f]
5			**62a**[f]

[a] Ref.214.
[b] Ref.218.
[c] Ref.199.
[d] Ref.200.
[e] Ref.234.
[f] Ref.235.

product mixtures. Also, it has been shown that cyclohexane can be dehydrogenated either to cyclohexene or benzene, depending on reaction conditions.[223,225] These dehydrogenation reactions also show some functional group tolerance; for example, tetrahydrofuran has been successfully dehydrogenated to give mixtures of dihydrofurans and furan (Table 16, entry 2),[199,200,214,218] and 2° and 3° amine substrates yield either imine[234] or enamine[235] products, respectively (Table 16, entries 3–5).

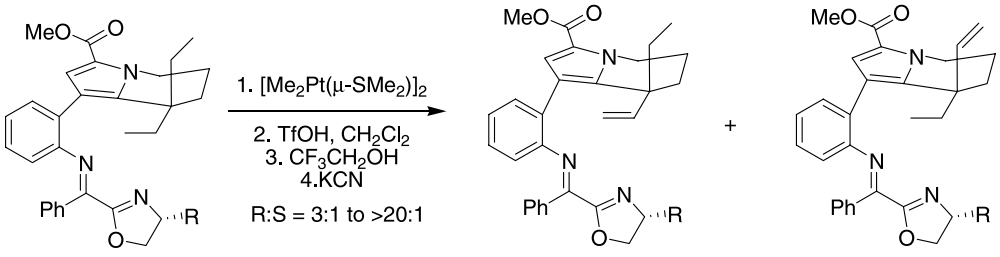
8.4. Application in natural product synthesis

The potential utility of efficient and selective alkane dehydrogenation reactions is illustrated in Sames' elegant construction of the antimitotic natural product rhazinilam.[236] The key transformation in this total synthesis involved imine/pyridine-directed dehydrogenation of an ethyl group of intermediate **67** at Pt^{II} to afford **68** in 79% yield over three steps (Eq. 21). This Pt product was then readily transformed into the natural product in eight straightforward steps.



(67) (68) (21)

Importantly, this route was also amenable to the asymmetric total synthesis of rhazinilam.[237] Substitution of the imine in **67** with a chiral oxazoline auxiliary led to stereoselective C–H activation/dehydrogenation, and diastereomeric ratios of up to 20:1 were obtained when R was large (e.g., *t*-Bu) and when the reaction temperature was lowered to 60 °C (Eq. 22).



(69) (R)-(70) (S)-(70) (22)

This work clearly demonstrates the potential of selective catalytic dehydrogenation, yet its requirement for stoichiometric Pt highlights the need for further advancements in catalyst reactivity, selectivity, and functional group tolerance.

In conclusion, alkane dehydrogenation represents a synthetically powerful approach to the oxidative functionalization of alkanes under mild conditions. In order to fully exploit this transformation, future work will require the development of catalysts that operate with high levels of regioselectivity in the context of more complex organic molecules. Additionally, new approaches to control competing olefin isomerization reactions will also be required to selectively isolate valuable terminal olefinic products.

9. Future challenges

While significant progress has been made in the development of efficient and highly selective transition metal catalysts for C–H bond oxidation, this field remains largely in its infancy, and a wide variety of exciting challenges remain. Future work will strive to develop more highly active transition metal catalysts that operate efficiently at milder temperatures and lower catalyst loadings. Such catalysts will likely find increased application in the chemical and pharmaceutical industries and should lead to enhanced kinetic control over the regio- and stereoselectivity of C–H bond oxidation. The development of catalysts that promote the selective intermolecular oxidation of unactivated C–H bonds without the requirement for activating or directing groups also remains an important ongoing goal. The borylation chemistry detailed in Section 7 represents an elegant example of the potential attainability and synthetic utility of such transformations. The development of new methods for the oxidative transformation of C–H bonds into other important functional groups, including carbon–fluorine, carbon–sulfur, and carbon–phosphorus bonds, remains an important frontier in this field. Finally, these new methods and catalysts will increasingly find application in the construction and functionalization of complex chemical systems and biologically active molecules.

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Biographical sketch

Allison R. Dick was born in Ames, Iowa, and received her BS in chemistry from Wheaton College (IL) in 2002, where she also minored in music. During that time, she completed an NSF-sponsored REU program at University of Pittsburgh in the laboratory of Professor David Waldeck. She began her graduate career at University of Michigan in August 2002, and is currently a fourth year graduate student working with Professor Melanie Sanford. Her research has focused on synthetic and mechanistic studies of palladium-catalyzed C–H bond oxidation reactions. Allison was the recipient of an Eli Lilly Graduate Fellowship in Organic Chemistry.

Melanie S. Sanford was born in New Bedford, MA and grew up in Providence, RI. She received her BS and MS degrees in chemistry at Yale University in 1996 where she carried out undergraduate research under the direction of Professor Robert Crabtree. She earned her PhD from California Institute of Technology in 2001, where she studied the mechanism of ruthenium-catalyzed olefin metathesis reactions under the direction of Professor Robert Grubbs. After 2 years as a National Institutes of Health post-doctoral fellow in the laboratories of Professor John Groves, she joined the faculty at the University of Michigan where she is currently an assistant professor of chemistry. Professor Sanford's research interests encompass the development and mechanistic study of new transition metal catalyzed reactions for applications in organic synthesis. She has been the recipient of a Camille and Henry Dreyfus New Faculty Award and an Arnold and Mabel Beckman Young Investigator Award as well as young investigator awards from Boehringer Ingelheim, Amgen, and Eli Lilly.

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Copper-free Sonogashira reaction using 7-chloro camptothecins

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Abstract—We studied copper-free Sonogashira reaction using 7-chloro camptothecins, and determined that *rac*-BINAP/Pd(OAc)$_2$ was an efficient catalyst for the coupling reaction. With this process, a number of 7-substituted camptothecins with a wide range of functional groups are potentially accessible. Besides, two drugs, SN-38 and BNP-1350, could be prepared by this method.

1. Introduction

Camptothecin (CPT **1**),[1] an alkaloid isolated from camptothecin acuminata by Wall and Wani in 1966, exhibits potent antitumor activity by inhibiting DNA topoisomerase I. However, the severe toxicity, the instability of the lactone and other defects[2] have promoted intensive efforts to study the structure–activity relationship (SAR) of CPT.

From SAR,[3] it appears that substituents in position 7 are very important to the activity of the CPT analogues. Recent studies have demonstrated that substitution in position 7 is no steric compromise.[4] A number of analogues with substituents in position 7 show enhanced biological profiles. One of them, SN-38 (**2**),[5] has been used in clinical practice to treat colon cancer. Others such as BNP-1350 (**3**),[6] silatecan (**4**),[7] ST-1481 (**5**),[8] lurtotecan (**6**)[9] are all in various stages of clinical development[10] (Fig. 1).

To date, the typical method to prepare 7-alkyl-substituted CPTs is the Minisci type reaction,[11] which proceeds via a carbon radical addition to electron-deficient heteroaromatics.[12] Although the Minisci type reaction has turned out to be fruitful, the radical reaction is potentially reactive to a broad range of functional groups.[13]

Thus, other processes are required to prepare 7-substituted CPTs. We envisioned that the Sonogashira coupling

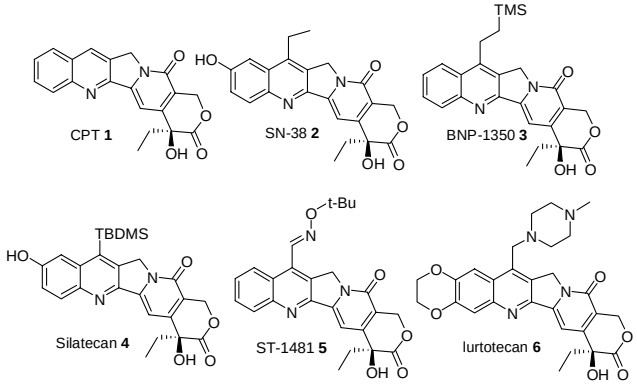

Figure 1.

reaction, which is carried out under mild reaction conditions and is compatible with a broad scope of functional groups,[14] could serve as a new approach to prepare 7-substituted CPT analogues. Although Hausheer and co-workers have reported coupling of 7-triflate camptothecins with a few alkynes under typical conditions,[15] the cocatalyst-free Sonogashira reaction using 7-chloride appears to be more appealing. In this paper, we report the development of a process to prepare 7-substituted CPT analogues by the copper-free Sonogashira coupling, and the application of our process to prepare SN-38 (**2**) and BNP-1350 (**3**).

2. Results and discussion

The synthesis of 7-chloride **8**, 7-bromide **9** and 7-iodide **10** CPT derivatives were accomplished as outlined in Scheme 1.

Keywords: Camptothecin; Topoisomerase I; Sonogashira coupling; Palladium; Catalysis.
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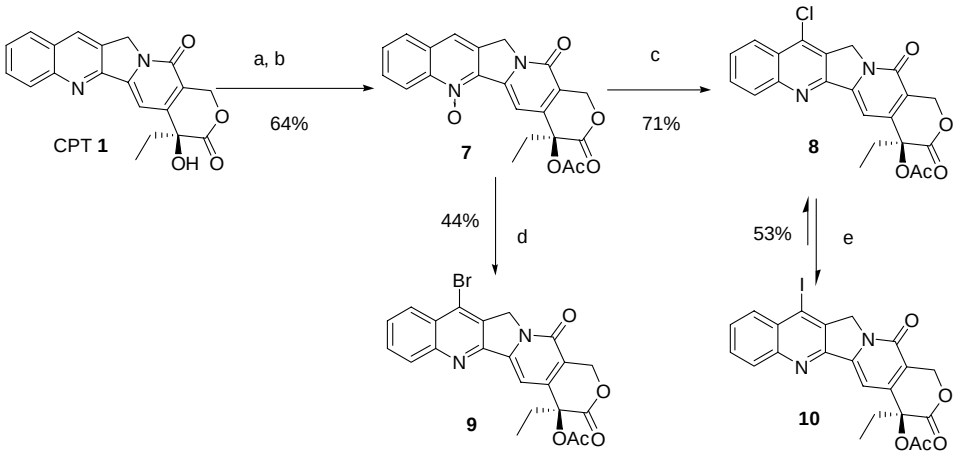
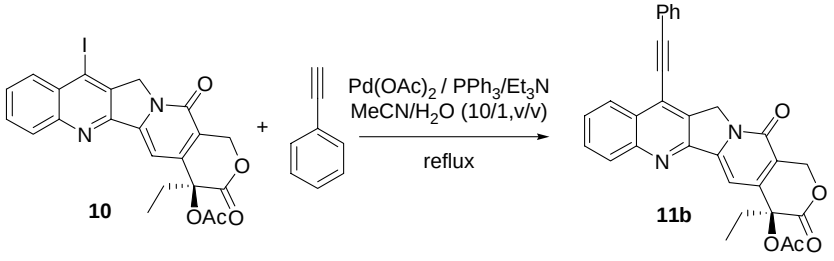


Scheme 1. Reagents and conditions: (a) Py/Ac_2O/DMAP; (b) 30% H_2O_2/AcOH; (c) DMF/$(COCl)_2$; (d) DMF/$POBr_3$; (e) NaI/AcCl/MeCN.



Scheme 2.

Thus, CPT (**1**) was acylated, and then oxidized in acetic acid with 30% hydrogen peroxide to give *N*-oxide **7**.[16] Then *N*-oxide **7** was treated with oxalyl chloride or phosphorus oxybromide in DMF to afford 7-chloride **8**[17] or 7-bromide **9** accordingly. The 7-iodide **10** was prepared by treating 7-chloride **8** with sodium iodide and acyl chloride in acetonitrile under reflux.[18] Unfortunately, an inseparable mixture of 7-iodide **10** and the starting material **8** was produced, because the chloride–iodide exchange is an equilibrium reaction. Longer reaction time did not change the results. The ^{1}H NMR indicated that the ratio of **10** to **8** was 4.8–1.

With these halides available, we attempted the Sonogashira reaction. Typical procedures for the Sonogashira reaction utilize catalytic amounts of palladium, a base and a copper salt as a cocatalyst.[19] Recent studies have shown that the copper cocatalyst induces homocoupling of terminal alkynes if the copper acetylide is exposed to oxidative agents or air.[20] In addition, we have previously reported that CPTs can be easily oxidized in air by catalytic amounts of copper (I) iodide.[21] Obviously, the copper-free Sonogashira reaction would be superior for our reaction. With respect to the organic halides, the following order of reactivity has been observed: aryl iodide > aryl bromide > aryl chloride.[22] As a result, we chose the inseparable mixture of iodide and chloride to test the coupling reaction with phenylacetylene under copper-free conditions. Thus, **11b** was synthesized smoothly using Sinou's protocol[23] (Scheme 2).

Although, 7-iodide **10** reacted with phenylacetylene smoothly, the inseparable 7-chloride **8** did not react with the alkyne under this condition, resulting in laborious separation after the reaction. Though 7-bromide **9** might be more reactive than 7-chloride **8**, the difficult availability of phosphorus oxybromide in large amounts and the low yield of **9** forced us to use the more easily available 7-chloride **8** to carry out the copper-free Sonogashira reaction.

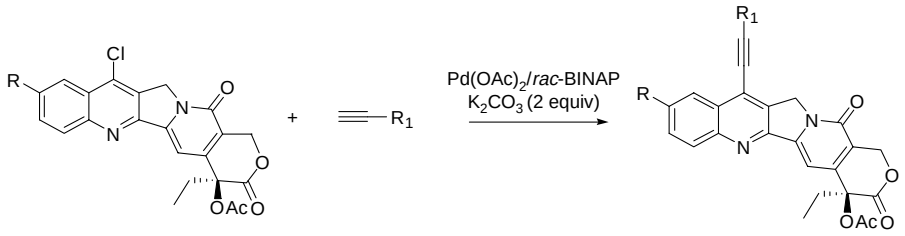
Although a significant volume of literature exists on copper-free Sonogashira reaction,[24] aryl chlorides are difficult to react under various conditions. Recently, a general protocol for employing aryl chlorides under copper-free conditions has been developed by Buchwald and co-workers.[25]

Table 1. Palladium-catalyzed Sonogashira coupling reaction of 7-chloride **8** with 1-heptyne[a]

Entry	Solvent	Base	Ligand	Yield (%)[b]
1[c]	Toluene	K_2CO_3	Tri-*o*-tolylphosphine	91
2[c]	Toluene	K_2CO_3	PPh_3	30
3	Toluene	K_2CO_3	DPPF	3
4	Toluene	K_2CO_3	DPPD	58
5	Toluene	K_2CO_3	DPPE	23
6	Toluene	K_2CO_3	*rac*-BINAP	95
7[d]	DMF	K_2CO_3	*rac*-BINAP	—
8	Toluene	$K_3PO_43H_2O$	*rac*-BINAP	82
9	Toluene	Cs_2CO_3	*rac*-BINAP	29
10	Toluene	DIEA	*rac*-BINAP	4
11[e]	Toluene	Tetramethyl guanidine	*rac*-BINAP	—

[a] Unless otherwise indicated, the reaction conditions were as following: 7-chloride **8** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), ligand (0.04 mmol), potassium carbonate (0.4 mmol), 1-heptyne (0.8 mmol), degassed toluene (17 mL) at 100 °C under Ar for 5 h.
[b] Isolated yields.
[c] 0.08 mmol ligand was used.
[d] Complete decomposition.
[e] Complicated products.

Table 2. The Sonogashira coupling catalyzed by $Pd(OAc)_2$/*rac*-BINAP[a]

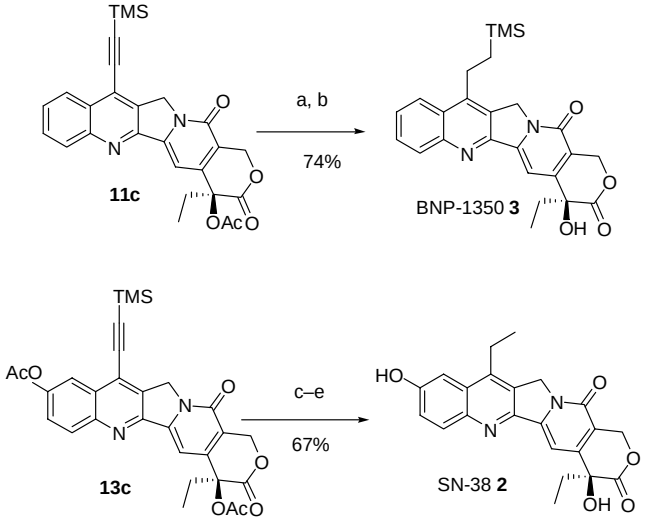


Entry	R	R_1	Time (h)	Product	Yield (%)[b]
1	H (8)	C_5H_{11}	5	11a	95
2	H (8)	Ph	9	11b	78
3[c]	H (8)	TMS	9	11c	68
4[d]	H (8)	2-Hydroxy-isopropyl	10	11d	75
5	OAc (12)	C_5H_{11}	5	13a	63
6	OAc (12)	Ph	9	13b	54
7[c]	OAc (12)	TMS	9	13c	60
8[d,e]	OAc (12)	2-Hydroxy-isopropyl	10	13d	—

[a] Unless otherwise indicated, the reaction conditions were as follows: 7-chloride (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), *rac*-BINAP (0.04 mmol), potassium carbonate (0.4 mmol), alkyne (0.8 mmol), degassed toluene (17 mL) at 100 °C under Ar for the indicated time.
[b] Isolated yields.
[c] $Pd(OAc)_2$ (0.04 mmol) and *rac*-BINAP (0.08 mmol) were used in a sealed tube.
[d] $Pd(OAc)_2$ (0.03 mmol) and *rac*-BINAP (0.06 mmol) were used.
[e] No reaction occurred.

However, the protocol has to use a ligand, which is not easily available. Thus, we had to establish the reaction condition for our reaction.

To screen for suitable reaction conditions, we chose to focus on the coupling of 7-chloride **8** with 1-heptyne as our test substrate. As shown in Table 1, among the six ligands tested, *rac*-BINAP was most effective in accomplishing the reaction. While tri-*o*-tolylphosphine was slightly less effective, it still provided a good yield. These data were in accordance with others' results that bulky, electron-rich phosphines could display unusually high reactivity in many coupling reactions. Among the five bases tested, anhydrous potassium carbonate was the best. In addition, DMF resulted in complete decomposition, while toluene furnished good yields.



Scheme 3. Reagents and conditions: (a) H_2/10% Pd/C; (b) $NaOCH_3$/CH_3OH; (c) KF/CH_3OH; (d) H_2/10% Pd/C; (e) $NaOCH_3$/CH_3OH.

Under these conditions, different camptothecin derivatives were coupled with a wide variety of terminal acetylenes (Table 2). Thus, 20-acetyl-7-chloro-camptothecin (**8**) reacted with an array of alkynes in moderate to good yields (entries 1–4). As illustrated in entries 5–7, the less reactive 10-acetoxyl-20-acetyl-7-chloro-camptothecin (**12**)[26] was also coupled with alkynes in moderate yields. Unfortunately, the $Pd(OAc)_2$/*rac*-BINAP catalytic system was ineffective for the coupling of **12** with 2-methyl-3-butyn-2-ol (entry 8).

After **11c** and **13c** were obtained, SN-38 (**2**) and BNP-1350 (**3**) were prepared as illustrated in Scheme 3. Compound **11c** was hydrogenated by 10% Pd/C, and then hydrolyzed with sodium methoxide in methanol to afford BNP-1350 (**3**) in 74% yield. Similarly, **13c** was treated with potassium fluoride in methanol, hydrogenated by 10% Pd/C, and then hydrolyzed with sodium methoxide in methanol to produce SN-38 (**2**) in 67% yield.

3. Conclusion

In summary, we have determined that *rac*-BINAP/$Pd(OAc)_2$ serves as an efficient catalyst for Sonogashira coupling to prepare 7-substituted CPT analogues. With this process, SN-38 (**2**) and BNP-1350 (**3**) have also been prepared. In addition, this study provides another example of the usefulness of bulky, electron-rich phosphines in palladium-catalyzed coupling reactions.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on either Gemini-300 or Bruker AM-400. Chemical shifts (δ ppm) were reported for signal center, and coupling constant J were

reported in units of Hz. High-resolution mass spectra were recorded on Varian MAT-711, MAT-95 or HT-5989 mass spectrometer. Column chromatograph was performed on 200–300 mesh silica gel. All reagents were used directly as obtained commercially, unless otherwise noted.

4.1.1. 20-Acetyl-7-(dec-1-ynyl)-camptothecin (11a). To a mixture of 7-chloride **8** (85 mg, 0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), *rac*-BINAP (0.04 mmol) and potassium carbonate (0.4 mmol), under an argon atmosphere, was added a solution of 1-heptyne (0.8 mmol) in degassed toluene (17 mL). The reaction mixture was heated at 100 °C for 5 h. Then the solvent was evaporated to give a residue, which was purified by flash column chromatography on silica gel (acetone/chloroform, 1:20) to give 92 mg of pure **11a** (95% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.93 (t, J=7.3 Hz, 6H), 1.38–1.57 (m, 4H), 1.71–1.82 (m, 2H), 2.21 (s, 3H), 2.10–2.30 (m, 2H), 2.66 (t, J=7.6 Hz, 2H), 5.26 (s, 2H), 5.40 (d, J=17.2 Hz, 1H), 5.68 (d, J=17.2 Hz, 1H), 7.18 (s, 1H), 7.68 (dd, J=8.0, 8.1 Hz, 1H), 7.81 (dd, J=7.9, 8.2 Hz, 1H), 8.17 (d, J=8.6 Hz, 1H), 8.32 (d, J=8.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=7.5, 13.9, 19.9, 20.7, 22.1, 28.1, 31.2, 31.8, 50.3, 67.1, 73.9, 75.8, 96.1, 107.5, 120.3, 126.0, 126.6, 127.9, 128.1, 129.8, 130.5, 130.7, 145.8, 146.4, 148.8, 151.5, 157.3, 167.5, 169.8. MS (EI): m/z=484, 396 (base peak). HRMS (EI): m/z calcd for $C_{29}H_{28}N_2O_5$ [M^+]: 484.1998; found: 484.1993.

4.1.2. 20-Acetyl-7-(2-phenylethynly)-camptothecin (11b). To a mixture of 7-chloride **8** (85 mg, 0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), *rac*-BINAP (0.04 mmol) and potassium carbonate (0.4 mmol), under an argon atmosphere, was added a solution of phenylacetylene (0.8 mmol) in degassed toluene (17 mL). The reaction mixture was heated at 100 °C for 9 h. Then the solvent was evaporated to give a residue, which was purified by flash column chromatography (acetone/chloroform, 1:20) to give 76 mg of pure **11b** (78% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.98 (t, J=7.4 Hz, 3H), 2.12–2.30 (m, 2H), 2.25 (s, 3H), 5.38 (s, 2H), 5.39 (d, J=17.2 Hz, 1H), 5.68 (d, J=17.2 Hz, 1H), 7.22 (s, 1H), 7.46–7.51 (m, 3H), 7.71–7.76 (m, 3H), 7.86 (dd, J=6.9, 7.1 Hz, 1H), 8.22 (d, J=8.5 Hz, 1H), 8.43 (d, J=8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=7.4, 20.6, 31.6, 50.1, 66.8, 75.8, 81.6, 95.9, 104.4, 120.2, 121.0, 125.2, 125.6, 127.1, 128.2, 128.6, 129.7, 130.1, 130.6, 132.1, 145.8, 146.2, 148.5, 151.4, 157.0, 167.4, 169.7. MS (EI): m/z=490, 430 (base peak). HRMS (EI): m/z calcd for $C_{30}H_{22}N_2O_5$ [M^+]: 490.1529; found: 490.1527.

4.1.3. 20-Acetyl-7-(2-trimethylsilylethynly)-camptothecin (11c). To a mixture of 7-chloride **8** (85 mg, 0.2 mmol), $Pd(OAc)_2$ (0.04 mmol), *rac*-BINAP (0.08 mmol) and potassium carbonate (0.4 mmol), under an argon atmosphere, was added a solution of trimethylsilylacetylene (0.8 mmol) in degassed toluene (17 mL). The reaction mixture was heated at 100 °C for 9 h in sealed tube. Then the solvent was evaporated to give a residue, which was purified by flash column chromatography (acetone/chloroform, 1:20) to give 66 mg of pure **11c** (68% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.38 (s, 9H), 0.97 (t, J=7.7 Hz, 3H), 2.11–2.29 (m, 2H), 2.22 (s, 3H), 5.31 (s, 2H), 5.40 (d, J=17.1 Hz, 1H), 5.68 (d, J=17.1 Hz, 1H), 7.19 (s, 1H), 7.73 (dd, J=6.9, 7.8 Hz, 1H), 7.85 (dd, J=7.0, 6.9 Hz, 1H), 8.20 (d, J=8.6 Hz, 1H), 8.34 (d, J=8.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=−0.2, 7.5, 20.7, 31.7, 50.2, 67.1, 75.8, 96.1, 96.6, 111.9, 120.5, 125.3, 125.9, 127.6, 128.5, 129.9, 130.8, 145.7, 146.2, 148.7, 151.6, 157.2, 167.5, 169.8. MS (EI): m/z=486, 149 (base peak). HRMS (EI): m/z calcd for $C_{27}H_{26}S_iN_2O_5$ [M^+]: 486.1611; found: 486.1618.

4.1.4. 20-Acetyl-7-(3,3-dimethly-3-hydroxyl-1-propylnyl)-camptothecin (11d). To a mixture of 7-chloride **8** (85 mg, 0.2 mmol), $Pd(OAc)_2$ (0.03 mmol), *rac*-BINAP (0.06 mmol) and potassium carbonate (0.4 mmol), under an argon atmosphere, was added a solution of 2-methyl-3-butyn-2-ol (0.8 mmol) in degassed toluene (17 mL). The reaction mixture was heated at 100 °C for 10 h. Then the solvent was evaporated to give a residue, which was purified by flash column chromatography (acetone/chloroform, 1:5) to give 71 mg of pure **11d** (75% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.97 (t, J=7.5 Hz, 3H), 1.78 (s, 6H), 2.10–2.31 (m, 2H), 2.22 (s, 3H), 5.29 (s, 2H), 5.39 (d, J=17.4 Hz, 1H), 5.67 (d, J=17.4 Hz, 1H), 7.19 (s, 1H), 7.71 (dd, J=7.8, 7.2 Hz, 1H), 7.84 (dd, J=8.7, 7.8 Hz, 1H), 8.20 (d, J=8.4 Hz, 1H), 8.29 (d, J=8.1 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=7.5, 20.5, 30.2, 31.2, 50.3, 64.1, 66.2, 73.7, 75.8, 95.2, 111.1, 119.2, 124.1, 125.4, 126.9, 128.6, 129.6, 130.9, 131.7, 145.5, 146.0, 147.8, 151.9, 156.5, 167.3, 169.6. MS (EI): m/z=472, 384 (base peak). HRMS (EI): m/z calcd for $C_{27}H_{24}N_2O_6$ [M^+]: 472.1634; found: 472.1674.

4.1.5. 10-Acetoxyl-20-acetyl-7-(dec-1-ynyl)-camptothecin (13a). To a mixture of 7-chloride **12** (97 mg, 0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), *rac*-BINAP (0.04 mmol) and potassium carbonate (0.4 mmol), under an argon atmosphere, was added a solution of 1-heptyne (0.8 mmol) in degassed toluene (17 mL). The reaction mixture was heated at 100 °C for 5 h. Then the solvent was evaporated to give a residue, which was purified by flash column chromatography (acetone/chloroform, 1:20) to give 68 mg of pure **13a** (63% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.92 (t, J=7.2 Hz, 6H), 1.36–1.54 (m, 4H), 1.67–1.77 (m, 2H), 2.09–2.27 (m, 2H), 2.18 (s, 3H), 2.36 (s, 3H), 2.62 (t, J=7.2 Hz, 2H), 5.22 (s, 2H), 5.35 (d, J=17.4 Hz, 1H), 5.63 (d, J=17.4 Hz, 1H), 7.13 (s, 1H), 7.53 (dd, J=9.0, 2.7 Hz, 1H), 7.98 (d, J=2.7 Hz, 1H), 8.13 (d, J=9.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=7.4, 13.8, 19.8, 20.5, 21.0, 22.0, 27.9, 31.0, 31.6, 50.2, 66.9, 73.5, 75.7, 95.9, 107.7, 116.9, 120.2, 125.9, 126.2, 128.4, 130.8, 131.1, 145.7, 146.2, 146.6, 149.9, 151.2, 157.1, 167.4, 169.1, 169.7. MS (EI): m/z=542, 482 (base peak). HRMS (EI): m/z calcd for $C_{31}H_{30}N_2O_7$ [M^+]: 542.2053; found: 542.2043.

4.1.6. 10-Acetoxyl-20-acetyl-7-(2-phenylethynly)-camptothecin (13b). To a mixture of 7-chloride **12** (97 mg, 0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), *rac*-BINAP (0.04 mmol) and potassium carbonate (0.4 mmol), under an argon atmosphere, was added a solution of phenylacetylene (0.8 mmol) in degassed toluene (17 mL). The reaction mixture was heated at 100 °C for 9 h. Then the solvent was evaporated to give a residue, which was purified by flash column chromatography (acetone/chloroform, 1:20) to give 59 mg of pure **13b** (54% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.98 (t, J=7.5 Hz, 3H), 2.11–2.33

(m, 2H), 2.22 (s, 3H), 2.41 (s, 3H), 5.36 (s, 2H), 5.40 (d, J=17.4 Hz, 1H), 5.68 (d, J=17.4 Hz, 1H), 7.17 (s, 1H), 7.43–7.49 (m, 3H), 7.60 (dd, J=9.0, 2.4 Hz, 1H), 7.69–7.72 (m, 2H), 8.13 (d, J=2.4 Hz, 1H), 8.21 (d, J=9.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=7.5, 20.6, 21.2, 31.7, 50.2, 66.9, 75.8, 81.4, 96.1, 104.9, 116.8, 120.5, 121.0, 125.3, 126.2, 128.0, 128.7, 130.2, 130.8, 131.3, 132.1, 145.8, 146.1, 146.7, 150.2, 151.5, 157.1, 167.4, 169.1, 169.8. MS (EI): m/z=548, 418 (base peak). HRMS (EI): m/z calcd for $C_{32}H_{24}N_2O_7$ [M^+]: 548.1584; found: 548.1597.

4.1.7. 10-Acetoxyl-20-acetyl-7-(2-trimethylsilylethynly)-camptothecin (13c). To a mixture of 7-chloride **12** (97 mg, 0.2 mmol), $Pd(OAc)_2$ (0.04 mmol), *rac*-BINAP (0.08 mmol) and potassium carbonate (0.4 mmol), under an argon atmosphere, was added a solution of trimethylsilylacetylene (0.8 mmol) in degassed toluene (17 mL). The reaction mixture was heated at 100 °C for 9 h in sealed tube. Then the solvent was evaporated to give a residue, which was purified by flash column chromatography (acetone/chloroform, 1:20) to give 65 mg of pure **13c** (60% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.38 (s, 9H), 0.97 (t, J=6.9 Hz, 3H), 2.10–2.31 (m, 2H), 2.20 (s, 3H), 2.42 (s, 3H), 5.30 (s, 2H), 5.40 (d, J=18 Hz, 1H), 5.68 (d, J=18 Hz, 1H), 7.17 (s, 1H), 7.60 (dd, J=9.3, 2.7 Hz, 1H), 8.05 (d, J=2.4 Hz, 1H), 8.20 (d, J=9.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=−0.3, 7.5, 20.7, 21.2, 31.7, 50.2, 67.0, 75.8, 96.1, 96.3, 112.4, 116.9, 120.6, 125.1, 126.2, 128.2, 131.3, 131.4, 145.8, 146.1, 146.7, 150.2, 151.6, 157.2, 167.4, 169.1, 169.8. MS (EI): m/z=544, 414 (base peak). HRMS (EI): m/z calcd for $C_{29}H_{28}SiN_2O_7$ [M^+]: 544.1666; found: 544.1670.

4.1.8. BNP-1350 (3). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.17 (s, 9H), 0.87–0.94 (m, 2H), 1.03 (t, J=7.2 Hz, 3H), 1.84–1.92 (m, 2H), 3.06–3.11 (m, 2H), 5.22 (s, 2H), 5.30 (d, J=16.8 Hz, 1H), 5.75 (d, J=16.8 Hz, 1H), 7.62–7.67 (m, 2H), 7.79 (dd, J=7.2, 7.8 Hz, 1H), 8.02 (d, J=8.4 Hz, 1H), 8.22 (d, J=8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=−1.8, 7.8, 17.7, 24.1, 31.5, 49.2, 66.3, 72.7, 98.0, 118.4, 123.2, 126.0, 126.6, 127.6, 129.9, 130.7, 147.0, 149.4, 150.1, 151.9, 157.6, 173.9. MS (EI): m/z=448, 448 (base peak). HRMS (EI): m/z calcd for $C_{25}H_{28}SiN_2O_4$ [M^+]: 448.1818; found: 448.1814.

4.1.9. SN-38 (2). ^{1}H NMR (300 MHz, DMSO-d_6): δ=0.85 (t, J=7.5 Hz, 3H), 1.28 (t, J=7.5 Hz, 3H), 1.80–1.88 (m, 2H), 3.06 (q, J=7.5 Hz, 2H), 5.25 (s, 2H), 5.39 (s, 2H), 7.23 (s, 1H), 7.38 (s, 1H), 7.40 (d, J=9.9 Hz, 1H), 8.01 (d, J=9.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=7.8, 13.4, 22.3, 30.2, 49.4, 65.3, 72.4, 95.9, 104.7, 118.1, 122.3, 127.9, 128.2, 131.6, 142.8, 143.6, 146.4, 148.8, 150.1, 156.5, 156.9, 172.6. MS (EI): m/z=392, 348 (base peak). HRMS (EI): m/z calcd for $C_{22}H_{20}N_2O_5$ [M^+]: 392.1372; found: 392.1383.

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26. 10-Acetoxyl-20-acetyl-7-chloro-camptothecin (**12**) was prepared in three steps from 10-hydroxyl-camptothecin in 50% yield by a process similarly with the preparation of 20-acetyl-7-chloro-camptothecin (**8**).

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Convenient synthesis of highly optically active 2,3,4,6-tetrasubstituted tetrahydropyrans via Prins cyclization reaction (PCR) of optically active homoallylic alcohols with aldehydes

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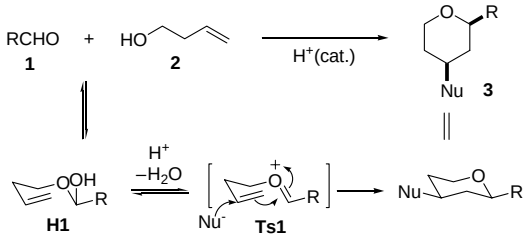
Abstract—Prins cyclization reaction (PCR) of optically active homoallylic alcohols, $R^aC^*H(OH)CH_2CH{=}CHCH_3$ (1-substituted but-2-en-1-ol), with aldehydes (R^bCHO) in the presence of an acid-catalyst (HX) affords (2-R^b,3-CH_3,4-X,6-R^a)-tetrasubstituted tetrahydropyrans highly stereoselectively in good yields.

1. Introduction

Many natural compounds bearing a substituted tetrahydropyran (THP) ring system have been discovered, and much attention has been paid for the synthesis of those structurally and biologically interesting compounds.[1] For the preparation of the tetrahydropyran (THP) ring **3**,[2c] a PCR of homoallylic alcohols with aldehydes in the presence of an acid is well-known as one of the most convenient methods.[2] For example, the homoallylic alcohol (but-3-en-1-ol) **2** reacts with the aldehyde **1** to give the THP derivative **3** in good yield via hemiacetal (**H1**) and then the oxocarbenium ion intermediate **Ts1** as shown in Scheme 1.

On the other hand, Willis et al.[3a] reported that a PCR of a homoallylic alcohol, such as 1-(4-methoxyphenyl)but-3-en-1-ol **2y**, with propanal **1p** gave the THP derivatives **3yp** and **3pp** in only 14 and 21% yields, respectively. They proposed that the formation of these two products (scrambling of the substituents at C2 and C6 positions in the THP ring) could be explained by assuming intermediary [3.3]-sigmatropic rearrangement, discovered and developed by Nokami,[4a] as shown in Scheme 2.

These substituent scramblings at C2 or C6 position on the THP ring has been reported from several laboratories, although there has been little discussion on the stereochemistry and the reaction pathway for the Prins cyclization



Scheme 1. PCR of homoallyl alcohol **2** with aldehyde **1** giving substituted-THP **3**.

products. The work of Willis et al., however, clearly shows that PCRs can proceed by allyl-transfer involving [3.3]-sigmatropic rearrangement.

We propose here a useful method for regio- and stereoselective synthesis of 2,3,4,6-trisubstituted THP derivatives by an acid-catalyzed PCR of aldehydes with homoallylic alcohols, which were prepared by our asymmetric allyl-transfer reactions.[4d–f]

2. Result and discussion

Recently, we discovered a new and convenient method for preparing optically pure (5*E*,3*R*)-1-phenylhept-5-en-3-ol **4a** (we abbreviate this type of homoallylic alcohol 'α-adduct'), by an allylation of aldehydes via an allyl-transfer reaction from the corresponding chiral allyl-donor.[4d] Therefore, we envisaged to synthesize optically active 2,3,4,

Keywords: Prins cyclization reaction; Enantiomeric excess; Nucleophile.
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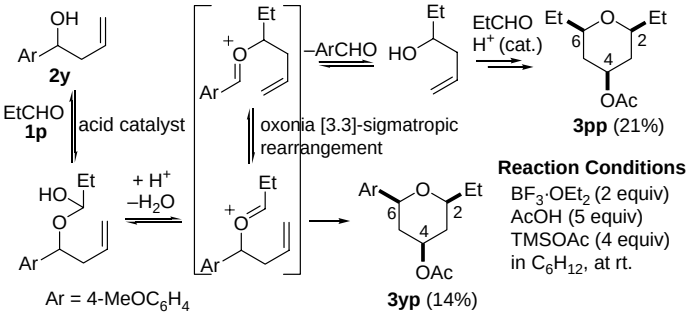


Scheme 2. Willis's proposed mechanism for PCR of homoallylic alcohol **2y** with propanal **1p**.

6-tetrasubstituted THP derivatives by PCR using this α-adduct. Here, we discovered that the desired products could be obtained in a satisfactory yield (63%), with minimal scrambling of C2- and C6-substituents on the THP ring, in the acid catalyzed reaction between **4a** and hexanal in acetic acid (Table 1, entry 1). On the other hand, PCR of 3-methylnon-1-en-4-ol (we abbreviate this type of homoallylic alcohol as 'γ-adduct') **2b** with an equimolar amount of 3-phenylpropanal **1a** in acetic acid (10 equiv) in the presence of 10 mol% of trifluoromethanesulfonic acid gave a mixture of a similar yield of four isomers of THP derivatives (**3ba**, **3bb**, **3ab**, **3aa**), in which two substituents (2-phenethyl and pentyl groups) at C2 and C6 on the THP ring were exchanged each other via an allyl-transfer reaction (entry 2). These results clearly show that the allyl-transfer from the γ-adduct to aldehydes to give an α-adduct (from γ- to α-) occurs more easily than that from α-adduct to γ-adduct, probably because the transition state **Ts2** is more stable than **Ts3** in an oxonia [3.3]-sigmatropic rearrangement step (Scheme 3).[5]

Subsequently, the selective synthesis of optically active 2,3,4,6-tetrasubstituted THP derivatives was attempted by utilizing the optically active α-adduct of homoallylic alcohols **4** instead of γ-adduct **2**.[2s]

When (5*E*,3*R*)-**4a** was treated with 3-phenylpropanal (**1a**, 1 equiv to **4a**) under similar reaction conditions as described above, (2*S*,3*S*,4*S*,6*R*)-4-acetoxy-3-methyl-2,6-di(2-phenethyl)tetrahydropyran **3aa** and its 4-hydroxy derivative **5aa** were obtained in 79% (>99% ee) and 5% yield, respectively, as shown in Table 2 (entry 1). In this table, the result of the reaction of (5*E*,3*R*)-**4a** with hexanal **1b** is listed again (entry 2) for easy comparison with the results of other aldehydes (entries 3–6). The formation of by-products such as **3aa** was minimized and the desired THP derivatives were obtained in satisfactory isolated yields with >99% ee. However, the formation of 4-hydroxy derivatives **5aa**–**fa** was unavoidable. This is because water was produced at the step of the formation of an oxocarbenium ion intermediate from hemiacetal at the beginning of the allyl-transfer reaction, which then served as nucleophile in the PCR to give these 4-hydroxy derivatives. These hydroxy derivatives could be easily converted to the corresponding acetates **3aa**–**fa** by acetylation of the hydroxy group.

Next, (5*Z*,3*S*)-**4a** was treated with various aldehydes (**1a**, **1b** and **1f**, 1 equiv to **4a**) under the same reaction conditions as above to give the corresponding THP derivatives where **7aa**, **7ba** and **7fa** were rather selectively obtained as shown in Table 3.

Finally, (5*E*,3*R*)-**4a** was treated with various aldehydes using trifluoroborane etherate, aluminum trichloride or *p*-toluenesulfonic acid as an acid catalyst, to give the corresponding 4-fluoro-, 4-chloro- and 4-tosyloxyTHP derivatives in good yields as shown in Table 4.

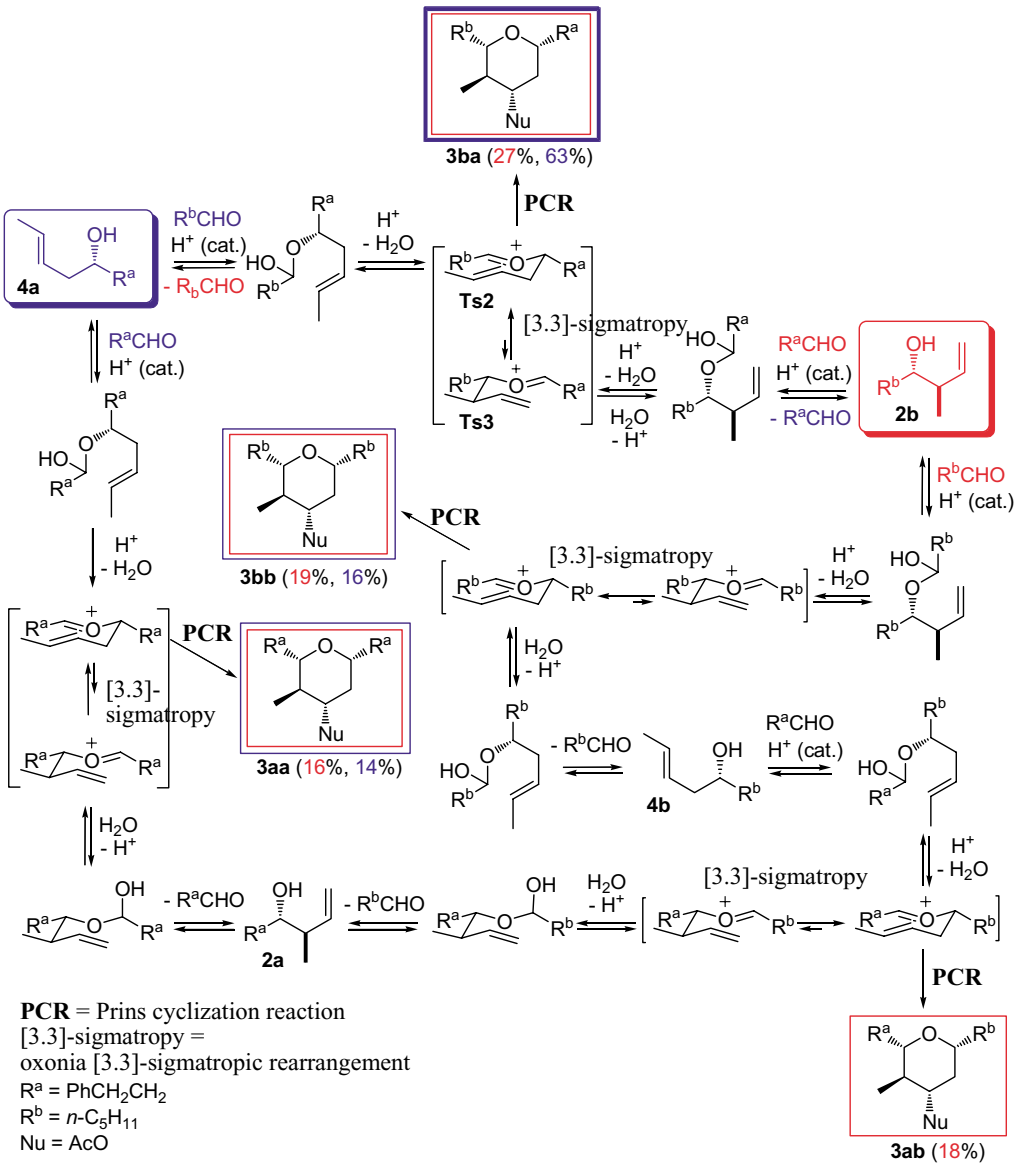
The reaction of (5*E*,3*R*)-**4a** with aldehydes was promoted by $BF_3 \cdot OEt_2$ (1.5 equiv) to give the corresponding (4*S*)-4-fluoro-2,3,6-trisubstituted THP derivative **10** stereoselectively in satisfactory yield, although the formation of the corresponding 4-hydroxy by-product **5** was again unavoidable. The reaction surely becomes a useful method to prepare optically pure 4-fluoroTHP derivatives,[2h,6] which are very useful compounds for further synthesis of fluorine containing bioactive compounds. It is noteworthy that *p*-toluenesulfonic acid gave the corresponding 4-tosyloxyTHP (46–72%) as well as 4-hydroxyTHP (12–18%) in better yield than in the case of the preparation of 4-acetoxyTHP (Table 1).

In conclusion, we have succeeded in a highly regio- and stereoselective preparation of various kinds of optically active 2,3,4,6-tetrasubstituted THP via PCR of optically

Table 1. Prins cyclization reaction (PCR) of homoallylic alcohol **2b** (γ-adduct) versus **4a** (α-adduct)[a]

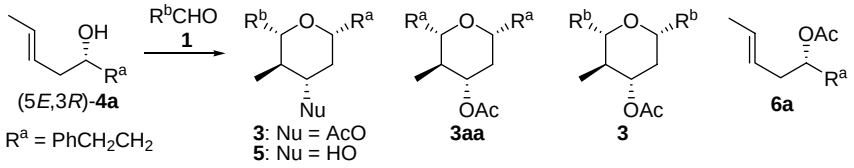
Entry	Homoallylic alcohol	Aldehyde	Yield of THP **3** (%)[b]			
			3ba	**3bb**	**3ab**	**3aa**
1	**4a**	Hexanal	63	16	0	14
2	**2b**[c]	3-Phenylpropanal	27	19	18	16

[a] Reactions were performed using homoallylic alcohol (0.3 mmol), aldehyde (0.3 mmol) and trifluoromethanesulfonic acid (0.03 mmol) in acetic acid (3 mmol) at 40 °C for 6 h.
[b] Isolated yield.
[c] Racemate.



Scheme 3. Synthetic route for THP derivatives by PCR of homoallylic alcohol (α- and γ-) with aldehydes.

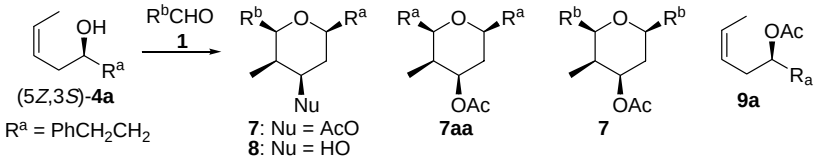
Table 2. PCR of (5*E*,3*R*)-**4a** with aldehydes giving THP derivatives[a]



Entry	Aldehyde **1**		Reaction time (h)	Yield (%)[b]			By-products (%)[b]			
		R^b		(%ee)			**3aa**			**6a**
1	**1a**	$PhCH_2CH_2$	20	**3aa**	79 (>99)[c]	**5aa**	5	—		—	0
2	**1b**	n-C_5H_{11}	6	**3ba**	63 (>99)[c]	**5ba**	3	14	**3bb**	16	Trace
3	**1c**[d]	$(CH_3CH_2)_2CH$	18	**3ca**	63	**5ca**	3	11	**3cc**	6	Trace
4	**1d**	$BnO(CH_2)_5$	6	**3da**	54	**5da**	9	7	**3dd**	15	Trace
5	**1e**[d]	Ph	5	**3ea**	77 (>99)[c]	**5ea**	7	8	**3ee**	Trace	Trace
6	**1f**	PhCH=CH	6	**3fa**	74 (>99)[e]	**5fa**	2	Trace	**3ff**	Trace	Trace

[a] Reactions were performed using (5*E*,3*R*)-**4a** (0.3 mmol), aldehyde **1** (0.3 mmol) and TfOH (0.03 mmol) in acetic acid (3 mmol) at 40 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis (CHIRALPAK AD-H, *n*-hexane/*i*-PrOH=100:1 as eluent).
[d] TfOH (0.06 mmol) was used.
[e] Determined by HPLC analysis (CHIRALCEL OD, *n*-hexane/*i*-PrOH=100:1 as eluent).

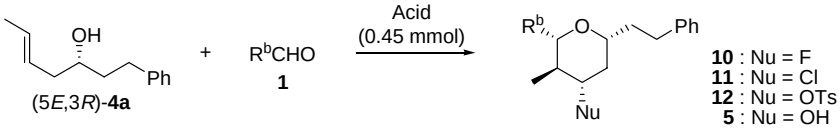
Table 3. PCR of (5*Z*,3*S*)-**4a** with aldehydes giving THP derivatives[a]



Entry	Aldehyde		Reaction time (h)	Yield (%)[b]				By-product (%)[b]			
		R^b		**7**	(% ee)	**8**		**7aa**			**9a**
1	**1a**	$PhCH_2CH_2$	6	**aa**	73 (>99)[c]	**aa**	8	—		—	5
2	**1b**	*n*-C_5H_{11}	6	**ba**	57 (>99)[c]	**ba**	5	10	**7bb**	10	0
3	**1f**	PhCH=CH	20	**fa**	57 (>99)[d]	**fa**	7	0	**7cc**	0	15

[a] Reactions were performed using (5*Z*,3*R*)-**4a** (0.2 mmol), aldehyde **1** (0.2 mmol) and TfOH (0.02 mmol) in acetic acid (2 mmol) at 40 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis (CHIRALPAK AD-H, *n*-hexane/*i*-PrOH=100:1 as eluent).
[d] Determined by HPLC analysis (CHIRALCEL OD, *n*-hexane/*i*-PrOH=100:1 as eluent).

Table 4. PCR of **4a** with aldehydes giving THP derivatives under various acidic conditions[a]



Entry	Aldehyde **1**		Acid	Reaction		Product yield (5)[b]			
	R^b			Temperature (°C)	Time (h)			**5**	
1	**1a**	$PhCH_2CH_2$	$BF_3\cdot OEt_2$	−20	1	**10aa**	63[c]	**aa**	15
2	**1b**	*n*-C_5H_{11}	$BF_3\cdot OEt_2$	−20	4	**10ba**	74	**ba**	14
3	**1d**	$BnO(CH_2)_5$	$BF_3\cdot OEt_2$	−20	4	**10da**	54	**da**	22
4	**1e**	Ph	$BF_3\cdot OEt_2$	−20	4	**10ea**	60	**ea**	19
5	**1f**	PhCH=CH	$BF_3\cdot OEt_2$	−20	4	**10fa**	37[d]	**fa**	18
6	**1a**	$PhCH_2CH_2$	$AlCl_3$	−20	1	**11aa**	74	**aa**	0
7	**1f**	PhCH=CH	$AlCl_3$	−20	4	**11fa**	50	**fa**	0
8	**1a**	$PhCH_2CH_2$	*p*-TsOH·H_2O	25	20	**12aa**	72[e]	**aa**	18[f]
9	**1c**	$(CH_3CH_2)_2CH$	*p*-TsOH·H_2O	25	20	**12ca**	60	**ca**	15
10	**1d**	$BnO(CH_2)_5$	*p*-TsOH·H_2O	25	20	**12da**	58	**da**	18
11	**1e**	Ph	*p*-TsOH·H_2O	25	20	**12ea**	63	**ea**	12
12	**1f**	PhCH=CH	*p*-TsOH·H_2O	25	20	**12fa**	70	**fa**	17
13	**1g**	$PhSCH_2CH_2$	*p*-TsOH·H_2O	25	20	**12ga**	46	**ga**	15

[a] Reactions were performed using (5*E*,3*R*)-**4a** (0.3 mmol), aldehyde (0.3 mmol) and acid (0.45 mmol) in CH_2Cl_2 (0.1 M for entries 1–7 and 0.5 M for entries 8–13).
[b] Isolated yield. HPLC analysis of ee was carried out for **10aa** (entry 1), **11aa** (entry 6), and **12aa** (entry 8).
[c] ee >99%. Determined by HPLC analysis (CHIRALCEL OD, *n*-hexane/*i*-PrOH=40:1 as eluent).
[d] Compound **10aa** (31% based on **4a**) was obtained.
[e] ee >99%. Determined by HPLC analysis (CHIRALCEL OD, *n*-hexane/*i*-PrOH=20:1 as eluent).
[f] ee >99%. Determined by HPLC analysis (CHIRALCEL OD, *n*-hexane/*i*-PrOH=5:1 as eluent).

pure homoallylic alcohols (α-adducts) with aldehydes, in the presence of an organic acid or Lewis acid as a catalyst.

For this purpose a homoallylic alcohol such as **4** (α-adduct) has proven to be more useful than the corresponding γ-adduct such as **2**.

3. Experimental

3.1. General

TLC was performed on aluminum-backed plates coated with silica gel 60 with F254 indicator. Column chromatography was carried out on silica gel BW-300 (200–400 mesh, Fuji Silysia Chemical Ltd). Infrared spectra were recorded on a Nicolet Series II Magna-IR system 550 spectrometer. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured on a JEOL JNMX 400 spectrometer. High-resolution mass spectra were obtained with a JEOL JMS-700 mass spectrometer. Elemental analyses were obtained on a Perkin-Elmer PE-2400 Series II CHN analyzer. Optical rotations were obtained on a JASCO DIP-370 polarimeter. The enantiomeric excess (ee) was determined by HPLC analysis. HPLC was performed on a Shimadzu HPLC system consisting of the following: pump, LC-6A; detector, SPD-6A; chromatopac, C-R3A, measured at 254 nm; column, DAICEL CHIRALPAK AD-H (0.46 cmϕ×25 cmL); eluent, *n*-hexane/*i*-PrOH=40:1; flow rate, 0.3 mL/min. The operation of HPLC was carried out at room temperature (15–27° C; without control of the column temperature).

3.1.1. PCR of α-adduct of homoallylic alcohol (5*E*,3*R*)-4a with hexanal 1b in acetic acid in the presence of TfOH to give 3ba (entry 1 in Table 1, entry 2 in Table 2). To a solution of (5*E*,3*R*)-1-phenylhept-5-en-3-ol **4a** (57.1 mg, 0.3 mmol) and hexanal **1b** (36.0 μL, 0.3 mmol) in acetic acid (172 μL, 3.0 mmol) was added trifluoromethanesulfonic acid (TfOH) (2.7 μL, 0.03 mmol) at 0 °C, and then the mixture was stirred for 6 h at 40 °C. To the reaction mixture was added chloroform and saturated sodium hydrogencarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give (2*S*,3*S*,4*S*,6*R*)-4-acetoxy-3-methyl-2-pentyl-6-(2-phenethyl)tetrahydropyran **3ba** (62.7 mg, 62.9%, R_f=0.67 (*n*-hexane/EtOAc=3:1)), (2*S*,3*R*,4*S*,6*R*)-4-hydroxy-3-methyl-2-pentyl-6-(2-phenethyl)tetrahydropyran **5ba** (2.6 mg, 3.0%, R_f=0.33 (*n*-hexane/EtOAc=3:1)), **3aa** (R_f=0.60 (*n*-hexane/EtOAc=3:1)), and **3bb** (R_f=0.72 (*n*-hexane/EtOAc=3:1)), as colorless oils.

Compound **3ba**: $[\alpha]_D^{25}$ 51.1 (*c* 0.45, $CHCl_3$); IR (neat) 3085, 3063, 3027, 2952, 2929, 2858, 1740, 1603, 1496, 1465, 1375, 1242, 1097, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (d, *J*=6.4 Hz, 3H), 0.92 (t, *J*=7.0 Hz, 3H), 1.25–1.50 (m, 8H), 1.58–1.73 (m, 3H), 1.82–1.91 (m, 1H), 1.98 (ddd, *J*=12.8, 4.6, 1.8 Hz, 1H), 2.05 (s, 3H), 2.64–2.71 (m, 1H), 2.76–2.83 (m, 1H), 2.97 (m, 1H), 3.29 (m, 1H), 4.55 (ddd, *J*=10.7, 10.7, 4.9 Hz, 1H), 7.16–7.19 (m, 3H), 7.27 (t, *J*=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 14.1, 21.2, 22.8, 25.3, 31.7, 31.9, 33.0, 37.6, 37.8, 40.9, 73.6, 75.9, 80.6, 125.7, 128.2, 128.4, 141.9, 170.7; HRMS (EI) *m*/*z* calcd for $C_{21}H_{32}O_3$ 332.2351. Found 332.2309.

Compound **5ba**: $[\alpha]_D^{25}$ 22.4 (*c* 0.42, $CHCl_3$); IR (Nujol) 3277, 3086, 3064, 3027, 2926, 2856, 1743, 1603, 1496, 1455, 1374, 1152, 1096, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J*=6.6 Hz, 3H), 0.95 (d, *J*=6.0 Hz, 3H), 1.19–1.43 (m, 8H), 1.60–1.74 (m, 4H), 1.83–1.92 (m, 2H), 2.69 (m, 1H), 2.80 (m, 1H), 2.89 (t, *J*=10.8 Hz, 1H), 3.21–3.31 (m, 2H), 7.16–7.19 (m, 3H), 7.25–7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 14.2, 22.8, 25.4, 31.8, 31.9, 33.0, 37.7, 41.5, 44.3, 73.8, 73.9, 80.6, 125.6, 128.2, 128.5, 142.1; HRMS (EI) *m*/*z* calcd for $C_{19}H_{30}O_2$ 290.2246. Found 290.2233.

Compound **3aa**: (shown in Section 3.1.3).

Compound **3bb**: $[\alpha]_D^{25}$ 15.5 (*c* 0.84, $CHCl_3$); IR (neat) 2956, 2931, 2872, 1743, 1467, 1377, 1243, 1088, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, *J*=7.2 Hz, 3H), 0.88 (t, *J*=6.8 Hz, 3H), 0.89 (t, *J*=6.8 Hz, 3H), 1.20–1.56 (m, 17H), 1.60–1.66 (m, 1H), 2.01 (ddd, *J*=12.1, 4.8, 1.9 Hz, 1H), 2.06 (s, 3H), 2.97 (ddd, *J*=9.4, 9.4, 2.4 Hz, 1H), 3.31 (m, 1H), 4.58 (ddd, *J*=10.8, 10.8, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 14.1, 14.2, 21.3, 22.7, 22.8, 25.2, 25.3, 31.7, 31.9, 32.9, 36.0, 37.8, 40.9, 75.0, 76.0, 80.7, 170.8; HRMS (EI) *m*/*z* calcd for $C_{18}H_{34}O_3$ 298.2508. Found 298.2512.

3.1.2. PCR of γ-adduct of homoallylic alcohol (±)-2b with 3-phenylpropanal 1a in acetic acid in the presence of acid-catalyst to give a mixture of four isomers 3ba, 3bb, 3aa, and 3ab (entry 2 in Table 1). To a solution of 3-phenylpropanal **1a** (43.8 μL, 0.30 mmol) and racemic 3-methylnon-1-en-4-ol (±)-**2b** (47.0 mg, 0.30 mmol) in acetic acid (173 μL, 3.0 mmol) was added trifluoromethanesulfonic acid (TfOH) (2.7 μL, 0.03 mmol) at 0 °C, and then the mixture was stirred for 6 h at 40 °C. To the reaction mixture was added chloroform and saturated sodium bicarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give 4-acetoxy-3-methyl-2-pentyl-6-(2-phenethyl)tetrahydropyran (±)-**3ba** (27.4 mg, 27.4%, R_f=0.67 (*n*-hexane/EtOAc=3:1)), 4-acetoxy-3-methyl-2,6-dipentyltetrahydropyran (±)-**3bb** (17.0 mg, 18.9%, R_f=0.72 (*n*-hexane/EtOAc=3:1)), 4-acetoxy-3-methyl-2,6-di(2-phenethyl)tetrahydropyran (±)-**3aa** (17.2 mg, 15.7%, R_f=0.60 (*n*-hexane/EtOAc=3:1)), and 4-acetoxy-3-methyl-6-pentyl-2-(2-phenethyl)-tetrahydropyran (±)-**3ab** (17.5 mg, 17.5%, R_f=0.67 (*n*-hexane/EtOAc=3:1)), as colorless oils.

Compound (±)-**3ab**: IR (neat) 3085, 3062, 3027, 2955, 2930, 2858, 1739, 1604, 1496, 1466, 1375, 1242, 1093, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (d, *J*=6.8 Hz, 3H), 0.91 (t, *J*=6.6 Hz, 3H), 1.23–1.62 (m, 10H), 1.72 (m, 1H), 1.90–1.98 (m, 1H), 2.01 (dd, *J*=12.0, 2.8 Hz, 1H), 2.05 (s, 3H), 2.66 (m, 1H), 2.88 (m, 1H), 2.94 (ddd, *J*=9.8, 9.8, 2.5 Hz, 1H), 3.33 (m, 1H), 4.56 (ddd, *J*=10.8, 10.8, 4.8 Hz, 1H), 7.18–7.20 (m, 3H), 7.27 (t, *J*=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 14.1, 21.2, 22.7, 25.4, 31.7, 31.8, 34.9, 36.0, 37.8, 40.9, 74.9, 75.8, 79.6, 125.7, 128.2, 128.4, 142.3, 170.7; HRMS (FAB^+) calcd for $[(C_{21}H_{32}O_3)+H]^+$ 333.2430. Found 333.2415.

3.1.3. Prins cyclization of α-adduct of homoallylic alcohol (*ER*)-4a with 3-phenylpropanal 1a in acetic acid in the presence of TfOH to give 3aa (entry 1 in Table 2). To a solution of (5*E*,3*R*)-1-phenylhept-5-en-3-ol (*ER*)-**4a** (57.1 mg, 0.3 mmol) and 3-phenylpropanal **1a** (43.8 μL, 0.3 mmol) in acetic acid (172 μL, 3.0 mmol) was added trifluoromethanesulfonic acid (TfOH) (2.7 μL, 0.03 mmol) at 0 °C, and then the mixture was stirred for 6 h at 40 °C. To the reaction mixture was added chloroform and saturated sodium hydrogencarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give (2*S*,3*S*,4*S*,6*R*)-4-acetoxy-3-methyl-2,6-di(2-phenethyl)-tetrahydropyran **3aa** (84.4 mg, 76.8%, R_f=0.60 (*n*-hexane/EtOAc=3:1)) and (2*S*,3*R*,4*S*,6*R*)-4-hydroxy-3-methyl-2,6-di(2-phenethyl)tetrahydropyran **5aa** (8.0 mg, 8.2%, R_f=0.23 (*n*-hexane/EtOAc=3:1)), as colorless oils.

Compound **3aa**: $[\alpha]_D^{25}$ 18.8 (*c* 1.30, $CHCl_3$); IR (neat) 3084, 3062, 3026, 2952, 2927, 2858, 1737, 1603, 1496, 1455, 1391, 1245, 1088, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (d, *J*=6.5 Hz, 3H), 1.33 (q, *J*=11.5 Hz, 1H), 1.50 (m, 1H), 1.69–1.80 (m, 2H), 1.87–2.03 (m, 3H), 2.05 (s, 3H), 2.66–2.76 (m, 2H), 2.82–2.90 (m, 1H), 2.92–3.02 (m, 2H), 3.34 (m, 1H), 4.54 (ddd, *J*=10.8, 10.8, 4.8 Hz, 1H), 7.17–7.31 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 21.2, 31.8, 34.9, 37.6, 37.7, 40.8, 73.8, 75.7, 79.8, 125.8,

128.3, 128.5, 142.0, 142.3, 170.8. Anal. Calcd for $C_{24}H_{30}O_3$: C, 78.65; H, 8.25. Found: C, 78.90; H, 8.34.

Compound **5aa**: $[\alpha]_D^{25}$ −6.4 (*c* 1.00, $CHCl_3$); IR (neat) 3389, 3061, 3026, 2925, 2856, 1603, 1495, 1451, 1373, 1326, 1266, 1844, 1149, 1083, 1043, 748, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (d, J=6.4 Hz, 3H), 1.21–1.35 (m, 2H), 1.7–1.8 (m, 2H), 1.89–2.02 (m, 3H), 2.66–2.78 (m, 2H), 2.83–2.99 (m, 3H), 3.25–3.32 (m, 2H), 7.16–7.23 (m, 6H), 7.26–7.31 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.8, 31.87, 31.91, 34.9, 37.7, 41.4, 44.1, 73.6, 74.0, 79.7, 125.66, 125.73, 128.3, 128.5, 142.1, 142.4. Anal. Calcd for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70. Found: C, 81.39; H, 8.76.

3.1.4. PCR of α-adduct of homoallylic alcohol (5*E*,3*R*)-4a with hexanal 1b in acetic acid in the presence of TfOH to give 3ba (entry 2 in Table 2, shown in Section 3.1.1).

3.1.5. PCR of α-adduct of homoallylic alcohol (5*E*,3*R*)-4a with 2-ethylbutanal 1c in acetic acid in the presence of TfOH to give 3ca (entry 3 in Table 2).

To a solution of (5*E*,3*R*)-1-phenylhept-5-en-3-ol **4a** (57.1 mg, 0.3 mmol) and 2-ethylbutanal **1c** (39.0 μL, 0.3 mmol) in acetic acid (172 μL, 3.0 mmol) was added trifluoromethanesulfonic acid (TfOH) (5.4 μL, 0.06 mmol) at 0 °C, and then the mixture was stirred for 18 h at 40 °C. To the reaction mixture was added chloroform and saturated sodium hydrogencarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give (2*S*,3*S*,4*S*,6*R*)-4-acetoxy-2-(1-ethylpropyl)-3-methyl-6-(2-phenethyl)tetrahydropyran **3ca** (53.6 mg, 53.8%, R_f=0.70 (*n*-hexane/EtOAc=3:1)), (2*S*,3*R*,4*S*,6*R*)-4-hydroxy-2-(1-ethylpropyl)-3-methyl-6-(2-phenethyl)-tetrahydropyran **5ca** (3.0 mg, 3.4%, R_f=0.37 (*n*-hexane/EtOAc=3:1)), **3aa**, and **3cc** as colorless oils.

Compound **3ca**: $[\alpha]_D^{25}$ 4.1 (*c* 0.83, $CHCl_3$); IR (neat) 3084, 3062, 3027, 2964, 2932, 2874, 1740, 1604, 1496, 1455, 1376, 1243, 1110, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.79 (d, J=6.4 Hz, 3H), 0.90–0.94 (m, 6H), 1.21–1.36 (m, 3H), 1.41–1.59 (m, 3H), 1.62–1.85 (m, 3H), 1.95 (ddd, J=12.2, 4.8, 2.0 Hz, 1H), 2.05 (s, 3H), 2.60–2.68 (m, 1H), 2.74–2.81 (m, 1H), 3.06 (d, J=10.4 Hz, 1H), 3.26 (m, 1H), 4.57 (ddd, J=10.7, 10.7, 4.5 Hz, 1H), 7.15–7.18 (m, 3H), 7.24–7.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.2, 12.6, 12.7, 20.8, 21.3, 23.2, 31.7, 37.5, 37.8, 37.9, 41.9, 73.8, 76.5, 81.2, 125.6, 128.2, 128.4, 142.1, 170.7. Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.75; H, 9.66.

Compound **5ca**: $[\alpha]_D^{25}$ 11.0 (*c* 0.42, $CHCl_3$); IR (Nujol) 3289, 3025, 2926, 2863, 1602, 1494, 1458, 1379, 1351, 1319, 1116, 1061, 1034, 1011, 747, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89–0.94 (m, 9H), 1.19–1.35 (m, 3H), 1.40–1.57 (m, 5H), 1.63–1.72 (m, 1H), 1.82 (m, 1H), 1.88 (ddd, J=12.2, 4.8, 1.8 Hz, 1H), 2.60–2.69 (m, 1H), 2.75–2.82 (m, 1H), 2.97 (dd, J=9.9, 1.7 Hz, 1H), 7.13–7.19 (m, 3H), 7.25–7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.1, 12.5, 20.8, 23.2, 31.7, 37.8, 40.7, 41.5, 41.9, 74.2, 74.3, 81.1, 125.6, 128.2, 128.5, 142.4. Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.45; H, 10.60.

Compound **3cc**: R_f=0.73 (*n*-hexane/EtOAc =3:1); $[\alpha]_D^{25}$ 19.4 (*c* 1.00, $CHCl_3$); IR (neat) 2963, 2935, 2875, 1743, 1464, 1378, 1241, 1091, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.79 (d, J=6.4 Hz, 3H), 0.82–0.92 (m, 12H), 1.18–1.53 (m, 11H), 1.66 (m, 1H), 1.93 (ddd, J=12.4, 4.8, 2.0 Hz, 1H), 2.06 (s, 3H), 3.02, (dd, J=9.6, 2.0 Hz, 1H), 3.23 (ddd, J=11.2, 5.2, 2.0 Hz, 1H), 4.62 (ddd, J=10.8, 10.8, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 11.7, 12.2, 12.6, 12.8, 20.9, 21.42, 21.38, 22.0, 23.2, 35.0, 37.6, 42.0, 45.7, 76.5, 76.7, 81.3, 170.6. Anal. Calcd for $C_{18}H_{34}O_3$: C, 72.44; H, 11.48. Found: C, 72.61; H, 11.60; HRMS (EI) *m/z* calcd for $C_{18}H_{34}O_3$ 298.2508. Found 298.2494.

3.1.6. PCR of α-adduct of homoallylic alcohol (5*E*,3*R*)-4a with 6-benzyloxyhexanal 1d in acetic acid in the presence of TfOH to give 3da (entry 4 in Table 2).

To a solution of (5*E*,3*R*)-1-phenylhept-5-en-3-ol **4a** (57.1 mg, 0.3 mmol) and 6-benzyloxyhexanal **1d** (61.9 mg, 0.3 mmol) in acetic acid (172 μL, 3.0 mmol) was added trifluoromethanesulfonic acid (TfOH) (2.7 μL, 0.03 mmol) at 0 °C, and then the mixture was stirred for 6 h at 40 °C. To the reaction mixture was added chloroform and saturated sodium bicarbonate (4 mL), and extracted with chloroform (3× 2 mL). The combined extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give (2*S*,3*S*,4*S*,6*R*)-4-acetoxy-2-(5-benzyloxypentyl)-3-methyl-6-phenethyltetrahydropyran **3da** (69.8 mg, 53.0%, R_f=0.60 (*n*-hexane/EtOAc=3:1)), (2*S*,3*R*,4*S*,6*R*)-4-hydroxy-2-(5-benzyloxypentyl)-3-methyl-6-(2-phenethyl)-tetrahydropyran **5da** (6.0 mg, 5.1%, R_f=0.23 (*n*-hexane/EtOAc=3:1)), and **3aa** as colorless oils.

Compound **3da**: $[\alpha]_D^{25}$ 36.5 (*c* 0.97, $CHCl_3$); IR (neat) 3085, 3063, 3027, 2947, 2927, 2856, 1741, 1603, 1496, 1454, 1372, 1240, 1097, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (d, J=6.4 Hz, 3H), 1.29 (q, J=11.5 Hz, 1H), 1.38–150 (m, 5H), 1.61–1.72 (m, 5H), 1.85 (m, 1H), 1.98 (ddd, J=12.2, 5.2, 1.4 Hz, 1H), 2.04 (S, 3H), 2.62–2.70 (m, 1H), 2.74–2.81 (m, 1H), 2.96 (m, 1H), 3.29 (m, 1H), 3.49 (t, J=6.6 Hz, 2H), 4.50 (s, 2H), 4.54 (ddd, J=10.8, 10.8, 4.6 Hz, 1H), 7.15–7.18 (m, 3H), 7.24–7.33 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 21.2, 25.5, 26.3, 29.8, 31.7, 33.0, 37.6, 37.7, 40.8, 70.4, 72.9, 73.7, 75.8, 80.5, 125.7, 127.4, 127.5, 128.2, 128.4, 138.6, 141.9, 1070.7. Anal. Calcd for $C_{28}H_{38}FO$: C, 76.68; H, 8.73. Found: C, 76.75; H, 8.73.

Compound **5da**: $[\alpha]_D^{25}$ 12.0 (*c* 0.45, $CHCl_3$); IR (neat) 3400, 3061, 3027, 2935, 2857, 1603, 1495, 1454, 1367, 1325, 1274, 1244, 1208, 1097, 1027, 906, 824, 749, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, J=6.5 Hz, 3H), 1.16–1.31 (m, 2H), 1.36–1.48 (m, 4H), 1.62–1.73 (m, 4H), 1.83–1.92 (m, 2H), 2.64–2.71 (m, 1H), 2.75–2.82 (m, 1H), 2.88 (m, 1H), 3.24–3.31 (m, 2H), 3.49 (t, J=6.6 Hz, 2H), 4.50 (s, 2H), 7.17–7.19 (m, 3H), 7.25–7.34 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 25.5, 26.2, 29.8, 31.7, 32.9, 37.7, 41.4, 44.1, 70.5, 72.8, 73.7, 73.8, 80.5, 125.7, 127.4, 127.6,

128.26, 128.3, 128.5, 138.7, 142.1. Anal. Calcd for $C_{26}H_{36}O_3$: C, 78.75; H, 9.15. Found: C, 78.53; H, 9.36.

3.1.7. PCR of α-adduct of homoallylic alcohol (5*E*,3*R*)-4a with benzaldehyde 1e in acetic acid in the presence of TfOH to give 3ea (entry 5 in Table 2). To a solution of (5*E*,3*R*)-1-phenylhept-5-en-3-ol **4a** (57.1 mg, 0.3 mmol) and benzaldehyde **1e** (31.1 μL, 0.3 mmol) in acetic acid (172 μL, 3.0 mmol) was added trifluoromethanesulfonic acid (TfOH) (5.4 μL, 0.06 mmol) at 0 °C, and then the mixture was stirred for 5 h at 40 °C. To the reaction mixture was added chloroform and saturated sodium bicarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give (2*R*,3*R*,4*S*,6*R*)-4-acetoxy-3-methyl-2-phenyl-6-(2-phenethyl)tetrahydropyran **3ea** (70.4 mg, 69.4%, R_f=0.63 (*n*-hexane/EtOAc=3:1)), (2*R*,3*R*,4*S*,6*R*)-4-hydroxy-3-methyl-2-phenyl-6-(2-phenethyl)tetrahydropyran **5ea** (6.9 mg, 7.8%, R_f=0.23 (*n*-hexane/EtOAc=3:1)), and **3aa** as colorless oils.

Compound **3ea**: $[\alpha]_D^{25}$ 7.1 (*c* 1.17, $CHCl_3$); IR (neat) 3086, 3063, 3028, 2964, 2928, 2852, 1738, 1603, 1496, 1455, 1372, 1241, 1101, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.66 (d, *J*=6.8 Hz, 3H), 1.51 (q, *J*=11.8 Hz, 1H), 1.74–1.86 (m, 2H), 1.89–1.98 (m, 1H), 2.06 (s, 3H), 2.12 (dd, *J*=11.6, 4.0 Hz, 1H), 2.62–2.76 (m, 2H), 3.54 (m, 1H), 3.96 (d, *J*=9.6 Hz, 1H), 4.74 (ddd, *J*=10.8, 10.8, 4.8 Hz, 1H), 7.13–7.18 (m, 3H), 7.25–7.38 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 21.2, 31.4, 37.4, 37.5, 42.0, 74.6, 75.8, 84.5, 125.7, 127.5, 127.9, 128.2, 128.3, 128.4, 140.2, 141.8, 170.6. Anal. Calcd for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 78.30; H, 7.83.

Compound **5ea**: $[\alpha]_D^{25}$ 67.9 (*c* 0.38, $CHCl_3$); IR (neat) 3270, 3063, 3026, 2925, 2863, 1602, 1494, 1457, 1354, 1240, 1148, 1112, 1052, 975, 943, 918, 750, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.77 (d, *J*=6.6 Hz, 3H), 1.48 (m, 1H), 1.57 (m, 1H), 1.75–1.85 (m, 1H), 1.96 (m, 1H), 2.03 (ddd, *J*=12.3, 4.6, 1.8 Hz, 1H), 2.71 (m, 2H), 3.43–3.51 (m, 2H), 3.88 (d, *J*=10.0 Hz, 1H), 7.15–7.19 (m, 3H), 7.24–7.37 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 31.4, 37.4, 40.9, 45.1, 73.9, 74.8, 84.5, 125.7, 127.6, 127.8, 128.3, 128.5, 140.6, 142.0. Anal. Calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.26; H, 8.32.

3.1.8. PCR of α-adduct of homoallylic alcohol (5*E*,3*R*)-4a with 3-phenylpropenal 1f in acetic acid in the presence of TfOH to give 3fa (entry 6 in Table 2). To a solution of (5*E*,3*R*)-1-phenylhept-5-en-3-ol **4a** (57.1 mg, 0.3 mmol) and 3-phenylpropenal **1f** (40.0 mg, 0.3 mmol) in acetic acid (172 μL, 3.0 mmol) was added trifluoromethanesulfonic acid (TfOH) (2.7 μL, 0.03 mmol) at 0 °C, and then the mixture was stirred for 6 h at 40 °C. To the reaction mixture was added chloroform and saturated sodium bicarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give (2*S*,3*R*,4*S*,6*R*)-4-acetoxy-3-methyl-2-(2-phenylethenyl)-6-(2-phenethyl)tetrahydropyran **3fa** (73.0 mg, 66.8%, R_f=0.60 (*n*-hexane/EtOAc=3:1)) as a colorless oil, (2*S*,3*R*,4*S*,6*R*)-4-hydroxy-3-methyl-2-(2-phenylethenyl)-6-(2-phenethyl)-tetrahydropyran **5fa** (9.0 mg, 9.3%, R_f=0.22 (*n*-hexane/EtOAc=3:1)) as a white solid, and **3aa** as a colorless oil.

Compound **3fa**: $[\alpha]_D^{25}$ 6.0 (*c* 1.04, $CHCl_3$); IR (Nujol) 3083, 3062, 3025, 2923, 2854, 1741, 1495, 1455, 1377, 1236, 1097, 1036, 965 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, *J*=6.4 Hz, 3H), 1.40 (q, *J*=11.6 Hz, 1H), 1.57–1.67 (m, 1H), 1.71–1.80 (m, 1H), 1.89–1.98 (m, 1H), 2.04–2.08 (m, 4H), 2.66–2.81 (m, 2H), 3.46 (m, 1H), 3.64 (dd *J*=10.0, 7.6 Hz, 1H), 4.65 (ddd, *J*=10.7, 10.7, 4.5 Hz, 1H), 6.19 (dd, *J*=16.2, 2.4 Hz, 1H), 6.64 (d, *J*=16.0 Hz, 1H), 7.16–7.18 (m, 3H), 7.24–7.33 (m, 6H), 7.41 (d, *J*=6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 21.2, 31.6, 37.41, 37.43, 40.9, 74.1, 75.5, 82.4, 125.7, 126.5, 127.7, 127.9, 128.2, 128.36, 128.43, 132.9, 136.5, 141.7, 170.6. Anal. Calcd for $C_{24}H_{28}O_3$: C, 79.09; H, 7.74. Found: C, 79.22; H, 7.72.

Compound **5fa**: $[\alpha]_D^{25}$ 66.7 (*c* 0.21, $CHCl_3$); IR (Nujol) 3294, 3060, 3023, 2923, 2856, 1601, 1493, 1457, 1375, 1148, 1038, 970, 746, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (d, *J*=6.5 Hz, 3H), 1.35–1.44 (m, 2H), 1.73–1.82 (m, 1H), 1.92–2.03 (m, 3H), 2.68–2.82 (m, 2H), 3.38–3.46 (m, 2H), 6.62 (dd, *J*=15.9, 7.5 Hz, 1H), 6.62 (d, *J*=15.9 Hz), 7.16–7.34 (m, 8H), 7.42 (d, *J*=7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 31.6, 37.5, 40.9, 44.1, 73.7, 74.3, 82.5, 125.7, 126.6, 127.7, 128.3, 128.5, 132.7, 136.7, 142.0. Anal. Calcd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13. Found: C, 81.82; H, 8.32.

3.1.9. PCR of α-adduct of homoallylic alcohol (5*Z*,3*S*)-4a with 3-phenylpropanal 1a in acetic acid in the presence of TfOH to give 7aa (entry 1 in Table 3). To a solution of (5*Z*,3*S*)-1-phenylhept-5-en-3-ol (*ZS*)-**4a** (57.1 mg, 0.3 mmol) and 3-phenylpropanal **1a** (43.8 μL, 0.3 mmol) in acetic acid (172 μL, 3.0 mmol) was added trifluoromethanesulfonic acid (TfOH) (2.7 μL, 0.03 mmol) at 0 °C, and then the mixture was stirred for 6 h at 40 °C. To the reaction mixture was added chloroform and saturated sodium bicarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give (2*R*,3*S*,4*R*,6*S*)-4-acetoxy-3-methyl-2,6-di(2-phenethyl)-tetrahydropyran **7aa** (78.9 mg, 73.1%, R_f=0.58 (*n*-hexane/EtOAc=3:1)) and (2*R*,3*R*,4*R*,6*S*)-4-hydroxy-3-methyl-2,6-di(2-phenethyl)-tetrahydropyran **8aa** (8.0 mg, 8.2%, R_f=0.23 (*n*-hexane/EtOAc=3:1)), as colorless oils.

Compound **7aa**: $[\alpha]_D^{25}$ 2.3(*c* 1.25, $CHCl_3$); IR (neat) 3082, 3075, 3059, 2968, 2928, 2852, 1739, 1602, 1496, 1455, 1373, 1242, 1089, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, *J*=6.8 Hz, 3H), 1.51 (q, *J*=11.9 Hz, 1H), 1.57–1.77 (m, 3H), 1.97 (m, 3H), 2.03 (s, 3H), 2.62–2.75 (m, 2H), 2.79–2.88 (m, 2H), 32.9–3.35 (m, 2H), 4.91 (ddd, *J*=12.0, 4.8, 4.8 Hz, 1H), 7.17–7.29 (m, 3H), 7.27 (t, *J*=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.9, 14.1, 21.4, 22.7, 25.8, 31.8, 31.9, 32.1, 32.6, 35.5, 37.6, 73.8, 74.8, 78.4, 125.7, 128.2, 128.4, 141.9, 170.3. Anal. Calcd for $C_{24}H_{30}O_3$: C, 78.65; H, 8.25. Found: C, 78.63; H, 8.39.

Compound **8aa**: $[\alpha]_D^{25}$ 17.0 (*c* 1.66, $CHCl_3$); IR (Nujol) 3302, 3086, 3062, 3026, 2924, 2853, 1603, 1496, 1456, 1376, 1349, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, J=6.8 Hz, 3H), 1.37 (q, J=11.9 Hz, 1H), 1.56–1.65 (m, 2H), 1.67–1.81 (m, 3H), 1.87–2.04 (m, 2H), 2.63–2.75 (m, 2H), 2.80–2.88 (m, 2H), 3.23 (m, 2H), 3.78 (ddd, J=12.0, 4.8, 4.8 Hz, 1H), 7.16–7.21 (m, 6H), 7.27 (t, J=8.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.1, 31.9, 32.4, 34.6, 35.4, 37.5, 38.4, 71.0, 74.9, 77.5, 125.62, 125.65, 128.19, 128.21, 128.36, 141.9, 142.0; HRMS (EI) *m*/*z* calcd for $C_{22}H_{28}O_2$ 324.2089. Found 324.2042.

3.1.10. (2*R*,3*S*,4*R*,6*S*)-4-Acetoxy-3-methyl-2-pentyl-6-(2-phenethyl)tetrahydropyran 7ba (entry 2 in Table 3). To a solution of (5*Z*,3*S*)-1-phenylhept-5-en-3-ol (*ZS*)-**4a** (57.1 mg, 0.3 mmol) and hexanal **1b** (36.0 μL, 0.3 mmol) in acetic acid (172 μL, 3.0 mmol) was added trifluoromethanesulfonic acid (TfOH) (2.7 μL, 0.03 mmol) at 0 °C, and then the mixture was stirred for 6 h at 40 °C. To the reaction mixture was added chloroform and saturated sodium bicarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts was dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give (2*R*,3*S*,4*R*,6*S*)-4-acetoxy-3-methyl-2-pentyl-6-(2-phenethyl)tetrahydropyran **7ba** (55.7 mg, 57.0%, R_f=0.67 (*n*-hexane/EtOAc=3:1)), (2*R*,3*R*,4*R*,6*S*)-4-hydroxy-3-methyl-2-pentyl-6-(2-phenethyl)tetrahydropyran **8ba** (3.9 mg, 4.5%, R_f=0.33 (*n*-hexane/EtOAc=3:1)) as colorless oils, and trace of **7aa** (R_f=0.58 (*n*-hexane/EtOAc=3:1)) and **7bb** (R_f=0.76 (*n*-hexane/EtOAc=3:1)).

Compound **7ba**: $[\alpha]_D^{25}$ 0.9 (*c* 0.85, $CHCl_3$); IR (neat) 3085, 3062, 3027, 2933, 2858, 1740, 1603, 1946, 1455, 1364, 1243, 1102, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88–0.92 (m, 6H), 1.32 (m, 6H), 1.46–1.55 (m, 2H), 1.60–1.73 (m, 3H), 1.85–1.99 (m, 2H), 2.04 (s, 3H), 2.65–2.72 (m, 1H), 2.78–2.83 (m, 1H), 3.31 (m, 3H), 4.91 (ddd, J=12.0, 4.8, 4.8 Hz, 1H), 7.17–7.19 (m, 3H), 7.27 (t, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.9, 14.1, 21.4, 22.7, 25.8, 31.8, 31.9, 32.1, 32.6, 35.5, 37.6, 73.8, 74.8, 78.4, 125.7, 128.2, 128.4, 141.9, 170.3. Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.67; H, 9.87.

Compound **7bb**: $[\alpha]_D^{25}$ 28.4 (*c* 0.45, $CHCl_3$); IR (neat) 2955, 2932, 2859, 1744, 1466, 1364, 1243, 1100, 1031 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86–0.90 (m, 9H), 1.28–1.16 (m, 15H), 1.53–1.58 (m, 2H), 1.66 (d, J=12.0 Hz, 1H), 1.99 (m, 1H), 2.05 (s, 3H), 3.29–3.34 (m, 2H), 4.94 (ddd, J=12.0, 4.8, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.8, 14.1, 21.4, 22.7, 25.3, 25.7, 31.8, 31.9, 32.1, 32.5, 35.4, 36.0, 73.9, 76.1, 78.5, 170.4. Anal. Calcd for $C_{18}H_{34}O_3$: C, 72.44; H, 11.48. Found: C, 72.20; H, 11.20.

Compound **8ba**: $[\alpha]_D^{25}$ 8.1 (*c* 0.30, $CHCl_3$); IR (neat) 3368, 3085, 3060, 3025, 2930, 2858, 1601, 1495, 1455, 1347, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, J=7.2 Hz, 3H), 0.91 (t, J=7.0 Hz, 3H), 1.25–1.42 (m, 8H), 1.58–1.72 (m, 4H), 1.83 (m, 1H), 1.91 (m, 1H), 2.70 (m, 1H), 2.80 (m, 1H), 3.21–3.27 (m, 2H), 3.84 (ddd, J=12.0, 4.8, 4.8 Hz, 1H), 7.16–7.20 (m, 3H), 7.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0, 14.2, 22.7, 25.9, 31.8, 31.9, 32.7, 35.5, 37.5, 38.3, 71.4, 74.8, 78.7, 125.6, 128.2, 128.4, 142.0; HRMS (EI) *m*/*z* calcd for $C_{19}H_{30}O_2$ 290.2246. Found 290.2272.

3.1.11. (2*R*,3*R*,4*R*,6*S*)-4-Acetoxy-3-methyl-2-(2-phenylethenyl)-6-(2-phenylethyl)-tetrahydropyran 7fa (entry 3 in Table 3). To a solution of (5*Z*,3*S*)-1-phenylhept-5-en-3-ol (*ZS*)-**4a** (40.0 mg, 0.21 mmol) and 3-phenylpropenal **1f** (28.3 mg, 0.21 mmol) in acetic acid (121 μL, 2.1 mmol) was added trifluoromethanesulfonic acid (TfOH) (1.9 μL, 0.021 mmol) at 0 °C, and then the mixture was stirred for 20 h at 40 °C. To the reaction mixture was added chloroform and saturated sodium bicarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give (2*R*,3*S*,4*R*,6*S*)-4-acetoxy-3-methyl-2-(2-phenylethenyl)-6-(2-phenethyl)tetrahydropyran **7fa** (43.5 mg, 56.8%, R_f=0.60 (*n*-hexane/EtOAc=3:1)), (2*R*,3*R*,4*R*,6*S*)-4-hydroxy-3-methyl-2-(2-phenylethenyl)-6-(2-phenethyl)-tetrahydropyran **8fa** (4.6 mg, 6.8%, R_f=0.22 (*n*-hexane/EtOAc=3:1)), as colorless oils. **7fa**: $[\alpha]_D^{25}$ −6.8 (*c* 0.53, $CHCl_3$); IR (neat) 3082, 3060, 3026, 2976, 2942, 2859, 1739, 1601, 1496, 1450, 1365, 1242, 1094, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, J=6.8 Hz, 3H), 1.60 (q, J=11.6 Hz, 1H), 1.72 (m, 1H), 1.80 (m, 1H), 1.95–2.03 (m, 1H), 2.06 (s, 3H), 2.19 (m, 1H), 2.71–2.87 (m, 2H), 3.47 (m, 1H), 4.14 (m, 1H), 5.04 (ddd, J=12.0, 4.8, 4.8 Hz, 1H), 6.16 (dd, J=16.0, 4.8 Hz, 1H), 6.64 (d, J=16.0 Hz, 1H), 7.17–7.41 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.4, 21.3, 31.6, 31.7, 36.7, 37.5, 73.3, 74.9, 78.4, 125.7, 126.3, 127.4, 128.3, 128.35, 128.40, 128.43, 130.0, 136.9, 141.8, 170.3. Anal. Calcd for $C_{24}H_{28}O_3$: C, 79.09; H, 7.74. Found: C, 79.09; H, 7.74.

Compound **8fa**: $[\alpha]_D^{25}$ −42.6 (*c* 1.16, $CHCl_3$); IR (Nujol) 3401, 3081, 3059, 3024, 2924, 2855, 1599, 1493, 1458, 1376, 1084, 1056, 1028, 970 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, J=6.8 Hz, 3H), 1.43–1.52 (m, 2H), 1.69 (m, 1H), 1.76–1.84 (m, 1H), 1.95–2.06 (m, 2H), 2.73–2.88 (m, 2H), 3.39 (m, 1H), 3.98 (m, 1H), 4.06 (m, 1H), 6.20 (dd, J=16.4, 5.2 Hz, 1H), 6.64 (d, J=16.4 Hz, 1H), 7.17–7.34 (m, 8H), 7.41 (d, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.5, 31.8, 35.1, 37.5, 39.6, 71.1, 74.9, 78.7, 125.7, 126.3, 127.3, 128.3, 128.5, 128.9, 129.8. Anal. Calcd for HRMS (EI) *m*/*z* calcd for $C_{22}H_{26}O_2$ 322.1933. Found 322.1920.

3.1.12. (2*S*,3*S*,4*S*,6*R*)-4-Fluoro-3-methyl-2,6-di(2-phenylethyl)tetrahydropyran 10aa (entry 1 in Table 4). To a solution of (5*E*,3*R*)-1-phenylhept-5-en-3-ol (*ER*)-**4a** (57.1 mg, 0.3 mmol) and 3-phenylpropanal **1a** (43.8 μL, 0.3 mmol) in dichloromethane (3 mL) was added boron trifluoride diethyl etherate ($Et_2O{\cdot}BF_3$) (120.3 μL, 0.45 mmol) at −20 °C, and then the mixture was stirred for 1 h at −20 °C. To the reaction mixture was added chloroform and saturated sodium bicarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1

as eluents) to give (2*S*,3*S*,4*S*,6*R*)-4-fluoro-3-methyl-2,6-di(2-phenethyl)-tetrahydropyran **10aa** (62.0 mg, 63.3%, R_f=0.72 (*n*-hexane/EtOAc=3:1)) and (2*S*,3*R*,4*S*,6*R*)-4-hydroxy-3-methyl-2,6-di(2-phenethyl)tetrahydropyran **5aa** (14.7 mg, 15.1%, R_f=0.23 (*n*-hexane/EtOAc=3:1)), as colorless oils.

Compound **10aa**: $[\alpha]_D^{25}$ −1.2 (*c* 0.84, $CHCl_3$); IR (neat) 3061, 3026, 2945, 2925, 2855, 1603, 1496, 1452, 1372, 1324, 1271, 1243, 1159, 1090, 1050, 995, 909, 875, 821, 751, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, *J*=5.2 Hz, 3H), 1.45–1.57 (m, 2H), 1.72–1.81 (m, 2H), 1.91–2.09 (m, 3H), 2.66–2.78 (m, 2H), 2.84–2.99 (m, 3H), 3.26 (m, 1H), 4.17 (dddd, *J*=49.6, 10.5, 10.5, 5.0 Hz, 1H), 7.18–7.23 (m, 6H), 7.26–7.31 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 31.9, 34.6, 37.7, 38.6 (d, $^2J_{CF}$=17 Hz), 42.3 (d, $^2J_{CF}$=16 Hz), 73.3 (d, $^3J_{CF}$=12 Hz), 79.0 (d, $^3J_{CF}$=8 Hz), 94.5 (d, $^1J_{CF}$=177 Hz), 125.6, 125.7, 128.19, 128.22, 128.3, 141.7, 142.0; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ −177.4 (d, *J*=75.3 Hz). Anal. Calcd for $C_{22}H_{27}FO$: C, 80.94; H, 8.34. Found: C, 80.73; H, 8.51.

3.1.13. (2*S*,3*S*,4*S*,6*R*)-4-Fluoro-3-methyl-2-pentyl-6-(2-phenethyl)tetrahydropyran 10ba (entry 2 in Table 4). To a solution of (5*E*,3*R*)-1-phenylhept-5-en-3-ol (*ER*)-**4a** (57.1 mg, 0.3 mmol) and hexanal **1b** (36.2 μL, 0.3 mmol) in dichloromethane (3 mL) was added boron trifluoride diethyl etherate ($Et_2O\cdot BF_3$) (59.8 μL, 0.45 mmol) at −20 °C, and then the mixture was stirred for 4 h at −20 °C. To the reaction mixture was added chloroform and saturated sodium hydrogencarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give (2*S*,3*S*,4*S*,6*R*)-4-fluoro-3-methyl-2-pentyl-6-(2-phenethyl)tetrahydropyran **10ba** (64.7 mg, 73.8%, R_f=0.80 (*n*-hexane/EtOAc=3:1)) and (2*S*,3*R*,4*S*,6*R*)-4-hydroxy-3-methyl-2,6-di(2-phenethyl)tetrahydropyran **5ba** (12.4 mg, 14.2%, R_f=0.33 (*n*-hexane/EtOAc=3:1)), as colorless oils.

Compound **10ba**: $[\alpha]_D^{25}$ 26.0 (*c* 1.27, $CHCl_3$); IR (neat) 3085, 3027, 3027, 2952, 2928, 2858, 1603, 1496, 1466, 1455, 1379, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J*=6.6 Hz, 3H), 0.97 (d, *J*=6.4 Hz, 3H), 1.29–1.54 (m, 8H), 1.58–1.76 (m, 3H), 1.91 (m, 1H), 2.02 (m, 1H), 2.69 (m, 1H), 2.80 (m, 1H), 2.88 (t, *J*=9.4 Hz, 3H), 4.15 (dddd, *J*=49.9, 10.5, 10.5, 5.1 Hz, 1H), 7.17–7.19 (m, 3H), 7.24–7.29 (M, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7 (d, $^3J_{CF}$=1.6 Hz), 14.2, 22.8, 25.3, 31.7, 31.9, 32.7 (d, $^4J_{CF}$=1.7 Hz), 37.6, 38.5 (d, $^2J_{CF}$=17.4 Hz), 42.3 (d, $^2J_{CF}$=15.7 Hz), 73.1 (d, $^3J_{CF}$=11.6 Hz), 80.0 (d, $^3J_{CF}$=8.2 Hz), 94.8 (d, $^1J_{CF}$=175.7 Hz), 125.7, 128.2, 128.5, 141.9; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ −177.2 (dt, *J*=49.7, 9.6 Hz). Anal. Calcd for $C_{19}H_{29}FO$: C, 78.04; H, 10.00. Found: C, 77.99; H, 10.18.

3.1.14. (2*S*,3*S*,4*S*,6*R*)-2-(5-Benzyloxypentyl)-4-fluoro-3-methyl-6-(2-phenethyl)tetrahydropyran 10da (entry 3 in Table 4). To a solution of (5*E*,3*R*)-1-phenylhept-5-en-3-ol (*ER*)-**4a** (57.1 mg, 0.3 mmol) and 6-benzyloxyhexanal **1d** (61.9 μL, 0.3 mmol) in dichloromethane (3 mL) was added boron trifluoride diethyl etherate ($Et_2O\times BF_3$) (120.3 μL, 0.45 mmol) at −20 °C, and then the mixture was stirred for 4 h at −20 °C. To the reaction mixture was added chloroform and saturated sodium bicarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give (2*S*,3*S*,4*S*,6*R*)-2-(5-benzyloxypentyl)-4-fluoro-3-methyl-6-(2-phenethyl)tetrahydropyran **10da** (65.0 mg, 54.3%, R_f=0.68 (*n*-hexane/EtOAc=3:1)) and (2*S*,3*R*,4*S*,6*R*)-2-(5-benzyloxypentyl)-4-hydroxy-3-methyl-6-(2-phenethyl)-tetrahydropyran **5da** (23.0 mg, 19.3%, R_f=0.23 (*n*-hexane/EtOAc=3:1)), as colorless oils.

Compound **10da**: $[\alpha]_D^{25}$ 19.7 (*c* 1.18, $CHCl_3$); IR (neat) 3062, 3028, 2934, 2857, 1603, 1495, 1454, 1366, 1323, 1269, 1196, 1162, 1098, 996, 905, 824, 741, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, *J*=6.4 Hz, 3H), 1.47–1.53 (m, 6H), 1.60–1.76 (m, 5H), 1.91 (m, 1H), 2.03 (m, 1H), 2.64–2.72 (m, 1H), 2.76–2.83 (m, 1H), 2.88 (t, *J*=9.1 Hz, 1H), 3.21 (m, 1H), 3.49 (t, *J*=6.6 Hz, 2H), 4.17 (dddd, *J*=49.5, 10.5, 10.5, 5.1 Hz, 1H), 4.51 (s, 2H), 7.16–7.20 (m, 3H), 7.25–7.34 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 25.5, 26.2, 29.8, 31.7, 32.6, 37.6, 38.4 (d, $^2J_{CF}$=17 Hz), 42.2 (d, $^2J_{CF}$=16 Hz), 70.4, 72.9, 73.1 (d, $^3J_{CF}$=12 Hz), 79.9 (d, $^3J_{CF}$=8 Hz), 94.8 (d, $^1J_{CF}$=176 Hz), 125.8, 127.4, 127.6, 128.3, 128.5, 138.6, 141.9; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ −177.3 (d, *J*=37.6 Hz); HRMS (EI) *m*/*z* calcd for $C_{22}H_{25}FO$ 398.2621. Found 398.2617.

3.1.15. (2*R*,3*S*,4*S*,6*R*)-4-Fluoro-3-methyl-2-phenyl-6-(2-phenethyl)tetrahydropyran 10ea (entry 4 in Table 4). To a solution of (5*E*,3*R*)-1-phenylhept-5-en-3-ol (*ER*)-**4a** (57.1 mg, 0.3 mmol) and 6-benzaldehyde **1e** (30.5 μL, 0.3 mmol) in dichloromethane (3 mL) was added boron trifluoride diethyl etherate ($Et_2O\cdot BF_3$) (120.3 μL, 0.45 mmol) at −20 °C, and then the mixture was stirred for 4 h at −20 °C. To the reaction mixture was added chloroform and saturated sodium bicarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give (2*R*,3*S*,4*S*,6*R*)-4-fluoro-3-methyl-2-phenyl-6-(2-phenethyl)-tetrahydropyran **10ea** (54.0 mg, 60.3%, R_f=0.70 (*n*-hexane/EtOAc=3:1)) and (2*R*,3*R*,4*S*,6*R*)-4-hydroxy-3-methyl-2-phenyl-6-(2-phenethyl)tetrahydropyran **5ea** (16.6 mg, 18.7%, R_f=0.23 (*n*-hexane/EtOAc=3:1)), as colorless oils.

Compound **10ea**: $[\alpha]_D^{25}$ 77.1 (*c* 1.10, $CHCl_3$); IR (neat) 3062, 3029, 2927, 2856, 1603, 1496, 1454, 1374, 1305, 1248, 1216, 1157, 1067, 1033, 1006, 915, 756, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.79 (d, *J*=6.5 Hz, 3H), 1.68 (quint, *J*=11.1 Hz, 1H), 1.77–1.88 (m, 2H), 1.99 (m, 1H), 2.18 (m, 1H), 2.71 (m, 2H), 3.46 (m, 1H), 3.87 (dd, *J*=10.1, 0.7 Hz, 1H), 4.36 (dddd, *J*=49.3, 10.2, 10.2, 4.8 Hz, 1H), 7.15–7.20 (m, 3H), 7.25–7.38 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 31.4, 37.3, 38.2 (d, $^2J_{CF}$=17 Hz), 43.4 (d, $^2J_{CF}$=16 Hz), 74.0 (d, $^2J_{CF}$=12 Hz), 83.8 (d, $^3J_{CF}$=9 Hz), 94.8 (d, $^1J_{CF}$=177 Hz), 125.8, 127.5, 128.0, 128.30, 128.34, 128.5, 139.9, 141.8; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ −177.1

(d, J=37.6 Hz). Anal. Calcd for $C_{20}H_{23}FO$: C, 80.50; H, 7.77. Found: C, 80.25; H, 7.96.

3.1.16. (2*S*,3*S*,4*S*,6*R*)-4-Fluoro-3-methyl-2-(2-phenylethenyl)-6-(2-phenethyl)tetrahydropyran 10fa (entry 4 in Table 4). To a solution of (5*E*,3*R*)-1-phenylhept-5-en-3-ol (*ER*)-**4a** (57.1 mg, 0.3 mmol) and 2-phenylpropenal **1f** (37.8 μL, 0.3 mmol) in dichloromethane (3 mL) was added boron trifluoride diethyl etherate ($Et_2O\cdot BF_3$) (120.3 μL, 0.45 mmol) at −20 °C, and then the mixture was stirred for 4 h at −20 °C. To the reaction mixture was added chloroform and saturated sodium bicarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give (2*S*,3*S*,4*S*,6*R*)-4-fluoro-3-methyl-2-(2-phenylethenyl)-6-(2-phenethyl)tetrahydropyran **10fa** (42.1 mg, 37.1%, R_f=0.68 (*n*-hexane/EtOAc=3:1)) as colorless oil and (2*S*,3*R*,4*S*,6*R*)-4-hydroxy-3-methyl-2-(2-phenylethenyl)-6-(2-phenethyl)-tetrahydropyran **5fa** (16.9 mg, 17.5%, R_f=0.22 (*n*-hexane/EtOAc=3:1)), as a white solid.

Compound **10fa**: $[\alpha]_D^{25}$ 80.9 (*c* 0.87, $CHCl_3$); IR (Nujol) 3063, 3019, 2924, 2856, 1600, 1493, 1457, 1376, 1316, 1157, 1093, 1066, 1031, 997, 970, 749, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, J=6.5 Hz, 3H), 1.52–1.71 (m, 2H), 1.75–1.83 (m, 1H), 1.99 (m, 1H), 2.11 (m, 1H), 2.68–2.82 (m, 2H), 3.37 (m, 1H), 3.55 (t, J=8.7 Hz, 1H), 4.26 (dddd, J=49.3, 10.5, 10.5, 5.0 Hz, 1H), 6.19 (dd, J=15.9, 7.4 Hz, 1H), 6.62 (d, J=15.9 Hz, 1H), 7.16–7.42 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 31.5, 37.3, 38.1 (d, $^2J_{CF}$=17 Hz), 42.3 (d, $^2J_{CF}$=16 Hz), 73.6 (d, $^3J_{CF}$=12 Hz), 81.8 (d, $^2J_{CF}$=9 Hz), 94.4 (d, $^1J_{CF}$=177 Hz), 125.8, 126.6, 127.6, 127.8, 128.3, 128.47, 128.52, 133.0, 136.5, 141.7; ^{19}F NMR (376.3 MHz, $CDCl_3$) δ −177.4 (d, J=75.3 Hz). Anal. Calcd for $C_{22}H_{25}FO$: C, 81.45; H, 7.77. Found: C, 81.59; H, 7.94.

3.1.17. (2*S*,3*S*,4*S*,6*R*)-4-Chloro-3-methyl-2,6-di(2-phenethyl)tetrahydropyran 11aa (entry 6 in Table 4). To a suspension of powdered anhydrous aluminum chloride (60 mg, 0.45 mmol) and molecular sieves (4 Å, 15 mg) in dichloromethane (1.5 mL) was added a solution of (5*E*,3*R*)-1-phenylhept-5-en-3-ol (*ER*)-**4a** (57.1 mg, 0.3 mmol) and 3-phenylpropanal **1a** (43.8 μL, 0.3 mmol) in dichloromethane (1.5 mL) at −20 °C, and then the mixture was stirred for 1 h at −20 °C. To the reaction mixture was added chloroform and saturated sodium hydrogencarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give (2*S*,3*S*,4*S*,6*R*)-4-chloro-3-methyl-2,6-di(2-phenethyl)tetrahydropyran **11aa** (75.9 mg, 74.4%, R_f=0.73 (*n*-hexane/EtOAc=3:1)) as a colorless oil.

Compound **11aa**: $[\alpha]_D^{25}$ 1.0 (*c* 1.00, $CHCl_3$); IR (neat) 3061, 3026, 2926, 2852, 1602, 1495, 1451, 1380, 1323, 1284, 1258, 1182, 1150, 1090, 963, 941, 878, 840, 753, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (d, J=6.5 Hz, 3H), 1.56 (m, 1H), 1.68–1.81 (m, 3H), 1.87–2.03 (m, 2H), 2.15 (ddd, J=12.8, 4.6, 1.6 Hz, 1H), 2.66–2.76 (m, 2H), 2.82–2.88 (m, 1H), 2.89–2.97 (m, 2H), 3.25 (m, 1H), 3.62 (ddd, J=11.2, 11.2, 6.5 Hz, 1H), 7.17–7.23 (m, 6H), 7.27–7.31 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 31.72, 31.76, 35.2, 37.4, 43.2, 44.8, 64.0, 75.1, 80.7, 125.77, 125.84, 128.35, 128.37, 128.5, 141.8, 142.2. Anal. Calcd for $C_{22}H_{27}ClO$: C, 77.06; H, 7.94. Found: C, 76.92; H, 7.95.

3.1.18. (2*S*,3*S*,4*S*,6*R*)-4-Chloro-3-methyl-2-(2-phenylethenyl)-6-(2-phenethyl)-tetrahydropyran 11fa (entry 7 in Table 4). To a suspension of powdered anhydrous aluminum chloride (60 mg, 0.45 mmol) and molecular sieves (4 Å, 15 mg) in dichloromethane (1.5 mL) was added a solution of (5*E*,3*R*)-1-phenylhept-5-en-3-ol (*ER*)-**4a** (57.1 mg, 0.3 mmol) and 3-phenylpropenal **1f** (37.8 μL, 0.3 mmol) in dichloromethane (1.5 mL) at −20 °C, and then the mixture was stirred for 1 h at −20 °C. To the reaction mixture was added chloroform and saturated sodium bicarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts was dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give (2*S*,3*S*,4*S*,6*R*)-4-chloro-3-methyl-2-(2-phenylethenyl)-6-(2-phenethyl)-tetrahydropyran **11fa** (51.4 mg, 50.2%, R_f=0.70 (*n*-hexane/EtOAc=3:1)) as a colorless oil.

Compound **11fa**: $[\alpha]_D^{25}$ 93.7 (*c* 0.48, $CHCl_3$); IR (neat) 3060, 3026, 2927, 2854, 1719, 1602, 1495, 1451, 1379, 1357, 1319, 1282, 1197, 1152, 1086, 1066, 1033, 968, 754, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (d, J=6.4 Hz, 3H), 1.64–1.84 (m, 3H), 1.94 (m, 1H), 2.20 (dd, J=12.6, 3.0 Hz, 1H), 2.67–2.81 (m, 2H), 3.38 (m, 1H), 3.59 (t, J=8.4 Hz, 1H), 3.72 (ddd, J=11.2, 11.2, 4.4 Hz, 1H), 6.19 (dd, J=16.2, 7.4 Hz, 1H), 6.63 (d, J=15.6 Hz, 1H), 7.17–7.20 (m, 3H), 7.24–7.35 (m, 5H), 7.42 (d, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.0, 31.5, 37.2, 42.8, 44.9, 63.6, 83.5, 125.8, 126.5, 127.8, 127.9, 128.3, 128.4, 128.5, 133.1, 136.4, 141.6. Anal. Calcd for $C_{22}H_{25}ClO$: C, 77.51; H, 7.39. Found: C, 77.39; H, 7.46.

3.1.19. (2*S*,3*S*,4*S*,6*R*)-3-Methyl-2,6-di(2-phenethyl)-4-tosyloxytetrahydropyran 12aa (entry 8 in Table 4). To a solution of (5*E*,3*R*)-1-phenylhept-5-en-3-ol (*ER*)-**4a** (57.1 mg, 0.3 mmol) and 3-phenylpropanal **1a** (43.8 μL, 0.3 mmol) in dichloromethane (0.6 mL) was added *p*-toluenesulfonic acid monohydrate ($TSA\cdot H_2O$) (77.5 mg, 0.45 mmol) at room temperature, and then the mixture was stirred for 20 h. To the reaction mixture was added chloroform and saturated sodium bicarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give (2*S*,3*S*,4*S*,6*R*)-3-methyl-2,6-di(2-phenethyl)-4-tosyloxytetrahydropyran **12aa** (103.7 mg, 72.2%, R_f=0.52 (*n*-hexane/EtOAc=3:1)) and (2*S*,3*R*,4*S*,6*R*)-4-hydroxy-3-methyl-2,6-di(2-phenethyl)tetrahydropyran **5aa** (17.7 mg, 18.2%, R_f=0.23 (*n*-hexane/EtOAc=3:1)), as colorless oils.

Compound **12aa**: $[\alpha]_D^{25}$ 16.6 (*c* 1.00, $CHCl_3$); IR (neat) 3061, 3027, 2926, 2855, 1600, 1495, 1452, 1365, 1179,

1093, 1045, 929, 884, 854, 815, 750, 698, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.70 (d, J=6.4 Hz, 3H), 1.45–1.58 (m, 2H), 1.68–1.76 (m, 2H), 1.84–1.97 (m, 2H), 2.04 (ddd, J=12.6, 4.8, 2.0 Hz, 1H), 2.43 (s, 3H), 2.62–2.73 (m, 2H), 2.78–2.93 (m, 3H), 3.23 (m, 1H), 4.23 (ddd, J=10.8, 10.8, 5.1 Hz, 1H), 7.16–7.21 (m, 6H), 7.25–7.33 (m, 6H), 7.78 (d, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 21.5, 31.5, 31.6, 34.7, 34.7, 37.3, 39.0, 41.2, 73.4, 79.3, 84.2, 125.6, 125.7, 127.5, 128.16, 128.18, 128.3, 129.6, 134.1, 141.5, 144.4. Anal. Calcd for $C_{29}H_{34}O_4S$: C, 72.77; H, 7.16. Found: C, 72.82; H, 7.03.

3.1.20. (2*S*,3*S*,4*S*,6*R*)-2-(1-Ethylpropyl)-3-methyl-6-(2-phenethyl)-4-tosyloxytetrahydropyran 12ca (Table 4, entry 9). To a solution of (5*E*,3*R*)-1-phenylhept-5-en-3-ol (*ER*)-**4a** (57.1 mg, 0.3 mmol) and 2-ethylbutanal **1c** (39.0 μL, 0.3 mmol) in dichloromethane (0.6 mL) was added *p*-toluenesulfonic acid monohydrate (TSA·H_2O) (77.5 mg, 0.45 mmol) at room temperature, and then the mixture was stirred for 20 h. To the reaction mixture was added chloroform and saturated sodium bicarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give (2*S*,3*S*,4*S*,6*R*)-2-(1-ethylpropyl)-3-methyl-6-(2-phenethyl)-4-tosyloxytetrahydropyran **12ca** (81.3 mg, 60.1%, R_f=0.68 (*n*-hexane/EtOAc=3:1)) and (2*S*,3*R*,4*S*,6*R*)-4-hydroxy-3-methyl-2-(1-ethylpropyl)-6-(2-phenethyl)-tetrahydropyran **5ca** (12.6 mg, 14.5%, R_f=0.37 (*n*-hexane/EtOAc=3:1)), as colorless oils.

Compound **12ca**: $[\alpha]_D^{25}$ 30.6 (*c* 1.00, $CHCl_3$); IR (neat) 3061, 3028, 2961, 2933, 2873, 1600, 1495, 1457, 1365, 1178, 1097, 1064, 1020, 933, 905, 856, 816, 754, 696, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.67 (d, J=6.5 Hz, 3H), 0.85–0.90 (m, 6H), 1.16–1.29 (m, 2H), 1.37–1.82 (m, 7H), 1.99 (ddd, J=12.3, 4.8, 1.7 Hz, 1H), 2.44 (s, 3H), 2.57–2.65 (m, 1H), 2.71–2.78 (m, 1H), 2.97 (d, J=10.0 Hz, 1H), 3.148 (m, 1H), 4.27 (ddd, J=10.7, 10.7, 4.8 Hz, 1H), 7.14 (d, J=7.2 Hz, 2H), 7.19 (d, J=7.2 Hz, 1H), 7.27 (m, 2H), 7.33 (d, J=8.1 Hz, 2H), 7.79 (d, J=8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.0, 12.4, 12.5, 20.6, 21.6, 23.0, 31.5, 37.4, 38.0, 39.1, 41.8, 73.5, 81.0, 85.3, 125.7, 127.7, 128.3, 128.5, 129.7, 141.9, 144.5. Anal. Calcd for $C_{26}H_{36}O_4S$: C, 70.23; H, 8.16. Found: C, 70.48; H, 8.31.

3.1.21. (2*S*,3*S*,4*S*,6*R*)-2-(5-Benzyloxypentyl)-3-methyl-6-(2-phenethyl)-4-tosyloxytetrahydropyran 12da (entry 10 in Table 4). To a solution of (5*E*,3*R*)-1-phenylhept-5-en-3-ol (*ER*)-**4a** (57.1 mg, 0.3 mmol) and 6-benxyloxyhexanal **1d** (61.9 mg, 0.3 mmol) in dichloromethane (0.3 mL) was added *p*-toluenesulfonic acid monohydrate (TSA·H_2O) (51.7 mg, 0.3 mmol) at room temperature, and then the mixture was stirred for 20 h. To the reaction mixture was added chloroform and saturated sodium bicarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts were dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give (2*S*,3*S*,4*S*,6*R*)-2-(5-benzyloxypentyl)-3-methyl-6-(2-phenethyl)-4-tosyloxytetrahydropyran **12da** (96.6 mg, 58.4%, R_f=0.50 (*n*-hexane/EtOAc=3:1)) and (2*S*,3*R*,4*S*,6*R*)-2-(5-benzyloxypentyl)-4-hydroxy-3-methyl-6-(2-phenethyl)tetrahydropyran **5da** (22.0 mg, 18.4%, R_f=0.23 (*n*-hexane/EtOAc=3:1)), as colorless oils.

Compound **12da**: $[\alpha]_D^{25}$ 24.8 (*c* 1.05, $CHCl_3$); IR (neat) 3061, 3029, 2933, 2857, 1708, 1599, 1495, 1453, 1364, 1179, 1097, 1025, 931, 849, 816, 749, 698, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.70 (d, J=6.5 Hz, 3H), 1.34–1.69 (m, 11H), 1.82 (m, 1H), 2.01 (ddd, J=12.4, 5.0, 1.1 Hz, 1H), 2.43 (s, 3H), 2.59–2.67 (m, 1H), 2.70–2.77 (m, 1H), 3.18 (m, 1H), 3.47 (t, J=6.6 Hz, 2H), 4.23 (ddd, J=10.7, 10.7, 4.8 Hz, 1H), 4.49 (s, 2H), 7.13–7.20 (m, 3H), 7.25–7.33 (m, 9H), 7.78 (d, J=8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.9, 14.2, 21.6, 25.3, 26.1, 29.7, 31.5, 32.9, 37.3, 39.0, 41.2, 60.4, 70.4, 72.8, 73.3, 80.3, 84.5, 125.8, 127.4, 127.6, 127.7, 128.3, 128.5, 129.7, 134.3, 138.6, 141.7, 144.6. Anal. Calcd for $C_{33}H_{42}O_5S$: C, 71.97; H, 7.69. Found: C, 71.77; H, 7.85.

3.1.22. (2*R*,3*S*,4*S*,6*R*)-3-Methyl-2-phenyl-6-(2-phenylethyl)-4-tosyloxytetrahydropyran 12ea (entry 11 in Table 4). To a solution of (5*E*,3*R*)-1-phenylhept-5-en-3-ol (*ER*)-**4a** (57.1 mg, 0.3 mmol) and benzaldehyde **1e** (30.5 μL, 0.3 mmol) in dichloromethane (0.3 mL) was added *p*-toluenesulfonic acid monohydrate (TSA·H_2O) (51.7 mg, 0.3 mmol) at room temperature, and then the mixture was stirred for 20 h. To the reaction mixture was added chloroform and saturated sodium bicarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts was dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc=20:1–2:1 as eluents) to give (2*R*,3*S*,4*S*,6*R*)-3-methyl-2-phenyl-6-(2-phenethyl)-4-tosyloxytetrahydropyran **12ea** (85.1 mg, 62.9%, R_f=0.50 (*n*-hexane/EtOAc=3:1)) and (2*R*,3*R*,4*S*,6*R*)-4-hydroxy-3-methyl-2-phenyl-6-(2-phenethyl)tetrahydropyran **5ea** (11.0 mg, 12.4%, R_f=0.23 (*n*-hexane/EtOAc=3:1)), as colorless oils.

Compound **12ea**: $[\alpha]_D^{25}$ 67.0 (*c* 1.00, $CHCl_3$); IR (Nujol) 2931, 2899, 2862, 1599, 1494, 1457, 1371, 1297, 1181, 1903, 1074, 1032, 942, 918, 897, 872, 833, 811, 753, 729, 696, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.52 (d, J=6.5 Hz, 3H), 1.67–1.85 (m, 3H), 1.91 (m, 1H), 2.16 (ddd, J=12.0, 4.8, 1.6 Hz, 1H), 2.45 (s, 3H), 2.66 (m, 2H), 3.42 (m, 1H), 3.87 (d, J=10.1 Hz, 1H), 4.40 (ddd, J=10.7, 10.7, 4.8 Hz, 1H), 7.11 (d, J=7.1 Hz, 2H), 7.18 (m, 1H), 7.24–7.35 (m, 9H), 7.81 (d, J=8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 21.6, 31.2, 37.0, 38.7, 42.3, 74.2, 84.27, 84.30, 125.8, 127.4, 127.7, 128.1, 128.26, 128.32, 128.4, 129.7, 139.2, 139.7, 141.6, 144.7. Anal. Calcd for $C_{27}H_{30}O_4S$: C, 71.97; H, 6.71. Found: C, 71.86; H, 6.53.

3.1.23. (2*S*,3*S*,4*S*,6*R*)-3-Methyl-2-(2-phenylethenyl)-6-(2-phenethyl)-4-tosyloxytetrahydropyran 12fa (entry 12 in Table 4). To a solution of (5*E*,3*R*)-1-phenylhept-5-en-3-ol (*ER*)-**4a** (57.1 mg, 0.3 mmol) and 3-phenylpropenal **1f** (37.8 μL, 0.3 mmol) in dichloromethane (0.3 mL) was added *p*-toluenesulfonic acid monohydrate (TSA·H_2O) (77.5 mg, 0.45 mmol) at room temperature, and then the mixture was stirred for 20 h. To the reaction mixture was added chloroform and saturated sodium bicarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts were dried over anhydrous sodium sulfate, and

concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give (2*S*,3*S*,4*S*,6*R*)-3-methyl-2-(2-phenylethenyl)-6-(2-phenethyl)-4-tosyloxytetrahydropyran **12fa** (99.8 mg, 69.8%, R_f=0.48 (*n*-hexane/EtOAc=3:1)) and (2*S*,3*R*,4*S*,6*R*)-4-hydroxy-3-methyl-2-(2-phenylethenyl)-6-(2-phenethyl)tetrahydropyran **5fa** (16.4 mg, 17.0%, R_f=0.22 (*n*-hexane/EtOAc=3:1)), as colorless oils.

Compound **12fa**: $[\alpha]_D^{25}$ 58.6 (*c* 1.00, $CHCl_3$); IR (Nujol) 3075, 2924, 2857, 1599, 1458, 1366, 1298, 1182, 1092, 1067, 965, 929, 903, 851, 812, 754, 695, 671 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.74 (d, J=6.5 Hz, 3H), 1.57–1.76 (m, 3H), 1.91 (m, 1H), 2.10 (ddd, J=12.4, 4.8, 1.6 Hz, 1H), 2.43 (s, 3H), 2.63–2.76 (m, 2H), 3.34 (m, 1H), 3.55 (dd, J=9.6, 7.8 Hz, 1H), 4.33 (ddd, J=10.7, 10.7, 4.8 Hz, 1H), 6.12 (dd, J=15.1, 7.5 Hz, 1H), 6.58 (d, J=15.9 Hz), 7.14–7.39 (m, 12H), 7.80 (d, J=8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 21.6, 31.4, 37.1, 38.6, 41.3, 73.7, 82.3, 84.0, 125.8, 126.5, 127.4, 127.7, 127.9, 128.3, 128.4, 128.5, 129.7, 133.3, 134.2, 136.3, 141.6, 144.7. Anal. Calcd for $C_{29}H_{32}O_4S$: C, 73.08; H, 6.77. Found: C, 73.14; H, 6.81.

3.1.24. (2*S*,3*S*,4*S*,6*R*)-3-Methyl-6-(2-phenethyl)-2-(2-phenylthioethyl)-4-tosyloxytetrahydropyran 12ga (entry 13 in Table 4). To a solution of (5*E*,3*R*)-1-phenylhept-5-en-3-ol (*ER*)-**4a** (57.1 mg, 0.3 mmol) and 3-phenylthiopropenal **1g** (49.9 mg, 0.3 mmol) in dichloromethane (0.6 mL) was added *p*-toluenesulfonic acid monohydrate (TSA·H_2O) (51.7 mg, 0.3 mmol) at room temperature, and then the mixture was stirred for 20 h. To the reaction mixture was added chloroform and saturated sodium hydrogencarbonate (4 mL), and extracted with chloroform (3×2 mL). The combined extracts was dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc=20:1–2:1 as eluents) to give (2*S*,3*S*,4*S*,6*R*)-3-methyl-6-(2-phenethyl)-2-(2-phenylthioethyl)-4-tosyloxytetrahydropyran **12ga** (70.1 mg, 45.8%, R_f=0.48 (*n*-hexane/EtOAc=3:1)) and (2*S*,3*R*,4*S*,6*R*)-4-hydroxy-3-methyl-6-(2-phenethyl)-2-(2-phenylthioethyl)-tetrahydropyran **5ga** (16.3 mg, 15.2%, R_f=0.20 (*n*-hexane/EtOAc=3:1)), as colorless oils.

Compound **12ga**: $[\alpha]_D^{25}$ 8.3 (*c* 1.15, $CHCl_3$); IR (neat) 3060, 3027, 2929, 2854, 1594, 1481, 1446, 1364, 1298, 1179, 1093, 1041, 1025, 932, 878, 852, 818, 744, 695, 672 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.66 (d, J=6.5 Hz, 3H), 1.41–1.56 (m, 2H), 1.62–1.97 (m, 4H), 2.04 (ddd, J=12.3, 4.8, 1.3 Hz, 1H), 2.44 (s, 3H), 2.60–2.68 (m, 1H), 2.70–2.78 (m, 1H), 2.98–3.05 (m, 1H), 3.05–3.18 (m, 2H), 3.22 (m, 1H), 4.23 (ddd, J=10.7, 10.7, 4.9 Hz, 1H), 7.14–7.19 (m, 4H), 7.25–7.34 (m, 8H), 7.78 (d, J=8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 21.6, 29.5, 31.6, 32.7, 37.3, 38.9, 41.0, 73.5, 78.7, 84.1, 125.9, 127.7, 128.4, 128.5, 128.9, 129.0, 129.8, 134.2, 136.4, 141.6, 144.7. Anal. Calcd for $C_{29}H_{34}O_4S_2$: C, 68.20; H, 6.71. Found: C, 68.14; H, 6.75.

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Formation of metal-lustrous organic crystals from 2-aryl-1-(4-methoxyphenyl)-5-(5-tricyanoethenyl-2-thienyl)pyrroles

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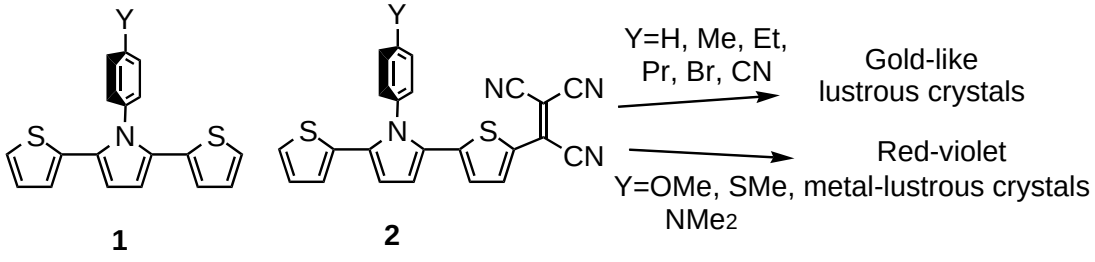
Abstract—Various 2-aryl-1-(4-methoxyphenyl)-5-(5-tricyanoethenyl-2-thienyl)pyrroles (**3**) were synthesized. When the 2-aryl group of **3** is phenyl, 4-tolyl, and 4-methoxyphenyl, organic crystals with greenish yellow metallic luster are formed. In contrast, a 2-(4-fluorophenyl) derivative of **3** gives gold-like lustrous crystals. The relation of their crystal structures with the appearance of metallic color is mentioned.

1. Introduction

Recently, we have reported a new class of π-electron rich compounds, 1-aryl-2,5-di(2-thienyl)pyrroles (**1**), which serve as strong π-electron donor.[1] Introduction of a stronger π-electron withdrawing tricyanoethenyl group into the skeleton of **1** can be achieved by the reaction with tetracyanoethylene to afford various 1-aryl-2-(2-thienyl)-5-(5-tricyanoethenyl-2-thienyl)pyrroles (**2**) in good yield.[2] Interestingly, the products (**2**) bearing halogen, cyano group, or a comparatively short alkyl substituent (less than propyl) at the *para*-position of the central *N*-phenyl group easily form stable crystals with gold-like metallic luster. X-ray structural analysis revealed that most of the gold-like lustrous crystals possess a coplanar sheet-like structure, in which the intermolecular C–H···N hydrogen bonds between the cyano nitrogen and the olefinic hydrogen (CN···H–C=C) were observed. This makes the adjacent π-systems intermolecularly close to each other to bring about their sufficient intermolecular contact (CN···C=C), which was suggested to play an important role in the appearance of gold-like metallic luster[2a] (Scheme 1).

The essential relationship between their vivid metallic colored appearance and their unique crystal structure motivated us to explore this work more systematically. Recently, we also reported that crystals with orange or red-violet metallic luster were obtained upon the introduction of methoxy group, methylthio group, or dimethylamino group into the 4-position of central *N*-phenyl group.[2b] In these crystals, the molecules are arranged into a heaving ribbon that is shown in Figure 1.

This is obviously different from the planar arrangement of the gold-like analogues that bear halogen, cyano, or short alkyl group at the *para*-position of the *N*-phenyl group. In the



Scheme 1.

Keywords: π-Conjugated molecule; 4-Methoxyphenyl group; Metallic luster; Ribbon-like molecular arrangement; Sheet-like molecular arrangement.
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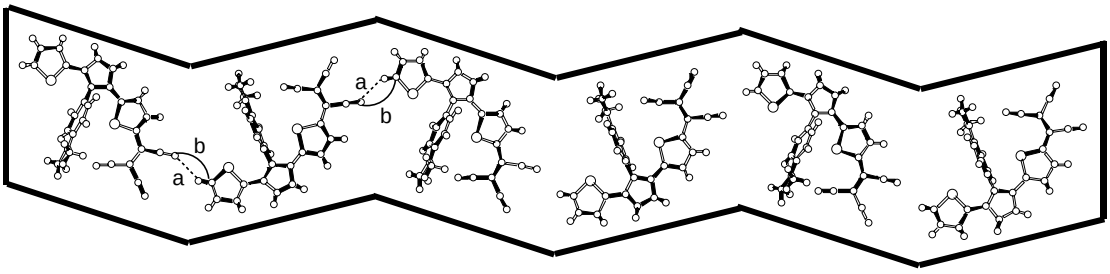
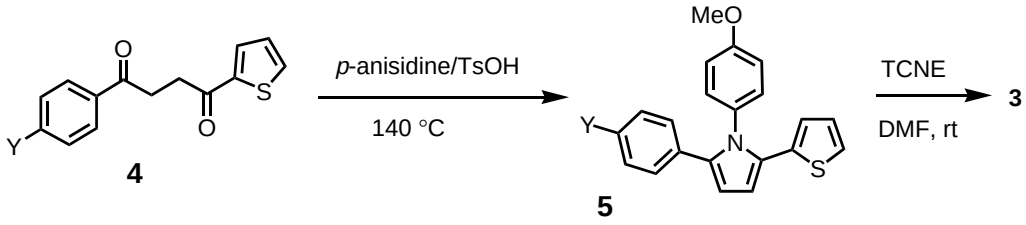


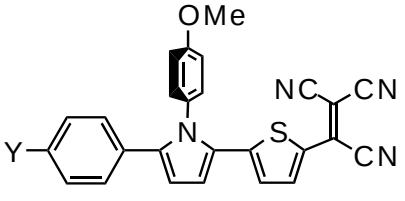
Figure 1. Heaving ribbon structure in crystal of **2** (Y=OMe). (a) 2.69 Å; (b) 3.48 Å.



Compound		4 → 5		5 → 3	
	Y	Time (h)	Yield (%)	Time (h)	Yield (%)
a	H	6.0	99	4.0	54
b	Me	2.5	99	2.0	99
c	OMe	3.0	61	24	61
d	F	2.0	99	4.0	98

Scheme 2.

heaving ribbon, an intermolecular C–H···N hydrogen bond between the terminal thiophene and cyano groups occurs to make the adjacent π-systems (CN···C=C) close enough. Thus, the terminal thiophene seems to be essential to the ribbon-like arrangement of the π-molecules in crystals. This consideration prompted us to examine what kind of crystal structure is constructed by crystallization of the π-molecule bearing an aryl group instead of the terminal thiophene of **2** (Y=OMe). Here, we report the synthesis of various 2-aryl-1-(4-methoxyphenyl)-5-(5-tricyanoethenyl-2-thienyl)pyrroles (**3**) and the metallic luster of their crystals.



2. Results and discussion

The compounds (**3**) were prepared according to the conventional procedures that we have published.[2] Reaction of 2-aryl-1-(4-methoxyphenyl)-5-(2-thienyl)pyrroles (**5**), which were easily derived from 1-aryl-4-(2-thienyl)-1,4-butanediones (**4**), with tetracyanoethylene occurred smoothly at an ambient temperature in *N*,*N*-dimethylformamide (DMF) to produce **3**, as summarized in Scheme 2.

The present compounds (**3**) are soluble in regular organic solvents such as chloroform, acetone, and THF to give a deep blue solution because they absorb visible light around the wavelength of 600–612 nm (Fig. 2). It is reasonably

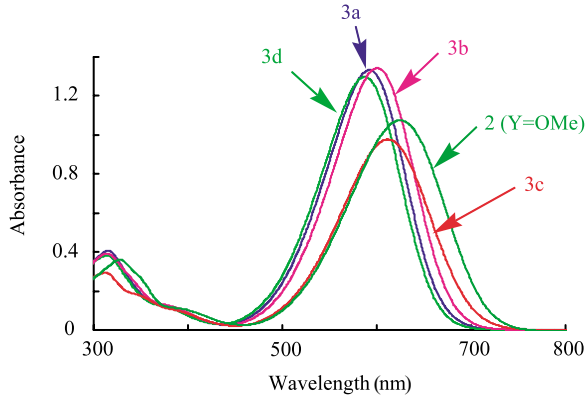


Figure 2. Solution UV–vis absorption spectra of **3** in THF (3.0×10^{-5} M). **3a**: λ_{max} 592 nm (ε 44,400); **3b**: 601 nm (ε 44,800); **3c**: 612 nm (ε 32,600); **3d**: 588 nm (ε 43,200); **2** (Y=OMe): 625 nm (ε 35,800).

thought by analogy with 1-aryl-1,2,2-tricyanothenes[3] that these absorption bands are due to intramolecular charge-transfer transition from the thiophene–pyrrole–thiophene part into the tricyanoethene part. It is noteworthy that **3c** (Y=OMe) shows its λ_{max} at a longer wavelength (612 nm) with a relatively lower extinction coefficient (32,600) in comparison with those of other compound (**3**). This behavior is attributable to the electron-donating property of the 4-methoxy group because the absorption of **2** (Y=OMe) appears at 625 nm with a comparable extinction coefficient (35,800).

By slow evaporation of the solvent, metal-lustrous crystals were formed. The color of the metallic luster is changeable according to the 4-substituent of 2-aryl group. Typical photographs are shown in Figure 3. Interestingly, crystals of **3d** (Y=F) look like gold metal, but **3a**, **3b**, and **3c** form greenish yellow or light greenish yellow metal-lustrous crystals.

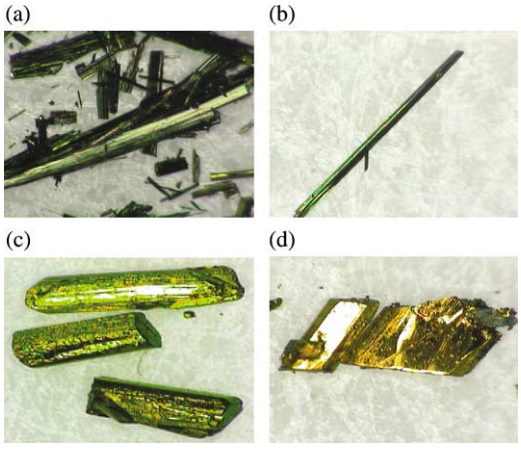


Figure 3. Photographs of metal-lustrous crystals of **3**. (a) **3a** (from acetone). (b) **3b** (from ethyl acetate). (c) **3c** (from chloroform). (d) **3d** (from ethyl acetate).

The solid-state UV–vis–NIR diffuse reflection–absorption spectra of these crystals were summarized in Figure 4. Apparently, the spectrum of gold-like lustrous crystals (**3d**) resemble to that of gold (Au) plate in the visible light region.

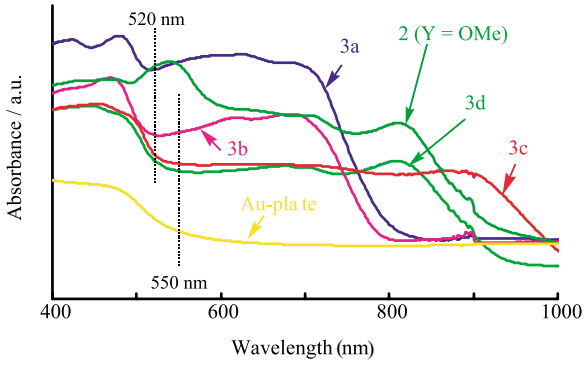


Figure 4. Solid UV–vis–NIR diffuse reflection–absorption spectra of **2** (Y = OMe), **3**, and Au-plate.

They display a peculiar broadened absorption band in the whole visible region (below 1000 nm for **3c** and below 930 nm for **3d**). This is reflected in the metallic luster that results from the intermolecular interaction between the π-systems.[2,4] In these spectra, the stronger absorption appears in the region of shorter wavelength than 550 nm. In contrast, the crystals of **3a**, **3b**, and **3c** show the corresponding strong absorption that covers the region of a relatively shorter wavelength than 510–520 nm, whose complementary color is greenish yellow. This is the reason why the crystals of **3a**, **3b**, and **3c** exhibit greenish yellow metallic luster.

The powder X-ray diffraction (PXRD) patterns of these crystals are summarized in Figure 5 that includes the PXRD pattern of **3d** for reference. From these patterns, it was not suggested that the crystals of **3a**, **3b**, and **3c** adopt the same structure.

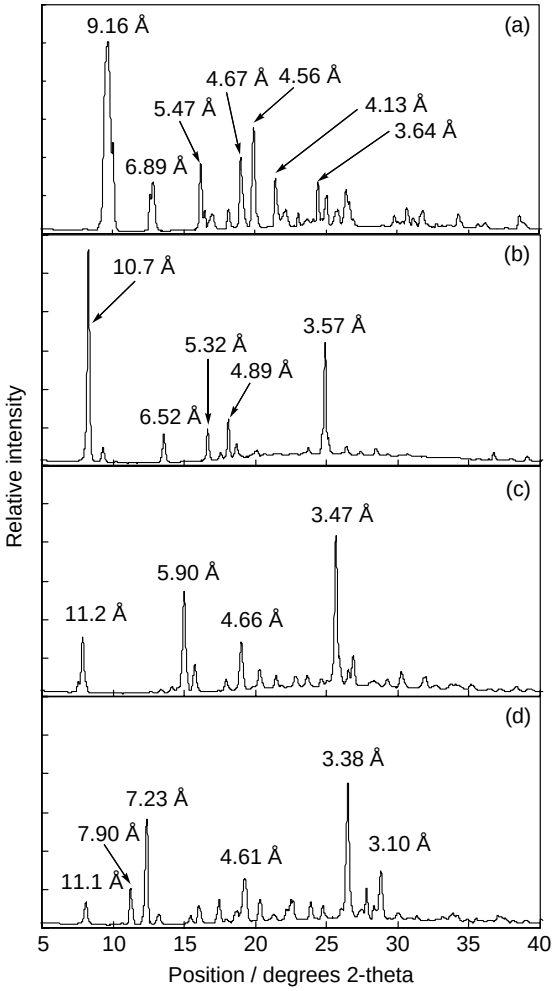


Figure 5. The PXRD patterns of **3**. (a) **3a**. (b) **3b**. (c) **3c**. (d) **3d**.

Among them, single crystals of **3a** with a good quality were fortunately obtained by crystallization from acetone. X-ray crystallographic analysis reveals that **3a** crystallize in a triclinic unit cell, containing two molecules. These two molecules are somewhat different from one another in conformation (note Conformer A and Conformer B).

Figure 6 shows an ORTEP plot of the crystal **3a** (Fig. 6a) together with **2** (Y=OMe) (Fig. 6c) that was reported in our previous study.[2b] Similar to the molecule of **2** (Y=OMe), the thiophene ring bearing tricyanoethenyl group is slightly but definitely distorted from the plane of pyrrole–thiophene conjugation (torsion angle: 28.0° (Conformer A) or 28.1° (Conformer B)), which is larger by 9.5° than that of **2** (Y=OMe). This particular torsion can be mainly ascribed to favorable formation of a CH/N type intramolecular C–H···N hydrogen bond[5–7] between the top of the cyano nitrogen and the hydrogen on methoxy group. The distance of the O–C–H···N hydrogen bond was 2.70 and 2.78 Å for Conformer A and Conformer B, respectively. Furthermore, the terminal phenyl group was also distorted by 33.7° (Conformer A) and 30.4° (Conformer B) from the central pyrrole ring, resulting in the edge-to-face interaction (CH/π interaction)[8] between the *N*-phenyl and the terminal phenyl groups (the distance between the *ipso* carbon of the central phenyl and the *ortho* hydrogen of the terminal phenyl: 2.64 Å).

To our surprise, the crystal structure of **3a** resembles to that of **2** (Y=OMe). The molecules of **3a** aggregate in a ribbon and the formed ribbons cross perpendicularly to each other to form a zig-zag layer as depicted illustratively in Figure 7. It is noteworthy that two kinds of ribbons exist: one ribbon consists of the molecules that adopt the conformation A. Another one consists of the molecules with the conformation B. These ribbons that are very similar to one another are arranged alternatively to form the zig-zag layer. The zig-zag layers stack to form a crystal. It is noteworthy that the present ribbon is flat. This is different from the heaving

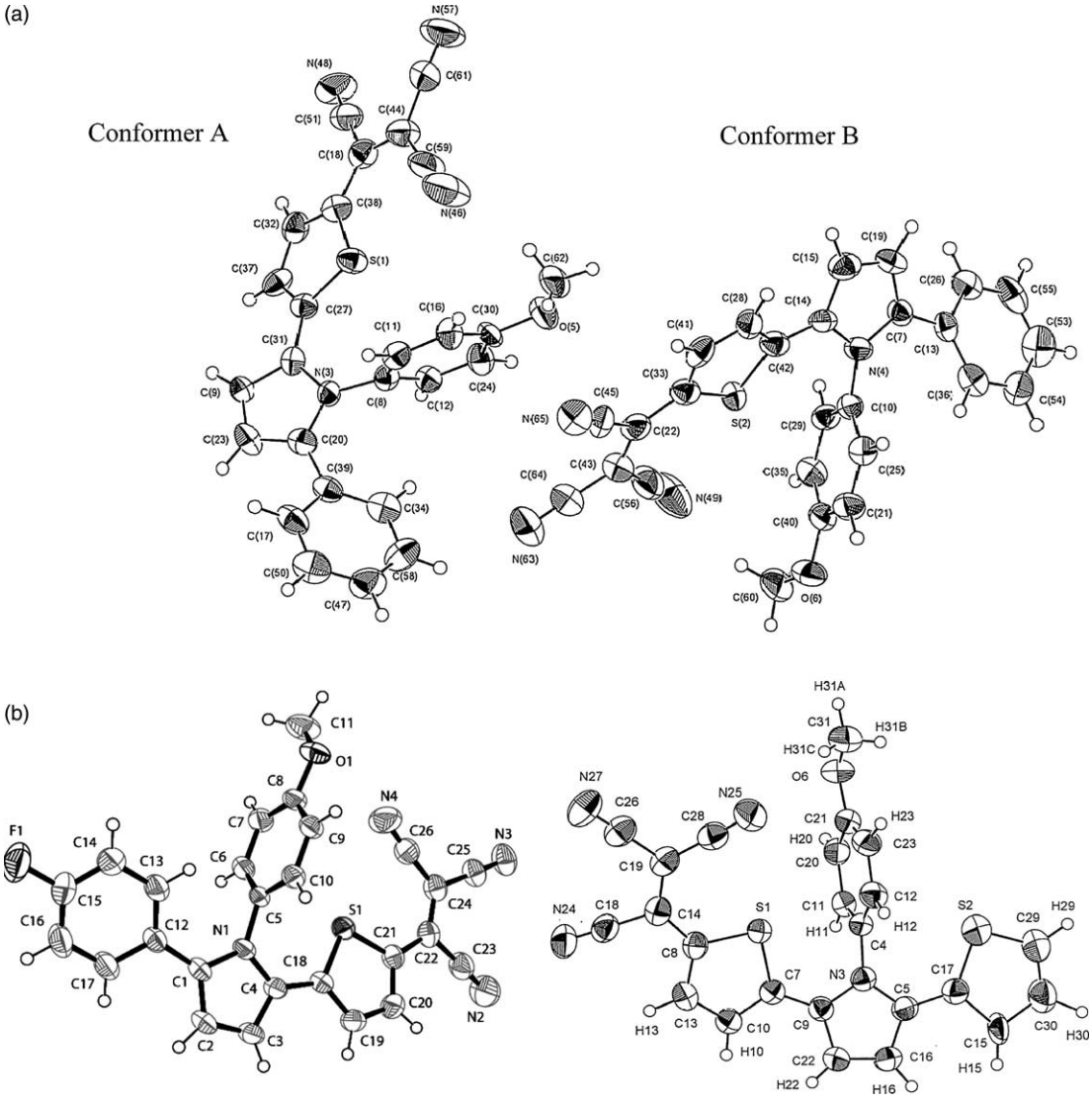


Figure 6. ORTEP polts of the crystals. (a) The crystal of **3a**, in which two conformers (A and B) exist. Selected torsion angles: [Conformer A] C(44)–C(18)–C(38)–S(1) 0.0°, N(3)–C(31)–C(27)–S(1) 28.0°, C(31)–N(3)–C(8)–C(12) 73.0°, N(3)–C(20)–C(39)–C(34) 33.7°. [Conformer B] C(43)–C(22)–C(33)–S(2) 3.20°, N(4)–C(14)–C(42)–S(2) 28.1°, C(14)–N(4)–C(10)–C(25) 76.8°, N(4)–C(7)–C(13)–C(36) 30.4°. Selected bond length: [Conformer A] N(46)–HC(62) 2.70 Å, C(8)–HC(34) 2.64 Å. [Conformer B] N(49)–HC(60) 2.78 Å, C(10)–HC(36) 2.64 Å. (b) The crystal of **3d**. Selected torsion angles: C(24)–C(22)–C(21)–S(1) 8.0°, N(1)–C(4)–C(18)–S(1) 10.1°, C(18)–N(1)–C(5)–C(10) 76.5°, N(1)–C(1)–C(12)–C(13) 21.4°. Selected bond length: N(4)–HC(11) 2.89 Å, C(5)–HC(13) 2.44 Å. (c) The crystal of **2** (Y=OMe).[2b]

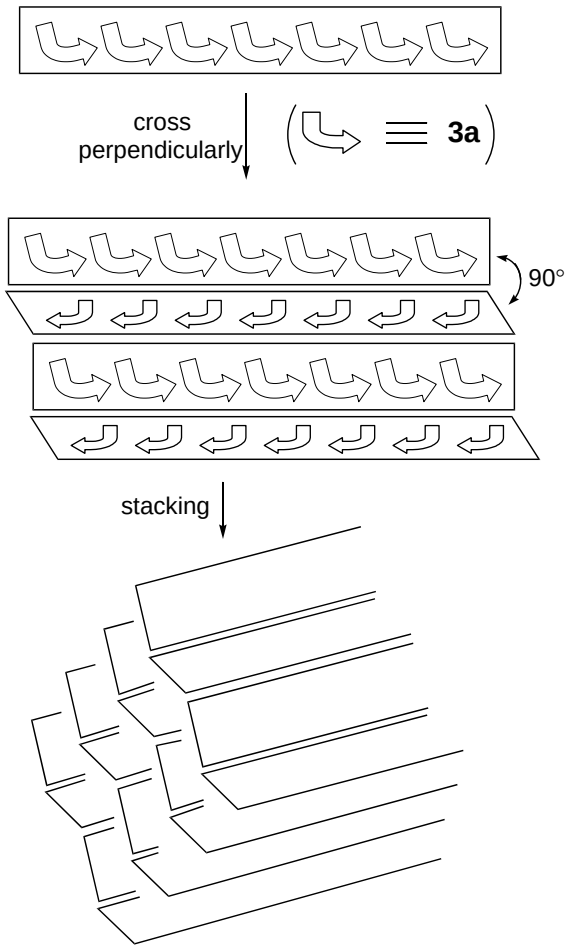


Figure 7. Schematic representation for the molecular arrangement style and the crystal formation of **3a**.

ribbon observed in the crystal of **2** (Y=OMe). In the ribbon, the molecules interact with head (tricyanoethenyl group) of itself to tail (central pyrrole ring) of the neighboring molecule by the intermolecular C–H···N interaction between the cyano nitrogen and the adjacent pyrrole hydrogen (CN···H–C=C, Fig. 8). The C–H···N interaction[6b,7] (distance: 2.54 and 2.80 Å) results in an edge-to-edge type CN···C=C contact (3.34 and 3.63 Å) between the π-electrons of pyrrole ring and cyano group, which substantially contribute to the crystal architecture of **3a** (Fig. 8c). This interaction extends repeatedly to provide successive rows of the flat ribbon. As shown in Figure 8d, weak intermolecular CH···N interaction works between the hydrogen of the terminal phenyl group of one ribbon and the cyano group of its perpendicularly adjacent analogue (CN···HC distance: 2.62 Å). Furthermore, the interlayer approach of the cyano groups was also observed (Fig. 8e): the cyano group of one molecule is close to that of the neighboring molecule of the adjacent ribbon layer in an inverse direction.

Next, we wish to describe the crystal structure of **3d**, which exhibits gold-like metallic luster. As mentioned in the introduction, **2** (Y=a small substituent such as H, halogen, or short alkyls) forms gold-like lustrous crystals. These crystals have a sheet structure and, in the sheet, the molecules are close to each other. In a similar manner to these crystals, a sheet structure was constructed in the crystals of **3d**. The sheets, which are slightly waving, stack to form a crystalline architecture, as shown in Figure 9b. Interestingly, the fluorine atom at the 4-position of the terminal phenyl plays a significant role in the formation of the sheet structure. The molecules of **3d** are arranged in a ribbon that is indicated by a pink quadrangle. The molecules interact with each other with head (tricyanoethenyl group) of itself to tail (central pyrrole ring) of the neighboring molecule by means of two intermolecular C–H···N interactions (b and c in Fig. 9a). These intermolecular interactions[6b,7] results in an edge-to-edge type CN···C=C contact (3.57 Å) between the π-electrons of pyrrole ring and cyano group. The interaction between the cyano nitrogen and the 3-hydrogen of the terminal 4-fluorophenyl should be noted. This is probably due to the strong inductive effect of the fluorine that makes the neighboring proton more acidic. Furthermore, the flat ribbons interact with each other by a side-by-side manner via the so-called hydrogen bonding[9] between the fluorine atom and the pyrrole hydrogen that is marked by the letter 'd' (C=CH···F 2.59 Å) in Figure 9a. This distance is smaller than the sum of the van der Waals radii[10] of fluorine and hydrogen atoms (1.47 and 1.20 Å).

3. Conclusion

In summary, we have successfully developed a new class of π-electron conjugated system, 2-aryl-1-(4-methoxyphenyl)-5-(5-tricyanoethenyl-2-thienyl)pyrrole (**3**), that forms crystals with metallic luster. The color of the metallic luster is changeable from greenish yellow to gold-like, depending on the substituent of the terminal aryl group. The greenish yellow metal-lustrous crystals were given by recrystallization of **3a** (aryl=phenyl) from acetone. The essential motif present in these crystals is an infinite, intermolecular, linear network of CN···H–C=C interaction, which organizes the molecules to arrange regularly in a row of the flat ribbon. The CN···H–C=C interaction originates from the unique effect of the tricyanoethenyl group, making the adjacent π-orbitals (CN···C=C) close enough to partially overlap with each other. Furthermore, the flat ribbons are arranged into a zig-zag layer. On the other hand, **3d** (aryl=4-fluorophenyl) formed gold-like lustrous crystals. X-ray crystallographic analysis revealed that the crystals adopt a slightly waving sheet structure. The sheet consists of the flat ribbons, in which the molecules interact with each other by two intermolecular C=C–H···NC hydrogen bonds to result in an edge-to-edge type CN···C=C contact. In these crystals, the fluorine atom of the terminal phenyl takes an important role in the connection of the flat ribbons to form a sheet. From these results, it is concluded that a 2-(5-tricyanoethenyl-2-thienyl)pyrrole moiety is essential to the appearance of metallic luster in the present π-system: the central pyrrole of one molecule is close to the cyano group of the adjacent molecule to make the π-systems contact to each other successively in a ribbon, while the terminal aryl group contributes to the formation of the crystal structure.

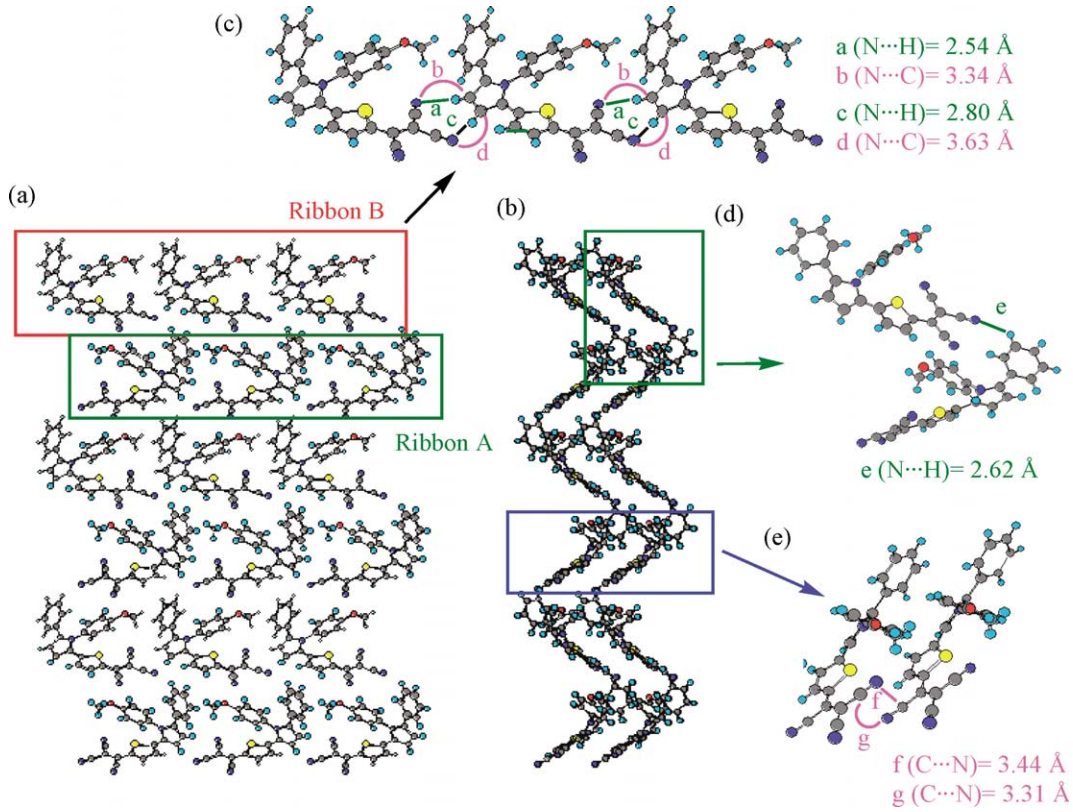


Figure 8. Crystal structure and CN···C═C overlapping mode of **3a**. (a) Molecular arrangement in a zig-zag layer. Ribbon A, which consists of conformer A molecules, and Ribbon B, which consists of conformer B molecules, are alternatively arranged. (b) The side view of two stacking zig-zag layers. (c) The molecular arrangement and intermolecular interactions in the ribbon. (d) Intermolecular interaction in the connection between the ribbons. (e) The approach of cyano groups between the neighboring layers.

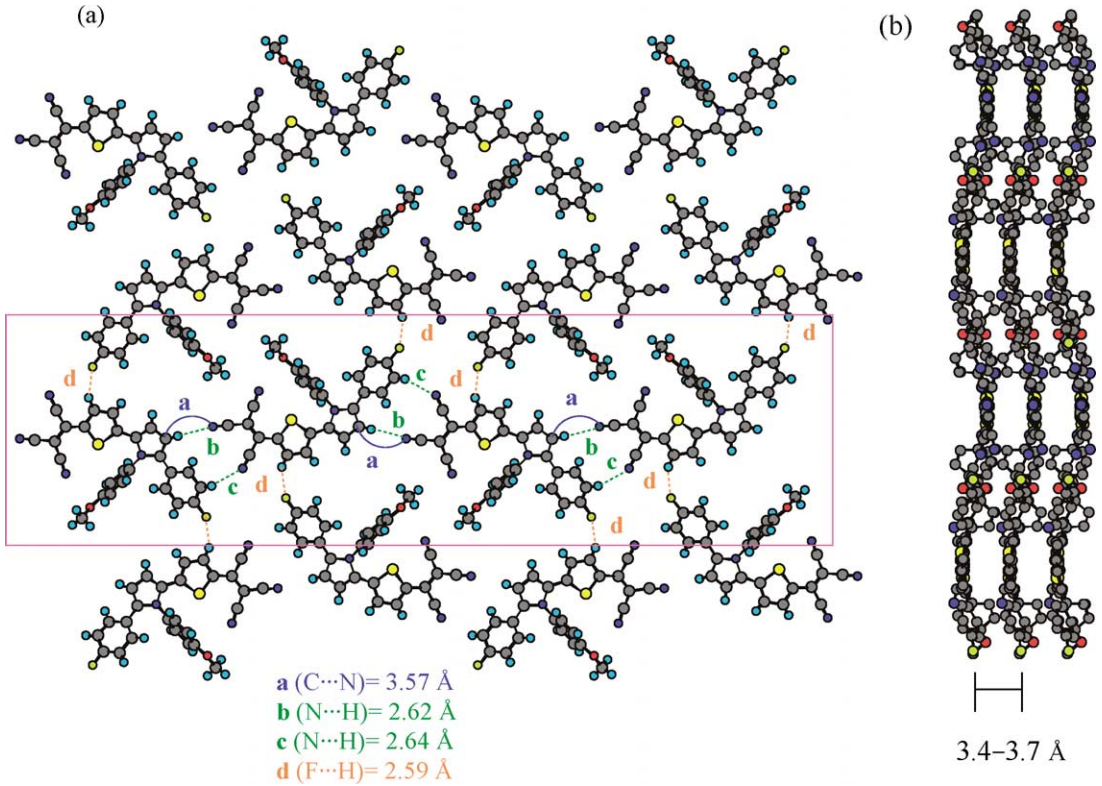


Figure 9. Crystal structure of **3d**. (a) Molecular arrangement in a waving layer. The area surrounded with four pink lines exhibits the ribbon, in which the molecules are arranged by head-to-tail interaction. (b) The side view of two stacking layers. The distance between the stacking layers was estimated to be 3.4–3.7 Å.

4. Experimental

Melting points are determined on a hot-stage microscope apparatus (Yamato MP-500D) and uncorrected. All chemicals were obtained from commercial suppliers and used without further purification. ^{1}H NMR spectra were recorded at 300 MHz using a Varian Gemini-2000 NMR spectrometer and chemical shifts were referenced to TMS as internal standard. UV–vis–NIR absorption spectra were recorded on a JASCO V-570 spectrophotometer. Infrared spectra were measured on a JASCO FT/IR-350 spectrophotometer. Elemental analyses were performed by Chemical Analysis Center of Chiba University.

4.1. Preparation of 1-(4-methoxyphenyl)-2-phenyl-5-(5-tricyanoethenyl-2-thienyl)pyrrole (3a). A typical procedure

A mixture of 1-phenyl-4-(2-thienyl)-1,4-butanedione (505 mg, 2.07 mmol), 4-methoxyaniline (714 mg, 5.94 mmol), and 4-toluenesulfonic acid monohydrate (117 mg, 0.616 mmol) was magnetically stirred at 140 °C for 6 h. After cooling to room temperature, the reaction mixture was purified by column chromatography on silica gel (eluent: toluene) to give **5a** as colorless crystals (678 mg; 99% yield).

4.1.1. Compound 5a. Colorless needles; mp 201.6–202.3 °C (from acetone); ^{1}H NMR ($CDCl_3$): δ 3.82 (s, 3H), 6.45 (d, J=3.6 Hz, 1H), 6.53 (dd, J=1.2, 3.6 Hz, 1H), 6.55 (d, J=3.8 Hz, 1H), 6.84 (d, J=8.8 Hz, 2H), 6.85 (dd, J=3.7, 4.8 Hz, 1H), 7.07 (dd, J=1.2, 5.1 Hz, 1H), 7.10 (d, J=9.0 Hz, 2H), 7.10–7.19 (m, 5H); IR (KBr) 1602, 1514, 1469, 1295, 1249, 1025, 833, 754, 698 cm^{-1}. Anal. Calcd for $C_{21}H_{17}NOS$: C, 76.10; H, 5.17; N, 4.23. Found: C, 76.17; H, 5.29; N, 4.09.

A solution of **5a** (446 mg, 1.34 mmol) and tetracyanoethylene (351 mg, 2.69 mmol) in 10 mL of anhydrous DMF was stirred for 2 h at room temperature. The reaction mixture was poured into brine (100 mL) and was extracted with toluene (100 mL×3). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The dark blue residue was purified by column chromatography on silica gel (eluent: a 4:1 mixture of chloroform and hexane) to give **3a** as greenish gold-like lustrous crystals (175 mg; 54% yield).

4.1.2. Compound 3a. Greenish gold-like lustrous crystals; mp 209.7–210.5 °C (from chloroform); ^{1}H NMR ($CDCl_3$): δ 3.88 (s, 3H), 6.63 (d, J=4.2 Hz, 1H), 6.99 (d, J=9.0 Hz, 2H), 7.07 (d, J=4.5 Hz, 1H), 7.10 (d, J=4.2 Hz, 1H), 7.18–7.25 (m, 5H), 7.22 (d, J=9.0 Hz, 2H), 7.76 (d, J=4.7 Hz, 1H); IR (KBr) 2217, 1513, 1497, 1449, 1421, 1346, 1249, 1198, 1102, 1057 cm^{-1}; UV (3.0×10^{-5} M in THF): λ_{max} 592 nm (ε 44,400); HRMS (FAB): calcd for $C_{26}H_{16}N_4OS$ 432.1045, found 432.1049. Anal. Calcd for $C_{26}H_{16}N_4OS\cdot0.1CHCl_3$: C, 70.70; H, 3.66; N, 12.64. Found: C, 70.77; H, 3.68; N, 12.74.

In a similar manner, compounds **3b**, **3c**, and **3d** were prepared.

4.1.3. Compound 5b. Colorless crystals; mp 168.2–168.3 °C (from acetone); ^{1}H NMR ($CDCl_3$): δ 2.27 (s, 3H), 3.82 (s, 3H), 6.41 (d, J=3.8 Hz, 1H), 6.52 (dd, J=1.2, 3.6 Hz, 1H), 6.54 (d, J=3.7 Hz, 1H), 6.83 (dd, J=3.6, 5.2 Hz, 1H), 6.84 (d, J=8.7 Hz, 2H), 6.96–7.03 (m, 4H), 7.06 (dd, J=1.2, 5.2 Hz, 1H), 7.10 (d, J=9.0 Hz, 2H); IR (KBr) 1515, 1500, 1459, 1295, 1249, 1027, 833, 769, 702 cm^{-1}. Anal. Calcd for $C_{22}H_{19}NOS$: C, 76.49; H, 5.54; N, 4.05. Found: C, 76.20; H, 5.61; N, 3.94.

4.1.4. Compound 5c. Colorless crystals; mp 174.5–174.9 °C (from ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3H), 3.82 (s, 3H), 6.37 (d, J=3.7 Hz, 1H), 6.51 (dd, J=1.2, 3.6 Hz, 1H), 6.53 (d, J=3.7 Hz, 1H), 6.72 (d, J=9.0 Hz, 2H), 6.83 (dd, J=3.5, 5.2 Hz, 1H), 6.84 (d, J=8.7 Hz, 2H), 7.04 (d, J=8.7 Hz, 2H), 7.06 (dd, J=1.2, 4.8 Hz, 1H), 7.09 (d, J=9.0 Hz, 2H); IR (KBr) 1516, 1498, 1284, 1248, 1178, 1030, 831, 766, 696 cm^{-1}. Anal. Calcd for $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.30; N, 3.88. Found: C, 72.97; H, 5.22; N, 3.73.

4.1.5. Compound 5d. Colorless crystals; mp 193.0–193.7 °C (from ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H), 6.40 (d, J=3.6 Hz, 1H), 6.53 (dd, J=1.4, 3.6 Hz, 1H), 6.54 (d, J=3.6 Hz, 1H), 6.82–6.87 (m, 2H), 6.84 (dd, J=3.6, 5.2 Hz, 1H), 6.88 (d, J=8.7 Hz, 2H), 7.05–7.10 (m, 2H), 7.08 (dd, J=1.2, 5.2 Hz, 1H), 7.08 (d, J=9.0 Hz, 2H); IR (KBr) 3006, 1547, 1514, 1495, 1294, 1248, 1221, 833, 768, 704 cm^{-1}. Anal. Calcd for $C_{21}H_{16}FNOS$: C, 72.18; H, 4.62; N, 4.01. Found: C, 72.38; H, 4.72; N, 3.95.

4.1.6. Compound 3b. Greenish metal-lustrous crystals; mp 229.9–230.4 °C (from ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H), 3.88 (s, 3H), 6.60 (d, J=4.2 Hz, 1H), 7.00 (d, J=9.0 Hz, 2H), 7.02–7.12 (m, 4H), 7.07 (d, J=4.5 Hz, 1H), 7.09 (d, J=4.5 Hz, 1H), 7.22 (d, J=9.0 Hz, 2H), 7.75 (d, J=4.5 Hz, 1H); IR (KBr) 2215, 1542, 1508, 1450, 1419, 1346, 1250, 1197, 1105, 1056 cm^{-1}; UV–vis (3.0×10^{-5} M in THF): λ_{max} 601 nm (ε 44,800); HRMS (FAB): calcd for $C_{27}H_{18}N_4OS$ 446.1201, found 446.1207. Anal. Calcd for $C_{27}H_{18}N_4OS\cdot0.2CH_3COOC_2H_5$: C, 71.94; H, 4.26; N, 12.07. Found: C, 71.85; H, 4.22; N, 12.18.

4.1.7. Compound 3c. Yellowish green metal-lustrous crystal; mp 216.0–216.5 °C (from ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 3.77 (s, 3H), 3.88 (s, 3H), 6.57 (d, J=4.2 Hz, 1H), 6.70 (d, J=9.0 Hz, 2H), 7.00 (d, J=9.0 Hz, 2H), 7.06 (d, J=4.5 Hz, 1H), 7.09 (d, J=4.2 Hz, 1H), 7.13 (d, J=9.0 Hz, 2H), 7.22 (d, J=9.0 Hz, 2H), 7.74 (d, J=4.5 Hz, 1H); IR (KBr) 2214, 1514, 1452, 1417, 1390, 1342, 1248, 1186, 1117 cm^{-1}; UV–vis (3.0×10^{-5} M THF): λ_{max} (ε) 612 (32,600); HRMS (FAB) calcd for $C_{27}H_{18}N_4O_2S$ 462.1150, found 462.1162. Anal. Calcd for $C_{27}H_{18}N_4O_2S$: C, 70.11; H, 3.92; N, 12.11. Found: C, 69.94; H, 3.99; N, 12.01.

4.1.8. Compound 3d. Gold-like lustrous crystals; mp 230.3–230.5 °C (from ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 3.88 (s, 3H), 6.57 (d, J=4.1 Hz, 1H), 6.89–6.95 (m, 2H), 6.99 (d, J=8.7 Hz, 2H), 7.05 (d, J=4.5 Hz, 1H), 7.07 (d, J=4.5 Hz, 1H), 7.14–7.19 (m, 2H), 7.19 (d, J=9.0 Hz, 2H), 7.76 (d, J=4.8 Hz, 1H); IR (KBr) 2213, 1515, 1496, 1414, 1301, 1250, 1191, 1165, 1102, 839 cm^{-1}. UV–vis (3.0×10^{-5} M THF) λ_{max} 588 nm (ε 43,200); HRMS (FAB): calcd for $C_{26}H_{15}FN_4OS$ 450.0951, found 450.0930. Anal. Calcd for $C_{26}H_{15}FN_4OS$: C, 69.32; H, 3.36; N, 12.44. Found: C, 69.47; H, 3.44; N, 12.39.

4.2. X-ray crystallography

4.2.1. Compound 3a. Data collection was performed on a Mac Science MXC18 four-circle diffractometer with graphite-monochromated Cu Kα ($\lambda=1.54178$) radiation using the 2θ-ω scan technique, and the X-ray intensities were measured up to $2\theta=140°$ at 298 K. The structures were solved by a direct method SIR92[11] and refined against F by a computer program package; maXus[12] from MAC Science. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated position.

Crystal data for **3a** $C_{26}H_{16}N_4OS$, $M_r=432.51$, greenish gold-like plates, triclinic, space group $P1$ (no. 1), $a=17.863(5)$ Å, $b=10.911(3)$ Å, $c=5.573(3)$ Å, $\alpha=86.60(3)°$, $\beta=89.89(3)°$, $\gamma=89.97(2)°$, $V=1084.3(6)$ Å^3, $Z=2$, $D_{calcd}=1.325$ g/cm^3, $F(000)=448$, $\mu=1.53$ cm^{-1}; 4589 observed reflections [$I>3\sigma(I)$], 563 parameters, $R=0.061$, $Rw=0.068$.

4.2.2. Compound 3d. Data collection was performed on a Bruker SMART-1000 CCD diffractmeter with graphite monochromated Mo Kα radiation ($\lambda=0.71013$ Å). Empirical absorption correction was applied using SADABS.[13] The structure was solved by a direct method (SHLEXS-97)[14] and refined by full-matrix least-squares method (SHLEXL-97)[15] against F^2. The non-hydrogen atoms were refined anisotropically. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated position. All calculations were performed using SHELEXTL[16] computer program package from Bruker AXS.

Crystal data for **3d** $C_{26}H_{15}FN_4OS$, $M_r=450.49$, gold prizsm, monoclinic, space group $P2_1/n$ (no. 14), $a=10.240(3)$ Å, $b=22.171(8)$ Å, $c=10.289(4)$ Å, $\beta=111.478(4)°$, $V=2173.8(13)$ Å^3, $Z=4$, $D_{calcd}=1.376$ g/cm^3, $F(000)=928$, $\mu=0.185$ cm^{-1}; 12702 observed reflections [$I>2\sigma(I)$], 299 parameters, $R=0.0417$, $Rw=0.0852$.

Crystallographic data (excluding structure factors) for two crystal structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 289278 (for **3d**) and 289279 (for **3a**). 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].

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An efficient aerobic oxidative aromatization of Hantzsch 1,4-dihydropyridines and 1,3,5-trisubstituted pyrazolines

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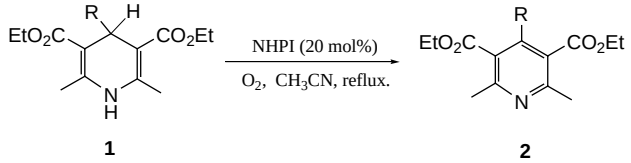
Abstract—4-Substituted Hantzsch 1,4-dihydropyridines and 1,3,5-trisubstituted pyrazolines were oxidized to the corresponding pyridines and pyrazoles, respectively, in high yields by molecular oxygen in the presence of catalytic amount of *N*-hydroxyphthalimide (NHPI) and $Co(OAc)_2$ in acetonitrile at room temperature.

1. Introduction

Hantzsch 1,4-dihydropyridines (DHPs), a class of model compounds of NADH coenzyme,[1] have been extensively studied in view of the biological pertinence of these compounds to the NADH redox process,[2] and their therapeutic functions for treatment of a variety of diseases,[3] such as cardiovascular disorders,[3a] cancer[3b] and AIDS.[3c] The oxidation of DHPs to the corresponding pyridine derivatives constitutes the principal metabolic route in biological systems,[1–2] as well as a facile access to the corresponding pyridine derivatives, which show antihypoxic and antiischemic activities,[4] from the easily available DHPs.[5] Therefore, oxidative aromatization of DHPs has attracted continuing interests of organic and medicinal chemists and a plethora of protocols has been developed.[6–8] Early works mostly used strong oxidants, such as HNO_3,[6b] $KMnO_4$,[6c] or CAN[6d] and I_2–MeOH.[6e] Recently, attention has been paid to more efficient and environmentally benign methods, such as electrochemical oxidation[7] and catalytic aerobic oxidation using $RuCl_3$,[8a] Pd/C,[8b] activated carbon[8c] or $Fe(ClO_4)_3$[8d] as the catalyst.

1,3,5-Trisubstituted pyrazolines are important five-membered heterocyclic compounds, which can be easily prepared from phenylhydrazine and chalcone derivatives. The oxidative aromatization of these dihydroheteroaromatics provides the corresponding pyrazoles, which are known to possess diverse biological activities, including antiinflammatory, antiarrhythmic, antidiabetic and antibacterial activities.[9] For this oxidative conversion of pyrazolines, various methods have been reported, which employed reagents such as $Pb(OAc)_4$,[10] MnO_2,[11] $KMnO_4$,[12] $Zr(NO_3)_4$,[13] iodobenzene diacetate,[14] silver nitrate,[15] Pd/C[8b] and activated carbon.[8c]

On a continuance of our interest in the DHP based chemistry, we reported a photochemical approach for the aromatization of DHPs.[16] Very recently, we found that *N*-hydroxyphthalimide (NHPI) could effectively catalyze the aerobic oxidative aromatization of DHPs in CH_3CN at refluxing temperature (Scheme 1).[17] This NHPI–O_2 system, which was first used by Ishii et al. for oxygenation of hydrocarbons, provides a simple, mild, and highly efficient approach for the aromatization of DHPs. Subsequent investigation showed that the capacity of this approach could be enhanced significantly in the presence of catalytic amount of $Co(OAc)_2$. This method is also applicable to the oxidative aromatization of 1,3,5-trisubstituted pyrazolines. Herein, we wish to report this work in detail.



1 2

Scheme 1.

2. Results and discussion

As demonstrated by Ishii et al., NHPI is a very effective organic catalyst for the functionalization of hydrocarbons

Keywords: Hantzsch 1,4-dihydropyridines; 1,3,5-Trisubstituted pyrazolines; Aerobic oxidative aromatization; *N*-Hydroxyphthalimide; Cobalt diacetate.
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Table 1. Catalytic aerobic aromatization of 1,4-dihydropyridines (**1**) by NHPI or NHPI–$Co(OAc)_2$

Entry	Method[a]	Substrate	R	Product[b]	Time (h)	Yield (%)[c]
1	A	**1a**	H	**2a**[8c]	0.5	99
2	B	**1a**	H	**2a**	0.5	99
3	A	**1b**	Me	**2b**[8c]	3	98
4	B	**1b**	Me	**2b**	4	98
5	A	**1c**	Ph	**2c**[8c,13]	4	99
6	B	**1c**	Ph	**2c**	4	99
7	A	**1d**	4-$MeOC_6H_4$	**2d**[6e]	1.5	98
8	B	**1d**	4-$MeOC_6H_4$	**2d**	3	99
9	A	**1e**	4-ClC_6H_4	**2e**[13]	5	96
10	B	**1e**	4-ClC_6H_4	**2e**	4	98
11	A	**1f**	2-Furyl	**2f**[6e]	7	93
12	B	**1f**	2-Furyl	**2f**, **2a**	3	91, 8
13	A	**1g**	4-$NO_2C_6H_4$	—	10	NR
14	B	**1g**	4-$NO_2C_6H_4$	**2g**[8c,13]	5	98

[a] Method A: an CH_3CN solution (3 mL) of Hantzsch 1,4-dihydropyridine **1** (1 mmol) and NHPI (0.2 mmol) was refluxed under stirring and oxygen atmosphere (1 atm). Method B: a mixture of 1,4-dihydropyridine **1** (1 mmol), NHPI (0.1 mmol) and $Co(OAc)_2 \cdot 4H_2O$ (0.005 mmol) in acetonitrile (3 mL) was stirred under an oxygen atmosphere (1 atm) at room temperature.

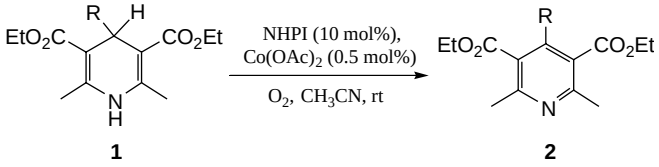
[b] The products were identified by comparing their ^1H, ^{13}C NMR and EI-MS spectral data and melting points with those reported in the cited references.

[c] Isolated yield.

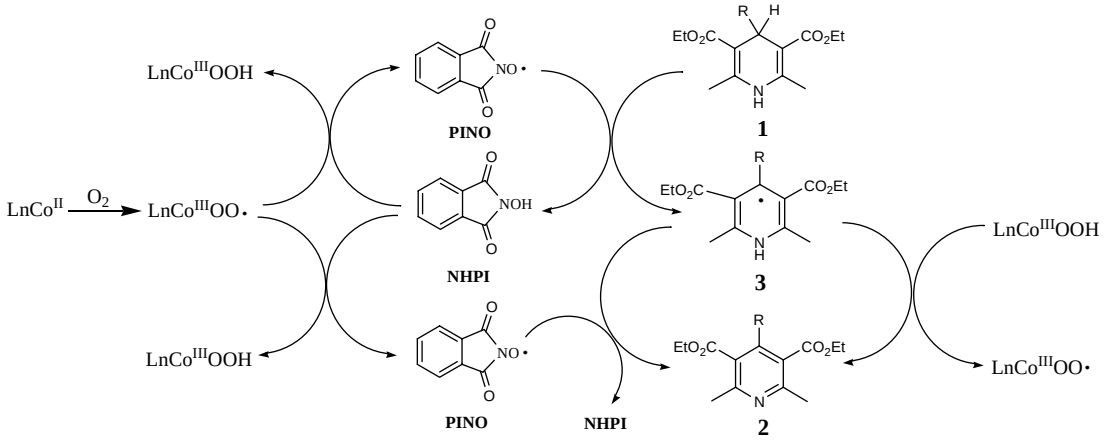
under O_2, NO, or NO_2 atmosphere to give oxygen-containing compounds, such as alcohols, ketones, carboxylic acids and nitroalkanes.[18] This process is believed to be via a NHPI mediated free radical mechanism. We envisioned that NHPI could also be used to catalyze the aerobic oxidation of DHPs. Indeed, when DHPs (**1**) was refluxed in acetonitrile under O_2 atmosphere in the presence of 20 mol% NHPI, the corresponding pyridine derivatives **2** was formed in excellent yields (Scheme 1, method A in Table 1). The only exception was **1g**, which gave no product after prolonged reflux (entry 13 in Table 1). Apparently, the strong electron-withdrawing nitro substituent renders **1g** unreactive.

It was found by Ishii et al. that the presence of a small amount of transition metals, such as Mn^{2+} and Co^{2+}, could significantly enhance the oxidizing capacity of the NHPI–O_2 system.[19] Accordingly, it was expected that the same effect could also be observed in our case for the oxidation of DHPs. Indeed, stirring substrate **1** with 10 mol% of NHPI and 0.5 mol% of $Co(OAc)_2$ in acetonitrile at room temperature for several hours led to the clean formation of pyridine product **2** in excellent yields (Scheme 2, method B in Table 1). By comparison, no appreciable reaction took place in the absence of $Co(OAc)_2$ under the otherwise same reaction conditions. Most significantly, even substrate **1g**, which was resistant to oxidation under the previous conditions,[17] was smoothly transformed to **2g** in 98% yield by this new treatment, demonstrating the high effectiveness of this NHPI–$Co(OAc)_2$–O_2 system (entry 14 in Table 1). In the case of **1f**, a small amount of C–C cleavaged product **2a** was formed along with the normal aromatization product **2f** (entry 12 in Table 1). This phenomenon was also observed in the previously reported aromatization of DHPs under other oxidative conditions.[16]

The NHPI catalyzed aerobic oxidation of DHPs was supposed to be following a free radical chain process,[17] similar to that proposed previously by Ishii et al.[18a] The initiation step was the generation of phthalimide-*N*-oxyl radical (PINO) by the hydrogen transfer from NHPI to O_2. Co^{2+} could accelerate this step by binding with O_2 to form a Co^{3+}–oxygen complex, which can abstract the hydrogen from NHPI much more effectively than oxygen (Scheme 3).[18a] Consequently, the whole process was remarkably accelerated in the presence of $Co(OAc)_2$, as demonstrated by the present result, as well as those observed



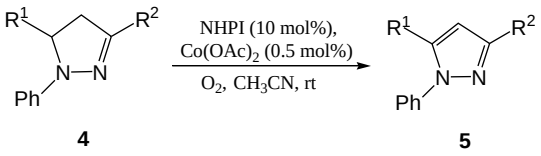
Scheme 2.



Scheme 3.

by others.[18] In the subsequent propagation step, PINO abstracted hydrogen from DHP to produce radical **3**. Generally, alkyl radicals would react with oxygen to form alkyl peroxyl radicals, which in turn, would produce oxygenated products. In the present case, however, the strong driving force of aromatization made the second hydrogen abstraction from radical **3** by PINO and/or Co^{3+}–oxygen complex very effective. Therefore, the pyridine derivative formed exclusively rather than the oxygenated products.

Having successfully achieved the aromatization of DHPs, we applied this method to the oxidative aromatization of 1,3,5-trisubstituted pyrazolines (Scheme 4, Table 2). As shown in Table 2, treatment of 1,3,5-trisubstituted pyrazolines (**4**) with the above mentioned procedure led to the formation of the corresponding pyrazoles (**5**) in high yields.



4 **5**

Scheme 4.

Table 2. Catalytic aerobic aromatization of 1,3,5-trisubstituted pyrazolines with NHPI–$Co(OAc)_2$[a]

Entry	Substrate	R^1	R^2	Time (h)	Product[b]	Yield (%)[c]
1	**4a**	Ph	Ph	7	**5a**[8c,13]	90
2	**4b**	4-$MeOC_6H_4$	Ph	9	**5b**[8c,13]	95
3	**4c**	4-ClC_6H_4	Ph	9	**5c**[8c,13]	88
4	**4d**	4-$NO_2C_6H_4$	Ph	7	**5d**[8c,13]	91
5	**4e**	Ph	Me	6	**5e**	89
6	**4f**	4-$MeOC_6H_4$	Me	6	**5f**	91

[a] Reaction condition: a mixture of 1,3,5-trisubstituted pyrazolines **4** (1 mmol), NHPI (0.1 mmol) and $Co(OAc)_2 \cdot 4H_2O$ (0.005 mmol) in acetonitrile (5 mL) was stirred under an oxygen atmosphere (1 atm) at room temperature.
[b] Compounds **5a–5d** were identified by comparing their ^1H, ^{13}C NMR and EI-MS spectral data and melting points with those reported in the cited references. **5e** and **5f** were two new compounds characterized by ^1H, ^{13}C NMR, EI-MS and HRMS spectra.
[c] Isolated yields.

In conclusion, the oxidative aromatization of substituted Hantzsch dihydropyridines and pyrazolines was achieved efficiently by using molecular oxygen as the terminal oxidant with NHPI and $Co(OAc)_2$ as the co-catalysts at room temperature. Extension of this method to the preparation of other heterocyclic compounds is under way in this laboratory.

3. Experimental

N-Hydroxyphthalimide (NHPI) (purity > 98%) was purchased from ALDRICH.

^1H and ^{13}C NMR spectra (300 and 75.5 MHz, respectively) were recorded on a Varian Mercury plus-300 spectrometer with TMS as the internal standard in $CDCl_3$. EI-MS spectra were measured on an HP 5988A spectrometer by direct inlet at 70 eV. The high resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEX II 47e spectrometer by ESI.

3.1. A typical procedure for the aromatization of 4-Hantzsch 1,4-dihydropyridines (1)

A mixture of 1,4-dihydropyridine **1a** (253 mg, 1.00 mmol), NHPI (16 mg, 0.10 mmol) and $Co(OAc)_2 \cdot 4H_2O$ (1 mg, 0.005 mmol) in acetonitrile (3 mL) was stirred under an oxygen atmosphere at room temperature for 4 h. After removal of the solvent under reduced pressure, the residue was column chromatographed (over silica gel) to afford the corresponding pyridine derivative **2a** 249 mg. Yield: 99%.

3.1.1. Diethyl 2,6-dimethyl-3,5-pyridinedicarboxylate (2a). Pale yellow solid; mp 70–71 °C (lit.[8c] 71–72 °C).

^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.42$ (t, 6H, $J = 7.2$ Hz), 2.85 (s, 6H), 4.40 (q, 4H, $J = 7.2$ Hz), 8.68 (s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.2$, 24.8, 61.3, 123.0, 140.8, 162.1, 165.8.

EI-MS: *m/z* (rel int., %) = 251 (39.8), 206 (100), 195 (19.6), 178 (53.8), 150 (29.0), 106 (21.6).

3.1.2. Diethyl 2,4,6-trimethyl-3,5-pyridinedicarboxylate (2b). Pale yellow oil (lit.[8c]).

^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.39$ (t, 6H, $J = 7.2$ Hz), 2.27 (s, 3H), 2.52 (s, 6H), 4.41 (q, 4H, $J = 7.2$ Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 14.1$, 16.9, 22.8, 61.5, 127.5, 142.0, 154.8, 168.3.

EI-MS: *m/z* (rel int., %) = 265 (31.4), 236 (45.9), 220 (100), 208 (43.2), 192 (25.9), 77 (34.5).

3.1.3. Diethyl 4-phenyl-2,6-dimethyl-3,5-pyridinedicarboxylate (2c). Pale yellow solid; mp 61–62 °C (lit.[8c] 60–61 °C).

^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.90$ (t, 6H, $J = 7.2$ Hz), 2.60 (s, 6H), 4.00 (q, 4H, $J = 7.2$ Hz), 7.2–7.4 (m, 5H).

^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 13.4$, 22.8, 61.2, 126.8, 127.9, 128.0, 128.3, 136.4, 146.0, 155.3, 167.7.

EI-MS: *m/z* (rel int., %) = 327 (71.2), 282 (48.1), 254 (42.4), 236 (100), 209 (29.4), 139 (33.8).

3.1.4. Diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (2d). Pale yellow solid; mp 49–50 °C (lit.[6e] 51–53 °C).

^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.89$ (t, 6H, $J = 7.2$ Hz), 2.50 (s, 6H), 3.72 (s, 3H), 3.96 (q, 4H, $J = 7.2$ Hz), 6.80 (d, 2H, $J = 6.9$ Hz), 7.10 (d, 2H, $J = 6.9$ Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.8, 22.9, 55.4, 61.4, 113.7, 127.4, 128.8, 129.6, 146.0, 155.3, 160.0, 168.2.

EI-MS: *m*/*z* (rel int., %)=357 (100), 312 (25.1), 282 (27.9), 266 (83.5), 135 (31.8), 84 (51.1).

3.1.5. Diethyl 4-(4-chlorophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (2e). Pale yellow solid; mp 65–66 °C (lit.[13] 65–66 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ=0.96 (t, 6H, J=7.2 Hz), 2.59 (s, 6H), 4.03 (q, 4H, J=7.2 Hz), 7.19 (d, 2H, J=8.4 Hz), 7.35 (d, 2H, J=8.4 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.5, 22.8, 61.4, 126.7, 128.2, 129.5, 134.6, 134.9, 144.7, 155.5, 167.5.

EI-MS: *m*/*z* (rel int., %)=363 (36.2), 361 (100), 316 (49.3), 288 (32.9), 270 (34.3), 139 (24.5), 43 (19.1).

3.1.6. Diethyl 4-(2-furyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (2f). Pale yellow oil (lit.[6e]).

^{1}H NMR (300 MHz, $CDCl_3$): δ=1.12 (t, 6H, J=6.9 Hz), 2.49 (s, 6H), 4.18 (q, 4H, J=6.9 Hz), 6.39 (d, 1H, J=3.3 Hz), 6.54 (d, 1H, J=3.3 Hz), 7.42 (br s, 1H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.7, 22.5, 61.5, 111.6, 111.7, 124.5, 133.5, 143.7, 147.8, 155.4, 167.9.

EI-MS: *m*/*z* (rel int., %)=317 (71.5), 272 (52.3), 243 (38.1), 214 (100), 95 (45.3).

3.1.7. Diethyl 4-(4-nitrophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylate (2g). Pale yellow solid; mp 114–115 °C (lit.[8c] 115–116 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ=1.00 (t, 6H, J=6.9 Hz), 2.64 (s, 6H), 4.05 (q, 4H, J=6.9 Hz), 7.47 (d, 2H, J=9.0 Hz), 8.27 (d, 2H, J=9.0 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.6, 23.0, 61.6, 123.1, 126.1, 129.3, 143.3, 143.9, 147.7, 156.1, 167.0.

EI-MS: *m*/*z* (rel int., %)=372 (48.8), 355 (29.5), 327 (100), 299 (39.5), 281 (32.5), 139 (23.2).

3.2. A typical procedure for the aromatization of 1,3,5-trisubstituted pyrazolines (4)

A mixture of 1,3,5-triphenylpyrazoline (**4a**) (298 mg, 1.00 mmol), NHPI (16 mg, 0.10 mmol) and $Co(OAc)_2 \cdot 4H_2O$ (1 mg, 0.005 mmol) in acetonitrile (5 mL) was stirred under an oxygen atmosphere at room temperature for 7 h. After removal of the solvent under reduced pressure, the residue was column chromatographed (over silica gel) to afford 1,3,5-triphenylpyrazole (**5a**) 267 mg. Yield: 90%.

3.2.1. 1,3,5-Triphenylpyrazole (5a). Pale yellow solid; mp 141–142 °C (lit.[13] 139–140 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ=6.83 (s, 1H), 7.3–7.5 (m, 13H), 7.93 (d, 2H, J=7.7 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ=105.2, 125.3, 125.8, 127.4, 128.0, 128.3, 128.4, 128.6, 128.7, 128.9, 130.5, 133.0, 140.0, 144.3, 151.9.

EI-MS *m*/*z* (rel int., %): 296 (48.6), 86 (64.2), 84 (100), 77 (91.5), 51 (55.2).

3.2.2. 1,3-Diphenyl-5-(4-methoxyphenyl)pyrazole (5b). Pale yellow solid; mp 79–80 °C (lit.[13] 78 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ=3.81 (s, 3H), 6.78 (s, 1H), 6.85 (d, 2H, J=9.0 Hz), 7.21 (d, 2H, J=9.0 Hz), 7.3–7.5 (m, 8H), 7.93 (d, 2H, J=7.5 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ=55.2, 104.7, 113.9, 122.9, 125.3, 125.7, 127.3, 127.9, 128.6, 128.9, 130.0, 133.0, 140.2, 144.2, 151.8, 159.5.

EI-MS *m*/*z* (rel int., %): 326 (23.1), 325 (4.1), 152 (14.5), 105 (61.5), 86 (100), 77 (36.6), 49 (61.4).

3.2.3. 5-(4-Chlorophenyl)-1,3-diphenylpyrazole (5c). Pale yellow solid; mp 113–114 °C (lit.[13] 114–115 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ=6.83 (s, 1H), 7.2–7.5 (m, 12H), 7.91 (d, 2H, J=8.1 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ=105.2, 125.2, 125.7, 127.6, 128.0, 128.6, 128.7, 128.9, 129.0, 129.9, 132.7, 134.3, 139.8, 143.1, 151.9.

EI-MS *m*/*z* (rel int., %): 332 (13.0), 330 (38.8), 329 (20.7), 105 (27.4) 84 (71.4), 77 (100), 51 (57.7).

3.2.4. 1,3-Diphenyl-5-(4-nitrophenyl)pyrazole (5d). Pale yellow solid; mp 142–144 °C (lit.[13] 142–143 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ=6.94 (s, 1H), 7.3–7.5 (m, 10H), 7.92 (d, 2H, J=8.4 Hz), 8.18 (d, 2H, J=8.4 Hz).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ=106.2, 123.8, 125.4, 125.8, 128.2, 128.3, 128.7, 129.2, 129.3, 132.4, 136.7, 139.5, 141.9, 147.2, 152.4.

EI-MS *m*/*z* (rel int.): 341 (20), 294 (30.1), 191 (11.5), 163 (13.2), 105 (63.8), 77 (100), 51 (21.8).

3.2.5. 1,5-Diphenyl-3-methyl-pyrazole (5e). Pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ=2.38 (s, 3H), 6.31 (s, 1H), 7.1–7.3 (m, 10H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.5, 107.7, 125.0, 127.0, 128.0, 128.3, 128.5, 128.8, 130.6, 140.0, 143.6, 149.4.

EI-MS *m*/*z* (rel int., %): 234 (100), 218 (14.3), 192 (13.8), 77 (31.5), 51 (20.5).

ESI-HRMS: *m*/*z* Calcd for $C_{16}H_{14}N_2+H^+$: 235.1230; found: 235.1228.

3.2.6. 1-Phenyl-3-methyl-5-(4-methoxyphenyl)pyrazole (5f). Pale yellow solid; mp 86–88 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ=2.37 (s, 3H), 3.77 (s, 3H), 6.25 (s, 1H), 6.80 (d, 2H, J=8.7 Hz), 7.13 (d, 2H, J=8.7 Hz), 7.2–7.4 (m, 5H).

^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.5, 55.1, 107.1, 113.8, 123.1, 125.0, 126.9, 128.7, 129.8, 140.2, 143.4, 149.3, 159.3.

MS *m/z* (rel int., %): 264 (100), 249 (39.5), 115 (18.4), 77 (58.1), 51 (28.7).

ESI-HRMS: *m/z* Calcd for $C_{17}H_{16}N_2O+H^+$: 265.1335; found: 265.1335.

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Synthesis of aromatic aldehydes by aerobic oxidation of hydroaromatic compounds and diarylalkanes using *N*-hydroxyphthalimide (NHPI) as a key catalyst

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Abstract—Aerobic oxidation of hydroaromatic compounds and diarylalkanes by *N*-hydroxyphthalimide (NHPI) under mild conditions afforded the corresponding hydroperoxides in high selectivity. Treatment of the resulting hydroperoxides with sulfuric acid followed by neutralization by a base resulted in phenol and aromatic aldehydes in high selectivity. This method provides a convenient synthetic route to aldehydes involving an aromatic moiety.

1. Introduction

Aerobic oxidation of alkylbenzenes is an important commercial process for the production of alkyl aromatic hydroperoxides, which are used as oxidants for epoxidation of alkenes like propene as well as raw materials for the production of phenols.[1] The Hock process is well known as a typical method for the concomitant synthesis of phenol and acetone from cumene hydroperoxide obtained by the aerobic oxidation of isopropylbenzene.[2] Currently, most phenols are manufactured by this method worldwide. Resorcinol and hydroquinone are also prepared by the aerobic oxidation of the *m*- and *p*-diisopropylbenzenes, respectively. However, there is little work reported on the aerobic oxidation of hydroaromatic compounds and diphenyl alkanes to prepare phenols and aldehydes, probably because of the difficulty in carrying out the oxidation selectively.[3] In previous papers, we have reported the aerobic oxidation of hydrocarbons catalyzed by NHPI in the presence or absence of transition metals such as cobalt and manganese salts. This oxidation provides a novel efficient catalytic method for the transformation of alkanes to oxygen-containing compounds like alcohols, ketones and carboxylic acids in high conversion and selectivity under mild conditions.[4] In continuation of our study, the present methodology was extended to the synthesis of various aromatic aldehydes by the aerobic oxidation of hydroaromatic compounds and diphenyl alkanes to hydroperoxides upon treatment with sulfuric acid.

Keywords: Aerobic oxidation; Hydroaromatic compounds; Hock process.
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2. Results and discussion

We first examined the aerobic oxidation of tetralin (**1**) under dioxygen atmosphere (1 atm) in the presence of a catalytic amount of AIBN and NHPI (Eq. 1). Table 1 shows the result for the oxidation of **1** with atmospheric dioxygen catalyzed by NHPI followed by treatment with triphenylphosphine.

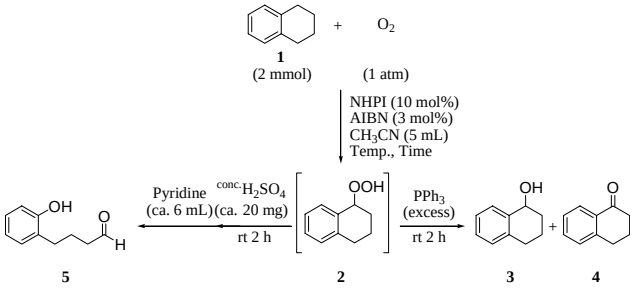
Table 1. Oxidation of tetralin (**1**) with O_2 (1 atm) by NHPI under various conditions[a]

Entry	Temperature (°C)	Time (h)	Conv. (%)	Select. (%)[b]	
				3	**4**
1	75	5	61	80	8
2	65	6	52	87	8
3[c]	50	6	50	92	4
4[d]	75	5	22	77	nd
5[e]	75	5	20	30	nd

[a] Compound **1** (2 mmol) was reacted with O_2 (1 atm) in the presence of AIBN (3 mol%) and NHPI (10 mol%) in CH_3CN (5 mL) followed by treatment with PPh_3 (ca. 10 mmol) at room temperature for 2 h.
[b] GC yield based on **1** reacted.
[c] BPP was used instead of AIBN.
[d] In the absence of AIBN.
[e] In the absence of NHPI.

Compound **1** was oxidized with O_2 (1 atm) in the presence of AIBN (3 mol%) and NHPI (10 mol%) in acetonitrile at 75 °C for 5 h. The resulting hydroperoxide (**2**) was treated with excess triphenylphosphine to give 1,2,3,4-tetrahydro-1-naphthol (α-tetralol) (**3**) and α-tetralone (**4**) in 80 and 8% selectivity, respectively, at 61% conversion of **1** (entry 1). The same reaction at 65 °C gave almost the same results as

that at 75 °C except for a slight decrease of the conversion (entry 2). In order to carry out the reaction at lower temperature, *t*-butyl peroxypivalate (BPP), which decomposes at 55 °C was employed as a radical initiator instead of AIBN. The oxidation can be performed at 50 °C to lead to **3** in high selectivity (92%) along with **4** (4%) at 50% conversion of **1** (entry 3). The reaction of **1** by NHPI alone at 75 °C took place at low conversion (22%) to give **3** (77% selectivity), but the reaction by AIBN in the absence of NHPI resulted in a complex mixture of products (entries 4 and 5). Quite recently, Xu et al. reported the oxidation of **1** with O_2 in the presence of anthraquinones and NHPI at 80 °C to give **4** (88%) and **3** (12%).[5]



(1)

In order to obtain further insight into the present reaction, the oxidation was followed by using NHPI/AIBN at 65 °C and using NHPI/BPP at 50 °C, respectively (Fig. 1). The time-conversion curves of **3** and **4** by both systems are similar. The oxidation proceeded smoothly for about 3 h, but it became very slow and was practically terminated after 8 h. This is believed to be due to the decomposition of the NHPI by a side-reaction with a radical species generated from the resulting hydroperoxide **2**. It is known that an increase in the concentration of hydroperoxides causes their steep self-decomposition.

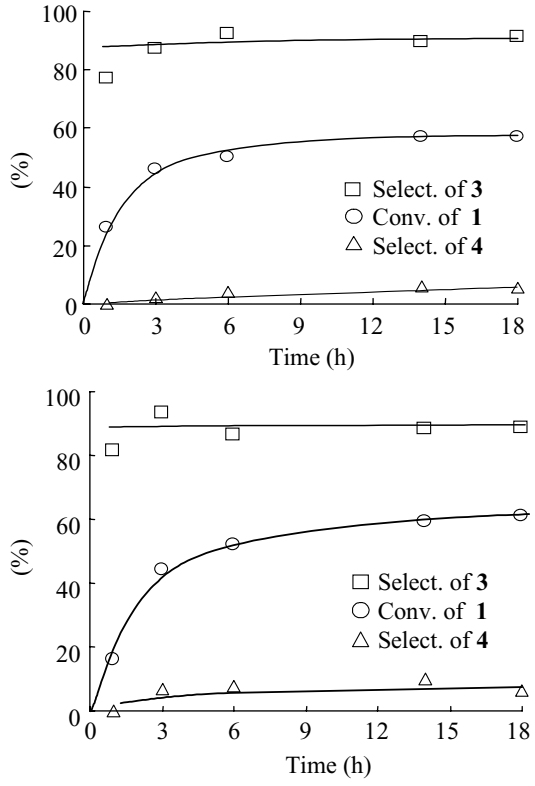


Figure 1. Time-dependence curves for aerobic oxidation of **1** (2 mmol) under O_2 (1 atm): (a) NHPI (10 mol%)/AIBN (3 mol%) in CH_3CN (5 mL) at 65 °C. (b) NHPI (10 mol%)/BPP (3 mol%) in CH_3CN (5 mL) at 50 °C.

We next tried the conversion of the resulting hydroperoxide **2** into aldehyde by treating with some acids (Table 2).

Table 2. Oxidation of **1** with O_2 (1 atm) by NHPI followed by treatment with sulfuric acid[a]

Entry	Temperature (°C)	Time (h)	Conv. (%)	Select. (%)[b]		
				3	**4**	**5**
1	75	3	49	2	4	94
2	75	6	64	3	8	89
3[c]	75	3	40	<1	7	92
4[d]	75	3	52	17	46	2
5[e]	50	3	31	nd	nd	87

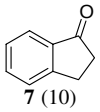
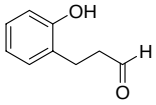
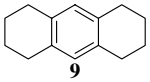
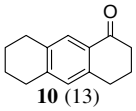
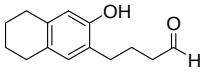
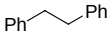
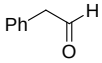
[a] Compound **1** (2 mmol) was reacted with O_2 (1 atm) in the presence of AIBN (3 mol%) and NHPI (10 mol%) in CH_3CN (5 mL). The reaction mixture was treated with H_2SO_4 (ca. 20 mg) at room temperature for 2 h followed by adding pyridine (ca. 6 mL).
[b] GC yield based on **1** reacted.
[c] $InCl_3 \cdot 4H_2O$ (50 mg) was used in place of H_2SO_4.
[d] $CeCl_3 \cdot 7H_2O$ (50 mg) was used in place of H_2SO_4.
[e] BPP (3 mol%) was used in place of AIBN.

The oxidation of **1** in the presence of AIBN and NHPI at 75 °C for 3 h followed by treatment with sulfuric acid at room temperature afforded 3-(2-hydroxyphenyl)butanal (**5**) (94%), **4** (4%), and **3** (2%) at 49% conversion of **1** (entry 1). When the reaction was prolonged to 6 h, the conversion was increased to 64% but the selectivity to **5** was slightly decreased (entry 2). Treatment of **2** with a Lewis acid like $InCl_3$, which does not decompose in aqueous medium, gave almost the same result as that of sulfuric acid (entry 3). However, when $CeCl_3$ was employed instead of $InCl_3$, tetralone **4** (46%) was formed as the principal product along with tetralol **3** (17%), but the desired **5** was formed in only 2% yield (entry 4). This shows that $CeCl_3$ serves as a metal ion, which promotes the redox decomposition of the hydroperoxide **2**. The reaction using BPP instead of AIBN at 50 °C led to **5** in 87% selectivity at 31% conversion of **1** (entry 5).

On the basis of these results, we examined the synthesis of aldehydes having an aromatic moiety from several hydroaromatic compounds and diphenyl alkanes (Table 3).

Indane (**6**) was reacted under the same conditions as entry 1 in Table 2 to afford 3-(2-hydroxyphenyl)propanal (**8**) (81%) and indanone (**7**) (10%) at 42% conversion of **6** (entry 1). In this reaction, a trace amount of 1-indanol was formed. *sym*-Octahydroanthracene (**9**) was easily oxidized under these conditions to give 1,2,3,4,6,7,8,9-octahydroanthracen-1-one (**10**) (13%) and 4-(5,6,7,8-tetrahydro-3-hydroxy-2-naphthyl)butanal (**11**) (73%) at higher conversion (85%) (entry 2). In this oxidation, however, no products in which both cyclohexyl rings in **9** are oxidized were obtained. It was found that diphenyl methane (**12**) was less reactive than **1**. Hence, benzonitrile, which is capable of raising the

Table 3. Conversion of hydroaromatic compounds and diphenyl alkanes into aldehydes[a]

Entry	Substrate	Temperature (°C)/Time (h) (Solvent)	Conv. (%)	Product (select. (%))[b]	
1	 **6**	75/3 (CH_3CN)	42	 **7** (10)	 **8** (81)
2	 **9**	75/3 (CH_3CN)	85	 **10** (13)	 **11** (73)
3	 **12**	100/5 (PhCN)	30	 **13** (98)	PhOH **14** (99)
4	 **15**	100/3 (PhCN)	37	 **16** (97)	**14** (62)
5	**15**	75/3 (CH_3CN)	23	**16** (96)	**14** (83)
6[c]	**15**	50/18 (CH_3CN)	33	**16** (99)	**14** (97)
7[c]	 **17**	50/3 (CH_3CN)	24	 **18** (>99)	**14** (67)

[a] Substrate (2 mmol) was reacted under the same conditions as entry 1 in Table 2.
[b] GC yield based on substrate reacted.
[c] BPP (*t*-butyl peroxypivalate) was used instead of AIBN.

reaction temperature to 100 °C, was used as a solvent. The reaction gave benzaldehyde (**13**) and phenol (**14**) in excellent selectivity at moderate conversion of **12** (entry 3). 1,2-Diphenylethane (**15**) reacted in the same way as **12** to give the corresponding aldehyde, phenylacetaldehyde (**16**), in high selectivity (97%) at 37% conversion (entry 4). Although long reaction time is needed for the oxidation of **15** at lower temperature (75 or 50 °C), **15** was found to be slowly oxidized even at 50 °C to give **16** in high selectivity (entry 6). However, oxidation of 1,1-diphenylethane (**17**) having a methine group more easily proceeded than that of **15** to give acetophenone (**18**) in high selectivity (99%) at 24% conversion (entry 7).

In conclusion, we have developed a method for aerobic oxidation of hydroaromatic compounds and diarylalkanes to the corresponding hydroperoxides selectively. Further treatment of the resulting hydroperoxides with sulfuric acid followed by neutralization with a base produced phenol derivatives and aromatic aldehydes in high selectivity. This method provides a convenient synthetic route to aldehydes involving an aromatic group.

3. Experimental

3.1. General procedure

^1H and ^{13}C NMR were measured at 270 and 67.5 MHz, respectively, in $CDCl_3$ with TMS as the internal standard. Infrared (IR) spectra were measured as thin films on NaCl plate or KBr press disk. A GLC analysis was performed with a flame ionization detector using a 0.2 mm×25 m capillary column (OV-17). Mass spectra were determined at an ionizing voltage of 70 eV. All starting materials, catalysts, and initiators were purchased from commercial sources and used without further treatment. The yields of products were estimated from the peak areas based on the internal standard technique.

3.2. General procedure for the oxidation of tetralin (1) to 1,2,3,4-tetrahydro-1-naphthol (α-tetralol) (3) and α-tetralone (4)

An acetonitrile (5 mL) solution of tetralin (**1**) (2 mmol), AIBN (3 mol%), and NHPI (10 mol%) was placed in a two-necked flask equipped with a balloon filled with O_2 at 50–75 °C for 5–6 h. The reaction mixture was treated with an excess amount of PPh_3 at 25 °C for 2 h.

3.3. General procedure for the oxidation of various substrates to aldehyde and ketone derivatives

An acetonitrile (5 mL) solution of substrate (2 mmol), AIBN (3 mol%), and NHPI (10 mol%) was placed in a two-necked flask equipped with a balloon filled with O_2 at 75 °C for 3 h. The reaction mixture was treated with H_2SO_4 (ca. 20 mg) in CH_3CN (1 mL) at 25 °C for 2 h. The mixture was neutralized by adding pyridine (ca. 6 mL). The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (*n*-hexane/

AcOEt=10:1) to give aldehydes and ketones. Products were characterized by ^{1}H and ^{13}C NMR, IR, and GC–MS.

3.3.1. 4-(2-Hydroxyphenyl)butanal (5).[6] ^{1}H NMR δ 9.79 (s, 1H), 7.09–6.79 (m, 4H), 5.66 (br, 1H), 2.62 (t, $J=7.2$ Hz, 2H), 2.55 (t, $J=6.7$ Hz, 2H), 1.95–1.90 (m, 2H); ^{13}C NMR δ 203, 130, 127, 120, 115, 42.9, 29.3, 22.1; IR (NaCl) 3420, 3066, 3034, 2937, 2723, 1716, 1593, 1503, 1454, 1231, 1175, 1107, 755 cm^{-1}; MS *m/e*=40, 51, 65, 77, 91, 107, 120, 133, 145, 164.

3.3.2. 1,2,3,4,6,7,8,9-Octahydroanthracen-1-one (10).[7] ^{1}H NMR δ 7.74 (s, 1H), 7.26 (s, 1H), 2.87 (t, $J=6.2$ Hz, 2H), 2.77 (t, $J=6.4$ Hz, 4H), 2.60 (t, $J=6.4$ Hz, 2H), 2.09 (q, $J=6.2$ Hz, 4H); ^{13}C NMR δ 198, 152, 143, 141, 135, 129, 128, 75; 53, 39, 29, 23; IR (NaCl) 2934, 2850, 1727, 1727, 1679, 1436, 1265, 1041, 894, 747 cm^{-1}; MS *m/e*= 40, 51, 63, 77, 91, 103, 115, 129, 144, 158, 172, 185, 200; HRMS (EI, M^{+}) calcd for $C_{14}H_{16}O$: 200.1201, found: 200.1204.

3.3.3. 4-(5,6,7,8-Tetrahydro-3-hydroxy-2-naphthyl)butanal (11). ^{1}H NMR δ 9.74 (s, 1H), 6.75 ppm (s, 1H), 6.48 (s, 1H), 2.63–2.48 (m, 8H), 1.89 (m, $J=6.8$ Hz, 2H), 1.70 (m, $J=7.3$ Hz, 4H), ^{13}C NMR δ 204, 152, 136, 131, 128, 124, 115, 43, 29, 28, 23, 22; IR (NaCl) 3412, 3004, 2927, 2855, 1712, 1620, 1517, 1424, 1247, 1191, 1094, 918, 858, 777 cm^{-1}; MS *m/e*=40, 55, 65, 77, 91, 105, 115, 133, 146, 161, 174, 187, 200, 218; HRMS (EI, M^{+}) calcd for $C_{14}H_{18}O_2$: 218.1307, found: 218.1332.

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Molecular recognition of viologen by zinc porphyrinic receptors with diarylurea sidearms. Toward construction of a supramolecular electron transfer system

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Abstract—A series of zinc porphyrinic receptors for a viologen substrate (hexyl viologen, $\mathbf{HV}^{2+}$) were synthesized, in which varying numbers of diarylurea moieties, from one to four, were appended at the porphyrin's *meso* positions. The increase in the number of the diarylurea moiety led to the increase in stability of the receptor–$\mathbf{HV}^{2+}$ complex, showing that the convergent dipoles set up on the porphyrin platform played an essential role in the complexation. In this system, formation of the stable electron donor–acceptor complex resulted in the effective electron transfer from the singlet excited state of the zinc porphyrin to $\mathbf{HV}^{2+}$.

1. Introduction

For a few past decades, photoinduced electron transfer systems employing organic molecules as well as metal complexes have received much attention because they do not only serve as models for photosynthetic electron relay systems but also give significant insights into the development of molecular-scale opto-electronic devices.[1] Especially, the supramolecular architecture of electron donor–acceptor complexes has been eagerly studied and established as one of powerful methods for construction of photochemically active ensembles,[2] where porphyrins and the related compounds have been widely used as electron donor components because of analogy to photosynthetic pigments. Thus, designing porphyrinic receptors for appropriate electron acceptors such as electron-deficient aromatics,[3] quinones,[4] fullerenes,[5] and viologens[6] has been one of major topics in supramolecular photochemistry. Many covalently-linked porphyrin–viologen donor–acceptor systems have so far been studied,[7] where the electron transfer effectively occurs via formation of a face-to-face donor–acceptor complex.[7d] However, despite such significance of the rational design of supramolecular porphyrin–viologen complexes, only a few examples of porphyrinic receptors for a bare viologen backbone have been so far reported.[6a,d,e]

We recently reported the doubly diarylurea-linked cofacial zinc porphyrin dimer (**DLD**), which formed a 1:1 complex with a viologen substrate (hexyl viologen perchlorate, $\mathbf{HV}^{2+}\cdot 2ClO_4^-$).[8] In this system, high stability of the complex ($K=546{,}000\ M^{-1}$ in

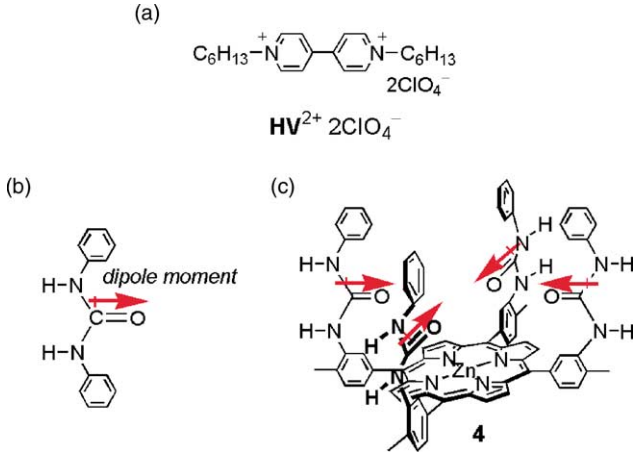

Figure 1. (a) Structure of a viologen substrate (hexyl viologen perchlorate), and illustrations of (b) the dipole moment on diphenylurea and (c) the convergent arrangement of four carbonyl dipoles in the receptor **4**.

Keywords: Molecular recognition; Diarylurea; Zinc porphyrin; Viologen; Photoinduced electron transfer; Supramolecular system.
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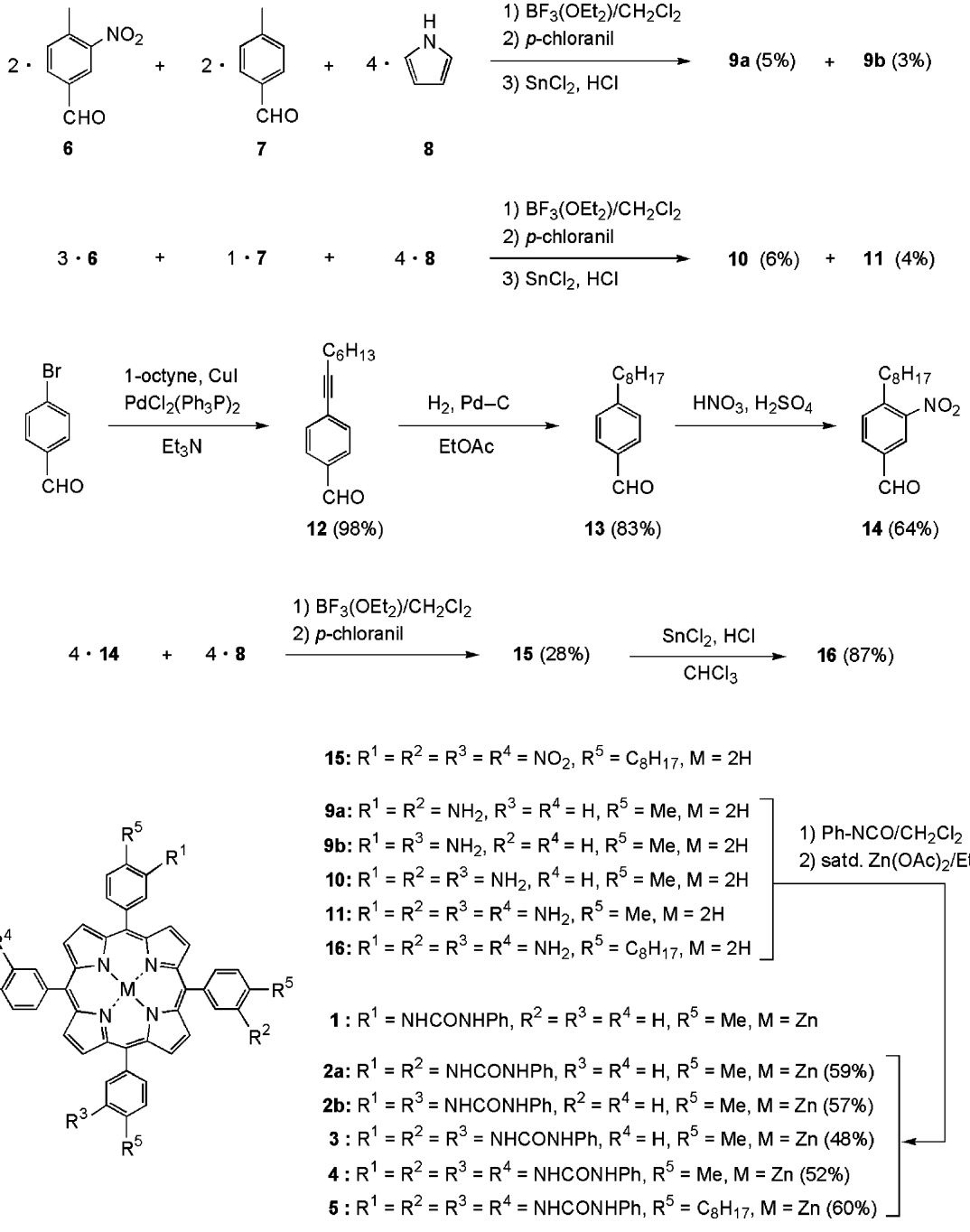
$CHCl_3$/DMSO, 10:1, v/v) was attributed to the dipole-cation interactions[9] between the diarylurea linkages and the viologen backbone. This interesting result impels us to design a more sophisticated porphyrinic receptor for viologen that is facilely prepared. Here we report complexation of a series of diarylurea-appended zinc porphyrins **1**–**4** with $\mathbf{HV}^{2+}$: arranging the carbonyl dipoles on the zinc porphyrin platform in a convergent manner should promise effective binding of $\mathbf{HV}^{2+}$ (Fig. 1). We also discuss the complexation-facilitated photoinduced electron transfer from steady-state fluorescence quenching studies and flash laser photolysis measurement.

2. Results and discussion

2.1. Synthesis of the zinc porphyrinic receptors

We have already reported the synthesis of the receptor **1** in the previous work.[10] In Scheme 1 are shown the syntheses of **2**–**5**. Acid-promoted ($BF_3 \cdot OEt_2$) condensation of 4-methyl-3-nitrobenzaldehyde **6**, *p*-tolualdehyde **7** and pyrrole **8** at the ratio of 2:2:4 (mol/mol/mol) followed by oxidation with chloranil afforded a mixture of 5,10-bis(3-nitro-4-methylphenyl)-15,20-bis(4-methylphenyl)porphyrin, and 5,15-bis(3-nitro-4-methylphenyl)-10,20-bis(4-methylphenyl)porphyrin, both of which were reduced



Scheme 1. Synthesis of porphyrinic receptors.

by $SnCl_2$ in concd HCl to yield a mixture of the corresponding amino-substituted porphyrins **9a** and **9b** in the yields of 3 and 5% based on **8**, respectively. Changing the ratio of the starting materials (**6**:**7**:**8**=3:1:4, mol/mol/mol), a similar procedure afforded **10** and **11** in 6 and 4% yields, respectively. The receptors **2**–**4** were easily obtained by the reactions of the corresponding amino-substituted porphyrins **9**–**11** with an excess amount of phenylisocyanate followed by zinc insertion in 48–60% yields. The more soluble, quadruply functionalized zinc porphyrin **5** was also prepared as an analogue of **4** for ^{1}H NMR spectroscopic studies. A Sonogashira cross-coupling reaction of 4-bromobenzaldehyde and 1-octyne yielded 4-(1-octyn-1-yl)benzaldehyde **12** in 98% yield, followed by hydrogenation on Pd–C to yield 4-octylbenzaldehyde **13** in 83% yield. Nitration of **13** by treatment with HNO_3 in H_2SO_4 yielded 3-nitro-4-octylbenzaldehyde **14** in 64% yield. Acid-promoted ($BF_3\cdot OEt_2$) condensation of **14** and **8** yielded a nitro-substituted porphyrin **15** in 28% yield, which was reduced to **16** in 87% yield. Treatment of **16** with a large excess of phenylisocyanate followed by zinc insertion yielded the receptor **5** in 60% yield. Each compound was identified by ^{1}H NMR, ^{1}H–^{1}H COSY, electronic absorption, IR, and FAB mass spectra as well as elemental analyses.

2.2. Complexation behavior of the zinc porphyrinic receptors with HV^{2+}

In Figure 2 are shown electronic absorption spectral changes of **4** in the Soret region upon addition of varying amounts of $\mathbf{HV}^{2+}\cdot 2ClO_4^-$. The red-shifted spectral changes with an isosbestic point at 434 nm showed saturation behavior. The stoichiometry of the **4**–$\mathbf{HV}^{2+}$ complex was confirmed as 1:1 by the Job's analysis using electronic absorption spectroscopy. The binding constant (K_{abs}) was determined as $(2.86\pm0.30)\times 10^6\ M^{-1}$ by the computer-assisted least squares analysis based on 1:1 complexation, which was larger than that of the **DLD**–$\mathbf{HV}^{2+}$ complex.[8] Similar complexation behavior was observed for **1**–**3** upon addition of $\mathbf{HV}^{2+}$, and K_{abs}s of **1**–**4** for $\mathbf{HV}^{2+}$ are summarized in Table 1. The increase in the number of the diarylurea moiety led to the increase in the stability of the complex, and the zinc porphyrin without any diarylurea moieties[11] did not exhibit any spectral changes even in the presence of an excess amount of $\mathbf{HV}^{2+}$. These results indicate that the diarylurea moieties play an essential role in binding of $\mathbf{HV}^{2+}$.

The complexation of $\mathbf{HV}^{2+}$ to the receptors was also confirmed by ^{1}H NMR titration experiments. In Figure 3 are shown ^{1}H NMR spectra of **5**, $\mathbf{HV}^{2+}$, and a 1:1 mixture of the both. The signals of H^a, H^b and H^c of $\mathbf{HV}^{2+}$ exhibited complexation-induced upfield shifts (1.4, 3.7, and 0.6 ppm, respectively) upon addition of an equimolar amount of **5**, and any other remarkable shifts of the signals of the alkyl protons in $\mathbf{HV}^{2+}$ were not observed (<0.2 ppm). As the proton was close to the center of viologen backbone, the upfield shift became large. These results were unambiguously due to ring-current anisotropy from the porphyrin π-plane, indicating that the bipyridinium backbone of $\mathbf{HV}^{2+}$ was located on the porphyrin ring. The free **5** exhibited the multiple signals of H^4 and two urea N–Hs as well as the broadened signals of H^1–H^6 (Fig. 3c), indicating that the receptor exists as a mixture of the atropisomers.[12]

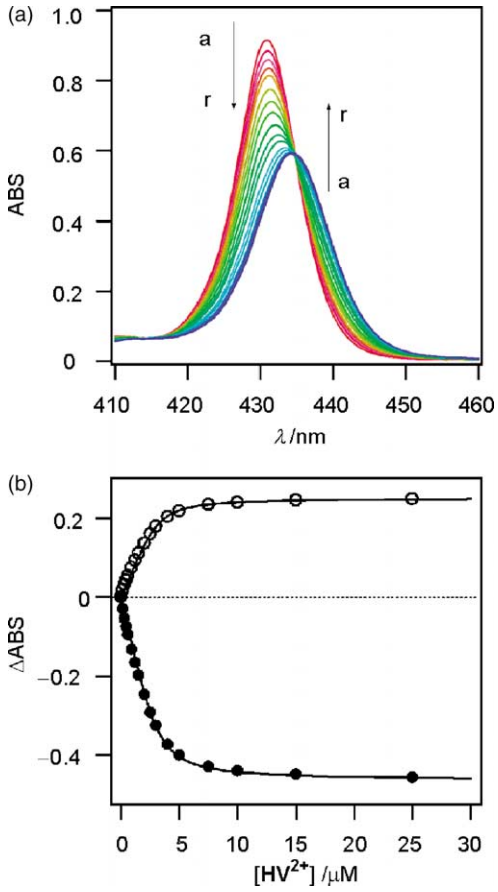


Figure 2. (a) Electronic absorption spectral changes of **4** (1.5 μM) upon addition of increasing amounts of $\mathbf{HV}^{2+}$ (a–r; 0, 0.15, 0.30, 0.45, 0.60, 0.90, 1.2, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 7.5, 10, 15, 25 and 50 μM) and (b) absorbance changes at 430 (●) and 438 nm (○) in $CHCl_3$–DMSO (10/1, v/v) at 293 K.

On the other hand, the complexed **5** exhibited singlet signals of H^4 and N–Hs as well as the sharp signals of H^1–H^6, although a small amount of metastable conformer was observed probably due to the flexibility of the diarylurea arms (Fig. 3b).[13] Taking it into consideration that the increase in the number of the diarylurea moiety gave rise to stabilization of the complex, one can see that all the diarylurea moieties participated in the binding of $\mathbf{HV}^{2+}$.

The contribution of the dipole-cation interaction to the complexation of $\mathbf{HV}^{2+}$ was quantitatively estimated by

Table 1. Binding constants of receptors **1**–**4** for $\mathbf{HV}^{2+}$ obtained by electronic absorption (K_{abs}) and fluorescence emission spectra (K_{em})[a]

Compound	K_{abs} (M^{-1})[b]	K_{em} (M^{-1})[c]	ΔG_{abs} (kJ mol^{-1})[d]
1	1100	2300	−17.1
2a	18,900	15,000	−24.0
2b	17,500	10,700	−23.8
3	195,000	216,000	−29.7
4	2,860,000	1,940,000	−36.2

[a] In $CHCl_3$–DMSO (10/1, v/v) at 293 K.
[b] Experimental errors were within 7% except for **4** (11%).
[c] Experimental errors were within 10% except for **4** (26%).
[d] ΔG_{abs}s were calculated from K_{abs}s.

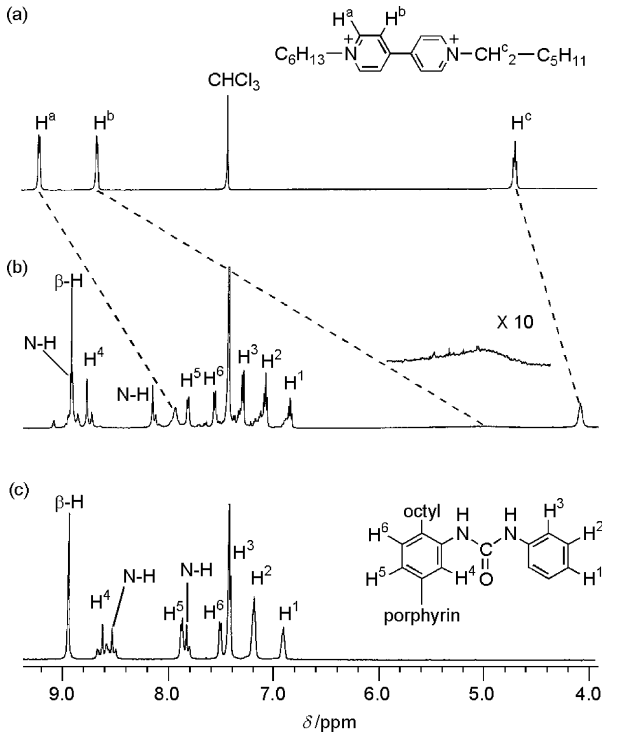


Figure 3. ^{1}H NMR spectral study of (a) $\mathbf{HV}^{2+}$ (1.8 mM), (b) $\mathbf{HV}^{2+}$ (1.8 mM) + **5** (1.8 mM), and **5** (1.8 mM) in $CDCl_3$–DMSO-d_6 (10/1, v/v) at 293 K.

plotting the free energy changes of the complexation (ΔG_{abs}s) against the number of the diarylurea moiety (Fig. 4). These plots showed good linearity, and the slope obtained (−6.28 kJ/mol) is attributed to the averaged free energy change given by one dipole-cation interaction between the diarylurea moiety and $\mathbf{HV}^{2+}$ (Fig. 5, ΔG_A). In addition, the intercept of the plots (−11.1 kJ/mol) is reasonably attributed to the free energy change of the interaction between the porphyrin platform and the viologen backbone (Fig. 5, ΔG_B), that is either electrostatic or solvophobic interaction, or the sum of both. It is noteworthy that such a good linear relationship also indicates that, in each receptor–$\mathbf{HV}^{2+}$ system, all diarylurea moieties contribute to binding of $\mathbf{HV}^{2+}$ in an induced-fit manner to achieve the multiple dipole-cation interaction.

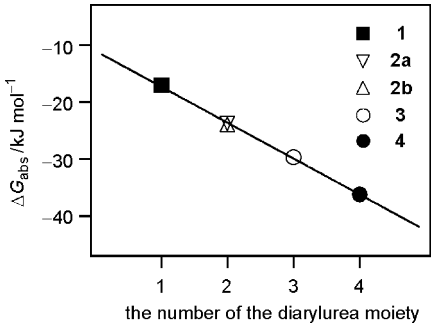


Figure 4. Plots for free energy changes on complexation of **1**–**4** with $\mathbf{HV}^{2+}$ against the number of the diarylurea moiety in the receptors in $CHCl_3$–DMSO (10/1, v/v) at 293 K. R^2 = 0.996.

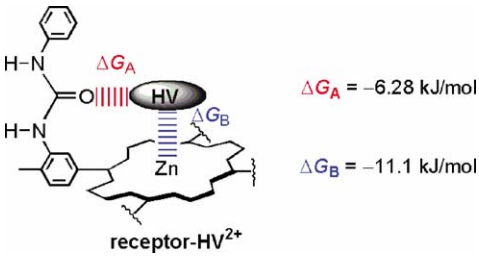


Figure 5. Schematic representation of contribution of the intermolecular interactions (ΔG_A and ΔG_B) to the complexation of the receptors **1**–**4** with $\mathbf{HV}^{2+}$.

2.3. Complexation-facilitated electron transfer from the zinc porphyrinic receptors to $\mathbf{HV}^{2+}$

Addition of $\mathbf{HV}^{2+}$ to solutions of **1**–**4** led to the fluorescence quenching due to photoinduced electron transfer from the zinc porphyrin unit to $\mathbf{HV}^{2+}$ (Fig. 6a).[6b,c,e,8] The binding constant K_{em} obtained from fluorescence emission spectroscopy validly corresponded with K_{abs} for each receptor (Table 1), indicating that fluorescence quenching occurred via formation of the electron donor–acceptor complex. As shown in Figure 6b, all titration curves finally reached plateaus but exhibited different fluorescence quenching efficiencies: the **3**–$\mathbf{HV}^{2+}$ and **4**–$\mathbf{HV}^{2+}$ systems showed quite efficient fluorescence quenching (97 and 100%, respectively, supposing that the receptor molecules fully complexed with $\mathbf{HV}^{2+}$), whereas the **2a**–$\mathbf{HV}^{2+}$ and **2b**–$\mathbf{HV}^{2+}$ showed quasi-effective (79 and 75%, respectively) and the **1**–$\mathbf{HV}^{2+}$ showed less effective quenching (24%). The **ZnPor**–$\mathbf{HV}^{2+}$ system hardly showed fluorescence quenching (**ZnPor**; [5,10,15,20-tetrakis(4-methylphenyl)-porphyrinato]zinc(II)). Therefore,

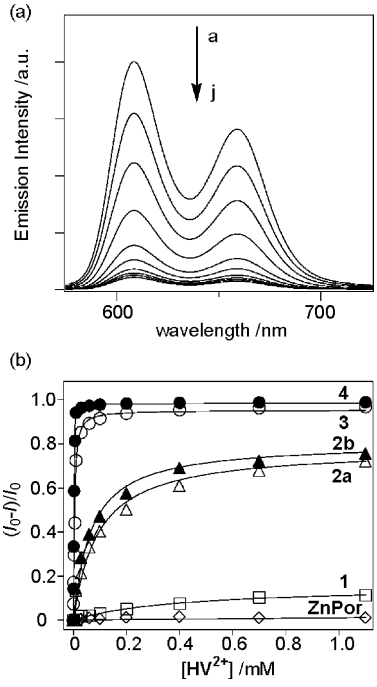


Figure 6. (a) Fluorescence emission spectral changes of **4** upon addition of increasing amounts of $\mathbf{HV}^{2+}$ (a–j; 0, 0.30, 0.60, 0.90, 1.2, 1.5, 2.0, 2.5, 3.0, and 4.0 μM; [**4**] = 1.5 μM) and (b) quenching titration profiles of **1**–**4** in $CHCl_3$–DMSO (10/1, v/v) at 293 K. λ_{ex} = 560 nm.

the increase in the thermodynamic stability of the receptor–$\mathbf{HV}^{2+}$ complex led to the increase of fluorescence quenching efficiency. These results indicated that multiple dipole-cation interactions as seen in **3**–$\mathbf{HV}^{2+}$ and **4**–$\mathbf{HV}^{2+}$ fixed $\mathbf{HV}^{2+}$ tightly on the receptor in a preferred manner to photoinduced electron transfer.

2.4. Photophysical properties of the 4–$\mathbf{HV}^{2+}$ complex

In order to clarify the efficient electron transfer in the **4**–$\mathbf{HV}^{2+}$ system, the detailed study on photophysics was carried out in a mixture of benzonitrile and tetrahydrofuran (1/1, v/v).[14] In this solvent system, the spectroscopic profiles of electronic absorption and fluorescence emission of **4** upon complexation with $\mathbf{HV}^{2+}$ were similar to those in $CHCl_3$–DMSO (10/1, v/v), although the binding constant of **4** to $\mathbf{HV}^{2+}$ significantly decreased to $3.98\times10^3\ M^{-1}$. The lifetime of the excited state of **4**, τ(**4**), was determined as 1.89 ns from the fluorescence emission decay at 650–700 nm, which was typical of the singlet excited state of zinc porphyrins.[15] Upon addition of $\mathbf{HV}^{2+}$(3.0 mM) to a solution of **4** (5.0 μM), the fast decay component τ_{CS} was observed (310 ps),[16] which was attributed to quenching by photoinduced electron transfer from the zinc porphyrin chromophore to $\mathbf{HV}^{2+}$. According to the Eqs. 1 and 2, the rate of charge separation k_{CS} and charge separation quantum yield Φ_{CS} were determined as $2.7\times10^9\ s^{-1}$ and 0.84, respectively:

$$k_{CS} = \tau_{CS}^{-1} - \tau(\mathbf{4})^{-1} \quad (1)$$

$$\Phi_{CS} = 1 - \tau_{CS}/\tau(\mathbf{4}) \quad (2)$$

The fast electron transfer from a porphyrin singlet state to a viologen in the stable complex has been reported by Willner et al.[6c] One can explain that the quite rapid charge separation process is caused by the intracomplex electron transfer in the **4**–$\mathbf{HV}^{2+}$ donor–acceptor ensemble.

Further information for the electron transfer process was obtained from the transient absorption spectra of **4**–$\mathbf{HV}^{2+}$ measured upon 558 nm laser irradiation. As shown in Figure 7a, the photoinduced electron transfer from **4** to $\mathbf{HV}^{2+}$ was confirmed by two characteristic bands of the viologen cation radical $\mathbf{HV}^{\bullet+}$ at 400 and 620 nm,[17] although the absorption of the porphyrin cation radical $\mathbf{4}^{\bullet+}$ at 640 nm[7c,18] was not clear because of the overlap with the absorption band of $\mathbf{HV}^{\bullet+}$. As seen in Figure 7b, the fast rise component of the viologen cation radical at 400 nm was indicative of the intracomplex electron transfer in the **4**–$\mathbf{HV}^{2+}$ complex.[6c] The slow rise component at 400 nm was also observed, which was attributed to the intermolecular electron transfer from the free **4** to the uncomplexed $\mathbf{HV}^{2+}$. The other characteristic band appeared at 470 nm, which was assigned to the zinc porphyrin triplet–triplet absorption.[6c,18c] The rate of the decay agreed well with the slow rise of the absorption of $\mathbf{HV}^{\bullet+}$, and thus, these results indicated that intermolecular electron transfer competitively occurred from the triplet state of **4**. However, as indicated by the fluorescence lifetime measurement, the efficient electron transfer should occur via the formation of the **4**–$\mathbf{HV}^{2+}$ complex. To clarify the intracomplex electron transfer process, the decay of the transient absorption of the triplet excited state of the porphyrinic receptor $^3\mathbf{4}^*$ was monitored in the presence of varying concentrations of $\mathbf{HV}^{2+}$(Fig. 8). The triplet–triplet absorption of **4** in the absence of $\mathbf{HV}^{2+}$ decayed obeying the first-order kinetics (190 μs^{-1}). The addition of $\mathbf{HV}^{2+}$ to a solution of **4** led to the decrease in the initial intensity of the triplet state absorption, along with the shortening of the triplet lifetime. This result clearly indicated that the rapid electron transfer disturbed the formation of $^3\mathbf{4}^*$ via the intersystem crossing. In other words, the complexation of **4** with $\mathbf{HV}^{2+}$ allowed the efficient electron transfer from the singlet state of **4** to $\mathbf{HV}^{2+}$. The charge recombination rate in the $\mathbf{4}^{\bullet+}$–$\mathbf{HV}^{\bullet+}$ supramolecular redox product could not be determined because the $\mathbf{HV}^{\bullet+}$ was formed via the two electron transfer pathways from both of the singlet and triplet excited states of **4**. However, it is noteworthy that the quick rise component at 400 nm (Fig. 7b) implies that the charge recombination rate is relatively slow. This is because the supramolecular redox product $\mathbf{4}^{\bullet+}$–$\mathbf{HV}^{\bullet+}$ dissociates to the individual redox species $\mathbf{4}^{\bullet+}$ and $\mathbf{HV}^{\bullet+}$ due to electrostatic repulsion.

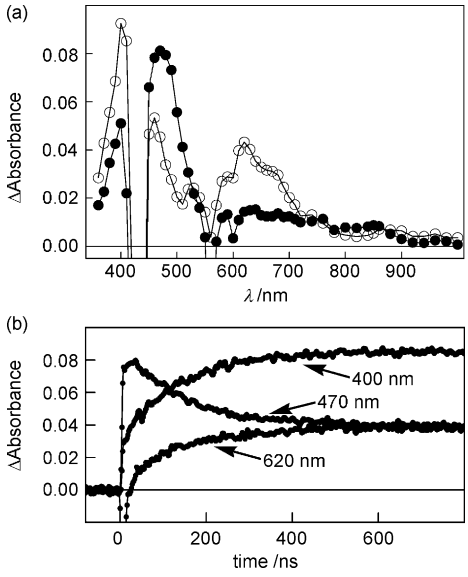


Figure 7. (a) Nanosecond transient absorption spectra of a mixture solution of **4** (5.0 μM) and $\mathbf{HV}^{2+}$ (3.0 mM) in Ar satd PhCN–THF (1/1, v/v) at 50 ns (●) and 500 ns (○) after the 558 nm-laser irradiation. (b) The absorption-time profiles monitored at 400, 470 and 620 nm.

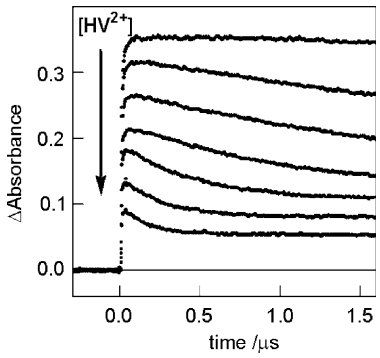


Figure 8. Decay dynamics of the triplet–triplet absorption due to $^3\mathbf{4}^*$ at 460 nm in Ar saturated PhCN–THF (1/1, v/v) upon addition of $\mathbf{HV}^{2+}$. [**4**]=5.0 μM, [$\mathbf{HV}^{2+}$]=0, 0.1, 0.2, 0.5, 1.0, 2.0, 3.0 mM.

3. Conclusions

The zinc porphyrinic receptors bearing diarylurea sidearms at the *meso* positions were newly synthesized, and their complexation behavior with $\mathbf{HV}^{2+}$ was investigated in detail. From the electronic absorption and ^{1}H NMR spectroscopic studies, the receptors bound $\mathbf{HV}^{2+}$ in an induced-fit manner, employing multiple dipole-cation interaction between the diarylurea sidearms and the viologen backbone. The energetic contribution of one dipole-cation interaction to the complexation was estimated as -6.28 kJ/mol. The interaction between the porphyrin platform and the viologen backbone (-11.1 kJ/mol) was also found to be essential to formation of the stable complex. The steady-state fluorescence titration study revealed that the increase in stability of the receptor–$\mathbf{HV}^{2+}$ complex brought about the increase in the efficiency of photoinduced electron transfer from the porphyrinic receptor to $\mathbf{HV}^{2+}$. From the investigation of the photophysics of the **4**–$\mathbf{HV}^{2+}$ system, the formation of the donor–acceptor complex significantly facilitated the electron transfer from the singlet excited state of **4** to $\mathbf{HV}^{2+}$ ($k_{CS}=2.7\times10^9\ s^{-1}$, $\Phi_{CS}=0.84$). In the supramolecular electron transfer system, relatively slow charge recombination was implied, which should be due to dissociation of the redox products caused by electrostatic repulsion. The results obtained in the present study should offer significant insights into construction of supramolecular photoinduced electron transfer systems.

4. Experimental

4.1. General methods

^{1}H NMR and ^{1}H–^{1}H COSY spectra were measured on a JEOL JNM-A500 (500 MHz) or a JEOL JNM-LA400 (400 MHz) spectrometer, using tetramethylsilane (0.00 ppm) and residual DMSO (2.49 ppm) as internal standards for $CDCl_3$ and DMSO-d_6, respectively. FAB mass spectra were recorded on a Finnigan MAT TSQ-70 mass spectrometer using 3-nitrobenzyl alcohol as a matrix. IR spectra were measured on a Shimadzu FTIR-8400S spectrometer using KBr pellets.

Electronic absorption spectra were measured on a Shimadzu Multispec-1500 spectrometer, and fluorescence emission spectra were recorded on a Shimadzu RF-5000 or a JASCO FP-6600 spectrophotometer. Solvents used for electronic absorption and fluorescence emission spectra were of spectroscopic grade. Just before acquisition of the spectra, the sample solutions were subjected to N_2 bubbling through a syringe needle for 10 min.

The time-resolved fluorescence spectra were measured by a single-photon counting method using a second harmonic generation (SHG, 410 nm) of a Ti:sapphire laser (Spectra-Physics, Tunami 3950-L2S, fwhm 1.5 ps) as an excitation source and using a streakscope (Hamamatsu Photonics, C4334-01) equipped with a polychromator as a detector.

Nanosecond transient absorption measurements were carried out using a SHG (532 nm) of the Nd:YAG laser (Spectra-Physics, Quanta-Ray GCR-130, fwhm 6 ns) as an excitation source. For measurements in the visible region and near-IR region (400–1000 nm), a monitoring light from a pulsed Xe lamp was detected with a Si–PIN photodiode (Hamamatsu Photonics, S1722-02). All the sample solutions in a quartz cell (1×1 cm) were deaerated by bubbling Ar gas through the solutions for 15 min.

4.2. Preparation of materials

All water-sensitive reactions were carried out under N_2 atmosphere, using dried solvent. Dichloromethane was dried over CaH_2 and distilled just prior to use. The preparation of 4-methyl-3-nitrobenzaldehyde **6** was previously reported in Ref. 8. 4-Methylbenzaldehyde, 4-bromobenzaldehyde and 1-octyne were commercially available. 4-Octylbenzaldehyde was prepared by the different method from those reported.[19] Size exclusion column chromatography was performed using BioRad Bio-Beads SX-1 with distilled THF as eluent.

4.3. Synthesis

4.3.1. Synthesis of 5,10-bis(3-amino-4-methylphenyl)-15,20-bis(4-methylphenyl)porphyrin (9a) and 5,15-bis(3-amino-4-methylphenyl)-10,20-bis(4-methylphenyl)porphyrin (9b). To a solution of chloranil (2.77 g, 11.3 mmol) in dry CH_2Cl_2 (500 mL) were added 4-methyl-3-nitrobenzaldehyde **6** (1.24 g, 7.51 mmol), 4-methylbenzaldehyde 7 (0.901 g, 7.50 mmol) and pyrrole **8** (1.01 g, 15.1 mmol) under N_2. After the mixture was stirred for a few minutes at ambient temperature under darkness, $BF_3\cdot OEt_2$ (0.95 mL, 7.56 mmol) was added, and then, the mixture was stirred for 1 h at the same temperature. The mixture was directly poured onto the top of an alumina column and allowed to pass through using CH_2Cl_2 as eluent. The resultant solution was concentrated to ca. 200 mL on a rotary evaporator, and then, washed with satd $NaHCO_3$ (100 mL$\times$3). The solution was dried over anhydrous Na_2SO_4, and the solvent was removed on a rotary evaporator. The residual dark purple solid was roughly purified by silica gel column chromatography (eluent; $CHCl_3$/hexane, 4:1, v/v) to obtain a fraction of a mixture of 5-(4-methyl-3-nitrophenyl)-10,15,20-tris(4-methylphenyl)porphyrin, 5,10-bis(4-methyl-3-nitrophenyl)-15,20-bis(4-methylphenyl)porphyrin, 5,15-bis(4-methyl-3-nitrophenyl)-10,20-bis(4-methylphenyl)-porphyrin. After removal of the solvent on a rotary evaporator, the residual dark purple solid was added to hot concd HCl (50 mL, 65 °C), followed by addition of $SnCl_2\cdot2H_2O$ (1.34 g, 5.94 mmol), and then, the reaction mixture was stirred at the same temperature for 2 h. After cooling, to the mixture was carefully added 27% aqueous NH_3 (70 mL) on an ice bath, and then, $CHCl_3$ (100 mL) was added. The mixture was stirred vigorously at ambient temperature for 2 h. The mixture was allowed to pass through a paper filter with Celite® mounted. The filtrate was washed with satd $NaHCO_3$ (100 mL), satd brine (100 mL), and water (100 mL). After dried over anhydrous Na_2SO_4, the solvent was removed by evaporation. Purification of the resultant mixture by silica gel column chromatography (eluent; $CHCl_3$/ethyl acetate, 5:1, v/v) yielded **9a** (142 mg, 0.203 mmol, 5%) and **9b** (83.7 mg, 0.119 mmol, 3%), both of which were dark purple solids. Porphyrins **9a** and

9b were discriminated from the ^{1}H NMR spectral patterns of the pyrrole β-Hs: two singlets and two coupled doublets were observed for the β-H signals of **9a**, while just two coupled doublets were observed for those of **9b**.[20]

4.3.2. 5,10-Bis(3-amino-4-methylphenyl)-15,20-bis(4-methylphenyl)porphyrin (9a). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) −2.79 (br, 2H, inner-N*H*), 2.51 (s, 6H, 5,10-Ar-CH_3), 2.70 (s, 6H, 15,20-Ar-CH_3), 3.87 (br, 4H, –NH_2), 7.39 (d, J=7.3 Hz, 2H, 5,10-Ar-*H*), 7.54–7.56 (m, 8H, 4H of 5,10-Ar-*H* and 4H of 15,20-Ar-*H*), 8.09 (d, J=7.6 Hz, 4H, 15,20-Ar-*H*), 8.83 (d, J=4.9 Hz, 2H, pyrrole β-*H*), 8.84 (s, 2H, pyrrole β-*H*), 8.92 (s, 2H, pyrrole β-*H*), 8.94 (d, J=4.9 Hz, 2H, pyrrole β-*H*); TLC (silica gel, eluent; $CHCl_3$/ethyl acetate, 5:1, v/v) R_f=0.41; IR (KBr) 1620, 3318, 3367, 3460 cm^{-1}; FAB MS *m/z* 700 (M^+). Anal. Calcd for $C_{48}H_{40}N_6$: C, 82.26; H, 5.75; N, 11.99. Found: C, 82.04; H, 5.92; N, 11.68.

4.3.3. 5,15-Bis(3-amino-4-methylphenyl)-10,20-bis(4-methylphenyl)porphyrin (9b). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) −2.80 (br, 2H, inner-N*H*), 2.50 (s, 6H, 5,15-Ar-CH_3), 2.70 (s, 6H, 10,20-Ar-CH_3), 3.85 (br, 4H, –NH_2), 7.39 (d, J=7.8 Hz, 2H, 5,15-Ar-*H*), 7.53–7.56 (m, 8H, 4H of 5,15-Ar-*H* and 4H of 10,20-Ar-*H*), 8.09 (d, J=7.8 Hz, 4H, 10,20-Ar-*H*), 8.83 (d, J=4.6 Hz, 4H, pyrrole β-*H*), 8.93 (d, J=4.6 Hz, 4H, pyrrole β-*H*); TLC (silica gel, eluent; $CHCl_3$/ethyl acetate, 5:1, v/v) R_f=0.67; IR (KBr) 1620, 3311, 3367, 3451 cm^{-1}; FAB MS *m/z* 700 (M^+). Anal. Calcd for $C_{48}H_{40}N_6\cdot H_2O$: C, 81.21; H, 5.82; N, 11.84. Found: C, 81.13; H, 5.67 N, 11.78.

4.3.4. {15,20-Bis(4-methylphenyl)-5,10-bis[4-methyl-3-(3-phenylureylen-1-yl)phenyl]porphyrinato}zinc(II) (2a). To a solution of **9a** (50.0 mg, 0.0713 mmol) in dry CH_2Cl_2 (30 mL) was added phenylisocyanate (41.0 , 0.344 mmol) under N_2, and the mixture was stirred for 3 h before another portion of phenylisocyanate (41.0 mg, 0.344 mmol) was added. After the reaction mixture was stirred at ambient temperature for 12 h, the solvent was removed on a rotary evaporator. The residue was dissolved in THF and filtered to remove insoluble materials. After removal of the solvent on a rotary evaporator, the residual dark purple solid was dissolved in $CHCl_3$ (20 mL), followed by addition of a saturated ethanolic solution of $Zn(OAc)_2$ (50 mL). The mixture was stirred at 50 °C for 1 h, and the solvent was removed by evaporation. The residue was dissolved in THF (20 mL) and filtered to remove insoluble materials. Purification of the resultant mixture by size-exclusion column chromatography (THF as eluent) and recrystallization from THF–hexane yielded **2a** as a purple solid (42.1 mg, 0.0420 mmol, 59%): ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.59 (s, 6H, 5,10-Ar-CH_3), 2.66 (s, 6H, 15,20-Ar-CH_3), 6.85–6.90 (m, 2H, Ph-*H*), 7.14–7.20 (m, 4H, Ph-*H*), 7.37–7.40 (m, 4H, Ph-*H*), 7.56–7.60 (m, 6H, 2H of 5,10-Ar-*H* and 4H of 15,20-Ar-*H*), 7.73–7.77 (m, 2H, 5,10-Ar-*H*), 8.04–8.07 (m, 4H, 15,20-Ar-*H*), 8.27 (br, 2H, –N*H*), 8.76–8.79 (m, 6H, 4H of pyrrole β-*H* and 2H of 5,10-Ar-*H*), 8.86–8.88 (m, 4H, pyrrole β-*H*), 9.17–9.20 (br, 2H, –N*H*); IR (KBr) 1663, 3366 cm^{-1}; FAB MS *m/z* 1000 ($[M]^+$), 1001 ($[M+1]^+$), 1002 ($[M+2]^+$), 1003 ($[M+3]^+$). Anal. Calcd for $C_{62}H_{48}N_8O_2Zn\cdot H_2O$: C, 72.97; H, 4.94; N, 10.98. Found: C, 72.62; H, 4.64; N, 11.05.

4.3.5. {5,15-Bis(4-methylphenyl)-10,20-bis[4-methyl-3-(3-phenylureylen-1-yl)phenyl]porphyrinato}zinc(II) (2b). To a solution of **9b** (50.0 mg, 0.0713 mmol) in dry CH_2Cl_2 (30 mL) was added phenylisocyanate (41.6 mg, 0.349 mmol) under N_2, and the mixture was stirred for 3 h before another portion of phenylisocyanate (41.6 mg, 0.349 mmol) was added. After the reaction mixture was stirred at ambient temperature for 15 h, the solvent was removed on a rotary evaporator, and the residue was dissolved in THF and filtrated to remove insoluble materials. After removal of the solvent on a rotary evaporator, the residual dark purple solid was added to $CHCl_3$ (30 mL) followed by addition of a saturated ethanolic solution of $Zn(OAc)_2$ (50 mL). The mixture was stirred at 50 °C for 1 h, and the solvent was removed by evaporation. Purification of the resultant mixture by silica gel chromatography (eluent; $CHCl_3$/methanol, 50:1, v/v) followed by size-exclusion column chromatography (THF as eluent) and recrystallization from THF–hexane yielded **2b** as a purple solid (40.5 mg, 0.0404 mmol, 57%): ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.59 (s, 6H, 5,15-Ar-CH_3), 2.65 (s, 6H, 10,20-Ar-CH_3), 6.88 (t, J=7.6 Hz, 2H, Ph-*H*), 7.18 (t, J=7.6 Hz, 4H, Ph-*H*), 7.39 (d, J=7.6 Hz, 4H, Ph-*H*), 7.56–7.60 (m, 6H, 2H of 5,15-Ar-*H* and 4H of 10,20-Ar-*H*), 7.74 (dd, J=1.5, 7.6 Hz, 2H, 5,15-Ar-*H*), 8.06 (d, J=7.6 Hz, 4H, 10,20-Ar-*H*), 8.29 (br, 2H, –N*H*), 8.76–8.79 (m, 6H, 4H of pyrrole β-*H* and 2H of 5,15-Ar-*H*), 8.86–8.88 (d, J=4.6 Hz, 4H, pyrrole β-*H*), 9.20 (br, 2H, –N*H*); IR (KBr) 1653, 3362 cm^{-1}; FAB MS *m/z* 1000 (M^+), 1001 ($[M+1]^+$), 1002 ($[M+2]^+$), 1003 ($[M+3]^+$). Anal. Calcd for $C_{62}H_{48}N_8O_2Zn\cdot H_2O$: C, 72.97; H, 4.94; N, 10.98. Found: C, 72.90; H, 4.65; N, 10.92.

4.3.6. Synthesis of 5,10,15-tris(3-amino-4-methylphenyl)-20-(4-methylphenyl)porphyrin (10) and 5,10,15,20-tetrakis(3-amino-4-methylphenyl)porphyrin (11). To a solution of chloranil (2.77 g, 11.3 mmol) in dry CH_2Cl_2 (500 mL) were added 4-methyl-3-nitrobenzaldehyde **6** (1.24 g, 7.51 mmol), 4-methylbenzaldehyde **7** (0.901 g, 7.50 mmol), and pyrrole **8** (1.01 g, 15.1 mmol) under N_2. After the mixture was stirred for a few minutes at ambient temperature under darkness, $BF_3\cdot OEt_2$ (0.95 mL, 7.56 mmol) was added, and then, the mixture was stirred for 1 h at the same temperature. The mixture was directly poured onto the top of an alumina column, and allowed to pass through using CH_2Cl_2 as eluent. The resultant solution was concentrated to ca. 200 mL on a rotary evaporator, and then, washed with satd $NaHCO_3$ (100 mL×3). The organic phase was dried over anhydrous Na_2SO_4, and the solvent was removed on a rotary evaporator. The residual dark purple solid was roughly purified by silica gel column chromatography (eluent; $CHCl_3$/hexane, 4:1, v/v) to obtain a fraction of a mixture of 10,15,20-tris(4-methyl-3-nitrophenyl)-5-(4-methylphenyl)porphyrin and 5,10,15,20-tetrakis(4-methyl-3-nitrophenyl)porphyrin. After removal of the solvent on a rotary evaporator, the residual dark purple solid was added to hot concd HCl (50 mL, 65 °C), followed by addition of $SnCl_2\cdot 2H_2O$ (1.34 g, 5.94 mmol), and then, the reaction mixture was stirred at the same temperature for 2 h. After cooling, to the mixture was carefully added 27% aqueous NH_3 (70 mL) on an ice bath, and then, $CHCl_3$ (100 mL) was added. The mixture was stirred vigorously at ambient temperature for 2 h. The

mixture was allowed to pass through a paper filter with Celite® mounted. The filtrate was washed with satd $NaHCO_3$ (100 mL), satd brine (100 mL) and water (100 mL). After dried over anhydrous Na_2SO_4, the solvent was removed by evaporation. Purification of a resultant mixture by silica gel column chromatography (eluent; $CHCl_3$/ethyl acetate, 4:1, v/v) yielded **10** (162 mg, 0.226 mmol, 6%) and **11** (112 mg, 0.150 mmol, 4%) as dark purple solids, respectively.

4.3.7. 5,10,15-Tris(3-amino-4-methylphenyl)-20-(4-methylphenyl)porphyrin (10). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) −2.81 (br, 2H, inner-N*H*), 2.46 (s, 9H, 5,10,15-Ar-CH_3), 2.69 (s, 3H, 20-Ar-CH_3), 3.78 (br, 6H, –NH_2), 7.36 (d, J=7.3 Hz, 3H, 5,10,15-Ar-*H*), 7.49–7.56 (m, 8H, 6H of 5,10,15-Ar-*H* and 2H of 20-Ar-*H*), 8.08 (d, J=7.5 Hz, 2H, 20-Ar-*H*), 8.82 (d, J=4.6 Hz, 2H, pyrrole β-*H*), 8.90–8.93 (m, 6H, pyrrole β-*H*); TLC (silica gel, eluent; $CHCl_3$/ethyl acetate, 5:1, v/v), R_f=0.15; IR (KBr) 1616, 3312, 3367, 3451 cm^{-1}; FAB MS *m/z* 715 (M^+). Anal. Calcd for $C_{48}H_{41}N_7 \cdot H_2O$: C, 78.55; H, 5.91; N, 13.36. Found: C, 78.79; H, 5.58; N, 13.36.

4.3.8. 5,10,15,20-Tetrakis(3-amino-4-methylphenyl)porphyrin (11). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) −2.82 (br, 2H, inner-N*H*), 2.51 (s, 12H, Ar-CH_3), 3.86 (br, 8H, –NH_2), 7.39 (d, J=7.6 Hz, 4H, Ar-*H*), 7.53–7.57 (m, 8H, Ar-*H*), 8.91 (s, 8H, pyrrole β-*H*); TLC (silica gel, eluent; $CHCl_3$/ethyl acetate, 5:1, v/v), R_f=0.05; IR (KBr) 1620, 3312, 3358, 3451 cm^{-1}; FAB MS *m/z* 730 (M^+). Anal. Calcd for $C_{48}H_{42}N_8 \cdot H_2O$: C, 76.98; H, 5.92; N, 14.96. Found: C, 77.20; H, 5.58 N, 14.84.

4.3.9. {20-(4-Methylphenyl)-5,10,15-tris[4-methyl-3-(3-phenylureylen-1-yl)phenyl]porphyrinato}zinc(II) (3). To a solution of **10** (50.0 mg, 0.0698 mmol) in dry CH_2Cl_2 (30 mL) was added phenylisocyanate (28.0 mg, 0.235 mmol) under N_2. After the reaction mixture was stirred at ambient temperature for 15 h, the solvent was removed on a rotary evaporator. $CHCl_3$ (50 mL) was poured to the residual dark purple solid, followed by addition of a saturated ethanolic solution of $Zn(OAc)_2$ (50 mL). The mixture was stirred at 50 °C for 1 h, and then, the solvent was removed by evaporation. The residue was dissolved in THF (20 mL) and filtered to remove insoluble materials. The resultant mixture was purified by size exclusion chromatography (THF as eluent). Further purification of the obtained solid by reprecipitation from THF into hexane yielded **3** as a purple solid (37.9 mg, 0.033 mmol, 48%): ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.59 (s, 9H, 5,10,15-Ar-CH_3), 2.66 (s, 3H, 20-Ar-CH_3), 6.85–6.90 (m, 3H, Ph-*H*), 7.14–7.21 (m, 6H, Ph-*H*), 7.37–7.41 (m, 6H, Ph-*H*), 7.56–7.60 (m, 5H, 3H of 5,10,15-Ar-*H* and 2H of 20-Ar-*H*), 7.73–7.77 (m, 3H, 5,10,15-Ar-*H*), 8.06–8.08 (m, 2H, 20-Ar-*H*), 8.27 (m, 3H, –N*H*), 8.76–8.78 (m, 5H, 2H of pyrrole β-*H* and 3H of 5,10,15-Ar-*H*), 8.87–8.88 (m, 6H, pyrrole β-*H*), 9.16–9.20 (br, 3H, –N*H*); IR (KBr) 1663, 3369 cm^{-1}; FAB MS *m/z* 1134 (M^+), 1135 ([M+1]$^+$), 1136 ([M+2]$^+$), 1137 ([M+3]$^+$). Anal. Calcd for $C_{69}H_{54}N_{10}O_3Zn \cdot H_2O$: C; 71.78, H; 4.89, N; 12.13. Found: C, 71.73; H, 4.68; N, 12.04.

4.3.10. {5,10,15,20-Tetrakis[4-methyl-3-(3-phenylureylen-1-yl)phenyl]porphyrinato}zinc(II) (4). To a solution of **11** (50.0 mg, 0.0684 mmol) in dry CH_2Cl_2 (50 mL) was added phenylisocyanate (35.0 mg, 0.294 mmol) under N_2. After the reaction mixture was stirred at ambient temperature for 4 h, the solvent was removed on a rotary evaporator. $CHCl_3$ (50 mL) was poured to the residue, followed by addition of a saturated ethanolic solution of $Zn(OAc)_2$ (50 mL). The mixture was stirred at 50 °C for 1 h, and then, the solvent was removed by evaporation. The residue was dissolved in THF (20 mL) and filtered to remove insoluble materials. The resultant mixture was purified by size exclusion chromatography (THF as a eluent). The reside was thoroughly purified by reprecipitation from THF into hexane to afford **4** as a purple solid (45.0 mg, 0.0354 mmol, 52%): ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 2.59 (s, 12H, 5,10,15,20-Ar-CH_3), 6.85–6.90 (m, 4H, Ph-*H*), 7.14–7.21 (m, 8H, Ph-*H*), 7.35–7.41 (m, 8H, Ph-*H*), 7.57 (m, 4H, 5,10,15,20-Ar-*H*), 7.75–7.77 (m, 4H, 5,10,15,20-Ar-*H*), 8.28 (br, 4H, –N*H*), 8.78–8.80 (m, 4H, 5,10,15,20-Ar-*H*), 8.88 (s, 8H, pyrrole β-*H*,), 9.16–9.20 (m, 4H, –N*H*); IR (KBr) 1662, 3363 cm^{-1}; FAB MS *m/z* 1268 (M^+), 1269 ([M+1]$^+$), 1270 ([M+2]$^+$), 1271 ([M+3]$^+$). Anal. Calcd for $C_{76}H_{60}N_{12}O_4Zn \cdot 2H_2O$: C, 69.85; H, 4.94; N, 12.86. Found: C, 69.96; H, 4.61; N, 12.62.

4.3.11. 4-(1-Octyn-1-yl)benzaldehyde (12). To a mixture of 4-bromobenzaldehyde (27.8 g, 150 mmol), bis(triphenylphosphine)palladium(II) dichloride (1.12 g, 1.60 mmol) and 1-octyne (18.8 g, 171 mmol) in Et_3N (200 mL) were added cupper(I) iodide (0.609 g, 3.20 mol). The mixture was stirred at 50 °C for 12 h under N_2. Insoluble materials were removed by filtration, and the filtrate was washed with satd brine (100 mL×3) and water (100 mL). Purification by flash chromatography (silica gel, hexane as eluent) afforded **12** (31.5 g, 147 mmol, 98%), which was used in the next reaction without further purification due to instability under air. The spectroscopic data was identical to the reported data:[21] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.90 (t, J=7.1 Hz, 3H, –CH_3), 1.28–1.64 (m, 8H, –CH_2–), 2.44 (t, J=7.1 Hz, 2H, –C≡C–CH_2–), 7.53 (d, J=8.3 Hz, 2H, Ar-*H*), 7.80 (d, J=8.3 Hz, 2H, Ar-*H*), 9.99 (s, 1H, –C*H*O); IR (KBr) 1704, 2225, 2855, 2929, 2955 cm^{-1}; FAB MS *m/z* 214 (M^+).

4.3.12. 4-Octylbenzaldehyde (13). H_2 gas was introduced into a vigorously stirred solution of **12** (31.5 g, 147 mmol) in ethyl acetate (200 mL) for 5 min via a syringe needle. To the solution was added a suspension of palladium/activated carbon (Pd 10%) (1.50 g) in ethyl acetate (30 mL). The mixture was stirred for 6 h under H_2, and then, allowed to pass through a filter with Celite® mounted. The Celite® was thoroughly washed with hexane (200 mL). The filtrate was combined with the washing, and the solvent was removed on a rotary evaporator to yield a dark yellow oil. Purification of the resultant oil by silica gel column chromatography (eluent; hexane/ethyl acetate, 20:1, v/v) yielded 4-octylbenzaldehyde **13** (26.8 g, 122 mmol, 83%), which was used in the next reaction without further purification due to instability under air: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.88 (t, J=7.1 Hz, 3H, –CH_3), 1.26–1.32 (m, 10H, –CH_2–), 1.61–1.67 (m, 2H, –CH_2–), 2.69 (t, J=7.1 Hz, 2H, Ar-CH_2–), 7.34 (d, J=7.8 Hz, 2H, Ar-*H*), 7.80 (d, J=7.8 Hz, 2H, Ar-*H*), 9.97 (s, 1H, –C*H*O); IR (KBr) 1704, 2856, 2924, 2955 cm^{-1}; FAB MS *m/z* 218 (M^+).

4.3.13. 3-Nitro-4-octylbenzaldehyde (14). To a mixture of fuming HNO_3 (1.7 mL) and concd sulfuric acid (12.4 mL) was added **13** (4.36 g, 20.0 mmol) dropwise on an ice bath with vigorous stirring under N_2. After completion of the addition of the aldehyde, the ice bath was removed, and the reaction mixture was stirred for 15 min. The mixture was poured onto ice, and then, the product was extracted into Et_2O. The organic phase was washed with satd $NaHCO_3$ (100 mL×3) and water (100 mL). After dried over anhydrous Na_2SO_4, the solvent was removed by evaporation. Purification of the residual mixture by silica gel column chromatography (eluent; hexane/$CHCl_3$, 10:1, v/v) yielded **14** (3.35 g, 12.7 mol, 64%), which was used in the next reaction without further purification due to instability under air: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.88 (t, J=7.1 Hz, 3H, –C*H*$_3$), 1.21–1.51 (m, 10H, –C*H*$_2$–), 1.57–1.63 (m, 2H, –C*H*$_2$–), 2.95 (t, J=7.1 Hz, 2H, Ar-C*H*$_2$–), 7.54 (d, J=7.8 Hz, 2H, Ar-*H*), 8.02 (d, J=7.8 Hz, 2H, Ar-*H*), 10.03 (s, 1H, –C*H*O); IR (KBr) 1348, 1529, 1701, 2853, 2922, 2955 cm^{-1}; FAB MS *m*/*z* 263 (M^+), 264 ($[M+1]^+$).

4.3.14. 5,10,15,20-Tetrakis(3-nitro-4-octylphenyl)porphyrin (15). In dry CH_2Cl_2 (500 mL) were dissolved **14** (2.23 g, 8.47 mmol) and pyrrole **8** (568 mg, 8.47 mmol), and the mixture was stirred for 15 min under N_2. $BF_3\cdot OEt_2$ (0.170 mL, 1.35 mmol) was added under darkness, and the mixture was stirred for 1 h. *p*-Chloranil (1.56 g, 6.34 mmol) was added at one portion, and the mixture was stirred for 1 h at the same temperature. Then, the resultant mixture was put on the top of an alumina column and allowed to pass through using CH_2Cl_2 as eluent. The solvent was removed on a rotary evaporator to yield a dark brown solid, which was purified by silica gel column chromatography (eluent; CH_2Cl_2/hexane, 3:2, v/v) to yield **15** as a dark purple solid (750 mg, 0.603 mmol, 28%): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) −2.87 (br, 2H, inner-N*H*), 0.94 (t, J=7.1 Hz, 12H, –C*H*$_3$), 1.36–1.65 (m, 40H, –C*H*$_2$–), 1.93–2.01 (m, J=7.8 Hz, 8H, Ar-CH$_2$C*H*$_2$–), 3.24 (t, J=7.1 Hz, 8H, Ar-C*H*$_2$–), 7.78 (d, J=6.4 Hz, 4H, Ar-*H*), 8.36 (d, J=6.4 Hz, 4H, Ar-*H*), 8.72 (s, 4H, Ar-*H*), 8.87 (s, 8H, pyrrole β-*H*); IR (KBr) 1344, 1529, 2853, 2926, 2953 cm^{-1}; FAB MS *m*/*z* 1243 (M^+), 1244 ($[M+1]^+$). Anal. Calcd for $C_{76}H_{90}N_8O_8$: C, 73.40, H, 7.29, N, 9.01. Found: C, 73.49; H, 7.53; N, 8.99.

4.3.15. 5,10,15,20-Tetrakis(3-amino-4-octyl-phenyl)porphyrin (16). To a stirred hot concd HCl (90 mL, 65 °C) was added **15** (500 mg, 0.402 mmol) and $CHCl_3$ (20 mL), followed by addition of $SnCl_2\cdot 2H_2O$ (1.90 g, 8.41 mmol). The reaction mixture was stirred at the same temperature for 2 h before another portion of $SnCl_2\cdot 2H_2O$ (2.01 g, 8.91 mmol) and $CHCl_3$ (20 mL) was added. The same process was repeated again ($CHCl_3$, 20 mL; $SnCl_2\cdot 2H_2O$, 1.83 g, 8.11 mmol), and then, the reaction mixture was stirred at the same temperature for 1 h. After cooling, to the mixture was carefully added 27% aqueous NH_3 (100 mL) on an ice bath, and then, $CHCl_3$ (100 mL) was added. The mixture was stirred vigorously at ambient temperature for 2 h and allowed to pass through a paper filter with Celite® mounted. The filtrate was washed with water (100 mL) three times. After dried over anhydrous $MgSO_4$, the solvent was removed by evaporation. Purification of the resultant solid by silica gel column chromatography (eluent; hexane/ethyl acetate, 20:1, v/v) yielded **16** as a purple solid (391 mg, 0.348 mmol, 87%): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) −2.81 (br, 2H, inner-N*H*), 0.94 (t, J=7.3 Hz, 12H, –C*H*$_3$), 1.34–1.65 (m, 40H, –C*H*$_2$–), 1.88–1.96 (m, 8H, Ar-CH$_2$C*H*$_2$–), 2.81 (t, J=7.3 Hz, 8H, Ar-C*H*$_2$–), 3.87 (br, 8H, –N*H*$_2$), 7.38 (d, J=7.3 Hz, 4H, Ar-*H*), 7.54 (s, 4H, Ar-*H*), 7.58 (d, J=7.3 Hz, 4H, Ar-*H*), 8.92 (s, 8H, pyrrole β-*H*); IR (KBr) 1618, 2854, 2924, 2953, 3321, 3362, 3441 cm^{-1}; FAB MS *m*/*z* 1123 (M^+), 1124 ($[M+1]^+$). Anal. Calcd for $C_{76}H_{98}N_8$: C, 81.24; H, 8.79; N, 9.97. Found: C, 81.11; H, 8.94; N, 10.01.

4.3.16. {5,10,15,20-Tetrakis[4-octyl-3-(3-phenylureylen-1-yl)phenyl]porphyrin (the precursor of 5). To a solution of **16** (200 mg, 0.178 mmol) in dry CH_2Cl_2 (20 mL) was added phenylisocyanate (170 mg, 1.43 mmol) under N_2. After the reaction mixture was stirred at ambient temperature for 15 h, the solvent was removed on a rotary evaporator. The residue was dissolved in THF (40 mL) and filtered to remove insoluble materials. The resultant mixture was purified by size exclusion column chromatography (THF as eluent). Reprecipitation of the obtained material from THF into hexane yielded {5,10,15,20-tetrakis[4-octyl-3-(3-phenylureylen-1-yl)phenyl]porphyrin as a purple solid (182 mg, 0.114 mmol, 64%), which was used in the next step without further purification: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) −2.90 (br, 2H, inner-N*H*), 0.86–0.90 (t, J=7.0 Hz, 12H, –C*H*$_3$), 1.30–1.58 (m, 40H, –C*H*$_2$–), 1.82–1.87 (m, 8H, Ar-CH$_2$–C*H*$_2$–), 2.90–2.95 (t, J=7.0 Hz, 8H, Ar-C*H*$_2$–), 6.85–6.89 (m, 4H, Ph-*H*), 7.12–7.21 (m, 8H, Ph-*H*), 7.39–7.42 (m, 8H, Ph-*H*), 7.55–7.58 (m, 4H, 5,10,15,20-Ar-*H*), 7.80–7.82 (m, 4H, 5,10,15,20-Ar-*H*), 8.24 (br, 4H, –N*H*), 8.70–8.71 (m, 4H, 5,10,15,20-Ar-*H*), 8.90 (s, 8H, pyrrole β-*H*), 9.14–9.16 (m, 4H, –N*H*); IR (KBr) 1653, 2856, 2926, 2953, 3320 cm^{-1}; FAB MS *m*/*z* 1599 (M^+), 1600 ($[M+1]^+$), 1601 ($[M+2]^+$).

4.3.17. {5,10,15,20-Tetrakis[4-(1-octyl)-3-(3-phenylureylen-1-yl)phenyl]porphyrinato}zinc(II) (5). {5,10,15,20-Tetrakis[4-(1-octyl)-3-(3-phenylureylen-1-yl)phenyl]porphyrin (100 mg, 0.0625 mmol) was dissolved in DMSO (10 mL), followed by addition of a saturated ethanolic solution of $Zn(OAc)_2$ (100 mL). The mixture was stirred at reflux for 1 h, and then, the ethanol was removed by evaporation. To the resultant mixture was added water (100 mL) followed by filtration to yield a purple solid. The solid was dried in vacuo, and then, dissolved in THF (50 mL) to remove insoluble materials by filtration. The filtrate was evaporated, and the residue was purified by size exclusion column chromatography (THF as eluent, two times). Further purification of the obtained solid by reprecipitation from THF into hexane yielded **5** as a purple solid (98.0 mg, 0.0589 mmol, 94%): ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 0.86 (m, 12H, –C*H*$_3$), 1.30–1.59 (m, 40H, –C*H*$_2$–), 1.85–1.89 (m, 8H, Ar-CH$_2$–C*H*$_2$–), 2.91–2.95 (m, 8H, Ar-C*H*$_2$–), 6.86–6.89 (m, 4H, Ph-*H*), 7.14–7.21 (m, 8H, Ph-*H*), 7.39–7.42 (m, 8H, Ph-*H*), 7.55–7.58 (m, 4H, 5,10,15,20-Ar-*H*), 7.79–7.82 (m, 4H, 5,10,15,20-Ar-*H*), 8.24 (br, 4H, –N*H*), 8.69–8.71 (m, 4H, 5,10,15,20-Ar-*H*), 8.90 (s, 8H, pyrrole β-*H*), 9.14–9.16 (m, 4H, –N*H*); IR (KBr) 1660, 2854, 2926, 2953, 3302 cm^{-1}; FAB MS *m*/*z* 1661 (M^+), 1662 ($[M+1]^+$), 1663 ($[M+2]^+$). Anal. Calcd for $C_{104}H_{116}N_{12}O_4Zn\cdot H_2O$: C, 74.28; H, 7.07; N, 10.00. Found: C, 74.08; H, 7.30; N, 9.90.

Acknowledgements

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Ytterbium-catalyzed dual intermolecular hydrophosphination: synthesis of bis(phosphinyl)dienes and bis(alkenyl)phosphine oxides

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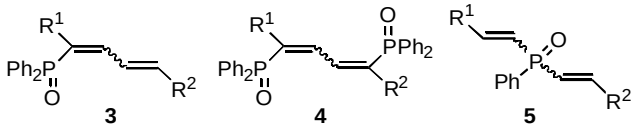
Abstract—Dual intermolecular hydrophosphination of conjugated diynes with 2 equiv of diphenylphosphine was catalyzed by ytterbium complexes, Yb(η^2-Ph_2CNPh)$(hmpa)_3$ (**1**) and Yb$[N(SiMe_3)_2]_3(hmpa)_2$ (**2**), to give the corresponding 1,4-bis(diphenylphosphinyl)buta-1,3-dienes in high yields after oxidative work-up. Distribution of the four possible stereoisomers sharply depended on substituents of the substrates. (*Z*,*Z*)-Isomers were predominantly obtained from the disubstituted diynes, together with minor (*Z*,*E*)-isomers. On the other hand, the reaction of the terminal diynes provided major (*E*,*Z*) and minor (*E*,*E*)-butadienes. 1,4-Di-*tert*-butylbuta-1,3-diyne was exclusively converted to an allenic compound. Moreover, the dual hydrophosphination using phenyphosphine was also performed with **1** and **2**. Thus, the reaction of 2 equiv of aromatic alkynes with $PhPH_2$ and subsequent oxidation gave bis(alkenyl)phosphine oxides in preference of the (*Z*,*Z*)-stereoisomers.

1. Introduction

α,β-Unsaturated phosphorus compounds are useful building blocks in organic synthesis.[1] Of their synthetic methods, addition reaction of $(RO)_2P(O)H$ and $R_2P(O)H$ to alkynes through oxidative addition of groups 9 and 10 catalysts to P–H bond has been recognized as the most promising and atom-economical process.[2] When this methodology was applied to the reaction of R_2PH, instead of pentavalent phosphorus, harsh conditions were necessary to promote the reaction, because of strong affinity of the late transition metals with the trivalent phosphines.[3] On the other hand, interaction between hard lanthanide metals and the soft phosphines could be so weak, and thus efficient intramolecular hydrophosphination of alkynyl and alkenylphosphines has been explored with lanthanocenes.[4]

Previously, we reported that a divalent ytterbium–imine complex, Yb(η^2-Ph_2CNPh)$(hmpa)_3$ (**1**), and a trivalent silylamide complex, Yb$[N(SiMe_3)_2]_3(hmpa)_2$ (**2**), served as highly effective precatalysts for intermolecular hydrophosphination of alkynes with diphenylphosphine and that the active species generated in situ were ytterbium phosphides, $Yb(PPh_2)_2$ and $Yb(PPh_2)_3$, which exhibited similar regio- and stereoselectivity irrespective of their valence state.[5] Based on this work, we intended to develop a simple method for the synthesis of potentially useful phosphorus compounds **3**–**5**. Diphenylphosphinyldienes **3** have been already prepared by the $Y[N(SiMe_3)_2]_3$-catalyzed dimerization of terminal alkynes, followed by hydrophosphination of the resulting enynes with Ph_2PH in one-pot.[6] Compound **4** would be synthesized with dual hydrophosphination of conjugated diynes with 2 equiv of Ph_2PH. However, two preliminary examples revealed that **4** was formed from primary alkyldiyne, but in contrast, tertiary alkyldiyne gave an allenic product.[5] Bis(alkeny)phosphines and their oxide **5** would be also prepared using $PhPH_2$, though it has been never used in the present system. To confirm these possibilities, we investigated the dual intermolecular hydrophosphination leading to **4** and **5**.



Keywords: Rare-earth catalysts; Dual hydrophosphination; Diynes.
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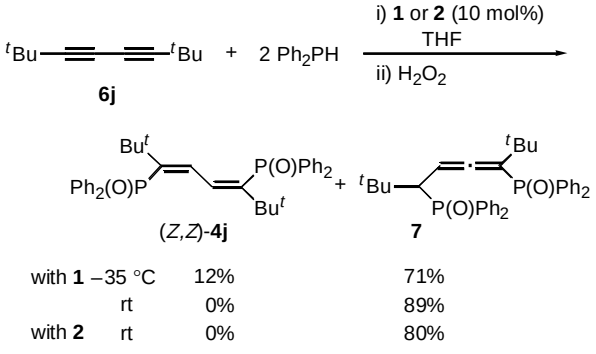
2. Results and discussion

When hexadeca-7,9-diyne (**6a**) was treated with 2 equiv of Ph_2PH in the presence of **1** (10 mol%) in THF at room temperature for 1 h, 7,10-bis(diphenylphosphinyl)hexadeca-7,9-diene (**4a**) was obtained in 80% total yield as a mixture of two stereoisomers (61:39) after oxidation with H_2O_2 (Table 1, run 1).[7] The major product showed one olefinic signal at 7.74 ppm with 34.8 Hz of *trans*-$^3J_{P-H}$ in ^1H NMR and one signal at 29.53 ppm in ^{31}P NMR. On the other hand, two olefinic signals at 6.83 (*cis*-$^3J_{P-H}=20.6$ Hz) and 7.13 ppm (*trans*-$^3J_{P-H}=35.0$ Hz) in ^1H NMR and two signals at 28.18 and 33.58 ppm in ^{31}P NMR were observed for the minor. Therefore, the major product was definitely assigned to the (*Z*,*Z*)-isomer, and the minor to the (*Z*,*E*)-isomer. The stereoselectivity was increased a little with decreasing temperature (run 2). The reaction was also conducted with the silylamide **2** effectively (run 3). Two cyclohexyl substituents in **6c** did not change the reaction mode, though its reactivity was somewhat decreased (run 5). Arylalkyldiynes **6d** and **6e** gave the (*Z*,*Z*) and (*Z*,*E*)-dienes **4d** and **4e**; in the latter substrate, a small amount of the (*E*,*Z*)-isomer was contaminated in the mixture (runs 6–9). 1,4-Diphenylbuta-1,3-diene (**6f**) was so reactive that no phosphinylated product **4f** was obtained with **1**, other than polymers even at −78 °C (run 10). In the absence of Ph_2PH, **6f** was recovered unchanged by the treatment with **1** at room temperature. Use of milder precatalyst **2** afforded (*E*,*E*)-**4f** in low yield (run 11). The reaction of terminal diynes **6g** and **6h** gave the expected products **4g** and **4h**, but their stereochemistry was drastically altered, (*E*,*Z*) and (*E*,*E*)-isomers being major and minor, respectively (runs 12–15). Aromatic terminal diyne **6i** was exclusively polymerized with both **1** and **2**, because of its higher reactivity (run 16).

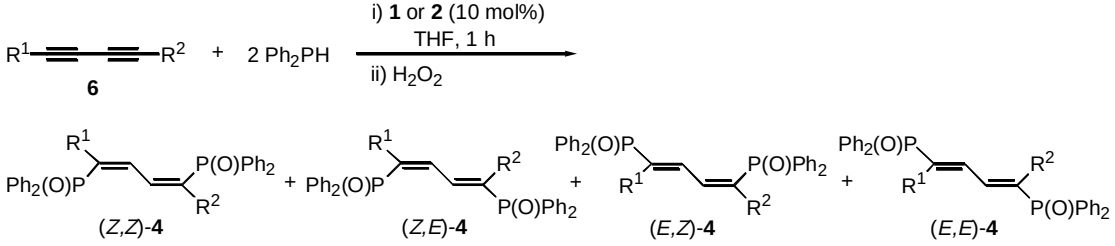
The behavior of di-*tert*-butyldiyne **6j** seems to be very different from that of others. Thus, the reaction with **1** at −35 °C gave bis(diphenylphosphinyl)allene **7** and (*Z*,*Z*)-diene **4j** in 71 and 12% yields, respectively (Eq. 1). When the reaction was performed at room temperature with **1** and **2**, the allene **7** was exclusively obtained in high yields.



(1)

Then, single hydrophosphination of unsymmetrical diynes **6d** and **6g** was carried out using equimolar amounts of Ph_2PH to learn the reaction process (Eq. 2). Apparently, the first reaction in **6d** took place at the α-alkyne carbon attached to the Ph group, with high selectivity for *anti*-addition, to yield (*Z*)-**8d**. This result contrasts well with the regio- and stereoselectivity observed for simple aromatic alkynes, in which *syn*-addition of Ph_2P occurred at the β-alkyne carbon to the aryl substituents, giving rise to

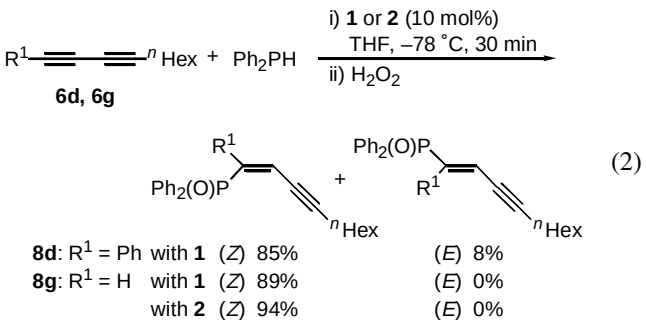
Table 1. Dual hydrophosphination of conjugated diynes with diphenylphosphine



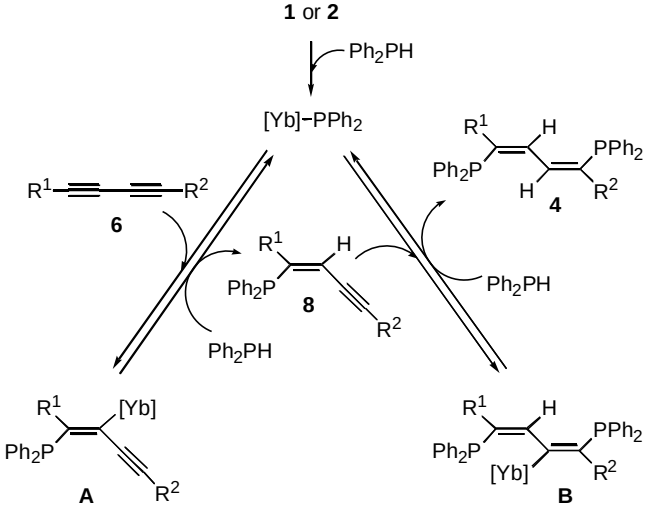
Run	6	R^1	R^2	Precatalyst	Temperature (°C)	4	Total yield (%)[a]	Ratio of isomers (*Z*,*Z*):(*Z*,*E*):(*E*,*Z*):(*E*,*E*)
1	**6a**	^{n}Hex	^{n}Hex	**1**	rt	**4a**	80	61:39:—:0
2				**1**	−15		82	74:26:—:0
3				**2**	−15		82	61:39:—:0
4	**6b**	^{n}Bu	^{n}Bu	**1**	−15	**4b**	92	67:33:—:0
5	**6c**	*c*-C_6H_{11}	*c*-C_6H_{11}	**1**	−15	**4c**	74	86:14:—:0
6	**6d**	Ph	^{n}Hex	**1**	−15	**4d**	98	73:27:0:0
7				**2**	−15		95	72:28:0:0
8	**6e**	4-MeOPh	^{n}Hex	**1**	−15	**4e**	85	73:19:8:0
9				**2**	−15		65	74:18:8:0
10	**6f**	Ph	Ph	**1**	−78	**4f**	0	Polymerization
11				**2**	−78		28	0:0:—:100
12	**6g**	H	^{n}Hex	**1**	−78[b]	**4g**	80	0:0:61:39
13				**2**	−78[b]		89	6:0:75:19
14	**6h**	H	^{n}Bu	**1**	−78[b]	**4h**	89	16:0:64:20
15				**2**	−78[b]		72	7:0:61:32
16	**6i**	H	Ph	**1** or **2**	−78	**4i**	0	Polymerization

[a] NMR yield.
[b] −78 °C for 1 h then room temperature for 2 h.

(*E*)-products.[5] In the reaction of the terminal diyne **6g**, enyne compound (*Z*)-**8g** was formed as a single isomer through *anti*-addition to the terminal position.



Combining these results with the reaction mechanism for the hydrophosphination of simple alkynes,[5] the process of the present system would be accounted for as follows (Scheme 1). At first, bis or tris(diphenylphosphino)ytterbium species, [Yb]-PPh_2, was generated in situ from the precatalysts **1** or **2** as previously proved. *anti*-Addition of the phosphide complex to the diyne **6** gave the intermediate **A**, which was readily protonated with Ph_2PH to yield the enyne compound **8** and regenerate the active phosphide species. The enyne **8** reacted further with the phosphide in a manner similar to the first cycle to yield the diene **4** via dienylytterbium **B**.



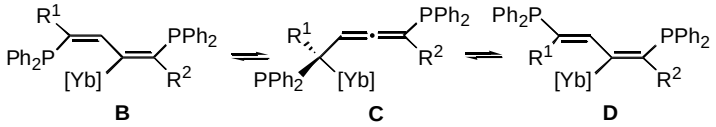
Scheme 1.

Regiochemistry was independent of the substituents of the diyne **6**, that is, two Ph_2P were introduced to the 1- and 4-position of the butadiyne moiety, whereas stereochemistry was significantly variable. As proposed in Scheme 1, repeated *anti*-addition of the Yb–phosphide complex could produce (*Z*,*Z*)-**4**, which is the case of the internal diynes **6a**–**6e**. In general, the overall stereoselectivity would be rationalized by the isomerization of the intermediate **B** formed by the second addition, which proceeds through allenic species **C** (Scheme 2). In the case of the terminal diynes **6g** and **6h**, **B** (R^1 = H) changes readily to other dienylytterbium **D** to avoid the steric repulsion between Ph_2P and Yb in the structure of **B**, giving rise to (*E*,*Z*)-**4g** and **4h** as major products. Moreover, it is likely that all four stereoisomeric dienylytterbiums such as **B** and **D** are interconvertible via **C**, but the equilibrium would not be attained completely, because of the rapid protonation of the intermediates with Ph_2PH. Therefore, stereoselectivity of the present reaction would be a reflection of both kinetic and thermodynamic factors.

Formation of the allene **7** from di-*tert*-butyldiyne **6j** substantiates the scenario described above. In this case, two tertiary substituents caused severe steric crowding in the form of a dienylytterbium species, and thus the allenic **C** should be the most stable intermediate, giving rise to **7** exclusively at room temperature. However, when the reaction was carried out at lower temperature, the (*Z*,*Z*)-diene **4j** derived from **B** was included as a minor product. Thus, **4j** and **7** could be kinetic and thermodynamic products, respectively.

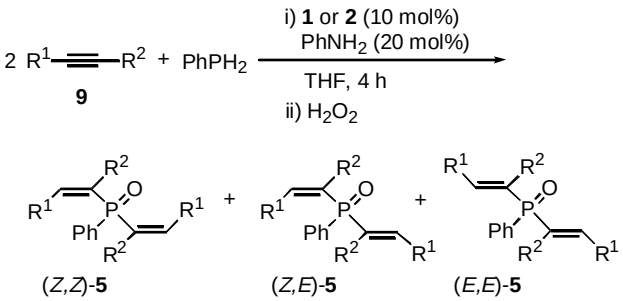
Next, we studied the dual hydrophosphination with phenylphosphine for the synthesis of bis(alkenyl)phosphines and their oxides **5**. The reaction of 1-phenylprop-1-yne (**9a**) (2 equiv) with $PhPH_2$ using the imine complex **1** (10 mol%) was slower than that with Ph_2PH, and required heating (Table 2, runs 1 and 2). After oxidative work-up with H_2O_2, three isomers of bis(β-methylstyryl)phenylphosphine oxide (**5a**) were formed in 43% total yield (run 2).[7] The silylamide precatalyst **2** gave better yield, which was further increased to 64% yield, though still non-selective, by addition of 20 mol% of aniline (runs 3 and 4). The reaction using equimolar amounts of the alkyne **9a** and $PhPH_2$ gave an intractable mixture, in which bis(1-methyl-2-phenylethyl)phenylphosphine oxide, a reduced product of **5a**, was mainly detected. In the reaction of phenylacetylene (**9b**), the aniline additive showed a significant effect for improvement of the selectivity as well as total yield of **5b** (run 5 vs 6). Thus, the (*Z*,*Z*)- and (*Z*,*E*)-isomers were obtained in 80 and 20% yields, respectively. Similarly, various aromatic alkynes **9c**–**9f** were converted to the expected products **5c**–**5f** in high yields (runs 7–10).

Unfortunately, this method was not applicable to the reaction of aliphatic alkynes, which resulted in recovery of the starting materials or exclusive consumption of $PhPH_2$ under various conditions. Moreover, the reaction of diphenylacetylene (**9g**) gave cyclic phosphine oxide **10**



Scheme 2.

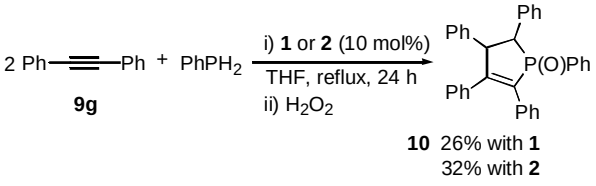
Table 2. Dual hydrophosphination of alkynes with phenylphosphine



Run	9	R^1	R^2	Precatalyst	Temperature (°C)	5	Total yield (%)[a]	Ratio of isomers (*Z*,*Z*):(*Z*,*E*):(*E*,*E*)
1	**9a**	Ph	Me	**1**[b]	rt[c]	**5a**	7	100:0:0
2				**1**[b]	Reflux		43	37:37:26
3				**2**[b]	Reflux		59	46:34:20
4				**2**	Reflux		64	36:34:30
5	**9b**	Ph	H	**2**[b]	rt	**5b**	75	48:52:0
6				**2**	rt		Quant	80:20:0
7	**9c**	4-MeOPh	H	**2**	rt	**5c**	Quant	82:18:0
8	**9d**	4-MePh	H	**2**	rt	**5d**	97	89:11:0
9	**9e**	4-ClPh	H	**2**	rt	**5e**	89	78:22:0
10	**9f**	4-BrPh	H	**2**	rt	**5f**	89	81:19:0

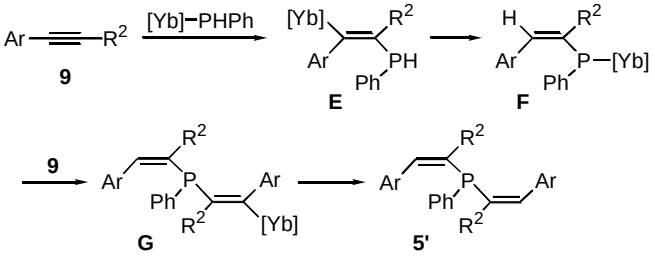
[a] NMR yield.
[b] In the absence of $PhNH_2$.
[c] Reaction period is 15 h.

unexpectedly in low yields, together with small amounts of *trans*-stilbene (Eq. 3).[8]



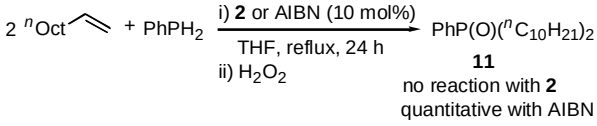
(3)

The present reaction would proceed in a mechanism analogous to that with diphenylphosphine as shown in Scheme 3. Addition of phenylphosphinoytterbium, [Yb]-PHPh, to aromatic alkyne **9**, followed by intramolecular proton transfer would yield alkenylphosphide species **F**, which reacts further with the second molecule of **9** to give bis(alkenyl)phosphine **5** through the intermediate **G**.



Scheme 3.

The regiochemistry was in agreement with that observed for the reaction with Ph_2PH, whereas the stereochemistry was reversed. Since isomerization of the intermediates and products is less likely in the present system, *anti*-addition of the phosphide species would take place preferentially to afford the (*Z*,*Z*)-isomers. The high (*Z*)-selectivity may be caused by a radical mechanism instead of the process proposed in Scheme 3.[9] However, this possibility was completely ruled out. Thus, the reaction of 2 equiv of 1-decene with $PhPH_2$ did not occur with **2**, but in contrast, addition product **11** was quantitatively formed under radical conditions (Eq. 4). Alternatively, the (*Z*)-selectivity would be attributed to the amine additive, which has been known to change the activity of the lanthanide catalysts and product selectivity in various reactions as a proton source and ligand.[6,10] In fact, aliphatic amines like amylamine decreased the yield and selectivity in contrast to aniline. However, the reason for the difference between the reaction with $PhPH_2$ and Ph_2PH is still unclear at present.



(4)

In summary, dual intermolecular hydrophosphination of conjugated diynes with 2 equiv of Ph_2PH has been achieved using ytterbium (II) and (III) precatalysts **1** and **2** to give bis(diphenylphosphinyl)dienes **4** in high yields. Addition reaction of the active species, Yb–phosphide, was found to proceed in an anti-fashion, but the resulting intermediates could isomerize via an allenic species. Thus, the stereochemistry of the products **4** was determined both kinetically and thermodynamically, depending on their substituents. Moreover, bis(alkenyl)phosphine oxides **5** were effectively obtained from 2 equiv of aromatic alkynes and $PhPH_2$ by the dual reaction in the presence of an aniline additive.

3. Experimental

3.1. General

^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded at 396, 99, and 160 MHz, respectively. IR spectra were taken on an FT-IR spectrophotometer. Mass spectra (EI) were obtained at 70 eV on a GC–MS apparatus. MALDI-TOF mass spectra were acquired using 1,8,9-trihydroxyanthracene as the matrix. Microanalyses were performed at our analytical laboratory. Melting points are uncorrected. All reactions were carried out under argon. THF was distilled from sodium/benzophenone ketyl immediately prior to use. HMPA was distilled from CaH_2 and stored over molecular sieves. The Yb-imine precatalyst **1** was generated in situ from Yb metal, $Ph_2C{=}NPh$, and HMPA (6 equiv) in THF as previously reported.[5] The silylamide precatalyst **2** was also generated by treatment of $Yb[N(SiMe_3)_2]_3(thf)_2$[11] with HMPA (2 equiv) in THF. Symmetrical diynes **6a–6c** and **6f**,[12] unsymmetrical diynes **6d** and **6e**,[13] and terminal diynes **6g–6i**[14] were prepared according to the literature methods. All other materials were commercially available and were used after drying and distillation.

3.2. Dual hydrophosphination of the conjugated diynes 6 with diphenylphosphine

Ph_2PH (2.0 mmol) was added to a solution of **1** or **2** (0.1 mmol) in THF (1 mL) and the mixture was stirred for 30 min at room temperature. After cooling the mixture to the appropriate temperature indicated in Table 1, diyne **6** (1.0 mmol) was added to the solution and stirring was continued for 1 h at this temperature. In the case of terminal diynes, the mixture was stirred for 1 h at −78 °C, and then for 2 h at room temperature to ensure the completion of the reaction. The reaction was quenched with H_2O (1 mL) and HCl solution (1 M, 1 mL), and the mixture was oxidized with H_2O_2 (30%, 1 mL) at 0 °C. Dimethyl terephthalate was added to the mixture as an internal standard. The reaction mixture was extracted with $CHCl_3$, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The product yield and ratio were determined by ^{1}H and ^{31}P NMR spectra of the crude mixture. Analytically pure compounds **4** were isolated by column chromatography on silica gel with chloroform–acetone eluent.

For determination of the stereochemistry of the products, the coupling constants between the olefinic protons and $Ph_2P(O)$ in ^{1}H NMR are informative; *trans*-$^{3}J_{P-H}$ (ca. 35 Hz), *cis*-$^{3}J_{P-H}$ (ca. 19 Hz), and $^{2}J_{P-H}$ (ca. 22 Hz). In addition, ^{31}P NMR signals of the olefinic (*Z*)-$Ph_2P(O)$ always appear in higher field than those of the (*E*).[9] For examples, (alkyl)[P(O)]C=CHR appears at ca. 29 (*Z*) and 33 ppm (*E*), (aryl)[P(O)]C=CHR at ca. 26 (*Z*) and 31 ppm (*E*), (H)[P(O)]C=CHR at ca. 22 (*Z*) and 25 ppm (*E*).

3.2.1. 7,10-Bis(diphenylphosphinyl)hexadeca-7,9-diene (4a). (*Z*,*Z*)-Isomer: white solid; mp 137–140 °C; IR (KBr) 1180 cm^{-1}; MS (MALDI) *m*/*z* 619.99 (M^+-2); MS *m*/*z* 622 (M^+), 551 ($M^+-C_5H_{11}$), 421 (M^+-Ph_2PO), 201 (Ph_2PO^+); ^{1}H NMR ($CDCl_3$) δ 0.75 (6H, t, J=7.2 Hz), 0.83–0.97 (12H, m), 1.00–1.09 (4H, m), 1.86–1.97 (4H, m), 7.45–7.55 (12H, m), 7.64–7.69 (8H, m), 7.76 (2H, d, J=35.0 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.3, 28.6, 29.3 (d, J=3.7 Hz), 31.2, 35.7 (d, J=12.3 Hz), 128.5 (d, J=8.3 Hz), 131.7 (d, J=2.5 Hz), 131.8 (d, J=10.7 Hz), 133.2 (d, J=101.7 Hz), 137.6 (d, J=86.2 Hz), 140.9 (dd, J=10.3, 3.7 Hz); ^{31}P NMR ($CDCl_3$) δ 29.53. Anal. Calcd for $C_{40}H_{48}O_2P_2$: C, 77.15; H, 7.77. Found: C, 77.03; H, 7.74. (*Z*,*E*)-Isomer: yellow oil; IR (neat) 1178 cm^{-1}; MS (MALDI) *m*/*z* 621.17 (M^+-1); ^{1}H NMR ($CDCl_3$) δ 0.81 (3H, t, J=7.0 Hz), 0.84 (3H, t, J=7.0 Hz), 1.09–1.37 (16H, m), 2.21 (2H, dt, J=13.8, 6.9 Hz), 2.50 (2H, dt, J=16.1, 7.7 Hz), 6.83 (1H, dd, J=20.6, 11.8 Hz), 7.13 (1H, ddd, J=35.0, 11.8, 1.2 Hz), 7.27–7.53 (20H, m); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.0, 22.4, 22.5, 28.7, 29.3, 29.5 (d, J=4.1 Hz), 30.5 (d, J=1.7 Hz), 31.3, 31.4, 36.4 (d, J=1.7 Hz), 36.5 (d, J=1.6 Hz), 128.3 (d, J=11.4 Hz), 128.5 (d, J=12.3 Hz), 131.1 (d, J=101.7 Hz), 131.5 (d, J=9.8 Hz), 131.62 (d, J=10.7 Hz), 131.63 (d, J=10.1 Hz), 131.8 (d, J=9.0 Hz), 132.7 (d, J=101.7 Hz), 136.7 (dd, J=19.7, 5.7 Hz), 136.9 (dd, J=14.0, 9.8 Hz), 140.1 (dd, J=96.0, 2.1 Hz), 140.9 (d, J=86.1 Hz); ^{31}P NMR ($CDCl_3$) δ 28.18, 33.58.

3.2.2. 5,8-Bis(diphenyphophinyl)dodeca-5,7-diene (4b). (*Z*,*Z*)-Isomer: white solid; mp 162–163 °C; IR (KBr) 1180 cm^{-1}; MS (MALDI) *m*/*z* 564.81 (M^+-2); ^{1}H NMR ($CDCl_3$) δ 0.56 (6H, t, J=6.9 Hz), 0.85–0.92 (8H, m), 1.92 (4H, dt, J=13.5, 6.7 Hz), 7.44–7.55 (12H, m), 7.64–7.69 (8H, m), 7.76 (2H, d, J=34.8 Hz); ^{13}C NMR ($CDCl_3$) δ 13.4, 21.9, 31.2, 35.3 (d, J=12.3 Hz), 128.4 (d, J=12.3 Hz), 131.72, (d, J=9.8 Hz), 131.73, 133.1 (d, J=100.9 Hz), 137.5 (dd, J=88.2, 2.1 Hz), 140.8 (dd, J=9.8, 4.1 Hz); ^{31}P NMR ($CDCl_3$) δ 29.57. Anal. Calcd for $C_{36}H_{40}O_2P_2$: C, 76.31; H, 7.12. Found: C, 76.51; H, 7.08. (*Z*,*E*)-Isomer: yellow oil; IR (neat) 1182 cm^{-1}; MS (MALDI) *m*/*z* 564.86 (M^+-2); ^{1}H NMR ($CDCl_3$) δ 0.74 (3H, t, J=7.2 Hz), 0.83 (3H, t, J=7.1 Hz), 1.14–1.37 (8H, m), 2.21 (2H, dt, J=13.7, 6.6 Hz), 2.53 (2H, dt, J=15.4, 7.6 Hz), 6.81 (1H, dd, J=20.6, 11.4 Hz), 7.13 (1H, dd, J=35.0, 11.4 Hz), 7.34–7.50 (20H, m); ^{13}C NMR ($CDCl_3$) δ 13.5, 13.6, 22.1, 22.7, 27.2 (d, J=9.0 Hz), 31.6 (d, J=4.1 Hz), 32.6, 36.1 (d, J=10.6 Hz), 128.3 (d, J=12.3 Hz), 128.4 (d, J=12.3 Hz), 131.1 (d, J=102.5 Hz), 131.4 (d, J=9.8 Hz), 131.61 (d, J=9.8 Hz), 131.62 (d, J=9.8 Hz), 131.7 (d, J=9.8 Hz), 132.6 (d, J=101.7 Hz), 136.5 (dd, J=19.7, 6.5 Hz), 136.8 (dd, J=14.7, 9.8 Hz), 140.0 (dd, J=96.8, 2.1 Hz), 140.9 (d, J=87.6 Hz); ^{31}P NMR ($CDCl_3$) δ 28.25, 33.71.

3.2.3. 1,4-Bis(diphenylphosphinyl)-1,4-dicyclohexylbuta-1,3-diene (4c). (*Z*,*Z*)-Isomer: white solid; mp 238–239 °C; IR (KBr) 1174 cm^{-1}; MS (MALDI) *m*/*z* 616.76 (M^+-2); ^{1}H NMR ($CDCl_3$) δ 0.68–0.74 (10H, m), 1.25–1.43 (10H, m), 2.00 (2H, quin, J=11.5 Hz), 7.43–7.55 (14H, m), 7.63–7.67 (8H, m); ^{13}C NMR ($CDCl_3$) δ 25.4, 26.3, 33.0 (d, J=10.6 Hz), 44.2 (d, J=10.6 Hz), 128.3 (d, J=12.3 Hz), 131.56, (d, J=9.8 Hz), 131.57, 133.4 (d, J=100.9 Hz), 138.2 (dd, J=10.7, 4.1 Hz), 143.0 (dd, J=87.0, 2.4 Hz); ^{31}P NMR ($CDCl_3$) δ 29.61. Anal. Calcd for $C_{40}H_{44}O_2P_2$: C, 77.65; H, 7.17. Found: C, 77.77; H, 7.21. (*Z*,*E*)-Isomer: isolated as a mixture with (*Z*,*Z*)-isomer; MS (MALDI) *m*/*z* 617.46 (M^+-1); ^{1}H NMR ($CDCl_3$) (clearly assignable peaks) δ 6.69 (1H, dd, J=22.1, 11.7 Hz); ^{13}C NMR ($CDCl_3$) δ 25.80, 25.83, 26.6, 26.9, 32.3 (d, J=3.3 Hz), 33.9 (d, J=4.1 Hz), 40.1 (d, J=9.0 Hz), 42.0 (d, J=11.5 Hz), 128.2

(d, J=11.5 Hz), 128.5 (d, J=12.3 Hz), 131.4 (d, J=2.4 Hz), 131.5 (d, J=42.7 Hz), 131.64 (d, J=9.8 Hz), 131.65 (d, J=2.4 Hz), 131.9 (d, J=9.8 Hz), 132.9 (d, J=101.7 Hz), 135.1 (dd, J=20.9, 5.3 Hz), 136.9 (dd, J=15.6, 9.8 Hz), 144.0 (dd, J=93.5, 1.6 Hz), 145.1 (d, J=86.1, 1.6 Hz); ^{31}P NMR ($CDCl_3$) δ 29.92, 35.16.

3.2.4. 1,4-Bis(diphenylphosphinyl)-1-phenyldeca-1,3-diene (4d). (Z,Z)-Isomer: white solid; mp 124–126 °C; IR (KBr) 1180 cm^{-1}; MS (MALDI) m/z 613.77 (M^+-1); ^{1}H NMR ($CDCl_3$) δ 0.77 (3H, t, J=7.4 Hz), 0.87–1.00 (6H, m), 1.07 (2H, quint, J=7.1 Hz), 1.95–2.00 (2H, m), 6.69 (2H, d, J=7.0 Hz), 6.94 (2H, t, J=7.4 Hz), 7.01 (1H, t, J=7.3 Hz), 7.32–7.68 (20H, m), 7.82 (1H, dd, J=35.5, 11.0 Hz), 7.89 (1H, dd, J=33.9, 11.0 Hz); ^{13}C NMR ($CDCl_3$) (clearly assignable peaks) δ 13.9, 22.2, 28.6, 29.1 (d, J=4.1 Hz), 31.1, 35.6 (d, J=11.5 Hz), 132.8 (d, J=101.7 Hz), 133.5 (d, J=102.5 Hz), 138.5 (dd, J=90.2, 2.1 Hz), 139.5 (d, J=9.8 Hz), 140.3 (dd, J=87.4, 2.0 Hz); ^{31}P NMR ($CDCl_3$) δ 26.13, 29.43. Anal. Calcd for $C_{40}H_{40}O_2P_2$: C, 78.16; H, 6.56. Found: C, 78.03; H, 6.68. (Z,E)-Isomer: colorless oil; IR (neat) 1182 cm^{-1}; MS (MALDI) m/z 613.04 (M^+-1); ^{1}H NMR ($CDCl_3$) δ 0.80 (3H, t, J=7.3 Hz), 1.09–1.45 (8H, m), 2.54 (2H, dd, J=16.0, 8.0 Hz), 6.99–7.01 (2H, m), 7.07–7.18 (4H, m), 7.27–7.53 (21H, m); ^{13}C NMR ($CDCl_3$) (clearly assignable peaks) δ 13.9, 22.4, 27.5 (d, J=9.0 Hz), 29.2, 30.4, 31.2, 136.5 (dd, J=14.8, 9.1 Hz), 139.9 (dd, J=9.9, 1.7 Hz), 141.8 (dd, J=88.6, 1.6 Hz), 143.0 (dd, J=95.2, 1.7 Hz); ^{31}P NMR ($CDCl_3$) δ 25.52, 33.38.

3.2.5. 1,4-Bis(diphenylphosphinyl)-1-(4-methoxyphenyl)deca-1,3-diene (4e). (Z,Z)-Isomer: white solid; mp 113–115 °C; IR (KBr) 1178 cm^{-1}; MS (MALDI) m/z 643.88 (M^+-1); ^{1}H NMR ($CDCl_3$) δ 0.77 (3H, t, J=7.2 Hz), 0.79–1.12 (8H, m), 1.91–2.00 (2H, m), 3.67 (3H, s), 6.48 (2H, d, J=8.2 Hz), 6.59 (2H, d, J=8.2 Hz), 7.35–7.68 (20H, m), 7.78 (1H, dd, J=35.3, 12.1 Hz), 7.83 (1H, dd, J=34.5, 12.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.3, 28.7, 29.2 (d, J=3.3 Hz), 31.2, 35.7 (d, J=10.7 Hz), 55.1, 113.1, 128.3 (d, J=12.3 Hz), 128.5 (d, J=11.5 Hz), 129.9 (d, J=4.9 Hz), 131.5 (d, J=2.4 Hz), 131.6 (d, J=9.8 Hz), 131.7 (d, J=9.8 Hz), 131.8 (d, J=2.4 Hz), 132.1 (d, J=10.7 Hz), 133.0 (d, J=101.7 Hz), 133.7 (d, J=102.5 Hz), 138.0 (dd, J=90.7, 2.1 Hz), 140.0 (dd, J=87.4, 2.1 Hz), 140.4 (dd, J=8.6, 4.5 Hz), 140.9 (dd, J=9.4, 5.3 Hz), 158.8; ^{31}P NMR ($CDCl_3$) δ 26.18, 29.41. Anal. Calcd for $C_{41}H_{42}O_3P_2$: C, 76.38; H, 6.57. Found: C, 75.96; H, 6.52. (Z,E)-Isomer: isolated as a mixture of (Z,E) and (E,Z)-isomer (65:35): yellow oil; MS (MALDI) m/z 643.88 (M^+-1); ^{1}H NMR ($CDCl_3$) δ 0.81 (3H, t, J=7.1 Hz), 0.99–1.39 (8H, m), 2.49–2.57 (2H, m), 3.72 (3H, s), 6.65 (2H, d, J=8.7 Hz), 6.93 (2H, d, J=8.7 Hz), 7.07 (1H, dd, J=20.4, 11.7 Hz), 7.28–7.57 (21H, m); ^{31}P NMR ($CDCl_3$) δ 25.69, 33.58. (E,Z)-Isomer: ^{1}H NMR ($CDCl_3$) (clearly assignable peaks) δ 0.77 (3H, t, J=7.4 Hz), 2.06–2.11 (2H, m), 3.75 (3H, s), 6.81 (2H, d, J=8.7 Hz), 7.22 (2H, d, J=8.9 Hz); ^{31}P NMR ($CDCl_3$) δ 28.33, 31.37.

3.2.6. (E,E)-1,4-Bis(diphenylphosphinyl)-1,4-diphenylbuta-1,3-diene (4f). White solid; mp 267–270 °C; IR (KBr) 1182 cm^{-1}; MS (MALDI) m/z 605.67 (M^+-1); ^{1}H NMR ($CDCl_3$) δ 6.76 (2H, d, J=16.9 Hz), 7.04–7.16 (10H, m), 7.27–7.43 (12H, m), 7.53–7.58 (8H, m); ^{13}C NMR ($CDCl_3$) δ 128.1 (d, J=30.4 Hz), 128.2 (d, J=2.4 Hz), 128.3 (d, J=2.4 Hz), 129.5 (d, J=2.4 Hz), 130.7 (d, J=104.2 Hz), 131.78 (d, J=9.0 Hz), 131.82 (d, J=7.4 Hz), 134.1 (d, J=4.5 Hz), 137.9 (d, J=14.4 Hz), 142.8 (dd, J=94.3, 1.4 Hz); ^{31}P NMR ($CDCl_3$) δ 29.97. Anal. Calcd for $C_{40}H_{32}O_2P_2$: C, 79.20; H, 5.32. Found: C, 79.13; H, 5.02.

3.2.7. 1,4-Bis(diphenylphosphinyl)deca-1,3-diene (4g). (Z,Z)-Isomer: white solid; mp 174–176 °C; IR (KBr) 1195, 1176 cm^{-1}; MS (MALDI) m/z 536.73 (M^+-2); ^{1}H NMR ($CDCl_3$) δ 0.76 (3H, t, J=7.1 Hz), 0.91–1.14 (8H, m), 1.98–2.05 (2H, m), 6.12 (1H, dd, J=24.6, 12.3 Hz), 7.45–7.53 (12H, m), 7.64–7.74 (8H, m), 8.15 (1H, dd, J=34.8, 12.3 Hz), 8.27 (1H, dt, J=37.4, 12.3 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.2, 28.6, 29.2 (d, J=4.1 Hz), 31.0, 35.7 (d, J=11.5 Hz), 124.0 (dd, J=96.8, 1.6 Hz), 124.4 (d, J=6.6 Hz), 128.5 (d, J=7.6 Hz) 130.9 (d, J=9.8 Hz), 131.6 (d, J=2.4 Hz), 131.7 (d, J=9.8 Hz), 131.8 (d, J=3.3 Hz), 132.5 (d, J=102.6 Hz), 133.8 (d, J=105.0 Hz), 140.9 (dd, J=10.2, 4.5 Hz), 141.0 (dd, J=84.5, 2.1 Hz), 144.7 (dd, J=9.4, 2.9 Hz); ^{31}P NMR ($CDCl_3$) δ 22.32, 30.73. Anal. Calcd for $C_{34}H_{36}O_2P_2$: C, 75.82; H, 6.74. Found: C, 75.46; H, 6.71. (E,Z)-Isomer: colorless oil; IR (neat) 1182 cm^{-1}; MS (MALDI) m/z 538.13 (M^+); ^{1}H NMR ($CDCl_3$) δ 0.81 (3H, t, J=7.1 Hz), 1.05–1.24 (6H, m), 1.32 (2H, quin, J=7.5 Hz), 2.20 (2H, dt, J=12.7, 7.5 Hz), 6.33 (1H, t, J=16.7 Hz), 6.91 (1H, dd, J=34.9, 11.4 Hz), 7.16 (1H, td, J=16.7, 11.4 Hz), 7.37–7.43 (8H, m), 7.48–7.55 (12H, m); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.3, 28.7, 29.4 (d, J=3.3 Hz), 31.2, 35.9 (d, J=9.8 Hz), 128.4 (d, J=12.3 Hz), 128.5, (d, J=11.5 Hz), 128.6 (br d, J=103.3 Hz) 131.3 (d, J=97.6 Hz), 131.4 (d, J=9.8 Hz), 131.5 (d, J=9.9 Hz), 131.8 (d, J=6.5 Hz), 132.4 (d, J=102.6 Hz), 141.5 (dd, J=22.5, 5.6 Hz), 142.7 (br d, J=86.1 Hz), 143.0 (dd, J=9.5, 6.2 Hz); ^{31}P NMR ($CDCl_3$) δ 26.31, 28.25. Anal. Calcd for $C_{34}H_{36}O_2P_2$: C, 75.82; H, 6.74. Found: C, 75.64; H, 6.53. (E,E)-Isomer: white solid; mp 212–214 °C; IR (KBr) 1186 cm^{-1}; MS (MALDI) m/z 537.94 (M^+-1); ^{1}H NMR ($CDCl_3$) δ 0.78 (3H, t, J=7.2 Hz), 0.96–1.17 (8H, m), 2.32–2.40 (2H, m), 6.53 (1H, dd, J=22.6, 17.0 Hz), 6.84 (1H, dd, J=19.3, 11.2 Hz), 7.37 (1H, td, J=17.0, 11.2 Hz), 7.46–7.57 (13H, m), 7.65–7.72 (7H, m); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.4, 28.9 (d, J=9.8 Hz), 29.3, 30.6, 31.2, 128.5 (d, J=11.5 Hz), 128.6 (d, J=12.3 Hz), 129.5 (d, J=100.9 Hz) 131.2 (d, J=102.5 Hz), 131.3 (d, J=9.9 Hz), 131.9 (d, J=9.9 Hz), 132.0 (d, J=2.4 Hz), 132.4 (d, J=67.3 Hz), 139.5 (dd, J=20.5, 10.7 Hz), 140.5 (dd, J=18.4, 3.7 Hz), 142.6 (br d, J=91.9 Hz); ^{31}P NMR ($CDCl_3$) δ 23.77, 31.68.

3.2.8. 1,4-Bis(diphenylphosphinyl)octa-1,3-diene (4h). (Z,Z)-Isomer: isolated as a mixture of (Z,Z) and (E,E)-isomer (52:48); white solid; IR (KBr) 1178 cm^{-1}; MS (MALDI) m/z 509.78 (M^+-1); ^{1}H NMR ($CDCl_3$) δ 0.60 (3H, t, J=7.2 Hz), 0.94–1.10 (4H, m), 1.97–2.04 (2H, m), 6.12 (1H, dd, J=25.3, 12.4 Hz), 7.44–7.73 (20H, m), 8.14 (1H, dd, J=34.6, 12.4 Hz), 8.26 (1H, dt, J=37.8, 12.4 Hz); ^{31}P NMR ($CDCl_3$) δ 22.41, 30.82. (E,Z)-Isomer: isolated as a mixture of (E,Z) and (E,E)-isomer (57:43); white solid; MS (MALDI) m/z 510.25 (M^+); ^{1}H NMR ($CDCl_3$) δ 0.71 (3H, t, J=7.2 Hz), 1.05–1.32 (4H, m), 2.16–2.23 (2H, m), 6.31 (1H, t, J=17.3 Hz), 6.89 (1H, dd, J=34.8, 11.1 Hz), 7.11 (1H, td, J=17.3, 11.1 Hz), 7.34–7.54 (16H, m),

7.63–7.70 (4H, m); ^{31}P NMR ($CDCl_3$) δ 26.71, 28.41. Anal. Calcd for $C_{32}H_{32}O_2P_2$: C, 75.28; H, 6.32. Found: C, 75.43; H, 6.30. (*E*,*E*)-Isomer: ^{1}H NMR ($CDCl_3$) (clearly assignable peaks) δ 0.66 (3H, t, J=7.2 Hz), 2.32–2.39 (2H, m), 6.53 (1H, dd, J=22.4, 16.8 Hz), 6.83 (1H, dd, J=19.5, 11.2 Hz), 7.36 (1H, td, J=16.8, 11.2 Hz); ^{31}P NMR ($CDCl_3$) δ 23.71, 31.70.

3.2.9. (*Z*,*Z*)-3,6-Bis(diphenylphosphinyl)-2,2,7,7-tetramethylocta-3,5-diene (4j). White solid; IR (Nujol) 1188 cm^{-1}; MS (EI) *m*/*z* 566 (M^+); ^{1}H NMR ($CDCl_3$) δ 0.85 (18H, s), 7.35–7.53 (14H, m), 7.68 (4H, tm, J=8.8 Hz), 7.90 (4H, tm, J=8.8 Hz); ^{13}C NMR ($CDCl_3$) (clearly assignable peaks) δ 29.7, 36.7. Anal. Calcd for $C_{36}H_{40}O_2P_2$: C, 76.31; H, 7.11. Found: C, 76.80; H, 7.47.

3.3. Dual hydrophosphination of aromatic alkynes 9 with phenylphosphine

The reaction was carried out in a manner similar to that of the diynes **6** described above, using the aromatic alkynes **9** (2.0 mmol), $PhPH_2$ (1.0 mmol), and **1** or **2** (0.1 mmol) in THF (1 mL). In the reaction with aniline, this additive and $PhPH_2$ were successively added to a solution of **1** or **2**, and the mixture was stirred for 30 min at room temperature.

3.3.1. Bis(β-methylstyryl)phenylphosphine oxide (5a). (*Z*,*Z*)-Isomer: IR (Nujol) 1178 cm^{-1}; MS (EI) *m*/*z* 358 (M^+); ^{1}H NMR ($CDCl_3$) δ 1.96 (6H, dd, J=12.2, 1.5 Hz), 7.03 (2H, dd, J=37.0, 1.5 Hz), 7.17–7.19 (6H, m), 7.28–7.40 (7H, m), 7.66–7.71 (2H, m); ^{13}C NMR ($CDCl_3$) δ 23.9 (d, J=13.1 Hz), 127.3, 127.9, 128.1, 128.4 (d, J=50.9 Hz), 129.5 (d, J=1.6 Hz), 131.1 (d, J=3.2 Hz), 131.5 (d, J=9.0 Hz), 132.5 (d, J=99.9 Hz), 136.0 (d, J=6.5 Hz), 144.6 (d, J=6.5 Hz); ^{31}P NMR ($CDCl_3$) δ 27.52. Anal. Calcd for $C_{24}H_{23}OP$: C, 80.43; H, 6.47. Found: C, 80.29; H, 6.51. (*Z*,*E*)-Isomer: MS (EI) *m*/*z* 358 (M^+); ^{1}H NMR ($CDCl_3$) δ 1.75 (3H, dd, J=14.0, 1.0 Hz), 2.09 (3H, dd, J=12.0, 1.2 Hz), 7.05–7.49 (15H, m), 7.66–7.71 (2H, m); ^{13}C NMR ($CDCl_3$) δ 14.4 (d, J=11.4 Hz), 23.8 (d, J=12.3 Hz), 127.3, 127.5, 127.9 (d, J=12.6 Hz), 128.1, 128.2 (d, J=11.5 Hz), 128.8 (d, J=90.9 Hz), 129.2, 129.5 (d, J=1.6 Hz), 131.0 (d, J=81.1 Hz), 131.1 (d, J=3.3 Hz), 131.3 (d, J=21.5 Hz), 132.0 (d, J=84.4 Hz), 135.8 (d, J=5.7 Hz), 136.0 (d, J=18.9 Hz), 141.3 (d, J=9.8 Hz), 145.4 (d, J=7.3 Hz); ^{31}P NMR ($CDCl_3$) δ 29.81. (*E*,*E*)-Isomer: MS (EI) *m*/*z* 358 (M^+); ^{1}H NMR ($CDCl_3$) δ 2.17 (6H, dd, J=13.2, 1.2 Hz), 7.25–7.57 (15H, m), 7.80–7.85 (2H, m); ^{13}C NMR ($CDCl_3$) δ 15.0 (d, J=9.8 Hz), 128.3, 128.4, 128.68, 128.71 (d, J=29.5 Hz), 129.4, 129.6 (d, J=41.7 Hz), 131.4 (d, J=92.6 Hz), 132.0 (d, J=9.8 Hz), 135.9 (d, J=18.0 Hz), 142.4 (d, J=10.6 Hz); ^{31}P NMR ($CDCl_3$) δ 38.40.

3.3.2. Bis(styryl)phenylphosphine oxide (5b). (*Z*,*Z*)-Isomer: white solid; mp 78–80 °C; IR (KBr) 1178 cm^{-1}; MS (EI) *m*/*z* 330 (M^+); ^{1}H NMR ($CDCl_3$) δ 6.07 (2H, dd, J=19.5, 14.0 Hz), 7.18–7.32 (11H, m), 7.65–7.72 (6H, m); ^{13}C NMR ($CDCl_3$) δ 123.9 (d, J=100.0 Hz), 127.8, 128.0, 129.1, 130.0, 130.7 (d, J=9.8 Hz), 131.0 (d, J=2.5 Hz), 133.7 (d, J=107.5 Hz), 135.2 (d, J=7.4 Hz), 148.0; ^{31}P NMR ($CDCl_3$) δ 15.03. Anal. Calcd for $C_{22}H_{19}OP$: C, 79.98; H, 5.80. Found: C, 79.87; H, 5.81. (*Z*,*E*)-Isomer: white solid; MS (EI) *m*/*z* 330 (M^+); ^{1}H NMR ($CDCl_3$) δ 6.22 (1H, dd, J=19.0, 13.9 Hz), 6.41 (1H, dd, J=22.9, 17.4 Hz), 7.11–7.54 (13H, m), 7.68–7.79 (4H, m); ^{13}C NMR ($CDCl_3$) δ 120.3 (d, J=105.0 Hz), 122.5 (d, J=100.1 Hz), 127.3, 127.8, 128.3, 128.5 (d, J=9.0 Hz), 129.2, 129.6, 129.8 (d, J=1.6 Hz), 130.4 (d, J=9.8 Hz), 131.3 (d, J=3.3 Hz), 133.5 (d, J=107.5 Hz), 134.9 (d, J=7.4 Hz), 135.1 (d, J=18.0 Hz), 146.0 (d, J=3.3 Hz), 148.9; ^{31}P NMR ($CDCl_3$) δ 17.56.

3.3.3. Bis(4-methoxystyryl)phenylphosphine oxide (5c). (*Z*,*Z*)-Isomer: IR (neat) 1180 cm^{-1}; MS (EI) *m*/*z* 390 (M^+); ^{1}H NMR ($CDCl_3$) δ 3.76 (6H, s), 5.92 (2H, dd, J=19.5, 14.0 Hz), 6.75–6.79 (4H, m), 7.17 (2H, dd, J=40.5, 14.0 Hz), 7.26–7.34 (3H, m), 7.70–7.76 (6H, m); ^{13}C NMR ($CDCl_3$) δ 55.2, 113.4, 121.1 (d, J=100.9 Hz), 128.07 (d, J=18.9 Hz), 128.09, 130.8 (d, J=9.8 Hz), 131.0 (d, J=3.3 Hz), 132.1 (d, J=1.6 Hz), 134.3 (d, J=106.6 Hz), 147.5 (d, J=1.6 Hz), 160.4; ^{31}P NMR ($CDCl_3$) δ 15.91. Anal. Calcd for $C_{24}H_{23}O_3P$: C, 73.83; H, 5.94. Found: C, 73.43; H, 5.98. (*Z*,*E*)-Isomer: MS (EI) *m*/*z* 390 (M^+); ^{1}H NMR ($CDCl_3$) δ 3.72 (3H, s), 3.80 (3H, s), 6.04 (1H, dd, J=19.4, 13.8 Hz), 6.30 (1H, dd, J=22.6, 17.2 Hz), 6.74–6.85 (4H, m), 7.29–7.48 (7H, m), 7.64–7.80 (4H, m); ^{13}C NMR ($CDCl_3$) δ 55.2, 55.3, 113.4, 114.1, 117.8 (d, J=107.5 Hz), 119.7 (d, J=100.9 Hz), 127.9 (d, J=7.4 Hz), 128.2, 128.4 (d, J=12.3 Hz), 129.1, 130.6 (d, J=9.8 Hz), 131.3 (d, J=2.4 Hz), 132.0, 134.2 (d, J=107.5 Hz), 145.5 (d, J=4.2 Hz), 148.4, 160.5, 160.9; ^{31}P NMR ($CDCl_3$) δ 18.57.

3.3.4. Bis(4-methylstyryl)phenylphosphine oxide (5d). (*Z*,*Z*)-Isomer: white solid; mp 98–99 °C; IR (KBr) 1178 cm^{-1}; MS (EI) *m*/*z* 358 (M^+); ^{1}H NMR ($CDCl_3$) δ 2.29 (6H, s), 6.00 (2H, dd, J=19.8, 14.0 Hz), 7.04–7.32 (10H, m), 7.61–7.72 (5H, m); ^{13}C NMR ($CDCl_3$) δ 21.3, 122.8 (d, J=100.9 Hz), 127.9 (d, J=11.5 Hz), 128.7, 130.2 (d, J=1.6 Hz), 130.8 (d, J=9.8 Hz), 130.9 (d, J=3.3 Hz), 132.5 (d, J=7.4 Hz), 134.2 (d, J=107.5 Hz), 139.4, 147.9 (d, J=1.6 Hz); ^{31}P NMR ($CDCl_3$) δ 15.29. Anal. Calcd for $C_{24}H_{23}OP$: C, 80.43; H, 6.47. Found: C, 80.21; H, 6.43. (*Z*,*E*)-Isomer: MS (EI) *m*/*z* 358 (M^+); ^{1}H NMR ($CDCl_3$) δ 2.24 (3H, s), 2.33 (3H, s), 6.14 (1H, dd, J=19.0, 14.0 Hz), 6.35 (1H, dd, J=22.8, 17.2 Hz), 6.92–7.79 (15H, m): ^{13}C NMR ($CDCl_3$) δ 21.2, 21.3, 119.3 (d, J=105.8 Hz), 121.5 (d, J=100.1 Hz), 127.4, 128.4 (d, J=12.3 Hz), 128.7, 129.3, 130.1, 130.6 (d, J=9.8 Hz), 131.3 (d, J=3.3 Hz), 132.4 (d, J=7.4 Hz), 132.7 (d, J=18.9 Hz), 134.0 (d, J=107.5 Hz), 139.5, 139.9, 145.9 (d, J=3.3 Hz), 148.9; ^{31}P NMR ($CDCl_3$) δ 18.09.

3.3.5. Bis(4-chlorostyryl)phenylphosphine oxide (5e). (*Z*,*Z*)-Isomer: white solid; mp 111–112 °C; IR ($CHCl_3$) 1175 cm^{-1}; MS (EI) *m*/*z* 398 (M^+); ^{1}H NMR ($CDCl_3$) δ 6.09 (2H, dd, J=19.6, 14.0 Hz), 7.15–7.39 (9H, m), 7.64–7.68 (6H, m); ^{13}C NMR ($CDCl_3$) δ 124.4 (d, J=100.0 Hz), 128.1, 128.3, 130.7 (d, J=9.8 Hz), 131.39, 131.44 (d, J=3.2 Hz), 133.2 (d, J=106.5 Hz), 133.5 (d, J=8.2 Hz), 135.3, 147.0; ^{31}P NMR ($CDCl_3$) δ 14.78. Anal. Calcd for $C_{22}H_{17}Cl_2OP$: C, 66.18; H, 4.29. Found: C, 66.12; H, 4.01. (*Z*,*E*)-Isomer: white solid; mp 150–151 °C; IR ($CHCl_3$) 1180 cm^{-1}; MS (EI) *m*/*z* 398 (M^+); ^{1}H NMR ($CDCl_3$) δ 6.25 (1H, dd, J=19.1, 13.8 Hz), 6.40 (1H, dd, J=22.7,

17.1 Hz), 7.20–7.50 (11H, m), 7.64–7.77 (4H, m); ^{31}P NMR ($CDCl_3$) δ 17.21. Anal. Calcd for $C_{22}H_{17}Cl_2OP$: C, 66.18; H, 4.29. Found: C, 66.19; H, 4.16.

3.3.6. Bis(4-bromostyryl)phenylphosphine oxide (5f). (*Z*,*Z*)-Isomer: white solid; mp 117–118 °C; IR ($CHCl_3$) 1180 cm^{-1}; MS (EI) *m*/*z* 486 (M^+); ^{1}H NMR ($CDCl_3$) δ 6.10 (2H, dd, J=19.7, 14.0 Hz), 7.20 (2H, dd, J=40.1, 14.0 Hz), 7.27–7.39 (7H, m), 7.58–7.68 (6H, m); ^{13}C NMR ($CDCl_3$) δ 123.8, 124.6 (d, J=99.2 Hz), 128.2 (d, J=12.3 Hz), 130.7 (d, J=9.8 Hz), 131.2, 131.5 (d, J=2.5 Hz), 131.6 (d, J=1.2 Hz), 133.2 (d, J=107.3 Hz), 134.0 (d, J=7.4 Hz), 147.1; ^{31}P NMR ($CDCl_3$) δ 12.14. Anal. Calcd for $C_{22}H_{17}Br_2OP$: C, 54.13; H, 3.51. Found: C, 54.18; H, 3.51. (*Z*,*E*)-Isomer: white solid; MS (EI) *m*/*z* 486 (M^+); ^{1}H NMR ($CDCl_3$) δ 6.25 (1H, dd, J=19.1, 14.0 Hz), 6.40 (1H, dd, J=23.0, 17.4 Hz), 7.19–7.76 (15H, m); ^{13}C NMR ($CDCl_3$) δ 121.0 (d, J=104.9 Hz), 123.4 (d, J=99.2 Hz), 124.1, 128.7 (d, J=12.2 Hz), 128.9, 129.1, 130.5 (d, J=10.7 Hz), 131.2, 131.6, 131.8, 132.0, 133.1 (d, J=112.0 Hz), 133.98, 134.03 (d, J=25.4 Hz), 145.1 (d, J=3.3 Hz), 147.8; ^{31}P NMR ($CDCl_3$) δ 14.61.

3.3.7. 3,6-Bis(diphenylphosphinyl)-2,2,7,7-tetramethylocta-3,4-diene (7). White solid; mp 202–204 °C; IR (KBr) 1203, 1186 cm^{-1}; MS (MALDI) *m*/*z* 564.01 (M^+-2); MS m/z 566 (M^+), 509 ($M^+-{}^t$Bu), 452 ($M^+-2{}^t$Bu), 365 (M^+-Ph_2PO), 308 (365-^{t}Bu$^+$), 201 (Ph_2PO^+); ^{1}H NMR ($CDCl_3$) δ 1.16 (9H, s), 1.33 (9H, s), 2.81 (1H, ddd, J=7.7, 5.9, 4.3 Hz), 5.30 (1H, ddd, J=16.7, 11.6, 7.7 Hz), 6.94–7.76 (20H, m); ^{13}C NMR ($CDCl_3$) δ 29.8 (d, J=5.7 Hz), 29.9 (d, J=4.1 Hz), 37.5 (d, J=6.6 Hz), 37.8 (d, J=5.7 Hz), 45.3 (dd, J=70.6, 4.9 Hz), 90.6 (d, J=13.9 Hz), 107.8 (d, J=96.8 Hz), 127.9 (d, J=11.5 Hz), 128.1 (d, J=100.9 Hz), 128.7, 130.2 (d, J=1.6 Hz), 130.8 (d, J=9.8 Hz), 130.9 (d, J=12.3 Hz), 128.3 (d, J=11.5 Hz), 128.4 (d, J=11.5 Hz), 130.0 (d, J=9.1 Hz), 130.5 (d, J=8.2 Hz), 130.7 (d, J=2.5 Hz), 131.1 (d, J=3.3 Hz), 131.4 (d, J=2.5 Hz), 131.5 (d, J=3.3 Hz), 131.6 (d, J=9.0 Hz), 132.0 (d, J=10.7 Hz), 132.9 (d, J=100.9 Hz), 134.0 (d, J=96.0 Hz), 135.6 (d, J=95.2 Hz), 137.8 (d, J=108.3 Hz), 207.1 (d, J=26.3 Hz); ^{31}P NMR ($CDCl_3$) δ 28.78 (d, J=5.9 Hz), 31.68 (d, J=5.9 Hz). Anal. Calcd for $C_{36}H_{40}O_2P_2$: C, 76.31; H, 7.11. Found: C, 76.53; H, 7.11.

3.3.8. 1-Diphenylphosphinyl-1-phenyldec-1-en-3-yne (8d). Isolated as a mixture of (*Z*) and (*E*)-isomer (91:9); yellow oil; IR (neat) 1190 cm^{-1}; MS (EI) *m*/*z* 412 (M^+); ^{1}H NMR ($CDCl_3$) δ (*Z*)-isomer: 0.84 (3H, t, J=6.9 Hz), 1.14–1.56 (8H, m), 2.53–2.61 (2H, m), 6.52 (1H, d, J=36.2 Hz), 6.87 (2H, d, J=7.0 Hz), 7.15–7.57 (9H, m), 7.70–7.86 (4H, m); (*E*)-isomer: 6.22 (d, J=18.1 Hz); ^{13}C NMR ($CDCl_3$) δ (*Z*)-isomer: 14.0, 22.4, 28.7, 29.4 (d, J=3.2 Hz), 31.5, 34.9 (d, J=8.2 Hz), 86.7 (d, J=10.6 Hz), 99.8 (d, J=1.6 Hz), 120.8 (d, J=6.5 Hz), 127.9, 128.3 (d, J=12.3 Hz), 128.5, 131.3, 131.73, 131.76 (d, J=10.7 Hz), 131.8, 132.5 (d, J=103.4 Hz), 146.8 (d, J=90.5 Hz); ^{31}P NMR ($CDCl_3$) δ (*Z*)-isomer: 27.76, (*E*)-isomer: 31.77. Anal. Calcd for $C_{28}H_{29}OP$: C, 81.53; H, 7.09. Found: C, 81.56; H, 7.22.

3.3.9. (*Z*)-1-Diphenylphosphinyldec-1-en-3-yne (8g). Yellow oil; IR (neat) 1188 cm^{-1}; MS (EI) *m*/*z* 336 (M^+); ^{1}H NMR ($CDCl_3$) δ 0.86 (3H, t, J=7.1 Hz), 1.15–1.27 (8H, m), 1.97–2.00 (2H, m), 6.47 (1H, dd, J=18.7, 13.2 Hz), 6.53 (1H, ddt, J=35.8, 13.2, 2.4 Hz), 7.43–7.53 (6H, m), 7.76–7.81 (4H, m); ^{13}C NMR ($CDCl_3$) δ 14.0, 19.6, 22.4, 27.7, 28.4, 31.2, 77.3 (d, J=12.3 Hz), 104.8, 128.3 (d, J=12.3 Hz), 128.4 (d, J=1.6 Hz), 131.26 (d, J=9.8 Hz), 131.30 (d, J=99.3 Hz), 131.6 (d, J=3.5 Hz), 133.0 (d, J=105.8 Hz); ^{31}P NMR ($CDCl_3$) δ 21.46. Anal. Calcd for $C_{22}H_{25}OP$: C, 78.55; H, 7.49. Found: C, 78.60; H, 7.58.

3.3.10. 1,2,3,4,5-Pentaphenyl-1-phosphacyclopent-2-ene 1-oxide (10). Isolated as a single isomer with unknown stereochemistry; white solid; mp 295–297 °C; IR (KBr) 1215 cm^{-1}; MS (MALDI) *m*/*z* 482.60 (M^+); ^{1}H NMR ($CDCl_3$) δ 3.98 (1H, dd, J=10.1, 8.2 Hz), 4.96 (1H, dd, J=27.3, 8.2 Hz), 7.01–7.39 (23H, m), 7.67–7.72 (2H, m); ^{13}C NMR ($CDCl_3$) δ 51.0 (d, J=69.7 Hz), 59.7 (d, J=7.3 Hz), 126.7, 127.0, 127.4, 127.7, 128.1, 128.27, 128.34, 128.40 (d, J=10.6 Hz), 128.85, 128.90, 129.7, 130.8 (d, J=7.5 Hz), 131.5 (d, J=9.8 Hz), 131.6 (d, J=2.4 Hz), 133.1 (d, J=119.6 Hz), 133.7 (d, J=1.0 Hz), 133.9, 134.0, 136.1 (d, J=92.6 Hz), 136.6 (d, J=15.5 Hz), 137.2, 157.9 (d, J=25.4 Hz); ^{31}P NMR ($CDCl_3$) δ 52.06. Anal. Calcd for $C_{34}H_{27}OP$: C, 84.63; H, 5.64. Found: C, 84.44; H, 5.68.

3.3.11. Di(decyl)phenylphosphine oxide (11). White solid; mp 56–57 °C; IR (KBr) 1165 cm^{-1}; MS (EI) *m*/*z* 406 (M^+); ^{1}H NMR ($CDCl_3$) δ 0.86 (6H, t, J=6.7 Hz), 1.21–2.17 (36H, m), 7.47–7.52 (3H, m), 7.66–7.71 (2H, m); ^{13}C NMR ($CDCl_3$) δ 14.1, 21.4 (d, J=4.1 Hz), 22.7, 29.1, 29.3, 29.4, 29.5 30.0 (d, J=68.1 Hz), 31.0 (d, J=13.8 Hz), 31.9, 128.6 (d, J=11.4 Hz), 130.4 (d, J=8.2 Hz), 131.4 (d, J=3.2 Hz), 132.3 (d, J=91.8 Hz); ^{31}P NMR ($CDCl_3$) δ 40.72. Anal. Calcd for $C_{26}H_{47}OP$: C, 76.80; H, 11.65. Found: C, 76.84; H, 11.65.

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7. The original phosphine products were isolable, but oxidized partially during the work-up and purification. Thus, they were isolated and characterized as phosphine oxides.
8. Although the mechanism leading to **10** is unknown at present, it may be formed by cyclization of (*Z*)-phosphinoalkenylyterbium species, (*Z*)-isomer corresponding to G depicted in Scheme 3.
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Substituent effects on the ^{31}P NMR chemical shifts of arylphosphorothionates

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Abstract—Six tris(aryloxy)phosphorothionates substituted in the *para* position of the aromatic rings were synthesized and studied by ^{31}P NMR, X-ray diffraction techniques and ab initio calculations at a RHF/6-31G** level of theory, in order to find the main structural factors associated with the δ^{31}P in these compounds. As the electron-withdrawing (EW) ability of the substituents was increased, an 'abnormal' shielding effect on δ^{31}P of the arylphosphorothionates was observed. The analyses of the geometrical properties obtained through both experimental and theoretical methods showed that a propeller-type conformation is preferred for the arylphosphorothionates, except in the case of the tris(*O*-4-methylphenyl)phosphorothionate, since one of the aromatic rings is not rotated in the same direction as the other two in the solid state. The main features associated with the δ^{31}P NMR of compounds **1**–**6** were a decrease of the averaged O–P–O angle and mainly the shortening of the P=S bond length, which is consistent with an increase of the thiophosphoryl bond order as δ^{31}P values go upfield. On the other hand, comparison of the experimental and calculated bond lengths and bond angles involving α bonded atoms to phosphorus of the six compounds suggested that stereoelectronic interactions of the type n_{π}O-$\sigma^*_{P=S}$, n_{π}O-$\sigma^*_{P\text{-}OAr}$ and n_{π}S-$\sigma^*_{P\text{-}OAr}$ could be present in the arylphosphorothionates **1**–**6**.

1. Introduction

During the last three decades, numerous groups have been interested in understanding the factors that contribute to the δ^{31}P chemical shift of organophosphorus compounds.[1] In this context, many correlations between chemical shifts and molecular structure have been performed.[2] Among them one of the most known is the relationship found by Gorenstein between the ^{31}P NMR chemical shift of cyclic and acyclic phosphate esters and OPO bond angles.[2a] In the case of organic phosphorus compounds with aromatic rings, the effect that an electron withdrawing (EW) or electron releasing (ER) group in the *para* position of the ring has on the ^{31}P chemical shift, seems related to the type of phosphorylated function present in the molecule and/or to the electronegativity of the α-atoms directly linked to phosphorus.[2i] However, these two factors cannot always be separated so as to understand their behavior. For instance, it has been reported that an increase in the EW power of the *para* substituent causes a deshielding of the ^{31}P signal in *N*-aryltriphenylphospha-λ^5-azenes[2m] and *O*-aryl diethylphosphinates,[2e] whereas the opposite behavior is observed in aryldihexylphosphates.[2j]

In spite of their commercial importance, few reports dealing with the correlation between ^{31}P chemical shift and the structure of thiophosphoryl compounds have appeared.[3] For instance, the phosphorothionates have been applied worldwide as insecticides[4] but also as motor and transmission oil additive, plasticizer, antioxidant[5] and lubricant of magnetic

Keywords: ^{31}P NMR; Ab initio; Back-bonding; Propeller-type conformation; X-ray crystal structures; Arylphosphorothionates.
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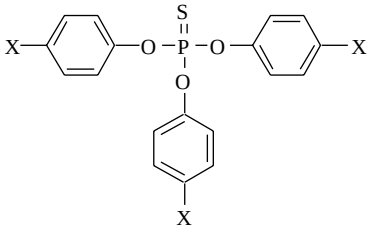
recording materials.[6] Reported in this work is the study of the electronic effect that EW and ER groups exert on the ^{31}P chemical shift of the arylphosphorothionates shown in Figure 1. The $\delta^{31}P$ of the six compounds are correlated with the Hammett constants (σ_p) within the context of LFER theory.[7] We analyzed thoroughly the experimental and theoretical structural parameters obtained through X-ray diffraction techniques of the resulting crystalline compounds and from the ab initio calculations of the complete series in order to find the principal structural features that determine the $\delta^{31}P$ of arylphosphorothionates.

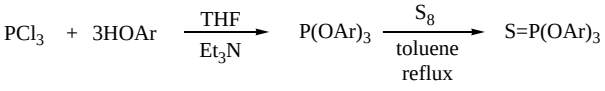


Compound	X
1	OMe
2	Me
3	H
4	Cl
5	CN
6	NO_2

Figure 1.

2. Results

The synthesis of arylphosphorothionates has been described before by several authors.[5,6,8] Treatment of thiophosphoryl chloride with 3 equiv of the corresponding substituted phenol is a one-step synthetic route to prepare triaryl phosphorothionates. However, phase transfer catalysts are needed due to the low reactivity of $PSCl_3$ with phenols, even under forcing conditions.[8c] In this work, the synthesis of arylphosphorothionates **1**–**6** was accomplished as summarized in Scheme 1. The use of THF as solvent in the first step of the synthesis contributes to increase the solubility of the corresponding phosphites, making easier its extraction (by filtration) from the triethylammonium chloride, produced during the reaction. Then, the phosphites were reacted with sulfur in toluene under reflux to produce the corresponding arylphosphorothionates. The desired products were purified from the crude of the reaction by chromatographic column.



Scheme 1.

The structures of the synthesized compounds were confirmed from the ^{31}P, ^{1}H, ^{13}C NMR spectra and EI mass spectrometry. The ^{31}P chemical shifts of the six arylphosphorothionates are given in Table 1. Homogeneous solutions with the same concentration (0.03 mol L^{-1}) of compounds **1**–**6** were prepared, and their corresponding ^{31}P NMR spectra were acquired in $CDCl_3$ at 25 °C. The reproducibility of the ^{31}P chemical shifts was evaluated through repeated measurements under similar conditions, and resulted better than ± 0.01 ppm. The effect of the concentration on ^{31}P chemical shift was measured for compound **5**. Only a small shielding of the signal (0.042 ppm) was observed when the concentration was increased from 0.03 to 0.14 mol L^{-1}.

Table 1. ^{31}P chemical shifts of *p*-X-arylphosphorothionates **1**–**6**

Compound	**1**	**2**	**3**	**4**	**5**	**6**
$\delta^{31}P$ (ppm)	56.56	54.92	53.71	53.81	50.47	50.09

Five of the six compounds were solids, only tris(*O*-4-methoxyphenyl)phosphorothionate (compound **1**) resulted a colorless oil. We were able to get crystals with quality enough for an X-ray diffraction study of compounds **2**, **3**, **4** and **5**. The ORTEP drawings of them are shown in Figures 2–5. Data collection and refinement parameters, bond lengths and bond angles are provided in Tables 2–4. Compounds **2**, **4** and **5** crystallized in the monoclinic system, the space group found was $P2_1/n$, in the cases of **2** and **4** and $P2_1/c$ for compound **5**. On the other hand, compound **3** crystallized in the non-centrosymetric space group $P2_12_12_1$ of the orthorhombic system.

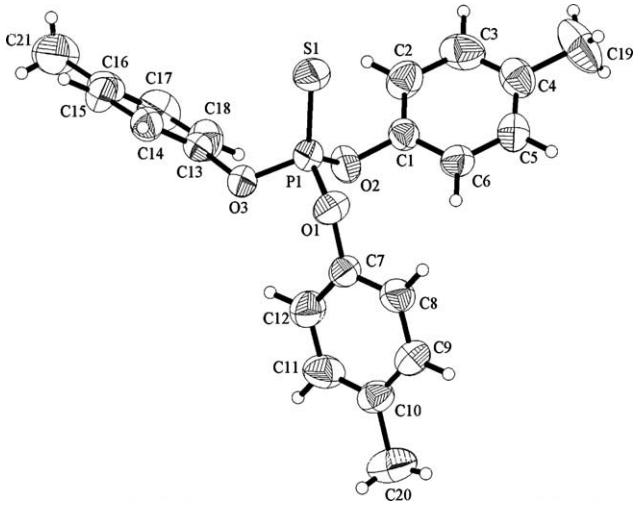


Figure 2. ORTEP drawing of tris(*O*-4-methylphenyl)phosphorothionate (**2**).

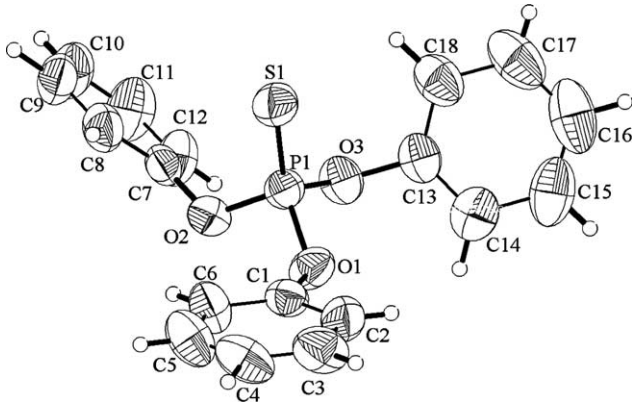


Figure 3. ORTEP drawing of tris(*O*-phenyl)phosphorothionate (**3**).

Geometry optimization of the six compounds was carried out at a RHF 6-31G** level of theory. The vibrational frequencies were computed for each molecule to characterize them as true minima. No imaginary frequencies were found. The RHF method and the 6-31G** basis set have been used before succesfully to describe related molecules.[9]

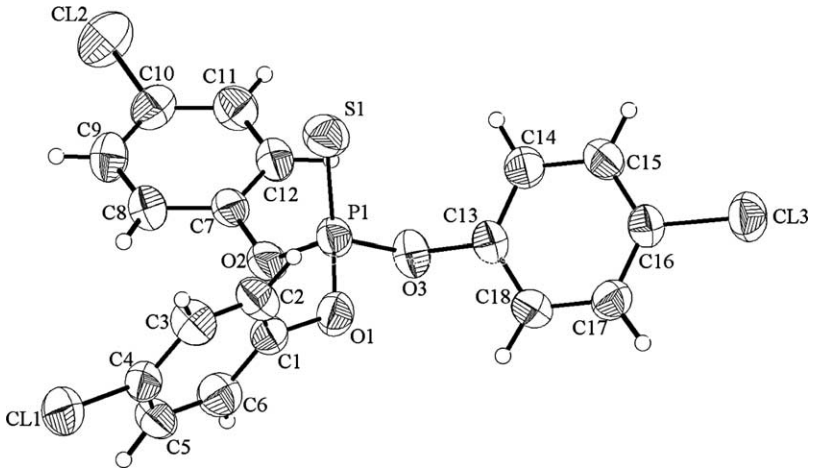


Figure 4. ORTEP drawing of tris(*O*-4-chlorophenyl)phosphorothionate (**4**).

The numerical results from our theoretical analyses are shown in Tables 5 and 6.

3. Discussion

3.1. Substituent effect on δ^{31}P NMR

The ^{31}P chemical shift for the six compounds reported here (Table 1) is distributed between 50.09 (X=NO_2) and 56.56 (X=OMe) ppm. The δ^{31}P of compounds **1**–**6** show an 'abnormal' shielding effect when the EW power of the substituent increases. A plot of Hammett σ_p constant versus δ^{31}P gives a straight line, whose slope is −5.66 with a correlation coefficient of 0.974 (Fig. 6).[10]

In analogy to these results, recently it was reported a similar reversible correlation between the Hammett σ_p constant and the ^{31}P NMR signals of the anancomeric axial and equatorial 2-*p*-X-aryloxy-2-thio-1,3,2λ^5-dioxaphosphorinanes (X=EW or ER groups).[3e] Through the structural data obtained with X-ray diffraction techniques for some of these heterocyclic compounds, it was observed a shortening of the P–$O_{endocyclic}$ bonds of the 1,3,2-dioxaphosphorinane ring as the EW power of the substituent increases, in agreement with the presence of the known n_πO-$\sigma^*_{P\text{-}OAr}$ and n_πO-$\sigma^*_{P=S}$ hyperconjugative interactions acting on the axial and equatorial thiophosphates, respectively, but also with the possible transfer of charge density by endocyclic oxygen atoms to phosphorus (Fig. 7).

In spite of the structural differences between the cyclic thiophosphates and the arylphosphorothionates **1**–**6**, it is interesting to note that the presence of an EW group in the aromatic ring causes the same shielding effect on the ^{31}P chemical shift in both kind of systems, which reveals that in addition to the transfer of charge density from the endocyclic oxygen atoms toward phosphorus nucleus proposed for the anancomeric dioxaphosphorinanes there are other structural and electronic factors that could contribute to observe the same behavior in the cyclic and acyclic thiophosphates.

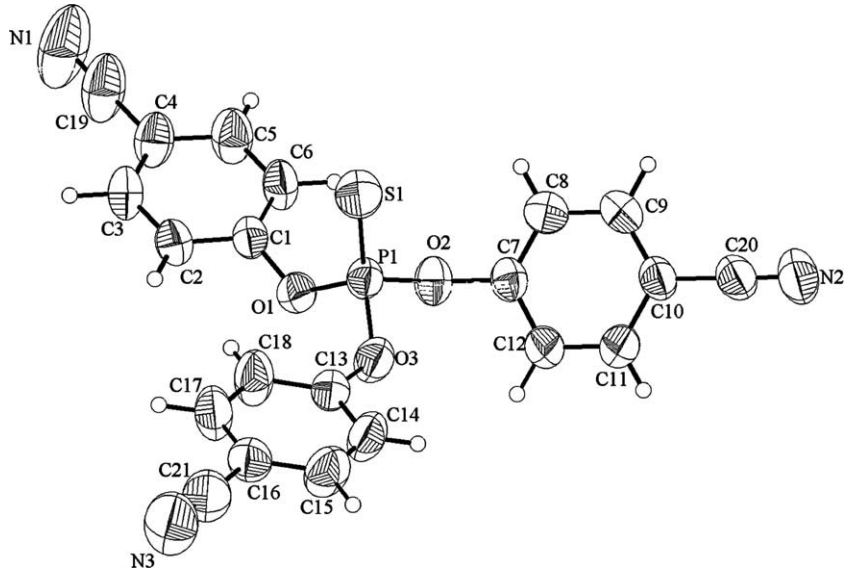


Figure 5. ORTEP drawing of tris(*O*-4-cyanophenyl)phosphorothionate (**5**).

Table 2. X-ray crystal data for arylphosphorothionates **2**, **3**, **4** and **5**[a]

	2	**3**	**4**	**5**
Formula	$C_{21}H_{21}O_3PS$	$C_{18}H_{15}O_3PS$	$C_{18}H_{12}C_{l3}O_3PS$	$C_{21}H_{12}N_3O_3PS$
*F*W	384.41	342.33	445.66	417.37
Crystal system	Monoclinic	Orthorhombic	Monoclinic	Monoclinic
Space group	*P* 1 21/*n* 1	*P* 2(1)2(1)2(1)	*P*2(1)/*n*	*P*1 21/*c* 1
Crystal size (mm^3)	0.392×0.28×0.28	0.4×0.4×0.4	0.7×0.5×0.5	0.75×0.45×0.45
Radiation	Mo Kα	Mo Kα	Mo Kα	Mo Kα
Wavelength (Å)	0.71073	0.71073	0.71073	0.71073
a (Å)	10.161(4)	7.941(2)	11.243(2)	8.8272(3)
b (Å)	12.68(14)	13.183(3)	17.469(4)	18.5137(5)
c (Å)	15.753(6)	16.133(3)	11.279 (2)	12.6684(5)
α	90.00	90.00	90.00	90.00
β	97.93 (3)	90.00	118.85(3)	91.7030(10)
γ	90.00	90.00	90.00	90.00
V ($Å^3$)	2010.2(13)	1688.9(7)	1940.3(7)	2069.41(12)
Z	4	4	4	4
$2\theta_{max}$(°)	54.98	55.24	54.98	55.02
D_{calcd} (Mg m^{-3})	1.270	1.346	1.526	1.340
Absortion coefficient (mm^{-1})	0.258	0.297	0.678	0.260
No. of reflections collected	2553	2234	9153	8793
No. of independent reflection	2433	2234	4446	4704
No. of observed reflections	2316	1374	2911	3064
$R1[F>4\sigma(F)]$	0.0556	0.0295	0.0534	0.0499
*WR*2	0.1178	0.0789	0.1334	0.1180
*R*1 (all data)	0.0587	0.0822	0.0881	0.0881
*WR*2	0.1197	0.0954	0.1446	0.1374
GOF on *F*2	1.096	1.016	1.034	1.014
Max. shift for final cycle of least squares Δ/σ	0.000	0.001	0.003	0.000
Max. peak in final difference syntheses ($e/Å^3$)	0.234	0.201	0.534	0.248
Max. difference hole ($e/Å^3$)	−0.263	−0.224	−0.355	−0.272

[a] Standard deviations are in parentheses.

Table 3. Selected bond lengths (Å) for arylphosphorothionates **2–5**[a]

	P═S	P–O1	P–O2	P–O3	O1–C	O2–C	O3–C
2	1.8987(16)	1.572(3)	1.581(3)	1.575(3)	1.412(4)	1.414(4)	1.414(4)
3	1.8981(12)	1.567(2)	1.579(2)	1.578(2)	1.414(3)	1.399(4)	1.406(3)
4	1.8968(10)	1.579(2)	1.5862(19)	1.5908(18)	1.418(3)	1.401(3)	1.418(3)
5	1.8888(8)	1.5704(16)	1.5869(17)	1.5811(16)	1.402(3)	1.394(3)	1.403(3)

[a] Standard deviations are in parentheses.

Table 4. Selected bond angles (θ) in degree for arylphosphorothionates **2–5**[a]

	O1PO2	O2PO3	O3PO1	SPO1	SPO2	SPO3
2	106.23(15)	100.98(15)	100.78(15)	111.91(12)	17.03(12)	117.98(11)
3	100.05(12)	99.14(12)	101.30(12)	117.01(10)	118.02(9)	117.98(9)
4	100.48(10)	99.85(10)	99.95(10)	118.04(8)	117.78(8)	117.36(8)
5	100.60(9)	99.06(9)	99.06(9)	117.51(7)	117.93(7)	117.64(7)

[a] Standard deviations are in parentheses.

Table 5. Selected calculated parameters of arylphosphorothionates **1–6**

	RHF 6-31G**					
	Bond	Lengths	(Å)	Bond	Angles	(Degrees)
	P═S	P–O[a]	O–C[a]	OPO	OPO	OPO
1	1.918	1.584	1.388	100.78	100.78	100.78
2	1.918	1.584	1.386	100.76	100.76	100.76
3	1.916	1.584	1.386	100.72	100.73	100.74
4	1.914	1.585	1.384	100.61	100.61	100.61
5	1.910	1.586	1.381	100.46	100.48	100.48
6	1.909	1.586	1.379	100.40	100.40	100.40

[a] The calculated P–O1, P–O2 and P–O3 bond lengths were identical in each case, an only one value is reported. It was the same case for C–O1, C–O2 and C–O3.

Table 6. Calculated natural charges on heteroatoms of arylphosphorothionates **1–6**

Compound	S	P	O[a]
1	−0.677	2.360	−0.917
2	−0.675	2.359	−0.917
3	−0.670	2.356	−0.917
4	−0.658	2.349	−0.914
5	−0.643	2.340	−0.913
6	−0.635	2.336	−0.912

[a] As the calculated molecules have a C_3 symmetry, O1, O2 and O3 are equivalent into each molecule, and as a consequence, the natural charges too.

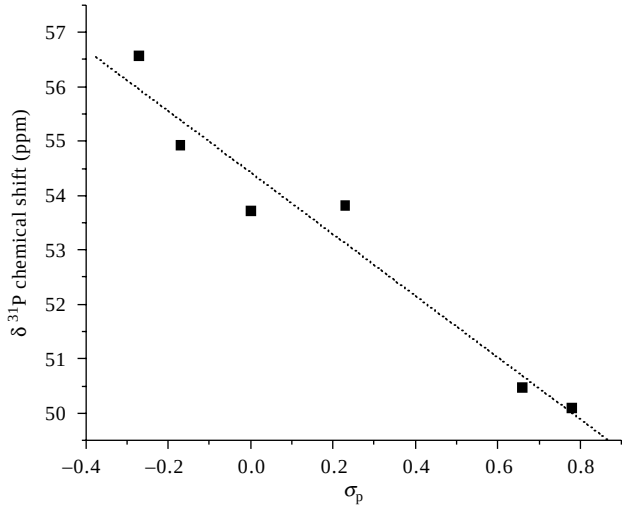


Figure 6. Relationship between the calculated σ_p and the experimental ^{31}P NMR chemical shift for arylphosphorothionates **1–6** (correlation coefficient = 0.974, slope = −5.66).

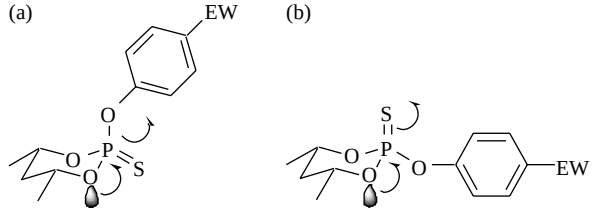


Figure 7.

3.2. Structural analysis

Three of the four arylphosphorothionates analyzed by X-ray diffraction techniques have almost a propeller-type conformation in solid state,[11] since the three OAr groups are rotated more or less in one direction, except in the case of the compound **2**, as can be visualized in the ORTEP drawings (Figs. 2–5). The optimized geometries of the six compounds gave also molecular propellers, but in this case all of them have C_3 symmetry, therefore the three OAr groups of each structure were equivalent among them.

The analysis of all the O–P–O bond angles found for the crystalline compounds **2–5** (Table 4), reveals that in most of them this angle is of around 100°, only O1–P–O2 in compound **2** is considerably more opened [106.23° (15)]. The averaged O–P–O bond angles found for compounds **2**, **3**, **4** and **5** are 102.66, 100.16, 100.09 and 99.57°, respectively. As can be observed, it is clear that this parameter reaches its greater value when the *para* substituent at the aromatic ring is an ER group and the smallest one when X is an EW group. In addition, the compounds **3** and **4** have almost the same averaged O–P–O bond angle, and it is interesting that the chemical shifts of both compounds have very close values (53.71 ppm for **3** and 53.81 ppm for **4**).

A similar behavior was found from the analysis of calculated O–P–O bond angles (Table 5). Since the geometry optimization of the six compounds gave in all the cases the same conformation, important changes between the averaged O–P–O bond angles of the six arylphosphorothionates were not found. However, as the EW power of the *para* substituent decreases, the averaged O–P–O angle is opened very slightly, from 100.40 degrees in compound **6** to 100.78 in compound **1**. A plot of the averaged O–P–O angle against ^{31}P chemical shift gave an acceptable correlation (the correlation coefficient was 0.947) (Fig. 8), showing that even a minimum difference in the OPO angle might also be correlated succesfully to the shielding effect observed for this kind of compound.

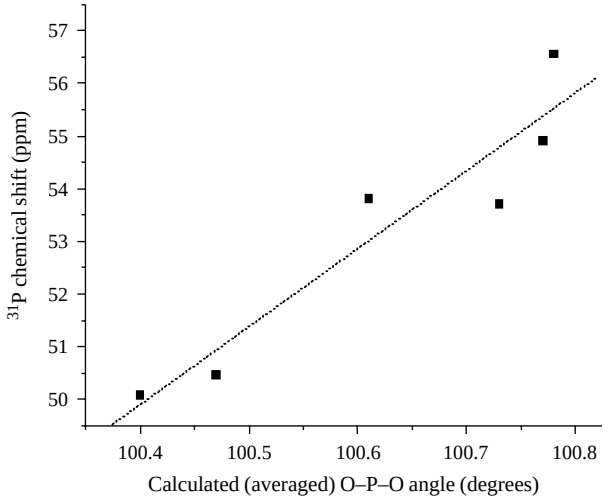


Figure 8. Relationship between the calculated O–P–O bond angle and the experimental ^{31}P NMR chemical shift for arylphosphorothionates **1–6** (correlation coefficient = 0.946, slope = 14.80).

On the other hand, although significant variations of the P═S bond length were not observed among the X-ray diffraction data of compounds **2**, **3** and **4** [the difference between the bond lengths are less than 2.7 σ(>99% confidence level[12])], when the *para* substituent is a strong EW group (X = CN in compound **5**) the P═S bond length become significantly shorter [1.8888(8) Å in **5** against 1.8987(16), 1.8981(12) and 1.8968(10) in **2**, **3** and **4**, respectively (see Table 3)]. This result supports the idea that a participation of sulfur in the transference of the charge density towards the phosphorus atom exists in the arylphosphorothionates when EW substituents are bonded to them. RHF calculations reinforce the experimental observation, the calculated P═S bond length (Table 5) is distributed

between 1.918 (compounds **1** and **2**) and 1.909 Å, (compound **6**). In addition, the linear regression of calculated P═S bond length against the experimental δ^{31}P chemical shift correlates satisfactorily, as can be visualized from Figure 9 (coefficient of correlation was 0.9634). The result suggests an increasing thiophosphoryl bond order as δ^{31}P values go upfield, which is in agreement with an effect of back-bonding from sulfur to phosphorus atom.[3a,e]

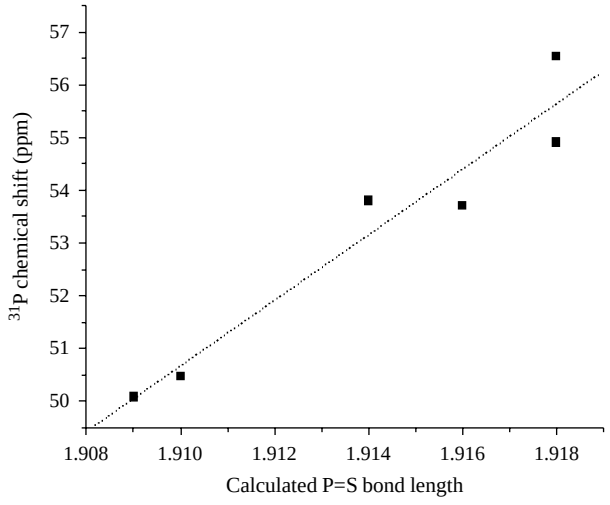
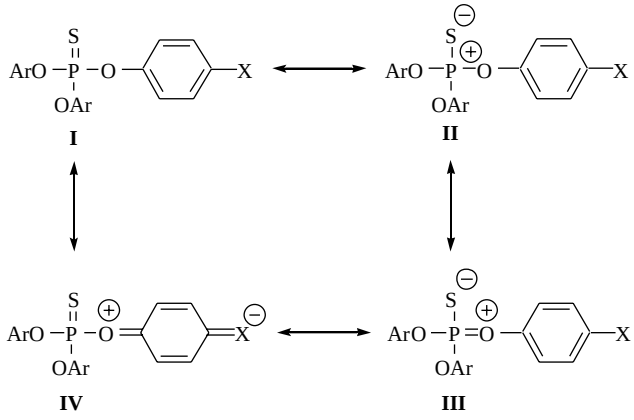


Figure 9. Relationship between the calculated P═S bond length and the experimental ^{31}P NMR chemical shift for arylphosphorothionates **1–6** (correlation coefficient = 0.964, slope = 621.70).

Nevertheless those significant differences among the averaged P–O bond lengths of compounds **2**, **3**, **4** and **5** (1.576, 1.575, 1.585 and 1.579 Å, respectively) were not observed in solid state. The fact that P–O1 bond length is shorter than P–O2 and P–O3 in compounds **3**, **4** and **5** [1.567(2) against 1.579(2) and 1.578(2) Å in **3**, 1.579 (2) against 1.5862 (19) and 1.5908 (18) Å in **4** and 1.5704 (16) against 1.5869 (17) and 1.5811 (16) Å in **5**] is consistent with the presence of at least a n_{π}O-$\sigma^*_{P\text{-}OAr}$ or n_{π}O-$\sigma^*_{P=S}$ interaction per molecule in solid state, as it has been proposed for analogous phosphorus containing compounds.[13] The changes in the calculated geometrical parameters of these systems also could be related to the existence of stereoelectronic interactions[9a,b] of the n_{π}O-$\sigma^*_{P=S}$ type, for example, since an increase of the ER power of the *para* substituent at the aromatic rings produces a slight shortening of the calculated averaged P–O bond lengths (from 1.584 Å in compounds **1–3** to 1.586 Å in compound **6**) accompanied by a lengthening of the P═S bond distance, as it was discussed above. However, a plot of the calculated averaged P–O bond lengths against the experimental δ^{31}P did not give a linear relationship.

The electronic effect of the *para* substituent (X) on arylphosphorothionates **1–6** can be summarized by the canonical structures **I–IV** (Scheme 2). Natural charges evaluated to the RHF 6-31G** level of theory (Table 6) are well described by these resonance structures. The charges at S are ca. −0.7 and those at P are ca. +2.4, whereas the calculated charges at O are ca. −0.9. These data are in agreement with the theoretical data reported before by Kuivalainen in the study of a series of *O*,*O*-dialkyl *O*-aryl phosphorothionates.[3a] The presence of EW groups on the aromatic rings of arylphosphorothionates lead to a decrease of the positive charge on phosphorus, accompanied also by a decreasing of the net charge on sulfur and oxygen atoms and the shortening of the P═S bond length, whereas the ER groups produce a slight shortening of the P–O bond length. As can be assumed, structures **I** and **IV** must be favored over the other two when X is an EW group, whereas **II** and **III** should have important contributions when X is an ER group.



Scheme 2.

The plot of natural charges on phosphorus and sulfur atoms against experimental ^{31}P chemical shift of compounds **1–6** gave good correlation coefficients (0.955 and 0.954, respectively) (Figs. 10 and 11), however an analogous plot of natural charges at oxygen atoms against δ^{31}P was not satisfactory (the correlation coefficient was 0.7), which suggests a minor participation of the aryl oxygen atoms to the 'abnormal' shielding of the ^{31}P chemical shift observed experimentally.

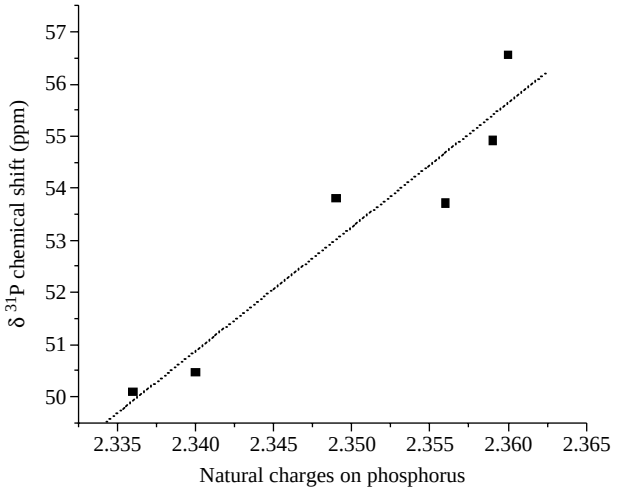


Figure 10. Relationship between the natural charge on phosphorus atom and the experimental ^{31}P NMR chemical shift for arylphosphorothionates **1–6** (correlation coefficient = 0.955, slope = 238.16).

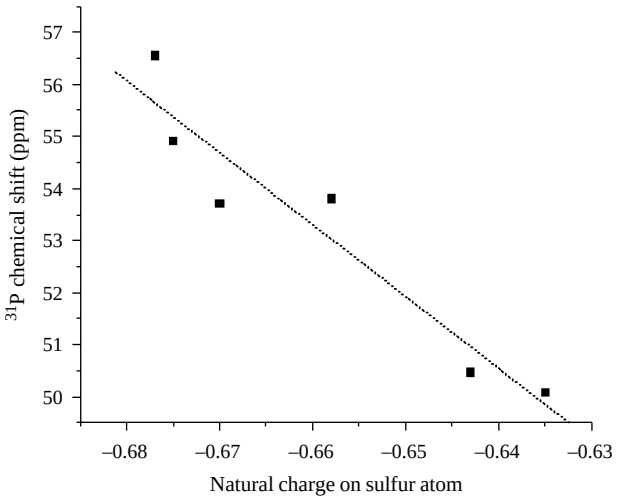


Figure 11. Relationship between the natural charge on sulfur atom and the experimental ^{31}P NMR chemical shift for arylphosphorothionates **1–6** (correlation coefficient = 0.954, slope = −137.89).

4. Conclusion

The ^{31}P chemical shifts of a series of *p*-X-arylphosphorothionates **1–6** are analyzed in terms of the electronic effect of the *p*-substituent. As the electronwithdrawing (EW) power of the X substituent increases, an 'abnormal' shielding on the ^{31}P NMR signal is observed, which is expressed in the reversible correlation between the Hammett constant σ_p and δ^{31}P. The detailed analyses of the experimental and theoretical structural parameters of the six arylphosphorothionates, obtained through X-ray diffraction techniques and ab initio calculations showed that the features associated with the shielding of the ^{31}P NMR signal of the arylphosphorothionates are the decreasing of the O–P–O averaged angle and the shortening of the P═S bond length. An increase of the thiophosphoryl bond order as a result of the back-bonding effect from sulfur toward the phosphorus atom is observed for arylphosphorothionate substituted with EW groups. Additionally, the changes observed in the experimental and theoretical structural parameters could be related to the presence of stereoelectronic interactions of the type n_πO-$\sigma^*_{P=S}$, and n_πO-$\sigma^*_{P\text{-}OAr}$, as has been proposed before for analogous systems. Further efforts in the theoretical study of this kind of compound are currently underway, and will be reported soon.

5. Experimental

Melting points are uncorrected. The ^{1}H, ^{13}C and ^{31}P spectra were recorded on a Bruker AVANCE 400 spectrometer operating at 400 MHz at a probe temperature of 25.0 °C. Bruker MSL-200 spectrometer operating at 50.32 MHz and Varian Mercury Plus (300 MHz) spectrometers, respectively, using deuterated $CDCl_3$ as solvent. Phosphorus NMR spectra are reported in ppm downfield (+) from 85% H_3PO_4 used as external standard. Mass spectra were measured on Varian Saturn Star 3400 CX spectrometer using electron impact (El) at 70 eV. The reactions were performed under an atmosphere of nitrogen in oven-dried glassware. Solvents and solutions were transferred by syringe-septum and cannula techniques. THF and toluene were of reagent grade and were dried and distilled immediately before use from sodium/benzophenone. Triethylamine was dried and distilled from $LiAlH_4$. Products were purified by flash column chromatography on silica gel 230–400 mesh using as eluent mixtures of AcOEt/hexanes. Yields are given for isolated products. AcOEt/hexanes or CH_2Cl_2/hexanes mixtures were used for recrystallization of **2–5**. Crystallographic work was performed in the difractometers Enraf-Nonius CAD-4 and Kappa CCDC. Data collection: CAD-4[14] and Kappa CCDC Software.[15] Cell refinement: CAD-4 and Kappa CCDC Software. Data reduction WinGX.[16] The structures were resolved by direct methods with SHELXS97[17] and refined with SHELXL97.[18] Molecular graphics: Diamond[19] and dihedral angles: PARST 95.[20] Crystallographic Data Center and the deposition numbers are: CCDC 284418 for compound **2**, CCDC 284416 for **3**, CCDC 284415 for compound **4** and CCDC 284417 for **5**. Ab initio calculations were performed employing the Gaussian 98 program.[21]

5.1. General procedure for the synthesis of compounds 1–6

In a three-necked 500 mL flask, fitted with dropping funnel, stir bar and rubber septa, were placed 34.2 mmol of *p*-X phenol, 5.28 mL of Et_3N (37.9 mmol) and 200 mL of dry THF. Then 1.57 g of PCl_3 (11.4 mmol) were added via syringe. The reaction mixture was stirred at room temperature for 24 h then, the resultant triethylammonium chloride was filtered off through a filter tipped cannula. The solid was washed two times with 15 mL of dry THF collecting the filtrate in a round-bottomed flask. The solvent was removed under reduced pressure to dryness to give the intermediate *p*-X-phenyl phosphite in ~80% yield as a thick oil, which was used in subsequent reaction without further purification.

In a round-bottomed 100 mL flask, fitted with a reflux condenser, stir bar and rubber septa, were placed 0.36 g (11.4 mmol) of elemental sulfur. A solution of the *p*-X-phenylphosphite (11.4 mmol) in dry toluene (80 mL) was added to the flask and the resulting suspension was stirred under reflux in an oil bath for 24 h. After cooling, the unreacted sulfur was filtered off and the suspension was concentrated under vaccum. The residue was washed with an aqueous solution of 10% sodium bicarbonate. The product was extracted with methylene chloride and the organic layer dried over sodium sulfate. The solvent was removed in a rotary evaporator and the oily residue was chromatographed on silica gel using hexanes/ethyl acetate as eluent.

5.1.1. Tris(*O*-4-methoxyphenyl)phosphorothionate (1).[8f]

According to the general procedure described above, 4.25 g (34.2 mmol) of *p*-MeO-phenol was treated with 1.57 g (11.4 mmol) of PCl_3 and 4.7 mL (34.2 mmol) of Et_3N. The resulting 3.64 g of phosphite (9.1 mmol) were reacted with 0.3 g (9.1 mmol) of elemental sulfur. Flash chromatography (hexanes/ethyl acetate 80:20) gave 3.1 g (80%) of a colorless oil. ^{1}H NMR δ 3.79 (s, 9H), 6.86 (d, $^3J_{HH}$ = 9.0 Hz, 6H), 7.13 (dd, $^3J_{HH}$ = 9.0 Hz, $^4J_{HP}$ = 1.7 Hz, 6H), RMN ^{13}C δ 55.48 (s, O*C*H$_3$), 114.57 (s, C$_m$), 121.76 (d,

$^3J_{CP}$=3.9 Hz, C_o), 144.24 (d, $^2J_{CP}$=8.1 Hz, C_i), 157.09 (s, C_p), RMN ^{31}P δ 56.56; MS (EI) *m/z* 432, 401, 309, 123. Anal. Calcd for $C_{21}H_{21}O_6PS$: C 58.33, H 4.89, S 7.42. Found: C 58.80, H 4.68, S 7.14.

5.1.2. Tris(*O*-4-methylphenyl)phosphorothionate (2).[8a,8d] According to the general procedure described above, 3.53 g (34.2 mmol) of *p*-Me-phenol were treated with 1.57 g (11.4 mmol) of PCl_3 and 4.7 mL (34.2 mmol) of Et_3N. The resulting 3.53 g (10.0 mmol) of phosphite were reacted with 0.3 g (10.0 mmol) of elemental sulfur. Flash chromatography (hexanes/ethyl acetate 95:5) gave 3.27 g (85%) of a white solid. Recrystallization from a mixture hexanes–$CHCl_3$ (90/10) gave colorless crystals (mp 89–90 °C). ^{1}H NMR δ 2.26 (s, 9H), 7.03 (dd, $^3J_{HH}$=8.7 Hz, $^4J_{HP}$=1.2 Hz, 6H), 7.07 (d, $^3J_{HH}$=8.7 Hz, 6H), RMN ^{13}C δ 20.75 (s, CH_3), 148.55 (d, $^2J_{CP}$=8.3 Hz, C_i), 135.20 (s, C_p), 120.44 (d, $^3J_{CP}$=4.4 Hz, C_o), 130.09 (s, C_m), RMN ^{31}P δ 54.92. MS (EI) *m/z* 384 (100), 293, 277, 107, 91. Anal. Calcd for $C_{21}H_{21}O_3PS$: C 65.61, H 5.51, S 8.34. Found: C 65.15, H 5.03, S 8.41.

5.1.3. Tris(*O*-phenyl)phosphorothionate (3).[5,8d] According to the general procedure described above, 3.2 g (34.2 mmol) of phenol were treated with 1.57 g (11.4 mmol) of PCl_3 and 4.7 mL (34.2 mmol) of Et_3N. The resulting 2.83 g (9.1 mmol) of phosphite were reacted with 0.3 g (9.1 mmol) of elemental sulfur. Flash chromatography (hexanes/ethyl acetate 98:2) gave 2.74 g (88%) of colorless needles. Recrystallization from a mixture of hexanes–ethyl acetate (80/20) gave colorless crystals (mp 53–54 °C). ^{1}H NMR δ 7.14 (m, 3H), 7.16 (d, $^3J_{HH}$=8.3 Hz, 6H), 7.29 (d, $^3J_{HH}$=8.3 Hz, 6H), ^{13}C NMR δ 121.13 (d, $^3J_{CP}$=4.4 Hz, C_o), 125.68 (s, C_p), 129.67 (s, C_m), 150.69 (d, $^2J_{CP}$=7.7 Hz, C_i), ^{31}P NMR δ 53.71. MS (EI) *m/z* 342 (100), 265, 249, 93. Anal. Calcd for $C_{18}H_{15}O_3PS$: C 63.15, H 4.42, S 9.37. Found: C 62.94, H 3.89, S 9.68.

5.1.4. Tris(*O*-4-chlorophenyl)phosphorothionate (4).[8a] According to the general procedure described above, 4.39 g (34.2 mmol) of *p*-chlorophenol were treated with 1.57 g (11.4 mmol) of PCl_3 and 4.7 mL (34.2 mmol) of Et_3N. The resulting 3.6 g (8.7 mmol) of phosphite were reacted with 0.27 g (8.7 mmol) of elemental sulfur. Flash chromatography (hexanes/ethyl acetate 80:20) gave 3.87 g (76%) of colorless crystals (mp 80–82 °C). ^{1}H NMR δ 7.15 (dd, $^3J_{HH}$=9.1 Hz, $^4J_{HP}$=2.0 Hz, 6H), 7.34 (dd, $^3J_{HH}$=9.1 Hz, $^5J_{HP}$=0.8 Hz, 6H), ^{13}C NMR δ 122.3 (d, $^2J_{CP}$=4.9 Hz, C_o), 129.7 (d, $^2J_{CP}$=1.7 Hz, C_m), 131.4 (s, C_p), 148.6 (d, $^2J_{CP}$=7.7 Hz, C_i), ^{31}P NMR δ 53.81. MS (EI) *m/z* 445, 333, 127. Anal. Calcd for $C_{18}H_{12}O_3PSCl_3$: C 48.51, H 2.71, S 7.19. Found: C 48.67, H 2.30, S 7.45.

5.1.5. Tris(*O*-4-cyanophenyl)phosphorothionate (5).[8c] According to the general procedure described above, 4.06 g (34.2 mmol) of *p*-cyanophenol were treated with 1.57 g (11.4 mmol) of PCl_3 and 4.7 mL (34.2 mmol) of Et_3N. The resulting 3.86 g (10.0 mmol) of phosphite were reacted with 0.32 g (10.0 mmol) of elemental sulfur. Flash chromatography (hexanes/ethyl acetate 80:20) gave 3.27 g (85%) of colorless needles. Recrystallization from a mixture of hexanes–ethyl acetate (80/20) gave colorless crystals (mp 155–156 °C). ^{1}H NMR δ 7.34 (dd, $^3J_{HH}$=8.6 Hz, $^4J_{HP}$=1.4 Hz, 6H), 7.73 (d, $^3J_{HH}$=8.6 Hz, 6H), ^{13}C NMR δ 110.37 (s, C_p), 117.58 (s, *C*N), 122.05 (d, $^3J_{CP}$=5.2 Hz, C_o), 134.25 (s, C_m), 152.99 (d, $^2J_{CP}$=7.4 Hz, C_i), ^{31}P NMR δ 50.47. MS (EI) *m/z* 417, 315, 299, 118, 102. Anal. Calcd for $C_{21}H_{12}N_3O_3PS$: N 10.07, C 60.43, H 2.90, S 7.68. Found: N 10.19, C 60.80, H 2.43, S 8.02.

5.1.6. Tris(*O*-4-nitrophenyl)phosphorothionate (6).[8a,8e] According to the general procedure described above, 4.06 g (34.2 mmol) of *p*-nitrophenol were treated with 1.57 g (11.4 mmol) of PCl_3 and 4.7 mL (34.2 mmol) of Et_3N. The resulting 2.57 g of phosphite were reacted with 0.18 g (5.7 mmol) of elemental sulfur. Flash chromatography (hexanes/ethyl acetate 60:40) gave 0.81 g (30%) of colorless needles. Recrystallization from a mixture hexanes–ethyl acetate (80/20) gave ligth yellow crystals (mp 175.0—175.1 °C) ^{1}H NMR δ 7.43 (dd, $^3J_{HH}$=9.0 Hz, $^4J_{HP}$=1.5 Hz, 6H), 8.35 (d, $^3J_{HH}$=9.0 Hz, 6H), ^{13}C NMR δ 121.83 (d, $^3J_{CP}$=4.3 Hz, C_o), 125.86 (s, C_m), δ 145.80 (s, C_p), 154.30 (d, $^2J_{CP}$=7.4 Hz, C_i), ^{31}P NMR δ 50.09. MS (EI) *m/z* 477, 355, 339, 138, 122. Anal. Calcd for $C_{18}H_{12}N_3O_9PS$: N 8.80, C 45.29, H 2.53, S 6.72. Found: N 8.74, C 45.38, H 2.11, S 6.95.

6. Supplementary material

Crystallographic data for the structural analysis have been deposited at the Cambridge Crystallographic Data Centre, CCDC.

Acknowledgements

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References and notes

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Regio- and stereocontrolled synthesis and conformational analysis of benzimidazole nucleosides

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Abstract—Regio- and stereocontrolled synthesis and conformational analysis of a series of benzimidazole nucleosides were achieved. A simple method by ^{1}H NMR 1D NOE experiment was developed for estimation of *syn* or *anti* conformation of benzimidazole nucleosides. Substituents at C2 of benzimidazole demonstrated to play a key role both in the unexpected regioselectivity of the glycosidic reaction and in the conformation distributions of the final products.

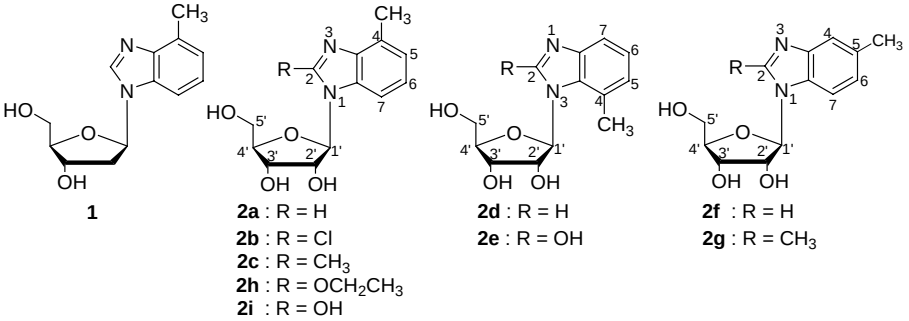
1. Introduction

Benzimidazole nucleosides, as a component of naturally occurring vitamin B12,[1] have shown considerable biological activities recently. For example, 1-[2-deoxy-β-D-erythro-pentofuanosyl]-4-methyl-1*H*-benzimidazole (**1**, Scheme 1) reported by Kool et al. was a close mimicry of 2′-deoxy-adenosine and was shown to be selectively inserted into DNA pairing with 2′-deoxy-thymidine.[2] A great number of benzimidazole nucleosides have been reported by Townsend et al. to show significant antiviral activities.[3] Thus, the unique structural features and pharmaceutical activities of benzimidazole nucleosides have rendered them attractive targets for development of efficient synthesis and conformational analysis. As 8-substituted purine nucleosides have been proved to be an effective class of antitumor reagents,[4] we were interested in their isosteres—2-substituted-4-methyl-benzimidazole nucleosides. Because the 2-substituted benzimidazole nucleosides (IUPAC numbering) may be considered analogous to the 8-substituted purine nucleosides (purine numbering), conformational analysis of these newly synthesized benzimidazole nucleosides may provide insights into the stereoelectronic factors that regulate the conformation of biologically important purine nucleosides.

2. Results and discussion

2.1. Synthesis

In our previous communication,[5] compound **2a–e** were synthesized regioselectively as mimicries of adenosine and the anticancer drug—8-Cl–adenosine. Under appropriate reaction conditions, either N1-isomer (**2a**) or N3-isomer (**2d**) of the benzimidazole nucleoside could be obtained selectively by reaction between 4-methyl-1*H*-benzimidazole and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose



Scheme 1.

Keywords: Nucleosides; Regioselectivity; Glycosylation; Stereoselectivity; Conformation.
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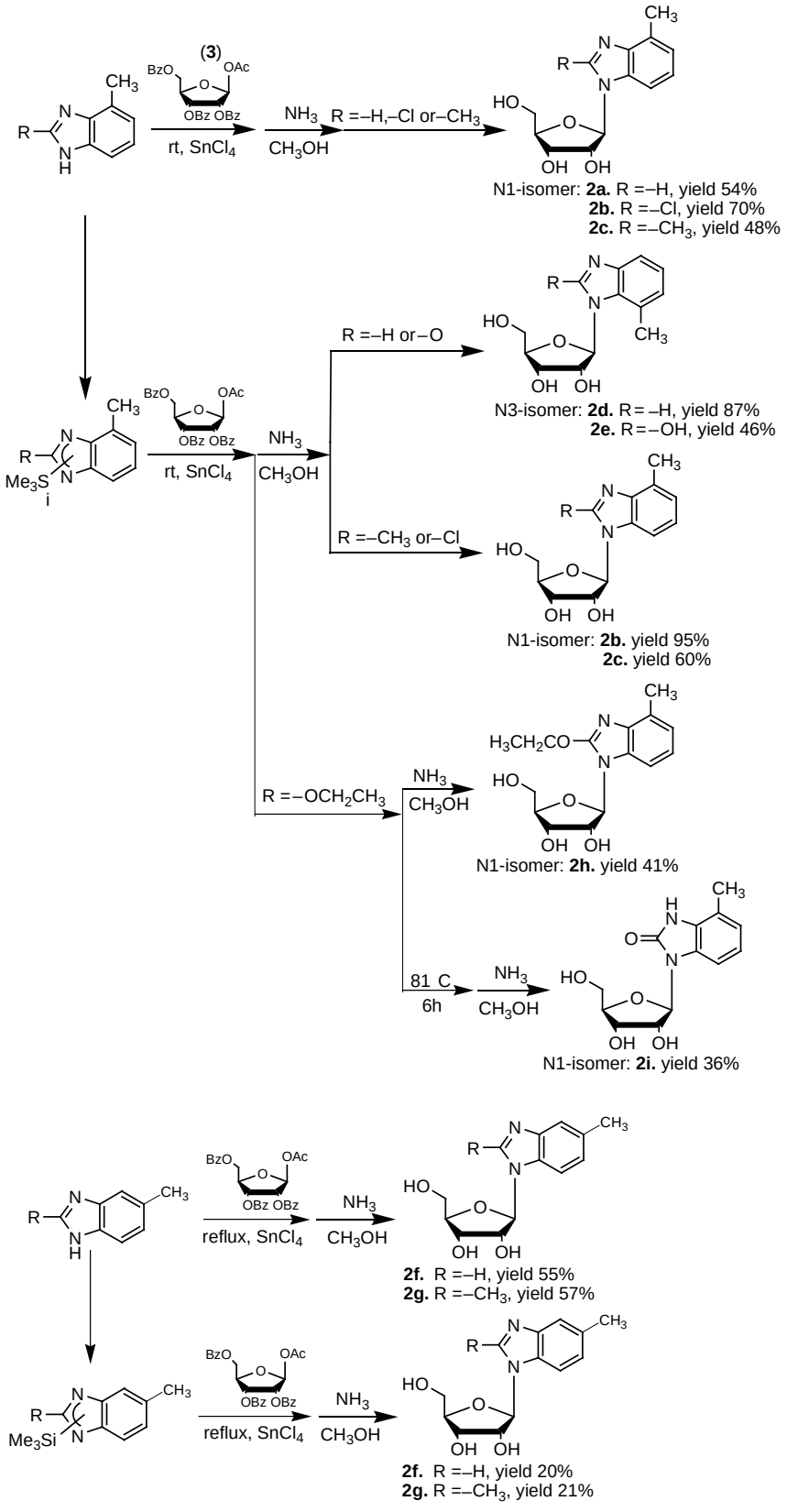
(**3**, Scheme 2). However, for the glycosidation between silylated 4-methyl-1*H*-benzimidazol-2-one and **3**, only N3-isomer (**2e**) was produced under acid-catalyzed conditions and no N1-isomer (**2i**) could be isolated by reaction between **3** and silylated or unsilylated 4-methyl-1*H*-benzimidazol-2-one under various conditions. We reasoned that the failure might be caused by the side reaction of the relatively active carbonyl group in 4-methyl-1*H*-benzimidazol-2-one.



Scheme 2. Regioselective synthesis of benzimidazole nucleosides.

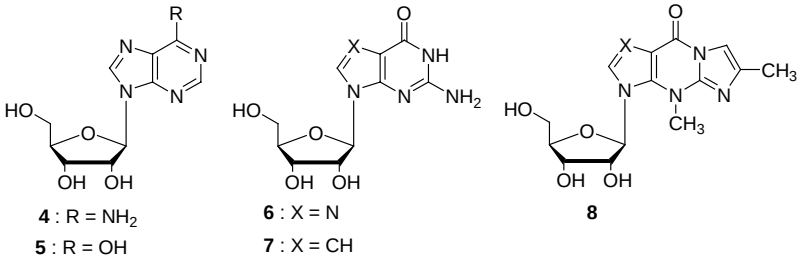
Accordingly, the 2-*O*-protected base (2-ethoxy-4-methyl-1*H*-benzimidazole) was silylated and tested for the glycosidation with **3**. To our pleasure, the reaction proceeded smoothly via N1-glycosidation, and the CH_3CH_2–O bond at 2-position of the product could be easily cleaved by heating the acid-containing reaction solution. N1-isomer **2h** was obtained after deprotection in 41% overall yield from **3** and silylated 2-ethoxy-4-methyl-1*H*-benzimidazole in the presence of $SnCl_4$ in acetonitrile at room temperature for 3 h, and N1-isomer **2i** was also obtained from **3** and silylated 2-ethoxy-4-methyl-1*H*-benzimidazole in presence of $SnCl_4$ in acetonitrile at room temperature for 3 h followed by reflux for further 6 h and deprotection in 36% overall yield (Scheme 2). Thus, the CH_3CH_2–O bond in 2-ethoxy-4-methyl-1*H*-benzimidazole moiety of the nucleoside showed a temperature-dependent cleavage by $SnCl_4$. Compounds **2f** and **2g** were synthesized as analogs of the 5-methyl-benzimidazole-α-riboside, which was isolated from the degradation of vitamin B12.[1b] In the preparation of some 4-methyl-benzimidazole nucleosides (**2b–e** and **2h–i**), silylation of the bases proved to be an effective step to improve the reaction yields and selectivities, however, in the preparation of 5-methyl-benzimidazole nucleosides (**2f–g**), unsilylated bases proved to be more effective than silylated base in the reaction (Scheme 2).

2.2. Conformational analysis

As activities of nucleosides and nucleotides might be correlated with their preferred structure in solution, the evaluation of their conformational parameters in solution is of key importance in elucidating the relevant mechanism of a biological process involving them. Concerning the overall shape of a nucleoside, the most important conformational parameters are the torsion angle around the glycosidic bond (χ) as well as the sugar puckering, which are interdependent to each other.[6] Considerable attention has been devoted towards understanding the glycosidic conformation of nucleosides, and the 1D ^{1}H Nuclear Overhauser enhancement (NOE) difference spectroscopy has been employed by Seela et al. as an efficient and straightforward approach to estimate qualitative or semiquantitative information about the preferred conformation of nucleosides in solution,[7] and they established a semiquantitative calibration graph method for estimation of *syn–anti* conformer populations of a variety of regular or modified nucleosides by comparison of their 1D ^{1}H NOE values (at H1′, H2′, and H3′ when H8 was irradiated) with the yardstick NOE values of the conformationally fixed model nucleosides N^3,5′-anhydroisoguanosine (*syn*) and 2′-deoxywyosine (*anti*). The results were applied as calibration benchmark in our conformational analysis of benzimidazole nucleosides. However, in most of the newly synthesized compounds (**2a–i**), H2 (IUPAC numbering, corresponding to H8 of purine nucleosides in purine numbering) was substituted by other groups, thus rendering them not to be amenable to the conformational analysis using the same method of Seela et al. by irradiating H2.[7] For these compounds, we took advantage of H7 in benzimidazole nucleosides, which does not exist in purine nucleosides, to develop a practical method for analysis of conformation of benzimidazole nucleosides. Molecular model studies of these compounds (Hyperchem 7.5) showed that in the *anti* conformation, H7 was much closer to H1′ than H2′ and H3′, whereas when rotated to *syn* conformation, H7 was much closer to H2′ than H1′ and H7 was closer to H3′ than in *anti* form. Therefore, when H7 was irradiated, the value x-H7 = η(H1′)/[η(H2′) + η(H3′)] (η is the enhancement at a certain hydrogen) can provide us a qualitative information on the *syn–anti* conformational distributions: the larger the x-H7 value, the more conformer population of *anti*. When H2 of the compounds **2a**, **2d** or **2f** was irradiated, the value x-H2 = η(H1′)/[η(H2′) + η(H3′)] can also provide us with qualitative information of the corresponding *syn–anti* conformation equilibria: the smaller the x-H2 value, the more conformer population of *anti* form.

Because H2 of benzimidazole nucleoside (IUPAC numbering) is equivalent to H8 of purine nucleosides (purine numbering), the x-H2 values of the reference compounds **8**, **7**, **6**, **5** and **4** (Scheme 3) were calculated using the literature NOE data and the results were given in Table 1 along with conformer populations estimated by Seela's method.[7] A calibration curve for estimation of *syn* and *anti* conformer populations of the β-nucleosides using their x-H2 values was easily established by simply linking the data points of **8**, **7**, **6**, **5** and **4** (Fig. 1), and the linearity was quite good within the two regions of **8–6** and **6–4**. Using this curve, the *anti* conformer populations of **2d**, **2a** and **2f** were estimated to be 98, 59 and 55%, respectively, based on their corresponding x-H2 values. By comparing the NOE values of **2e** and **2d** when 4-CH_3 is irradiated (Table 2), **2e** was concluded to have a larger *anti* conformer population than **2d**, between 98 and 100% *anti* (Molecular model studies showed that in the *anti* conformation, 4-CH_3 is much closer to H1′ than H2′, whereas when rotated to *syn* conformation, 4-CH_3 was much closer to H2′ than H1′). As seen from Table 2, x-H7 values of **2b**, **2c**, **2g**, **2h** and **2i** were extremely small comparing to the x-H7 value of **2f**, which adopted a 55% *anti* conformation. Therefore, **2b**, **2c**, **2g**, **2h** and **2i** were concluded to adopt predominantly *syn* conformations.

In order to obtain a semiquantitative estimation of *syn–anti* conformation for **2b**, **2c**, **2g**, **2h** and **2i** using the results of



Scheme 3. Compound taken from literature[7] as calibrations.

Table 1. Data from literature[7]

Compound	Irradiated	NOE (%)	*x*-H2	*anti* (%)
4	H8	H1′ (6.7), H2′ (3.2), H3′ (0.8)	1.68	40
5	H8	H1′ (4.1), H2′ (4.2), H3′ (1.5)	0.72	65
6	H8	H1′ (3.6), H2′ (5.7), H3′ (1.1)	0.53	70
7	H8	H1′ (2.1), H2′ (7.3), H3′ (1.3)	0.24	86
8	H8	H1′ (0.5), H2′ (7.4), H3′ (2.1)	0.05	100

anti (%) Values were from their analysis results.

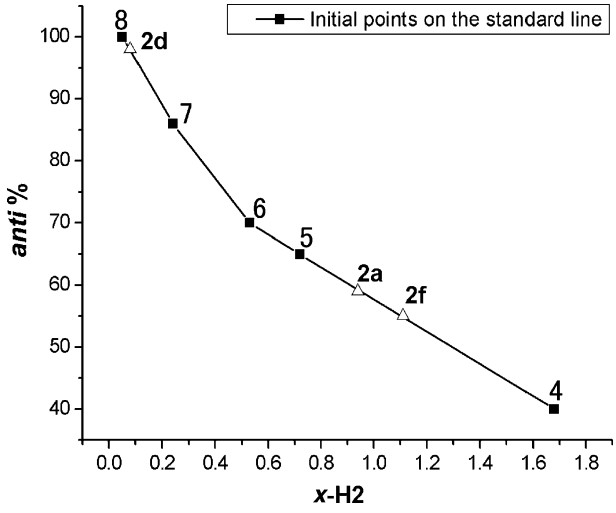


Figure 1. Conformation evaluation of **2d**, **2a** and **2f** on the standard line.

Table 2. ^{1}H 1D NOE data measured in DMSO and the calculated *x* values

Compound	Irradiated	NOE (%)	*x*-H2	*x*-H7
2e	CH_3	H1′ (11.85), H2′ (0.84), H3′ (0.33)		
2d	CH_3	H1′ (10.5), H2′ (1.14)		
2d	H2	H1′ (0.61), H2′ (5.85), H3′ (1.58)	0.08	
2a	H2	H1′ (2.91), H2′ (2.42), H3′ (0.68)	0.94	
2a	H7	H1′ (3.48), H2′ (2.26), H3′ (0.30)		1.36
2f	H2	H1′ (2.10), H2′ (1.57), H3′ (0.33)	1.11	
2f	H7	H1′ (3.54), H2′ (2.48), H3′ (0.30)		1.27
2b	H7	H1′ (1.51), H2′ (6.63), H3′ (0.51)		0.21
2c	H7	H1′ (1.78), H2′ (5.60), H3′ (0.79)		0.28
2g	H7	H1′ (1.05), H2′ (3.73), H3′ (0.73)		0.24
2h	H7	H1′ (1.29), H2′ (3.67), H3′ (0.24)		0.32
2i	H7	H1′ (1.76), H2′ (3.34), H3′ (0.57)		0.45

Seela et al.[7] as calibration, we sought for some type of relationship between the value of *x*-H2 and *x*-H7. As seen from data of **2a** and **2f** in Table 2, when *x*-H2 values increased, *x*-H7 values decreased almost by the same extent. So we hypothesized that *x*-H2 value and *x*-H7 value were added up to a constant: $x\text{-H2}+x\text{-H7}=c$. From the data of **2a** and **2f**, the constant *c* was calculated by average to be 2.34. Although the expression may not be accurate, it was considered to be adequate for a semiquantitative estimation as the final results of the conformational analysis were in good agreement with the experimental data (1D and 2D NOE data, X-ray single crystal diffraction analysis). The *x*-H2 value of **2b**, **2c**, **2g**, **2h** and **2i** were calculated by the expression ($x\text{-H2}+x\text{-H7}=2.34$) and the conformer populations were estimated by inserting the calculated *x*-H2 value listed in Table 3 into the extended calibration curve (Fig. 2).

Table 3. Measured *J* values, calculated *x*-H2 values and conformation analysis results

Compound	*x*-H2	*anti* (%)	$J_{1'2'}$	$J_{3'4'}$	*S* (%)
2b	2.13	28	7.5	2.4	76
2c	2.06	30	7.5	2.7	74
2g	2.10	29	7.8	2.4	76
2h	2.02	31	6.9	3.0	70
2i	1.89	34	6.9	2.4	74
2a	0.94	59	6.3	3.3	66
2f	1.11	55	6.0	2.7	69
2d	0.08	98	5.1	3.9	67
2e	—	98–100	5.7	4.2	56

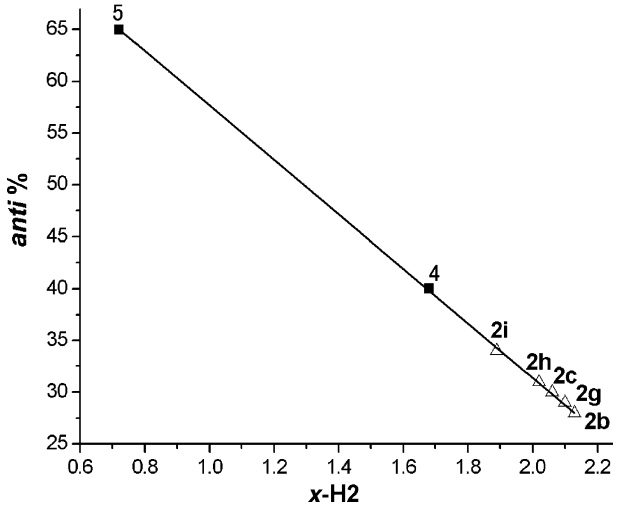


Figure 2. Conformation estimation of **2b**, **2c**, **2g**, **2h** and **2i** on the standard line.

As shown in Table 3, N3-isomers (**2d**, **2e**) had extremely high *anti* conformer populations, while the glycosidic orientations of N1-isomer depended on the 2-substituents. When the 2-positions of N1-isomers were not substituted, the nucleosides (**2a**, **2f**) adopted preferably *anti* conformation. However, when the 2-positions of N1-isomers were substituted (by groups bigger than –H), the nucleosides (**2b**, **2c**, **2g**, **2h**, **2i**) adopted primarily *syn* conformation. Thus, the blockage of 4-methyl and 2-substituents of the nucleosides played a key role in their conformation distributions.

The sugar puckering of **2a–i** in DMSO solution were determined by the literature method.[8] The coupling constants were measured with assist of NMR double-resonance experiment (Table 3) and *S*% was calculated using the following expression: $S\%=100\,J_{1'2'}/(J_{1'2'}+J_{3'4'})$. As seen from the results listed in Table 3, all of the nine nucleosides adopted primarily *S* type sugar puckering. Substituents at 2-position seemed to affect the sugar puckering of the nucleosides greatly. The nucleosides with substituents (bigger than –H) at 2-position (**2b**, **2c**, **2g**, **2h**, **2i**) generally had more *S* conformer population than the nucleosides without substituents at 2-position (**2a**, **2d**, **2f**). However, there was an exception of **2e**, which had the lowest *S* conformer population.

Although conformation of nucleosides in solution is generally considered to be of more importance, X-ray

crystal structure of nucleosides always provide the most accurate and reliable information of their solid-state structure and the two types of data can effectively supplement each other to furnish an integrated structure picture of the investigated compound. In the experiment compounds **2e**[9] and **2h** were obtained as single crystals and their solid-state structures were elucidated by X-ray crystallographic analyses.

The crystal structure of **2e** was showed in Figure 3 with the atom-labeling scheme. In the sugar ring, atom C10 was displaced by 0.538 Å on the same side of the C9/O2/C12/C11 plane as atom C13, suggesting that the sugar ring was in a C2′-*endo* envelope (*S*) conformation. The glycosidic torsion angle χ=O2–C9–N2–C1 was 69.8°, suggested that the glycosidic bond rotation was *anti*. The formation of hydrogen bond C10–H10···O1 (equivalent to C2′–H2′···O2 in normal numbering system) was consistent with the observation that H2′ in **2e** showed an extraordinarily high chemical shift (4.98) of ^{1}H NMR spectra in DMSO solution.[10] The existence of this hydrogen bond confirmed the *anti* glycosidic orientation of compound **2e** in DMSO solution, consistent with the conformational analysis result mentioned above. The conformation of the C5′–O5′ bond around the C4′–C5′ bond was *gauche–gauche*, the dihedral angles O5–C13–C12–O2 and O5–C13–C12–C11 being −70.0 and 49.0°, respectively. It was also evident from the crystal structure data that the benzimidazole moiety of **2e** existed in the ketonic form rather than the enol form (C1–O1 bond length is 1.232 Å).

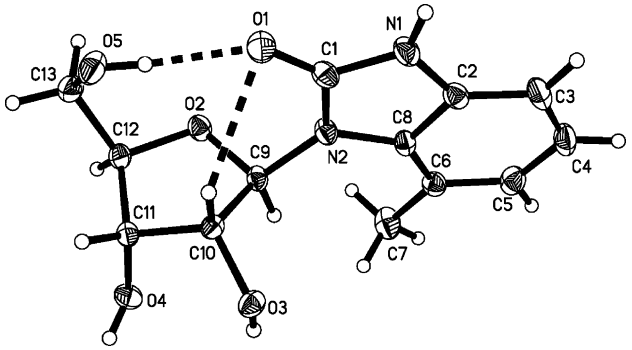


Figure 3. The structure of **2e**, showing 30% probability displacement ellipsoids and the atom-labeling scheme. Hydrogen bonds were shown as dashed lines.

Compound **2h** crystallized with 1 equiv of water included. A perspective view of **2h** with the atom-labelling scheme was shown in Figure 4. In the furanose ring, the atom C2 and C3 were displaced by 0.586 and 0.867 Å, respectively, on the same side of the C1/O1/C4 plane as the C5 atom. Therefore, the furanose ring was in neither envelope conformation nor twist conformation but in a nontypical *N* conformation. The glycosidic torsion angle χ= O1–C1–N1–C6 was 138.2°, suggesting a *syn* glycosidic orientation. Thus, compound **2h** exibited similar glycosidic orientation in crystal state and in DMSO solution. The torsion angles O4–C5–C4–O1 and O4–C5–C4–C3 were

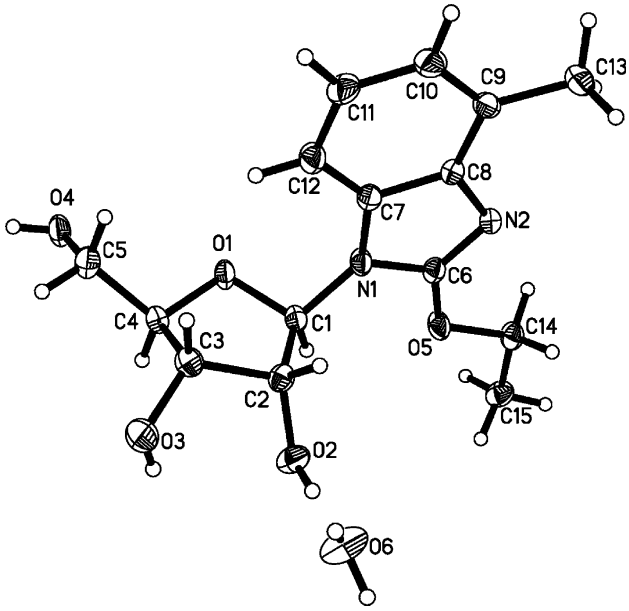
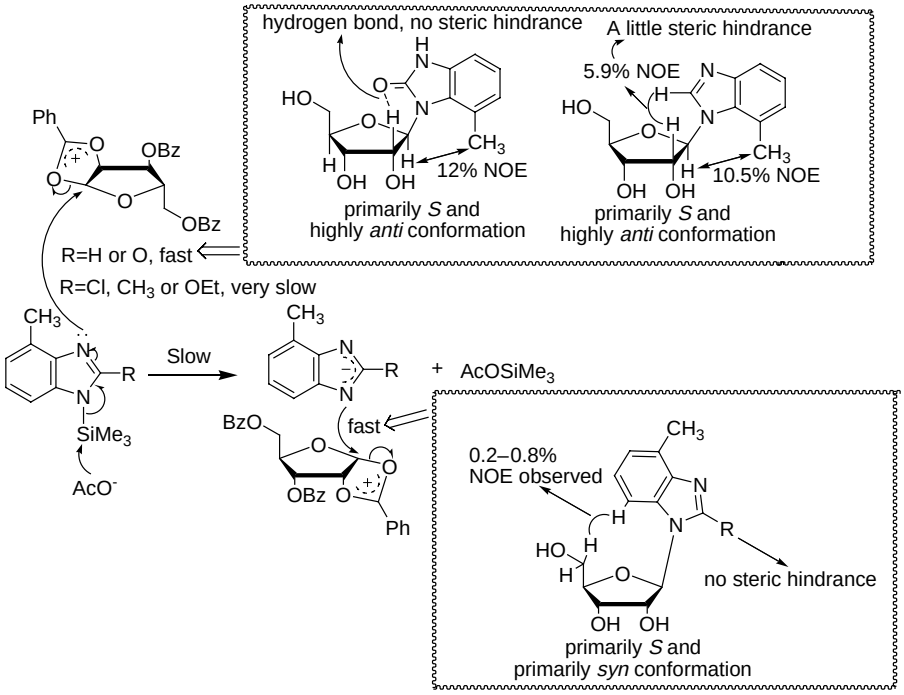


Figure 4. The structure of **2h** (with one molecule water), showing 30% probability displacement ellipsoids and the atom-labeling scheme. Hydrogen bonds were shown as dashed lines.

67.8 and −177.1°, respectively, defining the conformation around C4–C5 as *gauche*-trans. No intramolecular hydrogen bond was found in **2h**. Atom O6 of water molecular formed three intermolecular hydrogen bonds, O2–H2···O6, O6–H6B···O2 and O6–H6A···O4. Atom O4 formed two intermolecular hydrogen bonds, O6–H6A···O4 and O4–H4···N2. Atom O2 also formed two intermolecular hydrogen bonds, O2–H2···O6 and O3–H3···O2. These intermolecular O–H···O and O–H···N hydrogen bonds linked the molecules into a three-dimensional network.

The conformational analysis was found helpful for understanding the reaction mechanism. In the previous communication,[5] a plausible mechanism for the unexpected regioselectivity in the synthesis of **2a–e** was proposed, which was further supported by the results of the conformational analysis of **2a–i** (Scheme 4). Since the N3-isomers (**2d**, **2e**) of the products were tightly restricted to a highly *anti* and primarily *S* conformation, a little increase in the size of the 2-substituents may cause great steric repulsion between 2-substituents and H2′, thus making it very difficult for formation of 2-substituted N3-isomers. In contrast, N1-isomers of the products adopted primarily *syn* and *S* conformation, so the 2-substituents could not cause too much steric hindrance. Therefore, N1-isomers were obtained for every 4-methyl-benzimidazole bases, but N3-isomers were obtained only when there were no bulky substituents at the 2-position of 4-methyl-benzimidazole base. For 5-methyl-benzimidazole-nucleosides, no N3-isomer was obtained. One possible explanation for this phenomenon was given as the followings: as an electron-donor substituent, methyl group could activate *ortho*- and *para*-position of the benzene ring and thus activate the substituents at *ortho*- and *para*-position. Therefore, N1 was more reactive than N3 in 5-methyl-benzimidazoles, and N1-isomer was easier to form than N3-isomer for 5-methyl-benzimidazole nucleoside.



Scheme 4. Possible reaction mechanism supported by conformation analysis results.

3. Summary

A series of benzimidazole nucleosides were synthesized with different regioselectivity and β-stereoselectivity. All the selected benzimidazoles exhibited N1-regioselective glycosidation with **3** using the Vorbrüggen procedure[11] except for the silylated 4-methyl-1*H*-benzimidazole and 4-methyl-1*H*-benzimidazol-2-one, which exhibited N3-regioselective glycosidation with **3**. The CH_3CH_2–O bond in 2-ethoxy-4-methyl-1*H*-benzimidazole moiety of the nucleoside showed a temperature-dependent cleavage by $SnCl_4$. Conformations of these newly synthesized nucleosides were analyzed by ^1H NMR spectroscopy in DMSO solution, and the solid-state conformations of **2e** and **2h** were studied by X-ray single crystallography. The N3 isomers of benzimidazole nucleosides (**2d**, **2e**) were in highly *anti* conformation while the N1 isomers exhibited predominantly *syn* conformation when 2-position was substituted (**2b**, **2c**, **2g**, **2h**, **2i**) but exhibited primarily *anti* conformation when 2-position was unsubstituted (**2a**, **2f**). The sugar moieties in all of the benzimidazole nucleoside products were of primarily *S* conformation in DMSO solution. The conformation analysis provided further evidences for the proposed reaction mechanism.

4. Experimental

4.1. General

Melting points were determined with Yanagimoto MP-35 melting point apparatus and uncorrected. The ^1H spetra (1D) were recorded with a Varian Mercury Vx400 and Vx300 spectrometer and the ^1H 1D NOE, ^1H 2D NOE, ^1H double-resonance and ^{13}C spetra were recorded with a Varian Mercury Vx300 spetrometer, both using tetramethylsilane as the internal standard. Coupling constants are given in Hertz. All NMR measurements were performed with 0.1 M DMSO-d_6 solution at 298 K. The Mass spectra were recorded on Thermo Finnigan LCQAdvantage spectrometer in ESI mode, I Spray Voltage 4.8 kV. A Yamaco CHN corder MT-3 apparatus was used for elemental analysis. Optical rotations were determined with WZZ-1 polarimeter made by Shanghai Physico-optical Instrument Factory. X-ray crystallographic analysis was performed on a Bruker SMART 1000 diffractometer.

2-Ethoxy-4-methyl-1*H*-benzimidazole was prepared by similar procedures as described by literature.[12] 5-Methyl-1*H*-benzimidazole and 2,5-dimethyl-1*H*-benzimidazole were purchased from Acros and used without further purification. Silylation of the benzimidazoles was followed the procedure described by Takuzo Nishimura and Issei Iwai.[13] Acetonitrile and 1,2-dichloroethane were distilled over CaH_2 and P_2O_5, respectively, while $SnCl_4$ was redistilled freshly.

4.1.1. 5-Methyl-1-(β-D-erythro-pentofuranosyl)-1*H*-benzimidazole (2f). 5-Methyl-1*H*-benzimidazole (3.8 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (3.6 mmol) were dissolved in acetonitrile (30 ml) and a solution of tin tetrachloride (0.84 ml) in acetonitrile (18 ml) was added dropwise with stirring under a nitrogen atmosphere at reflux temperature. The solution was refluxed for 6 h and cooled to room temperature. Sodium bicarbonate (7.5 g) in water (50 ml) was added and stirring was continued for another 1 h. The resulting solution was extracted three times with chloroform. The organic layers were combined, dried over anhydrous sodium sulfate,

filtered, and evaporated to give a solid. The solid was dissolved in methanol (40 ml) and the solution was saturated with ammonia gas and stirred overnight in a sealed container. The resulting solution was evaporated to dryness to give the crude product, which was purified by silica-gel column chromatography using chloroform–methanol (9/1 v/v) as eluent to give 0.52 g target compound as a white powder, yield 55%. $[\alpha]_D^{20}$ −39.3 (*c* 0.2, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.39 (s, 1H, H2), 7.61 (d, J=8.0 Hz, 1H, H7), 7.56–7.53 and 7.46 (ms, 1H, H4), 7.07 (t, J=8.4 Hz, 1H, H6), 5.82 (d, J=5.3 Hz, 1H, H1′), 5.47 (d, J=5.3 Hz, 1H, 2′-OH), 5.22 (d, J=4.8 Hz, 1H, 3′-OH), 5.15–5.10 (m, 1H, 5′-OH), 4.39–4.33 (m, 1H, H2′), 4.13–4.08 (m, 1H, H3′), 3.97–3.94 (m, 1H, H5′), 3.70–3.57 (m, 2H, H5′), 2.41 (s, 3H, 5-CH_3); ^{13}C NMR (300 MHz, DMSO-d_6) δ 144.9, 143.0, 142.5, 131.7, 124.7, 120.0, 111.7, 89.3, 86.0, 74.2, 70.8, 61.9, 21.8; MS (ESI) *m*/*z* 265 $[M+H]^+$. Anal. Calcd for $C_{13}H_{16}N_2O_4$: C 59.08, H 6.10, N 10.60. Found: C 58.99, H 5.97, N 10.55.

4.1.2. 2,5-Dimethyl-1-(β-D-erythro-pentofuranosyl)-1*H*-benzimidazole (2g). 2,5-Dimethyl-1*H*-benzimidazole (3.8 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (3.6 mmol) were dissolved in 1,2-dichloroethane (30 ml) and a solution of tin tetrachloride (0.84 ml) in 1,2-dichloroethane (18 ml) was added dropwise with stirring under a nitrogen atmosphere at reflux temperature. The solution was refluxed for 5 h and cooled to room temperature. Sodium bicarbonate (7.5 g) in water (50 ml) was added and stirring was continued for another 1 h. The resulting solution was extracted three times with chloroform. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and evaporated to give a solid. The solid was dissolved in methanol (40 ml) and the solution was saturated with ammonia gas and stirred overnight in a sealed container. The resulting solution was evaporated to dryness to give the crude product, which was purified by silica-gel column chromatography using chloroform–methanol (9/1 v/v) as the eluent to give 0.57 g **2g** as a white powder, yield 57%. $[\alpha]_D^{20}$ −54.5 (*c* 0.3, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.69 and 7.67 (sd, J=4.9 Hz, 1H, H7), 7.38 and 7.31 (ds, J=7.9 Hz, 1H, H4), 6.95 (t, J=9.3 Hz, 1H, H6), 5.71 (d, J=7.4 Hz, 1H, H1′), 5.34 (d, J=7.0 Hz, 1H, 2′-OH), 5.24 (d, J=3.8 Hz, 1H, 3′-OH), 5.19–5.12 (m, 1H, 5′-OH), 4.38–4.30 (m, 1H, H2′), 4.12–4.06 (m, 1H, H3′), 3.94–3.91 (m, 1H, H4′), 3.72–3.67 (m, 2H, H5′), 2.54 (s, 3H, 2-CH_3), 2.37 (s, 3H, 5-CH_3); ^{13}C NMR (300 MHz, DMSO-d_6) δ 152.4, 143.7, 134.3, 131.1, 123.6, 118.9, 112.8, 89.1, 86.2, 72.4, 70.3, 62.1, 21.8, 15.1; MS (ESI) *m*/*z* 279 $[M+H]^+$. Anal. Calcd for $C_{14}H_{18}N_2O_4$: C 60.42, H 6.52, N 10.07. Found: C 60.16, H 6.25, N 9.82.

4.1.3. 2-Ethoxy-4-methyl-1-(β-D-erythro-pentofuranosyl)-1*H*-benzimidazole (2h). Silylated 2-ethoxy-4-methyl-1*H*-benzimidazole (3.8 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (3.6 mmol) were dissolved in acetonitrile (30 ml) and a solution of tin tetrachloride (0.84 ml) in acetonitrile (18 ml) was added dropwise with stirring under a nitrogen atmosphere at room temperature. The solution was stirred for 3 h at room temperature. Sodium bicarbonate (7.5 g) in water (50 ml) was added and stirring was continued for another 1 h. The resulting solution was extracted three times with chloroform. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and evaporated to give a solid. The solid was dissolved in methanol (40 ml) and the solution was saturated with ammonia gas and stirred overnight in a sealed container. The resulting solution was evaporated to dryness to give the crude product, which was purified by silica-gel column chromatography using chloroform–methanol (9/1 v/v) as eluent to give 0.45 g target compound as a white powder, yield 41%. Single crystals suitable for X-ray diffraction measurements were obtained by slow evaporation of its aqueous solution at room temperature. $[\alpha]_D^{20}$ −20.8 (*c* 0.1, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.42 (d, J=7.5 Hz, 1H, H7), 6.98–6.91 (m, 2H, H6 and H5), 5.71 (d, J=6.9 Hz, 1H, H1′), 5.31 (d, J=6.6 Hz, 1H, 2′-OH), 5.14 (d, J=4.8 Hz, 1H, 3′-OH), 5.02–4.99 (m, 1H, 5′-OH), 4.58–4.47 (m, 2H, H2′ and 2-O–CH_2), 4.09–4.05 (m, 1H, H3′), 3.87–3.83 (m, 1H, H4′), 3.62–3.58 (m, 2H, H5′), 2.43 (s, 3H, 4-CH_3), 1.41 (s, 3H, CH_3 of 2-OEt); ^{13}C NMR (300 MHz, DMSO-d_6) δ 156.9, 139.6, 132.3, 127.1, 122.8, 121.3, 109.4, 87.4, 85.6, 71.1, 70.6, 66.7, 62.3, 17.1, 15.1; MS (ESI) *m*/*z* 309 $[M+H]^+$. Anal. Calcd for $C_{15}H_{20}N_2O_5$: C 58.43, H 6.54, N 9.09. Found: C 58.17, H 6.81, N 8.84.

4.1.4. 4-Methyl-1-(β-D-erythro-pentofuranosyl)-3*H*-benzimidazol-one (2i). Silylated 2-ethoxy-4-methyl-1*H*-benzimidazole (3.8 mmol) and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (3.6 mmol) were dissolved in acetonitrile (30 ml) and a solution of tin tetrachloride (0.84 ml) in acetonitrile (18 ml) was added dropwise with stirring under a nitrogen atmosphere at room temperature. The solution was stirred for 3 h at room temperature then refluxed for 6 h and cooled to room temperature. Sodium bicarbonate (7.5 g) in water (50 ml) was added and stirring was continued for another 1 h. The resulting solution was extracted three times with chloroform. The organic layers were combined, dried over anhydrous sodium sulfate, filtered, and evaporated to give a solid. The solid was dissolved in methanol (40 ml) and the solution was saturated with ammonia gas and stirred overnight in a sealed container. The resulting solution was evaporated to dryness to give the crude product, which was purified by silica-gel column chromatography using chloroform–methanol (9/1 v/v) as the eluent to give 0.36 g **2i** as a white powder, yield 36%. $[\alpha]_D^{20}$ −30.4 (*c* 0.1, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.05 (s, 1H, H3), 7.20 (d, J=7.5 Hz, 1H, H7), 6.90–6.81 (m, 2H, H6 and H5), 5.66 (d, J=6.8 Hz, 1H, H1′), 5.20 (d, J=6.0 Hz, 1H, 2′-OH), 5.05 (d, J=4.8 Hz, 1H, 3′-OH), 4.99–4.95 (m, 1H, 5′-OH), 4.58–4.51 (m, 1H, H2′), 4.09–4.04 (m, 1H, H3′), 3.84–3.81 (m, 1H, H4′), 3.65–3.52 (m, 2H, H5′), 2.28 (s, 3H, 4-CH_3); ^{13}C NMR (300 MHz, DMSO-d_6) δ 154.8, 128.8, 127.9, 123.2, 121.3, 119.2, 108.3, 86.7, 85.4, 70.7, 70.1, 62.4, 16.8; MS (ESI) *m*/*z* 279 $[M-H]^-$. Anal. Calcd for $C_{13}H_{16}N_2O_5$: C 55.71, H 5.75, N 9.99. Found: C 55.46, H 5.38, N 9.98.

Acknowledgements

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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.2005.12.047. Supplementary material includes NMR ^{1}H 2D NOE spetra of compound **2a–i**. CCDC 280082 contain the supplementary crystallographic data and collection parameters for **2h**. These data can be obtained free of charge via www.ccdc.cam.ac,uk/conts/retrieving.html.

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Hydroxyl ionic liquid (HIL)-immobilized quinuclidine for Baylis–Hillman catalysis: synergistic effect of ionic liquids as organocatalyst supports

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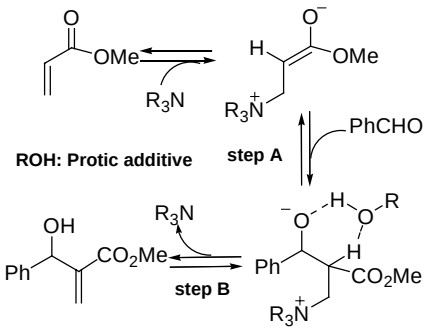
Abstract—Hydroxyl ionic liquid (HIL) has been explored as a novel support for Baylis–Hillman catalyst. The HIL-supported catalyst showed a better catalytic activity compared to other IL-immobilized catalyst that has no hydroxyl group attached to the IL scaffold. The hydroxyl group linked on IL played an important role in facilitating efficient catalysis under solvent-free conditions. The corresponding Baylis–Hillman and aza-Baylis–Hillman adducts were obtained in good to excellent yields in all cases examined. The HIL-supported quinuclidine can be readily recovered and reused for six times without significant loss of catalytic activity.

1. Introduction

The tertiary amine-catalyzed C–C bond-forming reaction of aldehydes with activated alkenes is widely referred to as Morita–Baylis–Hillman reaction, which has become one of the most popular C–C bond-forming reactions due to its many advantages regarding to atomic economy, non-metal catalysis, mild conditions, as well as the promising utility of the multifunctional products.[1] Recent efforts in this area have been focused largely on developing efficient reaction systems and exploring asymmetric Baylis–Hillman reactions.[1b,2] These studies have shown that the use of protic solvents or protic additives could accelerate the coupling reaction quite significantly and provide the presently most efficient Baylis–Hillman reactions.[3,4] In addition, a general inspection of the successful asymmetric catalysts reveals that the catalysts all bear a common structure motif with a 'proton'-donating moiety, which may be viewed as a critical determinant for chiral transduction.[2] Altogether, it seems likely that the involvement of a protic medium or a protic additive may be the prerequisite for developing efficient Baylis–Hillman synthesis and asymmetric catalysis. The recent finding that a protic additive could mediate intramolecular proton transfer (Scheme 1, step B) rather than enolate–aldehyde coupling (step A) as the rate-determining step in the initial stage of a Baylis–Hillman reaction,[5] is clearly in line with this proposal.



Scheme 1.

Another important area of current research is the development of supported Baylis–Hillman reactions and the recyclable catalysts.[6] This became of our recent focus because excess or stoichiometric small Lewis base catalysts have to be used under normal homogeneous B–H conditions. Progresses in literature along this line now include the exploration of poly-DMAP and the synthesis of supported phosphines for Baylis–Hillman catalysis.[6a,b] In our previous work, we have developed ionic liquid-supported quinuclidines for Baylis–Hillman catalysis on

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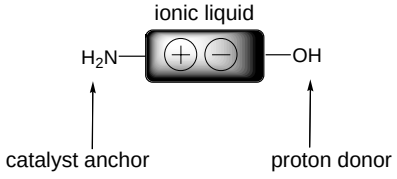
the basis of the biphasic strategy.[7] An inspection revealed that optimal result was achieved when using methanol as reaction medium, which is similar to the accelerating effect of protic solvent in other Baylis–Hillman reactions as highlighted above.[3,4] We could then speculate that the use of a hydroxyl containing ionic liquid alone may exert a similar accelerating effect. If this is the case, it will offer additional advantages such as elimination of a protic solvent, reduction of the catalyst loading, and a more efficient catalyst recycling for the Baylis–Hillman reactions. This deduction was considered to be reasonable because it was observed previously that a hydroxyl group in an amine type catalyst did exert accelerating effect on some coupling reactions.[8,9] In the present work, we explored the use of HILs as organocatalyst support. To our delight, we indeed observed a significant beneficial effect of the HIL catalyst over its non-hydroxyl counterpart. The first example of such type of Baylis–Hillman catalysts and their successful applications are hereby reported.

The ionic liquid precursor consists of a hydroxyl group and an amino group at the two ends of each alkyl chain, respectively, of which the amino group was linked to a quinuclidine moiety (Scheme 2). The synthesis of the HIL-supported quinuclidines was straight forward as depicted in Scheme 3. Reductive amination of 3-quinuclidinone with the synthetic bifunctional ionic liquid afforded the desired HIL-bound quinuclidines (**1a**–**1c**, **2a**–**2c**) as colorless or pale yellow viscous liquid. This new type of ionic liquids was characterized by ^{1}H, ^{13}C NMR, IR and MS.[10]

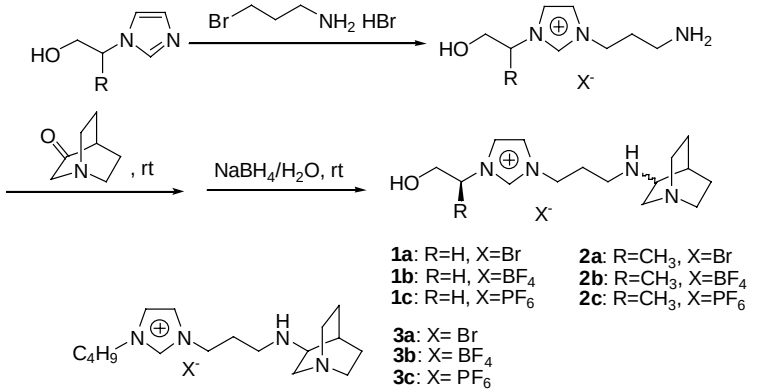


Scheme 2.

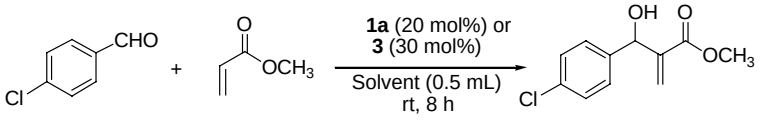
First, catalytic capability of the hydroxyl ionic liquid-immobilized quinuclidines was tested using **1a** as a representative catalyst and the reaction of *p*-chlorobenzaldehyde and methyl acrylate as a model B–H reaction (Scheme 4); the results were summarized in Table 1. As therein revealed, the reactions proceeded quite smoothly in the presence of 20 mol% of **1a** and showed a significant acceleration effect when conducted in protic solvents. For example, the reaction in methanol afforded 72% yield of the desired Baylis–Hillman product in 8 h, while the same reaction in THF provided only 32% of yield (Table 1, entry 1 vs entry 4).

It was also show that the HIL-supported quinuclidine **1a** had a better catalytic activity than its non-hydroxyl-bearing counterpart **3a** (or **3b**), regardless of the reaction media (Table 1). Considering the similarity of their structures of **1a** and **3**, it was envisioned that the hydroxyl group in the ionic liquid support **1a** must be responsible for its higher activity. It was conceived that the HIL support itself may serve as a protic additive to promote the Baylis–Hillman reaction in a manner similar to the protic additives in conventional cases. Indeed, further optimization of reaction conditions revealed that the reaction under solvent-free conditions provided the best result (90% in 8 h, Table 1, entry 11). In sharp contrast, the same reaction in the presence of a similar amount of non-HIL **3** was very sluggish and afforded less than 10% of the B–H product in 8 h under solvent-free conditions (Table 1, entry 11). These results indicated that the hydroxyl group linked on the ionic liquid played a critical role in promoting the reaction.[5]

Previously, ionic liquids have been shown in a few cases to exert positive effect on the Baylis–Hillman reaction rate when serving as reaction media.[6d–i,11] In our study, the use of hydroxyl containing ionic liquid as reaction media was found to give moderate accelerating effect in the presence of non-HIL-supported catalyst **3a** (Scheme 5, compared with Table 1, entries 7–11). Based on these results, further exploration led to the identification of hydroxyl containing



Scheme 3.



Scheme 4.

Table 1. Reactions of *p*-chlorobenzaldehyde with methyl acrylate in the presence of ionic liquid-supported quinuclidine **1a** (0.2 equiv) or **3** (0.3 equiv) in 0.5 mL of solvent for 8 h[a]

Entry	Solvent	Catalyst/yield (%)[b]	
		1a	**3a**
1	CH_3OH	72	37
2	C_2H_5OH	63	36
3	CH_3CN	43	18
4	THF	32	8
5	CH_2Cl_2	48	5
6	$CHCl_3$	29	9
7	$[BMIM]BF_4$	43	13[c]
8	$[BMIM]PF_6$	47	13[c]
9	$[bupy]BF_4$	69	21[c]
10	$[BMMIM]BF_4$	53	15[c]
11	None	90[d]	<10[c,d]

[a] Carried out on 0.5 mmol scale in the presence of 0.2 equiv of the catalyst **1a** at room temperature. Molar ratio of *p*-chlorobenzaldehyde/methyl acrylate=1:1.5.
[b] Isolated yields of pure product.
[c] Compound **3b** was employed instead of **3a**.
[d] Molar ratio of *p*-chlorobenzaldehyde/methyl acrylate=1:2.0.

IL-immobilized quinuclidine **1** as highly efficient Baylis–Hillman catalyst. The observations that the hydroxyl-bearing ionic liquids as catalyst supports could significantly promote the B–H reactions may be interpreted by suggesting a key role of the hydroxyl group on the IL support in activating aldehyde carbonyl or promoting an intramolecular proton transfer (or both) in a similar way to that suggested by Aggarwal.[5] However, the detailed mechanism as to how exactly the hydroxyl group is functioning in the B–H transition state is still unclear at the present stage and will need further investigation. Nevertheless, the finding that the HILs could serve as a synergistic reagent and support as well as a recoverable medium for Baylis–Hillman reactions provides a useful clue for designing highly efficient and recyclable catalysts for Baylis–Hillman reactions.

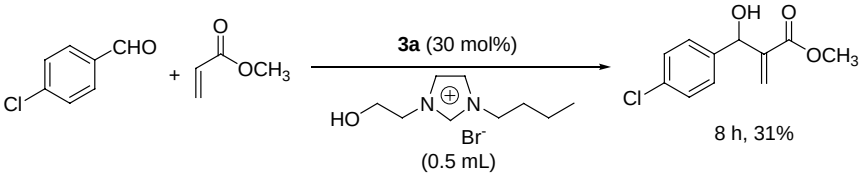
Under solvent-free conditions, several other hydroxyl ionic liquid-supported quinuclidines were also examined (Scheme 6, Table 2). The HILs with different counter ions showed little effect on the reactions (Table 2, entries 1–5). Among all the HILs examined, **1a** provided slightly better results in terms of reaction yields, and thus was selected as the catalyst for subsequent experiments. Increasing the loading of the catalyst did not lead to an increase in the yields (Table 2, entries 2 and 3), probably due to the formation of byproducts.

The immobilized chiral ionic liquids **2** were synthesized starting from L-alanine. The diastereoisomers obtained were inseparable and used directly as the B–H catalyst. As revealed in Table 2, the HIL-supported quinuclidines **2** maintained a comparable activity as **1** (Table 2, entries 6–8), but with poor enantioselectivity (<10% ee). The low selectivity may arise from an improper distance between the nucleophilic center and the protic moiety,[2a,b] thus the structure of catalyst should be further optimized.

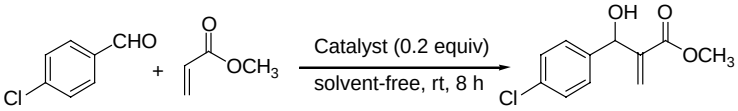
The HIL-supported catalysts can be readily recovered after the reaction using the biphasic strategy (i.e., homogeneous reaction and heterogeneous separation). The catalyst can then be reused directly for the following runs. It was found that **1a** could be recycled for at least six times without significant loss of its catalytic activity (Table 2, entries 9–13).

Under the optimized conditions established above, we then examined the Baylis–Hillman reactions of acrylates with a variety of aldehydes under solvent-free conditions (Scheme 7, Table 3). As shown therewith, both aliphatic and aromatic aldehydes can undergo very efficient Baylis–Hillman reactions with acrylates in the presence of 20 mol% of **1a**, giving the corresponding Baylis–Hillman adducts **4a**–**4s** in good to excellent yields (55–98%, 0.5–24 h). These results demonstrated that the HIL-supported quinuclidines were excellent Baylis–Hillman catalysts, with activities comparable to or better than some of the currently best catalytic systems in the literature.[3h] For example, the present system with 20 mol% of **1a** could provide fairly good isolated B–H adduct yields even for the reactions of inert substrates *p*-anisaldehyde (55%, Table 3, entry 11). In comparison, a similar reaction of *p*-anisaldehyde under the optimal conditions of the literature in the presence of 100 mol% quinuclidine gave 67% yield after 48 h.[3h] In addition, no apparent side reactions of aldehydes (such as aldol) were observed.

The analogous reactions of acrylonitrile with various aromatic aldehydes were also investigated (Scheme 8, Table 4). High yields were achieved for all the reactions in less reaction time. As shown in Table 4, catalyst **1a** was much more effective than **3b** in the cases tested. For example, for the commonly known inert substrate *p*-anisaldehyde, the yield of 83% was achieved in 8 h in the presence of 20 mol% of **1a** (Table 4, entry 4). In contrast, only 69% yield was obtained after 24 h when using **3b** (30 mol%) as the catalyst. For more active aldehydes such



Scheme 5.

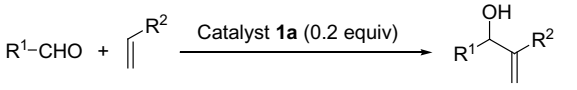


Scheme 6.

Table 2. Reactions of *p*-chlorobenzaldehyde with methyl acrylate in the presence of various HIL-supported quinuclidines[a]

Entry	Catalyst	Time (h)	Yield (%)[b]
1	**1a**	8	90
2	**1a**[c]	8	88
3	**1a**[d]	4	74
4	**1b**	8	86
5	**1c**	8	86
6	**2a**	8	79
7	**2b**	8	84
8	**2c**	8	86
9[e]	**1a** (2nd)	8	88
10[e]	**1a** (3rd)	8	88
11[e]	**1a** (4th)	8	82
12[e]	**1a** (5th)	12	86
13[e]	**1a** (6th)	12	84

[a] Carried out on 0.5 mmol scale in the presence of 0.2 equiv of the catalyst (except those specified) at room temperature. Molar ratio of *p*-chlorobenzaldehyde/methyl acrylate = 1:2.
[b] Isolated yields of pure product.
[c] 0.3 equiv of **1a** was used.
[d] 0.5 equiv of **1a** was used.
[e] Reuse of catalyst **1a** from 1 to 6 run.



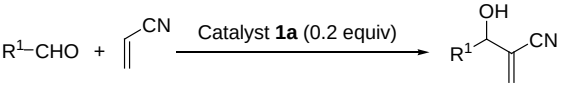
4a 4r (55 98%)

Scheme 7.

Table 3. Baylis–Hillman reactions of aldehydes (1.0 equiv) and acrylates (2.0 equiv) catalyzed by ionic liquid-supported quinuclidine **1a** (0.2 equiv) at room temperature[a]

Entry	R^1	R^2	Time (h)	Product	Yield (%)[b]
1	*n*-C_3H_7	$COOCH_3$	12	**4b**	79
2	*i*-C_4H_9	$COOCH_3$	12	**4c**	74
3	*n*-C_6H_{13}	$COOCH_3$	12	**4d**	80
4	Ph	$COOCH_3$	8	**4e**	94
5	*p*-ClPh	$COOC_2H_5$	8	**4f**	88
6	*p*-ClPh	$COOC_4H_9$	8	**4g**	86
7	*o*-ClPh	$COOCH_3$	8	**4h**	91
8	*m*-ClPh	$COOCH_3$	8	**4i**	84
9	*p*-CH_3Ph	$COOCH_3$	8	**4j**	72
10	*p*-*i*PrPh	$COOCH_3$	10	**4k**	70
11	*p*-CH_3OPh	$COOCH_3$	24	**4l**	55
12	*o*-NO_2Ph	$COOCH_3$	1	**4m**	97
13	*m*-NO_2Ph	$COOCH_3$	1	**4n**	94
14	2-Pyridyl	$COOCH_3$	0.5	**4o**	95
15	3-Pyridyl	$COOCH_3$	0.5	**4p**	98
16	4-Pyridyl	$COOCH_3$	0.5	**4q**	97
17	2-Furyl	$COOCH_3$	1	**4r**	93

[a] The reaction was carried out in 0.5 mmol scale.
[b] Isolated yields.



5a–5h (83–97%)

Scheme 8.

Table 4. Baylis–Hillman reactions of aldehydes (1.0 equiv) and acrylonitrile (2.0 equiv) in the presence of **1a** (0.2 equiv) at room temperature[a]

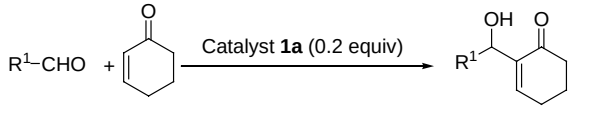
Entry	R^1	Time (h)	Product	Yield (%)[b]
1	Ph	1.5	**5a**	96
2	*p*-ClPh	1.5	**5b**	97
3	*p*-CH_3Ph	4	**5c**	91
4	*p*-CH_3OPh	8 (24)[c]	**5d**	83 (69)[c]
5	*p*-NO_2Ph	0.5	**5e**	85
6	2-Pyridyl	10 min	**5f**	98
7	3-Pyridyl	10 min	**5g**	98
8	4-Pyridyl	10 min	**5h**	98

[a] Carried out on 0.5 mmol scale.
[b] Isolated yields.
[c] Results using 30 mol% of **3b** as catalyst in 2.0 equiv of methanol.

as pyridinecarboxaldehydes, almost all substrates were quantitatively converted to the desired Baylis–Hillman products in only 10 min (Table 4, entries 6–8).

The Baylis–Hillman reactions involving the poor Michael acceptors, cyclic enones, were usually quite sluggish under normal conditions. Many attempts have been made to explore efficient catalysts to accelerate this kind of reaction.[7,12] In our previous work, we found that the reaction of 2-cyclohexenone could undergo quite effective (fair to high yields) B–H reactions in methanol using ionic liquid-supported quinuclidine **3b** as the catalyst.[7] In the present work, comparable or better results were obtained in the presence of 20 mol% of **1a** (Scheme 9, Table 5). No apparent aldol byproducts, except for the case of piperanol (Table 5, entry 5), were observed. In contrast, there were substantial aldol adducts in most cases when using **3b** as the catalyst.[7] Furthermore, the inert *p*-anisaldehyde could also undergo quite efficient Baylis–Hillman reaction with the inert Michael acceptor 2-cyclohexenone, giving 51% yield in quite a short reaction time (Table 5, entry 4). These results indicated that the HIL-bound catalyst **1a** of the present work was a very efficient catalyst for the Baylis–Hillman reactions involving 2-cyclohexenone.

The aza-Baylis–Hillman reaction was also examined (Scheme 10, Table 6). With 20 mol% of **1a**, the aza-



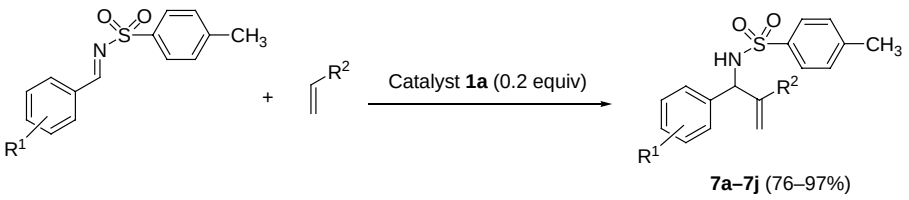
6a–6e (51–84%)

Scheme 9.

Table 5. Baylis–Hillman reactions of aldehydes (1.0 equiv) and 2-cyclohexenone (2.0 equiv) in the presence of **1a** (0.2 equiv) at room temperature[a]

Entry	R^1	Time (h)	Product	Yield (%)[b]
1	Ph	8	**6a**	77
2	*p*-ClPh	8	**6b**	84
3	*p*-CH_3Ph	12	**6c**	65
4	*p*-CH_3OPh	16	**6d**	51
5	Piperonal	16	**6e**	73 (9)[c]

[a] Carried out on 0.5 mmol scale.
[b] Isolated yields.
[c] The number in parentheses is the yield of aldol byproduct.



Scheme 10.

Baylis–Hillman reactions of *N*-sulfonated imines (i.e., *N*-arylmethylidene-4-methylbenzenesulfonamides) with various B–H substrates such as methyl acrylate and acrylonitrile were promoted to give exclusively the desired aza-Baylis–Hillman adducts (76–97%). Even the relatively inert *N*-4-methyoxyphenylmethylidene-4-methylbenzenesulfonamide could undergo efficient aza-B–H reaction with methyl acrylate and acrylonitrile in good to excellent yields (Table 6, entries 5 and 10).

Table 6. Aza-Baylis–Hillman reactions of aldehydes (1.0 equiv) and electrophiles (5.0 equiv) in the presence of **1a** (0.2 equiv) at room temperature[a]

Entry	R^1	R^2	Time (h)	Product	Yield (%)[b]
1	4-Cl	$COOCH_3$	4	**7a**	91
2	H	$COOCH_3$	2	**7b**	76
3	2-Cl	$COOCH_3$	4	**7c**	84
4	4-CH_3	$COOCH_3$	4	**7d**	88
5	4-CH_3O	$COOCH_3$	8	**7e**	96
6	4-Cl	CN	2	**7f**	94
7	H	CN	1	**7g**	90
8	2-Cl	CN	2	**7h**	92
9	4-CH_3	CN	2	**7i**	83
10	4-CH_3O	CN	4	**7j**	97

[a] Carried out on 0.2 mmol scale.
[b] Isolated yields.

In summary, we have disclosed HILs as novel supports for Baylis–Hillman catalyst. The HIL-bound quinuclidine demonstrated better catalytic activity than its non-hydroxyl ionic liquid analogues and was well applied to a range of Baylis–Hillman substrates under solvent-free conditions. This beneficial matrix effect of HIL was ascribed to the presence of hydroxyl group in the proximity of active sites, which accelerated the reaction via hydrogen-bonding activation and/or assisting intramolecular proton transfer. The HIL-bound catalysts possess all the advantages of the non-HIL-bound catalysts and can be readily recovered from the reaction mixture and reused for at least six times without significant loss of catalytic activity. The solvent-free reaction system provided a highly efficient Baylis–Hillman synthesis under environmentally friendly conditions.

2. Experimental

2.1. General procedure

In a 5 mL vial, **1a** (36 mg, 0.1 mmol), aldehyde (0.5 mmol) and activated alkene (1.0 mmol) were mixed. The resulted homogeneous solution was stirred at ambient temperature and monitored by TLC. After the indicated reaction time, the solution was extracted with diethyl ether. The ether extract was rotary-evaporated and the crude product was purified by flash chromatography on silica gel to afford the desired product. The remaining layer was further vacuumed to dryness and the resulting catalyst was reused directly for next run. The reactions using the recycled catalyst were conducted in the same manner.

2.1.1. Synthesis of HIL-bound quinuclidine 1a (R=H, X=Br). The synthesis of hydroxyl containing amino ionic liquid (R=H) followed our previous procedure:[7] to a stirred solution of 2-imidazol-1-yl ethanol (5.6 g, 50 mmol) in 50 mL of dry ethanol was added 3-bromopropylamine hydrobromide (10.95 g, 50 mmol). The solution was heated to reflux for 24 h. The ethanol was then removed under vacuo and the solid residue was dissolved in a minimal quantity of water and was brought to about pH=10 by the addition, in small portions, of solid KOH. The water solution was then concentrated to dryness and the residue was extracted with ethanol–THF. The combined extracts were concentrated to give the desired product (11.33 g, 91%) as a pale yellow viscous liquid. ^{1}H NMR (CD_3OD, 300 MHz): 7.20 (s, 1H), 6.98 (s, 1H), 4.15 (t, 2H, J=4.8 Hz), 3.91 (t, 2H, J=5.1 Hz), 3.83 (t, 2H, J=5.1 Hz), 2.73–2.69 (m, 2H), 2.08 (t, 2H, J=7.2 Hz); ^{13}C NMR (CD_3OD, 75 MHz): δ 139.2, 124.2, 123.6, 62.5, 60.8, 53.5, 39.1, 33.9; MS for $C_8H_{16}N_3O^+$ (M^+), calcd 170.13, found 170.47; Br^- (M^-), calcd 78.92, found 78.93.

To a solution of the synthetic hydroxyl containing amino imidazolium bromide (2.5 g, 10 mmol) in 20 mL of dry methanol was added 3-quinuclidinone (1.88 g, 15 mmol). After stirring for 12 h at ambient temperature, the reaction was cooled to 0 °C and sodium borohydride (0.855 g, 22.5 mmol) was added in small portions. The solution was stirred for 4 h, followed by adding small quantity of water. The resulting mixture was then stirred for additional 30 min and concentrated to dryness. The residue was extracted with chloroform and the extracts was concentrated, followed by extensive washing with diethyl ether to provide the expected product **1a** (3.09 g, 86%) as a pale yellow viscous liquid. IR (KBr, cm^{-1}): 3397, 2945, 1581, 1457, 1399, 1164, 1075. ^{1}H NMR (CD_3CN, 300 MHz): 7.51 (s, 1H), 7.06 (s, 1H), 6.89 (s, 1H), 4.27 (t, 2H, J=5.4 Hz), 3.90 (t, 2H, J=4.5 Hz), 3.17–3.09 (m, 2H), 2.86–2.73 (m, 4H), 2.68–2.60 (m, 3H), 2.45–2.39 (m, 2H), 2.13–2.08 (m, 3H), 1.90–1.85 (m, 2H), 1.76–1.71 (m, 1H), 1.61–1.53 (m, 2H), 1.48–1.40 (m, 2H); ^{13}C NMR (CD_3CN, 75 MHz): δ 138.8, 124.1, 123.6, 68.1, 62.5, 61.0, 58.1, 56.7, 55.8, 53.3, 44.6, 31.2, 26.7, 25.7, 20.3; MS for $C_{15}H_{27}N_4O^+$ (M^+), calcd 279.22, found 279.61; Br^- (M^-), calcd 78.92, found 78.98; HRMS for $C_{15}H_{27}N_4O^+$ (M^+), calcd 279.2185, found 279.2179.

2.1.2. Synthesis of hydroxyl based ionic liquid-bound quinuclidine 1b (R=H, X=BF_4). The sodium tetrafluoroborate (2.47 g, 22.5 mmol) was added to a solution of the synthetic hydroxyl containing amino imidazolium bromide (R=H, 3.75 g, 15 mmol) in ethanol/THF and stirred for 3 days. The suspension was filtered to remove the precipitated bromide salt and the organic phase was concentrated. The residue was then re-dissolved in a small amount of chloroform, and filtered to remove the inorganic salt. The solvent was removed under vacuo to afford a pale yellow liquid (3.12 g, 57%). ^{1}H NMR (CD_3OD, 300 MHz): 7.19 (s, 1H), 6.98 (s, 1H), 4.13 (t, 2H, J=5.1 Hz), 3.91 (t, 2H, J=4.8 Hz), 3.82 (t, 2H, J=5.4 Hz), 2.91–2.83 (m, 2H), 2.18 (t, 2H, J=7.2 Hz); ^{13}C NMR (CD_3OD, 75 MHz): δ 139.2, 124.3, 123.5, 62.5, 61.0, 53.4, 38.3, 31.6; MS for $C_8H_{16}N_3O^+$ (M^+), calcd 170.13, found 170.40; BF_4^- (M^-), calcd 87.00, found 87.03.

The synthesis of **1b** followed similar procedure as that of **1a**. With 3.12 g of imidazolium tetrafluoroborate (8.5 mmol), 2.57 g of **1b** (82%) was obtained as a colorless viscous liquid. IR (KBr, cm^{-1}): 3396, 2947, 1501, 1396, 1164, 1091. ^{1}H NMR (CD_3OD, 300 MHz): 7.19 (s, 1H), 6.98 (s, 1H), 4.35 (t, 2H, J=4.8 Hz), 3.92 (t, 2H, J=4.8 Hz), 3.17–3.10 (m, 2H), 2.82–2.77 (m, 4H), 2.68–2.59 (m, 3H), 2.46–2.44 (m, 2H), 2.14–1.09 (m, 3H), 1.93–1.89 (m, 2H), 1.77–1.72 (m, 1H), 1.61–1.55 (m, 2H), 1.48–1.40 (m, 2H); ^{13}C NMR (CD_3OD, 75 MHz): δ 138.8, 124.1, 123.6, 68.3, 62.5, 61.0, 58.1, 56.7, 55.9, 53.4, 44.6, 31.2, 26.7, 25.6, 20.3; MS for $C_{15}H_{27}N_4O^+$ (M^+), calcd 279.22, found 279.57; BF_4^- (M^-), calcd 87.00, found 87.03; HRMS for $C_{15}H_{27}N_4O^+$ (M^+), calcd 279.2185, found 279.2177.

2.1.3. Synthesis of hydroxyl based ionic liquid-bound quinuclidine 1c (R=H, X=PF_6). The potassium hexafluorophosphate (2.76 g, 15 mmol) was added to a solution of the synthetic hydroxyl containing amino imidazolium bromide (R=H, 2.5 g, 10 mmol) in ethanol/THF and stirred for 3 days. The suspension was filtered to remove the precipitated bromide salt and the organic phase was concentrated. The residue was then re-dissolved in a small amount of chloroform, and filtered to remove the inorganic salt. The solvent was removed under vacuo to afford a pale yellow liquid (2.15 g, 51%). ^{1}H NMR (CD_3OD, 300 MHz): 7.19 (s, 1H), 6.98 (s, 1H), 4.12 (t, 2H, J=5.4 Hz), 3.89 (t, 2H, J=4.8 Hz), 3.82 (t, 2H, J=4.8 Hz), 2.91–2.86 (m, 2H), 2.19 (t, 2H, J=7.2 Hz); ^{13}C NMR (CD_3OD, 75 MHz): δ 137.7, 124.2, 123.5, 65.6, 60.4, 56.8, 38.5, 31.8, 18.6; MS for $C_8H_{16}N_3O^+$ (M^+), calcd 170.13, found 170.42; PF_6^- (M^-), calcd 144.96, found 145.13.

The synthesis of **1c** followed the similar procedure as that of **1a**. With 2.15 g of imidazolium hexafluorophosphate (5.1 mmol), 2.67 g of **1c** (92%) was obtained as a colorless viscous liquid. IR (KBr, cm^{-1}): 3158, 2946, 1561, 1457, 1398, 1164, 1078, 847. ^{1}H NMR (CD_3OD, 300 MHz): 7.18 (s, 1H), 6.98 (s, 1H), 4.33 (t, 2H, J=5.1 Hz), 3.90 (t, 2H, J=5.1 Hz), 3.16–3.10 (m, 2H), 2.85–2.73 (m, 4H), 2.70–2.60 (m, 2H), 2.45–2.40 (m 2H), 2.12–2.07 (m, 3H), 1.93–1.88 (m, 2H), 1.77–1.73 (m, 1H), 1.61–1.55 (m, 2H), 1.48–1.40 (m, 2H); ^{13}C NMR (CD_3OD, 75 MHz): δ 138.8, 124.1, 123.6, 68.2, 62.5, 61.0, 58.1, 56.6, 55.8, 53.3, 44.6, 31.2, 26.7, 25.7, 20.3; HRMS for $C_{15}H_{27}N_4O^+$ (M^+), calcd 279.2185, found 279.2179; MS for $C_{15}H_{27}N_4O^+$ (M^+), calcd 279.22, found 279.55; BF_4^- (M^-), calcd 144.96, found 145.15.

2.1.4. Synthesis of hydroxyl based ionic liquid-bound quinuclidine 2a (R=CH_3, X=Br). The synthesis of hydroxyl containing amino ionic liquid (R=CH_3) still followed our previous procedure: to a stirred solution of 2-(1-imidazolyl)propanol (8.64 g, 68 mmol) in 68 mL of dry ethanol was added 3-bromopropylamine hydrobromide (14.88 g, 68 mmol). The solution was heated to reflux for 24 h. The ethanol was then removed in vacuo and the solid residue was dissolved in a minimal quantity of water and brought to about pH=10 by the addition, in small portions, of solid KOH. The water solution was then concentrated to dryness and the residue was extracted with ethanol–THF. The combined extracts were concentrated to give the desired product (R=CH_3, 17.29 g, 96%) as a pale red viscous liquid. ^{1}H NMR (CD_3OD, 300 MHz): 7.24 (s, 1H), 6.98 (s, 1H), 4.69–4.58 (m, 1H), 4.43–4.38 (m, 2H), 3.78–3.71 (m, 2H), 3.66–3.59 (m, 2H), 2.26–2.13 (m, 2H), 1.60 (d, 3H, J=6.9 Hz); ^{13}C NMR (CD_3OD, 75 MHz): δ 137.7, 123.7, 126.6, 65.6, 60.4, 56.8, 38.5, 31.8, 18.6; MS for $C_9H_{18}N_3O^+$ (M^+), calcd 184.14, found 184.42; Br^- (M^-), calcd 78.92, found 78.97.

To a solution of the synthetic hydroxyl containing amino imidazolium bromide (R=H, 2.64 g, 10 mmol) in 20 mL of dry methanol was added 3-quinuclidinone (1.88 g, 15 mmol). After stirring for 12 h at ambient temperature, the reaction was cooled to 0 °C and sodium borohydride (0.855 g, 22.5 mmol) was added in small portions. The solution was stirred for 4 h, followed by adding a small quantity of water. The resulting mixture was then stirred for an additional 30 min and concentrated to dryness. The residue was extracted with chloroform and the extract was concentrated, followed by extensive washing with diethyl ether to provide the expected product **2a** (3.48 g, 93%) as a pale yellow viscous liquid. IR (KBr, cm^{-1}): 3137, 2944, 2874, 2312, 1558, 1457, 1400, 1167, 1046. ^{1}H NMR (CD_3OD, 300 MHz): 7.90 (s, 1H), 7.01 (s, 1H), 6.97 (s, 1H), 4.61–4.56 (m, 1H), 4.38–4.33 (m, 2H), 3.89–3.84 (m, 1H), 3.75–3.58 (m, 2H), 3.33 (br, 1H), 3.18–3.11 (m, 1H), 2.80 (br, 3H), 2.66–2.59 (m, 3H), 2.45–2.41 (m, 1H), 2.10 (t, 2H, J=6.9 Hz), 1.90 (br, 2H), 1.74 (br, 2H), 1.59 (d, 3H, J=6.9 Hz); ^{13}C NMR (CD_3OD, 75 MHz): δ 136.2, 122.0, 120.8, 67.3, 64.5, 58.9, 58.9, 56.3, 54.9, 48.0, 47.4, 46.4, 28.3, 24.8, 19.0; HRMS for $C_{16}H_{29}N_4O^+$ (M^+), calcd 293.2336, found 293.2339; MS for $C_{16}H_{29}N_4O^+$ (M^+), calcd 293.23, found 293.49; Br^- (M^-), calcd 78.92, found 78.93.

2.1.5. Synthesis of hydroxyl based ionic liquid-bound quinuclidine 2b (R=CH_3, X=BF_4). The sodium tetrafluoroborate (3.29 g, 30 mmol) was added to a solution of the synthetic hydroxyl based amino imidazolium bromide (R=CH_3, 5.28 g, 20 mmol) in ethanol/THF and stirred for 3 days. The suspension was filtered to remove the precipitated bromide salt and the organic phase was concentrated. The residue was then re-dissolved in a small amount of chloroform, and filtered to remove the inorganic salt. The solvent was removed under vacuo to afford a pale yellow liquid (2.51 g, 46%). ^{1}H NMR (CD_3OD, 300 MHz):

7.79 (s, 1H), 7.61 (s, 1H), 4.69–4.59 (m, 1H), 4.45–4.40 (m, 2H), 3.89–3.85 (m, 2H), 3.66–3.59 (m, 2H), 2.37–2.27 (m, 2H), 1.59 (d, 3H, $J=8.4$ Hz); ^{13}C NMR (CD_3OD, 75 MHz): δ 137.0, 124.1, 122.7, 65.8, 60.3, 58.4, 37.8, 29.2, 18.5; MS for $C_9H_{18}N_3O^+$ (M^+), calcd 184.14, found 184.37; BF_4^- (M^-), calcd 87.00, found 87.05.

The synthesis of **2b** followed a similar procedure to that of **2a**. With 2.22 g of imidazolium tetrafluoroborate (8.2 mmol), 1.92 g of **2b** (86%) was obtained as a colorless viscous liquid. IR (KBr, cm^{-1}): 3132, 2942, 2871, 1558, 1457, 1400, 1115, 1045. ^{1}H NMR (CD_3OD, 300 MHz): 7.22 (s, 1H), 6.98 (s, 1H), 4.63–4.58 (m, 1H), 4.39–4.34 (m, 2H), 3.89–3.85 (m, 1H), 3.76–3.70 (m, 2H), 3.37 (br, 1H), 3.18–3.10 (m, 1H), 2.79 (br, 3H), 2.68–2.56 (m, 3H), 2.46–2.40 (m, 1H), 2.12 (t, 2H, $J=$ 6.9 Hz), 1.90 (br, 2H), 1.74 (br, 2H), 1.59 (d, 3H, $J=6.9$ Hz); ^{13}C NMR (CD_3OD, 75 MHz): δ 137.6, 123.6, 122.3, 68.1, 66.8, 60.3, 58.1, 56.7, 55.8, 48.1, 47.5, 47.1, 29.1, 25.3, 19.6; HRMS for $C_{16}H_{29}N_4O^+$ (M^+), calcd 293.2336, found 293.2336; MS for $C_{16}H_{29}N_4O^+$ (M^+), calcd 293.23, found 293.56; BF_4^- (M^-), calcd 87.00, found 87.06.

2.1.6. Synthesis of hydroxyl based ionic liquid-bound quinuclidine 2c ($R=CH_3$, $X=PF_6$). The potassium hexafluorophosphate (4.14 g, 22.5 mmol) was added to a solution of the synthetic hydroxyl based amino imidazolium bromide ($R=CH_3$, 3.96 g, 15 mmol) in ethanol/THF and stirred for 3 days. The suspension was filtered to remove the precipitated bromide salt and the organic phase was concentrated. The residue was then re-dissolved in a small amount of chloroform, and filtered to remove the inorganic salt. The solvent was removed under vacuo to afford a pale yellow liquid (2.96 g, 60%). ^{1}H NMR (CD_3OD, 300 MHz): 7.24 (s, 1H), 6.98 (s, 1H), 4.60–4.54 (m, 1H), 4.39–4.34 (m, 2H), 3.88–3.84 (m, 2H), 3.62–3.53 (m, 2H), 2.31–2.21 (m, 2H), 1.58 (d, 3H, $J=6.9$ Hz); ^{13}C NMR (CD_3OD, 75 MHz): δ 137.6, 123.5, 122.5, 65.5, 60.3, 56.8, 38.4, 31.6, 17.9; MS for $C_9H_{18}N_3O^+$ (M^+), calcd 184.14, found 184.34; PF_6^- (M^-), calcd 144.96, found 145.14.

The synthesis of **2c** followed a similar procedure to that of **2a**. With 2.8 g of imidazolium hexafluorophosphate (8.5 mmol), 2.58 g of **2c** (92%) was obtained as a colorless viscous liquid. IR (KBr, cm^{-1}): 3162, 2946, 2875, 2310, 1558, 1457, 1396, 1166, 1052, 845. ^{1}H NMR (CD_3OD, 300 MHz): 7.22 (s, 1H), 6.97 (s, 1H), 4.60–4.54 (m, 1H), 4.36–4.31 (m, 2H), 3.87–3.83 (m, 1H), 3.75–3.69 (m, 2H), 3.37 (br, 1H), 3.17–3.13 (m, 1H), 2.78 (br, 3H), 2.67–2.54 (m, 3H), 2.44–2.40 (m, 1H), 2.10 (t, 2H, $J=6.9$ Hz), 1.89 (br, 2H), 1.76 (br, 2H), 1.58 (d, 3H, $J=6.9$ Hz); ^{13}C NMR (CD_3OD, 75 MHz): δ 137.6, 123.6, 122.3, 68.2, 66.5, 60.3, 58.1, 56.6, 55.7, 47.5, 47.0, 44.6, 29.0, 26.7, 20.3; MS for $C_{16}H_{29}N_4O^+$ (M^+), calcd 293.23, found 293.58; Br^- (M^-), calcd 144.96, found 145.13.

All the Baylis–Hillman products are known compounds.[4,7,13]

Acknowledgements

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A facile access to spiro furanone skeleton based on Pd(II)-mediated cyclization–carbonylation of propargylic esters

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Abstract—The oxidative cyclization–carbonylation of propargylic esters mediated by Pd(II) afforded cyclic orthoesters, which were hydrolyzed into γ-acetoxy-β-ketoesters. Based on the NMR experiments, it was presumed that the cyclization reaction was initiated by a nucleophilic attack of carbonyl oxygen to the alkyne carbon coordinated to palladium(II). When the γ-acetoxy-β-ketoesters were treated with a basic condition, Knoevenagel–Claisen type condensation took place, and spiro furanone derivatives were obtained in good yields. We applied these reactions to steroid derivatives, and steroid derivatives having a spiro furanone fragment were synthesized. Among them, the spiro furanone **4j** had vasorelaxant and bradycardiac activities. Compounds **2i**–**4k** had inhibitory effect on CYP3A.

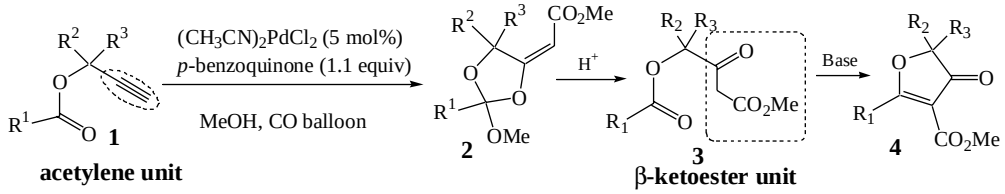
1. Introduction

Palladium(II)-catalyzed reactions are fundamentally important in organic transformations.[1] Propargylic esters undergo a number of palladium catalyzed transformations,[2] such as nucleophilic substitution,[3] oxidative rearrangement[4] and carbonylation reactions.[5] Recently, we have reported cyclization–carbonylation of 4-yne-1-ols,[6] 4-yne-1-ones[7] and propargylic esters.[8] These reactions are considered to be a useful method for the conversion of the acetylene unit to a β-ketoester unit.[9] We would like to report here mechanistic insight into the Pd(II)-mediated cyclization–carbonylation of propargylic esters and an application to the construction of a spiro furanone skeleton by using Knoevenagel–Claisen type condensation of γ-acetoxy-β-ketoesters (Scheme 1).

2. Results and discussion

2.1. Cyclization–carbonylation of propargylic esters

The cyclization–carbonylation of propargylic acetate **1a**–**d** in the presence of $(CH_3CN)_2PdCl_2$/*p*-benzoquinone in methanol at 0 °C–rt under carbon monoxide atmosphere (balloon) afforded methoxycarbonylated orthoesters **2a**–**d** in 61–71% yields (Scheme 2, Table 1, entries 1–4). In the case



Scheme 1.

Keywords: Palladium; Orthoester; Cyclization–carbonylation; Propargylic ester; β-Ketoesters; Spiro furanone; 3(2*H*)-Furanone; Ethisterone; Mestranol; Ethynylestradiol.
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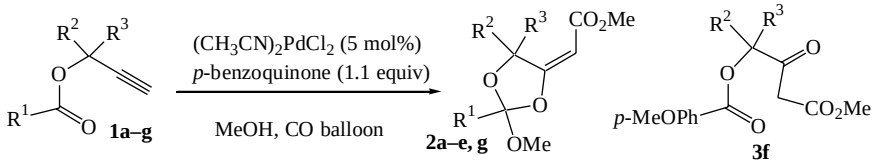


Scheme 2.

Table 1. The cyclization–alkoxycarbonylation of propargylic esters

Entry	1	Condition	R^1	R^2	R^3	Product	Yield (%)
1	**1a**	0 °C, 7 h	Me		$-(CH_2)_6-$	**2a**	65
2	**1b**	0 °C, 3 h	Me		$-(CH_2)_5-$	**2b**	65
3	**1c**	0 °C, 5 h	Me		$-(CH_2)_2NBoc(CH_2)_2-$	**2c**	71
4	**1d**	rt, 0.5 h	Me	Me	CH_2CH_2Ph	**2d**[a]	61
5	**1e**	0 °C, 4.5 h	Ph		$-(CH_2)_5-$	**2e**	80
6	**1f**	rt, 1 h	*p*-MeOPh		$-(CH_2)_5-$	**3f**	83
7	**1g**	rt, 1 h	*p*-NO_2Ph		$-(CH_2)_5-$	**2g**	21

[a] The product **2d** was obtained as a 2:1 diastereomeric mixture.

of benzoates **1e–g**, electronic effect of the *p*-substituents on the phenyl group was observed. When benzoate **1e** and *p*-methoxy derivative **1f** bearing an electron-donating group were subjected to similar reaction conditions, the yields of the products **2e** and **3f** were improved in comparison with acetate **1a** (entries 5 and 6). However, the reaction of *p*-nitrobenzoate **1g** having an electron-withdrawing group scarcely proceeded and **2g** was obtained in 21% yield together with recovery of the substrate (65%) (entry 7). In addition, in the case of a phenylacetylene derivative of **1b** and a TBDMS ether derivative of **1d**, the reactions did not proceed under similar reaction conditions. These results suggested that the presence of neighboring group participation and nucleophilicity of the carbonyl oxygen play an important role for initiating the reaction. The substrate **1h** bearing two phenyl groups in propargylic position afforded different products **5**[10] (36%) and **6** (23%) from those of Table 1 (Fig. 1). These products **5** and **6** should be produced by S_N1-type substitution of the acetoxy group with MeOH and by oxidative rearrangement of propargylic acetate,[4] respectively.

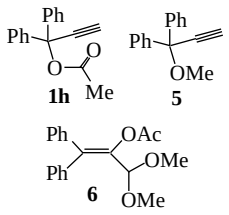


Figure 1.

Selected data of the NMR spectra measured in CD_3-$COCD_3$ of **2b** are shown in Figure 2. The quaternary carbon of orthoester appeared in 124 ppm and its HMBC correlations with proton of the methyl group (1.6 ppm) and with proton of the methoxy group (3.24 ppm) were clearly observed. These results indicated the presence of an orthoester structure. In addition, the structure of **2c** was unequivocally determined by X-ray crystallographic analysis.

Two kinds of mechanistic pathways have been proposed for the intramolecular cyclization of alkynes with a C=O group. Yamamoto et al. reported the cyclization of alkynyl aldehydes takes place via a hemiacetal intermediate based on NMR experiment,[11] and then we have also reported the asymmetric cyclization–carbonylation of 2-alkynyl-1,3-diketone proceeded through a similar pathway.[12] On the other hand, in the case of alkynyl ketones and propargylic esters, we have proposed an alternative pathway.[7,8] The reaction could be initiated by a nucleophlic attack of the C=O group to the triple bond coordinated to palladium(II) followed by orthoester formation. Recently, Bacchi et al. have reported oxidative cyclization–alkoxycarbonylation of prop-2-ynyl α-ketoesters afforded the products, resulting from MeOH attack on the ester carbonyl group followed by cyclization and carbonylation.[5a] Thus, to clarify the mechanism of the Pd(II)-mediated cyclization of propargylic esters, NMR studies of a 1:1 mixture of **1b** and $(CH_3CN)_2PdCl_2$ in CD_2Cl_2 at rt were carried out according to the precedent.[11] The ^1H and ^{13}C NMR spectra clearly showed the disappearance of acetylenic proton (δ 2.61) and carbons (δ 84.2, 74.3), newly generated proton (δ 5.46) and carbons appeared. The three secondary carbon signals (δ 37.3, 25.5, 22.8) split into five secondary carbon resonances (δ 34.9, 31.8, 30.0, 27.3, 26.5), which suggest that the symmetry of the cyclohexane moiety was lost. To our regret, the mixtures became black after 30 min. We tentatively proposed the above mixtures to be vinyl palladium complex **A** such as shown in Figure 3.[13,14] Although the structure of the above mixtures could not be clarified,[15] it is possible that the reaction is initiated by a nucleophilic attack of the carbonyl oxygen to the triple bond coordinated with palladium(II).

A plausible mechanism of the present reactions would be proposed as shown in Scheme 3. Propargylic acetate **1** reacts with Pd(II) to generate vinyl palladium intermediate **B**, which was subjected to the nucleophilic attack of MeOH on the carbon atom of the carbonyl group followed by CO insertion to provide the orthoester products **2**. In the case of benzoate **1e** and *p*-methoxybenzoate **1f**, the cationic intermediate **B** (R_3=Ph and *p*-MeO–Ph) should be stabilized by an electron-donating group, and

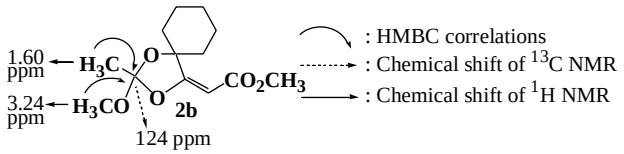


Figure 2. Selected data of ^{1}H, ^{13}C NMR and HMBC spectra of **2b**.

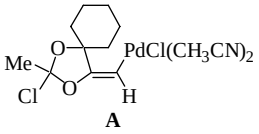
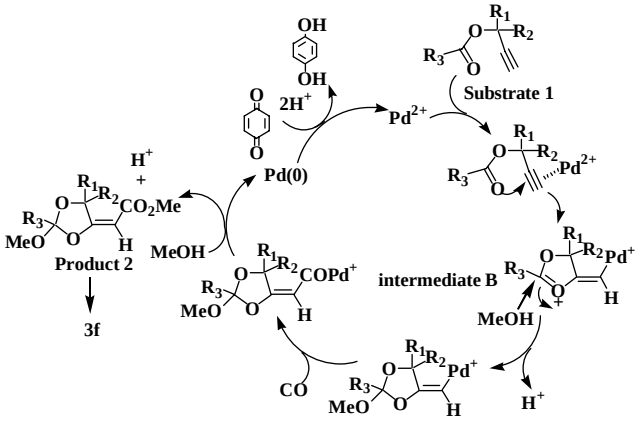


Figure 3. Proposed vinyl palladium complexes **A**.



Scheme 3.

nucleophilicity of the carbonyl oxygen should be increased. Therefore, the yield of the products could be improved. While the electron-withdrawing effect of the nitro group caused decreased nucleophilicity of the carbonyl oxygen in **1g**, the reaction scarcely proceeded. In the case of *p*-methoxybenzoate **1f**, the orthoester bond of **2f** (R_3 = *p*-MeO–Ph) should be easily cleaved, to afford β-ketoester **3f** directly.

2.2. Synthesis of spiro furanones

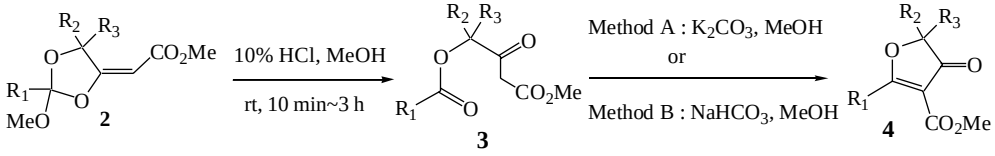
3(2*H*)-Furanones are of pharmacological significance and represent important building blocks for natural product synthesis.[16] A number of syntheses[17] and biological activities, such as selective inhibitory activity on COX-2 (cyclooxygenase-2),[18] inhibitory activity on MAO (monoamine oxidase),[19] anti-cataract effect on spontaneous cataract rats,[20] cytotoxic activity against human tumor cell[21] and antiallergic activity[22] have been reported. As an application of the above cyclization–carbonylation reaction, the facile synthesis of 3(2*H*)-furanones have been achieved (Scheme 4, Table 2). The cyclic orthoesters **2** were converted to the corresponding γ-acetoxy-β-ketoesters **3** by acid treatment in good yields. When γ-acetoxy-β-ketoesters **3** were treated with a base, Knoevenagel–Claisen type condensation took place, furanones **4** were obtained in good yields. In some cases (**3c** and **3d**), though the use of K_2CO_3 leads to decrease in yield, it has been improved by using $NaHCO_3$.

2.3. Synthesis of steroid derivatives containing spiro furanone fragment

Next, we applied these reaction sequences to steroid derivatives, acetates of ethisterone, mestranol and ethynylestradiol. The cyclization–carbonylation of propargylic acetate **1i** and **1j** in the presence of $(CH_3CN)_2PdCl_2$/*p*-benzoquinone in methanol at 0 °C under carbon monoxide atmosphere (balloon) afforded the corresponding orthoesters **2i** and **2j** in 100 and 86% yields, respectively (Scheme 5, Table 3). In the case of diacetate **1k**, partial deacetylation was observed, **2k** was obtained in 30% yield together with acetate **2l** (43% yield). Treatment of **2i–2k** with 10% HCl in MeOH gave the corresponding β-ketoesters **3i–3k** in 88–98% yields. The spiro furanones **4i–4k** were obtained by treatment of **3i–3k** under basic conditions in 92–99% yields.

2.4. Biological activity

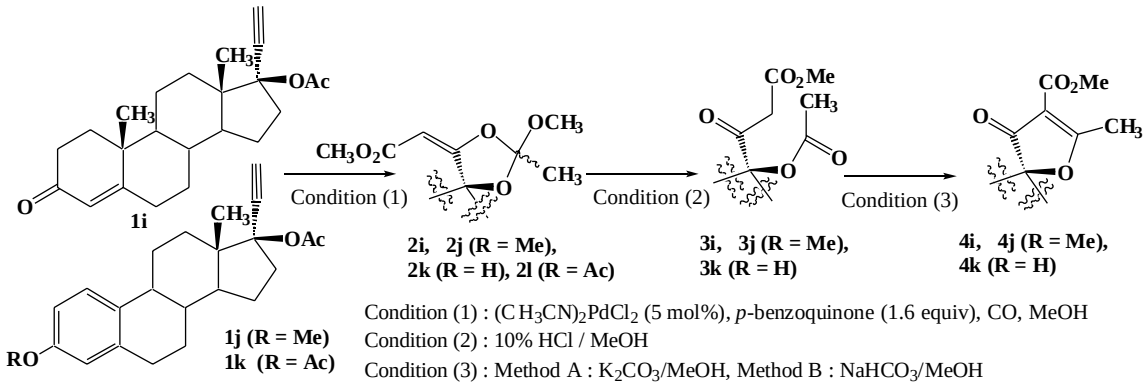
Steroid compounds in general are known for their effects on various receptors, ion channels and enzymes. In the present



Scheme 4.

Table 2. The conversion of orthoesters **2** into furanones **4**

Entry	**2**	R^1	R^2	R^3	Product **3** (yield %)	Condition (method A or B)	Product **4** (yield %)
1	**2a**	Me		$-(CH_2)_6-$	**3a** (98)	rt 3 h (A)	**4a** (quant.)
2	**2b**	Me		$-(CH_2)_5-$	**3b** (96)	rt 3 h (A)	**4b** (96)
3	**2c**	Me		$-(CH_2)_2NBoc(CH_2)_2-$	**3c** (quant.)	rt 1.5 h (A) rt 24 h (B)	**4c** (57) **4c** (96)
4	**2d**	Me	Me	$PhCH_2CH_2$	**3d** (83)	rt 3 h (A) rt 24 h (B)	**4d** (28) **4d** (89)
5	**2e**	Ph		$-(CH_2)_5-$	**3e** (91)	rt 48 h (B)	**4e** (84)



Scheme 5.

Table 3. The reaction of 17-alkynylsteroid derivatives **1i–1k**

Entry	**1**	Condition (1)	Product **2** (yield %)	Condition (2)	Product **3** (yield %)	Condition (3)	Product **4** (yield %)
1	**1i**	0 °C, 15 h	**2i** (quant.)	rt, 0.5 h	**3i** (88)	Method A, rt, 1 h	**4i** (92)
2	**1j**	0 °C, 72 h	**2j** (86)	rt, 3 h	**3j** (98)	Method B, rt, 24 h	**4j** (99)
3	**1k**	0 °C, 24 h	**2k** (30) (R=H) and **2l** (43) (R=Ac)	rt, 1 h	**3k** (95 from **2k**)	Method B, rt, 24 h	**4k** (94 from **3k**)

study, we examined the effects of synthesized compounds **2i–4k** on isolated cardiovascular preparations and on CYP3A activity.

(1) Cardiovascular effect: in aortic rings precontracted with 10^{-5} M norepinephrine, test compounds (10^{-5} M), showed endothelium-independent relaxant effects. The relaxation was expressed as a percentage of the maximum relaxation by 10^{-4} M papaverine and summarized (Table 4). The spontaneous beating rate of isolated right atria was 193–200 beats per minute. The test compounds (10^{-5} M) slightly affected the beating rate. The change in beating rate was expressed as a percentage of the basal beating rate and summarized (Table 4). Among them, the spiro furanone **4j** had vasorelaxant and bradycardiac activities.

Table 4. Cardiovascular effects of test compounds

Compound no.	Relaxation (%)	Changes in heart rate (%)
2i	9.0±1.4	1.2±1.1
3i	5.4±2.6	1.0±3.0
4i	4.2±2.3	−1.3±1.1
2j	10.0±3.7	2.9±2.6
3j	9.5±1.6	−1.7±7.2
4j	18.7±3.4	−11.4±1.8
4k	7.9±2.2	−2.7±3.9
2l	1.3±1.0	3.9±1.9
2k	13.0±1.9	0.4±3.2
2a	3.1±0.5	5.7±5.1
Estradiol	29.2±5.8	−0.03±5.3

Values are the mean±standard error of the mean from 3 to 5 preparations.

Table 5. Effect of test compounds **2i–4k** on midazolam hydroxylation

Compound no.	Activity
2i	63.8±2.5
3i	69.8±13.9
4i	92.2±2.8
2j	45.2±10.4
3j	47.3±3.2
4j	57.1±3.5
4k	61.5±5.6
2l	60.8±6.5
2k	44.9±5.4

Values are the mean±standard deviation of three experiments.

(2) Inhibitory effect on CYP 3A activity: test compounds **2i–4k** have inhibitory effect on CYP3A activity assessed by midazolam 1′-hydroxylation. Preincubated with 3×10^{-5} M of the test compounds, the activity of rat hepatic microsomes was decreased to 40–90% of control values (Table 5). Some steroid compounds such as 17α-ethynylestradiol and danazol containing a terminal acetylene moiety on the C17 position have been known to decrease CYP3A activity and cause drug–drug interactions in the clinical situation. Though compounds **2i–4k** do not contain the terminal acetylene moiety, they also have inhibitory effect on CYP3A. These results might be a clue to clarifying the mechanism of the inhibition.

3. Conclusion

We have reported Pd(II)-mediated cyclization–carbonylation of propargylic esters. This reaction is considered to be a useful method for the conversion of the acetylene unit to a γ-acetoxy-β-ketoester unit. Based on the NMR experiments, it was presumed that the cyclization reaction was initiated by a nucleophilic attack of carbonyl oxygen to the alkyne carbon coordinated to palladium(II). As an application of this reaction, we have developed a new method for the construction of a spiro furanone skeleton, and steroid derivatives having a spiro furanone fragment were synthesized. Among them, the spiro furanone **4j** had vasorelaxant and bradycardiac activities. Compounds **2i–4k** had inhibitory effect on CYP3A.

4. Experimental

4.1. General experimental methods

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^{1}H, ^{13}C NMR and HMBC spectra were recorded on JEOL AL 400 and JEOL Lambda 500 spectrometer in $CDCl_3$ with Me_4Si as an internal reference. In the case of acetone-d_6, solvent peak were used as a reference (2.04 ppm for ^{1}H and 29.8 ppm for ^{13}C). High-resolution mass spectra (HR-MS) and the fast atom bombardment mass spectra (FAB MS) were obtained with a JEOL GC mate II and a JEOL JMS 600 H spectrometer, respectively. IR spectra were recorded with a JASCO FT/IR-300 spectrometer. All reagents were purchased from commercial sources and used without purification. All evaporations were performed under reduced pressure. For column chromatography, silica-gel (Kieselgel 60) was employed.

4.2. Preparation of substrates

The substrates **1** were prepared by acetylation (Ac_2O/pyridine) of the corresponding alcohols. The acetates **1** except **1f** were known compounds.[23]

4.2.1. 1-Ethynyl-1-cyclohexyl 4-methoxybenzoate 1f. Colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.37–1.57 (2H, m), 1.63–1.75 (4H, m), 2.05–2.24 (4H, m), 2.64 (1H, s), 3.84 (3H, s), 6.90 (2H, d, J=6.8 Hz), 7.99 (2H, d, J=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 22.4 (2C), 25.2, 37.1 (2C), 55.4, 74.2, 75.1, 84.0, 113.5 (2C), 123.4, 131.6 (2C), 163.3, 164.4; HRMS-EI *m/z*: [M^+] calcd for $C_{16}H_{18}O_3$ 258.1256; found 258.1246; IR (KBr) 2937, 1719, 1606, 1253 cm^{-1}. Anal. Found: C, 73.95; H, 7.02 Calcd for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02%.

4.3. General procedure for the cyclization–carbonylation of propargylic esters 1a–1h

A 30 mL two-necked round-bottomed flask, containing a magnetic stirring bar, $(CH_3CN)_2PdCl_2$ (0.05 mmol), *p*-benzoquinone (1.1 mmol) and MeOH (6 mL) was fitted with a rubber septum and three-way stopcock connected to a balloon filled with carbon monoxide. The apparatus was purged with carbon monoxide by pumping–filling via the three-way stopcock. A solution of the substrate **1** (1 mmol) in MeOH (3 mL) was added dropwise to the stirred mixture via a syringe at 0 °C. After being stirred for the appropriate period of time, the mixture was diluted with CH_2Cl_2 (30 mL), washed with 5% NaOH aq (40 mL), and dried over $MgSO_4$. The solution was concentrated under reduced pressure. The crude product was purified by column chromatography on silica-gel. The fraction eluted with hexane–ethyl acetate (100/1–30/1) afforded **2** or **3f**.

4.3.1. Methyl (2*E*)-(2-methoxy-2-methyl-1,3-dioxaspiro[4.6]undec-4-ylidene)acetate 2a. Hexane/ethyl acetate=50:1. Colorless needles. Mp 42 °C (MeOH); ^{1}H NMR (CD_3COCD_3) δ 1.58–1.82 (9H, m), 1.60 (3H, s), 1.90–1.97 (1H, m), 2.53–2.60 (1H, m), 2.67–2.76 (1H, m), 3.24 (3H, s, orthoester), 3.61 (3H, s, ester), 5.21 (1H, s); ^{13}C NMR (CD_3COCD_3) δ 3.2, 23.2, 25.4, 27.9, 27.9, 36.4, 37.6, 49.6 (O*Me* of orthoester), 51.1 (O*Me* of ester), 88.1 (quaternary, O–*C*), 90.2 (OC=*C*H), 124.3 (quaternary, orthoester), 167.1 (*C*O of ester), 176.7 (O*C*=CH); EI-MS *m/z*: 270 (M^+); IR (KBr) 2932, 1714, 1642, 1141, 1044 cm^{-1}. Anal. Found: C, 61.88; H, 8.29 Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20%.

4.3.2. Methyl (2*E*)-(2-methoxy-2-methyl-1,3-dioxaspiro[4.5]dec-4-ylidene)acetate 2b. Hexane/ethyl acetate=50:1. Colorless oil. ^{1}H NMR (CD_3COCD_3) δ 1.33–1.41 (1H, m), 1.60 (3H, s), 1.56–1.70 (6H, m), 1.75–1.81 (1H, m), 2.48–2.57 (1H, m), 2.61–2.69 (1H, m), 3.24 (3H, s, O*Me* of orthoester), 3.61 (3H, s, O*Me*), 5.27 (1H, s); ^{13}C NMR (CD_3COCD_3) δ 22.5, 22.7, 25.2, 25.2, 32.1, 33.2, 49.7 (O*Me* of orthoester), 51.1 (O*Me* of ester), 87.4 (quaternary, O–*C*), 89.2 (OC=*C*H), 124.1 (quaternary, orthoester), 167.0 (*C*O of ester), 171.6 (O*C*=CH); EI-MS *m/z*: 256 (M^+); IR (KBr) 2862, 1716, 1649, 1075, 1052, 977 cm^{-1}. Anal. Found: C, 61.22; H, 8.12 Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87%.

4.3.3. *tert*-Butyl (4*E*)-2-methoxy-4-(2-methoxy-2-oxoethylidene)-2-methyl-1,3-dioxa-8-azaspiro[4.5]-decane-8-carboxylate 2c. Hexane/ethyl acetate=30:1. Colorless needles. Mp 78 °C (hexane); ^{1}H NMR (CD_3COCD_3) δ 1.46 (9H, s), 1.58–1.64 (1H, m), 1.65 (3H, s), 1.73–1.79 (1H, m), 2.67–2.85 (2H, m), 2.94–3.10 (2H, m), 3.27 (3H, s), 3.61 (3H, s), 4.01–4.12 (2H, m), 5.34 (1H, s); ^{13}C NMR (CD_3COCD_3) δ 24.8, 28.6, 31.9, 32.9, 40.5 (br), 41.2 (br), 49.9, 51.2, 79.4, 85.4, 89.9, 124.1, 154.8, 166.6, 172.5; FAB-MS *m/z*: 380 (M^++Na); IR (KBr) 1690, 1652, 1135, 1077, 1045 cm^{-1}. Anal. Found: C, 57.27; H, 7.47 Calcd for $C_{17}H_{27}NO_7$: C, 57.13; H, 7.61%.

4.3.3.1. X-ray crystallographic analysis. X-ray diffraction data for **2c** were collected on a Bruker SMART APEX CCD diffractometer equipped with a graphite crystal and

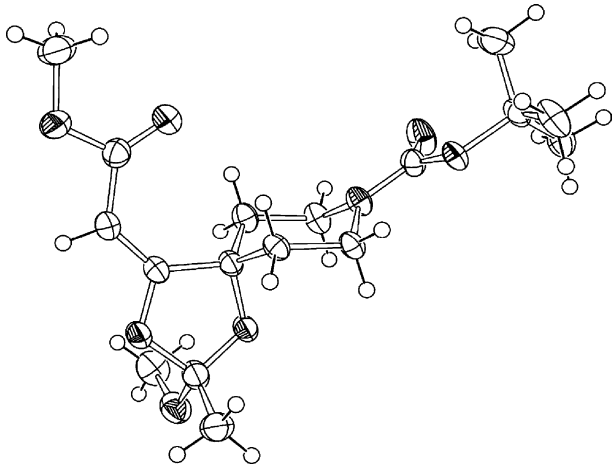


Figure 4.

incident beam monochromator using Mo Kα radiation (λ=0.71073 Å). The structures were solved by the direct method (SHELXS 97[24]) and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. The crystal contains two crystallographically independent molecules, one of which exhibits disorder with respect to

the methyl and methoxy substituents attached to the five-membered ring. An ORTEP[25] diagram of the disorder-free molecule is shown in Figure 4. Crystallographic parameters: $C_{17}H_{27}NO_7$, $M_W=357.40$, triclinic, space group $P\bar{1}$, with unit cell $a=10.4863(7)$ Å, $b=12.5804(8)$ Å, $c=15.345(1)$ Å, $\alpha=74.778(1)°$, $\beta=74.247(1)°$, $\gamma=79.900(1)°$, and $V=1868.2(2)$ Å^3. $Z=4$, $D_{calcd}=1.271$ g cm^{-3}, $T=173$ K, λ(Mo Kα)$=0.71073$ Å. $R1(I>2\sigma(I))=0.0574$, $wR2=0.1602$, $R1$(all data)$=0.0730$, $wR2=0.1732$, 9154 independent reflections (R(int)$=0.0154$), 488 parameters refined on F^2. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre.

4.3.4. Methy (2*E*)-[2-methoxy-2,5-dimethyl-5-(phenylethyl)-1,3-dioxolan-4-ylidene]acetate 2d. Hexane/ethyl acetate=50:1. Colorless oil. Mixture of two diastereomers (ratio=2:1). ^{1}H NMR (CD_3COCD_3) (major diastereomer) δ 1.69 (3H, s), 1.77 (3H, s), 2.25–2.51 (2H, m), 2.55–2.77 (2H, m), 3.31 (3H, s), 3.62 (3H, s), 5.37 (1H, s), 7.13–7.28 (5H, m); (minor diastereomer) δ 1.65 (3H, s), 1.73 (3H, s), 3.35 (3H, s), 3.61 (3H, s), 5.32 (1H, s); ^{13}C NMR (CD_3COCD_3) (major diastereomer) δ 22.9, 23.7, 30.9, 40.0, 50.5, 51.2, 88.1, 89.9, 124.0, 126.6, 129.2, 129.2, 142.7, 167.1, 174.1; EI-MS *m*/*z*: 275 (M^+-OMe); IR (KBr) 2946, 1715, 1652, 1142, 1104, 1055 cm^{-1}. Anal. Found: C, 66.52; H, 7.32 Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24%.

4.3.5. Methyl (2*E*)-(2-methoxy-2-phenyl-1,3-dioxaspiro[4.5]dec-4-ylidene)acetate 2e. Hexane/ethyl acetate=100:1. Colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.40–1.50 (2H, m), 1.63–1.75 (5H, m), 1.91–1.94 (1H, m), 2.44 (1H, dt, $J=5.2$, 13.2 Hz), 2.66–2.71 (1H, m), 3.32 (3H, s), 3.64 (3H, s), 5.43 (1H, s), 7.36–7.37 (3H, m), 7.55–7.58 (2H, m); ^{13}C NMR ($CDCl_3$) δ 21.9, 22.1, 24.4, 31.7, 31.7, 50.5, 51.0, 87.6, 89.6, 122.1, 125.8, 128.3, 129.5, 137.6, 166.7, 173.5; FAB-MS *m*/*z*: 319 (M^++H); IR (KBr) 2934, 1715, 1652, 1135, 1043 cm^{-1}. Anal. Found: C, 68.19; H, 6.82 Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97%.

In the case of *p*-methoxybenzoate **1f**, γ-acetoxy-β-ketoester **3f** was obtained directly.

4.3.6. 1-(3-Methoxy-1,3-dioxopropyl)cyclohexyl 4-methoxy-benzoate 3f. Hexane/ethyl acetate=30:1. Colorless oil. ^{1}H NMR (CD_3COCD_3) δ 1.29–1.38 (1H, m), 1.58–1.81 (7H, m), 2.20–2.23 (2H, m), 3.59 (2H, s), 3.62 (3H, s), 3.90 (3H, s), 7.06 (2H, d, $J=8.8$ Hz), 8.05 (2H, d, $J=8.8$ Hz); ^{13}C NMR (CD_3COCD_3) δ 22.1 (2C), 25.6, 31.4 (2C), 43.5, 52.2, 56.0, 85.8, 114.9 (2C), 122.7, 132.7 (2C), 165.0, 165.9, 168.2, 202.1; HRMS-FAB *m*/*z*: [M^++H] calcd for $C_{13}H_{23}O_6$ 335.1495; found 335.1495; IR (KBr) 2939, 1752, 1707, 1605, 1255 cm^{-1}. Anal. Found: C, 63.41; H, 6.52 Calcd for $C_{18}H_{22}O_6 1/2H_2O$: C, 62.96; H, 6.75%.

4.3.7. Methyl (2*E*)-[2-methoxy-2-(4-nitrophenyl)-1,3-dioxaspiro[4.5]dec-4-ylidene]acetate 2g. Hexane/ethyl acetate=70:1. Colorless oil. ^{1}H NMR (CD_3COCD_3) δ 1.39–1.42 (2H, m), 1.61–1.76 (5H, m), 1.93–1.97 (1H, m), 2.47 (1H, dt, $J=5.2$, 13.2 Hz), 2.67–2.76 (1H, m), 3.39 (3H, s), 3.64 (3H, s), 5.48 (1H, s), 7.85 (2H, d, $J=8.8$ Hz), 8.31 (2H, d, $J=8.8$ Hz); ^{13}C NMR ($CDCl_3$) δ 22.5, 22.7, 25.1, 32.3, 32.4, 50.7, 51.4, 88.6, 90.8, 121.9, 124.4, 128.0, 145.5, 149.6, 166.8, 173.4; HRMS-FAB *m*/*z*: [M^++H] calcd for $C_{18}H_{22}NO_7$ 364.1396; found 364.1385; IR (KBr) 2934, 1716, 1655, 1528, 1354, 1134 cm^{-1}. Anal. Found: C, 57.65; H, 5.82; N, 3.41 Calcd for $C_{18}H_{21}NO_7 1/2H_2O$: C, 58.06; H, 5.96%; N, 3.76.

4.3.8. 1,1′-(1-Methoxy-2-propynylidene)bisbenzene 5. Hexane/ethyl acetate=50:1. Colorless oil. Spectral data was identical with that of literature's.[10]

4.3.9. 3,3-Dimethoxy-1,1-diphenyl-1-propen-2-ol acetate 6. Hexane/ethyl acetate=50:1. Colorless needles. Mp 74 °C (hexane); ^{1}H NMR ($CDCl_3$) δ 1.97 (3H, s), 3.36 (6H, s), 4.77 (1H, s), 7.20–7.40 (10H, m); ^{13}C NMR ($CDCl_3$) δ 20.8, 54.9, 101.1, 127.6, 127.9, 128.1, 128.3, 129.8, 135.7, 138.1, 138.3, 140.7, 168.4; FAB-MS *m*/*z*: 281 (M^+-MeO); IR (KBr) 1764, 1193, 1074, 1228 cm^{-1}. Anal. Found: C, 72.80; H, 6.44 Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45.

4.4. Preparation of γ-hydroxy-β-ketoesters 3

A solution of the orthoester **2** (1 mmol) in MeOH (10 mL), H_2O (2 mL) and 10% HCl aq (1 mL) was stirred for the appropriate period of time, the mixture was diluted with EtOAc (30 mL) and H_2O (30 mL). The organic layer was dried over $MgSO_4$. The solution was concentrated under reduced pressure. The crude product was purified by column chromatography on silica-gel. The fraction eluted with hexane–ethyl acetate (10/1–4/1) afforded **3**.

4.4.1. Methyl 3-(1-acetoxycycloheptyl)-3-oxopropanoate 3a. Hexane/ethyl acetate=10:1. Colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.59 (9H, br s), 1.94–2.10 (3H, m), 2.11 (3H, s), 3.48 (2H, s), 3.72 (3H, s); ^{13}C NMR ($CDCl_3$) δ 21.1, 22.7, 29.4, 34.2, 42.7, 52.4, 89.2, 167.7, 170.5, 201.0; FAB-MS *m*/*z*: 257 (M^++H); IR (KBr) 2931, 1737, 1247 cm^{-1}. Anal. Found: C, 60.62; H, 7.82 Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87%.

4.4.2. Methyl 3-(1-acetoxycyclohexyl)-3-oxopropanoate 3b. Hexane/ethyl acetate=10:1. Colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.22–1.32 (1H, m), 1.47–1.61 (2H, m), 1.66–1.73 (5H, m), 2.02–2.06 (2H, m), 2.13 (3H, s), 3.50 (2H, s), 3.72 (3H, s); ^{13}C NMR ($CDCl_3$) δ 20.9, 21.2, 24.9, 30.7, 42.8, 52.4, 85.2, 167.6, 170.4, 201.2; EI-MS *m*/*z*: 242 (M^+); IR (KBr) 2942, 1739, 1234 cm^{-1}. Anal. Found: C, 59.28; H, 7.48 Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49%.

4.4.3. Methyl 3-(4-acetoxy-1-*tert*-butoxycarbonylpiperidin-4-yl)-3-oxopropanoate 3c. Hexane/ethyl acetate=4:1. Colorless needles. Mp 99 °C (hexane); ^{1}H NMR ($CDCl_3$) δ 1.46 (9H, s), 1.89–2.04 (4H, m), 2.15 (3H, s), 3.03–3.10 (2H, m), 3.51 (2H, s), 3.73 (3H, s), 3.89–4.02 (2H, m); ^{13}C NMR ($CDCl_3$) δ 20.8, 28.4, 30.4, 38.8 (br), 42.8, 52.5, 80.0, 83.0, 154.6, 167.3, 170.3, 199.9; FAB-MS *m*/*z*: 344 (M^++H); IR (KBr) 1754, 1682, 1273, 1228 cm^{-1}. Anal. Found: C, 55.91; H, 7.27; N, 3.83 Calcd for $C_{16}H_{25}NO_7$: C, 55.97; H, 7.34; N, 4.08%.

4.4.4. Methyl 4-acetyloxy-4-methyl-3-oxo-6-phenylhexanoate 3d. Hexane/ethyl acetate=10:1. Colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.60 (3H, s), 2.04–2.28 (2H, m), 2.06

(3H, s), 2.56–2.67 (2H, m), 3.50 (1H, d, $J=15.6$ Hz), 3.58 (1H, d, $J=15.6$ Hz), 3.72 (3H, s), 7.14–7.21 (3H, m), 7.26–7.30 (2H, m); ^{13}C NMR ($CDCl_3$) δ 20.4, 21.0, 29.5, 37.7, 43.4, 52.4, 86.1, 126.2, 128.3, 128.5, 140.8, 167.4, 170.3, 201.0; FAB-MS *m/z*: 293 ($M^+ + H$); IR (KBr) 2951, 1741, 1249 cm^{-1}. Anal. Found: C, 65.44; H, 6.88 Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90%.

4.4.5. 1-(3-Methoxy-1,3-dioxopropyl)cyclohexyl benzoate 3e. Hexane/ethyl acetate=50:1. Colorless oil. ^{1}H NMR (CD_3COCD_3) δ 1.30–1.37 (1H, m), 1.58–1.85 (7H, m), 2.23–2.26 (2H, m), 3.57 (2H, s), 3.71 (3H, s), 7.47–7.51 (2H, m), 7.58–7.64 (1H, m), 8.07–8.10 (2H, m); ^{13}C NMR (CD_3COCD_3) δ 21.4 (2C), 25.0, 31.8 (2C), 42.8, 52.4, 85.7, 128.6, 129.4, 129.9, 133.7, 165.6, 167.7, 201.3; EI-MS *m/z*: 304 (M^+); IR (KBr) 2940, 1752, 1717, 1292 cm^{-1}. Anal. Found: C, 67.12; H, 6.80 Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62%.

4.5. Preparation of furanones 4a–4e

(*Method A*). A solution of the γ-hydroxy-β-ketoester **3** (1 mmol) in MeOH (8 mL) and K_2CO_3 (138 mg, 1 mmol) was stirred for the period of time, the mixture was diluted with EtOAc (30 mL) and H_2O (30 mL). The organic layer was dried over $MgSO_4$. The solution was concentrated under reduced pressure. The crude product was purified by column chromatography on silica-gel. The fraction eluted with hexane–ethyl acetate (20/1–3/1) afforded **4**.

(*Method B*). $NaHCO_3$ (2 equiv) was used instead of K_2CO_3 (1 equiv).

4.5.1. Methyl 2-methyl-4-oxo-1-oxaspiro[4.6]undec-2-en-3-carboxylate 4a. Hexane/ethyl acetate=5:1. Colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.61–1.76 (10H, m), 1.87–1.95 (2H, m), 2.60 (3H, s), 3.83 (3H, s); ^{13}C NMR ($CDCl_3$) δ 18.0, 22.3, 29.2, 35.2, 51.5, 95.0, 106.4, 163.7, 195.3, 201.2; HRMS-EI *m/z*: [M^+] calcd for $C_{13}H_{18}O_4$ 238.1205; found 238.1210; IR (KBr) 2929, 1710, 1594, 1441, 1205, 1146 cm^{-1}.

4.5.2. Methyl 2-methyl-4-oxo-1-oxaspiro[4.5]dec-2-en-3-carboxylate 4b. Hexane/ethyl acetate=2:1. Colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.33–1.42 (1H, m), 1.57–1.81 (9H, m), 2.63 (3H, s), 3.83 (3H, s); ^{13}C NMR ($CDCl_3$) δ 18.0, 21.4, 24.3, 31.6, 51.5, 92.2, 107.1, 163.7, 195.3, 201.2; HRMS-EI *m/z*: [M^+] calcd for $C_{12}H_{16}O_4$ 224.1049; found 224.1048; IR (KBr) 2939, 1709, 1593, 1442, 1199 cm^{-1}.

4.5.3. Methyl 8-*tert*-butoxycarbonyl-2-methyl-4-oxo-1-oxa-8-azaspiro[4.5]dec-2-en-3-carboxylate 4c. Hexane/ethyl acetate=2:1. Colorless needles. Mp 110 °C (hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 1.48 (9H, s), 1.50–1.63 (2H, d-like, br), 1.89–1.97 (2H, m), 2.66 (3H, s), 3.15 (2H, br), 3.84 (3H, s), 4.11 (2H, br); ^{13}C NMR ($CDCl_3$) δ 18.0, 28.4, 31.3, 39.3 (br), 51.7, 80.1, 89.4, 107.5, 154.5, 163.2, 195.5, 198.7; HRMS-EI *m/z*: [M^+] calcd for $C_{16}H_{23}NO_6$ 325.1525; found 325.1536; IR (KBr) 2871, 1705, 1604, 1426, 1167 cm^{-1}.

4.5.4. Methyl 2,5-dimethyl-4-oxo-5-(1-phenylethyl)-4,5-dihydrofuran-3-carboxylate 4d. Hexane/ethyl acetate=5:1. Colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.44 (3H, s), 2.04–2.17 (2H, m), 2.53 (2H, t, $J=8.0$ Hz), 2.60 (3H, s), 3.85 (3H, s), 7.12–7.28 (5H, m); ^{13}C NMR ($CDCl_3$) δ 17.8, 22.1, 29.3, 38.1, 51.6, 92.4, 107.9, 126.2, 128.3, 128.5, 140.5, 163.3, 196.0, 199.8; HRMS-FAB *m/z*: [$M^+ + H$] calcd for $C_{16}H_{19}O_4$ 275.1283; found 275.1285; IR (KBr) 2950, 1709, 1592, 1443, 1199 cm^{-1}. Anal. Found: C, 69.6; H, 6.70 Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61%.

4.5.5. Methyl 4-oxo-2-phenyl-1-oxaspiro[4.5]dec-2-en-3-carboxylate 4e. Hexane/ethyl acetate=20:1. Colorless needles. Mp 63 °C (hexane); ^{1}H NMR ($CDCl_3$) δ 1.38–1.47 (1H, m), 1.65–1.87 (9H, m), 3.83 (3H, s), 7.46–7.63 (3H, m), 7.91–7.94 (2H, m); ^{13}C NMR ($CDCl_3$) δ 21.6 (2C), 24.4, 31.9 (2C), 51.9, 91.3, 106.8, 128.3, 129.3, 129.4, 133.1, 163.6, 187.3, 201.2; FAB-MS *m/z*: 287 ($M^+ + H$); IR (KBr) 2947, 1702, 1604, 1567, 1387, 1089 cm^{-1}. Anal. Found: C, 71.28; H, 6.39 Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34%.

4.6. Reaction of steroids

The cyclization–carbonylation of propargylic esters **1i–1k**

A 100 mL two-necked round-bottomed flask, containing a magnetic stirring bar, $(CH_3CN)_2PdCl_2$ (0.025 mmol), *p*-benzoquinone (0.8 mmol) and MeOH (7 mL) was fitted with a rubber septum and three-way stopcock connected to a balloon filled with carbon monoxide. The apparatus was purged with carbon monoxide by pumping–filling via the three-way stopcock. A solution of the substrate **1** (0.5 mmol) in MeOH (35 mL) was added dropwise to the stirred mixture via a syringe at 0 °C. After being stirred for the appropriate period of time at 0 °C, the mixture was diluted with CH_2Cl_2 (70 mL), washed with 5% NaOH aq (50 mL), and dried over $MgSO_4$. The solution was concentrated under reduced pressure. The crude product was purified by column chromatography on silica-gel. The fraction eluted with hexane–ethyl acetate (30/1–10/1) afforded **2**.

4.6.1. Steroidal spiro orthoester 2i. Hexane/ethyl acetate=10:1. Colorless needles. Mp 70 °C (MeOH); mixture of two diastereomaers (ratio=5:1). ^{1}H NMR ($CDCl_3$) (major diastereomer) δ 0.84–1.05 (2H, m), 0.98 (3H, s), 1.19 (3H, s), 1.35–1.50 (3H, m), 1.59–1.74 (4H, m), 1.66 (3H, s), 1.91–2.03 (4H, m), 2.14–2.47 (5H, m), 2.85–2.93 (1H, m), 3.19 (3H, s), 3.65 (3H, s), 5.62 (1H, s), 5.73 (1H, s); (minor diastereomer) δ 0.96, 1.19, 1.59, 3.38, 3.64 (s each, Me), 5.52, 5.73 (s each, C=C*H*); ^{13}C NMR ($CDCl_3$) (major diastereomer) δ 14.8, 17.3, 20.8, 24.5, 24.5, 31.8, 32.1, 32.8, 33.4, 33.9, 35.6, 36.6, 38.5, 48.8, 49.7, 50.5, 51.3, 53.2, 93.5, 98.1, 120.8, 123.9, 166.5, 169.9, 171.0, 199.4; HRMS-EI *m/z*: [M^+] calcd for $C_{26}H_{36}O_6$ 444.2512; found 444.2512; IR (KBr) 2946, 1721, 1675, 1437, 1196 cm^{-1}.

4.6.2. Steroidal spiro orthoester 2j. Hexane/ethyl acetate=30:1. Colorless needles. Mp 129 °C (MeOH); mixture of two diastereomaers (ratio=5:1). ^{1}H NMR ($CDCl_3$) (major diastereomer) δ 0.98 (3H, s), 1.32–1.60 (5H, m), 1.67 (3H, s), 1.71–2.32 (7H, m), 2.84–3.00 (3H, m), 3.21 (3H, s), 3.64 (3H, s), 3.77 (3H, s), 5.65 (1H, s), 6.63 (1H, br s), 6.69 (1H, dd, $J=8.8$, 1.6 Hz), 7.15 (1H, d, $J=8.8$ Hz); (minor diastereomer) δ 0.95, 1.61, 3.40, 3.63, 3.77 (s each, Me), 5.54

(s, C=C*H*); ^{13}C NMR ($CDCl_3$) (major diastereomer) δ 14.8, 24.1, 24.6, 26.4, 27.6, 29.8, 32.3, 33.8, 39.2, 43.4, 48.8, 50.3 (2C), 51.2, 55.2, 93.4, 98.3, 111.5, 113.8, 120.9, 126.2, 132.3, 138.0, 157.5, 166.7, 169.9; EI-MS *m/z*: 442 (M^+); IR (KBr) 2937, 1722, 1650, 1252, 1082, 1049 cm^{-1}. Anal. Found: C, 70.37; H, 7.83 Calcd for $C_{26}H_{34}O_6$: C, 70.56; H, 7.74%.

4.6.3. Steroidal spiro orthoester 2k. Hexane/ethyl acetate=20:1. Colorless needles. Mp 172 °C (hexane/$CHCl_3$); mixture of two diastereomaers (ratio=5:1). ^{1}H NMR ($CDCl_3$) (major diastereomer) δ 0.96 (3H, s), 1.24–1.74 (7H, m), 1.67 (3H, s), 1.91–2.28 (5H, m), 2.73–2.98 (3H, m), 3.20 (3H, s), 3.63 (3H, s), 4.80 (1H, br), 5.63 (1H, s), 6.53 (1H, d, J=2.4 Hz), 6.59 (1H, dd, J=8.4, 2.4 Hz), 7.07 (1H, d, J=8.4 Hz); (minor diastereomer) δ 0.93, 1.59, 3.38, 3.62 (s each, Me), 5.54 (s, C=C*H*); ^{13}C NMR ($CDCl_3$) (major diastereomer) δ 14.8, 24.1, 24.6, 26.4, 27.5, 29.6, 32.3, 33.8, 39.1, 43.3, 48.8, 50.2 (2C), 51.3, 93.4, 98.3, 112.6, 115.2, 120.9, 126.4, 132.3, 138.2, 153.4, 166.8, 169.9; EI-MS *m/z*: 428 (M^+); IR (KBr) 3444, 2932, 1723, 1689, 1644, 1199, 1126 cm^{-1}. Anal. Found: C, 68.31; H, 7.61 Calcd for $C_{25}H_{32}O_6 1/2H_2O$: C, 68.68; H, 7.60%.

4.6.4. Steroidal spiro orthoester 2l. Hexane/ethyl acetate=20:1. Colorless needles. Mp 129 °C (MeOH); mixture of two diastereomaers (ratio=5:1). ^{1}H NMR ($CDCl_3$) (major diastereomer) δ 0.95 (3H, s), 1.30–1.55 (6H, m), 1.67 (3H, s), 1.70–1.81 (1H, m), 1.93–2.23 (5H, m), 2.25 (3H, s), 2.82–2.98 (3H, m), 3.19 (3H, s), 3.62 (3H, s), 5.63 (1H, s), 6.77 (1H, d, J=2.4 Hz), 6.82 (1H, dd, J=8.4, 2.4 Hz), 7.21 (1H, d, J=8.4 Hz); (minor diastereomer) δ 0.93, 1.59, 2.02, 3.38 (s each, Me), 5.54 (s, C=C*H*); ^{13}C NMR ($CDCl_3$) (major diastereomer) δ 14.7, 21.1, 24.1, 24.6, 26.2, 27.3, 29.5, 32.3, 33.7, 38.8, 43.5, 48.8, 50.2, 50.2, 51.2, 93.4, 98.2, 118.5, 120.9, 121.5, 126.2, 137.7, 138.2, 148.4, 166.7, 169.8 (2C); EI-MS *m/z*: 470 (M^+); IR (KBr) 2931, 1767, 1721, 1651, 1206, 1082, 1047 cm^{-1}. Anal. Found: C, 68.86; H, 7.33 Calcd for $C_{27}H_{34}O_7$: C, 68.92; H, 7.28%.

4.7. Preparation of γ-hydroxy-β-ketoesters 3i–3k

A solution of the orthoester **2** (0.27 mmol) in MeOH (10 mL), H_2O (0.5 mL) and 10% HCl aq (0.5 mL) was stirred for the appropriate period of time, the mixture was diluted with EtOAc (30 mL) and H_2O (30 mL). The organic layer was dried over $MgSO_4$. The solution was concentrated under reduced pressure. The crude product was purified by column chromatography on silica-gel. The fraction eluted with hexane–ethyl acetate (10/1–2/1) afforded **3i–3k**.

4.7.1. Methyl 17-acetoxy-3,20-dioxo-pregna-4-en-21-carboxylate 3i. Hexane/ethyl acetate=2:1. Colorless needles. Mp 61 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 0.85–1.47 (6H, m), 1.02 (3H, s), 1.15 (3H, s), 1.55–1.98 (8H, m), 2.10 (3H, s), 2.22–2.42 (4H, m), 2.72–2.80 (1H, m), 3.34 (1H, d, J=15.6 Hz), 3.52 (1H, d, J=15.6 Hz), 3.70 (3H, s), 5.69 (1H, s); ^{13}C NMR ($CDCl_3$) δ 15.0, 17.3, 20.6, 21.0, 24.5, 31.4, 32.6, 33.2, 33.3, 33.9, 35.6, 35.7, 38.4, 45.9, 46.9, 47.8, 52.3, 52.7, 95.9, 124.0, 167.3, 170.4, 171.3, 199.2, 202.5; HRMS-EI *m/z*: [M^+] calcd for $C_{25}H_{34}O_6$ 430.2355; found 430.2371; IR (KBr) 2948, 1741, 1671, 1253, 1029 cm^{-1}.

4.7.2. Methyl 17-acetoxy-3-methoxy-20-oxo-19-nor-pregna-1,3,5(10)-trien-21-carboxylate 3j. Hexane/ethyl acetate=10:1. Colorless needles. Mp 168 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 1.04 (3H, s), 1.35–1.69 (7H, m), 1.88–1.91 (3H, m), 2.10–2.17 (1H, m), 2.13 (3H, s), 2.31–2.46 (1H, m), 2.79–2.87 (3H, m), 3.41 (1H, d, J=15.6 Hz), 3.61 (1H, d, J=15.6 Hz), 3.74 (3H, s), 3.76 (3H, s), 6.62 (1H, d, J=2.4 Hz), 6.69 (1H, dd, J=8.4, 2.4 Hz), 7.14 (1H, d, J=8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 15.0, 21.1, 24.3, 26.2, 27.3, 29.7, 33.4, 33.6, 38.9, 43.0, 46.0, 46.5, 48.4, 52.3, 55.2, 96.2, 111.5, 113.8, 126.2, 132.1, 137.9, 157.5, 167.4, 171.4, 202.7; EI-MS *m/z*: 428 [M^+]; IR (KBr) 2946, 1754, 1610, 1501, 1251, 1033 cm^{-1}. Anal. Found: C, 69.97; H, 7.57 Calcd for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53%.

4.7.3. Methyl 17-acetoxy-3-hydroxy-20-oxo-19-nor-pregna-1,3,5(10)-trien-21-carboxylate 3k. Hexane/ethyl acetate=3:1. Colorless needles. Mp 189 °C (hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 1.02 (3H, s), 1.29–1.69 (7H, m), 1.82–2.03 (4H, m), 2.14 (3H, s), 2.21–2.26 (1H, m), 2.77–2.86 (3H, m), 3.43 (1H, d, J=15.6 Hz), 3.62 (1H, d, J=15.6 Hz), 3.75 (3H, s), 5.18 (1H, br), 6.55 (1H, d, J=2.4 Hz), 6.61 (1H, dd, J=8.4, 2.4 Hz), 7.04 (1H, d, J=8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 15.0, 21.1, 24.3, 26.1, 27.2, 29.5, 33.4, 33.6, 38.8, 42.8, 46.1, 46.5, 48.4, 52.4, 96.2, 112.7, 115.3, 126.4, 132.0, 138.1, 153.6, 167.8, 171.5, 202.8; HRMS-EI *m/z*: [M^+] calcd for $C_{24}H_{30}O_6$ 414.2042; found 414.2034; IR (KBr) 3467, 2947, 1739, 1252, 1024 cm^{-1}. Anal. Found: C, 69.08; H, 7.26 Calcd for $C_{24}H_{30}O_6 1/4H_2O$: C, 68.80; H, 7.34%.

4.8. Preparation of spiro furanones 4i–4k

4.8.1. 4′-Methoxycarbonyl-5′-methyl-(17*S*)-spiro[androst-4-ene-17,2′-(3′*H*)-furan]-3,3′-dione 4i. Hexane/ethyl acetate=2:1. Colorless needles. Mp 194 °C (hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 0.92–1.17 (2H, m), 1.00 (3H, s), 1.13 (3H, s), 1.29–1.63 (6H, m), 1.78–1.96 (3H, m), 2.00–2.40 (8H, m), 2.57 (3H, s), 3.77 (3H, s), 5.69 (1H, s); ^{13}C NMR ($CDCl_3$) δ 15.1, 17.4, 17.6, 20.3, 23.9, 31.2, 31.2, 31.4, 32.6, 33.8, 35.4, 35.6, 38.4, 47.5, 48.6, 51.4, 52.7, 100.5, 107.7, 124.0, 163.3, 170.5, 196.2, 199.2, 200.5; EI-MS *m/z*: (M^+); 412; IR (KBr) 2941, 1704, 1584, 1438, 1402 cm^{-1}. Anal. Found: C, 72.86; H, 7.74 Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82%.

4.8.2. 4′-Methoxycarbonyl-5′-methyl-(17*S*)-spiro[3-methoxyestra-1,3,5-(10)-triene-17,2′(3′*H*)-furan]-3′-one 4j. Hexane/ethyl acetate=5:1. Colorless needles. Mp 144 °C (hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 1.03 (3H, s), 1.40–1.64 (6H, m), 1.88–2.22 (4H, m), 2.23–2.39 (3H, m), 2.62 (3H, s), 2.84–2.87 (2H, m), 3.77 (3H, s), 3.82 (3H, s), 6.62 (1H, d, J=1.6 Hz), 6.69 (1H, dd, J=8.8, 1.6 Hz), 7.14 (1H, d, J=8.8 Hz); ^{13}C NMR ($CDCl_3$) δ 15.2, 17.7, 23.8, 26.0, 27.4, 29.8, 31.4, 31.6, 38.7, 42.9, 47.2, 49.3, 51.5, 55.2, 101.0, 107.7, 111.5, 113.8, 126.3, 132.3, 137.9, 157.5, 163.5, 196.2, 200.8; EI-MS *m/z*: 410 (M^+); IR (KBr) 2939, 1741, 1706, 1601, 1402, 1146 cm^{-1}. Anal. Found: C, 73.09; H, 7.41 Calcd for $C_{25}H_{30}O_5$: C, 73.15; H, 7.37%.

4.8.3. 4′-Methoxycarbonyl-5′-methyl-(17*S*)-spiro[3-hydroxyestra-1,3,5-(10)-triene-17,2′(3′*H*)-furan]-3′-one 4k. Hexane/ethyl acetate=2:1. Colorless needles. Mp 272 °C (hexane/AcOEt); ^{1}H NMR ($CDCl_3$) δ 1.01 (3H, s),

1.34–1.66 (6H, m), 1.85–1.95 (3H, m), 2.05–2.30 (4H, m), 2.62 (3H, s), 2.79–2.81 (2H, m), 3.84 (3H, s), 5.47 (1H, br), 6.59–6.62 (2H, m), 7.00 (1H, d, $J=7.6$ Hz); ^{13}C NMR ($CDCl_3$) δ 15.3, 17.8, 23.8, 25.8, 27.3, 29.6, 31.3, 31.5, 38.4, 42.6, 47.2, 49.4, 51.5, 101.2, 107.7, 113.0, 115.7, 126.4, 132.0, 137.8, 153.6, 163.4, 196.4, 201.3; HRMS-EI *m/z*: [M^+] calcd for $C_{24}H_{28}O_5$ 396.1937; found 396.1934; IR (KBr) 3349, 2918, 1707, 1684, 1584, 1443, 1160 cm^{-1}. Anal. Found: C, 72.3; H, 7.12 Calcd for $C_{24}H_{28}O_5$: C, 72.7; H, 7.12%.

4.9. NMR experiments

To a stirred solution of **1b** (10 mg, 0.06 mmol) in CD_2Cl_2 (0.5 mL) was added $(CH_3CN)_2PdCl_2$ (16 mg, 0.06 mmol). After the $(CH_3CN)_2PdCl_2$ dissolved completely (ca. 5 min), the spectra was measured immediately.

^{1}H NMR (CD_2Cl_2) δ 1.41–1.64 (5H, m), 1.77–1.94 (4H, m), 1.97 (6H, s, C*H*$_3$CN), 1.99–2.07 (1H, m), 2.29 (3H, s), 5.47 (1H, s); ^{13}C NMR (CD_2Cl_2) δ 2.0, 20.5, 26.5, 27.3, 30.0, 31.8, 34.9, 72.4, 94.1, 116.9, 128.0, 168.5.

4.10. Method for the biological activity test (1)

All experiments comply with the Guiding Principles for the Care and Use of Laboratory Animals Approved by the Japanese Pharmacological Society. The right atria was rapidly isolated from 1 to 3 day old chicks and beating rate measurements were performed as described previously.[26] The aorta was rapidly isolated from male rats (350–450 g) and contractile force measurements with endothelium-denuded aortic rings were performed as described previously.[26] The test compounds were dissolved in DMSO and small alliquots were applied to the organ bath to yield a final concentration of 10^{-5} M.

4.11. Method for the biological activity test (2)

Assay for CYP3A activity (midazolam 1′-hydroxylation) was assessed according to a previously published procedure.[27] Hepatic microsomes isolated from male Splague–Dawley rats (250 g) was preincubated with 3×10^{-5} M of the test compounds and 1 mM NADPH at 37 °C for 20 min, before assaying for CYP3A activity.

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References and notes

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Experimental and theoretical study on the substitution reactions of aryl 2,4-dinitrophenyl carbonates with quinuclidines

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Abstract—The reactions of quinuclidines with phenyl, 4-methylphenyl, and 4-chlorophenyl 2,4-dinitrophenyl carbonates are kinetically evaluated in aqueous solution. The Brønsted-type plots (log k_N vs pK_a of quinuclidinium ions) are linear. The magnitude of the slopes and validated theoretical scales of electrophilicity and nucleophilicity confirm the concerted nature of these reactions.

1. Introduction

The kinetics and mechanisms of the aminolysis of carbonyl compounds are well documented.[1–9] Some of these reports concern the reactions of pyridines with some aryl methyl carbonates, with aryl=phenyl, 4-nitrophenyl, 2,4-dinitrophenyl, and 2,4,6-trinitrophenyl, (hereafter MPC, MNPC, MDNPC, and MTNPC, respectively),[1] the reactions of MNPC, MDNPC, and MTNPC with secondary alicyclic (SA) amines,[2] the reactions of MNPC and MDNPC with quinuclidines[2c] and the reactions of MDNPC with anilines.[2a] Other reactions involving SA amines with phenyl, 4-methylphenyl, and 4-chlorophenyl 2,4-dinitrophenyl carbonates (PDNPC, MPDNPC and ClPDNPC, respectively)[2c,5a,c] and with 4-methylphenyl and 4-chlorophenyl 4-nitrophenyl carbonates (MPNPC and ClPNPC, respectively)[5a,b] have been the subject of experimental studies. Also investigated have been the reactions of phenyl 4-nitrophenyl carbonate (PNPC), MPNPC, ClPNPC, and PDNPC with quinuclidines[4,5] and those of MPDNPC and ClPDNPC with anilines.[5c]

Some of these processes have been described as stepwise, going through a zwitterionic tetrahedral intermediate ($T^{\pm}$). This conclusion has been drawn based on the biphasic Brønsted-type plots obtained (reactions of SA amines with MNPC,[2c] MPNPC,[5a] and ClPNPC[5b] and those of pyridines with MDNPC[1b] and MTNPC[1d]). These biphasic plots show two linear portions, at low (with slope β ca. 1) and high (β ca. 0.3) pK_a values of the conjugate acid of the amine, which have been assigned to rate-determining breakdown and formation of $T^{\pm}$, respectively. In other reactions linear Brønsted plots with slopes within the β range of 0.7–1.1 have been found. These reactions have been associated with stepwise processes, where the breakdown to products is the rate-determining step. This is the case of the reactions of MPC[1c] and MNPC[1a] with pyridines, those of MDNPC with anilines,[2a] and those of MNPC,[2c] PNPC,[4] MPNPC,[5b] and ClPNPC[5b] with quinuclidines. The change in the rate-determining step has been discussed as a function of the different leaving group abilities. In the case of the diaryl carbonates, this change has been argued in terms of the electron withdrawing or electron releasing abilities of the nonleaving groups.

Other aminolysis of carbonates have been found to be concerted. This is the case of the reactions of SA amines with MDNPC,[2c] MTNPC,[2b] PDNPC,[2c] MPDNPC,[5a] and ClPDNPC[5c] and the reactions of MPDNPC and ClPDNPC toward anilines.[5c] These reactions exhibit linear Brønsted-type plots with slopes $\beta=0.4$–0.7 or slightly curved plots. The Brønsted β value alone is not sufficient for the diagnosis of a concerted mechanism. A definitive proof that the title

Keywords: Aminolysis of diaryl carbonates; Electrophilicity scale; Nucleophilicity scale; Electrophilicity/nucleophilicity difference; Reaction mechanisms.
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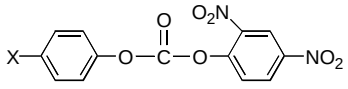
reactions are concerted implies the prediction of the pK_a position at the break of the biphasic Brønsted-type plot (pK_a^0) for a hypothetical stepwise mechanism. It would be further necessary to show that this value falls within the pK_a range of the amines employed.[10] It is also important to obtain a large number of data, which cover a substantial pK_a range above and below the pK_a^0 value.[11]

A pertinent alternative is to complement the experimental study with reliable theoretical and computational models of chemical reactivity in order to establish the global reactivity patterns at the ground state of the substrates. We propose in this work such an analysis based on theoretical scales of global electrophilicity/nucleophilicity for the reference series of diaryl carbonates and alkyl aryl carbonates and related amines,[12] respectively.

In order to further extend our investigations on the kinetics and mechanisms of the aminolysis of diaryl carbonates, in this work we report kinetic results for the quinuclidinolysis of PDNPC, MPDNPC, and ClPDNPC (see structures below) in water. By comparing these reactions with the aminolyses of similar carbonates in aqueous ethanol and in water, the influence of the leaving and nonleaving groups, as well as solvent effects and amine nature on the kinetics and mechanism may be completely examined. Another objective of this work is to confirm the mechanism of the title reactions by theoretical studies.[12]



PDNPC (X = H)
MPDNPC (X = Me)
ClPDNPC (X = Cl)

2. Results and discussion

Under amine excess over the substrate, pseudo-first-order rate coefficients (k_{obsd}) were obtained for all reactions. The experimental conditions of the reactions and the values of k_{obsd} are shown in Tables 1–3.

2.1. Experimental studies of the mechanism based on the analysis of the Brønsted-type plots

The kinetic law obtained under the reaction conditions is that described by Eq. 1, where $DNPO^-$ is 2,4-dinitrophenoxide anion and S is the substrate.

$$\frac{d[DNPO^-]}{dt} = k_{obsd}[S] \quad (1)$$

Plots of k_{obsd} against concentration of free quinuclidine (except for DABCO, see below) at constant pH were linear in accordance with Eq. 2, where k_0 and k_N are the rate coefficients for hydrolysis and aminolysis of the substrates, respectively. The values of k_0 and k_N were obtained as the intercept and slope, respectively, of plots of Eq. 2, and were pH-independent.

$$k_{obsd} = k_0 + k_N[\text{free amine}] \quad (2)$$

The reactions with mixtures of DABCO and $DABCOH^+$ ion were studied at the pH range 5.0–7.0, where a mixture of both amines are present. In these cases the k_N values were obtained through Eqs. 3 and 4. In these equations k_{Nobsd} is a global nucleophilic rate constant (corresponding to the mixture of nucleophiles), $[N]_{tot}$ is the total amine (DABCO + $DABCOH^+$) concentration, F_N and F_{NH} are the molar fractions of DABCO and $DABCOH^+$, respectively, and k_N and k_{NH} are their corresponding nucleophilic

Table 1. Experimental conditions and k_{obsd} values for the reactions of quinuclidines with phenyl 2,4-dinitrophenyl carbonate (PDNPC)[a]

Amine	pH	F_N[b]	$10^4[N]_{tot}/M$[c]	$10^2 k_{obsd}/s^{-1}$	No. of runs
Quinuclidine	11.4	0.5	28.8–962	204–7210	6
3-Hydroxyquinuclidine	9.3	0.24	1.00–10.0	0.648–3.16	6
	9.8	0.5	1.00–962	0.881–3140	11
	10.1	0.67	2.00–11.9	1.74–11.1	6
3-Chloroquinuclidine	8.7	0.33	1.00–10.0	0.414–3.70	6
	9.0	0.50	1.00–24.0	0.361–2650	13
	9.3	0.67	1.00–6.00	0.574–4.76	4
DABCO + $DABCOH^+$	5.0	[d]	31.8–271	0.0427–0.155	6
	5.3	[e]	32.1–225	0.0565–0.188	5
	5.6	[f]	81.5–277	0.137–0.321	4
	6.0	[g]	269–1080	1.32–5.50	5
	6.3	[h]	99.1–991	0.640–5.33	7
	6.5	[i]	92.8–834	1.12–6.62	5
	6.8	[j]	107–1070	2.62–15.2	6
3-Quinuclidinone	7.2	0.33	20.0–120	1.18–9.49	6
	7.5	0.50	20.0–3600	1.47–394	12
	7.8	0.67	20.0–120	3.00–15.2	6

[a] In water, at 25 °C, ionic strength 0.2 M (KCl).
[b] Free amine fraction.
[c] Concentration of total amine (free base plus protonated forms).
[d] Free DABCO and $DABCOH^+$ ion fractions are 0.0001498 and 0.98995, respectively.
[e] Free DABCO and $DABCOH^+$ ion fractions are 0.0003004 and 0.994714, respectively.
[f] Free DABCO and $DABCOH^+$ ion fractions are 0.0006007 and 0.996895, respectively.
[g] Free DABCO and $DABCOH^+$ ion fractions are 0.0015098 and 0.997493, respectively.
[h] Free DABCO and $DABCOH^+$ ion fractions are 0.0030093 and 0.996491, respectively.
[i] Free DABCO and $DABCOH^+$ ion fractions are 0.004762 and 0.994923, respectively.
[j] Free DABCO and $DABCOH^+$ ion fractions are 0.009458 and 0.990385, respectively.

Table 2. Experimental conditions and k_{obsd} values for the reactions of quinuclidines with 4-chlorophenyl 2,4-dinitrophenyl carbonate (ClPDNPC)[a]

Amine	pH	F_N[b]	$10^4[N]_{tot}/M$[c]	$10^2 k_{obsd}/s^{-1}$	No. of runs
Quinuclidine	11.4	0.5	38.4–41.0	430–7070	5
3-Hydroxyquinuclidine	9.36	0.24	1.00–10.0	0.393–3.20	6
	9.8	0.5	1.00–1920	0.965–7160	11
	10.1	0.67	2.00–12.0	1.66–18.2	6
3-Chloroquinuclidine	8.7	0.33	2.00–12.0	0.585–4.80	6
	9.0	0.50	1.00–3360	0.517–6410	13
	9.3	0.67	4.00–12.0	2.55–8.32	5
DABCO + $DABCOH^+$	5.0	[d]	31.8–271	0.043–0.146	6
	5.3	[e]	32.1–273	0.062–0.22	6
	5.6	[f]	81.5–326	0.183–0.397	6
	6.0	[g]	269–915	1.43–4.70	5
	6.3	[h]	99.1–991	0.713–5.18	7
	6.5	[i]	92.8–834	1.25–6.53	5
	6.8	[j]	107–1070	2.50–14.5	7
3-Quinuclidinone	7.2	0.33	20.4–121	2.42–12.8	6
	7.5	0.50	20.2–3600	3.03–585	12
	7.8	0.67	20.2–121	3.48–19.8	6

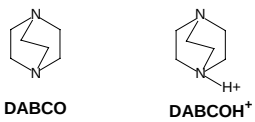
[a] In water, at 25 °C, ionic strength 0.2 M (KCl).
[b] Free amine fraction.
[c] Concentration of total amine (free base plus protonated forms).
[d] Free DABCO and $DABCOH^+$ ion fractions are 0.0001498 and 0.98995, respectively.
[e] Free DABCO and $DABCOH^+$ ion fractions are 0.0003004 and 0.994714, respectively.
[f] Free DABCO and $DABCOH^+$ ion fractions are 0.0006007 and 0.996895, respectively.
[g] Free DABCO and $DABCOH^+$ ion fractions are 0.0015098 and 0.997493, respectively.
[h] Free DABCO and $DABCOH^+$ ion fractions are 0.0030093 and 0.996491, respectively.
[i] Free DABCO and $DABCOH^+$ ion fractions are 0.004762 and 0.994923, respectively.
[j] Free DABCO and $DABCOH^+$ ion fractions are 0.009458 and 0.990385, respectively.

Table 3. Experimental conditions and k_{obsd} values for the reactions of quinuclidines with 4-methylphenyl 2,4-dinitrophenyl carbonate (MPDNPC)[a]

Amine	pH	F_N[b]	$10^4[N]_{tot}/M$[c]	$10^2 k_{obsd}/s^{-1}$	No. of runs
Quinuclidine	11.4	0.5	28.8–962	196–5740	6
3-Hydroxyquinuclidine	9.8	0.5	240–3600	1110–11400	6
3-Chloroquinuclidine	9.0	0.5	120–2400	102–2530	6
DABCO + $DABCOH^+$	5.6	[d]	179–326	0.222–0.378	4
	6.0	[e]	269–1080	0.861–3.80	5
	6.3	[f]	99.1–991	0.463–3.54	7
	6.5	[g]	92.8–834	0.738–4.67	4
	6.8	[h]	268–750	2.94–8.37	4
	7.0	[i]	100–703	2.07–11.7	5
3-Quinuclidinone	7.5	0.5	240–3600	16.7–3240	6

[a] In water, at 25 °C, ionic strength 0.2 M (KCl).
[b] Free amine fraction.
[c] Concentration of total amine (free base plus protonated forms).
[d] Free DABCO and $DABCOH^+$ ion fractions are 0.0006007 and 0.996895, respectively.
[e] Free DABCO and $DABCOH^+$ ion fractions are 0.0015098 and 0.997493, respectively.
[f] Free DABCO and $DABCOH^+$ ion fractions are 0.0030093 and 0.996491, respectively.
[g] Free DABCO and $DABCOH^+$ ion fractions are 0.004762 and 0.994923, respectively.
[h] Free DABCO and $DABCOH^+$ ion fractions are 0.009458 and 0.990385, respectively.
[i] Free DABCO and $DABCOH^+$ ion fractions are 0.014908 and 0.984993, respectively.

rate constants. The values of k_{Nobsd} were obtained as the slopes of linear plots of k_{obsd} versus $[N]_{tot}$ at constant pH. The k_N and k_{NH} values for the reactions with DABCO and $DABCOH^+$, respectively, were determined graphically through Eqs. 3 and 4.



$$k_{obsd} = k_0 + k_{Nobs}[N]_{tot} \quad (3)$$

$$k_{Nobsd} = F_N k_N + F_{NH} k_{NH} \quad (4)$$

The values of k_N for the reactions of DABCO and $DABCOH^+$ ion with the three aryl carbonates, as well as those of the pK_a of the their conjugate acids, were statistically corrected with $q=2$ and $p=2$, respectively. The reactions with the other quinuclidines were not corrected statistically ($q=1$ and $p=1$). The statistical parameter q is the number of equivalent basic sites of the amine and p is the number of equivalent protons of the conjugate acid of the amine.[13]

Table 4 shows the corrected values of pK_a of the quinuclidinium ions and those of the corrected k_N values for the reactions under study. The pK_a values and those of k_N for the quinuclidinolysis of PDNPC, both obtained at ionic strength 0.2 M, agree well with those reported at ionic strength 1.0 M in the same solvent and temperature.[4] With these corrected values the Brønsted-type plots of Figure 1 were obtained. These plots are linear with slopes (β_N) 0.54, 0.57, and 0.57 for the reactions with PDNPC, MPDNPC, and ClPDNPC, respectively.

Table 4. Values of corrected pK_a for the conjugate acids of quinuclidines and corrected k_N values for the reactions of these amines with phenyl 2,4-dinitrophenyl carbonate (PDNPC), 4-methylphenyl 2,4-dinitrophenyl carbonate (MPDNPC), and 4-chlorophenyl 2,4-dinitrophenyl carbonate (ClPDNPC)[a]

Amine	Corrected pK_a	k_N q^{-1}/s^{-1} M^{-1}		
		PDNPC	MPDNPC	ClPDNPC
Quinuclidine	11.4	1510±50	1210±20	2190±80
3-Hydroxyquinuclidine	9.8	670±10	590±40	738±4
3-Chloroquinuclidine	9.0	203±6	210±10	329±4
DABCO	8.6	66±13	56±6	69±11
3-Quinuclidinone	7.5	21.6±0.5	18.4±0.6	27.6±0.4
DABCOH$^+$	3.2[b]	0.09±0.05	0.05±0.04	0.07±0.04

[a] Both the pK_a and k_N values were determined in aqueous solution, at 25.0 °C, ionic strength 0.2 (KCl).
[b] pK_a value from Ref. 14, corrected with $p=2$ (see text).

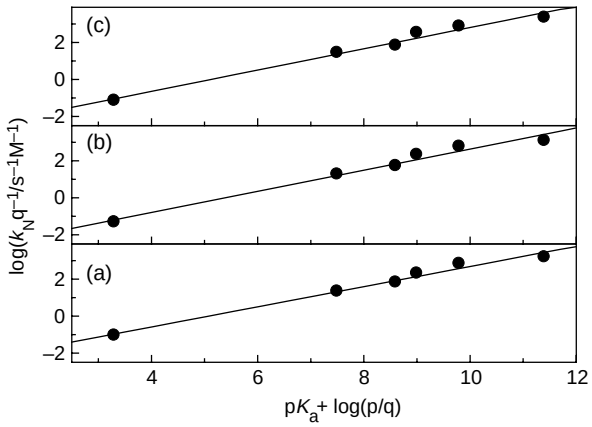


Figure 1. Brønsted-type plots obtained in the reactions of quinuclidines with (a) phenyl 2,4-dinitrophenyl carbonate (PDNPC), (b) 4-methylphenyl 2,4-dinitrophenyl carbonate (MPDNPC) and (c) 4-chlorophenyl 2,4-dinitrophenyl carbonate (ClPDNPC), in water, at 25.0 °C and an ionic strength of 0.2 M.

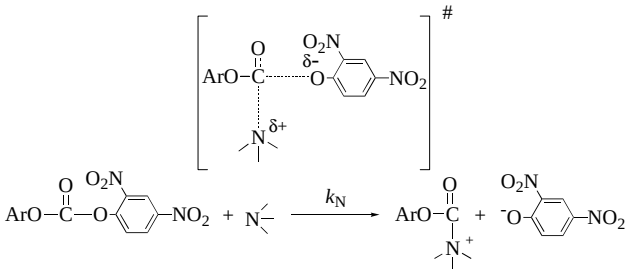
The values of β found for the reactions of quinuclidines with PDNPC, MPDNPC, and ClPDNPC (Fig. 1) are in agreement with those obtained in the following concerted aminolyses in water: SA amines with 2,4,6-trinitrophenyl acetate,[2b] methyl 2,4,6-trinitrophenyl carbonate,[2b] methyl 2,4-dinitrophenyl carbonate,[2c] and phenyl 2,4-dinitrophenyl carbonate[2c] ($\beta=0.41$, 0.36, 0.48, and 0.39, respectively). The slopes are also in agreement with those obtained for the reactions of SA amines with *S*-(2,4-dinitrophenyl) and *S*-(2,4,6-trinitrophenyl) *O*-ethyl thiocarbonates ($\beta=0.56$ and 0.48, respectively),[15] the reactions of quinuclidines with these two substrates ($\beta=0.54$ and 0.47, respectively),[16] and those of anilines with the latter compound ($\beta=0.54$).[17] These β values are also in agreement with those found in the concerted reactions of SA amines and anilines with MPDNPC and ClPDNPC in 44 wt% ethanol–water ($\beta=$ 0.44–0.68),[5a,c] and the concerted methoxycarbonyl group transfer between isoquinoline and pyridines in water ($\beta=$ 0.58).[10a]

The pyridinolysis of methyl 2,4-dinitrophenyl carbonate in water exhibits a biphasic Brønsted-type plot with a pK_a^0 value of 7.8.[1b] It is known that quinuclidines are better nucleofuges from a tetrahedral intermediate than isobasic pyridines,[16,18] which implies a larger pK_a^0 value for the former amines. On the other hand, the change of methoxy or ethoxy to phenoxy as the nonleaving group also enhances the pK_a^0 value.[19] Therefore, the pK_a^0 value for the quinuclidinolysis of PDNPC should be larger than 7.8 if this reaction were stepwise. If the predicted pK_a^0 value were within the pK_a range for the quinuclidines employed in this work, a biphasic Brønsted plot would be expected. As seen in Figure 1 this is not the case. If, on the other hand, the pK_a^0 value were much larger than 7.8 and outside the pK_a range for the quinuclidines, the rate-determining step for the quinuclidinolysis of PDNPC would be the breakdown to products of the tetrahedral intermediate ($T^{\pm}$). Nevertheless, the Brønsted slope obtained for this reaction (Fig. 1) is small compared to the slopes observed when decomposition to products of $T^{\pm}$ is the rate limiting step ($\beta=0.8$–1.1).[1b,2c,4,5a,b,16,20]

Furthermore, there are additional proofs that the title reactions are concerted: (1) the reactions of SA amines with methyl 4-nitrophenyl carbonate (MNPC) in water are stepwise,[2c] in contrast to those of the same amines with methyl 2,4-dinitrophenyl carbonate in the same solvent, which are concerted.[2c] (2) Similarly, the mechanism for the reactions of quinuclidines in water changes from stepwise to concerted by the same change of carbonates.[2c] (3) Other examples are: the stepwise SA aminolysis of MPNPC[5a] and ClPNPC[5b] in aqueous ethanol, in contrast to the concerted reactions of the same amines with MPDNPC[5a] and ClPDNPC[5c] in the same solvent. Namely, in these reactions the addition of a second nitro substituent in the leaving group of the substrate shifts the mechanism from a two-steps to a single-step process.[21] On the other hand, the quinuclidinolysis of phenyl 4-nitrophenyl carbonate in water is stepwise (see above).[4] Therefore, it is likely that the addition of a second nitro substituent to the leaving group of the latter carbonate (to give PDNPC) changes the mechanism from stepwise to concerted. Furthermore, the change of the carbonate from MNPC to PDNPC, MPDNPC or ClPDNPC in their reactions with SA amines changes the mechanism from stepwise to concerted.[2c,5a,c] Since the quinuclidinolysis of MNPC is stepwise, it is reasonable that the quinuclidinolysis of the title substrates would be concerted.

Taking into account the slopes of the Brønsted plots obtained, the arguments given above, the kinetic law and product studies, the most likely mechanism for the reactions under scrutiny is the concerted process. Scheme 1 shows the single-step reaction, with its transition state. In this Scheme,

Ar is 4-X-phenyl (X=H, Me, Cl) and N represents a quinuclidine.



Scheme 1.

In order to evaluate the influence of the nonleaving group of the substrate on the kinetics and mechanism of the aminolysis studied, Brønsted plots (not shown) were obtained. These plots were drawn with the corrected k_N values found in this work (Table 4) and the pK_a values of the conjugate acids of the nonleaving groups (the latter are 10.1, 9.9, and 9.4 for 4-methylphenol, phenol, and 4-chlorophenol, respectively). The β_{nlg} values are negative for all the quinuclidines, ranging from −0.13 to −0.36, with a mean value −0.22. The latter value is acceptable for a concerted mechanism and is in accordance with that found for the concerted phenolysis of diaryl carbonates ($\beta_{nlg}=-0.27$).[22]

The slightly greater reactivity of ClPDNPC with respect to PDNPC and MPDNPC (Table 4) may be traced to the negative value of β_{nlg} and the larger value of the pK_a of 4-methylphenol and phenol as compared to that of 4-chlorophenol. This result is in agreement with theoretical studies.[12,21]

Figure 2 shows a comparison of the Brønsted-type plots obtained for the concerted quinuclidinolysis of PDNPC (this work) and methyl 2,4-dinitrophenyl carbonate (MDNPC),[2c] both in aqueous solution.

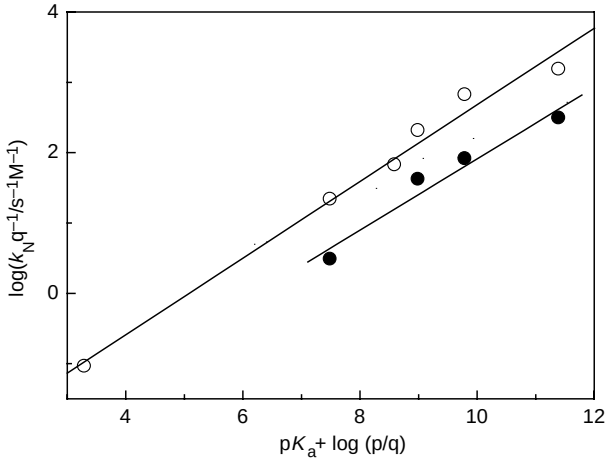


Figure 2. Brønsted-type plots (statistically corrected) for the quinuclidinolysis of phenyl 2,4-dinitrophenyl carbonate (PDNPC) (○, this work) and MDNPC (●, Ref. 2c), in water, at 25.0 °C and an ionic strength of 0.2 M.

The k_N values for the quinuclidinolysis of PDNPC (this work) are larger than those found for the same aminolysis of MDNPC[2c] in the same solvent. This result is in line with the behaviour of the concerted reactions of the same substrates with SA amines[2c] and can be explained by the greater electron withdrawing effect of the PhO as compared to MeO as the nonleaving group in the substrate.

2.2. Nature of the reaction mechanisms based on the theoretical electrophilicity/nucleophilicity indices

As mentioned above, a definitive proof that the title reactions are concerted, implies the prediction of the pK_a position at the break of the biphasic Brønsted-type plot (pK_a^0) for an hypothetical stepwise mechanism, which demands this value to fall within the pK_a range of the amines employed.[10] Another pertinent alternative is to complement the experimental study with reliable theoretical studies of chemical reactivity in order to establish the relative stability of the hypothetical tetrahedral intermediates involved in analogous reactions. We propose here such an analysis based on theoretical scales of global electrophilicity/nucleophilicity for the reference series of diaryl carbonates and alkyl aryl carbonates and related amines,[12] respectively. Validated theoretical scales of electrophilicity/nucleophilicity[21,23–29] have proven to be useful tools to rationalize the observed reaction mechanisms in related systems.[12,21] They may be further used to predict the degree of polar character of the process at the transition state.[30,31] Within this framework, we have previously proposed a useful empirical rule, based on theoretical electrophilicity/nucleophilicity indexes to rationalize the reaction mechanism for a series of carbonates[12] and thiocarbonates[21] derivatives with neutral and charged reagents of varying nucleophilicity.[12] This rule states that the greater the electrophilicity–nucleophilicity difference, the greater concerted character the reaction mechanism will possess. Conversely, a small electrophilicity/nucleophilicity gap will in general be associated with a stepwise reaction mechanism. Other attempts to relate reactivity indexes and reactions mechanisms have been reported.[28,29] Beyond the electrophilicity/nucleophilicity scales, some mechanistic change from stepwise to concerted may be attributed to the different leaving abilities of the nucleofuge.[1b–d,2c,4,5a–c,12,21]

The global electrophilicity index, ω, which measures the stabilization in energy when the system acquires and additional electronic charge (ΔN) from the environment, has been given the following expression:[32]

$$\omega = \frac{\mu^2}{2\eta} \tag{5}$$

Conceptually, the electrophilicity index encompasses two classical concepts involved in the propensity of any atomic or molecular system to bind an extra electronic charge from the environment, namely, the electronegativity $\chi=-\mu$ (where μ is the electronic chemical potential) and the chemical hardness η, measuring the resistance of the system to exchange electronic charge with the environment. Both quantities are easily obtained from a finite difference method together with Koopman's theorem, in terms of the one electron energy levels of the frontier molecular orbitals HOMO and LUMO,[32] as

shown in Eqs. 6 and 7, respectively

$$\mu = \frac{\varepsilon_H + \varepsilon_L}{2} \quad (6)$$

$$\eta \cong \varepsilon_L - \varepsilon_H \quad (7)$$

With μ and η values at hand, the electrophilicity index was evaluated using Eq. 5. The global electrophilicity is not sensitive to solvent effects,[33] and therefore the gas phase value suffices to establish an absolute hierarchy of the electron accepting ability of these systems. Ab inito HF/3-21G calculations were performed using the Gaussian 98 suite of programs[34] in order to evaluate the electronic quantities required to estimate the ground state electrophilicity index for the series of carbonates derivatives considered in the present study.

The experimental and theoretical scales of electrophilicity/nucleophilicity are useful tools to discuss reaction feasibility,[24] inter and intramolecular reactivity[25] and reaction mechanisms.[12,21] The nucleophilicity number ω^- has been represented using the critical points of the molecular electrostatic potential.[12] For the aminolysis of carbonates[12] and thiocarbonates,[21] we reported an empirical rule stating that the larger the electrophilicity/nucleophilicity difference, the greater the concerted character of the reaction mechanism. Conversely, a small electrophilicity/nucleophilecity gap will be associated, in general, with a stepwise reaction mechanism. This model uses the nucleophilicity–electrophilicity difference index, $\Delta_{NE}=|\varpi^- - \omega|$, as a criterion to predict the degree of polar character of the electrophile/nucleophile interaction.[12,21] The parameter ϖ^- is the average nucleophilicity evaluated for a set of secondary alicyclic amines, that are allowed to react with a series of carbonates (electrophiles).[12]

Table 5. Energy of the frontier molecular orbitals HOMO and LUMO (ε_H and ε_L), electronic chemical potential (μ), and chemical hardness (η)

Carbonate	ε_{HOMO} (a.u.)	ε_{LUMO} (a.u.)	μ (eV)	η (eV)
MTNPC	−0.43551	−0.09719	−6.08	11.80
MDNPC	−0.40089	0.00293	−5.41	10.99
ClPDNPC	−0.35179	0.00745	−4.68	9.77
MPDNPC	−0.34269	−0.01218	−4.83	8.99
PDNPC	−0.34412	0.01174	−4.52	9.68
PNPC	−0.34372	0.04075	−4.12	10.46
ClPNPC	−0.35396	0.04445	−4.21	10.84
MPNPC	−0.34020	0.04849	−3.97	10.58
MNPC	−0.37142	0.05283	−4.33	11.54
(*m*)PNPC	−0.35183	0.07957	−3.70	11.74

Table 5 shows the energy values of the frontier molecular orbitals HOMO and LUMO (ε_H and ε_L), electronic chemical potential (μ), and chemical hardness (η) for the series of carbonates and Table 6 shows the electrophilicity index (ω) for the series of carbonates and the corresponding Δ_{NE} values for the substitution reactions that have been kinetically evaluated for reactions with secondary (SA) and tertiary (Q) alicyclic amines, via either concerted or stepwise mechanisms.[2b,c,4,5a–c] As can be seen, those electrophiles that react via a stepwise pathway display Δ_{NE} values smaller than or approximately equal to 1.1 eV. Carbonates that have been evaluated to react via a concerted pathway, on the other hand, consistently show Δ_{NE} values greater than 1.1 eV. However, the dividing line around $\Delta_{NE}=1.1$ eV is certainly arbitrary. A more reliable criterion may be obtained by taking an interval between the maximum and minimum values around the border line. Based on these results, the empirical rule can be applicable for the nucleophilic substitution reactions examined here. These results can be used either to predict the mechanism of the aminolysis of compounds not kinetically evaluated to date or to validate the kinetically proposed mechanism.

Table 6. Nucleophilicity–electrophilicity differences (Δ_{NE})[a] and predicted and experimenthal mechanisms for the reactions of secondary alicyclic (SA) amines and quinuclidines (Q) with diaryl carbonates and alkyl aryl carbonates

HF/3-21G				Mechanism	
Carbonate	ω (eV)	Amine series	Δ_{NE} (eV)[a]	Exptl	Pred.
MTNPC	1.57	SA	1.80	Conc[2b]	Conc
		Q	1.68		Conc
MDNPC	1.33	SA	1.56	Conc[2c]	Conc
		Q	1.44	Conc[2c]	Conc
ClPDNPC	1.30	SA	1.53	Conc[5c]	Conc
		Q	1.41	Conc[b]	Conc
MPDNPC	1.16	SA	1.39	Conc[5a]	Conc
		Q	1.27	Conc[b]	Conc
PDNPC	1.10	SA	1.33	Conc[2c]	Conc
		Q	1.21	Conc[b]	Conc
PNPC	0.86	SA	1.09		Stepwise
		Q	0.97	Stepwise[4]	Stepwise
ClPNPC	0.84	SA	1.07	Stepwise[5b]	Stepwise
		Q	0.95	Stepwise[5b]	Stepwise
MPNPC	0.84	SA	1.07	Stepwise[5a]	Stepwise
		Q	0.95	Stepwise[5b]	Stepwise
MNPC	0.81	SA	1.04	Stepwise[2c]	Stepwise
		Q	0.92	Stepwise[2c]	Stepwise
(*m*)PNPC	0.58	Q	0.81	Stepwise[4]	Stepwise

[a] $(\Delta_{NE})=|\omega^- - \omega|$; $\varpi^- = -0.228$ and -0.1075 eV for SA and Q, respectively.
[b] This work.

3. Experimental

3.1. Materials

The series of quinuclidines were purified as reported.[4] The carbonates, PDNPC,[4] MPDNPC,[5a] and ClPDNPC,[5c] were prepared as described.

3.2. Kinetic measurements

These were carried out by means of either a HP-8453 diode array spectrophotometer or a Applied Photophysics DX17MV stopped flow spectrophotometer in aqueous solution, at 25.0±0.1 °C, ionic strength 0.2 M (KCl). The reactions were studied by monitoring the appearance of 2,4-dinitrophenoxide anion at 360 nm.

The reactions in the stopped flow spectrophotometer were carried out with unequal mixing. The carbonate dissolved in dry acetonitrile was placed in the smaller syringe (0.1 mL) and the larger syringe (2.5 mL) was filled with the amine aqueous solution. The total acetonitrile concentration was 3.85% (v/v).

All the reactions were examined under excess amine over the substrate. The initial substrate concentration was 5×10^{-5} M, and the pH was maintained by partial protonation of the quinuclidines.

Pseudo-first-order rate coefficients (k_{obsd}) were found throughout and determined by means of the spectrophotometer kinetic software for first order reactions.

3.3. Determination of pK_a values

The pK_a value of the conjugated acid of DABCO was determined by a potentiometric method, in water, at 25.0±0.1 °C, and an ionic strength of 0.2 M (maintained with KCl). The value obtained was 8.9±0.1.

3.4. Product studies

One of the products of the reactions under scrutiny was identified as 2,4-dinitrophenoxide anion, as shown by a comparison of the UV–vis spectra after completion of the reactions with an authentic sample under the same experimental conditions.

4. Concluding remarks

In this work, we have experimentally and theoretically examined the reactivity of diaryl carbonates (PDNPC, MPDNPC and ClPDNPC) toward alicyclic amines. For the reactions of quinuclidines with these substrates the Brønsted-type plots (log k_N vs pK_a of quinuclidinium ions) are linear. The magnitude of the slopes and other arguments suggest that these mechanisms are concerted. The electrophilicity of the diaryl carbonates may be conveniently described in terms of the electronic reactivity index proposed by Parr et al.[32] The global electrophilicity index assesses well the substituent effects of the strong electron withdrawing –NO_2 group, which is known to have its greatest effectiveness at the *para* position[21] of the phenyl ring. The increasing substitutions by one and two –NO_2 groups increases the electrophilicity number and makes an almost additive contribution by group.[21] These analyses are consistent with the available experimental data[35] and also with the recently proposed Hammett substituent constants.[21] On the other hand, the electrophilicity/nucleophilicity scales may also be used to rationalize reaction mechanisms in these systems: while highly electrophilic diaryl carbonates will in general undergo aminolysis via a concerted route, those marginally electrophilic will react with quinuclidines via a stepwise route. This thereby confirms that the quinuclidinolysis of aryl dinitrophenyl carbonates is a concerted process.

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Synthesis of novel tricyclic pyrimidine-fused 5,6-dihydrobenzodiazepines via a Pictet–Spengler-like cyclization

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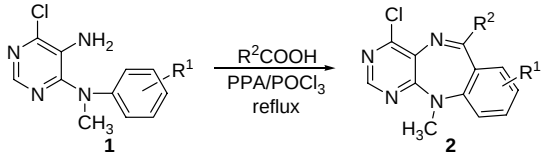
Abstract—Novel pyrimidine-fused 5,6-dihydrobenzodiazepines were prepared via a Pictet–Spengler-like cyclization. It was based on the intramolecular electrophilic substitution of the phenyl ring of 5-amino-6-chloro-4-(*N*-methylanilino)pyrimidine **1** by the iminium intermediate formed with an aldehyde in one pot. The products may be further transformed by subsequent nucleophilic substitution of the chloro atom. This strategy may provide an efficient method to access a library of compounds based on privileged substructures that are of interest in drug discovery.

1. Introduction

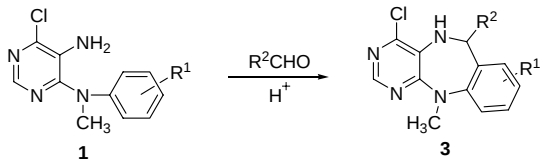
Heterocyclic compounds are often considered privileged structures in medicinal chemistry[1,2] due to their various biological effects. Benzodiazepines represent a class of heterocycles with important activities in the central nervous system and medicinal chemistry efforts in this field have led to the discovery of several CNS drugs. For example, clozapine, olanzapine and quetiapine are used in the clinic for treating schizophrenia, while clonazepam, diazepam, lorazepam, nitrazepam, and oxazepam are used as anti-anxiety drugs. In addition, there are numerous reports of heterocyclic scaffolds containing the benzodiazepine moiety, which show additional biological activities.[3–5]

Another class of heterocycles has often been used as scaffolds in medicinal chemistry are pyrimidines. Consequently, synthetic methodologies for synthesis of novel pyrimidines or pyrimidine-fused compounds are of particular interests to organic and medicinal chemists. For example, synthetic methods have been reported for the efficient syntheses of purines,[6] pyrrolopyrimidines,[7] pyrazolopyrimidines,[8] pyrimidopyrimidines,[9] imidazopyrimidines[10] and furopyrimidines.[11] Recently, we reported a new methodology for the synthesis of pyrimidine-fused benzodiazepines **2**, which entailed an intramolecular Friedel–Crafts type reaction (Scheme 1).[12]



Scheme 1.

As part of our on-going efforts to develop new synthetic methods to prepare novel heterocyclic scaffolds, we envisioned that a Pictet–Spengler-like cyclization[13] of pyrimidine **1** with an aldehyde in place of the carboxylic acid should lead to tricyclic 4-chloro-5,6-dihydropyrimido[4,5-*b*][1,4]benzodiazepines **3** (Scheme 2). This methodology could be complementary to the recently reported one for pyrimido[4,5-*b*][1,4]benzodiazepines.[12] To the best of our knowledge, this is the first approach to fuse pyrimidine with a benzodiazepine by a Pictet–Spengler-like cyclization.[14] Herein, the detailed results from our investigation including exploration of the scope of the cyclization are described.



Scheme 2.

Keywords: Aldehyde; Benzodiazepines; Pyrimidines.
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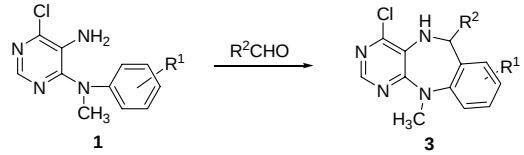
Table 1. Syntheses of 4-chloro-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepines

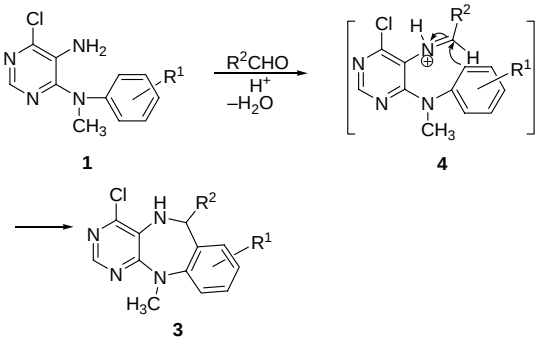


Pyrimidines	R^1	R^2	Products	Yield (%)	Time
1.1	H	$CH_3CH_2CH_2$	**3.1**	65	27 h
1.1	H	CH_3CH_2	**3.2**	47	34 h
1.1	H	Ph	**3.3**	65	48 h
1.1	H	4′-CH_3–C_6H_4	**3.4**	44	24 h
1.1	H	4′-F–C_6H_4	**3.5**	88	29 h
1.1	H	4′-NO_2–C_6H_4	**3.6**	97	16 h
1.2	*p*-CH_3	$CH_3CH_2CH_2$	**3.7**	72	24 h
1.2	*p*-CH_3	CH_3CH_2	**3.8**	57	17 h
1.2	*p*-CH_3	Ph	**3.9**	72	26 h
1.2	*p*-CH_3	4′-CH_3–C_6H_4	**3.10**	46	17 h
1.2	*p*-CH_3	4′-F–C_6H_4	**3.11**	75	35 h
1.2	*p*-CH_3	4′-NO_2–C_6H_4	**3.12**	97	18 h
1.3	*m*-CH_3	$CH_3CH_2CH_2$	**3.13**	81	23 h
1.3	*m*-CH_3	CH_3CH_2	**3.14**	74	21 h
1.3	*m*-CH_3	Ph	**3.15**	71	24 h
1.3	*m*-CH_3	4′-CH_3–C_6H_4	**3.16**	45	17 h
1.3	*m*-CH_3	4′-F–C_6H_4	**3.17**	91	21 h
1.3	*m*-CH_3	4′-NO_2–C_6H_4	**3.18**	99	22 h
1.4	*p*-F	Ph	**3.19**	19	6 days

2. Result and discussion

The starting pyrimidines **1** were readily prepared by a known two-step process from commercially available 5-nitro-4,6-dichloro-pyrimidine and *N*-methylanilines in high yields.[12] Initially, the cyclization reactions of pyrimidine **1.1** (R^1=H) with various aldehydes were investigated. These reactions proceeded smoothly to yield products **3.1**–**3.6** in the presence of excess amount of trifluoroacetic acid in refluxing acetonitrile (Table 1).

A plausible mechanism similar to Pictet–Spengler type reactions was proposed as shown in Scheme 3. It was envisioned that the cyclization reaction proceeded through an iminium intermediate **4** formed between the amino group of pyrimidine **1** and an aldehyde under acid-catalyzed conditions. Iminium **4** underwent an intramolecular electrophilic substitution of the adjacent electron-rich phenyl ring of the anilino moiety to yield the seven-membered ring of the final cyclized product. This is an unusual case since most



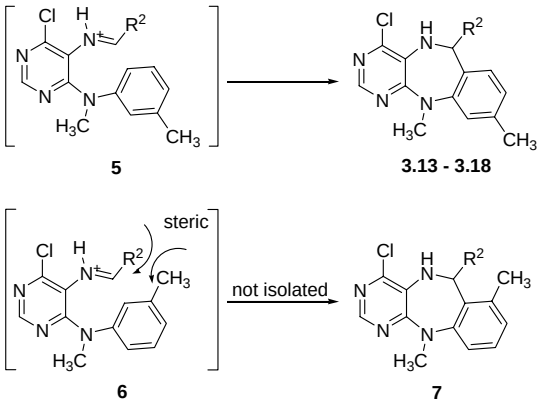
Scheme 3.

Pictet–Spengler reactions in the literature involve an aliphatic amine instead of an aromatic one.

As shown in Table 1, the desired cyclization products were obtained in moderate to excellent yields (44–95%). Higher yields were isolated when electron-withdrawing groups were present in aromatic aldehydes (**3.5**, **3.6**), which may be attributed to their higher reactivity towards imine formation and stabilization effect on the imine intermediates. The scope of the cyclization was further expanded to various pyrimidine derivatives (**1.2**–**1.4**) and the results were also listed in Table 1.

The effect of R^1 substituents on the reactivity of pyrimidine **1** was explored by varying its position and changing the electronegativity. *para*- and *meta*-Methyl substitutions of the anilino phenyl in pyrimidine **1.2** were well tolerated and the desired cyclized products **3.7**–**3.18** were isolated in good to excellent yields. However, a *para*-fluoro substitution (pyrimidine **1.4**) led to a significant decrease in the reaction rate and only 19% of the desired product **3.19** was isolated after 6 days of reaction. These results were consistent with the reaction mechanism that entailed an intramolecular electrophilic substitution of the anilino phenyl ring by iminium ion intermediate **4**. Therefore, when R^1 is an electron-donating group (e.g., CH_3) the phenyl group is more reactive towards an electrophile; while the phenyl group has reduced electron density leading to lower reactivity when R^1 is an electron-withdrawing group (e.g., F). Conversely, when an aromatic aldehyde containing an electron-withdrawing group on its phenyl ring should increase the electro-deficiency of the carbonyl, thereby facilitate imine formation. For instance, **3.6**, **3.12**, **3.18** (R^2=4′-NO_2–C_6H_4) were isolated with excellent yields. It was noteworthy that when R^1 was an *m*-CH_3 two possible regioisomers could be formed. However, only

one regioisomer was isolated (products **3.13–3.18**) suggesting that this reaction could be highly regioselective when a non-symmetrical phenyl ring was present in pyrimidines **1**. This observation may be attributed to the difference in steric effects between the two regioisomers as shown in Scheme 4.

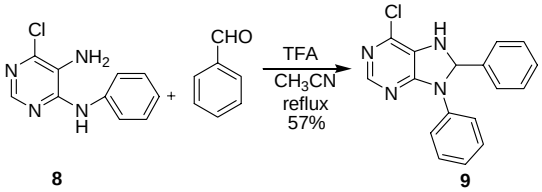


Scheme 4.

When aromatic aldehydes were used regioisomers **7** was not even detected by LC–MS; while the molecular ions of isomers **7** could barely be observed on LC–MS when aliphatic aldehydes were employed. However, the amount was too small to be isolated.

Given the success of this cyclization reaction of pyrimidines **1** with various aldehydes, it was logical to attempt to further expand the scope of this cyclization reaction to ketones. Unfortunately, all attempts on the reactions between **1.1** and various ketones, such as acetone, butan-2-one and acetophenone, failed to generate the desired products.

To investigate whether the 4-anilino group had to be blocked (currently with a methyl group in pyrimidines **1.1–1.4**), the reaction of pyrimidine **8** and benzaldehyde was conducted under the above condition (Scheme 5). No desired cyclization product was observed instead only the dihydropurine compound **9** was obtained in 57% yield. The formation of compound **9** was presumably due to the nucleophilic attack on the iminium ion by the 4-amino group that was more nucleophilic compared to the phenyl ring and the formation of a five-membered ring system was kinetically more favored compared to that of a seven-membered ring system.



Scheme 5.

3. Conclusion

In conclusion, an efficient method was developed for the construction of a novel heterocyclic scaffold, 5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepines. This new method complements the existing chemistries for the preparation of benzodiazepine derivatives. The resulting 4-chloro-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepines may be suitable for further manipulations such as nucleophilic substitution reactions of the 4-chloro group to yield products with more diversity. Therefore, this new reaction is applicable to the preparation of large libraries of novel scaffolds that are of interest in drug discovery.

4. Experimental

4.1. General

The starting compound **1** were prepared by a modified procedure reported by us.[12] Phosphoryl oxychloride was freshly distilled. All other commercial reagents were used as received without additional purification. Melting point was uncorrected. Mass spectra and HPLC (ELSD) data was recorded on an 1100 LC/MS system (Agilent Technology Corporation) with Alltech ELSD 2000, using a 4.6×50 mm Column (CenturySIL C-18 AQ^+, 5μ) with a linear gradient 30–90% (v/v) acetonitrile–water with 0.035% trifluoro-acetic acid over 8 min with a flow rate of 3.5 mL/min. Analytical TLC was performed using 2.5×5 cm plated coated with a 0.25 mm thickness of silica gel 60 F_{254}. Column chromatography was performed using silica gel G (200–300 mesh). All ^1H NMR spectra (300 MHz) are reported as follows: chemical shifts in ppm downfield from TMS as internal standard (δ scale) and $CDCl_3$ or DMSO-d_6 as the solvent. Multiplicities are indicated as the following: multiplicity [s=singlet, d=doublet, t=triplet, m=multiplet, integration and coupling constant (Hz)]. All ^{13}C NMR spectra (75 MHz) were determined with complete proton decoupling and reported in ppm.

4.2. General procedure for 4-chloro-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepines

5-Amino-6-chloro-4-*N*-methyl-anilino-pyrimidine (**1**) (0.85 mmol), the appropriate aldehyde or its derivatives (1.275 mmol) and TFA (0.8 mL) were dissolved in CH_3CN (10.0 mL), and stirred under reflux for 16–48 h. The reaction mixture was concentrated in vacuo, diluted with EtOAc (15 mL), and washed with saturated $NaHCO_3$ (3×15 mL). The water layer was extracted with EtOAc (3×10 mL). The combined EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by flash chromatography (elution with EtOAc/petroleum ether=1:10 for the compound **3.6**, **3.12**, **3.18**, elution with EtOAc/petroleum ether=1:30 for the others).

4.2.1. 4-Chloro-11-methyl-6-propyl-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.1). Yellow oil, yield: 65%, ES-MS: 289.2 [$(M+1)^+$]. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.01 (s, 1H), 7.29–7.34 (m, 1H), 7.03–7.17 (m, 3H), 4.54–4.59 (m, 1H), 4.48 (d, J=4.2 Hz, 1H), 3.49 (s, 3H), 1.97–2.07 (m, 2H), 1.39–1.54 (m, 2H), 1.02

(t, J=7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.9, 145.8, 145.6, 142.5, 135.5, 128.4, 128.1, 126.0, 123.8, 122.3, 57.3, 40.0, 35.1, 20.1, 13.9. Anal. Calcd for $C_{15}H_{17}ClN_4$: C, 62.39; H, 5.93; N, 19.40. Found C, 62.37; H, 5.69; N, 19.40.

4.2.2. 4-Chloro-11-methyl-6-ethyl-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepin (3.2). Yellow oil, yield: 47%, ES-MS: 275.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01 (s, 1H), 7.29–7.34 (m, 1H), 7.03–7.16 (m, 3H), 4.52 (d, J=3.9 Hz, 1H), 4.41–4.48 (m, 1H), 3.49 (s, 3H), 1.98–2.14 (m, 2H), 1.05 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.0, 145.9, 145.6, 142.6, 135.4, 128.5, 128.1, 126.1, 123.9, 122.4, 59.4, 40.1, 26.1, 11.5.

4.2.3. 4-Chloro-11-methyl-6-phenyl-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.3). Yellow oil, yield: 65%, ES-MS: 323.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99 (s, 1H), 7.31–7.40 (m, 4H), 7.24–7.27 (m, 2H), 7.16 (d, J=7.8 Hz, 1H), 7.06 (td, J=7.5, 0.9 Hz, 1H), 6.95 (dd, J=7.5 Hz, 1H), 5.82 (d, J=4.2 Hz, 1H), 4.97 (d, J=3.9 Hz, 1H), 3.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.3, 146.4, 146.0, 143.0, 140.1, 135.7, 129.0, 128.8, 128.0, 127.8, 127.7, 126.3, 124.0, 122.8, 60.8, 39.7. Anal. Calcd for $C_{18}H_{15}ClN_4$: C, 66.98; H, 4.68; N, 17.36. Found C, 67.02; H, 4.95; N, 17.07.

4.2.4. 4-Chloro-11-methyl-6-(4′-methyl-phenyl)-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.4). Yellow oil, yield: 44%, ES-MS: 337.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99 (s, 1H), 7.32–7.38 (m, 1H), 7.14–7.20 (m, 5H), 7.04 (td, J=7.2, 1.2 Hz, 2H), 6.92 (dd, J=7.5, 1.5 Hz, 1H), 5.84 (d, J=3.9 Hz, 1H), 4.91 (d, J=3.3 Hz, 1H), 3.32 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.3, 146.4, 146.0, 142.9, 137.5, 136.9, 135.9, 129.4, 128.9, 128.2, 127.6, 126.4, 123.9, 122.7, 60.5, 39.9, 21.1.

4.2.5. 4-Chloro-11-methyl-6-(4′-fluoro-phenyl)-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.5). Yellow oil, yield: 88%, ES-MS: 341.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 (s, 1H), 7.35–7.40 (m, 1H), 7.16–7.23 (m, 3H), 6.97–7.10 (m, 4H), 5.74 (d, J=3.0 Hz, 1H), 4.96 (d, J=3.3 Hz, 1H), 3.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.0 (d, J=245.0 Hz, 1C), 151.2, 146.5, 145.8, 143.1, 136.1, 136.1, 135.4, 129.2, 127.9 (d, J=5.7 Hz, 2C), 127.7, 124.1, 122.8, 115.5 (d, J=21.8 Hz, 2C), 60.3, 39.7.

4.2.6. 4-Chloro-11-methyl-6-(4′-nitro-phenyl)-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.6). Orange solid, yield: 97%, ES-MS: 368.1 [$(M+1)^+$]. Mp 174.5–175.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.16 (d, J=8.7 Hz, 2H), 8.00 (s, 1H), 7.41–7.46 (m, 1H), 7.35 (d, J=8.4 Hz, 2H), 7.20–7.16 (m, 3H), 5.60 (d, J=5.7 Hz, 1H), 5.19 (d, J=5.7 Hz, 1H), 3.11 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.1, 148.3, 147.2, 146.8, 145.7, 143.5, 134.5, 129.8, 128.4, 126.8, 126.6, 124.5, 123.8, 123.1, 60.8, 39.1. Anal. Calcd for $C_{18}H_{14}ClN_5O_2$: C, 58.78; H, 3.84; N, 19.04. Found C, 58.86; H, 3.74; N, 18.93.

4.2.7. 4-Chloro-8,11-dimethyl-6-propyl-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.7). Yellow oil, yield: 72%, ES-MS: 303.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 (s, 1H), 7.12 (d, J=8.4 Hz, 1H), 7.04 (d, J=8.4 Hz, 1H), 6.94 (d, J=1.8 Hz, 1H), 4.45–4.54 (m, 2H), 3.47 (s, 3H), 2.32 (s, 3H), 1.96–2.04 (m, 2H), 1.36–1.53 (m, 2H), 1.00 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.1, 145.9, 143.0, 142.5, 135.2, 133.5, 128.9, 128.0, 126.7, 122.2, 57.5, 40.0, 35.2, 20.7, 20.2, 13.9.

4.2.8. 4-Chloro-8,11-dimethyl-6-ethyl-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.8). Yellow oil, yield: 57%, ES-MS: 289.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 (s, 1H), 7.11 (d, J=8.1 Hz, 1H), 7.04 (d, J=8.1 Hz, 1H), 6.93 (s, 1H), 4.49 (s, 1H), 4.37–4.41 (m, 1H), 3.47 (s, 3H), 2.32 (s, 3H), 1.98–2.12 (m, 2H), 1.05 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.0, 145.8, 142.8, 142.4, 134.9, 133.4, 128.8, 127.8, 126.7, 122.1, 59.4, 39.9, 26.0, 20.6, 11.4.

4.2.9. 4-Chloro-8,11-dimethyl-6-phenyl-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.9). Yellow oil, yield: 72%, ES-MS: 337.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.97 (s, 1H), 7.27–7.39 (m, 3H), 7.23–7.26 (m, 2H), 7.16 (dd, J=8.7 Hz, 1.5 Hz, 1H), 7.05 (d, J=8.7 Hz, 1H), 6.79 (d, J=1.5 Hz, 1H), 5.73 (d, J=3.9 Hz, 1H), 4.98 (d, J=3.9 Hz, 1H), 3.23 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.5, 146.5, 143.3, 142.9, 140.2, 135.3, 133.8, 129.5, 128.6, 128.5, 127.8, 127.6, 126.3, 122.7, 60.9, 39.7, 20.8.

4.2.10. 4-Chloro-8,11-dimethyl-6-(4′-methyl-phenyl)-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.10). Yellow oil, yield: 46%, ES-MS: 351.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.97 (s, 1H), 7.12–7.19 (m, 4H), 7.06 (d, J=8.1 Hz, 2H), 6.75 (s, 1H), 5.76 (d, J=3.6 Hz, 1H), 4.91 (d, J=3.6 Hz, 1H), 3.28 (s, 3H), 2.36 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.5, 146.4, 143.3, 142.9, 137.3, 137.0, 135.5, 133.7, 129.4, 129.3, 128.2, 127.9, 126.3, 122.6, 60.6, 39.8, 21.1, 20.8.

4.2.11. 4-Chloro-8,11-dimethyl-6-(4′-fluoro-phenyl)-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.11). Yellow solid, yield: 75%, ES-MS: 355.1 [$(M+1)^+$]. Mp 153.7–155.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.98 (s, 1H), 7.16–7.22 (m, 3H), 7.00–7.07 (m, 3H), 6.81 (d, J=1.5 Hz, 1H), 5.66 (d, J=4.8 Hz, 1H), 4.96 (d, J=4.8 Hz, 1H), 3.22 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.0 (d, J=245.0 Hz, 1C), 151.4, 146.6, 143.2, 143.1, 136.1, 135.0, 133.9, 129.6, 128.5, 127.8 (d, J=8.0 Hz, 2C), 127.4, 122.8, 115.5 (d, J=21.8 Hz, 2C), 60.4, 39.6, 20.7. Anal. Calcd for $C_{19}H_{16}ClFN_4$: C, 64.32; H, 4.55; N, 15.79. Found C, 64.14; H, 4.49; N, 15.52.

4.2.12. 4-Chloro-8,11-dimethyl-6-(4′-nitro-phenyl)-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.12). Orange solid, yield: 97%, ES-MS: 382.1 [$(M+1)^+$]. Mp 225.6–227.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.16 (d, J=8.7 Hz, 2H), 7.98 (s, 1H), 7.34 (d, J=8.1 Hz, 2H), 7.23 (d, J=8.1 Hz, 1H), 7.06 (d, J=8.1 Hz, 1H), 7.00 (s, 1H), 5.53 (d, J=5.7 Hz, 1H), 5.18 (d, J=6.0 Hz, 1H), 3.07 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.3, 148.4,

147.1, 146.8, 143.4, 142.9, 134.4, 134.2, 130.2, 129.0, 126.6, 123.7, 123.0, 60.8, 39.0, 20.7.

4.2.13. 4-Chloro-9,11-dimethyl-6-propyl-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.13). Yellow oil, yield: 81%, ES-MS: 303.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 (s, 1H), 7.01 (d, J=7.8 Hz, 1H), 6.96 (s, 1H), 6.88 (dd, J=7.8, 1.2 Hz, 1H), 4.51–4.56 (m, 1H), 4.45–4.46 (m, 1H), 3.48 (s, 3H), 2.34 (s, 3H), 1.94–2.06 (m, 2H), 1.33–1.55 (m, 2H), 0.99 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.0, 145.8, 145.5, 142.5, 138.2, 132.6, 128.2, 125.9, 124.5, 122.9, 57.0, 40.0, 35.2, 21.2, 20.1, 13.9.

4.2.14. 4-Chloro-9,11-dimethyl-6-ethyl-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.14). Yellow oil, yield: 74%, ES-MS: 289.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 (s, 1H), 7.01 (d, J=7.5 Hz, 1H), 6.96 (s, 1H), 6.88 (d, J=7.5 Hz, 1H), 4.49–4.50 (m, 1H), 4.38–4.45 (m, 1H), 3.48 (s, 3H), 2.34 (s, 3H), 1.98–2.14 (m, 2H), 1.05 (t, J=7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.0, 145.8, 145.4, 142.5, 138.2, 132.4, 128.1, 126.1, 124.5, 122.9, 59.1, 40.0, 26.2, 21.2, 11.5. Anal. Calcd for $C_{15}H_{17}ClN_4$: C, 62.39; H, 5.93; N, 19.40. Found C, 62.56; H, 6.12; N, 19.22.

4.2.15. 4-Chloro-9,11-dimethyl-6-phenyl-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.15). Yellow oil, yield: 71%, ES-MS: 337.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.98 (s, 1H), 7.30–7.38 (m, 3H), 7.24–7.27 (m, 2H), 6.98 (s, 1H), 6.86 (d, J=7.8 Hz, 1H), 6.82 (d, J=7.8 Hz, 1H), 5.78 (d, J=3.9 Hz, 1H), 4.95 (d, J=3.9 Hz, 1H), 3.27 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.3, 146.3, 145.8, 142.9, 140.4, 139.0, 132.8, 128.7, 128.1, 127.7, 127.6, 126.3, 124.7, 123.4, 60.5, 39.7, 21.2.

4.2.16. 4-Chloro-9,11-dimethyl-6-(4′-methyl-phenyl)-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.16). Yellow oil, yield: 45%, ES-MS: 351.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.98 (s, 1H), 7.11–7.16 (m, 4H), 6.98 (s, 1H), 6.85 (d, J=8.4 Hz, 1H), 6.79 (d, J=8.4 Hz, 1H), 5.80 (d, J=3.3 Hz, 1H), 4.89 (d, J=3.3 Hz, 1H), 3.30 (s, 3H), 2.36 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.3, 146.3, 145.8, 142.9, 138.8, 137.4, 137.1, 133.0, 129.4, 128.2, 127.6, 126.4, 124.6, 123.3, 60.2, 39.9, 21.2, 21.1.

4.2.17. 4-Chloro-9,11-dimethyl-6-(4′-fluoro-phenyl)-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.17). Yellow oil, yield: 91%, ES-MS: 355.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.99 (s, 1H), 7.19–7.23 (m, 2H), 7.98–7.06 (m, 3H), 6.87 (s, 2H), 5.70 (d, J=4.2 Hz, 1H), 4.94 (d, J=4.2 Hz, 1H), 3.25 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.0 (d, J=245.0 Hz, 1C), 151.3, 146.4, 145.6, 143.1, 139.1, 136.3, 132.4, 127.9, 127.8 (d, J=3.4 Hz, 2C), 127.7, 124.7, 123.5, 115.5 (d, J=21.8 Hz, 2C), 60.0, 39.6, 21.2.

4.2.18. 4-Chloro-9,11-dimethyl-6-(4′-nitro-phenyl)-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.18). Orange solid, yield: 99%, ES-MS: 382.1 [$(M+1)^+$]. Mp 82.4–88.7 °C (no clear melting point observed). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.16 (d, J=8.4 Hz, 2H), 7.99 (s, 1H), 7.34 (d, J=8.4 Hz, 2H), 7.07 (d, J=7.2 Hz, 1H), 6.98 (s, 1H), 6.96 (d, J=7.5 Hz, 1H), 5.56 (d, J=5.4 Hz, 1H), 5.17 (d, J=5.4 Hz, 1H), 3.09 (s, 3H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.2, 148.6, 147.1, 146.7, 145.5, 143.4, 139.9, 131.6, 128.2, 126.9, 126.1, 125.1, 123.7, 123.6, 60.5, 39.0, 21.3.

4.2.19. 4-Chloro-8-fluoro-11-methyl-6-phenyl-5,6-dihydro-pyrimido[4,5-*b*][1,4]benzodiazepine (3.19). 5-Amino-6-chloro-4-*N*-methyl anilinopyrimidine (**1.4**) (200 mg, 0.85 mmol), the benzaldehyde (0.14 mL, 1.275 mmol) and TFA (0.8 mL) were dissolved in CH_3CN (10.0 mL), and stirred under reflux for 6 days. The reaction mixture was concentrated in vacuo, diluted with EtOAc (15 mL), and washed with saturated $NaHCO_3$ (3×15 mL). The water layer was extracted with EtOAc (3×10 mL). The combined EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by flash chromatography to give **3.19** (55 mg, 19%) as a yellow oil (elution with EtOAc/petroleum ether=1:30). Yield: 19%, ES-MS: 341.1 [$(M+1)^+$]. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01 (s, 1H), 7.36–7.43 (m, 3H), 7.28–7.33 (m, 2H), 7.11–7.16 (m, 1H), 7.02 (td, J=8.7, 3.0 Hz, 1H), 6.60–6.63 (dd, J=8.7, 3.0 Hz, 1H), 5.87 (d, J=3.3 Hz, 1H), 4.87 (d, J=3.0 Hz, 1H), 3.28 (s, 3H).

4.2.20. 6-Chloro-8,9-diphenyl-8,9-dihydro-7*H*-purine (9). 6-Chloro-4-*N*-phenylpyrimidine-4,5-diamine (**8**) (200 mg, 0.91 mmol), benzaldehyde (0.14 mL, 1.275 mmol) and TFA (0.8 mL) were dissolved in CH_3CN (10.0 mL), and stirred under reflux for 23 h. The reaction mixture was concentrated in vacuo, diluted with EtOAc (15 mL), and washed with saturated $NaHCO_3$ (3×15 mL). The water layer was extracted with EtOAc (3×10 mL). The combined EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by flash chromatography to give **9** (160 mg, 57%) as a yellow solid (elution with EtOAc/petroleum ether=1:10). ES-MS: 309.1 [$(M+1)^+$]. Mp 72.4–75.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.93 (s, 1H), 7.28–7.31 (m, 5H), 7.12–7.15 (m, 2H), 6.91–6.97 (m, 3H), 5.61 (d, J=4.5 Hz, 1H), 5.13 (d, J=4.8 Hz, 1H).

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Psoracorylifols A–E, five novel compounds with activity against *Helicobacter pylori* from seeds of *Psoralea corylifolia*

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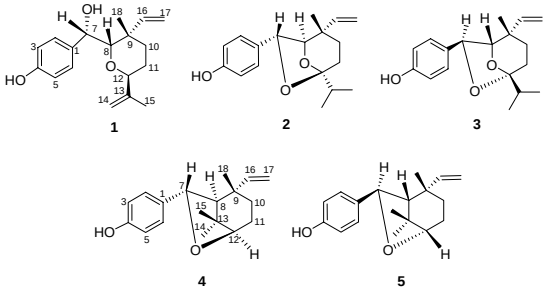
Abstract—Five novel compounds, psoracorylifols A–E (**1**–**5**) with important activity against *Helicobacter pylori* have been isolated from a well-known traditional Chinese medicine (TCM), the seeds of *Psoralea corylifolia*. The structures of compounds **1**–**5**, including their absolute configurations, were established on the basis of spectral methods and biogenetic reason. The structure of **1** was confirmed by a single-crystal X-ray diffraction. Psoracorylifols D and E (**4** and **5**) represent an unprecedented carbon skeleton. The biogenetic origin of psoracorylifols A–E (**1**–**5**) was also postulated.

1. Introduction

Five natural *Helicobacter pylori* inhibitors, psoracorylifols A–E (**1**–**5**) were isolated from the seeds of *Psoralea corylifolia* L. (Fabaceae), which is a well-known traditional Chinese medicine (TCM), and has been applied to cure gynecological bleeding, vitiligo and psoriasis.[1] A series of compounds[2,3] isolated from this TCM showed important biological activities, such as antibacterial,[2a,b,4] antiplatelet,[5a] DNA polymerase and topoisomerase II inhibition.[5b] *H. pylori* infection is closely associated with gastritis, peptic ulcer, and gastric cancer, and eradication of the infection is now recommended as the primary therapy for patients with peptic ulcer disease.[6] Psoracorylifols A–E (**1**–**5**) showed important inhibitory activity against two strains of *H. pylori* (SS1 and ATCC 43504) at the level of MICs of 12.5–25 μg/mL, especially against *H. pylori*-ATCC 43504, a drug resistant strain with the MIC of 128 μg/mL to resist metronidazole. Metronidazole is a main ingredient for the combination therapies of *H. pylori* infection. However, metronidazole resistant *H. pylori* has been reported worldwide and drug resistance has now become one of major reasons for the failure of antimicrobial therapies.[6]

The structures of psoracorylifols A–E (**1**–**5**) were elucidated by spectral methods. Their absolute configurations were proposed on the basis of biogenetic reason and demonstrated by CD spectra. The structure of **1** was confirmed by a single-crystal X-ray diffraction. The origin of psoracorylifols A–E (**1**–**5**) could be biogenetically traced back to (*S*)-(+)-bakuchiol (**6**), a coexisting major compound. We describe herein the isolation, structure elucidation and biosynthetic ways of these antimicrobial compounds.



2. Results and discussion

Psoracorylifol A (**1**) showed the molecular formula of $C_{18}H_{24}O_3$ as deduced by HREIMS. The IR absorptions indicated the presence of hydroxyls (3473 and 3265 cm^{-1}) and aromatic ring (1616 and 1518 cm^{-1}). From its ^1H and ^{13}C NMR data (Tables 1 and 2), six typical aromatic carbons for a 1,4-substituted benzene ring were easily distinguished, the remaining twelve carbons were attributable to the functionalities of two methyls, four methylenes (two olefinic), four methines (one olefinic and three oxygenated) and two quaternary carbons (one olefinic), indicating existence of two terminal double bonds. The structural assignment of **1** was fully achieved by interpretation of 2D NMR including HMQC, HMBC and NOESY (Fig. 1a)

Keywords: Psoracorylifols A–E; Anti *Helicobacter pylori*; Structure elucidation; Biosynthesis; Natural products.
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Table 1. ^{1}H NMR data of compounds **1–5** (CD_3OD)[a]

Protons	1	2	3	4	5
2/6	7.12 (d, 8.4)	7.12 (d, 8.5)	7.12 (d, 8.5)	7.17 (dd, 0.8, 8.6)	7.12 (d, 8.3)
3/5	6.70 (d, 8.4)	6.67 (d, 8.5)	6.70 (d, 8.5)	6.72 (d, 8.6)	6.70 (d, 8.3)
7	4.63 (d, 5.3)	5.04 (br s)	4.93 (br s)	5.23 (br s)	4.93 (br s)
8	3.38 (d, 5.3)	3.83 (br s)	3.88 (br s)	2.09 (br s)	2.05 (br s)
10α	1.62 (d, 7.5)[b]	1.63 (m)	2.02[b]	1.99 (dd, 6.7, 14.4)	1.98[b]
10β	1.60 (d, 7.5)[b]	1.76 (m)	1.46 (m)	1.58 (m)	1.47 (m)
11α	1.98 (m)	1.72 (m)	1.66 (m)	1.83 (m)	1.80 (m)
11β	1.85 (m)	1.52 (m)	1.81 (m)	1.66 (m)	1.99[b]
12	4.40 (t, 4.5)			3.84 (d, 4.2)	3.88 (d, 4.3)
13		1.95 (m)	2.02[b]		
14	*a* 4.89 (br s)	0.94 (3H, d, 6.9)	1.02 (3H, d, 7.0)	1.13 (3H, s)	0.76 (3H, s)
	b 4.91 (br s)				
15	1.55 (3H, s)	0.93 (3H, d, 6.9)	1.07 (3H, d, 7.0)	0.73 (3H, s)	1.29 (3H, s)
16	6.40 (dd, 11.0, 17.7)	6.03 (dd, 10.9, 17.7)	5.85 (dd, 11.0, 17.6)	6.10 (dd, 10.9, 17.8)	6.00 (dd, 10.9, 17.6)
17a	4.97 (dd, 1.5, 17.7)	4.99 (dd, 1.1, 10.9)	5.15 (dd, 1.0, 11.0)	4.93 (dd, 0.8, 10.9)	4.98 (d, 10.9)
17b	5.02 (dd, 1.5, 11.0)	5.06 (dd, 1.1, 17.7)	5.08 (dd, 1.0, 17.6)	5.05 (d, 17.8)	4.95 (d, 17.6)
18	0.84 (3H, s)	0.98 (3H, s)	1.18 (3H, s)	1.08 (3H, s)	1.31 (3H, s)

[a] Data were recorded at 400 MHz, chemical shifts are in ppm, and the coupling constant *J* is in Hz (in parentheses).
[b] Signals were overlapped in the same vertical column.

Table 2. ^{13}C NMR data of compounds **1–5** (CD_3OD)[a]

Carbons	1	2	3	4	5
1	135.6	135.3	135.2	138.0	138.1
2/6	130.0	129.0	129.0	126.6	126.7
3/5	116.0	116.3	116.3	116.2	116.2
4	158.2	158.3	158.3	157.0	157.0
7	74.5	79.6	80.2	81.9	83.9
8	83.6	90.5	89.7	60.9	60.2
9	40.0	40.0	40.2	42.5	42.9
10	35.7	30.1	28.4	28.3	29.4
11	24.5	27.7	27.3	27.7	27.3
12	76.9	113.5	113.9	85.8	85.8
13	145.9	37.0	37.0	44.6	44.6
14	113.3	18.1	18.1	25.3	30.9
15	20.4	18.7	18.7	30.0	24.9
16	144.7	145.5	146.2	151.2	153.4
17	112.7	113.0	114.6	109.5	111.1
18	25.3	24.1	23.4	32.9	29.3

[a] Data were recorded at 100 MHz, chemical shifts (δ) are in ppm.

spectra, and was finally confirmed by a single-crystal X-ray diffraction (Fig. 1b).

Psoracorylifol B (**2**) gave the molecular formula $C_{18}H_{24}O_3$ as determined by HREIMS. IR implied the existence of hydroxyl (3332 cm^{-1}) and aromatic ring (1616 and 1518 cm^{-1}). Analysis of its ^{1}H and ^{13}C NMR data (Tables 1 and 2) has led to identification of all the functionalities. One benzene ring and a terminal double bond accounted for five degrees of unsaturation, according to the molecular formula, two additional rings in **2** were required. HMQC and ^{1}H–^{1}H COSY spectra revealed three structural fragments of –CH=CH_2, –CH_2CH_2– and –$CH(CH_3)_2$. The linkage of structural fragments, quaternary carbons, oxygen atoms and other functional groups were furnished by HMBC spectrum (Fig. 2) to outline the skeleton of **2**. In the HMBC, H-7 correlated with C-1 and C-2/6 to attach the benzene ring to the C-7; H-8 correlated with C-7, and H-7 correlated with C-9 to tentatively link C-7 and C-9 to C-8 (although C-7 and C-8 are bearing protons, the correlation between H-7 and H-8 was not observed in the ^{1}H–^{1}H COSY due to the unfavorable dihedral angle between the two protons); H-10, H-16 and H-18 showed correlations with the quaternary carbon C-9 to locate C-10, C-16 and C-18 at C-9; H_2-11 and H-13 correlated with the quaternary carbon C-12 at δ 113.5 to connect the whole carbon backbone together; both H-7 and H-8 at the oxygenated carbons correlating with C-12 strongly, indicated that C-7, C-8 and C-12 were connected via a ketal group. The presence of one ketal group was supported by the quaternary carbon at δ 113.5 (C-12) and two tertiary carbon signals at 79.6 (C-7) and 90.5 (C-8).[7,8,10]

The relative configuration and the conformation of **2** were mainly assigned by NOESY spectrum (Fig. 3). The H-16 correlated with H-11α, indicating that H-11α and vinyl moiety taking axial bonds were at the same side of the six-membered ring, and were arbitrarily fixed as α-orientation. For the compounds with a 6,8-dioxabicyclo[3,2,1]octane

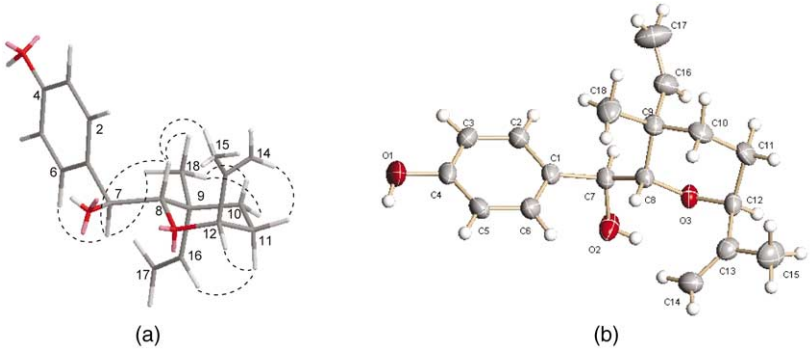


Figure 1. (a) Selected NOESY correlations of **1**; (b) single-crystal X-ray structure of **1**.

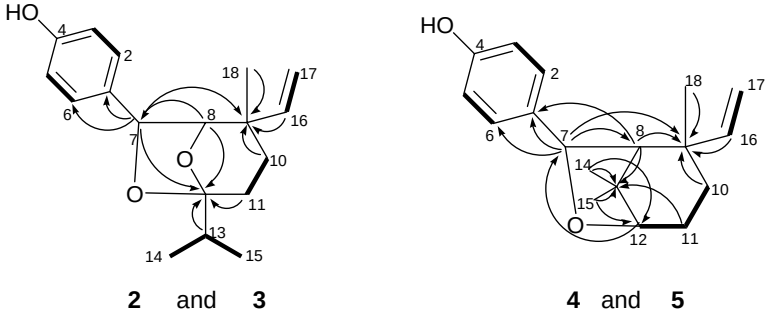


Figure 2. Selected HMBC (H→C) and ^{1}H–^{1}H COSY (—) of **2**–**5**.

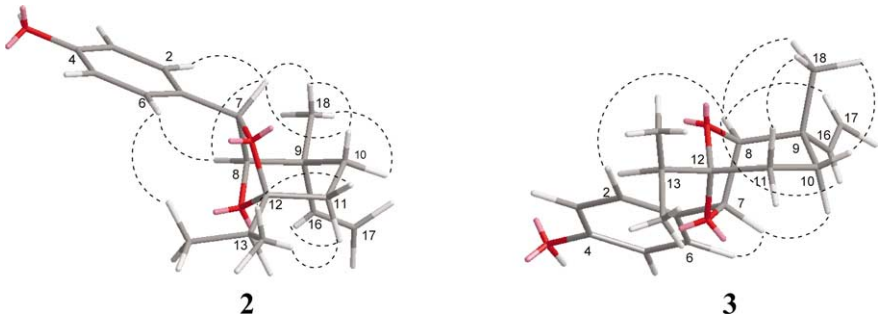


Figure 3. Key NOESY correlations of **2** and **3** (⌒).

core,[7–10] like **2**, the six-membered ring always takes a chair conformation, and the five-membered ring occupying two axial bonds at the six-membered ring should be envelope conformation. Accordingly, C-7 and its bonding oxygen atom in the five-membered ring might take the two axial bonds at C-8 and C-12 to form the bottom of the envelope, and was definitely assigned as in β-orientation. H-7 correlating with both Me-18 and H-10β showed that the 4-hydroxyphenyl was on the opposite side toward C-10.

Psoracorylifol C (**3**) was determined to share a common planar structure with that of **2** by HREIMS and 2D NMR spectra (Fig. 2, Tables 1 and 2). The relative stereochemistry of **3** was also established by NOESY (Fig. 3). The Me-18 correlating with H-11β indicated that both them took the axial bonds, and were randomly designated as β-configuration. CH-7 and its bonding oxygen atom in the five-membered ring occupying two axial bonds at C-8 and C-12 were accordingly assigned as α-configured. H-7 correlated with H-10α allowed us to locate the 4-hydroxyphenyl on the opposite direction toward the C-10. In a similar way as that in **2**, the solution conformation of **3** was also determined as a chair conformation for the six-membered ring and envelope conformer for the five-membered ring.

Psoracorylifols D (**4**) and E (**5**) were stereoisomers with a new carbon skeleton, as established by HREIMS and spectral analysis, especially by the strategic application of combined 2D NMR spectra (Fig. 2, Tables 1 and 2). The correlation between H-7 and H-8 in **4** was not observed in the ^{1}H–^{1}H COSY due to the unfavorable dihedral angle between the two protons.[7–10] In the HMBC of **4**, H-7 correlated with C-1 and C-2/6 enabled us to attach 4-hydroxyphenyl to the C-7. The HMBC correlations of H-7 with C-8 and C-9, and H-8 with C-9 indicated a linkage of C-7, C-8 and C-9. The Me-18, H-16 and H_2-10 were all correlated with the quaternary carbon C-9 to attach Me-18, vinyl group and C-10 to C-9. The C-8, C-14 and C-15 were located to another quaternary carbon C-13 by HMBC correlations of H-8, Me-14 and Me-15 with C-13. The strong HMBC correlation between H-12 and C-7 established the linkage of a 7,12-epoxy. Even though the HMBC correlation between H-12 and C-13 was not observed in **4**, the correlations of H-11β/C-13, H-14/C-12 and H-15/C-12 could still direct a connection of C-12 and C-13, which was the only possibility after the other linkages were settled.

The relative configuration and conformation of **4** were established by NOESY (Fig. 4). The NOESY correlation between Me-14 and H-16 indicated that Me-14 and vinyl moiety might take the axial bonds, and were designated as α-configuration. CH-7 and its bonding oxygen formed the bottom of furan envelope might occupy the two axial bonds at C-8 and C-12, respectively, and were accordingly β-oriented. The H-7 correlating with both Me-18 and H-10β (δ 1.58, m) showed that 4-hydroxyphenyl group was far away from the C-10.

The relative stereochemistry of **5** was fixed by using NOESY and NOE difference spectra (Fig. 4). In the NOESY, H-7 correlating with H-10α showed that the 4-hydroxyphenyl was far away from the six-membered ring, and H-10α occupying the axial bond was randomly put in α-oriented; the Me-15 correlated with H-8 and H-11β, indicating that they were at the same side and were β-oriented; both Me-18 and H-16 showed correlations with H-8, and the correlation of Me-15 and Me-18 showed uncertainty as they were nearly overlapped. The NOE difference spectra of **5** were thus performed to assign the relative configuration of Me-18, in which, the interactions of Me-15 (after irradiation) with Me-14 and Me-18, and the interactions of Me-18 (after irradiation) with Me-15 and

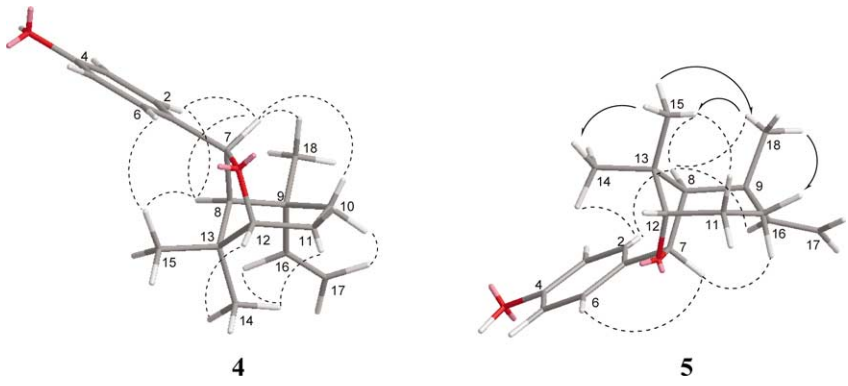
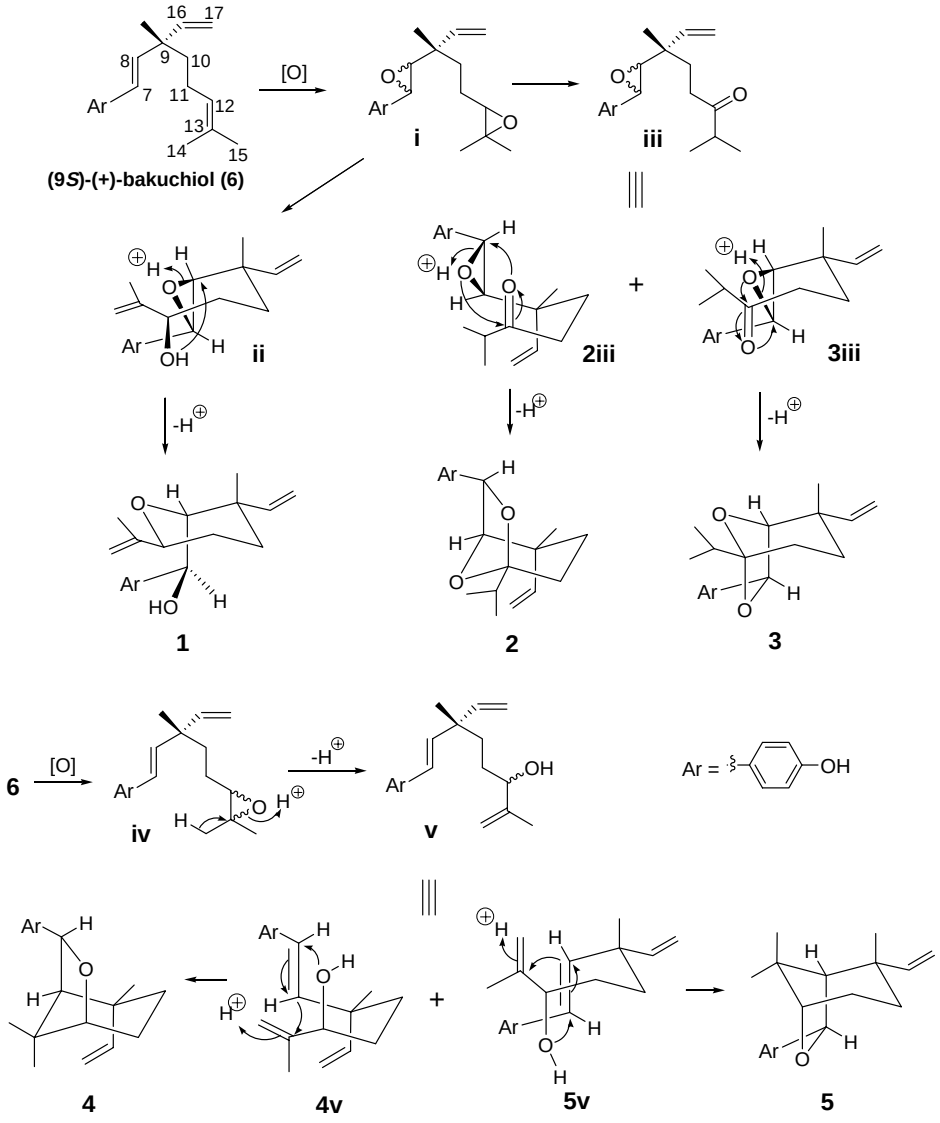


Figure 4. Key NOESY correlations of **4** and **5** (⟷). NOE difference of **5** (irradiated H⌒enhanced H).

H-10β indicated that the Me-18 taking axial bond was β-configuration. These results also indicated that the cyclohexane ring took a chair conformation, and the furan ring was envelope.[7–10]

The origin of psoracorylifols A–E (**1**–**5**) could be rationalized biogenetically (Scheme 1), and traced back to (9*S*)-(+)-bakuchiol (**6**),[2b] a coexisting major compound (up to 3–6% in the seeds). After oxidation, **6** could be transformed into an intermediate **i**, which would then undergo rearrangements to give two key intermediates **ii** and **iii**. The **ii** could be transformed to **1** by an acid induced intramolecular rearrangement. The intermediate **iii** had two isomers **2iii** and **3iii** (at the epoxy), which could be



Scheme 1. Biogenetic pathways proposed for psoracorylifols A–E (**1**–**5**).

Table 3. Absolute configuration and Cotton effects of compounds **1–5**

Compounds	Chiral centers				Cotton effects	
	C-7	C-8	C-9	C-12	270 nm	227 nm
1	*S*	*S*	*S*	*S*	+	−
2	*R*	*R*	*S*	*R*	−	+
3	*S*	*S*	*S*	*S*	+	−
4	*S*	*S*	*S*	*R*	+	−
5	*R*	*R*	*S*	*S*	−	+

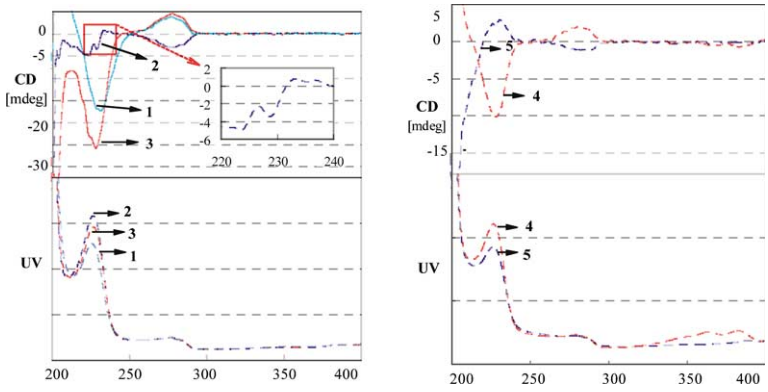


Figure 5. CD and UV spectra of psoracorylifols A–E (**1–5**).

transformed to **2** and **3**, respectively, by intramolecular cyclizations triggered by an acidic catalysis. The **iv** produced by epoxidation of **6** would be transformed to the key intermediate **v** via an acid inducing rearrangement. The key intermediate **v** (12-hydroxyisobakuchiol[11]), a mixture of two isomers **4v** and **5v**, was also isolated in the current research. The intermediates **4v** and **5v** could be transformed to **4** and **5**, respectively, also by an acid catalyzed intramolecular cyclization.

The absolute configurations of psoracorylifols A–E (**1–5**) (Table 3) were proposed on the basis of biogenetic reason and demonstrated by CD spectra. The origin of **1–5** was proposed to be (9*S*)-(+)-bakuchiol (**6**), whose absolute configuration was determined by a total synthesis,[2b] and a hypothesis was thus made that the 9*S*-configuration were retained at the biosynthetic procedures of **1–5**. Accordingly, the absolute configuration of **1–5** could be predicted by referring to (9*S*)-(+)-bakuchiol (**6**). Observation of CD spectra of **1–5** (Fig. 5), the patterns of Cotton effects corresponding to the UV absorptions around 270 and 227 nm seemed to be closely related with the chiral centers of C-7 and C-8.[12] Although it was not determined whether C-7/ and C-8 were corresponded to these Cotton effects, compounds **1**, **3** and **4** proposed as 7*S*,8*S*-configurations showed positive chirality (positive first Cotton effect around 270 nm and negative second Cotton effect centered at 227 nm); while compounds **2** and **5** with 7*R*,8*R*-configurations gave negative chirality (Cotton effects are totally reversed by comparing with those of **1**, **3** and **4**). The CD spectra of **1–5** showed good consistency with the absolute structures predicted on the biogenetic reason.

Psoracorylifols A–E (**1–5**) were tested on the antimicrobial assay against *H. pylori* (Hp) in vitro, and metronidazole was used as the positive control (Table 4). All the tested compounds showed significant inhibitory activity against two strains of *H. pylori* (SS1 and ATCC 43504) at the level of MICs of 12.5–25 μg/mL, the latter one was a drug (metronidazole) resistant Hp strain.[6] It is remarkable that psoracorylifols A–E (**1–5**) are more stronger (5–10 times) than metronidazole, a critical ingredient for combination therapies of *H. pylori* infection, against *H. pylori* ATCC 43504.

Table 4. Inhibitory activities of compounds **1–5** against *H. pylori*

Samples	MICs (μg/mL)	
	Hp ATCC 43504	Hp SS1
1	25	25
2	12.5	12.5
3	12.5	12.5
4	12.5	12.5
5	25	25
Metronidazole	128	0.5

3. Experimental

3.1. General experimental procedures

Melting points were measured with an SGWX-4 apparatus and uncorrected. Optical rotation was determined on a Perkin-Elmer 341 polarimeter, and CD was obtained on a Jasco 810 spectrometer. UV was measured on Varian Cary 300 BIO spectrometer. IR spectra were recorded on a Perkin-Elmer 577 spectrometer. NMR spectra were measured on a Bruker AM-400 spectrometer with TMS as internal standard. EIMS (70 eV) were carried out on a

Finnigan MAT 95 mass spectrometer. Semi-preparative HPLC was performed on a Waters 515 pump with a Waters 2487 detector (254 nm), and a YMC-Pack ODS-A column (250×10 mm, S-5 μm, 12 nm) was used.

3.2. Plant material

The seeds of *P. corylifolia* were harvested in September 1999 from Anhui Province of China, and authenticated by Dr. Y. Xiang of Shanghai Institute of Materia Medica, where a voucher specimen has been deposited (Accession number Pc-1999-1Y).

3.3. Extraction and isolation

The dried seeds powder of *P. corylifolia* (2.0 kg) was extracted with 95% EtOH to give 592 g crude, and part of which (392 g) was suspended in 2.5 L water and then partitioned with petroleum ether and ethyl acetate successively to give petroleum ether soluble fraction PE (143 g) and ethyl acetate soluble fraction EA (120 g). EA (100 g) was subjected to silica gel column chromatography (CC) eluted with an increasingly gradient of acetone in petroleum ether to obtain nine fractions Frs 1–9 according to TLC monitor. Frs 1–4 (total 46 g) mainly contained bakuchiol (**6**) (Scheme 1). Fr 5 (4.5 g) was further separated on a silica gel CC eluted with $CHCl_3$ to afford subfractions Frs 5a–5e. Fr 5c was purified on a silica gel column eluted with petroleum ether–EtOAc (6/1) to offer **1** (31 mg, recrystallized in acetone). Fr 5a (0.72 g) was treated on a Sephadex LH-20 column eluted with EtOH to obtain a major mixture, which was then separated on a silica gel CC eluted with petroleum ether–EtOAc (15/1–3/1) to give two major gum-like mixtures Frs 5a-1 and 5a-2, each of them was purified by preparative HPLC with the mobile phase of 60% CH_3CN in water (at flow rate of 3 mL/min), Fr 5a-1 yielded compounds **2** (12.3 mg) and **3** (10.2 mg), and Fr 5a-2 gave compounds **4** (7.5 mg) and **5** (5.4 mg).

3.3.1. Psoracorylifol A (1). Colorless needles from MeOH; mp 152–154 °C; $[\alpha]_D^{20}$ +39.5 (*c* 1.30, MeOH); UV (MeOH): λ_{max} (log ε)=226 (4.00), 277 (3.19) nm; IR (KBr): ν_{max}=3473, 3265, 1616, 1518, 1452 cm^{-1}; ^1H and ^{13}C NMR: see Tables 1 and 2; EIMS (70 eV): *m/z* (%): 288 $[M]^+$ (2), 270 (13), 189 (10), 165 (34), 123 (100), 107 (26); HREIMS: *m/z* 288.1729 $[M]^+$ (calcd for $C_{18}H_{24}O_3$: 288.1725).

3.3.2. Psoracorylifol B (2). Colorless gum; $[\alpha]_D^{20}$ 0 (*c* 0.61, MeOH); UV (MeOH): λ_{max} (log ε)=227 (4.06), 277 (3.23) nm; IR (KBr disc): ν_{max}=3332, 1616, 1518, 1448 cm^{-1}; ^1H and ^{13}C NMR: see Tables 1 and 2; EIMS (70 eV): *m/z* (%): 288 $[M]^+$ (3), 200 (34), 185 (100), 172 (9), 153 (9), 136 (16), 123 (10), 107 (29); HREIMS: *m/z* 288.1717 $[M]^+$ (calcd for $C_{18}H_{24}O_3$: 288.1725).

3.3.3. Psoracorylifol C (3). Colorless gum; $[\alpha]_D^{20}$ −30.7 (*c* 0.39, MeOH); UV (MeOH): λ_{max} (log ε)=227 (4.09), 277 (3.19) nm; IR (KBr): ν_{max}=3357, 1612, 1516, 1443 cm^{-1}; ^1H and ^{13}C NMR: see Tables 1 and 2; EIMS (70 eV): *m/z* (%): 288 $[M]^+$ (3), 200 (32), 185 (100), 172 (9), 153 (19), 136 (21), 123 (8), 107 (38); HREIMS: *m/z* 288.1722 $[M]^+$ (calcd for $C_{18}H_{24}O_3$: 288.1725).

3.3.4. Psoracorylifol D (4). Colorless gum; $[\alpha]_D^{20}$ +21.0 (*c* 0.22, MeOH); UV (MeOH) λ_{max} (log ε)=226 (3.95), 280 (3.17) 363 (3.14), 381 (3.10) nm; IR (KBr): ν_{max}=3394, 1614, 1514, 1469 cm^{-1}; ^1H and ^{13}C NMR: see Tables 1 and 2; EIMS (70 eV): *m/z* (%): 272 $[M]^+$ (8), 150 (30), 135 (78), 121 (25), 107 (100); HREIMS: *m/z* 272.1780 $[M]^+$ (calcd for $C_{18}H_{24}O_2$: 272.1776).

3.3.5. Psoracorylifol E (5). Colorless gum; $[\alpha]_D^{20}$ −69.0 (*c* 0.16, MeOH); UV (MeOH): λ_{max} (log ε)=226 (3.86), 279 (3.12) nm; IR (film): ν_{max}=3346, 1614, 1514, 1444 cm^{-1}; ^1H and ^{13}C NMR: see Tables 1 and 2; EIMS (70 eV): *m/z* (%): 272 $[M]^+$ (18), 257 (18), 187 (76), 149 (100), 135 (44), 121 (94), 107 (70); HREIMS: *m/z* 272.1767 $[M]^+$ (calcd for $C_{18}H_{24}O_2$: 272.1776).

3.4. X-ray crystallographic analysis of 1

Single-crystals suitable for X-ray analysis were obtained by recrystallization from methanol. All measurements were made on a Rigaku AFC7R four circle diffractometer employing graphite monochromated Mo Kα radiation (λ=0.71073 Å) at 293 K and operating in the ϕ–ω scan mode. Crystal data: $C_{18}H_{24}O_3$, (M_r 288.17), monoclinic, space group *P*2(1), *a*=10.896(15) Å, *b*=6.162(8) Å, *c*=11.850(16) Å, β=98.899(2)°, *V*=786.03(18) $Å^3$, *Z*=2, D_{calcd}=1.22 g/cm^3, *F*(000)=312 and μ(Mo Kα)=0.081 mm^{-1}. The structure was solved by direct methods (SHELXS-97) and refined with full-matrix least-squares calculations on F^2 using SHELXL-97. Copies of the data can be obtained, free of charge, on application to CCDC (CCDC deposition number: 275109), 12 Union Road, Cambridge CB2 1EZ, UK [fax: 44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.5. In vitro test of anti-*H. pylori* activity by agar dilution method[6]

A series of agar plates were prepared with the base of Campylobacter selective agar (Merck) containing 5% of fetal bovine serum, and various concentrations of two-fold diluted samples (**1**–**5**) were dispersed into the culture medium. To the well-prepared agar plates, *H. pylori* (Hp SS1 or ATCC 43504 strain) cells suspended in saline at the density of 10^8 CFU/mL were inoculated and incubated at 37 °C for 96 h under an atmosphere of 5% O_2, 10% CO_2 and 85% N_2. The blank controls (*H. pylori* cultures in the agar plates, no test samples were dispersed) and the positive controls (*H. pylori* cultures in the agar plates dispersed with various concentrations of two-fold diluted metronidazole) were incubated under the same condition. The MIC was defined as the lowest concentration of test samples, at which the visible growth was completely inhibited. All measurements were repeated three times under the same condition.

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Rapid solution and solid phase synthesis of monodisperse oligo[(1,4-phenyleneethynylene)-alt-(2,5-thiopheneethynylene)]s

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Abstract—Monodisperse oligo[(1,4-phenyleneethynylene)-alt-(2,5-thiopheneethynylene)]s, new candidates for molecular wires, were rapidly synthesized via an iterative divergent/convergent doubling strategy in solution as well as on Merrifield's resin.

1. Introduction

Conjugated oligomers of precise length and constitution have received considerable attention both as models for analogous bulk polymers and as candidates for molecular wires and molecular scale electronic devices.[1] Monodisperse, well-defined oligo(1,4-phenyleneethynylene)s and oligo(2,5-thiopheneethynylene)s are of particular interest due to their linear conjugated molecular structures as well as their interesting electronic characteristics.[2–8] Recently, we reported the first synthesis of monodisperse alternating cooligomers of oligo(1,4-phenyleneethynylene)s and oligo(2,5-thiopheneethynylene)s, new candidates for molecular wires, which may possess interesting characteristics different from previously reported oligo(1,4-phenyleneethynylene)s, oligo(2,5-thiopheneethynylene)s and their block cooligomers.[9] We describe here the synthetic details for the synthesis of monodisperse oligo[(1,4-phenyleneethynylene)-alt-(2,5-thiopheneethynylene)]s by means of an iterative divergent/convergent doubling strategy in solution as well as on Merrifield's resin.

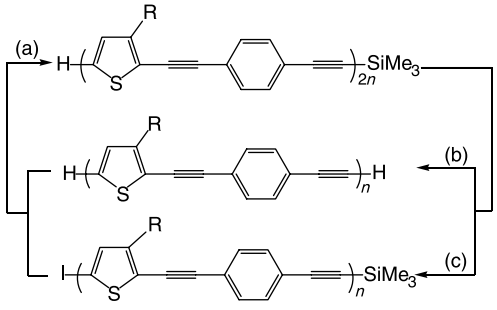
2. Results and discussion

2.1. Failed synthetic route

We initially designed a synthetic route outlined in Scheme 1 to the synthesis of monodisperse oligo[(1,4-phenyleneethynylene)-alt-(2,5-thiopheneethynylene)]s. However, the strategy failed because the products of the iodination reaction were too complicated to purify. Then, we designed another successful synthetic route described below to achieve our goal.

2.2. Oligomer synthesis in solution

The successful solution phase iterative divergent/convergent synthetic route was outlined in Scheme 2. Compound **1** was conveniently synthesized analogous to previously reported procedure.[5] 4-Iodoaniline was converted to the diethyltriazene **2**,[4] followed by coupling to trimethylsilylacetylene and then desilylation to afford **3**, which was then coupled with **1** to give **4**, the desired 'starting monomer' for the iterative divergent/convergent doubling strategy. Compound **4** was divided into two parts. One part was treated with base to give the desilylation terminal alkyne **5**, and the other was converted to the aryl iodide **6** with methyl iodide. Then, compound **5** was coupled with **6** yielding compound **7**. Iteration of above reaction sequence doubled the molecular length of compound **7** to afford **10**. The dimer



Scheme 1. (a) $Pd(dba)_2$, CuI, PPh_3, THF/Et_3N; (b) K_2CO_3, MeOH; (c) LDA, Et_2O, −78 to 0 °C then I_2, −78 °C.

Keywords: Molecular wires; Monodisperse oligomers; Resin; Synthesis.
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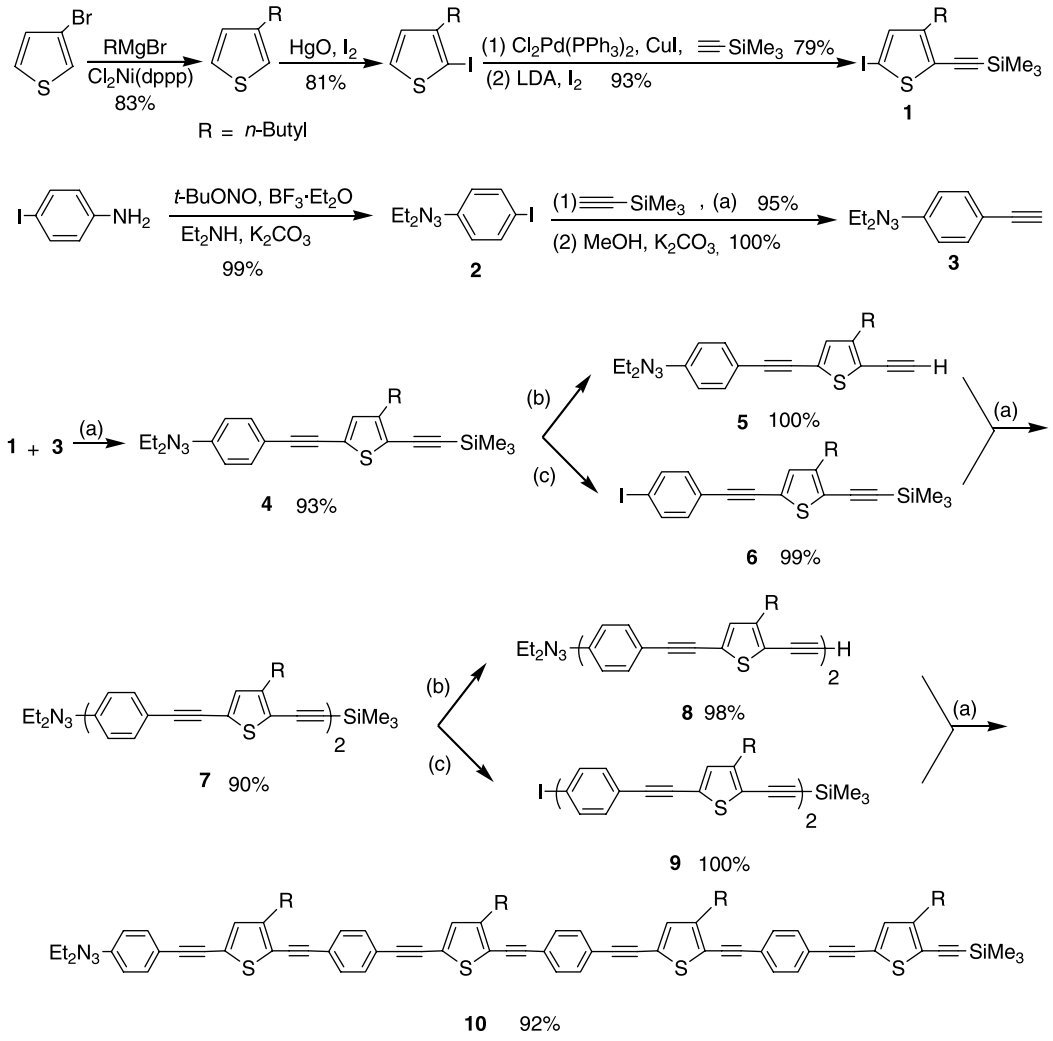


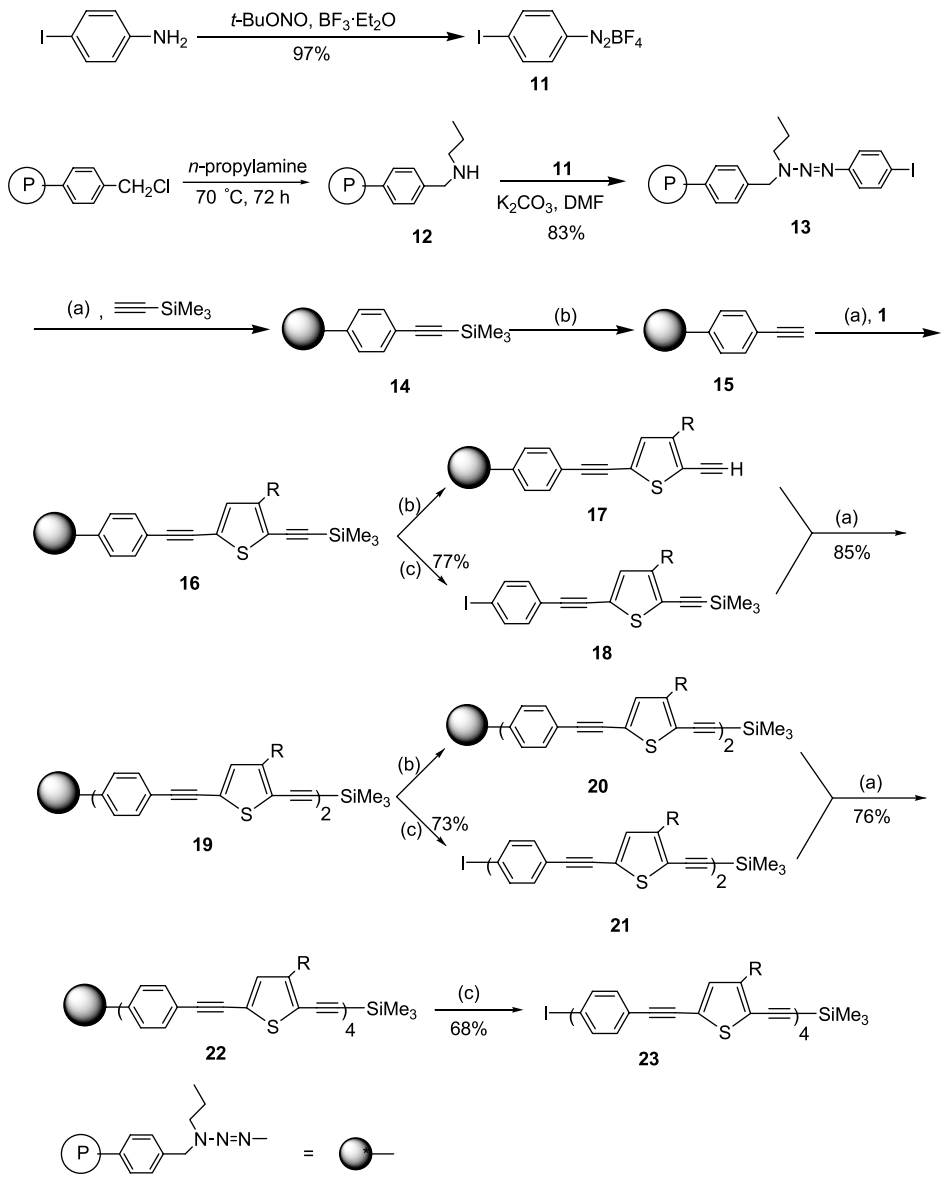
Scheme 2. (a) $Pd(dba)_2$, CuI, PPh_3, THF, Et_3N; (b) K_2CO_3, MeOH; (c) MeI.

4, tetramer **7** and octamer **10** were quite soluble in common organic solvents such as THF, $CHCl_3$ and so on. Both triazene–iodide conversion and trimethylsilyl deprotection reactions were almost in quantitative yields, and the coupling reactions were also in high yields (>90%). Note that any product bearing triazene in this report was easily decomposed when silica gel was used for chromatographic purification! Fortunately, chromatographic purification on neutral alumina has proven to be efficient.

2.3. Oligomer synthesis on Merrifield's resin

Since solid phase synthetic method has many remarkable advantages especially including simplified purification, we also synthesized monodisperse oligo[(1,4-phenyleneethynylene)-alt-(2,5-thiopheneethynylene)]s on Merrifield's resin. The synthetic route was outlined in Scheme 3. 4-Iodoaniline was converted to the diazonium tetrafluoroborate salt **11** in high yield.[10] Merrifield's resin was converted to resin **12** by reaction with degassed dry *n*-propylamine in a sealed vessel under argon at 70 °C for 3 days.[11] Compound **11** was attached to resin **12** in the presence of potassium carbonate at 0 °C, followed by coupling to trimethylsilylacetylene and then desilylation by treatment with tetrabutylammonium fluoride (TBAF) in THF at room temperature to give the resin-supported terminal acetylene **15**. Resin **16**, the desired 'starting monomer' for the iterative divergent/convergent doubling strategy, was prepared by coupling resin **15** with compound **1** using the above Pd/Cu catalyst system. One-third of **16** underwent desilylation with TBAF to afford the resin **17**. The remaining two-thirds of **16** were treated with MeI at 115 °C for 24 h to afford liberated compound **18**. Resin **17** was then coupled with all of the liberated iodide **18** under Pd/Cu cross coupling conditions to afford the resin **19**. The sequence was repeated to generate the resin **22**. Compound **23** was liberated from resin **22** by treatment with MeI at 115 °C for 12 h. The dimer **18**, tetramer **21** and octamer **23** were quite soluble in common organic solvents such as THF, $CHCl_3$ and so on.

During the synthesis, reagents attached to the resin were used in large excess amounts (usually 2–3 equiv) to drive the conversion completely and could be easily removed and recovered by filtration. Completion of each resin-supported reaction was monitored by FTIR analysis of the resin-supported substrate according to previously reported method.[4] Because the yield calculations for solid phase



Scheme 3. (a) $Pd(dba)_2$, CuI, PPh_3, Et_3N; (b) THF, TBAF; (c) MeI.

synthesis were quite difficult, the yields marked in Scheme 3 were therefore only rough estimations based on the weight changes of the resin after each reaction.

3. Conclusions

Monodisperse oligo[(1,4-phenyleneethynylene)-alt-(2,5-thiopheneethynylene)]s, new candidates for molecular wires, were rapidly synthesized via an iterative divergent/convergent doubling strategy in solution as well as on Merrifield's resin.

4. Experimental

4.1. General

All reagents were purchased from Aldrich, Sigma or Acros, and used as received unless otherwise noted. All operations, if not otherwise mentioned, were carried out under a dry, oxygen-free argon atmosphere. Tetrahydrofuran (THF) and ether were distilled under argon from sodium benzophenone ketyl. Triethylamine, iodomethane and diisopropylamine were distilled over calcium hydride. Diethylamine was distilled prior to use. Merrifield's resin was purchased from Sigma (chloromethylated polystyrene, 1% crosslinked with divinyl-benzene, 200–400 mesh, 0.83 mequiv Cl/g). 3-*n*-Butyl-2-[(trimethylsilyl)ethynyl]thiophene was synthesized according to literature procedure.[5] ^1H NMR (400 or 600 MHz) and ^{13}C NMR spectra (100 or 150 MHz) were measured on a Bruker AV600 or Varian Unity 400. Infrared spectroscopy was carried out on a Bio-Rad FTS - 135 FTIR or Bruker Tensor27 FTIR spectrometer. Matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) were recorded on LDI 1700, Linear Scientific Inc. USA, using a dithranol matrix in positive ion mode. Thin-layer chromatography (TLC) was performed on silica gel coated aluminum foils (Merck alumina foils 60F254). The terminal alkynes larger than the dimer stage were

oxidatively unstable, and used immediately after preparation. Unless otherwise noted, all compounds were >95% pure as judged by NMR.

General procedure for the coupling of a terminal alkyne with an aryl iodide (procedure A). Analogous to literature procedure[4] with some modifications. All of the reagents were thoroughly dried and flushed with argon before use. To a flame-dried vessel were added the alkyne, the iodide (1.0 equiv based on per alkyne), bis(dibenzylideneacetone)-palladium(0) (5 mol% per alkyne), triphenylphosphine (25 mol% per alkyne), copper(I) iodide (10 mol% per alkyne) and THF–Et_3N (2/1) at room temperature under argon. The vessel was sealed and allowed to stir at room temperature for 2–3 days. The reaction mixture was then poured into water, and the aqueous layer was extracted three times with ethyl acetate. After drying the combined organic layers over magnesium sulfate, the solvent was removed in vacuum to afford a crude product, which was then purified by column chromatography (neutral alumina, 200–300 mesh). Eluents and other slight modifications were described below for each reaction.

General procedures for the desilylation of alkynes (procedure B). Analogous to literature procedure[4] with slight modifications. The silylated alkyne was dissolved in methanol and dichloromethane. Potassium carbonate (2 equiv) was then added, and the reaction was stirred overnight. The reaction mixture was poured into water and the aqueous layer was extracted with ethyl acetate. After drying the combined organic layers over magnesium sulfate, the solvent was removed in vacuum. The product was used without further purification.

General procedure for iodide formation from triazenes (procedure C). Analogous to literature procedure[4] with slight modification. To a thick-walled flame-dried tube were added the corresponding triazene and iodomethane (10 equiv). The tube was flushed with argon, sealed, and heated to 120 °C overnight. The reaction was cooled to room temperature, and the solvent was removed in vacuum. The crude product was then passed through a plug of silica gel with ethyl acetate.

General procedure for the coupling of a resin-supported terminal alkyne with an aryl iodide (procedure D). Analogous to literature procedure[4] but with great modification. All of the reagents were thoroughly dried and flushed with argon before use. To a thick-walled flame-dried sealed tube were added the resin-supported terminal alkyne, the aryl iodide (2.0–3.0 equiv based on per alkyne), bis(dibenzylideneacetone)palladium(0) (8 mol% per alkyne), triphenylphosphine (40 mol% per alkyne) and copper(I) iodide (16 mol% per alkyne) at room temperature. The tube was flushed with argon, and then injected with THF–Et_3N (2/1–4/1) (ca. 10 mL/g of resin) that were thoroughly degassed with argon before use. The tube was sealed and kept at 65 °C for 48–72 h, and it was shaken periodically. The resin was then poured onto a glass filter, and dichloromethane was used to transfer the remaining resin sticking to the sides of the tube. The resin was then washed sequentially (ca. 30 mL/g of resin) with the following: CH_2Cl_2, DMF, 0.05 M solution of sodium diethyl dithiocarbamate in 99:1 DMF/diisopropylethylamine, DMF, CH_2Cl_2, MeOH, and dried to constant mass in vacuum at 60 °C. Completion of each resin-supported coupling reaction was monitored by the disappearance of the 3310 cm^{-1} band (characteristic of the terminal alkynyl carbon–hydrogen stretch) and the appearance of the 2156 cm^{-1} band (characteristic of the carbon–carbon stretch of the trimethylsilylated terminal alkyne) measured by FTIR analysis of the resin.

General procedure for the desilylation of resin-supported silylated alkynes (procedure E). Analogous to literature procedure[4] with slight modification. To a round-bottomed flask were added the resin-supported (trimethylsilyl)alkyne (1.0 equiv), THF (10 mL/g of resin) and TBAF (2.0 equiv). The suspension was stirred slowly for 15–45 min at room temperature. The resin was then poured onto a glass filter, and washed sequentially (ca. 30 mL/g resin) with THF, MeOH, and dried to constant mass in vacuum at 60 °C. Completion of each resin-supported desilylation reaction was monitored by the appearance of the 3310 cm^{-1} band (characteristic of the terminal alkynyl carbon–hydrogen stretch) and the disappearance of the 2156 cm^{-1} band (characteristic of the carbon–carbon stretch of the trimethylsilylated terminal alkyne) measured by FTIR analysis of the resin.

General procedure for the liberation of resin-supported oligomers (procedure F). Analogous to literature procedure[4] with slight modification. To a thick-walled flame-dried tube were added the resin-supported oligomer and iodomethane (7–10 mL/g of resin). The tube was flushed with argon, sealed, and heated to 120 °C for 12–24 h without stirring. The reaction mixture was cooled to room temperature and then filtered through a glass filter. The resin was washed with hot CH_2Cl_2 (ca. 20 mL/g of resin) to extract any residual product trapped in the resin. The combined filtrate was evaporated under vacuum. The crude product was then passed through a plug of silica gel with ethyl acetate.

4.1.1. 5-Iodo-3-*n*-butyl-2-[(trimethylsilyl)ethynyl]thiophene (1). To a solution of diisopropylamine (3.42 g, 33.81 mmol) in ether (25 mL) at −78 °C was added dropwise *n*-butyllithium (19.35 mL, 30.96 mmol, 1.60 M in hexane), and then stirred at −78 °C for 15 min. The mixture was warmed to 0 °C for 30 min and then recooled to −78 °C. 3-*n*-Butyl-2-[(trimethylsilyl)ethynyl]thiophene (3.66 g, 15.48 mmol) in ether (15 mL) at room temperature was then added dropwise, and the solution was warmed from −78 to 0 °C for 15 min. After recooling to −78 °C, iodine (8.58 g, 33.81 mmol) in ether (40 mL) was added via cannula, and the solution was then warmed to room temperature and stirred overnight. The mixture was quenched with water, and the aqueous layer was extracted with ether. The organic layer was washed with brine and aqueous sodium thiosulfate, and then dried over magnesium sulfate. The solvent was removed under vacuum, and the crude product was purified by flash chromatography (silica gel, hexane) to afford 5.22 g (93%) of **1** as a yellow liquid. ^1H NMR (600 MHz, $CDCl_3$) δ 6.83 (s, 1H), 2.68 (t, $J=7.6$ Hz, 2H), 1.59 (quint, $J=7.6$ Hz, 2H), 1.35 (sext, $J=7.2$ Hz, 2H), 0.86 (t, $J=7.2$ Hz, 3H), 0.26 (s, 9H).

4.1.2. 4-(Diethyltriazenyl)-1-iodobenzene (2). To an oven-dried vessel containing boron trifluoride etherate (3.81 mL, 30 mmol) at −15 °C was added 4-iodoaniline (3.29 g, 15 mmol) in dichloromethane (40 mL) followed by *tert*-butyl nitrite (3.60 mL, 30 mmol) in dichloromethane (5 mL). The mixture was stirred at −15 °C for 30 min, and then warmed to 0 °C for 30 min. Diethylamine (12.35 mL, 120 mmol) and potassium carbonate (13.82 g, 100 mmol) were sequentially added. The reaction was stirred at 0 °C for 2 h. The reaction mixture was then poured into water and the aqueous layer was extracted three times with ethyl acetate. After drying the combined organic layers over magnesium sulfate, the solvent was removed in vacuum to afford a crude product, which was then purified by flash chromatography on neutral alumina (9:1; hexane/dichloromethane) to afford 4.72 g (99%) of **1** as a light yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J=8.8 Hz, 2H), 7.17 (d, J=8.8 Hz, 2H), 3.75 (q, J=7.2 Hz, 4H), 1.26 (t, J=7.2 Hz, 6H).

4.1.3. 4-Ethynyl-1-diethyltriazenylbenzene (3). First, 4-[(trimethylsilyl)ethynyl]-1-diethyltriazenylbenzene was synthesized according to procedure A. Used were **2** (1.65 g, 5.4 mmol), triethylamine (8.0 mL), (trimethylsilyl)-acetylene (0.92 mL, 6.50 mmol), bis(dibenzylideneacetone)palladium(0) (0.155 g, 0.27 mmol), triphenylphosphine (0.354 g, 1.35 mmol) and copper iodide (0.103 g, 0.54 mmol) for 1 day. The crude product was purified by flash chromatography on neutral alumina by first using 20:1 hexane/dichloromethane and then slowly increasing to 8:1 hexane/dichloromethane to afford 1.40 g (95%) of 4-[(trimethylsilyl)ethynyl]-1-diethyltriazenylbenzene as a yellow–orange waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J=8.8 Hz, 2H), 7.34 (d, J=8.8 Hz, 2H), 3.76 (q, J=7.2 Hz, 4H), 1.26 (t, J=7.2 Hz, 6H), 0.25 (s, 9H).

Then, **3** was synthesized according to procedure B. 4-[(Trimethylsilyl)ethynyl]-1-diethyltriazenylbenzene (0.42 g, 1.50 mmol), methanol (25 mL), and potassium carbonate (0.69 g, 5 mmol) afforded 0.30 g (100%) of **3** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J=8.8 Hz, 2H), 7.36 (d, J=8.8 Hz, 2H), 3.77 (q, J=7.2 Hz, 4H), 2.95 (s, 1H), 1.27 (t, J=7.2 Hz, 6H).

4.1.4. Dimer (4). See procedure A. Compound **1** (2.54 g, 7.0 mmol), **3** (1.31 g, 6.5 mmol), bis(dibenzylideneacetone)-palladium(0) (0.20 g, 0.35 mmol), triphenylphosphine (0.46 g, 1.75 mmol), copper(I) iodide (0.13 g, 0.70 mmol) and triethylamine (30 mL) for 36 h afforded 2.69 g (95%) of **4** as a yellow sticky liquid after flash chromatography on neutral alumina (hexane). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, J=8.4 Hz, 2H), 7.39 (d, J=8.4 Hz, 2H), 6.98 (s, 1H), 3.77 (q, J=7.2 Hz, 4H), 2.65 (t, J=7.8 Hz, 2H), 1.60 (quint, J=7.2 Hz, 2H), 1.35 (sext, J=7.2 Hz, 2H), 1.27 (br s, 6H), 0.94 (t, J=7.2 Hz, 3H), 0.26 (s, 9H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 151.27, 148.64, 132.34, 132.18, 123.44, 120.44, 119.42, 118.69, 101.82, 97.05, 94.33, 82.39, 32.16, 32.05, 29.05, 22.18, 13.91, 13.81. LDI-MS (*m*/*z*): 436 (M^+), 407 ($M-C_2H_5$), 363 (M−TMS), 336 ($M-Et_2N_3$). Anal. Calcd for $C_{25}H_{33}N_3SSi$: H, 7.64; C, 68.93; N, 9.65. Found: H, 7.58; C, 69.02; N, 9.43.

4.1.5. Terminal alkynyl dimer (5). See procedure B. Compound **4** (0.54 g, 1.24 mmol), methanol (10 mL), dichloromethane (5 mL) and potassium carbonate (0.82 g, 5.0 mmol) afforded 0.45 g (100%) of **5** as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J=8.4 Hz, 2H), 7.39 (t, J=8.4 Hz, 2H), 6.99 (s, 1H), 3.79 (q, J=7.2 Hz, 4H), 3.46 (s, 1H), 2.67 (t, J=7.6 Hz, 2H), 1.59 (quint, J=7.6 Hz, 2H), 1.35 (d, J=8.4 Hz, 2H), 1.28 (br s, 6H), 0.94 (t, J=7.2 Hz, 3H).

4.1.6. Iodide dimer (6). See procedure C. Compound **4** (0.48 g, 1.10 mmol) and iodomethane (5 mL) for 24 h afforded 0.51 g (99%) of **6** as a yellow liquid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, J=8.4 Hz, 2H), 7.21 (d, J=8.4 Hz, 2H), 7.01 (s, 1H), 2.65 (t, J=7.6 Hz, 2H), 1.59 (quint, J=7.6 Hz, 2H), 1.36 (sext, J=7.4 Hz, 2H), 0.95 (t, J=7.2 Hz, 3H), 0.26 (s, 9H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 148.65, 137.57, 137.43, 132.99, 132.84, 130.23, 122.47, 122.21, 120.28, 102.33, 96.79, 94.52, 92.58, 84.12, 32.05, 29.11, 22.19, 13.93. LDI-MS (*m*/*z*): 462 (M^+), 336 (M−I). Anal. Calcd for $C_{21}H_{23}ISSi$: H, 5.02; C, 54.54. Found: H, 5.06; C, 54.49.

4.1.7. Tetramer (7). See procedure A. Compound **5** (0.35 g, 0.97 mmol), **6** (0.43 g, 0.97 mmol), bis(dibenzylideneacetone)palladium(0) (0.0288 g, 0.05 mmol), triphenylphosphine (0.0629 g, 0.24 mmol), copper(I) iodide (0.0184 g, 0.09 mmol), THF (6 mL) and triethylamine (1 mL) for 2 days afforded 0.62 g (90%) of **7** as a yellow waxy solid after flash chromatography on neutral alumina by first using hexane and then slowly increasing to 9:1 hexane/dichloromethane. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, J=8.4 Hz, 2H), 7.46 (s, 4H), 7.40 (d, J=8.4 Hz, 2H), 7.03 (s, 1H), 7.01 (s, 1H), 3.77 (q, J=7.2 Hz, 4H), 2.72 (t, J=7.2 Hz, 2H), 2.65 (t, J=7.2 Hz, 2H), 1.65–1.59 (m, 4H), 1.41–1.34 (m, 4H), 1.26 (br s, 6H), 0.97–0.93 (m, 6H), 0.26 (s, 9H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 151.24, 148.63, 148.00, 132.91, 132.48, 132.12, 131.97, 131.28, 131.11, 124.02, 123.07, 122.56, 122.41, 120.41, 120.24, 120.18, 119.10, 118.59, 102.25, 96.80, 95.71, 94.89, 93.30, 84.70, 84.44, 82.38, 32.19, 31.99, 29.16, 28.98, 22.20, 22.13, 13.87, 13.78. LDI-MS (*m*/*z*): 698 (M^+), 669 ($M-C_2H_5$), 598 ($M-Et_2N_3$). Anal. Calcd for $C_{43}H_{47}N_3S_2Si$: H, 6.79; C, 74.00; N, 6.02. Found: H, 6.88; C, 73.87; N, 5.76.

4.1.8. Terminal alkynyl tetramer (8). See procedure B. Compound **7** (0.30 g, 0.43 mmol), methanol (10 mL), dichloromethane (5 mL) and potassium carbonate (0.24 g, 1.73 mmol) afforded 0.266 g (98%) of **8** as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (br s, 6H), 7.40 (d, J=8.4 Hz, 2H), 7.04 (s, 2H), 3.27 (q, J=7.2 Hz, 4H), 3.47 (s, 1H), 2.73–2.68 (m, 4H), 1.65–1.61 (m, 4H), 1.41–1.37 (m, 4H), 1.28 (m, 12H), 0.97–0.92 (m, 6H).

4.1.9. Iodide tetramer (9). See procedure C. Compound **7** (0.30 g, 0.43 mmol) and iodomethane (10 mL) for 24 h afforded 0.31 g (100%) of **9** as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, J=8.4 Hz, 2H), 7.47 (s, 4H), 7.22 (d, J=8.4 Hz, 2H), 7.07 (s, 1H), 7.02 (s, 1H), 2.73 (t, J=7.2 Hz, 2H), 2.65 (t, J=7.2 Hz, 2H), 1.65–1.59 (m, 4H), 1.40–1.35 (m, 4H), 0.97–0.93 (m, 6H), 0.26 (s, 9H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 148.69, 148.07, 137.59, 133.21, 133.00, 132.83, 131.37, 131.22, 123.05, 122.95, 122.66,

122.54, 122.18, 120.31, 120.02, 102.36, 96.80, 96.05, 94.55, 93.23, 93.07, 84.82, 84.16, 84.08, 32.22, 32.04, 29.19, 29.04, 22.24, 22.18, 13.89, 13.80. LDI-MS (*m/z*): 725 (M^+), 697 ($M-C_2H_5$), 598 ($M-I$). Anal. Calcd for $C_{39}H_{37}IS_2Si$: H, 5.15; C, 64.63. Found: H, 5.23; C, 64.46.

4.1.10. Octamer (10). See procedure A. Compound **8** (0.26 g, 0.42 mmol), **9** (0.30 g, 0.42 mmol), bis(dibenzylideneacetone)palladium(0) (0.0121 g, 0.021 mmol), triphenylphosphine (0.0275 g, 0.105 mmol), copper(I) iodide (0.0080 g, 0.042 mmol), THF (10 mL) and triethylamine (2 mL) for 3 days afforded 0.47 g (92%) of **10** as a yellow solid after flash chromatography on neutral alumina by first using hexane and then slowly increasing to 9:1 hexane/dichloromethane. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49–7.47 (m, 14H), 7.40 (d, $J=8.4$ Hz, 2H), 7.09 (s, 2H), 7.05 (s, 1H), 7.02 (s, 1H), 3.78 (q, $J=7.2$ Hz, 4H), 2.75–2.72 (m, 6H), 2.66 (t, $J=7.2$ Hz, 2H), 1.69–1.57 (m, 8H), 1.41–1.32 (m, 8H), 1.27–1.20 (m, 6H), 0.98–0.94 (m, 12H), 0.26 (s, 9H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 151.32, 148.70, 148.12, 133.23, 133.01, 132.56, 132.19, 131.37, 131.23, 124.09, 123.20, 123.17, 123.04, 122.98, 122.65, 122.61, 122.56, 122.46, 120.45, 120.30, 120.05, 120.01, 119.16, 118.67, 102.35, 96.80, 96.10, 95.73, 94.90, 93.84, 93.78, 93.24, 84.81, 84.71, 84.51, 84.28, 84.21, 82.39, 32.24, 32.04, 29.21, 29.04, 22.25, 22.18, 13.90, 13.80. MALDI-MS (*m/z*): 1223 (M^+), 1123 ($M-Et_2N_3$). Anal. Calcd for $C_{79}H_{75}N_3S_4Si$: H, 6.19; C, 77.61; N, 3.44. Found: H, 6.35; C, 77.36; N, 3.18.

4.1.11. 4-Iodobenzenediazonium tetrafluoroborate (11). To an oven-dried three-neck round-bottomed flask containing boron trifluoride etherate (25.36 mL, 200 mmol) precooled below −20 °C was added dropwise over 15 min a solution of 4-iodoaniline (13.14 g, 60 mmol) in dry THF (50 mL). A solution of *tert*-butyl nitrite (21.03 mL, 175.4 mmol) in dry THF (100 mL) was then added dropwise over 50 min to the chilled reaction mixture at −20 °C. The reaction was stirred an additional 30 min at −20 °C, and then slowly warmed to 5 °C. After reaction at 5 °C for 20 min, *n*-pentane (250 mL) was added to the reaction mixture and a white solid immediately precipitated. The suspension was cooled to 0 °C, stirred for 10 min, and then poured onto a glass filter. The solid was thoroughly washed with ethanol (30 mL) pre-cooled to 0–5 °C, and then dried in vacuum to give 18.50 g (97%) of **11** as a white powder. ^{1}H NMR (CD_3CN, 300 MHz) δ 8.37 (d, $J=9.1$ Hz, 2H), 8.18 (d, $J=9.1$ Hz, 2H).

4.1.12. Propylaminomethylated polystyrene (12). Compound **12** was prepared according to literature procedure.[11] Chloromethyl polystyrene (30 g, 0.83 mmol Cl/g resin) and *n*-propylamine (100 mL, 1.22 mol) afforded 30.48 g (0.67 mmol N/g resin) of **12** as white beads.

4.1.13. Resin-supported iodide (13). Analogous to literature procedure[11] with some modifications. To a chilled (0 °C) suspension of **12** (15.00 g, ca. 10 mmol N) and DMF (200 mL) was added sequentially potassium carbonate (5.53 g, 40 mmol) followed by **11** (6.36 g, 20 mmol) in portions over 30 min. The suspension was slowly stirred at 0 °C for 2 h, and then warmed to room temperature for 1 h. The suspension was transferred onto a glass filter using DMF and washed sequentially with 150 mL of the following solvents: CH_3CN, MeOH, H_2O, MeOH, THF, MeOH, and dried in vacuum to a constant mass to give 16.79 g (0.67 mmol I/g resin, 83%) of **13** as light yellow beads.

4.1.14. Resin-supported silylated alkynes (14). See procedure D. Compound **12** (8.16 g, ca. 4 mmol I), (trimethylsilyl)acetylene (1.14 mL, 8 mmol), bis(dibenzylideneacetone)-palladium(0) (0.1833 g, 0.32 mmol), copper(I) iodide (0.1238 g, 0.64 mmol), triphenylphosphine (0.4196 g, 1.60 mmol), triethylamine (15 mL) and THF (45 mL) for 2 days afforded 8.06 g (0.67 mmol Si/g resin) of **14** as mustard-colored beads. IR (CCl_4, neat) 2156 cm^{-1}.

4.1.15. Resin-supported terminal alkynyl (15). See procedure E. Compound **14** (8.05 g, 4 mmol Si), THF (80 mL) and TBAF (2.52 g, 8 mmol) afforded 7.78 g (0.51 mmol terminal alkynyl/g resin) of **15** as brown beads. IR (CCl_4, neat) 3317, 2107 cm^{-1}.

4.1.16. Resin-supported dimer (16). See procedure D. Compound **15** (16.00 g, 8.22 mmol terminal alkynyl), **1** (5.96 g, 16.44 mmol), bis(dibenzylideneacetone)palladium(0) (0.38 g, 0.66 mmol), copper(I) iodide (0.25 g, 1.32 mmol), triphenylphosphine (0.86 g, 3.29 mmol) and triethylamine (150 mL) for 2 days afforded 17.66 g (0.46 mmol Si/g resin, 86%) of **16** as brown beads. IR (CCl_4, neat) 2156 cm^{-1}.

4.1.17. Resin-supported terminal alkynyl dimer (17). See procedure E. Compound **16** (4.38 g, 2.04 mmol Si), THF (50 mL) and TBAF (1.29 g, 4.08 mmol) afforded 4.24 g (0.48 mmol terminal alkynyl/g resin) of **17** as brown beads. IR (CCl_4, neat) 3313, 2105 cm^{-1}.

4.1.18. Iodide dimer liberated from resin 16 (18). See procedure F. Compound **16** (13.14 g, 6.11 mmol Si) and iodomethane (120 mL) for 20 h afforded 2.17 g (77%) of **18** as a yellow liquid, which was analytically identical to **6**.

4.1.19. Resin-supported tetramer (19). See procedure D. Compound **17** (4.20 g, 2.02 mmol terminal alkynyl), **18** (2.00 g, 4.32 mmol), bis(dibenzylideneacetone)palladium(0) (0.099 g, 0.16 mmol), copper(I) iodide (0.061 g, 0.32 mmol), triphenylphosphine (0.212 g, 0.81 mmol) and triethylamine (50 mL) for 2 days afforded 4.77 g (0.36 mmol Si/g resin, 85%) of **19** as brown beads. IR (CCl_4, neat) 2155 cm^{-1}.

4.1.20. Resin-supported terminal alkynyl tetramer (20). See procedure E. Compound **19** (0.92 g, 0.33 mmol Si), THF (10 mL) and TBAF (0.21 g, 0.66 mmol) afforded 0.90 g (0.37 mmol terminal alkynyl/g resin) of **20** as brown beads. IR (CCl_4, neat) 3311, 2103 cm^{-1}.

4.1.21. Iodide tetramer liberated from resin 19 (21). See procedure F. Compound **19** (3.68 g, 1.32 mmol Si) and iodomethane (40 mL) for 16 h afforded 0.70 g (73%) of **21** as a yellow solid, which was analytically identical to **9**.

4.1.22. Resin-supported octamer (22). See procedure D. Compound **20** (0.86 g, 0.32 mmol terminal alkynyl), **21**

(0.66 g, 0.91 mmol), bis(dibenzylideneacetone)palladium(0) (0.0145 g, 0.025 mmol), copper(I) iodide (0.0096 g, 0.051 mmol), triphenylphosphine (0.0332 g, 0.126 mmol), THF (8 mL) and triethylamine (2 mL) for 3 days afforded 1.00 g (0.24 mmol Si/g resin, 76%) of **22** as brown beads. IR (CCl_4, neat) 2155 cm^{-1}.

4.1.23. Iodide octamer liberated from resin 22 (23). See procedure F. Compound **22** (0.96 g, 0.23 mmol Si) and iodomethane (10 mL) for 12 h afforded 0.19 g (68%) of **23** as a yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, J=8.4 Hz, 2H), 7.48 (s, 12H), 7.21 (d, J=8.4 Hz, 2H), 7.07 (ss, 2H), 7.03 (ss, 2H), 2.74 (br s, 6H), 2.66 (t, J=7.2 Hz, 2H), 1.67–1.60 (m, 8H), 1.42–1.35 (m, 8H), 0.97–0.93 (m, 12H), 0.26 (s, 9H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 148.69, 148.11, 137.58, 133.22, 133.00, 132.82, 132.56, 132.19, 132.03, 131.65, 131.36, 131.23, 123.15, 122.99, 122.96, 122.61, 122.55, 122.44, 122.16, 120.43, 120.29, 120.05, 119.15, 118.69, 102.34, 96.80, 96.10, 95.73, 94.88, 94.55, 93.77, 93.24, 93.08, 84.81, 84.71, 84.51, 84.21, 84.08, 82.41, 32.22, 32.11, 32.03, 29.69, 29.35, 29.20, 29.03, 22.25, 22.17, 13.89, 13.80. MALDI-MS (*m*/*z*): 1250 (M^+), 1220 ($M-C_2H_3$), 1122 ($M-I$). Anal. Calcd for $C_{75}H_{65}IS_4Si$: H, 5.25; C, 72.10. Found: H, 5.39; C, 71.75.

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Substituent effect on anthracene-based bisboronic acid glucose sensors

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Abstract—Earlier we communicated an anthracene-based bisboronic acid sensor for glucose. Aimed at understanding the substituent effect, we have introduced various functional groups, such as the cyano, nitro, and fluoro group on the boronic acid moiety of this glucose sensor. Fluorescent binding studies indicated that the cyano-substituted sensor (**4a**) has the highest affinity (K 2540 M^{-1}) for glucose, but the lowest selectivity (three-fold over fructose); the fluoro-substituted compound (**4c**) shows the lowest affinity (630 M^{-1}) and a modest selectivity (15-fold over fructose); and the unsubstituted one (**1a**) shows the highest selectivity over fructose (43-fold) and a modest affinity (1472 M^{-1}).

1. Introduction

Carbohydrates are considered critical to various biological processes.[1–5] The most prominent among them is glucose, which is a critical energy supplier to cells, and its elevated concentration is the primary symptom of diabetes.[6] Just as important are oligosaccharides (glycans) that are part of glycoproteins or glycolipids.[1,2] Sensors for these biologically important carbohydrates have the potential to be used as diagnostics, new imaging agents, as well as therapeutics.[7–9] In this area, there is especially strong interest in developing boronic acid-based sensors[10–16] because of the ability of the boronic acid group to form reversible and tight complexes with diol-containing compounds.[10,13,14,17–25] Boronic acids have been used to develop fluorescent sensors,[11,13,14,21,22,26–28] color sensors,[8,11–13,15,16,26,29–36] sensors for cell recognition based on surface carbohydrate biomarkers,[22] carbohydrate transporters,[37–42] and chromatographic stationary materials.[43–48] Because monoboronic acids have certain intrinsic preference for various carbohydrates, the design of selective sensors for a particular sugar often relies on the introduction of additional functional group interactions, such as a second boronic acid unit, with a proper scaffold to afford selectivity.[22] Such an approach has been successfully used in various examples.[10,11,15,32,49] Modulation of the affinity of a monoboronic acid for diols can be achieved through the introduction of various substituents on an arylboronic acid. Generally speaking, arylboronic acids with lower pK_a values tend to have higher affinities for diols, although one also needs to consider the pH of the solution and other factors.[19] For example, 2-fluoro-5-nitrophenylboronic acid has a pK_a of about 6.0, which is 2.8 pK_a units lower than that of phenylboronic acid. Consequently, the binding constant between glucose and 2-fluoro-5-nitrophenylboronic acid at physiological pH is about ten-fold higher than that of phenylboronic acid.[19] However, to the best of our knowledge there have not been studies that directly probe the effect of substituents on the affinity and selectivity of bisboronic acid sensors. Recently, our group reported a highly selective anthracene-based boronic acid sensor for glucose (**1a**, Fig. 1).[22] The sensor design used the Shinkai fluorescent reporter,[10] which showed an increase in

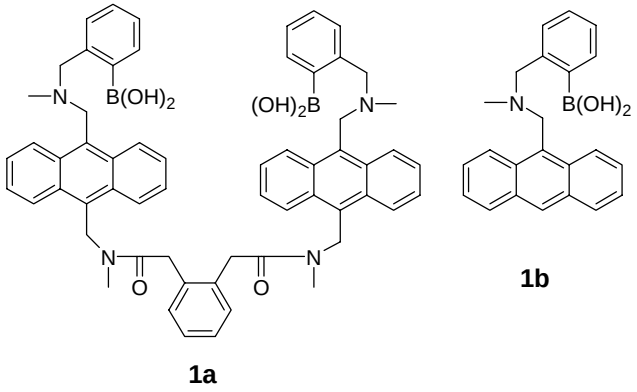

Figure 1. Dianthraceneboronic acid (**1a**) and anthracenemonoboronic acid (**1b**).

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fluorescence intensity upon binding with a diol due to protonation of the amine nitrogen upon binding.[50] Compound **1a** showed about 43-fold selectivity for glucose over fructose and 49-fold selectivity over galactose.

In this study, we have introduced various electron-withdrawing substituents on the arylboronic acid portion of the bisboronic acid sensor aimed at achieving a better understanding of the substituent effect. Specifically, there are two questions we wish to answer: (1) will the affinity-enhancing effect of electron-withdrawing groups such as fluoro, nitro, and cyano substituents be translated into enhanced affinity of the bisboronic acid sensors for saccharide and (2) how will such electron-withdrawing groups affect the selectivity of the parent boronic acid sensors **1a** and **1b**. With that in my mind we synthesized three analogs of **1a**[22] and **1b**[10] with the cyano, nitro, and fluoro functional groups placed at a position para to the boronic acid. Their binding constants with various sugars have also been determined.

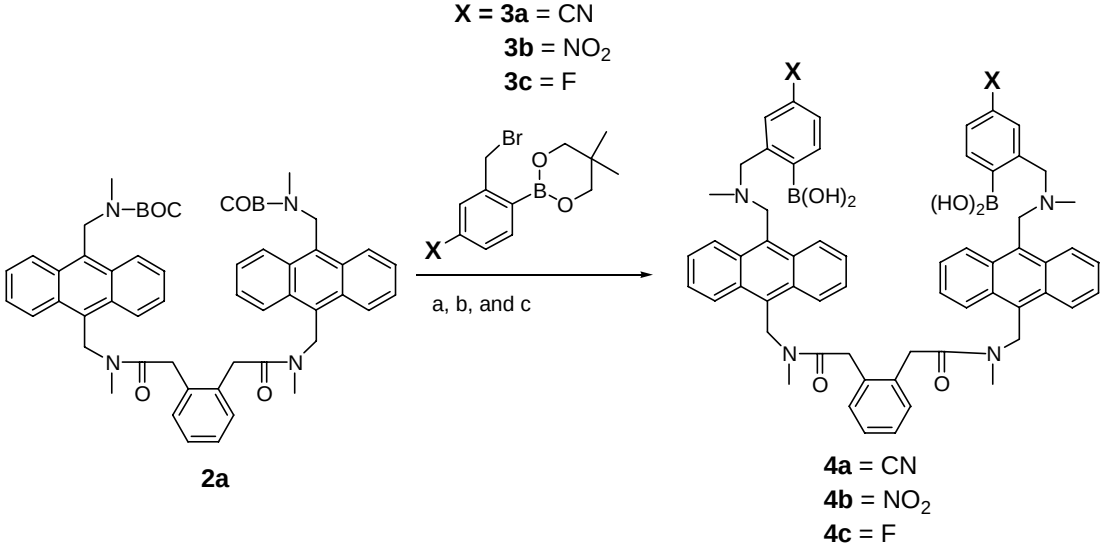
2. Results and discussions

2.1. Synthesis

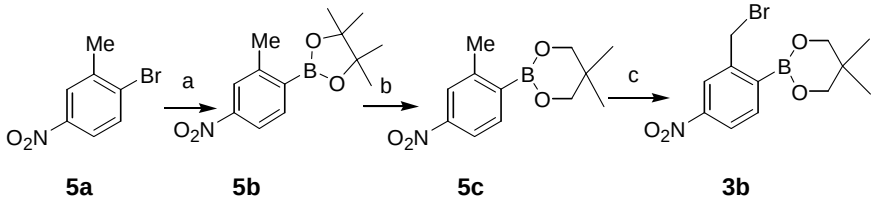
Three dianthraceneboronic acid compounds, **4a–c**, and three anthracenemonoboronic acid compounds, **6a–6c** with cyano, nitro, and fluoro groups, respectively, were prepared by following the procedure for the synthesis of the parent compounds (Schemes 1 and 3).[22,36] The key to the synthesis of these analogs was the preparation of protected arylboronic acids (**3a–c**) with various substitutions, which were used in the preparation of the bisboronic (**4a–c**) and monoboronic (**6a–6c**) acid products through alkylation (Schemes 1 and 3). The nitro-substituted pinacolato boronate **5b** was obtained by borylation of commercially available bromo-2-methyl-4-nitro-benzene using pinacolatodiboron in the presence of a palladium catalyst at 80 °C. The pinacolato protecting group of **5b** was then converted to the neopentyl glycol (**5c**)[51,52] protecting group for the ease of deprotection at the end of the synthesis. This was accomplished by reaction with neopentyl glycol at 250 °C. Bromination of **5c** in presence of NBS and AIBN yielded **3b**[51] (Scheme 2) in 82% yield. The cyano and fluoro-substituted boronates **3a** and **3c** were synthesized according to literature procedures.[51]

For the synthesis of the bisboronic acid sensors, compound **2a** was prepared following procedure reported earlier and deprotected using trifluoroacetic acid (Scheme 1). The deprotected amino group was then reacted with **3a–c** in the presence of K_2CO_3 in acetonitrile at rt to give the corresponding boronate esters of **4a–c**. Hydrolysis of the protected boronic acids under basic conditions in the presence of $NaHCO_3$ gave the free boronic acids **4a** and **4b**; whereas free boronic acid **4c** was obtained under acidic condition in the presence of HCl.[22]

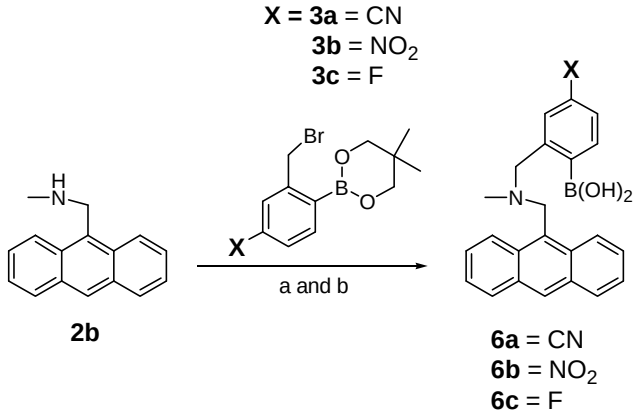
For the synthesis of the monoboronic acids, commercially available anthracen-9-ylmethyl-methylamine (**2b**) was reacted with **3a–c** in the presence of K_2CO_3 in acetonitrile at rt to give the corresponding boronate esters (Scheme 3).



Scheme 1. (a) TFA, DCM; (b) **3**(**a–c**), K_2CO_3, KI, CH_3CN; (c) **4a** and **4b**: DCM, 10% $NaHCO_3$, H_2O; **4c**: acetone–H_2O (4/1), 1 N HCl.



Scheme 2. (a) $PdCl_2$(dppf), KOAc, DMSO, (pinacolato)diboron, 80 °C; (b) neopentyl glycol, 250 °C; (c) NBS, AIBN, benzene, reflux.



Scheme 3. (a) **3**(**a**–**c**), K_2CO_3, KI, CH_3CN; (b) **6a** and **6b**: DCM, 10% $NaHCO_3$, H_2O; **6c**: acetone–H_2O (4/1), 1 N HCl.

Hydrolysis of the protected boronic acids was done under the same conditions as mentioned above to obtain free boronic acids **6a**–**c**.[22]

2.2. Fluorescent studies

As discussed earlier, these compounds were expected to increase fluorescence upon sugar binding. Furthermore, we were interested in seeing whether substitutions would change the binding affinity of the bisboronic acid sensors for diols parallel to that of the monoboronic acid unit. Therefore, fluorescence experiments were conducted to determine the appropriate binding constants of **4a**–**c** and **6a**–**c** for various sugars. Since the anthracene-based compounds are fairly lipophilic, a 1:1 mixture of methanol and phosphate buffer (pH 7.4) was used as the solvent with a sensor concentration of about 1×10^{-6} M. The sugars studied include glucose, fructose, and galactose. As expected, upon sugar addition, all three substituted glucose sensor analogs (**4a**–**c**) showed dramatically increased fluorescence intensity. Figure 2 shows two typical sets of fluorescent spectral changes upon sugar addition using compound **4a**–**b** as examples. In the past, it was proposed that the increase in fluorescence intensity for such anthracene-based boronic acids upon addition of a saccharide was due to increased B–N bond strength upon sugar binding, which in turn resulted in reduced fluorescence quenching by photoinduced electron transfer (PET).[10] Recently, our group has proposed a different mechanism, the hydrolysis mechanism, for the increase in the fluorescence intensity upon addition of a sugar.[50] As shown in Scheme 4, without sugar addition, there is a weak B–N bond. Under such a circumstance PET can happen from the amine lone pair electrons to the anthracence ring in the excited state. Upon sugar addition, the increased acidity of the boron[18,19] results in a pK_a switch so that the first pK_a is that of the boron. In such a case, the addition of a sugar allows for the breaking of the weak B–N bond and the formation of the anionic boron species **8b**, which helps to stabilize the protonated form of the amine nitrogen. Such protonation abolishes the PET process, turns off the fluorescence quenching, and results in increased fluorescence intensities. One would expect these new analogs to have a similar mechanism in inducing the fluorescent changes upon sugar binding, although this was not specifically studied.

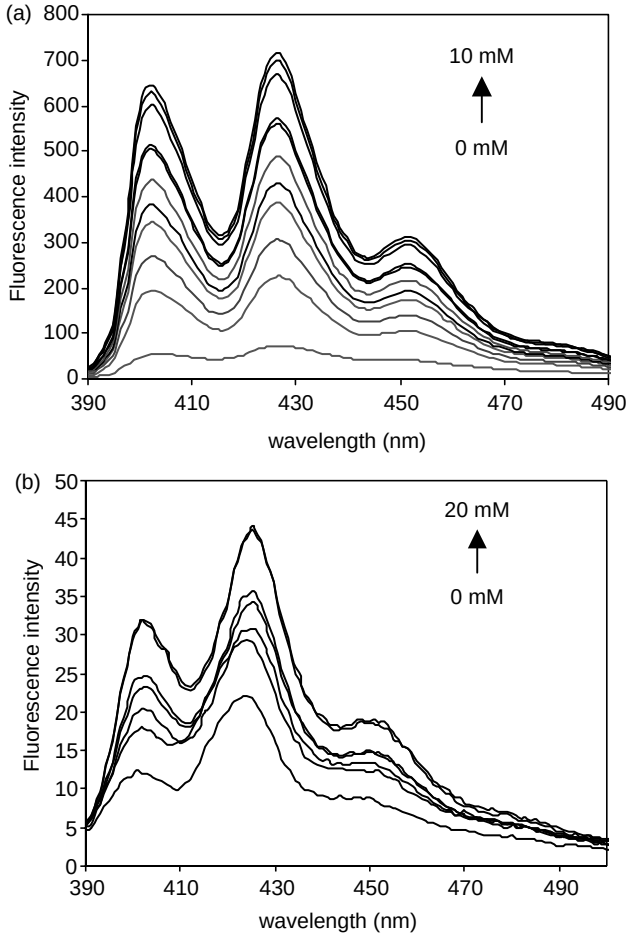
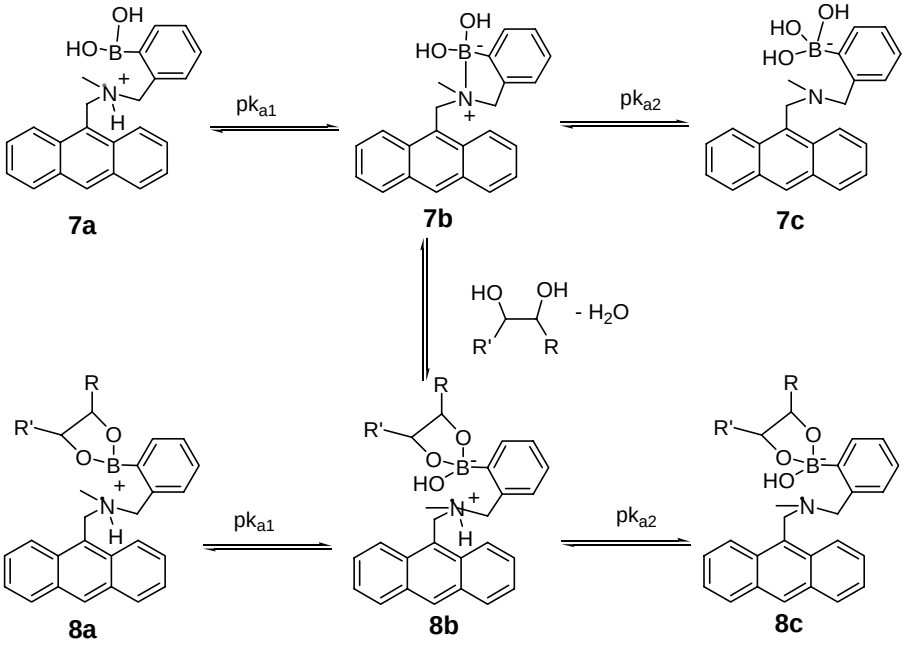


Figure 2. (a) Fluorescence spectra of **4a** (1.0×10^{-6} M) with D-glucose (0–10 mM); (b) fluorescence spectra of **4b** (1.0×10^{-6} M) with D-glucose (0–20 mM) at 25 °C in 50% MeOH/0.1 M aqueous phosphate buffer at pH 7.4: $\lambda_{ex}=370$ nm.

With the four analogs of dianthraceneboronic acid in hand, the cyano-substituted compound (**4a**) showed the highest change in fluorescence intensity with a ten-fold increase upon glucose addition. It also showed the highest binding affinity with an apparent binding constant (K_a) of 2540 M^{-1} for glucose (Table 1). It is interesting to see that the nitro-substituted compound (**4b**) showed the lowest fluorescent intensity changes (a maximum of two folds), while having the second highest affinity for glucose (1808 M^{-1}). The fluoro-substituted analog (**4c**) showed only four-fold fluorescent intensity changes with a binding constant (630 M^{-1}) that is even smaller than that of the parent compound (**1a**, 1472 M^{-1}). The binding of these bisboronic acids was compared with that of the corresponding monoboronic acid analogs (**6a**–**6c**, Table 2). It is interesting to note that the cyanophenylboronic acid compound (**6a**) also showed much higher affinity than either the nitro (**6b**) or fluoro (**6c**) substituted ones. Therefore, the results of the bisboronic acids parallel that of the monoboronic acids in this case.

However, the comparison between the nitro and fluoro-substituted compounds did not yield the same conclusions. In the monoboronic acid series, the nitro and fluoro-substituted boronic acids (**6b** and **6c**) had similar



Scheme 4. A hydrolysis mechanism for the fluorescence intensity changes of Shinkai's anthraceneboronic acid.

affinities for both fructose and glucose. On the other hand, in the bisboronic acid series, the nitro-substituted compound (**4b**) showed a much higher affinity than the fluoro-substituted one (**4c**). It is also worth noting that the fluoro-substituted bisboronic acid has an even lower affinity than that of the unsubstituted control (**1a**). Such results were somewhat unexpected because fluoro-substitution is electron-withdrawing. Furthermore, the size of the fluorine atom is small and one would not expect much perturbation of the conformation of the bisboronic acid compound by the fluorine atom. Consequently, one would expect **4c** to have a higher affinity for glucose than does **1a**.

The results of the selectivity studies were also somewhat surprising. Sensor **4a**, although having the highest affinity for glucose, showed the lowest selectivity with a three-fold preference for glucose over fructose in terms of the binding constants. This is in direct contrast to the 43-fold selectivity of **1a** for the same pair of sugars.[22] Compounds **4b** and **4c** were somewhere in between. In comparison with the monoboronic acids, it seems that the cyano-substituted one has a low selectivity problem too, only in this case it was the selectivity for fructose. Such results could mean that the cyano-substituted boronic acids have a lower propensity to discriminate among different sugars. However, the underlying reason for this is not clear.

Overall, the results indicate that the substituent effect on monoboronic acids can only be partially translated into the same kind effect when used for the preparation of bisboronic acid compounds. Other factors such as conformational changes may also need to be considered in designing analogs aimed at optimizing the affinity and selectivity of the interested sensors.

There is one additional point that is worth discussing, that is, why the substituent electron-withdrawing ability did not correlate with the apparent binding constants of the monoboronic acids (**1b**, and **6–c**) (Tables 1 and 2).

Table 1. Binding constant (K_a) for compounds **4a–4c** and **1a** with different saccharides

Compound	K_a (M^{-1}) D-glucose	K_a (M^{-1}) D-fructose	K_a (M^{-1}) D-galactose	Selectivity $K_{a\ glucose}/K_{a\ fructose}$	Fluorescence intensity changes for glucose
4a	2540±90.1	968±126.6	271±37.5	3	Ten-fold increase
4b	1808±130.6	198±32.8	132±60.5	9	Two-fold increase
4c	630±48.6	42±7.2	46±6.6	15	Four-fold increase
1a	1472	34	30	43	Seven-fold increase

Table 2. Binding constant (K_a) for monoboronic acids **6a–6c** and **1b** with different saccharides

Compound	K_a (M^{-1}) fructose	K_a (M^{-1}) glucose	Selectivity $K_{a\ fructose}/K_{a\ glucose}$	Fluorescence intensity changes for fructose
6a	1350±68.4	101±5.2	13	2.3-Fold increase
6b	714±51.3	40±4.0	18	Two-fold increase
6c	650±29.2	26±8.3	25	2.3-Fold increase
1b	940	50	18	Two-fold increase

As has been reported previously, the apparent binding constant of a particularly boronic acid can be affected by several factors including (1) the pK_a values of the boronic acid and the diol; (2) the optimal pH for a particular complexation reaction; (3) steric factors; (4) the concentration and nature of the buffer; (5) whether trivalent interaction is involved and (6) other idiosyncratic factors that have not been identified.[19] Among these factors, a shift of the optimal pH away from 7.4 to a lower pH is most likely the reason for the diminished intrinsic affinity of **6b** and **6c** for diols at pH 7.4 compared with the unsubstituted one (**1b**). Similar examples have been reported before, especially with boronic acids that have a very low pK_a value.[19]

3. Conclusions

We have synthesized three new anthracene-based bisboronic fluorescent sensors (**4a**–**4c**) and three monoboronic fluorescent sensors (**6a**–**c**). Both cyano- (**4a**) and nitro-substituted (**4b**) sensors had higher apparent binding constant for glucose (K 2540 and 1808 M^{-1}, respectively) than the parent sensor (**1a**) (1472 M^{-1}). Whereas fluoro-substituted bisfluoroboronic acid (**4c**) had a lower apparent binding constant (K 630 M^{-1}) but it has the most appropriate affinity and selectivity for glucose sensing under physiological conditions. The selectivity between glucose and fructose did diminish for all the new sensors (**4a**–**4c**) compared to **1a**. The monoboronic acid sensors (**6a**–**c**) also showed similar trend in the affinity for saccharides compared with their bisboronic acid analogs. Again, monofluoroboronic acid sensor (**6c**) had the lowest binding constant but showed a greater selectivity (25-fold) than **6a** for fructose over glucose. Overall, the introduction of an electron-withdrawing group does not always directly translate into enhanced affinity, and the affinity of the bisboronic sensors only partially tracks that of the monoboronic building blocks. The effect of the electron-withdrawing group in the selectivity of the bisboronic acid sensors is hard to predict.

4. Experimental

4.1. General procedures

Commercially available reagents were used without additional purification unless otherwise indicated. Dichloromethane was distilled from CaH_2. THF was distilled from sodium and benzophenone. Mass spectrometry (MS) analyses were performed by the Mass Spectrometry Laboratories of Georgia State University. ^1H and ^{13}C NMR spectra were recorded at 75 and 100 MHz. Chemical shifts (δ) are given in ppm relative to TMS for ^1H spectra and relative to residual solvent for ^{13}C spectra.

4.2. Fluorescence binding study procedure

A Shimadzu RF-5301PC fluorometer was used for all the fluorescent studies. For a typical fluorescent measurement, a 2 ml of sensor stock solution in methanol (2.0×10^{-6} M) was mixed with 2 ml of saccharide solution in 0.1 M of phosphate buffer (pH 7.4) at various concentrations. The pH was checked and corrected if necessary. The mixture was allowed to mix for 20 min and fluorescence intensity was recorded. Triplicate measurements were taken for each sugar. The correlation coefficients for all determinations in fitting the 1:1 model were over 0.99.

4.2.1. 4,4,5-Trimethyl-2(2-methyl-4-nitro-phenyl)-[1,3,2]dioxaboroloane (5b). A mixture of bromo-2-methyl-4-nitro-benzene (**5a**, 11.6 mmol), $PdCl_2$(dppf) (0.1 mmol), KOAc (14.6 mmol), and bis(pinacolato)diboron (12.7 mmol) in DMSO was heated to 80 °C overnight. The reaction mixture was pour into 25 ml ice-water slush and extracted with ethyl acetate (3×10 ml) and dried over $MgSO_4$. After evaporation of solvent, crude product was chromatographed on silica column using hexane–ethyl acetate as the eluent to give **5b** in 53%. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.05 (6H, s), 2.59 (3H, s), 3.80 (4H, s), 7.86 (1H, d, J=8.0 Hz), 7.96 (2H, d, J=8.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.8, 22.3, 31.6, 72.4, 119.3, 124.1, 135.7, 145.7, 148.9 ppm. HRMS (EI): calcd for $C_{12}H_{18}BNO_4$ [M^+] 263.1329, found 263.1336.

4.2.2. 5-Methyl-2-(2-methyl-4-nitro-phenyl)-[1,3,2]-dioxaborinane (5c). Compound **5b** (4.7 mmol) and neopentyl glycol (62.5 mmol) were mixed and heated to 250 °C for 2 h and then reaction was cooled to rt. Crude product was chromatographed on silica column using hexane–ethyl acetate as eluent to give **5c** in 82%. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.36 (12H, s), 2.62 (2H, s), 7.90 (1H, d, J=8.0 Hz), 7.95 (1H, s), 7.98 (1H, s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.4, 25.1, 84.5, 119.6, 124.2, 136.9, 146.8, 149.6 ppm. HRMS (ESI−): calcd for $C_{12}H_{16}BNO_4$ [M+CH_3OH] 280.1256, found 280.1252.

4.2.3. Compound (4a). Boc protected compound **2** (127 mg, 14 mmol) was dissolved in 4 ml dry DCM and 2 ml of trifluoroacetic acid (TFA) was added to the flask. Reaction was stirred for 30 min at rt and solvent was removed and dried under vacuum. The deprotected product, **3a** (156 mg, 0.50 mmol), potassium carbonate (175 mg, 1.27 mmol) and KI (6 mg) was dissolved in dried acetonitrile and mixed for 12 h at rt. Solvent was removed and resulted yellow precipitate was dissolved in (10 ml) DCM and 5 ml 10% $NaHCO_3$ and stirred for 1 h at rt. The organic phase was washed with water (2×10 ml), and dried over $MgSO_4$ and solvent was removed in vacuo. The resulted residue was re-precipitated from DCM–ether to give **4a** in 39%. ^1H NMR (400 MHz, CD_3OD) δ: 2.37 (6H, s), 2.63 (6H, s), 3.81 (4H, s), 4.22 (4H, s), 5.06 (4H, s), 5.74 (4H, s), 7.24 (4H, s), 7.57 (9H, t, J=8.8 Hz), 7.83 (4H, d, J=7.2 Hz), 8.31 (4H, d, J=7.6 Hz), 8.45 (4H, d, J=8 Hz) ppm. HRMS (ESI+): calcd for $C_{62}H_{58}B_2N_6O_6$: 1005.4663; found: 1005.4663. We were unable to remove cleaved neopentyl glycol, in order to confirm the structure; the boronic acid was oxidized in the presence of acetic acid–water (1/1) and H_2O_2 to obtain pure NMR. ^1H NMR (400 MHz, CD_3Cl_3) δ: 2.41 (6H, s), 2.64 (6H, s), 3.81 (8H, s), 4.71 (4H, s), 5.72 (4H, s), 6.66 (2H, d, J=8.4 Hz), 7.23 (6H, s), 7.34–7.32 (3H, dd, J=2, 6.4 Hz), 7.54 (4H, t, J=8.8 Hz), 7.63 (4H, t, J=6.4 Hz), 8.44 (8H, q, J=9.2, 12 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.58, 29.62, 33.37, 39.35, 41.85, 53.59, 59.52, 102.32, 116.85, 119.12, 122.84, 124.37, 124.76, 125.28, 125.64, 126.26, 126.42, 127.32, 128.55, 129.98, 130.52, 130.89, 131.17, 132.22, 132.42, 132.98, 133.12,

134.42, 161.58, 170.77 ppm. HRMS (ESI+): calcd for $C_{62}H_{56}N_6O_4$: 949.4442; found: 949.4479.

4.2.4. Compound (4b). The procedure was same as the preparation of **4a** from **2**. Yield (20%). ^{1}H NMR (400 MHz, $CD_3OD/CDCl_3$) δ: 2.37 (6H, s), 2.63 (6H, s), 3.80 (4H, s), 4.21 (10H, s), 5.73 (4H, s), 7.23 (4H, s), 7.56 (6H, t, J= 8.0 Hz), 7.86 (2H, d, J=8.0 Hz), 8.07 (2H, s), 8.12 (2H, d, J=8 Hz), 8.30 (4H, d, J=8.4 Hz), 8.43 (4H, d, J= 8.4 Hz) ppm. HRMS (ESI+): calcd for $C_{60}H_{58}B_2N_6O_{10}$: 1045.4479; found: 1045.4523. We were unable to remove cleaved neopentyl glycol, in order to confirm the structure; the boronic acid was oxidized in the presence of acetic acid–water (1/1) and H_2O_2 to obtain pure NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.44 (6H, s), 2.64 (6H, s), 3.80 (4H, s), 3.88 (4H, s), 4.73 (4H, s), 5.72 (4H, s), 6.64 (2H, d, J= 6 Hz), 7.26 (3H, s), 7.52 (4H, t, J=8 Hz), 7.62 (4H, t, J= 6.8 Hz), 7.87 (2H, s), 7.95–7.93 (4H, dd, J=2.4, 2.4 Hz), 8.41 (4H, t, J=10 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.71, 33.48, 39.36, 41.66, 42.01, 53.50, 59.39, 116.17, 121.81, 124.36, 124.65, 125.22, 125.32, 126.36, 126.57, 127.44, 128.38, 130.04, 130.82, 131.10, 134.35, 140.05, 163.70, 170.74 ppm. HRMS (ESI+): calcd for $C_{60}H_{56}N_6O_8$: 989.4238; found: 989.4252.

4.2.5. Compound (4c). The procedure was same as the preparation of **4a** from **2**, but the hydrolysis was done in solution of acetone–water (1/4) in total volume of 150 ml and 1 N HCl (10 ml). The reaction was stirred vigorously for 1 h at rt. The organic phase was washed with water (2× 10 ml), and dried over $MgSO_4$ and solvent was removed in vacuo. The resulted residue was re-precipitated from DCM–ether to give **4c** in 20%. ^{1}H NMR (400 MHz, $CD_3OD/CDCl_3$) δ: 2.21 (6H, s), 2.42 (6H, s), 3.72 (4H, s), 4.11 (4H, s), 4.60 (4H, s), 5.68 (4H, s), 7.09 (4H, q, J=8.4, 9.6 Hz), 7.24 (4H, s), 7.48 (8H, s), 7.68 (2H, s), 8.27 (4H, s), 8.42 (4H, d, J=6.4 Hz) ppm. HRMS (ESI+): calcd for $C_{60}H_{58}B_2F_2N_4O_6$–H_2O: 973.4483; found: 973.4464. We were unable to remove cleaved neopentyl glycol, in order to confirm the structure; the boronic acid was oxidized in the presence of acetic acid–water (1/1) and H_2O_2 to obtain pure NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.34 (6H, s), 2.61 (6H, s), 3.79 (8H, s), 4.67 (4H, s), 5.29 (4H, s), 6.62 (2H, q, J=4.4, 4.8 Hz), 6.71 (2H, dd, J=2.8 Hz), 6.77 (2H, d, J= 2.8 Hz), 7.23 (4H, s), 7.52 (4H, t, J=8.4 Hz), 7.60 (4H, t, J=8.4 Hz), 8.40–8.42 (8H, dd, J=2.4, 2.8 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.71, 39.31, 41.66, 41.75, 53.59, 59.97, 114.78 (s (d_{C-F}), J=14 Hz), 115.01 (s (d_{C-F}), J=14 Hz), 116.49 (s (d_{C-F}), J=8 Hz), 122.69, 122.75, 124.63, 125.19, 126.29, 127.42, 129.14, 129.58, 130.08, 130.85, 131.07, 134.38, 153.11, 157.15 (s (d_{C-F}), J= 220 Hz), 170.72 ppm. HRMS (ESI+) calcd for $C_{60}H_{56}F_2N_4O_4$: 935.4348; found: 935.4351.

4.2.6. 2-[(Anthracen-9-ylmethyl-methyl-amino)-methyl]-4-cyano-boronic acid (6a). Anthracen-9-ylmethyl-methyl-amine (120 mg, 0.54 mmol), **3a** (183 mg, 0.60 mmol), potassium carbonate (299 mg, 2.17 mmol) and KI (7.2 mg) was dissolved in dried acetonitrile and mixed for 12 h at rt. Solvent was removed and resulted yellow precipitate was dissolved in (10 ml) DCM and 5 ml 10% $NaHCO_3$ and stirred for 1 h at rt. The organic phase was washed with water (2×10 ml), and dried over $MgSO_4$ and solvent was removed in vacuo. The resulted residue was re-precipitated from DCM–hexane to give **6a** in 12%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.44 (3H, s), 4.23 (2H, s), 5.03 (2H, s), 7.55 (4H, m), 7.67 (1H, d, J=7.8 Hz), 7.89 (1H, d, J=7.5 Hz), 8.10–8.19 (4H, dd, J=8.4 Hz), 8.59 (1H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 43.15, 51.55, 112.24, 119.33, 124.92, 125.88, 128.08, 128.34, 129.08, 129.32, 130.09, 131.00, 131.39, 131.72, 133.79, 144.71 ppm. HRMS (ESI+): calcd for $C_{24}H_{21}BN_2O_2$: 381.1774; found: 381.1774.

4.2.7. 2-[(Anthracen-9-ylmethyl-methyl-amino)-methyl]-4-nitro-boronic acid (6b). The procedure was same as the preparation of **6a**. Yield (29%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.25 (3H, s), 4.54 (2H, s), 5.15 (2H, s), 7.58 (4H, m), 7.97 (1H, d, J=8 Hz), 8.14 (2H, d, J=8 Hz), 8.24–8.28 (4H, dd, J=5.6, 6 Hz), 8.64 (1H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$) δ: 42.29, 121.80, 124.24, 124.90, 126.08, 126.77, 128.57, 129.17, 131.38, 131.95, 135.88, 141.96, 143.07, 148.50 ppm. HRMS (ESI+): calcd for $C_{23}H_{21}BN_2O_4$: 401.1672; found: 401.1670.

4.2.8. 2-[(Anthracen-9-ylmethyl-methyl-amino)-methyl]-4-fluoro-boronic acid (6c). The procedure was same as the preparation of **6a**. Yield (53%). ^{1}H NMR (300 MHz, CD_3OD) δ: 2.24 (3H, s), 3.98 (2H, s), 4.57 (2H, s), 7.06 (2H, m), 7.42–7.44 (4H, dd, J=2.7, 3.3 Hz), 7.79 (1H, s), 7.94–8.00 (4H, dd, J=3, 13.2 Hz), 8.39 (1H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3/CD_3OD$) δ: 38.39, 61.24, 112.81 (s (d_{C-F}), J=18 Hz), 115.52 (s (d_{C-F}), J= 19 Hz), 122.32, 123.64, 125.38, 127.84, 128.28, 130.01, 130.16, 134.69, 141.96, 162.69 (s (d_{C-F}), J=243 Hz) ppm. HRMS (ESI+): calcd for $C_{23}H_{21}BFNO_2$: 374.1727; found: 374.1717.

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52. Compound **5c** synthesis has been reported in literature but not fully characterized. See Section 4 for full characterization of **5c**.

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Efficient one-pot, two-step synthesis of (*E*)-cinnmaldehydes by dehydrogenation–oxidation of arylpropanes using DDQ under ultrasonic irradiation☆

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Abstract—A general, efficient and new approach to the synthesis of cinnamaldehydes with trans-selectivity has been accomplished starting from arylpropanes. One-pot, two-step dehydrogenation and oxidation of arylpropanes with excess DDQ in dioxane containing a few drops of acetic acid gave (*E*)-cinnmaldehydes under ultrasound irradiation.

1. Introduction

Cinnamaldehyde derivatives are common in nature[1] and they possess remarkable biological properties[2] such as antibacterial, antifungal, antitermitic, antioxidant and anti-cancer activities. Moreover, cinnamaldehydes are used to prevent darkening of skin[3] caused by UV rays of sun and also prevent hair-loss and promote hair growth.[4] Cinnamaldehydes are often used as starting materials for the synthesis of many bioactive compounds[5] including cytostatic[6] and anti-viral[7] drugs.

A number of reagents and processes are available for the preparation[8] of cinnmaldehydes including Wittig olefination reaction,[9] oxidation of arylpropene,[10] palladium cluster[11] or potassium dichromate[12] catalysed oxidation of allylic alcohols and most importantly, chain lengthening[13] of arylaldehydes (C_6–C_1 unit) by a C_2-unit. However, most of these methods mainly suffer from poor yield, harsh reaction conditions and contamination with small amounts of the undesirable *Z*-isomer.[14] Recently, some straightforward strategies have also been reported for the synthesis of cinnamaldehydes with trans-selectivity[15] and the most common approach is the Heck[16] reaction. Since the inception of the Heck reaction, a number of modifications[17] in the original protocols have been reported, however, problems such as side product formation, low yields and polymerization of acrolein incited chemists to look for alternatives. Direct oxidative[18] coupling of aromatic compounds with α,β-unsaturated aldehydes by palladium acetate/molybdovanadophosphoric acid/oxygen[19] system is a meticulous entry, however, expensive reagents and side product formation limit adoption of the protocol.

All these synthetic methods have also been exploited for introduction of α,β-unsaturated aldehyde moiety in the aromatic ring during the synthesis of various bioactive compounds[20] and natural products.[21] However, limitations such as harsh reaction conditions, heavy burden of protection–deprotection steps and lengthy protocols warrant alternative efficient and environmentally friendly procedures for the synthesis of (*E*)-cinnamaldehydes. The application of ultrasound irradiation[22] has emerged as a useful synthetic tool. In this paper, we report the DDQ-assisted one-pot, two-step dehydrogenation–oxidation of arylpropanes in dioxane, containing a few drops of acetic acid, into cinnamaldehydes with 100% (*E*)-selectivity under ultrasonic irradiation (Scheme 1).

2. Results and discussion

The methods for formation of cinnamaldehyde basically fall into three categories[8–19] (a) combination of a C_6 unit with a C_3 unit, (b) combination of a C_6–C_1 unit with a C_2 unit, and (c) modification of an already existing C_6–C_3 unit. Among these three, use of a C_6–C_3 unit would ensure waste minimization through atom economy[23] as C_6–C_3 system in

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Keywords: Arylalkane; Cinnamaldehyde; DDQ; trans-Selectivity; Dehydrogenation–oxidation.
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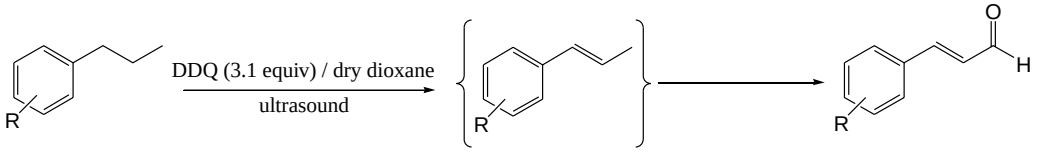


Where
R= OMe, OEt, –OCH_2O–, OH etc.

Scheme 1.

the substrate is retained in the product. Recently, we have reported[24] that arylpropane[25] effectively undergoes oxidation with DDQ[26] in wet dioxane leading to the formation of propiophenone while dehydrogenation of arylpropane with DDQ in anhydrous dioxane to form (*E*)-arylpropene[24] along with traces of (*E*)-cinnamaldehyde.[27] Hence, we decided to pursue both dehydrogenation and oxidation in one-pot for the formation of cinnamaldehydes. This would be achieved through the DDQ-assisted conversion of arylpropane directly into cinnamaldehyde via formation of intermediate (*E*)-arylpropene under ultrasound irradiation.

Thus, treatment of 3-(2,4,5-trimethoxyphenyl)propane[24] **1a** with 2 equiv of DDQ in dioxane for 6 h under ultrasonication provided (*E*)-2,4,5-trimethoxycinnamaldehyde[15c] **2a** in 48% yield along with some amount of starting **1a**. Subsequently, it was found that 3.1 equiv of DDQ was optimum for providing 73% yield of the product **2a** in 3.5 h under ultrasonication. Finally, conditions were optimized and we observed that addition of a catalytic amount of acetic acid (2–3 drops) increased the yield of **2a** up to 82% in 2 h. Acetic acid was found best among other homogeneous and heterogeneous acid catalysts (Table 1). After success of the above reactions for conversion of **1a** into **2a**, the same methodology was employed towards dehydrogenation–oxidation of other arylpropanes (**1b**–**1i**), which successfully provided the corresponding cinnmaldehydes (**2b**–**2i**) in moderate to good yield (Table 2). It is obvious from Table 2 that higher yields are obtained with the more electron rich aromatics and no cinnamaldehyde was formed in the case of unsubstituted phenylpropane **1j**. To make a comparative analysis, dehydrogenation and oxidation of **1a** with DDQ (3.1 equiv) in dioxane containing a few drops of acetic acid at room temperature (20 h) or reflux temperature (8 h) provided **2a** in 76% yield under conventional method. The results clearly showed that ultrasound activation afforded a better yield in a shorter reaction time compared to the classical method. We also found that small alterations in the reaction conditions such as changing the amount of DDQ and using hydrated or anhydrous conditions[24] provide a range of products as shown in Scheme 2.

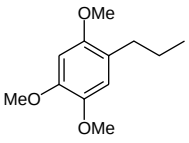
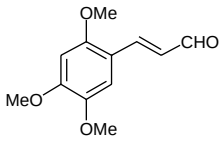
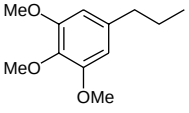
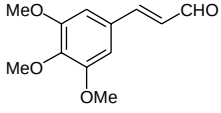
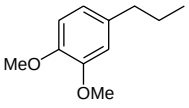
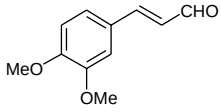
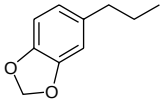
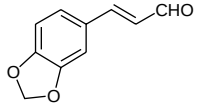
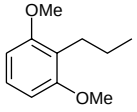
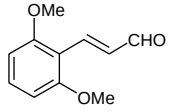
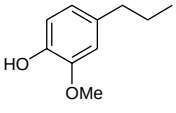
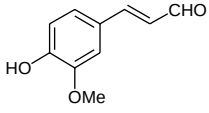
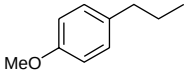
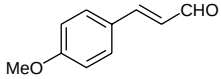
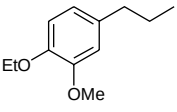
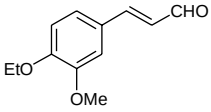
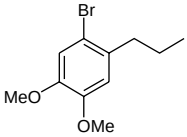
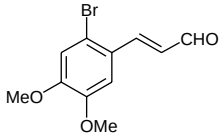
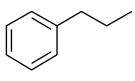
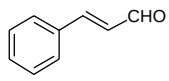
Table 1. Effect of catalyst on the yield of cinnamaldehyde (**1b**) under ultrasonic irradiation

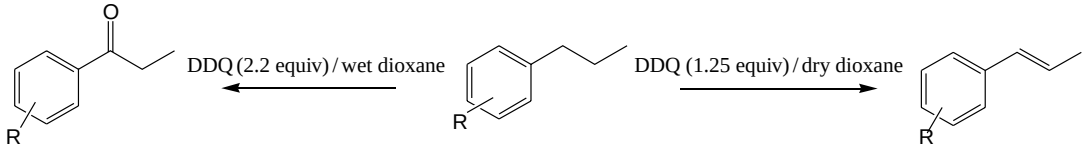
Support	Reaction time (in hours)	Product yield (%)
Acetic acid	2	82
Silica gel	2	78
Alumina (acidic)	2	76
Hydrochloric acid	2	42

3. Conclusion

In conclusion, we have realised a convenient synthetic approach towards the preparation of a number of *(E)*-cinnmaldehydes (**2a**–**2i**) via dehydrogenation–oxidation

Table 2. DDQ assisted dehydrogenation–oxidation of arylpropanes (**1**) into cinnamaldehydes (**2**)

S. no.	Substrate (**1**)	Product (**2**)	Yield (%)
a			82
b			79
c			78
d			76
e			72
f			32
g			72
h			72
i			74
j			0



Scheme 2.

of available arylpropanes (**1a–1i**) with DDQ utilizing ultrasound irradiation. The merits of the protocol lie in one-pot, two-steps methodology, economical substrate, atom economy and consequent waste minimization, ultrasound irradiation and 100% (*E*)-selectivity. The method may be useful in natural product synthesis due to mild nature of the protocol.

4. Experimental

4.1. General methods

All melting points were determined with a Metler FP80 micromelting point apparatus. IR spectra were recorded on a Perkin-Elmer spectrophotometer. ^{1}H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were taken on a Bruker AM-300 spectrometer, using TMS as internal reference standard in $CDCl_3$. HRMS spectra were determined using a Micromass Q-TOF Ultima spectrometer. Sonication (20 kHz, 400 W; pulse length:10 s; 75% duty) was used for all the given reactions. Commercial reagents and solvents were of analytical grade and were purified by standard procedures prior to use. Column chromatographic separations have been carried out on neutral alumina (Qualigens India).

4.2. General procedure for ultrasound-assisted dehydrogenation–oxidation of arylpropanes (1a–1i) into cinnamaldehydes (2a–2i)

To a solution of **1a–1i** (0.017 mol) in dry dioxane (100 mL), a catalytic amount of acetic acid (2–4 drops) and DDQ (0.053 mol) was added. The reaction mixture was sonicated for 2 h or till disappearance of starting material on TLC plate. After completion of the reaction, the precipitated solid $DDQH_2$ was removed by filtration and the filtrate was evaporated. The residue was taken in ethyl acetate (70 mL) and was washed with water (2×10 mL), 2% sodium bicarbonate (2×5 mL), brine (2×10 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated to afford a crude yellow liquid, which was chromatographed on neutral alumina using hexane–ethyl acetate mixture with increasing proportion of ethyl acetate up to 40% to provide **2a–2i** whose spectral data agreed well with the reported values.[1a–d,2b,8e,15b–c,19,24]

4.2.1. (*E*)-2,4,5-Trimethoxycinnamaldehyde[1c,15c,31] (2a). Yellow solid; 3.09 g (82% yield); mp 139–140 °C (lit.[15c,31] 140–141 °C).

4.2.2. (*E*)-3,4,5-Trimethoxycinnamaldehyde[1a,31] (2b). Yellow solid; 2.98 g (79% yield); mp 110 °C (lit.[31] 109–111 °C).

4.2.3. (*E*)-3,4-Dimethoxycinnamaldehyde[2b,8e] (2c). Yellow solid; 2.54 g (78% yield); mp 81–82 °C (lit.[8e] mp 83–84 °C).

4.2.4. (*E*)-3,4-Methylenedioxycinnamaldehyde[9,31] (2d). Yellow solid; 2.27 g (76% yield); mp 78 °C (lit.[9] mp 77–79 °C, lit.[31] mp 83–84 °C).

4.2.5. (*E*)-2,6-Dimethoxycinnamaldehyde[1b] (2e). Yellow solid; 2.35 g (72% yield); mp 78 °C (lit.[1b] mp 77–78 °C).

4.2.6. (*E*)-4-Hydroxy-3-methoxycinnamaldehyde[1d,31] (2f). Yellow solid; 0.97 g (32% yield); mp 83–84 °C (lit.[31] mp 84 °C).

4.2.7. (*E*)-4-Methoxycinnamaldehyde[15b,19,31] (2g). Light yellow solid; 1.98 g (72% yield); mp 58 °C (lit.[15b,31] mp 58–59 °C).

4.2.8. (*E*)-4-Ethoxy-3-methoxycinnamaldehyde (2h). Yellow solid; 2.52 g (72% yield); mp 78–80 °C; IR (KBr) 1670 cm^{-1} (conjugated carbonyl); ^{1}H NMR ($CDCl_3$): δ 9.59 (1H, d, J=7.8 Hz, H-3′), 7.36 (1H, d, J=15.8 Hz, H-1′), 7.07 (1H, d, J=8.1 Hz, H-6), 7.00 (1H, s, H-2), 6.83 (1H, d, J=8.1 Hz, H-5), 6.56 (1H, dd, J=15.8, 7.8 Hz, H-2′), 4.11 (2H, q, J=6.9 Hz, 4-OCH_2), 3.83 (3H, s, 3-OCH_3), 1.44 (3H, t, J=6.9 Hz, 4-CH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 193.6 (C-3′), 152.9 (C-1′), 151.4 (C-4), 149.5 (C-3), 126.8 (C-2′), 126.6 (C-1), 123.4 (C-6), 112.1 (C-5), 110.2 (C-2), 64.4 (4-OCH_2), 56.0 (3-OCH_3), 14.6 (4-CH_3); HRMS (M+Na) *m/z*: 229.2335 (Calcd for $C_{12}H_{14}O_3Na$: 229.2321).

4.2.9. (*E*)-2-Bromo-4,5-dimethoxycinnamaldehyde (2i). Yellow solid; 3.41 g (74% yield); mp 136–138 °C; IR (KBr) 1671 cm^{-1} (conjugated carbonyl); ^{1}H NMR ($CDCl_3$): δ 9.66 (1H, d, J=7.8 Hz, H-3′), 7.75 (1H, d, J=15.8 Hz, H-1′), 7.19 (1H, s, H-3), 7.02 (1H, s, H-6), 6.53 (1H, dd, J=15.8, 7.8 Hz, H-2′), 3.84 (3H, s, 4-OCH_3), 3.82 (3H, s, 5-OCH_3); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 193.4 (C-3′), 152.1 (C-1′), 150.5 (C-5), 148.8 (C-4), 128.6 (C-1), 125.8 (C-2′), 118.0 (C-3), 115.7 (C-6), 109.3 (C-2), 56.3 (4-OCH_3), 56.1 (5-OCH_3); HRMS (M+Na) *m/z*: 294.1006 (Calcd for $C_{11}H_{11}O_3BrNa$: 294.1012).

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25. The arylpropane derivatives are prepared either by catalytic reduction[28] of abundantly available isomeric mixture of arylpropenes (α,β and γ-isomers) or hydrogenolysis[29] of arylpropanol.
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27. To our best knowledge, formation of (*E*)-cinnamaldehyde is detected for the first time as a side product[24] along with expected (*E*)-arylpropene during dehydrogenation of arylpropane with 1.25 equiv of DDQ–SiO_2 in anhydrous dioxane under ultrasonication. It is presumed that formation of cinnamaldehyde could be due to the presence of atmospheric oxygen/moisture in the reaction mixture during sonication, which would form highly reactive peroxy radicals[30] to further oxidize (*E*)-arylpropene into (*E*)-cinnamaldehyde.
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A new route for the preparation of the 22,23-dioxocholestane side chain from diosgenin and its application to the stereocontrolled construction of the 22*R*,23*S*-diol function

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Abstract—The new (22*R*,23*S*,25*R*)-3β,16β,26-triacetoxy-cholest-5-ene-22,23-diol (**11a**) was synthesized from diosgenin (**3**) through a synthetic route based on chemoselective RuO_4 oxidation of (25*R*)-3β,16β-diacetoxy-23-ethyl-23^1,26-epoxycholesta-5,23(23^1)-dien-22-one (**9**) that afforded (20*S*,25*R*)-3β,16β,26-triacetoxycholest-5-ene-22,23-dione (**10**) which was stereoselectively reduced using $NaBH_4$. Compound **9** was obtained from the known isomeric 22,26-epoxycholest-5-ene steroidal skeleton **8b** by treatment with *p*-TsOH in toluene, amberlyst-15 or directly from diosgenin by treatment with $BF_3 \cdot OEt_2/Ac_2O$. Chemoselective reduction of the 23-keto group of **10**, was attained using $NaBH_4/ZnCl_2$ at −70 °C to give 23*S*-**14**. The NMR spectra of all compounds were unambiguously assigned based on one and two dimensional experiments and the C-22 and C-23 stereochemistry in the diacetate derivative **11b**, as well as the structure of epoxycholestene **9** were further established by X-ray diffraction analyses. The new route for the functionalization of the side chain of diosgenin can find application in the synthesis of norbrassinosteroid analogues.

1. Introduction

In recent years there has been increasing interest in the selective functionalization and derivatization of spirostan sapogenins owing to their applications in the synthesis of potent anticancer agents such as OSW-1,[1] cephalostatins and ritterazines,[2] oxysterols[3] and steroidal natural products.[4] Since ring opening of the spiroketal is pivotal for the selective transformation of the side chain, a great variety of catalysts and reaction conditions have been explored providing a wide variety of products,[5] sometimes under similar reaction conditions.

For many years it was believed that cleavage of the spiroketal side chain always occurs at the F ring, leading to furostene derivatives.[6] This erroneous conception led to incorrect structural assignment in several old and recent reports. For example, although Zderic[7] obtained **8b** by treatment of diosgenin(**3**) with excess $BF_3 \cdot OEt_2/Ac_2O$, the structure was incorrectly assigned as (*E*)-(25*R*)-23-acetyl-furosta-5,22-diene-3β,16β-diyl diacetate (**4a**) (Fig. 1). Singh[8] described that under catalysis of the same Lewis acid (8 equiv, 1 h reflux), but in the absence of acetic acid, diosgenin undergoes regioselective cleavage of ring E, not F, to give a new derivative, the 22,26-epoxycholesta-3,5-diene-16-one (**5**). In a similar experiment, Tian[9] reported that the 20-epimeric furostenes **4a** and **4b**, as well as (*E*)-(20*S*,25*R*)-20,23-diacetylfurosta-5,22-diene-3β,16β-diyl diacetate (**6**) are obtained when an equivalent of the Lewis was added at 0 °C, and stirred for 3 h at room temperature. However, the same author[10] reinvestigated the reaction and corrected the structures proposed for the furostenes, which correspond to epoxycholestenes (25*R*)-23-acetyl-3β,16β-diacetoxy-22,26-epoxycholesta-5,22-diene (**8a**, **8b**). The regioselective opening of ring E in spirostan

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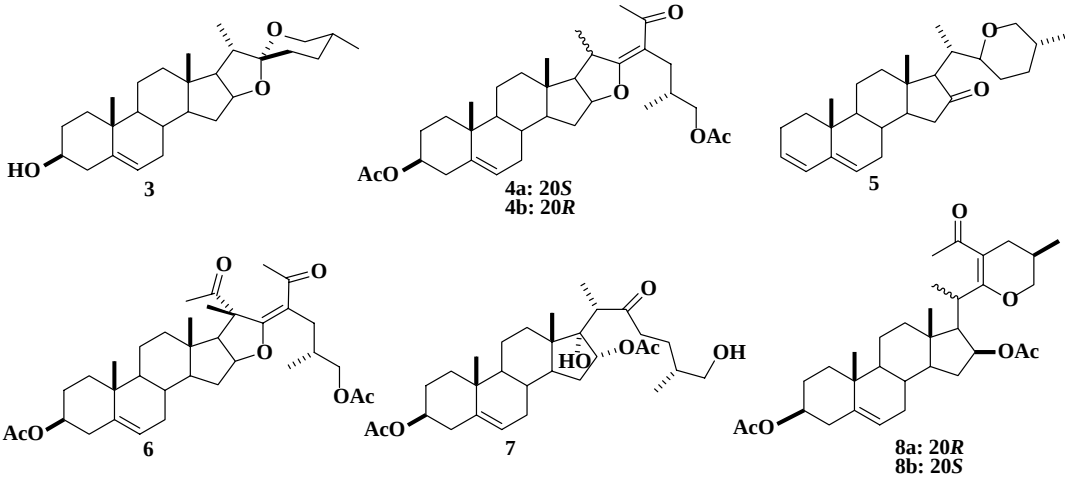


Figure 1. Products from $BF_3 \cdot OEt_2$ catalyzed transformations of sapogenins.

sapogenins to give an epoxy derivative analogous to **8a** has been described by González.[11] In turn, Strigina[12] reported that, with the same Lewis acid, 17α-hydroxydiosgenin (pennogenin) produced (20*S*,25*R*)-22-oxocholest-5-ene-3β,16α,17α,26-tetraol-3,16-diacetate (**7**) or a dimeric furostene, depending on the reaction conditions.

We have described the highly regioselective cleavage[13a] of ring E in sapogenins from the 25*R* serie whereby treatment of diosgenin (**3**) yielded 23-acetyl-3β,16β-diacetoxy-22,26-epoxycholesta-5,22-diene (**8b**) in 85%, as established by spectroscopic methods and X-ray diffraction analysis. In contrast, sarsasapogenin (25*S* serie), yields a mixture of furostenes and epoxy derivative due to steric hindrance of the methyl group at position 25.[13b,14] More recently, reduction of the vinylogous ester moiety in compound **8b** with 9-BBN provided steroidal derivatives[15] with vinyl substituents on C-23.

In continuation of our studies on the modification of the side chain of sapogenins we report the construction of a cholestane side chain supporting a *trans*-22,23-diol functionality from diosgenin, by stereoselective reduction of the corresponding 22,23-dioxocholestane. This functionality is analogous to the one present in plant growth hormones known as brassinosteroids where it has been recognized that the stereochemistry of the carbon atoms supporting the substituents on the side chain, plays an important role on the biological activity, thus all native brassinosteroids present a (22*R*,23*R*)-diol moiety.

Due to the high bioactivity of brassinosteroids, a variety of analogues have been prepared and tested, and great efforts have been devoted to the construction of the side chain that supports the (22*R*,23*R*)-diol function; for this reason, many synthetic pathways have been published.[16–20] In general, spectral characterization of the new native or synthetic derivatives is based on comparison with the reported NMR studies described for brassinolide (**1**) and 24-*epi*-brassinolide[21,22] (**2**) (Fig. 2).

The present work describes a new approach based on the construction of the 22,23-dioxocholestane from the intact side chain of diosgenin, an important raw materials for the synthesis of hormones and other biologically interesting steroids. It should be mentioned that diosgenin (**3**) has also been used for the preparation of brassinosteroids analogues with spirostanic or furostanic side chains.[23]

The structures of all compounds were established by detailed 1D and 2D NMR studies. Moreover, comparison of the data reported for a series of brassinosteroids derivatives revealed that assignment of the configuration of diol **11a** based solely on chemical shifts and coupling constants from the ^1H spectrum is not easy due to conformational changes [24–26] in the side chain. Thus, the configurations at the newly formed stereogenic centers were unambiguously established as 22*R*,23*S* by X-ray diffraction analysis of the diacetate derivative **11b**. Stereoselective formation of diol **11a** was attributed to steric hindrance at C-22 caused by Me-18, Me-21 and the acetate at C-16. This in turn allowed regioselective reduction of the carbonyl group at position 23.

The new methodology described herein could find application in the synthesis of brassinosteroids analogues and, to our knowledge, this constitutes the first report where the 22,23-functionality is constructed from the intact side chain of diosgenin. Moreover, stepwise reduction offers the possibility of stereoselective formation of specific 22,23-diol functions. Finally the new derivatives have potential for the preparation of labeled samples required in biosynthetic studies.

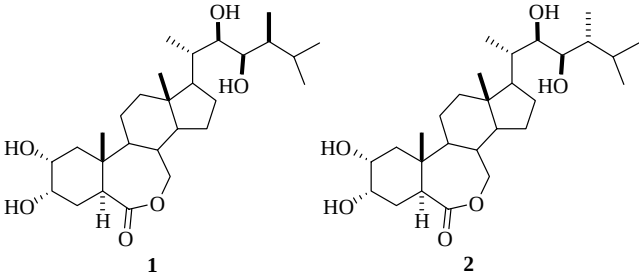
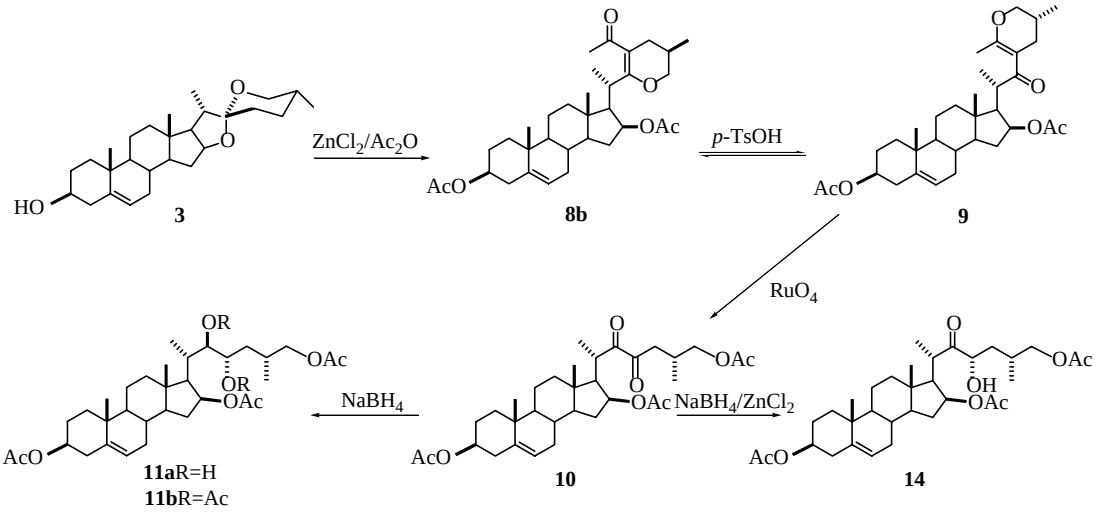


Figure 2. Native C-24 epimeric brassinolides.



Scheme 1. Synthetic route for the preparation of *trans*-diol **11a**.

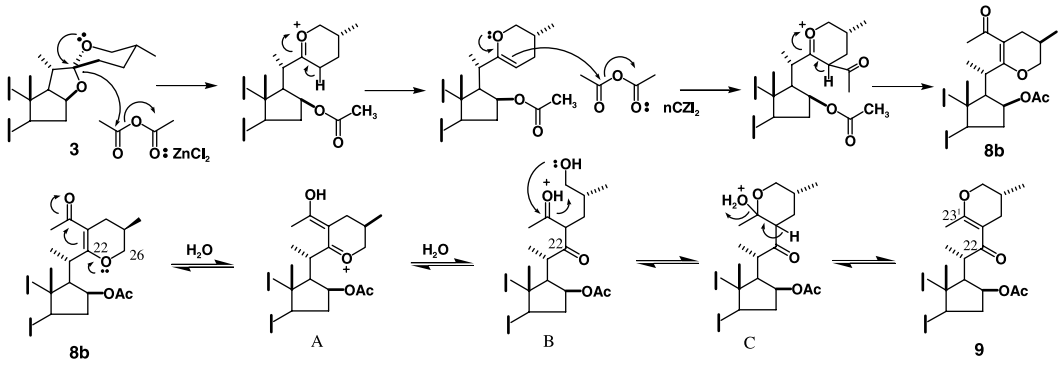
2. Results and discussion

In view of the synthetic value of **8b** for the construction of steroidal frameworks, the acetolysis reaction of diosgenin was reinvestigated using $ZnCl_2/Ac_2O$ instead of $BF_3\cdot OEt_2/Ac_2O$; this allowed to increase the yield to 95% (Scheme 1). The mechanism for the formation of **8b** (Scheme 2) is analogous to that described previously.[13a]

An important modification reported herein is the transformation of **8b** into the isomeric epoxycholesta-5,23(23[1])-dien-22-one (**9**). This reaction was carried out using different types of acids such as H_3PO_4, HCl, $BF_3\cdot OEt_2$, amberlyst-15 and *p*-TsOH (in hexane, acetone, benzene and toluene). The best results were obtained with *p*-TsOH acid in toluene or amberlyst-15 in water[27] which allowed to obtain the new β-alkoxy-α,β-unsaturated ketone **9** in 60% yield. The existence of an equilibrium between **8b** and **9** (4:6 ratio, determined by ^{1}H NMR) was confirmed by reacting epoxy **9** under the same conditions. Moreover, increasing the reaction times did not alter the product ratio and only reduced the yield. Alternatively, compound **9** could be obtained directly by treatment of diosgenin (**3**) with $BF_3\cdot OEt_2/Ac_2O$ provided quenching of the reaction is performed by slowly adding small portions of ice.

The acid catalyzed rearrangement of epoxycholestene **8b** can be explained through formation of oxonium ion **A** (Scheme 2), which is attacked by a molecule of H_2O giving a hemiketal, which tautomerizes to the β-diketone **B**. A new pyran ring is formed by nucleophilic attack of the hydroxyl group on C-26 to the carbonyl at C-23[1] (intermediate **C**). Protonation of the hemiketal followed by sequential elimination of water and proton gives the new product **9**. This mechanism is similar to the one proposed for the reaction of vinyl ethers with water in acidic solution.[28]

Compound **9** was obtained as colorless crystals, mp 255–256 °C; $[\alpha]_D^{20}$ −39, quite different from those of **8b**, mp 95–96 °C, and $[\alpha]_D^{20}$ −24. The mass spectrum of both **8b** and **9** showed the molecular ion at 540 amu with different fragmentation patterns. In the IR spectrum, characteristic carbonyl absorptions were observed at 1734 and 1671 for **9**, compared to 1732 and 1660 for **8b**. The ^{1}H NMR data for the isomeric derivatives **8b** and **9** showed similar chemical shifts for Me-21 (1.10 ppm in **9** and 1.19 ppm in **8b**), Me-18 (0.89 ppm in **9** and 0.92 in **8b**) and H-16α (5.02 in **9** and 5.14 in **8b**). However, the fact that the proton at C-20 is considerably shifted to low frequencies in **9** (3.20 ppm) compared to **8b** (4.08 ppm), could easily lead to the erroneous conclusion that the compounds are epimeric at



Scheme 2. Plausible mechanism for the formation of isomeric **8b** and **9**.

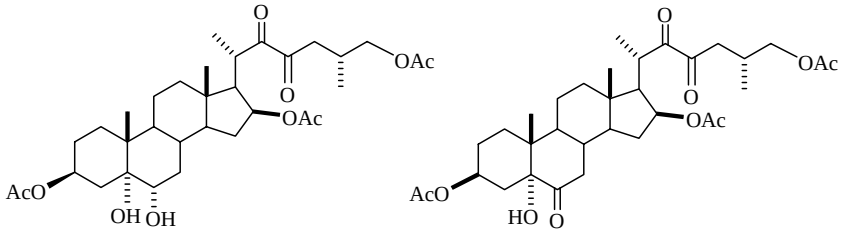


Figure 3. Δ^5 Oxidation of epoxy **9** with RuO_4.

C-20. Similarly, the ^{13}C NMR spectrum showed only slight chemical shifts differences except for the signals in the region from 160–175 ppm, which showed signals in 171.2, 170.4 and 170.3 for **8b**; 170.3, 169.6 and 164.2 for **9**, as well as C-20, which appears at 32.7 in **8b** and 38.6 in **9**.

Dione **10** was obtained by treatment of **9** with RuO_4 during 4 min at 0 °C in 63% yield[29d] (Scheme 1), together with recovered unreacted material. The chemoselectivity of the oxidation was confirmed by observation of the vinylic proton (H-6) at 5.36 ppm in the ^1H NMR spectrum. The diastereotopic protons at position 26 appear as dd at 4.03 and 3.88 ppm while the ones at position 24 are at 2.87 and 2.59 ppm. Conclusive evidence was obtained from the ^{13}C NMR spectrum that showed the presence of two carbonyl signals at 200.2 and 198.2 ppm and the double bond at 139.6 and 122.1 ppm.

The mass spectrum of **10** showed the pseudo molecular ion at 573 [$M^+ + 1$]. In the IR spectrum, carbonyl absorptions were observed at 1734 (C=O). The UV spectrum shows an absoption at 429 nm ($\varepsilon = 32$), characteristic of α-diketones.

When the epoxy derivative **9** was allowed to react with RuO_4 for 3 h other oxidation products were formed. In this way, 5,6-diol **12** and trione **13** were obtained, by further oxidation of the double bond in C-5 (Fig. 3). The ^1H NMR spectrum of 5,6-diol **12** showed the presence of a doublet of doublets for a proton geminal to an alcohol at 3.65 ppm, indicative of the oxidation of Δ^5. The corresponding ^{13}C NMR showed signals at 76.3 and 70.3 ppm for C-5 and C-6, respectively. The stereochemistry of the hydroxyl groups was established by a ROESY experiment, which showed correlation between H-6 and Me-19 that evidences a 6β disposition among them, therefore, the cis hydroxylation of the Δ^5 double bond occurs from the alpha side.[29] The UV spectrum of **12** shows a band at 275 nm ($\varepsilon = 1734$) for the α-diketone and IR bands at 1736 cm^{-1} (C=O) and 3480 cm^{-1} (OH). The mass spectrum shows the pseudo molecular ion at 607.

In the ^1H NMR spectrum of trione **13**, the new signal at 2.78 ppm (dd, $J_{7,8} = 12.7$ Hz), typical for a proton α to a carbonyl group, was assigned to H-7_{ax} while H-7_{eq} is shifted upfield and overlapped with other signals. The remaining signals had chemical shifts similar to those of dione **12**. Similarly, no vinylic signals were evident in the ^{13}C NMR spectrum, which shows three carbonyl signals at 211.5, 200.1 and 198.1 ppm. The high frequency signal was assigned to C-6 by comparison with the shift obtained for the corresponding carbons in dione **10**, while the remaining carbonyl groups at C-22 and C-23 were ascribed based on long range coupling constants from the HMBC experiment, which shows correlation between the carbonyl carbon at position 22 and Me-21. The signal at 80.1 ppm was assigned to the quaternary C-5.

The UV spectrum of **13** gives a band at 379 nm ($\varepsilon = 264$) characteristic of α-diketones. The carbonyl absorption appears at 1737 cm^{-1} and the hydroxyl groups at 3468 cm^{-1}, in the IR spectrum. The mass spectrum showed a pseudo molecular ion at $m/z = 605$.

The final step involved reduction of **10** with $NaBH_4$ in MeOH at room temperature, during 30 min, to give (22*R*,23*S*)-3β,16β,26-triacetoxycholest-5-ene-22,23-diol (**11a**). The proton NMR spectrum of **11a** showed multiplets for H-16 and H-3 at 5.27 and 4.60 ppm. The diastereotopic protons at C-26 showed the same pattern as in dione **10**, and their chemical shifts were also very similar (4.06 and 3.95 ppm). The broad dd at 3.66 ppm, was assigned to H-23 ($J_{22,23} = 8$ Hz) and the broad doublet ($J = 8$ Hz, $W_{1/2} = 7$ Hz) at 3.22 to H-22. The mass spectrum of **11a** showed the [$M^+ - 18$] ion at 558. In the IR spectrum, the hydroxyl band was observed at 3503 cm^{-1}. The UV spectrum shows an absorption at 269 nm ($\varepsilon = 413$).

In order to assign the configuration at C-22 and C-23, the coupling constant values reported for brassinosteroids and analogs (Fig. 4) were compared with those of diol **11a**, however, it is evident that these values are dependent on the configuration of C24, as well as the conformation of the side chain.[24–26] Evidence for the stereochemistry of the new stereogenic centers was obtained from a NOESY experiment, which showed through space interaction between H-22 and H-16, thus suggesting a (22*R*) configuration.

The ROESY spectrum for **11a** showed correlation between H-22 and H-16; H-22 and H-17, therefore H-22 is on the same side as H-16 and H-17. Also, an interaction between H-23 and H-20 was observed; since H-20 is beta, this suggests that H-23 is on the same face. This allowed to propose a (22*R*,23*S*) stereochemistry for **11a**, which is in agreement with the couplings constants reported for (23*S*,24*R*)-diepiteasterone, (22*S*,24*R*)-diepiteasterone and brassinolide (**1**) (Fig. 4).

In order to unambiguously establish the stereochemistry at C22 and C23, several diol derivatives, which include the boronic ester, acetonide and diacetate **11b** were prepared, the latter provided adequate crystals for X-ray analysis. Thus, the absolute configuration of the carbons at positions

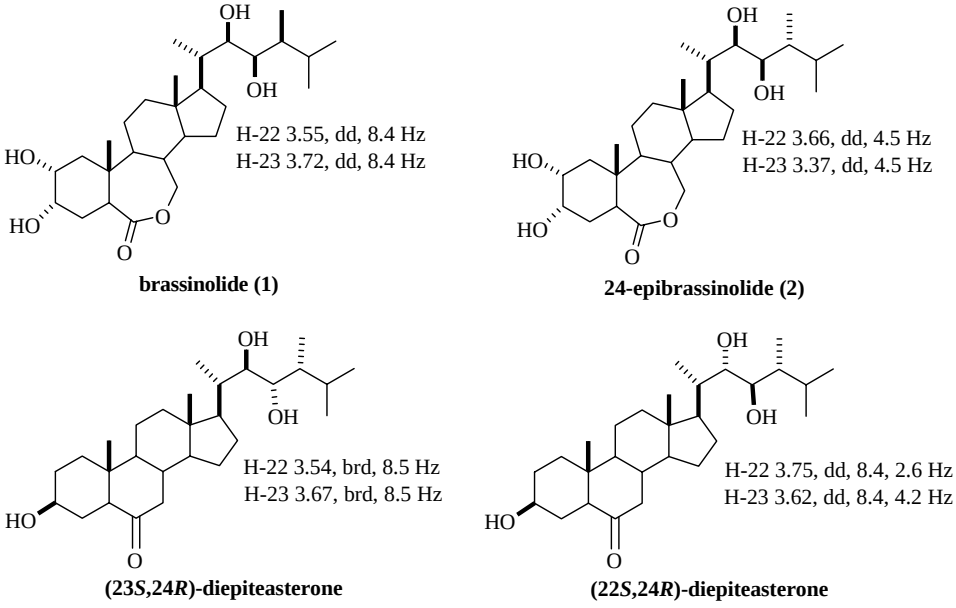


Figure 4. Chemical shifts and coupling constants for 22,23-dihydroxylated brassinosteroids.[24]

22 and 23 were established as *R* and *S*, respectively, confirming our previous assignments base on NMR studies.

The X-ray crystal structure analyses of compounds **9** and **11b** showed that the stereochemistry at C20 and C25 (*S*,*R* configuration, respectively) is retained (Fig. 5). In both compounds, the steroid nucleus shows that rings A and C adopt chair conformations. The C5–C6 (Csp^2–Csp^2) distance of 1.32 (4) Å confirms the position of the double bond, and ring B adopts a half-chair conformation. The cyclopentane ring D adopts an envelope conformation with torsion angles of 23.3° for the C15–C16–C17–C13 fragment. Bond lengths and angles for C-22 and C-23 unambiguously stand for sp^2 hybridized atoms in the case of **9**, while a sp^3 hybridization is observed in the case of **11b**. The dihedral angle for the H22–C22–C23–H23 fragment is 166.4° indicating a quasi *anti* conformation for the 22,23-diol.

Regioselective reduction of the carbonyl group at C-23 was attained by treatment of **10** with $NaBH_4$ in the presence of $ZnCl_2$, at −70 °C during 3 h, to give keto-ol **14**. The ^1H NMR spectrum showed the multiplets assigned to H-3 and H-16 at 4.57 and 4.78 ppm; the diastereotopic protons at C-26 are slightly downfield shifted (4.12 and 4.03 ppm) in comparison with those of the diol **11a** (4.06 and 3.95 ppm) or with respect to those in the diketone **10** (4.03 and 3.88 ppm). A dq at 3.02 ppm was assigned to H-20, the multiplet at 2.29 ppm to H-24 and the broad doublet at 4.23 ppm to H-23. The fact that H-20 (3.02 ppm) in **14** is shifted to high frequency with respect to diosgenin or the diol-**11a** evidences the presence of a carbonyl group at C-22; the same proton in dione-**10** is observed at 3.77 ppm. Moreover, the ^{13}C NMR spectrum of **14** showed only one carbonyl signal at 215.18 ppm and a new signal at 75.45 ppm for C-23. The results evidence that the stereoselectivity of the reduction of the carbonyl group at C-23 is due to a large steric hindrance caused by Me-18, and Me-21.

In conclusion, we have developed a new route for the preparation of 22,23-dioxocholestane frameworks via chemoselective oxidation of **9**. The sequence described provides a new route to norbrassinosteroid analogues by exploiting the intact skeleton of sapogenins. It is important to mention that there have been intensified efforts toward the synthesis of these phytohormones in view of their application for enhancement of crop yields.

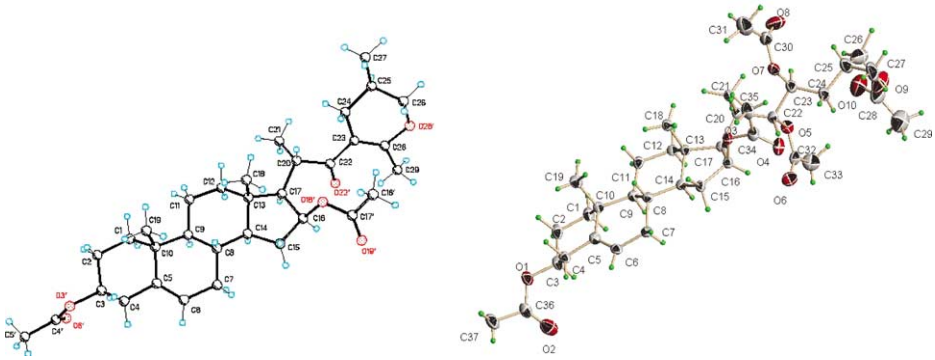


Figure 5. Perspective views of compounds **9** and **11b** (ellipsoids at 50% probability).

3. Experimental

3.1. General

1D and 2D ^{1}H and ^{13}C NMR spectra (DEPT, COSY, HMQC, HMBC, INADEQUATE) were recorded on Bruker DMX 500 and JEOL eclipse +400 spectrometers. Chemical shifts are stated in ppm (δ), and referred to the residual ^{1}H signal ($\delta=7.27$) or to the central ^{13}C triplet signal, ($\delta=77.0$) for $CDCl_3$. Infrared absorption spectra were obtained with Perkin Elmer 16F-PC-FT-IR and Perkin Elmer Spectrum GX spectrophotometers using KBr pellets. Mass spectra (EI) were obtained on a HP 5989A spectrometer adapted to a HP 6890A gas chromatograph.

Ultraviolet absorption spectra were determined on a Perkin Elmer Lambda 12 and Varian Cary UV–vis spectrophotometers; wavelengths (λ) are expressed in nm. Optical rotations were determined on a Perkin-Elmer 241 polarimeter at room temperature using chloroform solutions. Melting points were obtained on an Electrothermal 9200 apparatus. Elemental analyses were determined on a Thermofinnigan flash EA 1112. X-ray diffraction analyses were performed on Bruker P4 and Enraf-Nonius-Kappa CCD diffractometers with Mo Kα-radiation, $\lambda=0.71073$ Å. Column chromatography were carried out on silica gel grade 60 (230–400 mesh). Thin layer chromatography analyses were performed on silica gel $60F_{254}$ sheets using a 7:3 hexane/ethyl acetate mixture. High-resolution mass spectra were obtained on a Jeol JMS-SX102A using polyethylene glycol-600.

3.2. Reaction of diosgenin with $ZnCl_2/Ac_2O$

To a suspension of 1.00 g (2.4 mmol) of **3** in 10 mL (106.0 mmol) of Ac_2O were added 0.33 g (2.4 mmol) of anhydrous $ZnCl_2$. The reaction mixture was stirred 40 h at room temperature and quenched with ice. The organic phase was extracted with ethyl acetate, neutralized with a saturated $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, and evaporated under vacuum to yield 1.23 g (95%, $R_f=0.50$) of **8b**.

3.2.1. (25*R*)-23-Acetyl-3β,16β-diacetoxy-22,26-epoxycholesta-5,22-diene (8b). Colorless crystals, mp 95–96 °C, lit. (95–96 °C) [11,13a] $[\alpha]_D^{20}$ −24 (*c* 0.65, $CHCl_3$); UV λ_{max} 275 nm (ε 10,300); IR $\bar{\nu}_{max}$: 1732 (OAc), 1660 and 1568 (C=C–C=O), 1248 (C–O) cm^{-1}; MS, *m/z* (%): 540 ([M$^{+\cdot}$], 3), 480 (9), 205 (100), 43 (91). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.36 (1H, d, $J=4.5$ Hz, H-6), 5.14 (1H, ddd, $J_{16-17\alpha}=J_{16-15\alpha}=7.5$ Hz, $J_{16-15\beta}=4.0$ Hz, H-16), 4.59 (1H, m, H-3), 4.08 (1H, dq, $J_{20-17}=11.0$ Hz, $J_{20-21}=7.0$ Hz, H-20), 4.01 (1H, ddd, $J_{gem}=10.5$ Hz, $J_{26eq-25ax}=3.5$ Hz, $J_{26eq-24eq}=2.0$ Hz, H-26$_{eq}$), 3.46 (1H, dd, $J_{gem}=J_{26ax-25ax}=10.5$ Hz, H-26$_{ax}$), 2.20 (3H, s, 23^2-$COCH_3$), 2.03 (3H, s, 3-OCOCH_3), 1.84 (3H, s, 16-OCOCH_3), 1.19 (3H, d, $J=7.0$ Hz, CH_3-21), 1.03 (3H, s, CH_3-19), 0.97 (3H, d, $J=6.5$ Hz, CH_3-27), 0.92 (3H, s, CH_3-18). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 197.9 (23^1-*CO*CH_3), 171.2 (C-22), 170.4 (16-O*CO*CH_3), 170.3 (3-O*CO*CH_3), 139.6 (C-5), 122.1 (C-6), 106.8 (C-23), 74.9 (C-16), 73.7 (C-3), 71.4 (C-26), 55.8 (C-17), 54.2 (C-14), 49.9 (C-9), 42.1 (C-13), 39.6 (C-12), 37.9 (C-4), 36.8 (C-1), 36.4 (C-10), 34.8 (C-15), 32.7 (C-20), 31.5 (C-24), 31.4 (C-7), 31.2 (C-8), 29.6 (23^2-$COCH_3$), 27.6 (C-2), 26.4 (C-25), 21.2 (3-OCO*C*H_3), 21.0 (16-OCO*C*H_3), 20.7 (C-11), 19.3 (C-21), 19.1 (C-19), 16.7 (C-27), 12.8 (C-18).

3.3. Reaction of diosgenin with $BF_3\cdot OEt_2/Ac_2O$

To a magnetically stirred suspension of 5.00 g (12.1 mmol) of **3** in 50 mL (531 mmol) of Ac_2O were added 10 mL (72.6 mmol) of $BF_3\cdot OEt_2$, at room temperature. The reaction mixture was stirred for 10 min and quenched by adding slowly small portions of ice over a period of 20 min (CARE most be taken because the reaction is highly exothermic) The organic phase was extracted with ethyl acetate, neutralized with saturated $NaHCO_3$ solution, dried over anhydrous $MgSO_4$ and evaporated under vacuum. The crude product (5.30 g) was chromatographed over silica gel using hexane/EtOAc 90:10 to give 1.00 g of **8b** (17% yield, $R_f=0.5$), 2.50 g of **9** (42% yield, $R_f=0.38$) contaminated with traces of furostene **4b** ($R_f=0.38$) pf 83–85 °C. All R_f are referenced to a hexane–ethyl acetate (7/3) mixture as mobile phase.

3.3.1. (25*R*)-3β,16β-Diacetoxy-23-ethyl-23^1,26-epoxycholesta-5,23(23^1)-dien-22-one (9). White crystals, mp 255–256 °C; $[\alpha]_D^{20}$ −39 (*c* 1.0, $CHCl_3$); UV λ_{max} 269 nm (ε 11,583); IR $\bar{\nu}_{max}$ (KBr) 2967 (CH), 1734 (OAc), 1671 (CO), 1576 (C=C), 1249 (C–O) cm^{-1}; MS, *m/z* (%): 540 ([M$^{+\cdot}$] 0.1), 139 (100). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.36 (1H, d, $J=5.2$ Hz, H-6), 5.02 (1H, m, H-16), 4.59 (1H, m, H-3), 4.06 (1H, ddd, $J_{gem}=10.4$ Hz, $J_{26eq-25ax}=3.0$ Hz, $J_{26eq-24eq}=1.9$ Hz, H-26$_{eq}$), 3.43 (1H, dd, $J_{gem}=J_{26ax-25ax}=10.4$ Hz, H-26$_{ax}$), 3.20 (1H, dq, $J_{20,17}=10.7$ Hz, $J_{20-21}=7.0$ Hz, H-20), 2.13 (3H, s, 23^2CH_3), 2.03 (3H, s, 3-OCOCH_3), 1.90 (3H, s, 16-OCOCH_3), 1.10 (3H, d, $J=7$ Hz, CH_3-21), 1.03 (3H, d, $J=6.4$ Hz, CH_3-27), 1.03 (3H, s, CH_3-19), 0.89 (3H, s, CH_3-18). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 203.8 (22-*CO*), 170.3 (3-O*CO*CH_3), 169.6 (16-O*CO*CH_3), 164.2 (C-23^1), 139.6 (C-5), 122.2 (C-6), 107.6 (C-23), 75.6 (C-16), 73.8 (C-3), 71.6 (C-26), 55.9 (C-17), 54.0 (C-14), 49.7 (C-9), 41.8 (C-13), 39.6 (C-12), 38.6 (C-20), 38.0 (C-4), 36.8 (C-1), 36.5 (C-10), 34.6 (C-15), 31.6 (C-7), 31.2 (C-8), 30.7 (C-24), 27.6 (C-2), 26.6 (C-25), 21.3 (3-OCO*C*H_3), 21.0 (16-OCO*C*H_3), 20.7 (C-11), 20.6 (C-23^2), 19.2 (C-19), 17.1 (C-21), 17.0 (C-27), 13.4 (C-18). Anal. Calcd for $C_{33}H_{48}O_6$: C 73.30, H 8.95, O 17.75. Found: C 73.26, H 9.03.

3.4. Acid catalyzed equilibration of 8b and 9

Method A. In a pressure tube were placed 2.00 g (3.70 mmol) of **8b** in 5 mL of toluene and 200 mg (1.05 mmol) *p*-toluenesulfonic acid and the mixture was heated at 120 °C for 30 min with vigorous stirring. The solvent was evaporated under vacuum and the organic phase extracted with ethyl acetate–water, neutralized with $NaHCO_3$ and dried over Na_2SO_4 to give a mixture of **8b** and **9** in a 4:6 ratio, as determined by ^{1}H NMR. The products were separated by chromatography as described previously. The same ratio of products was obtained starting from epoxy **9**.

Method B. In a pressure tube were placed 1.00 g (1.85 mmol) of **8b**, 5 mL of water and 30 mg of Amberlyst-15 and the mixture was heated at 120 °C for

7 h with vigorous stirring. The catalyst was separated by filtration, the solution evaporated under vacuum and the organic phase extracted with ethyl acetate–water, dried over Na_2SO_4 and evaporated to dryness to give a mixture of **8b** and **9** in a 4:6 ratio as determined by ^{1}H NMR. The products were separated by chromatography as described previously.

3.4.1. (20*S*,25*R*)-3β,16β,26-Triacetoxycholest-5-ene-22,23-dione (10). A solution of 0.27 g (0.50 mmol) of **9** in 7 mL of CH_2Cl_2, 3 mL of acetone, 3 mL of MeCN, was vigorously stirred at 5 °C and treated with half of a solution of RuO_4 prepared from 0.32 g of $NaIO_4$ (1.5 mmol), 0.018 g of $RuCl_3\cdot 3H_2O$ (0.085 mmol), in 1.2 mL of H_2O. The reaction mixture was stirred at 5 °C for 2 min, the remaining RuO_4 solution was added and the reaction mixture was stirred for 2 additional minutes after which it was quenched with 5 mL of a 20% solution of $Na_2S_2O_5$ and stirred for 5 min. All the solvents were evaporated under vacuum and the residue was extracted with CH_2Cl_2 (2×50 mL). The extracts were washed with H_2O, dried with anhydrous Na_2SO_4, and concentrated under vacuum to give 0.25 g of dione **10** containing traces of starting material (determined by NMR). Pure dione **10** was obtained by washing the crude product with MeOH (isolated yield 63%) since **9** is not soluble in this solvent. Attempts to purify the remaining mixture of dione **10** and epoxy **9** by column chromatography on silica gel led to extensive decomposition of dione **10**, thus the subsequent reduction was performed on the crude product.

Yellowish-green powder, mp 110–112 °C; $[\alpha]_D^{20}$ −21.2 (*c* 1.0, $CHCl_3$); UV ($CHCl_3$) λ_{max} 429 nm (ε=32); IR ν_{max} (KBr) 2937 (CH), 1734 (OAc), 1248 (C–O); MS, *m*/*z* (%): 573 ([$M^{+\cdot}$+1], 0.4), 387 (25), 327 (37), 253 (45), 101 (39), 43 (100). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.36 (1H, d, J=4.9 Hz, H-6), 4.99 (1H, ddd, $J_{16-17\alpha}$=7.7 Hz, $J_{16-15\alpha}$=7.5 Hz, $J_{16-15\beta}$=4.6 Hz, H-16), 4.60 (1H, m, H-3), 4.03 (1H, dd, J_{gem}=10.9 Hz, J_{26-25}=5.6 Hz, H-26), 3.88 (1H, dd, J_{gem}=10.9 Hz, J_{26-25}=6.5 Hz, H-26), 3.77 (1H, dq, J_{20-17}=11.3 Hz, J_{20-21}=7.2 Hz, H-20), 2.87 (1H, dd, J_{gem}=18.1 Hz, J_{24-25}=5.6 Hz, H-24), 2.59 (1H, dd, J_{gem}=18.1 Hz, J_{24-25}=7.7 Hz, H-24), 2.05 (3H, s, 26-OCOCH_3), 2.03 (3H, s, 3-OCOCH_3), 1.85 (3H, s, 16-OCOCH_3), 1.09 (1H, d, J_{21-20}=7.2 Hz, CH_3-21), 1.03 (3H, s, CH_3-19), 0.97 (3H, d, J_{27-25}=6.8 Hz, CH_3-27), 0.92 (3H, s, CH_3-18). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 200.2 (22-*C*=*O*), 198.2 (23-*C*=*O*), 170.9 (26-O*CO*CH_3), 170.4 (3-O*CO*CH_3), 170.0 (16-O*CO*CH_3), 139.6 (C-5), 122.1 (C-6), 74.7 (C-16), 73.7 (C-3), 68.1 (C-26), 54.6 (C-17), 54.0 (C-14), 49.7 (C-9), 42.1 (C-13), 39.9 (C-24), 39.5 (C-12), 38.0 (C-4), 36.8 (C-1), 36.6 (C-10), 35.0 (C-20), 34.2 (C-15), 31.8 (C-7), 31.5 (C-8), 28.1 (C-25), 27.6 (C-2), 21.3 (3-OCO*C*H_3), 20.8 (16-OCO*C*H_3), 20.7 (26-OCO*C*H_3), 20.6 (C-11), 19.2 (C-19), 16.7 (C-27), 15.8 (21), 13.0 (C-18). Anal. Calcd for $C_{33}H_{48}O_8$: C 69.28, H 8.45, O 22.35. Found: C 69.48, H 8.71.

3.4.2. (22*R*,23*S*,25*R*)-3β,16β,26-Triacetoxy-cholest-5-ene-22,23-diol (11a). A solution of 100 mg (0.18 mmol) of dione **10** in 10 mL MeOH was treated with 100 mg (2.60 mmol) of $NaBH_4$ and the solution was stirred 30 min at room temperature. The excess hydride was quenched with water, the methanolic suspension was concentrated and the organic phase was extracted twice with ethyl acetate, washed with water, dried over Na_2SO_4 and evaporated to dryness to give 60 mg (59% yield, R_f=0.38), the R_f was missing 19) of **11a**.

White powder, mp 194–195 °C ($CHCl_3$–CH_3OH); $[\alpha]_D^{20}$ −22.3 (*c* 0.2, $CHCl_3$); UV ($CHCl_3$) λ_{max} 269 nm (ε=413); IR $\bar{\nu}_{max}$ (KBr): 3503 (OH) 2930 (CH), 1732 (CO), 1252 (C–O); MS, *m*/*z* (%): 558 ([$M^{+\cdot}$−18], 0.1), 303 (27), 254 (30), 253 (100). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.36 (1H, d, J=4.9 Hz, H-6), 5.27 (1H, ddd, $J_{16-17ax}$=7.7 Hz, $J_{16-15eq}$=4.1 Hz, H-16), 4.60 (1H, m, H-3), 4.06 (1H, dd, J_{gem}=10.9 Hz, J_{26-25}=5.3 Hz, H-26), 3.95 (1H, dd, J_{gem}=10.9 Hz, J_{26-25}=6.2 Hz, H-26), 3.66 (1H, dd, J=8.0 Hz, H-23), 3.2 (1H, br d, J=8.0 Hz, H-22), 2.38 (1H, m, H-17), 2.30 (1H, m, H-4), 2.06 (3H, s, 3-OCO*C*H_3), 2.03 (3H, s, 16-OCO*C*H_3), 2.02 (3H, s, 26-OCO*C*H_3), 1.03 (1H, s, CH_3-19), 1.02 (3H, d, J=7.2 Hz, CH_3-27), 0.98 (3H, d, J=6.8 Hz, CH_3-21), 0.92 (3H, s, CH_3-18). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.4 (3-O*CO*CH_3), 170.9 (16-O*CO*CH_3), 170.5 (26-O*CO*CH_3), 139.7 (C-5), 122.1 (C-6), 76.7 (C-22), 75.2 (C-16), 74.7 (C-3), 70.0 (C-23), 68.7 (C-26), 55.6 (C-17), 54.6 (C-14), 49.8 (C-9), 42.4 (C-13), 39.5 (12), 38.1 (24), 38.0 (4), 36.9 (1), 36.5 (C-10), 34.8 (C-15), 31.5 (7), 31.4 (C-8), 30.7 (C-20), 29.4 (C-25), 27.6 (2), 21.3 (16-OCO*C*H_3), 21.3 (26-OCO*C*H_3), 20.9 (3-OCO*C*H_3), 20.6 (C-11), 19.2 (C-19), 18.5 (C-27), 12.5 (C-21), 11.4 (C-18).

HRMS: Calculated for $C_{33}H_{52}O_8$ $[M+H]^+$: 577.3737. Found 577.3740.

3.4.3. (22*R*,23*S*,25*R*)-3β,16β,22,23,26-Pentacetoxy-cholest-5-ene (11b). Diol **11a** (100 mg, 0.172 mmol) was dissolved in mL of 1 mL pyridine, 1.0 mL (10.6 mmol) of Ac_2O were added and the reaction was stirred for 5 h at room temperature. The reaction mixture was poured over iced water and the organic phase extracted with CH_2Cl_2/dilute HCl, neutralized with Na_2CO_3 and evaporated to dryness to give 100 mg (75% yield, R_f=0.31), the R_f was missing 20) of **11b**.

White powder, mp 152–153°C; $[\alpha]_D^{20}$ −25.8 (*c* 0.18, $CHCl_3$); IR $\bar{\nu}_{max}$ (KBr): 2970 (CH), 1737 (CO), 1241 (C–O); MS, *m*/*z* (%): 540 ([$M^{+\cdot}$−120], 4.0), 434 (2.0), 405 (10), 278 (5.0), 253 (100), 158 (10.0), 109 (5.0), 43 (6.0). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.34 (1H, d, J=4.9 Hz, H-6), 5.20 (1H, m, H-16), 5.16 (1H, dd, m, H-23), 4.87 (1H, d, J_{22-23}=7.6 Hz, H-22), 4.59 (1H, m, H-3), 3.94 (1H, dd, J_{gem}=11.0 Hz, J=5.4 Hz, H-26), 3.86 (1H, dd, J_{gem}=11.0 Hz, J=5.8 Hz, H-26), 2.08, 2.07, 2.06, 2.02 and 2.05 (3H each, s, 3-, 16-, 22-, 23-, 26-OCO*C*H_3), 0.99 (1H, s, CH_3-19), 0.98 (3H, d, J=7.2 Hz, CH_3-21), 0.94 (3H, d, J=6.8 Hz, CH_3-27), 0.85 (3H, s, CH_3-18). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.17, 170.58, 170.51, 170.18, 170.1 (3-, 16-, 22-, 23-, 26-O*CO*CH_3), 139.7 (C-5), 122.36 (C-6), 75.5 (C-16), 75.03 (C-22), 73.89 (C-3), 70.27 (C-23), 68.34 (C-26), 55.99 (C-17), 54.42 (C-14), 49.87 (C-9), 42.46 (C-13), 39.66 (C-12), 38.11 (C-4), 36.97 (C-24), 36.58 (C-10), 35.32 (C-1), 35.23 (C-15), 31.58 (C-7), 31.45 (C-25), 30.64 (C-8), 29.28 (C-20), 27.78 (C-2), 21.50, 21.50, 21.46, 21.22, 20.96 (3-, 16-, 22-, 23-, 26-O*CO*CH_3), 20.78 (C-11), 19.36 (C-19), 18.22 (C-27), 12.77 (C-21), 12.4 (C-18).

HRMS: Calculated for $C_{37}H_{57}O_{10}$ $[M+H]^+$: 661.3948. Found 661.3952.

3.4.4. (25*R*)-3β,16β,26-Triacetoxy-5,6α-dihydroxy-5α-cholestane-22,23-dione (12). Treatment of **9** as described previously, for 6 min gave 0.49 g of a mixture of dione **10** and 5,6-diol **12**, which were separated by column chromatography. Compound **10** (133 mg, 23%, $R_f=0.5$) eluted using a 9:1 mixture of hexane/ethyl acetate and **12** (230 mg, 40%, $R_f=0.33$) was eluted with an 8:2 mixture of the same solvents.

Yellow powder, mp 98–101 °C; $[\alpha]_D^{20}$ +6.59 (*c* 0.2, $CHCl_3$); UV ($CHCl_3$) λ_{max} 275 nm ($\varepsilon=1734$); IR $\bar{\nu}_{max}$ (KBr) 3480 (OH), 2941 (CH), 1736 (CO), 1244 (C–O); MS, *m/z* (%): 607 ([$M^{+\cdot}+1$] 0.6), 421 (76), 343 (83), 269 (100), 251 (44). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.10 (1H, dddd, $J_{3ax-2ax}=J_{3ax-4ax}=11.4$ Hz, $J_{3ax-2eq}=J_{3ax-4eq}=5.4$ Hz, H-3), 4.99 (1H, ddd, $J_{16-15ax}=J_{17-16}=8.0$ Hz, $J_{16-15eq}=4.9$ Hz, H-16), 4.02 (1H, dd, $J_{gem}=10.9$ Hz, $J_{26-25}=5.6$ Hz, H-26), 3.88 (1H, dd, $J_{gem}=10.9$ Hz, $J_{26-25}=6.5$ Hz, H-26), 3.76 (1H, dq, $J_{20-17}=11.2$ Hz, $J_{20-21}=7.1$ Hz, H-20), 3.65 (1H, dd, $J_{6ax-7ax}=11.3$ Hz, $J_{6ax-7eq}=5.1$ Hz, H-6), 2.86 (1H, dd, $J_{gem}=18.1$ Hz, $J_{24-25}=5.6$ Hz, H-24) 2.59 (1H, dd, $J_{gem}=18.1$ Hz, $J_{24-25}=7.7$ Hz, H-24), 2.04 (3H, s, 26-OCO*CH*$_3$), 2.02 (3H, s, 16-OCO*CH*$_3$), 1.84 (3H, s, 3-OCO*CH*$_3$), 1.07 (1H, d, $J_{21-20}=7.1$ Hz, CH_3-21), 0.97 (3H, s, CH_3-19), 0.96 (3H, d, $J_{27-25}=6.8$ Hz, CH_3-27), 0.88 (3H, s, CH_3-18). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 200.2 (22-*CO*), 198.2 (23-*CO*), 171.0 (3-O*CO*CH_3), 170.9 (16-O*CO*CH_3), 170.0 (26-O*CO*CH_3), 76.3 (C-5), 74.7 (C-16), 71.1 (C-3), 70.3 (C-6), 68.2 (C-26), 54.7 (C-17), 53.2 (C-14), 44.02 (C-9), 42.46 (C-13), 39.94 (C-24), 39.59 (C-4), 39.15 (C-10), 35.06 (C-20), 34.80 (C-7), 34.38 (C-1), 34.15 (C-15), 33.05 (C-8), 30.69 (C-2), 28.17 (C-25), 26.56 (C-12), 21.42 (3-OCO*CH*$_3$), 20.83 (16-OCO*CH*$_3$), 20.77 (26-OCO*CH*$_3$), 20.34 (C-11), 16.82 (C-27), 15.79 (C-21), 15.36 (C-19) 13.34 (C-18).

Anal. Calcd for: C 65.33, H 8.31, O 26.36. Found: C 65.03, H 8.39.

3.4.5. (25*R*)-3β,16β,26-Triacetoxy-5-hydroxy-5α-cholesta-6,22,23-trione (13). A solution of 0.54 g (1.0 mmol) of **9** in 18.4 mL of CH_2Cl_2, 8.1 mL of acetone, 8.1 mL of MeCN, was vigorously stirred at 5 °C and treated with a solution of RuO_4 at once prepared from 1.8 g of $NaIO_4$ (7.9 mmol), 0.49 g of $RuCl_3\cdot 3H_2O$ (2.3 mmol), in 10.8 mL of H_2O. The reaction mixture was stirred at 5 °C for 3 h, after which it was quenched with 13.2 mL of a 20% solution of $Na_2S_2O_5$ and stirred for 10 min. All the solvents were evaporated under vacuum and the residue was extracted with CH_2Cl_2 (2×50 mL). The extracts were washed with H_2O, dried with anhydrous Na_2SO_4, and concentrated under vacuum to give (0.52 g) of a mixture of the trione **13** and traces of 5,6-diol **12**, which were separated by column chromatography. Compound **13** (0.45 g, 74.5%, $R_f=0.53$) eluted using a 7:3 mixture of hexane acetate and **12** (0.12 g, 19.8%, $R_f=0.33$) eluted with an 5:5 mixture of the same solvents.

Yellow powder, mp 100–105 °C; $[\alpha]_D^{20}$ −33.7 (*c* 0.2, $CHCl_3$); UV ($CHCl_3$) λ_{max} 379 nm ($\varepsilon=264$); IR $\bar{\nu}_{max}$ (KBr) 3468 (OH), 2947 (CH), 1737 (–CO), 1243 (C–O); MS, *m/z* (%): 605 ([$M^{+\cdot}+1$] 0.4), 419 (51), 341 (66), 267 (100), 101 (47), 43 (95). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.03 (1H, dddd, $J_{3ax-2ax}=J_{3ax-4ax}=11.2$ Hz, $J_{3ax-2eq}=J_{3ax-4eq}=5.0$ Hz, H-3), 4.99 (1H, ddd, $J_{16-15ax}=J_{17-16}=8.0$ Hz, $J_{16-15eq}=5.2$ Hz, H-16), 4.02 (1H, dd, $J_{gem}=10.9$ Hz, $J_{26-25}=5.6$ Hz, H-26), 3.88 (1H, dd, $J_{gem}=10.9$ Hz, $J_{26-25}=6.5$ Hz, H-26), 3.77 (1H, dq, $J_{20-17}=11.3$ Hz, $J_{20-21}=7.1$ Hz, H-20), 2.86 (1H, dd, $J_{gem}=18.2$ Hz, $J_{24-25}=5.6$ Hz, H-24) 2.78 (1H, dd, $J_{gem}=J_{7ax-8ax}=12.7$ Hz, H-7), 2.60 (1H, dd, $J_{gem}=18.2$ Hz, $J_{24-25}=7.7$ Hz, H-24), 2.04 (3H, s, 26-OCO*CH*$_3$), 2.00 (3H, s, 16-OCO*CH*$_3$), 1.84 (3H, s, 3-OCO*CH*$_3$), 1.08 (1H, d, $J_{21-20}=7.1$ Hz, CH_3-21), 0.97 (3H, d, $J_{27-25}=6.8$ Hz, CH_3-27), 0.88 (3H, s, CH_3-18), 0.82 (3H, s, CH_3-19). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 211.5 (C-6), 200.1 (22-*C*O), 198.1 (23-*C*O), 171.0 (3-O*CO*CH_3), 170.1 (16-O*CO*CH_3), 170.0 (26-O*CO*CH_3), 80.1 (C-5), 74.3 (C-16), 70.6 (C-3), 68.2 (C-26), 54.6 (C-17), 53.6 (C-14), 44.1 (C-9), 42.8 (C-10), 42.4 (C-13), 41.3 (C-7), 39.9 (C-24), 39.4 (C-4), 36.5 (C-8), 35.0 (C-20), 33.9 (C-15), 32.3 (C-1), 29.4 (C-2), 28.1 (C-25), 26.2 (C-12), 21.3 (C-11), 21.0 (3-OCO*CH*$_3$), 20.9 (16-OCO*CH*$_3$), 20.9 (26-OCO*CH*$_3$), 16.8 (C-27), 15.7 (C-21), 13.8 (C-19) 13.3 (C-18).

HRMS: Calculated for $C_{33}H_{49}O_{10}$ $[M+H]^+$605.3326. Found 605.3329.

3.4.6. (23*S*,25*R*)-3β,16β,26-Triacetoxy-23-hydroxy-cholest-5-en-22-one (14). A solution of dione **10** (100 mg, 0.17 mmol) in 3 mL of methanol at −70 °C was treated with $ZnCl_2$ (48 mg, 0.35 mmol) and $NaBH_4$ (50 mg, 1.32 mmol) and the mixture was stirred for 3 h. The reaction was quenched with NH_4Cl and the organic layer was extracted with CH_2Cl_2, washed with water, dried with anhydrous $NaSO_4$ and concentrated under vacuum. The residue (93 mg) was purified by chromatography on silica gel (hexane/EtOAc 8:2) to yield (68 mg, 67.6%, $R_f=0.28$) of **14**.

White powder, mp 138–139°C ($CHCl_3$–CH_3OH); $[\alpha]_D^{20}$ +23.4 (*c* 0.2, $CHCl_3$); IR ν_{max} (KBr): 3461 (OH) 2938 (CH), 1735 (CO), 1245 (C–O); MS, *m/z* (%): 515 ([$M^{+\cdot}-59$], 0.3), 282 (32), 327 (14), 372 (16), 253 (100), 311 (16), 313 (67). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.33 (1H, d, $J=4.4$ Hz, H-6), 4.78 (1H, ddd, $J_{16-17ax}=8.1$ Hz, $J_{16-15eq}=3.3$ Hz, H-16), 4.57 (1H, m, H-3), 4.23 (1H, br d, $J=10.6$ Hz, H-23), 4.12 (1H, dd, $J_{gem}=11.0$ Hz, $J_{26-25}=6.2$ Hz, H-26), 4.03 (1H, dd, $J_{gem}=11.0$ Hz, $J_{26-25}=7.0$ Hz, H-26), 3.02 (1H, dq, $J_{17-20}=13.9$ Hz, $J_{20-21}=6.6$ Hz, H-20), 2.39 (1H, m, H-15), 2.29 (1H, m, H-24), 2.06 (3H, s, 3-OCO*CH*$_3$), 2.0 (3H, s, 16-OCO*CH*$_3$), 1.97 (3H, s, 26-OCO*CH*$_3$), 1.15 (3H, d, $J_{21-20}=6.6$ Hz, CH_3-21), 1.02 (1H, d, $J_{27-25}=6.6$ Hz, CH_3-27), 1.00 (3H, s, CH_3-19), 0.87 (3H, s, CH_3-18). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 215.18 (22-*C*O), 171.26 (3-O*CO*CH_3), 170.59 (16-O*CO*CH_3), 170.02 (26-O*CO*CH_3), 139.67 (C-5), 122.26 (C-6), 75.84 (C-16), 75.45 (C-23), 73.85 (C-3), 67.72 (C-26), 56.90 (C-17), 53.93 (C-14), 49.77 (C-9), 42.3 (C-13), 39.83 (C-12), 38.86 (C-20), 38.09 (C-4), 37.43 (C-24), 36.94 (C-1), 36.6 (C-10), 34.97 (C-15), 31.6 (C-7), 31.38 (C-8), 29.4 (C-25), 27.76 (C-2), 21.5 (16-OCO*CH*$_3$), 21.07 (26-OCO*CH*$_3$), 21 (3-OCO*CH*$_3$), 20.82 (C-11), 19.36 (C-19), 18.4 (C-27), 17.33 (C-21), 13.57 (C-18).

HRMS: Calculated for $C_{33}H_{50}O_8$ $[M+H]^+$ 575.3584. Found 575.3586.

3.5. X-ray data

Copy of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033) or e-mail: deposit@ccdc.cam.ac.uk No. 253082 for compound **9** and 269385 for **11b**.

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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.2005.12.036.

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4*H*-Thiopyran-1-oxides. Conformational analysis and photochemical isomerization

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Abstract—The stereochemical aspects and photochemistry of a series of 2,4,4,6-tetrasubstituted-4*H*-thiopyran-1-oxides are described. Substitution-induced changes to the sulfinyl group stereomutation and the ring conformation are investigated. The sulfoxides were configurationally stable at a wide thermal range, but underwent photocatalysed stereomutation at sulfur without concomitant isomerization at C-4. In almost all cases the trans isomer predominated at equilibrium. The theoretical studies are in close agreement with experimental results.

1. Introduction

Increasing interest has been focused on the stereochemical aspects of sulfoxides. The conformational analysis of cyclic sulfoxides is an area of attraction for many groups.[1–6] Significant attention was earlier directed toward the conformational analysis of substituted thiane-1-oxides.[7–9] It is known, for example, that the sulfinyl group prefers an axial orientation in a chair conformation. The conformational integrity of the sulfoxide has also generated interest in the various conditions under which it may undergo stereoisomerization. Here we restrict the discussion to photochemical isomerization. A large number of aliphatic, aromatic and cyclic sulfoxides are photochemicaly investigated.[10–17] Although extensive studies on sulfoxides have disclosed their chemical and physico-chemical properties, little is known about the properties of the sulfinyl groups in unsaturated cyclic sulfoxides.

Herein we report the results of our studies on the preparation of some 4*H*-thiopyran-1-oxides by oxidation of the corresponding 4*H*-thiopyran derivatives, their stereochemical analysis via a combined NMR, molecular modelling and X-ray crystallographic approach, and their photochemical behavior. Various 4,4-disubstituted 4*H*-thiopyran-1-oxide derivatives were chosen in order to attempt to relate the substitution-induced changes to the sulfinyl group stereomutation.

Keywords: Conformation analysis; Photochemistry; Stereomutation; Sulfoxides; 4*H*-Thiopyran-1-oxide.
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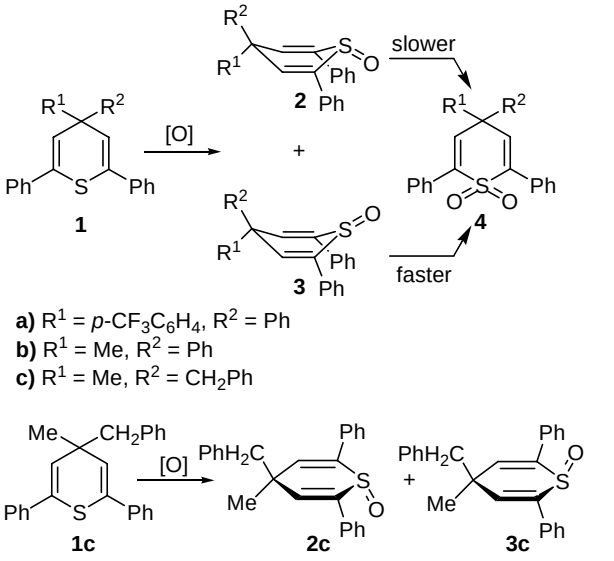
2. Results and discussion

To investigate the photochemical behavior of 4*H*-thiopyran-1-oxides **2a**–**2c** and **3a**–**3c**, these compounds were synthesized by oxidation of their corresponding 4*H*-thiopyran derivatives **1a**–**1c**. Oxidation of compounds **1a**–**1c** with various oxidants such as sodium periodate, *m*-CPBA, and hydrogen peroxide were carried out and two stereoisomeric monoxides obtained. The isomeric sulfoxides were separated by PLC, where in all cases the cis isomer in which the sulfinyl oxygen is cis to the higher priority substituent at C-4, eluted prior to the trans one. Sodium periodate proved the oxidant of choice, giving the oxidized products in highest yields.

At least four types of stereoisomers were considered for each compound, where X-ray crystallographic analysis confirmed unambiguously two cis- and trans-stereoisomers with boat (**2a** and **3a**), rather flattened boat (**2b** and **3b**) and planar (**2c** and **3c**) conformations.[18–20] It is evident that appropriate substitution can lead to a wide variation in geometry. For example, these compounds prefer a planar conformation bearing small alkyl substituents, or presumably no substituents at the C-4 position of the ring where, with a single large substituent, they become nearly flattened. With two large aryl substituents, close packing in the crystal is difficult so a boat conformation is established. It appears as though small substituents cause little distortion from planarity, whereas a bulky substituent may produce a boat-shaped conformation as the energy minimum. The boat conformations differ in that one stereoisomer has the sulfoxide oxygen in an equatorial position, whereas



Scheme 1. Oxidation of compounds **1a**–**1c** to their corresponding stereoisomeric monoxides.

the other in a pseudoaxial one (**2a**–**2b** and **3a**–**3b**, respectively, Scheme 1). The planar ones differ in that the cis isomer has the sulfinyl and more bulky group in the same side of the ring plane, while in the trans isomer, they are on opposite sides (**3c** and **2c**, respectively, Scheme 1). Surprisingly, treatment of **1a**–**1c** with sodium periodate gave predominantly the cis sulfoxides **2a**, **3b**, and **3c**, respectively (1.5:1 ratios obtained almost in all cases). Diastereomeric ratios were determined by integration of the signals corresponding to the H-3,-5 protons in the ^{1}H NMR spectra of the crude products. In all cases, analysis of the products by ^{1}H and ^{13}C NMR spectroscopy allows the unambiguous determination of the configurational and stereochemical properties of these molecules. Assignment of the signals corresponding to each of the diastereomers **2a**–**2c** and **3a**–**3c** was based on X-ray crystallography. In the ^{1}H NMR spectra, the methyl protons for trans isomers **2b**–**2c** (δ 1.86 and 1.56, respectively) are significantly downfield of that of cis isomers **3b**–**3c** (δ 1.76 and 1.33, respectively). The downfield shift relative to their counterparts is a consequence of methyl projection into a region of the molecule where the deshielding anisotropies of the sulfoxide group are exerting their effect. Further evidence is provided through the observation that the cis sulfoxides **3b**–**3c**, exhibit resonances at δ 6.75 and 6.65 attributed to H-3,-5, respectively, whereas the trans ones, **2b**–**2c** isomers exhibit the corresponding resonances at δ 6.71 and 6.52. Therefore, the major isomer is attributed to the cis isomer, with the sulfinyl and more hindered groups oriented in the same side. Furthermore, the diagnostic absorptions due to the S–O stretching vibration were observed with the equatorial ones placed at shorter wavelengths.

A surprising result during the oxidation of **1b** was an inversion in the arrangement of substitutions at C-4 position of the ring. In the flattened boat conformation of the compound, confirmed by X-ray crystallography[21] (Fig. 1), the methyl and phenyl groups were in the pseudoaxial and equatorial positions, respectively, whereas in their sulfoxide stereoisomers, the arrangement of the methyl and phenyl groups was reversed (i.e., the methyl and phenyl groups in equatorial and pseudoaxial positions, respectively) (Scheme 2). The result suggests a ring inversion in the course of oxidation of **1b**.

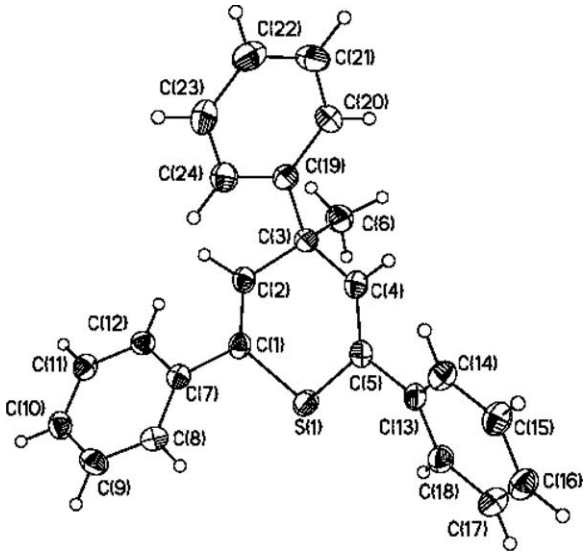
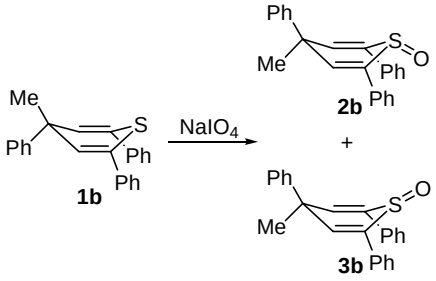


Figure 1. ORTEP plot of compound **1b** with atom labeling.



Scheme 2. The course of oxidation of compound **1b**.

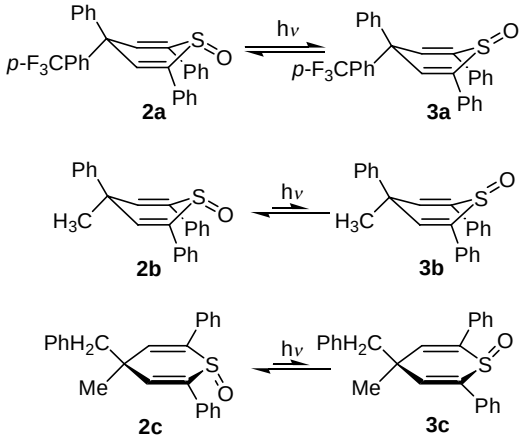
However, it was realized that adoption of a specific near-boat conformation (**1a**–**1c**) would render the sulfur lone-pairs non-equivalent, such that preferential reactivity of either the axial or equatorial sulfur lone-pair would be a feasible approach to stereoselective oxidation. It seemed plausible, given that these oxidants operate through a direct mechanism in which the sulfur attacks the electrophilic oxygen, that the selectivity of these reactions is governed by a preferential attack of the equatorial sulfur lone-pair. The sulfoxides **3a**–**3b** possess an equatorial sulfur lone-pair, which is more reactive toward the oxidant than the axial lone-pair of **2a**–**2b**, such that the sulfoxides **3a**–**3b** are oxidized more quickly to the sulfones **4a**–**4b** (Scheme 1).

In order to study the photochemical transformation behavior of the compounds **2a**–**2c** and **3a**–**3c**, a pure sample of either isomer in DMSO-d_6 (3×10^{-2} M solutions) was irradiated with a low pressure mercury lamp at $\lambda=254$ nm (85% transmission of 254 nm and 15% transmission of light from 254–579 nm) under an argon atmosphere at room temperature. The time dependence of transformations was studied by ^{1}H NMR. During the earlier times of irradiation, cis- and trans-sulfoxides isomerized to each other via

a photoinduced stereomutation. On prolonged irradiation, an equilibrium mixture of sulfoxides was accomplished for each stereoisomer. The molar ratios of the compounds at different time intervals were obtained from the intensities of the relative signals in the ^{1}H NMR spectra. The relative variations of each stereoisomer during 240 min of irradiation under identical experimental conditions are summarized in Table 1. The results demonstrate the gradual stereomutation at sulfur, where interconversion of *cis*-**3b–3c** to *trans*-**2b–2c** stereoisomers is faster, and the trans isomers are favored at equilibrium (Scheme 3). This isomerization is rational in terms of the greater thermodynamic stability of the *trans*-**2b–2c** than *cis*-**3b–3c** compounds. The greater stability of these isomers could be attributed to a combination of repulsive van der Waals interactions between the oxygen and phenyl hydrogens and a more favorable interaction between the π-orbitals of 4*H*-thiopyran ring and equatorial S–O bond. These observations suggest that only one of the stereoisomers is adopted to any significant extent. Two similar aryl groups at the C-4 position of the rings **2a** and **3a** do not cause a significant energy difference between the two isomers, so neither one of them predominates in the equilibrium (Table 1).

Table 1. The relative variations of stereoisomers **2a–2c** with respect to **3a–3c** during 240 min of irradiation

	15	30	90	120	180	240
2a/3a	7.5	2.6	1.1	1.1	1.0	1.0
2b/3b	5.7	3.3	1.6	1.5	1.4	1.4
2c/3c	8.4	4.6	1.9	1.6	1.3	1.3



Scheme 3. Photolysis of compounds **2a–2c** and **3a–3c**.

The variable temperature ^{1}H NMR spectra (−80 to 180 °C) for stereoisomeric monoxides **2a–2c** as well as **3a–3c** were recorded, where it seems that ring inversion (boat flipping) probably occurs rapidly, and it is inversion at the sulfur center, which must be slow.

In order to ascertain a rationale for the apparent stability of the trans isomers of **2b–2c**, we performed computer modelling studies on the boat conformers of sulfoxides **2b–2c** and **3b–3c**, using HF calculations utilizing the GAMESS programs.[22] The equilibrium geometries and zero point energies of the two stereoisomeric monoxides were computed using the Restricted Hartree Fock functional in conjunction with the 6-31G(d) basis set and the energetics were compared (see Supplementary material). In the gas phase, the computations predict **2b–2c** with the trans configuration to be the most stable isomers. The best estimate for the energy differences are 0.2 and 1.14 Kcal mol^{-1}, respectively. The computed equilibrium geometries are almost in close agreement with the X-ray data. The difference between theory and experiment for the heavy atom distances is generally within ∼0.005 Å, the largest difference being for the S–C distances. The most discrepancies between the crystallographic structures and the calculated ones were the orientation of phenyl groups (at C-2 and C-6 positions) with respect to the sulfur ring, which arise from packing requirements. For example, the calculated structure of **3b** with symmetric orientation of the phenyl groups was 0.88 Kcal mol^{-1} more stable than the crystal structure with asymmetric orientation of these groups. Dipole moment considerations (4.23 vs 4.33) were in accordance with the conformations observed in the solid state.

It is well established that carbon–sulfur bond homolysis (α-cleavage) is an extremely common photochemical reaction of sulfoxides, and recombination of radical pairs or biradicals so-generated necessarily provides a mechanism for stereomutation. Nonetheless, it has been asserted that photochemical stereomutation occurs through a direct inversion of the sulfur center, even though some results demand that carbon–sulfur bond rupture occurs in the process of epimerization of the sulfur. Authors through the years have long suspected that there is a direct inversion pathway that does not involve formation of any radicals. Since no other byproducts were observed as a result of α-cleavage, we supposed a noncleavage mechanistic approach for photochemical stereomutation in 4*H*-thiopyran-1-oxides. The evidence points to photocatalyzed inversion at sulfur.

3. Conclusion

In conclusion, we succeeded in the first isolation and structure determination of unsaturated cyclic sulfoxides with planar to boat conformations, relative to the substituents. They adopt cis- and trans-configurations with the latter showing a lower energy and higher efficiency. These types of configurations have not been considered previously. Furthermore, 4*H*-thiopyran-1-oxides are subject to photochemical stereomutation in high yield and the compounds with trans-configuration and equatorial sulfinyl groups are favored at equilibrium. In light of experimental results, it is proposed that cis–trans isomerization derives from geometrical relaxation in the excited state, that results in a flattened sulfur center. Upon returning to the ground electronic state, relaxation to the cis- and trans-configurations is competitive. A good agreement between theoretical and experimental data has been found, and reveals that the favored conformations predicted by theoretical calculations are also found in the crystal.

4. Experimental

4.1. General

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 500 or 300 MHz and 125.6 and 75 MHz, respectively. Infrared absorption spectra were obtained using a Shimadzu 4300 FTIR spectrometer as a thin film between potassium bromide plates. High resolution mass spectra were recorded on a Karatos MS 25 RFA, ion source energy 70 eV. All photolysis were carried out using a low pressure mercury lamp with a transition maximum at $\lambda=254$ nm (85% transmission) and transmitted light from 254–579 nm (15% transmission). TLC was performed on neutral alumina plates.

4.2. Syntheses

The 4*H*-thiopyrans **1a**–**1c** were synthesized according to the procedures previously described.[23,24] The 4*H*-thiopyran-oxides **2a**–**2c** and **3a**–**3c** were synthesized according to the following method: to a solution of 4*H*-thiopyrans **1a**–**1c** (0.5 mmol) in methanol (10 mL) and acetone (5 mL) was added a solution of sodium metaperiodate (1 mmol) in water (5 mL). The resulting mixture was left to stir at room temperature overnight. The reaction mixture was diluted with water (20 mL) and extracted into CH_2Cl_2 (3×10 mL). The combined organic fractions were dried ($MgSO_4$), and the solvent evaporated in vacuo to give a yellow oil consisting of unreacted starting material and two stereoisomeric monoxides in different ratios. Purification by PLC on neutral alumina (30% ethyl acetate/petroleum ether) followed by crystallization afforded the corresponding cis- and trans-sulfoxides as white crystalline solids. The unreacted starting material was collected for further oxidation.

4.2.1. *cis*-4-(*p*-Trifluoromethylphenyl)-2,4,6-triphenyl-4*H*-thiopyran-1-oxide (2a). (Ninety milligrams, 37%), colorless crystals, mp 219–220 °C; [Found: C, 73.89; H, 4.64; S, 6.40, $C_{30}H_{21}OSF_3$ requires C, 74.06; H, 4.35; S, 6.59%]; ν_{max} (KBr) 1061 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.26–7.68 (19H, m, Ph), 6.75 (2H, s, =C*H*); δ_C (75 MHz, $CDCl_3$) 147, 143.3, 139.3, 135.3, 134.7, 129.6, 129.4, 129.3, 129, 128.7, 128, 127.9, 127.8, 126.1, 126, 125.9, 125.8, 122.1, 54.4; *m*/*z* 486 (3, M^+), 105 (97), 77 (100%); HRMS (EI): M^+, found 486.1252, $C_{30}H_{21}OSF_3$ requires 486.1265.

4.2.2. *trans*-4-(*p*-Trifluoromethylphenyl)-2,4,6-triphenyl-4*H*-thiopyran-1-oxide (3a). (Sixty one milligrams, 25%), colorless crystals, mp 175–176 °C; [Found: C, 73.85; H, 4.61; S, 6.42, $C_{30}H_{21}OSF_3$ requires C, 74.06; H, 4.35; S, 6.59%]; ν_{max} (KBr) 1039 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.26–7.68 (19H, m, Ph), 6.73 (2H, s, =C*H*); δ_C (75 MHz, DMSO) 149.2, 143, 138.8, 135.7, 129.6, 129.5, 129.4, 129.3, 128.6, 128.5, 128.2, 128.1, 126.4, 126.3, 126.2, 126.1, 123.1, 54.2; *m*/*z* 486 (5, $M^{\cdot+}$), 470 (100), 438 (40), 325 (47), 149 (19%); HRMS (EI): M^+, found 486.1249, $C_{30}H_{21}OSF_3$ requires 486.1265.

4.2.3. *trans*-4-Methyl-2,4,6-triphenyl-4*H*-thiopyran-1-oxide (2b). (Forty milligrams, 22%), colorless crystals, mp 181–182 °C; [Found: C, 80.72; H, 5.61; S, 8.76, $C_{24}H_{20}OS$ requires C, 80.86; H, 5.66; S, 8.99%]; ν_{max} (KBr) 1033 cm^{-1}; δ_H (300 MHz, DMSO) 7.36–7.68 (15H, m, Ph), 6.71 (2H, s, =C*H*), 1.86 (3H, s, *Me*); δ_C (75 MHz, DMSO) 144.1, 137.7, 137.6, 135.9, 129.4, 129.3, 129.2, 128.1, 127.6, 126.9, 45.5, 26; *m*/*z* 356 (24, $M^{\cdot+}$), 310 (24), 263 (26), 149 (18), 134 (100%); HRMS (EI): M^+, found 356.1230, $C_{24}H_{20}OS$ requires 356.1234.

4.2.4. *cis*-4-Methyl-2,4,6-triphenyl-4*H*-thiopyran-1-oxide (3b). (Sixty three milligrams, 35%), colorless crystals, mp 187–188 °C; [Found: C, 80.64; H, 5.68; S, 8.62, $C_{24}H_{20}OS$ requires C, 80.86; H, 5.66; S, 8.99%]; ν_{max} (KBr) 1009 cm^{-1}; δ_H (300 MHz, DMSO) 7.33–7.67 (15H, m, Ph), 6.75 (2H, s, =C*H*),1.75 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 140.7, 137.8, 137.4, 135.7, 129.1, 129, 128.9, 127.7, 127.6, 127.1, 45.2, 26.4; *m*/*z* 356 (8, $M^{\cdot+}$), 340 (20), 325 (100), 263 (30), 149 (24%); HRMS (EI): found 356.1228, $C_{24}H_{20}OS$ requires 356.1234.

4.2.5. *trans*-4-Benzyl-4-methyl-2,6-diphenyl-4*H*-thiopyran-1-oxide (2c). (Fifty nine milligrams, 32%), colorless crystals, mp 141–142 °C; [Found: C, 81.17; H, 6.03; S, 8.45, $C_{25}H_{22}OS$ requires C, 81.04; H, 5.99; S, 8.65%]; ν_{max} (KBr) 1020 cm^{-1}; δ_H (300 MHz, DMSO) 6.94–7.44 (15H, m, Ph), 6.52 (2H, s, =C*H*), 2.99 (2H, s, CH_2Ph), 1.56 (3H, s, *Me*); δ_C (75 MHz, DMSO) 140.6, 137.1, 137, 136.3, 131.1, 129.2, 129, 127.9, 127.8, 126.9, 48.1, 44, 27.2; *m*/*z* 370 (4, $M^{\cdot+}$), 339 (10), 279 (21), 264 (54), 263 (100%); HRMS (EI): found 370.1394, $C_{25}H_{22}OS$ requires 370.1391.

4.2.6. *cis*-4-Benzyl-4-methyl-2,6-diphenyl-4*H*-thiopyran-1-oxide (3c). (Thirty three milligrams, 18%), colorless crystals, mp 127–128 °C; [Found: C, 81.14; H, 5.94; S, 8.51, $C_{25}H_{22}OS$ requires C, 81.04; H, 5.99; S, 8.65%]; ν_{max} (KBr), 1030 cm^{-1}; δ_H (300 MHz, DMSO) 7.30–7.56 (15H, m, Ph), 6.65 (2H, s, =C*H*), 3.10 (2H, s, CH_2Ph), 1.32 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 138.8, 138.5, 136.2, 136, 130.4, 128.9, 128.4, 127.7, 127.2, 48, 41.7, 27.5; *m*/*z* 371 (29, $M^{\cdot+}+1$), 370 (2, $M^{\cdot+}$), 339 (3), 279 (23), 264 (53), 263 (100), 105 (95%); HRMS (EI): found 370.1396, $C_{25}H_{22}OS$ requires 370.1391.

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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.2005.12.025. ^{1}H NMR spectra for compounds **2a**–**2c** and **3a**–**3c**, their spectra at different time intervals of irradiation, analytical, and spectroscopic data as well as crystallographic information file of **1b**, and optimized coordinates and total energies of **2b**–**2c** and **3b**–**3c**, are available from the authors upon request.

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Synthesis of methylenecyclopropane analogues of antiviral nucleoside phosphonates

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Abstract—Synthesis of methylenecyclopropane analogues of nucleoside phosphonates **6a**, **6b**, **7a** and **7b** is described. Cyclopropyl phosphonate **8** was transformed in four steps to methylenecyclopropane phosphonate **16**. The latter intermediate was converted in seven steps to the key *Z*- and *E*-methylenecyclopropane alcohols **23** and **24** separated by chromatography. Selenoxide eliminations (**15**→**16** and **22**→**23**+**24**) were instrumental in the synthesis. The *Z*- and *E*-isomers **23** and **24** were transformed to bromides **25a** and **25b**, which were used for alkylation of adenine and 2-amino-6-chloropurine to give intermediates **26a**, **26b**, **26c** and **26d**. Acid hydrolysis provided the adenine and guanine analogues **6a**, **6b**, **7a** and **7b**. Phosphonates **6b** and **7b** are potent inhibitors of replication of Epstein-Barr virus (EBV).

1. Introduction

Analogues of nucleoside 5′-phosphates have been a fruitful topic of research for many years.[1–3] Phosphonate derivatives, which unlike nucleotides are chemically and enzymatically stable occupy a prominent place in this effort. Another important feature of these compounds is that they are capable of circumventing the first phosphorylation step in the activation of nucleoside analogues. This is frequently a limiting event in the phosphorylation sequence, which ultimately leads to triphosphates. One of the first groups of such analogues, which yielded biologically effective compounds are acyclic nucleoside phosphonates[1] exemplified by structures **1a** and **1b** (Chart 1). Thus, compound **1a** (adefovir) and the guanine counterpart **1b** are just two examples of potent antiviral agents from this class of analogues. Because acyclic chain of **1a** and **1b** has five rotatable bonds, limiting their number will improve the entropic factor and this may lead to new biologically active analogues. Indeed, an insertion of two methylene groups between carbons 2′ and 3′ of the guanine derivative **1b** led to furanose cis- and trans-phosphonates **2** and **3** with only three rotatable bonds. Both analogues were effective[4–6] against human cytomegalovirus (HCMV) and the trans-isomer **3** is an antitumor agent.[7–9]

Our previous investigations have shown that isosteric replacement of C–O–C grouping of antiviral drugs acyclovir **4a** (B=Gua) and ganciclovir **4b** (B=Gua) with a rigid methylenecyclopropane moiety led to a new class of nucleoside analogues **5a** and **5b** (Chart 2) effective in particular against HCMV and Epstein-Barr virus (EBV).[10–13] Therefore, it seemed possible that a similar replacement of the C–O–C function in acyclic phosphonates **1a** and **1b** (Chart 1) might provide new analogues with biological activity. Regardless of the results, the antiviral testing of these analogues will provide further insight into the structure–activity relationships of methylenecyclopropane analogues. For these reasons, we have synthesized phosphonates **6a**, **6b**, **7a** and **7b**.

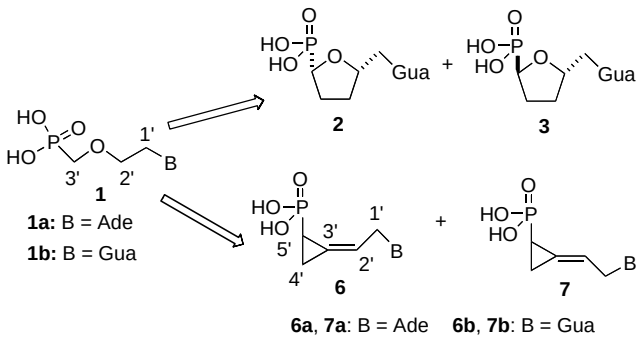

Chart 1.

Keywords: Cyclopropylphosphonates; Methylenecyclopropanes; Selenoxide eliminations; Nucleotide analogues; Antivirals.
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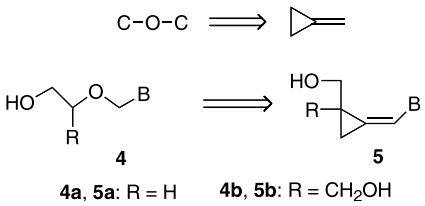


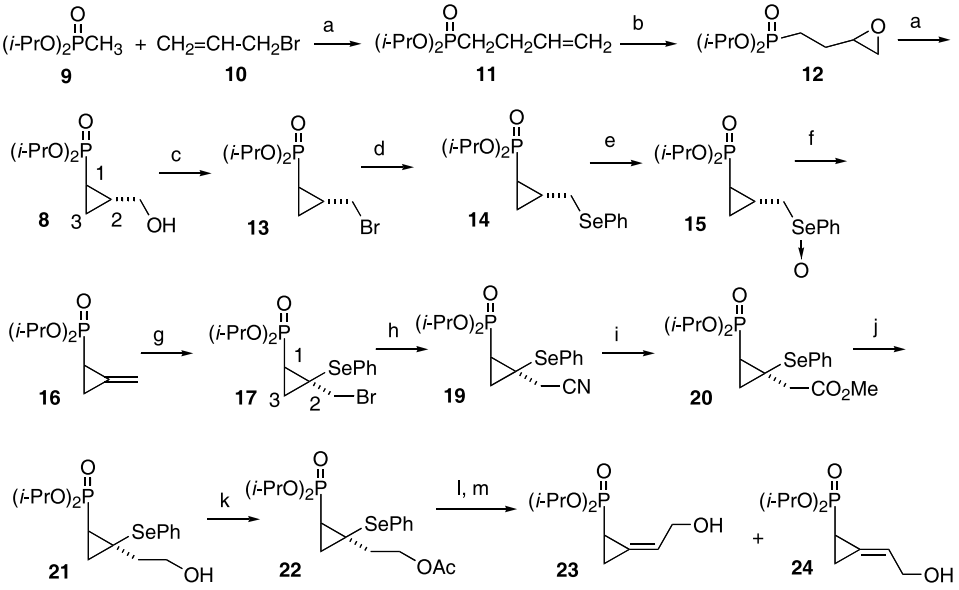
Chart 2.

2. Results and discussion

Diisopropyl (*E*)-2-hydroxymethyl-1-phosphonate[14] (**8**) was chosen as a starting material. The reproduction of the synthetic sequence on the scale of 0.27 mol was problem-free although little details were originally provided.[14] The commercially available diisopropyl methylphosphonate (**9**) and allyl bromide (**10**) were transformed to unsaturated phosphonate **11** in 70% yield (Scheme 1). Compound **11** was transformed to oxirane **12** (91%) and, finally, by an intramolecular opening of the oxirane ring to cyclopropane **8** in 80% yield. Phosphonate **8** was converted to bromo derivative **13** using Ph_3P–Br_2 reagent but the product was inseparable from the triphenylphosphine oxide formed during the reaction and, therefore, it was used as such in the next step. Reaction with PhSeNa generated from Ph_2Se_2 and $NaBH_4$ gave phenylselenenyl derivative **14** still contaminated with triphenylphosphine oxide. Although it was possible to obtain pure **14** by chromatography on a small scale, this was impractical for the intended purpose. Therefore, crude **14** was oxidized with H_2O_2 to give, after chromatography, selenoxide **15** in 76% yield after three steps (**8**→**13**→**14**→**15**). β-Elimination catalyzed by *i*-Pr_2NEt gave after a prolonged reflux in toluene (50 h) methylenecyclopropane phosphonate **16** (65%). Elimination of phenylselenoxide from cyclopropanes to give methylenecyclopropanes was reported.[15–17] Electrophilic addition of phenylselenyl bromide[18] (prepared in situ from Ph_2Se_2 and NBS) afforded intermediate **17** (88%) as a single stereoisomer as shown by NMR. It is likely that the phosphonate group of **16** directs the addition of selenium reagent to the *syn* face of double bond similar to methylenecyclopropane carboxylate function[18] to give the cis (*Z*) isomer of **17** via phenylselenonium intermediate **18** (Scheme 2).

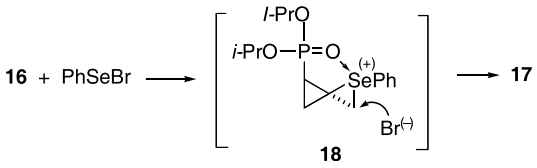
Carbon chain extension was performed using nitrile **19**, which was obtained from **17** using Me_3SiCN and Bu_4NF method[19] in 45% yield. Methanolysis (HCl in MeOH) afforded ester **20** (72%), which was reduced with $LiBH_4$ to alcohol **21** (74%). Acetylation gave acetate **22**, which was oxidized with H_2O_2, subsequently refluxed for 24 h and then deacetylated to give the *Z*- and *E*-methylenecyclopropane phosphonates **23** and **24**. Both isomers were readily separated by chromatography to give the less polar (faster moving) *Z*-isomer **23** followed by the *E*-isomer **24** in 32 and 29% overall yield, respectively, after four steps.

Separated isomers **23** and **24** were converted to bromo derivatives **25a** and **25b** using Ph_3P and CBr_4 (67%, Scheme 3). Alkylation of adenine with **25a** or **25b** using K_2CO_3 in DMF at rt gave intermediates **26a** or **26b** in 70 and 67% yield, respectively. Hydrolysis in refluxing 6 M HCl for 20 min provided free target phosphonates **6a** (83%) and **7a** (71%). In a similar fashion, alkylation of 2-amino-6-chloropurine with bromides **25a** and **25b** afforded diisopropyl phosphonates **26c** and **26d** in 62 and 67% yield, respectively. The corresponding 7-isomers **27a** and **27b** were obtained as more polar by-products in 15% yield. Attack of the 7-position of a purine ring is a frequent

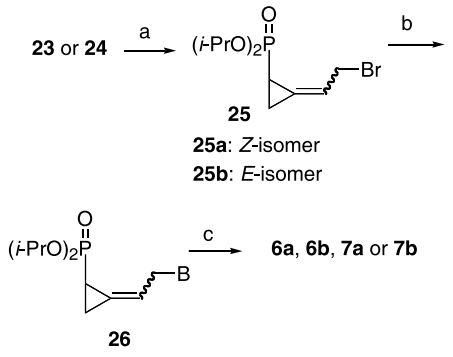


(a) BuLi, THF, −78 °C. (b) MCPBA, CH_2Cl_2. (c) Ph_3P, Br_2, CH_2Cl_2. (d) (i) $(PhSe)_2$, EtOH, (ii) NaOH, $NaBH_4$. (e) H_2O_2, THF. (f) (*i*-Pr)$_2$NEt, toluene, ². (g) $(PhSe)_2$, NBS, CH_2Cl_2. (h) Me_3SiCN, Bu_4NF, MeCN. (i) HCl (g), MeOH. (*j*) $LiBH_4$, THF. (k) Ac_2O, pyridine. (l) 1. H_2O_2, THF. 2. ². (m) K_2CO_3, MeOH/H_2O.

Scheme 1.



Scheme 2.



Scheme 3.

side-reaction in alkylations of 2-amino-6-chloropurine.[20] The assignment of the 7-isomers followed from a general rule[21] that the H_8, C_8 and $C_{1'}$ signals of the 7-isomers are located at a lower field than in 9-isomers whereas the opposite is true for the C_5 resonances (Table 1). Hydrolysis of phosphonate esters and hydrolytic dechlorination of **26c** and **26d** were perfomed simultaneously to give target phosphonates **6b** (85%) and **7b** (73%) after chromatography on Dowex 1.

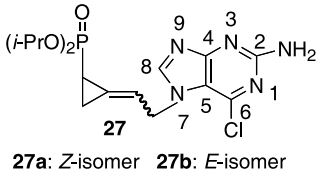


Table 1. Selected chemical shifts of the ^1H (δ) and ^{13}C NMR (ppm) of the 9- and 7-isomers **26c**, **27a**, **26d** and **27b** in $CDCl_3$

Compound	H_8	C_8	C_5	$C_{1'}$
(*Z*,9)-**26c**	7.96	142.9	125.3	44.6
(*Z*,7)-**27a**	8.23	148.9	116.3	47.9
(*E*,9)-**26d**	7.80	142.6	125.0	44.5
(*E*,7)-**27b**	8.04	148.8	116.5	47.9

A preliminary *Z*- and *E*-isomeric assignment was based on a chromatographic mobility of compounds **23** and **24** on silica gel, which conformed with the general observation in the series of methylenecyclopropane analogues that the *Z*-isomers are less polar (faster moving) than *E*-isomers.[3,10,12,13] The NOE experiments with phosphonates **6a** and **7a** confirmed these assignments (Table 2).

Table 2. Selected NOE data of the *Z*- and *E*-isomers **6a** and **7a**

Isomer	H_{irr} (δ)	H_{obs} (δ)	%NOE
Z-**6a**	$H_{2'}$ (5.83)	$H_{4'}$ (1.40)	0.3
	$H_{4'}$ (1.40)	$H_{2'}$ (5.83)	1.35
E-**7a**	$H_{2'}$ (5.96)	$H_{5'}$ (1.29)	1.11
	$H_{5'}$ (1.29)	$H_{2'}$ (5.96)	0.89

As expected, NOE enhancements were found between the cis-orientated hydrogens, $H_{2'}$ and $H_{4'}$ in the *Z*-isomer **6a** and $H_{2'}$ and $H_{5'}$ in the *E*-isomer **7a**.

Phosphonates **6a**, **6b**, **7a** and **7b** were tested against the following viruses in culture: HSV-1, HSV-2, HCMV, EBV, VZV, HIV-1 and HBV. Guanine analogues **6b** and **7b** were potent inhibitors of replication of EBV in Daudi cells with EC_{50}/CC_{50} (μM) 1.1 and $<0.03/>300$, respectively.[22] Acyclovir (**4a**, B=Gua) used as a control had EC_{50}/CC_{50} $0.33/>100$. No activity was found against other tested viruses.

3. Conclusions

Synthesis of methylenecyclopropane phosphonates **6a**, **6b**, **7a** and **7b** is described. Selenoxide eliminations (Scheme 1) were key steps in the synthesis. The described methodology may find application for synthesis of cyclopropyl-phosphonates beyond the area of nucleotide analogues. The *Z*- and *E*-guanine analogues **6b** and **7b** were potent inhibitors of replication of Epstein-Barr virus (EBV).

4. Experimental

4.1. General methods

The NMR spectra were determined at 300 or 400 MHz (^1H), 75 or 100 MHz (^{13}C) and 162 MHz (^{31}P). Mass spectra were measured in electron-impact (EI-MS) or elecrospray ionization (ESI-MS, methanol–NaCl) mode. For synthesis of **11**, **12** and **8** a general procedure[14] was followed.

4.1.1. Diisopropyl 3-butenyl-1-phosphonate (11). BuLi (330 mL, 0.66 mol, 2.0 M in hexanes) was slowly added to a stirred solution of diisopropyl methylphosphonate (**9**, 78 mL, 0.40 mol) in THF (200 mL) at −78 °C under N_2. The stirring was continued for 30 min, the solution of the Li reagent was allowed to warm to rt and then it was carefully transferred to a 1-L addition funnel. The reagent was added to a solution of allyl bromide (**10**, 75 mL, 0.86 mol) in THF (200 mL) at −78 °C within 30 min under N_2. The stirring was continued for 30 min whereupon the reaction was carefully quenched by adding saturated aqueous NH_4Cl solution (300 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2×150 mL). The combined organic phases were washed with brine (300 mL) and dried (Na_2SO_4). Evaporation of solvents gave a crude product, which was chromatographed on a silica gel column in hexanes/EtOAc=4:1–2:1 to afford phosphonate **11** as an oil (61.6 g, 70%). ^1H NMR ($CDCl_3$) δ 5.78 (ddt, 1H, J= 17.2, 10.4, 6.4 Hz, CH=), 4.98 (ddt, 1H, J=17.2, 1.6 Hz), 4.92 (dd, 1H, J=10.0, 1.6 Hz, CH_2=), 4.62 (m, 2H, CHO

of *i*-PrO), 2.28 (m, 2H, CH_2), 1.71 (m, 2H, CH_2P), 1.25 (2d, $J=5.6$ Hz, 12H, CH_3). ^{13}C NMR 137.6 (d, $J=18.6$ Hz, CH=), 115.1 (CH_2=), 70.1 (d, $J=6.7$ Hz, CHO of *i*-PrO), 26.9 (d, $J=4.4$ Hz, CH_2), 26.4 (d, $J=141.8$ Hz, CH_2P), 24.3 ($J=4.4$ Hz, CH_3). ^{31}P NMR 30.44.

4.1.2. Diisopropyl (*E*)-2-(oxiranyl)ethylphosphonate (12). MCPBA (126 g, 0.56 mol, 77%) was added in small portions to a solution of compound **11** (60.0 g, 0.27 mol) in CH_2Cl_2 (1 L) with stirring at 0 °C. The stirring was continued at rt for 11 h. The solution was then cooled to 0 °C again and the reaction was quenched with saturated aqueous solutions of $NaHCO_3$ (500 mL) and 250 $Na_2S_2O_3$ (250 mL). The organic layer was separated and aqueous phase was extracted with CH_2Cl_2 (3×250 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (3×200 mL) and brine (200 mL). After drying (Na_2SO_4) the solvents were evaporated to give a crude product, which was chromatographed on silica gel in hexanes/EtOAc=3:1–0:100 and then CH_2Cl_2/MeOH=10:1 leaving oxirane **12** (58.5 g, 91%) as an oil. ^1H NMR ($CDCl_3$) δ 4.63 (m, 2H, CHO of *i*-Pr), 2.93 (t, $J=5.2$ Hz), 2.70 (m), 2.45 (dd, 3H, $J=5.6$, 2.4 Hz, oxirane), 1.87–1.67/m, 4H, $(CH_2)_2$/, 1.24 (m, 12H, CH_3). ^{13}C NMR 70.3 (d, $J=6.7$ Hz, CHO of *i*-PrO), 52.1 (d, $J=19.3$ Hz) and 47.3 (oxirane), 26.1 (d, $J=5.2$ Hz, CH_2), 24.2 (m, CH_3), 23.3 (d, $J=144.7$ Hz, CH_2P). ^{31}P NMR 29.91. EI-MS 237 (M+H, 2.8), 135 (100.0).

4.1.3. Diisopropyl (*E*)-2-hydroxymethyl-1-cyclopropylphosphonate (8). BuLi (120 mL, 0.30 mol, 2.5 M in hexanes) was added slowly to a solution of compound **12** (58.0 g, 0.24 mol) in THF (400 mL) under N_2 at −78 °C within 30 min. The stirring was continued for 30 min whereupon the reaction was quenched with saturated aqueous NH_4Cl (100 mL) and the mixture was allowed to warm to rt. After addition of CH_2Cl_2 (600 mL), the layers were separated and the organic phase was washed with saturated aqueous NH_4Cl solution (400 mL). The combined aqueous phase was saturated with solid NaCl and it was extracted with CH_2Cl_2 (3×300 mL). The organic phase was washed with brine (500 mL) and it was dried (Na_2SO_4). Evaporation of the solvent afforded the crude product, which was chromatographed on silica gel in CH_2Cl_2/MeOH=100:1–50:1–30:1 providing compound **8** (48.0 g, 83%). ^1H NMR ($CDCl_3$) δ 4.64 (m, 2H, CHO of *i*-PrO), 3.56 (ddd, $J=11.4$, 6.4, 1.6 Hz) and 3.50 (dd, 2H, $J=11.4$, 6.4 Hz, CH_2O), 2.61 (m, 1H, OH),1.64–1.53 (m), 1.09–1.00 (m), 0.83–0.72 (m, 4H, cyclopropane), 1.30 (m, 12H, CH_3). ^{13}C NMR 70.6, 70.5 (2d, $J=8.3$ Hz, CHO of *i*-PrO), 64.9 (d, $J=4.4$ Hz, CH_2O), 24.6 (d, $J=3.8$ Hz, CH_3), 19.7 (d, $J=3.7$ Hz), 10.2 (d, $J=196.3$ Hz), 8.4 (d, $J=5.2$ Hz, cyclopropane). ^{31}P NMR 28.71. EI-MS 237 (M+H, 4.0), 153 (100.0). HRMS calcd for $C_{10}H_{22}O_4P$: 237.1256, found 237.1254.

4.1.4. Diisopropyl (*E*)-2-(phenylselenenylmethyl)-1-cyclopropylphosphonate (14). A solution of Br_2 (22 mL, 0.42 mol) in CH_2Cl_2 (80 mL) was added with stirring to PPh_3 (107 g, 0.41 mol) in CH_2Cl_2 (300 mL) at −35 to −25 °C within 15 min under N_2. The stirring was continued for 15 min, a solution of compound **8** (48.0 g, 0.20 mol) in CH_2Cl_2 (200 mL) was added, the resulting mixture was agitated for 15 min and then at rt for another 15 min. Saturated $NaHCO_3$ solution (200 mL) followed by saturated $Na_2S_2O_3$ solution (100 mL) were slowly added at 0 °C. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (2×200 mL). Combined organic phase was washed with water (500 mL) and brine (500 mL) whereupon it was dried (Na_2SO_4). The solvent was evaporated to give crude product **13** (170 g) containing Ph_3PO (ratio 1:2.7, estimated yield of **13** was 88%), which was employed in the next step. ^1H NMR ($CDCl_3$) δ 7.61–7.56 (m, 16H), 7.46–7.42 (m, 8H) and 7.38–7.34 (m, 16H, Ph_3PO), 4.66–4.54 (m, 2H, CHO of *i*-PrO), 3.31–3.20 (m, 2H, CH_2Br), 1.80–1.68 (m, 1H), 1.20–1.15 (m, 1H), 0.82–0.78 (m, 2H, cyclopropane), 1.25 (2d), 1.24 (2d, $J=5.6$ Hz, 12H, CH_3). ^{13}C NMR 133.3, 132.2, 132.1, 128.8 and 128.6 (Ph), 70.7 and 70.5 (2d, $J=6.3$ Hz, CHO of *i*-PrO), 36.3 (d, $J=3.8$ Hz), 24.4–24.3 (4 peaks, CH_3), 20.0 (d, $J=3.7$ Hz), 15.1 (d, $J=194.8$ Hz), 12.7 (d, $J=4.5$ Hz, cyclopropane). ^{31}P NMR 30.12 (Ph_3PO), 26.63.

A solution of $(PhSe)_2$ (34.9 g, 0.112 mol) in EtOH (350 mL) was refluxed till all selenide was dissolved (30 min). After cooling to rt, 4 M NaOH (56 mL, 0.225 mol) was added followed by $NaBH_4$ (7.67 g, 0.225 mol). The mixture was refluxed for 30 min and then it was cooled to rt. The crude product **13** from the previous experiment (170 g) in EtOH (300 mL) was added and the mixture was stirred at rt for 5 h. The solvent was evaporated, saturated aqueous solution of $NaHCO_3$ (200 mL) was added and the mixture was extracted with EtOAc (2×400 mL). The organic phase was washed with brine (200 mL) and it was dried over Na_2SO_4. The solvent was evaporated and the residue was chromatographed on a silica gel column in hexanes/EtOAc=100:0–4:1 and then EtOAc/MeOH=10:1 giving crude product **14** (185 g) containing Ph_3PO. A 200-mg sample of this product was rechromatographed in hexanes/EtOAc=1:1–CH_2Cl_2/MeOH=100:1 to afford compound **14** (70 mg) as an oil. ^1H NMR ($CDCl_3$) δ 7.51–7.48 (m, 2H), 7.26–7.21 (m, 3H, Ph), 4.67–4.56 (m, 2H, CHO of *i*-PrO), 2.98 (dd, 1H, $J=12.4$, 7.0 Hz), 2.81 (ddd, 1H, $J=12.4$, 7.0, 1.6 Hz, CH_2Se), 1.69–1.57 (m, 1H), 1.15–1.06 (m, 1H), 0.77–0.66 (m, 2H, cyclopropane), 1.29–1.25 (4d, 12H, $J=5.6$ Hz, 12H, CH_3). ^{13}C NMR 133.3, 130.2, 129.30, 127.34 (Ph), 70.5, 70.4 (2d, $J=6.0$ Hz, CHO of *i*-PrO), 32.0 (d, $J=4.4$ Hz, CH_2Se), 24.4–24.3 (2 overlapped d, CH_3), 18.1 (d, 1H, $J=3.7$ Hz), 14.2 (d, 1H, $J=193.9$ Hz), 12.2 (d, 2H, $J=5.2$ Hz, cyclopropane). ^{31}P NMR 27.80. EI-MS 376, 374 (M, 3.6, 2.1), 135 (100.0). HRMS calcd for $C_{16}H_{25}O_3P^{80}Se$: 376.0707, found 376.0709. Anal. Calcd for $C_{16}H_{25}O_3PSe$: C, 51.20; H, 6.71. Found: C, 51.37; H, 6.80.

4.1.5. Diisopropyl (*E*)-2-(phenylselenenylmethyl)-1-cyclopropylphosphonate Se-oxide (15). Hydrogen peroxide (30%, 220 mL) was added slowly to a solution of the crude product **14** from the previous experiment (185 g) in THF (800 mL) at 0 °C with stirring, which was continued for 1 h. The mixture was then stirred at rt for 16 h. Saturated aqueous $NaHCO_3$ (200 mL) was slowly added and the mixture was extracted with EtOAc (6×200 mL). Combined organic phase was dried (Na_2SO_4), the solvent was evaporated and the residue was chromatographed on a silica gel column in hexanes/EtOAc/MeOH=30:60:1 to EtOAc/MeOH=5:1 leaving compound **15** (60 g, 76% in

three steps) as an oil. ^{1}H NMR ($CDCl_3$) δ 7.71–7.65 (m, 2H), 7.44–7.43 (m, 3H, Ph), 4.78–4.61 (m, 2H, CHO of *i*-PrO), 3.03 (dd, J=12.4, 5.8 Hz), 2.86 (dd, J=12.4, 7.4 Hz, 2H), 2.70 (ddd, J=12.0, 8.0, 1.6 Hz), (dd, 2H, J=12.0, 9.6 Hz, CH_2Se), 1.52–1.46 (m), 1.39–1.31 (m), 1.19–1.01 (m), 0.84–0.77 (m), 0.76–0.63 (m, 4H, cyclopropane), 1.23–1.16 (4 overlapped d, 12H, J=6.4 Hz, CH_3). ^{13}C NMR 140.1, 131.69, 131.67, 129.8, 126.3, 126.1 (Ph), 70.8–70.7 (2 overlapped d, CHO of *i*-PrO), 58.1 (d, J=3.0 Hz), 57.9 (d, J=3.7 Hz, CH_2Se), 24.3, 24.2 (2 overlapped d peaks, J=5.2, 4.5 Hz, CH_3), 13.48 (d, J=194.6 Hz), 13.45 (d, J=195.6 Hz), 12.0 (d, J=3.7 Hz), 11.9 (d, J=3.7 Hz), 11.8 (d, J=5.2 Hz), 11.2 (d, J=5.1 Hz, cyclopropane). ^{31}P NMR 26.23, 25.99. ESI-MS 415, 413 (M+Na, 41.1, 20.2), 393, 391 (M+H, 49.7, 100.0). Anal. Calcd for $C_{16}H_{25}O_4PSe$: C, 49.11; H, 6.44. Found: C, 49.41; H, 6.42.

4.1.6. Diisopropyl 2-methylene-1-cyclopropylphosphonate (16). A mixture of compound **15** (60 g, 0.153 mol) and *i*-Pr_2NEt (50 mL, 0.30 mol) in toluene (500 mL) was refluxed for 50 h. The solvent was evaporated in vacuo at rt, the residue was dissolved in THF (400 mL) and H_2O_2 (30%, 120 mL) was added to oxidize compound **14** formed as a by-product. The reaction was run at 0 °C for 1 h and at rt for 24 h. It was worked up as described in the previous experiment. Column chromatography afforded product **16** (14 g) as an oil and the starting material **15** (31 g, 79.5 mmol). The latter was subjected to another round of elimination as described above to give additional compound **16** (7.8 g), total yield 21.8 g (65%). ^{1}H NMR ($CDCl_3$) δ 5.47 (m, 2H, CH_2=), 4.60 (m, 2H, CHO of *i*-PrO), 1.60–1.45 (m, 3H, cyclopropane), 1.26–1.21 (4 overlapped d, 12H, J=6.4 Hz, CH_3). ^{13}C NMR 127.0 (d, J=9.0 Hz, C=), 105.2 (d, J=5.2 Hz, CH_2=), 70.7, 70.5 (2d, J=6.0, 6.7 Hz, CHO of *i*-PrO), 24.3–24.0 (3d, J=5.2 Hz, CH_3), 10.9 (d, J=188.8 Hz, C_1), 8.2 (d, J=5.2 Hz, C_3). ^{31}P NMR 24.23. EI-MS 219 (M+H, 0.8), 134 (100.0). HRMS calcd for $C_{10}H_{20}O_3P$ (M+H) 219.1150, found 219.1155. Anal. Calcd for $C_{10}H_{19}O_3P$: C, 55.03; H, 8.77. Found: C, 54.80; H, 8.53.

4.1.7. Diisopropyl (*Z*)-2-bromomethyl-2-phenylselenenyl-1-cyclopropylphosphonate (17). NBS (13.5 g, 75.8 mmol) was added in portions to a stirred solution of compound **16** (14.0 g, 64.2 mmol) and $(PhSe)_2$ (24.0 g, 77.0 mmol) in CH_2Cl_2 (500 mL) under N_2 at 0 °C. The stirring was continued for 1 h whereupon water (100 mL) was added followed by saturated aqueous $Na_2S_2O_3$ (100 mL). The layers were separated and the organic phase was washed with 2 M NaOH (2×200 mL) and brine (200 mL). It was dried (Na_2SO_4), the solvent was evaporated and the residue was chromatographed on silica gel in hexanes/EtOAc=10:1–1.5:1 to give product **17** (26.5 g, 91%) as an oil. ^{1}H NMR ($CDCl_3$) δ 7.63–7.61 (m, 2H), 7.27–7.26 (m, 3H, Ph), 4.74 (m, 2H, CHO of *i*-PrO), 3.78 (dd, J=11.2, 1.6 Hz), 3.47 (d, 2H, J=11.2 Hz, CH_2Br), 1.72–1.64, 1.61–1.55, 1.48–1.44 (3m, 3H, cyclopropane), 1.34–1.30 (cluster of d, 12H, J=7.0 Hz, CH_3). ^{13}C NMR 134.7, 129.4, 128.7, 128.4 (Ph), 71.1, 71.0 (2d, J=6.6, 5.9 Hz, CHO of *i*-PrO), 42.1 (d, J=3.7 Hz, CH_2Br), 27.1 (d, J=4.4 Hz, C_2), 21.0 (d, J=196.3 Hz, C_1), 21.1 (d, J=6.0 Hz, C_3), 24.4–24.3 (clusters of d, CH_3). ^{31}P NMR 23.46. EI-MS 452, 454, 456 (M, 3.7, 7.7, 5.8), 213 (100.0). HRMS calcd for $C_{16}H_{24}^{79}BrO_3P^{80}Se$: 453.9812, found 453.9815. Anal. Calcd for $C_{16}H_{24}BrO_3PSe$: C, 42.31; H, 5.32. Found: C, 42.28; H, 5.12.

4.1.8. Diisopropyl (*Z*)-2-cyanomethyl-2-phenylselenenyl-1-cyclopropylphosphonate (19). A mixture of compound **18** (26.0 g, 57.2 mmol), Me_3SiCN (16.0 mL, 120 mmol) and Bu_4NF (1.0 M in THF, 120 mL, 120 mmol) in MeCN (500 mL) was stirred at rt for 60 h. The volatile components were evaporated in vacuo at rt and the residue was chromatographed on silica gel in hexanes/EtOAc=1:1–1:2 to give product **19** (10.3 g, 45%) as an oil. ^{1}H NMR ($CDCl_3$) δ 7.67–7.64 (m, 2H), 7.31–7.28 (m, 3H, Ph), 4.75 (m, 2H, CHO of *i*-PrO), 2.86, 2.61 (2dd, 2H, J=17.2, 1.6 Hz, CH_2CN), 1.71–1.63 (m), 1.53–1.47 (m, 1H), 1.36–1.32 (m, 15H, cyclopropane and CH_3). ^{13}C NMR 135.1, 129.6, 128.8, 128.0 (Ph), 116.9 (CN), 71.4, 71.3 (2d, CHO of *i*-PrO), 30.2 (d, J=3.0 Hz, *CH_2*CN), 21.0 (d, J=4.5 Hz, C_2), 20.8 (d, J=197.0 Hz, C_1), 20.4 (d, J=5.2 Hz, C_3), 24.4–24.2 (cluster of d, CH_3). ^{31}P NMR 22.47. EI-MS 399, 401 (M, 3.5, 7.0). HRMS calcd for $C_{17}H_{24}NO_3P^{80}Se$: 401.0651, found 401.0654. Anal. Calcd for $C_{17}H_{24}NO_3PSe$: C, 51.00; H, 6.04; N, 3.49. Found: C, 51.04; H, 6.07; N, 3.59.

4.1.9. Diisopropyl (*Z*)-2-(methoxycarbonylmethyl)-2-phenylselenenyl-1-cyclopropylphosphonate (20). A solution of compound **19** (9.8 g, 24.5 mmol) in MeOH (200 mL, saturated with gaseous HCl) was stirred at 0 °C for 1 h. The stirring was continued at rt for 20 h. The reaction was monitored by ^{31}P NMR spectra. Volatile components were evaporated at rt and the crude product was dissolved in MeOH–2 M HCl (1/1, 200 mL) and the solution was kept at rt for 22 h. Water (200 mL) was added and the mixture was extracted with EtOAc (2× 200 mL). The organic phase was washed with saturated $NaHCO_3$ solution (100 mL), brine (100 mL) and it was dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silica gel in hexanes/EtOAc=1:2 to afford compound **20** (7.6 g, 72%) as an oil. ^{1}H NMR ($CDCl_3$) δ 7.64–7.61 (m, 2H), 7.26–7.24 (m, 3H, Ph), 4.82–4.67 (m, 2H, CHO of *i*-PrO), 3.61 (s, 3H, CH_3O), 2.80 (dd, J=15.8, 4.2 Hz), 2.32 (d, 2H, J=15.8 Hz, CH_2CO_2Me), 1.63–1.56 (m, 1H), 1.39–1.28 (m, 14H, cyclopropane overlapped with CH_3). ^{13}C NMR 170.9 (C=O), 135.0, 129.2, 128.1 (Ph), 71.0, 70.7 (2d, J=6.9, 6.0 Hz, CHO of *i*-PrO), 51.9 (CH_3O), 46.1 (d, J=3.0 Hz, $CH_2CO_2CH_3$), 24.4, 24.3 (2d, J=5.3, 6.6 Hz, CH_3), 23.0 (d, J=4.9 Hz, C_2), 22.1 (d, J=197.4 Hz, C_1), 21.0 (d, J=4.9 Hz, C_3). ^{31}P NMR 23.58. EI-MS 432, 434 (M, 2.6, 4.8), 193 (100.0). HRMS calcd for $C_{18}H_{27}O_5P^{80}Se$: 434.0761, found 434.0759. Anal. Calcd for $C_{18}H_{27}O_5PSe$: C, 49.89; H, 6.27. Found: C, 49.78; H, 6.29.

4.1.10. Diisopropyl (*Z*)-2-(2-hydroxyethyl)-2-phenylselenenyl-1-cyclopropylphosphonate (21). $LiBH_4$ (2 M in THF, 35 mL, 70 mmol) was added via syringe to a solution of compound **20** (7.0 g, 16.1 mmol) in THF (100 mL) under N_2 at 0 °C and the resulting mixture was stirred for 1 h. The stirring was continued at rt for 23 h. The solution was re-cooled to 0 °C, and MeOH (50 mL) was added to quench the reaction. The saturated NH_4Cl solution (120 mL) was then added slowly (CAUTION, gas

evolution!) at 0 °C. The mixture was extracted with EtOAc (2×150 mL), the organic phase was washed with saturated aqueous NH_4Cl solution and brine. It was dried (Na_2SO_4), the solvent was evaporated and the residue was chromatographed in hexanes/EtOAc=1:1–1:2 and then EtOAc/MeOH=15:1 leaving product **21** (4.8 g, 74%) as an oil. ^{1}H NMR ($CDCl_3$) δ 7.61–7.58 (m, 2H), 7.26–7.25 (m, 3H, Ph), 4.78–4.71 (m, 2H, CHO of *i*-PrO), 4.02–3.96, 3.83–3.78 (2m, 2H, CH_2O), 2.64 (br s, 1H, OH), 2.05–1.99 (m, 1H), 1.62 (ddd, J=18.4, 7.2, 4.8 Hz, 1H), 1.38–1.28 (m, 16H, cyclopropane, CH_2CH_2O, CH_3). ^{13}C NMR 133.8, 129.8, 129.2, 127.6 (Ph), 71.0 (d, J=5.9 Hz, CHO of *i*-PrO), 61.5 (CH_2O), 42.7 (d, J=3.0 Hz, CH_2CH_2O), 25.4 (d, J=5.2 Hz, C_2), 21.5 (d, J=5.2 Hz, C_3), 21.4 (d, J=197.0 Hz, C_1), 24.5–24.2 (4d, J=5.2 Hz, CH_3). ^{31}P NMR 25.14. EI-MS 404, 406 (M, 5.4, 10.5), 147 (100.0). HRMS calcd for $C_{17}H_{27}O_4P^{80}Se$: 406.0812, found 406.0819. Anal. Calcd for $C_{17}H_{27}O_4PSe$: C, 50.38; H, 6.71. Found: C, 49.93; H, 6.31.

4.1.11. Diisopropyl (*Z*)- and (*E*)-(2-hydroxyethylidene)-1-cyclopropylphosphonate (23) and (24). A mixture of compound **21** (4.5 g, 11.1 mmol) and Ac_2O (20 mL) in pyridine (40 mL) was stirred at rt for 6 h. The volatile components were evaporated in vacuo at rt and the residue was dissolved in EtOAc (200 mL). The organic phase was washed with 1 M HCl (2×80 mL), brine (100 mL) and it was dried Na_2SO_4). The solvent was evaporated and the crude acetate **22** was dissolved in THF (120 mL). Hydrogen peroxide (30%, 40 mL) was then added with stirring at 0 °C, which was continued for 1 h and then at rt for 13 h, whereupon the solution was refluxed for 24 h. After cooling, water (200 mL) was added and the mixture was extracted with EtOAc (2×150 mL). Aqueous layer was saturated with NaCl and it was extracted again with EtOAc (2×100 mL). The combined organic phase was washed with saturated $NaHCO_3$ (2×100 mL), brine (100 mL) and it was dried (Na_2SO_4). The solvent was evaporated and the residue was dissolved in MeOH (50 mL) followed by addition of K_2CO_3 (1.22 g, 8.9 mmol in water (10 mL). The mixture was stirred at rt for 10 min. Water (100 mL) was added and the resulting mixture was extracted with EtOAc (2×150 mL). The organic phase was washed with brine (100 mL) and it was dried (Na_2SO_4). The solvent was evaporated and the crude product was chromatographed on a silica gel column in hexanes/EtOAc=1:1–1:2 followed by EtOAc (100%) and, finally, EtOAc/MeOH=25:1 to furnish the faster moving *Z*-isomer **23** (890 mg, 32%) followed by *E*-isomer **24** (810 mg, 29%) as oils.[24]

Z-Isomer **23**. ^{1}H NMR ($CDCl_3$) δ 6.13 (m, 1H, CH=), 4.71, 4.61 (2m, 2H, CH_2O), 4.40–4.27 (m, 2H, CHO of *i*-PrO), 2.89 (br s, 1H, OH), 1.79 (m, 1H), 1.55–1.49 (m, 2H, cyclopropane), 1.36–1.23 (4d, 12H, J=5.6 Hz, CH_3). ^{13}C NMR 120.7 (d, J=5.2 Hz, CH=), 117.7 (d, J=9.7 Hz, C=), 71.7, 71.3 (2d, J=6.6, 6.7 Hz, CHO of *i*-PrO), 62.3 (CH_2O), 24.3, 24.2, 24.1, 23.8 (4 overlapped d, J=3.7, 5.1, 3.7, 5.2 Hz, CH_3), 10.5 (d, J=190.3 Hz, C_1), 7.0 (d, J=5.2 Hz, C_3). ^{31}P NMR 25.42.

E-Isomer **24**. ^{1}H NMR ($CDCl_3$) δ 6.04 (m, 1H, CH=), 4.63–4.56 (2m, 2H, CHO of *i*-PrO), 4.19 (m, 2H, CH_2O), 3.54 (br s, 1H, OH), 1.61–1.54 (m, 3H, cyclopropane), 1.29–1.24 (m, 12H, CH_3). ^{13}C NMR 120.1, 120.2 (2 overlapped d, C=, CH=), 71.0, 70.8 (2d, J=6.0, 6.7 Hz, CHO of *i*-PrO), 62.5 (CH_2O), 24.3–24.1 (3 overlapped d, CH_3), 9.7 (d, J=188.7 Hz, C_1), 7.3 (d, J=4.5 Hz, C_3). ^{31}P NMR 24.98.

4.1.12. Diisopropyl (*Z*)-(2-bromoethylidene)-1-cyclopropylphosphonate (25a). A mixture of compound **23** (820 mg, 3.29 mmol), PPh_3 (2.62 g, 10.0 mmol) and CBr_4 (3.31 g, 10.0 mmol) in CH_2Cl_2 (60 mL) was stirred at rt for 4 h. The solvent was evaporated in vacuo at rt and the residue was chromatographed on silica gel in hexanes/EtOAc=3:1 to give product **25a** (690 mg, 67%) as an oil.[25] ^{1}H NMR ($CDCl_3$) δ 6.13 (m, 1H, CH=), 4.66 (m, J=6.4 Hz, 2H, CHO of *i*-PrO), 4.21–4.10 (m, 2H, CH_2Br), 1.71–1.60 (m, 3H, cyclopropane), 1.31–1.26 (poorly resolved 3d, 12H). ^{13}C NMR 124.0 (d, J=10.4 Hz, C=), 117.2 (d, J=5.9 Hz, CH=), 71.2 and 70.8 (2d, J=6.0, 6.7 Hz, CHO of *i*-PrO), 31.3 (CH_2Br), 24.4–24.3 (2 overlapped d), 24.2, 24.1 (2d, J=3.7, 4.4 Hz, CH_3), 10.8 (d, J=188.8 Hz, C_1), 8.4 (d, J=4.4 Hz, C_3). ^{31}P NMR 23.45. EI-MS 311, 313 (M+H, traces), 147 (100.0). HRMS calcd for $C_{11}H_{21}O_3P^{79}Br$ (M+H) 311.0412, found 311.0412. Anal. Calcd for $C_{11}H_{20}BrO_3P\cdot 0.5H_2O$: C, 41.27; H, 6.61. Found: C, 41.50, H, 6.36.

4.1.13. Diisopropyl (*E*)-(2-bromoethylidene)-1-cyclopropylphosphonate (25b). The procedure described above for the *Z*-isomer **25a** was performed with *E*-isomer **24** (740 mg, 2.97 mmol) to give *E*-isomer **25b** (620 mg, 67%) as an oil.[25] ^{1}H NMR ($CDCl_3$) δ 6.14 (m, 1H, CH=), 4.63 (m, 2H, CHO of *i*-PrO), 4.06 (d, J=7.2 Hz, 2H, CH_2Br), 1.71–1.54 (2m, 3H, H_1, H_3), 1.29–1.25 (4 overlapped d, J=6.2 Hz, 12H, CH_3). ^{13}C NMR 124.5 (d, J=8.9 Hz, C=), 116.8 (d, J=5.2 Hz, CH=), 71.1 and 70.8 (2d, J=5.9, 6.6 Hz, CHO of *i*-PrO), 31.3 (CH_2Br), 24.3–24.1 (3 overlapped d, CH_3), 11.2 (d, J=188.8 Hz, C_1), 7.3 (d, J=5.2 Hz, C_3). ^{31}P NMR 23.09. EI-MS 313, 311 (M, traces), 147 (100.0). HRMS calcd for $C_{11}H_{21}O_3P^{79}Br$ (M+H) 311.0412, found 311.0404. Anal. Calcd for $C_{11}H_{20}BrO_3P$: C, 42.46; H, 6.47. Found: C, 42.25; H, 6.51.

4.1.14. Diisopropyl (*Z*)-2-[2-(adenin-9-yl)ethylidene]-1-cyclopropylphosphonate (26a). A mixture of compound **25a** (350 mg, 1.12 mmol), adenine (302 mg, 2.25 mmol) and K_2CO_3 (470 mg, 3.36 mmol) in DMF (50 mL) was sonicated for 5 min and then it was stirred at rt for 10 h. Solvent was evaporated in vacuo and the residue was chromatographed on silica gel in CH_2Cl_2/MeOH=10:1 to afford compound **26a** (281 mg, 70%), mp 126–128 °C. UV_{max} (EtOH) 262 nm (ε 13,800). ^{1}H NMR (CD_3SOCD_3) δ 8.13 and 8.09 (2s, 2H, H_8 and H_2), 7.22 (s, 2H, NH_2), 6.14 (m, 1H, $H_{2'}$), 4.94 and 4.78 (AB, J=12.8–14.8 Hz), 4.93 and 4.80 (A′B′, J=14.0–14.4 Hz, 2H, $H_{1'}$), 4.62–4.50 (m, 2H, CHO of *i*-PrO), 1.99 (dt, 1H, $H_{5'}$), 1.71 (dd, J=18.0, 8.8 Hz, 1H) and 1.54 (m, 1H, $H_{4'}$), 1.24–1.18 (4 overlapped d, J=6.0 Hz, 12H, CH_3). ^{13}C NMR 156.6, 153.2, 149.9, 140.9, 119.3 (adenine), 125.4 (d, J=8.9 Hz, $C_{3'}$), 114.6 (d, J=5.9 Hz, $C_{2'}$), 70.9 and 70.6 (2d, J=6.0, 6.7 Hz, CHO of *i*-PrO), 44.4 ($C_{1'}$), 24.5, 24.4, 24.2 (3d, J=3.6–4.5 Hz, CH_3), 10.6 (d, J=187.2 Hz, $C_{5'}$), 8.3 (d, J=5.1 Hz, $C_{4'}$). ^{31}P NMR 24.04. EI-MS 365 (M, 5.2), 200 (100.0). HRMS calcd for $C_{16}H_{24}\cdot N_5O_3P$: 365.1617, found 365.1612. Anal. Calcd for $C_{16}H_{24}N_5O_3P$: C, 52.59; H, 6.62; N, 19.16. Found: C, 52.80; H, 6.51; N, 19.20.

4.1.15. Diisopropyl (*E*)-2-[2-(adenin-9-yl)ethylidene]-1-cyclopropylphosphonate (26b). The procedure described above for the *Z*-isomer **26a** was performed with *E*-isomer **25b** (190 mg, 0.61 mmol) to give *E*-isomer **26b** (148 mg, 67%), mp 165–167 °C. UV_{max} (EtOH) 262 nm (ε 14,300). ^1H NMR (CD_3SOCD_3) δ 8.11 and 8.07 (2s, 2H, H_8 and H_2), 7.21 (s, 2H, NH_2), 6.11 (m, 1H, $H_{2'}$), 4.90 (s, 2H, $H_{1'}$), 4.46 (m, 2H, CHO of *i*-PrO), 1.75 (dt, 1H) and 1.34–1.08 (m, 14H, $H_{5'}$, $H_{4'}$ and CH_3). ^{13}C NMR 156.6, 153.2, 150.2, 141.4, 119.2 (adenine), 123.1 (d, J=8.9 Hz, $C_{3'}$), 115.0 (d, J=5.2 Hz, $C_{2'}$), 70.6 and 70.4 (2d, J=5.9, 6.0 Hz, CHO of *i*-PrO), 44.1 ($C_{1'}$), 24.4 (2 overlapped d) and 24.2 (d, J=4.7 Hz), 9.7 (d, J=185.0 Hz, $C_{5'}$), 7.2 (d, J=5.2 Hz, $C_{4'}$). ^{31}P NMR 23.60. EI-MS 365 (M, 3.9), 200 (100.0). HRMS calcd for $C_{16}H_{24}N_5O_3P$: 365.1617, found 365.1617. Anal. Calcd for $C_{16}H_{24}N_5O_3P$: C, 52.59; H, 6.62; N, 19.16. Found: C, 52.71; H, 6.50; N, 18.92.

4.1.16. (*Z*)-2-[2-(Adenin-9-yl)ethylidene]-1-cyclopropylphosphonate (6a). Compound **26a** (185 mg, 0.50 mmol) was refluxed in 6 M HCl (12 mL) for 20 min. The volatile components were evaporated in vacuo at 40 °C. Water (3 mL) was added to the residue, the solid was filtered off, washed with water (1 mL) and it was dried in vacuo to give product **6a** (128 mg, 83%), mp 288–290 °C. UV_{max} (H_2O) 262 nm (ε 13,500). ^1H NMR (D_2O, sodium salt) δ 7.99 and 7.89 (2s, 2H, H_8 and H_2), 5.83 (br s, 1H, $H_{2'}$), 4.77 (s, $H_{1'}$ overlapped with HDO), 1.63 (t, 1H, $H_{5'}$), 1.40–1.31 (m, 2H, $H_{4'}$). ^{13}C NMR 155.0, 151.9, 148.1, 142.3, 118.1 (adenine), 130.1 (d, J=8.3 Hz, $C_{3'}$), 111.0 (d, J=5.3 Hz, $C_{2'}$), 45.4 ($C_{1'}$), 13.5 (d, J=166.4 Hz, $C_{5'}$), 7.3 (d, $C_{4'}$). ^{31}P NMR 17.84. ESI-MS 282 (M, 100.0). Negative ESI-MS 282 (M, 1.5), 281 (M−H, 13.2), 280 (M−2H, 100.0). Anal. Calcd for $C_{10}H_{12}N_5O_3P\cdot 0.8H_2O$: C, 40.63; H, 4.64; N, 23.69. Found: C, 40.87; H, 4.88; N, 23.57.

4.1.17. (*E*)-2-[2-(Adenin-9-yl)ethylidene]-1-cyclopropylphosphonate (7a). The procedure for the *Z*-isomer **6a** was followed with *E*-isomer **26b** (92 mg, 0.25 mmol) to afford *E*-isomer **7a** (50 mg, 71%), mp 297–300 °C. UV_{max} (H_2O) 261 nm (ε 13,800). ^1H NMR (D_2O, sodium salt) δ 8.00 and 7.98 (2s, 2H, H_8 and H_2), 5.96 (br s, 1H, $H_{2'}$), 4.78 (s, $C_{1'}$ overlapped with HDO), 1.29 (br s, 1H, $H_{5'}$), 0.71 (m, 2H, $H_{4'}$). ^{13}C NMR 155.3, 152.3, 148.9, 143.0, 118.1 (adenine), 127.7 (d, J=8.1 Hz, $C_{3'}$), 110.4 (d, J=4.2 Hz, $C_{2'}$), 44.9 ($C_{1'}$), 12.7 (d, J=164.2 Hz, $C_{5'}$), 5.7 (d, J=3.6 Hz, $C_{4'}$). ^{31}P NMR 17.40. Negative ESI-MS 282 (M, 4.2), 281 (M−H, 8.7), 280 (M−2H, 59.3), 113 (100.0). Anal. Calcd for $C_{10}H_{12}N_5O_3P\cdot 0.8H_2O$: C, 40.63; H, 4.64; N, 23.69. Found: C, 40.57; H, 4.19; N, 23.38.

4.1.18. Diisopropyl (*Z*)-2-[2-(2-amino-6-chloropurin-9-yl)ethylidene]-1-cyclopropyl-phosphonate (26c) and 7-isomer 27a. A mixture of compound **25a** (450 mg, 1.46 mmol), 2-amino-6-chloropurine (510 mg, 3.07 mmol) and K_2CO_3 (621 mg, 4.53 mmol) in DMF (50 mL) was sonicated for 2 min at rt and then it was stirred for 24 h. The solvent was evaporated in vacuo at rt and the crude product was chromatographed on a silica gel column in EtOAc/MeOH=30:1–10:1 followed by CH_2Cl_2/MeOH=10:1 to give (*Z*,9)-isomer **26c** (340 mg, 62%) as a followed by (*Z*,7)-isomer **27a** (84 mg, 15%) as sirups.

(Z,9)-Isomer **26c**. UV_{max} (EtOH) 224 nm (ε 27,200), 249 (ε 5,900), 311 (ε 7,700). ^1H NMR ($CDCl_3$) δ 7.96 (s, 1H, H_8), 6.08 (m, 1H, $H_{2'}$), 5.27 (br s, 2H, NH_2), 4.93 (poorly resolved half of 2AB's), 4.80 and 4.79 ($J_{AB}=J_{A'B'}$= 14.4 Hz, 2H, $H_{1'}$), 4.75–4.63 (m, 2H, CHO of *i*-PrO), 1.77–1.63 (m, 3H, $H_{5'}$ and $H_{4'}$), 1.32–1.24 (3d, J=6.0–6.4 Hz, 12H, CH_3). ^{13}C NMR 159.3, 153.7, 151.2, 142.9, 125.3 (purine), 125.7 (d, J=9.6 Hz, $C_{3'}$), 113.8 (d, J=5.2 Hz, $C_{2'}$), 71.4, 71.1 (2d, J=6.6 Hz, CHO of *i*-PrO), 44.6 ($C_{1'}$), 24.3–24.1 (cluster of d, CH_3), 11.1 (d, J=191.1 Hz, $C_{5'}$), 8.4 (d, J=5.2 Hz, $C_{4'}$). ^{31}P NMR 23.19. EI-MS 399, 401 (24.3, 8.7), 234 (100.0). HRMS calcd for $C_{16}H_{23}N_5O_3P^{35}Cl$: 399.1227, found 399.1226. Anal. Calcd for $C_{16}H_{23}ClN_5O_3P$: C, 48.06; H, 5.79; N, 17.51. Found: C, 47.93; H, 5.86; N, 17.36.

(Z,7)-Isomer **27a**. ^1H NMR ($CDCl_3$) δ 8.23 (s, 1H, H_8), 6.17 (m, 1H, $H_{2'}$), 5.46 (br s, 2H, NH_2), 5.19 (poorly resolved half of 2AB's), 5.07 and 5.05 (J_{AB}=14.8 Hz, $J_{A'B'}$= 14.4 Hz, 2H, $H_{1'}$), 4.73–4.60 (m, 2H, CHO of *i*-PrO), 1.74–1.60 (m, 3H, $H_{5'}$ and $H_{4'}$), 1.31–1.19 (4 partly overlapped d, J=6.4 Hz, 12H, CH_3). ^{13}C NMR 164.1, 159.6, 148.9, 143.7, 116.3 (purine), 126.0 (d, J=8.9 Hz, $C_{3'}$), 114.4 (d, J=5.2 Hz, $C_{2'}$), 71.4 and 71.2 (2d, J=6.7 Hz, CHO of *i*-PrO), 47.9 ($C_{1'}$), 24.4–24.2 (3 partly overlapped d) and 24.1 (d, J=5.2 Hz, CH_3), 11.1 (d, J=190.3 Hz, $C_{5'}$), 8.5 (d, J=5.2 Hz, $C_{4'}$). ^{31}P NMR 22.90.

4.1.19. Diisopropyl (*E*)-2-[2-(2-amino-6-chloropurin-9-yl)ethylidene]-1-cyclopropylphosphonate (26d) and 7-isomer 27b. The experiment was performed as described for the *Z*-isomer **26c** with compound **25b** (280 mg, 1.8 mmol), 2-amino-6-chloropurine (305 mg, 1.8 mmol) and K_2CO_3 (373 mg, 2.7 mmol) in DMF (50 mL). Column chromatography on silica gel in CH_2Cl_2–MeOH (20/1) gave the *E*-isomer **26d** (244 mg, 67%) as a sirup and 7-isomer **27b** (56 mg, 15%).

(E,9)-Isomer **26d**. UV_{max} (EtOH) 224 nm (ε 27,100), 248 (ε 5,900), 310 (ε 7,700). ^1H NMR ($CDCl_3$) δ 7.80 (s, 1H, H_8), 6.10 (m, 1H, $H_{2'}$), 5.20 (br s, 2H, NH_2), 4.83 (br s, 2H, $H_{1'}$), 4.67–4.59 (m, 2H, CHO of *i*-PrO), 1.62 (poorly resolved dt), 1.52–1.44 (m) and 1.38–1.23 (m, 15H, $H_{5'}$, $H_{4'}$ and CH_3). ^{13}C NMR 159.4, 153.9, 151.4, 142.6, 125.0 (purine), 124.4 (d, J=8.9 Hz, $C_{3'}$), 113.6 (d, J=5.2 Hz, $C_{2'}$), 71.08 and 70.93 (2d, J=6.7 Hz, CHO of *i*-PrO), 44.5 ($C_{1'}$), 24.32–24.11 (cluster of d, CH_3), 10.5 (d, J=189.5 Hz, $C_{5'}$) and 7.3 (d, J=4.4 Hz, $C_{4'}$). ^{31}P NMR 22.98. EI-MS 399, 401 (34.6, 14.3), 234 (100.00). HRMS calcd for $C_{16}H_{23}N_5O_3P^{35}Cl$: 399.1227, found 399.1222. Anal. Calcd for $C_{16}H_{23}ClN_5O_3P$: C, 48.06; H, 5.79; N, 17.51. Found: C, 48.23; H, 5.97; N, 17.35.

(E,7)-Isomer **27b**. ^1H NMR ($CDCl_3$) δ 8.04 (s, 1H, H_8), 6.14 (br s, 1H), 5.59 (br s, 2H, NH_2), 5.09 (br s, 2H, $H_{1'}$), 4.61 (m, 2H, CHO of *i*-PrO), 1.60 (poorly resolved t, 1H, $H_{5'}$), 1.45–1.37 (m, 1H) and 1.27–1.22 (m, 13H, $H_{4'}+CH_3$). ^{13}C NMR 164.0, 159.7, 148.8, 143.9, 116.5 (purine), 124.4 (d, J=9.8 Hz, $C_{3'}$), 114.4 (d, J=5.2 Hz, $C_{2'}$), 71.1 and 70.9 (2d, J=6.7 Hz, CHO of *i*-PrO), 47.9 ($C_{1'}$), 24.3–24.1 (m, CH_3), 10.3 (d, J=189.6 Hz, $C_{5'}$), 7.3 (d, J=5.2 Hz, $C_{4'}$). ^{31}P NMR 22.86.

4.1.20. (*Z*)-2-[2-(Guanin-9-yl)ethylidene]-1-cyclopropylphosphonate 6b. A solution of compound **26c** (270 mg, 0.67 mmol) in 6 M HCl (9 mL) was refluxed for 20 min. The volatile components were evaporated in vacuo at 40 °C, the residue was dissolved water (5 mL) and the pH was adjusted with NH_4OH to 9.0. The solution was put on the top of Dowex 1×2 column (200 mesh, $AcO^{(-)}$), which was eluted first with water (300 mL) and then 0.5 M AcOH (900 mL). The UV absorbing fractions were collected and they were evaporated to dryness. The residue was dried in vacuo to give product **6b** (170 mg, 85%), mp 222–224 °C. UV_{max} (H_2O) 253 nm (ε 13,300), 270 (shoulder, ε 10,300). ^1H NMR (D_2O, sodium salt) δ 7.61 (s, 1H, H_8), 5.67 (s, 1H, $H_{2'}$), 4.63 (overlapped with HDO, 2H, CH_2N), 1.44 (m, 1H, $H_{5'}$) and 1.16 (m, 2H, $H_{4'}$). ^{13}C NMR 158.5, 153.5, 150.6, 139.4, 115.6 (purine), 131.3 (d, J=7.1 Hz, $C_{3'}$), 110.1 ($C_{2'}$), 45.2 ($C_{1'}$), 13.9 (d, J=164.2 Hz, $C_{5'}$), 7.2 ($C_{4'}$). ^{31}P NMR 17.66. Negative ESI-MS 296 (M−H, 100.0), 297 (M, 13.5). Anal. Calcd for $C_{10}H_{12}N_5O_3P\cdot 1.4H_2O$: C, 37.25; H, 4.62; N, 21.72. Found: C, 37.15; H, 4.23; N, 22.08.

4.1.21. (*E*)-2-[2-(Guanin-9-yl)ethylidene]-1-cyclopropylphosphonate 7b. The experiment was performed as described for the *Z*-isomer **6b**. From the *E*-isomer **26d** (100 mg, 0.25 mmol) 55 mg (73%) of **7b** was obtained, mp 254–256 °C. UV_{max} (H_2O) 253 nm (ε 12,800), 270 (shoulder, ε 9,500). ^1H NMR (D_2O, sodium salt) δ 7.71 (s, 1H, H_8), 5.98 (m, 1H, $H_{2'}$), 4.80 (overlapped with HDO, 2H, $H_{1'}$), 1.30 (poorly resolved t, 1H, $H_{5'}$) and 0.79 (m, 2H, $H_{4'}$). ^{13}C NMR 165.2, 158.7, 151.6, 139.7, 116.9 (purine), 126.9 (d, J=7.1 Hz, $C_{3'}$), 110.8 ($C_{2'}$), 44.4 ($C_{1'}$), 12.5 (d, J=164.2 Hz, $C_{5'}$), 5.6 (d, $C_{4'}$). ^{31}P NMR 17.52. Negative ESI-MS 296 (M−H, 100.0), 297 (M, 19.8). Anal. Calcd for $C_{10}H_{12}N_5O_3P\cdot 1.5H_2O$: C, 37.04; H, 4.67; N, 21.59. Found: C, 37.26; H, 4.42; N, 21.60.

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25. Compounds **25a** and **25b** are stable neat at −10 °C but they are unstable in solution.

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An eco-friendly protocol for synthesis of thiourea derivatives: 1-benzoyl-3-benzylguanidine and 1-benzoyl-3-benzyl-*O*-ethylisourea. A possible non-purely thermal microwave assisted reaction

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Abstract—1-Benzoyl-3-benzylguanidine and 1-benzoyl-3-benzyl-*O*-ethylisourea were synthesized in good yields (68 and 76%, respectively) from 1-benzoyl-3-benzylthiourea and benzoyl-ethylthiocarbamate in dry media conditions using $KF–Al_2O_3$ under microwave irradiation. Strong nucleophilic amines promoted the sulfur elimination by attack on the thiocarbonyl group in both thiourea and thiocarbamates to afford guanidines and isourea, respectively. Transesterification products were obtained from *p*-TsOH catalyzed reaction of thiocarbamate with alcohols under MW-solvent-free conditions. Very important non-purely thermal MW specific effects were evidenced and attributed to stabilization by coulombic interactions between materials and waves.

1. Introduction

Substituted guanidines are interesting compounds that are utilized in medicine[1–3] as analgesic[4] and antihypertensive[5] compounds. In analytical chemistry, guanidines have been used as extraction agents for periodate ions.[6] In addition, guanidines are also useful in organic synthesis.[7–9]

The substituents on the guanidine group influence the physico-chemical properties and biological activities of these molecules. For instance, the introduction of an acyl group on one of the guanidine nitrogen atoms markedly reduces the guanidine basicity.[10]

Several methods have been reported for the preparation of guanidines in solution.[11–15] Recently, the conversion of *N*-benzoylthioureas into guanidines has been disclosed in good yields using $Bi(NO_3)_3 \cdot 5H_2O$ as a catalyst.[16] Solid-phase syntheses of trisubstituted guanidines[17] and *N*-acyl-*N*′-carbamoylguanidines[18] have been also reported.

Microwave (MW) activation has been used for guanidines preparation under both dry[19] and in solution.[20] However, in the first case, several reaction steps and the use of the very toxic isocyanates were required, whereas the second work described the use of non-volatile solvents and hazardous diamines as guanidine precursors at high temperatures (> 150 °C).

Alkylisoureas like **2a** are hydantoin derivatives. This class of compounds has been used as anti-convulsants in the treatment of epilepsy and heart arrhythmia.[21–22] On the other hand, alkylisoureas are useful materials for ester preparation by O-alkylation of carboxylic acids.[23] The first synthesis of hydantoins was described as early as 1911, using KOH–EtOH, which resulted in very low yields.[24] Recently, the synthesis of phenytoin, a hydantoin analogue, has also been reported by using MW activation.[25] Classical preparations of alkylisoureas require of carbodiimides as starting materials and long reaction times.[26] Improvements were introduced by using of the solid supported carbodiimides[27] and microwave irradiation.[26]

The use of MW technology together with solvent-free conditions allows improvements in yields, selectivity and

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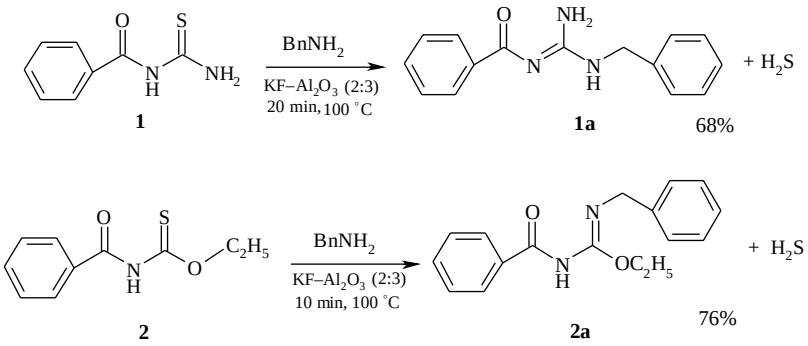
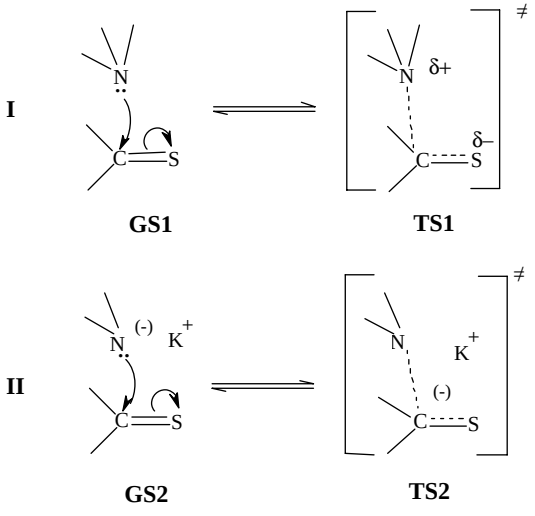


Scheme 1. Synthesis of 1-benzoyl-3-benzylguanidine **1a** and 1-benzoyl-3-benzyl-*O*-ethylisourea **2a**.

work up, with shortened reaction times when compared with classical methods.[28–34]

This work describes the synthesis of 1-benzoyl-3-benzylguanidine **1a** and 1-benzoyl-3-benzyl-*O*-ethylisourea **2a** from the corresponding thiourea derivatives **1** and **2**, respectively, under MW irradiation under solvent-free conditions using potassium fluoride impregnated onto alumina as the catalyst (Scheme 1) (Scheme 2). A special aim of the present work is the reaction of thiocarbamates **2** with alcohols to yield the transesterification products **2b** and **2c** (Scheme 3), which constitutes an extension of the previous non-classical synthesis of thiourea related compounds.[35–36]



Scheme 2. Rate determining steps in the mechanism of amine addition to the thiocarbonyl functionality in neutral **I** or basic **II** medium.

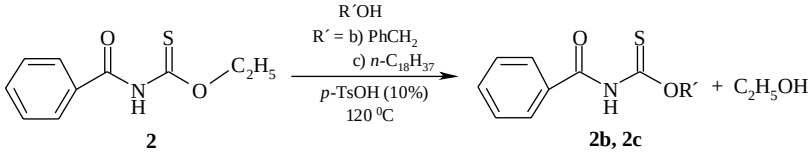
2. Results and discussions

Microwave experiments were carried out in open vessels with an efficient mechanical stirring (which avoids all problems of non-homogeneity in temperature). Several inorganic supports were tested in order to achieve the best product yields. The support/substrate relative amounts were previously optimized. Experiments were replicated to ensure reproducibility. In order to check the possible intervention of the specific non-purely thermal MW effects,[37,38] the same reactions were performed using an oil bath controlled using a thermostat under similar conditions. Table 1 shows the results obtained for the synthesis of **1a** or/and **2a**. A single-mode focused MW reactor was used to ensure a higher reproducibility and a better control of the reaction parameters (power, temperature).

The best yields (68 and 76% for guanidine **1a** and alkylisourea **2a**, respectively) were obtained using KF impregnated on alumina. Experiments performed at higher output power and for longer exposure times were unsuccessful (higher yields were not observed and decomposition products were detected by TLC analysis). No reaction was observed below 100 °C. Figure 1 showed the profiles of rises in temperature and emitted power during microwave assisted synthesis of **1a**. An emitted MW power value of 60 W was sufficient to maintain a constant temperature of 120 °C.

In all cases, it has been found that reactions proceed with considerable lower yields under similar temperature conditions by conventional heating demonstrating that the effect of MW is evidently not only purely thermal.

Microwaves are electromagnetic waves generated by an alternating electric field of high frequency. The energy



Scheme 3. Acid-catalyzed transesterification of **2** under MW irradiation without solvent.

Table 1. Synthesis of **1a** and **2a** under MW irradiation by reacting **1** and **2** with benzylamine

Reagent (2 mmol)	Support[a]	t (min)	T (°C)	Product	Activation mode	Yield (%)[b]
					Δ[c]	MW
1	No support	20	120		—	51
		20	100	**1a**	<10	168
	$KF–Al_2O_3$	15	120		—	59
2	No support	3	100		<10	40
		5	120		21	52
	$KF–Al_2O_3$	3	100	**2a**	17	67
		10	100		—	76

[a] $KF–Al_2O_3$=3/2 w/w.
[b] Yields of isolated products.
[c] Conventional heating controlled using a thermostat oil bath wash under similar conditions.

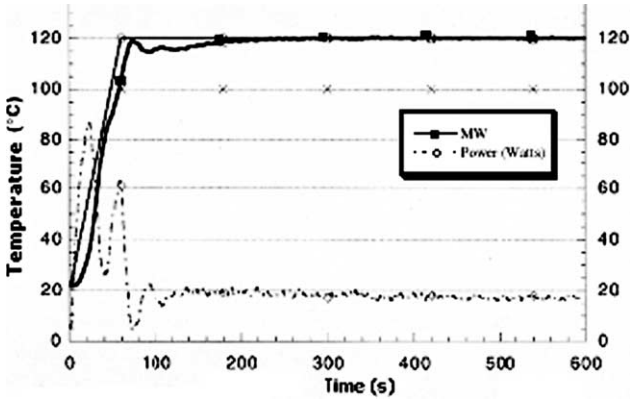


Figure 1. Profile of rise in temperature for the MW assisted solvent-free synthesis of **1a**.

associated with a MW photon (1 J mol^{-1} by application of Planck's law: $E=h\nu$ with $\nu=2450$ MHz) is far too small to induce any excitation of molecules. It can, however, induce thermal effects due to some internal friction between polar molecules during their changes in orientation with each alternation of the electric field. In addition, they can induce some electrostatic interactions with polar materials by dipole–dipole interactions, rather similar to the behavior of a dipolar solvent.[39]

By analogy and extension of the interpretation of solvent effects, the reactions can be facilitated when there is an increase of the polarity of the system during the progress of the reaction between the ground state and the transition state. An increase in MW efficiency could result therefore from both thermal effects (which provide adequate thermal energy) and specific polar electrostatic (non-purely thermal) effects.[34]

The specific MW effects we have evidenced here are consistent with the consideration of the mechanism and with the assumption that MW effects are increased when the polarity of a system is increased during the progress of the reaction (Scheme 2): [37,38,40,41]

– For the support (base)-free reaction, the rate determining step is the nucleophilic attack of the amine on thiocarbonyl moiety **I**. One can thus expect an important MW effect due to the enhancement of polarity of the system provided by the dipolar transition state TS1 when compared to neutral ground state GS1.[37–42]

– For the base-activated reaction (i.e., of KF–alumina), the enhancement of polarity of the system during the reaction is provided by ionic dissociation of the ion pairs from GS2 toward TS2 **II**, which is more polar due to the negative charge delocalization.[43]

In both cases, the most important phenomenon is the stabilization of the transition states by dipole–dipole electrostatic interactions with the electric field, which therefore could be responsible for an enhancement of reactivity by a decrease of the activation energy (Scheme 2).

A special interest lies in the reaction of **2** with $BnNH_2$ yielding the corresponding **2a** with H_2S elimination. On the other hand, when catalyzed by *p*-TsOH, the reaction of compound **2** with alcohols leads to the transesterification product, without sulfur elimination. Thus, two other thiocarbamates **2b** and **2c** were synthesized through transterification of **2** (Scheme 3) in order to confirm the reactivity of thiocarbamates toward molecules with different nucleophilic strength. This reaction has afforded the corresponding thiocarbamates in high yields and short reaction times (Table 2). Therefore, the present microwave assisted-acid catalyzed transesterification of thiocarbamate was more efficient than the reported classical procedure.[44]

The main results for thiocarbamates transesterification are displayed in Table 2.

The dielectric environment during MW-assisted transesterification of **2** aid the formation of polar intermediates formed during the acid-catalyzed transesterification reaction. The rapid microwave induced volatilization of the leaving alcohol (ethanol) molecule would shift the equilibrium favorably to formation of the transesterification product.[45]

Reactions carried out without acid catalysis showed low yields of the transesterification product presumably due the elimination of the ethanol molecule and formation of the isothiocyanate occurring before the nucleophilic attack of the benzyl alcohol (reactions 1–4 in Table 2). This thermal process seems to be more rapid under microwaves irradiation (reactions 1–2 in Table 2) and showed a strong dependence on the exposition time (reactions 3–4 in Table 2) yielding decomposition at 20 and 180 min of irradiation. When the reaction was conducted under classical heating (120 °C) for 24 h a 61% of **2b** was obtained together some decomposition products. This

Table 2. Results of synthesis of thiocarbamates **2b** and **2c** by reaction of **2** (2 mmol) with benzyl and octadecyl alcohol under MW irradiation

R′OH (mmol)	Catalyst (mmol)	Time (min)	*T* (°C)	MW, yield (%)	Δ, Yield (%)
BnOH (2)	—	10	100	52	—
	—	10	120	64	25
	—	20	100	—[a]	28
	—	180	120	—	52[b]
	0.2	10	100	64	—
	1	5	120	70	45
	1	10	120	88	50
BnOH (**4**)	1	**10**	**120**	**94**	**48**
n-$C_{18}H_{37}OH$ (2)	—	20	120	61	27
***n*-$C_{18}H_{37}OH$ (2)**[c]	1	**20**	**120**	**85**	**41**

Comparison with classical heating (Δ).
[a] Decomposition products.
[b] Δ 24 h → 120 °C, 61%.
[c] Higher alcohol amounts did not affect the product yield.

behavior will be carefully investigated and the results will be opportunely communicated.

3. Conclusion

In conclusion, we describe herein an efficient and eco-friendly protocol for the synthesis of 1,3-substituted guanidines, alkylisoureas and thiocarbamates in good yields. Special interests lie in the procedures for preparation of guanidines and alkylisoureas, where a non-purely thermal effect of the microwave irradiation is evidenced. In addition, transesterification of ethyl thiocarbamate with benzyl and octadecyl alcohols give the corresponding transesterificated products, resulting in a useful procedure toward other thiocarbamates.

4. Experimental

4.1. General methods

Reactions were performed in a Prolabo monomode reactor Synthewave™ 402 device.[30] The temperature was measured during the reaction by an optical fiber introduced inside the stirrer or by infrared detection, which indicates the surface temperature after previous calibration of emissivity in each case with an optical fiber (FTI-10 device from Fiso). All reactions were carried out in a cylindrical Pyrex tube with mechanical stirring to establish homogeneity in temperature. The emitted power was monitored (between 15 and 300 W) to maintain a constant temperature.

Melting points were obtained using Electrothermal 9100 apparatus. ^{1}H NMR spectra were recorded on a Bruker AC spectrometer at 250 MHz. ^{13}C NMR spectra and DEPT experiments were determined at 62 MHz. Chemical shifts are expressed in δ (ppm) using tetramethylsilane (TMS), which was used as an internal standard. IR spectra (ν_{max} cm^{-1}) were recorded on Bruker IR S48 using KBr pellets. EI mass (70 eV) spectra were obtained on HP5989A spectrometers. The reactions were followed by silica-gel plates (Merck $60F_{250}$) TLC performed using chloroform–ethyl acetate (8/2) as the eluent. All the chemicals were purchased from Aldrich and used as received.

4.2. Typical procedure for synthesis of 1a and 2a from benzoylthiourea 1 and thiocarbamate 2 under microwave irradiation

Benzoylthiourea **1** (2 mmol) or ethyl benzoylthiocarbamate **2** was dissolved in acetone. An equimolar amount of benzylamine was added and the mixtures were smoothly mixed with 1 g of KF–alumina (3/2). The solvent was removed under reduced pressure. The resulting mixture was placed into a Pyrex-glass open vessel and irradiated in the monomode MW reactor for the reaction times and temperatures as indicated in Table 1. The products were extracted from the support with acetone and precipitated using ice water.

Benzoylthiourea **1** and ethyl-*N*-benzoylthiocarbamate **2** were obtained according to the standard procedure previously reported in the literature.[35–36]

4.3. Typical procedure for microwave assisted transesterification of thiocarbamate 2. Synthesis of 2b and 2c

Equimolar amounts (2 mmol) of alcohol and ethyl benzoylthiocarbamate **2** were dissolved in acetone. The solvent was removed under reduced pressure. 1 mmol of *p*-TsOH was added slowly. The resulting mixture was placed into a Pyrex-glass open vessel and irradiated in a monomode MW reactor for reaction times and temperatures as indicated in Table 2. The reaction mixture was extracted with petroleum ether (bp 60 °C)–cyclohexane (1/1), yielding a white compound. The product was dissolved in dichloromethane and filtered to separate insoluble *p*-TsOH. After solvent evaporation, the white precipitate was purified by a column silica gel chromatography using toluene–methanol (5/1) as eluent.

4.4. Comparison between microwave activation and conventional heating for compounds 1a, 2a–c

In order to compare the results of MW irradiation versus conventional heating (Δ), the same reactions were performed inside a preheated thermostated oil bath at the same temperature as under MW irradiation. The reaction was achieved for the same reaction time. The temperature was controlled with the same optical fiber thermometer as for the calibration of MW's emissivity and the profile of temperature rise was adjusted to be similar to that registered

under microwave irradiation. The treatment and analysis remained identical.

4.5. Spectroscopic data

4.5.1. *N*-Benzoylthiourea 1. Yield 73% (from acetone–H_2O). Mp 178–179 °C; lit.[46] mp 186–187 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ=7.92–7.46 (m, 5H), 9.7 (d, 2H), 11.25 (s, 1H); ^{13}C NMR (DMSO-d_6, 62 MHz) δ=128.4 (CH), 129.4 (CH), 131.8 (CH), 134.9 (C_{ipso}), 161.9 (CO), 179.4 (CS); FT-IR (KBr): ν_{max} (cm^{-1})=3205, 3100, 1680, 1600, 1550, 1390; EI-MS *m/z*: 181.2 $(M+H)^+$.

4.5.2. *N*-Benzoyl-ethylthiocarbamate 2. Yield 64% (from acetone–H_2O). Mp 59–61 °C; lit.[47] 65–74 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ=1.40 (t, 3H), 4.60 (m, 2H), 7.45–7.90 (m, 5H), 9.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 62 MHz) δ=13.6 (CH_3), 69.2 (CH_2), 127.6 (CH), 128.8 (CH), 132.8 (CH), 133.0 (C_{ipso}), 162.8 (CO), 189.3 (CS); FT-IR (KBr): ν_{max} (cm^{-1})=3257, 3100, 1697, 1599, 1522, 1295; EI-MS *m/z*: 210.2 $(M+H)^+$.

4.5.3. 1-Benzoyl-3-benzylguanidine 1a. Mp 184–185 °C; lit.[48] 186–190 °C; ^{1}H NMR (DMSO-d_6, 250 MHz): δ=4.42 (m, 2H, broad signal), 4.45 (d, 2H), 7.23–8.22 (m, 10H), 9.1 (t, 1H); ^{13}C NMR (DMSO-d_6, 62 MHz) δ=49.2 (CH_2), 127.1 (CH), 127.2 (CH), 127.3 (CH), 127.4 (CH), 128.2 (CH), 128.3 (C_{ipso}), 133.0 (C_{ipso}), 136.0 (CH), 161.8 (CO), 177.2 (CN); FT-IR (KBr): ν_{max} (cm^{-1})=3234, 3105, 1679, 1590, 1498; EI-MS *m/z*: 252.1 $(M+H)^+$.

4.5.4. 1-Benzoyl-3-benzyl-*O*-ethylisourea 2a. Mp 159–160 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ=1.36 (t, 3H), 4.51 (s, 2H), 4.52 (m, 2H), 7.23–8.24 (m, 10H), 10.3 (s, 1H); ^{13}C NMR ($CDCl_3$, 62 MHz) δ=14.4 (CH_3), 44.8 (CH_2), 63.7 (CH_2), 127.0 (CH), 127.3 (CH), 127.6 (CH), 128.1 (CH), 129.1 (CH), 131.1 (CH), 134.0 (C_{ipso}), 134.2 (C_{ipso}), 162.8 (CO), 177.6 (CN); FT-IR (KBr): ν_{max} (cm^{-1})= 3234, 3105, 1679, 1612, 1590, 1498; EI-MS *m/z*: 283.1 $(M+H)^+$.

4.5.5. *N*-Benzoyl-benzylthiocarbamate 2b. Mp 104–106 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ=5.62 (s, 2H), 7.25–7.83 (m, 10H), 9.24 (s, 1H); ^{13}C NMR ($CDCl_3$, 62 MHz): δ=74.2 (CH_2), 127.1 (CH), 127.3 (CH), 127.7 (CH), 128.3 (CH), 129.0 (CH), 131.1 (C_{ipso}), 137.4 (C_{ipso} and CH), 188.9 (CS), 162.8 (CO); FT-IR (KBr): ν_{max} (cm^{-1})=3314, 3073, 1693, 1601, 1519, 1456, 1377; EI-MS *m/z*: 272.2 $(M+H)^+$.

4.5.6. *N*-Benzoyl-stearylthiocarbamate 2c. Mp 67.5–68.5 °C; ^{1}H NMR ($CDCl_3$, 250 MHz): δ=0.9 (m, 3H), 1.0–1.5 (m, 30H), 1.8 (m, 2H), 4.6 (m, 2H), 7.4–7.9 (m, 5H), 9.18 (s, 1H); ^{13}C NMR ($CDCl_3$, 62 MHz): δ=14.1 (CH_3), 22.7 (CH_2), 31.9 (CH_2), 31.9 (CH_2), 73.8 (OCH_2), 127.7 (CH), 129.0 (CH), 133.1 (C_{ipso} and CH), 162.7 (CO), 189.7 (CS); FT-IR (KBr): ν_{max} (cm^{-1})=3256, 3021, 1704, 1604, 1538, 1300. Anal. Calcd for $C_{26}H_{43}NO_2S$ (433.54): C, 72.02; H, 9.98; N, 3.22. Found: C, 72.12; H, 9.88; N, 3.17.

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Reactions of carbanions derived from α-substituted-methyl tolyl sulfones with quinone methides as Michael acceptors

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Abstract—Nucleophilic addition of α-halo-4-tolylsulfonyl methyl anions to quinone methides and subsequent reactions were studied. Three kinds of consecutive reaction products were isolated, depending on the substrate structures and reaction conditions. Two of them were identified as rearrangement products and one as the vicarious nucleophilic substitution (VNS) product. An unexpected 1,2-migration of the tosyl group was observed. The mechanism of the reactions is briefly discussed.

1. Introduction

Aryl substituted quinone methides are appropriate reference electrophiles for determination of the nucleophilicities of powerful nucleophiles such as carbanions.[1] Consequently, the nucleopilicites of numerous carbanions were determined toward these Michael acceptors.[2–5] Recently, we tried to determine reactivities of carbanions bearing leaving groups such as a halogen or thiophenol at the α-position. This kind of carbanion constitutes an important class of compounds, widely used in organic synthesis, for example, in the Darzens condensation[6–9] or in the vicarious nucleophilic substitution (VNS)[10–12] as well as in the synthesis of heterocyclic compounds.[13–16] Hence, knowledge of the nucleophilicities of the examined class of carbanions might be an invaluable synthetic tool. However, at the beginning of our studies we encountered that instead of the regular Michael adducts, as previously observed for other carbanions,[2] we isolated products of consecutive reactions. Here we present the results of our preliminary synthetic investigations.

2. Results and discussion

2.1. Michael addition

The reaction of X-4-tolylsulfonyl methyl anions **2a–d** (generated in situ by adding 1 equiv of *t*-BuOK to CH-acids) with quinone methides **1a–c** leads to the formation of the Michael adducts (Scheme 1).

Thus, the quinone methide **1a** reacts with carbanions **2a**,**c** or **2d** to give diastereoisomeric mixtures (Table 1). The products **3ac** and **3ac′**, from the addition of electrophile **1a** and nucleophile **2c**, were chromatographically separable and examined by X-ray crystallography (Figs. 1 and 2).

The addition of anion **2b** to quinone methide **1a** reveals stereoselectivity, and leads to formation of diastereoisomer **3ab**. The quinone methide **1b** with carbanions **2b**,**c** forms diasteroisomeric adducts, from which **3bb** and **3bb′** were chromatographically separable. The addition of anion **2a** to quinone methide **1b** shows stereoselectivity and leads to formation of diastereoisomer **3ba**. The less electrophilic quinone methide in this series **1c** ($E=-17.29$)[17] needed higher dilution for the reaction, because its solubility in DMF is very poor. We isolated the adducts of carbanions **2c** and **2d** to quinone methide **1c**, from which diastereoisomers **3cc** and **3cc′** were separable by column chromatography. The adducts of carbanions **2a** and **2b** to quinone methide **1c** were unfortunately unstable and decomposed under standard workup conditions.

The yields of the addition reactions of quinone methides **1a–c** and carbanions **2a–d** were moderate to good. In general, initially formed Michael adducts (diastereoisomer mixtures in anionic form) are sensitive to external base and prolonged reaction time. These factors cause changes in the ratio of diastereoisomers, probably via consecutive deprotonation at the position stabilized by sulfone group,

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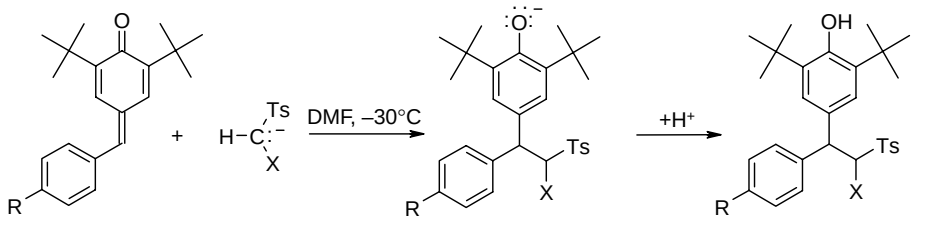


R	
H	**1a**
OMe	**1b**
NMe_2	**1c**

X	
Cl	**2a**
Br	**2b**
Ph	**2c**
SPh	**2d**

R	X	
H	Cl	**3aa**
	Br	**3ab**
	Ph	**3ac**, **3ac'**
	SPh	**3ad**
OMe	Cl	**3ba**
	Br	**3bb**, **3bb'**
	Ph	**3bc**
	SPh	**3bd**
NMe_2	Ph	**3cc**, **3cc'**
	SPh	**3cd**

Scheme 1. The Michael addition of α-substituted-4-tolylsulfonyl methyl anions and quinone methides.

Table 1. Michael adducts of α-substituted-4-tolylsulfonyl methyl anions and quinone methides isolated after protonation

Entry	Quinone methide		Carbanion		Michael adduct
	R	No.	X	No.	No. yield %
1	H	**1a**	Cl	**2a**	**3aa**[a] 38
2		**1a**	Br	**2b**	**3ab** 43
3		**1a**	Ph	**2c**	**3ac** 44, **3ac′** 14
4		**1a**	SPh	**2d**	**3ad**[b] 53
5	OMe	**1b**	Cl	**2a**	**3ba** 89
6		**1b**	Br	**2b**	**3bb** 19, **3bb′**17
7		**1b**	Ph	**2c**	**3bc**[c] 90
8		**1b**	SPh	**2d**	**3bd**[d] 52
9	NMe_2	**1c**	Ph	**2c**	**3cc** 30, **3cc′** 16[e]
10		**1c**	SPh	**2d**	**3cd**[f] 14

[a] Diastereoisomer ratio 2:1.
[b] Diastereoisomer ratio 6:1.
[c] Diastereoisomer ratio 6:1.
[d] Diastereoisomer ratio 3:1, the excess base causes isolation of, only the minor diastereoisomer exclusively.
[e] Higher dilution was necessary, due to very low solubility of quinone methide.
[f] Diastereoisomer ratio 2:1, the product of elimination of 2,6-di-*tert*-butyl-phenol as the side product **7cd** was isolated (see Section 3).

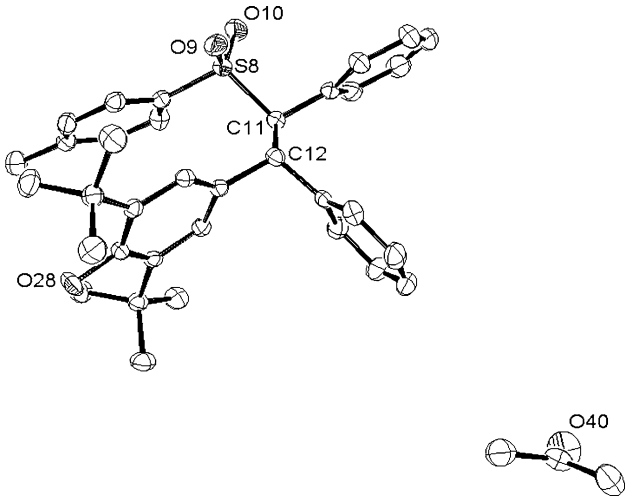


Figure 1. X-ray structure of the adduct **3ac** with acetone. Compound name: 2,6-di-*tert*-butyl-4-((1*S*,2*S*)1,2-diphenyl-2-(toluene-4-sulfonyl)ethyl)phenol and 2,6-di-*tert*-butyl-4-((1*R*,2*R*)1,2-diphenyl-2-(toluene-4-sulfonyl)ethyl)phenol acetone solvate. Summary of data CCDC 241140.

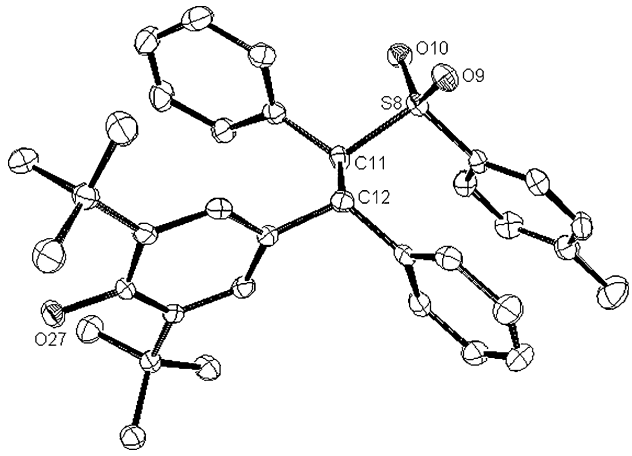


Figure 2. X-ray structure of the adduct **3ac′**. Compound name: 2,6-di-*tert*-butyl-4-((1*S*,2*R*)1,2-diphenyl-2-(toluene-4-sulfonyl)ethyl)phenol and 2,6-di-*tert*-butyl-4-((1*R*,2*S*)1,2-diphenyl-2-(toluene-4-sulfonyl)ethyl)phenol. Summary of data CCDC 236493.

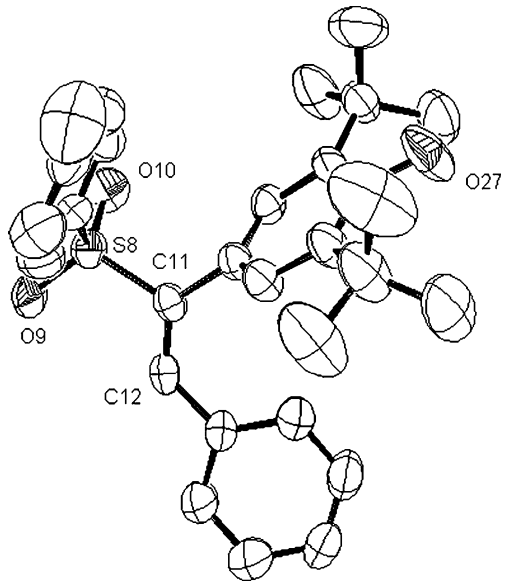


Figure 3. X-ray structure of the product **4a**. Compound name: 2,6-di-*tert*-butyl-4-[(*E*)-2-phenyl-1-(toluene-4-sulfonyl)vinyl]phenol. Summary of data CCDC 213205.

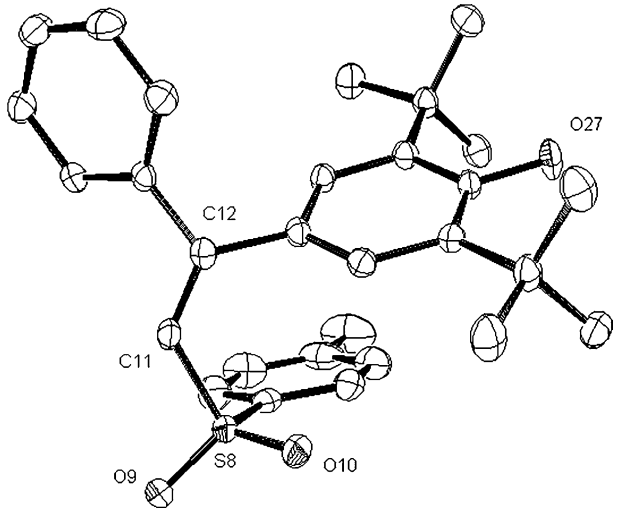


Figure 4. X-ray structure of the product **5a**. Compound name: 2,6-di-*tert*-butyl-4-[(*Z*)-1-phenyl-2-(toluene-4-sulfonyl)vinyl]phenol. Summary of data CCDC 213206.

and subsequent inversion of the configuration at carbanionic center, followed by protonation at the quench stage.

2.2. Consecutive processes

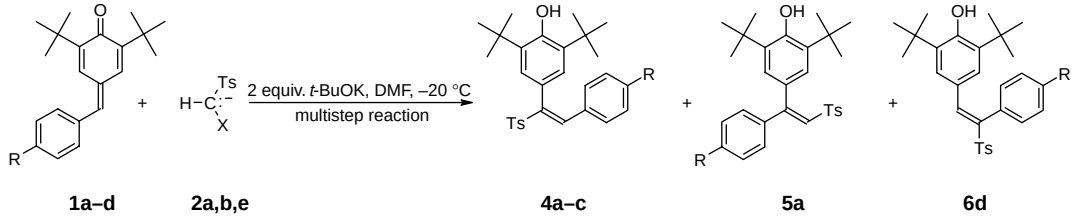
Although we expected only one product of hydrogen VNS to be formed in the reaction of anion **2a** with quinone methide **1a**, conducted in the presence of *t*-BuOK, a mixture of two products of the addition–elimination reaction cascade were identified. Both products possess very similar spectroscopic properties and the same elemental analysis. However, they were separable by column chromatography. The structures were determined by X-ray analysis (Figs. 3 and 4). The major product **4a**, which represents the unexpected product of rearrangement (1,2-shift of 2,6-di-*tert*-butylphenyl group), and the minor product **5a**, which is the product of the VNS reaction (Scheme 2).

On the other hand, anion **2b** and iodo substituted analogue **2e** reacted with quinone methide **1a** to give only the rearrangement product **4a**. Also, quinone methides **1b–c** substituted with electron-donating (Me_2N, MeO) groups reacted with anions **2a–b** to yield only the rearrangement products **4b–c**. Different chemical behavior was observed in the case of quinone methide **1d**, substituted with the electron-withdrawing nitro group, and carbanion **2a**. Here, we observed formation of another rearrangement product **6d** (Scheme 2, Table 2). In this case, migration of the 4-tolylsulfonyl group occurred. The structure of product **6d** was confirmed by X-ray crystallography (Fig. 5).

The adducts formed from carbanion **2d** and quinone methides **1a–c** did not undergo subsequent elimination, neither intramolecular nor via base promoted 1,2-elimination, due to insufficient nucleofugality of thiophenolate group.

2.3. Reaction mechanism

The first step is the Michael addition of the carbanion to the electrophilic double bond of the quinone methide, which results in the formation of the corresponding phenolate anions (Scheme 1). The addition reactions are irreversible. This can be explained by taking into account the electrophilicity of quinone methides ($-17.3<E<-15$)[5] as well as the high nucleophilicity of the applied α-substituted-4-tolyl-sulfonyl methyl anions (estimated *N* values 25 ± 3).[3] The expected rates of the addition reactions, predicted using Mayr's equation: $\log k = s(N+E)$,[18] should be faster than $10^5\ M^{-1}\ s^{-1}$. The presence of a very good leaving group such as a halogen atom at the β-position to the phenolate ring of the initially formed Michael adducts can lead to intramolecular cyclization (C-alkylation) with formation of spirodienones (Scheme 3). The formation of structurally similar compounds, isolated with good yields of 60–85%, under basic conditions has been reported previously.[19] However, in the case of our substrates we were unable to isolate these intermediates.



Scheme 2. Products of the reaction of α-halo-4-tolylsulfonyl methyl anions with quinone methides, conducted with an excess of external base.

Table 2. Products of the reactions of α-halo-4-tolylsulfonyl methyl anions with quinone methides conducted with an excess of external base

Entry	Quinone methide		Carbanion		Products-no. yield %		
	R	No.	X	No.			
1	H	**1a**	Cl	**2a**	**4a** 44	**5a** 12	
2		**1a**	Br	**2b**	**4a** 69		
3		**1a**	I	**2e**	**4a** 62		
4	OMe	**1b**	Cl	**2a**	**4b** 61		
5		**1b**	Br	**2b**	**4b** 60		
6[a]	NMe_2	**1c**	Cl	**2a**	**4c** 89		
7[a]		**1c**	Br	**2b**	**4c** 59		
8[b]	NO_2	**1d**	Cl	**2a**			**6d** 31

[a] The reactions were carried out at 0 °C and higher dilution, because of poor solubility of quinone methide in DMF.
[b] Additionally, the product (**7d**) of the consecutive VNS reaction in the nitrobenzene ring was isolated with 33% yield.

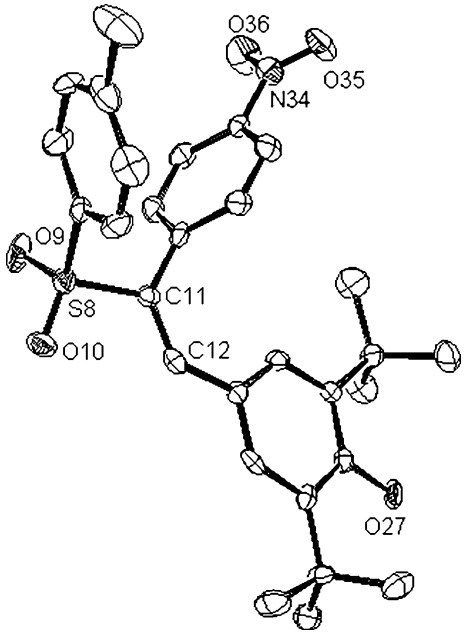


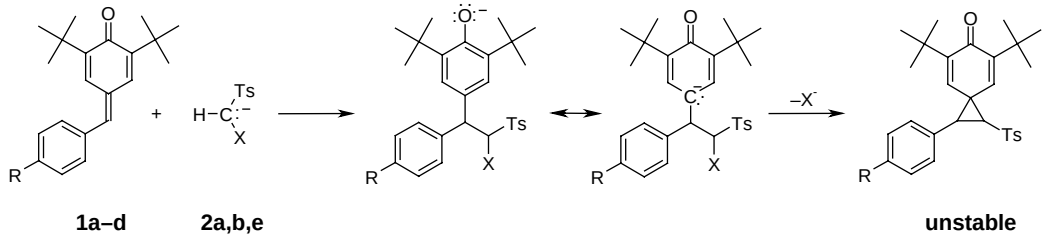
Figure 5. X-ray structure of the product **6d**. Compound name: 2,6-di-*tert*-butyl-4-[(*E*)-2-(4-nitrophenyl)-2-(toluene-4-sulfonyl)vinyl]phenol. Summary of data CCDC 267465.

The spirodienones can undergo spontaneous ring opening reactions with formation of mesomericaly stabilized carbocation (path A—Scheme 4)[20] or can be deprotonated by base (*t*-BuOK) at the position α to the tosyl group with formation of stabilized carbanion (path B—Scheme 4). Both reaction paths lead to formation of rearrangement products **4a–c**. In both cases, the intramolecular π–π interactions between the electron-rich phenolate ring and the neighboring aryl group determine the final geometry at the double bond of the product.

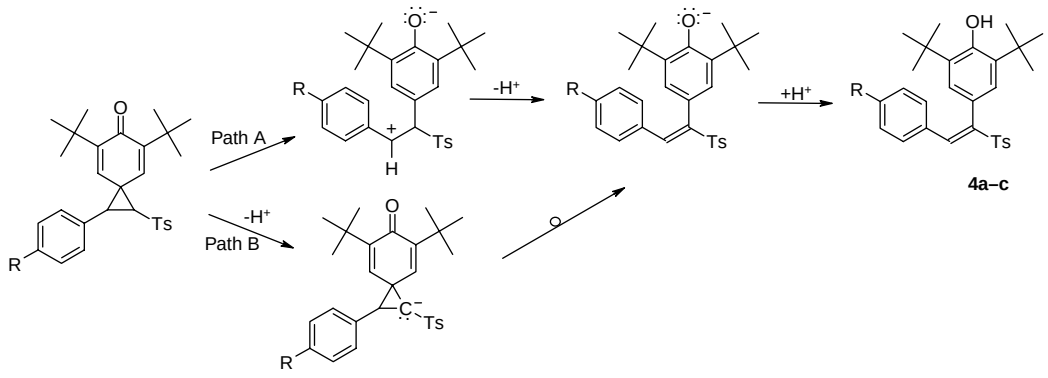
The formation of product **5a** can be explained via the base promoted 1,2-elimination of HCl from the initially formed Michael adduct. The overall path of the formation of this product is a new example of the VNS reaction, performed on an electrophilic alkene (Scheme 5). VNS reaction is known for certain Michael acceptors such as benzylidene-malonodinitriles, β-nitrostyrenes, dimethyl maleate, fumarate etc.[21] However, in some cases, cyclopropanation and a consecutive ring opening process takes place.

The course of the consecutive reaction of the initially formed Michael adducts is probably determined by nucleofugality of the leaving group at the β-position to the phenolate ring. Thus, the strongest nucleofuges in this series (bromine and iodide) increase the rate of intramolecular cyclization, leading to the formation of spirodienone and finally to formation of the rearrangement products (Table 2). Chlorine, a slightly weaker nucleofuge, decreases the rate of the intramolecular cyclization and allows for the competing base promoted 1,2-elimination of HCl. In this case, two products are formed: the rearrangement product **4a** and VNS product **5a** (Table 2). The sluggish and bulky—thiophenolate leaving group opposes elimination, neither intramolecular nor via base promoted 1,2-elimination. Thus, the consecutive reactions do not occur. Here also, steric factors can hinder the elimination processes. Another factor, discriminating between intramolecular cyclization and the VNS, is the concentration of base. The higher base concentration can increase the rate of the 1,2-elimination of the HX from the initially formed adducts, which extend the participation of the VNS in the competition.

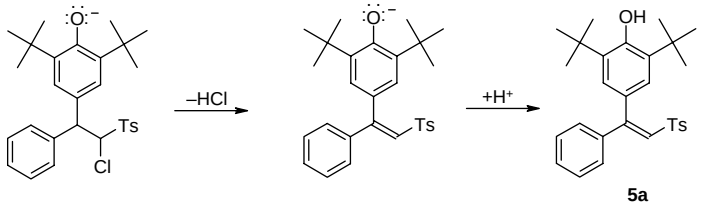
The most difficult is the rationalization of the mechanism for formation of products **6d** and **7d** formation (Scheme 2, Table 2). In this case, the spirodienone shown in Scheme 3 also has to become an intermediate. But the presence of



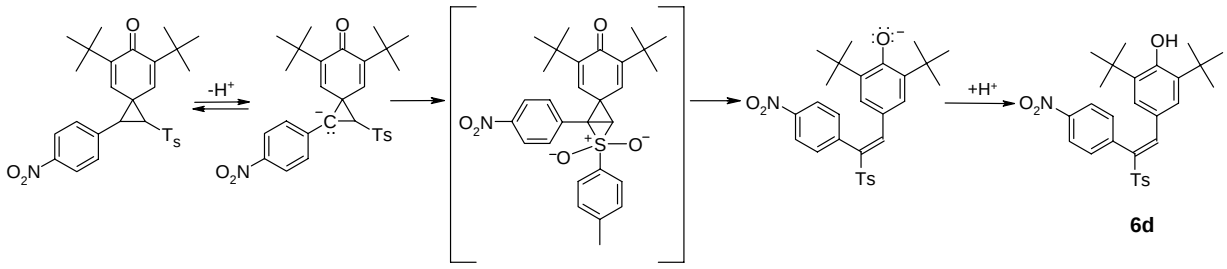
Scheme 3. Addition of α-halo-4-tolylsulfonyl methyl anions to quinone methides with formation of phenolate anion, followed by possible intramolecular cyclization to form spirodienones.



Scheme 4. Spontaneous or base promoted ring opening reaction of spirodienones with formation of products **4a–c**.



Scheme 5. The formation of product **5a** via base-induced elimination of HCl from the initially formed Michael adduct—the VNS of hydrogen in quinone methide.



Scheme 6. The formation of product **6d** via deprotonation of spirodienone intermediate and 1,2-intramolecular migration of tosyl group.

a nitro group at the *para* position increases the acidity of the proton at the benzylic position. For comparison, the pK_a value for *para*-nitrotoluol is 20.4 (DMSO).[22] This facilitates deprotonation (Scheme 6). The next step could involve a 1,2-shift of the tosyl group via a hypervalent sulfur intermediate.[23–25] We have previously observed similar 1,2-migration of a tosyl group attached to a three-membered ring in reactions of salicylic aldehydes with anion **2a**.[16]

After the product **6d** formation (in anionic form), a consecutive-parallel and reversible (in the first step) VNS reaction of the carbanion **2a** with compound **6d** occurs in the remaining nitrobenzene ring. This leads to the formation of product **7d**. The consecutive VNS reaction must be much slower than the first nucleophilic attack of **2a** on **1d** due to lower electrophilicity of the nitrobenzene ring in comparison to the double bond of the quinone–methide.

2.4. Concluding discussion

The expected Michael addition products were obtained, when the reaction was conducted under mild conditions, for example, without excess of base, short reaction time and at low temperature. Interestingly, when an excess of base (*t*-BuOK) was used and the reaction time was prolonged and the reaction was carried out at higher temperature, in addition to the expected elimination product, several rearrangements products were obtained depending on the substrates used. Quantitative determination of the nucleophilicites for studied carbanions would, however, be possible in our opinion, but with using a stopped flow system and conducting the measurements at low temperature, which ensures sufficient stability of the carbanions and decelerates the reaction rates.[11,12,26]

3. Experimental

3.1. Instruments and materials

Chemical shifts in ^{1}H and ^{13}C NMR spectra are expressed in ppm and refer to Me_4Si ($\delta_H=0.00$ ppm), ($\delta_C=0.00$ ppm). Coupling constants are in Hz. Melting points are uncorrected. The yields refer to isolated products without

optimization of the procedures. DMF was dried over CaH_2 and distilled under reduced pressure. The X-ray structures were determined on the 'KappaCCD' (Nonius) diffractometer. Quinone methides[27,28] and carbanion[29,30] precursors were prepared according to literature procedures. Quinone methide **1d** (40% yield) was prepared via an analogous route to that described in the literature.[27,28] Substrates **2a** was commercial available, sulfone **2c** was synthesized from sodium 4-tolylsulfinate and benzyl chloride, respectively, under PTC conditions and recrystallized. Silica gel 230–400 mesh was used for column chromatography.

3.2. General reaction procedure

Addition reactions of **1** *and* **2**. To a stirred solution of *t*-BuOK (0.113 g, 1 mmol) in DMF (5 mL) at −30 °C and under argon atmosphere was added, via cannula, a solution of CH-acid **2** (1 mmol) in DMF (3 mL). The mixture was stirred for 2 min before dropwise addition a solution of quinone methide **1** (1 mmol) in DMF (5 mL). After 5 min, the mixture was allowed to warm up to 0 °C and poured into cooled 3% aqueous HCl (100 mL). The precipitate was filtered off, washed with water and dried in the air. The crude products **3** were isolated as yellow powders, and purified by column chromatography with hexane–ethyl acetate eluent and recrystallized.

3.2.1. 2,6-Di-*tert*-butyl-4-[2-chloro-1-phenyl-2-(toluene-4-sulfonyl)ethyl]phenol (3aa). Diasteroisomer ratio 2:1, mp 155–159 °C (190 mg, 38%, AcOEt/heptane); ν_{max} (KBr) 1033, 1083, 1139, 1153 (SO_2), 1237 (C–OH), 1598 (C=C arom), 3627 (OH) cm^{-1}; δ_H (300 MHz, acetone-d_6) major diasteroisomer 1.25 (18H, s, C(*Me*)$_3$), 2.37 (3H, s, C*Me*), 4.68 (1H, d, J=9.9 Hz, TsCH–C*H*), 5.89 (1H, s, O*H*), 6.38 (1H, d, J=9.9 Hz, TsC*H*), 7.16 (2H, s, C*H*CC(Me)$_3$), 7.16–7.60 (9H, m, *Ph* and SO_2-*p*-C_6H_4Me), minor diasteroisomer 1.39 (18H, s, C(*Me*)$_3$), 2.42 (3H, s, C*Me*), 4.83 (1H, d, J=8.1 Hz, TsCH–CH), 5.96 (1H, s, O*H*), 6.14 (1H, d, J=8.1 Hz, TsC*H*), 7.16 (2H, s, C*H*CC(Me)$_3$), 7.16–7.60 (9H, m, *Ph* and SO_2-*p*-C_6H_4Me); δ_C (75 MHz, acetone-d_6) major diasteroisomer 20.2, 29.2, 33.7, 52.6, 77.5, 124.7, 126.1, 127.8, 127.8, 128.4, 128.8, 130.1, 133.9, 136.9, 144.0, 140.6, 152.4, minor diasteroisomer 20.3, 29.3, 33.8, 54.7, 77.6, 125.2, 126.2, 127.8, 127.8, 128.7, 129.1, 130.4, 135.0, 136.9, 141.9, 144.5, 152.4; *m/z* (EI, 70 eV) 498 ($(M-H)^+$, 4), 342 ($(M-Ts)^+$, 47), 308 (45), 295 (100), 293 (25), 91 (12).

3.2.2. 4-[2-Bromo-1-phenyl-2-(toluene-4-sulfonyl)ethyl]-2,6-di-*tert*-butylphenol (3ab). Mp 148–150 °C (234 mg, 43%, EtOH); ν_{max} (KBr) 1083, 1120, 1138 (SO_2), 1300 (C–OH), 1601 (C=C arom), 3557 (OH) cm^{-1}; λ_{max}=201 nm, log ε=4.7 (EtOH); δ_H (400 MHz, $CDCl_3$) 1.27 (18H, s, C(*Me*)$_3$), 2.28 (3H, s, C*Me*), 4.40 (1H, d, J=5.9 Hz, TsC*H*), 4.90 (1H, d, J=5.9 Hz, TsCH–C*H*), 5.02 (1H, s, O*H*), 7.15 (2H, s, C*H*CC(Me)$_3$), 7.03–7.58 (9H, m, *Ph* and SO_2-*p*-C_6H_4Me); δ_C (100 MHz, $CDCl_3$) 21.6, 29.9, 34.3, 51.6, 77.6, 126.4, 127.1, 128.1, 128.6, 129.1, 130.0, 131.1, 135.4, 138.3, 140.8, 144.8, 153.1.

3.2.3. (1*S*,2*S*)/(1*R*,2*R*)-2,6-Di-*tert*-butyl-4-[1,2-diphenyl-2-(toluene-4-sulfonyl)ethyl]phenol (3ac). Major diasteroisomer, mp 182–183 °C (238 mg, 44%, acetone/heptane); [Found: C, 77.85; H, 7.64; S, 5.88. $C_{35}H_{40}O_3S$ requires C, 77.74; H, 7.46; S, 5.93%]; ν_{max} (KBr) 1084, 1141 (SO_2), 1237 (C–OH), 1598 (C=C arom), 2956 (C–H), 3636 (OH) cm^{-1}; λ_{max}=202 nm, log ε=4.8, λ_{max}=230 nm, log ε=4.3 (EtOH); δ_H (600 MHz, $CDCl_3$) 1.32 (18H, s, C(*Me*)$_3$), 2.28 (3H, s, C*Me*), 4.96 (1H, s, O*H*), 5.03 (1H, d, J=10.1 Hz, TsCH–CH), 5.06 (1H, d, J=10.1 Hz, TsC*H*), 6.92 (2H, AA′XX′, J=7.7 Hz), 6.94–7.04 (10H, m, 2×*Ph*), 7.05 (2H, s, C*H*CC(Me)$_3$), 7.26 (2H, AA′XX′, J=7.7 Hz); δ_C (150 MHz, $CDCl_3$) 21.6, 30.2, 34.2, 52.4, 75.8, 125.1, 126.0, 128.1, 128.1, 128.2, 128.3, 128.6, 128.9, 131.0, 131.8, 132.5, 135.5, 137.8, 142.5, 143.3, 152.6; *m/z* (EI, 70 eV) 540 (M^+, 4), 385 (6), 384 (8), 296 (24), 295 (100), 279 (6), 179 (4), 91 (9). HRMS (EI, 70 eV) M^+, found 540.2693. $C_{35}H_{40}O_3S$ requires 540.2698.

3.2.4. (1*S*,2*R*)/(1*R*,2*S*)-2,6-Di-*tert*-butyl-4-[1,2-diphenyl-2-(toluene-4-sulfonyl)ethyl]phenol (3ac′). Minor diasteroisomer, mp 189–190 °C (76 mg, 14%, acetone/heptane); [Found: C, 77.67; H, 7.43; S, 6.06. $C_{35}H_{40}O_3S$ requires C, 77.74; H, 7.46; S, 5.93%]; ν_{max} (KBr) 1083, 1147 (SO_2), 1287 (C–OH), 1598 (C=C arom), 2956 (C–H), 3555 (OH) cm^{-1}; λ_{max}=202 nm, log ε=4.8 (EtOH); δ_H (600 MHz, $CDCl_3$) 1.23 (18H, s, C(*Me*)$_3$), 2.27 (3H, s, C*Me*), 4.83 (1H, s, O*H*), 4.94 (1H, d, J=9.9 Hz, TsCH–CH), 5.03 (1H, d, J=9.9 Hz, TsC*H*), 6.82 (2H, s, C*H*CC(Me)$_3$), 7.02–7.41 (10H, m, 2×*Ph*), 6.97 (2H, AA′XX′, J=8.0 Hz), 7.26 (2H, AA′XX′, J=8.0 Hz); δ_C (150 MHz, $CDCl_3$) 21.5, 30.1, 34.1, 51.8, 75.8, 125.5, 126.5, 127.7, 127.8, 128.1, 128.4, 128.5, 128.9, 130.9, 131.8, 133.1, 135.2, 136.6, 142.5, 143.5, 151.8.

3.2.5. 2,6-Di-*tert*-butyl-4-[1-phenyl-2-phenylsulfanyl-2-(toluene-4-sulfonyl)ethyl]phenol (3ad). Diasteroisomer ratio 6:1, mp 146–149 °C (303 mg, 53%, MeOH/water); ν_{max} (KBr) 1083, 1146, 1124 (SO_2), 1237 (C–OH), 1596 (C=C arom), 3631 (OH) cm^{-1}; δ_H (600 MHz, $CDCl_3$) major diasteroisomer 1.35 (18H, s, C(*Me*)$_3$), 2.33 (3H, s, C*Me*), 4.71 (1H, d, J=4.3 Hz, TsCH–CH), 5.10 (1H, s, O*H*), 5.14 (1H, d, J=4.3 Hz, TsC*H*), 7.15 (2H, s, C*H*CC(Me)$_3$), 6.85–7.23 (14H, m, *Ph*, S*Ph* and SO_2-*p*-C_6H_4Me), minor diasteroisomer 1.38 (18H, s, C(*Me*)$_3$), 2.34 (3H, s, C*Me*), 4.73 (1H, d, J=4.9 Hz, TsCH–CH), 5.11 (1H, s, O*H*), 5.11 (1H, d, J=4.9 Hz, TsC*H*), 7.15 (2H, s, C*H*CC(Me)$_3$), 6.85–7.23 (14H, m, *Ph*, S*Ph* and SO_2-*p*-C_6H_4Me); δ_C (150 MHz, $CDCl_3$) major diasteroisomer 21.6, 30.3, 34.2, 51.1, 82.1, 126.7, 126.9, 128.2, 128.5, 128.7, 128.8, 128.8, 128.8, 130.1, 132.0, 132.7, 134.8, 135.4, 141.6, 143.9, 153.0, minor diasteroisomer 21.5, 30.2, 34.3, 50.4, 81.2, 125.5, 127.0, 127.9, 128.1, 128.5, 128.8, 129.0, 129.5, 129.8, 131.6, 134.6, 135.0, 135.9, 138.9, 144.1, 152.8; *m/z* (EI, 70 eV) 572 (M^+, 4), 416 (23), 308 (67), 295 (100), 293 (23), 279 (7), 178 (4), 91 (4). HRMS (EI, 70 eV) M^+, found 572.2418. $C_{35}H_{40}O_3S_2$ requires 572.2419.

3.2.6. 2,6-Di-*tert*-butyl-4-[2-chloro-1-(4-methoxyphenyl)-2-(toluene-4-sulfonyl)ethyl]phenol (3ba). Mp 152–154 °C (470 mg, 89%, acetone/heptane); ν_{max} (KBr) 1034 (O–Me), 1084, 1146 (SO_2), 1252 (C–OH), 1597, 1611 (C=C arom), 3606 (OH) cm^{-1}; δ_H (400 MHz, acetone-d_6) 1.35 (18H, s, C(*Me*)$_3$), 2.36 (3H, s, C*Me*), 3.74 (3H, s, O*Me*), 4.65 (1H, d, J=9.5 Hz, TsCH–CH), 5.88 (1H, s, O*H*), 6.26 (1H, d, J=9.5 Hz, TsC*H*), 6.80 (2H, AA′XX′, J=8.7 Hz), 7.14 (2H, s,

C*H*CC(Me)$_3$), 7.25 (2H, AA′XX′, J=8.0 Hz), 7.39 (2H, AA′XX′, J=8.7 Hz), 7.51 (2H, AA′XX′, J=8.0 Hz); δ_C (100 MHz, acetone-d_6) 21.6, 30.7, 35.1, 54.1, 55.4, 79.1, 114.4, 125.9, 129.9, 130.0, 130.4, 132.0, 135.0, 136.5, 137.9, 145.3, 153.8, 159.4; *m/z* (EI, 70 eV) 528 (M^+, 6), 374 (10), 372 (26), 357 (9), 326 (28), 325 (100), 309 (4), 91 (3). HRMS (EI, 70 eV) M^+, found 528.2105. $C_{30}H_{37}O_4SCl$ requires 528.2101.

3.2.7. 4-[2-Bromo-1-(4-methoxyphenyl)-2-(toluene-4-sulfonyl)ethyl]-2,6-di-*tert*-butylphenol (3bb). Major diasteroisomer, mp 124–125 °C (109 mg, 19%, acetone/heptane); ν_{max} (KBr) 1028 (O–Me), 1080, 1119, 1129 (SO_2), 1282 (C–OH), 1599, 1611 (C=C arom), 3598 (OH) cm^{-1}; λ_{max}=201 nm, log ε=4.9, λ_{max}=226 nm, log ε=4.5 (EtOH); δ_H (400 MHz, $CDCl_3$) 1.27 (18H, s, C(*Me*)$_3$), 2.32 (3H, s, C*Me*), 3.71 (3H, s, O*Me*), 4.05 (1H, d, J=3.4 Hz, TsCH–CH), 5.14 (1H, s, O*H*), 5.83 (1H, d, J=3.4 Hz, TsC*H*), 6.90 (2H, s, C*H*CC(Me)$_3$), 6.71 (2H, AA′XX′, J=9.7 Hz), 7.03 (2H, AA′XX′, J=9.7 Hz), 7.10 (2H, AA′XX′, J=8.2 Hz), 7.40 (2H, AA′XX′, J=8.2 Hz); δ_C (100 MHz, $CDCl_3$) 21.5, 30.1, 34.1, 55.2, 55.2, 71.2, 113.5, 119.6, 127.8, 128.1, 128.8, 129.1, 132.3, 135.3, 135.5, 144.2, 154.1, 159.2.

3.2.8. 4-[2-Bromo-1-(4-methoxyphenyl)-2-(toluene-4-sulfonyl)ethyl]-2,6-di-*tert*-butylphenol (3bb′). Minor diasteroisomer, (97 mg, 17%); δ_H (400 MHz, $CDCl_3$) 1.26 (18H, s, C(*Me*)$_3$), 2.32 (3H, s, C*Me*), 3.73 (3H, s, O*Me*), 4.91 (1H, d, J=6.3 Hz, TsCH–CH), 5.28 (1H, s, O*H*), 5.45 (1H, d, J=6.3 Hz, TsC*H*), 6.75 (2H, AA′XX′, J=8.8 Hz), 7.01–7.17 (4H, m, H-arom), 7.12 (2H, s, C*H*CC(Me)$_3$), 7.48 (2H, AA′XX′, J=8.4 Hz); δ_C (100 MHz, $CDCl_3$) 21.4, 30.2, 34.2, 55.3, 55.3, 71.8, 113.8, 126.2, 127.6, 128.8, 129.0, 129.1, 132.1, 135.9, 136.4, 143.5, 154.4, 160.8.

3.2.9. 2,6-Di-*tert*-butyl-4-[1-(4-methoxyphenyl)-2-phenyl-2-(toluene-4-sulfonyl)ethyl]phenol (3bc). Diasteroisomer ratio 6:1, mp 200–216 °C (513 mg, 90%, acetone/heptane); ν_{max} (KBr) 1034 (O–Me), 1084, 1143 (SO_2), 1258 (C–OH), 1597, 1612 (C=C arom), 2964 (C–H), 3560 and 3625 (OH) cm^{-1}; δ_H (400 MHz, $CDCl_3$) major diasteroisomer 1.22 (18H, s, C(*Me*)$_3$), 2.29 (3H, s, C*Me*), 3.74 (3H, s, O*Me*), 4.82 (1H, s, O*H*), 4.89 (1H, d, J=10.2 Hz, TsCH–C*H*), 4.96 (1H, d, J=10.2 Hz, TsC*H*), 6.72 (2H, AA′XX′, J=8.5 Hz), 6.80 (2H, s, C*H*CC(Me)$_3$), 6.96–7.04 (5H, m, *Ph*), 6.98 (2H, AA′XX′, J=8.1 Hz), 7.28 (2H, AA′XX′, J=8.1 Hz), 7.23–7.26 (2H, buried m, arom); δ_C (100 MHz, $CDCl_3$) 21.4, 30.1, 34.1, 51.2, 55.1, 76.0, 113.9, 125.1, 127.5, 127.8, 128.5, 128.8, 128.9, 129.1, 130.9, 132.2, 133.2, 135.2, 136.9, 143.4, 151.8, 158.3, minor diasteroisomer 1.32 (18H, s, C(*Me*)$_3$), 2.27 (3H, s, C*Me*), 3.64 (3H, s, O*Me*), 4.82 (1H, s, O*H*), 4.95 (1H, d, J=9.3 Hz, TsCH–C*H*), 5.05 (1H, d, J=9.3 Hz, TsC*H*), 6.59 (2H, AA′XX′, J=8.7 Hz), 6.97 (2H, AA′XX′, J=8.1 Hz), 7.01 (2H, s, C*H*CC(Me)$_3$), 7.00–7.29 (9H, buried m, arom); *m/z* (EI, 70 eV) 570 (M^+, 2), 505 (2), 414 (6), 325 (100), 309 (5), 200 (4), 91 (2). HRMS (EI, 70 eV) M^+, found 570.2820. $C_{36}H_{42}O_4S$ requires 570.2804.

3.2.10. 2,6-Di-*tert*-butyl-4-[1-(4-methoxyphenyl)-2-phenylsulfanyl-2-(toluene-4-sulfonyl)-ethyl]phenol (3bd). Diasteroisomer ratio 3:1, mp 174–175 °C (313 mg, 52%, MeOH); [Found: C, 71.94; H, 6.94; S, 10.68. $C_{36}H_{42}O_4S_2$ requires C, 71.73; H, 7.02; S, 10.64%]; ν_{max} (KBr) 1021 (O–Me), 1086, 1119, 1147 (SO_2), 1248 (C–OH), 1582, 1596, 1609 (C=C arom), 3626, 3634 (OH) cm^{-1}; λ_{max}= 202 nm, log ε=4.6 (EtOH); δ_H (400 MHz, $CDCl_3$) major diasteroisomer 1.32 (18H, s, C(*Me*)$_3$), 2.31 (3H, s, C*Me*), 3.78 (3H, s, O*Me*), 4.66 (1H, d, J=4.0 Hz, TsCH–C*H*), 5.09 (1H, s, O*H*), 5.11 (1H, d, J=4.0 Hz, TsC*H*), 6.77 (2H, AA′XX′, J=8.7 Hz), 6.80 (2H, AA′XX′, J=8.3 Hz), 6.98–7.10 (5H, m, S*Ph*), 7.12 (2H, s, C*H*CC(Me)$_3$), 7.34 (2H, AA′XX′, J=8.7 Hz), 7.50 (2H, AA′XX′, J=8.2 Hz); δ_C (100 MHz, $CDCl_3$) 21.5, 30.2, 34.4, 49.3, 55.2, 81.3, 113.5, 125.4, 127.8, 128.7, 129.0, 129.6, 130.9, 131.0, 131.8, 132.0, 134.8, 135.1, 135.9, 144.1, 152.8, 158.7, minor diasteroisomer 1.34 (18H, s, C(*Me*)$_3$), 2.30 (3H, s, C*Me*), 3.76 (3H, s, O*Me*), 4.68 (1H, d, J=5.3 Hz, TsCH–CH), 5.01 (1H, d, J=5.3 Hz, TsC*H*), 5.06 (1H, s, O*H*), 6.75–6.81 (4H, buried m, arom), 6.87–7.22 (7H, buried m, arom), 7.12 (2H, s, C*H*CC(Me)$_3$), 7.42 (2H, AA′XX′, J=8.3 Hz); *m/z* (EI, 70 eV) 602 (M^+, 1), 447 (17), 338 (57), 325 (100), 309 (19), 267 (12), 91 (8). HRMS (EI, 70 eV) M^+, found 602.2532. $C_{36}H_{42}O_4S_2$ requires 602.2525.

3.2.11. 2,6-Di-*tert*-butyl-4-[1-(4-dimethylaminophenyl)-2-phenyl-2-(toluene-4-sulfonyl)ethyl]phenol (3cc). Major diasteroisomer, mp 230–232 °C (175 mg, 30%, MeOH); ν_{max} (KBr) 1083, 1144 (SO_2), 1237 (C–OH), 1359 (N–(Me)$_2$), 1523 (C=C arom), 2952 (C–H), 3608 (OH) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.31 (18H, s, C(*Me*)$_3$), 2.27 (3H, s, C*Me*), 2.77 (6H, s, N(*Me*)$_2$), 4.92 (1H, s, O*H*), 4.95 (1H, d, J=9.4 Hz, TsCH–C*H*), 5.01 (1H, d, J=9.4 Hz, TsC*H*), 6.43 (2H, AA′XX′, J=8.7 Hz), 6.97 (2H, AA′XX′, J=8.5 Hz), 6.95–7.00 (2H, m, arom), 7.01 (2H, s, C*H*CC(Me)$_3$), 7.13–7.29 (7H, m, arom); δ_C (75 MHz, $CDCl_3$) 21.6, 30.2, 34.2, 40.4, 51.1, 76.2, 112.3, 125.0, 128.0, 128.1, 128.2, 128.9, 129.4, 130.1, 131.2, 132.6, 132.9, 135.3, 137.8, 143.1, 148.7, 152.3; *m/z* (EI, 70 eV) 583 (M^+, 1), 427 (8), 339 (26), 338 (100), 322 (6), 91 (6). HRMS (EI, 70 eV) M^+, found 583.3081. $C_{37}H_{45}NO_3S$ requires 583.3120.

3.2.12. 2,6-Di-*tert*-butyl-4-[1-(4-dimethylaminophenyl)-2-phenyl-2-(toluene-4-sulfonyl)ethyl]phenol (3cc′). Minor diasteroisomer, mp 239–240 °C (93 mg, 16%, AcOEt); ν_{max} (KBr) 1083, 1144 (SO_2), 1237 (C–OH), 1359 (N–(Me)$_2$), 1523 (C=C arom), 2952 (C–H), 3608 (OH) cm^{-1}; δ_H (300 MHz, $CDCl_3$) 1.23 (18H, s, C(*Me*)$_3$), 2.28 (3H, s, C*Me*), 2.87 (6H, s, N(*Me*)$_2$), 4.79 (1H, s, O*H*), 4.87–4.94 (2H, m, TsCH–C*H* and TsC*H*), 6.53 (2H, AA′XX′, J=8.7 Hz), 6.81 (2H, s, C*H*CC(Me)$_3$), 6.96 (2H, AA′XX′, J=8.1 Hz), 7.18 (2H, AA′XX′, J=8.7 Hz), 7.28 (2H, AA′XX′, J=8.1 Hz), 7.04 (5H, m, *Ph*); δ_C (75 MHz, $CDCl_3$) 21.4, 30.1, 34.1, 40.6, 51.2, 76.3, 112.7, 125.3, 127.7, 127.7, 128.4, 128.8, 128.9, 128.9, 130.9, 132.6, 133.3, 135.0, 137.2, 143.0, 149.3, 151.6; *m/z* (EI, 70 eV) 583 (M^+, 1), 427 (4), 339 (26), 338 (100), 322 (5), 91 (6). HRMS (EI, 70 eV) M^+, found 583.3133. $C_{37}H_{45}NO_3S$ requires 583.3120.

3.2.13. 2,6-Di-*tert*-butyl-4-[1-(4-dimethylaminophenyl)-2-phenylsulfanyl-2-(toluene-4-sulfonyl)ethyl]phenol (3cd). Diasteroisomer ratio 2:1, mp 174–175 °C (86 mg, 14%, MeOH); ν_{max} (KBr) 1082, 1121, 1145 (SO_2), 1289

(C–OH), 1316, 1358 (N–(Me)$_2$), 1613 (C═C arom), 3631 (OH) cm^{-1}; δ_H (200 MHz, acetone-d_6) major diastereoisomer 1.32 (18H, s, C(*Me*)$_3$), 2.36 (3H, s, C*Me*), 2.86 (6H, s, N–(Me)$_2$), 5.84 (1H, s, O*H*), 4.75–4.99 (1H, m, TsCH–C*H*), 6.48–6.64 (1H, m, TsC*H*), 6.47–6.64 (8H, m, arom), 6.98–7.80 (5H, m, S*Ph*), 7.09 (2H, s, C*H*CC(Me)$_3$), minor diasteroisomer 1.28 (18H, s, C(*Me*)$_3$), 2.28 (3H, s, C*Me*), 2.82 (6H, s, N–(Me)$_2$), 5.84 (1H, s, O*H*), 4.75–4.99 (1H, m, TsCH–C*H*), 6.48–6.64 (1H, m, TsC*H*), 6.98–7.80 (8H, m, arom), 6.98–7.80 (5H, m, S*Ph*), 7.07 (2H, s, C*H*CC(Me)$_3$).

3.2.14. Dimethyl-{4-[2-phenylsulfanyl-2-(toluene-4-sulfonyl)vinyl]phenyl}amine (7cd). Mp 207–209 °C (29 mg, 7%, acetone/heptane); ν_{max} (KBr) 1085, 1141 (SO$_2$), 1606 (C═C arom), 1375 (N–(Me)$_2$) cm^{-1}; δ_H (500 MHz, acetone-d_6) 2.35 (3H, s, C*Me*), 3.04 (6H, s, N(*Me*)$_2$), 6.57 (2H, AA′XX′, J=9.2 Hz), 7.03–7.15 (5H, m, *Ph*), 7.28 (2H, AA′XX′, J=8.0 Hz), 7.78 (2H, AA′XX′, J=8.0 Hz), 7.90 (2H, AA′XX′, J=9.2 Hz), 8.44 (1H, s, vinyl C*H*); δ_C (125 MHz, acetone-d_6) 21.4, 39.9, 112.2, 120.3, 124.6, 126.6, 127.1, 129.5, 129.7, 130.2, 134.5, 135.4, 138.1, 144.6, 149.1, 153.8; *m/z* (EI, 70 eV) 409 (M$^+$, 70), 254 (100), 239 (40), 210 (22), 144 (25), 91 (12). HRMS (EI, 70 eV) M$^+$, found 409.1167. $C_{23}H_{23}NO_2S_2$ requires 409.1170.

3.3. General reaction procedure

Reactions of **1** *and* **2** *in the excess of base*. To a stirred solution of *t*-BuOK (0.675 g, 6 mmol) in DMF at −20 °C and under argon atmosphere was added dropwise, via cannula, a solution of CH-acid **2** (2 mmol) and quinone methide **1** (2 mmol) in DMF (5 mL). After 20 min, the mixture was allowed to warm up to room temperature and poured into cooled 3% aqueous HCl (100 mL). The yellow precipitate was filtered off, washed with water and dried in the air. The crude products were purified by column chromatography on silica gel with hexane–ethyl acetate as eluent and recrystallized.

3.3.1. 2,6-Di-*tert*-butyl-4-[(*E*)-2-phenyl-1-(toluene-4-sulfonyl)vinyl]phenol (4a). Mp 132–135 °C (EtOH); ν_{max} (KBr) 1087, 1152 (SO$_2$), 1291 (C–OH), 1598 (C═C arom), 3613 (OH) cm^{-1}; δ_H (500 MHz, CDCl$_3$) 1.28 (18H, s, C(*Me*)$_3$), 2.38 (3H, s, C*Me*), 5.32 (1H, s, O*H*), 7.11 (2H, AA′XX′, J=7.3 Hz), 7.14–7.25 (5H, m, *Ph*), 7.71 (2H, s, C*H*CC(Me)$_3$), 7.49 (2H, AA′XX′, J=7.3 Hz), 7.87 (1H, s, TsCC*H*); δ_C (125 MHz, CDCl$_3$) 21.4, 30.1, 35.2, 121.8, 127.4, 128.3, 128.8, 129.1, 129.7, 130.4, 133.3, 136.0, 136.1, 136.4, 142.6, 143.7, 154.5; *m/z* (EI, 70 eV) 462 (M$^+$, 8), 307 (100), 306 (49), 291 (40), 249 (5), 215 (4), 91 (4). HRMS (EI, 70 eV) M$^+$, found 462.2223. $C_{29}H_{34}O_3S$ requires 462.2229.

3.3.2. 2,6-Di-*tert*-butyl-4-[(*Z*)-1-phenyl-2-(toluene-4-sulfonyl)vinyl]phenol (5a). Mp 172–174 °C (111 mg, 12%, EtOH); [Found: C, 75.25; H, 7.47; S, 7.04. $C_{29}H_{34}O_3S$ requires C, 75.29; H, 7.41; S, 6.93%]; ν_{max} (KBr) 1080, 1142, 1312 (SO$_2$), 1297 (C–OH), 1597 (C═C arom), 3589 (OH) cm^{-1}; δ_H (500 MHz, CDCl$_3$) 1.37 (18H, s, C(*Me*)$_3$), 2.32 (3H, s, C*Me*), 6.27 (1H, s, O*H*), 6.88 (2H, s, C*H*CC(Me)$_3$), 7.05 (1H, s, TsC*H*), 7.13 (2H, AA′XX′, J=8.8 Hz), 7.30–7.40 (5H, m, *Ph*), 7.39 (2H, AA′XX′, J=8.8 Hz); δ_C (125 MHz, CDCl$_3$) 21.5, 30.4, 34.9, 127.7, 128.1, 128.3, 129.3, 129.3, 129.7, 130.0, 130.9, 137.1, 140.0, 140.9, 143.8, 143.8, 156.8; *m/z* (EI, 70 eV) 462 (M$^+$, 100), 391 (95), 307 (9), 235 (20), 139 (15), 91 (30). HRMS (EI, 70 eV) M$^+$, found 462.2217. $C_{29}H_{34}O_3S$ requires 462.2229.

3.3.3. 2,6-Di-*tert*-butyl-4-[(*E*)-2-(4-methoxyphenyl)-1-(toluene-4-sulfonyl)vinyl]phenol (4b). Mp 145–146 °C (hexane/ethyl acetate); [Found: C, 73.20; H, 7.47; S, 6.69. $C_{30}H_{36}O_4S$ requires C, 73.14; H, 7.37; S, 6.51%]; ν_{max} (KBr) 1033 (O–Me), 1087, 1150, 1290 (C–OH), 1304 (SO$_2$), 1605 (C═C arom), 3575 (OH) cm^{-1}; λ_{max}= 213 nm, log ε=4.7, λ_{max}=296 nm, log ε=4.6, (EtOH); δ_H (300 MHz, acetone-d_6) 1.29 (18H, s, C(*Me*)$_3$), 2.37 (3H, s, C*Me*), 3.75 (3H, s, O*Me*), 6.24 (1H, s, O*H*), 6.73 (2H, s, C*H*CC(Me)$_3$), 6.75 (2H, AA′XX′, J=8.9 Hz), 7.13 (2H, AA′XX′, J=8.9 Hz), 7.28 (2H, AA′XX′, J=8.3 Hz), 7.47 (2H, AA′XX′, J=8.3 Hz), 7.80 (1H, s, TsCC*H*); δ_C (75 MHz, acetone-d_6) 20.8, 29.9, 34.5, 55.1, 114.1, 123.0, 126.1, 127.7, 128.9, 129.5, 132.4, 135.8, 137.2, 138.2, 140.7, 144.0, 154.9, 161.4; *m/z* (EI, 70 eV) 492 (M$^+$, 8), 338 (24), 337 (100), 336 (82), 265 (3), 231 (31), 202 (4), 139 (3), 91 (6). HRMS (EI, 70 eV) M$^+$, found 492.2335. $C_{30}H_{36}O_4S$ requires 492.2334.

3.3.4. 2,6-Di-*tert*-butyl-4-[(*E*)-2-(4-dimethylaminophenyl)-1-(toluene-4-sulfonyl)vinyl]phenol (4c). Mp 163–165 °C (MeOH); [Found: C, 73.58; H, 8.07; N, 2.81; S, 6.35. $C_{31}H_{39}NO_3S$ requires C, 73.63; H, 7.77; N, 2.77; S, 6.34%]; ν_{max} (KBr) 1082, 1138, 1299 (SO$_2$), 1289 (C–OH), 1379 (NMe$_2$), 1601 (C═C arom), 3553 (OH) cm^{-1}; λ_{max}= 213 nm, log ε=4.7, λ_{max}=239 nm, log ε=4.7, λ_{max}= 361 nm, log ε=4.8 (EtOH); δ_H (300 MHz, acetone-d_6) 1.29 (18H, s, C(*Me*)$_3$), 2.37 (3H, s, C*Me*), 2.93 (6H, s, N*Me*$_2$), 6.25 (1H, s, O*H*), 6.51 (2H, AA′XX′, J=10.0 Hz), 6.71 (2H, s, C*H*CC(Me)$_3$), 7.02 (2H, AA′XX′, J=10.0 Hz), 7.28 (2H, AA′XX′, J=8.0 Hz), 7.45 (2H, AA′XX′, J=8.0 Hz), 7.72 (1H, s, TsCC*H*); δ_C (75 MHz, acetone-d_6) 20.9, 30.0, 34.5, 39.5, 111.7, 121.0, 123.7, 128.0, 128.8, 129.5, 132.3, 136.8, 137.3, 137.9, 138.1, 143.7, 151.9, 154.8.

3.3.5. 2,6-Di-*tert*-butyl-4-[(*E*)-2-(4-nitrophenyl)-2-(toluene-4-sulfonyl)vinyl]phenol (6d). Mp 204–207 °C (315 mg, 31%, MeOH); [Found: C, 68.49; H, 6.48; N, 2.65. $C_{29}H_{33}NO_5S$ requires C, 68.61; H, 6.55; N, 2.76%]; ν_{max} (KBr) 1087, 1146, 1302 (C–OH), 1313 (SO$_2$), 1344, 1528 (NO$_2$), 1599 (C═C arom), 3617 (OH) cm^{-1}; λ_{max}= 210 nm, log ε=4.6, λ_{max}=235 nm, log ε=4.5, λ_{max}= 310 nm, log ε=4.5 (EtOH); δ_H (300 MHz, acetone-d_6) 1.22 (18H, s, C(*Me*)$_3$), 2.38 (3H, s, C*Me*), 6.36 (2H, AA′XX′, J= 8.8 Hz), 6.50 (1H, s, O*H*), 7.03 (2H, s, C*H*CC(Me)$_3$), 7.32 (2H, AA′XX′, J=7.5 Hz), 7.55 (2H, AA′XX′, J=7.5 Hz), 7.97 (1H, s, TsCC*H*), 8.24 (2H, AA′XX′, J=8.8 Hz); δ_C (75 MHz, acetone-d_6) 21.0, 29.6, 34.5, 123.9, 124.2, 128.6, 128.8, 130.0, 133.0, 136.5, 136.9, 137.6, 140.0, 140.5, 144.7, 148.5, 156.9; *m/z* (EI, 70 eV) 507 (M$^+$, 96), 492 (54), 436 (11), 353 (60), 351 (88), 323 (100), 280 (17), 215 (6), 202 (6), 91 (12). HRMS (EI, 70 eV) M$^+$, found 507.2093. $C_{29}H_{33}NO_5S$ requires 507.2079.

3.3.6. 2,6-Di-*tert*-butyl-4-[(*E*)-2-[4-nitro-3-(toluene-4-sulfonylmethyl)phenyl]-2-(toluene-4-sulfonyl)vinyl]-phenol (7d). Mp 229–230 °C (446 mg, 33%, MeOH/petroleum ether); [Found: C, 66.01; H, 6.12; N, 2.11. $C_{37}H_{41}NO_7S_2$ requires C, 65.75; H, 6.11; N, 2.07%]; ν_{max} (KBr) 1087, 1154, 1303 (SO_2), 1291 (C–OH), 1349, 1528 (NO_2), 1596 (C=C arom), 3610 (OH) cm^{-1}; λ_{max}= 205 nm, log ε=5.8, λ_{max}=229 nm, log ε=4.7, λ_{max}= 312 nm, log ε=4.5 (EtOH); δ_H (300 MHz, acetone-d_6) 1.25 (18H, s, C(*Me*)$_3$), 2.40 (6H, s, C*Me*), 5.00 (2H, s, CH_2), 6.62 (1H, s, O*H*), 7.05 (2H, s, C*H*CC(Me)$_3$), 7.13 (1H, d, J= 1.9 Hz), 7.25 (1H, dd, J=8.14 Hz, J=1.9 Hz), 7.26 (2H, AA′XX′, J=8.3 Hz), 7.36 (2H, AA′XX′, J=8.2 Hz), 7.54 (2H, AA′XX′, J=8.3 Hz), 7.56 (2H, AA′XX′, J=8.3 Hz), 7.91 (1H, s, TsCC*H*), 8.04 (1H, d, J=8.4 Hz); δ_C (75 MHz, acetone-d_6) 21.0, 21.1, 29.7, 34.6, 57.9, 123.9, 124.7, 126.2, 128.6, 128.7, 129.0, 130.1, 130.2, 133.3, 135.8, 136.4, 136.9, 137.0, 137.8, 138.7, 140.2, 144.8, 145.5, 150.2, 157.1; *m/z* (EI, 70 eV) 675 (M^+, 42), 604 (17), 521 (32), 365 (28), 351 (94), 350 (100), 339 (36), 336 (53), 294 (11), 91 (94). HRMS (EI, 70 eV) M^+, found 675.2229. $C_{37}H_{41}NO_7S_2$ requires 675.2324.

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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.2005.12.040. Crystal data and structure refinement.

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Studies on quinones. Part 40: Synthesis and cytotoxicity evaluation of anthraquinone epoxides and isomerization products☆

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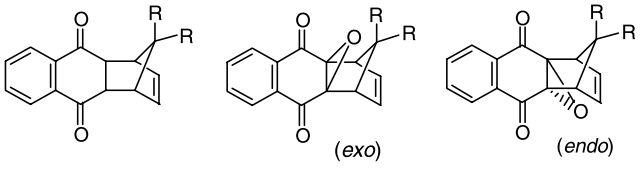
Abstract—Aerobic oxidation of 1,4,4a,10a-tetrahydro-1,4-alkano-5,10-anthraquinones and thiophene-analogues in dichloromethane–DBU yielded the corresponding dihydroalkanoquinones which, depending on their structures, react with in situ generated hydroperoxide anion to give quinone epoxides and/or hydroperoxides. The calcium hydroxide-induced rearrangement of quinone epoxides yielded furan-containing angular quinones. The cytotoxic activities of quinone epoxides and their isomerization products were evaluated in vitro against normal human lung fibroblasts (MRC-5) and human cancer gastric epithelial cells (AGS).

1. Introduction

Epoxidation of quinone double bonds is of great interest because of the synthetic utility of the resulting epoxides for further functionalization of the quinones. Aqueous hydrogen peroxide is the usual common epoxidation reagent because it is both inexpensive and safe, yielding water as the byproduct. Nevertheless, this epoxidation procedure is not applicable to base-sensitive quinones due to the strongly alkaline conditions required (NaOH; KOH; K_2CO_3).[2–5]

We have recently reported a quinone epoxidation procedure under non-aqueous conditions using the urea–hydrogen peroxide complex (UHP) in basic media (DBU; K_2CO_3), which is potentially useful for the epoxidation of base-sensitive quinones.[6]

In 1972 Giles[4a] reported that treatment of 1,4-naphthoquinone-spirocyclopentadiene adduct **1** with aqueous methanolic sodium hydroxide in the presence of air yielded a mixture of isomeric quinone epoxides **3**+**5** together with a minor quantity of angular quinone **7**. Their findings show that compound **7** arises from epoxides through a photo-induced rearrangement. Later, Marchand[7] described the formation of quinone epoxides **4**+**6**, together with small amounts of quinone **8**, by aerobic oxidation of adduct **2** under conditions similar to those reported by Giles.[4b]



1. R = $(CH_2)_2$
2. R = H
3. R = $(CH_2)_2$
4. R = H
5. R = $(CH_2)_2$
6. R = H

7 **8**

Taking into account the aerobic oxidation of phenols in aqueous sodium hydroxide reported by Hewgill,[8] the probable oxidation mechanism of adducts **1** and **2** involves semiquinone radical and hydroperoxide anion species

☆ For Part 39, see Ref. 1.

Keywords: Diels–Alder adducts; Aerobic epoxidation; Rearrangement; Angular quinones; Cytotoxicity.
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generated by redox reactions of oxygen with phenolate anion intermediates.

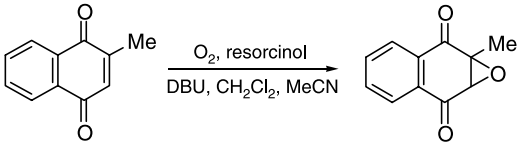
As part of our continuous interest in the synthesis and biological evaluation of quinones,[9] we decided to study the oxidation of Diels–Alder adducts such as **2** aimed at the following objectives: (i) to explore a quinone epoxidation procedure by aerobic oxidation under non-aqueous basic conditions, potentially useful for base-sensitive quinone epoxides, and (ii) to use the resulting quinone epoxides in the synthesis of tetracyclic angular quinones such as **7**, for cytotoxicity evaluation. The synthesis of new angular quinones is of current interest due to the fact that a wide variety of compounds containing an angular tetracyclic skeleton arrangement have antitumoral activities.[10]

In this work, we report the results of our studies on aerobic oxidation of Diels–Alder adducts of naphthoquinones and benzothiophenequinones with cyclopentadiene and cyclohexadiene, and their base-induced isomerization to angular quinones. We also report on the in vitro evaluation of the products against normal fibroblasts (MRC-5) and gastric cancer cells (AGS).

2. Results and discussion

In agreement with reports on the generation of superoxide anions and perhydroxyl radicals by electron-transfer reduction of molecular oxygen with phenolate anion[11,12] and semiquinone radicals,[13,14] we examined the eventual formation of hydroperoxide anions by aerobic oxidation of phenolates in organic solvents. Menadione **9** was used for trapping the hydroperoxide anion formed in situ, which was generated via reduction of oxygen in these basic media.

The trials were run in an open flask containing a vigorously stirred solution of menadione **9**, with 1 equiv of the corresponding phenol and 1 equiv of DBU in organic solution (CH_2Cl_2, MeCN, MeOH). The assays were conducted at rt and the following phenols were tested: phenol, hydroquinone, resorcinol and 4-*tert*-butyl-2 methoxyphenol. In these experiments, resorcinol exhibited the best capability to give menadione epoxide **10** in CH_2Cl_2 and MeCN. Thus, the aerobic treatment of menadione with 1 equiv of resorcinol and 1 equiv of DBU in dichloromethane or acetonitrile for 30 and 80 min, respectively, produced menadione epoxide **10** in 35 and 22% isolated yields. These experiments demonstrate the epoxidation capability of organic aerobic solutions containing phenolate anions.

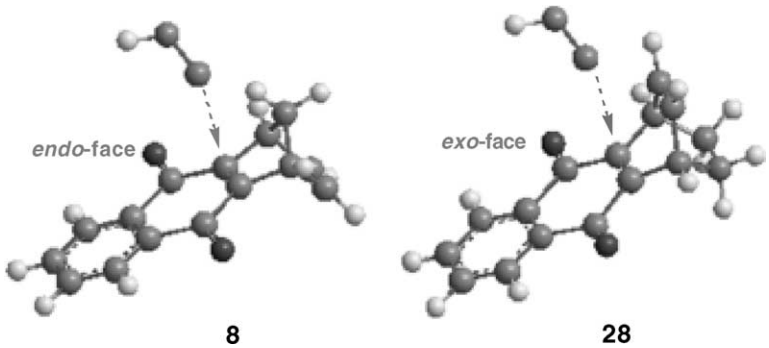


9 **10**

On the basis of these results, we attempted to extend this aerobic procedure to the synthesis of quinone epoxides from Diels–Alder adducts **2**, **14**–**18**. These compounds were prepared by reaction of either cyclopentadiene or cyclohexa-1,3-diene with dienophiles **11**–**13** using standard procedures. It is appropriate to point out that base-induced enolization of Diels–Alder adducts with DBU in organic media would provide the phenolate anions required for the molecular oxygen reduction.

Aerobic oxidation of Diels–Alder adducts **2**, **14**–**18** were conducted under standard conditions using 2 equiv of DBU in dichloromethane. We first examined the behavior of Diels–Alder adducts **2** and **15**, derived from cyclopentadiene. Oxidation of adduct **2** for 4 h yielded a 4.6:1 mixture of *exo*- and *endo*-epoxides **4**+**6** in 68% yield, together with small amounts of hydroperoxide **25**. The *exo*/*endo* ratio was determined by ^{1}H NMR using the vinylic proton signals of the isomers at δ 6.53 and 6.10 ppm, respectively. Quinone epoxides **4** and **6** were identified by comparing their ^{1}H and ^{13}C NMR spectra with those reported by Giles[4b] and Marchand.[7] The behavior of adduct **2** to aerobic oxidation in dichloromethane–DBU is similar to the oxidation of **2** with aqueous hydrogen peroxide in ethanol–Na_2CO_3 reported by Paquette,[5] which yielded a 3:1 mixture of *exo*- and *endo*-quinone epoxides **4**+**6** along with trace amounts of hydroperoxide **25**. Oxidation of adduct **15** gave a 20:1 mixture of *exo*- and *endo*-epoxides **21**+**22** in 62% yield, together with trace amounts of hydroperoxides **26**+**27** (detected by ^{1}H NMR). The *exo*/*endo* ratio was determined by ^{1}H NMR using the vinylic proton signals of the isomers at δ 6.52 and 6.15 ppm, respectively.

The formation of *exo*-epoxides as the main isomer in the air oxidations of adducts **2** and **15** implies that the *endo* face of the quinone intermediates are more sterically crowded



8 **28**

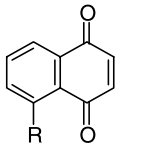
Figure 1. Molecular models showing the nucleophilic attack of the hydroperoxide anion on the quinone double bond through the less hindered face of quinone **8** and **28**.

towards the approach of the hydroperoxide anion. Figure 1 shows the favorable attack of the hydroperoxide anion on the quinone double bond through the less hindered *exo* face of quinone intermediate **8**.

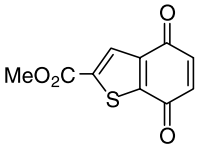
Aerobic oxidation of Diels–Alder adducts **14** and **16** derived from cyclohexadiene was examined. The reaction of compound **14** gave a mixture of quinone **28** and *endo*-epoxide **20** in approximately equal amounts (^{1}H NMR), together with trace amounts of *exo*-epoxide **19**. The structure of compounds **19**, **20** and **28** were established by comparing their spectral data with those reported in literature.[5] Due to our interest in the synthesis of angular quinones by isomerization of quinone epoxides, the reaction mixture arising from the aerobic oxidation of **14** was treated with urea hydrogen peroxide (UHP) to give *endo*-epoxide **20** in 84% isolated yield.

couplings for the proton at C-3 (δ 7.90) with carbon atoms at C-4 (δ 188.2) and C-4a (δ 82.2), respectively. Further reaction of **30** with 2 equiv of DBU in dichloromethane did not result in the formation of quinone epoxides.

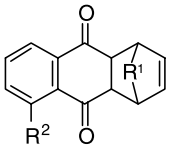
A different reactivity was seen for the aerobic oxidation of **18** with respect to **17**. In fact, the reaction of adduct **18** gave a 1:11 mixture of the *exo*/*endo* quinone epoxides **31**+**32**. The *exo*/*endo* ratio was determined by ^{1}H NMR analysis using the vinylic proton signals of the isomers at δ 6.44 and 6.06 ppm, respectively.



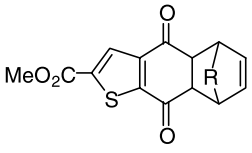
11. R= H
12. R= OH



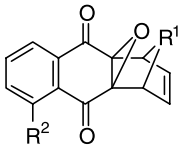
13



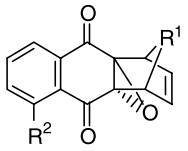
14. $R^1 = (CH_2)_2$, R^2 = H
15. $R^1 = CH_2$, R^2 = OH
16. $R^1 = (CH_2)_2$, R^2 = OH



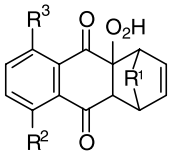
17. R = CH_2
18. R = $(CH_2)_2$

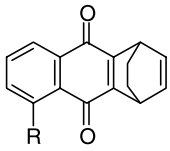


(*exo*)



(*endo*)





19. $R^1 = (CH_2)_2$, R_2 = H
21. $R^1 = CH_2$, R_2 = OH
23. $R^1 = (CH_2)_2$, R_2 = OH

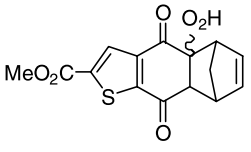
20. $R^1 = (CH_2)_2$, R^2 = H
22. $R^1 = CH_2$, R^2 = OH
24. $R^1 = (CH_2)_2$, R^2 = OH

25. $R_1 = CH_2$, $R^2 = R^3$ = H
26. $R_1 = CH_2$, R^2 = H, R^3 = OH
27. $R_1 = CH_2$, R^2 = OH, R^3 =H

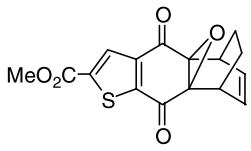
28. R = H
29. R = OH

A similar result was seen in the aerobic oxidation of adduct **16**, which yielded a mixture of quinone **29** and *endo*-epoxide **24** in nearly equal amounts, together with trace quantities of *exo*-epoxide **23**. Further treatment of the reaction mixture resulting from the aerobic oxidation of **16** with UHP yielded *endo*-epoxide **24** in 72% isolated yield. It should be noted that aerobic oxidation of **16** in refluxing dichloromethane gave quinone **29** in 87% yield and no *endo*-epoxide **24** was detected. Apparently, under these conditions, formation of **29** by aerobic oxidation of **16** is much faster than its subsequent epoxidation reaction to give **24**.

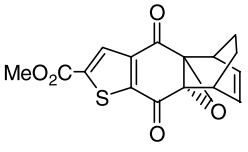
The aerobic oxidation of Diels–Alder adduct **17** showed a different reactivity with respect to adducts **2** and **15**. Thus, treatment of adduct **17** gave a complex mixture of highly polar products. The ^{1}H NMR of the crude product displays signals for the main product in agreement with hydroperoxide **30** (unstable orange oil). Assignment of the regiochemistry of **30** was established by 2D NMR experiments (HMBC, 400 MHz) that displayed $^3J_{C,H}$ and $^4J_{C,H}$



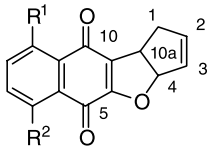
30



31 (*exo*)



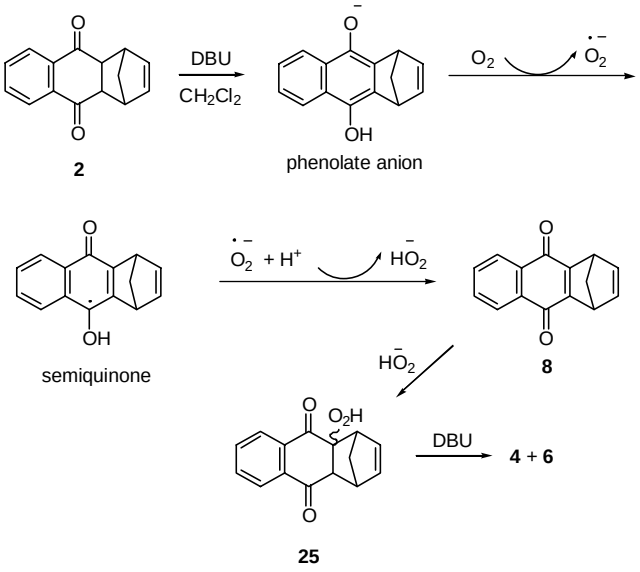
32 (*endo*)



33. R^1= R^2= H
34. R^1=H, R^2 = OH
35. R^1=OH,R^2 = H

According to our results on the aerobic oxidation of Diels–Alder adducts **2**, **14**–**18** in dichloromethane–DBU, the probable mechanism for the formation of quinone epoxides is initiated by a sequence of two electron transfer processes mediated by phenoxide anion and semiquinone radical

intermediates. The hydroperoxide anion generated by these redox reactions undergoes conjugate addition to give a hydroperoxide intermediate that, by further cyclisation, yielded quinone epoxides (Scheme 1). The formation of *endo*-epoxides as the main isomers in the aerobic oxidations of adducts **14**, **16** and **18** indicates that the *endo*-face of the quinone intermediates is less sterically crowded towards the approach of the hydroperoxide anion (Fig. 1).



Scheme 1. Probable mechanism of the aerobic oxidation of Diels–Alder adduct **2** in DBU–dichloromethane.

During the isolation of compounds **4**+**6** by column chromatography, angular quinone **33** was detected. This compound was also detected when the **4**+**6** mixture was analyzed by thin-layer chromatography. These evidences suggest that quinone epoxides **4**+**6** undergo rearrangements to quinone **33** via photochemical[4] or ionic pathways.

In order to verify the first assumption, solutions of epoxides **4**+**6** in $CDCl_3$ contained in NMR tubes were exposed to sunlight. The ^1H NMR analyses of the samples showed that no reaction had occurred after 1 week of irradiation. Interestingly, when epoxides **4**+**6** were stirred with silica gel/gypsum in dichloromethane at rt, they underwent smooth rearrangement to produce, after 7 days, quinone **33** in 45% isolated yield, thus confirming an ionic process involved in the rearrangement of quinone epoxides **4** and **6**. Conversion of epoxides **4**+**6** to quinone **33** was improved (68% yield) by treatment of **4**+**6** with calcium hydroxide in CH_2Cl_2 for 3 days at rt.

Quinone epoxide **21** was subjected to rearrangement with calcium hydroxide, yielding angular quinones **34** and **35** in 9 and 19% isolated yields, respectively. The structure of the major regioisomer **35** was established by HMBC experiments, which showed $^3J_{C,H}$ between the carbon atom of the hydrogen-bonded carbonyl group at C-10 (δ 188.4 ppm) with the proton at C-10b (δ 4.17 ppm).

We tried to induce the rearrangement of quinone epoxides **20** and **32** by microwave irradiation of the epoxides loaded on calcium hydroxide and on silica gel/gypsum. However, no rearrangement products were detected.

The stable epoxides **20**, **24**, **32** and quinones **29**, **33**, **34** and **35** were evaluated in vitro on normal fibroblast and gastric cancer cell lines. The results are reported in Table 1 as IC_{50} (concentration of compound expressed in μg/mL required to inhibit cell growth by 50% after 24 h of drug exposure). Vinblastine and camptothecin were used as reference drugs.

Table 1. Cytotoxic activity of quinones and quinone epoxides* against MRC-5 fibroblasts and AGS gastric cells

Entry	Compound[b]	IC_{50} (μM)[a]	
		Human normal lung fibroblasts (MRC-5)	Human gastric cancer epithelial cells (AGS)
1	**20**	>100	>100
2	**24**	>100	>100
3	**29**	41.6±1.4	15.0±2.3
4	**32**	>100	>100
5	**33**	53.5±2.2	29.3±1.6
6	**34**	6.3±0.2	4.1±0.3
7	**35**	13.3±0.3	4.9±0.2
9	Camptothecin	>100	>100
10	Vinblastine	76.6±2.7	>100

[a] Values are means±standard error of the mean.
[b] All compounds were quite stable in DMSO solution.

The screening indicates that quinone epoxides **20**, **24**, and **32** (entries 1, 2 and 4) do not display cytotoxic effects on these cell lines. Quinones **29**, **33**, **34** and **35** showed cytotoxic effects at micromolar concentrations, low selectivity (i.e., ratio between cytotoxic effect on normal fibroblast and on gastric cancer cells) and were more cytotoxic than the reference drugs.

Comparison of the activities of angular quinones **33**, **34** and **35** (entries 6 and 7) indicates that the presence of a hydroxyl group on the aromatic ring induces a significant increase in cytotoxicity. It seems possible that the influence of the hydroxyl groups on the biological activity is due to hydrophobic interactions with biological targets and/or to the increase of the redox potential of the quinone system.

The cytotoxic activities of compounds **29**, **33**, **34** and **35** are probably due to the generation of reactive oxygen species after redox cycling and/or alkylation of cellular nucleophiles.[15] In the case of angular quinones **33**, **33** and **34**, intercalation in DNA or binding to a DNA–enzyme complex could also be important aspects involved in the bioactivity.[10,16]

In summary, we have reported the aerobic oxidation of 1,4,4a,9a-tetrahydro-1,4-alkano-9,10-anthra-quinones in dichloromethane–DBU solution, which yields the corresponding 1,4-alkanoanthraquinones, which by further epoxidation with in situ generated hydroperoxide anion or with UHP yielded the corresponding quinone epoxides. This approach to the synthesis 1,4,4a,10a-tetrahydro-1,4-alkano-5,10-anthraquinone epoxides from Diels–Alder adducts offers an alternative to previously reported preparation procedures for this class of quinone epoxides. The salient

aspects of this new procedure are simple workup, in situ generation of the epoxidation reagent (i.e., **4**, **6**, **21**, **22**) and compatibility with base-sensitive functional groups (OH, CO_2CH_3).[3,6]

Furthermore, we have shown that quinone epoxides with the methano bridge undergo isomerization with calcium hydroxide to the corresponding angular quinones, but quinone epoxides containing the ethano bridge are inert to this rearrangement. Anthraquinone **29** and the furan-containing angular quinones **33**, **34** and **35** showed cytotoxic activities, in the 4–54 μM concentration range, against normal fibroblasts and gastric cancer AGS cells. Since compounds **29**, **33** and **35** showed selective activity, being more cytotoxic towards AGS cells than to fibroblasts they might be good prototypes for the development of new anticancer drugs.

3. Experimental

All reagents were of commercial quality reagent grade and were used without further purification. Melting points were determined on a Köfler hot-stage apparatus and are uncorrected. IR spectra were recorded on an FT Bruker spectrophotometer using KBr discs, and wave numbers are given in cm^{-1}. ^1H NMR spectra were measured on Bruker AM-200 and AM-400 equipment in $CDCl_3$. Chemical shifts are expressed in ppm downfield relative to TMS (δ scale) and coupling constants (J) are reported in Hz. ^{13}C NMR spectra were obtained in deuteriochloroform at 50 and 100 MHz. 2D NMR techniques (COSY, HMBC) and DEPT were used for signal assignment. Chemical shifts are reported in δ ppm downfield from tetramethylsilane (TMS), and J values are given in Hz. Silica gel 60 (70–230 mesh), and TLC aluminiun foil 60 F254 (Merck) were used for preparative column and analytical TLC, respectively. Heterocyclic quinone **13** was prepared from commercially available 2,5-dimethoxybenzaldehyde as reported previously.[17]

3.1. Aerobic epoxidation of menadione 9 in basic organic media. Typical procedure

A solution of quinone **9** (200 mg, 1.16 mmol), resorcinol (128 mg, 1.16 mmol) DBU (176 mg, 1.16 mmol) in dichloromethane (15 mL) was vigorously stirred at rt in an open flask for 30 min. The mixture was evaporated under reduced pressure and the dark residue chromatographed on silica gel (CH_2Cl_2) to give 2,3-epoxy-2-methyl-2,3-dihydro-1,4-naphthoquinone **10** (76 mg, 35%). The spectral properties were in full agreement with those reported in the literature.[6]

3.1.1. *endo*-1,4,4a,9a-Tetrahydro-1,4-methano-9,10-anthraquinone 2. A solution of quinone **11** (180 mg, 1.14 mmol), cyclopentadiene (100 mg, 1.52 mmol) in CH_2Cl_2 (15 mL) was left for 2 h at rt. The mixture was evaporated under reduced pressure and the residue chromatographed on silica gel, eluting with CH_2Cl_2, to give *endo*-cycloadduct **2** (220 mg, 86%) as a yellow solid, mp 119–120 °C (*exo*-cycloadduct: lit.[18] mp 160 °C); IR: ν_{max} 1675 (C═O); ^1H NMR: δ 1.53 (m, 2H, 11-H), 3.44 (m, 2H, 4a- and 9a-H), 3.63 (s, 2H, 1- and 4-H), 5.95 (s, 2H, 2- and 3-H), 7.68 (m, 2H, 6- and 7-H), 8.00 (m, 2H, 5- and 8-H); ^{13}C NMR: δ 49.2, 49.5, 126.8, 134.1, 135.5, 135.8, 197.8. Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found: C, 79.99; H, 5.39.

3.1.2. *endo*-5-Hydroxy-1,4,4a,9a-tetrahydro-1,4-methano-9,10-anthraquinone 15. A solution of quinone **12** (250 mg, 1.44 mmol), cyclopentadiene (100 mg, 1.52 mmol) in CH_2Cl_2 (15 mL) was left for 2 h at rt. The mixture was evaporated under reduced pressure and the residue chromatographed on silica gel, eluting with CH_2Cl_2 to give adduct **15** (330 mg, 95%) as a yellow solid, mp 132–133 °C; IR: ν_{max} 3449 (OH), 1673 and 1632 (C═O); ^1H NMR: δ 1.54 (m, 2H, 11-H), 3.42 (m, 2H, 4a- and 9a-H), 3.65 (s, 2H, 1- and 4-H), 6.00 (s, 2H, 2- and 3-H), 7.20 (m, 1H, 6-H), 7.55 (m, 2H, 7- and 8-H), 12.59 (s, 1H, OH); ^{13}C NMR: δ 48.9, 49.3, 49.7, 49.9, 118.2, 123.5, 135.1, 135.8, 137.0, 162.1, 196.9, 204.8. Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.76; H, 5.01.

3.1.3. *endo*-4,9-Dioxo-4,4a,5,8,8a,9-hexahydro-5,8-methano-2-methoxycarbonylnaphtho[2,3-*b*]tiophene 17. Following the procedure described for the adducts of cyclopentadiene, compound **17** was obtained (150 mg, 96%) from 4,7-dihydro-2-methoxycarbonyl-4,7-dioxo-benzo[*b*]thiophene **13** (120 mg, 0.54 mmol), cyclopentadiene (100 mg, 2.28 mmol) in CH_2Cl_2 (15 mL), mp 129–131 °C; IR: ν_{max} 1725, 1712 and 1666 (C═O); ^1H NMR: δ 1.55 (m, 2H, 10-H), 3.44 (m, 2H, 5- and 8-H), 3.62 (t, 2H, J=1.7 Hz, 4a- and 9a-H), 3.91 (s, 3H, OCH_3), 6.01 (t, 2H, J=1.7 Hz, 6- and 7-H), 8.00 (s, 1H, 3-H); ^{13}C NMR: δ 49.2, 49.3, 49.5, 51.0, 53.0, 131.0, 134.1, 135.2, 141.3, 145.2, 151.9, 161.4, 1925, 192.6. Anal. Calcd for $C_{15}H_{12}O_4S$: C, 62.49; H, 4.20; S, 11.12. Found: C, 62.18; H, 4.31; S, 10.94.

3.1.4. *endo*-1,4,4a,9a-Tetrahydro-1,4-ethano-9,10-anthraquinone 14. A solution of 1,4-naphthoquinone **11** (250 mg, 1.58 mmol), 1,3-cyclohexadiene (170 mg, 2.1 mmol) in CH_2Cl_2 (15 mL), was left for 9 days at rt. Removal of the solvent followed by column chromatography (CH_2Cl_2/petroleum ether, 1:1) of the residue yielded adduct **14** as yellow solid (110 mg, 29%), mp 132.5–133.0 °C; IR: ν_{max} 1679 (C═O); ^1H NMR: δ 1.24 (m, 2H, 12-H), 1.64 (m, 2H, 11-H), 3.07 (d, 2H, J=1.1 Hz, 1- and 4-H), 3.17 (t, 2H, J=1.3 Hz, 4a- and 9a-H), 5.97 (c, 2H, J=1.36, 3.1 Hz, 2- and 3-H), 7.52 (m, 2H, 6- and 7-H), 7.84 (m, 2H, 5- and 8-H); ^{13}C NMR: δ 22.8, 23.9, 38.8, 81.5, 122.6, 126.0, 126.3, 127.8, 131.6, 133.0, 133.2, 134.2, 135.2, 160.0, 178.4, 182.4. Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.67; H, 5.99.

3.1.5. *endo*-1,4,4a,9a-Tetrahydro-5-hydroxy-1,4-ethano-9,10-anthraquinone 16. A solution of **12** (310 mg, 1.78 mmol), cyclohexadiene (250 mg, 3.1 mmol) in CH_2Cl_2 (15 mL) was refluxed for 12 days. The mixture was evaporated under reduced pressure and the residue chromatographed on silica gel (CH_2Cl_2/petroleum ether, 1:1) to give adduct **16** (220 mg, 49%) as an orange solid, mp 90–91 °C (lit.[19] mp 89–90 °C); IR: ν_{max} 3438 (OH), 1671, 1623 (C═O); ^1H NMR: δ 1.38 (dd, 2H, J=1.52, 6.0 Hz, 12-H), 1.76 (d, 2H, J=7.2 Hz, 11-H), 3.22 (m, 2H, 1- and 4-H), 3.35 (s, 2H, 4a- and 9a-H), 6.18 (t, 2H, J=3.78 Hz, 2- and

3-H), 7.19 (q, 1H, $J=1.8$, 5.7 Hz, 7-H), 7.57 (q, 2H, $J=3.1$, 6.8 Hz, 6- and 8-H), 12.58 (s, 1H, OH); ^{13}C NMR: δ 24.8, 25.0, 36.0, 36.1, 49.8, 50.2, 118.2, 123.3, 133.3, 134.0, 135.4, 137.0, 161.9, 197.2, 204.6. Anal. Calcd $C_{16}H_{14}O_3$: C, 75.57; H, 5.55. Found: C, 75.29; H, 5.31.

3.1.6. *endo*-4,9-Dioxo-4,4a,5,8,8a,9-hexahydro-5,8-ethano-2-methoxycarbonylnaphtho[2,3-*b*]thiophene 18. A solution of 4,7-dihydro-2-methoxycarbonyl-4,7-dioxobenzo[*b*]thiophene (130 mg, 0.59 mmol), cyclohexadiene (250 mg, 3.15 mmol), in CH_2Cl_2 (15 mL) was left for 4 days at rt. Removal of the solvent and purification by chromatography (CH_2Cl_2) yielded adduct **18** (180 mg, 95%) as a yellow solid, mp 102.5–103.5 °C; IR: ν_{max} 1727, 1713, 1667 (C=O); ^{1}H NMR: δ 1.37 (m, 2H, 11-H), 1.73 (m, 2H, 10-H), 3.15 (c, 2H, $J=2.15$, 2.54 Hz, 5- and 8-H), 3.31 (s, 2H, 4a- and 8a-H), 3.90 (s, 3H, OCH_3), 6.15 (m, 2H, 6- and 7-H), 8.00 (s, 1H, 3-H); ^{13}C NMR: δ 21.0, 24.9, 35.8, 35.9, 51.6, 53.0, 60.4, 131.2, 133.3, 133.7, 141.1, 144.9, 151.5, 161.4, 192.7, 192.9. Anal. Calcd for $C_{16}H_{14}O_4S$: C, 63.56; H, 4.67; S, 10.61. Found: C, 63.77; H, 4.03; S, 9.98.

3.1.7. Aerobic oxidation of adduct 2 in dichlomethane–DBU. A solution of adduct **2** (220 mg, 0.98 mmol), DBU (298 mg, 1.96 mmol) in CH_2Cl_2 (15 mL) was vigorously stirred in an open flask for 4 h. The mixture was evaporated under reduced pressure and the residue was chromatographed on silica gel. Elution with petroleum ether yielded a 4.6:1 mixture of *exo*- and *endo*-1,4,4a,9a-tetrahydro-4a,9a-epoxy-1,4-methano-9,10-anthraquinone **4+6** (160 mg, 68%) as a pale yellow solid, mp 120–123 °C. The spectral properties of epoxides **4+6** were in good agreement with those reported in the literature.[7]

Further elution with CH_2Cl_2–EtOAc (1/1) gave 1,4,4a,9a-tetrahydro-4a-hydroperoxy-1,4-methano-9,10-anthraquinone **25** (18 mg, 7%) as a viscous orange oil; ^{1}H NMR: δ 1.95 (m, 2H, 11-H), 2.90 (s, 1H, 1-H), 3.22 (s, 1H, 4-H), 3.77 (d, 1H, $J=1.4$ Hz, 4a-H), 3.97 (s, 1H, OH), 6.28 (q, 1H, $J=2.67$, 2.91 Hz, 3-H), 6.50 (q, 1H, $J=2.7$, 2.9 Hz, 2-H), 7.45 (m, 2H, 6- and 7-H), 7.84 (m, 2H, 5- and 8-H).

3.1.8. Aerobic oxidation of adduct 15 in DBU–dichloromethane solution. A solution of adduct **15** (230 mg, 0.96 mmol), DBU (292 mg, 1.92 mmol) in CH_2Cl_2 (15 mL) was vigorously stirred under aerobic conditions for 4 h at rt. The mixture was evaporated under reduced pressure and the residue subjected to column chromatography. Elution with CH_2Cl_2 yielded a 20:1 mixture of *exo*- and *endo*-5-hydroxy-1,4,4a,9a-tetrahydro-4a,9a-epoxy-1,4-methano-9,10-anthraquinone **21+22**. Further elution with AcOEt yielded a mixture of 8-hydroxy-1,4,4a,9a-tetrahydro-4a-hydroperoxy- and 8-hydroxy-1,4,4a,9a-tetrahydro-9a-hydroperoxy-1,4-methano-9,10-anthraquinone **26+27** (27 mg, 10%), as an unstable viscous orange oil. Column chromatography of the mixture **21+22** yielded **21** (150 mg, 62%) as a yellow solid, mp 103–105 °C; IR: ν_{max} 3190 br (OH), 1692 and 1642 (C=O), 1294 and 910 (C–O epoxide); ^{1}H NMR: δ 1.71 (m, 2H, 11-H), 3.59 (t, 2H, $J=1.5$ Hz, 1- and 4-H), 3.68, 6.59 (dd, 2H, $J=3.6$, 1.5 Hz, 2- and 3-H), 7.22 (m, 1H, 6-H), 7.53 (m, 2H, 7- and 8-H), 11.09 (s, 1H, OH); ^{13}C NMR: δ 41.6, 42.0, 42.6, 72.6, 115.9, 119.5, 124.1, 134.5, 136.6, 141.4, 142.4, 161.5, 190.4, 196.3. Anal. Calcd for $C_{15}H_{10}O_4$: C, 70.86; H, 3.96. Found: C, 70.53; H, 3.77.

3.1.9. *endo*-1,4,4a,9a-Tetrahydro-4a,9a-epoxy-1,4-ethano-9,10-anthraquinone 20. A solution of **14** (119 mg, 0.5 mmol), DBU (152 mg, 1.00 mmol) and CH_2Cl_2 (15 mL) was vigorously stirred for 4 h at rt. UHP (100 mg, 1.06 mmol) was added to the solution and the mixture was allowed to stand for 24 h at rt. The solvent was removed, yielding a 1:18 mixture of *exo*- and *endo*-1,4,4a,9a-tetrahydro-4a,9a-epoxy-1,4-ethano-9,10-anthraquinone **19+20**. The *exo*/*endo* ratio was determined using the vinylic proton signals of the isomers at δ 6.52 and 6.06 ppm, respectively. Column chromatography of the mixture over silica gel yielded *endo*-epoxide **20** (106 mg, 84%), mp 143–144 °C (lit.[5] 144–145 °C). The spectral properties of epoxide **20** were in full agreement with those reported in the literature.[5]

3.1.10. *endo*-5-Hydroxy-1,4,4a,9a-tetrahydro-4a,9a-epoxy-1,4-ethano-9,10-anthraquinone 24. A solution of **16** (120 mg, 0.47 mmol), DBU (143 mg, 0.94 mmol) and CH_2Cl_2 (15 mL) was vigorously stirred for 4 h at rt. UHP (100 mg, 1.06 mmol) was added to the solution and the mixture was left for 24 h at rt. Evaporation of the solvent yielded a 1:20 mixture of *exo*- and *endo*-5-hydroxy-1,4,4a,9a-tetrahydro- 4a,9a-epoxy-1,4-ethano-9,10-anthraquinone **23+24**. The ratio of isomers **23+24** was evaluated using the vinylic proton signals of the isomers at δ 6.55 and 6.06 ppm, respectively. The mixture was column chromatographed on silica gel to give *endo*-epoxide **24** (90 mg, 72%) as a yellow solid, mp 132.5–133 °C; IR: ν_{max} 1687 (C=O), 1246, 887, 814 (C–O epoxide); ^{1}H NMR: δ 11.27 (s, 1H, OH), 7.59 (m, 2H, 6- and 8-H), 7.25 (dd, 1H, $J=1.5$, 7.5 Hz, 7-H), 6.06 (t, 2H, $J=4.0$ Hz, 2- and 3-H,), 3.85 (s, 2H, 3a- and 10a-H), 1.49 (m, 4H, 11- and 12-H); ^{13}C NMR: δ 21.3, 21.4, 29.0, 29.5, 60.3, 60.8, 115.7, 119.4, 124.2, 129.1, 129.4, 133.8, 136.9, 161.4, 190.1, 196.3. Anal. Calcd for $C_{16}H_{12}O_4$: C, 71.64; H, 4.51. Found: C, 71.23; H, 4.12.

3.1.11. 1,4-Dihydro-5-hydroxy-1,4-ethano-9,10-anthraquinone 29. A solution of adduct **16** (120 mg, 0.47 mmol), DBU (143 mg, 0.94 mmol) in CH_2Cl_2 (15 mL) was refluxed for 24 h. Removal of the solvent followed by column chromatography of the residue (CH_2Cl_2) yielded quinone **29** (103 mg, 87%) as an orange solid, mp 158–159 °C; IR: ν_{max} 3449 (OH), 1658 and 1638 (C=O); ^{1}H NMR: δ 12.12 (s, 1H, OH), 7.57 (m, 2H, 6- and 8-H), 7.23 (t, 1H, $J=7$ Hz, 7-H), 6.45 (m, 2H, 2- and 3-H), 4.54 (s, 2H, 1- and 4-H), 1.49 (m, 4H, 11- and 12-H); ^{13}C NMR: δ 24.57, 24.65, 33.54, 34.32, 114.91, 119.12, 124.18, 132.49, 133.70, 133.81, 135.85, 150.44, 151.92, 161.52, 180.60, 186.60. Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 76.28; H, 4.95.

3.1.12. 3b,10a-Dihydronaphtho[2,3-*b*]-1*H*-cyclopenta[*d*]-furan-5,10-dione 33. *Method A*. A suspension of epoxides **4+6** (151 mg, 0.64 mmol), silica gel/gypsum (1 g) in dichloromethane (20 mL) was stirred for 7 days at rt. The mixture was filtered and the solid washed thoroughly with dichloromethane. The filtrate was concentrated under reduced pressure and the residue chromatographed over

silica gel. Elution with CH_2Cl_2 yielded quinone **33** (70 mg, 45%) as a yellow solid, mp 190–191 °C (lit.[4,20] 189–190 °C; 191–193 °C). The ^1H and ^{13}C NMR properties were in agreement with those reported for **33**.[4,20]

Method B. A suspension of epoxides **4**+**6** (106 g, 0.44 mmol), calcium hydroxide (1.0 g) in dichloromethane (20 mL) was stirred for 3 days at rt. Work-up followed by column chromatography gave quinone **33** (71 mg, 68%).

3.1.13. 6- and 9-Hydroxy-3b,10a-dihydronaphtho[2,3-*b*]-1*H*-cyclopenta[*d*]furan-5,10-dione 34 and 35. A suspension of quinone epoxide **22** (126 mg, 0.5 mmol), silica gel/gypsum (1 g) in dichloromethane (15 mL) was stirred for 7 days. Work up and column chromatography (CH_2Cl_2) gave compound **35** (25 mg, 19%) as orange solid, mp 137.5–138 °C; IR (KBr): ν_{max} 3443 (OH), 1694 and 1682 (C=O); ^1H NMR: δ 2.80 (m, 1H, 1-H), 2.98 (m, 1H, 1-H), 4.17 (dt, 1H, J=2.2, 8.6 Hz, 10b-H), 5.98 (m, 1H, 2- or 3-H), 6.17 (m, 1H, 3a-H), 7.19 (dd, 1H, J=1.2, 8.4 Hz, 3- or 2-H), 7.53 (t, 1H, J=7.9 Hz, 6-H), 7.63 (dd, 2H, J=1.2, 7.5 Hz, 7- and 8-H), 12.31 (s, 1H, OH); ^{13}C NMR: δ 38.2, 41.7, 96.6, 115.0, 119.4, 125.7, 126.5, 127.7, 131.9, 135.0, 137.6, 159.4, 161.2, 177.8, 188.4. Anal. Calcd for $C_{15}H_{10}O_4$: C, 70.86; H, 3.96. Found: C, 70.67; H, 3.80.

Further elution with dichloromethane yielded quinone **34** (12 mg, 9%) as a yellow solid, mp 145–146 °C; IR (KBr): ν_{max} 3443 (OH), 1694 and 1682 (C=O); ^1H NMR: δ 2.79 (m, 1H, 1-H), 2.97 (m, 1H, 1-H), 4.08 (dt, 1H, J=2.2, 8.6 Hz, 4-H), 5.98 (s, 1H, 10a-H), 6.12 (d, 1H, J=8.9 Hz, 2-H), 6.21 (m, 1H, 3-H), 7.23 (dd, 1H, J=2.1, 7.6 Hz, 6-H), 7.64 (m, 2H, 7- and 8-H), 11.70 (s, 1H, OH); ^{13}C NMR: δ 38.2, 42.7, 96.3, 114.8, 119.0, 124.0, 127.7, 127.8, 133.5, 136.9, 137.7, 158.4, 162.0, 181.5, 183.3.

3.1.14. Aerobic oxidation of adduct 18 in dichloromethane–DBU. A solution of adduct **18** (113 mg, 0.43 mmol), DBU (130 mg, 0.86 mmol) in dichloromethane (15 mL) was vigorously stirred under aerobic conditions for 48 h at rt. Column chromatography of the residue (CH_2Cl_2) yielded a 1:11 mixture of *exo*- and *endo*-4,9-dioxo-4,4a,5,8,8a,9-hexahydro-4a,8a-epoxy-5,8-ethano-2-methoxycarbonylnaphtho-[2,3-*b*]thiophene **31**+**32**. Further column chromatography of the crude product gave pure *endo*-epoxide **32** (110 mg, 81%) as a yellow solid, mp 129.5–130.5 °C; IR: ν_{max} 1728 (C=O ester), 1710 and 1670 (C=O enone); ^1H NMR: δ 1.24 (d, 2H, J=5 Hz, 11-H), 1.46 (s, 2H, 10-H), 3.80 (s, 2H, 5- and 8-H), 3.95 (s, 3H, OCH_3), 6.06 (dd, 2H, J=1.37, 3.49 Hz, 6- and 7-H), 8.07 (s, 1H, 3-H); ^{13}C NMR: δ 21.2, 21.3, 29.4, 29.7, 53.1, 61.1, 61.3, 129.2, 129.3, 131.0, 140.8, 141.6, 161.1, 184.9, 185.3. Anal. Calcd for: $C_{16}H_{12}O_5S$: C, 60.75; H, 3.82; S, 10.14. Found: C, 60.69; H, 3.80; S, 9.98.

3.2. Cytotoxicity screening

MRC-5 cell culture. Human normal lung fibroblasts MRC-5 (ATCC CCL-171) were grown as monolayers in minimum essential Eagle medium, with Earle's salts, 2 mM L-glutamine and 2.2 g/L sodium hydrogencarbonate, supplemented with 10% heat-inactivated fetal bovine serum (FBS), 100 IU/mL penicillin and 100 μg/mL streptomycin in a humidified incubator with 5% CO_2 in air at 37 °C. Cell passage was maintained between 10 and 16, and the medium was changed every 2 days.

AGS cell culture. Human gastric cancer epithelial cells AGS (ATCC CRL-1739) were grown as monolayers in Ham F-12 medium containing 1 mM L-glutamine and 1.5 g/L sodium hydrogencarbonate, supplemented with 10% heat-inactivated FBS, 100 IU/mL penicillin and 100 μg/mL streptomycin in a humidified incubator with 5% CO_2 in air at 37 °C. Cell passage was maintained between 42–48, and the medium was changed every 2 days.

Cytotoxicity assay. Confluent cultures of MRC-5 as well as AGS cells were treated during 24 h with medium containing the compounds or the reference compounds at concentrations ranging from 0 up to 100 μM. The substances were first dissolved in DMSO (1% final concentration) and then in the corresponding culture medium supplemented with 2% FBS. Untreated cells were used as controls. At the end of the incubation, the neutral red assay was carried out as described previously.[21] To calculate the concentration that produces a 50% inhibitory effect on the cell viability (IC_{50}), results were converted to percentage of controls and the IC_{50} values were graphically obtained from the dose-response curves.

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Azidosubstituted arylboronic acids: synthesis and Suzuki–Miyaura cross-coupling reactions

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Abstract—Arylboronic acids having a remote azido group were prepared from the corresponding azidosubstituted aryl bromides via lithiation and treatment with trialkyl borates. Preparative yields were achieved when the starting aryl bromides possessed *ortho*-alkoxy groups, which would stabilize the intermediate aryllithium species. Conventional Suzuki cross-coupling of the arylboronic acids proceeded generally well with retention of azido group; however, sometimes azidomethyl fragment underwent oxidative transformation into a nitrile.

1. Introduction

During the last decade the Suzuki–Miyaura cross-coupling leading to biaryls[1] has become a widely used technology in target synthesis, and in particular, medicinal chemistry.[2] In the synthesis of complex molecules, the organoboron component is usually less structurally complex than the more complicated aryl halide, which is due to the difficulties in preparing arylboronic acids bearing certain functional groups.[3] On the other hand, the employment of sophisticated arylboronic acids will be useful for combinatorial chemistry, that is, they may serve as multifunctional templates for the preparation of a broad variety of related compounds. The application of such arylboronic acids in medicinal chemistry is not unprecedented.[3]

The preparation of structurally diverse arylboronic acids bearing functional groups of electrophilic type from the corresponding aryl halides using organolithium protocol remained limited until Li and Nelson proposed an improved 'in situ quench' procedure when *n*-butyllithium was added to a mixture of aryl halide and triisopropyl borate.[4] Using this technique, arylboronic acids with nitrile, ester and nitro groups, as well as certain hetarylboronic acids, were prepared directly from the aryl/hetaryl halide precursors in reasonable yields.

To the best of our knowledge, organoboronic acids bearing an azido group are not documented in the literature.[5] The azido group is a well known precursor to various nitrogen containing compounds.[6] On the other hand, it is very convenient from the point of view of multistep synthesis: it may tolerate a variety of reagents and conditions, and its low polarity does not bring complications to isolation and purification.

2. Results and discussion

In our investigations we targeted compounds possessing a 2,3-dihydrobenzo[*b*]furan core, which is of interest in medicinal chemistry.[7] Aryl-substituted 2,3-dihydrobenzo-[*b*]furans are rare within the literature.[8] We proposed that the compounds of interest could be readily prepared from commercially available bromophenols **1**. Claisen rearrangement of their allyl ethers **2**, followed by oxidative cyclization of *o*-allylphenols **3** (Scheme 1), gave rise to 2-hydroxymethyldihydrobenzofurans **4**. The latter compounds were readily converted via mesylation into the key bromo azides **5**.

The conversion of aryl bromides **5** into the corresponding boronic acids by sequential *n*-BuLi–$B(OMe)_3$ treatment was found to be substrate dependent. Two 7-bromo derivatives **5a**,**b** gave boronic acids **6a**,**b** in good yields (Scheme 2), while 5-bromosubstituted compound furnished the target product in poor yield (Scheme 3).

Keywords: Azides; Boronic acids; Cross-coupling; 2,3-Dihydrobenzo[*b*]-furans; Nitriles.
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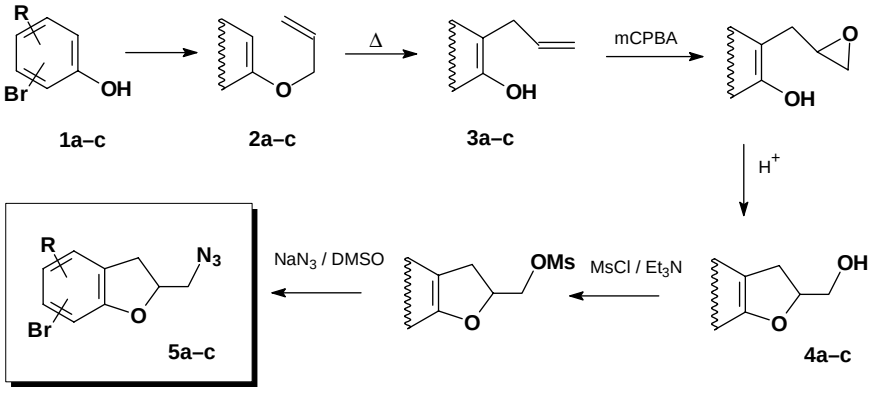
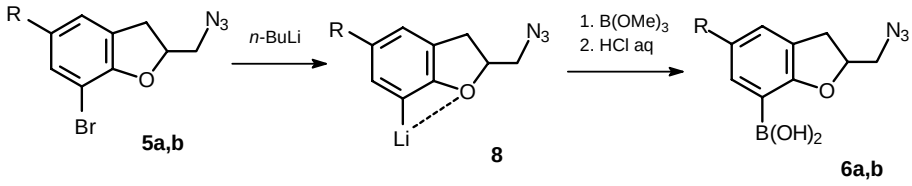
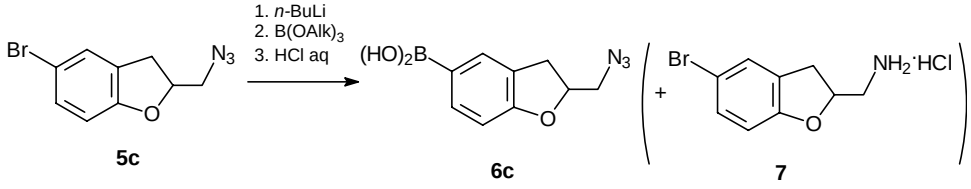


Scheme 1.

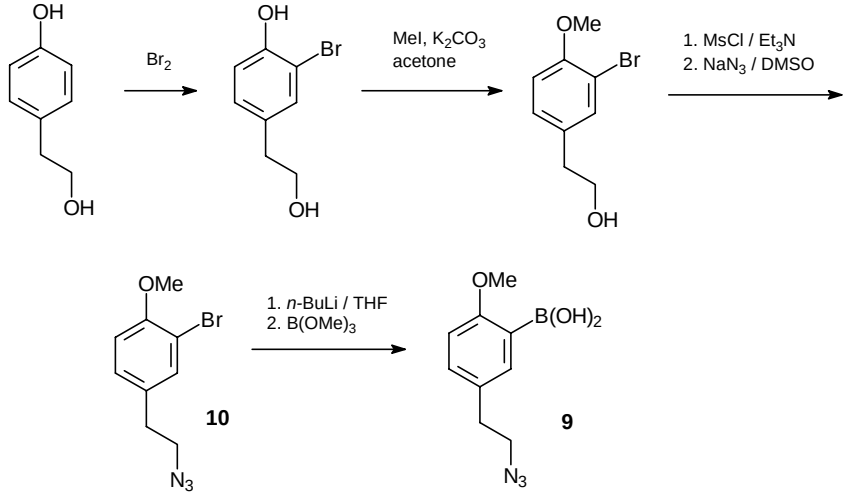


Scheme 2. R = H (**5a**,**6a**), Cl (**5b**,**6b**).



Scheme 3.

For the preparation of compound **6c**, two synthetic protocols were attempted, this is, sequential addition of *n*-BuLi and $B(OMe)_3$ to a THF solution of bromide **5c** and addition of *n*-BuLi to a THF/toluene solution of bromide **5c** and $B(O\text{-}i\text{-}Pr)_3$. Both procedures gave the target material **6c** in low yield ($\sim$10%),[9] while some differences were observed. In the first case, during the addition of *n*-BuLi prior to quenching with the electrophile, precipitation of a polymeric material took place and this material brought serious complications during the work up of the reaction mixture. Probably, the aryllithium, formed initially, may attack the azido function of another molecule (organoazides are known to react with organolithium compounds to form triazenes[6]). In the second case, the polymeric material was not formed in a large amount, while the major product was bromoamine **7** (isolated as the hydrochloride). Here, *n*-BuLi may preferentially add to the azido group rather than undergo the bromine–lithium exchange reaction.



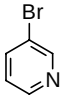
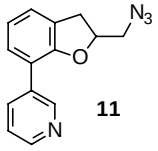
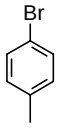
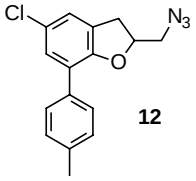
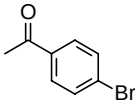
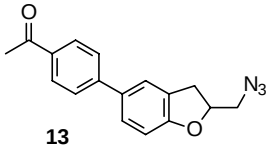
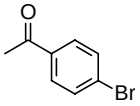
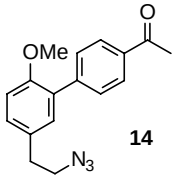
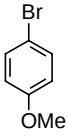
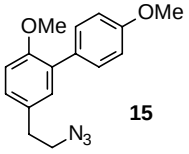
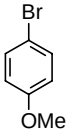
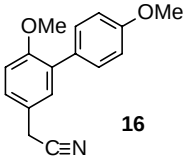
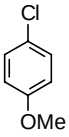
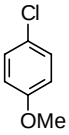
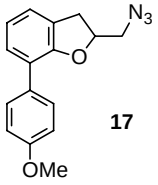
Scheme 4.

Butyltriazene, which may form, decomposes during the work-up of the reaction mixture and provides the amine **7** (cf. Ref. 10).

It is of particular note that bromides **5a**,**b** possessing alkoxy substitutents *ortho* to bromine atom give the organoboronic acids in good yields. This ether function presumably coordinates to the organolithium species, and after bromine–lithium exchange, it forms a stabilized chelate complex **8** (Scheme 2). Similarly, boronic acid **9** was prepared in good yield from *o*-bromoanisol derivative **10**, bearing a remote azido group (Scheme 4).

Organoboronic acids **6a–c** and **9** were screened using standard Suzuki cross-coupling reactions ($Pd(PPh_3)_4$, DME, Na_2CO_3 aq, 90 °C)[11] with several of aryl halides. It was important to let the aryl halide react with and $Pd(PPh_3)_4$ in DME for ca. 40 min prior to addition of other reaction components; during this period oxidative addition of aryl halide to palladium should take place. Most commonly, with

Table 1. Cross-coupling of azidosubstituted arylboronic acids with aryl halides

Entry	Boronic acid	Aryl halide	Catalyst[a]	Product	Isolated yield (%)
1	**5a**		$Pd(PPh_3)_4$	 **11**	71
2	**5b**		$Pd(PPh_3)_4$	 **12**	86
3	**5c**		$Pd(PPh_3)_4$	 **13**	77
4	**9**		$Pd(PPh_3)_4$	 **14**	68
5	**9**		$Pd(PPh_3)_4$	 **15**	78
6	**9**		$Pd(PPh_3)_4$	 **16**	32
7	**9**		$Pd(OAc)_2 \cdot 2L$	**16**	26
8	**5a**		$Pd(OAc)_2 \cdot 2L$	 **17**	34

[a] $Pd(PPh_3)_4$ with Na_2CO_3 (aq) in DME; $Pd(OAc)_2 \cdot 2L$ (L=2-dicyclohexylphosphino-2′-dimethylaminobiphenyl) with K_3PO_4 in toluene.

typical aryl bromides the reaction proceeded smoothly and the biaryl compounds **11**–**15** were obtained in good yields (Table 1, entries 1–5), with the azido group remaining intact. However, in some cases the analogous nitriles were obtained instead of azides. For example, nitrile **16** was obtained in a yield of 32% in a parallel experiment involving boronic acid **9** and 4-bromoanisol, when all the reagents were loaded simultaneously into the reaction vessel (entry 6). In some other experiments, this phenomenon could occur when the reaction mixture was accidently exposed to air, or when less active and sterically hindered hetaryl chlorides were used, that is, when the catalyst system has been somewhat different. Palladium-catalysed conversion of azidomethyl group into nitrile is not unprecedented (Pd/C or Pd black), although rare,[12,13] the yields being generally modest. Detailed investigations revealed that this reaction is balanced to 2/3 of nitrile and 1/3 of amine that may suggest red-ox disproportionation of the azidomethyl moiety; the use of an oxidant, however, did not allow raising the yield of the nitrile product.[12]

New possibilities of palladium chemistry over the past 5 years facilitate the employment of a broad variety of inactivated aryl chlorides in Suzuki reaction using bulky phosphines[14] or *N*-heterocyclic carbene[15] ligands (derived from imidazolium salts). Therefore, we attempted to couple azido-containing boronic acids **9** and **6a** with essentially inactive 4-chloroanisol (Table 1, entries 7 and 8 correspondingly) using efficient Buchwald catalytic system $Pd(OAc)_2$–2-dicyclohexylphosphino-2′-dimethylaminobiphenyl.[14a] The yields of biaryls appeared to be quite modest. Acid **9** was converted into nitrile **16** (yield 26%), while acid **6a** turned into azido-containing biaryl **17** (yield 34%, trace amounts of corresponding nitrile were also detected in the lower fractions during column chromatography). Probably, azido-group possessing certain oxidative properties would destroy this catalytic system based on Pd(II) and electron-rich phosphine while the rate of cross-coupling is slow.

3. Conclusion

To conclude, we have demonstrated that arylboronic acids bearing a remote azido group can be prepared in reasonable yields from the corresponding aryl bromides containing an *ortho*-positioned functional group, which can stabilize the intermediate organolithium species by intramolecular chelation. The azido-substituted arylboronic acids are useful substrates for Suzuki–Miyaura reactions, which could promote their use as perspective templates in combinatorial chemistry and some related fields. However, their application is limited to active aryl halides.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at 400.13 MHz (^1H) or 100.62 MHz (^{13}C) using a DRX 400 Avance (Bruker) instrument. ^{11}B NMR spectra were recorded using an AMX 400 (Bruker) spectrometer at 128.3 MHz, the chemical shifts were referred to $Et_2O\cdot BF_3$ ($\delta_B=0.0$ ppm). Elemental analyses were performed at the Analytical Laboratory of the Nesmeyanov Institute of Organoelement Compounds, Moscow. The starting bromophenols and 4-(2-hydroxyethyl)phenol were commercially available and used as purchased. Trimethyl and triisopropyl borates were freshly distilled. All solvents used in reactions and as eluents for column chromatography were freshly distilled, THF was distilled from $LiAlH_4$ under argon.

4.1.1. *o*-Allylphenols 3a–c. A mixture of bromophenol **1** (50 mmol), allyl bromide (4.8 mL, 55 mmol), freshly powdered K_2CO_3 (15.2 g, 110 mmol) and acetone (100 mL) was stirred at reflux for 2.5 h (TLC monitoring) up to the complete consumption of the starting phenol **1**. The mixture was cooled, filtered and the filter cake was washed with acetone. Concentrating of the filtrate in vacuo gave the essentially pure aryl allyl ether **2**. The material obtained was heated under argon in a flask connected to a Vigreux column on an oil bath at 200–220 °C for 2–4 h (TLC monitoring). The product was then distilled from the same flask under reduced pressure.

4.1.1.1. 2-Allyl-6-bromophenol (3a). Bp 85–90 °C (1 Torr). Yield: 7.6 g (71%). Physicochemical properties were in agreement with the literature.[16]

4.1.1.2. 2-Allyl-6-bromo-4-chlorophenol (3b). Bp 101–105 °C (1 Torr). Yield: 8.9 g (83%). Physicochemical properties were in agreement with the literature.[16a]

4.1.1.3. 2-Allyl-4-bromophenol (3c). Bp 120 °C (1 Torr). Yield: 9.3 g (75%). Physicochemical properties were in agreement with the literature.[17]

4.1.2. 7-Bromo-2-hydroxymethyl-2,3-dihydrobenzo[*b*]-furan (4a). To a warm (35 °C) solution of 2-allyl-6-bromophenol (**3a**) (7.6 g, 35.7 mmol) in CH_2Cl_2 (60 mL), *m*-chloroperoxybenzoic acid (10 g of 75% material, 43 mmol) was added in portions, and the mixture was refluxed for 4 h and then cooled to ambient temperature. Methanesulfonic acid (1 mL) in CH_2Cl_2 (5 mL) was carefully added, and the mixture was vigorously stirred for 2 h (TLC control). The mixture was then treated with 5% NaOH (aq). The organic layer was separated and washed successively with solutions of $Na_2S_2O_3$, $NaHCO_3$, NaCl and dried with Na_2SO_4. The solution was concentrated in vacuo and the residue was subjected to column chromatography (gradient 0→100% CH_2Cl_2 in CCl_4 and then 0→2% MeOH in CH_2Cl_2) to afford 4.8 g (58%) of the title compound as a colourless oil. ^1H NMR δ 2.33 (br s, 1H), 3.16 (dd, 1H, $J=15.5$, 7.8 Hz), 3.31 (dd, 1H, $J=15.5$, 9.5 Hz), 3.75 (dd, 1H, $J=12.2$, 5.6 Hz), 3.90 (dd, 1H, $J=12.2$, 3.2 Hz), 4.97 (m, 1H), 6.72 (t, 1H, $J=7.8$ Hz), 7.08 (d, 1H, $J=7.1$ Hz), 7.25 (d, 1H, $J=8.1$ Hz). ^{13}C NMR δ 32.0t, 64.4t, 83.6d, 102.5s, 121.9d, 123.9d, 128.1d, 128.1s, 131.1s, 156.6s.

4.1.3. 7-Bromo-5-chloro-2-hydroxymethyl-2,3-dihydro-benzo[*b*]furan (4b). The title compound was prepared similarly to compound **4a** in a 61% yield, mp 69–70 °C. ^1H NMR δ 2.18 (br s, 1H), 3.17 (dd, 1H, $J=16.0$, 8.0 Hz), 3.30 (dd, 1H, $J=16.0$, 9.4 Hz), 3.74 (dd, 1H, $J=12.4$, 5.3 Hz), 3.91 (dd, 1H, $J=12.4$, 3.3 Hz), 4.99 (m, 1H), 7.05 (s, 1H), 7.25 (s, 1H). ^{13}C NMR δ 32.0t, 64.2t, 84.2d, 102.5s, 124.2d, 125.8s, 129.4s, 130.5d, 155.6s. Anal. Calcd for

$C_9H_8BrClO_2$: C, 41.02; H, 3.06; Cl+Br, 43.77. Found: C, 40.83; H, 3.02; Br+Cl, 43.86.

4.1.4. 5-Bromo-2-hydroxymethyl-2,3-dihydrobenzo[*b*]-furan (4c). The title compound was prepared similarly to compound **4a** in a 74% yield. ^{1}H NMR data were in good agreement with the literature.[18]

4.1.5. 2-Azidomethyl-7-bromo-2,3-dihydrobenzo[*b*]-furan (5a). To a stirred solution of alcohol **4a** (4.8 g, 21 mmol) and triethylamine (4 mL) in CH_2Cl_2 (20 mL), methanesulfonyl chloride (1.9 mL, 23 mmol) was slowly added at 0–5 °C. The reaction was accompanied by precipitation of solid triethylammonium chloride. After the mesylate formation was complete (ca. 1 h, TLC control), the mixture was treated with $NaHCO_3$ (aq), and the organic layer was separated and washed successively with solutions of HCl, NaCl, $NaHCO_3$ and dried with Na_2SO_4. Evaporating the solvent furnished the crude mesylate. This material was dissolved in a mixture of MeCN (23 mL) and DMSO (7 mL), 18-crown-6 ether (0.15 g) was added, and then sodium azide (2.8 g, 43 mmol) was added with stirring in one portion. The mixture was heated to a gentle reflux for 7–8 h (TLC monitoring). After the reaction was complete, the most of acetonitrile was distilled off, water (50 mL) was added to the residue, and the organic components were extracted with CH_2Cl_2. The combined extracts were washed with brine, dried with $CaCl_2$ and concentrated in vacuo. The remainder was subjected to column chromatography (gradient 0→25% CH_2Cl_2 in CCl_4) to afford 3.88 g (72%) of the title azide as a colourless oil. ^{1}H NMR δ 3.15 (dd, 1H, J=16.0, 6.6 Hz), 3.41 (dd, 1H, J=16.0, 9.5 Hz), 3.50 (dd, 1H, J=13.1, 5.4 Hz), 3.56 (dd, 1H, J=13.1, 4.2 Hz), 5.04 (m, 1H), 6.75 (t, 1H, J=7.8 Hz), 7.10 (dd, 1H, J=7.3, 1.0 Hz), 7.28 (br d, 1H, J=7.8 Hz). ^{13}C NMR δ 33.5t, 54.1t, 81.4d, 102.8s, 122.2d, 123.9d, 127.2s, 131.4d, 156.3s. Anal. Calcd for $C_9H_8BrN_3O$: C, 42.54; H, 3.17; Br, 31.45; N, 16.54. Found: C, 42.54; H, 3.05; Br, 31.42; N, 16.55.

4.1.6. 2-Azidomethyl-7-bromo-5-chloro-2,3-dihydrobenzo[*b*]furan (5b). The title compound was synthesized similarly to compound **5a** in a 66% yield, white solid, mp 66 °C. ^{1}H NMR δ 3.14 (dd, 1H, J=16.6, 6.9 Hz), 3.39 (dd, 1H, J=16.1, 9.8 Hz), 3.48 (dd, 1H, J=13.1, 5.4 Hz), 3.58 (dd, 1H, J=13.1, 4.2 Hz), 5.06 (m, 1H), 7.03 (br s, 1H), 7.28 (br s, 1H). ^{13}C NMR δ 33.4t, 54.0t, 82.0d, 102.7s, 124.1d, 126.1s, 128.5s, 130.7d, 155.3s. Anal. Calcd for $C_9H_7BrClN_3O$: C, 37.47; H, 2.45; Br, 27.69; Cl, 12.29; N, 14.56. Found: C, 37.58; H, 2.39; Br, 27.76; Cl, 12.41; N, 14.51.

4.1.7. 2-Azidomethyl-5-bromo-2,3-dihydrobenzo[*b*]-furan (5c). The title compound was synthesized similarly to compound **5a** in a 69% yield, oil. ^{1}H NMR δ 3.02 (dd, 1H, J=16.1, 6.6 Hz), 3.31 (dd, 1H, J=16.1, 9.5 Hz), 3.46 (dd, 1H, J=13.0, 6.1 Hz), 3.52 (dd, 1H, J=13.0, 4.2 Hz), 4.96 (m, 1H), 6.69 (d, 1H, J=8.5 Hz), 7.23 (br d, 1H, J=8.5 Hz), 7.28 (br s, 1H). ^{13}C NMR δ 32.6t, 54.3t, 81.6d, 111.1d, 112.6s, 127.9d, 128.3s, 131.1d, 158.2s. Anal. Calcd for $C_9H_8BrN_3O$: C, 42.54; H, 3.17; Br, 31.45; N, 16.54. Found: C, 42.52; H, 3.13; Br, 31.64; N, 16.62.

4.1.8. Synthesis of 5-(2-azidoethyl)-1-bromo-2-methoxybenzene (10). a. *2-Bromo-4-(2-hydroxyethyl)phenol*. To a stirred mixture of 4-(2-hydroxyethyl)phenol (4.14 g, 30 mmol), finely powdered $NaHCO_3$ (3.5 g, 42 mmol), CH_2Cl_2 (15 mL), MeOH (6 mL) a solution of bromine (1.53 mL, 30 mmol) in CH_2Cl_2 (6 mL) was added dropwise at 0–5 °C. According to TLC data, some unreacted starting material was left, along with the formation of another component with a higher R_f, presumably 2,6-dibromo derivative. Water was added to the reaction mixture, and the organic components were extracted with EtOAc. The extract was dried ($MgSO_4$), concentrated in vacuo and the residue was subjected to column chromatography using CH_2Cl_2 as an eluent to afford 2.9 g (44%) of the title monobromo derivative as a white solid, mp 91–93 °C. ^{1}H NMR (DMSO-d_6) δ 2.60 (t, 2H, J=6.9 Hz), 3.54 (t, 2H, J=6.9 Hz), 4.56 (br s, 1H), 6.85 (d, 1H, J=8.2 Hz), 7.0 (dd, 1H, J=8.2, 1.7 Hz), 7.31 (d, 1H, J=1.7 Hz), 9.89 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 37.6t, 62.2t, 108.9s, 116.1d, 129.1d, 131.9s, 132.9d, 152.1s. Anal. Calcd for $C_8H_9BrO_2$: C, 44.27; H, 4.18; Br, 36.81. Found: C, 44.24; H, 4.20; Br, 36.85.

b. *1-Bromo-5-(2-hydroxyethyl)-2-methoxybenzene*. A mixture of 2-bromo-4-(2-hydroxyethyl)phenol (2.9 g, 13.4 mmol) from the previous step, methyl iodide (1.1 mL, 17.5 mmol), freshly powdered K_2CO_3 (2.42 g, 17.5 mmol) and acetone (20 mL) was stirred at 40 °C for 5 h until the full conversion of starting phenol (TLC monitiring). Acetone was then removed by distillation, water was added to the residue, and the organic components were extracted with ether. The extracts were dried ($MgSO_4$), concentrated in vacuo and the remainder was subjected to column chromatography using CH_2Cl_2 as an eluent to afford 2.9 g (93%) of the title methyl ether as a viscous oil, which would solidify on standing. ^{1}H NMR ($CDCl_3$) δ 1.63 (br s, 1H), 2.77 (t, 2H, J=6.6 Hz), 3.80 (t, 2H, J=6.6 Hz), 3.86 (s, 3H), 6.84 (d, 1H, J=8.3 Hz), 7.12 (dd, 1H, J=8.3, 2.1 Hz), 7.41 (d, 1H, J=2.1 Hz). ^{13}C NMR ($CDCl_3$) δ 37.8t, 56.2q, 63.4t, 111.6s, 112.0d, 128.9d, 132.2s, 133.6d, 154.5s. Anal. Calcd for $C_9H_{11}BrO_2$: C, 46.78; H, 4.80, Br, 34.58. Found: C, 46.82; H, 5.16; Br, 34.71.

c. *5-(2-Azidoethyl)-1-bromo-2-methoxybenzene* (**10**). Colourless viscous oil was obtained in a 75% yield from the preceding alcohol via its mesylation and azide substitution for mesylate group (see synthesis of compound **5a**). ^{1}H NMR ($CDCl_3$) δ 2.81 (t, 2H, J=7.1 Hz), 3.47 (t, 2H, J=7.1 Hz), 3.88 (s, 3H), 6.85 (d, 1H, J=8.3 Hz), 7.12 (dd, 1H, J=8.3, 2.2 Hz), 7.40 (d, 1H, J=2.2 Hz). ^{13}C NMR ($CDCl_3$) δ 34.1t, 52.3t, 56.3q, 111.7s, 112.1d, 128.7d, 131.6s, 133.5d, 154.8s. Anal. Calcd for $C_9H_{10}BrN_3O$: C, 42.21; H, 3.94; Br, 31.20; N, 16.43. Found: C, 42.28; H, 3.81; Br, 31.46; N, 16.37.

4.2. Boronic acids 6a–c and 9

A solution of bromoarene **5a–c** or **10** (14 mmol) in THF (47 mL) was placed under argon into a one-neck flask equipped with a magnetic stirring bar and adapter with a rubber septum and a gas inlet, which was connected to a manifold. The solution was cooled to ca. −80 °C and the traces of oxygen were removed by three-fold pumping—filling with argon. *n*-Butyllithium (8.4 mL of 1.7 M solution

in hexane, 14.3 mmol) was added dropwise during 10 min at the same temperature, and the mixture was stirred for additional 20 min. Trimethyl borate (6.3 mL, 55 mmol) was quickly added in one potion, and the mixture was allowed to reach ambient temperature. The flask was then put on a rotary evaporator and the most of volatile components were distilled off, the excess of trimethyl borate being removed by subsequent co-evaporation with toluene. The yellow viscous residue was shaken with water and ether and the layers were separated. The ethereal layer was treated with 5% NaOH (aq), and the alkaline solution was combined with the previous aqueous layer. The rest of neutral organic components were extracted from this aqueous phase with ether. The aqueous layer was cooled to 0–5 °C and acidified with 10% HCl (pH∼1), which caused precipitation of a solid material (sometimes the product emerged as oil, which would solidify on trituration). The product was collected by filtration, washed with water and dried in air. Usually, the material thus obtained was essentially pure. If a product required purification by column chromatography (2% MeOH in CH_2Cl_2 as eluent), one should note that during this operation boronic acids would form liquid methyl esters. To recover the acids, the material was triturated with water (solid was formed quickly) and then dried.

4.2.1. (2-Azidomethyl-2,3-dihydrobenzo[*b*]furan-7-yl)-boronic acid (6a). Yield 72%, mp 105–6 °C. ^{1}H NMR (DMSO-d_6) δ 2.94 (dd, 1H, J=16.0, 6.9 Hz), 3.29 (dd, 1H, J=16.0, 9.5 Hz), 3.54 (dd, 1H, J=13.5, 5.9 Hz), 3.68 (dd, 1H, J=13.5, 3.7 Hz), 5.03 (m, 1H), 6.84 (t, 1H, J=7.3 Hz), 7.27 (dd, 1H, J=7.3, 1.0 Hz), 7.41 (br d, 1H, J=7.3 Hz), 7.46 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 31.6t, 53.8t, 81.3d, 120.3d, 125.5s, 127.3d, 133.6d, 163.5s. ^{11}B NMR (DMSO-d_6) δ 29.7. Anal. Calcd for $C_9H_{10}BN_3O_3$: C, 49.36; H, 4.60; B, 4.94; N, 19.19. Found: C, 49.30; H, 4.50; B, 5.03; N, 19.00.

4.2.2. (2-Azidomethyl-5-chloro-2,3-dihydrobenzo[*b*]-furan-7-yl)boronic acid (6b). Yield 69%, mp 159–60 °C. ^{1}H NMR (DMSO-d_6) δ 2.95 (dd, 1H, J=16.4, 6.6 Hz), 3.30 (dd, 1H, J=16.4, 9.8 Hz), 3.53 (dd, 1H, J=13.5, 5.9 Hz), 3.70 (dd, 1H, J=13.5, 3.4 Hz), 5.05 (m, 1H), 7.30 (s, 1H), 7.33 (s, 1H), 7.68 (s, 2H). ^{13}C NMR (DMSO-d_6) δ 31.5t, 53.7t, 82.0d, 124.1s, 126.8d, 128.6s, 132.5d, 162.2s. ^{11}B NMR (DMSO-d_6) δ 28.5. Anal. Calcd for $C_9H_9BClN_3O_3$: C, 42.65; H, 3.58. Found: C, 42.80; H, 3.60.

4.2.3. (2-Azidomethyl-2,3-dihydrobenzo[*b*]furan-5-yl)-boronic acid (6c). Yield 11%, mp 101–2 °C. ^{1}H NMR (DMSO-d_6) δ 2.93 (dd, 1H, J=15.9, 6.8 Hz), 3.29 (dd, 1H, J=15.9, 9.5 Hz), 3.50 (dd, 1H, J=13.2, 6.4 Hz), 3.64 (dd, 1H, J=13.2, 3.4 Hz), 4.99 (m, 1H), 6.74 (d, 1H, J=8.1 Hz), 7.59 (br d, 1H, J=8.1 Hz), 7.65 (br s, 1H), 7.76 (br s, 2H). ^{13}C NMR (DMSO-d_6) δ 31.8t, 54.0t, 81.4d, 108.3d, 125.7s, 131.1d, 134.8d, 160.7s. ^{11}B NMR (DMSO-d_6) δ 29.0. Anal. Calcd for $C_9H_{10}BN_3O_3$: C, 49.36; H, 4.60; B, 4.94; N, 19.19. Found: C, 49.60; H, 4.65; B, 4.78; N, 19.00.

4.2.4. 5-(2-Azidoethyl)-2-methoxyphenylboronic acid (9). Yield 64%, mp 54–5 °C. ^{1}H NMR (DMSO-d_6) δ 2.77 (t, 2H, J=7.1 Hz), 3.50 (t, 2H, J=7.1 Hz), 3.79 (s, 3H), 6.92 (d, 1H, J=8.3 Hz), 7.28 (dd, 1H, J=8.3, 2.1 Hz), 7.46 (d, 1H, J=2.1 Hz), 7.66 (br s, 2H). ^{13}C NMR (DMSO-d_6) δ 33.7t, 51.9t, 55.4q, 110.4d, 129.8s, 131.9d, 135.9d, 162.4s. ^{11}B NMR (DMSO-d_6) δ 30.1. Anal. Calcd for $C_9H_{12}BN_3O_3$: C, 48.91; H, 5.47; B, 4.89; N, 19.01. Found: C, 48.92; H, 5.70; B, 4.74; N, 18.85.

4.2.5. 2-Aminomethyl-5-bromo-2,3-dihydrobenzo[*b*]-furan hydrochloride (7). *n*-Butyllithium (14 mL of 1.7 M solution in hexane, 24 mmol) was added during 40 min at −80 °C to a stirred deaerated mixture of 2-azidomethyl-5-bromo-2,3-dihydrobenzo[*b*]furan (**5c**) (5.08 g, 20 mmol), triisopropyl borate (5.6 g, 30 mmol), toluene (32 mL) and THF (8 mL). The thick reaction mixture was allowed to reach the ambient temperature. The flask was put on a rotary evaporator and the most of volatile components were distilled off. The residue was treated with 5% NaOH to give three layers. The aqueous layer was separated and treated as described above in the syntheses of boronic acids **6**; the yield of (2-azidomethyl-2,3-dihydrobenzo[*b*]furan-5-yl)boronic acid (**6c**) was 208 mg (5%). The other two organic layers were vigorously shaken with 10% HCl, which finally led to the formation of two layers. The aqueous layer was separated, and the rest of neutral components were extracted with ether. Solid KOH pellets were added to reach alkaline pH, and the oil thus liberated was taken into ether. The extract was concentrated in vacuo, and then treated with minimum concd HCl. The slurry thus formed was mixed with *n*-butanol and evaporated to ca. 5 mL volume. The residue was triturated with ether and the precipitate was filtered off, washed with ether and dried in air to afford 1.83 g (34%) of the title compound as a white solid, mp 230 °C (dec). ^{1}H NMR (DMSO-d_6) δ 2.90–3.10 (several peaks, 2H), 3.31–3.42 (several peaks, 2H), 5.10 (m, 1H), 6.75 (d, 1H, J=8.4 Hz), 7.27 (dd, 1H, J=8.4, 2.2 Hz), 7.41 (d, 1H, J=2.2 Hz), 8.50 (br s, 3H). ^{13}C NMR (DMSO-d_6) δ 32.4t, 42.2t, 79.8d, 111.3d, 111.8s, 128.1d, 129.6s, 130.6d, 157.8s. Anal. Calcd for $C_9H_{11}BrClNO$: C, 40.86; H, 4.19; N, 5.29. Found: C, 40.78; H, 4.14; N, 5.17.

4.3. Cross-coupling reactions (general procedure)

All reactions were performed in a two-necked flask equipped with a rubber septum and a reflux condenser connected to a manifold, which was connected to suction and argon lines. To a degassed solution of aryl bromide (2 mmol) in 1,2-dimethoxyethane (2–3 mL), $Pd(PPh_3)_4$ (70 mg, ca. 3 mol%) was added, and the mixture was stirred for ca. 40 min. Boronic acid (1.5 mmol) was added, and the mixture was degassed by pumping—argon filling. Then a freshly prepared deaerated solution of sodium carbonate (0.848 g) in water (3.2 mL) was injected through the septum, and the mixture was refluxed for 6 h. The mixture was diluted with water, the organic products were extracted with ether, and the extracts were dried ($CaCl_2$ or Na_2SO_4) and concentrated in vacuo. The residue was subjected to column chromatography using hexane–ethyl acetate mixtures as eluents.

4.3.1. 2-Azidomethyl-7-(pyrid-3-yl)-2,3-dihydrobenzo[*b*]-furan (11). The title compound was prepared in a 71% yield from 3-bromopyridine and boronic acid **6a**, oil. ^{1}H NMR ($CDCl_3$) δ 3.12 (dd, 1H, J=15.7, 7.3 Hz), 3.38 (dd, 1H, J=15.7, 9.3 Hz), 3.53 (several peaks, 2H), 5.01 (m, 1H), 6.99 (t, 1H, J=7.6 Hz), 7.20 (dd, 1H, J=7.3, 1.0 Hz), 7.29–7.36

(several peaks, 2H), 8.03 (dt, 1H, J=7.8, 1.9 Hz), 8.54 (dd, 1H, J=4.7, 1.8 Hz), 8.92 (d, 1H, J=1.8 Hz). ^{13}C NMR ($CDCl_3$) δ 32.7t, 54.3t, 81.3d, 120.2s, 121.7d, 123.1d, 124.9d, 127.0s, 127.7d, 132.7s, 135.6d, 148.1d, 149.2d, 156.3s. Anal. Calcd for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.43; H, 4.73; N, 21.98.

4.3.2. 2-Azidomethyl-5-chloro-7-(4-methylphenyl)-2,3-dihydrobenzo[*b*]furan (12). The title compound was prepared in a 86% yield from 3-bromopyridine and boronic acid **6b**, mp 44–46 °C. ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 3.10 (dd, 1H, J=15.9, 7.3 Hz), 3.33 (dd, 1H, J=15.9, 9.3 Hz), 3.52 (several peaks, 2H), 5.00 (m, 1H), 7.10 (br s, 1H), 7.24 (d, J=8.3 Hz), 7.28 (br s, 1H), 7.56 (d, 2H, J=8.3 Hz). ^{13}C NMR ($CDCl_3$) δ 21.2q, 32.7t, 54.3t, 81.4d, 123.5d, 124.9s, 126.0s, 127.6d, 128.1d, 128.4s, 129.2d, 132.8s, 137.6s, 154.8s. Anal. Calcd for $C_{16}H_{14}ClN_3O$: C, 64.11; H, 4.71; Cl, 11.83; N, 14.02. Found: C, 64.14; H, 4.66; Cl, 12.00; N, 14.07.

4.3.3. 5-(4-Acetylphenyl)-2-azidomethyl-2,3-dihydrobenzo[*b*]furan (13). The title compound was prepared in a 77% yield from 4-bromoacetophenone and boronic acid **6c**, mp 75–75 °C. ^{1}H NMR ($CDCl_3$) δ 2.62 (s, 3H), 2.90 (dd, 1H, J=15.9, 6.9 Hz), 3.39 (dd, 1H, J=15.9, 9.5 Hz), 3.51 (dd, 1H, J=13.0, 5.9 Hz), 3.56 (dd, 1H, J=13.0, 3.9 Hz), 5.02 (m, 1H), 6.90 (d, 1H, J=8.3 Hz), 7.42 (d, 1H, J=8.3 Hz), 7.45 (s, 1H), 7.61 (d, 2H, J=8.3 Hz), 7.99 (d, 2H, J=8.3 Hz). ^{13}C NMR ($CDCl_3$) δ 26.5q, 32.6t, 54.5t, 81.7d, 109.9d, 123.9d, 126.6s, 127.7d, 128.9d, 133.0s, 135.3s, 145.6s, 159.4s, 197.6s. Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.49; H, 5.18; N, 14.33.

4.3.4. 4-Acetyl-5′-(2-azidoethyl)-2′-methoxybiphenyl (14). The title compound was prepared in a 68% yield from 4-bromoacetophenone and boronic acid **9**, oil. ^{1}H NMR ($CDCl_3$) δ 2.63 (s, 3H), 2.89 (t, 2H, J=7.3 Hz), 3.52 (t, 2H, J=7.3 Hz), 3.81 (s, 3H), 6.96 (d, 1H, J=8.3 Hz), 7.18–7.24 (several peaks, 2H), 7.63 (d, 2H, J=8.3 Hz), 8.00 (d, 2H, J=8.3 Hz). ^{13}C NMR ($CDCl_3$) δ 26.6q, 34.4t, 52.6t, 55.7q, 111.6d, 128.0d, 129.5d, 129.7d, 130.4s, 131.0d, 135.6s, 143.3s, 155.4s, 197.7s; one quaternary C is missing. Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.14; H, 5.80; N, 14.23. Found: C, 68.69; H, 5.75; N, 14.11.

4.3.5. 5-(2-Azidoethyl)-2,4′-dimethoxybiphenyl (15). The title compound was prepared in a 78% yield from 4-bromoanisol and boronic acid **9**, oil. ^{1}H NMR ($CDCl_3$) δ 2.89 (t, 2H, J=7.3 Hz), 3.52 (t, 2H, J=7.3 Hz), 3.81 (s, 3H), 3.86 (s, 3H), 6.92–6.99 (several peaks, 3H), 7.13–7.18 (several peaks, 2H), 7.45–7.50 (several peaks, 2H). ^{13}C NMR ($CDCl_3$) δ 34.5t, 52.7t, 55.3q, 55.7q, 111.5d, 113.5d, 128.2d, 130.2s, 130.5d, 130.6s, 130.7s, 131.0d, 155.4s, 158.7s. Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.83; H, 6.05; N, 14.83. Found: C, 67.91; H, 6.07; N, 14.68.

4.3.6. 4-Methoxy-3-(4-methoxyphenyl)phenylacetonitrile (16). To a degassed solution of 4-bromoanisol (249 mg, 1.33 mmol) and boronic acid **9** (221 mg, 1 mmol) in 1,2-dimethoxyethane (2.5 mL), $Pd(PPh_3)_4$ (35 mg, ca. 3 mol%) was added, and the mixture was degassed again by pumping—argon refilling. Then a freshly prepared deaerated solution of sodium carbonate (0.8 g) in water (3 mL) was injected through the septum, and the mixture was refluxed for 8 h (palladium black precipitated when the mixture reached an elevated temperature). The mixture was diluted with water, the organic products were extracted with ether, and the extracts were dried ($CaCl_2$) and concentrated in vacuo. The residue was subjected to column chromatography (gradient 2→20% EtOAc in hexane) to afford 82 mg (32%) of the title compound as a white solid, mp 65–67 °C. ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 2H), 3.82 (s, 3H), 3.85 (s, 3H), 6.94–6.98 (several peaks, 3H), 7.22–7.25 (several peaks, 2H), 7.43–7.48 (several peaks, 2H). ^{13}C NMR ($CDCl_3$) δ 22.8t, 55.3q, 55.7q, 111.7d, 113.6d, 118.1s, 122.0s, 127.5d, 130.0s, 130.2d, 130.5d, 131.1s, 156.2s, 158.9s. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.91; H, 5.87; N, 5.43.

The same compound **16** was obtained in 26% yield using boronic acid **9** and 4-chloroanisol essentially as described for compound **17** (see below).

4.3.7. 2-Azidomethyl-7-(4-methoxyphenyl)-2,3-dihydrobenzo[*b*]furan (17). A mixture of boronic acid **6a** (164 mg, 0.75 mmol), 4-chloroanisol (214 mg, 1.5 mmol), toluene (2 mL), $Pd(OAc)_2$ (11 mg, 0.045 mmol), 2-dicyclohexylphosphino-2′-dimethylaminobiphenyl (35 mg, 0.09 mmol) and K_3PO_4 (508 mg) was stirred under argon at 95 °C for 5 h. The reaction mixture was cooled, suspended in toluene (10 mL), silica gel (ca. 3 mL) was added, and the volatile components were removed under reduced pressure. The material thus obtained was loaded on a top of chromatography column packed with silica gel, and the products were eluted with gradient 0→10% EtOAc in hexane to give 72 mg (34%) of the title compound as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 3.10 (dd, 1H, J=15.5, 7.1 Hz), 3.35 (dd, 1H, J=15.5, 9.5 Hz), 3.48–3.57 (several peaks, 2H), 3.85 (s, 3H), 4.98 (m, 1H), 6.93–6.99 (several peaks, 3H), 7.12 (br d, 1H, J=7.3 Hz), 7.28 (br d, 1H, J=7.8 Hz), 7.65 (d, 2H, J=8.8 Hz). ^{13}C NMR ($CDCl_3$) δ 32.9t, 54.5t, 55.3q, 80.9d, 113.8d, 121.4d, 123.4d, 123.6s, 126.5s, 127.7d, 129.4s, 129.5d, 155.9s, 158.9s. Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.18; H, 5.37; N, 14.72.

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Influence of *N*-amino protecting group on aldolase-catalyzed aldol additions of dihydroxyacetone phosphate to amino aldehydes

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Dedicated to Professor Francisco Camps on the occasion of his 70th birthday.

Abstract—This work examines the influence of *N*-protecting groups on the conversion and stereoselectivity of dihydroxyacetone phosphate (DHAP) dependent aldolase-catalyzed aldol additions of DHAP to *N*-protected-3-aminopropanal. Phenylacetyl-(PhAc-), *tert*-butyloxycarbonyl- (^{t}Boc-) and fluoren-9-ylmethoxycarbonyl- (Fmoc-)-3-aminopropanal were evaluated as substrates for D-fructose 1,6-bisphosphate aldolase from rabbit muscle (RAMA), and L-rhamnulose-1-phosphate aldolase (RhuA) and L-fuculose-1-phosphate aldolase (FucA), both from *Escherichia coli*. Using PhAc and ^{t}Boc ca. 70% conversions to the aldol adduct were achieved, whereas Fmoc gave maximum conversions of ca. 25%. The stereoselectivity of the DHAP-aldolases did not depend on the *N*-protected-3-aminopropanal derivative. Moreover, inversion of FucA stereoselectivity relative to that obtained with the natural L-lactaldehyde was observed. Both *N*-PhAc and ^{t}Boc adduct product derivatives were successfully deprotected by penicillin G acylase (PGA)-catalyzed hydrolysis at pH 7 and by treatment with aqueous TFA (6% v/v), respectively. However, the corresponding cyclic imine sugars could not be isolated, presumable due to the presence of a highly reactive primary amine and a keto group in the molecule, which lead to a number of unexpected reactions.

1. Introduction

Aldolases are a class of lyases that catalyze stereoselective aldol additions of aldehydes and ketones,[1,2] constituting powerful tools in the asymmetric synthesis of both conventional and uncommon carbohydrates as well as other complex hydroxylated products.[1–4]

We recently reported aldol additions of DHAP to *N*-benzyloxycarbonyl (Cbz) amino aldehydes catalyzed by D-fructose-1,6-diphosphate aldolase from rabbit muscle (RAMA), and L-rhamnulose-1-phosphate aldolase (RhuA) and L-fuculose-1-phosphate aldolase (FucA), both from *Escherichia coli*.[5,6] These enzymatic reactions afforded, after cleavage of the phosphate group, the corresponding 2-keto-*N*-Cbz-amino-3,4-diols, which can be converted into iminocyclitols, potent inhibitors of glycoprocessing enzymes, by reductive amination.

In the course of our ongoing project on the chemoenzymatic synthesis of iminocyclitols we investigated whether other *N*-blocking groups of the amino aldehyde may also be suitable for the synthesis of these compounds. Furthermore, alternative *N*-protecting groups to suit any further synthetic strategies upon the *N*-protected amino-2-keto-3,4-diols was also pursued. To this end, three *N*-protecting groups for the model aldehyde 3-aminopropanal were selected: phenylacetyl (PhAc), *tert*-butyloxycarbonyl (^{t}Boc) and fluoren-9-ylmetoxycarbonyl (Fmoc). PhAc is structurally similar to Cbz, and it can be cleaved by penicillin amidase (PGA)-catalyzed hydrolysis under mild and selective conditions.[7] Removal of ^{t}Boc requires acidic conditions but less strenuous than simple amides like acetyl.[8] Fmoc group can be eliminated in the presence of secondary amines, such as piperidine, by base induced β-elimination.

Herein, we report on the reactivity and stereoselectivity of RAMA, RhuA and FucA DHAP aldolases as catalysts for aldol additions of DHAP to aldehydes: *N*-(PhAc)-(**1**), *N*-(^{t}Boc)- (**2**) and *N*-(Fmoc)-3-aminopropanal (**3**) (Scheme 1). In this study, we focused on three aspects. First, the influence of two reactions media, namely emulsion

Keywords: DHAP dependent aldolases; Aldol additions; Fmoc group; Boc group; PhAc group; Penicillin amidase.
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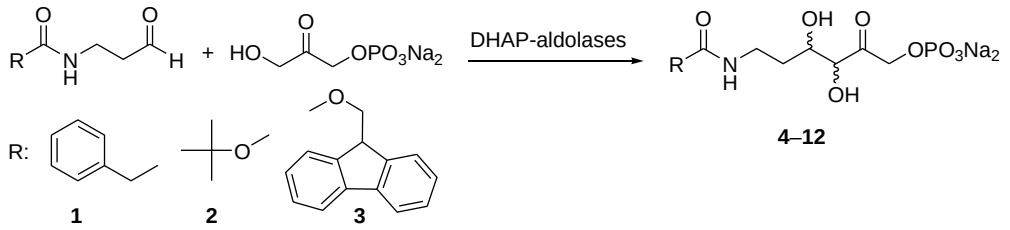


Scheme 1. RAMA, RhuA and FucA DHAP aldolases catalyzed synthesis of products **4–12**.

systems developed and assayed in previous works[9] and cosolvent DMF/H_2O 1:4 mixtures, on the reaction conversion to aldol adducts was investigated. Second, to assess the stereoselectivity of the aldolases towards the three *N*-protected-3-aminopropanal derivatives, the aldol adducts were prepared under the best reaction conditions and their structure and stereochemistry determined. Third, the deprotection reactions of *N*-blocked-2-keto-aminodiol adducts obtained in higher yield were studied.

2. Results and discussion

2.1. Aldolase-catalyzed reactions

Aldol additions of DHAP to aldehydes **1–3** catalyzed by RAMA, RhuA and FucA were investigated in two reaction systems namely high water content emulsions and DMF–H_2O (1/4) cosolvent mixture (Table 1). Three emulsion formulations were employed: $H_2O/C_{14}E_4$/tetradecane, $H_2O/C_{14}E_4$/hexadecane and $H_2O/C_{14}E_4$/squalane always in 90/4/6 wt%, where $C_{14}E_4$ is a technical grade tetra(ethyleneglycol)tetradecyl ether surfactant ($C_{14}H_{29}(OCH_2CH_2)_4OH$), with an average of 4 mol of ethylene oxide per surfactant molecule.[5,9] Both PhAc and the sterically more demanding ^{t}Boc derivatives **1** and **2** were good substrates (Table 1, entries 1, 2, 4, 5, 7 and 8), the conversions to aldol adduct being similar to those achieved with benzyloxycarbonyl (Cbz) *N*-protecting group.[5,6] The most hydrophobic and bulky Fmoc derivative **3** was also tolerated as substrate, although it gave the lowest conversions with the three aldolases (Table 1, entries 3, 6 and 9).

Diastereomeric ratio of aldol adducts **4–12** were assessed by NMR spectroscopy and are summarized in Table 1, last column. The absolute configuration of the newly formed stereogenic centers was assigned assuming that the stereochemistry at the C-3 position depended exclusively on the DHAP aldolase and was conserved upon reaction with any electrophile.[10–16] Hence, epimeric products at C-4 arose from attack on the inverted face of the *N*-protected-3-aminopropanal carbonyl group relative to that on the natural aldehyde. RAMA catalyst was the most stereoselective towards the *N*-protected-3-aminopropanal derivatives, both ^{t}Boc and Fmoc giving the highest diastereomeric excesses (de $>$ 80%). The stereoselectivity of RhuA enzyme was lower (de 40–60%) than that of RAMA, the de with both PhAc and Fmoc being similar to that obtained with the corresponding Cbz derivative.[5] The NMR spectra of the aldol adducts obtained with FucA catalyst were indistinguishable from those observed with RhuA enzyme. Similarly to *N*-Cbz-3-aminopropanal,[6] an inversion of FucA stereoselectivity towards the *N*-protected amino aldehydes **1–3** was observed.

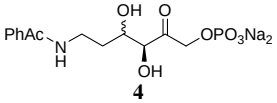
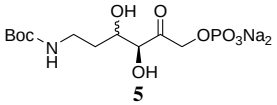
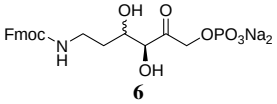
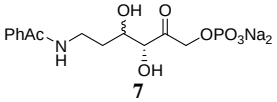
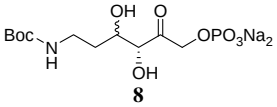
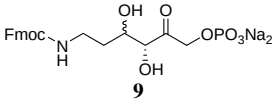
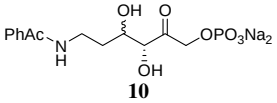
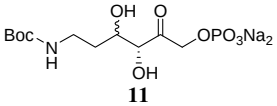
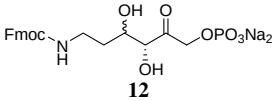
The conversions and diastereomeric ratios shown in Table 1 remained constant up to 24 h of reaction, therefore it was assumed that they reflect the final equilibrium compositions. In a previous paper,[6] we suggested that the stereochemical outcome of the aldol addition of DHAP to Cbz-3-aminopropanal catalyzed by FucA was thermodynamically controlled. To assess if the diastereomeric ratios of the aldol adducts generated from DHAP and PhAc-, ^{t}Boc- and Fmoc-3-aminopropanal correlate with the thermodynamic stability of the corresponding diastereoisomers, an extensive exploration of the conformational space available to adducts **4–12** was carried out. Only the linear forms of these products were considered, since the relative abundance by NMR of the corresponding cyclic forms was always low. The results of these calculations showed that the lowest energy minima conformers of the (3*S*,4*R*), or (3*R*,4*S*), diastereoisomers of adducts **4–12** were always more stable, by approximately 1.5 kcal/mol, than the corresponding (3*S*,4*S*), or (3*R*,4*R*), isomers independently of the protecting group present. Assuming that the entropic contributions to ΔG cancel out, this energetic difference suggests a predicted (3*S*,4*R*):(3*S*,4*S*) or (3*R*,4*S*):(3*R*,4*R*) ratio close to 93:7 at 25 °C, in general good agreement with the ratios shown in Table 1, particularly for the reactions catalyzed by RAMA. The maximal deviation (67:33) was observed for the FucA catalyzed reactions with substrates **1** and **2**.

Altogether, these results suggest that, under our reactions conditions, the major products of the aldolic condensation of aldehydes **1–3** with DHAP catalyzed by RAMA, RhuA and FucA are those thermodynamically favoured, similarly to what was previously observed for the condensation of different *N*-Cbz-aminoaldehydes catalyzed by FucA.[6] Thus, while for RAMA and RhuA catalysts the stereofacial selectivity observed with the natural substrates (glyceraldehyde-3-phosphate and L-lactaldehyde, respectively) was conserved, the contrary was true for FucA and the main adducts formed are those from the 'wrong' face attack (i.e., relative to that with the natural substrate, L-lactaldehyde).

Docking simulations carried out with the different diastereoisomers of products **4–12** bound into the active centre of RAMA and RhuA[†] suggest that in all cases the bulky *N*-protecting group cannot get into the catalytic site of the

[†] We did not attempt to model the FucA complexes because of the difficulty to predict the conformation of the flexible C-terminal tail of the protein.[17]

Table 1. DHAP-dependent aldolase-catalyzed aldol addition of DHAP to *N*-protected-3-aminopropanal derivatives **1–3**

Entry	Acceptor aldehyde	Aldolase (U mL^{-1})	DHAP concn[a] (mM)	Conversion,[b] % (Time, h)		Product	Diastereomeric ratio (C-4) *R*:*S*
				A[c]	B[d]		
1	**1**	RAMA 20	86	66 (3)	65 (2)	 **4**	89:11
2	**2**	RAMA 20	97	66 (4)	70 (6)	 **5**	93:7
3	**3**	RAMA 20	53	25 (1)	19 (2)	 **6**	92:8
4	**1**	RhuA 0.4	100	47 (2)	28 (4)	 **7**	19:81
5	**2**	RhuA 0.4	91	63 (7)	45 (7)	 **8**	30:70
6	**3**	RhuA 0.4	53	15 (6)	15 (6)	 **9**	23:77
7	**1**	FucA 8	45	72 (3)	71 (4)	 **10**	33:67
8	**2**	FucA 8	45	70 (3)	70 (4)	 **11**	33:67
9	**3**	FucA 8	53	20 (2)	18 (2)	 **12**	21:79

[a] Acceptor aldehyde (1.8 equiv mol^{-1}); reaction volume 5 mL. $T=25$ °C.
[b] Molar percent conversion to the aldol adduct (**4**–**12**) with respect to the starting DHAP concentration, determined by HPLC from the crude reaction mixture using purified standards.
[c] High water content emulsions. Reaction conversions to the corresponding aldol adduct in emulsions were similar regardless of the formulation used, therefore, the mean values obtained in the three emulsion systems, $H_2O/C_{14}E_4$/tetradecane, $H_2O/C_{14}E_4$/hexadecane and $H_2O/C_{14}E_4$/squalane 90/4/6 wt%, are always given.
[d] DMF/H_2O 1:4 v/v.

protein and probably remains at the entrance of the cavity, partially exposed to the solvent. This is shown in Figure 1 for the major 3*S*,4*R*-isomers of adducts bearing *N*-PhAc, ^{t}Boc and Fmoc bound in the active centre of RAMA and for the corresponding 3*R*,4*S*- enantiomers in the active center of RhuA. That would explain the little effect of the *N*-protecting groups with different size and shape on the stereochemical outcome of the reactions, since those groups would remain far from the reactive atoms. In addition, it also suggests that the lower yields observed for the Fmoc containing adducts (**6**, **9**, **12**) could be due to the steric hindrance arising from the bulkiest Fmoc moiety, which could difficult the approach of the aldehyde group to the reactive enzyme-bound DHAP.

2.2. Deprotection of the phenylacetyl and *tert*-butyloxycarbonyl groups

The results obtained showed that both PhAc and ^{t}Boc, provided the highest reaction conversions with similar stereoselectivities. At this point, it was also important to establish proper reaction conditions for the *N*-protecting group removal. To this end *N*-PhAc and *N*-^{t}Boc aminopolyols **4** and **5**, and their corresponding unphosphated derivatives, were treated with penicillin acylase at pH 7 and aqueous trifluoroacetic acid, respectively.

Removal of PhAc and ^{t}Boc was achieved quantitatively under the aforementioned conditions (see Section 4). The formation of the six-membered imine sugar, in equilibrium

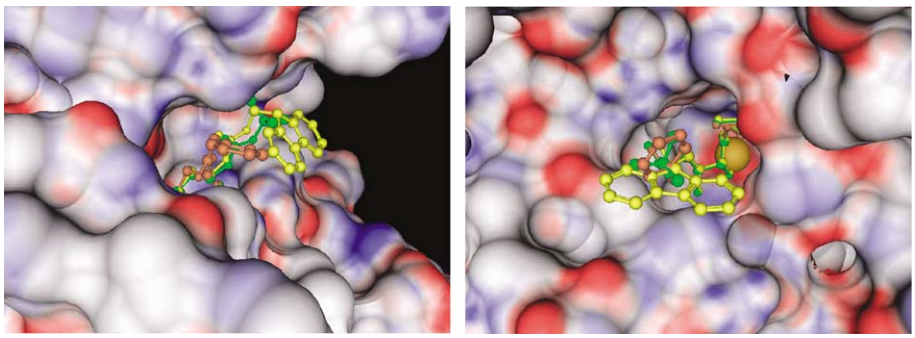


Figure 1. Structures of aldol adducts bearing PhAc (brown), ^{t}Boc (green) and Fmoc (yellow) protecting groups docked into the active center of RAMA (left panel) and RhuA (right panel). Structures on the left panel correspond to the (3*S*,4*R*) diastereoisomers, while those on the right panel correspond to the (3*R*,4*S*) diastereoisomers.

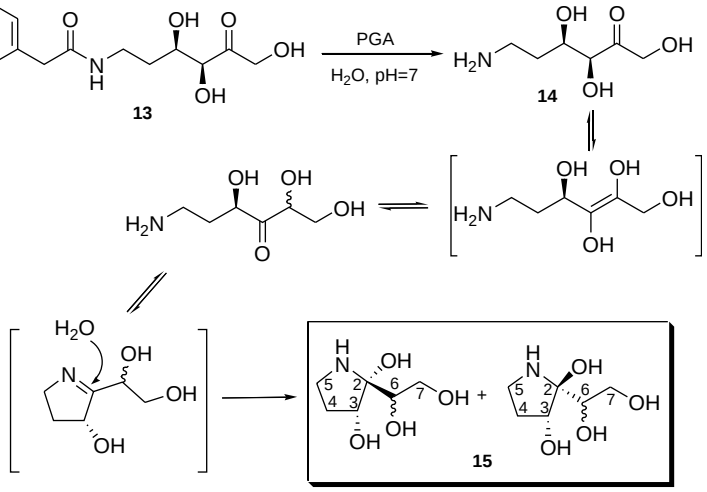
with the corresponding unprotected aminoketopolyol, was the product expected after the deprotection reaction. However, the cyclic imine sugar could not be isolated in any reaction condition. Hence, the NMR spectrum of the residue obtained after PhAc removal of **4** and work up was complex with signals that presumably belong to a number of decomposition products since they can hardly be assigned to any single structure. To avoid any possible influence of the work up on the stability of the final product, the deprotection reaction was performed into an NMR tube and monitored continuously. This experiment confirmed the previous observation: the signals corresponding to the product disappeared while no major product was formed with the exception of phenylacetic acid. On the other hand, the deprotection of unphosphated derivative **13** gave the hemiaminal mixture **15** as the major products. A possible mechanism for the formation of **15** is outlined in Scheme 2. The key step was the enolization of **14** and subsequent shift of the ketone to position 3.

Deprotection of ^{t}Boc blocking group was accomplished by aqueous TFA. It has been reported that treatment of *N*-formyl-aminopolyol with aqueous acid at pH 1 efficiently cleaves the amide, and that at pH 3 the same compound is stable.[8] On this basis and being aware of the sensitivity of these compounds to acids, we decided to perform the deprotection at the lowest possible TFA concentration. We surveyed different TFA concentrations from 1 to 6% and we found that 6% aqueous TFA lead to complete Boc cleavage in 24 h. The reaction was monitored by NMR and, in agreement with the expectations, the spectra revealed the presence of the linear compound **16** in equilibrium with the cyclic imine **17** (Scheme 3).

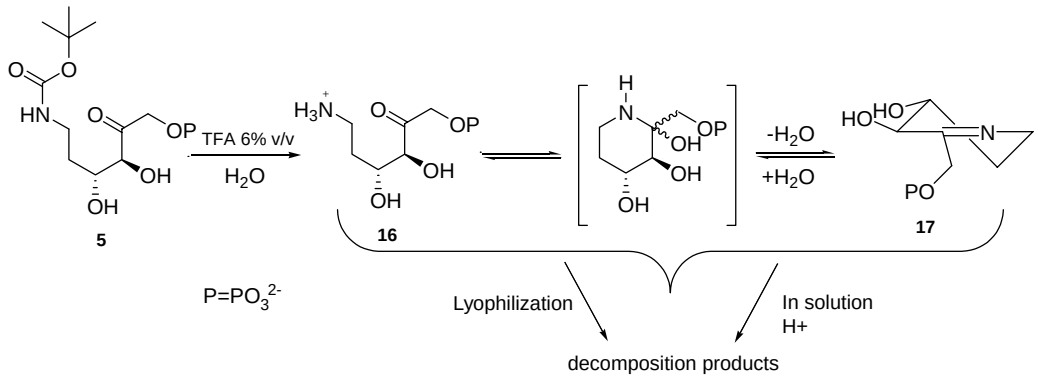
Nevertheless, the resulting imine could not be isolated and after lyophilization, the NMR spectrum revealed a mixture of decomposition products. Besides, when the reaction mixture was left for more than 10 days, the solution turned dark and no single compound could be assigned by NMR. A similar result was also found for the ^{t}Boc deprotection of unphosphated derivative of **5**.

3. Conclusions

The results obtained demonstrated that DHAP-aldolases tolerate a variety of *N*-protecting groups for the 3-amino-propanal. The outcome of the reaction performance, however, depended on the protecting group. Thus, ca. 70% conversion to aldol adduct were achieved with PhAc



Scheme 2. Deprotection of **13** by penicillin G acylase.



Scheme 3. Deprotection of **5** by aqueous TFA (6%).

and ^{t}Boc, similar to those obtained before with Cbz, whereas Fmoc gave ca. 20% conversion. Modifications on the protecting group structure, however, did not affect the stereoselectivity of the aldolases to a significant extent, nor the inversion of FucA stereoselectivity towards the *N*-protected derivatives of 3-aminopropanal. *N*-PhAc and ^{t}Boc adduct product derivatives were successfully deprotected by PGA-catalyzed hydrolysis at pH 7 and with aqueous TFA (6% v/v) respectively. However, the corresponding six-membered imine sugar could not be isolated, even though under the mild reactions conditions used with the PGA. When, *N*-PhAc was deprotected from the unphosphated derivatives a five-membered iminocyclytol was identified. When both phosphated or Boc derivatives were deprotected a complex NMR spectra were recorded after lyophilization with signals that presumably belong to a number of decomposition products. This behaviour may be due to the presence of a highly reactive primary amine and a keto group in the molecule, which lead to a number of unexpected reactions. The situation was different with the previously reported benzyloxycarbonyl group (Cbz).[5,6] In this case, the hydrogenolysis of the Cbz and the reductive amination took place in one pot reaction, safely catching the imine intermediate being less prone to side reactions.

Protecting groups such as PhAc, ^{t}Boc and, Cbz provide also a range of removal conditions to fulfill most of the required orthogonalities for functional group manipulation on the 2-ketoaminodiols.

4. Experimental

4.1. Materials

Fructose-1,6-diphosphate aldolase from rabbit muscle (RAMA; EC 4.1.2.13, crystallized, lyophilized powder, 19.5 U mg^{-1}) was from Fluka (Buchs, Switzerland). Rhamnulose 1-phosphate aldolase (RhuA; EC 4.1.2.19, suspension 100 U mL^{-1}) was kindly donated by Boehringer Mannhein (Mannhein, Germany). L-Fuculose-1-phosphate aldolase (FucA, EC 4.1.2.17, lyophilized 500–800 U g^{-1}) was from Departament d'Enginyeria Química of the Universitat Autònoma de Barcelona, produced from a recombinant *E. coli* (ATCC no. 86984) and purified by affinity chromatography. Acid phosphatase (PA, EC 3.1.3.2, 5.3 U mg^{-1}) was from Sigma (St. Louis, USA). Penicillin Amidase, immobilized on Eupergit® C from *E. coli* (EC 3.5.1.11, 100 U g^{-1} immobilized preparation) was from Fluka. Non-ionic polyoxyethylene ether surfactant with an average of 4 mol of ethylene oxide per surfactant molecule ($C_{14}E_4$) was from Albright and Wilson (Barcelona, Spain). The precursor of dihydroxyacetone phosphate (DHAP), dihydroxyacetone phosphate dimer bis (ethyl ketal), was synthesized in our lab using a procedure described by Jung et al.[18] with slight modifications.

Molecular modelling. Molecular simulations were conducted with the programs MOE (v. 2004.03, Chemical Computing Group, Montreal). The conformational space of all the possible diastereoisomers of adducts **4–6** was exhaustively searched using the systematic conformational search algorithm implemented in MOE, and the conformations generated were minimized and ranked according to their energy, as previously decribed.[5] These energy calculations were carried out using the implemented MMFF94x force field with its standard atomic charges and parameters,[19] and the Born continuum solvation model[20–22] without cut-offs. Geometries were optimized up to an RMS gradient <0.01.

Docked structures of the stereoisomers of products **4–6** in the active centres of RAMA and RhuA were determined by sampling the conformational space of the products in the enzyme environment. The methodology used was similar to that previously described.[5] However, in this case we used the above mentioned MMFF94x force field and the Born continuum salvation model, with a smoothed cut-off between 14 and 15 Å to model the nonbonded interactions.

4.2. General methods

HPLC analyses. HPLC analyses were performed on a RP-HPLC cartridge, 250×4 mm filled with Lichrosphere® 100, RP-18, 5 μm from Merck (Darmstadt, Germany). Samples (50 mg) were withdrawn from the reaction medium, dissolved with methanol to stop any enzymatic reaction, and analyzed subsequently by HPLC. The solvent system was the following: solvent A: 0.1% v/v trifluoroacetic acid (TFA) in H_2O, solvent B: 0.095% v/v TFA in H_2O/CH_3CN 1:4. Elution conditions for *N*-PhAc and *N*-^{t}Boc derivatives: isocratic 10% B during 2 min followed by a gradient from 10 to 33% B over 18 min; elution conditions for *N*-Fmoc derivatives: gradient from 30 to 90% B over 30 min, always

at a flow rate of 1 mL min^{-1} and detection at 215 nm. Retention factors (k') for the acceptor aldehydes and condensation products are given below.

NMR analysis. High field ^1H and ^{13}C nuclear magnetic resonance (NMR) analyses were carried out at the Servei de Ressonància Magnètica Nuclear, Universitat Autònoma de Barcelona using an AVANCE 500 BRUKER spectrometer for D_2O solutions. Full characterization of the described compounds was performed using typical gradient-enhanced 2D experiments: COSY, NOESY, HSQC and HMBC, recorded under routine conditions. When possible, NOE data was obtained from selective 1D NOESY versions using a single pulsed-field-gradient echo as a selective excitation method and a mixing time of 500 ms. When necessary, proton and NOESY experiments were recorded at different temperatures in order to study the different behaviour of the exchange phenomena to avoid the presence of false NOE cross-peaks that difficult both structural and dynamic studies. ^1H (300 MHz) and ^{13}C NMR (75 MHz) spectra were carried out at the Instituto de Investigaciones Químicas y Ambientales-CSIC.

Elemental analyses. Elemental analyses were performed by the Servei de Microanàlisi Elemental IIQAB-CSIC.

4.3. Synthesis of *N*-protected amino aldehydes

The synthesis of *N*-protected amino aldehydes was carried out in two steps. First, the *N*-protected 3-aminopropanol was obtained and second the oxidation of the alcohol group to aldehyde was performed.

4.4. Synthesis of *N*-protected amino alcohols

4.4.1. *N*-(3-Hydroxypropyl)-2-phenylacetamide. To a cooled (−20 °C) solution of 3-amino-1-propanol (9.2 mL, 122.5 mmol) in CH_2Cl_2 (40 mL) was added dropwise phenylacetyl chloride (8 mL, 60.1 mmol) in CH_2Cl_2 (4 mL) and, simultaneously, an aqueous solution of NaOH (2.4 g, 60 mmol) in water (8 mL) under vigorous stirring. After the addition was complete, the reaction was kept at −20 °C for 2 h and then allowed to warm to room temperature under stirring overnight. Then, the crude reaction mixture was evaporated under vacuum to dryness, the residue was dissolved with ethyl acetate and washed successively with citric acid 5% w/v (3×50 mL), $NaHCO_3$ 10% w/v (3×50 mL) and brine (3×50 mL). After being dried over Na_2SO_4, the organic layer was evaporated under reduced pressure to yield **3** as a white solid (8.1 g, 70%, 99% pure by HPLC). The ^1H and ^{13}C NMR spectra were consistent with those reported in the literature.[23]

4.4.2. *tert*-Butyl-3-hydroxypropylcarbamate. To a solution of 3-amino-1-propanol (4.3 mL, 57.1 mmol) in CH_2Cl_2 (3 mL) at 25 °C was added dropwise a solution of $(Boc)_2O$ (12.5 g, 57.1 mmol) in CH_2Cl_2 (7 mL). After 12 h, the mixture was worked up as described above to yield **4** as a colourless oil (6.4 g, 64%, 99% pure by HPLC), whose ^1H and ^{13}C NMR spectra matched those reported.[24]

4.4.3. Fluoren-9-yl-3-hydroxypropylcarbamate. The synthesis of the title compound was performed by a procedure described previously in our lab using Fmoc-OSu as acylating agent.[5] The compound was obtained as a white solid (3.6 g, 90%, 99% pure by HPLC). The ^1H NMR spectrum matched that reported.[25] ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 157.3 (CONH), 143.7, 141.2, 127.6, 126.9, 124.9 (Fmoc), 66.5 (OCH_2), 59.3 (CH_2OH), 47.2 ($NHCH_2$), 37.4 (*C*H), 32.5 (CH_2CH_2OH).

4.5. Synthesis of *N*-protected aminoaldehydes

The synthesis of *N*-protected amino aldehydes was achieved by 2-iodoxobenzoic acid (IBX) oxidation method.[26,27] Caution! IBX has been reported to detonate upon heavy impact and/or heating over 200 °C. To a solution of the *N*-protected amino aldehyde (10–19 mmol) in DMSO (60–120 mL), IBX (24–48 mmol) was added. The reaction was monitored by HPLC until no alcohol was detected. At this point, the reaction mixture was diluted with water (30–60 mL) and the mixture was extracted with ethyl acetate (3×75–100 mL). The organic layers were pooled, washed with $NaHCO_3$ 5% (w/w) (3×100 mL) and brine (3×100 mL), dried over Na_2SO_4 and evaporated under reduced pressure.

4.5.1. *N*-(3-Oxopropyl)-2-phenylacetamide (PhAc-aminopropanal) (1). The title compound (1.04 g) was obtained as a white solid in 52% yield by using the above general procedure. HPLC $k'=7.05$. ^1H NMR (300 MHz, $CDCl_3$, ppm): $\delta=9.7$ (1H, s, CHO), 3.5 (2H, s, CH_2CO), 3.4 (2H, q, $NHCH_2$), 2.6 (2H, t, CH_2CHO). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 201.0 (CHO), 171.1 (CONH), 43.6 ($NHCH_2$), 33.0 (CH_2CHO).

4.5.2. *tert*-Butyl-3-oxoethylcarbamate (^{t}Boc-aminopropanal) (2). The title compound (1.7 g) was obtained as a pale yellow oil in 90% yield by using the above general procedure. HPLC $k'=9.17$. ^1H NMR[28] (300 MHz, $CDCl_3$, ppm): 9.7 (1H, s, CHO), 5.0 (1H, br, NH), 3.3 (2H, q, $NHCH_2$), 2.6 (2H, t, CH_2CHO), 1.3 (9H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 201 (CHO), 155.7 (CONH), 79.3 ($OC(CH_3)_3$), 44.2 ($NHCH_2$), 33.9 (CH_2CHO), 28.3 (CH_3).

4.5.3. Fluoren-9-yl-3-oxoethylcarbamate (Fmoc-aminopropanal) (3). The title compound (1.7 g) was obtained as a pale yellow solid in 98% yield by using the above general procedure. HPLC $k'=9.42$. The ^1H NMR spectrum matched that reported.[29] ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 201.2 (CHO), 157.0 (CONH), 143.7, 141.2, 127.5, 126.9, 124.9 (Fmoc), 66.6 (OCH_2), 47.1 (CH_2CHO), 43.9 (*C*H), 34.3 ($NHCH_2$).

4.6. Enzymatic aldol condensations

Enzymatic aldol condensations in emulsions. Reactions were carried out in 10 mL test tubes with screw caps. The aldehyde (0.23–0.90 mmol), the oil (6% w/w) and the surfactant (4% w/w) were mixed vigorously. Then, the DHAP solution (0.13–0.50 mmol) at pH 6.9, freshly prepared as described by Effenberger et al.,[30] was added dropwise while stirring at 25 °C with a vortex mixer. The final reaction volume was 5 mL. Finally, RAMA (100 U), RhuA (2 U) or FucA (40 U) was added and mixed again.

The test tubes were placed on a horizontal shaking bath (100 rpm) at constant temperature (25 °C). The reactions were followed by HPLC until the peak of the product reached a maximum. The enzymatic reactions were stopped by addition of MeOH. Then, the methanol was evaporated and the aqueous solution washed with ethyl acetate to remove the unreacted *N*-protected amino-aldehyde. The aqueous layer was collected and lyophilized. The residue was dissolved in water, adjusted to pH 3 with trifluroacetic acid (TFA) and purified by reversed phase HPLC on a Perkin-Elmer semipreparative 250×25 mm column, filled with C18, 10 μm type stationary phase and eluted using a CH_3CN gradient (8–56% in 30 min; 24–72% in 30 min for the Fmoc derivative) in 0.10% (v/v) aqueous TFA. The best fractions were pooled, diluted, re-loaded onto the column and eluted with a CH_3CN gradient (0% 10 min and then 0–56% in 30 min) in plain water to eliminate the TFA. The pure fractions were pooled and lyophilized.

Enzymatic aldol condensations in mixtures water/dimethylformamide 4:1. Reactions were carried out in 10 mL test tubes with screw caps. The aldehyde (0.4–0.9 mmol) was dissolved in DMF 20% (v/v). Then, the DHAP solution (0.23–0.50 mmol), prepared as described above, was added dropwise while mixing. The rest of the experimental procedure was identical to that described for the reaction in emulsions.

The yields of the compounds **4**–**12** correspond to the amounts from of the aldol enzymatic reactions at semipreparative level. Most of them contained salts from the purification process. The purification procedures were not optimized.

4.6.1. (3*S*,4*R*)-5,6-Dideoxy-[(phenylacetyl)amino]-1-*O*-phosphonohex-2-ulose sodium salt and (3*S*,4*S*)-5,6-dideoxy-[(phenylacetyl)amino]-1-*O*-phosphonohex-2-ulose sodium salt (4). The title compounds were obtained as a mixture in a proportion of 89:11, respectively, following the general methodology described above. 219 mg, 35%, 99.5% purity by HPLC ($k'=2.79$). $[\alpha]_D^{20}$ +6.7 (*c* 1 in H_2O/MeOH 5:95) and $[\alpha]_D^{20}$ +12.9 (*c* 1 in H_2O/MeOH 1:1). ^1H NMR (500 MHz, D_2O, ppm): δ 7.24 (5H, m, Ph), 4.55 (2H, dd, $J=6.3$, 18.8 Hz, CH_2OP), 4.27 (1H, d, $J=1.7$ Hz, C*H*OH), 4.00 (1H, br t, $J=5.9$ Hz, C*H*(*R*)OH), 3.47 (2H, s, PhCH_2), 3.18 (2H, t, $J=6.9$ Hz, NHCH_2), 1.66 (2H, m, NHCH$_2$CH_2C(*R*)HOH); minor signals corresponding to the diastereomer 3*S*,4*S*: δ 3.79 (1H, m, C*H*(*S*)OH), 1.56 (2H, m, NHCH$_2$CH_2CH(*S*)OH). ^{13}C NMR (125 MHz, D_2O, ppm): δ 211.1 (CO), 174.5 (OCONH), 134.9 (C ar), 128.9 (CH ar), 128.7 (CH ar), 127.1 (CH ar), 77.4 (CHOH), 69.0 (CHOH), 67.8 (CH_2OP), 42.2 (CH_2), 36.1 (CH_2), 31.6 (CH_2). (Found: C, 38.22; H, 4.62; N, 3.22. $C_{14}H_{18}NO_8Na_2P\cdot 1/2H_2O\cdot 1/2NaCl$ requires: C, 37.92; H, 4.32; N, 3.16%).

4.6.2. (3*S*,4*R*)-5,6-Dideoxy-{[(*tert*-butyloxy)carbonyl]amino}-1-*O*-phosphonohex-2-ulose sodium salt and (3*S*,4*S*)-5,6-dideoxy-{[(*tert*-butyloxy)carbonyl]amino}-1-*O*-phosphonohex-2-ulose sodium salt (5). The title compounds were obtained as a mixture in a proportion of 93:7, respectively, following the general methodology described above. 203 mg, 47%, 99.5% purity by HPLC ($k'=3.81$). $[\alpha]_D^{20}$ +18.8 (*c* 1 in H_2O/MeOH 5:95). ^1H NMR (500 MHz, D_2O, ppm): δ 4.56 (2H, dd, $J=5.9$, 6.3, 18.9 Hz, CH_2OP), 4.21 (1H, d, $J=1.4$ Hz, C*H*OH), 4.03 (1H, br t, $J=7.7$ Hz, C*H*(*R*)OH), 3.06 (2H, m, NHCH_2), 1.64 (2H, br m, CH_2), 1.30 (9H, s, CH_3); minor signals corresponding to the diastereoisomer 3*S*,4*S*: δ 4.3 (1H, s, C*H*(*S*)OH), 3.84 (1H, m, C*H*OH), 1.53 (2H, m, CH_2). ^{13}C NMR (125 MHz, D_2O, ppm): δ 210.1 (CO), 158.0 (OCONH), 80.6 (C), 77.5 (CHOH), 68.9 (CHOH), 67.70 (CH_2OP), 36.6 (CH_2), 32.2 (CH_2), 27.5 (CH_3); minor signals corresponding to the diastereoisomer 3*S*,4*S*: 77.6 (CHOH), 69.4 (CHOH), 68.4 (CH_2OP). (Found: C, 31.83; H, 5.62; N, 3.34. $C_{11}H_{20}NNa_2O_9P\cdot 3/2H_2O$ requires: C, 31.89; H, 5.60; N, 3.38%).

4.6.3. (3*S*,4*R*)-5,6-Dideoxy-{[(fluoren-9-ylmetoxy)carbonyl]amino}-1-*O*-phosphonohex-2-ulose sodium salt and (3*S*,4*S*)-5,6-dideoxy-{[(fluoren-9-ylmetoxy)carbonyl]-amino}-1-*O*-phosphonohex-2-ulose sodium salt (6). The title compounds were obtained as a mixture in a proportion of 92:8, respectively, following the general methodology described above. 31 mg, 23%, 99.5% purity by HPLC ($k'=$ 7.48 broad peak). Due to signal overlapping and for the sake of simplicity, the NMR spectra were recorded for the unphosphated derivatives of **6**. ^1H NMR (500 MHz, D_2O, ppm): δ 7.84 (2H, d, $J=7.5$ Hz, Ph), 7.66 (2H, d, $J=$ 7.4 Hz, Ph), 7.41 (2H, t, $J=7.4$ Hz, Ph), 7.33 (2H, t, $J=$ 7.4 Hz, Ph), 4.50 (2H, dd, $J=19.3$, 46.6 Hz, CH_2OP), 4.37 (2H, m, CH_2O), 4.22 (H, t, $J=6.8$ Hz, C*H*–CH_2O), 4.14 (H, d, $J=2.1$ Hz, C*H*(R)OH), 4.01–3.98 (1H, m, C*H*OH), 3.29–3.22 (2H, m, NHCH_2), 1.82–1.72 (2H, m, NHCH$_2$-CH_2C(*R*)HOH). Signals corresponding to the diastereomer (4*S*): 4.10 (H, d, $J=5.7$ Hz, C*H*(R)OH), 3.87 (1H, br, C*H*OH). ^{13}C NMR (125 MHz, D_2O, ppm): δ 215.8 (CO), 161.4 (OCONH), 147.8 (C), 145.0 (C) 131.2, 130.6, 128.6, 123.4 (arom), 81.9 (*C*H(OH)CO), 73.8 (*C*H(OH)-CH(OH)CO), 70.3 (*C*H$_2$–O–CO), 70.1 (*C*H$_2$OH), 48.22 (*C*H–CH$_2$–O–), 41.0 (CH_2), 36.8 (CH_2). (Found: C, 22.36; H, 1.15; N, 0.48. $C_{21}H_{22}NNa_2O_9P\cdot 7NaCl\cdot 7CF_3COONa$ requires: C, 22.47; H, 1.19; N, 0.75%). Unphosphated derivative: (Found: C, 62.28; H, 6.44; N, 3.64. $C_{21}H_{23}NO_6\cdot H_2O$ requires: C, 62.52; H, 6.27; N, 3.45%).

4.6.4. (3*R*,4*S*)-5,6-Dideoxy-[(phenylacetyl)amino]-1-*O*-phosphonohex-2-ulose sodium salt and (3*R*,4*R*)-5,6-dideoxy-[(phenylacetyl)amino]-1-*O*-phosphonohex-2-ulose sodium salt (7). The title compounds were obtained as a mixture in a proportion of 81:19, respectively, following the general methodology described above. 376 mg, 49%, 99.5% purity by HPLC ($k'=2.79$). $[\alpha]_D^{20}$ −12.0 (*c* 1 in H_2O/MeOH 5:95). NMR spectra were undistinguishable from those obtained for the corresponding diastereoisomers **4**. (Found: C, 34.31; H, 3.68; N, 2.47 $C_{14}H_{18}NNa_2O_8P\cdot CF_3COONa$ NaCl requires: C, 34.36; H, 3.60; N, 2.50%).

4.6.5. (3*R*,4*S*)-5,6-Dideoxy-{[(*tert*-butyloxy)carbonyl]amino}-1-*O*-phosphonohex-2-ulose sodium salt and (3*R*,4*R*)-5,6-dideoxy-{[(*tert*-butyloxy)carbonyl]amino}-1-*O*-phosphonohex-2-ulose sodium salt (8). The title compounds were obtained as a mixture in a proportion of 70:30, respectively, following the general methodology

described above. 115 mg, 37%, 99.5% purity by HPLC ($k'=3.81$). $[\alpha]_D^{20}$ −11.8 (*c* 1 in H_2O/MeOH 5:95). NMR spectra were undistinguishable from those obtained for the corresponding diastereoisomers **5**. (Found: C, 30.53; H, 5.40; N, 3.14. $C_{11}H_{20}NNa_2O_9P\cdot 1/2H_2O\cdot NaCl$ requires: C, 30.53; H, 5.12; N, 3.24%).

4.6.6. (3*R*,4*S*)-5,6-Dideoxy-{[(fluoren-9-ylmetoxy)carbonyl]amino}-1-*O*-phosphonohex-2-ulose sodium salt and (3*R*,4*R*)-5,6-dideoxy-{[(fluoren-9-ylmetoxy)carbonyl]-amino}-1-*O*-phosphonohex-2-ulose sodium salt (9). The title compounds were obtained as a mixture in a proportion of 77:23, respectively, following the general methodology described above. 12 mg, 4%, 99.5% purity by HPLC ($k'=$ 7.48 broad peak). Due to signal overlapping and for the sake of simplicity, the NMR spectra were recorded for the unphosphated derivatives and were undistinguishable from those obtained for the corresponding diastereoisomers **6**. (Found: C, 34.97; H, 4.23; N, 2.15. $C_{21}H_{22}NNa_2O_9P\cdot 5H_2O\cdot 2NaCl$ requires: C, 35.21; H, 4.50; N, 1.96%); Unphosphated derivative: (Found: C, 59.21; H, 6.36; N, 3.07. $C_{21}H_{23}NO_6\cdot 9/4H_2O$ requires: C, 59.22; H, 6.51; N, 3.29%).

4.6.7. (3*R*,4*R*)-5,6-Dideoxy-[(phenylacetyl)amino]-1-*O*-phosphonohex-2-ulose sodium salt and (3*R*,4*S*)-5,6-dideoxy-[(phenylacetyl)amino]-1-*O*-phosphonohex-2-ulose sodium salt (10). The title compounds were obtained as a mixture in a proportion of 33:67, respectively, following the general methodology described above. 255 mg, 35%, 99.5% purity by HPLC ($k'=2.79$). $[\alpha]_D^{20}$ −11.4 (*c* 1 in H_2O/MeOH 5:95). NMR spectra were undistinguishable from those obtained for the corresponding diastereoisomers **4**. (Found: C, 34.52; H, 4.32; N, 3.14. $C_{14}H_{18}NNa_2O_8P\cdot 3/2H_2O$ NaCl requires: C, 34.27; H, 4.31; N, 2.85%).

4.6.8. (3*R*,4*R*)-5,6-Dideoxy-{[(*tert*-butyloxy)carbonyl]-amino}-1-*O*-phosphonohex-2-ulose sodium salt and (3*R*,4*S*)-5,6-dideoxy-{[(*tert*-butyloxy)carbonyl]amino}-1-*O*-phosphonohex-2-ulose sodium salt (11). The title compounds were obtained as a mixture in a proportion of 33:67, respectively, following the general methodology described above. 143 mg, 22%, 99.5% purity by HPLC ($k'=3.81$). $[\alpha]_D^{20}$ −10.4 (*c* 1 in H_2O/MeOH 5:95). NMR spectra were undistinguishable from those obtained for the corresponding diastereoisomers **5**. (Found: C, 30.58; H, 5.63; N, 3.30. $C_{11}H_{20}NNa_2O_9P\cdot 5/2H_2O$ requires: C, 30.56; H, 5.83; N, 3.24%).

4.6.9. (3*R*,4*R*)-5,6-Dideoxy-{[(fluoren-9-ylmetoxy)carbonyl]amino}-1-*O*-phosphonohex-2-ulose sodium salt and (3*R*,4*S*)-5,6-dideoxy-{[(fluoren-9-ylmetoxy)carbonyl]-amino}-1-*O*-phosphonohex-2-ulose sodium salt (12). The title compounds were obtained as a mixture in a proportion of 21:79, respectively, following the general methodology described above. 41 mg, 22% (contained some salts), 99.5% purity by HPLC ($k'=7.48$ broad peak). Due to signal overlapping and for the sake of simplicity, the NMR spectra were recorded for the unphosphated derivatives and were undistinguishable from those obtained for the corresponding diastereoisomers **6**. (Found: C, 21.70; H, 1.75; N, 0.82. $C_{21}H_{22}NNa_2O_9P\cdot H_2O\cdot 10NaCl\cdot 2CF_3COONa$ requires: C, 21.70; H, 1.72; N, 1.01%). Unphosphated derivative: (Found: C, 61.12; H, 6.65; N, 3.13. $C_{21}H_{23}NO_6\cdot 3/2H_2O$ requires: C, 61.16; H, 6.35; N, 3.40%).

4.7. Removal of protecting groups

4.7.1. Removal of phosphate group. The phosphate group of compounds **4**–**12** was removed by hydrolysis catalyzed by acid phosphatase following the procedure described by Bednarski et al.[31] The reaction was followed by HPLC until no starting material was detected. Then the crude was desalted by HPLC and lyophilized.

4.7.2. Removal of *N*-phenylacetyl (PhAc) protecting group by penicillin G acylase. Compound **4**, or the corresponding unphosphated analogue (0.320 mmol, 90 mg) was dissolved in plain water (5 mL). To this solution was added penicillin amidase immobilized on Eupergit® (100 mg). The pH was controlled by a pH meter and maintained between 6.5 and 7 by additions of NaOH 0.1 M. Samples were withdrawn every 45 min and analyzed by HPLC, a peak corresponding to the phenylacetic acid appeared. When no signal of the starting material was detected, the immobilized enzyme was filtered off. Then, the phenylacetic acid was eliminated by anion exchange chromatography on a Macroprep High-Q support eluting with plain water. Finally, the product, which was not retained under the elution conditions, was lyophilized.

4.7.3. Removal of *N*-*tert*-butyloxycarbonyl (^{t}Boc) protecting group by trifluoroacetic acid. Compound **5**, or the corresponding unphosphated analogue, (0.162 mmol) was dissolved in plain water (9 mL). To this solution was added an aqueous solution of TFA (1.2 mL, 1:1 TFA/H_2O). Samples were withdrawn every 45 min and analyzed by HPLC. After 14 h, no signal of the starting material was detected. Then the crude was lyophilized.

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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.2005.12.031. ^{1}H NMR and ^{13}C spectra of **4**–**12**, ^{1}H NMR spectrum of the residue after work up and lyophilization of the penicillin acylase-catalyzed removal of phenylacetyl amino protecting group of **5**; ^{1}H NMR reaction monitoring of the deprotection reaction using penicillin acylase and ^{1}H NMR spectrum of **15**–**17** are supplied.

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Diastereoselective synthesis of aziridine esters via amino selanyl esters

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Abstract—A synthesis of aziridine esters based on the cyclisation of amino selanyl esters induced by the selanyl group activation was developed with either the Meerwein salt or NBS. Two asymmetric approaches are proposed: the diastereoselective reductions of α-selanyl β-iminoesters derived from α-oxoesters, which lead to cis chiral aziridine esters **6** and **6′**; and the diastereoselective conjugate additions of a chiral amide to α,β-unsaturated esters providing trans chiral aziridine esters **6** and **6″**.

1. Introduction

The aziridine moiety is present in a wide variety of natural biologically active compounds like antitumor and antibiotic agents.[1] Synthetic aziridines exhibit multiple biological properties, such as enzyme inhibitors[2] and DNA alkylation agents since their ring strain. They are, in particular, susceptible for regio- and stereoselective ring opening.[3] Thus, they are useful precursors for diverse nitrogen containing compounds,[4] notably chiral amino acids.[5]

Several reviews have surveyed the asymmetric synthesis of aziridines.[6] One pathway to obtain chiral aziridines consists of the addition of nitrenoid compounds to alkenes,[7] or of carbenes to imines,[8] in presence of asymmetric catalysts. Nonetheless, the conceptually simplest approach relies on the nucleophilic attack of a nitrogen atom on an adjacent carbon atom bearing a leaving group.[9] In this manner, enantiomerically pure starting materials such as amino acids, carbohydrates or hydroxy acids can be used and lead to aziridines after displacement of the hydroxyl group through a S_N2 process.[10] Similarly, aziridine synthesis by derivation of a sulfonium group has been reported.[11]

The selanyl group is known to be easily displaced under mild conditions by nucleophiles when it has an activated IV oxidation state, such as selenone or selenonium salt.[12] Thus, epoxides formation from β-hydroxy selenides through intramolecular substitution is well documented.[13] Our laboratory is interested in selenium methodology, which has provided useful synthetic tools for organic chemists.[14] Previously reported work, bifunctional synthons such as α-selanyl carbonyl derivatives have especially been investigated.[15] We developed specific methods to prepare α-selanyl imines, which after reduction led to the corresponding β-selanyl amines that are potential precursors of aziridines. We first promoted the cyclisation of β-selanyl amines using Meerwein salt, which was subsequently improved using *N*-bromosuccinimide (NBS).[16,17] The synthesis of non-functionalized aziridines from α-selanyl aldehydes and α-selanyl ketones has recently been reported.[17b]

We next focussed our attention on the preparation of chiral aziridine esters. Indeed we had observed a *syn* diastereoselection during the reduction of imines derived from β-selanyl α-oxoesters.[16] Treatment of the *syn* configured β-selanyl α-aminoesters by the Meerwein salt provided corresponding *cis* aziridine esters. In continuation of this work, herein we report a comparison between the Meerwein salt and NBS activation of these substrates, and our attempt to access chiral aziridine esters by introducing an additional asymmetric centre on the amine group (path A, Scheme 1). We also propose a new pathway that would provide aziridine esters via β-amino α-selanylesters prepared from α,β-unsaturated esters (path B, Scheme 1).

2. Results and discussion

β-Selanyl α-oxoesters **1** were first converted into *N*-benzyl imines in presence of titanium tetrachloride (Scheme 2).

Keywords: Selenium activation; Synthetic aziridines; Meerwein salt; N. Bromosuccinimide.
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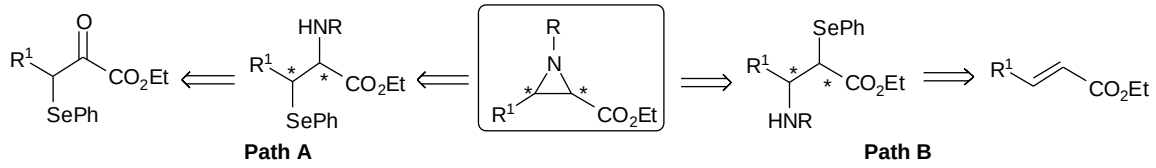
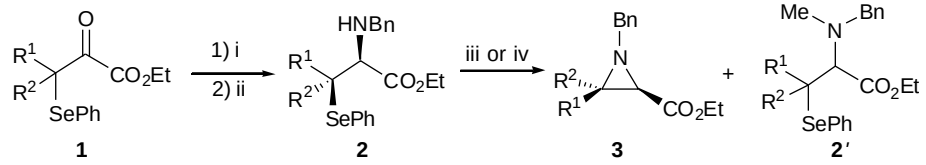


Scheme 1.



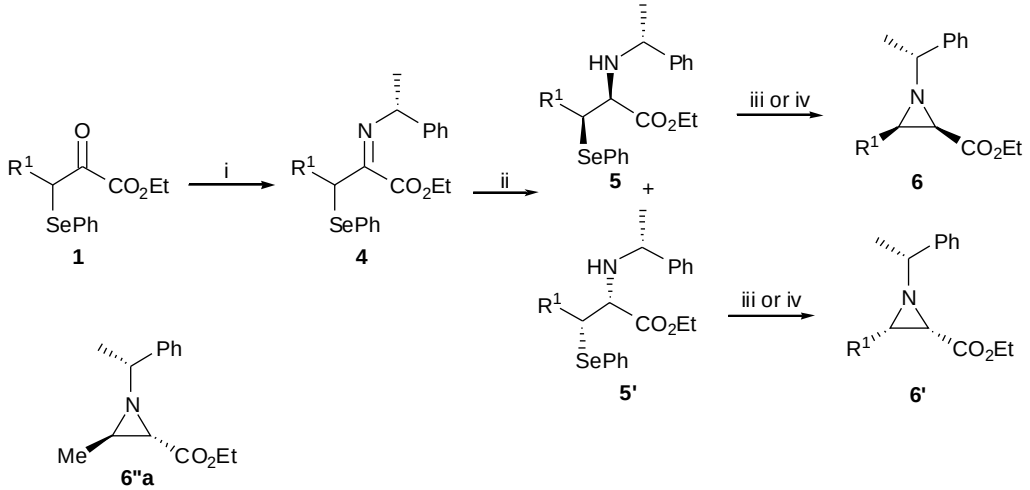
Scheme 2. (i) $BnNH_2$ (4 equiv), $TiCl_4$, Et_2O, 20 °C, 4 h; (ii) $NaBH_3CN$ (0.5 equiv), AcOH, EtOH, 0 °C, 1 h; (iii) Me_3OBF_4 (2 equiv), CH_2Cl_2, 12 h then NaOH aq 1 N; (iv) NBS (1.1 equiv), CH_3CN, 5 min then Na_2CO_3.

Reduction to the amine was performed with sodium cyanoborohydride as it had been shown that this reducing agent limits the deselenenylation of the substrates.[15a] Only one diastereomer was observed in the NMR for the corresponding β-selanyl α-aminoesters **2**. Methylation of the selanyl group with the Meerwein salt and treatment with base led to aziridine esters **3** in 48–61% yields (Table 1). The characteristic aziridine coupling constant J_{H2-H3} allowed us to unambiguously assign the cis stereochemistry of aziridines **3** ($J_{H2-H3}=6.3$–6.8 Hz).[18] Considering that the cyclisation proceeds through an S_N2 mechanism we deduced a *syn* configuration for the β-selanyl α-aminoesters **2**. However, with the hindered substrate **2f**, no aziridine was obtained after the Meerwein salt action. Only a N-methylation reaction was observed yielding **2′f**. This undesired reaction, due to the nature of the activator and which also occurred during the cyclisation of hindered β-selanyl amines derived from α-selanyl aldhehydes, can be suppressed by the use of NBS. Indeed treatment of compound **2f** with this reagent provided the desired aziridine **3f** in 65% yield. In addition, the cyclisation reactions are much faster with NBS than with the Meerwein salt (5 min instead of 12 h) and the aziridine yields are slightly higher.

In order to access chiral aziridine esters, an additional asymmetric centre has been introduced by replacing the benzylamine by the (*R*)-phenylethylamine ((*R*)-PEA). The resulting imines **4** were formed as two diastereomers in equal proportion. Due to their instability, it

Table 1. Synthetic yields of aziridine esters **3** via Scheme 2

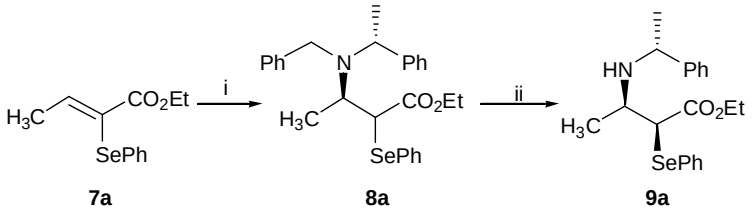
Substrate			**1**→**2** Yield (%)	Cyclisation of **2** products, yield (%)	
No.	R^1	R^2		Via iii	Via iv
1a	Me	H	47	**3a**, 49	**3a**, 45
1b	Et	H	54	**3b**, 57	**3b**, 66
1c	*n*Pr	H	51	**3c**, 61	**3c**, 67
1d	*i*Pr	H	46	**3d**, 54	**3d**, 61
1e	Bn	H	52	**3e**, 48	**3e**, 52
1f	Me	Me	55	**2f***N*-Me, 51	**3f**, 65



Scheme 3. (i) (*R*)-PEA (4 equiv), $TiCl_4$, Et_2O, 20 °C, 4 h; (ii) $NaBH_3CN$ (0.5 equiv), AcOH, EtOH, 0 °C, 1 h; (iii) Me_3OBF_4 (2 equiv), CH_2Cl_2, 12 h then NaOH aq 1 N; (iv) NBS (1.1 equiv), CH_3CN, 5 min then Na_2CO_3.

Table 2. Synthetic yields of aziridine esters **6** and **6′** via Scheme 3

Substrate		**1**→**5**-*syn*/**5′**-*syn* Yield (%), (**5**/**5′**)	Cyclisation of **5** products, yield (%)		Cyclisation of **5′** products, yield (%)	
No.	R^1		Via iii	Via iv	Via iii	Via iv
1a	Me	47, (50/50)	**6a**, 47	**6″a**, 57	**6′a**, 49	**6′a**, 51
1b	Et	53, (50/50)	**6b**, 50	**6b**, 55	**6′b**, 56	**6′b**, 49
1c	*n*Pr	51, (50/50)	**6c**, 55	**6c**, 61	**6′c**, 52	**6′c**, 58
1e	Bn	50, (50/50)	**6e**, 41	**6e**, 48	**6′e**, 44	**6′e**, 52



7a **8a** **9a**

Scheme 4. (i) [(*R*)-BPEA (1.3 equiv), *n*-BuLi (1.3 equiv)], THF, −78 °C, 40 min; (ii) CAN (2.1 equiv), CH_3CN/H_2O, 20 °C, 1 h.

was not possible to separate them and these were reduced as a crude mixture to provide β-selanyl α-aminoesters **5** and **5′** in equal proportion (Scheme 3, Table 2).[†] Substrates **5** and **5′** were separated by silica gel chromatography and subjected to the cyclisation conditions. Activation of the selanyl group of **5a** and **5′a** (R^1=Me) by the Meerwein salt led to the expected formation of *cis* aziridine **6a** and **6′a**, respectively. However, when **5′a** was treated with NBS, **6′a** was obtained, but surprisingly *trans* aziridine **6″a** was exclusively formed from **5a**. This might be explained by an enol equilibrium leading to the more stable aziridine.[19] Considering these results all the cyclisation substrates were then subjected to both activators. Nevertheless, only *cis* aziridine esters were obtained starting from **5b–e** and **5′b–e** no matter what the activation conditions were. This confirmed the *syn* stereochemistry of substrates **5** and **5′**. At this point of our study, we only knew the relative stereochemistry of products **5**, **5′**, **6** and **6′** but could not attribute their absolute configuration.

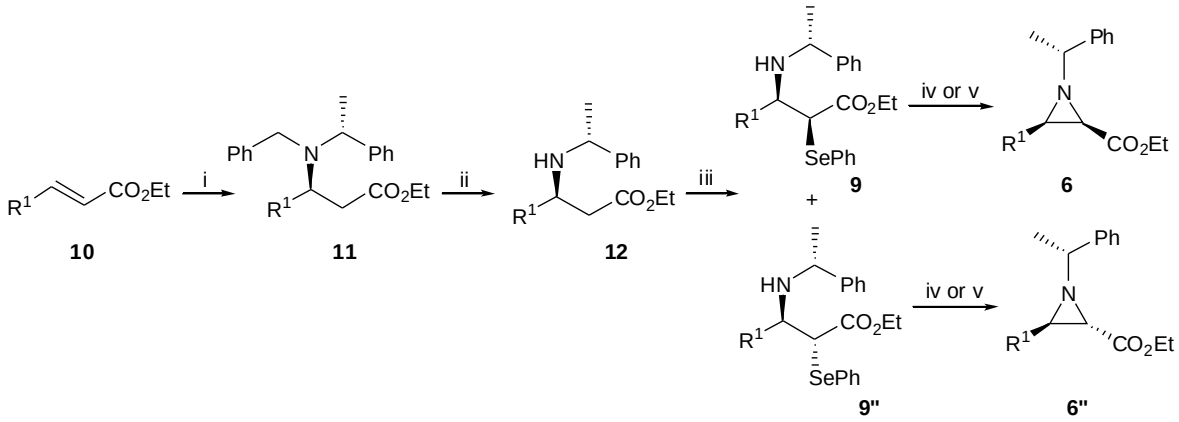
We thus developed another pathway to access similar aziridine esters from α,β-unsaturated esters. Indeed, Davies and co-workers have developed very efficient methods for the diastereoselective conjugate additions of the lithium amide derived from (*R*)-*N*-benzyl-*N*-phenylethylamine ((*R*)-BPEA).[20] Initially addition of this chiral lithium amide to the α-selanyl-α,β-unsaturated ester **7a** gave an unstable adduct **8a**, which decomposed on silica gel or alumina (Scheme 4). Thus **8a** was used without any purification in a debenzylation step with cerium ammonium nitrite (CAN)[21] to provide amine **9a** as a single *syn* diastereomer albeit in 28% yield over two steps, probably due to a competitive retro-Michael reaction. Finally, the selanyl group was introduced at the end of the reaction sequence.

After addition of the chiral lithium amide on α,β-unsaturated esters **10** only one diastereomer (*R*,*R*) was observed in the NMR for products **11**. Based on computational studies, Davies and co-workers have shown that the *Si* face is the most favourable for the amide attack because of the minimisation of steric interactions.[22] The debenzylation with CAN is selective and afforded amines **12** in 48–68% yields. After deprotonation with LDA and addition of benzene selenienyl bromide, β-amino α-selanylesters were obtained as two diastereomers chromatographically separable **9** and **9″** in proportions ranging from 50/50 to 70/30 depending on R^1. The use of camphor selenienyl bromide[23] as a chiral electrophile did not increase the diastereoselectivity. The cyclisation of substrates **9″a–g** by the Meerwein salt provided *trans* aziridine esters **6″a–g** (J_{H2-H3}=2.7–2.8 Hz) which implied an *anti* configuration for precursors **9″**. *cis* Aziridine esters **6a–g** (J_{H2-H3}=6.6–6.9 Hz) were observed from treatment of compounds **9a–g** with the same activator. Similar results were obtained when the cyclisations were carried out with NBS, except with three substrates. Indeed, the activation with this reagent of the selanyl group of compounds **9b** (R^1=Et) led to a mixture of *cis*/*trans* aziridines **6b/6″b** in a ratio 43/57 and compounds **9a**,**g** (R^1=Me, Ph) provided only the *trans* aziridines **6″a**,**g**. As during the cyclisation of β-selanyl α-aminoesters **5a**, these partial or total C2 epimerisations occurred only when the cyclisations were promoted by NBS and not by the Meerwein salt. Considering that the configuration of one of the stereogenic carbons was established by the diastereoselective addition of the chiral amide, we were able to attribute the absolute configuration of aziridines **6**, **6″** and with these results in hand, we deduced the absolute configuration for their precursors **9**, **9″** (Scheme 5, Table 3).

The fact, that *cis* aziridines **6** are the common product of both pathways A and B (Scheme 1), allowed us to distinguish between the two *cis* aziridines **6** and **6′** obtained previously from α-oxo esters **1** (path A) and, as a consequence, to determine the absolute configuration of β-selanyl α-aminoesters **5** and **5′**.

In conclusion, we have developed a synthesis of aziridine esters based on the cyclisation of amino selanyl esters induced by the selanyl group activation with either the Meerwein salt or NBS. Two asymmetric approaches are proposed: the diastereoselective reductions of α-selanyl β-iminoesters derived from α-oxoesters, which lead to *cis*

[†] When R^1=*i*Pr (**1d**), a complex mixture was obtained and no desired amine could be isolated.



Scheme 5. (i) [(*R*)-BPEA (1.3 equiv), *n*-BuLi (1.3 equiv)], THF, −78 °C, 40 min; (ii) CAN (2.1 equiv), CH_3CN/H_2O, 20 °C, 1 h; (iii) LDA (2.1 equiv), THF, −78 °C then PhSeBr (1.3 equiv), −78 °C, 20 min; (iv) Me_3OBF_4 (2 equiv), CH_2Cl_2, 12 h then NaOH aq 1 N; (v) NBS (1.1 equiv), CH_3CN, 5 min then Na_2CO_3.

Table 3. Synthetic yields of aziridines esters **6** and **6″** via Scheme 5

Substrate		**10→11** Yield (%)	**11→12** Yield (%)	**12→9**-*syn*/**9″**-*anti* Yield %, (**9**/**9″**)	Cyclisation of **9** products, yield (%)		Cyclisation of **9″** products, yield (%)	
No.	R^1				Via iv	Via v	Via iv	Via v
10a	Me	79	68	65, (50/50)	**6a**, 51	**6″a**, 58	**6″a**, 53	**6″a**, 59
10b	Et	75	66	59, (50/50)	**6b**, 53	**6b**/**6″b** (43/57), 48	**6″b**, 47	**6″b**, 51
10c	*n*Pr	72	63	56, (50/50)	**6c**, 47	**6c**, 61	**6″c**, 50	**6″c**, 51
10d	*i*Pr	82	53	58, (60/40)	**6d**, 44	**6d**, 49	**6″d**, 48	**6″d**, 53
10e	Bn	78	62	61, (70/30)	**6e**, 42	**6e**, 53	**6″e**, 39	**6″e**, 48
10g	Ph	89	48	57, (70/30)	**6g**, 49	**6″g**, 55	**6″g**, 52	**6″g**, 55

chiral aziridine esters **6** and **6′**; and the diastereoselective conjugate additions of a chiral amide to α,β-unsaturated esters providing trans chiral aziridine esters **6** and **6″**. The comparison of the aziridine esters obtained by these two synthetic ways allowed the attribution of the absolute configuration to all the synthesized compounds.

3. Experimental

THF was distilled over sodium/benzophenone. Ether was dried over sodium. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.4 MHz) spectrum were recorded on a Brucker DPX 300 instrument and carried out in $CDCl_3$. Chemical shifts (δ) were quoted in ppm downfield from tetramethylsilane (TMS). Elemental analyses were obtained on a Carlo-Erba 1106 analyser and Mass Spectra on a HP5890 (electronic impact 70 eV) using GC–MS coupling with a Jeol AX 500.

3.1. Synthesis of α-(phenylselanyl)α-aminoesters 2

Preparation of β-(phenylselanyl)α-iminoesters. Titanium chloride (708 mg, 3.75 mmol, 0.75 equiv) in heptane (2 mL) was slowly added to a solution of β-(phenylselanyl) α-oxoester (5 mmol, 1 equiv) and amine (20 mmol, 4 equiv) in anhydrous ether (70 mL), under argon, at 0 °C. The mixture was stirred 30 min at 0 °C and then 3 h at room temperature. The titanium salts were filtered and rinced with ether. The organic phase was dried over $MgSO_4$ and concentrated to afford the desired β-(phenylselanyl)α-iminoesters.

Reduction of β-(phenylselanyl)α-iminoesters. To the α-(phenylselanyl)α-iminoester (5 mmol) in ethanol (60 mL) at 0 °C, under argon, were added successively sodium cyanoborohydride (314 mg, 5 mmol) and acetic acid (300 mg, 5 mmol). The reaction mixture was stirred for 1 h at 0 °C and quenched with water (70 mL). After dichloromethane (100 mL) addition, the aqueous phase was separated and washed with dichloromethane (2×80 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel chromatography (cyclohexane/ether: 85:15).

3.1.1. *syn*-Ethyl 2-benzylamino-3-(phenylselanyl)-butanoate 2a.[16] Oil, yield=47%. ^{1}H NMR δ: 1.11 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.37 (d, 3H, J=7.1 Hz, H-4), 2.19 (s, 1H, N*H*), 3.23 (d, 1H, J=5.7 Hz, H-2), 3.53 (qd, 1H, J=5.7, 7.1 Hz, H-3), 3.59 (d, 1H, J=13.2 Hz, CH_2Ph), 3.85 (d, 1H, J=13.2 Hz, CH_2Ph), 3.86 (dq, 1H, J=7.1, 10.8 Hz, OCH_2CH_3), 3.98 (dq, 1H, J=7.1, 10.8 Hz, OCH_2CH_3), 7.17–7.47 (m, 10H, Ph). ^{13}C NMR δ: 14.6 (OCH_2CH_3), 20.6 (C-4), 43.2 (C-3), 52.8 (CH_2Ph), 61.3 (OCH_2CH_3), 65.7 (C-2), 127.5, 128.1, 128.7, 128.8, 129.3, 129.4, 135.7, 140.2 (Ph), 173.6 (C-1).

3.1.2. *syn*-Ethyl 2-benzylamino-3-(phenylselanyl)-pentanoate 2b.[16] Oil, yield=54%. ^{1}H NMR δ: 0.92 (t, 3H, J=7.3 Hz, H-5), 1.03 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.73 (m, 2H, H-4), 2.10 (s, 1H, N*H*), 3.31 (td, 1H, J=3.9, 7.2 Hz, H-3), 3.35 (d, 1H, J=3.9 Hz, H-2), 3.62 (d, 1H, J=13.3 Hz, CH_2Ph), 3.71 (dq, 1H, J=7.2, 10.8 Hz, OCH_2CH_3), 3.90 (d, 1H, J=13.3 Hz, CH_2Ph), 3.92 (dq, 1H, J=7.2, 10.8 Hz,

OCH_2CH_3), 7.15–7.45 (m, 10H, Ph). ^{13}C NMR δ: 13.1 (OCH_2CH_3), 14.4 (C-5), 27.5 (C-4), 52.8 (C-3), 52.9 (CH_2Ph), 61.2 (OCH_2CH_3), 63.6 (C-2), 126.3, 126.9, 127.3, 127.4, 127.8, 128.8, 133.7, 140.4 (Ph), 173.6 (C-1).

3.1.3. *syn*-Ethyl 2-benzylamino-3-(phenylselanyl)-hexanoate 2c.[16] Oil, yield=51%. ^1H NMR δ: 0.79 (t, 3H, J=7.3 Hz, H-6), 1.02 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.21–1.31 (m, 1H, H-5), 1.39–1.49 (m, 1H, H-5), 1.66–1.70 (m, 2H, H-4), 2.26 (s, 1H, NH), 3.32 (d, 1H, J=3.9 Hz, H2), 3.39 (td, 1H, J=3.9, 7.2 Hz, H-3), 3.57 (d, 1H, J=13.2 Hz, CH_2Ph), 3.70 (dq, 1H, J=7.2, 10.8 Hz, OCH_2CH_3), 3.89 (d, 1H, J=13.2 Hz, CH_2Ph), 3.91 (dq, 1H, J=7.2, 10.8 Hz, OCH_2CH_3), 7.11–7.45 (m, 10H, Ph). ^{13}C NMR δ: 12.7 (C-6), 13.0 (OCH_2CH_3), 20.1 (C-5), 35.1 (C-4), 49.3 (C-3), 51.4 (CH_2Ph), 59.7 (OCH_2CH_3), 62.3 (C-2), 126.0, 126.3, 127.2, 127.3, 127.8, 128.6, 133.7, 139.0 (Ph), 172.2 (C-1).

3.1.4. *syn*-Ethyl 2-benzylamino-4-methyl-3-(phenylselanyl)pentanoate 2d.[16] Oil, yield=46%. ^1H NMR δ: 0.85 (d, 3H, J=6.7 Hz, H-5), 0.96 (t, 3H, J=7.3 Hz, OCH_2CH_3), 1.09 (d, 3H, J=6.7 Hz, H-5), 1.96–2.04 (m, 1H, H-4), 2.16 (s, 1H, NH), 3.17 (dd, 1H, J=3.8, 7.4 Hz, H-3), 3.50 (d, 1H, J=3.8 Hz, H-2), 3.55 (d, 1H, J=13.3 Hz, CH_2Ph), 3.61 (dq, 1H, J=7.3, 10.7 Hz, OCH_2CH_3), 3.86 (dq, 1H, J=7.2, 10.8 Hz, OCH_2CH_3), 3.87 (d, 1H, J=13.3 Hz, CH_2Ph), 7.09–7.44 (m, 10H, Ph). ^{13}C NMR δ: 15.2 (OCH_2CH_3), 22.4 (C-5), 23.0 (C-5), 33.2 (C-4), 53.7 (CH_2Ph), 61.1 (C-3), 61.9 (OCH_2CH_3), 64.2 (C-2), 128.2, 128.3, 129.5, 129.7, 130.1, 133.3, 135.4, 141.3 (Ph), 174.7 (C-1).

3.1.5. *syn*-Ethyl 2-benzylamino-4-phenyl-3-(phenylselanyl)butanoate 2e.[5b,16] Oil, yield=52%. ^1H NMR δ: 1.00 (t, 3H, J=7.2 Hz, OCH_2CH_3), 2.21 (s, 1H, NH), 3.10 (dd, 1H, J=7.2, 13.9 Hz, H-4), 3.15 (dd, 1H, J=7.3, 13.9 Hz, H-4), 3.29 (d, 1H, J=2.9 Hz, H-2), 3.49 (d, 1H, J=12.8 Hz, CH_2Ph), 3.66 (dt, 1H, J=2.9, 7.2 Hz, H-3), 3.69 (dq, 1H, J=7.2, 10.7 Hz, OCH_2CH_3), 3.86 (dq, 1H, J=7.2, 10.7 Hz, OCH_2CH_3), 3.88 (d, 1H, J=12.8 Hz, CH_2Ph), 7.05–7.43 (m, 15H, Ph). ^{13}C NMR δ: 13.0 (OCH_2CH_3), 39.4 (C-4), 50.6 (C-3), 51.5 (CH_2Ph), 59.8 (OCH_2CH_3), 61.3 (C-2), 125.4, 126.0, 126.5, 127.3, 127.4, 127.8, 128.2, 128.4, 129.1, 133.7, 138.6, 139.1 (Ph), 172.1 (C-1).

3.1.6. Ethyl 2-benzylamino-3-methyl-3-(phenylselanyl)-butanoate 2f.[16] Oil, yield=55%. ^1H NMR δ: 1.15 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.22 (s, 3H, H-4), 1.35 (s, 3H, H-4), 2.22 (s, 1H, NH), 3.21 (s, 1H, H-2), 3.55 (d, 1H, J=13.1 Hz, CH_2Ph), 3.78 (d, 1H, J=12.8 Hz, CH_2Ph), 4.11 (q, 2H, J=7.1 Hz, OCH_2CH_3), 7.16–7.42 (m, 10H, Ph). ^{13}C NMR δ: 13.3 (OCH_2CH_3), 25.2 (C-4), 26.9 (C-4), 47.6 (C-3), 51.6 (CH_2Ph), 59.6 (OCH_2CH_3), 68.3 (C-2), 126.1, 126.8, 127.0, 127.3, 127.5, 127.6, 137.4, 138.5 (Ph), 172.0 (C-1).

3.2. Cyclisation of β-(phenylselanyl)α-aminoesters 2

Procedure A with Me_3OBF_4. To the β-(phenylselanyl) α-aminoester **2** (1 mmol) in dichloromethane (10 mL) was added Me_3OBF_4 (310 mg, 2.1 mmol) at room temperature. After 12 h of stirring, the mixture was washed with a solution of sodium hydroxide 1 N (10 mL). The aqueous phase was extracted with dichloromethane (2×10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel chromatography (cyclohexane/ether: 75:25) to afford aziridine **3**.

Procedure B with NBS. To the β-(phenylselanyl) α-aminoester **2** (1 mmol) in acetonitrile (10 mL) was added NBS (195 mg, 1.1 mmol) at room temperature. After 5 min of stirring, the mixture became red-brown and sodium bicarbonate (212 mg, 2 mmol) was introduced. The mixture turned rapidly yellow. Water (10 mL) was added and the aqueous phase was extracted with dichloromethane (2×10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel chromatography (cyclohexane/ether: 75:25) to afford aziridine **3**.

3.2.1. *cis*-Ethyl 1-benzyl-3-methylaziridine-2-carboxylate 3a.[3j,16,18] Oil, yield=49% (A), yield=45% (B). ^1H NMR δ: 1.18 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.21 (d, 3H, J=5.5 Hz, CH_3), 1.90–1.95 (m, 1H, H-3), 2.13 (d, 1H, J=6.8 Hz, H-2), 3.54 (d, 1H, J=13.9 Hz, CH_2Ph), 3.61 (d, 1H, J=13.9 Hz, CH_2Ph), 4.08 (dq, 1H, J=7.2, 10.7 Hz, OCH_2CH_3), 4.11 (dq, 1H, J=7.2, 10.7 Hz, OCH_2CH_3), 7.13–7.28 (m, 5H, Ph). ^{13}C NMR δ: 13.5 (CH_3), 14.7 (OCH_2CH_3), 42.1 (C-3), 43.1 (C-2), 61.3 (OCH_2CH_3), 64.0 (CH_2Ph), 127.5, 128.1, 128.6, 138.4 (Ph), 170.0 (C=O).

3.2.2. *cis*-Ethyl 1-benzyl-3-ethylaziridine-2-carboxylate 3b.[16] Oil, yield=57% (A), yield=66% (B). ^1H NMR δ: 0.82 (t, 3H, J=7.4 Hz, CH_2CH_3), 1.20 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.42–1.49 (m, 1H, CH_2CH_3), 1.56–1.63 (m, 1H, CH_2CH_3), 1.81 (q, 1H, J=6.8 Hz, H-3), 2.17 (d, 1H, J=6.8 Hz, H-2), 3.52 (s, 2H, CH_2Ph), 4.13 (q, 2H, J=7.2 Hz, OCH_2CH_3), 7.16–7.28 (m, 5H, Ph). ^{13}C NMR δ: 11.9 (CH_2CH_3), 14.7 (OCH_2CH_3), 21.5 (CH_2CH_3), 43.0 (C-2), 48.5 (C-3), 61.3 (OCH_2CH_3), 64.3 (CH_2Ph), 127.6, 128.5, 128.7, 138.4 (Ph), 170.2 (C=O). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.38; H, 8.55; N, 6.19.

3.2.3. *cis*-Ethyl 1-benzyl-3-propylaziridine-2-carboxylate 3c.[16] Oil, yield=61% (A), yield=67% (B). ^1H NMR δ: 0.80 (t, 3H, J=7.2 Hz, $CH_2CH_2CH_3$), 1.19 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.28–1.63 (m, 4H, $CH_2CH_2CH_3$), 1.85 (q, 1H, J=6.8 Hz, H-3), 2.17 (d, 1H, J=6.8 Hz, H-2), 3.49 (d, 1H, J=13.7 Hz, CH_2Ph), 3.56 (d, 1H, J=13.7 Hz, CH_2Ph), 4.13 (q, 2H, J=7.2 Hz, OCH_2CH_3), 7.19–7.27 (m, 5H, Ph). ^{13}C NMR δ: 12.7 ($CH_2CH_2CH_3$), 13.3 (OCH_2CH_3), 19.6 ($CH_2CH_2CH_3$), 28.7 ($CH_2CH_2CH_3$), 41.6 (C-2), 45.6 (C-3), 59.8 (OCH_2CH_3), 62.9 (CH_2Ph), 126.1, 127.0, 127.3, 136.9 (Ph), 168.8 (C=O). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.67. Found: C, 72.81; H, 8.66; N, 5.89.

3.2.4. *cis*-Ethyl 1-benzyl-3-*iso*-propylaziridine-2-carboxylate 3d.[16] Oil, yield=54% (A), yield=61% (B). ^1H NMR δ: 0.72 (d, 3H, J=6.2 Hz, $CH(CH_3)_2$), 0.79 (d, 3H, J=6.2 Hz, $CH(CH_3)_2$), 1.15 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.48–1.53 (m, 2H, H-3, $CH(CH_3)_2$), 2.15 (d, 1H, J=6.3 Hz, H-2), 3.43 (d, 1H, J=13.9 Hz, CH_2Ph), 3.47

(d, 1H, J=13.9 Hz, CH_2Ph), 4.10 (q, 2H, J=7.1 Hz, OCH_2CH$_3$), 7.10–7.25 (m, 5H, Ph). ^{13}C NMR δ: 13.3 (OCH$_2$CH$_3$), 18.6 (CH(CH$_3$)$_2$), 19.9 (CH(CH$_3$)$_2$), 26.2 (CH(CH$_3$)$_2$), 42.0 (C-2), 52.4 (C-3), 59.8 (OCH$_2$CH$_3$), 63.2 (CH$_2$Ph), 127.5, 128.1, 128.6, 138.4 (Ph), 170.0 (C=O). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.67. Found: C, 73.31; H, 8.99; N, 6.02.

3.2.5. *cis*-Ethyl 1,3-dibenzylaziridine-2-carboxylate 3e.[5b,16] Oil, yield=48% (A), yield=52% (B). ^{1}H NMR δ: 1.18 (t, 3H, J=7.1 Hz, OCH$_2$CH$_3$), 2.10 (q, 1H, J=6.8 Hz, H-3), 2.22 (d, 1H, J=6.8 Hz, H-2), 2.77 (dd, 1H, J=6.8, 14.7 Hz, CH$_2$Ph), 2.98 (dd, 1H, J=5.9, 14.7 Hz, CH$_2$Ph), 3.48 (d, 1H, J=13.7 Hz, CH$_2$Ph), 3.56 (d, 1H, J=13.7 Hz, CH$_2$Ph), 4.14 (q, 2H, J=7.1 Hz, OCH$_2$CH$_3$), 7.07–7.23 (m, 10H, Ph). δ_C (75.4 MHz, CDCl$_3$): 13.3 (OCH$_2$CH$_3$), 33.0 (CH$_2$Ph), 41.4 (C-2), 46.4 (C-3), 60.0 (OCH$_2$CH$_3$), 62.6 (CH$_2$Ph), 125.3, 126.1, 127.0, 127.3, 127.6, 128.4, 136.7, 137.7 (Ph), 168.6 (C=O).

3.2.6. Ethyl 1-benzyl-3,3-dimethylaziridine-2-carboxylate 3f. Oil, yield=65% (B). ^{1}H NMR δ: 1.20 (t, 3H, J=7.2 Hz, OCH$_2$CH$_3$), 1.26 (s, 3H, CH$_3$), 1.28 (s, 3H, CH$_3$), 2.05 (s, 1H, H-2), 3.68 (d, 1H, J=14.8 Hz, CH$_2$Ph), 3.75 (d, 1H, J=14.8 Hz, CH$_2$Ph), 4.14 (q, 2H, J=7.2 Hz, OCH$_2$CH$_3$), 7.15–7.26 (m, 5H, Ph). ^{13}C NMR δ: 14.5 (OCH$_2$CH$_3$), 18.0 (CH$_3$), 21.9 (CH$_3$), 44.8 (C-3), 49.4 (C-2), 56.0 (CH$_2$Ph), 60.9 (OCH$_2$CH$_3$), 126.8, 127.4, 128.4, 139.3 (Ph), 170.4 (C=O). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.14; H, 7.79; N, 6.34.

3.3. Synthesis of β-(phenylselanyl)α-aminoesters 5

3.3.1. Preparation of β-(phenylselanyl)α-iminoesters 4. The protocol is the same as the one for the synthesis of α-(phenylselanyl)α-aminoesters **2**. The β-(phenylselanyl) α-iminoesters **4** were isolated but not purified because of decomposition. That is why we just reported their ^{1}H NMR spectrum.

3.3.1.1. Ethyl-2-((*R*)-1-phenylethylimino)-3-(phenylselanyl)butanoate 4a. Oil, two diastereomers: 50/50, conv.=100%. ^{1}H NMR δ: 1.34–1.63 (m, 9H, H-4, CH(Ph)CH$_3$, OCH$_2$CH$_3$), 4.14, 4.16 (2×q, 1H, J=6.9 Hz, H-3), 4.30–4.40 (m, 2H, OCH$_2$CH$_3$), 4.70, 4.73 (2×q, 1H, J=6.4 Hz, CH(Ph)CH$_3$), 7.24–7.65 (m, 10H, Ph).

3.3.1.2. Ethyl 2-((*R*)-1-phenylethylimino)-3-(phenylselanyl)pentanoate 4b. Oil, two diastereomers: 50/50, conv.=100%. ^{1}H NMR δ: 0.98 (t, 3H, J=7.4 Hz, H-5), 1.19–1.31 (m, 6H, CH(Ph)CH$_3$, OCH$_2$CH$_3$), 1.68–1.78 (m, 1H, H-4), 1.90–2.02 (m, 1H, H-4), 3.83, 3.88 (2×t, 1H, J=7.4 Hz, H-3), 4.23, 4.28 (2×q, 2H, J=7.2 Hz, OCH$_2$CH$_3$), 4.60, 4.62 (2×q, 1H, J=6.4 Hz, CH(Ph)CH$_3$), 6.95–7.45 (m, 10H, Ph).

3.3.1.3. Ethyl 2-((*R*)-1-phenylethylimino)-3-(phenylselanyl)hexanoate 4c. Oil, two diastereomers: 50/50, conv.=100%. ^{1}H NMR δ: 0.83, 0.85 (2×t, 3H, J=7.2 Hz, H-6), 1.19–1.31 (m, 6H, CH(Ph)CH$_3$, OCH$_2$CH$_3$), 1.32–1.60 (m, 2H, H-5), 1.62–1.89 (m, 1H, H-4), 1.87–2.03 (m, 1H, H-4), 3.88, 3.93 (2×t, 1H, J=7.9 Hz, H-3), 4.23, 4.28 (2×q, 2H, J=7.2 Hz, OCH$_2$CH$_3$), 4.60, 4.62 (2×q, 1H, J=6.4 Hz, CH(Ph)CH$_3$), 6.95–7.42 (m, 10H, Ph).

3.3.1.4. Ethyl 2-((*R*)-1-phenylethylimino)-4-phenyl-3-(phenylselanyl)butanoate 4e. Oil, two diastereomers: 50/50, conv.=100%. ^{1}H NMR δ: 1.54–1.32 (m, 6H, CH(Ph)CH$_3$, OCH$_2$CH$_3$), 2.98–3.09 (m, 1H, H-4), 3.32–3.45 (m, 1H, H-4), 4.16–4.29 (m, 3H, H-3, OCH$_2$CH$_3$), 4.58–4.69 (m, 1H, CH(Ph)CH$_3$), 7.11–7.45 (m, 15H, Ph).

3.3.2. Reduction of α-(phenylselanyl)α-iminoesters 4. The protocol is the same as the one for the synthesis of α-(phenylselanyl)α-aminoesters **2**.

3.3.2.1. Ethyl 2-((*R*)-1-phenylethylamino)-3-(phenylselanyl)butanoate 5a, 5′a. Oil, **5a/5′a**: 50/50, yield=47%.

(2R,3R)-Ethyl 2-((R)-1-phenylethylamino)-3-(phenylselanyl)butanoate **5′a**. (First eluted). ^{1}H NMR δ: 1.19 (t, 3H, J=7.2 Hz, OCH$_2$CH$_3$), 1.34 (d, 3H, J=6.6 Hz, CH(Ph)CH$_3$), 1.46 (d, 3H, J=6.9 Hz, H-4), 2.37 (s, 1H, NH), 3.36 (d, 1H, J=5.9 Hz, H-2), 3.57 (qd, 1H, J=5.9, 6.9 Hz, H-3), 3.77 (q, 1H, J=6.6 Hz, CH(Ph)CH$_3$), 3.89 (q, 2H, J=7.2 Hz, OCH$_2$CH$_3$), 7.25–7.52 (m, 10H, Ph). ^{13}C NMR δ: 14.2 (OCH$_2$CH$_3$), 20.0 (C-4), 23.3 (CH(Ph)CH$_3$), 43.3 (C-3), 57.5 (CH(Ph)CH$_3$), 61.0 (OCH$_2$CH$_3$), 64.5 (C-2), 127.2, 127.3, 127.7, 128.5, 128.9, 129.1, 135.3, 145.4 (Ph), 173.4 (C-1). $[\alpha]_D^{25}$ +14.8 (c 1.0 in CHCl$_3$).

(2S,3S)-Ethyl 2-((R)-1-phenylethylamino)-3-(phenylselanyl)butanoate **5a**. (Second eluted). ^{1}H NMR δ: 1.14 (t, 3H, J=7.2 Hz, OCH$_2$CH$_3$), 1.37 (d, 3H, J=6.9 Hz, H-4), 1.38 (d, 3H, J=6.4 Hz, CH(Ph)CH$_3$), 2.19 (s, 1H, NH), 3.09 (d, 1H, J=5.1 Hz, H-2), 3.54 (qd, 1H, J=5.1, 6.9 Hz, H-3), 3.73 (q, 1H, J=6.4 Hz, CH(Ph)CH$_3$), 4.01 (dq, 1H, J=7.2, 10.7 Hz, OCH$_2$CH$_3$), 4.18 (dq, 1H, J=7.2, 10.7 Hz, OCH$_2$CH$_3$), 7.23–7.47 (m, 10H, Ph). ^{13}C NMR δ: 14.3 (OCH$_2$CH$_3$), 20.5 (C-4), 25.4 (CH(Ph)CH$_3$), 43.2 (C-3), 57.0 (CH(Ph)CH$_3$), 60.9 (OCH$_2$CH$_3$), 63.9 (C-2), 126.9, 127.2, 127.7, 128.5, 128.9, 129.1, 135.2, 145.4 (Ph), 173.7 (C-1). $[\alpha]_D^{25}$ −17.1 (c 1.0 in CHCl$_3$).

3.3.2.2. Ethyl 2-((*R*)-1-phenylethylamino)-3-(phenylselanyl)pentanoate 5b, 5′b. Oil, **5b/5′b**: 50/50, yield=53%.

(2S,3S)-Ethyl 2-((R)-1-phenylethylamino)-3-(phenylselanyl)pentanoate **5b**. (First eluted). ^{1}H NMR δ: 0.86 (t, 3H, J=7.2 Hz, H-5), 1.08 (t, 3H, J=7.2 Hz, OCH$_2$CH$_3$), 1.40 (d, 3H, J=6.4 Hz, CH(Ph)CH$_3$), 1.64–1.92 (m, 2H, H-4), 2.28 (s, 1H, NH), 3.24 (d, 1H, J=3.3 Hz, H-2), 3.39 (td, 1H, J=3.3, 7.2 Hz, H-3), 3.62–3.78 (m, 2H, OCH$_2$CH$_3$, CH(Ph)CH$_3$), 3.82–2.92 (m, 1H, OCH$_2$CH$_3$), 7.09–7.48 (m, 10H, Ph). ^{13}C NMR δ: 12.8 (C-5), 14.1 (OCH$_2$CH$_3$), 25.3 (CH(Ph)CH$_3$), 27.4 (C-4), 53.1 (C-3), 56.9 (CH(Ph)CH$_3$) 60.7 (OCH$_2$CH$_3$), 61.8 (C-2), 127.2, 127.4, 127.5, 128.4, 128.9, 130.0, 134.7, 145.4 (Ph), 173.7 (C-1). $[\alpha]_D^{25}$ −16.3 (c 1.0, CHCl$_3$).

(2R,3R)-Ethyl 2-((R)-1-phenylethylamino)-3-(phenylselanyl)pentanoate **5′b**. (Second eluted). ^{1}H NMR δ: 1.08 (t, 3H, J=7.2 Hz, OCH$_2$CH$_3$), 1.11 (t, 3H, J=7.2 Hz, H-5), 1.34 (d, 3H, J=6.6 Hz, CH(Ph)CH$_3$), 1.81–1.98 (m, 2H,

H-4), 2.38 (s, 1H, N*H*), 3.41 (ddd, 1H, J=4.1, 6.4, 7.7 Hz, H-3), 3.53 (d, 1H, J=4.1 Hz, H-2), 3.72–3.78 (m, 2H, C*H*(Ph)CH$_3$, OC*H*$_2$CH$_3$), 3.79–3.84 (m, 1H, OC*H*$_2$CH$_3$), 7.24–7.54 (m, 10H, Ph). ^{13}C NMR δ: 12.9 (C-5), 14.1 (OCH$_2$*C*H$_3$), 23.3 (CH(Ph)*C*H$_3$), 37.2 (C-4), 53.3 (C-3), 57.3 (*C*H(Ph)CH$_3$), 60.9 (O*C*H$_2$CH$_3$), 62.2 (C-2), 126.8, 127.2, 127.4, 128.4, 128.9, 134.4, 134.7, 145.6 (Ph), 173.5 (C-1). $[\alpha]_D^{25}$ +12.1 (*c* 1.0, CHCl$_3$).

3.3.2.3. Ethyl 2-((*R*)-1-phenylethylamino)-3-(phenylselanyl)hexanoate 5c, 5′c. Oil, **5c/5′c**: 50/50, yield=51%.

(2S,3S)-Ethyl 2-((R)-1-phenylethylamino)-3-(phenylselanyl)hexanoate **5c**. (First eluted). ^{1}H NMR δ: 0.71 (t, 3H, J=7.2 Hz, H-6), 0.98 (t, 3H, J=7.2 Hz, OCH$_2$C*H*$_3$), 1.18–1.32 (m, 2H, H-5), 1.30 (d, 3H, J=6.4 Hz, CH(Ph)C*H*$_3$), 1.57–1.73 (m, 2H, H-4), 2.16 (s, 1H, N*H*), 3.11 (d, 1H, J=3.3 Hz, H-2), 3.83 (td, 1H, J=3.3, 7.2 Hz, H-3), 3.63 (dq, 1H, J=7.2, 10.7 Hz, OC*H*$_2$CH$_3$), 3.68 (q, 1H, J=6.4 Hz, C*H*(Ph)CH$_3$), 3.86 (dq, 1H, J=7.2, 10.7 Hz, OC*H*$_2$CH$_3$), 7.11–7.41 (m, 10H, Ph). ^{13}C NMR δ: 13.7 (C-6), 14.1 (OCH$_2$*C*H$_3$), 21.2 (C-5), 25.3 (CH(Ph)*C*H$_3$), 36.4 (C-4), 50.7 (C-3), 57.0 (*C*H(Ph)CH$_3$), 60.8 (O*C*H$_2$CH$_3$), 61.9 (C-2), 127.2, 127.4, 127.5, 128.4, 129.0, 130.1, 134.7, 145.5 (Ph), 173.8 (C-1). $[\alpha]_D^{25}$ −14.2 (*c* 1.0 in CHCl$_3$).

(2R,3R)-Ethyl 2-((R)-1-phenylethylamino)-3-(phenylselanyl)hexanoate **5′c**. (Second eluted). ^{1}H NMR δ: 0.84 (t, 3H, J=7.2 Hz, H-6), 0.98 (t, 3H, J=7.2 Hz, OCH$_2$C*H*$_3$), 1.24 (d, 3H, J=6.4 Hz, CH(Ph)C*H*$_3$), 1.31–1.61 (m, 2H, H-5), 1.68–1.85 (m, 2H, H-4), 2.29 (s, 1H, N*H*), 3.36–3.43 (m, 2H, H-2, H-3), 3.67–3.82 (m, 3H, C*H*(Ph)CH$_3$, OC*H*$_2$CH$_3$), 7.15–7.45 (m, 10H, Ph). ^{13}C NMR δ: 13.9 (C-6), 14.1 (OCH$_2$*C*H$_3$), 21.3 (C-5), 23.4 (CH(Ph)*C*H$_3$), 36.3 (C-4), 51.1 (C-3), 57.3 (*C*H(Ph)CH$_3$), 60.9 (O*C*H$_2$CH$_3$), 62.5 (C-2), 126.9, 127.2, 127.3, 127.4, 128.4, 128.5, 134.7, 145.7 (Ph), 173.5 (C-1). $[\alpha]_D^{25}$ +11.7 (*c* 1.0 in CHCl$_3$).

3.3.2.4. Ethyl 2-((*R*)-1-phenylethylamino)-4-phenyl-3-(phenylselanyl)butanoate 5e, 5′e. Oil, **5e/5′e**: 50/50, yield=50%.

(2S,3S)-Ethyl 2-((R)-1-phenylethylamino)-4-phenyl-3-(phenylselanyl)butanoate **5e**. (First eluted). ^{1}H NMR δ: 0.95 (t, 3H, J=7.2 Hz, OCH$_2$C*H*$_3$), 1.35 (d, 3H, J=6.6 Hz, CH(Ph)C*H*$_3$), 2.39 (s, 1H, N*H*), 2.86 (dd, 1H, J=6.9, 14.1 Hz, H-4), 2.99 (dd, 1H, J=7.9, 14.1 Hz, H-4), 3.18 (d, 1H, J=2.8 Hz, H-2), 3.47–3.51 (m, 1H, H-3), 3.65–3.69 (m, 2H, C*H*(Ph)CH$_3$, OC*H*$_2$CH$_3$), 3.84 (dq, 1H, J=7.2, 10.7 Hz, OC*H*$_2$CH$_3$), 6.78–7.22 (m, 15H, Ph). ^{13}C NMR δ: 14.1 (OCH$_2$*C*H$_3$), 25.2 (CH(Ph)*C*H$_3$), 39.8 (C-4), 52.9 (C-3), 57.2 (*C*H(Ph)CH$_3$), 59.9 (O*C*H$_2$CH$_3$), 61.9 (C-2), 126.3, 127.2, 127.3, 127.5, 127.7, 128.3, 128.4, 128.9, 129.4, 134.8, 139.8, 145.4 (Ph), 173.6 (C-1). $[\alpha]_D^{25}$ −15.4 (*c* 1.0 in CHCl$_3$).

(2R,3R)-Ethyl 2-((R)-1-phenylethylamino)-4-phenyl-3-(phenylselanyl)butanoate **5′e**. (Second eluted). ^{1}H NMR δ: 1.04 (t, 3H, J=7.2 Hz, OCH$_2$C*H*$_3$), 1.26 (d, 3H, J=6.4 Hz, CH(Ph)C*H*$_3$), 2.37 (s, 1H, N*H*), 3.21 (dd, 1H, J=7.4, 14.1 Hz, H-4), 3.30 (dd, 1H, J=7.9, 14.1 Hz, H-4), 3.49 (d, 1H, J=3.1 Hz, H-2), 3.73–3.79 (m, 3H, H-3, C*H*(Ph)CH$_3$, OC*H*$_2$CH$_3$), 3.87 (dq, 1H, J=7.2, 10.7 Hz, OC*H*$_2$CH$_3$), 7.15–7.42 (m, 15H, Ph). ^{13}C NMR δ: 14.0 (OCH$_2$*C*H$_3$), 23.0 (CH(Ph)*C*H$_3$), 40.4 (C-4), 51.9 (C-3), 56.9 (*C*H(Ph)CH$_3$), 60.9 (O*C*H$_2$CH$_3$), 61.1 (C-2), 126.5, 126.8, 127.1, 127.4, 127.5, 128.1, 128.3, 128.5, 129.4, 134.8, 139.7, 145.5 (Ph), 173.2 (C-1). $[\alpha]_D^{25}$ +13.6 (*c* 1.0 in CHCl$_3$).

3.4. Cyclisation of β-(phenylselanyl)α-aminoesters 5, 5′

The protocols are the same as for the cyclisation of β-(phenylselanyl)α-aminoesters **2**.

Procedure A with Me$_3$OBF$_4$. β-(Phenylselanyl)α-aminoesters **5** (or **5′**) afforded aziridines **6** (or **6′**).

Procedure B with NBS. β-(Phenylselanyl)α-aminoester **5** (or **5′**) afforded aziridines **6** (or **6′**), except for **5a**, which lead to **6″a**.

3.4.1. (2*R*,3*R*)-Ethyl 3-methyl-1-((*R*)-1-phenylethyl)-aziridine-2-carboxylate 6a.[5b] Oil, yield=47% (A). ^{1}H NMR δ: 1.11 (d, 3H, J=5.6 Hz, C*H*$_3$), 1.23 (t, 3H, J=7.2 Hz, OCH$_2$C*H*$_3$), 1.37 (d, 3H, J=6.4 Hz, CH(Ph)C*H*$_3$), 1.78–1.82 (m, 1H, H-3), 2.15 (d, 1H, J=6.6 Hz, H-2), 2.56 (q, 1H, J=6.4 Hz, C*H*(Ph)CH$_3$), 4.15 (dq, 1H, J=7.2, 10.7 Hz, OC*H*$_2$CH$_3$), 4.17 (dq, 1H, J=7.2, 10.7 Hz, OC*H*$_2$CH$_3$), 7.17–7.33 (m, 5H, Ph). ^{13}C NMR δ: 13.3 (*C*H$_3$), 14.6 (OCH$_2$*C*H$_3$), 23.1 (CH(Ph)*C*H$_3$), 41.3 (C-3), 43.3 (C-2), 61.0 (O*C*H$_2$CH$_3$), 69.8 (*C*H(Ph)CH$_3$), 126.9, 127.2, 128.5, 143.9 (Ph), 170.0 (C=O). MS *m*/*z*: 233 (M$^+$, 2), 128 (68), 105 (100). IR ν_{max} (neat) cm^{-1}: 2967, 1744, 1450, 1186. Anal. Calcd for C$_{14}$H$_{19}$NO$_2$: C, 72.10; H, 8.21; N, 6.00. Found: C, 72.45; H, 8.19; N, 6.33. $[\alpha]_D^{25}$ +57.3 (*c* 1.0 in CH$_2$Cl$_2$).

3.4.2. (2*S*,3*S*)-Ethyl 3-methyl-1-((*R*)-1-phenylethyl)-aziridine-2-carboxylate 6′a.[5b] Oil, yield=49% (A), yield=51% (B). ^{1}H NMR δ: 1.13 (t, 3H, J=7.2 Hz, OCH$_2$C*H*$_3$), 1.28 (d, 3H, J=5.4 Hz, C*H*$_3$), 1.36 (d, 3H, J=6.6 Hz, CH(Ph)C*H*$_3$), 1.94–2.00 (m, 1H, H-3), 2.02 (d, 1H, J=6.9 Hz, H-2), 2.57 (q, 1H, J=6.6 Hz, C*H*(Ph)CH$_3$), 4.06 (dq, 1H, J=7.2, 10.7 Hz, OC*H*$_2$CH$_3$), 4.08 (dq, 1H, J=7.2, 10.7 Hz, OC*H*$_2$CH$_3$), 7.15–7.31 (m, 5H, Ph). ^{13}C NMR δ: 13.8 (*C*H$_3$), 14.5 (OCH$_2$*C*H$_3$), 23.9 (CH(Ph)*C*H$_3$), 42.4 (C-3), 42.7 (C-2), 59.9 (O*C*H$_2$CH$_3$), 69.8 (*C*H(Ph)CH$_3$), 126.7, 127.1, 128.5, 143.3 (Ph), 168.1 (C=O). MS *m*/*z*: 233 (M$^+$, 2), 128 (84), 105 (100). IR ν_{max} (neat) cm^{-1}: 2967, 1744, 1450, 1186. Anal. Calcd for C$_{14}$H$_{19}$NO$_2$: C, 72.10; H, 8.21; N, 6.00. Found: C, 71.81; H, 8.08; N, 6.13. $[\alpha]_D^{25}$ −20.9 (*c* 1.0 in CH$_2$Cl$_2$).

3.4.3. (2*R*,3*R*)-Ethyl 1-((*R*)-1-phenylethyl)-3-ethyl-aziridine-2-carboxylate 6b. Oil, yield=50% (A), yield=55%(B). ^{1}H NMR δ: 0.58 (t, 3H, J=7.4 Hz, CH$_2$C*H*$_3$), 1.25 (t, 3H, J=7.2 Hz, OCH$_2$C*H*$_3$), 1.39 (d, 3H, J=6.6 Hz, CH(Ph)C*H*$_3$), 1.38–1.55 (m, 2H, C*H*$_2$CH$_3$), 1.70 (q, 1H, J=6.6 Hz, H-3), 2.17 (d, 1H, J=6.6 Hz, H-2), 2.53 (q, 1H, J=6.6 Hz, C*H*(Ph)CH$_3$), 4.16 (dq, 2H, J=7.2, 12.3 Hz, OC*H*$_2$CH$_3$), 7.16–7.41 (m, 5H, Ph). ^{13}C NMR δ: 11.4 (CH$_2$*C*H$_3$), 14.4 (OCH$_2$*C*H$_3$), 21.2 (*C*H$_2$CH$_3$), 22.6 (CH(Ph)*C*H$_3$), 43.0 (C-2), 47.7 (C-3), 60.9 (O*C*H$_2$CH$_3$), 70.0 (*C*H(Ph)CH$_3$), 127.2, 127.3, 128.3, 143.6 (Ph), 170.0

(C═O). MS *m/z*: 247 (M^+, 16), 142 (16), 105 (100). IR ν_{max} (neat) cm^{-1}: 2968, 1744, 1451, 1185. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 58.29; H, 8.50; N, 5.66. Found: C, 58.39; H, 8.71; N, 5.48. $[\alpha]_D^{25}$ +56.9 (*c* 1.0, CH_2Cl_2).

3.4.4. (2*S*,3*S*)-Ethyl 1-((*R*)-1-phenylethyl)-3-ethylaziridine-2-carboxylate 6′b. Oil, yield=56% (A), yield=49% (B). ^1H NMR δ: 0.97 (t, 3H, *J*=7.4 Hz, CH_2CH_3), 1.16 (t, 3H, *J*=7.2 Hz, OCH_2CH_3), 1.38 (d, 3H, *J*=6.6 Hz, CH(Ph)CH_3), 1.39–1.73 (m, 2H, CH_2CH_3), 1.84 (dt, 1H, *J*=6.9, 6.1 Hz, H-3), 2.05 (d, 1H, *J*=6.9 Hz, H-2), 2.56 (q, 1H, *J*=6.6 Hz, CH(Ph)CH_3), 4.07 (dq, 1H, *J*=7.2, 10.5 Hz, OCH_2CH_3), 4.09 (dq, 1H, *J*=7.2, 10.5 Hz, OCH_2CH_3), 7.11–7.41 (m, 5H, Ph). ^{13}C NMR δ: 11.9 (CH_2CH_3), 14.3 (OCH_2CH_3), 21.4 (CH_2CH_3), 23.8 (CHαCH_3), 42.5 (C-2), 48.9 (C-3), 60.8 (OCH_2CH_3), 69.5 (CH(Ph)CH_3), 126.6, 127.0, 128.4, 143.8 (Ph), 169.7 (C═O). MS *m/z*: 247 (M^+, 2), 142 (100), 105 (84). IR ν_{max} (neat) cm^{-1}: 2967, 1744, 1450, 1186. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 58.29; H, 8.50; N, 5.66. Found: C, 58.72; H, 8.84; N, 5.27. $[\alpha]_D^{25}$ −19.1 (*c* 1.0, CH_2Cl_2).

3.4.5. (2*R*,3*R*)-Ethyl 1-((*R*)-1-phenylethyl)-3-propylaziridine-2-carboxylate 6c. Oil, yield=55% (A), yield=61% (B). ^1H NMR δ: 0.64 (t, 3H, *J*=7.4 Hz, $CH_2CH_2CH_3$), 0.95–1.08 (m, 2H, $CH_2CH_2CH_3$), 1.21 (t, 3H, *J*=7.2 Hz, OCH_2CH_3), 1.38–1.54 (m, 2H, $CH_2CH_2CH_3$), 1.40 (d, 3H, *J*=6.4 Hz, CH(Ph)CH_3), 1.70–1.76 (m, 1H, H-3), 2.15 (d, 1H, *J*=6.9 Hz, H-2), 2.51 (q, 1H, *J*=6.4 Hz, CH(Ph)CH_3), 4.14 (dq, 1H, *J*=7.2, 10.7 Hz, OCH_2CH_3), 4.16 (dq, 1H, *J*=7.2, 10.7 Hz, OCH_2CH_3), 7.23–7.32 (m, 5H, Ph). ^{13}C NMR δ: 13.7 ($CH_2CH_2CH_3$), 14.4 (OCH_2CH_3), 20.5 ($CH_2CH_2CH_3$), 22.7 (CH(Ph)CH_3), 29.9 ($CH_2CH_2CH_3$), 43.2 (C-2), 46.1 (C-3), 60.9 (OCH_2CH_3), 70.2 (CH(Ph)CH_3), 127.3, 127.4, 128.4, 143.7 (Ph), 170.1 (C═O). MS *m/z*: 261 (M^+, 5), 156 (100), 105 (81), 82 (49). IR ν_{max} (neat) cm^{-1}: 2978, 1744, 1453, 1184. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.69; H, 9.07; N, 5.38. $[\alpha]_D^{25}$ +41.2 (*c* 1.0 in CH_2Cl_2).

3.4.6. (2*S*,3*S*)-Ethyl 1-((*R*)-1-phenylethyl)-3-propylaziridine-2-carboxylate 6′c. Oil, yield=52% (A), yield=58% (B). ^1H NMR δ: 0.90 (t, 3H, *J*=7.2 Hz, $CH_2CH_2CH_3$), 1.14 (t, 3H, *J*=7.2 Hz, OCH_2CH_3), 1.18–1.63 (m, 4H, $CH_2CH_2CH_3$), 1.38 (d, 3H, *J*=6.4 Hz, CH(Ph)CH_3), 1.84–1.91 (m, 1H, H-3), 2.05 (d, 1H, *J*=6.9 Hz, H-2), 2.56 (q, 1H, *J*=6.4 Hz, CH(Ph)CH_3), 4.08 (dq, 1H, *J*=7.2, 10.7 Hz, OCH_2CH_3), 4.11 (dq, 1H, *J*=7.2, 10.7 Hz, OCH_2CH_3), 7.16–7.32 (m, 5H, Ph). ^{13}C NMR δ: 14.0 ($CH_2CH_2CH_3$), 14.4 (OCH_2CH_3), 21.0 ($CH_2CH_2CH_3$), 23.8 (CH(Ph)CH_3), 30.2 ($CH_2CH_2CH_3$), 42.5 (C-2), 47.4 (C-3), 60.8 (OCH_2CH_3), 69.7 (CH(Ph)CH_3), 126.7, 127.1, 128.3, 143.9 (Ph), 169.7 (C═O). IR ν_{max} (neat) cm^{-1}: 2978, 1744, 1453, 1184. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.85; H, 9.12; N, 5.54. $[\alpha]_D^{25}$ −18.4 (*c* 1.0 in CH_2Cl_2).

3.4.7. (2*R*,3*R*)-Ethyl 3-benzyl-1-((*R*)-1-phenylethyl)-aziridine-2-carboxylate 6e.[5b] Oil, yield=41% (A), yield=48% (B). ^1H NMR δ: 1.20 (t, 3H, *J*=7.2 Hz, OCH_2CH_3), 1.38 (d, 3H, *J*=6.6 Hz, CH(Ph)CH_3), 2.00–2.05 (m, 1H, H-3), 2.22 (d, 1H, *J*=6.4 Hz, H-2), 2.57 (q, 1H, *J*=6.6 Hz, CH(Ph)CH_3), 2.73 (dd, 1H, *J*=7.3, 14.7 Hz, CH_2Ph), 2.85 (dd, 1H, *J*=5.4, 14.7 Hz, CH_2Ph), 4.16 (q, 2H, *J*=7.2 Hz, OCH_2CH_3), 6.88–7.28 (m, 10H, Ph). ^{13}C NMR δ: 14.4 (OCH_2CH_3), 22.7 (CH(Ph)CH_3), 34.2 (CH_2Ph), 42.8 (C-2), 47.1 (C-3), 61.1 (OCH_2CH_3), 70.1 (CH(Ph)CH_3), 126.2, 126.7, 127.2, 127.4, 128.5, 128.7, 138.8, 143.4 (Ph), 170.0 (C═O). MS *m/z*: 309 (M^+, 1), 218 (11), 130 (100), 105 (72). IR ν_{max} (neat) cm^{-1}: 2968, 1743, 1455, 1183. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.60; H, 7.49; N, 4.53. Found: C, 77.89; H, 7.53; N, 4.68. $[\alpha]_D^{25}$ +36.1 (*c* 1.0 in CH_2Cl_2).

3.4.8. (2*S*,3*S*)-Ethyl 3-benzyl-1-((*R*)-1-phenylethyl)-aziridine-2-carboxylate 6′e.[5b] Oil, yield=44% (A), yield=52% (B). ^1H NMR δ: 1.13 (t, 3H, *J*=7.2 Hz, OCH_2CH_3), 1.20 (d, 3H, *J*=6.6 Hz, CH(Ph)CH_3), 2.08–2.12 (m, 1H, H-3), 2.10 (d, 1H, *J*=6.6 Hz, H-2), 2.55 (q, 1H, *J*=6.6 Hz, CH(Ph)CH_3), 2.85 (dd, 1H, *J*=4.6, 14.3 Hz, CH_2Ph), 2.99 (dd, 1H, *J*=4.3, 14.3 Hz, CH_2Ph), 4.09 (dq, 1H, *J*=7.2, 10.7 Hz, OCH_2CH_3), 4.12 (dq, 1H, *J*=7.2, 10.7 Hz, OCH_2CH_3), 7.17–7.28 (m, 10H, Ph). ^{13}C NMR δ: 14.4 (OCH_2CH_3), 23.8 (CH(Ph)CH_3), 34.7 (CH_2Ph), 42.5 (C-2), 48.5 (C-3), 59.9 (OCH_2CH_3), 69.6 (CH(Ph)CH_3), 126.6, 126.7, 127.2, 128.5, 128.6, 129.0, 139.1, 139.8 (Ph), 169.6 (C═O). MS *m/z*: 309 (M^+, 1), 218 (11), 130 (100), 105 (72). IR ν_{max} (neat) cm^{-1}: 2968, 1743, 1455, 1183. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.60; H, 7.49; N, 4.53. Found: C, 77.92; H, 7.74; N, 4.76. $[\alpha]_D^{25}$ −11.3 (*c* 1.0 in CH_2Cl_2).

3.5. Synthesis of β-aminoesters 11

n-Butyllithium 2.5 M in hexane (5.4 mL, 13 mmol, 1.3 equiv) was added dropwise to a solution of (*R*)-*N*-benzyl-*N*-((*R*)-1-phenylethyl)amine (2.74 g, 13 mmol, 1.3 equiv) in THF (75 mL) at 0 °C under argon. After 15 min at 0 °C, the mixture was cooled to −78 °C. α,β-Unsaturated ester **10** (10 mmol, 1 equiv) in solution in THF (5 mL) was then introduced. After 40 min of stirring at −78 °C, the mixture was quenched with a saturated aqueous solution of ammonium chloride (5 mL) and allowed to reach room temperature. Water (90 mL) and ether (30 mL) were added. The aqueous phase was separated and extracted with ether (2×80 mL). The combined organic phases were washed with an aqueous solution of hydrochloric acid 0.5 N (200 mL) and then with a saturated aqueous solution of sodium chloride (200 mL). After drying over $MgSO_4$ and concentration, the crude product was purified by silica gel chromatography (cyclohexane/ether: 90:10).

3.5.1. (*R*)-Ethyl 3-(*N*-benzyl-*N*-((*R*)-1-phenylethyl)-amino)butanoate 11a.[24] Oil, yield=79%. ^1H NMR δ: 1.18 (d, 3H, *J*=6.6 Hz, H-4), 1.20 (t, 3H, *J*=7.2 Hz, OCH_2CH_3), 1.39 (d, 3H, *J*=6.9 Hz, CH(Ph)CH_3), 2.15 (dd, 1H, *J*=7.9, 14.1 Hz, H-2), 2.40 (dd, 1H, *J*=5.9, 14.1 Hz, H-2), 3.46–3.53 (m, 1H, H-3), 3.73 (d, 1H, *J*=14.6 Hz, CH_2Ph), 3.77 (d, 1H, *J*=14.6 Hz, CH_2Ph), 3.94–4.03 (m, 2H, CH(Ph)CH_3, OCH_2CH_3), 4.08 (dq, 1H, *J*=7.2, 10.8 Hz, OCH_2CH_3), 7.26–7.48 (m, 10H, Ph). ^{13}C NMR δ: 14.2 (OCH_2CH_3), 18.0 (CH(Ph)CH_3), 18.7 (C-4), 39.9 (C2), 49.7 (CH_2Ph), 50.2 (C-3), 57.8 (CH(Ph)CH_3), 60.2 (OCH_2CH_3), 126.7, 126.9, 127.8, 128.1, 128.2, 128.4, 141.9, 144.4 (Ph), 172.5 (C-1). Anal. Calcd for

$C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30. Found: C, 77.72; H, 8.56; N, 4.61. $[\alpha]_D^{25}$ +4.9 (*c* 1.0 in $CHCl_3$).

3.5.2. (*R*)-Ethyl 3-(*N*-benzyl-*N*-((*R*)-1-phenylethyl)-amino)pentanoate 11b. Oil, yield=75%. ^{1}H NMR δ: 0.93 (t, 3H, *J*=7.2 Hz, H-5), 1.11 (t, 3H, *J*=7.2 Hz, OCH_2CH_3), 1.28 (d, 3H, *J*=6.9 Hz, $CH(Ph)CH_3$), 1.40–1.50 (m, 2H, H-4), 1.92 (d, 2H, *J*=6.4 Hz, H-2), 3.12–3.21 (m, 1H, H-3), 3.46 (d, 1H, *J*=14.9 Hz, CH_2Ph), 3.71 (d, 1H, *J*=14.9 Hz, CH_2Ph), 3.76 (q, 1H, *J*=6.9 Hz, $CH(Ph)CH_3$), 3.87–4.00 (m, 2H, OCH_2CH_3), 7.15–7.40 (m, 10H, Ph). ^{13}C NMR δ: 12.1, 14.3 (C-5, OCH_2CH_3), 19.7 ($CH(Ph)CH_3$), 26.4 (C-4), 36.9 (C-2), 50.1 (CH_2Ph), 55.8 (C-3), 57.8 ($CH(Ph)CH_3$), 60.2 (OCH_2CH_3), 126.7, 127.0, 128.1, 128.2, 128.4, 141.8, 143.2 (Ph), 173.1 (C-1). Anal. Calcd for $C_{22}H_{29}NO_2$: C, 77.83; H, 8.61; N, 4.12. Found: C, 77.52; H, 8.46; N, 3.87. $[\alpha]_D^{25}$ +4.3 (*c* 1.0 in $CHCl_3$).

3.5.3. (*R*)-Ethyl 3-(*N*-benzyl-*N*-((*R*)-1-phenylethyl)-amino)hexanoate 11c.[24,25] Oil, yield=72%. ^{1}H NMR δ: 0.79 (t, 3H, *J*=7.2 Hz, H-6), 1.11 (t, 3H, *J*=7.2 Hz, OCH_2CH_3), 1.15–1.21 (m, 1H, H-5), 1.26 (d, 3H, *J*=6.9 Hz, $CH(Ph)CH_3$), 1.47–1.53 (m, 3H, H-4, H-5), 1.90 (dd, 1H, *J*=8.2, 14.6 Hz, H-2), 1.97 (dd, 1H, *J*=4.9, 14.6 Hz, H-2), 3.18–3.31 (m, 1H, H-3), 3.46 (d, 1H, *J*=14.9 Hz, CH_2Ph), 3.71 (d, 1H, *J*=14.9 Hz, CH_2Ph), 3.75 (q, 1H, *J*=6.9 Hz, $CH(Ph)CH_3$), 3.89 (dq, 1H, *J*=7.2, 10.7 Hz, OCH_2CH_3), 3.94 (dq, 1H, *J*=7.2, 10.7 Hz, OCH_2CH_3), 7.15–7.37 (m, 10H, Ph). ^{13}C NMR δ: 14.2, 14.3 (C-6, OCH_2CH_3), 19.9 ($CH(Ph)CH_3$), 20.3 (C-5), 36.0 (C-4), 37.0 (C-2), 50.2 (CH_2Ph), 54.0 (C-3), 58.1 ($CH(Ph)CH_3$), 60.2 (OCH_2CH_3), 126.7, 127.0, 127.4, 128.1, 128.2, 128.4, 142.0, 143.4 (Ph), 173.1 (C-1). $[\alpha]_D^{25}$ +4.1 (*c* 1.0 in $CHCl_3$).

3.5.4. (*R*)-Ethyl 3-(*N*-benzyl-*N*-((*R*)-1-phenylethyl)-amino)-4-methylpentanoate 11d. Oil, yield=82%. ^{1}H NMR δ: 0.85 (d, 3H, *J*=6.6 Hz, H-5), 1.08 (d, 3H, *J*=6.6 Hz, H-5), 1.20 (t, 3H, *J*=7.2 Hz, OCH_2CH_3), 1.37 (d, 3H, *J*=6.9 Hz, $CH(Ph)CH_3$), 1.62–1.79 (m, 1H, H-4), 1.89 (dd, 1H, *J*=2.3, 15.9 Hz, H-2), 2.06 (dd, 1H, *J*=9.2, 15.9 Hz, H-2), 3.17–3.29 (m, 1H, H-3), 3.50 (d, 1H, *J*=14.8 Hz, CH_2Ph), 3.75 (q, 1H, *J*=6.9 Hz, $CH(Ph)CH_3$), 3.78 (d, 1H, *J*=14.8 Hz, CH_2Ph), 4.04 (q, 2H, *J*=7.2 Hz, OCH_2CH_3), 7.18–7.50 (m, 10H, Ph). ^{13}C NMR δ: 14.3 (OCH_2CH_3), 19.7 (C-5), 20.3 ($CH(Ph)CH_3$), 21.1 (C-5), 32.9 (C-4), 35.0 (C-2), 51.4 (CH_2Ph), 58.1 ($CH(Ph)CH_3$), 58.6 (C-3), 60.2 (OCH_2CH_3), 126.1, 126.7, 127.1, 128.7, 141.7, 142.4 (Ph), 173.4 (C-1). Anal. Calcd for $C_{23}H_{31}NO_2$: C, 78.15; H, 8.84; N, 3.96. Found: C, 78.42; H, 9.13; N, 4.22. $[\alpha]_D^{25}$ +5.3 (*c* 1.0 in $CHCl_3$).

3.5.5. (*R*)-Ethyl 3-(*N*-benzyl-*N*-((*R*)-1-phenylethyl)-amino)-4-phenylbutanoate 11e. Oil, yield=78%. ^{1}H NMR δ: 1.09 (t, 3H, *J*=7.2 Hz, OCH_2CH_3), 1.12 (d, 3H, *J*=6.9 Hz, $CH(Ph)CH_3$), 2.03 (d, 2H, *J*=6.9 Hz, H-4), 2.55 (dd, 1H, *J*=6.9, 13.6 Hz, H-2), 2.79 (dd, 1H, *J*=7.0, 13.6 Hz, H-2), 3.54–3.67 (m, 1H, H-3), 3.57 (d, 1H, *J*=14.8 Hz, CH_2Ph), 3.76–3.98 (m, 3H, $CH(Ph)CH_3$, OCH_2CH_3), 3.82 (d, 1H, *J*=14.8 Hz, CH_2Ph), 7.09–7.32 (m, 15H, Ph). ^{13}C NMR δ: 14.2 (OCH_2CH_3), 19.0 ($CH(Ph)CH_3$), 36.9 (C-4), 39.8 (C-2), 50.1 (CH_2Ph), 56.6 (C-3), 57.8 ($CH(Ph)CH_3$), 60.2 (OCH_2CH_3), 126.1, 126.8, 127.0, 128.0, 128.2, 128.3, 128.4, 128.6, 129.6, 140.1, 141.3, 143.2 (Ph), 172.6 (C-1). Anal. Calcd for $C_{27}H_{31}NO_2$: C, 80.76; H, 7.78; N, 3.49. Found: C, 81.02; H, 8.04; N, 3.76. $[\alpha]_D^{25}$ +3.9 (*c* 1.0 in $CHCl_3$).

3.5.6. (*R*)-Ethyl 3-(*N*-benzyl-*N*-((*R*)-1-phenylethyl)-amino)-3-phenylpropanoate 11g. Oil, yield=89%. ^{1}H NMR δ: 0.96 (t, 3H, *J*=6.9 Hz, OCH_2CH_3), 1.15 (d, 3H, *J*=6.7 Hz, $CH(Ph)CH_3$), 2.47 (dd, 1H, *J*=9.4, 14.6 Hz, H-2), 2.58 (dd, 1H, *J*=5.6, 14.6 Hz, H-2), 3.58 (d, 1H, *J*=14.6 Hz, CH_2Ph), 3.66 (d, 1H, *J*=14.6 Hz, CH_2Ph), 3.65 (q, 2H, *J*=6.9 Hz, OCH_2CH_3), 3.93 (q, 1H, *J*=6.7 Hz, $CH(Ph)CH_3$), 4.36 (dd, 1H, *J*=5.6, 9.4 Hz, H-3), 7.17–7.33 (m, 15H, Ph). ^{13}C NMR δ: 14.1 (OCH_2CH_3), 16.0 ($CH(Ph)CH_3$), 37.9 (C-2), 51.0 (CH_2Ph), 57.0 ($CH(Ph)CH_3$), 59.6 (C-3), 60.4 (OCH_2CH_3), 126.7, 126.9, 127.3, 127.9, 128.2, 128.3, 141.6, 141.9, 144.2 (Ph), 171.9 (C-1). Anal. Calcd for $C_{29}H_{25}NO_2$: C, 80.59; H, 7.54; N, 3.61. Found: C, 80.94; H, 7.69; N, 3.87. $[\alpha]_D^{25}$ +6.8 (*c* 1.0 in $CHCl_3$).

3.6. Synthesis of β-aminoesters 12

Cerium and ammonium nitrate (5.74 g, 10.5 mmol, 2.1 equiv) was added to β-amino ester **11** (5 mmol, 1 equiv) in a mixture of acetonitrile/water: 5:1 (50 mL) at 0 °C. After 1 h of stirring at room temperature, a saturated aqueous solution of sodium carbonate (40 mL) was introduced. The solid was filtered and washed with ether (2×25 mL). The aqueous phase was separated and extracted with ether (2×40 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel chromatography (cyclohexane/ether: 70:30).

3.6.1. (*R*)-Ethyl 3-(*N*-((*R*)-1-phenylethyl)amino)butanoate 12a.[26] Oil, yield=68%. ^{1}H NMR δ: 0.97 (d, 3H, *J*=6.6 Hz, H-4), 1.17 (t, 3H, *J*=7.2 Hz, OCH_2CH_3), 1.24 (d, 3H, *J*=6.4 Hz, $CH(Ph)CH_3$), 2.30 (dd, 1H, *J*=6.4, 14.6 Hz, H2), 2.35 (dd, 1H, *J*=5.6, 14.6 Hz, H-2), 2.86–2.94 (m, 1H, H-3), 3.80 (q, 1H, *J*=6.4 Hz, $CH(Ph)CH_3$), 4.05 (q, 2H, *J*=7.2 Hz, OCH_2CH_3), 7.17–7.25 (m, 5H, Ph). ^{13}C NMR δ: 14.4 (OCH_2CH_3), 21.6 (C-4), 24.7 ($CH(Ph)CH_3$), 41.0 (C-2), 47.9 (C-3), 55.1 ($CH(Ph)CH_3$), 60.3 (OCH_2CH_3), 126.6, 127.0, 128.5, 146.2 (Ph), 172.4 (C-1). $[\alpha]_D^{25}$ +31.1 (*c* 1.0, $CHCl_3$).

3.6.2. (*R*)-Ethyl 3-(*N*-((*R*)-1-phenylethyl)amino)-pentanoate 12b. Oil, yield=66%. ^{1}H NMR δ: 0.78 (t, 3H, *J*=7.4 Hz, H-5), 1.18 (t, 3H, *J*=7.1 Hz, OCH_2CH_3), 1.24 (d, 3H, *J*=6.4 Hz, $CH(Ph)CH_3$), 1.31–1.38 (m, 2H, H-4), 1.45 (s, 1H, NH), 2.28 (dd, 1H, *J*=5.6, 14.6 Hz, H-2), 2.38 (dd, 1H, *J*=5.9, 14.6 Hz, H-2), 2.60–2.69 (m, 1H, H-3), 3.81 (q, 1H, *J*=6.4 Hz, $CH(Ph)CH_3$), 4.06 (q, 2H, *J*=7.1 Hz, OCH_2CH_3), 7.14–7.30 (m, 5H, Ph). ^{13}C NMR δ: 10.5 (C-5), 14.4 (OCH_2CH_3), 25.0 ($CH(Ph)CH_3$), 28.1 (C-4), 38.4 (C-2), 53.7 (C-3), 55.2 ($CH(Ph)CH_3$), 60.3 (OCH_2CH_3), 126.8, 127.0, 128.5, 146.2 (Ph), 172.7 (C-1). $[\alpha]_D^{25}$ +29.3 (*c* 1.0, $CHCl_3$).

3.6.3. (*R*)-Ethyl 3-(*N*-((*R*)-1-phenylethyl)amino)-hexanoate 12c.[26b] Oil, yield=63%. ^{1}H NMR δ: 0.72 (t, 3H, *J*=6.9 Hz, H-6), 1.18 (t, 3H, *J*=7.2 Hz, OCH_2CH_3), 1.11–1.29 (m, 10H, H-4, H-5), 1.24 (d, 3H, *J*=6.4 Hz,

CH(Ph)CH_3), 1.46 (s, 1H, N*H*), 2.27 (dd, 1H, J=5.4, 14.6 Hz, H-2), 2.37 (dd, 1H, J=5.6, 14.6 Hz, H-2), 2.67–2.78 (m, 1H, H-3), 3.81 (q, 1H, J=6.4 Hz, C*H*(Ph)CH_3), 4.06 (q, 2H, J=7.2 Hz, OCH_2CH_3), 7.18–7.25 (m, 5H, Ph). ^{13}C NMR δ: 14.2 (C-6), 14.4 (OCH_2*C*H_3), 19.3 (C-5), 25.1 (CH(Ph)*C*H_3), 37.8 (C-4), 38.8 (C-2), 52.0 (C-3), 55.2 (*C*H(Ph)CH_3), 60.3 (O*C*H_2CH_3), 126.9, 127.0, 128.1, 146.2 (Ph), 172.7 (C-1). $[\alpha]_D^{25}$ +28.9 (*c* 1.0, $CHCl_3$).

3.6.4. (*R*)-Ethyl 3-(*N*-((*R*)-1-phenylethyl)amino)-4-methylpentanoate 12d.[26] Oil, yield=53%. ^{1}H NMR δ: 0.79 (d, 3H, J=6.6 Hz, H-5), 0.87 (d, 3H, J=6.9 Hz, H-5), 1.26 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.31 (d, 3H, J=6.6 Hz, CH(Ph)CH_3), 1.44 (s, 1H, N*H*), 1.62–1.75 (m, 1H, H-4), 2.32 (dd, 1H, J=6.4, 14.6 Hz, H-2), 2.43 (dd, 1H, J=5.4, 14.6 Hz, H-2), 2.61–2.67 (m, 1H, H-3), 3.84 (q, 1H, J=6.6 Hz, C*H*(Ph)CH_3), 4.13 (q, 2H, J=7.2 Hz, OCH_2CH_3), 7.21–7.35 (m, 5H, Ph). ^{13}C NMR δ: 14.4 (OCH_2*C*H_3), 18.5 (C-5), 18.8 (C-5), 24.9 (CH(Ph)*C*H_3), 31.5 (C-4), 36.2 (C-2), 55.6 (*C*H(Ph)CH_3), 57.8 (C-3), 60.3 (O*C*H_2CH_3), 126.9, 127.0, 128.4, 146.4 (Ph), 173.2 (C-1). $[\alpha]_D^{25}$ +25.4 (*c* 1.0, $CHCl_3$).

3.6.5. (*R*)-Ethyl 3-(*N*-((*R*)-1-phenylethyl)amino)-4-phenylbutanoate 12e. Oil, yield=62%. ^{1}H NMR δ: 1.18 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.20 (d, 3H, J=6.6 Hz, CH(Ph)CH_3), 1.52 (s, 1H, N*H*), 2.32 (d, 2H, J=6.1 Hz, H-4), 2.58 (dd, 1H, J=7.4, 13.6 Hz, H-2), 2.66 (dd, 1H, J=6.4, 13.6 Hz, H-2), 2.92–3.02 (m, 1H, H-3), 3.78 (q, 1H, J=6.6 Hz, C*H*(Ph)CH_3), 4.06 (q, 2H, J=7.2 Hz, OCH_2CH_3), 6.97–7.19 (m, 10H, Ph). ^{13}C NMR δ: 14.4 (OCH_2*C*H_3), 24.8 (CH(Ph)*C*H_3), 38.7 (C-4), 41.6 (C-2), 53.7 (C-3), 55.3 (*C*H(Ph)CH_3), 60.4 (O*C*H_2CH_3), 126.4, 126.6, 126.9, 128.3, 128.4, 129.5, 138.9, 145.7 (Ph), 172.4 (C-1). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.36; H, 9.41; N, 4.74. $[\alpha]_D^{25}$ +26.3 (*c* 1.0, $CHCl_3$).

3.6.6. (*R*)-Ethyl 3-(*N*-((*R*)-1-phenylethyl)amino)-3-phenylpropanoate 12g.[26] Oil, yield=48%. ^{1}H NMR δ: 1.10 (t, 3H, J=7.2 Hz, OCH_2*C*H_3), 1.26 (d, 3H, J=6.4 Hz, CHα*C*H_3), 1.77 (s, 1H, N*H*), 2.56 (dd, 1H, J=6.1, 15.1 Hz, H-2), 2.64 (dd, 1H, J=7.7, 15.1 Hz, H-2), 3.58 (q, 1H, J=6.4 Hz, C*H*(Ph)CH_3), 3.99 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.12 (dd, 1H, J=6.1, 7.7 Hz, H-3), 7.16–7.21 (m, 10H, Ph). ^{13}C NMR δ: 14.3 (OCH_2*C*H_3), 22.4 (CH(Ph)*C*H_3), 43.0 (C-2), 54.7 (*C*H(Ph)CH_3), 57.0 (C-3), 60.6 (O*C*H_2CH_3), 126.7, 126.9, 127.0, 127.1, 128.5, 128.7, 142.9, 146.1 (Ph), 171.9 (C-1). Anal. Calcd for $C_{19}H_{21}NO_2$: C, 76.75; H, 7.80; N, 4.71. Found: C, 76.95; H, 8.13; N, 5.02. $[\alpha]_D^{25}$ +21.7 (*c* 1.0, $CHCl_3$).

3.7. Synthesis of α-(phenylselanyl)β-aminoesters 9, 9″

n-Butyllithium 2.5 M in hexane (1.26 mL, 3.15 mmol, 2.1 equiv) was added dropwise to a solution of diisopropylamine (318 mg, 3.15 mmol, 2.1 equiv) in THF (20 mL) at 0 °C, under argon. After 15 min of stirring at 0 °C, the mixture was cooled to −78 °C and a solution of the β-aminoester **12** (1.5 mmol, 1 equiv) in THF (2 mL) was slowly introduced. After 20 min at −78 °C, a solution of PhSeBr (460 mg, 1.95 mmol, 1.3 equiv) in THF (2 mL) was added. After 20 min of stirring at −78 °C the mixture was quenched with a saturated aqueous solution of ammonium chloride (5 mL) and allowed to reach the room temperature. Water (30 mL) and ether (15 mL) were added. The aqueous phase was separated and extracted with ether (2×30 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by silica gel chromatography (cyclohexane/ether: 90:10).

3.7.1. Ethyl 3-((*R*)-1-phenylethylamino)-2-(phenylselanyl)butanoate 9a, 9″a. Oil, **9a/9″a**: 50/50, yield=65%.

3.7.1.1. (2*S*,3*R*)-Ethyl 3-((*R*)-1-phenylethylamino)-2-(phenylselanyl)butanoate 9a. (Second eluted). ^{1}H NMR δ: 1.10 (d, 3H, J=6.4 Hz, H-4), 1.15 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.31 (d, 3H, J=6.6 Hz, CH(Ph)CH_3), 1.70 (s, 1H, N*H*), 3.11 (quint, 1H, J=6.4 Hz, H-3), 3.83 (d, 1H, J=6.4 Hz, H-2), 3.86 (q, 1H, J=6.6 Hz, C*H*(Ph)CH_3), 4.04–4.10 (m, 2H, OCH_2CH_3), 7.26–7.55 (m, 10H, Ph). ^{13}C NMR δ: 14.2 (OCH_2*C*H_3), 19.3 (C-4), 24.5 (CH(Ph)*C*H_3), 51.4, 52.7 (C-2, C-3), 55.7 (*C*H(Ph)CH_3), 61.1 (O*C*H_2CH_3), 126.7, 126.9, 128.2, 128.5, 129.1, 129.3, 135.2, 146.3 (Ph), 172.1 (C-1). $[\alpha]_D^{25}$ −18.5 (*c* 1.0 in $CHCl_3$).

3.7.1.2. (2*R*,3*R*)-Ethyl 3-((*R*)-1-phenylethylamino)-2-(phenylselanyl)butanoate 9″a. (First eluted). ^{1}H NMR δ: 1.13 (d, 3H, J=6.4 Hz, H-4), 1.16 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.22 (d, 3H, J=6.4 Hz, CH(Ph)CH_3), 1.64 (s, 1H, N*H*), 3.13 (quint, 1H, J=6.4 Hz, H-3), 3.73 (d, 1H, J=6.4 Hz, H-2), 3.77 (q, 1H, J=6.4 Hz, C*H*(Ph)CH_3), 4.9 (q, 2H, J=7.2 Hz, OCH_2CH_3), 7.24–7.62 (m, 10H, Ph). ^{13}C NMR δ: 14.2 (OCH_2*C*H_3), 19.4 (C-4), 24.0 (CH(Ph)*C*H_3), 52.5, 52.6 (C-2, C-3), 55.8 (*C*H(Ph)CH_3), 61.0 (O*C*H_2CH_3), 126.7, 127.0, 128.1, 128.5, 129.2, 129.7, 134.8, 146.4 (Ph), 172.8 (C-1). $[\alpha]_D^{25}$ −33.4 (*c* 1.0 in $CHCl_3$).

3.7.2. Ethyl 3-((*R*)-1-phenylethylamino)-2-(phenylselanyl)pentanoate 9b, 9″b. Oil, **9b/9″b**: 50/50, yield=59%.

3.7.2.1. (2*S*,3*R*)-Ethyl 3-((*R*)-1-phenylethylamino)-2-(phenylselanyl)pentanoate 9b. (Second eluted). ^{1}H NMR δ: 0.84 (t, 3H, J=7.2 Hz, H-5), 1.19 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.34 (d, 3H, J=6.6 Hz, CH(Ph)CH_3), 1.66–1.80 (m, 3H, H-4, N*H*), 2.32–2.41 (m, 1H, H-3), 3.87 (q, 1H, J=6.6 Hz, C*H*(Ph)CH_3), 4.01 (d, 1H, J=5.4 Hz, H-2), 4.04–4.19 (m, 2H, OCH_2CH_3), 7.19–7.60 (m, 10H, Ph). ^{13}C NMR δ: 10.5 (C-5), 14.2 (OCH_2*C*H_3), 24.7 (CHα*C*H_3), 25.2 (C-4), 49.9 (C-2), 55.5 (*C*H(Ph)CH_3), 58.4 (C-3), 61.2 (O*C*H_2CH_3), 126.8, 128.1, 128.4, 128.6, 129.1, 129.2, 135.2, 146.1 (Ph), 172.2 (C-1). $[\alpha]_D^{25}$ −17.9 (*c* 1.0, $CHCl_3$).

3.7.2.2. (2*R*,3*R*)-Ethyl 3-((*R*)-1-phenylethylamino)-2-(phenylselanyl)pentanoate 9″b. (First eluted). ^{1}H NMR δ: 0.73 (t, 3H, J=7.2 Hz, H-5), 1.16 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.21 (d, 3H, J=6.4 Hz, CH(Ph)CH_3), 1.39–1.58 (m, 2H, H-4), 1.73 (s, 1H, N*H*), 2.85–3.91 (m, 1H, H-3), 3.74 (q, 1H, J=6.4 Hz, C*H*(Ph)CH_3), 3.81 (d, 1H, J=5.9 Hz, H2), 3.96–4.13 (m, 2H, OCH_2CH_3), 7.22–7.70 (m, 10H, Ph). ^{13}C NMR δ: 10.1 (C-5), 14.1 (OCH_2*C*H_3), 24.0 (CH(Ph)*C*H_3), 25.4 (C-4), 50.2 (C-2), 55.6 (*C*H(Ph)CH_3), 57.8 (C-3), 61.0 (O*C*H_2CH_3), 126.8, 127.0, 128.0, 128.4, 129.3, 129.4, 134.7, 146.3 (Ph), 172.9 (C1). $[\alpha]_D^{25}$ −30.7 (*c* 1.0, $CHCl_3$).

3.7.3. Ethyl 3-((*R*)-1-phenylethylamino)-2-(phenylselanyl)hexanoate 9c, 9″c. Oil, **9c/9″c**: 50/50, yield=56%.

3.7.3.1. (2*S*,3*R*)-Ethyl 3-((*R*)-1-phenylethylamino)-2-(phenylselanyl)hexanoate 9c. (Second eluted). ^{1}H NMR δ: 0.67 (t, 3H, J=7.2 Hz, H-6), 1.10 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.21 (d, 3H, J=6.4 Hz, $CH(Ph)CH_3$), 1.15–1.29 (m, 2H, H-5), 1.48–1.42 (m, 2H, H-4), 1.68 (s, 1H, N*H*), 2.75–2.79 (m, 1H, H-3), 3.75 (q, 1H, J=6.4 Hz, $CH(Ph)CH_3$), 3.93 (d, 1H, J=4.8 Hz, H-2), 4.03 (dq, 1H, J=7.2, 10.7 Hz, OCH_2CH_3), 4.06 (dq, 1H, J=7.2, 10.7 Hz, OCH_2CH_3), 7.16–7.45 (m, 10H, Ph). ^{13}C NMR δ: 14.0, 14.2 (C-6, OCH_2CH_3), 19.4 (C-5), 24.8 ($CH(Ph)CH_3$), 34.7 (C-4), 50.0 (C-2), 55.4 ($CH(Ph)CH_3$), 56.7 (C-3), 61.2 (OCH_2CH_3), 126.9, 127.5, 127.9, 128.2, 128.6, 129.2, 135.4, 146.0 (Ph), 172.1 (C-1). $[\alpha]_D^{25}$ −17.4 (*c* 1.0 in $CHCl_3$).

3.7.3.2. (2*R*,3*R*)-Ethyl 3-((*R*)-1-phenylethylamino)-2-(phenylselanyl)hexanoate 9″c. (First eluted). ^{1}H NMR δ: 0.76 (t, 3H, J=7.2 Hz, H-6), 1.15 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.22 (d, 3H, J=6.4 Hz, $CH(Ph)CH_3$), 1.16–1.34 (m, 2H, H-5), 1.43–1.49 (m, 2H, H-4), 1.68 (s, 1H, N*H*), 2.95–3.01 (m, 1H, H-3), 3.79 (q, 1H, J=6.4 Hz, $CH(Ph)CH_3$), 3.90 (d, 1H, J=5.4 Hz, H-2), 4.01 (q, 2H, J=7.2 Hz, OCH_2CH_3), 7.27–7.63 (m, 10H, Ph). ^{13}C NMR δ: 14.2, 14.3 (C-6, OCH_2CH_3), 19.1 (C-5), 24.2 ($CH(Ph)CH_3$), 35.3 (C-4), 51.0 (C-2), 55.6 ($CH(Ph)CH_3$), 56.4 (C-3), 61.1 (OCH_2CH_3), 127.0, 127.1, 128.1, 128.5, 129.2, 129.5, 134.8, 146.7 (Ph), 172.9 (C-1). $[\alpha]_D^{25}$ −29.8 (*c* 1.0 in $CHCl_3$).

3.7.4. Ethyl 3-((*R*)-1-phenylethylamino)-4-methyl-2-(phenylselanyl)pentanoate 9d, 9″d. Oil, **9d/9″d**: 60/40, yield=58%.

3.7.4.1. (2*S*,3*R*)-Ethyl 3-((*R*)-1-phenylethylamino)-4-methyl-2-(phenylselanyl)pentanoate 9d. (First eluted). ^{1}H NMR δ: 0.78 (d, 3H, J=6.9 Hz, H-5), 0.81 (d, 3H, J=6.9 Hz, H-5), 1.04 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.38 (d, 3H, J=6.6 Hz, $CH(Ph)CH_3$), 1.55 (s, 1H, N*H*), 1.83 (septd, 1H, J=3.8, 6.9 Hz, H-4), 2.95 (dd, 1H, J=3.8, 6.9 Hz, H-3), 3.89 (q, 1H, J=6.6 Hz, $CH(Ph)CH_3$), 3.91 (dq, 1H, J=7.2, 10.4 Hz, OCH_2CH_3), 3.95 (dq, 1H, J=7.2, 10.4 Hz, OCH_2CH_3), 4.05 (d, 1H, J=6.9 Hz, H-2), 7.26–7.62 (m, 10H, Ph). ^{13}C NMR δ: 14.0 (OCH_2CH_3), 17.9 (C-5), 19.9 (C-5), 24.1 ($CH(Ph)CH_3$), 31.6 (C-4), 51.1 (C-2), 56.8 ($CH(Ph)CH_3$), 59.8 (C-3), 61.1 (OCH_2CH_3), 127.0, 127.1, 128.1, 128.4, 129.0, 130.0, 135.6, 146.2 (Ph), 172.8 (C-1). $[\alpha]_D^{25}$ −19.6 (*c* 1.0 in $CHCl_3$).

3.7.4.2. (2*R*,3*R*)-Ethyl 3-((*R*)-1-phenylethylamino)-4-methyl-2-(phenylselanyl)pentanoate 9″d. (Second eluted). ^{1}H NMR δ: 0.68 (d, 3H, J=6.9 Hz, H-5), 0.79 (d, 3H, J=6.9 Hz, H-5), 1.16 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.28 (d, 3H, J=6.4 Hz, $CH(Ph)CH_3$), 1.65 (s, 1H, N*H*), 2.01 (septd, 1H, J=4.3, 6.9 Hz, H-4), 2.96 (dd, 1H, J=4.3, 6.9 Hz-3), 3.82 (d, 1H, J=6.9 Hz, H-2), 3.92 (q, 1H, J=6.4 Hz, $CH(Ph)CH_3$), 4.06 (dq, 1H, J=7.2, 10.7 Hz, OCH_2CH_3), 4.09 (dq, 1H, J=7.2, 10.7 Hz, OCH_2CH_3), 7.28–7.63 (m, 10H, Ph). ^{13}C NMR δ: 14.1 (OCH_2CH_3), 17.6 (C-5), 20.1 (C-5), 24.2 ($CH\alpha CH_3$), 31.4 (C-4), 49.9 (C-2), 56.7 ($CH(Ph)CH_3$), 61.0 (OCH_2CH_3), 61.7 (C-3), 127.2, 127.3, 128.3, 128.6, 129.2, 130.0, 135.8, 146.4 (Ph), 173.3 (C-1). $[\alpha]_D^{25}$ −33.5 (*c* 1.0 in $CHCl_3$).

3.7.5. Ethyl 4-phenyl-3-((*R*)-1-phenylethylamino)-2-(phenylselanyl)butanoate 9e, 9″e. Oil, **9e/9″e**: 70/30, yield=61%.

3.7.5.1. (2*S*,3*R*)-Ethyl 4-phenyl-3-((*R*)-1-phenylethylamino)-2-(phenylselanyl)butanoate 9e. (Second eluted). ^{1}H NMR δ: 1.06 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.19 (d, 3H, J=6.6 Hz, $CH(Ph)CH_3$), 1.67 (s, 1H, N*H*), 2.61 (dd, 1H, J=7.9, 13.7 Hz, H-4), 2.94 (dd, 1H, J=5.1, 13.7 Hz, H-4), 3.09–3.15 (m, 1H, H-3), 3.78 (q, 1H, J=6.6 Hz, $CH(Ph)CH_3$), 3.85 (d, 1H, J=4.9 Hz, H-2), 3.95 (dq, 1H, J=7.2, 10.7 Hz, OCH_2CH_3), 3.97 (dq, 1H, J=7.2, 10.7 Hz, OCH_2CH_3), 6.84–7.07 (m, 15H, Ph). ^{13}C NMR δ: 14.2 (OCH_2CH_3), 24.6 ($CH(Ph)CH_3$), 38.9 (C-4), 49.6 (C-2), 55.6 ($CH(Ph)CH_3$), 58.5 (C-3), 61.1 (OCH_2CH_3), 126.4, 126.6, 126.8, 128.1, 128.3, 128.4, 128.5, 129.1, 129.7, 135.0, 138.7, 145.6 (Ph), 172.3 (C-1). $[\alpha]_D^{25}$ −29.6 (*c* 1.0 in $CHCl_3$).

3.7.5.2. (2*R*,3*R*)-Ethyl 3-((*R*)-1-phenylethylamino)-2-(phenylselanyl)butanoate 9″e. (First eluted). ^{1}H NMR δ: 1.10 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.16 (d, 3H, J=6.4 Hz, $CH(Ph)CH_3$), 1.87 (s, 1H, N*H*), 2.75 (d, 2H, J=6.6 Hz, H-4), 3.19 (td, 1H, J=5.4, 6.6 Hz, H-3), 3.66 (d, 1H, J=5.4 Hz, H-2), 3.74 (q, 1H, J=6.4 Hz, $CH(Ph)CH_3$), 4.04 (q, 2H, J=7.2 Hz, OCH_2CH_3), 6.94–7.48 (m, 15H, Ph). ^{13}C NMR δ: 14.2 (OCH_2CH_3), 23.9 ($CH(Ph)CH_3$), 39.2 (C-4), 49.6 (C-2), 55.9 ($CH(Ph)CH_3$), 58.3 (C-3), 61.0 (OCH_2CH_3), 126.4, 126.7, 126.9, 128.0, 128.4, 128.5, 129.1, 129.5, 129.9, 134.6, 138.5, 146.0 (Ph), 172.8 (C-1). $[\alpha]_D^{25}$ −16.3 (*c* 1.0 in $CHCl_3$).

3.7.6. Ethyl 3-phenyl-3-((*R*)-1-phenylethylamino)-2-(phenylselanyl)propanoate 9g, 9″g. Oil, **9g/9″g**: 50/50, yield=57%.

3.7.6.1. (2*S*,3*R*)-Ethyl 3-phenyl-3-((*R*)-1-phenylethylamino)-2-(phenylselanyl)propanoate 9g. (First eluted). ^{1}H NMR δ: 0.86 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.34 (d, 3H, J=6.6 Hz, $CH(Ph)CH_3$), 2.17 (s, 1H, N*H*), 3.56 (q, 1H, J=6.6 Hz, $CH(Ph)CH_3$), 3.73 (dq, 1H, J=7.2, 10.7 Hz, OCH_2CH_3), 3.75 (dq, 1H, J=7.2, 10.7 Hz, OCH_2CH_3), 3.98 (d, 1H, J=9.7 Hz, H-2), 4.25 (d, 1H, J=9.7 Hz, H-3), 7.24–7.62 (m, 15H, Ph). ^{13}C NMR δ: 13.8 (OCH_2CH_3), 21.8 ($CH(Ph)CH_3$), 52.7 (C-2), 54.6 ($CH(Ph)CH_3$), 60.8 (OCH_2CH_3), 60.9 (C-3), 126.7, 126.8, 127.6, 127.8, 128.1, 128.3, 128.4, 128.5, 129.0, 135.9, 140.5, 146.1 (Ph), 171.1 (C-1). $[\alpha]_D^{25}$ −15.7 (*c* 1.0 in $CHCl_3$).

3.7.6.2. (2*R*,3*R*)-Ethyl 3-phenyl-3-((*R*)-1-phenylethylamino)-2-(phenylselanyl)propanoate 9″g. (Second eluted). ^{1}H NMR δ: 1.10 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.28 (d, 3H, J=6.4 Hz, $CH(Ph)CH_3$), 2.35 (s, 1H, N*H*), 3.61 (q, 1H, J=6.4 Hz, $CH(Ph)CH_3$), 3.89 (d, 1H, J=8.6 Hz, H-2), 4.03 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.31 (d, 1H, J=8.6 Hz, H-3), 7.18–7.25 (m, 15H, Ph). ^{13}C NMR δ: 14.1 (OCH_2CH_3), 22.1 ($CH(Ph)CH_3$), 51.7 (C-2), 55.1 ($CH(Ph)CH_3$), 61.0 (OCH_2CH_3), 62.0 (C-3), 126.7, 126.8, 127.1, 127.6, 127.7, 128.1, 128.4, 128.5, 128.9, 135.2, 140.4, 146.3 (Ph), 172.2 (C-1). $[\alpha]_D^{25}$ −23.8 (*c* 1.0 in $CHCl_3$).

3.8. Cyclisation of α-(phenylselanyl)β-aminoesters 9, 9″

The protocols are the same as for the cyclisation of β-(phenylselanyl)α-aminoesters **2**.

Procedure A with Me_3OBF_4. α-(Phenylselanyl)β-aminoesters **9** (or **9″**) afforded aziridines **6** (or **6″**).

Procedure B with NBS. α-(Phenylselanyl)β-aminoesters **9** (or **9″**) afforded aziridines **6** (or **6″**), except for **9a** and **9f**, which lead, respectively, to **6″a** and **6″f**.

3.8.1. (2*R*,3*R*)-Ethyl 3-methyl-1-((*R*)-1-phenylethyl)-aziridine-2-carboxylate 6a.[5b] Yield=51% (A).

3.8.2. (2*S*,3*R*)-Ethyl 3-methyl-1-((*R*)-1-phenylethyl)-aziridine-2-carboxylate 6″a. Oil, two invertomers: 60/40, yield=53% (A), yield=59% (B). Major: ^{1}H NMR δ: 1.04 (d, 3H, J=5.4 Hz, CH_3), 1.18 (d, 3H, J=6.6 Hz, CH(Ph)CH_3), 1.26 (t, 3H, J=7.2 Hz, OCH$_2$CH_3), 2.12–2.20 (m, 1H, H-3), 2.44 (d, 1H, J=2.8 Hz, H-2), 3.77 (q, 1H, J=6.6 Hz, CH(Ph)CH$_3$), 4.16 (dq, 1H, J=7.2, 10.7 Hz, OCH_2CH$_3$), 4.19 (dq, 1H, J=7.2, 10.7 Hz, OCH_2CH$_3$), 7.23–7.32 (m, 5H, Ph). ^{13}C NMR δ: 14.5 (OCH$_2$CH_3), 18.0 (CH_3), 23.5 (CH(Ph)CH_3), 41.7 (C-2), 42.1 (C-3), 59.1 (Cα), 61.3 (OCH$_2$CH$_3$), 127.4, 128.7, 128.8, 145.3 (Ph), 170.0 (C=O). Minor: δ_H (300 MHz, CDCl$_3$): 1.14 (d, 3H, J=7.2 Hz, OCH$_2$CH_3), 1.36 (d, 3H, J=6.4 Hz, CHαCH_3), 1.40 (t, 3H, J=6.1 Hz, CH_3), 1.77 (d, 1H, J=2.8 Hz, H-2), 2.56–2.65 (m, 1H, H-3), 3.27 (q, 1H, J=6.4 Hz, CH(Ph)CH$_3$), 4.05 (q, 2H, J=7.2 Hz, OCH_2CH$_3$), 7.23–7.32 (m, 5H, Ph). ^{13}C NMR δ: 10.9 (CH_3), 14.6 (OCH$_2$CH_3), 24.9 (CH(Ph)CH_3), 41.4 (C-3), 43.7 (C-2), 60.4 (CH(Ph)CH$_3$), 61.2 (OCH$_2$CH$_3$), 127.0, 128.7, 128.8, 145.3 (Ph), 170.2 (C=O). MS *m*/*z*: 233 (M$^+$, 2), 128 (77), 105 (100). IR ν_{max} (neat) cm^{-1}: 2979, 1728, 1449, 1190. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.10; H, 8.21; N, 6.00. Found: C, 71.87; H, 8.23; N, 5.89. $[\alpha]_D^{25}$ +34.1 (*c* 1.0 in CH_2Cl_2).

3.8.3. (2*R*,3*R*)-Ethyl 1-((*R*)-1-phenylethyl)-3-ethyl-aziridine-2-carboxylate 6b. Yield=53% (A).

3.8.4. (2*S*,3*R*)-Ethyl 1-((*R*)-1-phenylethyl)-3-ethyl-aziridine-2-carboxylate 6″b. Oil, yield=47% (A), yield=51% (B). ^{1}H NMR δ: 0.62 (t, 3H, J=7.4 Hz, CH$_2$CH_3), 1.30 (d, 3H, J=6.6 Hz, CH(Ph)CH_3), 1.37 (t, 3H, J=7.2 Hz, OCH$_2$CH_3), 1.17–1.52 (m, 2H, CH_2CH$_3$), 2.17 (ddd, 1H, J=2.8, 5.4, 6.7 Hz, H-3), 2.56 (d, 1H, J=2.8 Hz, H-2), 3.83 (q, 1H, J=6.6 Hz, CH(Ph)CH$_3$), 4.12–4.22 (m, 2H, OCH_2CH$_3$), 7.22–7.49 (m, 5H, Ph). ^{13}C NMR δ: 11.0 (CH$_2$CH_3), 14.4 (OCH$_2$CH_3), 22.8 (CH(Ph)CH_3), 25.7 (CH_2CH$_3$), 40.7 (C-2), 48.2 (C-3), 59.4 (CH(Ph)CH$_3$), 61.2 (OCH$_2$CH$_3$), 127.3, 127.4, 128.4, 144.7 (Ph), 170.0 (C=O). MS *m*/*z*: 247 (M$^+$, 14), 142 (34), 105 (100). IR ν_{max} (neat) cm^{-1}: 2970, 1728, 1450, 1190. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 58.29; H, 8.50; N, 5.66. Found: C, 58.85; H, 8.67; N, 5.31. $[\alpha]_D^{25}$ +22.6 (*c* 1.0, CH_2Cl_2).

3.8.5. (2*R*,3*R*)-Ethyl 1-((*R*)-1-phenylethyl)-3-propyl-aziridine-2-carboxylate 6c. Yield=47% (A), yield=61% (B).

3.8.6. (2*S*,3*R*)-Ethyl 1-((*R*)-1-phenylethyl)-3-propyl-aziridine-2-carboxylate 6″c. Oil, yield=50% (A), yield=51% (B). ^{1}H NMR δ: 0.69 (t, 3H, J=7.2 Hz, CH$_2$CH$_2$CH_3), 0.98–1.07 (m, 2H, CH$_2$CH_2CH$_3$), 1.24–1.41 (m, 2H, CH_2CH$_2$CH$_3$), 1.30 (d, 3H, J=6.4 Hz, CH(Ph)CH_3), 1.34 (t, 3H, J=7.2 Hz, OCH$_2$CH_3), 2.15–2.23 (m, 1H, H-3), 2.53 (d, 1H, J=2.8 Hz, H-2), 3.80 (q, 1H, J=6.4 Hz, CH(Ph)CH$_3$), 4.23 (dq, 1H, J=7.2, 10.7 Hz, OCH_2CH$_3$), 4.25 (dq, 1H, J=7.2, 10.7 Hz, OCH_2CH$_3$), 7.25–7.41 (m, 5H, Ph). ^{13}C NMR δ: 13.7 (CH_3CH$_2$CH$_2$), 14.4 (OCH$_2$CH_3), 20.1 (CH$_3$CH_2CH$_2$), 22.8 (CH(Ph)CH_3), 34.8 (CH$_3$CH$_2$CH_2), 41.1 (C-2), 46.7 (C-3), 59.5 (CH(Ph)CH$_3$), 61.2 (OCH$_2$CH$_3$), 127.3, 127.5, 128.4, 144.7 (Ph), 170.0 (C=O). MS *m*/*z*: 261 (M$^+$, 1), 156 (91), 105 (100), 82 (69). IR ν_{max} (neat) cm^{-1}: 2968, 1728, 1455, 1189. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.75; H, 9.01; N, 5.48. $[\alpha]_D^{25}$ +17.3 (*c* 1.0 in CH_2Cl_2).

3.8.7. (2*R*,3*R*)-Ethyl 1-((*R*)-1-phenylethyl)-3-*iso*-propyl-aziridine-2-carboxylate 6d. Oil, yield=44% (A), yield=49% (B). ^{1}H NMR δ: 0.42 (d, 3H, J=6.4 Hz, CH(CH_3)$_2$), 0.67 (d, 3H, J=6.4 Hz, CH(CH_3)$_2$), 1.22 (t, 3H, J=7.2 Hz, OCH$_2$CH_3), 1.38–1.40 (m, 4H, CH(CH$_3$)$_2$, CH(Ph)CH_3), 1.41–1.48 (m, 1H, H-3), 2.15 (d, 1H, J=6.4 Hz, H-2), 2.45 (q, 1H, J=6.6 Hz, CH(Ph)CH$_3$), 4.15 (q, 2H, J=7.2 Hz, OCH_2CH$_3$), 7.19–7.33 (m, 5H, Ph). ^{13}C NMR δ: 14.4 (OCH$_2$CH_3), 19.8 (CH(CH_3)$_2$), 20.6 (CH(CH_3)$_2$), 22.1 (CH(Ph)CH_3), 27.2 (CH(CH$_3$)$_2$), 43.2 (C-2), 53.2 (C-3), 59.9 (OCH$_2$CH$_3$), 70.4 (CH(Ph)CH$_3$), 127.6, 127.8, 128.4, 143.4 (Ph), 170.2 (C=O). MS *m*/*z*: 261 (M$^+$, 3), 218 (11), 156 (100), 105 (74), 82 (85). IR ν_{max} (neat) cm^{-1}: 2978, 1744, 1453, 1184. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.87; H, 9.03; N, 5.16. $[\alpha]_D^{25}$ +48.5 (*c* 1.0 in CH_2Cl_2).

3.8.8. (2*S*,3*R*)-Ethyl 1-((*R*)-1-phenylethyl)-3-*iso*-propyl-aziridine-2-carboxylate 6″d. Oil, yield=48% (A), yield=53% (B). ^{1}H NMR δ: 0.37 (d, 3H, J=6.6 Hz, CH(CH_3)$_2$), 0.71 (d, 3H, J=6.6 Hz, CH(CH_3)$_2$), 1.18–1.20 (m, 1H, CH(CH$_3$)$_2$), 1.21 (d, 3H, J=6.4 Hz, CH(Ph)CH_3), 1.27 (t, 3H, J=7.2 Hz, OCH$_2$CH_3), 1.92 (dd, 1H, J=2.8, 7.7 Hz, H-3), 2.47 (d, 1H, J=2.8 Hz, H-2), 3.69 (q, 1H, J=6.4 Hz, CH(Ph)CH$_3$), 4.12–4.23 (m, 2H, OCH_2CH$_3$), 7.18–7.32 (m, 5H, Ph). ^{13}C NMR δ: 14.4 (OCH$_2$CH_3), 19.5 (CH(CH_3)$_2$), 19.6 (CH(CH_3)$_2$), 22.3 (CH(Ph)CH_3), 31.2 (CH(CH$_3$)$_2$), 39.9 (C-2), 53.5 (C-3), 59.9 (CH(Ph)CH$_3$), 61.2 (OCH$_2$CH$_3$), 127.9, 128.4, 128.6, 144.6 (Ph), 170.1 (C=O). MS *m*/*z*: 261 (M$^+$, 3), 156 (60), 105 (83), 82 (100). IR ν_{max} (neat) cm^{-1}: 2968, 1723, 1449, 1190. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.53; H, 8.94; N, 5.28. $[\alpha]_D^{25}$ −22.8 (*c* 1.0 in CH_2Cl_2).

3.8.9. (2*R*,3*R*)-Ethyl 3-benzyl-1-((*R*)-1-phenylethyl)-aziridine-2-carboxylate 6e.[5b] Yield=42% (A), yield=53% (B).

3.8.10. (2*S*,3*R*)-Ethyl 3-benzyl-1-((*R*)-1-phenylethyl)-aziridine-2-carboxylate 6″e. Oil, yield=39% (A), yield=48% (B). ^{1}H NMR δ: 1.19 (d, 3H, J=6.4 Hz, CH(Ph)CH_3), 1.25 (t, 3H, J=6.9 Hz, OCH$_2$CH_3), 2.39 (td, 1H, J=2.8, 5.9 Hz, H-3), 2.53 (dd, 1H, J=5.9, 14.6 Hz, CH_2Ph), 2.58 (d, 1H, J=2.8 Hz, H-2), 2.62 (dd, 1H, J=5.9,

14.6 Hz, CH_2Ph), 3.75 (q, 1H, J=6.4 Hz, CH(Ph)CH_3), 4.12 (dq, 1H, J=6.9, 10.5 Hz, OC$H_2$$CH_3$), 4.16 (dq, 1H, J=6.9, 10.5 Hz, OC$H_2$$CH_3$), 6.86–7.31 (m, 10H, Ph). ^{13}C NMR δ: 14.4 (OCH$_2$$CH_3$), 23.0 (CH(Ph)$CH_3$), 38.8 ($CH_2$Ph), 40.6 (C-2), 47.3 (C-3), 59.4 (CH(Ph)CH_3), 61.3 (O$CH_2$$CH_3$), 126.2, 126.6, 127.2, 127.3, 128.4, 128.6, 138.2, 144.4 (Ph), 169.7 (C=O). IR ν_{max} (neat) cm^{-1}: 2978, 1723, 1449, 1190. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.60; H, 7.49; N, 4.53. Found: C, 77.88; H, 7.76; N, 4.69. $[\alpha]_D^{25}$ +13.8 (c 1.0 in CH_2Cl_2).

3.8.11. (2*R*,3*R*)-Ethyl 3-phenyl-1-((*R*)-1-phenylethyl)-aziridine-2-carboxylate 6g.[5b] Oil, yield=49% (A).

3.8.12. (2*S*,3*R*)-Ethyl 3-phenyl-1-((*R*)-1-phenylethyl)-aziridine-2-carboxylate 6″g. Oil, yield=52% (A), yield=55% (B). ^{1}H NMR δ: 1.22–1.31 (m, 6H, CH(Ph)CH_3, OCH$_2$CH_3), 2.75 (d, 1H, J=2.8 Hz, H-2), 3.15 (d, 1H, J=2.8 Hz, H-3), 4.01 (q, 1H, J=6.4 Hz, CH(Ph)CH_3), 4.15 (m, 2H, OC$H_2$$CH_3$), 7.12–7.32 (m, 10H, Ph). ^{13}C NMR δ: 14.2 (OCH$_2$$CH_3$), 23.5 (CH(Ph)$CH_3$), 44.6 (C-2), 47.9 (C-3), 60.6 (CH(Ph)CH_3), 61.2 (O$CH_2$$CH_3$), 126.9, 127.3, 127.8, 128.0, 128.5, 129.1, 135.7, 144.5 (Ph), 167.9 (C=O). M.S. m/z: 295 (M$^+$, 1), 190 (100), 117 (79), 105 (47). IR ν_{max} (neat) cm^{-1}: 2977, 1724, 1455, 1184. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.03; H, 7.17; N, 4.74. Found: C, 77.17; H, 7.35; N, 4.93. $[\alpha]_D^{25}$ +22 (c 1.0 in CH_2Cl_2).

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New macrocycles derived from biphenyl for pH-switched solvent extraction

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Abstract—Four new fluorescent macrocyclic ligands derived from biphenyl are described. The new compounds have been used in liquid–liquid extraction experiments and the influence of pH has been studied in those ligands containing carboxylic groups. The results obtained for the latter ligands have been compared with those observed in the presence of an external acid.

1. Introduction

Solvent extraction belongs to one of the most important processes in water treatment and hydrometallurgical metal winning. The design of the complexing agents plays an important role in such processes. In the solvent extraction of metal ions it is now well established that a variety of ligand types can be employed as the extracting agent and, for example, can form chelate or solvated complexes with metal ions.[1] In particular, macrocyclic ligands, such as certain crown compounds, complex cations selectively and have played an important role in the separation and recovery of toxic metals from waste water.[2] For macrocyclic polyethers, the strong influence of the ligand topology on the extraction efficiency has been well established.[3] On the other hand, the presence of additional functional groups sensitive to the medium pH have been used to regulate complexation and to improve extraction under chosen conditions.[4] In particular, crowns with pendant acidic arms can bind and extract metal ions in the form of their neutral complexes.[5]

For several years our research group has been interested in the preparation of crown ethers derived from biphenyl for use, not only in cation sensing, but also in solvent extraction as well as for use as ionophores for transport experiments across organic membranes.[6] We now report the preparation of five new functionalized ligands of the above type in order to study their efficiency in extraction experiments under different pH conditions (Chart 1).

2. Discussion and results

Ligand **1** has been previously reported. Ligands **3** and **4** were easily prepared by direct reaction of 2-chlorocarbonyl-2′-methoxycarbonyl-4,4′-dinitrobiphenyl with 2-hydroxymethyl-18-crown-6 and 4,13-diaza-18-crown-6, respectively. Hydrolysis of ligands **1** and **4** gave rise to compounds **2** and **5**, respectively, in high yield (Scheme 1).

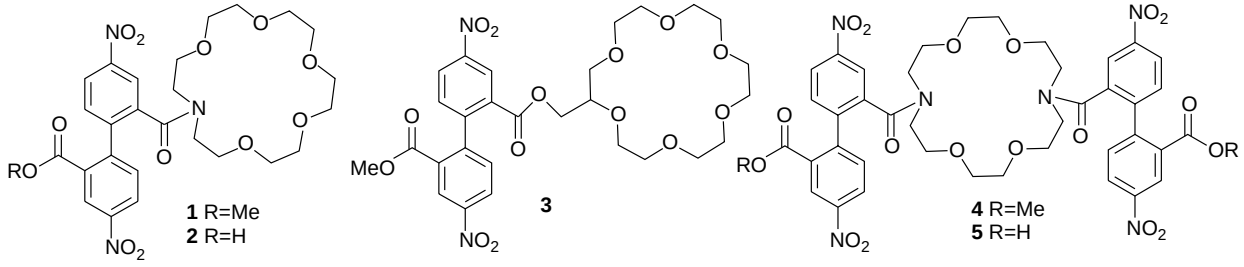

Chart 1.

Keywords: Extraction; pH-switched ligands; Biphenyl; Cations.
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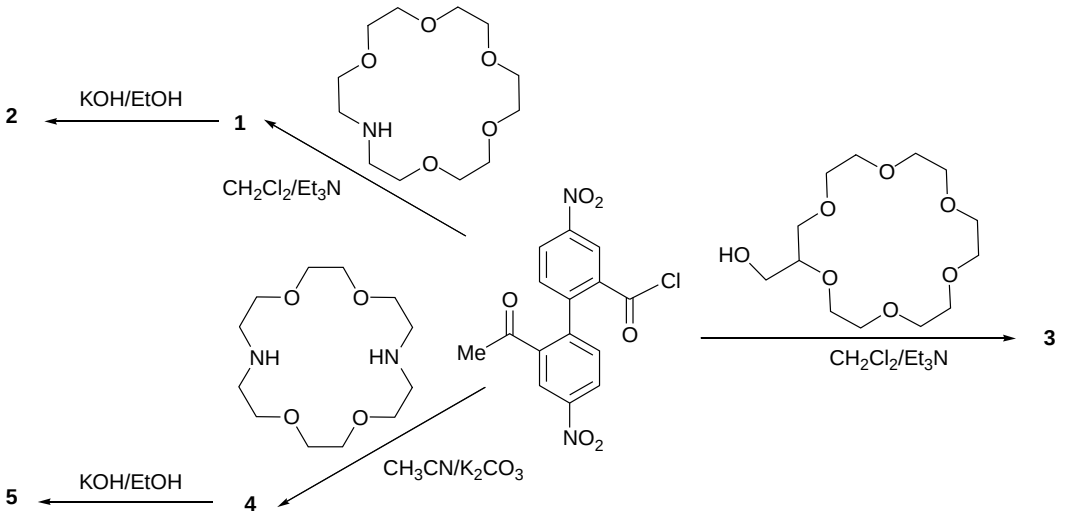

Scheme 1.

2.1. Liquid–liquid extraction studies

In order to evaluate the potential of the newly prepared compounds as extracting agents and also the influence of pH on the extraction efficiency, liquid–liquid extraction of several metal cations (Na^+, Cs^+, Ag^+, Zn^{2+}, Eu^{3+}) were conducted using the extraction system metal salt/acid–buffer–H_2O/ligand–chloroform. It is well established that the efficiency of extraction by a lipophilic ligand is influenced by the nature of counter anions, which accompany the cation–ligand complex.[7] To compare the efficiency of the ionophores, experimental conditions need to be carefully controlled as does the nature of the companion anions. The experiments were carried out under different pH conditions in order to determine the influence of the free carboxylic groups on extraction efficiency. Preliminary extraction experiments showed a very poor efficiency for all ligands towards the alkali cations Na^+ and Cs^+. The influence of pH was studied between pH=2.7 and 7.6 and also the effect of different counter anions (picrate, NO_3^-, ClO_4^- and Cl^-) was investigated but no substantial change in extraction were observed. Only ligand **3** was found to extract cesium picrate with an efficiency that was independent of the pH. However, the extraction with this ligand **3** was more than seven times lower than for 18-C-6. The loss of efficiency observed with ligand **3** can be related to the presence of the biphenyl unit that tends to inhibit complexation. The stoichiometry of the complexes formed with both ligands (18-C-6 and **3**) and cesium picrate was in each case 1:1 and the extraction constants were log K_{ex}=4.5 and 3.6, respectively. Experiments carried out with sodium salts demonstrated that the extraction was always negligible even though a range of experimental conditions were used. In addition, experiments for Ag^+ also showed most efficient extraction occurs for **3** to form a 1:1 complexes with silver picrate with a log K_{ex}=3.8.

The results obtained in the experiments involving Zn^{2+} and Eu^{3+} were more interesting. Thus, the extractability showed by ligands **1**–**5** at pH=2.4 (HPic) was negligible; however, clearly different results were observed under basic conditions. Thus, data for extraction of $ZnCl_2$ with ligands **1**–**5**, at pH=8.6–8.7, are presented in Figure 1. Under basic conditions, extractabilities using **2** and **5** were strongly enhanced when compared with the behaviour of **1** and **4**, respectively (from 0.7% for **1** to 75.5% for **2** and from 5.4% for **4** to 90.3% for **5**).

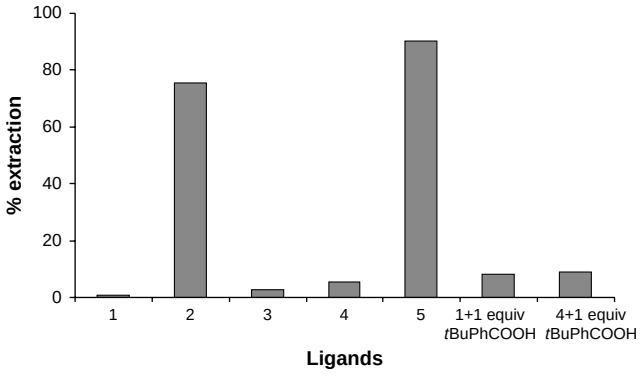

Figure 1. Extraction of Zn^{2+} from aqueous AMP buffer solutions (pH=8.6–8.7) with ligands **1**–**5** in chloroform. $[ZnCl_2]=2.10^{-4}$ M, $[L]=10^{-3}$ M.

To confirm that the presence of additional carboxylic groups in the ligands is responsible of the observed strong extraction increments, additional experiments for **1** and **4** in the presence of external acid were carried out.[8] The results obtained (shown in Fig. 1) demonstrate that the effect of the carboxylic groups is only important when they are included as part of the ligand structure and complex through intramolecular interactions.

Similar studies were carried out with $Eu(ClO_4)_3$ under different pH conditions and the results obtained are illustrated in Figure 2.

As was expected, the influence of the pH on extraction with ligands **1** and **4** is essentially negligible, with only a small increment being observed at higher pH. In contrast, the ligands incorporating carboxylic groups in their structures are more sensitive to pH. Thus, **2** leads to a clear increase in

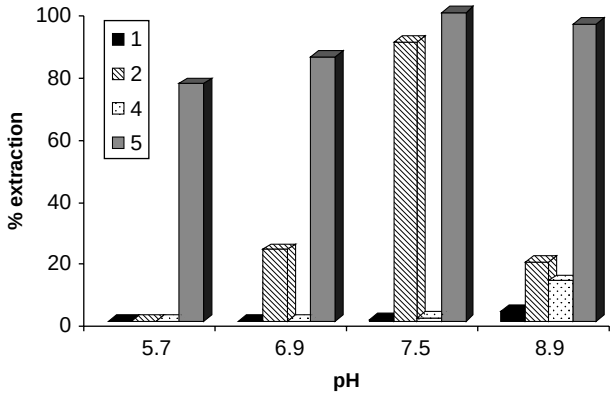

Figure 2. Extraction of $Eu(ClO_4)_3$ from aqueous solution with ligands **1**, **2**, **4** and **5** in chloroform at different pH values. $[Eu(ClO_4)_3]=10^{-4}$ M, $[L]=10^{-3}$ M.

extraction when the pH was higher than 7. Similar behaviour was observed with ligand **5**; this gives rise to high extraction values even at pH=5.7. This behaviour is in accord with pK_a values for **2** ($pK_a=5.28\pm0.3$) and **5** ($pK_a1=4.76\pm0.2$ and $pK_a2=6.06\pm0.3$) determined by potentiometry in dioxane/water 70:30.

Additional experiments were carried out to investigate the type of complexes formed by **2** and **5** under different conditions and the results are summarised in Table 1.[9] Thus, it was determined that the complex formed by **2** had a L_2M stoichiometry with $\log K_{ex}=8.7$ when the buffer was HEPES (Fig. 3). By contrast, when the buffer was AMP no extraction was observed even though the pH of the solution was the same.

Table 1. $Eu(ClO_4)_3$ extraction studies with ligands **2** and **4**

Ligand	Acid	Buffer	pH	Extraction (%)	Stoichiometry	Log K_{ex}
2	$HClO_4$	AMP	5.3	0	—	—
2	$HClO_4$	HEPES	5.2	3.96	2:1	8.7
4	$HClO_4$	AMP	4.6	8.99	2:1	4.7
4	$HClO_4$	HEPES	5.3	99.34	1:1	11.2

Complex stoichiometry and log K determinations under different experimental conditions.

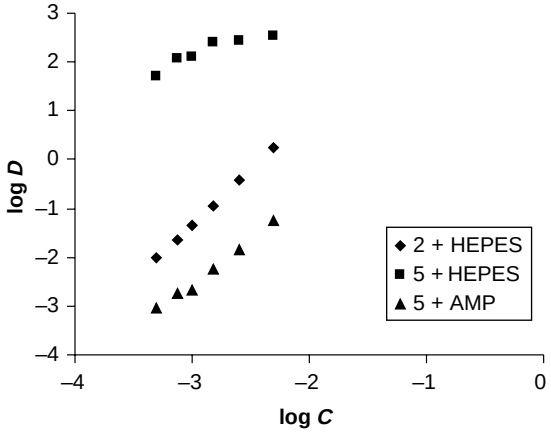

Figure 3. Plot of log D versus log c_L for $Eu(ClO_4)_3$ extraction for ligands **2** and **4** at different pH values.

In the case of **4**, more interesting behaviour was observed since the stoichiometry appears to be a function of pH. Thus, a 2:1 stoichiometry was assigned at pH=4.6, changing to 1:1 at pH=5.3.

2.2. Spectroscopic studies

In order to obtain additional information about the structure of these ligands a number of spectroscopic measurements were carried out. ^{1}H NMR spectra in CD_3CN were obtained for the complexes formed by **2** and **5** with $Eu(ClO_4)_3$. Figure 4 shows the ^{1}H NMR spectra of free **5** and this ligand after addition of 0.5 equiv of Eu^{3+} in CD_3CN. Significant upfield shifts were observed for the protons on the crown moiety suggesting that the complexation involves the crown cavity. In addition, a broadening on the signals corresponding to one of the aromatic rings in the biphenyl systems was also observed. The other aromatic protons are less affected (Table 2). Similar proton NMR shifts and line broadening have been reported for the complexation of Eu^{3+} with a crown ether.[10]

The IR absorption spectral data of the free ligands **2** and **5** and their Eu^{3+} complexes are summarized in Table 3. The shift of the CC–O stretching frequencies arising from the polyether ring, 1115 cm^{-1} in **2** and 1110 cm^{-1} in **5** to 1096 and 1098 cm^{-1}, respectively, for their corresponding complexes, is in keeping with complexation of Eu^{3+} with the cavity oxygens. On the other hand, the amide band I in the 2:1 complexes compared to the bands for the free ligands shows a displacement to lower frequencies, suggesting some coordination by the carbonyl oxygen atom.[11] In comparison, almost no change was observed in the frequency of the acid carbonyl group under the above conditions.

Finally, a clearly different situation was observed for the 1:1 complex formed between **5** and $Eu(ClO_4)_3$. In this complex, the most affected carbonyl frequency is that of the acid group (1728 cm^{-1} in the free ligand and 1714 cm^{-1} in the complex). Also clear shifts were observed in the amide II band; this appears to be related more to a conformational change of the ligand rather than arising from a contribution of the amide nitrogen atom to complex formation.

3. Conclusions

The extraction experiments carried out with ligands **1**–**5** clearly demonstrate that these systems are not useful for alkali cation extraction. In contrast, high extraction was observed for **2** and **5** towards Zn^{2+} and Eu^{3+}. In addition, the presence of carboxylic groups in these systems allows pH control of extraction. This effect is undoubtedly influenced by the pK_a value for the carboxylic groups. On the other hand, ligand **5** forms two types of complexes depending on the pH. Thus, when only one carboxylic group is deprotonated a L_2M complex is formed but at higher pH values deprotonation of both acid groups occurs to yield a LM complex.

Structural modelling suggests interactions between the crown cavity and the different carbonyl groups present in

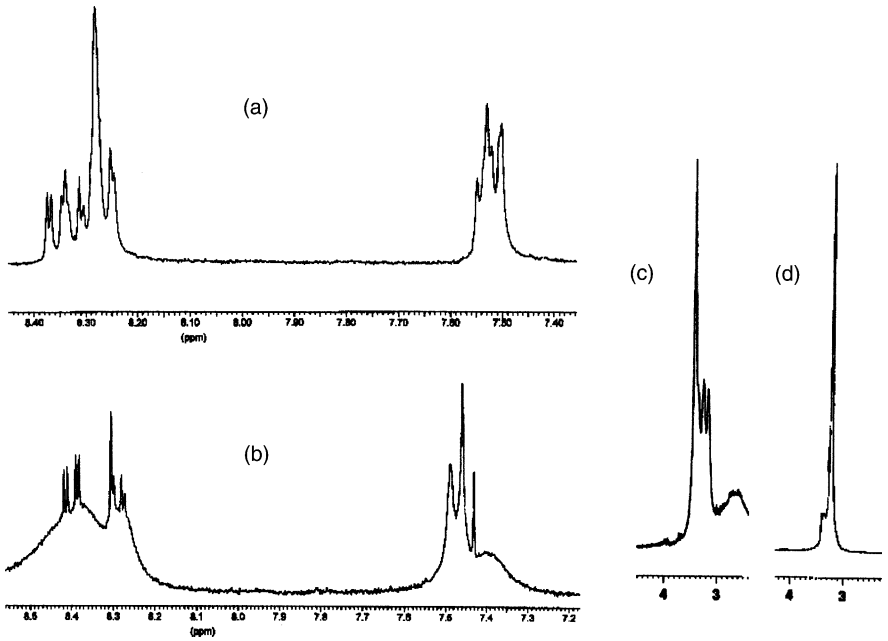

Figure 4. ^{1}H NMR spectra in CD_3CN (a) aromatic region for free **5**, (b) aromatic region for **5** plus 0.5 equiv of $Eu(ClO_4)_3$, (c) crown ether region for free **5**, (d) crown ether region for **5** plus 0.5 equiv of $Eu(ClO_4)_3$.

Table 2. ^{1}H NMR shifts for **2** and **5** and their complexes with $Eu(ClO_4)_3$ in CD_3CN

	$H_a/H_{a'}$	$H_b/H_{b'}$	$H_c/H_{c'}$	Crown	$H_d/H_{d'}$
2	8.62/8.34	8.28/8.37	7.57/7.53	3.51	3.24/3.30
2·$Eu(ClO_4)_3$ 1:1	—/—	—/—	7.53/—	3.40	3.07/3.29
5	8.63/8.28	8.38/8.30	7.54/7.51	3.41	3.27/3.26
5·$Eu(ClO_4)_3$ 2:1	8.29/—	8.39/—	7.47/—	2.94	3.45
5·$Eu(ClO_4)_3$ 1:1	8.29/—	8.40/—	7.47/7.41	3.24	3.42

Table 3. Assignments in the IR absorptions for the free ligands **2** and **5** and their $Eu(ClO_4)_3$ complexes

	Acid (C=O)	Amide I	Amide II	NO_2 as	NO_2 *si*	CC–O	δ (C=C)
2	1723	1633	1606	1523	1348	1115	658
2·$Eu(ClO_4)_3$ 2:1	1724	1610	1606	1524	1349	1096	652
5	1728	1635	1604	1524	1349	1110	652
5·$Eu(ClO_4)_3$ 2:1	1724	1610	1606	1524	1349	1098	627
5·$Eu(ClO_4)_3$ 1:1	1714	1644	1598	1518	1348	1084	626

ligands **2** and **5**. This fact is in agreement with the information obtained by ^{1}H NMR and IR spectroscopic measurements.

4. Experimental

4.1. General methods

All commercially available reagents were used without further purification. Water sensitive reactions were performed under argon. Column chromatography was carried out on SDS activated neutral aluminium oxide (0.05–0.2 mm; activity degree 1). IR spectra were recorded on a Perkin-Elmer 1750 FT-IR and a Bruker Equinox 55 FT-IR. NMR spectra were recorded with Bruker Avance 300/400/500 spectrometers. Chemical shifts are reported in parts per million downfield from TMS. Spectra were referenced to residual undeuterated solvent. High-resolution mass spectra were taken with a Fisons VG-AUTOSPEC.

4.1.1. Synthesis of 2. To a stirred suspension of KOH/EtOH (10%) heated at 60 °C was added a solution of **1**[3] (0.423 g, 0.715 mmol) in absolute EtOH (10 ml). When the addition was finished, the heating was continued until the completion of the reaction (TLC, 25 min). Then the reaction was quenched with a solution of HCl (10%) until pH=1. A white powder appeared in the solution and it was removed by filtration. After that, the solution was concentrated under reduced pressure and redissolved in a CH_2Cl_2/H_2O mixture. The organic phase was washed with three portions of H_2O (3×25 ml) and dried over anhydrous Na_2SO_4. The organic solvent was distilled to give a yellow solid. (0.396 g, 0.686 mmol). (96% yield). ^{1}H NMR (300 MHz, CD_3COCD_3) δ_H 8.77 (1H, s, Ar-H), 8.49 (1H, dd, J_1= 2.3 Hz, J_2=8.5 Hz, Ar-H), 8.40 (1H, d, J=2.3 Hz, Ar-H), 8.33 (1H, dd, J_1=2.3 Hz, J_2=8.5 Hz, Ar-H), 7.74 (1H, d, J=8.5 Hz, Ar-H), 7.66 (1H, d, J=8.5 Hz, Ar-H), 3.65–3.45 (20H, m, $-CH_2O-$), 3.41 (2H, m, $-NCH_2-$), 3.34 (2H, m, $-NCH_2-$). ^{13}C NMR (75 MHz, CD_3COCD_3) δ_C 169.15 ($-CON(CH_2)_2-$), 166.53 ($-COOCH_3-$), 149.09 (C_{Ar}),

148.64 (C_{Ar}), 146.11 (C_{Ar}), 145.05 (C_{Ar}), 138.43 (C_{Ar}), 133.98 (2C_{Ar}), 132.42 (C_{Ar}), 127.03 (C_{Ar}), 126.21 (C_{Ar}), 124.24 (C_{Ar}), 123.49 (C_{Ar}), 73.76 (–OCH_2–), 72.12 (–OCH_2–), 71.79 (–OCH_2–), 71.70 (–OCH_2–), 71.68 (–OCH_2–), 71.62 (–OCH_2–), 71.31 (–OCH_2–), 71.28 (–OCH_2–), 69.80 (–OCH_2–), 69.72 (–OCH_2–), 50.78 (–NCH_2–), 45.92 (–NCH_2–). IR ν_{max} (KBr) 3088 (Ar-H), 2871 (–(C=O)–*OH*), 1724 (–(*C*=*O*)–OH), 1633 (amide I), 1606 (amide II), 1523 (–NO_{2asym}), 1349 (–NO_{2sym}). EM (EI^+): M^+ found 577.19077. $C_{26}H_{31}N_3O_{12}$ required 577.19077. Mp: 65–67°.

4.1.2. Synthesis of 3. 2-Chlorocarbonyl-2′-methoxycarbonyl-4,4′-dinitrobiphenyl (0.307 g, 0.886 mmol) was added to an excess of thionyl chloride (30 ml). The suspension was refluxed with magnetic stirring until a clear solution had formed (2 h). Then the excess of thionyl chloride was distilled, dry benzene was added and the solution was redistilled. The solid obtained was dissolved in dry CH_2Cl_2 (25 ml) and added dropwise to a stirred mixture of 2-(hydroxymethyl)-18-crown-6 (0.261 g, 0.886 mmol) and dry triethylamine (99%) (0.0897 g, 0.886 mmol) in dry CH_2Cl_2 (20 ml) at 0 °C, under an inert atmosphere of Ar. When the addition was finished, the stirring was continued at room temperature. After completion of the reaction (TLC, 12 h), the solution was washed with three portions of HCl (10%) (3×15 ml) and dried over anhydrous Na_2SO_4. Then the organic phase was concentrated under reduced pressure and the crude reaction product was purified by chromatography through an alumina neutral column using CH_2Cl_2–AcOEt (7/3) as eluent to give the desired compound as a yellow oil. (0.358 g, 0.575 mmol). (65% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.94 (2H, d, J=2.5 Hz, Ar-H), 8.43 (2H, dd, J_1=2.5 Hz, J_2=8.5 Hz, Ar-H), 7.38 (1H, d, J=8.5 Hz, Ar-H), 7.37 (1H, d, J=8.5 Hz, Ar-H), 4.31 (1H, m, –CH_2–), 4.17 (1H, m, –CH_2–), 3.75 (3H, s, –$COOCH_3$), 3.68–3.57 (23H, m, crown). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 164.96 (–*CO*OCH_3), 164.48 (–*CO*OCH_2–), 148.45 (2C_{Ar}), 147.83 (2C_{Ar}), 131.18 (2C_{Ar}), 130.76 (C_{Ar}), 130.66 (C_{Ar}), 126.81 (2C_{Ar}), 125.86 (2C_{Ar}), 71.39 (–$(OCH_2)_2$–*CH*–OCH_2–), 71.27 (–OCH_2–), 71.22 (–OCH_2–), 71.09 (–OCH_2–), 71.05 (–OCH_2–), 71.01 (–OCH_2–), 70.19 (–OCH_2–), 69.00 (–OCH_2–), 67.06 (–OCH_2–), 65.82 (–OCH_2–), 65.77 (–$COOCH_2$–), 65.27 (–OCH_2–), 62.30 (–OCH_2–), 53.09 (–$COOCH_3$). IR ν_{max} (KBr) 3401 (Ar-H), 1731 (–(*C*=*O*)–OCH_3), 1524 (–NO_{2asym}), 1349 (–NO_{2sym}), 1106 (–(O=*C*)–*O*CH_3). EM (FAB^+): M+1 found 623.208829. $C_{28}H_{35}N_2O_{14}$ required 623.20882.

4.1.3. Synthesis of 4. 2-Chlorocarbonyl-2′-methoxycarbonyl-4,4′-dinitrobiphenyl (0.504 g, 1.45 mmol) was added to an excess of thionyl chloride (30 ml). The suspension was refluxed under magnetic stirring until it became a clear solution (2 h). The excess of thionyl chloride was removed by distillation, dry benzene was added and the solution was redistilled. The solid obtained was dissolved in dry CH_2Cl_2 (25 ml) and this solution was added dropwise to a stirred mixture of 4,13-diaza-18-crown-6 (0.190 g, 0.725 mmol) and dry triethylamine (99%) (0.147 g, 1.45 mmol) in dry CH_2Cl_2 (20 ml) at 0 °C under an inert atmosphere of Ar. When the addition was finished, the stirring was continued at a room temperature. After completion of the reaction (TLC, 12 h) the solution was washed with three portions of HCl (10%) (3×15 ml) and dried over anhydrous Na_2SO_4. Then the organic phase was concentrated under reduced pressure and the crude reaction product was purified by chromatography using an alumina neutral column and CH_2Cl_2–AcOEt (8/2) as eluent to give the desired compound as a white solid. (0.445 g, 0.484 mmol). (67% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.85 (1H, d, J=2.3 Hz, Ar-H), 8.84 (1H, d, J=2.3 Hz, Ar-H), 8.39 (1H, dd, J_1=2.3 Hz, J_2=8.0 Hz, Ar-H), 8.37 (1H, dd, J_1=2.3 Hz, J_2=8.0 Hz, Ar-H), 8.31–8.26 (4H, m, Ar-H), 7.62 (2H, d, J=8.0 Hz, Ar-H), 7.40 (2H, d, J=8.0 Hz, Ar-H), 3.80 (3H, s, –$COOCH_3$), 3.79 (3H, s, –$COOCH_3$), 3.51–3.36 (24H, m, crown). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 168.24 (2-*CO*$N(CH_2)_2$–), 165.25 (2-*CO*OCH_3–), 148.13 (2C_{Ar}), 147.72 (C_{Ar}), 145.38 (C_{Ar}), 145.33 (C_{Ar}), 143.54 (C_{Ar}), 137.16 (C_{Ar}), 130.99 (C_{Ar}), 126.42 (C_{Ar}), 125.96 (C_{Ar}), 123.72 (C_{Ar}), 122.75 (C_{Ar}), 70.92 (2-O*CH*$_2$*CH*$_2$O–), 69.86 (4-NCH$_2$*CH*$_2$O–), 53.33 (2-COO*CH*$_3$), 49.96 (2-N*CH*$_2$CH$_2$O–), 46.05 (2-N*CH*$_2$CH$_2$O–). IR ν_{max} (KBr) 3090 (Ar-H), 1731 (–(*C*=*O*)–OCH_3), 1635 (amide I), 1608 (amide II), 1524 (–NO_{2asym}), 1349 (–NO_{2sym}), 1123 cm^{-1} (–(O=*C*)–*O*CH_3). EM (FAB^+): M+1 found 919.263384. $C_{42}H_{43}N_6O_{18}$ required 919.26338. Mp: 179–180 °C.

4.1.4. Synthesis of 5. This product was prepared following the same method used to obtain **2**, but in this case starting from **4** (0.384 g, 0.379 mmol). The compound was isolated as a yellow solid (0.360 g, 0.405 mmol). (97% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 8.91 (2H, d, J=2.3 Hz, Ar-H), 8.45 (2H, dd, J_1=2.3 Hz, J_2=8.5 Hz, Ar-H), 8.35 (2H, dd, J_1=2.3 Hz, J_2=8.5 Hz, Ar-H), 8.21 (2H, d, J=2.3 Hz, Ar-H), 7.66 (2H, d, J=8.5 Hz, Ar-H), 7.49 (2H, d, J=8.5 Hz, Ar-H), 3.59–3.23 (24H, m, crown). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 176.11 (–*CO*OH), 171.71 (–*CO*OH), 169.92 (–*CO*$N(CH_2)_2$–), 168.08 (–*CO*$N(CH_2)_2$–), 148.18 (C_{Ar}), 147.69 (C_{Ar}), 146.23 (C_{Ar}), 144.26 (C_{Ar}), 136.73 (C_{Ar}), 134.37 (C_{Ar}), 131.26 (C_{Ar}), 127.47 (C_{Ar}), 126.52 (C_{Ar}), 126.10 (C_{Ar}), 124.04 (C_{Ar}), 121.81 (C_{Ar}), 70.71 (2-O*CH*$_2$-CH$_2$O–), 70.22 (2-OCH$_2$*CH*$_2$O–), 67.64 (4-NCH$_2$*CH*$_2$O–), 48.46 (4-N*CH*$_2$CH$_2$O–). IR ν_{max} (KBr) 3089 (Ar-H), 2870 (–(C=O)–*OH*), 1728 (–(*C*=*O*)–OH), 1636 (amide I), 1605 (amide II), 1524 (–NO_{2asym}), 1349 (–NO_{2sym}). EM (FAB^+): M+1 found 891.232084. $C_{40}H_{39}N_6O_{18}$ required 891.23207. Mp: 142–143 °C.

4.2. Potentiometric titrations

They were carried out under nitrogen in dioxane–water (70/30 v/v) using a reaction vessel water-thermostatted at 25.0±0.1 °C (0.1 mol dm^{-3} tetrabutylammonium perchlorate). The titrant was added by means of a Crison microburete 2031. The potentiometric measurements were made using a Crison 2002 pH-meter and a combined glass electrode. The titration system was automatically controlled by a PC computer using a program that monitors the e.m.f. values and the volume of titrant added. The electrode was dipped in dioxane–water (70/30 v/v) for half an hour before use. It was calibrated for hydrogen concentration by titration of a known amount of HCl with CO_2 free LiOH solution and determining the equivalent point by the Gran's method; this gives the standard potential E'° and the ionic product of water (K'_w=[H+][OH–], pK=

15.9±0.1).[12] The computer program SUPERQUAD[13] was used to calculate the protonation constants.

4.3. Liquid–liquid extraction experiments

The liquid–liquid extraction experiments were carried out at 22±2 °C in polypropylene microcentrifuge tubes (2 ml) with a phase ratio $V_{(w)}$:$V_{(org)}$ of 1:1 (each phase 0.5 ml). The aqueous phase contained the metal ion (at 10^{-4} M), a supporting anion, HPic, HNO_3, $HClO_4$ or HCl, at different concentrations and a selected buffer (HEPES or AMP, used to maintain the chosen pH). The organic phase contained a known concentration of ligand in $CHCl_3$ (normally 10^{-3} M except variable concentration experiments were employed). All experiments involved mechanical shaking of the vials for 30 min. At the end of these periods, the phases were separated, centrifuged (to ensure full phase separation) and then duplicate 100 μl samples of both phases were removed for analysis.

The metal concentration in both phase was determined radiometrically by means of γ-counting using a NaI(Tl) scintillation counter (Cobra II, Canberra-Packard). The following radioisotopes were employed: ^{22}Na, ^{137}Cs, ^{65}Zn, ^{110m}Ag and ^{152}Eu.

The distribution ratio D_M for each metal was calculated by the following equation:

$$D_M = \frac{[M^{n+}]_{(org)}}{[M^{n+}]_{(w)}}$$

With this parameter it was possible to calculate the extractability E using the equation:

$$E(\%) = \frac{D_M}{D_M + 1} 100$$

All the extraction reactions are described by the following two equilibria:

$$M^{n+}(w) + nA^-(w) + sL(org) \overset{K_{ex}}{\rightleftharpoons} ML_sA_n(w),(org)$$

$$M^{n+}_{(w)} + sH_nL_{(org)} \rightleftarrows ML_{s(org)} + nsH^+_{(w)}$$

$$K_{ex} = \frac{[ML_sA_n]_{(org)}}{[M^{n+}]_{(w)}[A^-]^n_{(w)}[L]^s_{(org)}}$$

$$\log D_M = \log K_{ex} + n \log[A^-]_{(w)} + s \log[L]_{(org)}$$

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Synthesis of 1,2,4-triazole dendrimers

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Abstract—A convergent synthetic strategy towards novel 1,2,4-triazole dendrimers, in which 3,5-dichloro-4-(4-methoxyphenyl)-4*H*-1,2,4-triazole was used as the heterocyclic building block, was successfully explored. Nucleophilic aromatic substitution at this novel AB_2-monomer was used as the key step in the propagation of the heterocyclic dendrons and these dendrons were attached to both a 1,3,5-triazine and a methylene core. The peripheral 1,2,4-triazole could be varied not only by nucleophilic aromatic substitution but also by Suzuki cross-coupling. The presented dendrimers are promising candidates to be used in applications where the large number of heteroatoms can be exploited or a better resistance to the applied conditions is required.

1. Introduction

Dendrimers are monodisperse, well-defined macromolecules that are prepared through divergent or convergent iterative procedures to different sizes or 'generations'. The unique properties associated with the perfectly branched dendritic architecture are highly appreciated and have hence been validated in a substantial amount of different application fields in recent years.[1–3]

In the synthesis of dendrimers, it is crucial to employ reactions with a high efficiency to reduce the probability of defects in the large structure and to simplify purification. Recently, we have started to use the nucleophilic aromatic substitution (NAS) of halides with phenolates as a new convergent strategy towards dendrimers.[4–8] In order to facilitate this substitution it is necessary to have an electron poor (e.g., heterocyclic) group in the *ortho*- or *para*-position of the aryl halide, but it is even more efficient to place the halide directly on a heterocyclic structure. Dendrimers consisting of 1,3,4-oxadiazoles, 1,3,5-triazines or pyrimidines were successfully synthesized using this approach (Fig. 1). The synthesis of the oxadiazole dendrimers was hampered by the poor reactivity of the system towards NAS,[6] while the triazine dendrimers were characterized by a lack of stability.[7] The pyrimidine system was of an intermediate reactivity combining an easy synthesis and an increased stability.[8] We now envisaged to enlarge the scope of our NAS strategy to 1,2,4-triazole dendrimers.

Some poly(1,2,3-triazole) dendrimers have already been prepared. Earlier work in our group focused on the synthesis of dendritic and hyperbranched polytriazoles through 1,3-dipolar cycloadditions,[9,10] while Fokin et al. recently described a highly efficient 'click-chemistry' route to 1,2,3-triazole dendrimers by a copper(I)-catalyzed ligation of azides and alkynes.[11] The only 1,2,4-triazole dendrimers described so far have been prepared by Diez-Barra et al., but their synthesis was limited to the first generation.[12,13]

Dendrimers are currently being studied as soluble supports in homogeneous catalysis since their large size enables recycling by membrane separation techniques.[14,15] The majority of applications of metallodendritic catalysts

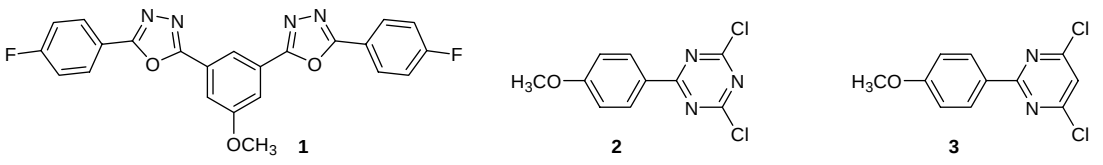

Figure 1. Heterocyclic monomers used for the synthesis of dendrimers through a NAS approach.

Keywords: Dendrimer synthesis; 1,2,4-Triazole; Convergent approach; Nucleophilic aromatic substitution; Suzuki cross-coupling.
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concerns hydroformylation, hydrogenation, C–C coupling reactions, polymerizations and related reactions in non-oxidizing atmospheres. With a few exceptions,[16] oxidation processes are absent from this spectrum, mainly because of the susceptibility of several of the previously used dendrimers to oxidative degradation. Clearly, there is a need for new, oxidatively stable dendritic macromolecules. Because of their increased stability, our pyrimidine dendrons could be used as (recyclable) dendritic catalysts for oxidation reactions by embedding catalytically active surface functionalities (benzimidazoles or porphyrins) at the dendrons periphery.[17,18] Incorporation of a benzimidazole metal complexing moiety resulted in a heterogeneous catalyst.[17] In our search for a completely homogeneous oxidation-resistant dendritic catalyst the presented 1,2,4-triazole dendrimers show great potential. Due to the large number of heteroatoms, polytriazole dendrimers are excellent candidates for complex formation and coordination of catalytically active metal atoms. The complexing azole moieties will now be suspended throughout the dendritic structure while the periphery can be functionalized independently to control solubility properties.

Conjugated triazole moieties (e.g., 3-(4-biphenylyl)-4-phenyl-5-(4-*tert*-butylphenyl)-1,2,4-triazole (TAZ)[19,20]) are known for their excellent electron transporting and hole blocking ability and have therefore been used (by itself or incorporated into a polymer (side) chain) in the construction of organic light-emitting diodes (OLEDs).[19–21] Suspension of triazole moieties throughout a dendritic backbone hence also shows potential in this field. The major advantage of dendrimers over analogous heterocyclic polymers is that their electronic and physical properties can be optimized independently.[22]

2. Results and discussion

2.1. Monomer synthesis

A 1,2,4-triazole system with the appropriate AB_2-symmetry (analogous to the previous heterocyclic monomers, Fig. 1) that is well-suited for the convergent dendrimer synthesis is 3,5-dichloro-4-(4-methoxyphenyl)-4*H*-1,2,4-triazole (**4**) (Scheme 1). The synthesis of this novel monomer was started by the cyclocondensation of 4-methoxyphenylisocyanate (**5**) with ethyl carbazate (**6**). The obtained semicarbazide **7** was then cyclized using potassium hydroxide after which the triazolidine-3,5-dione (or 'urazole') **8**[23–25] could be transformed into the desired monomer **4** using phosphorus oxychloride (in 74% yield).

2.2. Propagation of the dendrons

The 1,2,4-triazole dendrimers were constructed using a convergent approach. Due to the presence of the electron poor (hetero)aryl chloride functions in monomer **4**, nucleophilic aromatic substitution at this heterocyclic building block was made possible and the NAS reaction was used as the key reaction for the synthesis of the 1,2,4-triazole dendrimers.

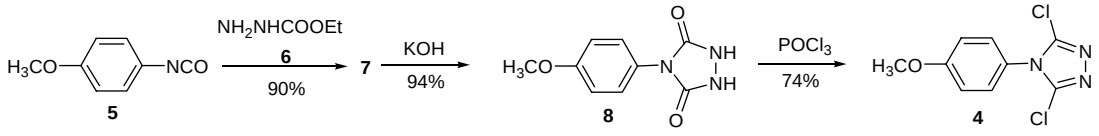
The dendron propagation was started with the substitution of the two chlorine functions by a phenolate with the desired peripheral groups. These peripheral groups have a major influence on the final properties of the dendron or dendrimer. In order to ensure an easy synthesis, purification and characterization of the dendritic structures we initially used 3,5-bis(*t*-butyl)phenol (**9**), which is commercially available at low cost, as a peripheral moiety (to enhance solubility). This phenol was reacted with monomer **4** to obtain a first generation dendron **10** (Scheme 2), but theoretically all compounds bearing a phenol moiety are insertable as peripheral groups.

The ideal circumstances for the NAS were investigated (different base-solvent systems). On using the reaction conditions optimized for the analogous triazine monomer **2** (triethylamine base in dichloromethane at room temperature) no reaction was observed. The use of potassium *t*-butoxide base in refluxing THF resulted in a mixture of mono- and disubstituted products, even after 5 days of reaction. Both G_1-dendrons could be separated by column chromatography and were obtained in poor yields (20% each). Another attempt using the conditions optimized for pyrimidine monomer **3** (potassium carbonate in refluxing acetonitrile) did not result in any improvement. Disubstitution of the 1,2,4-triazole monomer **4** finally succeeded when quite harsh conditions, potassium carbonate in a refluxing mixture of DMF and toluene (2/1) while azeotropically removing water, were used. After 3 days of reaction, the disubstituted G_1-dendron **10** could be obtained in an acceptable 80% yield. To ensure complete substitution 2.2 equiv of the peripheral phenol **9** were used and G_1-dendron **10** was purified by column chromatography to ensure the absence of 3,5-bis(*t*-butyl)phenol or monosubstituted product and hence avoiding defects in the higher generations.

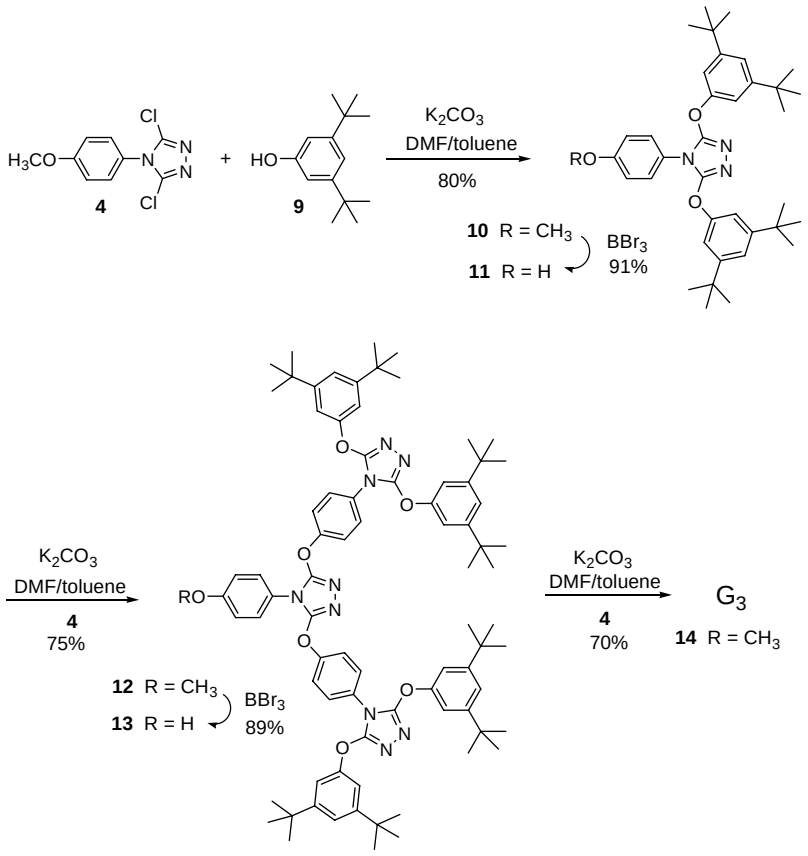
The obtained first generation dendron **10** could be activated again for a second substitution by a (high-yielding) deprotection step using boron tribromide.[6–8] Reiteration of the NAS with the deprotected first generation dendron **11** and monomer **4** gave the second generation dendron **12**. This sequence was repeated up to the third generation triazole dendron **14** (Scheme 2).

2.3. Peripheral functionalization by Suzuki cross-coupling

1,2,4-Triazole monomer **4** was also subjected to a Suzuki cross-coupling reaction. To our knowledge, Suzuki reactions have never been employed before on halogenated



Scheme 1. Synthesis of 1,2,4-triazole monomer **4**.



Scheme 2. Convergent propagation strategy towards 1,2,4-triazole dendrons.

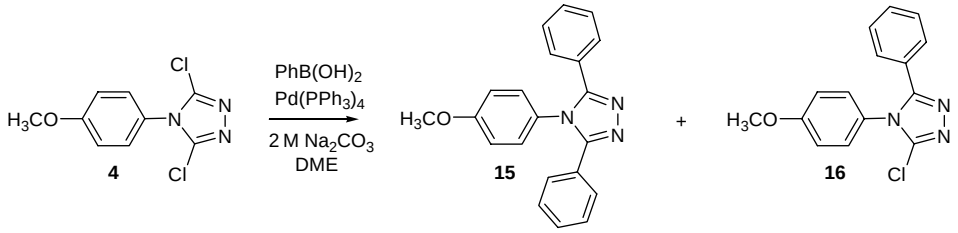
triazole moieties. By applying this reaction the scope by which the periphery of the dendrons can be functionalized could be extended. While using a standard set of Suzuki conditions (3 equiv of phenylboronic acid, $Pd(PPh_3)_4$ catalyst, Na_2CO_3 (2 M) base in refluxing DME) we obtained (after 48 h reaction), besides the desired disubstituted product **15** (37%), still a substantial amount of the monosubstituted triazole **16** (47%) (Scheme 3). Optimization of the Suzuki procedure (Pd source, ligand, solvent, base, …) will likely provide a higher yield for the disubstituted triazole.

1,2,4-Triazole derivative **15** could now be regarded as an alternative G_1-dendron and could be subjected to the same NAS propagation strategy as employed for G_1-dendron **10**, resulting in an enlarged scope of peripheral functionalization possibilities.

2.4. Dendrimer synthesis

The convergent approach to dendrimer synthesis implies that the synthesized dendritic wedges are attached to a central core in the final step. In our case, any core molecule that can be coupled with a phenol functionality, either by NAS or by some other methodology, can be applied.

2.4.1. Dendrimers with a 1,3,5-triazine core. The trifunctional, reactive heterocycle 2,4,6-trichloro-1,3,5-triazine has already been used before as a dendritic core (by NAS).[7] On applying this core, two dendritic generations (**17** and **18**, respectively) were synthesized easily and in high yields using mild NAS conditions (triethylamine base in dichloromethane at room temperature) (Fig. 2).



Scheme 3. Suzuki cross-coupling on 1,2,4-triazole monomer **4**.

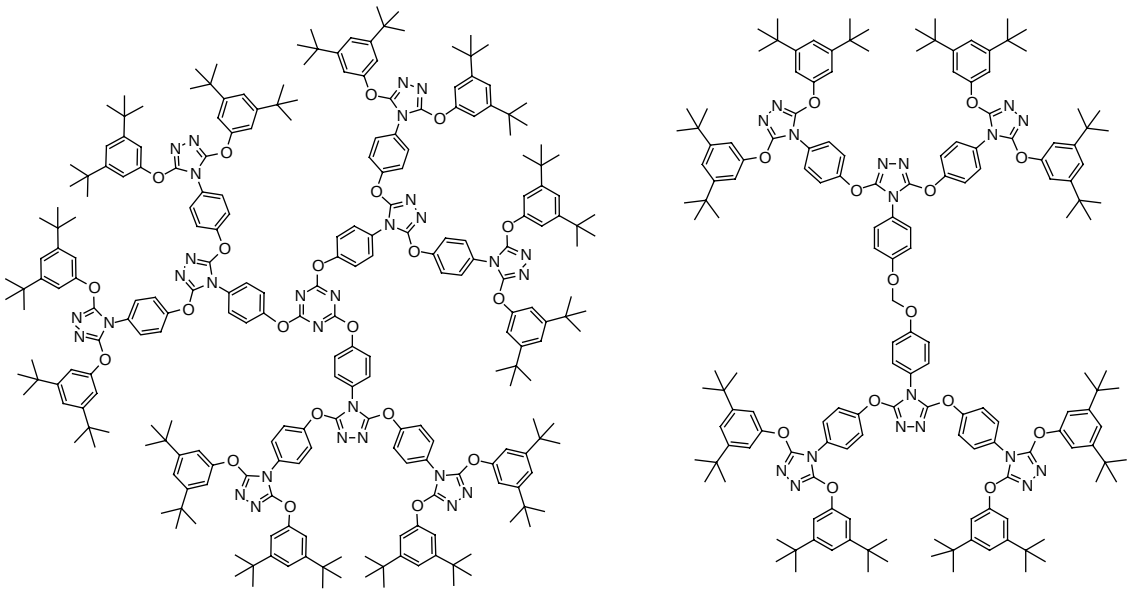


Figure 2. G_2-dendrimers **18** and **20**.

2.4.2. Dendron solvolysis in dichloromethane. While performing NAS reactions in the dendron propagation sequence it was observed that the presence of trace amounts of dichloromethane in the reaction mixture (due to work-up or sample transfer) resulted in the formation of novel dendrimers by a substitution of the chlorine groups of dichloromethane. While this reaction is obviously undesired during the dendron propagation, it shows the potential of dichloromethane to be used as a difunctional dendritic core. When adding dichloromethane to a solution of the deprotonated dendron (NaH) **11** (G_1) or **13** (G_2) in DMF, substitution occurs rapidly, resulting in the difunctional dendrimers **19** and **20**, respectively (Fig. 2). Despite the huge excess of dichloromethane used, no sign of mono-substituted species could be observed.

2.5. Characterization

Compounds **4**, **10**–**13** and **15**–**20** were fully characterized using NMR spectroscopy (^{1}H and ^{13}C) and mass spectrometry (CI or ESI).

The ^{1}H NMR spectra of the different generation dendrons clearly show the signals corresponding with the different monomer layers and the integration indicates which generation is involved.

Although the formation of G_3-dendron **14** could be demonstrated by both mass spectrometry and NMR spectroscopy, successful purification of this third generation triazole dendron (from the excess of G_2-dendron, necessary to drive the reaction to completion, and possibly the monosubstituted analogue) could not be achieved by column chromatography.

Since no core protons are available to prove full core functionalization of the triazine core dendrimers (**17** and **18**) by ^{1}H NMR spectroscopy, this had to be done by ^{13}C NMR spectroscopy and mass spectrometry (ESI). On the other hand, dendrimers **19** and **20** are easily identifiable by their characteristic methylene core giving rise to a singlet at 5.8 ppm in the ^{1}H NMR spectrum corresponding with a methylene ^{13}C NMR signal at 91 ppm.

Analytical scale gel permeation chromatography (GPC) indicated that all dendrimers were obtained pure and monodisperse (PDI <1.06).

The glass transition temperatures (T_g) of the dendrimers were determined by differential scanning calorimetry (DSC). First generation dendrimer **17** showed a glass transition at 85 °C at first heating, immediately followed by an exotherm at 107 °C (probably due to crystallization), while the analogous G_1-dendrimer **19** showed only a clear T_g at 145 °C. The second generation dendrimers (**18** and **20**) showed very broad glass transitions ($T_g=133$ and 135 °C, respectively). Moreover, degradation of the dendrimers was observed at temperatures of approximately 165–180 °C.

The UV–vis absorption spectrum of the triazole monomer **4** showed a broad absorption peak centered at 234 nm. Phenyl substitution on the monomer resulted in a red-shift of the absorption maximum.

3. Conclusions

By implementing a convergent nucleophilic aromatic substitution approach, the synthesis of novel heterocyclic 1,2,4-triazole dendrimers was accomplished. 3,5-Dichloro-4-(4-methoxyphenyl)-4*H*-1,2,4-triazole **4** was used as an AB_2-monomer and different cores, including a methylene core resulting from substitution on dichloromethane, have been employed to prepare the dendrimers. The reactivity of

the 1,2,4-triazole monomer towards NAS was proven to be moderate since quite harsh conditions had to be employed to promote complete substitution. As a result the propagation sequence could only be carried out up to the third generation triazole dendron. The peripheral 1,2,4-triazole could be varied further by applying standard Suzuki conditions. The presented polytriazole system provides a promising alternative for applications in the preparation of novel rigid homogeneous dendritic (oxidation) catalysts or the construction of organic light-emitting diodes.

4. Experimental

4.1. General

NMR spectra were acquired on commercial instruments (Bruker Avance 300 MHz or Bruker AMX 400 MHz) and chemical shifts (δ) are reported in parts per million referenced to tetramethylsilane (TMS) (^{1}H) or the carbon signal of deuterated solvents (^{13}C). Mass spectra were run using a HP MS-Engine 5989A apparatus (chemical ionization (CI), CH_4) or a Micromass Quattro II apparatus (electrospray ionization (ESI), usual solvent mixture: CH_2Cl_2/MeOH+NH_4OAc). Analytical scale GPC was performed on a Shimadzu GPC with a Plgel mixed-D column (Polymer Laboratories); RI and UV detector, mobile phase THF or $CHCl_3$, flow rate 1 mL min^{-1}, 30 °C, calibrated with linear polystyrene standards. UV–vis spectra were taken on a Perkin-Elmer Lambda 20 spectrometer. IR spectra were obtained on a Perkin-Elmer 1600 instrument as KBr pellets. Melting points (not corrected) were determined using a Reichert Thermovar apparatus. Differential scanning calorimetry was run on a DSC 7 (Perkin Elmer) at a heating rate of 2 K min^{-1}. Elemental analysis (C, H and N) of powdered samples was performed on a CE Instrument EA-1110 elemental analyzer. For column chromatography 70–230 mesh silica 60 (E.M. Merck) was used as the stationary phase. Chemicals received from commercial sources were used without further purification. DMF was dried on molecular sieves 4 Å.

4.1.1. Synthesis of the 1,2,4-triazole monomer (4) [3,5-dichloro-4-(4-methoxyphenyl)-4*H*-1,2,4-triazole]. $POCl_3$ (25 mL) was added to triazolidine-3,5-dione **8** (3.14 g, 15.1 mmol) and the mixture was heated at reflux for 18 h. After being cooled to room temperature, the mixture was poured on ice (150 g). The aqueous solution was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were dried with $MgSO_4$, filtered and evaporated. The crude product was further purified by precipitation from an ethyl acetate solution and monomer **4** was obtained as a white solid (which could be recrystallized from ethyl acetate) (2.74 g, 74%). R_f (ethyl acetate) 0.70; mp 200.5–201.5 °C; MS (CI) *m*/*z* 244.0 (100%), 246.0 (67%) and 248.0 (11%) (MH^+); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25 (d, J=8.7 Hz,[†] 2H), 7.07 (d, J=8.7 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.6 (C_i–OCH_3), 143.6 (C–Cl), 128.8 (CH_m–OCH_3), 124.2 (C_i-triaz.), 115.6 (CH_o–OCH_3), 56.1 (CH_3); IR ν_{max} (cm^{-1}) 3065, 2930, 2848, 1732, 1610, 1513, 1442, 1290, 1257, 1172, 1027, 986, 839; UV–vis (CH_2Cl_2) λ_{max} (log ε) 234.0 (3.986). Anal. Calcd for $C_9H_7Cl_2N_3O$: C, 44.29; H, 2.89; N, 17.22. Found: C, 44.35; H, 3.04; N, 17.20.

[†] For all *p*-substituted benzene parts (AA′XX′ higher-order spin system) of the described compounds, the given coupling constant J is actually the sum of the *ortho* (J_{AX}) and *para* ($J_{AX'}$) coupling.

4.2. General procedure for the synthesis of the protected dendrons (R=CH_3)

The G_x-dendron (3,5-bis(*t*-butyl)phenol (**9**), **11** or **13**) (2.2 equiv) in a DMF–toluene (2/1) solution was stirred at room temperature for 0.5 h with an excess of K_2CO_3 (3 equiv). After another 0.5 h of reflux, 1,2,4-triazole monomer **4** (1 equiv) was added and the mixture was heated at reflux for 3–5 days while azeotropically removing water. After evaporation of the solvents, CH_2Cl_2 was added and the mixture was washed with water. The organic fraction was dried with $MgSO_4$, filtered and evaporated to dryness. The 1,2,4-triazole dendrons were purified by column chromatography (silica) and obtained as white solids.

4.2.1. G_1-dendron (10). Eluent CH_2Cl_2–ethyl acetate (15/1); R_f 0.80; yield 80%; MS (CI) *m*/*z* 584.5 (MH^+); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, J=8.7 Hz, 2H), 7.20 (t, J=1.8 Hz, 2H), 7.20 (d, J=1.8 Hz, 4H), 6.99 (d, J=8.7 Hz, 2H), 3.85 (s, 3H), 1.28 (s, 36H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.2 (C_i–OCH_3), 154.3, 154.0, 152.7 (C_i–*t*-Bu), 127.9 (CH_m–OCH_3), 124.6 (C_i-triaz.), 119.6 (CH), 115.0 (CH_o–OCH_3), 113.7 (CH), 55.9 (CH_3–O), 35.4, 31.7 (CH_3). Anal. Calcd for $C_{37}H_{49}N_3O_3$: C, 76.12; H, 8.46; N, 7.20. Found: C, 75.96; H, 8.61; N, 7.03.

On using non-optimized NAS conditions or shorter reaction times the monosubstituted G_1-dendron could be isolated as a side product. R_f 0.60; MS (CI) *m*/*z* 414.2 (100%) and 416.2 (40%) (MH^+); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, J=8.7 Hz, 2H), 7.23 (t, J=1.8 Hz, 1H), 7.04 (d, J=1.8 Hz, 2H), 7.02 (d, J=8.7 Hz, 2H), 3.86 (s, 3H), 1.28 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.5, 161.0 (C_i–OCH_3), 153.6, 153.1 (C_i–*t*-Bu), 128.6 (CH_m–OCH_3), 124.3 (C_i-triaz.), 120.1 (CH), 115.3 (CH_o–OCH_3), 113.9 (CH), 56.0 (CH_3–O), 35.4, 31.7 (CH_3). Anal. Calcd for $C_{23}H_{28}ClN_3O_2$: C, 66.74; H, 6.82; N, 10.15. Found: C, 67.12; H, 7.10; N, 9.60.

4.2.2. G_2-dendron (12). Eluent ethyl acetate–petroleum ether (1/5); R_f 0.15; yield 75%; MS (ESI) *m*/*z* 1312.1 [M+H]$^+$, 656.4 [M+2H]$^{2+}$; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (d, J=9.0 Hz, 4H), 7.49 (d, J=9.0 Hz, 4H), 7.35 (d, J=9.0 Hz, 2H), 7.23 (t, J=1.5 Hz, 4H), 7.16 (d, J=1.5 Hz, 8H), 7.03 (d, J=9.0 Hz, 2H), 3.85 (s, 3H), 1.30 (s, 72H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.4 (C_i–OCH_3), 153.6, 153.5, 153.4, 153.3, 152.7 (C_i–*t*-Bu), 128.6, 127.5 (CH), 127.3 (CH_m–OCH_3), 123.4, 119.8 (CH), 119.3 (CH), 115.0 (CH_o–OCH_3), 113.3 (CH), 55.6 (CH_3–O), 35.0, 31.3 (CH_3).

4.2.3. G_3-dendron (14). Yield 70%; MS (ESI) *m*/*z* 2764.1 [M+H]$^+$, 1382.7 [M+2H]$^{2+}$, 1296.1 [G_2], 570.6 [G_1]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (m_{br}, 28H), 7.23 (s_{br}, 8H), 7.16 (s_{br}, 16H), 3.88 (s, 3H), 1.29 (s, 144H).

4.3. General procedure for the synthesis of the deprotected dendrons (R=H)

To a solution of the protected G_x-dendron **10** or **12** (1 equiv) in CH_2Cl_2 an excess of BBr_3 (1 M in CH_2Cl_2, 5 equiv/generation) was added at −78 °C under dry conditions and the mixture was placed in the freezer (−18 °C). After 4 days of reaction at −18 °C, ice water was added. After separation of the organic layer, the aqueous phase was extracted with CH_2Cl_2. The organic layers were collected, dried with $MgSO_4$, filtered and evaporated in vacuum. The dendrons were purified by column chromatography (silica) and obtained as white solids.

4.3.1. G_1-dendron (11). Eluent ethyl acetate–petroleum ether (1/4); R_f 0.35; yield 91%; MS (CI) *m/z* 570.7 (MH^+); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39 (d, J=8.7 Hz, 2H), 7.24 (t, J=1.8 Hz, 2H), 7.08 (d, J=1.8 Hz, 4H), 6.88 (d, J=8.7 Hz, 2H), 4.37 (s, 1H, OH), 1.26 (s, 36H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 158.1 (C_i–OH), 153.5, 153.4, 152.2, 127.9 (CH_m–OH), 121.9 (C_i-triaz.), 118.7 (CH), 115.8 (CH_o–OH), 113.1 (CH), 34.6, 31.0 (CH_3).

4.3.2. G_2-dendron (13). Eluent ethyl acetate–petroleum ether (1/3); R_f 0.25; yield 89%; MS (ESI) *m/z* 1296.9 $[M+H]^+$, 649.1 $[M+2H]^{2+}$; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.77 (s_{br}, 1H, OH), 7.52 (m, 8H), 7.22 (t, J=1.5 Hz, 4H), 7.14 (d, J=1.5 Hz, 8H), 7.13 (d, J=8.8 Hz, 2H), 6.84 (d, J=8.8 Hz, 2H), 1.27 (s, 72H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.5 (C_i–OH), 153.7, 153.6, 153.4, 153.2, 152.7 (C_i–*t*-Bu), 128.2, 127.4 (CH), 127.1 (CH_m–OH), 121.8, 119.9 (CH), 119.5 (CH), 116.6 (CH_o–OH), 113.4 (CH), 35.0, 31.3 (CH_3).

4.4. Suzuki reaction on 1,2,4-triazole monomer 4

To a mixture of 1,2,4-triazole **4** (100 mg, 410 μmol, 1 equiv) and $Pd(PPh_3)_4$ (3 mol%) in DME (2.5 mL), phenylboronic acid (150 mg, 1.23 mmol, 3 equiv) was added, immediately followed by aqueous Na_2CO_3 (2 M, 1.25 mL). The mixture was flushed with N_2 for 5 min and the reaction mixture was then heated under reflux for 48 h. After cooling, the reaction mixture was evaporated to dryness under reduced pressure, CH_2Cl_2 (25 mL) was added and the organic fraction was washed with water (3× 25 mL). The organic layer was dried with $MgSO_4$, filtered and evaporated in vacuum. Purification by column chromatography (silica, CH_2Cl_2/ethyl acetate 1/1) furnished disubstituted triazole **15** (50 mg, 37%) and monosubstituted triazole **16** (55 mg, 47%) as white solids (which could be crystallized from CH_2Cl_2/heptane).

4.4.1. G_1-dendron (15). R_f 0.30; mp 255.5–256.5 °C; MS (CI) *m/z* 328.3 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.50–7.25 (m, 10H), 7.06 (d, J=8.8 Hz, 2H), 6.90 (d, J=8.8 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.0 (C_i–OCH_3), 154.9 ($C_{triaz.}$), 129.5 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 127.7, 127.0, 115.0 (CH_o–OCH_3), 55.5 (CH_3); UV–vis (CH_2Cl_2) λ_{max} (log ε) 228.7 (4.294), 261.2 (4.210). Anal. Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84. Found: C, 76.96; H, 5.30; N, 12.77.

Monosubstituted G_1-dendron **16**. R_f 0.60; mp 148.0–149.0 °C; MS (CI) *m/z* 286.3 (100%) and 288.3 (34%) (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45–7.25 (m, 5H), 7.16 (d, J=8.8 Hz, 2H), 7.01 (d, J=8.8 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.6 (C_i–OCH_3), 155.3 ($C_{triaz.}$), 143.3 (C–Cl), 130.1 (CH), 128.6 (CH), 128.5 (CH), 128.0 (CH), 126.3, 125.9, 115.1 (CH_o–OCH_3), 55.6 (CH_3); UV–vis (CH_2Cl_2) λ_{max} (log ε) 232.1 (4.243), 248.0 (4.132). Anal. Calcd for $C_{15}H_{12}ClN_3O$: C, 63.05; H, 4.23; N, 14.71. Found: C, 62.97; H, 4.38; N, 14.65.

4.5. General procedure for the synthesis of the triazine dendrimers

To a solution of G_x-dendron **11** or **13** (3.3 equiv) in CH_2Cl_2, Et_3N (3.6 equiv) was added and the mixture was stirred for 0.5 h at room temperature. 2,4,6-Trichloro-1,3,5-triazine (1 equiv) was added to this solution and the mixture was stirred for another 6 h and then evaporated in vacuum. After purification through column chromatography (silica) the title compounds (white solids) were obtained.

4.5.1. G_1-dendrimer (17). Eluent ethyl acetate–petroleum ether (1/3); R_f 0.70; yield 92%; MS (ESI, CH_3CN) *m/z* 1807.7 $[M+Na]^+$, 1785.4 $[M+H]^+$, 904.5 $[M+Na+H]^{2+}$, 893.0 $[M+2H]^{2+}$; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.61 (d, J=8.7 Hz, 6H), 7.38 (d, J=8.7 Hz, 6H), 7.24 (s_{br}, 6H), 7.18 (s_{br}, 12H), 1.29 (s, 108H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4 ($C_{triazine}$), 153.5, 153.2, 152.7 (C_i–*t*-Bu), 151.1, 129.7, 127.2 (CH), 122.5 (CH), 119.5 (CH), 113.5 (CH), 35.0, 31.3 (CH_3); GPC (THF) M_w=2087, PDI=1.034; IR ν_{max} (cm^{-1}) 3075, 2961, 2869, 1812, 1737, 1569, 1514, 1453, 1424, 1368, 1292, 1208, 1121, 1081, 1006, 935, 870, 705; T_g 85 °C.

4.5.2. G_2-dendrimer (18). Eluent ethyl acetate–petroleum ether (1/2); R_f 0.70; yield 81%; MS (ESI, CH_3CN+NH_4OAc) *m/z* 3966.0 $[M+H]^+$, 1983.1 $[M+2H]^{2+}$, 1322.6 $[M+3H]^{3+}$; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.58 (m, 30H), 7.45 (d, J=9.0 Hz, 6H), 7.23 (t, J=1.8 Hz, 12H), 7.16 (d, J=1.8 Hz, 24H), 1.28 (s, 216H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.4 ($C_{triazine}$), 153.5, 153.2, 153.0, 153.0, 152.6 (C_i–*t*-Bu), 151.5, 129.1, 128.9, 127.5 (CH), 127.2 (CH), 122.8 (CH), 120.1 (CH), 119.4 (CH), 113.4 (CH), 35.0, 31.3 (CH_3); GPC ($CHCl_3$) M_w=3806, PDI=1.032; IR ν_{max} (cm^{-1}) 3076, 2961, 2870, 1733, 1570, 1510, 1454, 1424, 1366, 1292, 1206, 1120, 1080, 1007, 936, 869, 705; T_g 133 °C.

4.6. General procedure for the synthesis of the dendrimers with a methylene core

To a solution of G_x-dendron **11** or **13** (88 μmol, 1 equiv) in DMF (2 mL), NaH (3 equiv) and CH_2Cl_2 (0.5 mL) were added. The mixture was stirred at 45 °C during 2 h and then evaporated in vacuum. CH_2Cl_2 (10 mL) was added, the organic phase was washed with water (3×10 mL), dried with $MgSO_4$, filtered and the solvent was removed under reduced pressure. After purification through column chromatography (silica) the title compounds (white solids) were obtained.

4.6.1. G_1-dendrimer (19). Eluent ethyl acetate–petroleum ether (1/3); R_f 0.50; yield 88%; MS (ESI) *m/z* 1174.1 $[M+Na]^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42 (d, $J=8.8$ Hz, 4H), 7.24 (d, $J=8.8$ Hz, 4H), 7.21 (t, $J=1.5$ Hz, 4H), 7.12 (d, $J=1.5$ Hz, 8H), 5.80 (s, 2H, CH_2), 1.28 (s, 72H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.8 (C_i–OCH_2), 153.7, 153.4, 152.5 (C_i–*t*-Bu), 127.5 (CH), 126.0, 119.2 (CH), 116.9 (CH), 113.3 (CH), 90.7 (CH_2), 34.9, 31.3 (CH_3); GPC (THF) $M_w=1293$, PDI=1.059; IR ν_{max} (cm^{-1}) 3073, 2961, 2869, 1810, 1741, 1599, 1514, 1459, 1423, 1363, 1293, 1243, 1206, 1121, 1081, 1000, 937, 900, 871, 840, 705; T_g 145 °C.

4.6.2. G_2-dendrimer (20). Eluent ethyl acetate–petroleum ether (1/3); R_f 0.50; yield 80%; MS (ESI) *m/z* 2606.0 $[M+H]^+$, 1303.3 $[M+2H]^{2+}$; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d_{br}, $J=9.0$ Hz, 8H), 7.52 (d_{br}, $J=9.0$ Hz, 8H), 7.44 (d_{br}, $J=8.8$ Hz, 4H), 7.31 (d_{br}, $J=8.8$ Hz, 4H), 7.23 (s_{br}, 8H), 7.16 (s_{br}, 16H), 5.80 (s_{br}, 2H, CH_2), 1.29 (s, 144H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.5 (C_i–OCH_2), 153.5, 153.3, 153.2, 153.1, 152.6 (C_i–*t*-Bu), 128.6, 127.5 (CH), 125.4, 119.9, 119.4 (CH), 117.4 (CH), 113.4 (CH), 91.3 (CH_2), 35.0, 31.3 (CH_3); GPC ($CHCl_3$) $M_w=2954$, PDI=1.031; IR ν_{max} (cm^{-1}) 3075, 2960, 2868, 1733, 1594, 1511, 1458, 1424, 1364, 1297, 1208, 1120, 1081, 1003, 936, 869, 843, 705; T_g 135 °C.

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Nucleophilic epoxidation of γ-alkoxy dienyl sulfoxide derivatives

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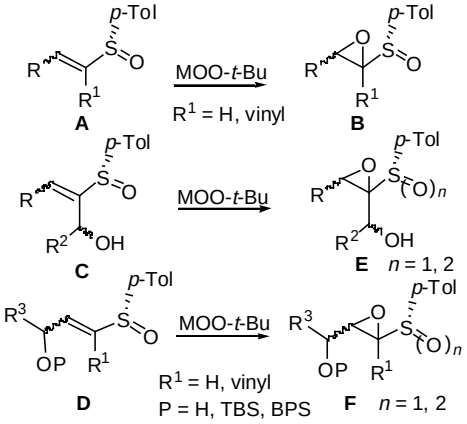
Abstract—(*E*,*E*) and (*Z*,*E*) γ-alkoxy dienyl sulfones undergo nucleophilic epoxidation with remarkable regio- and stereoselectivity to render *syn* oxiranes in a process mainly controlled by the alkoxy stereocenter. Upon epoxidation γ-hydroxy dienyl sulfoxides provide sulfinyl and sulfonyl oxiranes along with bis-epoxides formed through a Payne rearrangement that can be prevented by silylation of the OH group. Interestingly, the presence of a γ-silyloxy group can invert the stereochemical trend of the molecule affording mainly an *anti* epoxidation process.

1. Introduction

The asymmetric epoxidation of electron deficient alkenes has attracted a great deal of attention in the last decade[1] as an efficient route towards enantiopure functionalized epoxides, very attractive building blocks.[2] In this context, our group has demonstrated that simple α,β-unsaturated sulfoxides **A** (R^1=H) undergo nucleophilic epoxidation by treatment with metalated hydroperoxides with complete preservation of double bond geometry and with moderate to excellent facial selectivity to produce enantio- and diastereomerically pure α,β-epoxy sulfoxides **B** (R^1=H). Related 2-sulfinyl dienes **A** (R^1=vinyl) have also resulted suitable substrates for these epoxidations and the facial diastereoselectivity may be controlled by the choice of the counterion (LiOO-*t*-Bu vs NaOO-*t*-Bu).[3] Subsequently, we have explored the behavior of α′-(1-hydroxyalkyl)vinyl sulfoxides **C**,[4] and γ-alkoxy vinyl sulfoxides **D** (R^1=H, P=TBS, BPS),[5] bearing an additional stereocenter and with a reinforcing/non-reinforcing scenario being operative. The above work has led to the development of a new method for the synthesis of enantiopure sulfinyl and sulfonyl oxiranes **B**, **E** and **F**.[6] In connection with these efforts, we have also examined the nucleophilic epoxidation of γ-hydroxy dienyl sulfoxides **D** (R^1=vinyl). Among others, we have studied the effect of the *E*/*Z* geometry on the electrophilic double bond, of the relative configuration of the hydroxyl and sulfinyl stereocenters, of the protection at the hydroxyl group as well as the reactivity of the related γ-hydroxy dienyl sulfones in this epoxidation. Now we report in full our results (Scheme 1).



Scheme 1.

2. Discussion and results

2.1. Preparation of the starting dienes

The set of dienyl sulfoxides and sulfones chosen for this study was synthesized following a procedure previously reported by us.[7] The method entails submitting the two diastereomeric *anti* sulfinyl chlorohydrins **G** to one-pot base-induced (KO-*t*-Bu) epoxide formation/rearrangement to generate enantiopure hydroxy 2-sulfinyl dienes **D** through the diasteromeric epoxy vinyl sulfoxides **H** that, if desired, can also be isolated. This efficient reaction allows for the selective synthesis of *E*/*E* or *Z*/*E* dienyl sulfoxides **D** depending on the relative stereochemistry of the sulfinyl

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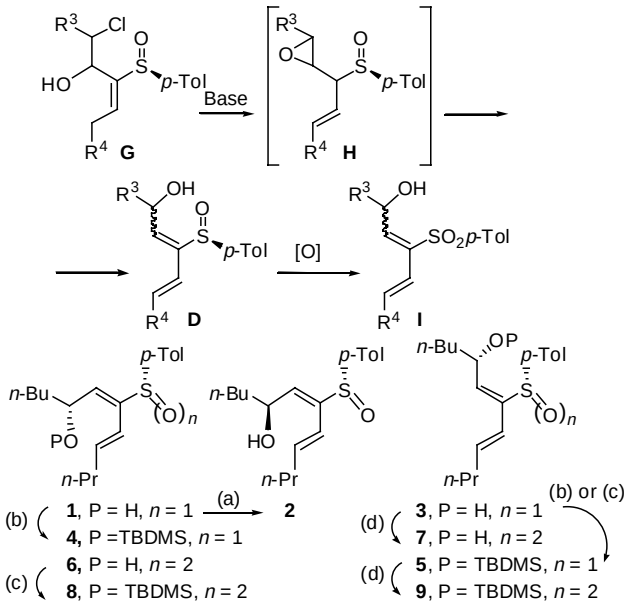


(a) i. PPh_3, DIAD, p-$NO_2C_6H_4CO_2H$, 0 °C THF, 90 min; ii. K_2CO_3, MeOH, 0 °C, 2 h, 72% overall yield. (b) TBDMSCl, imidazole, CH_2Cl_2, 0 °C to rt, 95 min, 79%. (c) TBDMSOTf, Et_3N, DMAP, 0 °C to rt, 23 min, 98%. (d) MMPP, MeOH, rt, 24 h, 60–64%.

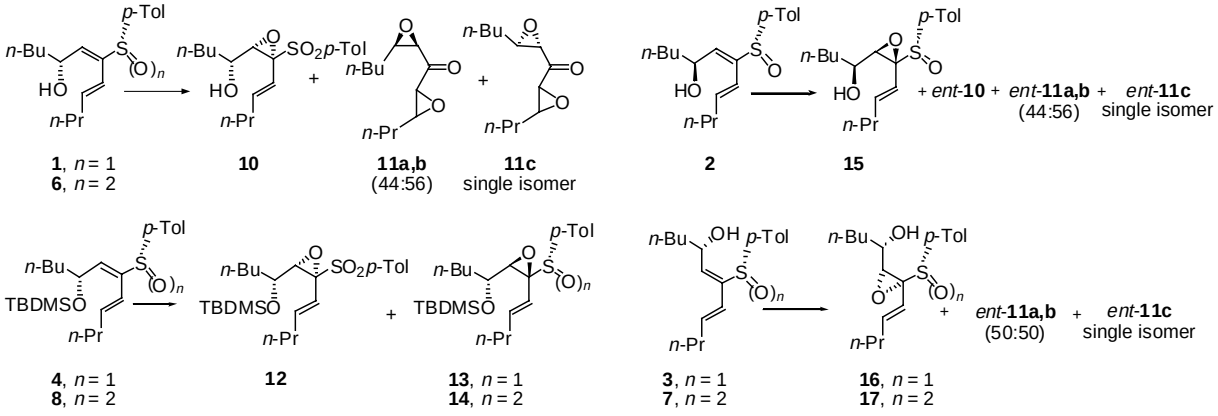
Scheme 2.

chlorohydrin precursor, **G**. Further oxidation (MMPP) allowed for the simple transformation of dienyl sulfoxides **D** into γ-hydroxy dienyl sulfones **I** without any detectable loss of stereochemical integrity. In particular, dienyl sulfoxides **1** and **3**, and dienyl sulfones **6** and **7** were prepared for the present work. In addition, (*E*,*E*)-γ-hydroxy dienyl sulfoxide **1** was submitted to Mitsunobu conditions followed by debenzoylation to give diastereomeric diene **2** in good yield and as a single isomer. Finally, to assess the influence of the hydroxyl group in the epoxidation process dienyl sulfoxide **1** as well as dienyl sulfone **6** were protected as silyl ethers in good yields to afford dienes **4** and **8**, respectively. Surprisingly, (*Z*,*E*)-dienyl sulfoxide **3** showed a low reactivity under silylation conditions and the resulting silyloxy diene **5** was unstable under standard chromatographic purification leading to *E*/*E* dienes and diastereomerization at sulfur.[8] However, with careful manipulation a small amount of **5** could be isolated and then treated with MMPP to afford γ-silyloxy dienyl sulfone **9** in good yield (Scheme 2).

2.2. Nucleophilic epoxidation of dienyl sulfoxides and sulfones

At the beginning of this study, we submitted (*E*,*E*)-dienyl sulfones **6** and **8** to epoxidation with NaOO-*t*-Bu to assess the effect of the alkoxy group as the only stereocenter in the molecule (Table 1, entries 1 and 2). The nucleophilic epoxidation of γ-hydroxy dienyl sulfone **6** was remarkably

Table 1. Nucleophilic epoxidation of γ-alkoxy dienyl sulfoxides and sulfones

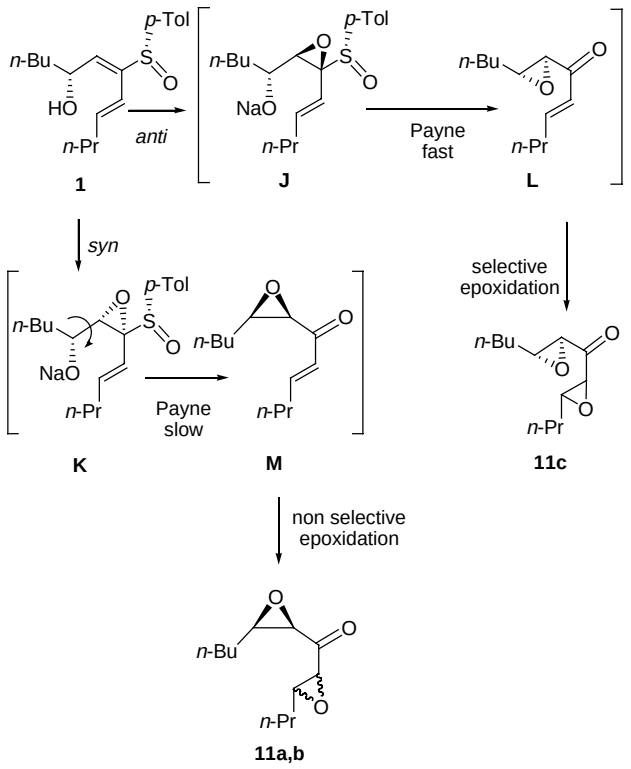


Entry	Compounds	Conditions[a]	*syn*						*anti*			Yield (%)[b]
			10/*ent*-**10**	**12**	**15**	**16**	**17**	**11a,b**/*ent*-**11a,b**[c]	**13**	**14**	**11c**/*ent*-**11c**[d]	
1	**6**	NaOO*t*-Bu, 105 m	100 (**10**)									89
2	**8**	NaOO*t*-Bu, 4 days		46						54		75[e]
3	**1**	NaOO*t*-Bu, 3 h	27 (**10**)					52 (**11a,b**)			21 (**11c**)	62
4	**4**	KOO*t*-Bu, 4 days		10					43	47		82[f]
5	**2**	NaOO*t*-Bu, 70 m	4 (*ent*-**10**)		80			11 (*ent*-**11a,b**)			5 (*ent*-**11c**)	93
6	**7**	NaOO*t*-Bu, 55 m					100					82
7	**3**	NaOO*t*-Bu, 45 m				72	4	2 (*ent*-**11a,b**)			22 (*ent*-**11c**)	61[g]

[a] All reactions were conducted in THF at 0 °C.
[b] Combined yield of isolated epoxides.
[c] As a 44:56 mixture of diastereomers except for entry 7 where an equimolecular mixture was detected.
[d] As a single isomer. The absolute configuration was not confirmed.
[e] Starting material (5%) in the crude reaction mixture (^{1}H NMR).
[f] Starting material (12%) in the crude reaction mixture (^{1}H NMR).
[g] Starting material (11%) in the crude reaction mixture (^{1}H NMR).

regio- and stereoselective affording *syn* sulfonyl oxirane **10** as a single diastereoisomer. In contrast, γ-silyloxy dienyl sulfone **8** underwent a slower epoxidation (>4 days) to give a 46:54 mixture of *syn* and *anti* sulfonyl oxiranes **12** and **14** under similar reaction conditions. To further probe the stereochemical assignment of the above sulfonyl oxiranes, **10** was silylated using TBDMSCl and imidazole rendering **12** with a moderate yield (29%) and conversion (70% recovered starting material), however, at this point we did not further optimize this reaction. The high stereodirecting capability of the free hydroxyl group was again observed for the nucleophilic epoxidation of (*Z*,*E*)-γ-hydroxy dienyl sulfone **7** (entry 6). Thus treatment of **7** with NaOO-*t*-Bu in THF afforded exclusively *syn* sulfonyl oxirane **17** in 55 min and with an excellent yield (82%).

Subsequently we examined the behavior of (*E*,*E*)-γ-hydroxy dienyl sulfoxides **1** and **2** with an additional stereocenter at sulfur (entries 3 and 5). Treatment of **1** with NaOO-*t*-Bu after 3 h provided as minor product sulfonyl oxirane **10** (27%) along with bis-epoxides **11ab** (52%, as a 44:55 mixture of diastereoisomers) and **11c** (21%, as a single diastereoisomer). Shortening the reaction time allowed for detection of variable amounts of the sulfinyl oxirane (**10′** not shown) precursor of **10**, however, starting material was always recovered. The formation of bis-epoxides **11a–c** has been rationalized in terms of a Payne rearrangement,[9] (Scheme 3) of sulfinyl oxiranes **J** (*anti*) and **K** (*syn*) to generate α,β-unsaturated epoxy ketones **L** and **M** that undergo in situ second selective or non selective nucleophilic epoxidation providing **11c** and **11ab**, respectively. In this context, minor *anti* oxirane **J** would suffer a rapid Payne process while major *syn* oxirane **K** would require rotation around Cβ–Cγ to adopt a suitable arrangement and this slows down the Payne rearrangement.



Scheme 3.

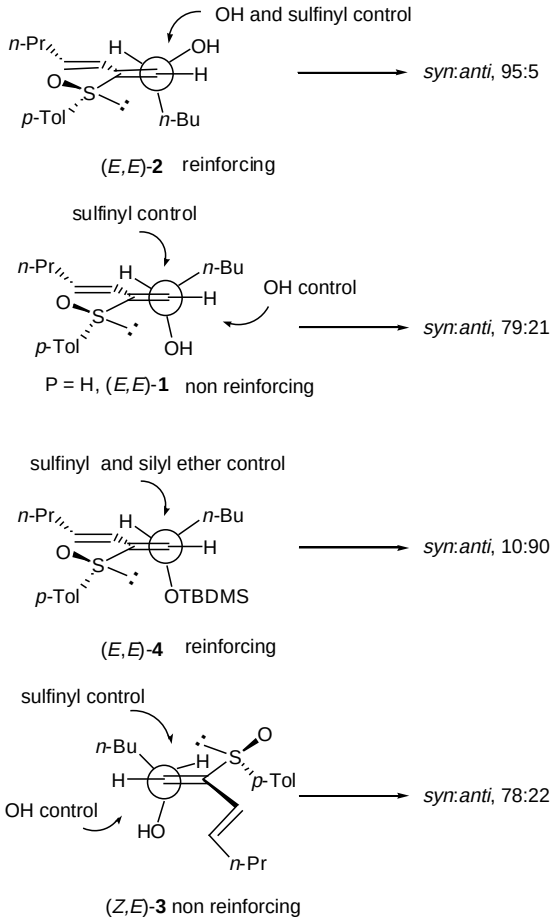
The behavior of dienyl sulfoxide **2** with opposite relative configuration at the stereocenters is parallel to **1**. Thus, nucleophilic epoxidation of **2** afforded after 70 min an 80:4:11:5 mixture of *syn* sulfinyl oxirane **15**, *syn* sulfonyl oxirane *ent*-**10** and bis-epoxides **11ab** (44:46) and **11c**. Stereochemical correlation between **15** and *ent*-**10** was easily provided by oxidation of **15** with MMPP to render *ent*-**10** in 59% yield. Taking into account the overall ratio of final epoxides, hydroxy dienyl sulfoxide **2** provides a 95:5 mixture of *syn* and *anti* epoxides[10] with a reinforcing combination of stereodirecting elements (hydroxyl and sulfinyl) while **1** provides a 79:21 *syn*:*anti* mixture with a non-reinforcing arrangement of the stereocenters.

As expected, protection of the hydroxyl group as silyl ether prevented the Payne rearrangement from taking place, however, a lower reactivity as well as a reversal of stereoselectivity was observed (entry 4). In fact, epoxidation of γ-silyloxy dienyl sulfoxide **4** was carried out with the more reactive KOO-*t*-Bu[3–5] affording a mixture of sulfonyl oxiranes **12** (10) and **14** (47) along with sulfinyl oxirane **13** (43). A chemical correlation between **13** and **14** was established by treatment of **13** with MMPP to give **14** in 74% yield. The inversion of the overall *syn*:*anti* ratio (10:90) compared with **1** (*syn*:*anti*, 79:29) is noteworthy.[11]

Finally, to assess the influence of the stereochemistry of the double bond, the nucleophilic epoxidation of (*Z*,*E*)-γ-hydroxy dienyl sulfoxide **3** was examined (Table 1, entry 7). The reaction mixture showed a mixture of *syn* sulfinyl and sulfonyl oxiranes **16** (72) and **17** (4) and again significant amounts of bis-epoxides *ent*-**11a**,**b** (2) and *ent*-**11c** (22) from the Payne rearrangement with an overall *syn*:*anti* ratio of 78:22. Further oxidation (MMPP) of **16** rendered **17** in 62% yield. At this point, we envisioned the protection of the free hydroxyl group to prevent the Payne process. However, the silylation of **3** was not a straightforward process due to the unstable nature of **5** and, surprisingly, γ-silyloxy dienyl sulfone **9** was unreactive under the nucleophilic epoxidation conditions examined. Therefore, we did not pursue any further the epoxidation of these (*Z*,*E*)-dienes.

The structural assignment of the epoxides was based mainly in their NMR data. The oxidation state at sulfur was determined by the slightly higher chemical shifts of *H-ortho* (*p*-TolS), *H* (epox) and *C* (arom)-S for sulfonyl oxiranes. The relative configuration of the sulfinyl and sulfonyl oxiranes was indirectly assessed through the cis/trans stereochemistry of bis epoxides (see Scheme 3): **11a**,**b** [$J^{1,3}$(*cis*-butyl oxirane)=4.8 Hz, *syn* epoxidation] and **11c** [$J^{1,3}$(*trans*-butyl oxirane)=1.9 Hz, *anti* epoxidation].

The stereochemical outcome of the nucleophilic epoxidation is primarily controlled by stereoelectronic effects and can be understood in terms of an initial nucleophilic attack of the metalated peroxide to the reactive conformers of the alkoxy dienes (Scheme 4). For (*E*,*E*)-dienyl sulfoxides **1** and **2**, an *s*-cis conformation for the unsaturated sulfoxide (Cα=Cβ/S-:),[12] along with an *s*-trans conformation for the dienyl



Scheme 4.

system would be probably adopted to minimize $A^{1,3}$ strain stronger than $A^{1,2}$ strain caused by the interaction between the sulfinyl and butenyl groups. Besides, in agreement with the observed coupling constant between allylic and vinylic protons for the dienes ($J=8$–9 Hz) the Cγ–H bond would be coplanar to the dienyl system with a dihedral angle of 180°.[13] In this context, the diastereofacial selectivity for each substrate (**1** and **2**) would be determined by the relative configuration of the two stereogenic centers, sulfoxide and hydroxyl group. A reinforcing scenario is working for **2** that produces a 95:5 mixture of epoxidation *syn* to the OH group, while a non reinforcing contribution of the sulfoxide diminishes the stronger stereodirecting ability of the hydroxyl group in **1** to provide a less selective epoxidation (*syn*:*anti*, 79:21). However, for this particular relative stereochemistry, the presence of a silyl ether (**4**) results in a reinforcing scenario and thus reverts the *syn*:*anti* outcome of the epoxidation (10:90).[11] Similarly, (*Z*,*E*)-dienyl sulfoxide **3** would adopt an *s*-cis reactive conformation for the dienyl system and the nucleophilic epoxidation would occur mainly *syn* (*syn*:*anti*, 78:22) to the hydroxyl group since a non reinforcing contribution of the stereodirecting elements is taking place.

In summary, we have demonstrated that (*E*,*E*) and (*Z*,*E*) γ-hydroxy dienyl sulfones undergo nucleophilic epoxidation with remarkable regio- and stereoselectivity to render *syn* epoxides in a process mainly controlled by the hydroxyl stereocenter. Upon epoxidation, γ-hydroxy dienyl sulfoxides provide sulfinyl and sulfonyl oxiranes, along with significant amounts of bis-epoxides probably formed through a Payne rearrangement that can be prevented by silylation of the OH group. In terms of stereochemistry, an additional stereocenter at sulfur implies a reinforcing/non-reinforcing scenario with the free hydroxyl group as the stronger *syn* stereodirecting element of the epoxidation. Interestingly, the presence of a γ-silyloxy group can invert the stereochemical outcome of the process affording mainly an *anti* epoxidation process.

3. Experimental

3.1. General procedures

Reagents and solvents were handled by using standard syringe techniques. Hexane, toluene, and CH_2Cl_2 were distilled from CaH_2, and Et_2O from sodium. DMF was dried over CaH_2 and filtered before distillation under reduced pressure. Then, it was collected over 4 Å molecular sieves and argon was bubbled through for 10 min before storing it. Et_3N was distilled from CaH_2. Crude products were purified by flash chromatography on Merck 230–400 mesh silica gel with distilled solvents. Analytical TLC was carried out on Merck (Kieselgel 60F-254) silica gel plates with detection by UV light, iodine, acidic vanillin solution, 10% phosphomolybdic acid solution in ethanol. All reagents were commercial products purchased from Aldrich, Acros, Fluka or Merck. Organolithium reagents were titrated by reaction with 3,4-dimethoxybenzaldehyde prior to use. NaH and KH (60% in mineral oil) were washed repeatedly with dry hexane and dried prior to use. Through this section, the volume of solvents is reported in mL/mmol of starting material. Infrared spectra (IR) were obtained on a Perkin-Elmer 681 and on a Perkin-Elmer Spectrum one. ^1H and ^{13}C NMR spectra were recorded on a Brüker AM-200 (200 MHz), Varian Gemini-200 (200 MHz), Varian INOVA-300 (300 MHz) and Varian INOVA-400 (400 MHz) using $CDCl_3$ as solvent and with the residual solvent signal as internal reference ($CDCl_3$, 7.24 and 77.0 ppm). The following abbreviations are used to describe peak patterns when appropriate: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Melting points were determined on a Reichert Kofler microscope and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 20 °C using a sodium lamp and in $CHCl_3$ solution. Low resolution mass spectra were recorded by direct injection on a Hewlett Packard 5973 MSD instrument using the electronic impact technique with an ionization energy of 70 eV or on a Hewlett Packard 1100 MSD instrument using the atmospheric pressure chemical ionization (APCI) or electrospray (ES) chemical ionization techniques in its positive or negative modes. Elemental analyses were carried out on a Perkin-Elmer 240 C and on a Heraus CHN-O-Rapid instruments at Instituto de Química Orgánica, CSIC (Madrid).

3.2. General procedure for silylation of sulfinyl alcohols

(a) With *tert*-butyldimethylsilyl chloride: under an atmosphere of argon, 1.1 equiv of *tert*-butyldimethylsilyl chloride was added to a cold (0 °C) solution of the sulfinyl

alcohol and 1.2 equiv of imidazole in CH_2Cl_2 (10 mL/mmol) and the reaction mixture was allowed to warm up to rt and monitored by TLC. Upon completion the reaction was quenched with H_2O (1 mL/mmol), diluted with CH_2Cl_2 (10 mL/mmol) and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (three times, 10 mL/mmol) and the combined organic extracts were washed with a saturated solution of NaCl (4 mL/mmol), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude product that was purified by column chromatography on silica gel using a gradient of the appropriate solvents. (b) With *tert*-butyldimethylsilyl triflate: under an atmosphere of argon, 2.0 equiv of freshly distilled *tert*-butyldimethylsilyl triflate was added to a cold (0 °C) solution of the sulfinyl alcohol, 2 equiv of Et_3N and 2–3 crystals of DMAP in THF (7 mL/mmol) and the reaction mixture was allowed to warm up to rt and monitored by TLC. Upon completion 3 equiv of Et_3N was added and the reaction was quenched with a saturated solution of $NaHCO_3$ (4 mL/mmol) and H_2O (4 mL/mmol), diluted with EtOAc (10 mL/mmol) and the layers were separated. The aqueous phase was extracted with EtOAc (three times, 10 mL/mmol) and the combined organic extracts were washed with a saturated solution of NaCl (4 mL/mmol), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude product that was purified by column chromatography on silica gel using a gradient of the appropriate solvents.

3.2.1. Synthesis of *tert*-butyldimethylsilyl ether of (+)-(5*R*,S_S)-(6*E*,8*E*)-7-(*p*-tolylsulfinyl)-6,8-dodecadien-5-ol, 4. From hydroxy dienyl sulfoxide **1** (15.8 mg, 0.049 mmol) in CH_2Cl_2 (0.50 mL), imidazole (4 mg, 0.06 mmol), *tert*-butyldimethylsilyl chloride (8.4 mg, 0.05 mmol) according to the general procedure (95 min), after chromatography (5–50% Et_2O–hexane), 16.8 mg (79%) of silylated diene **4** was obtained as a colorless oil. Data for **4**: R_f=0.37 (30% EtOAc–hexane). $[\alpha]_D^{20}$ +81.1 (*c* 0.90). ^{1}H NMR (300 MHz) δ −0.05 (s, 3H, TBDMS), −0.02 (s, 3H, TBDMS), 0.77 (t, 3H, *J*=7.4 Hz), 0.83–0.85 (m, 3H), 0.84 (s, 9H, TBDMS), 1.21–1.36 (m, 6H), 1.45–1.62 (m, 2H), 1.99 (m, 2H), 2.35 (s, 3H, CH_3–*p*-Tol), 4.46 (ddd, 1H, *J*=8.7, 7.2, 5.5 Hz, H-5), 5.83 (m, 2H, H-8, H-9), 6.32 (d, 1H, *J*=8.7 Hz, H-6), 7.21 (dd, 2H, *J*=8.5, 0.6 Hz, ArH), 7.45 (d, 2H, *J*=8.3 Hz, ArH). ^{13}C NMR (50 MHz) δ −4.8, −4.3, 13.4, 14.0, 18.1, 21.4, 22.1, 22.6, 25.8 (3C), 27.3, 35.5, 37.7, 69.2, 119.5, 125.5 (2C), 129.6 (2C), 135.5, 138.6, 140.6, 141.4. IR (CCl_4): 2920, 2900, 2820, 1620, 1570, 1480, 1440, 1240, 1060, 1030, 990, 820, 790 cm^{-1}. Anal. Calcd for $C_{25}H_{42}O_2SSi$: C, 69.07; H, 9.74; S, 7.38. Found: C, 69.13; H, 9.55; S, 7.23.

3.2.2. Synthesis of *tert*-butyldimethylsilyl ether of (−)-(5*S*,S_S)-(6*Z*,8*E*)-7-(*p*-tolylsulfinyl)-6,8-dodecadien-5-ol, 5, *tert*-butyldimethylsilyl ether of (5*S*,S_S)-(6*E*,8*E*)-7-(*p*-tolylsulfinyl)-6,8-dodecadien-5-ol, 5′, and *tert*-butyldimethylsilyl ether of (5*S*,R_S)-(6*E*,8*E*)-7-(*p*-tolylsulfinyl)-6,8-dodecadien-5-ol, *ent*-4. Three different procedures (a), (b), and (c) were employed for the synthesis of **5**. (a) From hydroxy dienyl sulfoxide **3** (25.5 mg, 0.08 mmol) in CH_2Cl_2 (1.0 mL), imidazole (6.5 mg, 0.10 mmol), *tert*-butyldimethylsilyl chloride (13.6 mg, 0.09 mmol) according to the general procedure (27 h), after chromatography (5–50% EtOAc–hexane), 11.6 mg (34%) of an inseparable mixture (20:80) of silylated dienes **5′** and *ent*-**4** was obtained as a colorless oil. (b) From hydroxy dienyl sulfoxide **3** (14.3 mg, 0.044 mmol) in DMF (1.0 mL), Et_3N (9 mg, 12 μL, 0.089 mmol), 2 crystals of DMAP, *tert*-butyldimethylsilyl triflate (18.1 mg, 16 μL, 0.067 mmol) according to the general procedure (3 h, two additions of reagents in the above amounts), after chromatography (5–30% EtOAc–hexane), 5.9 mg (32%) of diene **5** was obtained as a colorless oil, rather unstable in silica gel, and 7.4 mg (52%) of starting material was obtained. (c) From hydroxy dienyl sulfoxide **3** (24.5 mg, 0.07 mmol) in THF (0.53 mL), Et_3N (15.2 mg, 21 μL, 0.15 mmol), 2 crystals of DMAP, *tert*-butyldimethylsilyl triflate (26 μL, 29.9 mg, 0.11 mmol) according to the general procedure (6 h 20 min, four additions of reagents in the above amounts), after chromatography (5–30% EtOAc–hexane), 15 mg (49%) of a 32:68 inseparable mixture of **5′** and *ent*-**4** was obtained. Data for **5**: R_f=0.42 (20% EtOAc–hexane). $[\alpha]_D^{20}$ −82.0 (*c* 0.68). ^{1}H NMR (300 MHz) δ 0.03 (s, 3H, TBDMS), 0.07 (s, 3H, TBDMS), 0.73 (t, 3H, *J*=7.4 Hz), 0.88 (t, 3H, *J*=5.9 Hz), 0.89 (s, 9H, TBDMS), 1.19–1.70 (m, 8H), 1.94 (q, 2H, *J*=6.7 Hz), 2.37 (s, 3H, CH_3–*p*-Tol), 5.07 (q, 1H, *J*=6.7 Hz, H-5), 5.74 (d, 1H, *J*=15.7 Hz, H-8), 5.95 (dt, 1H, *J*=15.7, 6.6 Hz, H-9), 6.08 (d, 1H, *J*=8.7 Hz, H-6), 7.25 (d, 2H, *J*=8.5 Hz, ArH), 7.44 (d, 2H, *J*=8.2 Hz, ArH). ^{13}C NMR (50 MHz) δ −4.2, −4.1, 13.4, 14.0, 19.1, 21.3, 22.6, 25.8 (3C), 27.1, 29.7, 35.0, 38.4, 69.0, 121.1, 124.7 (2C), 129.6 (2C), 136.9, 139.5, 140.5, 140.6, 141.4. IR (CCl_4): 2930, 2900, 2820, 1720, 1480, 1450, 1240, 1060, 1030, 1000, 780 cm^{-1}. MS (APCI): 425 [M+Na]$^-$, 171 (100%). Data for **5′** from a 38:68 mixture of **5′** and *ent*-**4**: R_f=0.40 (20% EtOAc–hexane). ^{1}H NMR (200 MHz) δ −0.06 (s, 3H, TBDMS), −0.03 (s, 3H, TBDMS), 0.75–0.92 (m, 6H, 2 CH_3), 0.82 (s, 9H, TBDMS), 1.16–1.36 (m, 6H), 1.40–1.61 (m, 2H), 1.98 (m, 2H), 2.36 (s, 3H, CH_3–*p*-Tol), 4.48 (m, 1H, H-5), 5.84 (m, 2H, H-8 and H-9), 6.31 (d, 1H, *J*=8.4 Hz, H-6), 7.21 (d, 2H, *J*=8.1 Hz, ArH), 7.47 (d, 2H, *J*=8.2 Hz, ArH). The data of *ent*-**4** was identical to its enantiomer.

3.2.3. Synthesis of *tert*-butyldimethylsilyl ether of (+)-(5*R*)-(6*E*,8*E*)-7-(*p*-tolylsulfonyl)-6,8-dodecadien-5-ol, 8. From hydroxy dienyl sulfone **6** (29.3 mg, 0.087 mmol) in THF (0.61 mL), Et_3N (26.3 mg, 36 μL), 2 crystals of DMAP, *tert*-butyldimethylsilyl triflate (34.5 mg, 30 μL, 0.130 mmol) according to the general procedure (23 min), after chromatography (5–50% EtOAc–hexane), 35.6 mg (98%) of **8** was obtained as a pale yellow oil. Data for **8**: R_f=0.43 (20% EtOAc–hexane). $[\alpha]_D^{20}$ +24.1 (*c* 0.85). ^{1}H NMR (300 MHz) δ −0.07 (s, 3H, TBDMS), −0.04 (s, 3H, TBDMS), 0.80 (t, 3H, *J*=7.3 Hz), 0.84 (s, 9H, TBDMS), 0.86 (t, 3H, *J*=7.0 Hz), 1.22–1.44 (m, 6H), 1.54–1.61 (m, 2H), 2.02 (q, 2H, *J*=6.9 Hz), 2.40 (s, 3H, CH_3–*p*-Tol), 4.38 (m, 1H, H-5), 5.81 (d, 1H, *J*=16.1 Hz, H-8), 5.87 (dt, *J*=15.9, 6.1 Hz, H-9), 6.74 (d, 1H, *J*=8.6 Hz, H-6), 7.26 (d, 2H, *J*=7.9 Hz, ArH), 7.66 (d, 2H, *J*=8.2 Hz, ArH). ^{13}C NMR (75 MHz) δ −4.9, −4.3, 13.5, 14.0, 18.1, 21.6, 22.0, 22.5, 25.7 (3C), 27.2, 35.4, 37.1, 69.0, 118.2, 128.2 (2C), 129.5 (2C), 136.8, 138.5, 141.2, 143.0, 144.0. IR (CCl_4): 2910, 2820, 1630, 1580, 1470, 1440, 1390, 1300, 1240, 1150, 1070, 920, 650 cm^{-1}. Anal. Calcd for $C_{25}H_{42}O_3SSi$: C, 66.62; H, 9.39; S, 7.11. Found: C, 66.74; H, 9.59; S, 7.03.

3.3. General procedure for oxidation of sulfoxides with MMPP

To a cold (0 °C) solution of sulfoxide in MeOH (10 mL/mmol) was added 1.5 equiv of magnesium monoperoxyphthalate hexahydrate (MMPP). The mixture was stirred from 0 °C to rt, monitored by TLC until completion and then quenched with a saturated solution of $NaHCO_3$ (4 mL/mmol). After removal of MeOH under reduced pressure, the mixture was diluted with EtOAc (5 mL/mmol), the layers were separated and the aqueous phase was extracted with EtOAc (three times, 4 mL/mmol). The combined organic layers were washed with a saturated solution of NaCl (1 mL/mmol), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a crude product that was purified by gradient column chromatography using EtOAc–hexane mixtures.

3.3.1. Synthesis of *tert*-butyldimethylsilyl ether of (+)-(5*S*)-(6*Z*,8*E*)-7-(*p*-tolylsulfonyl)-6,8-dodecadien-5-ol, 9. From sulfinyl diene **5** (10.5 mg, 0.026 mmol) in MeOH (0.30 mL) and MMPP (64.3 mg, 0.104 mmol), according to the general procedure (24 h), after chromatography (2–15% EtOAc–hexane), dienyl sulfone **9** (7 mg, 64%) was obtained as a colorless oil. Data for **9**: R_f=0.30 (2×15% EtOAc–exane). ^{1}H NMR (300 MHz) δ −0.06 (s, 3H, TBDMS), 0.04 (s, 3H, TBDMS), 0.81 (t, 3H, J=7.3 Hz), 0.85 (s, 9H, TBDMS), 0.88 (t, 3H, J=5.9 Hz), 1.24–1.38 (m, 8H, 4CH_2), 2.01 (qd, 2H, J=7.3, 1.5 Hz, H-4), 2.40 (s, 3H, CH3–*p*-Tol), 5.31 (dt, 1H, J=7.9, 3.8 Hz, H-5), 5.77 (dt, 1H, J=15.5, 7.0 Hz, H-9), 6.06 (d, 1H, J=8.1 Hz, H-6), 6.05 (d, 1H, J=15.0 Hz, H-8), 7.28 (d, 2H, J=8.5 Hz, ArH), 7.70 (d, 2H, J=8.3 Hz, ArH). ^{13}C NMR (50 MHz) δ −4.8, −4.4, 13.5, 14.0, 18.1, 21.6, 22.0, 22.6, 25.8 (3C), 27.4, 34.8, 37.7, 68.3, 124.3, 127.7 (2C), 129.5 (2C), 134.0, 137.0, 137.6, 144.2, 144.7.

3.4. General procedure for nucleophilic epoxidation of dienyl sulfoxides and sulfones

A two-necked round-bottomed flask fitted with a tube in T for entrance and exit of argon and a polyethylene stopper, was charged with anhydrous THF (5 mL/mmol) and 2–4 equiv of oil free NaH or KH (washed with hexane and dried), the mixture was cooled to 0 °C and then 2–4 equiv of *t*-BuOOH (80% in *t*-BuOO-*t*-Bu) was added. After stirring at rt for 20–30 min, the resulting solution was cooled to 0 °C and a solution of 1 equiv of the corresponding dienyl sulfoxide or sulfone in THF (7 mL/mmol), previously dried over 4 Å sieves, was added dropwise. The reaction mixture was stirred at 0 °C until starting material disappearance, monitored by TLC. Subsequently, a 10% solution of $Na_2S_2O_4$ (4 mL/mmol) and EtOAc (8 mL/mmol) was added. After separation, the aqueous layer was extracted with EtOAc (3×10 mL/mmol). The combined organic extracts were washed with brine and dried with anhydrous $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure provided a crude product that was purified by column chromatography on silica gel.

3.4.1. Synthesis of (−)-(2*S*,3*S*,1′*R*)-(*E*)-3-(1′-hydroxypentyl)-2-(1-pentenyl)-2-(*p*-tolylsulfonyl)oxirane, 10. From NaH (7 mg, 0.31 mmol) in THF (1.50 mL), *t*-BuOOH (40 μL, 35.1 mg, 0.31 mmol) and a solution of dienyl sulfone **6** (26.2 mg, 0.078 mmol) in THF (0.50 mL), according to the general procedure (0 °C, 105 min), hydroxy sulfonyl oxirane **10** was obtained. Purification by chromatography (5–30% EtOAc–hexane) gave 24.5 mg (89%) of **10** as a colorless oil. Data for **10**: R_f=0.34 (30% EtOAc–hexane). $[\alpha]_D^{20}$ −43.5 (*c* 1.01). ^{1}H NMR (300 MHz) δ 0.75 (t, 3H, J=7.3 Hz), 0.88 (t, 3H, J=7.3 Hz), 1.20–1.32 (m, 6H), 1.46–1.70 (m, 2H), 1.92 (br s, 1H, OH), 1.96 (ap q, 2H, J=6.6 Hz), 2.42 (s, 3H, CH_3–*p*-Tol), 3.28 (dt, 1H, J=8.0, 5.6 Hz, H-1′), 3.81 (d, 1H, J=8.2 Hz, H-3), 5.65 (dt, 1H, J=15.6, 6.7 Hz, H-2″), 5.79 (dt, 1H, J=15.5, 1.2 Hz, H-1″), 7.30 (dd, 2H, J=8.5, 0.6 Hz, ArH), 7.68 (dd, 2H, J=8.4, 1.9 Hz, ArH). ^{13}C NMR (75 MHz) δ 13.4, 13.8, 21.7 (2C), 22.5, 26.8, 33.0, 34.2, 65.1, 69.6, 76.0, 116.3, 129.4 (2C), 129.6 (2C), 132.4, 141.3, 145.3. IR (CCl_4): 3460, 2920, 2900, 2840, 1640, 1580, 1450, 1240, 1170, 640 cm^{-1}. MS (APCI): 353 $[M+1]^+$, 197 (100%). Anal. Calcd for $C_{19}H_{28}O_4S$: C, 64.74; H, 8.01; S, 9.10. Found: C, 64.55; H, 8.22; S, 9.09.

3.4.2. Synthesis of (2*S*,3*S*,1′*R*)-(*E*)-3-[1′-(*tert*-butyldimethylsilyloxy)-*n*-pentyl]-2-(1-pentenyl)-2-(*p*-tolylsulfonyl)oxirane, 12, and (2*R*,3*R*,1′*R*)-(*E*)-3-[1′-(*tert*-butyldimethylsilyloxy)-*n*-pentyl]-2-(1-pentenyl)-2-(*p*-tolylsulfonyl)oxirane, 14. From NaH (6.4 mg, 0.26 mmol) in THF (1.30 mL), *t*-BuOOH (33 μL, 30 mg, 0.26 mmol) and a solution of dienyl sulfone **8** (27.8 mg, 0.066 mmol) in THF (0.46 mL), according to the general procedure (4 days, 6 h), a 44:51:5 mixture of sulfonyl oxiranes **12** and **14** and starting material was obtained. Purification by chromatography (5–30% EtOAc–hexane) gave 22.3 mg (75%) of an inseparable mixture of **12** and **14** as a colorless oil, and 2 mg (5%) of starting material. Spectral data measured for **12** and **14** was identical to those described below.

3.4.3. Synthesis of (−)-(2*S*,3*S*,1′*R*,S_S)-(*E*)-3-(1′-hydroxypentyl)-2-(pentenyl)-2-(*p*-tolylsulfinyl)oxirane, 10′, (−)-(2*S*,3*S*,1′*R*)-(*E*)-3-(1′-hydroxypentyl)-2-(1-pentenyl)-2-(*p*-tolylsulfonyl)oxirane, 10, (7*R*,8*R*)-6-oxadodecanyl-4,7-bis-oxirane, 11c, (7*S*,8*R*)-6-oxadodecanyl-4,7-bis-oxirane, 11a,b. From NaH (7.8 mg, 0.32 mmol) in THF (1.60 mL), *t*-BuOOH (41 μL, 37 mg, 0.32 mmol) and a solution of dienyl sulfoxide **1** (26 mg, 0.081 mmol) in THF (0.56 mL), according to the general procedure (1 h), a 46:9:18:9:18 mixture of **10′**, **11c**, **11a**,**b**, **10** and **1** was obtained (^{1}H NMR of an aliquot). After 2 h (total reaction time), a 26:10:38:16:10 mixture of **10′**, **11c**, **11a**,**b**, **10** and **1** was obtained. Purification by chromatography (5–50% EtOAc–hexane) gave 4.25 mg (25%) of bis oxiranes **11c** and **11a**,**b**, 3.25 mg (11%) of sulfonyl oxirane **10**, 4.15 mg (21%) of sulfinyl oxirane **10′** and 3.7 mg (7%) of starting material as colorless oils. Alternatively, from NaH (13.5 mg, 0.40 mmol) in THF (2.15 mL), *t*-BuOOH (55 μL, 50 mg, 0.40 mmol) and a solution of dienyl sulfoxide **1** (35.2 mg, 0.11 mmol) in THF (0.76 mL), according to the general procedure (3 h) a 21:52:27 mixture of bis oxiranes **11c** and **11a**,**b** and sulfonyl oxirane **10** was obtained. Purification by chromatography (5–50% Et_2O–hexane) gave 4 mg (18%) of **11c** and 10 mg (44%) of **11a**,**b**. Data for **10′**: R_f=0.21 (2×30% EtOAc–hexane). $[\alpha]_D^{20}$ −17.9 (*c* 0.41). ^{1}H NMR (300 MHz) δ 0.78 (t, 3H, J=7.4 Hz), 0.83 (t, 3H, J=7.1 Hz), 1.16–1.59 (m, 9H), 1.96 (qd, 2H, J=7.1, 1.5 Hz),

2.40 (s, 3H, CH_3–*p*-Tol), 3.33 (dt, 1H, J=7.9, 5.4 Hz, H-1′), 3.67 (d, 1H, J=8.0 Hz, H-3), 5.43 (dt, 1H, J=15.6, 1.5 Hz, H-1″), 5.72 (dt, 1H, J=15.6, 6.8 Hz, H-2″), 7.28 (d, 2H, J=7.8 Hz, ArH), 7.46 (d, 2H, J=8.3 Hz, ArH). ^{13}C NMR (75 MHz) δ 13.5, 13.8, 21.5, 21.8, 22.5, 26.8, 33.0, 34.5, 64.6, 69.8, 76.5, 115.1, 125.4 (2C), 129.5 (2C), 136.7, 141.4, 142.2. IR (CCl_4): 3360, 2920, 2900, 2820, 1630, 1470, 1440, 1240, 1070, 1000, 770 cm^{-1}. Data for **11a**,**b** (as an inseparable 44:56 mixture of diastereomers): R_f=0.46 (50% Et_2O–hexane). ^{1}H NMR (400 MHz) δ 0.88 (t, 3H, J=7.3 Hz, CH_3), 0.92–1.0 (m, 9H, CH_3), 1.23–1.70 (m, 20H), 3.08 (td, 1H, J=5.9, 1.9 Hz), 3.20–3.26 (m, 3H), 3.39 (d, 1H, J=1.9 Hz, CH–CO), 3.47 (d, 1H, J=1.9 Hz, CH–CO), 3.58 (d, 1H, J=4.8 Hz, CH–CO), 3.77 (d, 1H, J=4.8 Hz, CH–CO). ^{13}C NMR (125 MHz) δ 13.7, 13.9, 19.1, 19.7, 22.3, 22.4, 26.7, 27.2, 27.8, 28.3, 28.4, 31.4, 31.5, 33.6, 33.7, 56.0, 56.4, 58.6, 58.7, 59.1, 59.3, 59.4, 211.7. IR (CCl_4): 2960, 2930, 2875, 1720, 1460, 1430, 1380, 1230, 1190, 1090, 1050, 1020, 880 cm^{-1}. MS (EI): 212 [M]$^+$, 169, 127, 97, 71, 55 (100%), 43, 41. Data for **11c**: R_f=0.52 (50% Et_2O–hexane). ^{1}H NMR (400 MHz) δ 0.90 (t, 3H, J=7.2 Hz), 0.96 (t, 3H, J=7.2 Hz), 1.34–1.66 (m, 10H), 3.07 (tt, 1H, J=5.6, 1.7 Hz), 3.16 (td, 1H, J=5.6, 1.7 Hz), 3.30 (d, 1H, J=1.9 Hz, CH–CO), 3.42 (d, 1H, J=2.1 Hz, CH–CO). ^{13}C NMR (50 MHz) δ 13.7, 13.9, 19.1, 22.3, 27.8, 31.5, 33.8, 56.8, 57.2, 57.3, 59.2, 211.7. IR (CCl_4): 2960, 2930, 2875, 1720, 1460, 1430, 1380, 1230, 1190, 1090, 1050, 1020, 880 cm^{-1}. MS (EI): 127, 97, 71, 55 (100%), 43, 41, 39. The data of **10** was identical to that found before.

3.4.4. Synthesis of (+)-(2*R*,3*R*,1′*S*,S_S)-(*E*)-3-(1′-hydroxypentyl)-2-(1-pentenyl)-2-(*p*-tolylsulfinyl)oxirane, 15, (+)-(2*R*,3*R*,1′*S*)-(*E*)-3-(1′-hydroxypentyl)-2-(1-pentenyl)-2-(*p*-tolylsulfonyl)oxirane *ent*-10, (7*R*,8*S*)-6-oxadodecanyl-4,7-bis-oxirane, *ent*-11a,b, (7*S*,8*S*)-6-oxado- decanyl-4,7-bis-oxirane, *ent*-11c. From NaH (2.2 mg, 0.094 mmol) in THF (0.47), *t*-BuOOH (12 μL, 11 mg, 0.094 mmol) and a solution of dienyl sulfoxide **2** (7.5 mg, 0.023 mmol) in THF (0.16 mL), according to the general procedure (70 min), an 80:4:11:5 of sulfinyl oxirane **15**, sulfonyl oxirane *ent*-**10**, and bis oxiranes *ent*-**11a**,**b** and *ent*-**11c**, was obtained. Purification by chromatography (5–50% EtOAc–hexane) gave 5.4 mg (76%) of **15**, 0.3 mg (4%) of *ent*-**10** and 0.5 mg (13%) of *ent*-**11c** and *ent*-**11a**,**b** as colorless oils. Data for **15**: R_f=0.25 (50% EtOAc–hexane). $[\alpha]_D^{20}$ +48.9 (*c* 0.60). ^{1}H NMR (300 MHz) δ 0.80 (t, 3H, J=7.4 Hz), 0.87 (t, 3H, J=7.2 Hz), 1.20–1.39 (m, 6H), 1.36–1.62 (m, 2H), 1.81 (d, 1H, J=2.4 Hz, OH), 1.99 (qd, 2H, J=7.0, 1.5 Hz), 2.39 (s, 3H, CH_3–*p*-Tol), 3.35 (m, 1H, H-1′), 3.61 (d, 1H, J=8.1 Hz, H-3), 5.40 (dt, 1H, J=15.7, 1.5 Hz, H-1″), 5.67 (dt, 1H, J=15.7, 6.8 Hz, H-2″), 7.26 (d, 2H, J=7.9 Hz, ArH), 7.46 (d, 2H, J=8.2 Hz, ArH). ^{13}C NMR (50 MHz) δ 13.5, 13.8, 21.5, 21.8, 22.5, 26.9, 33.0, 34.5, 64.5, 69.8, 78.8, 117.4, 126.1 (2C), 129.3 (2C), 135.6, 141.1, 142.3. IR (CCl_4): 3350, 2920, 2890, 2820, 2840, 1730, 1540, 1470, 1450, 1380, 1240, 1070, 1000, 770, 640 cm^{-1}. Anal. Calcd for $C_{19}H_{28}O_3S$: C, 67.82; H, 8.39; S, 9.53. Found: C, 67.65; H, 8.42; S, 9.44. The data for *ent*-**10**, *ent*-**11c** and *ent*-**11a**,**b** was identical to that of their enantiomers.

3.4.5. Synthesis of (+)-(2*R*,3*R*,1′*R*,S_S)-(*E*)-3-[1′-(*tert*-butyldimethylsilyloxy)-*n*-pentyl]-2-(1-pentenyl)-2-(*p*-tolylsulfinyl)oxirane, 13, (2*S*,3*S*,1′*R*)-(*E*)-3-[1′-(*tert*-butyldimethylsilyloxy)-*n*-pentyl]-2-(1-pentenyl)-2-(*p*-tolylsulfonyl)oxirane, 12, (+)-(2*R*,3*R*,1′*R*)-(*E*)-3-[1′-(*tert*-butyldimethylsilyloxy)-*n*-pentyl]-2-(1-pentenyl)-2-(*p*-tolylsulfonyl)oxirane, 14. From KH (10.7 mg, 0.26 mmol) in THF (1.30 mL), *t*-BuOOH (33 μL, 30 mg, 0.26 mmol) and a solution of dienyl sulfoxide **4** (29 mg, 0.06 mmol) in THF (0.46 mL), according to the general procedure (94 h), a 9:41:37:12 of sulfonyl oxiranes **12** and **14**, sulfinyl oxirane **13** and starting material was obtained. Purification by chromatography (5–15% EtOAc–CH_2Cl_2) gave 11.3 mg (38%) of **13**, 14 mg (44%) of an 82:18 inseparable mixture of **14** and **12** and 3.1 mg (11%) of starting material, as colorless oils. Data for **13**: R_f=0.45 (2×15% EtOAc–hexane). $[\alpha]_D^{20}$ +80.1 (*c* 1.11). ^{1}H NMR (300 MHz) δ −0.06 (s, 3H, TBDMS), −0.02 (s, 3H, TBDMS), 0.79 (t, 3H, J=7.4 Hz), 0.85 (s, 9H, TBDMS), 0.87 (t, 3H, J=7.2 Hz), 1.24–1.51 (m, 8H), 2.00 (q, 2H, J=6.8 Hz), 2.37 (s, 3H, CH_3–*p*-Tol), 3.36 (dt, 1H, J=8.0, 5.6 Hz, H-1′), 3.60 (d, 1H, J=7.9 Hz, H-3), 5.48 (d, 1H, J=15.5 Hz, H-1″), 5.60 (dt, 1H, J=15.5, 6.3 Hz, H-2″), 7.24 (d, 2H, J=7.9 Hz, ArH), 7.47 (d, 2H, J=8.2 Hz, ArH). ^{13}C NMR (75 MHz) δ −4.4, −4.2, 13.6, 14.0, 18.0, 21.5, 21.9, 22.7, 25.7 (3C), 26.3, 34.5, 35.1, 63.8, 68.2, 78.5, 117.1, 125.9 (2C), 129.3 (2C), 136.1, 140.7, 142.0. IR (CCl_4): 2920, 2900, 2820, 1530, 1440, 1240, 1060, 990, 770 cm^{-1}. Data for **12**: R_f=0.48 (15% EtOAc–hexane). ^{1}H NMR (300 MHz) δ −0.04 (s, 3H, TBDMS), 0.05 (s, 3H, TBDMS), 0.76 (t, 3H, J=7.3 Hz), 0.80–0.90 (m, 3H), 0.86 (s, 9H, TBDMS), 1.23–1.60 (m, 8H), 1.96 (q, 2H, J=6.3 Hz), 2.42 (s, 3H, CH_3–*p*-Tol), 3.22 (dt, 1H, J=8.1, 4.9 Hz, H-1′), 3.77 (d, 1H, J=8.2 Hz, H-3), 5.65 (dt, 1H, J=15.5, 7.0 Hz, H-2″), 5.82 (d, 1H, J=15.5 Hz, H-1″), 7.29 (d, 2H, J=8.4 Hz, ArH), 7.68 (d, 2H, J=8.4 Hz, ArH). Data for **14**: R_f=0.37 (15% EtOAc–hexane). $[\alpha]_D^{20}$ +6.6 (*c* 0.83). ^{1}H NMR (300 MHz) δ −0.02 (s, 3H, TBDMS), 0.03 (s, 3H, TBDMS), 0.76 (t, 3H, J=7.3 Hz), 0.80–0.90 (m, 3H), 0.86 (s, 9H, TBDMS), 1.22–1.39 (m, 6H), 1.52–1.56 (m, 2H), 1.99 (m, 2H), 2.41 (s, 3H, CH_3–*p*-Tol), 3.30 (ddd, 1H, J=7.9, 6.1, 5.3 Hz, H-1′), 3.82 (d, 1H, J=7.9 Hz, H-3), 5.55 (dt, 1H, J=15.5, 7.0 Hz, H-2″), 5.93 (dt, 1H, J=15.5, 1.5 Hz, H-1″), 7.29 (d, 2H, J=8.7 Hz, ArH), 7.69 (d, 2H, J=8.3 Hz, ArH). ^{13}C NMR (75 MHz) δ −4.5, −4.1, 13.5, 14.0, 21.7, 21.8, 22.6, 25.7 (3C), 26.4, 29.7, 34.2, 35.1, 65.1, 67.6, 76.6, 116.5, 129.4 (2C), 129.5 (2C), 132.9, 140.8, 145.5. IR (CCl_4): 2920, 2890, 2820, 1440, 1310, 1240, 1130, 1070, 1000, 640 cm^{-1}. MS (APCI): 489 [M+Na]$^-$, 244 (100%).

3.4.6. Synthesis of (−)-(2*S*,3*R*,1′*S*)-(*E*)-3-(1′-hydroxypentyl)-2-(1-pentenyl)-2-(*p*-tolylsulfonyl)oxirane, 17. From NaH (3.7 mg, 0.15 mmol) in THF (0.80 mL), *t*-BuOOH (19 μL, 17 mg, 0.15 mmol) and a solution of dienyl sulfone **7** (13 mg, 0.038 mmol) in THF (0.26 mL), according to the general procedure (55 min), sulfonyl oxirane **17** was obtained. Purification by chromatography (5–50% Et_2O–hexane) gave 11 mg (82%) of **17**, as a colorless oil. Data for **17**: R_f=0.28 (50% Et_2O–hexane). $[\alpha]_D^{20}$ −39.2 (*c* 0.76). ^{1}H NMR (300 MHz) δ 0.68 (t, 3H, J=7.4 Hz), 0.92 (t, 3H, J=7.3 Hz), 1.18 (sext, 2H, J=7.3 Hz), 1.34–1.54 (m, 4H), 1.65–1.69 (m, 2H), 1.81–1.90 (m, 2H),

2.32 (d, 1H, J=3.6 Hz, OH), 2.42 (s, 3H, CH_3–p-Tol), 3.04 (d, 1H, J=7.8 Hz, H-3), 4.62 (m, 1H, H-1′), 5.59 (dt, 1H, J=15.5, 6.6 Hz, H-2″), 5.73 (dt, 1H, J=15.5, 1.2 Hz, H-1″), 7.31 (d, 2H, J=7.9 Hz, ArH), 7.71 (d, 2H, J=8.3 Hz, ArH). ^{13}C NMR (75 MHz) δ 13.3, 14.0, 21.5, 21.7, 22.5, 27.0, 33.6, 33.8, 67.7, 73.1, 76.8, 120.5, 129.1 (2C), 129.5 (2C), 134.4, 138.1, 145.2. IR (CCl_4): 3500, 2920, 2900, 2830, 1640, 1580, 1450, 1310, 1240, 1150, 1060, 990, 780, 660 cm^{-1}. Anal. Calcd for $C_{19}H_{28}O_4S$: C, 64.74; H, 8.01; S, 9.10. Found: C, 64.66; H, 8.25; S, 9.01.

3.4.7. Synthesis of (+)-(2*S*,3*R*,1′*S*,S_S)-(*E*)-3-(1′-hydroxypentyl)-2-(1-pentenyl)-2-(*p*-tolylsulfinyl)oxirane, 16, (−)-(2*S*,3*R*,1′*S*)-(*E*)-3-(1′-hydroxypentyl)-2-(1-pentenyl)-2-(*p*-tolylsulfonyl)oxirane, 17, (7*S*,8*S*)-6-oxadodecanyl-4,7-bis-oxirane, *ent*-11c, (7*R*,8*S*)-6-oxadodecanyl-4,7-bis-oxirane, *ent*-11a,b. From NaH (9.9 mg, 0.41 mmol) in THF (2.0 mL), *t*-BuOOH (51 μL, 46 mg, 0.41 mmol) and a solution of dienyl sulfoxide **3** (33 mg, 0.102 mmol) in THF (0.71 mL), according to the general procedure (45 min) a 65:4:18:2:11 mixture of **16**, **17**, *ent*-**11c**, *ent*-**11a**,**b** and **3** was obtained. Purification by chromatography (5–50% Et_2O–hexane, then 5–20% EtOAc–toluene) gave 14.8 mg (44%) of sulfinyl oxirane **16**, 1 mg (3%) of sulfonyl oxirane **17**, 3 mg (14%) of bis oxiranes *ent*-**11c** and *ent*-**11a**,**b** and 3 mg (10%) of starting material, as colorless oils. Data for **16**: R_f=0.30 (2×30% EtOAc–hexane). $[\alpha]_D^{20}$ +7.3 (*c* 1.17). ^{1}H NMR (300 MHz) δ 0.71 (t, 3H, J=7.4 Hz), 0.94 (t, 3H, J=7.3 Hz), 1.21 (sext, 2H, J=7.4 Hz), 1.40–1.84 (m, 6H), 1.90 (q, 2H, J=7.0 Hz), 2.10 (br s, 1H, OH), 2.38 (s, 3H, CH_3–p-Tol), 3.13 (d, 1H, J=8.2 Hz, H-3), 4.16 (dt, 1H, J=8.0, 5.5 Hz, H-1′), 5.51 (dt, 1H, J=15.5, 6.8 Hz, H-2″), 5.74 (dt, 1H, J=15.6, 1.5 Hz, H-1″), 7.27 (d, 2H, J=7.9 Hz, ArH), 7.46 (d, 2H, J=8.3 Hz, ArH). ^{13}C NMR (75 MHz) δ 13.4, 13.9, 21.4, 21.7, 22.6, 27.0, 33.3, 34.1, 69.9, 71.2, 76.4, 116.6, 125.1 (2C), 129.4 (2C), 136.1, 138.6, 141.8. IR (CCl_4): 3360, 2930, 2900, 2840, 1720, 1640, 1580, 1470, 1450, 1360, 1240, 1060, 1020, 990, 770 cm^{-1}. Anal. Calcd for $C_{19}H_{28}O_3S$: C, 67.82; H, 8.39; S, 9.53. Found: C, 67.98; H, 8.56; S, 9.71. The data for **17**, *ent*-**11c**, and *ent*-**11a**,**b** was identical to those found before.

3.4.8. Synthesis of (2*S*,3*S*,1′*R*)-(*E*)-3-[(1′-*t*-butyldimethylsilyloxy)-*n*-pentyl]-2-(1-pentenyl)-2-(*p*-tolylsulfonyl)-oxirane, 12. From hydroxy sulfonyl oxirane **10** (12.4 mg, 0.03 mmol) in CH_2Cl_2 (0.30 mL), imidazole (2.9 mg, 0.042 mmol), *t*-butyldimethylsilyl chloride (6 mg, 0.038 mmol) according to the general procedure (25 h), after chromatography (5–30% EtOAc–hexane), 4.5 mg (29%) of silylated oxirane **12** and 8.75 mg (70%) of starting material, was obtained as colorless oils. The data for **12** was identical to those found before.

3.4.9. Synthesis of (+)-(2*R*,3*R*,1′*R*)-(*E*)-3-[(1′-*tert*-butyldimethylsilyloxy)-*n*-pentyl]-2-(1-pentenyl)-2-(*p*-tolylsulfonyl)oxirane, 14. From sulfinyl oxirane **13** (11 mg, 0.02 mmol) in MeOH (0.24 mL) and MMPP (22.7 mg, 0.036 mmol), according to the general procedure (2 h), after chromatography (5–30% EtOAc–hexane), sulfonyl oxirane **14** (8.3 mg, 74%) was obtained as a colorless oil. The data for **14** was identical to those found before.

3.4.10. Synthesis of (+)-(2*R*,3*S*,1′*S*)-(*E*)-3-(1′-hydroxypentyl)-2-(1-pentenyl)-2-(*p*-tolylsulfonyl)oxirane, *ent*-10. From sulfinyl oxirane **15** (6 mg, 0.017 mmol) in MeOH (0.17 mL) and MMPP (16.5 mg, 0.026 mmol), according to the general procedure (90 min), after chromatography (5–30% EtOAc–hexane), sulfonyl oxirane *ent*-**10** (3.5 mg, 59%) was obtained as a colorless oil with data identical to that of its enantiomer except for the sign of the optical rotation ($[\alpha]_D^{20}$ +32.6 (*c* 0.35)).

3.4.11. Synthesis of (−)-(2*S*,3*R*,1′*S*)-(*E*)-3-(1′-hydroxypentyl)-2-(1-pentenyl)-2-(*p*-tolylsulfonyl)oxirane, 17. From sulfinyl oxirane **16** (10.8 mg, 0.032 mmol) in MeOH (0.32 mL) and MMPP (29.8 mg, 0.048 mmol), according to the general procedure (23 h), after chromatography (5–20% EtOAc–hexane), sulfonyl oxirane **17** (7.0 mg, 62%) was obtained as a colorless oil with data identical to that found before.

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Polyhydroxylated pyrrolidines. Part 4: Synthesis from D-fructose of protected 2,5-dideoxy-2,5-imino-D-galactitol derivatives☆

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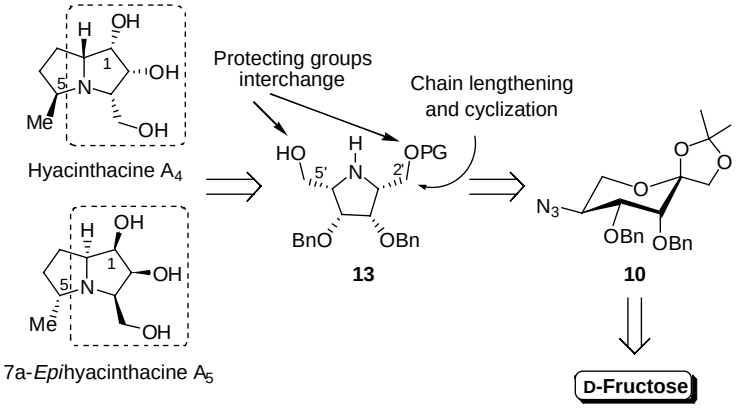
Abstract—The readily available 3-*O*-benzoyl-4-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-methanesulfonyl-β-D-fructopyranose (**5**) was straightforwardly transformed into its D-*psico* epimer (**8**), after *O*-debenzoylation followed by oxidation and reduction, which caused the inversion of the configuration at C(3). Compound **8** was treated with lithium azide yielding 5-azido-4-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-L-tagatopyranose (**9**) that was transformed into the related 3,4-di-*O*-benzyl derivative **10**. Cleavage of the acetonide in **10** to give **11**, followed by regioselective 1-*O*-pivaloylation to **12** and subsequent catalytic hydrogenation gave (2*R*,3*S*,4*R*,5*S*)-3,4-dibenzyloxy-2,5-bis(hydroxymethyl)-2′-*O*-pivaloylpyrrolidine (**13**). Stereochemistry of **13** could be determined after *O*-deacylation to the symmetric pyrrolidine **14**. Total deprotection of **14** gave 2,5-imino-2,5-dideoxy-D-galactitol (**15**, DGADP).

1. Introduction

In a very recent paper, our group reported on preparation of orthogonally protected derivatives of 2,5-dideoxy-2,5-imino-D-*allo*- (DADP) and -D-*altro*-hexitol (DALDP),[1] in a stereoselective manner, using commercially available D-fructose as the chiral starting material. Continuing with our efforts on this topic, we reported herein on the highly stereoselective synthesis of the D-galacto isomer (**13**) of the above mentioned 2,5-iminohexitols.

Scheme 1 shows the synthetic potentiality of (2*R*,3*S*,4*R*,5*S*)-3,4-dibenzyloxy-2,5-bis(hydroxymethyl)-2′-*O*-pivaloylpyrrolidine (**13**) displaying the retrosynthesis of hyacinthacines A_4 and 7a-*epi*-A_5, the former recently isolated from *Scilla sibirica*,[2] where clearly is shown that **13** must be considered an appropriate chiral starting material for the synthesis of such target molecules. Thus, *O*-protecting groups interchange between the hydroxyl groups at C(2′)–C(5′), carbon-chain lengthening at either C(2′) (the original C(1) of D-fructose) or C(5′) in a two more carbon atoms fragment



Scheme 1. Retrosynthesis of natural hyacinthacine A_4 and 7a-*epi*-A_5.

☆ For Part III, see Ref. 1.

Keywords: D-Fructose; Stereoselective synthesis; Polyhydroxylated pyrrolidines; 2,5-Dideoxy-2,5-iminohexitols; DGADP.
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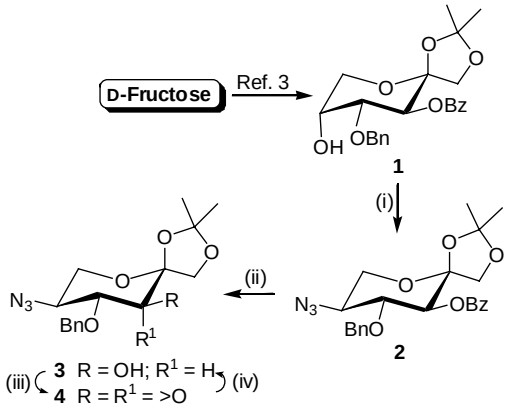
suitably functionalized, followed by a further cyclization, could lead to pyrrolizidines, which stereochemistry at C(1,2,3,7a) belonging either to that of the natural hyacinthacine A_4 or the 7a-*epi*-A_5.

2. Results and discussion

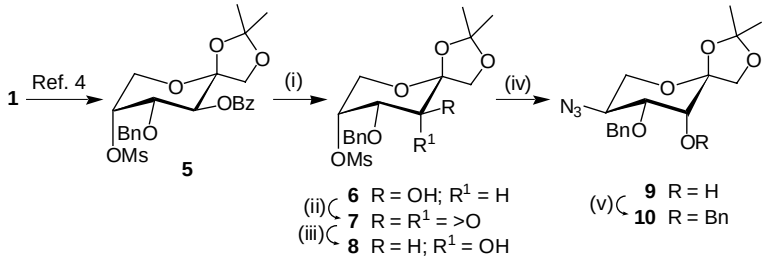
A first attempt of synthesizing the required key intermediate 3,4-di-*O*-benzy1-1,2-*O*-isopropylidene-α-L-tagatopyranose (**10**) according to the synthetic route outlined in Scheme 2, where the well known 3-*O*-benzoyl-4-*O*-benzy1-1,2-*O*-isopropylidene-β-D-fructopyranose (**1**)[3] was chosen as the chiral starting material was unsuccessful. Even though the transformation of **1** into the already reported 5-azido-5-deoxy-α-L-sorbopyranose derivative **2**,[4] after its treatment with diphenylphorphoryl azide (DPPA)/Ph_3P/DEAD,[5] occurred with total stereocontrol and high yield, as well as its 3-*O*-debenzoylation to **3**, and subsequent oxidation to the corresponding 2,3-diulose **4**, the sodium borohydride reduction of the latter took place with high stereoselectivity but by the α-face regenerating **3**.[6]



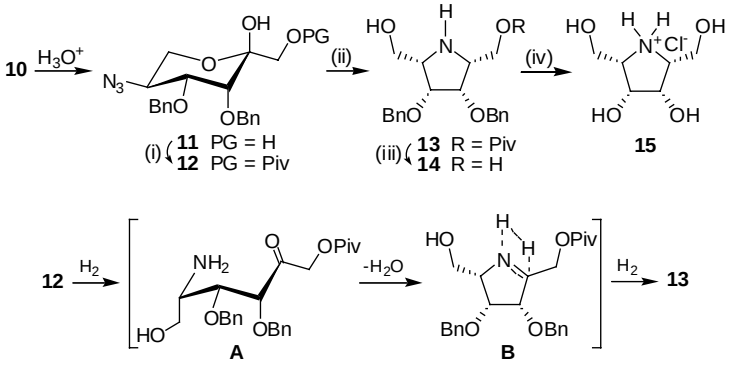
Scheme 2. Synthesis of **3** from **1**. Reagents and conditions: (i) Ph_3P/DEAD/$(PhO)_2PON_3$/THF; (ii) NaMeO/MeOH; (iii) Dess–Martin periodinane/Cl_2CH_2; (iv) $NaBH_4$/MeOH.

On the basis of the above results, an alternative synthetic route was explored (see Scheme 3). Thus, **1** was straightforwardly transformed into the corresponding 5-*O*-methanesulfonyl derivative **5**,[4] which was de-*O*-benzoylated to **6** by standard Zemplen conditions without observing any substitution or elimination of the mesyloxy group at C(5). Oxidation of **6** with the Dess–Martin reagent gave the not fully characterized 2,3-diulose **7**, which was exclusively reduced to 4-*O*-benzy1-1,2-*O*-isopropylidene-5-*O*-methanesulfonyl-β-D-psicopyranose (**8**). Reaction of **8** with lithium azide in DMF gave 5-azido-4-*O*-benzy1-5-deoxy-1,2-*O*-isopropylidene-α-L-tagatopyranose (**9**), which was finally benzylated to the required **10**.

Deacetonation of **10** in acid medium (see Scheme 4) yielded the corresponding free hexulose **11** that was shown as the crystalline α-epimer in a $^2C_5$ conformation with H(4,5,6ax) in trans-diaxial disposition in accordance with the $J_{4,5}$ and $J_{5,6ax}$ values of 10.0 and 11.2 Hz, respectively. Reaction of **11** with pivaloyl chloride gave in a highly regioselective manner 5-azido-3,4-di-*O*-benzyl-5-deoxy-1-*O*-pivaloyl-α-L-tagatopyranose (**12**). Hydrogenation of **12** under the presence of Raney nickel catalyst occurred in moderate yield but with high stereoseletivity affording (2*R*,3*S*,4*R*,5*S*)-3,4-dibenzyloxy-2,5-bis(hydroxylmethyl)-2′-*O*-pivaloyl-pyrrolidine (**13**). Formation of **13** must occur through the intermediate aminocarbonyl sugar **A** that reacted in a fast



Scheme 3. Synthesis of **10** from **1**. Reagents and conditions: (i) MeOH/MeONa (cat.), rt; (ii) Dess–Martin/Cl_2CH_2, rt; (iii) $NaBH_4$/MeOH, 0 °C; (iv) LiN_3/DMF, 100 °C; (v) NaH/DMF/BnBr, rt.



Scheme 4. Synthesis of polyhydroxylated pyrrolidines **13**–**15**. Reagents and conditions: (i) PivCl/TEA/Cl_2CH_2, rt; (ii) Raney Ni/H_2/MeOH; (iii) NaMeO/MeOH; (iv) 10% Pd–C/H_2/MeOH/HCl.

intramolecular process to its cyclic imine intermediate **B**, which was finally hydrogenated to **13**. The stereochemistry of **13** could be easily established after its 2′-de-*O*-acylation to **14**, which ^{1}H- and ^{13}C NMR spectra contained signals only consistent with the presence of a symmetry plane in the molecule and hence with a D-*galacto* configuration in **13**. The total removal of the protection group in **14** yielded (2*R*,3*S*,4*R*,5*S*)-3,4-dihydroxy-2,5-bis(hydroxymethyl)pyrrolidine hydrochloride [2,5-dideoxy-2,5-imino-D-galactitol (DGADP)] (**15**), which analytical and spectroscopic data were in agreement with those previously reported.[7] Compound **15** has been also described as the free base.[8]

Comments merit the high stereoselectivity found in the catalytic hydrogenation of intermediate Δ^{1}-pyrroline **B** (see Scheme 4), where the entry of the hydrogen molecule took place by the β-face resulting in a cis-disposition for all substituents. These results are in accordance with those previously reported, where the authors[9] stated that in five-membered ring systems the stereochemistry at the new stereogenic centre [C(2)] is controlled by that existing at C(4), in such a way that the substituents at both carbon atoms resulted cis-positioned.

Compound **15** was reported[8a] as a potent inhibitor of α-galactosidase from coffee bean with K_i 5×10^{-8} M.

3. Conclusions

D-Fructose is an appropriate chiral starting material for the stereoselective synthesis of orthogonally protected polyhydroxylated pyrrolidines alkaloids. Highly diastereoselective hydrogenation of a 5-azido-5-deoxy-α-L-tagatose derivative is an excellent synthetic route to the partially protected target molecule DGADP.

4. Experimental

4.1. General procedures

Melting points were determined with a Gallenkamp apparatus and are uncorrected. Solutions were dried over $MgSO_4$ before concentration under reduced pressure. The ^{1}H and ^{13}C NMR spectra were recorded with Bruker AMX-300, AM-300, and ARX-400 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). IR spectra were recorded with a Perkin-Elmer 782 instrument and mass spectra with a Micromass Mod. Platform II and Autospec-Q mass spectrometers. Optical rotations were measured for solutions in $CHCl_3$ (1-dm tube) with a Jasco DIP-370 polarimeter. TLC was performed on precoated E. Merck silica gel 60 F_{254} aluminium sheets with detection by charring with H_2SO_4 or employing a mixture of 10% ammonium molybdate (w/v) in 10% aqueous sulphuric acid containing 0.8% cerium sulphate (w/v) and heating. Column chromatography was performed on silica gel (E. Merck, 7734). The no crystalline compounds, for which elemental analyses were not obtained, were shown to be homogeneous by chromatography and characterized by NMR spectroscopy and FAB-HRMS with thioglycerol matrix.

4.1.1. 5-Azido-3-*O*-benzoyl-4-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-L-sorbopyranose (2). To an ice-water cooled and stirred solution of 3-*O*-benzoyl-4-*O*-benzyl-1,2-*O*-isopropylidene-β-D-fructopyranose[3] (**1**, 1.1 g, 3.6 mmol) in dry THF (30 mL) were consecutively added triphenylphosphine (1 g, 3.8 mmoL), a 40% solution of DEAD in toluene (1.75 mL, 3.8 mmol) and after 10 min DPPA (1 mL, 4.6 mmol). The mixture was allowed to reach room temperature and then left overnight. TLC (3:2, ether/hexane) then revealed a new faster running compound. The mixture was concentrated, supported on silica gel and then submitted to chromatography (1:3, ether/hexane) to afford pure crystalline **2** (1.23 g, 78%), which analytical and spectroscopy data were in accordance with those previously reported.[4]

4.1.2. 4-*O*-Benzyl-1,2-*O*-isopropylidene-5-*O*-methanesulfonyl-β-D-fructopyranose (6). To a solution of 3-*O*-benzoyl-4-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-methanesulfonyl-β-D-fructopyranose[4] (**5**, 4.93 g, 10 mmol) in anhydrous methanol (20 mL) was treated with 0.1 M NaOMe in methanol (5 mL) overnight. TLC (4:1, ether/hexane) then revealed the absence of **5** and the presence of a slower-running compound. The reaction mixture was neutralized with AcOH, concentrated and the residue dissolved in Cl_2CH_2 (25 mL) washed with water and concentrated again. Flash chromatography (1:1, ether/hexane) of the residue afforded pure syrupy **6** (3.67 g, 94%); $[\alpha]_D^{26}$ −150 (*c* 1.1); IR (neat): υ 3520 cm^{-1} (OH). ^{1}H NMR (300 MHz): δ 7.40–7.30 (m, 5H, Ph), 5.10 (dt, 1H, H-5), 4.82 and 4.68 (2d, 2H, J=11.0 Hz, CH_2Ph), 4.21 and 4.02 (2d, 2H, $J_{1,1'}$=8.8 Hz, H-1,1′), 4.00 (dd, 1H, $J_{5,6}$=1.6 Hz, $J_{6,6'}$=13 Hz, H-6), 3.94 (dd, 1H, $J_{5,6'}$=1.6 Hz, H-6′), 3.86 (d, 1H, $J_{3,4}$=9.8 Hz, H-3), 3.69 (dd, 1H, $J_{4,5}$=3.2 Hz, H-4), 3.02 (s, 3H, Ms), 1.90 (br s, 1H, OH), 1.49 and 1.44 (2s, 6H, CMe_2). ^{13}C NMR: δ 137.27, 128.68, and 128.28 (Ph), 112.37 (CMe_2), 105.71 (C-2), 77.46 (C-4), 76.79 (C-5), 72.94 (CH_2Ph), 71.99 (C-1), 63.12 (C-6), 39.11 (Ms), 26.57 and 26.31 (CMe_2). HRMS: *m*/*z* 411.1088 [M^++Na]. For $C_{17}H_{24}O_8NaS$ 411.1089 (deviation +0.3 ppm).

4.1.3. 4-*O*-Benzyl-1,2-*O*-isopropylidene-5-*O*-methanesulfonyl-β-D-psicopyranose (8). To a stirred suspension of Dess–Martin periodinane (5.93 g, 13.9 mmol) in dry CH_2Cl_2 (25 mL) was added dropwise a solution of **6** (4 g, 10.3 mmol) in the same solvent (25 mL) under Ar. The mixture was stirred at room temperature overnight. TLC (4:1, ether/hexane) then revealed the presence of a faster-running product. The reaction mixture was filtered and the filtrate washed with 10% aqueous Na_2CO_3, brine and water, then concentrated. The residue was percolated (3:2, ether/hexane) through a short column of silica gel to afford fractions containing presumably ketone **7** [3.8 mg, 96%; IR (neat): υ 1757 cm^{-1}], that was used in the next step.

To a stirred and ice-water cooled solution of **7** (3.8 g, 9.8 mmol) in dry methanol (25 mL) $NaBH_4$ (0.44 g, 11.5 mmol) was added portionwise. After 1 h, TLC (4:1, ether/hexane) showed no ketone **7** and the presence of a new product of lower mobility. The reaction mixture was neutralized with AcOH, concentrated and the residue was dissolved in Cl_2CH_2, washed with water then concentrated.

Flash chromatography (1:1, ether/hexane) afforded crystalline **8** (2.9 g, 76%); mp 93–94 °C (from ether/hexane); $[\alpha]_D^{28}$ −97 (*c* 1.2); *ν* (KBr) 3549 (OH), 3089, 726 and 696 cm^{-1} (aromatic). ^1H NMR (300 MHz): *δ* 7.40–7.30 (m, 5H, Ph), 4.97 (dt, 1H, H-5), 4.73 and 4.66 (2d, 2H, $J=11.3$ Hz, CH_2Ph), 4.20 and 4.14 (2d, 2H, $J_{1,1'}=9.6$ Hz, H-1,1′), 4.04 (d, 2H, $J_{5,6}=1.7$ Hz, H-6,6), 3.88–3.83 (m, 2H, H-3,4), 3.04 (s, 3H, Ms), 1.46 and 1.37 (2s, 6H, CMe_2). ^{13}C NMR: *δ* 136.98, 128.69, 128.32, and 128.12 (Ph), 112.68 (*C*Me_2), 105.47 (C-2), 77.06 (C-5), 73.62 (C-1), 71.90 (C-4), 70.66 (*C*H_2Ph), 70.40 (C-3), 63.33 (C-6), 39.03 (Ms), 26.61 and 26.42 (C*Me*$_2$). Anal. Calcd for $C_{17}H_{24}O_8S$: C, 52.57; H, 6.23; S, 8.25. Found: C, 52.86; H, 6.53; S, 8.07.

4.1.4. 5-Azido-4-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-L-tagatopyranose (9). A stirred solution of **8** (3.8 g, 9.7 mmol) and lithium azide (1.43 g, 29.2 mmol) in dry DMF (20 mL) was heated at 100 °C for 2 h. TLC (4:1, ether/hexane) then revealed a faster-running compound. The mixture was concentrated to a residue that was dissolved in ether (40 mL), washed with brine and concentrated. Flash chromatography (2:1, ether/hexane) of the residue afforded crystalline **9** (2.7 g, 82%); mp 74–76 °C (from ether–hexane); $[\alpha]_D^{26}$ −112.5 (*c* 0.9); IR (neat): *υ* 3492 (OH), 3064 (aromatic), 2105 (N_3), 1384 and 1372 (CMe_2), 752 and 699 cm^{-1} (aromatic). ^1H NMR (400 MHz): *δ* 7.45–7.30 (m, 5H, Ph), 4.73 and 4.67 (2d, 2H, $J=11.2$ Hz, CH_2Ph), 4.11 and 4.02 (2d, 2H, $J_{1,1'}=9.4$ Hz, H-1,1′), 3.87–3.73 (m, 4H, H-3,4,5,6eq), 3.51 (t, 1H, $J_{5,6ax}=J_{6ax,6eq}=11.1$ Hz, H-6ax), 1.46 and 1.37 (2s, 6H, CMe_2). ^{13}C NMR: *δ* 137.15, 128.75, 128.40, and 128.22 (Ph), 112.29 (*C*Me_2), 104.54 (C-2), 78.96 (C-3), 73.26 (*C*H_2Ph), 72.31 (C-1), 69.98 (C-4), 61.60 (C-6), 57.10 (C-5), 26.60 and 26.44 (C*Me*$_2$). HRMS: *m*/*z* 358.1377 $[M^+ + Na]$. For $C_{16}H_{21}N_3O_5Na$ 358.1379 (deviation +0.4 ppm).

4.1.5. 5-Azido-3,4-di-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-α-L-tagatopyranose (10). To a stirred suspension of NaH (60% oil dispersion, 387 mg, 16.1 mmol) in dry DMF (5 mL), compound **9** (2.7 g, 8.0 mmol) in the same solvent (10 mL) was added at room temperature. After 15 min, the mixture was cooled (ice-water), benzyl bromide (1.2 mL, 10.4 mmol) was added and the mixture was allowed to reach room temperature, then left for 4 h. TLC (1:2, ether/hexane) then showed the presence of a faster-running compound. The mixture was cautiously poured into ice-water, and extracted with ether (4×30 mL). The combined extracts were washed with brine, water, and concentrated. Flash chromatography (1:5, ether/hexane) of the residue gave **10** (2.9 g, 85%) as a colourless syrup; $[\alpha]_D^{26}$ −65 (*c* 1); *ν* (neat) 3031 (aromatic), 2110 (N_3), 1382 and 1372 (CMe_2), 736 and 697 cm^{-1} (aromatic). ^1H NMR (300 MHz): *δ* 7.46–7.26 (m, 10H, 2 Ph), 4.93 and 4.57 (2d, 2H, $J=11.5$ Hz, CH_2Ph), 4.80 and 4.75 (2d, 2H, $J=11.4$ Hz, CH_2Ph), 4.01 (dt, 1H, H-5), 3.96 and 3.73 (2d, 2H, $J_{1,1'}=9.3$ Hz, H-1,1′), 3.83 (dd, 1H, $J_{4,5}=9.7$ Hz, H-4), 3.79 (dd, 1H, $J_{5,6eq}=5.5$ Hz, $J_{6ax,6eq}=11.1$ Hz, H-6eq), 3.66 (d, 1H, $J_{3,4}=2.6$ Hz, H-3), 3.49 (t, 1H, $J_{5,6ax}=11.1$ Hz, H-6ax), 1.43 and 1.31 (2s, 6H, CMe_2). ^{13}C NMR: *δ* 137.95, 137.73, 128.65, 128.53, 128.25, 128.12, and 128.06 (Ph), 112.21 (*C*Me_2), 105.21 (C-2), 80.28 (C-3), 76.92 (C-4), 74.70 and 72.96 (*C*H_2Ph), 73.42 (C-1), 62.30 (C-6), 57.98 (C-5), 26.70 and 26.44 (C*Me*$_2$). HRMS: *m*/*z* 448.1842 $[M^+ + Na]$. For $C_{23}H_{27}N_3O_5Na$ 448.1848 (deviation +1.5 ppm).

4.1.6. 5-Azido-3,4-di-*O*-benzyl-5-deoxy-α-L-tagatopyranose (11). A solution of **10** (3.74 g, 8.8 mmol) in 70% aqueous TFA (10 mL) was kept at room temperature for 24 h. TLC (2:1, ether/hexane) then revealed a slower running compound. The mixture was concentrated and repeatedly codistilled with water and then dissolved in dichloromethane, washed with 10% aqueous sodium carbonate and water, then concentrated. Column chromatography (1:5→1:1, ether/hexane) gave pure crystalline **11** (2.62 g, 78%) as α-anomer; mp 83–85 °C; $[\alpha]_D^{25}$ −36 (*c* 0.9); *ν* (KBr) 3386 (OH), 3088 (aromatic), 2106 (N_3), 749 and 699 cm^{-1} (aromatic). ^1H NMR (300 MHz): *δ* 7.45–7.28 (m, 10H, 2 Ph), 4.90 and 4.54 (2d, 2H, $J=11.5$ Hz, CH_2Ph), 4.78 and 4.74 (2d, 2H, $J=11.9$ Hz, CH_2Ph), 4.03 (br dt, 1H, H-5), 3.93 (dd, 1H, $J_{3,4}=2.5$ Hz, $J_{4,5}=10.0$ Hz, H-4), 3.78 (d, 1H, H-3), 3.78 and 3.21 (2d, 2H, $J_{1,1'}=11.6$ Hz, H-1,1′), 3.76 (dd, 1H, $J_{5,6eq}=5.6$ Hz, $J_{6ax,6eq}=11.2$ Hz, H-6eq), 3.55 (t, 1H, $J_{5,6ax}=11.2$ Hz, H-6ax), 3.42 (br s, 1H, OH). ^{13}C NMR (inter alia): *δ* 97.54 (C-2), 79.87 (C-3), 75.17 (C-4), 74.78 and 72.76 (*C*H_2Ph), 66.39 (C-1), 61.91 (C-6), 58.25 (C-5). HRMS: *m*/*z* 408.1540 $[M^+ + Na]$. For $C_{20}H_{23}N_3O_5Na$ 408.1535 (deviation −1.0 ppm).

4.1.7. 5-Azido-3,4-di-*O*-benzyl-5-deoxy-1-*O*-pivaloyl-α-L-tagatopyranose (12). To an ice-water cooled and stirred solution of **11** (0.5 g, 1.3 mmol) in dry Cl_2CH_2 (15 mL) were added TEA (200 μL, 1.5 mmol) and pivaloyl chloride (175 μL, 1.5 mmol) and the mixture was left at room temperature for 5 h. TLC (2:1, ether/hexane) then showed a faster-running compound. MeOH (0.5 mL) was added and after 15 min the reaction mixture was washed with water, then concentrated to a residue that was submitted to flash-chromatography (1:2, ether/hexane) to afford syrupy **12** (535 mg, 88%) as a colourless syrup; $[\alpha]_D^{24}$ −30 (*c* 1); *ν* (neat) 3440 (OH), 3065 (aromatic), 2110 (N_3), 1734 (ester C=O), 734 and 698 cm^{-1} (aromatic). ^1H NMR (300 MHz): *δ* 7.45–7.25 (m, 10H, 2 Ph), 4.92 and 4.56 (2d, 2H, $J=11.0$ Hz, CH_2Ph), 4.79 and 4.72 (2d, 2H, $J=11.5$ Hz, CH_2Ph), 4.39 and 4.02 (2d, 2H, $J_{1,1'}=11.7$ Hz, H-1.1′), 4.01 (dt, 1H, H-5), 3.91 (dd, 1H, $J_{3,4}=2.6$ Hz, $J_{4,5}=9.9$ Hz, H-4), 3.76 (dd, 1H, $J_{5,6eq}=5.5$ Hz, $J_{6ax,6eq}=11.1$ Hz, H-6eq), 3.75 (d, 1H, H-3), 3.58 (t, 1H, $J_{5,6ax}=11.1$ Hz, H-6ax), 3.18 (br s, 1H, HO), and 1.20 (s, 9H, CMe_3). ^{13}C NMR (inter alia): *δ* 179.49 (ester C=O), 97.97 (C-2), 79.52 (C-4), 75.13 and 72.83 (2 *C*H_2Ph), 74.93 (C-3), 65.78 (C-6), 61.81 (C-6), 58.00 (C-5), 39.02 (C*Me*$_3$) and 27.24 (*C*Me_3). HRMS: *m*/*z* 492.2112 $[M^+ + Na]$. For $C_{25}H_{31}N_3O_6Na$ 492.2111 (deviation −0.3 ppm).

4.1.8. Hydrogenation of 12. Compound **12** (1.4 g, 3 mmol) in MeOH (40 mL) was hydrogenated at 60 psi over wet Raney nickel (500 mg, Fluka) for 5 h. TLC (5:1, ether/methanol) then revealed the presence of a slower-running compound. The catalyst was filtered off, washed with MeOH, and the combined filtrate and washings were concentrated to a residue that was submitted to column chromatography (ether→10:1, ether/methanol) to afford syrupy (2*R*,3*S*,4*R*,5*S*)-3,4-dibenzyloxy-2,5-bis(hydroxymethyl)-2′-*O*-pivaloylpyrrolidine (**13**, 680 mg, 53%); $[\alpha]_D^{26}$ −11 (*c* 0.5); *ν* (neat) 3268 (OH, NH), 3064, (aromatic),

1726 (ester C=O), 736 and 698 cm^{-1} (aromatic). ^1H NMR (300 MHz): δ 7.40–7.24 (m, 10H, 2 Ph), 4.76 and 4.63 (2d, 2H, $J=11.2$ Hz, CH_2Ph), 4.69 and 4.56 (2d, 2H, $J=11.8$ Hz, CH_2Ph), 4.31 (dd, 1H, $J_{2,2'a}=6.4$ Hz, $J_{2'a,2'b}=11.1$ Hz, H-2′a), 4.22 (dd, 1H, $J_{2,2'b}=7.0$ Hz, H-2′b), 4.14 (dd, 1H, $J_{3,4}=4.0$ Hz, $J_{4,5}=7.6$ Hz, H-4), 4.01 (t, 1H, $J_{2,3}=4.2$ Hz, H-3), 3.82 (dd, 1H, $J_{5,5'a}=4.5$ Hz, $J_{5'a,5'b}=11.5$ Hz, H-5′a), 3.65 (dd, 1H, $J_{5,5'b}=4.8$ Hz, H-5′b), 3.47 (dt, 1H, H-5), 3.41 (dt, 1H, H-2), 2.35 (br s, 1H, OH), and 1.18 (s, 9H, CMe_3). ^{13}C NMR (inter alia): δ 178.44 (COCMe_3), 81.46 (C-4), 78.36 (C-3), 74.05 and 73.24 (2 CH$_2$Ph), 64.29 (C-2′), 61.64 (C-5′), 58.82 (C-5), 57.69 (C-2), 38.85 (COCMe$_3$), and 27.30 (COCMe_3). HRMS: *m*/*z* 450.2250 [M^++Na] for $C_{25}H_{33}NO_5Na$ 450.2256 (deviation +1.4 ppm).

4.1.9. (2*R*,3*S*,4*R*,5*S*)-3,4-Dibenzyloxy-2,5-bis(hydroxymethyl)pyrrolidine (14). A solution of **13** (680 mg, 1.59 mmol) in anhydrous MeOH (5 mL), was treated with 0.5 M MeONa in the same solvent (0.3 mL) for 6 h at room temperature. TLC (1.5:1, ether/methanol) then showed the presence of a more polar compound. The reaction mixture was concentrated and the residue submitted to column chromatography (5:2, ether/methanol) to yield **14** (330 mg, 61%) as a colourless syrup; ν (neat) 3324 (OH, NH), 3088, 736 and 697 cm^{-1} (aromatic). ^1H NMR (300 MHz): δ 7.38–7.25 (m, 10H, 2 Ph), 4.70 and 4.57 (2d, 4H, $J=11.7$ Hz, 2 CH_2Ph), 4.07 (m, 2H, H-3,4), 3.92 (br s, 2H, OH,NH), 3.86 (dd, 2H, $J_{2,2'a}=J_{5,5'a}=6.0$ Hz, $J_{2'a,2'b}=J_{5'a,5'b}=11.7$ Hz, H-2′a,5′a), 3.71 (dd, 2H, $J_{2,2'b}=J_{5,5'b}=4.7$ Hz, H-2′b,5′b), and 3.38 (br q, 2H, H-2,5). ^{13}C NMR: δ 137.68, 128.64, 128.07, and 127.71 (Ph), 79.85 (C-3,4), 73.64 (2 CH$_2$Ph), 61.33 (C2′,5′), and 59.76 (C-2,5). HMRS: *m*/z 366.1687 [M^++Na] for $C_{20}H_{25}NO_4Na$ 366.1681 (deviation −1.4 ppm).

4.1.10. (2*R*,3*S*,4*R*,5*S*)-3,4-Dihydroxy-2,5-bis(hydroxymethyl)pyrrolidine hydrochloride [2,5-dideoxy-2,5-imino-D-galactitol (DGADP, 15)]. Compound **14** (94 mg, 0.27 mmol) was hydrogenated in MeOH (5 mL) and concd HCl (5 drops) over 10% Pd–C (50 mg) in an H_2 atmosphere overnight. TLC (3:3:0.5, ether/methanol/TEA) then showed the presence of a compound of lower mobility. The catalyst was filtered off, washed with MeOH and the combined filtrate and washings concentrated to a residue that was repeatedly washed with Cl_2CH_2 to yield **15** hydrochloride (30 mg, 56%) as a colourless foam. ^1H NMR (400 MHz, MeOH-d_4): δ 4.37 (br d, 2H, $J=5.0$ Hz, H-3,4), 3.94 (dd, 2H, $J_{2,2'a}=J_{5,5'a}=5.0$ Hz, $J_{2'a,2'b}=J_{5'a,5'b}=11.9$ Hz H-2′a,5′a), 3.89 (dd, 2H, $J_{2,2'b}=J_{5,5'b}=8.2$ Hz, H-2′b,5′b), and 3.65 (m, 2H, H-2,5). ^{13}C NMR: δ 71.57 (C-3,4), 63.22 (C-2,5), and 59.29 (C-2′,5′). Lit.[7] ^1H NMR (500 MHz, D_2O): δ 3.76–3.81 (m, 2H), 3.92 (dd, 2H, $J=8.8$, 12.2 Hz), 4.01 (dd, 2H, $J=4.9$, 12.2 Hz), 4.51 (d, $J=4.9$ Hz). ^{13}C NMR: δ 60.66, 64.30, 72.86.

Acknowledgements

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Cyclization versus oligomerization of S_P- and R_P-5′-OH-N^4-benzoyl-2′-deoxycytidine-3′-*O*-(2-thio-4,4-pentamethylene-1,3,2-oxathiaphospholane)s

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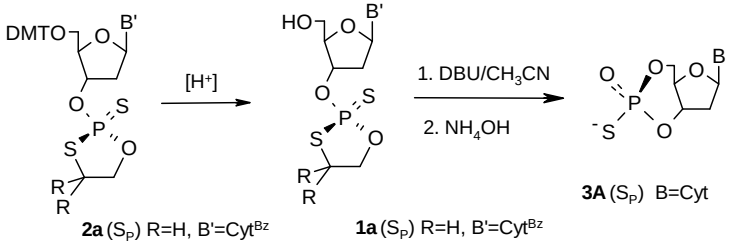
Dedicated to Professor David Shugar on the occasion of his 80th birthday

Abstract—The S_P-isomer of 5′-OH-N^4-benzoyl-2′-deoxycytidine-3′-*O*-(2-thio-4,4-pentamethylene-1,3,2-oxathiaphospholane) undergoes DBU-promoted intramolecular cyclization providing as a sole product S_P-deoxycytidine cyclic 3′,5′-*O*,*O*-phosphorothioate. Unexpectedly, the R_P-counterpart yields a mixture of products consisting of R_P-deoxycytidine cyclic 3′,5′-*O*,*O*-phosphorothioate and macrocyclic oligo(deoxycytidine phosphorothioate)s. The results of molecular modeling indicate that the dychotomy observed for the R_P substrate may result from remarkably higher energy of the corresponding transition states, caused by the presence of bulky 'spiro' pentamethylene substituent at the position C4 in the oxathiaphospholane ring.

1. Introduction

Nucleoside cyclic 3′,5′-*O*,*O*-phosphorothioates[1] (cNMPS, **3**, Scheme 1) are valuable tools for studying the mechanism of action of enzymes involved in the metabolism of cyclic nucleotides and are potent agonists or antagonists of the latter compounds. Due to assymetry of the phosphorus atom, cNMPS exist in the form of S_P and R_P diastereomers, which usually have markedly different biological properties.[1,2] The first reported synthesis of cNMPS involved cyclization of nucleoside 5′-*O*-(bis(4-nitrophenyl)phosphorothioate)s under treatment with *t*-BuOK in DMF, followed by hydrolytic removal of the remaining 4-nitrophenoxyl group. The resulting cNMPS were then chromatographically separated into individual diastereomers.[3] Reported to date stereocontrolled methods of synthesis of R_P- or S_P-cNMPS rely upon preparation of appropriately protected diastereomerically pure nucleoside cyclic 3′,5′-*O*,*O*-phosphoranilidates or phosphoranilidothioates and their stereoretentive conversion into corresponding



Scheme 1.

Keywords: Cyclic oligonucleotides; Phosphorothioate analogues of DNA; Oxathiaphospholane method.
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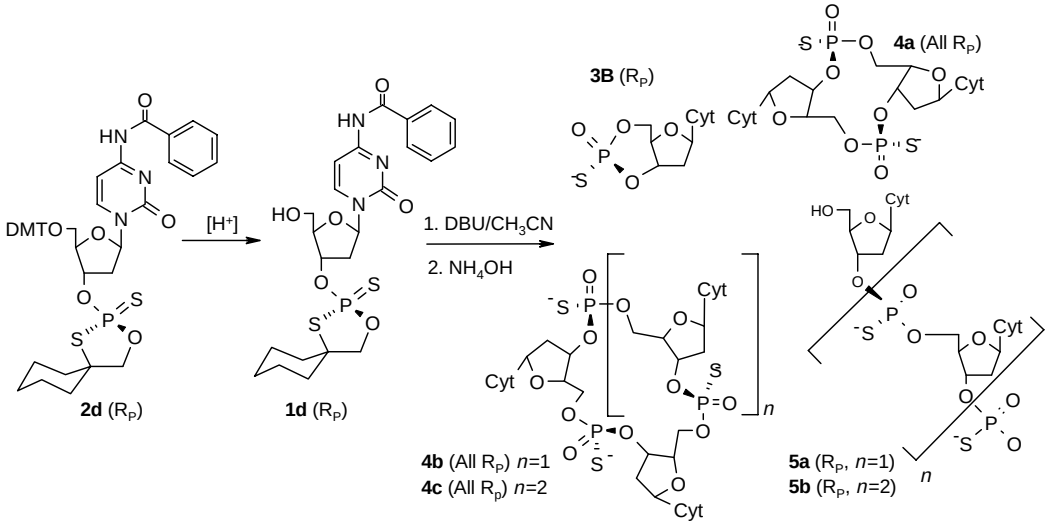


Scheme 2.

phosphorothioates using NaH/CS_2 or NaH/CO_2, respectively.[4] Here we describe highly efficient synthesis of S_P- and R_P-deoxycytidine cyclic 3′,5′-*O*-*O*-phosphorothioates (**3A** and **3B**, B = Cyt) in a stereospecific manner by oxathiaphospholane approach, as well as unexpected formation of stereodefined macrocyclic and linear oligonucleotides of general formula **4** and **5**, respectively (see Scheme 2). The macrocyclic oligo(deoxycytidine phosphorothioate)s **4** belong to the family of circular oligonucleotides, possessing interesting DNA, RNA, and protein binding properties and potential therapeutic applications.[5] To the best of our knowledge, the only two published examples of stereodefined macrocyclic phosphorothioate oligonucleotides were chimeric R_P-, and S_P-cyclic diribonucleotide c($G_{PS}G_{PO}$), which can be considered the analogues of cyclic diguanylic acid involved in regulatory system of cellulose synthesis in *Acetobacter xylinum*,[6] and R_P,R_P- and S_P,R_P-cyclic di(deoxycytidine phosphorothioate)s obtained by Battistini et al.[7]

2. Results and discussion

In the oxathiaphospholane method, which was originally designed for the stereocontrolled synthesis of oligo(nucleoside phosphorothioate)s, chromatographically separated P-diastereomers of 5′-*O*-DMT-nucleoside-3′-*O*-(2-thio-1,3,2-oxathiaphospholane)s (**2a**,**b**, R = H) and their ring-substituted analogues (**2c**,**d**, R,R = –$(CH_2)_5$–) are used.[8] Their reaction with 5′-OH-nucleoside component (usually performed in CH_3CN solution in the presence of strong non-nucleophilic base, preferably DBU), proceeds according to the adjacent type mechanism, where pseudorotation of a P^V intermediate (such a process is marked with Ψ in Scheme 1S, Supplementary data) results in retention of configuration at the phosphorus atom.[8c,9] We anticipated that diastereomerically pure oxathiaphospholane substrates after acidolytic removal of the 5′-*O*-dimethoxytrityl protecting group may undergo a DBU-promoted intramolecular reaction in analogous stereospecific manner to give the desired cNMPS (see Scheme 1). Notably, intramolecular ring-opening reactions of oxathiaphospholanes were not reported in the literature, albeit it was known from our earlier work that structurally related N^6-benzoyl-2′-*O*-tetrahydropyranyl-adenosine-5′-*O*-(2-thio-1,3,2-dithiaphospholane) can be effectively transformed into adenosine cyclic 3′,5′-*O*,*O*-phosphorodithioate via intramolecular cyclization by treatment with *t*-BuOK in DMF solution, followed by removal of protecting groups.[4d] As model compounds we chose diastereomerically pure S_P- and R_P-N^4-benzoyl-deoxycytidine-3′-*O*-(2-thio-1,3,2-oxathiaphospholane)s (**1a** and **1b**, respectively, $B = Cyt^{Bz}$, R = H), which were prepared from chromatographically separated S_P- and R_P-5′-*O*-DMT-precursors **2a** and **2b**, by treatment with *p*-toluenesulfonic acid in methylene chloride. The reactions of **1a** and **1b** were performed on a 66 μmol scale by addition of equimolar amount of DBU into magnetically stirred solutions of the substrates in anhydrous acetonitrile. After 5 min at room temperature ^{31}P NMR spectra showed quantitative formation of single products. After ammoniacal deprotection these products were identified by ^{31}P NMR and HPLC comparison with genuine sample,[4d] as S_P- and R_P-deoxycytidine cyclic 3′,5′-*O*,*O*-phosphorothioate (**3A** and **3B**). Thus, the reaction of intramolecular cyclization occurred with retention of configuration at phosphorus, most likely by the mentioned earlier adjacent mechanism.

The results obtained for **1a** and **1b** fulfilled our expectations, but for practical reasons we intended to use their ‘spiro’ analogues possessing 4,4-pentamethylene substituent in the oxathiaphospholane ring (**1c** and **1d**, $B = Cyt^{Bz}$, R,R = –$(CH_2)_5$–), which were known for considerably better chromatographic properties of their precursors **2c** and **2d** in respect to their separation into pure P-diastereoisomers.[8d] The reactions of diastereoisomerically pure S_P-**1c** and R_P-**1d** (obtained by detritylation of **2c** and **2d**, respectively) were performed exactly as for **1a**,**b**. While the S_P-substrate yielded the expected cyclic 3′,5′-*O*,*O*-phosphorothioate **3A** virtually quantitatively, the R_P-counterpart provided a mixture of products with several resonances (difficult for precise integration) within a range 55–57 ppm in a ^{31}P NMR spectrum. After ammoniacal deprotection the products were separated by RP HPLC and identified by MALDI-TOF MS (see Table 1). Approximate quantification of their distribution, expressed as percentage of the consumption of

Table 1. Identification and quantification of HPLC-separated products of cyclization/oligomerization of R_P-**1d** (DBU/CH_3CN procedure)

Compounds	HPLC t_R (min)[a]	Content (%)[b]	Molecular weight[c]	^{31}P NMR δ (ppm)
3B	10.61	41.8	304/305.3	55.23
4a	21.40	26.3	609/610.5	54.68
4b	26.39	20.1	915/915.8	55.76
4c	22.97	6.1	1222/1221.0	55.79
4d	23.45	1.7	1526/1526.3	ND[d]
4e	24.52	1.1	1833/1831.5	ND[d]
5a	14.27	1.7	627/628.5	ND[d]
5b	18.33	1.2	933/933.8	ND[d]

[a] HPLC was performed using Econosphere C_{18} (5 μ) 4.6×250 mm column (Alltech) with a linear gradient of acetonitrile in 0.1 M TEAB: 0–20 min—0.5%/min; 20–32 min—0.3%/min; flow 1 mL/min.
[b] Calculated from electronically integrated chromatograms (UV detection at 255 nm).
[c] Calculated/measured *m/z*; by MALDI-TOF MS, negative ion mode (Voyager™ Elite), calculated for free acids (Da).
[d] Not determined.

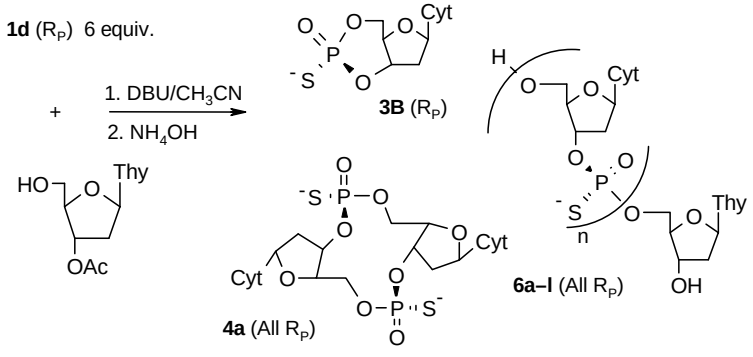
Table 2. HPLC-separation and identification of products of cyclization/oligomerization of R_P-**1d** in the presence of 3′-*O*-acetylthymidine

Compounds	HPLC t_R (min)[a]	Quantity of products[b]	Molecular weight	
			Measured[c]	Calculated[d]
3B	12.42	30.5	304.1	305.25
4a	30.84	15.1	610.0	610.50
6a ($n=1$)	26.00	13.0	546.9	547.48
6b ($n=2$)	31.44	18.0	852.3	852.73
6c ($n=3$)	35.30	7.9	1157.8	1157.98
6d ($n=4$)	38.44	16.1	1463.1	1463.20
6e ($n=5$)	41.12	3.9	1768.0	1768.49
6f ($n=6$)	43.33	3.0	2073.2	2073.70
6g ($n=7$)	45.26	2.1	2378.5	2378.95
6h ($n=8$)	47.01	1.5	2683.5	2684.20
6i ($n=9$)	48.61	1.1	2989.9	2989.45
6j ($n=10$)	50.22	1.0	3293.1	3294.70
6k ($n=11$)	51.82	1.0	3599.2	3599.95
6l ($n=12$)	53.20	0.8	3903.6	3905.20

[a] HPLC was performed using PTH C_{18} (5 μ) 2.1×220 mm column (Brownlee) with a linear gradient of acetonitrile in 0.1 M TEAB: 0–60 min—0.47%/min; flow 0.3 mL/min (UV detection at 255 nm).
[b] Given in optical density (measured at 260 nm).
[c] *m/z*; Measured by MALDI-TOF MS (Voyager™ Elite).
[d] Calculated for free acids (Da).

the starting material **1d**, was accomplished by integration of peaks in the HPLC profile. The inspection of the data (listed in Table 1) reveals that the main product of self-condensation of **1d** (41.8% conversion of the starting material) was R_P-deoxycytidine cyclic 3′,5′-*O*,*O*-phosphorothioate (**3B**) as proved by MALDI-TOF MS, HPLC and ^{31}P NMR. In addition to **3B**, several oligomeric products were identified, including macrocyclic (**4a–e**) and linear oligo(deoxycytidine phosphorothioate)s (**5a**,**b**) (see Scheme 2). Obviously, expected highly favorable entropy of intramolecular cyclization did not assure full regioselectivity. The major macrocyclic products include those containing two (**4a**, 26.3% of total UV absorption), three (**4b**, 20.1%) and four deoxycytidine phosphorothioate units (**4c**, 6.1%). Minor products containing five (**4d**, 1.7%) and six units in macrocyclic ring (**4e**, 1.1%) were also identified. In fact, the formation of 'macrocyclic' fraction consumed over 55% of the oxathiaphospholane substrate. The formation of macrocyclic products **4** can be explained by conversion of substrate **1d** into corresponding linear oligomers (all with the oxathiaphospholane function at the 3′-end) followed by their inter- or intramolecular cyclization. In addition to the macrocyclic products, two minor linear products were isolated and identified by HPLC/MS as 3′-*O*-phosphorothioylated dinucleotide (**5a**, 1.7%) and trinucleotide (**5b**, 1.2%) (see Table 1 and Scheme 2). It seems reasonable to assume that the 3′-terminal oxathiaphospholane function was hydrolyzed with traces of moisture yielding inert phophorothioate group in **5a**,**b**. Similar results were obtained when a N^2-isobutyryl-deoxyguanosine 3′-*O*-(2-thio-'spiro'-4,4-pentamethylene-1,3,2-oxathiaphospholane) (a mixture of P-diastereoisomers ca. 1:1) was a substrate for DBU-promoted cyclization. After ammoniacal deprotection the obtained mixture was analyzed by ^{31}P NMR (in D_2O) showing the presence of four major products: S_P-deoxyguanosine cyclic 3′,5′-*O*,*O*-phosphorothioate[4c] (δ 52.8 ppm, 50% of total integral), its R_P-epimer (δ 54.6 ppm, 16%), deoxyguanosine analogue of 'dimeric' compound **4a** (δ 55.2 ppm, 12%), and deoxyguanosine 3′-*O*-phosphorothioate (δ 47.4 ppm, 5%). These products were separated on HPLC and their structures were confirmed by MALDI-TOF MS analysis.

The observed predominant formation of macrocyclic oligo(deoxycytidine phosphorothioate)s **4a–e** prompted us to perform the reaction in the presence of limited amount of 3′-*O*-acetylthymidine (1/6 mol equiv) acting as a '3′-end forming unit' to prevent 'macrocyclization' and facilitate the formation of linear products. The deprotected products were isolated by RP HPLC, quantified by UV absorption at 260 nm and identified by MALDI-TOF MS (Table 2, Scheme 3). It was found, that although the main product of the reaction was R_P-cyclic nucleotide **3B** (26.6% of total UV absorption) and among other prominent products



Scheme 3.

macrocyclic dimer **4a** was identified (13.1%), the major fraction of the products (60.3%) consisted of a mixture of linear phosphorothioate oligonucleotides **6a–l** ranging from 2 to 13 nucleotides in length and containing thymidine at the 3′-terminus. The trimer **6b** (15.7%), pentamer **6d** (14.0%), and dimer **6a** (11.3%) were most abundant, whereas each of those containing 8 or more nucleotides in the chain constituted less than 2% of the mixture of products.

The autoradiogram for PAGE analysis of compounds enzymatically radiolabeled with [^{32}P]phosphate group (Fig. 1) showed the expected pattern of bands of oligonucleotides **6a–l** and the lack of radioactive label in macrocyclic dinucleotide **4a**. The 5′-radiolabeled heptamer

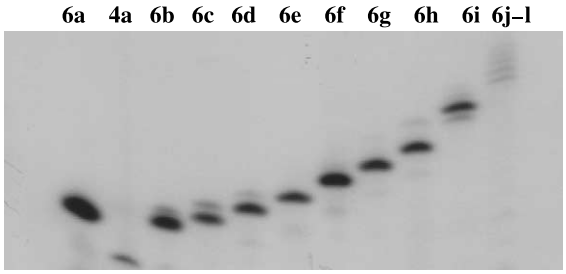
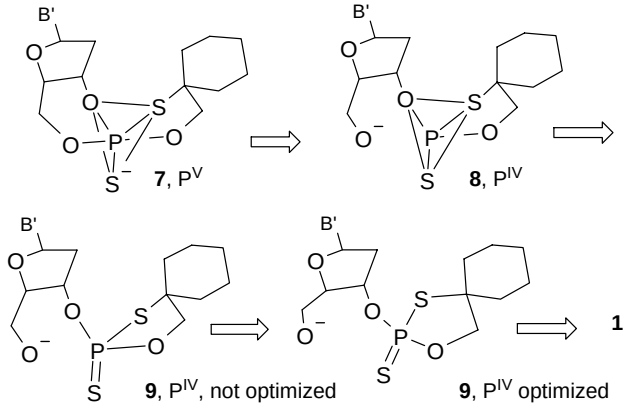


Figure 1. PAGE analysis (20% polyacrylamide/7 M urea) of HPLC-separated and ^{32}P-labeled products **6a–l** of DBU-promoted self-condensation of **1d** performed in the presence of ca. 1/6 mol equiv of 3′-*O*-acetylthymidine.



Scheme 4.

6f (0.1 OD_{260}) was treated with R_P-specific snake venom phosphodiesterase (svPDE)[10] and S_P-specific nuclease P1 (*n*P1).[11] It was found that **6f** was completely degraded on 10 min incubation with 50 μg of svPDE at 37 °C, whereas no degradation was observed after 2 h incubation of identical sample of **6f** with 1 μg of *n*P1 at room temperature. These results confirm that DBU-promoted self-condensation of R_P-oxathiaphospholane **1d** leads to homochiral oligomeric products **6a–l** with R_P-configuration at each internucleotide bond. Undoubtedly, the same absolute configuration must be assigned to phosphorus atoms in the macrocyclic compounds **4**. Notably, although it is known, that nucleases present in 50% human serum are able to hydrolyze phosphorothioate oligonucleotides of R_P-configuration,[12] using RP HPLC technique we found that both tested cyclic oligomers **4a** and **4b** were stable under these conditions for more than 24 h (data not shown).

Analysis of the mechanistic aspects of the condensation suggests that the observed intermolecular oligomerization or macrocyclization might successfully compete with entropically favored intramolecular cyclization for **1d** provided that the latter process was significantly slowed-down. This may happen due to higher energy barrier for the transition of **1d** to the corresponding P^V intermediate product **7** (Scheme 4). Conformational search (HyperChem 7.5 package, parameter set Amber99, HyperCube, Inc.) done for four P^V intermediates **7a–d**, derived from **1a–d**, respectively, showed that the pentacoordinate intermediates **7** adopt two basic structures with the 1,3,2-dioxaphosphorinane ring in either energetically favored chair conformation, or disfavored boat conformation. The numbering of atoms in **7**, a list of torsion angles varied during the search and the geometrical restraints imposed on bonds around P-atom in **7** are shown on Figure 2. Negative charge was assigned to the equatorial sulfur atom (S35). The obtained structures were analyzed in respect to the absolute configuration of the starting **1** and the relevant energies and torsion angles for those resulting from S_P-**1c** and R_P-**1d** are collected in Tables 1S and 2S, respectively (Supplementary data). Then, within the sets of the lowest energy conformers of **7a–b** (#1–33, in a range of 150.0–158.9 kcal/mol) and **7c–d** (#1–28, 157.0–164.4 kcal/mol, see Tables 1S and 2S) the apical bonds P–$O^{5'}$ were cleaved and geometries of the resulting molecules were optimized in two steps, that is, with geometrical restraints for P^V atom either kept (**8**) or

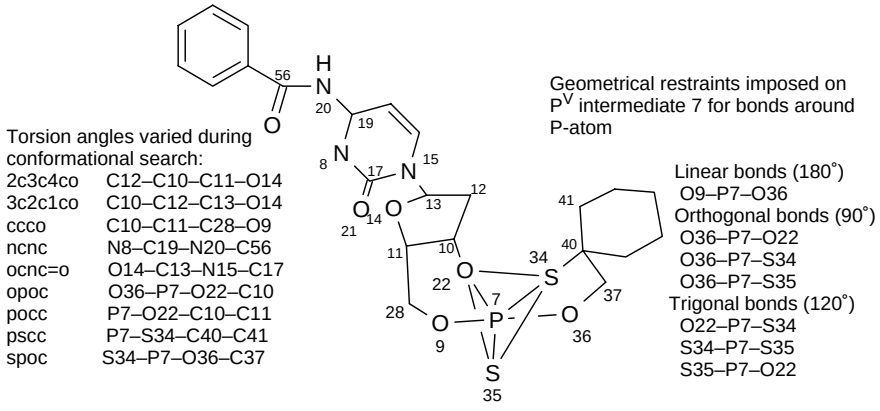


Figure 2. The numbering of atoms in **7**, a list of torsion angles varied during the conformational search and the geometrical restraints imposed on bonds around the P-atom.

released (**9**), giving on this 'retro' way information about relative energies of the structures **8** resembling corresponding transition states. Subsequent analysis of the profiles **1a**,**b**→**9**→**8a**,**b**→**7a**,**b** showed no significant differences in the energy barrier for both diastereomers. This finding corresponds with quantitative conversion of both P-diastereomeric substrates **1a** and **1b** into cyclic 3′,5′-*O*,*O*-phosphorothioates. Interestingly, among the profiles **1c**,**d**→**9**→**8c**,**d**→**7c**,**d** a very favorable profile was found for one of the chair conformers of **7c** (#5) with the energy barrier for its formation by 9.2 kcal/mol lower than for its **7d** counterpart (#4). The structures **7c**, #5 and **7d**, #4 are shown on Figures 1S and 2S, respectively, and related to them structures **8c**,**d** on Figure 3. Notably, in a case of **8d** we observed repulsion interactions along a narrow groove, indicated with the red arrow. This steric hindrance may result in higher energy barrier leading to the formation of **7d**. The calculated energy profiles for the intermediates formed from **1c** and **1d** during cyclization are shown on Figures 3S and 4S, respectively. Comparison of the lowest energy profiles for the cyclization **1c**,**d**→**9**→**8c**,**d**→**7c**,**d**, each ending with **7** adopting either the boat or chair conformations of the dioxaphosphorinane ring, is shown on Figure 4, while relevant energy values are collected in Tables 3S and 4S. Since the conformational search for R_P- and S_P-isomers of anionic **1** (it was assumed that DBU devoided the reacting substrate of 5′-OH proton) showed that for both pairs of diastereomers the energies of conformers suitable for cyclization are within 1 kcal/mol of those of the lowest energy (Tables 5S and 6S), apparently, a conformation of the substrate molecules is not a decisive factor in the problem under consideration.

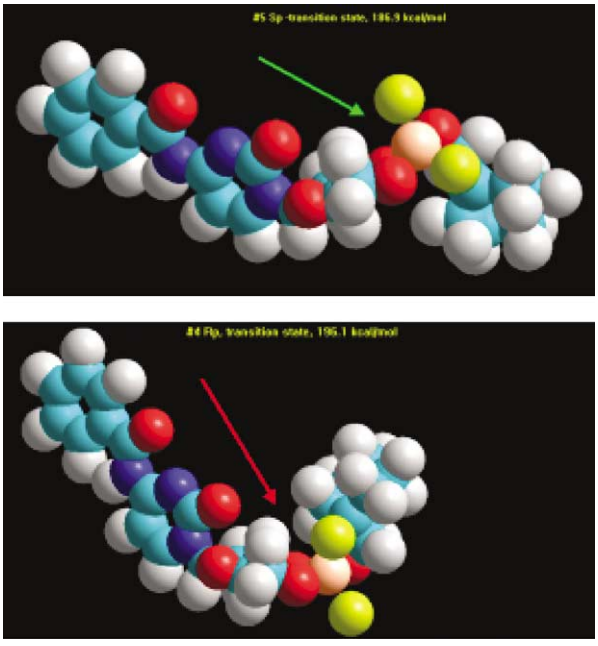


Figure 3. The calculated lowest energy barrier conformations of P^{IV}-intermediate **8c** (upper panel) and **8d** (bottom panel) formed during cyclization **1c**,**d**→**9**→**8c**,**d**→**7c**,**d** with the chair conformation of the 1,3,2-dioxaphosphorinane ring. The geometrical restraints present in **7c**,**d** were kept during geometry optimization. The green and red arrows indicate the grooves without and with repulsion interactions, respectively. Assignment of colors: hydrogen—white, carbon—blue, nitrogen—dark blue, oxygen—red, sulfur—yellow, phosphorus—pink.

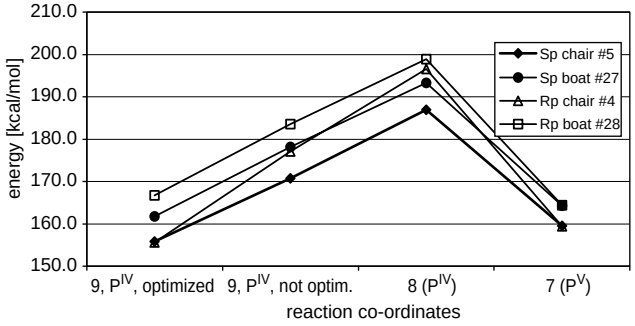


Figure 4. Comparison of the calculated profiles with the lowest energy barrier (for structures **8c**,**d** adopting either the chair or boat conformation of the dioxaphosphorinane ring) during the cyclization **1c**,**d**→**9**→**8c**,**d**→**7c**,**d**.

Although performed calculation does not reflect interactions with solvent molecules nor with DBU activator, these numbers suggest that despite of strong entropy factor facilitating intramolecular reaction, due to remarkably higher energy barrier **1**→**9**→**8** the cyclization of **1d** is slowed-down, compared to **1c**, and intermolecular reaction leads to linearized products.

3. Conclusions

The DBU-promoted intramolecular cyclization of diastereomerically pure S_P- and R_P-isomers of 5′-OH-N^4-benzoyl-2′-deoxycytidine-3′-*O*-(2-thio-1,3,2-oxathiaphospholane) provides quantitatively corresponding S_P- and R_P-deoxycytidine cyclic 3′,5′-*O*,*O*-phosphorothioate, respectively. The same applies to the S_P-isomer of 5′-OH-N^4-benzoyl-2′-deoxycytidine-3′-*O*-(2-thio-4,4-pentamethylene-1,3,2-oxathiaphospholane), while its R_P-counterpart yields a mixture of products consisting of R_P-deoxycytidine cyclic 3′,5′-*O*,*O*-phosphorothioate and macrocyclic oligo(deoxycytidine phosphorothioate)s. This difference can be explained in terms of steric hindrance (caused by bulky pentamethylene substituent) observed during formation of first pentacoordinate intermediate, which slows- down the intramolecular process and allows the intermolecular macrocyclization to compete. Similar dychotomy was observed for cyclization of deoxyguanosine derivatives. This approach is suitable for synthesis of stereodefined macrocyclic oligonucleotides—the analogues of cyclic diguanylic acid involved in regulatory system of cellulose synthesis in *A. xylinum*.

4. Experimental

4.1. General

4.1.1. 5′-*O*-DMT-N^4-benzoyl-deoxycytidine-3′-*O*-(2-thio-1,3,2-oxathiaphospholane) (2a,b, B=Cyt^{Bz}, R=H). The title compound was synthesized and separated into pure P-diastereomers (by ^{31}P NMR and TLC) as described.[8b]

4.1.2. 5′-*O*-DMT-N^4-benzoyl-deoxycytidine-3′-*O*-(2-thio-4,4-pentamethylene-1,3,2-oxathiaphospholane) (2c,d, B=Cyt^{Bz}, R=–(CH$_2$)$_5$–). The title compound was synthesized and separated into pure P-diastereomers (diastereomeric purity assessed by ^{31}P NMR and TLC) as described.[8d]

4.1.3. 5′-*O*-DMT-N^2-isobutyryl-deoxyguanosine 3′-*O*-(2-thio-'spiro'-4,4-pentamethylene-1,3,2-oxathiaphospholane). The title compound was synthesized as described.[8d]

4.1.4. S_P-N^4-benzoyl-deoxycytidine-3′-*O*-(2-thio-1,3,2-oxathiaphospholane)s (1a, B = Cyt^{Bz}, R = H). Into the solution of fast-5′-*O*-DMT-N^4-benzoyl-deoxycytidine-3′-*O*-(2-thio-1,3,2-oxathiaphospholane) (110 mg, 0.14 mmol) in methylene chloride (30 mL), *p*-toluenesulfonic acid monohydrate (120 mg, 0.66 mmol) was added with stirring at room temperature. The reaction progress was monitored by TLC (silica gel, chloroform/methanol 9:1 v/v, R_f substrate 0.78; R_f product 0.45). After 40 min, the reaction mixture was concentrated and the oil residue was applied on a silica gel column (20×100 mm, silica gel 60, 230–400 mesh, Merck). The column was eluted with a gradient of chloroform/2-propanol 100:0→50:50. Appropriate fractions were collected and evaporated to dryness to yield **1a** (35 mg, 0.075 mmol, 53%). δ ^{31}P NMR 104.11 ppm (CD_3CN). Compounds **1b**, **1c** and **1d** were obtained in analogous way.

4.1.5. The intramolecular cyclization reaction of 1a. Into the solution of fast-N^4-benzoyl-deoxycytidine-3′-*O*-(2-thio-1,3,2-oxathiaphospholane) (31 mg, 0.066 mmol) in anhydrous acetonitrile (0.3 mL) equimolar amount of DBU (10 μL) was added. After 5 min at room temperature the reaction mixture was diluted with CD_3CN (0.3 mL) and ^{31}P NMR spectra showed quantitative formation of single product resonating at δ 51.5 ppm (CD_3CN). After removal of the benzoyl protecting groups (treatment with 30% aqueous ammonia at 55 °C for 16 h) the product was identified by ^{31}P NMR and HPLC comparison with genuine sample,[4d] as S_P-deoxycytidine cyclic 3′,5′-*O*,*O*-phosphorothioate (**3A**). Its structure was also confirmed by FAB MS (*m*/*z* 304.1 (negative ions); calculated M_W 305.25 (free acid)). The cyclization of **1b**, **1c** and **1d** was performed in analogous way. For **1b** and **1c** single products were observed, while for **1d** several resonances were found within a range 55–57 ppm.

4.1.6. The condensation reaction of 1d in the presence of 3′-*O*-acetylthymidine. A solution of **1d** (70 mg, 130 μmol) and 3′-*O*-acetylthymidine (6 mg, 21 μmol) in anhydrous acetonitrile (0.4 mL) was treated, with stirring at room temperature, with DBU (22 μL, 145 μmol). After 7 min the reaction mixture was diluted with CD_3CN (0.3 mL) and ^{31}P NMR showed several peaks within 56–58 ppm range. The deprotected products (treatment with 30% aqueous ammonia at 55 °C for 16 h) were isolated by preparative RP HPLC (PTH C_{18}, 5 μ, 2.1×220 mm column (Brownlee) with a linear gradient of acetonitrile in 0.1 M TEAB: 0–60 min—0.47%/min; flow 0.3 mL/min (UV detection at 255 nm)), quantified by UV absorption at 260 nm and identified by MALDI-TOF MS.

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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.2005.12.022. Text containing detailed description of molecular modeling performed; Scheme 1S—mechanism of oxathiaphospholane ring-opening cyclization; Tables 1S, 2S—torsion angles found for 28 lowest energy conformers of P^V intermediate **7c**,**d** formed from **1c**,**d**; Figures 1S, 2S—the #4 and #5 conformations of P^V-intermediates **7**; Figures 3S, 4S—the energy profiles for intermediates formed from **1c**,**d** during cyclization **1**→**9**→**8**→**7**; Tables 3S, 4S—energies calculated for intermediates **8** and **9** leading to lowest energy conformers of **7c**,**d** derived from **1c**,**d**; Tables 5S, 6S—energies and torsion angles found in conformational search for ten lowest energy conformers of anionic form of **1c**,**d**.

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Influence of an 8-trifluoroacetyl group on flavanol couplings

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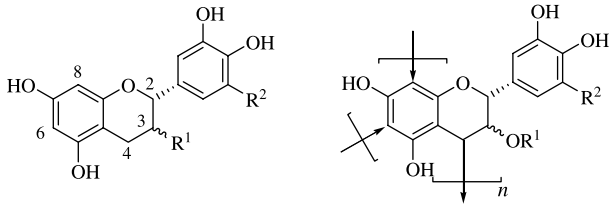
Abstract—The effect of an electron attracting substituent in the Lewis acid catalyzed oligomerization of flavanols was investigated. The results showed that the presence of a $COCF_3$, at the 8 position of a (+)-catechin unit strongly influenced the attack of the 6 free nucleophile flavanol position by the electrophile generated from a 4-*O*-alkyloxy protected catechin unit. This was observed either with $TiCl_4$ or TMSOTf as Lewis acids in which the carbon–carbon bond formation was inhibited and the corresponding dimer was detected in small amount. On the contrary, the formation of a carbon–oxygen bond was observed and the corresponding C-4→*O*→C-3 ether linked procyanidin dimer was isolated in a good yield. In order to avoid the participation of the C-3 hydroxyl group in the dimerization reaction, the two flavanol units were forced into C-4→C-8 coupling by use of an internal link. The structural elucidation of the isolated compounds was achieved through MS and NMR spectroscopy.

1. Introduction

Proanthocyanidins (condensed tannins) are a class of bioactive polyphenolic natural compounds found in a variety of plant foods and beverages. They have been attributed numerous therapeutic properties and many clinical researches suggest that their pronounced biological activities might prevent age-related chronic diseases, cancers and heart diseases.[1–3] These beneficial health effects have led to several investigations on their chemical structures and have initiated a number of synthetic efforts to access condensed tannins.[4–12] Proanthocyanidins are generally mixtures of oligomers and polymers of flavan-3-ol units, linked either through carbon–carbon and/or carbon–oxygen bonds. The most encountered flavan-3-ols involved in proanthocyanidin formation are derived from catechin **1a**, epicatechin **1b**, gallocatechin **1c**, or epigallocatechin **1d** (Fig. 1). The synthesis of proanthocyanidins **2** is generally achieved by coupling the C-4 of an electrophilic flavanyl unit to a C-6/C-8 of a nucleophilic flavanyl unit. The nucleophilicity of the aromatic A ring may play a crucial role in these coupling reactions during which a new bond is established between the C-4 position of the electrophile and the C-6/C-8 of the nucleophile unit.



1a: R^1 = α-OH, R^2=H catechin
1b: R^1 = β-OH, R^2=H epicatechin
1c: R^1 = α-OH, R^2=OH gallocatechin
1d: R^1 = β-OH, R^2=OH epigallocatechin

2: *n*=2 to >100
R^1=H, G alloyl
R^2=H, OH

Figure 1. Structures of flavan-3-ols monomers (**1a**–**1d**) and oligo/polymers (**2**).

The stability of proanthocyanidins is primarily dependent on that of this newly established linkage, which is sensitive to acidic and alkalinic conditions and might a priori also be influenced by the type of flavanol unit. Additionally, the reactivity of the electrophilic/nucleophilic species involved in the coupling reaction could also be influenced by the flavanol types. While the synthesis of proanthocyanidins from natural flavanols is well documented,[4–12] little is known about the effect of an A ring substitution on the reactivity of a flavanol unit involved either as nucleophilic or electrophilic species during the coupling reaction and its impact on the proanthocyanidin synthesis course.[13] In an ongoing program directed to the synthesis of modified proanthocyanidins, we described the preparation of modified catechin derivatives involving introduction of substituents either at C-6 and/or C-8 positions.[14,15] In this paper, we report the results dealing with

Keywords: Flavanol; C–C coupling; Dimerization; Substituent effects; Lewis acids; Regioselectivity.
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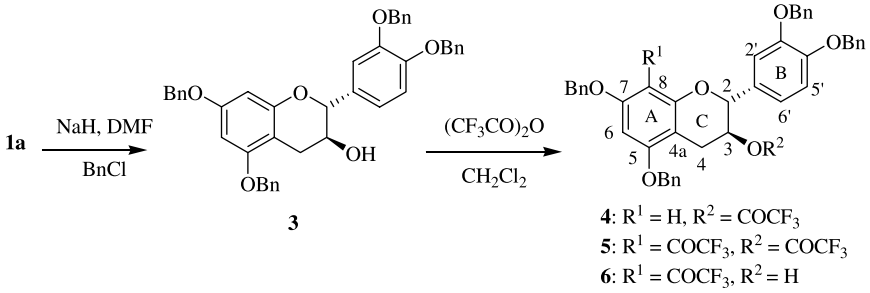


Scheme 1. Formation of tetrabenzylated trifluroacylated catechin derivatives **4**, **5**, **6**.

the effect of an electron deficient substituent linked to the C-8 position of a flavanol subunit on the Lewis acid catalyzed dimerisation of flavanols and offer new information on the reactivity of modified flavanols during such coupling reactions.

2. Results and discussion

2.1. Synthesis of modified flavanols

In the course of a program dealing with the synthesis and the reactivity of modified condensed tannins, we started an investigation on the synthesis of new procyanidin derivatives with modified monomeric subunits derived from catechin. Our objectives were to explore the impact of the A ring substitution on the course of Lewis acid catalyzed classic procyanidin formation reaction. For this study, the 8-trifluoroacetyltetrabenzyloxycatechin **6** was used as the electrophile acceptor in coupling reactions with a C-4 activated catechin derivative. Compound **6** was prepared by action of trifluoacetic anhydride on tetrabenzylated catechin **3** according to Scheme 1. During this reaction, the trifluoroacylation occurred first at the 3-OH giving the ester **4**. Compound **5** was then formed following a Friedel–Craft's reaction on the 8 nucleophile position. Hydrolysis of compound **5** gave the target product **6** with a yield of 64%. The structures of the three trifluoroacylated derivatives **4**, **5** and **6** were determined through UV, MS and NMR spectroscopy. Structure elucidation of compound **6**, which was used in the synthesis described below, was initiated by UV spectroscopy, which showed, in addition to the usual 280 nm flavan-3-ols maximum, another maximum located around 300 nm more probably due to the presence of the $COCF_3$ group. Its ESMS spectrum recorded in the positive ion mode showed signals located at *m/z*: 747, 764 and 769 amu corresponding to $[M+H]^+$, $[M+NH_4]^+$ and $[M+Na]^+$ ions, respectively, and indicating a molecular weight of 746 amu in agreement with the structure of compound **6**. The usual flavan-3-ols characteristic RDA fragmentation was also observed at *m/z*: 415 amu, $[M+H-332]^+$ ion and corresponding to the protonated A moiety (Fig. 2).

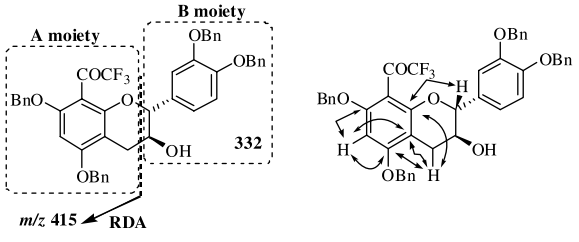


Figure 2. Main fragmentations and ^1H–^{13}C long range characteristic correlations observed for compound **6**.

The position of the $COCF_3$ group on the aromatic A ring was elucidated by 2D NMR HMBC analysis. The usual pyran ring protons H-4 (2.67 and 3.08 ppm), H3 (3.95 ppm) and H-2 (4.78 ppm) were easily assigned by ^1H NMR analysis. The three B ring protons were observed between 6.89 and 7.01 ppm. For the aromatic A ring, only one proton signal appearing as a singlet at 6.28 ppm was present indicating a monosubstitution. The presence of the $COCF_3$ group was confirmed through ^{13}C NMR analysis showing a quartet at 184.31 ppm and corresponding to the carbonyl group. The protonated carbon chemical shifts were assigned through NMR DEPT analysis.

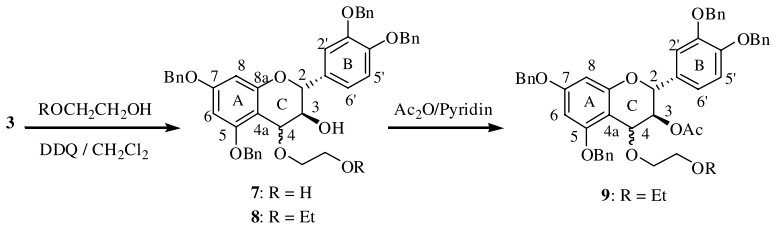
The definitive structure elucidation of compound **6** was achieved by HMBC experiment, which allowed assignment of all hydrogen and carbon atoms. In addition to their correlations with C-2 (81.94 ppm) and C-3 (67.63 ppm), H-4 protons (2.67 and 3.08 ppm) correlated with 3 carbons located at 103.19, 154.18 and 157.77 ppm. Carbons C-4a, C-8a and C-5 are in a favorable position to give such correlations. The signal observed at 103.19 ppm was attributed to C-4a due to its chemical shift position compared to C-8a and C-5, which are linked to an oxygen atom. The carbon signal located at 154.18 ppm also gave a correlation with H-2, which pointed to the C-8a carbon and thus the remaining signal observed at 157.77 ppm was attributed to C-5. The C-8a signal thus attributed did not show any correlation with the residual A ring aromatic protons, which is thus H-6. This was confirmed by the presence of a correlation between C-5 and the residual aromatic proton (Fig. 2).

2.2. Synthesis of activated catechin derivatives

Oxidation at the benzylic C-4 position of flavanols is a fundamental step in proanthocyanidin synthesis. Over the years, three main reagents have been used in the literature for this purpose, namely $K_2S_2O_8$, lead(IV) acetate and DDQ, which is now the most widely used.[16–22] In this study, DDQ was used as oxidant of tetrabenzylated catechin **3** in presence of ethylene glycol or 2-ethoxyethanol giving access to the corresponding 4-*O*-alkylated catechin **7**, **8** with yields up to 70% (Scheme 2).

2.3. $TiCl_4$-catalyzed flavanol coupling reaction

Lewis acids have been employed in literature to synthesize proanthocyanidins. Thus, $TiCl_4$, $AgBF_4$, $SnCl_4$, TMSOTf have been used to synthesize dimeric and oligomeric procyanidins of (+)-catechin and (−)-epicatechin

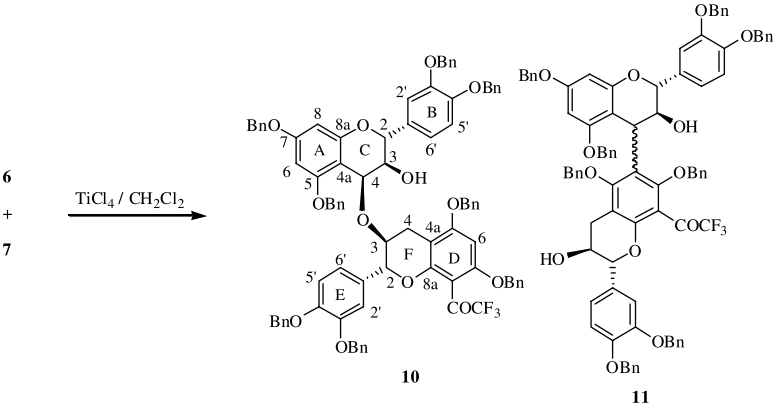


Scheme 2. Synthesis of the 4-activated catechin derivatives **7**, **8**, **9**.

units.[8,9,13,23–26] In these reactions, the role of Lewis acids is to promote the formation of the benzylic carbocation at C-4 of a flavanol subunit starting from a C-4 hetero substituted flavanol, which thereafter undergoes a Friedel–Craft-like addition on a second flavanol subunit. For this preliminary study, the Lewis acid $TiCl_4$ was first used as a carbocation promoting agent from the 4-(2-hydroxyethyloxy) flavan-3-ol **7**. Coupling reaction between compound **6** and **7** in a 6/1 molar ratio was investigated in CH_2Cl_2 according to Scheme 3. The reaction was monitored by CCM and HPLC and showed the disappearance of compound **6** and appearance of new compounds. Among the products formed, compound **10** was obtained in sufficient amounts to allow its structure investigation. This was achieved through UV, LC/ESMS, ES CAD MS/MS and NMR analysis.

The UV spectrum of compound **10** exhibited similar maxima (285 and 305 nm) to that of compound **6**, indicating that the original flavan structure with the $COCF_3$ group was retained. The mass spectrum obtained in the positive ion mode (Fig. 3) showed signals at *m/z*: 1395, 1412, 1417 and 1433 amu corresponding, respectively, to $[M+H]^+$, $[M+NH_4]^+$, $[M+Na]^+$ and $[M+K]^+$ indicating a molecular weight of 1394 amu in agreement with a dimeric structure consisting of tetrabenzylated (+)-catechin **3** linked to its trifluoroacylated derivative **6**. However, the remaining problem was the establishment of the position of linkage to compound **6**, as the tetrabenzylated catechin moiety is linked through its 4 position.

In addition to the signals indicated above, the mass spectrum of compound **10** also showed signals at *m/z*: 747 and 649 amu



Scheme 3. $TiCl_4$-catalyzed formation of compounds **10**, **11**.

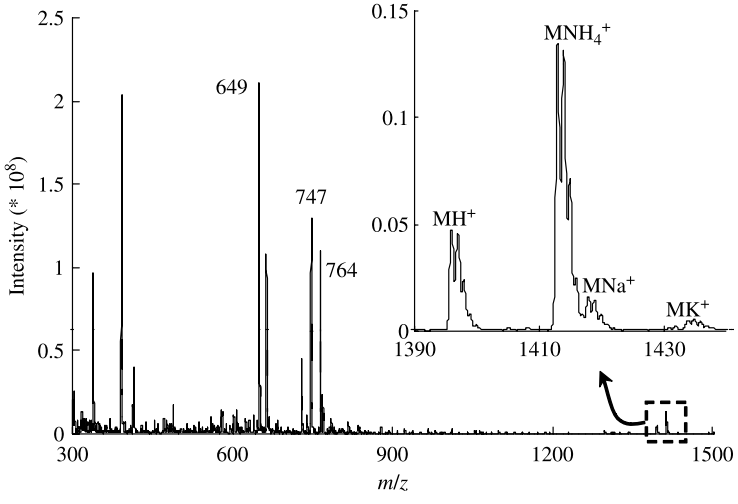


Figure 3. MS spectrum of **10** recorded in a positive ion mode.

corresponding to the fission of the bond between the two constitutive units. Among the other observed signals two of them were located at *m/z*: 1063 and 981 amu and were also observed in the spectrum obtained through positive ES CAD MS/MS fragmentation of the signal located at *m/z*: 1395 amu ($[M+H]^+$ ion). The signal observed at *m/z*: 1063 amu was attributed to the characteristic RDA fragmentation corresponding to the $[M+H-332]^+$ ion as what was observed for compound **6** through a loss of the B moiety. The second fragmentation observed at *m/z*: 981 amu correspond in fact to the $[M+H-414]^+$ ion, meaning a loss of the A moiety of compound **6** unit (Fig. 4) and corresponding to another RDA fragmentation. The occurrence of this fission indicated the presence of the A moiety in the structure of compound **10**. In other words, this means that the isolated compound is not a C-4→C-6 dimer since only one RDA fragmentation corresponding to the $[M+H-332]^+$ ion could be possible in this case. The possible linkage is thus expected to occur via the 2 or 3 position of the F ring or possibly the 2′, 5′ or 6′ positions of the ring E.

Through NMR analysis, the presence of two distinct catechin proton systems was observed. This was confirmed through 1D ^{1}H and 2D ^{1}H–^{1}H COSY NMR spectra, which showed the presence of an AMX and AA'MX spin systems corresponding to the two catechin units. Thus, the signals, which resonate at 2.52, 2.71, 4.48 and 4.90 ppm could be readily assigned to the H-4 (α and β), H-3 and H-2 of the F ring, while those located at 3.82, 4.85 and 5.10 ppm were assigned, respectively, to the H-3, H-4 and H-2 of the C ring.

In the HETCOR spectra, these aliphatic protons correlate with carbons located at 27.15, 70.80 and 76.69 ppm, respectively, for the first system and at 66.03, 70.17 and 80.52 ppm, respectively, for the second system. The furthest upfield carbon chemical shifts is in agreement with a carbon resonance deshielded by the presence of an oxygen atom. In addition, the HETCOR spectra showed correlations between the B and E rings protons and their corresponding carbons, which were thus assigned in connection with the results also obtained through ^{13}C and DEPT NMR analysis.

In the aromatic proton chemical shift region, the spectrum also showed two doublets ($J=1.8$ Hz) integrating one proton each located at 6.10 and 6.26 ppm and a singlet integrating one proton located at 6.20 ppm. The first doublets were assigned to H-6 and H-8 protons of the A ring while the singlet was assigned to H-6 of the D ring. This indicated that the interflavanyl linkage did not involve the D ring confirming thus the conclusion deduced from the MS results described above. It did not neither involve the E ring since the three corresponding protons were observed through ^{13}C and DEPT NMR spectra.

In conjunction with the absence of a doubly benzylic methylene proton characteristic of a C4→C6 linkage and taking into account the dimeric structure of the compound as supported by MS analysis, the NMR data collectively indicated a dimeric structure with an interflavanyl ether bond connecting the two heterocyclic C and F rings. Taking into account the fact that the linkage did not involve the H-2, H-3, H-4 F ring protons since they were all evidenced through NMR analysis, a (4-*O*-3) mode of linkage was thus concluded to occur between the two flavan-3-ols units. This was also confirmed by comparison of the chemical shifts of the H-4 and H-3 resonances of both the C and the F rings with those of their precursors. Finally, the structure of compound was univocally confirmed through HMBC analysis where several long range correlations were observed. In particular correlations involving proton and carbon of both C and F rings via the oxygen atom were observed and confirmed thus the ether linkage involved in compound **10**. Full assignment of the protons and carbon chemical shifts was achieved through HMBC analysis. Figure 4 showed some of the main correlations involving H/C of the C and F rings in agreement with the proposed structure.

It was concluded that a (4-*O*-3) linkage was occured between the two flavan-3-ol units. Moreover, coupling constants for the AMX spin system of the C ring protons ($J_{3,4}=3.2$ Hz) indicated a 3,4 cis relative configuration for this ring, that is a 4β linkage between both flavanol units. The complete stereoselectivity of the reaction remains, however, to be explained and should presumably be due to a participation of the hydroxy group at C-3 of **6**. However, its involvement in the stereochemical course of the reaction cannot be, in our case, related to the formation of a protonated

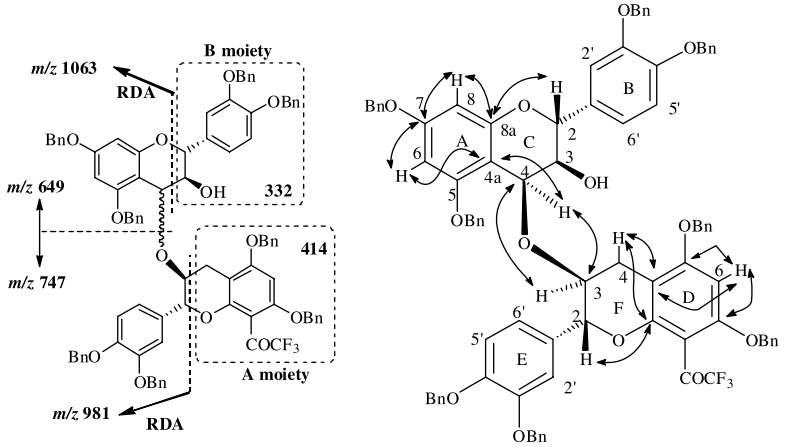


Figure 4. Main fragmentations and ^{1}H–^{13}C long range characteristic correlations observed for compound **10**.

epoxide similar to that reported by Bennie et al.,[27] in a work dealing with the dimerization of epioritin-4-ol derivatives.

Indeed, the stereochemical outcome of the reaction in our case should be rather more consistent with a chelation process of the Lewis acid by both hydroxy groups of **7** and **6**, therefore inducing the approach of the nucleophile from the β face of **7**. The possible participation of the oxygen atoms of the ethylene glycol moiety of **7**, in such a chelation process, thereby inducing a quasi-concerted process has also to be considered.

In order to verify the presence of other dimeric structures the mixture was explored by HPLC coupled to a mass spectrometry detection operating in the positive ion mode. An extracted ion current chromatogram recorded at *m/z*: 1395 and 1412 amu (Fig. 5) and corresponding to a dimeric structure molecular weight showed the presence, in addition to compound **10**, of a minor compound, which is possibly the carbon–carbon coupled dimer **11**. The fragmentations observed for compound **11** were in agreement with the proposed dimeric structure consisting of tetrabenzylated (+)-catechin **3** coupled to its trifluroacylated derivative **6** through a C4→C6 linkage (Fig. 6).

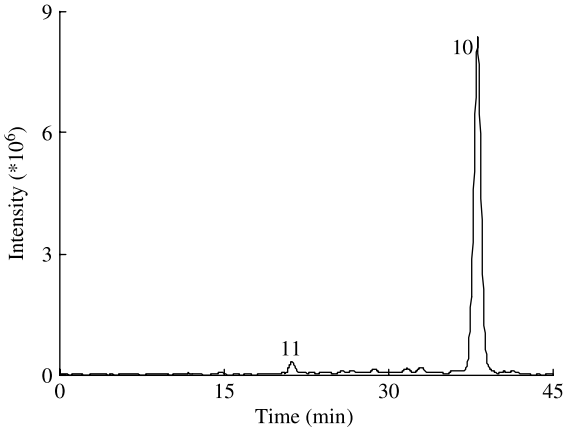


Figure 5. XIC recorded at *m/z*: 1395 amu showing the presence of the main 4-*O*-3 ether **10** and the probable C-4→C-6 linked dimers **11**.

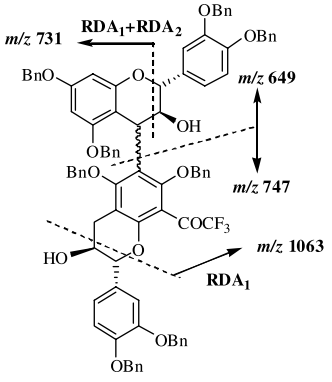


Figure 6. Main fragmentations observed for compound **11**.

The almost exclusive, high yielding formation, in these conditions of the novel ether linked procyanidins as main compound rather than its carbon–carbon C-4→C-6 coupled analogue reflects the importance of electronic features in the formation of flavan-3-ol dimers. The poor nucleophilicity of the A ring monomeric precursor, caused by the presence of the $COCF_3$ group, permits alternative centers to participate in the interflavanyl bond formation.

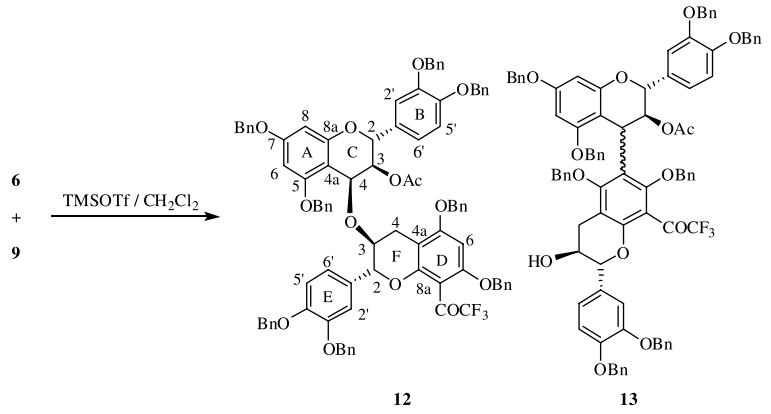
2.4. TMSOTf-catalyzed flavanol coupling reaction

As indicated above, various Lewis acids were used as coupling agents for proanthocyanidin synthesis. After having used $TiCl_4$, the same reaction was investigated using TMSOTf, which was recently used to synthesize octabenzylated procyanidin-B3 with high levels of setereoselectivity and in excellent isolated yields.[7,8,28] The reaction was conducted by using the acetylated compound **9** as electrophile, which was prepared through DDQ mediated oxidation of tetrabenzylated catechin **3** in presence of ethoxyethanol followed by an acetylation using acetic anhydride (Scheme 2). The structures of the compounds obtained were confirmed by MS and NMR analysis. The coupling reaction in the presence of TMSOTf was achieved at −78 °C using the same 8-trifluoroacetylated adduct **6** as nucleophile. After isolation by column chromatography eluting with ethylacetate/cyclohexane mixture, the major compound obtained was submitted to spectral analysis. The mass spectrum obtained in the positive ion mode showed signals at *m/z*: 1437, 1454 and 1459 amu and corresponding to $[M+H]^+$, $[M+NH_4]^+$ and $[M+Na]^+$ ions, respectively, in agreement with a dimeric structure consisting of an acetoxy-tetrabenzyloxy- and a trifluoroacetyl-tetrabenzyloxy catechin. The full structure elucidation of compound **12** was achieved using 1D and 2D NMR analysis. The presence of the three A and D rings aromatic protons was observed indicating that they were not involved during the coupling reaction and that the interflavanic bond was not a C-4→C-6 type. Further NMR analysis similar to those described for compounds **10** was used to confirm the regiochemistry of the reaction and indicated the predominant formation of a C-4→*O*→C-3 ether bond type between the two flavanol moieties. The 3,4 stereochemistry of the upper unit was also determined by NMR and was shown to be cis (Scheme 4).

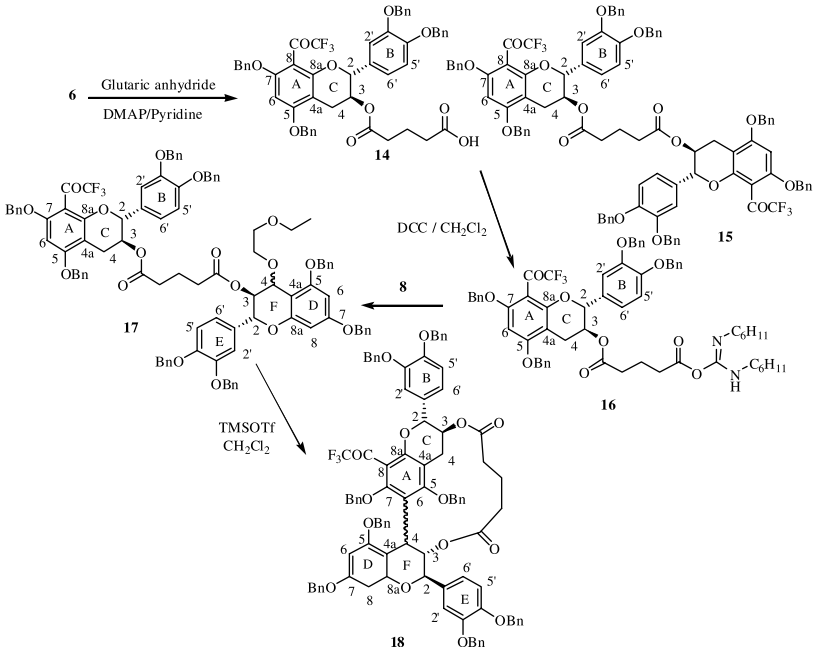
The formation of the ether linked procyanidins as main products of dimerisation rather than the carbon–carbon C-4→C-6 coupled analogues showed that the inhibition effect of the trifluoroacetyl group when using $TiCl_4$ as catalysing Lewis acid was also observed in the case of TMSOTf. This confirms the effect of the A ring substitution on the nucleophilicity of the flavanol, so allowing other nucleophilic centers to participate to the coupling reaction.

2.5. TMSOTf-catalyzed intramolecular flavanol coupling reaction

After having tested these two Lewis acid in the condensation reaction and after having showed the participation of the 3-hydroxyl group as a nucleophilic site in interflavanyl linkage formation, we decided to protect this group and to try to achieve coupling reaction with increased C–C linkage formation yield. To avoid the undesirable intervention of the 3-hydroxyl group in the chain elongation process, this group was protected in both the electrophilic and the nucleophilic



Scheme 4. TMSOTf-catalyzed formation of compounds **12**, **13**.



Scheme 5. TMSOTf-catalyzed formation of compounds **18**.

reaction partner by a diester linker glutaric anhydride in two steps (Scheme 5) and the TMSOTf-catalyzed condensation reaction was reinvestigated.

The 8-trifluoroacetyl derivative **6** was first treated with glutaric anhydride to yield the corresponding esterified compound **14**, in addition to which compound **15** resulting from a double esterification was also obtained. The isolated carboxylic mono-ester **14** was further coupled with the electrophile unit **8** in presence of DCC to give the desired diester **17**. In this reaction, the intermediate **16** was also isolated and identified. Having the 4-*O*-alkoxy derivative **17** in hand, the stage was set for its possible conversion to the corresponding C–C coupled adduct **18** (Scheme 5) through intramolecular TMSOTf-catalyzed coupling reaction.[7] The reaction was conducted in CH_2Cl_2 at −78 °C to give coupled product **18** with a low yield. In order to increase the reaction yield, several attempts were made in various conditions; however the C–C bond formation was always observed with a low yield. The mass spectrum of compound **18** showed signals at *m/z*: 1491 and 1598 amu corresponding to $[M+H]^+$ and $[M+NH_4]^+$ ions, respectively, and where the fragment *m/z*: 731 resulting from two successive RDA scissions was observed showing the presence of the C-4→C-6 linkage. In the ^1H NMR spectrum, the particular disappearance of the H-6A proton was observed confirming such C–C linkage. The low yield obtained in the coupling reaction confirms once again the negative effect of the 8-trifluoroacetyl substituent on the nucleophilicity of the C-6 center. This could also be due to geometrical factors, which are obviously important in such coupling reaction.

3. Conclusion

Our results delineate thus the influence of an electron deficient substituent on C-8 of the aromatic A ring of a catechin subunit on the course of the Lewis acid catalyzed classical procyanidin formation reaction. The results obtained showed that the presence of a $COCF_3$ substituent linked to the 8 position of a (+)-catechin unit strongly influenced the attack on the flavanol moiety by the electrophile generated from a 4-*O*-alkyloxy protected catechin unit and indicates the importance of electronic

features in the establishment of the carbon–carbon interflavanic bond. When using either $TiCl_4$ or TMSOTf as Lewis acids, C–C bond formation was inhibited and the corresponding C→C dimer was detected only in a very small amount. By contrast the formation of a carbon–oxygen bond was observed and the corresponding C-4→*O*→C-3 ether linked procyanidin dimer was isolated in a good yield. The poor nucleophilicity of the A ring electrophile acceptor subunit probably caused by the presence of the electron deficient $COCF_3$ group, allows alternative nucleophilic sites of the molecules to participate in interflavanyl bond formation.

Our results report the production of ether linked dimeric procyanidins based on (+)-catechin skeleton and obtained in good yield. Its formation is a new concept in proanthocyanidin synthesis since until now only flavanols with pyrogallol moiety were described as precursors of 4-*O*-4 and 4-*O*-3 ether linked proanthocyanidins. They finally open perspectives for further investigations of similar compounds. A number of properties such as temperature and hydrolytic stability, in addition to its biological activities, remain of a high interest, and will be investigated.

4. Experimental

4.1. General

All reactions were performed under argon and monitored by TLC and analytical HPLC. Unless otherwise indicated, the ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a Varian Gemini-300 spectrometer at 300 and 75 MHz, respectively (proton decoupling mode for carbon). ^1H NMR spectra were referenced to the signal at $\delta=$ 7.27 ppm of residual $CHCl_3$. ^{13}C NMR spectra were referenced to signals of $CDCl_3$ ($\delta=77.0$ ppm). Resonances of the benzyl group are not mentioned. FT-IR spectra were recorded with a Nicolet Avatar 320 FT-IR spectrophotometer. UV–visible spectra were recorded with a Kontron Uvikon 930 spectrophotometer fitted with a quartz cell.

Analytical TLC was performed on Merck silica gel 60 F254 plates. Column chromatography was performed using a mixture of ethyl acetate/cyclohexane as eluent on silica gel 60 Å 70–200 μm (SDS, 13124 PEYPIN, France). Analytical HPLC analysis was performed on a Varian apparatus including a 9012 solvent delivery system, a 9100 autosampler and a 9065 polychrom diode array detector. Analysis were performed on a C18 column eluting with a mixture of solvents A: acetonitrile and B: water with 0.5% orthophosphoric acid eluting from 15 to 100% A in 18 min followed by a washing and a reequilibrating of the column. LC/MS analysis were performed with a chromatographic system (Alliance) consisted of a Waters 2695 separations module equipped with an autosampler and a Waters 2487 dual lambda absorbance detector (Waters, Milford, MA, USA). The column was a 150×2.1 mm Interchrom UP5ODB#15E (Uptisphere 5 μm ODB) with a 10× 2.1 mm precolumn from Interchim (Montluçon, France). Chromatography was ran in isocratic mode using a 60/40 mixture of acetonitrile (RS-Plus quality for HPLC from Carlo Erba) and water with 0.2% acetic acid. The flow rate was 0.2 mL/min, the analyses were performed with the column and the samples kept at ambient temperature and 5.0–10 μL was injected for each analysis. The effluent from the UV detector was introduced without any split into the mass spectrometer. The HPLC system was coupled on line to a Quattro LC MS/MS triple quadrupole mass spectrometer (Micromass, Manchester, UK) equipped with a pneumatically assisted electrospray source ionisation (ESI). Data acquisition and processing were performed using a MassLynx NT 3.5 data system. The electrospray source parameters were fixed as follow: electrospray capillary voltage 3.25 kV in positive mode and 3 kV in negative mode, source block temperature 120 °C, desolvation gas temperature 400 °C. Nitrogen was used as drying gas and nebulising gas at flow rates of approximately 50 and 450 L/h.

4.2. Synthesis

4.2.1. 3′,4′,5,7-Tetrabenzyloxycatechin (3). To a stirred suspension of NaH (144.5 mmol) in dry DMF (170 mL) under nitrogen at −78 °C, was sequentially added a solution of (+)-catechin **1a** (10 g, 34 mmol) in anhydrous DMF (170 mL) and benzyl chloride (170 mmol). The mixture was stirred at −78 °C for 15 min then at room temperature for 7 h. Progress of the reaction was monitored by TLC and was quenched by addition of 1 N HCl and water. The aqueous layer was extracted with EtOAc and the organic layer washed with water, dried over $MgSO_4$ and concentrated under reduced pressure. Purification by silica gel chromatography (eluent, cyclohexane/EtOAc, 80:20) afforded 3′,4′,5,7-tetrabenzyloxycatechin **3** (33 mmol, 97%) as white amorphous powder. Spectral data were similar to those previously described.[29]

4.2.2. 3′,4′,5,7-Tetrabenzyloxy-8-trifluoroacetylcatechin (6). To a solution of tetra-*O*-benzylated catechin **3** (2 g, 3.0 mmol) in CH_2Cl_2 (12 mL) was added dropwise $(CF_3CO)_2O$ (20 mL) at 0 °C. The mixture was stirred at room temperature and the progress of the reaction was followed by TLC. The formation of **4** as primary product of the reaction was first observed. The formation of compound **5** was then observed. Hydrolysis of compound **5** gave the target product **6**. The crude mixture so obtained was concentrated and chromatographed on silica gel (eluent, cyclohexane/EtOAc, 80:20) giving 1.43 g (1.9 mmol, 64%) of 3′,4′,5,7-tetrabenzyloxy-8-trifluoroacetylcatechin **6**. The purity of **6** was controlled through analytical HPLC. ^1H NMR (300 MHz, $CDCl_3$) 7.01 (d, $J=1.6$ Hz, 1H, H-2′), 6.89 (dd, $J=1.6$, 8.4 Hz, 1H, H-6′), 6.95 (d, $J=8.4$ Hz, 1H, H-5′), 6.28 (s, 1H, H-6), 4.72 (d, $J=7.8$ Hz, 1H, H-2), 3.95 (m, 1H, H-3), 3.08 (dd, $J=5.4$, 16.5 Hz, 1H, H-4β), 2.67 (dd, $J=8.7$, 16.5 Hz, 1H, H-4α). ^{13}C NMR (125 MHz, $CDCl_3$) 184.3 (CO), 160.6 (C-7), 157.8 (C-5), 154.2 (C-8a), 149.5 (C-4′), 149.2 (C-3′), 130.4 (C-1′), 121.1 (CF_3), 120.4 (C-6′), 115.1 (C-5′), 113.8 (C-2′), 105.7 (C-8), 103.2 (C-4a), 81.9 (C-2), 91.3 (C-6), 67.6 (C-3), 27.5 (C-4). ESI-MS *m/z*: 747 $[M+H]^+$, 764 $[M+NH_4]^+$, 769 $[M+Na]^+$.

4.2.3. 3′,4′,5,7-Tetrabenzyloxy-4-(2-hydroxyethoxy)-catechin (7). To a solution of 3′,4′,5,7-tetrabenzyloxycatechin **3** (1.3 g, 2.0 mmol) in anhydrous CH_2Cl_2 (13 mL) was added at room temperature 0.6 mL (11.5 mmol) of

ethylene glycol and then all at once and with a good stirring 0.9 g (3.9 mmol) of DDQ. A black-green colour appeared instantaneously and gradually faded to a dark brown. After 120 min of vigorous stirring at room temperature under a $CaCl_2$ tube, excess of 4-(dimethylamino)-pyridine was added to the solution at 0 °C and the mixture was stirred for 5 min. The resulting purple solid was removed by filtration and the filtrate was washed with water and brine, and dried ($MgSO_4$). Filtration, concentration and silica gel column chromatography (eluent, hexane/EtOAc, 1:2–2:3) gave 3′,4′,5,7-tetrabenzyloxy-4-(2-hydroxyethoxy)catechin **7** (990 mg, 1.4 mmol, 70%) as white foam. ^{1}H NMR (300 MHz, $CDCl_3$) 7.13 (d, J=1.6 Hz, 1H, H-2′B), 7.08 (d, J=8.1 Hz, 1H, H-5′B), 7.02 (dd, J=1.6, 8.1 Hz, 1H, H-6′B), 6.50 (d, J=2.1 Hz, 1H, H-6A), 6.25 (d, J=2.1 Hz, 1H, H-8A), 5.10 (d, J=10.0 Hz, 1H, H-2C), 4.95 (m, 1H, H-3C), 4.82 (d, J=7.1 Hz, 1H, H-4C), 3.50–3.90 (m, 4H, OCH_2-CH_2O). ^{13}C NMR (125 MHz, $CDCl_3$) 161.5 (C-7A), 160.7 (C-5A), 157.6 (C-8aD), 147.5 (C-3′B), 147.3 (C-4′B), 131.2 (C-1′B), 121.2 (C-6′B), 116.3 (C-5′B), 113.8 (C-2′B), 105.8 (C-4aA), 94.2 (C-8A), 93.2 (C-6A), 78.8 (C-2C), 74.2 (C-3C), 71.3 (C-4C), 68.3 (OCH$_2$CH$_2$OH), 61.8 (OCH$_2$$CH_2$-OH). ESI-MS m/z: 711 $[M+H]^+$, 728 $[M+NH_4]^+$, 733 $[M+Na]^+$.

4.2.4. 3′,4′,5,7-Tetrabenzyloxy-4-(2-ethoxyethoxy)-catechin (8). DDQ oxidation according to the above procedure using 3′,4′,5,7-tetrabenzyloxycatechin **3** (500 mg, 0.77 mmol), DDQ (350 mg, 1.54 mmol) and 2-ethoxyethanol (1.5 mL) in CH_2Cl_2 (15 mL) for 2 h afforded **8** as a pale yellow solid, which was crystallized from hexane/EtOAc to give 550 mg (0.75 mmol, 97%) of 3′,4′,5,7-tetrabenzyloxy-4-(2-ethoxyethoxy)catechin **8** as colourless needles. ^{1}H NMR (300 MHz, $CDCl_3$) 7.20 (d, J=1.7 Hz, 1H, H-2′B), 7.01 (d, J=8.0 Hz, 1H, H-5′B), 6.97 (dd, J=1.7, 8.0 Hz, 1H, H-6′B), 6.17 (d, J=2.0 Hz, 1H, H-6A), 6.03 (d, J=2.0 Hz, 1H, H-8A), 4.98 (d, J=10.05 Hz, 1H, H-2C), 4.89 (m, 1H, H-3C), 4.85 (d, J=7.0 Hz, 1H, H-4C), 3.50–3.90 (m, 4H, OCH_2CH_2O), 3.30 (q, J=7.0 Hz, 2H, OCH_2CH$_3$), 1.20 (t, J=7.0 Hz, 2H, OCH$_2$CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) 161.2 (C-7A), 160.3 (C-5A), 156.6 (C-8aD), 148.3 (C-3′B), 148.1 (C-4′B), 131.1 (C-1′B), 121.1 (C-6′B), 115.6 (C-5′B), 114.1 (C-2′B), 104.7 (C-4aA), 94.5 (C-8A), 93.6 (C-6A), 76.5 (C-2C), 74.2 (C-3C), 72.1 (C-4C), 70.8 (OCH$_2$), 70.2 (CH$_2$O), 66.5 (CH$_2$CH$_3$), 14.0 (CH$_2$$CH_3$). ESI-MS m/z: 739 $[M+H]^+$, 756 $[M+NH_4]^+$, 761 $[M+Na]^+$.

4.2.5. 3-Acetoxy-3′,4′,5,7-tetrabenzyloxy-4-(2-ethoxy-ethoxy)catechin (9). Acetylation using 3′,4′,5,7-tetrabenzyloxy-4-(2-ethoxyethoxy)catechin **8** (500 mg, 0.67 mmol), Ac_2O and 4-(dimethylamino)pyridine afforded 510 mg (0.65 mmol) of 3-acetoxy-3′,4′,5,7-tetrabenzyloxy-4-(2-ethoxyethoxy)catechin **9** as white foam. ^{1}H NMR (300 MHz, $CDCl_3$) 7.30 (d, J=1.6 Hz, 1H, H-2′B), 7.10 (d, J=8.1 Hz, 1H, H-5′B), 6.96 (dd, J=1.6, 8.1 Hz, 1H, H-6′B), 6.20 (d, J=2.0 Hz, 1H, H-6A), 6.10 (d, J=2.0 Hz, 1H, H-8A), 5.30 (m, 1H, H-3C), 5.20 (d, J=10.17 Hz, 1H, H-2C), 4.80 (d, J=7.4 Hz, 1H, H-4C), 3.30–3.7 (m, 4H, OCH_2CH_2O), 3.20 (q, J=7.0 Hz, 2H, OCH_2CH$_3$), 1.7 (s, 3H, CH_3CO), 1.10 (t, J=7.0 Hz, 3H, OCH$_2$CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) 170.2 (CH$_3$$C$O), 161.0 (C-7A), 160.5 (C-5A), 156.8 (C-8aD), 147.5 (C-3′B), 147.0 (C-4′B), 130.6 (C-1′B), 120.9 (C-6′B), 116.5 (C-5′B), 114.5 (C-2′B), 105.3 (C-4aA), 94.2 (C-8A), 93.4 (C-6A), 76.3 (C-3C), 75.8 (C-3C), 71.2 (C-4C), 70.1 (OCH$_2$), 70.0 (CH$_2$O), 66.3 (CH$_2$CH$_3$), 20.1 (CH$_3$CO), 14.2 (CH$_2$$CH_3$). ESI-MS m/z: 7381 $[M+H]^+$, 803 $[M+Na]^+$.

4.2.6. 3′,4′,5,7-Tetrabenzyloxycatechin-(4β→*O*→3)-3′,4′,5,7-tetrabenzyloxy-8-trifluoroacetylcatechin (10). To a solution of 3′,4′,5,7-tetrabenzyloxy-8-trifluoroacetylcatechin **6** (895 mg, 1.2 mmol, 6 equiv) and 3′,4′,5,7-tetrabenzyloxy-4-(2-hydroxyethoxy)catechin **7** (142 mg, 0.2 mmol) in CH_2Cl_2 (40 mL) was added dropwise 0.2 mmol of $TiCl_4$ at 0 °C. The reaction mixture was stirred for 5 min and then quenched with saturated sodium hydrogen carbonate. The aqueous solution was extracted with EtOAc and the combined organic phase was washed with water and brine, and dried over $MgSO_4$. Filtration, concentration and silica gel column chromatography (eluent cyclohexane/EtOAc, 80:20) afforded 180 mg of **10** (0.13 mmol, 66%). The purity of **10** was controlled through analytical HPLC. ^{1}H NMR (500 MHz, $CDCl_3$) 7.08 (d, J=1.8 Hz, 1H, H-2′B), 7.01 (d, J=8.2 Hz, 1H, H-5′B), 7.00 (dd, J=1.8, 8.2 Hz, 1H, H-6′B), 6.80 (d, J=8.2 Hz, 1H, H-5′E), 6.78 (d, J=1.3 Hz, 1H, H-2′E), 6.63 (dd, J=1.3, 8.2 Hz, 1H, H-6′E), 6.27 (d, J=2.2 Hz, 1H, H-6A), 6.20 (s, 1H, H-6D), 6.12 (d, J=2.2 Hz, 1H, H-8A), 5.06 (m, 1H, H-4C), 4.99 (m, 1H, H-2F), 4.85 (d, J=10 Hz, 1H, H-2C), 4.49 (m, 1H, H-3F), 3.83 (m, 1H, H-3C), 2.78 (dd, J=4.4, 16.7 Hz, 1H, H-4βF), 2.61 (dd, J=4.4, 16.7 Hz, 1H, H-4αF). ^{13}C NMR (125 MHz, $CDCl_3$) 188.9 (CO, q, J=38 Hz), 165.6 (C-7A), 165.3 (C-5D), 162.7 (C-5A), 161.9 (C-7D), 161.0 (C-8aA), 158.8 (C-8aD), 153.7 (C-3′B), 153.6 (C-4′B), 153.4 (C-3′E), 152.9 (C-4′E), 136.7 (C-1′B), 136.2 (C-1′E), 125.3 (C-6′B), 123.5 (C-6′E), 119.1 (C-5′B), 118.6 (C-5′E), 118.6 (C-2′B), 116.4 (C-2′E), 115.7 (CF_3, q, J=292 Hz), 109.6 (C-8D), 106.8 (C-4aA), 106.6 (C-4aD), 98.8 (C-8A), 97.6 (C-6A), 95.2 (C-6D), 84.6 (C-2F), 80.8 (C-2C), 74.6 (C-3F), 74.0 (C-3C), 70.3 (C-4C), 27.2 (C-4F). ESI-MS m/z: 1395.9 $[M+H]^+$, 1412 $[M+NH_4]^+$, 1417 $[M+Na]^+$, 1433 $[M+K]^+$.

4.2.7. 3-Acetoxy-3′,4′,5,7-tetrabenzyloxycatechin-(4β→*O*→3)-3′,4′,5,7-tetrabenzyloxy-8-trifluoroacetylcatechin (12). To a solution of 3′,4′,5,7-tetrabenzyloxy-8-trifluoroacetylcatechin **6** (895 mg, 1.2 mmol, 6 equiv) and 3-acetoxy-3′,4′,5,7-tetrabenzyloxy-4-(2-ethoxyethoxy)catechin **9** (156 mg, 0.2 mmol) in dry CH_2Cl_2 (40 mL) was added dropwise TMSOTf (0.4 mL, 0.2 mmol, 0.5 M solution in CH_2Cl_2) at −78 °C. After stirring for 5 min, the reaction mixture was quenched with saturated sodium hydrogen carbonate. The aqueous solution was extracted with EtOAc and the organic phase was washed with water and brine, and dried over $MgSO_4$. Filtration, concentration and silica gel column chromatography (cyclohexane/EtOAc, 80:20) afforded 143 mg of **12** (0.1 mmol, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) 7.11 (m, 2H, H-2′B, H-5′E), 7.00 (m, 2H, H-6′B, H-2′E), 6.81 (d, J=8.7 Hz, 1H, H-5′B), 6.63 (m, 1H, H-6′E), 6.26 (d, J=2.0 Hz, 1H, H-8A), 6.20 (s, 1H, H-6D), 6.10 (d, J=2.0 Hz, 1H, H-6A), 5.10 (m, 1H, H-2F), 4.90 (m, 1H, H-4C), 4.85 (d, J=10.2 Hz, 1H, H-2C), 4.48 (m, 1H, H-3F), 3.82 (m, 1H, H-3C), 2.71 (dd, J=6.6, 16.5 Hz, 1H, H-4βF), 2.52 (dd, J=4.5, 16.5 Hz, 1H, H-4αF), 1.9 (s, 3H, CH_3CO). ^{13}C NMR (125 MHz,

$CDCl_3$) 184.5 (CF_3CO), 169.8 (CH_3CO), 161.3 (C-7D), 160.8 (C-7A), 158.4 (C-5D), 157.6 (C-5A), 156.7 (C-8aD), 154.3 (C-8aA), 149.5 (C-4′E), 149.3 (C-4′B), 149.2 (C-3′E), 148.8 (C-3′B), 132.1 (C-1′E), 131.8 (C-1′B), 122.2 (CF_3), 121.4 (C-6′E), 119.7 (C-6′B), 115.1 (C-5′E), 114.9 (C-5′B), 114.8 (C-2′E), 112.6 (C-2′B), 110.2 (C-4aA), 105.6 (C-8D), 102.7 (C-4aD), 94.3 (C-6A), 93.3 (C-8A), 92.5 (C-6D), 80.5 (C-2C), 76.7 (C-2F), 70.8 (C-3F), 70.2 (C-4C), 66.0 (C-3C), 27.2 (C-4F), 21.1 (CH_3CO). ESI-MS *m/z*: 1437 $[M+H]^+$, 1454 $[M+NH_4]^+$, 1459 $[M+Na]^+$.

4.2.8. 3′,4′,5,7-Tetrabenzyloxy-8-trifluoroacetylcatechin-3-yl glutarate (14). A mixture of 3′,4′,5,7-tetrabenzyloxy-8-trifluoroacetylcatechin **6** (400 mg, 0.53 mmol), glutaric anhydride (183 mg, 1.6 mmol) and 4-(dimethylamino)-pyridine (5 mg) in pyridine (15 mL) was stirred at 0 °C for 1 h. After stirring for 48 h at room temperature, the reaction was quenched with water, and extracted with EtOAc. The combined organic acid phases were washed with brine, and dried ($MgSO_4$). Filtration, concentration and silica gel column chromatography (eluent, hexane/EtOAc, 1:1) gave 210 mg (0.24 mmol, 45%) of **14** and 160 mg of **15** (0.1 mmol, 19%). ^{1}H NMR of **14** (300 MHz, $CDCl_3$) 6.99 (d, $J=1.5$ Hz, 1H, H-2′), 6.91 (d, $J=8.4$ Hz, 1H, H-5′), 6.84 (dd, $J=1.5$, 8.4 Hz, 1H, H-6′), 6.24 (s, 1H, H-6), 5.3 (m, 1H, H-3), 4.95 (d, $J=7.8$ Hz, 1H, H-2), 2.81 (dd, $J=5.1$, 16.0 Hz, 1H, H-4β), 2.72 (dd, $J=5.7$, 16.0 Hz, 1H, H-4α), 2.4 (m, 4H, CH_2COOR, CH_2COOH), 1.7 (m, 2H, CH_2-CH_2CH_2). ^{13}C NMR (125 MHz, $CDCl_3$) 184.7 ($COCF_3$), 177.5 (COOH), 172.2 (COOR), 159.6 (C-7), 158.0 (C-5), 153.2 (C-8a), 149.2 (C-3′), 148.7 (C-4′), 130.4 (C-1′), 124.3 (C-6′), 117.8 (CF_3), 116.5 (C-5′), 114.4 (C-2′), 105.6 (C-8), 102.0 (C-4a), 91.1 (C-6), 78.5 (C-2), 68.4 (C-3), 35.5 (CH_2COOH), 33.6 (CH_2COOR), 27.9 (C-4), 19.9 (CH_2-CH_2COOH). ESI-MS *m/z*: 861 $[M+H]^+$, 883 $[M+Na]^+$.

4.2.9. Di-(5,7,3′,4′-tetrabenzyloxy-8-trifluoroacetylcatechin-3-yl) glutarate (15). ^{1}H NMR (300 MHz, $CDCl_3$) 7.10 (d, $J=1.5$ Hz, 2H, H-2′), 6.96 (d, $J=8.2$ Hz, 2H, H-5′), 6.90 (dd, $J=1.5$, 8.2 Hz, 2H, H-6′), 6.20 (s, 2H, H-6), 5.20 (d, $J=7.8$ Hz, 2H, H-2), 4.89 (m, 2H, H-3), 3.02 (dd, $J=5.1$, 15.0 Hz, 2H, H-4β), 2.72 (dd, $J=5.7$, 15.0 Hz, 2H, H-4α), 2.3 (m, 4H, CH_2CO), 1.8 (m, 2H, $CH_2CH_2CH_2$). ^{13}C NMR (125 MHz, $CDCl_3$) 185.0 ($COCF_3$), 172.1 (COOR), 160.6 (C-7), 158.0 (C-5), 153.7 (C-8a), 149.2 (C-3′), 148.5 (C-4′), 130.2 (C-1′), 121.0 (C-6′), 117.9 (CF_3), 117.5 (C-5′), 115.1 (C-2′), 105.6 (C-8), 102.0 (C4a), 91.1 (C-6), 78.5 (C-2), 68.4 (C-3), 33.5 (CH_2CO), 27.5 (C-4), 20.5 (CH_2CH_2CO). ESI-MS *m/z*: 1589 $[M+H]^+$, 1611 $[M+Na]^+$.

4.2.10. 3′,4′,5,7-Tetrabenzyloxy-4-(2-ethoxyethoxy)-catechin-3-yl-3′,4′,5,7-tetrabenzyloxy-8-trifluoroacetylcatechin-3-yl glutarate (17). A solution of 3′,4′,5,7-tetrabenzyloxy-4-(2-ethoxyethoxy)catechin **8** (150 mg, 0.20 mmol), 3′,4′,5,7-tetrabenzyloxy-8-trifluoroacetylcatechin-3-yl glutarate **14** (300 mg, 0.40 mmol), DCC (82.6 mg, 0.40 mmol) and DMAP (10.00 mg) in CH_2Cl_2 (20 mL) was stirred at 0 °C for 1 h. After stirring for 12 h at room temperature, the reaction mixture was quenched with water, and extracted with CH_2Cl_2. The combined organic phases were washed with brine, and dried ($MgSO_4$). Filtration, concentration and silica gel column chromatography (eluent, cyclohexane/EtOAc, 80:20) gave 50 mg (0.05 mmol, 12.5%) of the intermediate compound **16** and 126 mg (0.08 mmol, 40%) of the target product **17**, which was obtained as amorphous powder. ^{1}H NMR (300 MHz, $CDCl_3$) 7.21 (d, $J=8.1$ Hz, 1H, H-5′E), 7.06 (d, $J=1.5$ Hz, 1H, H-2′E), 6.95 (dd, $J=1.5$, 8.1 Hz, 1H, H-6′E), 6.84 (d, $J=1.7$ Hz, 1H, H-2′B), 6.74 (d, $J=8.4$ Hz, 1H, H-5′B), 6.26 (dd, $J=1.7$, 8.4 Hz, 1H, H-6′B), 6.19 (s, 1H, H-6A), 6.16 (d, $J=2$ Hz, 1H, H-6D), 6.03 (d, $J=2$ Hz, 1H, H-8D), 4.95–5.31 (m, 4H, H-2C, H-3C, H-2F, H-3F), 4.87 (d, $J=3$ Hz, 1H, H-4F), 3.4 (q, $J=7$ Hz, 2H, CH_2CH_3), 3.33–3.52 (m, 4H, OCH_2CH_2O), 2.82 (dd, $J=6.4$, 16.2 Hz, 1H, H-4βC), 2.65 (dd, $J=5.4$, 16.2 Hz, 1H, H-4αC), 1.98–2.40 (m, 6H, $CH_2CH_2CH_2$), 1.1 (t, $J=7$ Hz, 3H, CH_3CH_2). ^{13}C NMR (125 MHz, $CDCl_3$) 185.6 ($COCF_3$), 171.3 (COO), 170.9 (COO), 160.6 (C-7A), 159.9 (C-7D), 158.1 (C-5A), 157.4 (C-5D), 155.4 (C-8aA), 153.0 (C-8aD), 148.9 (C-3′B), 148.5 (3C, C-4′B, C-3′E, C-4′E), 130.1 (C-1′B), 129.9 (C-1′E), 120.9 (C-6′B), 118.8 (C-6′E), 117.4 (CF_3), 114.4 (2C, C-5′B, C-5′E), 114.3 (2C, C-2′B, C-2′E), 103.3 (C-4aA), 101.4 (C-4aD), 94.0 (C-8D), 93.4 (C-6D), 90.5 (C-6A), 78.2 (C-2C), 77.6 (C-2F), 74.5 (C-3C), 72.8 (C-3F), 70.2 (OCH_2CH_2O), 70.0 (OCH_2CH_2O), 66.5 (OCH_2CH_3), 35.1 (2C, CH_2CO), 27.1 (C-4), 19.8 ($CH_2CH_2CH_2$), 13.9 (CH_3CH_2). ESI-MS *m/z*: 1581 $[M+H]^+$, 1603 $[M+Na]^+$.

4.2.11. 3′,4′,5,7-Tetrabenzyloxy-8-trifluoroacetylcatechin-3-yl-dicyclohexyl-carbodiimidoyl-glutarate (16). ^{1}H NMR (300 MHz, $CDCl_3$) 7.05 (d, $J=1.5$ Hz, 1H, H-2′), 6.95 (d, $J=8.4$ Hz, 1H, H-5′), 6.78 (dd, $J=1.5$, 8.2 Hz, 1H, H-6′), 6.20 (s, 1H, H-6), 5.1 (d, $J=7.8$ Hz, 1H, H-2), 4.90 (m, 1H, H-3), 2.90 (dd, $J=5.1$, 16.0 Hz, 1H, H-4β), 2.60 (dd, $J=5.7$, 16.0 Hz, 1H, H-4α), 2.4 (m, 4H, CH_2CO), 1.6 (m, 2H, $CH_2CH_2CH_2$), 1.1–2.8 (m, 22H, H Cyclo). ^{13}C NMR (125 MHz, $CDCl_3$) 184.6 ($COCF_3$), 172.5 (COO), 172.2 (COOC=N), 160.6 (C-7), 158.0 (C-5), 154.1 (C-8a), 153.7 (C=N), 149.2 (C-3′), 149.1 (C-4′), 130.6 (C-1′), 120.6 (C-6′), 117.4 (CF_3), 116.5 (C-5′), 114.3 (C-2′), 105.6 (C-8), 102.0 (C-4a), 91.1 (C-6), 78.4 (C-2), 68.4 (C-3), 55.7 (CH–N=), 50.0 (CH–NH), 34.1 (CH_2–CO), 33.8 (CH_2–CO), 33.5 (CH_2 Cyclo), 33.5 (CH_2 Cyclo), 32.8 (CH_2 Cyclo), 32.7 (CH_2 Cyclo), 31.1 (CH_2 Cyclo), 31.0 (CH_2 Cyclo), 27.3 (C-4), 25.6 (CH_2 Cyclo), 25.5 (CH_2 Cyclo), 24.9 (CH_2 Cyclo), 23.2 (CH_2 Cyclo), 20.5 ($CH_2CH_2CH_2$). ESI-MS *m/z*: 1067.6 $[M+H]^+$, 1089.6 $[M+Na]^+$.

4.2.12. Octabenzyloxy-3,3′-*O*-glutarylcatechin-(4→6)-8-trifluoroacetylcatechin (18). To a solution of **17** (100 mg, 0.06 mmol) in CH_2Cl_2 (20 mL) was added dropwise TMSOTf (0.11 mL, 0.06 mmol, 0.5 M solution in CH_2Cl_2) at 0 °C. After stirring for 5 min, the pale yellow reaction mixture was quenched with saturated sodium hydrogen carbonate. The aqueous solution was extracted with $CHCl_3$ and the organic phase was washed with water and brine, and dried ($MgSO_4$). Filtration, concentration and short silica gel column chromatography (eluent, cyclohexane/EtOAc, 80:20) afforded 2 mg (0.001 mmol, 2.2%) of **18** as amorphous powder. ^{1}H NMR (300 MHz, $CDCl_3$) 7.01 (1H, d, $J=1.5$ Hz, 1H, H-2′E), 6.90 (1H, dd, $J=1.5$, 8.1 Hz, 1H, H-6′E), 6.75 (1H, d, $J=1.6$ Hz, 1H, H-2′B), 6.70 (1H, d, $J=8.1$ Hz, 1H, H-5′E), 6.40 (1H, dd, $J=1.6$, 8.3 Hz, 1H, H-6′B), 6.21 (1H, d, $J=8.3$ Hz, 1H, H-5′B), 6.10 (1H, d, $J=2.0$ Hz, 1H, H-6D), 6.05 (1H, d, $J=2.0$ Hz, 1H, H-8D),

5.05 (m, 1H, H-2F), 4.95 (m, 1H, H-4F), 4.80 (d, J= 10.2 Hz, 1H, H-2C), 4.42 (m, 1H, H-3F), 3.85 (m, 1H, H-3C), 2.76 (dd, J=6.6, 16.3 Hz, 1H, H-4βF), 2.45 (dd, J= 4.5, 16.3 Hz, 1H, H-4αF), 2.20–2.40 (m, 4H, $CH_2CH_2CH_2$), 1.70–1.92 (m, 2H, $CH_2CH_2CH_2$). ESI-MS *m/z*: 1491 $[M+H]^+$, 1513 $[M+Na]^+$.

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A facile chemoenzymatic approach to natural cytotoxic ellipsoidone A and natural ellipsoidone B☆

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Abstract—Starting from citraconic anhydride (**3**) a facile four-step synthesis of deoxyellipsoidone **8** has been reported with 37% overall yield. An elegant six-step access to naturally occurring cytotoxic ellipsoidone A (**1**) and ellipsoidone B (**2**) has been reported with good overall yields, via the conversion of itaconic anhydride (**9**) to the acetoxymethylmaleic anhydride (**11**), regioselective sodium borohydride reduction of anhydride **11** to acetoxymethylbutyrolactone **12**, Knoevenagel condensation of lactone **12** with 5-methylfurfural, selenium dioxide induced oxidation of the formed butenolide **13** and an Amano PS catalyzed deacylation of the formed diacetoxybutenolide **14** as a pathway.

1. Introduction

Plants of the genus *Hemsleya* are distributed throughout the southwest region of China and the tubers of these plants have been used in Chinese folk medicine system.[1] As a part of survey of Chinese medicinal resources, Nomura et al. in collaboration with group of researchers from China isolated the new compounds ellipsoidones A (**1**) and B (**2**) along with the known glucosidyl butenolide, siphonoside from the tubers of *Hemsleya ellipsoidea*[2] (Fig. 1). One can easily make out that siphonoside[3] is a biological precursor of **1** and **2**. Siphonoside on loss of three water molecules would generate **1** and **2** via an intramolecular condensation and dehydrative ring contraction pathway. The structural assignment of **1** and **2** was done on the basis of UV, ^{1}H NMR, ^{13}C NMR, 2D NMR, NOE and HRFABMS data. The two new acetogenins **1** and **2** are geometric stereoisomers of each other and ellipsoidone A (**1**) possesses cytotoxic activity against P-388 cells [IC_{50} 47 mg/mL].[2] A large number of structurally interesting butenolides have been isolated previously as bioactive natural products and several elegant methods for synthesis of this class of compounds are known in the literature.[4] Synthesis of these two geometric isomers **1** and **2** with two hydroxymethyl moieties is a challenging task as Nature derives them from the sugar, siphonodin 6-*O*-β-D-glycopyranoside.[3] In continuation of our studies on cyclic anhydrides to structurally interesting

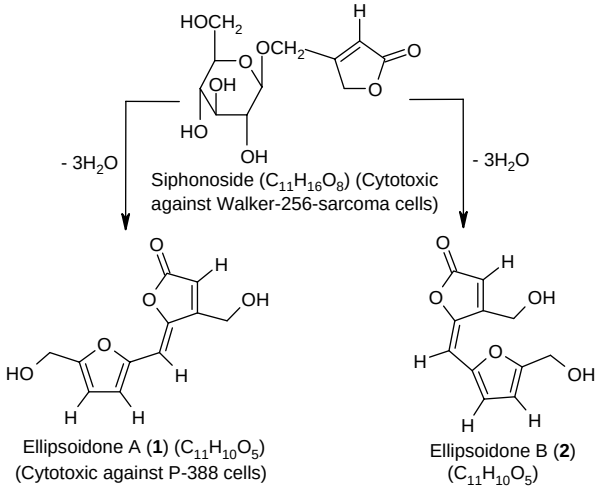

Figure 1. Bioactive natural products from *Hemsleya ellipsoidea*.

bioactive natural and unnatural products, now herein, we report a facile chemoenzymatic route to **1** and **2** using acetoxymethylmaleic anhydride (**11**) as a precursor[4,5] (Schemes 1 and 2).

2. Results and discussion

Selenium dioxide oxidation of the β-methyl group of α,β-unsaturated esters and several types of allylic/benzylic methyl groups are known in the literature.[6–8] We felt that the butenolide **5** would be a potential starting material for the synthesis of ellipsoidones A (**1**) and B (**2**) and selenium dioxide oxidation of both the allylic methyl groups in **5** would

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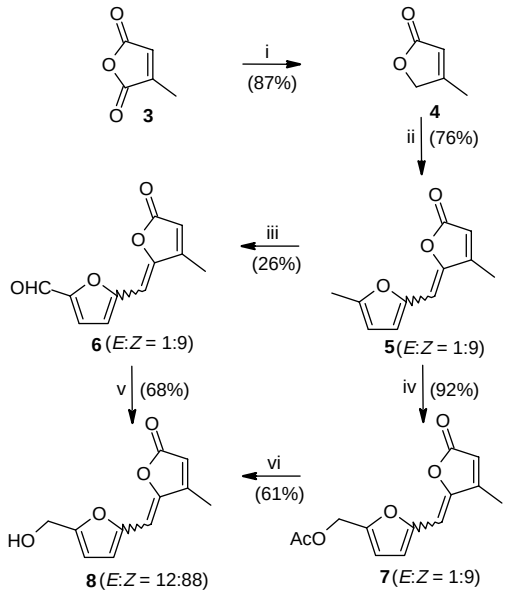
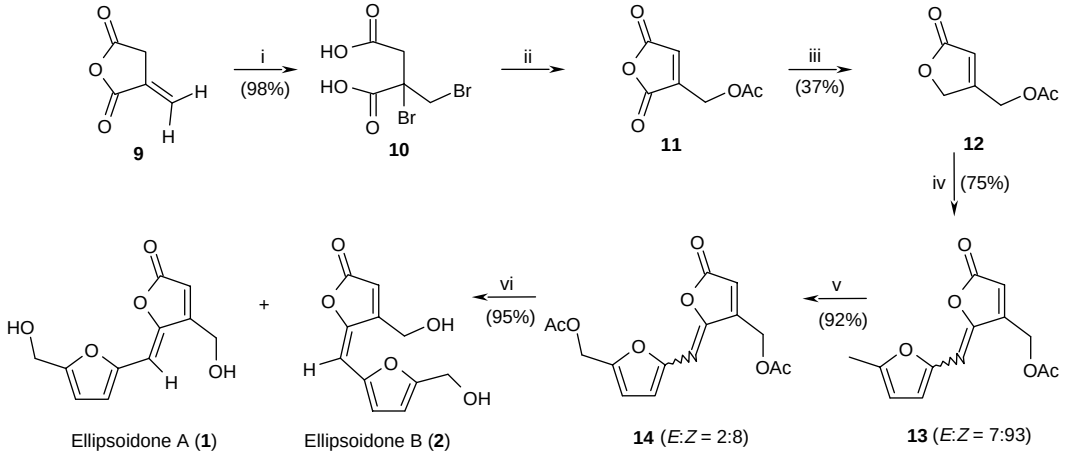


Scheme 1. Reagents, conditions and yields: (i) (a) $NaBH_4$, THF, 0 °C, 2 h, (b) H^+/HCl (87%); (ii) 5-methylfurfural, piperidine, CH_3OH, rt, 15 h (76%); (iii) SeO_2, CH_3COOH, reflux, 2 h (26%); (iv) SeO_2, CH_3COOH (anhydrous), reflux, 1.5 h (92%); (v) (a) $NaBH_4$, C_2H_5OH, rt, 1 h, (b) H^+/HCl (68%); (vi) K_2CO_3, CH_3OH, 0 °C to rt, 2 h (61%).

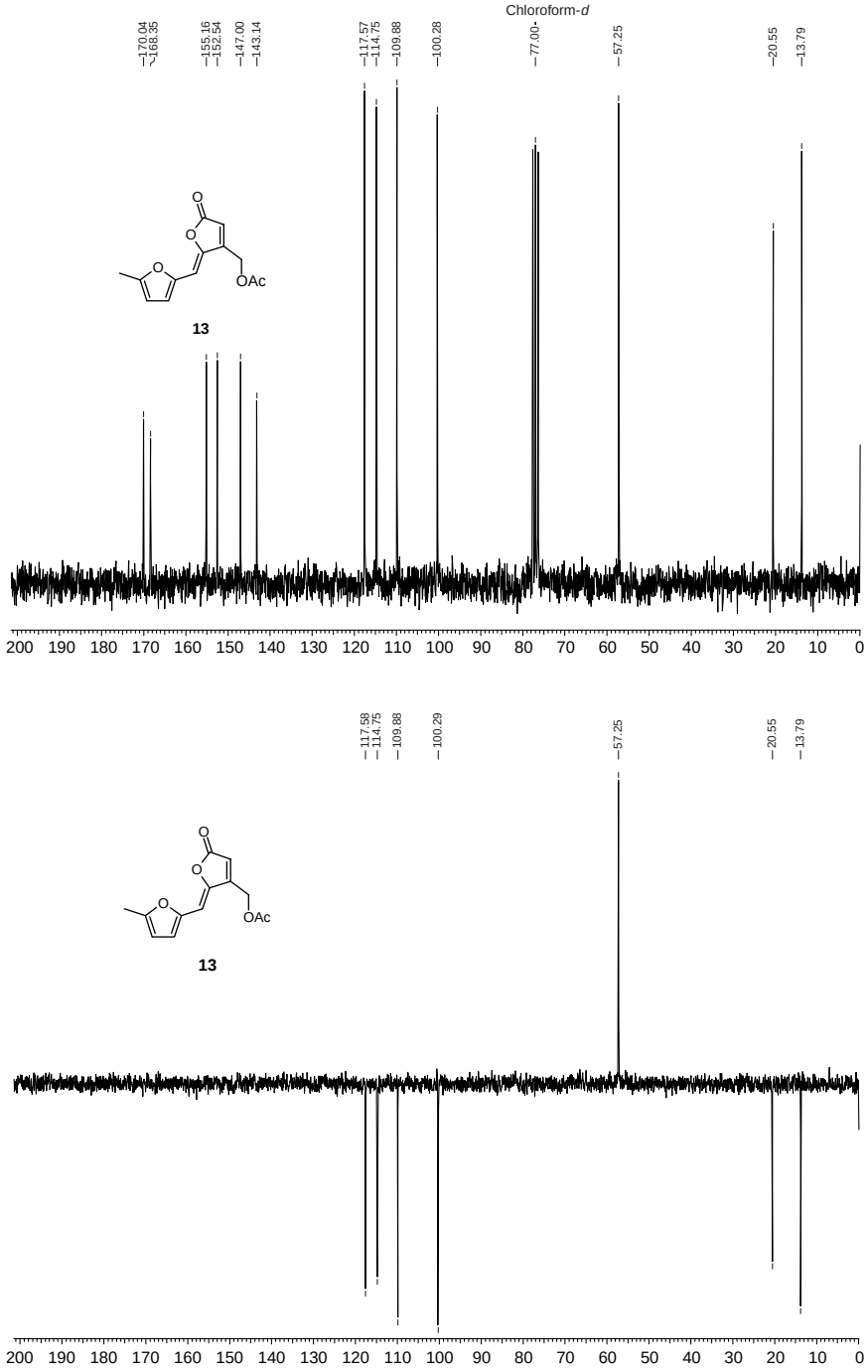
provide a simple and efficient access to these natural products. In this context, for the preparation of **5**, we performed the sodium borohydride reduction of citraconic anhydride (**3**) and obtained the known[9] butyrolactone **4** in 87% yield (Scheme 1). Piperidine catalyzed Knoevenagel condensation of lactone **4** with 5-methylfurfural gave the desired butenolide **5** in 76% yield (*E*:*Z*=1:9, by ^{1}H NMR). The butenolide **5** was strongly resistant to selenium dioxide oxidation in refluxing ethanol and 1,4-dioxane solutions and the starting material was recovered after 12 h reflux time. The SeO_2 oxidation of **5** in 98% acetic acid directly furnished the aldehyde **6**, but only in 26% yield, wherein both the hydroxylation and further oxidation of the alcohol to the aldehyde took place in one pot. To arrest the SeO_2 oxidation of **5** at the alcohol stage, we performed the reaction in a freshly dried anhydrous acetic acid and exclusively obtained the monoacetoxymethylbutenolide **7** in 92% yield. The aldehyde **6** on $NaBH_4$ reduction as well as the monoacetate **7** on base catalyzed deacylation gave the deoxyellipsoidone **8** (*E*:*Z*=12:88, by ^{1}H NMR) in 68 and 61% yields, respectively. Most of the naturally occurring butenolides of such type exist as the thermodynamically more stable *Z*-isomer[4] and herein, we could assign the *Z*-geometry to the exocyclic carbon–carbon double bonds in compounds **5** to **8** on the basis of ^{1}H NMR data. As expected, in compounds **5** to **8** the lactone methyl group signals for the minor *E*-isomers in ^{1}H NMR spectra were more deshielded (ca. δ 2.51) than the corresponding major *Z*-isomer signals (ca. δ 2.22), due to the anisotropic effect of the furan ring. All our attempts to oxidize the allylic methyl group of the lactone moiety in **5** met with failure. We feel that, on the formation of new exocyclic carbon–carbon double bond in **5**, the allylic methyl group hydrogens lose the sacrificial hyperconjugation with the lactone carbonyl group and hence it becomes inactive to the SeO_2-oxidation. Therefore, we altered our strategy and decided to start the synthesis of **1** and **2** from acetoxymethylbutenolide **12**.

We envisaged the preparation of acetoxymethyllactone **12** from itaconic anhydride (**9**). The bromination of itaconic anhydride (**9**) furnished the dibromodiacid **10**[10] in 98% yield (Scheme 2). The diacid **10** on treatment with Ac_2O/NaOAc mixture at room temperature for 6 h followed by removal of acetic anhydride in vacuo gave the crude acetoxymethylmaleic anhydride (**11**). Herein all the three-steps, the ring closure of acid **10** to the intermediate succinic anhydride derivative, dehydrobromination to form the second intermediate bromomethylmaleic anhydride and the allylic substitution of the bromide with the acetoxy group took place in one pot. The acetoxymethylmaleic anhydride (**11**) was very unstable and we were unable to purify it. The structure of the anhydride **11** was established on the basis of IR, ^{1}H NMR data of crude **11**. The direct regioselective $NaBH_4$ reduction of the crude anhydride **11** in THF furnished the desired lactone **12** in 37% yield (two-steps), without deacylation of the acetate moiety in **11/12**. Alternately, the desired lactone **12** can also be obtained from dihydroxy acetone in four-steps with 38% overall yield.[11] The Knoevenagel condensation of lactone **12** with 5-methylfurfural gave the required monoacetoxymethylbutenolide **13** (*E*:*Z*=7:93, by ^{1}H NMR) in 75% yield. Herein, the regioselective carbanion formation on an internal butyrolactone methylene group, rather than the external



Scheme 2. Reagents, conditions and yields: (i) Br_2, CCl_4, rt, 24 h (98%); (ii) Ac_2O, AcONa, rt, 6 h; (iii) (a) $NaBH_4$, THF, 0 °C, 2 h, (b) H^+/HCl (two steps, 37%); (iv) 5-methylfurfural, piperidine, rt, 15 h (75%); (v) SeO_2, AcOH (anhydrous), reflux, 6 h (92%); (vi) Amano PS, hexane–benzene (2/1), phosphate buffer pH 7.0, rt, 40 h (95%, **1**:**2**=86:14).

acetoxymethyl moiety is noteworthy and could be due to the generation of the stable oxyfurananion in the former case. As expected, here too the methylene proton signals from the $-CH_2OAc$ groups on lactone moieties for the minor *E*-isomers in compounds **13** and **14** appeared more downfield than the corresponding signals for their major *Z*-isomers. The SeO_2 oxidation of **13** in anhydrous acetic acid gave the desired diacetoxymethylbutenolide **14** in 92% yield. To obtain the natural products **1** and **2**, we systematically studied the deacylation of **14**, both under acidic and basic conditions and observed that the starting material **14** and formed products **1** and **2** are not very stable under these conditions. In our hands, we always got a complex mixture of products and this could be due to the intermolecular reactions of the two hydroxymethyl groups with the reactive enol-lactone. Finally, we carried out the Amano PS catalyzed double deacylation of **14** at pH 7 and obtained the mixture of desired products **1** and **2** (**1**:**2**=86:14, by ^{1}H NMR) in 95% yield. All our attempts to obtain the pure major isomer **1** from the **1** plus **2** mixture by recrystallization were unsuccessful. Finally, we did the HPLC separation of **1** plus **2** mixture using the known procedure[2] and obtained pure **1** and **2** with quantitative recovery. The analytical and spectral data obtained for **1** and **2** were in complete agreement with the reported data.[2] In the present six-step synthesis, starting from itaconic anhydride (**9**), the overall yield of ellipsoidone A (**1**) and ellipsoidone B (**2**) were 20.4 and 3.3%, respectively. The photochemical conversion of ellipsoidone B to ellipsoidone A is known.[2]



3. Conclusion

In summary, we have demonstrated the first total synthesis of isomeric natural cytotoxic ellipsoidone A (**1**) and natural ellipsoidone B (**2**) using regioselective reduction of acetoxymethylmaleic anhydride (**11**), selenium dioxide hydroxylation of butenolide **13** and an enzymetic deacylation of diacetoxybutenolide **14** as key reactions. In the present stepwise approaches, we could design the acetyl derivatives of both the unnatural deoxyellipsoidone regioisomers. In the present synthesis, the enzymatic hydrolysis of diacetate **14** to obtain the labile multifunctional ellipsoidones A and B in 95% yield is noteworthy. We feel that the present approach to **1** and **2** is general in nature and it would be useful to design the analogs and congeners of these bioactive natural products for the structure–activity relationship studies.

4. Experimental

4.1. General

Melting points are uncorrected. Column chromatographic separations were carried out on ACME silica gel (60–120 mesh). Commercially available citraconic anhydride, sodium borohydride, 5-methylfurfural, piperidine, selenium dioxide, bromine, sodium acetate, and Amano PS-1310 U from Amano Pharmaceuticals, Japan were used. The activity of the lipase powder[12] used is expressed in terms of units, 1 unit corresponding to micromoles of butyric acid liberated (estimation by GC) from glyceryl tributyrate per minute per milligram of enzyme powder. Dry acetic acid was obtained by refluxing it over active $CuSO_4$ for 12 h, followed by distillation.

4.1.1. 4-Methyl-5*H*-furan-2-one (4). To a stirred solution of citraconic anhydride **3** (800 mg, 7.14 mmol) in THF (15 mL), was added $NaBH_4$ (675 mg, 17.85 mmol) at 0 °C and the reaction mixture was further stirred at 0 °C for 2 h. The reaction was quenched with water, acidified with dilute HCl and extracted with ethyl acetate (50 mL×3). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (3:7) furnished pure **4**.[9]

Compound **4**: 609 mg (87% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.16 (s, 3H), 4.76 (s, 2H), 5.83 (q, J= 2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.5, 73.5, 115.5, 166.4, 173.8; IR ($CHCl_3$) ν_{max} 1782, 1751, 1647, 1215 cm^{-1}. Anal. Calcd for $C_5H_6O_2$: C, 61.22; H, 6.17. Found: C, 61.37; H, 6.21.

4.1.2. 4-Methyl-5-(5-methyl-furan-2-ylmethylene)-5*H*-furan-2-one (5). To a stirred solution of lactone **4** (300 mg, 3.06 mmol) in methanol were added piperidine (0.21 mL, 2.14 mmol) and 5-methylfurfural (0.30 mL, 3.06 mmol) at room temperature and the reaction mixture was stirred for 15 h. Removal of solvent in vacuo followed by column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (0.5:9.5) furnished **5** as a yellow crystalline solid.

Compound **5**: 442 mg (76% yield); mp 103–105 °C; ^{1}H NMR ($CDCl_3$, 200 MHz), major *Z*-isomer: δ 2.19 (d, J= 1 Hz, 3H), 2.35 (s, 2.7H), 5.91 (br s, 1H), 6.04 (s, 0.9H), 6.15 (d, J=4 Hz, 0.9H), 6.94 (d, J=4 Hz, 0.9H), [the following four signals for the minor *E*-isomer showed splitting and appeared at δ 2.49 (d, J=1 Hz, 0.3H), 6.10 (d, J=4 Hz, 0.1H), 6.44 (s, 0.1H), 6.49 (d, J=4 Hz, 0.1H)]; ^{13}C NMR ($CDCl_3$, 50 MHz), major *Z*-isomer: δ 11.5, 13.7, 98.9, 109.6, 114.8, 116.6, 146.7, 147.5, 154.5, 154.7, 169.2; IR ($CHCl_3$) ν_{max} 1773, 1751, 1651, 1520, 1215 cm^{-1}. Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.22; H, 5.51.

4.1.3. 5-(3-Methyl-5-oxo-5*H*-furan-2-ylidenemethyl)-furan-2-carbaldehyde (6). To a stirred solution of lactone **5** (100 mg, 0.53 mmol) in acetic acid (5 mL) was added SeO_2 (117 mg, 1.05 mmol) and the reaction mixture was refluxed for 2 h. The reaction mixture was filtered through Celite and acetic acid was removed in vacuo. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:4) to furnish **6** as a yellow crystalline solid.

Compound **6**: 28 mg (26% yield); mp 187–190 °C; ^{1}H NMR ($CDCl_3$, 200 MHz), major *Z*-isomer: δ 2.26 (s, 2.7H), 6.10 (s, 1H), 6.19 (s, 0.9H), 7.23 (d, J=4 Hz, 1H), 7.34 (d, J= 4 Hz, 0.9H), 9.65 (s, 1H), [the following three signals for the minor *E*-isomer showed splitting and appeared at δ 2.58 (s, 0.3H), 6.53 (s, 0.1H), 6.71 (d, J=4 Hz, 0.1H)]; ^{13}C NMR ($CDCl_3$, 50 MHz), major *Z*-isomer: δ 11.6, 97.2, 116.1, 117.3, 123.5, 151.7, 152.0, 153.8, 154.9, 168.0, 177.3; IR ($CHCl_3$) ν_{max} 1782, 1676, 1215 cm^{-1}. Anal. Calcd for $C_{11}H_8O_4$: C, 64.71; H, 3.95. Found: C, 64.67; H, 4.04.

4.1.4. Acetic acid 5-(3-methyl-5-oxo-5*H*-furan-2-ylidene methyl)-furan-2-ylmethyl ester (7). To a stirred solution of lactone **5** (100 mg, 0.53 mmol) in dry acetic acid (5 mL) was added SeO_2 (117 mg, 1.05 mmol) and the reaction mixture was refluxed for 1.5 h. The reaction mixture was filtered through Celite and acetic acid was removed in vacuo. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:9) to furnish **7** as a yellow crystalline solid.

Compound **7**: 120 mg (92% yield); mp 84–86 °C; ^{1}H NMR ($CDCl_3$, 200 MHz), major *Z*-isomer: δ 2.10 (s, 2.7H), 2.22 (d, J=2 Hz, 3H), 5.08 (s, 2H), 5.97 (s, 1H), 6.09 (s, 1H), 6.55 (d, J=4 Hz, 0.9H), 7.02 (d, J=4 Hz, 1H), [the following two signals for the minor *E*-isomer showed splitting and appeared at δ 2.48 (s, 0.3H), 6.50 (d, J=4 Hz, 0.1H)]; ^{13}C NMR ($CDCl_3$, 50 MHz), major *Z*-isomer: δ 11.6, 20.8, 57.9, 98.4, 113.7, 115.6, 115.7, 148.1, 149.4, 150.6, 154.8, 168.9, 170.5; IR ($CHCl_3$) ν_{max} 1774, 1751, 1651, 1601, 1234 cm^{-1}. Anal. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 63.03; H, 4.62.

4.1.5. 5-(5-Hydroxymethyl-furan-2-ylmethylene)-4-methyl-5*H*-furan-2-one (8). To a stirred solution of lactone **7** (70 mg, 0.28 mmol) in methanol (5 mL) was added K_2CO_3 (5 mg, 0.04 mmol) and the reaction mixture was

stirred at room temperature for 1 h. Methanol was removed in vacuo at room temperature and water (10 mL) was added to the reaction mixture. The reaction mixture was acidified to pH 4 using 2 N HCl and immediately extracted with ethyl acetate (15 mL×4). The combined organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by silica gel column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (2:8) as an eluent gave **8**.

Butenolide **6** (25 mg, 0.12 mmol) on $NaBH_4$ (5 mg, 0.14 mmol) reduction in EtOH (3 mL) at room temperature for 1 h followed by acidification with 2 N HCl gave **8** in 68% yield as a yellow crystalline solid.

Compound **8**: 35 mg (61% yield); mp 95–96 °C; ^{1}H NMR ($CDCl_3$, 200 MHz), major *Z*-isomer: δ 2.20 (s, 2.64H), 4.64 (s, 3H), 5.94 (s, 1H), 6.07 (s, 1H), 6.43 (d, J=4 Hz, 0.88H), 6.95 (d, J=4 Hz, 1H), [the following two signals for the minor *E*-isomer showed splitting and appeared at δ 2.49 (s, 0.36H), 6.53 (d, J=4 Hz, 0.12H)]; ^{13}C NMR ($CDCl_3$, 50 MHz), major *Z*-isomer: δ 11.6, 57.5, 98.6, 111.0, 115.4, 115.8, 147.7, 148.8, 154.9, 155.6, 169.1; IR ($CHCl_3$) ν_{max} 3449, 1780, 1755, 1649, 1599, 1217 cm^{-1}. Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 63.91; H, 4.99.

4.1.6. 2-Bromo-2-(bromomethyl)succinic acid (10). To a stirred solution of itaconic anhydride **9** (4.0 g, 35.70 mmol) in carbon tetrachloride (30 mL) was added a solution of bromine (3.60 mL, 71.40 mmol) in carbon tetrachloride (20 mL) at room temperature over a period of 20 min. The reaction mixture was further stirred for 24 h and then it was concentrated in vacuo. The obtained crude residue was recrystallized from petroleum ether plus ethyl acetate (1:1) mixture to obtain pure **10**[10] as a white crystalline solid.

Compound **10**: 10.13 g (98% yield); mp 163–165 °C (lit.[10] mp 167–168 °C); ^{1}H NMR (D_2O, 200 MHz) δ 3.27 (dd, J=18, 4 Hz, 2H), 4.03 (s, 2H); ^{13}C NMR (D_2O, 50 MHz) δ 40.0, 44.7, 59.5, 173.5, 174.8; IR (Nujol) ν_{max} 2700–2500, 1720, 1713, 1462 cm^{-1}.

4.1.7. Acetic acid 5-oxo-2,5-dihydro-furan-3-ylmethyl ester (12). To a stirred solution of acid **10** (2.0 g, 6.90 mmol) in Ac_2O (15 mL) was added NaOAc (1.70 g, 20.70 mmol) and the reaction mixture was stirred at room temperature for 6 h. Acetic anhydride was removed in vacuo to obtain crude **11**. To the stirred solution of this residue in THF (20 mL) was added $NaBH_4$ (522 mg, 13.80 mmol) at 0 °C. The reaction mixture was further stirred at 0 °C for 2 h and then quenched with water and acidified with dilute HCl and extracted with ethyl acetate (50 mL×3). The organic layer was washed with water, brine and dried over Na_2SO_4. Concentration of the organic layer in vacuo followed by the silica gel column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (3:7) furnished **12**.[11]

Compound **11** (crude): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.19 (s, 3H), 5.05 (d, J=2 Hz, 2H), 6.83 (t, J=2 Hz, 1H); IR (neat) ν_{max} 1771, 1738, 1730 cm^{-1}.

Compound **12**: 400 mg (37% yield); thick oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.11 (s, 3H), 4.81 (d, J=2 Hz, 2H), 4.93 (d, J=2 Hz, 2H), 6.01 (quintet, J=2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.3, 59.2, 71.0, 116.6, 163.6, 170.0, 172.7; IR (neat) ν_{max} 1782, 1747, 1651, 1229 cm^{-1}. Anal. Calcd for $C_7H_8O_4$: C, 53.85; H, 5.16. Found: C, 53.77; H, 5.04.

4.1.8. Acetic acid 2-(5-methyl-furan-2-ylmethylene)-5-oxo-2,5-dihydro-furan-3-ylmethyl ester (13). To a stirred solution of lactone **12** (300 mg, 1.92 mmol) in methanol was added piperidine (0.13 mL, 1.35 mmol) and 5-methyl-furfural (0.19 mL, 1.92 mmol) at room temperature and the reaction mixture was stirred for 15 h. Removal of solvent in vacuo followed by column chromatographic purification of the residue using a mixture of ethyl acetate and petroleum ether (1:9) furnished **13** as a faint yellow solid.

Compound **13**: 358 mg (75% yield); mp 83–85 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.16 (s, 2.79H), 2.23 (s, 0.21H), 2.35 (s, 2.79H), 2.43 (s, 0.21H), 5.06 (d, J=2 Hz, 1.86H), 5.43 (d, J=2 Hz, 0.14H), 6.08 (s, 0.93H), 6.11 (s, 0.93H), 6.17 (d, J=4 Hz, 0.93H), 6.23 (s, 0.07H), 6.26–6.31 (m, 0.07H), 6.50 (br s, 0.07H), 6.53 (d, J=4 Hz, 0.07H), 6.97 (d, J=4 Hz, 0.93H); ^{13}C NMR ($CDCl_3$, 50 MHz), major *Z*-isomer: δ 13.8, 20.6, 57.3, 100.3, 109.9, 114.8, 117.6, 143.1, 147.0, 152.5, 155.2, 168.4, 170.0; IR ($CHCl_3$) ν_{max} 1773, 1751, 1653, 1597, 1215 cm^{-1}. Anal. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 63.02; H, 4.95.

4.1.9. Acetic acid 2-(5-acetoxymethyl-furan-2-ylmethylene)-5-oxo-2,5-dihydro-furan-3-ylmethyl ester (14). To a stirred solution of lactone **13** (300 mg, 1.21 mmol) in dry acetic acid (10 mL) was added SeO_2 (268 mg, 2.42 mmol) and the reaction mixture was refluxed for 6 h. The reaction mixture was filtered through Celite and acetic acid was removed in vacuo. The residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (0.5:9.5) to furnish **14** as a faint yellow solid.

Compound **14**: 341 mg (92% yield); mp 93–96 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.10 (s, 3H), 2.18 (s, 3H), 5.07 (d, J=1 Hz, 1.6H), 5.08 (s, 1.6H), 5.11 (s, 0.4H), 5.42 (d, J=1 Hz, 0.4H), 6.13 (s, 0.8H), 6.19 (d, J=2 Hz, 0.8H), 6.30–6.35 (m, 0.2H), 6.50–6.60 (m, 0.6H), 6.56 (d, J=4 Hz, 0.8H), 7.05 (d, J=4 Hz, 0.8H); very clean two sets of ^{13}C carbon signals were obtained for the major and minor isomers, ^{13}C NMR ($CDCl_3$, 125 MHz), major isomer: δ 20.6, 20.8, 57.2, 57.9, 99.8, 113.8, 116.1, 116.6, 144.9, 149.0, 151.3, 152.7, 167.9, 170.0, 170.4, minor isomer: δ 20.6, 20.7, 57.7, 60.8, 103.5, 113.3, 117.2, 118.4, 145.4, 147.6, 152.0, 152.1, 167.6, 169.9, 170.5; IR ($CHCl_3$) ν_{max} 1776, 1746, 1676, 1653, 1605, 1219 cm^{-1}. Anal. Calcd for $C_{15}H_{14}O_7$: C, 58.83; H, 4.61. Found: C, 58.72; H, 4.80.

4.1.10. 4-Hydroxymethyl-5-(5-hydroxymethyl-furan-2-ylmethylene)-5*H*-furan-2-one (ellipsoidone A, 1 and ellipsoidone B, 2). A solution of diacetate **14** (100 mg, 0.33 mmol) in petroleum ether–benzene (2/1) mixture (12 mL) was added to a suspension of Amano PS lipase (40 mg) in aqueous sodium phosphate (0.01 M, 4 mL) at pH 7. The reaction mixture was stirred at room temperature for 40 h. The reaction mixture was filtered through Celite

and the aqueous layer was extracted with ethyl acetate (20 mL×4). The combined organic layer was washed with water, brine and dried over Na_2SO_4. The organic layer was concentrated in vacuo and the residue was purified by silica gel column chromatography using a mixture of ethyl acetate and petroleum ether (1:1) as an eluent to furnish ellipsoidone A (**1**) plus ellipsoidone B (**2**) in 95% yield. HPLC separation of **1** plus **2** mixture was done using the known literature procedure.[2]

Compound **1**: 59 mg (81.4% yield); yellow crystalline solid; mp 141–143 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 4.57 (s, 2H), 4.73 (s, 2H), 6.20 (s, 1H), 6.31 (s, 1H), 6.49 (d, J= 5 Hz, 1H), 6.90 (d, J=5 Hz, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 57.1, 57.3, 99.8, 111.0, 114.2, 116.4, 145.7, 149.3, 158.5, 161.5, 169.2; IR (Nujol) ν_{max} 3329, 3211, 1749, 1638, 1462 cm^{-1}. Anal. Calcd for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54. Found: C, 59.52; H, 4.63.

Compound **2**: 9.6 mg (13.2% yield); yellow crystalline solid; mp 159–161 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 4.63 (s, 2H), 4.97 (d, J=2 Hz, 2H), 6.41 (m, 1H), 6.46 (d, J=1 Hz, 1H), 6.62 (s, 1H), 6.74 (d, J=2 Hz, 1H); ^{13}C NMR (acetone-d_6, 125 MHz) δ 57.3, 60.0, 103.6, 110.5, 117.8, 117.9, 146.1, 147.8, 159.0, 160.5, 168.4; IR (Nujol) ν_{max} 3331, 3302, 1736, 1638, 1460 cm^{-1}. Anal. Calcd for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54. Found: C, 59.31; H, 4.60.

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Excimer emission and energy transfer in cofacial boradiazaindacene (BODIPY) dimers built on a xanthene scaffold

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Abstract—Using a rigid xanthene scaffold, a series of boradiazaindacene derivatives were synthesized. In some of these compounds, two boradiazaindacene derivatives were placed cofacially, resulting in significant inter-chromophoric interactions, including excimer emission. A simple modification of boradiazaindacene structure leads to formation of an ICT dye, which has distinct spectral properties. Energy transfer between two BODIPY dyes was demonstrated as well. In addition, the spectral properties of ICT dye can be modulated by the addition of the acid leading to an acid switchable energy transfer cassette.

1. Introduction

Boradiazaindacenes (a.k.a, BODIPY dyes, BDPs, difluorobora-dipyrromethenes, etc.) are well known fluorescent dyes with remarkable spectral properties like high quantum yields, large extinction coefficients and narrow emission bands.[1] These properties facilitated their application in many fields, such as fluorescent labeling of biomolecules,[2] ion sensing and signaling,[3] energy transfer cassettes,[4] light harvesting systems[5] and fluorescent stains.[1] Especially considering the relative ease of derivatization, it should not be difficult to predict further diversification of applications in the near future. Dimeric boradiazaindacenes should be particularly interesting as a new subclass of these dyes. It is well known that when biomolecules are labeled with boradiazaindacene dyes at relatively large dye/protein ratios, two boradiazaindacene moieties can come very close to each other and interactions yield quenching of the emission and/or formation of a bathochromically shifted excimer band.[6] The existence of two structurally distinct dimers were proposed and based on these observations, a BODIPY dimer obtained by the labeling of diaminocyclohexane was studied.[7] However, in all of these dimeric systems, boradiazaindacene units are highly flexible and in principle can adopt a number of different excited state structures. Thus, it would be very interesting to assemble two boradiazaindacene units in a rigid cofacial arrangement on a suitable scaffold. Here, there is just one possible transition dipole, which might lead to a very clearly understandable experimental results. The xanthene unit seems to provide such a structural feature because functionalization at positions 4 and 5 looks straightforward (Fig. 1). In recent literature, there are reports of cofacially arranged porphyrin and perylenediimide dyes,[8] but no examples of cofacial boradiazaindacene dimers were found. In this paper, we present the synthesis, energy transfer and acid switching of spectral properties of novel boradiazaindacene dimers built on a xanthene scaffold.

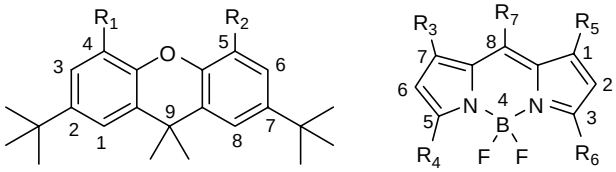

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Figure 1. Structures of 2,7-di-*tert*-butyl-9,9-dimethyl-9*H*-xanthane I and difluorobora-dipyrromethene II.

2. Results and discussion

The synthesis of the dyes **4**, **5** and **9** starts with the chloromethylation of the *t*-butylated xanthene derivative **1** (Scheme 1). Paraformaldehyde and concd HCl was used to carry out this transformation. Following a standard work-up, the product was usually obtained in satisfactory purity and

Keywords: BODIPY dyes; Energy transfer; Multichromophoric systems; Molecular switches.
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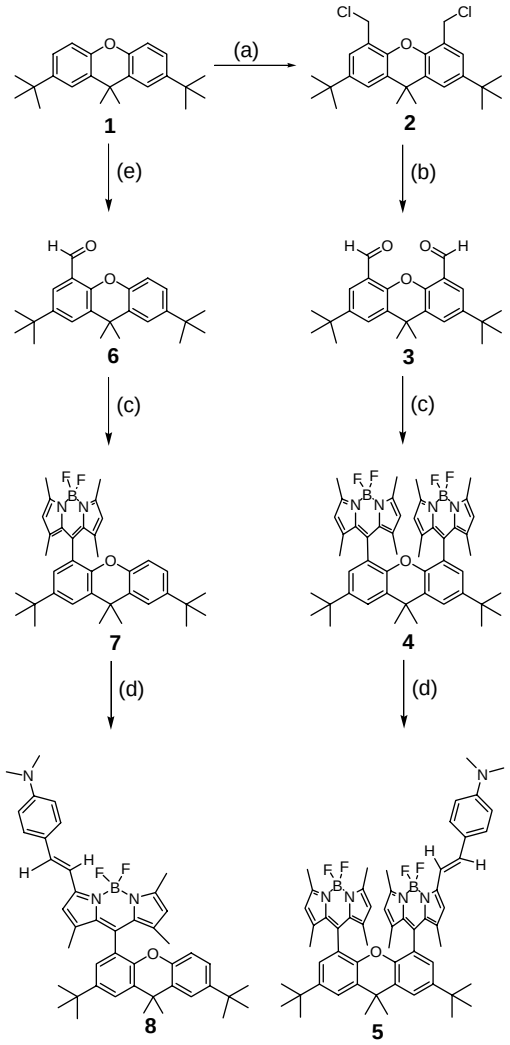
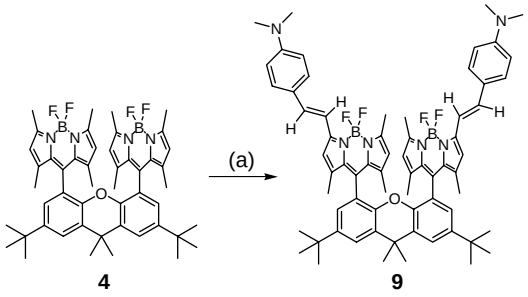


Scheme 1. Synthesis of BODIPY dyes **4**, **5**, **7** and **8**. Reagents and conditions: (a) HCl, $(CH_2O)_n$, Δ, CH_3COOH, *o*-phosphoric acid; (b) DMSO, $NaHCO_3$, Δ; (c) 2,4-dimethylpyrrole, TFA, Et_3N, BF_3:OEt_2, rt; (d) piperidine, CH_3COOH, *N*,*N*-dimethyl-4-aminobenzaldehyde; (e) HMTA, TFA, reflux.

used directly in the next step, which is the oxidation to bis-aldehyde **3** using DMSO. This aldehyde was then utilized in the construction of two boradiazaindacene units on the xanthene scaffold. This was done in analogy to the literature procedures, using 2,4-dimethylpyrrole as the source for the pyrrole unit. Following the purification steps, a bright green fluorescent dye **4** was obtained in 24% yield. Due to the acidity of the methyl groups at positions 3 and 5 of the boradiazaindacene heterocyclic system, extension of conjugation is possible by the condensation with aromatic aldehydes.[3e,9] We chose *p*-dimethylaminobenzaldehyde as the aldehyde in this reaction, because the electron donor capacity of the dialkylamino group can be modified by the protonation/deprotonation equilibrium, which could result in significant spectral changes. Thus, compounds **5** and **9** were obtained by refluxing the aldehyde together with the dye **4** in a Dean–Stark apparatus (Scheme 2). The second methyl group in each boradiazaindacene unit is presumably less reactive. In order to accurately assess the inter-chromophoric interactions including resonance energy transfer, we also synthesized xanthene derivatives carrying just one boradiazaindacene unit (compounds **7** and **8**).



Scheme 2. Synthesis of BODIPY dye **9**. Reagents and conditions: (a) piperidine, CH_3COOH, *N*,*N*-dimethyl-4-aminobenzaldehyde.

The normalized absorption spectra of compounds **4** and **7** in THF are shown in Figure 2. There are remarkable changes in the absorption spectrum. In the cofacial dimer **4**, the absorption peak is blue shifted to 478 nm with a shoulder at 504 nm. Compound **5**, as expected, shows two peaks, one for the standard boradiazaindacene absorption (455 nm) and one for the extended conjugation chromophore 575 nm. When a few drops of TFA is added, the long wavelength ICT absorption shifts to shorter wavelengths (530 nm) reflecting lower electron donor characteristics of the protonated dialkylamino groups (Fig. 3). Also, the absorption spectra of compounds **5**, **8** and **9** are shown separately in Figure 4. Extension of conjugation, as expected, results in a broad longer wavelength absorption at 571 nm. This is in accordance with the internal charge transfer (ICT) character of the dyes. The emission spectra are even more interesting: while monochromophoric **7** yields a very strong emission at 500 nm when excited at 480 nm, **4** results in highly quenched emission with two

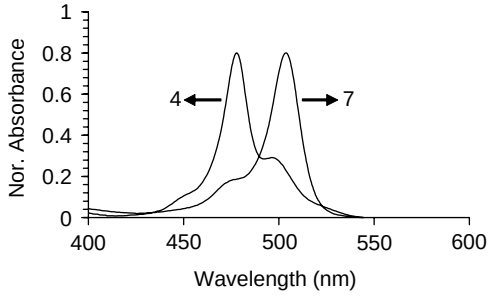


Figure 2. Normalized absorption spectra of compounds **4** and **7**. Normalized (performed at the maxima (478 and 504 nm, respectively)) to an arbitrary value of 0.8.

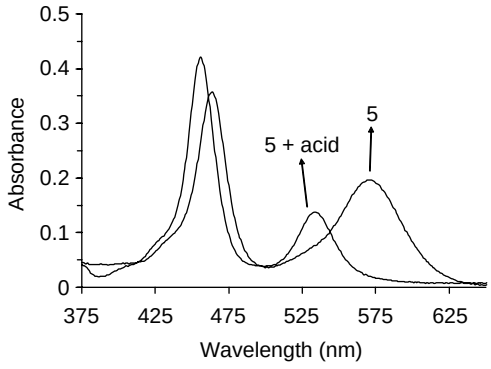


Figure 3. Absorption spectra of compound **5** and its acidified form. Upon acidification with a few drops of TFA, a significant blue shift is observed.

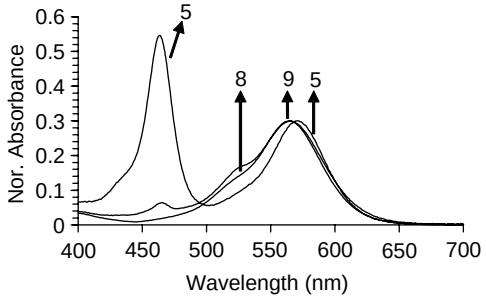


Figure 4. Normalized absorption spectra of compounds **5**, **8** and **9**. Normalization was done at the long wavelength peaks to an arbitrary value of 0.3.

peaks one at 505 nm and a broader excimer emission with a peak at 590 nm (Fig. 5). This is in accordance with the earlier observations made with less rigid boradiazaindacene dimers and organized media like micelles. In Figure 6, emission characteristics of **4**, **5** and **8** were compared. When the absorptions at the excitation wavelength (480 nm) for **4** and **5** were adjusted to 0.1, the emission spectra give more quantitative information about the quantum yields and the efficiency of the energy transfer relative emission. Very clearly, in compound **5**, the emission from the green emitting boradiazaindacene unit is further quenched, and some emission at long wavelength can be seen, this is due to energy transfer between the donor and the acceptor chromophore. The absorption of compound **8** was also adjusted at the long wavelength peak (near 550 nm) to that of compound **5**. But, since this chromophore does not absorb at 480 nm effectively, the emission is very weak. When analyzed together, it becomes obvious that in compound **5** there is efficient energy transfer. The efficiency can be

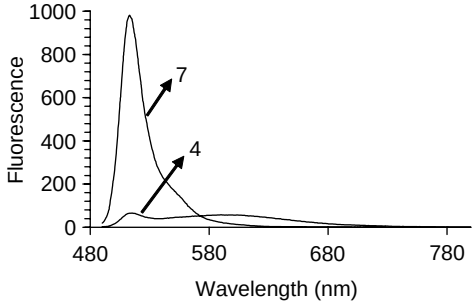


Figure 5. Emission spectra of compounds **4** and **7**. The absorption values at the excitation wavelength (480 nm) was adjusted to 0.1.

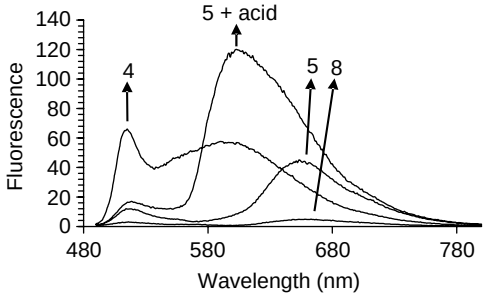


Figure 6. Emission spectrum of **4**, **5**, **8**. Absorption values of the dyes **4** and **5** were set at 0.1, whereas the absorption peaks at the long wavelength region (near 550 nm) were set to be comparable for the dyes **5** and **8**.

further improved by the protonation of the dialkylaminogroups by the addition of a few drops of TFA. The increase in intensity is probably in part due to the increased spectral overlap caused by the blue shift in the absorption spectrum of compound **5**.

3. Conclusion

We have synthesized and characterized xanthene derivatives with boradiazaindacene units attached orthogonally and in a very rigid arrangement. The cofacial chromophores were separated from each other only by a distance of approximately 4.5 Å, so both energy transfer and excimer formation can be observed in these systems. These derivatives can be excellent models to study the role of orientation of dipole moments during excitation. A careful inspection of the structure of compound **9** reveals that *syn–anti* stereoisomerism is possible. Although isolation of both isomers would be very useful in the study relative chromophore orientations in energy transfer, we were able to isolate only one isomer, most likely the *anti*-isomer. Based on our modeling studies, and considering the steric requirements of the condensation reaction, the *anti*-isomer is expected to be the major, if not the sole product.

The bichromophoric systems described here, have some potential as energy transfer cassettes, as well. In principle, these compounds can be excited at 480 nm, and the emission can be collected at 650 nm. As novel fluorophore systems, it is also likely that water soluble derivatives can be used in labeling biomolecules and in novel fluorescent chemosensors for cations or anions.

4. Experimental

4.1. General

The compounds were characterized and analyzed by nuclear magnetic resonance spectroscopy (NMR), UV/vis spectroscopy, and fluorescence spectroscopy. ^{1}H and ^{13}C nuclear magnetic resonance spectra of all compounds were recorded in $CDCl_3$ with Bruker Gmbh DPX-400, 400 MHz High Performance Digital FT-NMR Spectrometer. UV/vis spectra were recorded by Varian Bio 100 UV/vis Spectrophotometer. Fluorescence spectra were recorded using Varian Cary Eclipse Fluorescence Spectrophotometer. All solvents were distilled over $CaCl_2$ before use. 2,7-Di-*tert*-butyl-9,9-dimethyl-xanthane and 2,4-dimethylpyrrole were obtained from Aldrich. Hexamethylenetetramine was purchased from MERCK-Schuchardt. Merck Silica Gel 60 F_{254} TLC Aluminum sheets were used in monitoring reactions by thin-layer chromatography. Merck Silica Gel 60 (particle size 0.040–0.0963 mm, 230–400 mesh ASTM) used in column chromatography.

4.1.1. 2,7-Di-*tert*-butyl-4,5-bis(chloromethyl)-9,9-dimethyl-9*H*-xanthene 2. A mixture of 2,7-di-*tert*-butyl-9,9-dimethyl-9*H*-xanthene (500 mg, 1.55 mmol), *p*-formaldehyde (200 mg), orthophosphoric acid (0.14 mL), HCl (0.6 mL) and acetic acid (8.2 mL) were heated in a pressure

tube at 85 °C for overnight. The reaction mixture was then diluted with $CHCl_3$ and the solution was washed with saturated $NaHCO_3$. Then, the organic phase was dried over anhydrous Na_2SO_4 and solvent was evaporated under reduced pressure to give bis(chloromethyl)xanthene **2** as white powder (585 mg, 90%). Used in the following steps without further purification. Mp 201–202 °C. IR (KBr) ν_{max}: 3022, 1110 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 18H, $C(CH_3)_3$), 1.57 (s, 6H, $C(CH_3)_2$), 4.75 (s, 4H, CH_2), 7.17 (s, 2H, Ar-H), 7.28 (s, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.9, 32.0, 32.8, 34.9, 42.5, 123.9, 124.4, 125.9, 130.0, 146.1, 146.4.

4.1.2. 2,7-Di-*tert*-butyl-9,9-dimethyl-9*H*-xanthene-4,5-dicarbaldehyde 3. 2,7-Di-*tert*-butyl-4,5-bis(chloromethyl)-9,9-dimethyl-9*H*-xanthene (1.2 g, 2.86 mmol) and $NaHCO_3$ (600 mg, 7.14 mmol) were heated in DMSO (200 mL) for 3 days. The reaction mixture was then diluted with $CHCl_3$, and the solution was washed with water until all the DMSO was removed. Then the mixture was dried over Na_2SO_4. The solvent was evaporated, and the residue was purified by silica gel column chromatography (CH_3OH/$CHCl_3$ 1:99) to give **3** (324.7 mg, 30%) as a white solid. Mp 248–249 °C. IR (KBr) ν_{max}: 3031, 1721, 1128 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 18H, $C(CH_3)_3$), 1.62 (s, 6H, $C(CH_3)_2$), 7.64 (d, J_{meta}=2.38 Hz, 2H, Ar-H), 7.74 (d, J_{meta}=2.39 Hz, 2H, Ar-H), 10.6 (s, 2H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.7, 32.6, 32.8, 35.1, 62.4, 123.8, 124.4, 129.8, 130.9, 147.0, 149.9, 189.2. Elemental analysis: Found: C, 79.13; H, 8.05. $C_{25}H_{30}O_3$ requires C, 79.33; H, 7.99.

4.1.3. Bis-(boradiazaindacenyl)-derivatized xanthene 4. 2,4-Dimethylpyrrole (456 mg, 4.8 mmol) was added to a solution of 2,7-di-*tert*-butyl-9,9-dimethyl-9*H*-xanthene-4,5-dicarbaldehyde (400 mg, 1.05 mmol) in argon bubbled CH_2Cl_2 (750 mL). Then a drop of CF_3COOH was added and the solution was allowed to stir for 4 h at room temperature. Then tetrachloro-1,4-benzoquinone (258.3 mg, 1.05 mmol) in absolute CH_2Cl_2 (50 mL), Et_3N (4 mL) and BF_3:OEt_2 (4 mL) were added in order to the solution and stirred for overnight at at room temperature for overnight. The solution was concentrated under reduced pressure and washed with water several times and dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography (CH_3OH/$CHCl_3$ 1:99) to obtain reddish product **4** (162.9 mg, 20%). IR (KBr) ν_{max}: 3027, 1178, 1133 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.25–1.29 (overlapping singlets, 18H+12H, $C(CH_3)_3$+pyr-CH_3), 1.57 (s, 6H, $C(CH_3)_2$), 2.03 (s, 12H, pyr-CH_3), 5.21 (s, 4H, pyr-H), 7.17 (d, J_{meta}=1.96 Hz, 2H, Ar-H), 7.33 (d, J_{meta}=2.0 Hz, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 14.7, 31.5, 33.5, 34.7, 62.5, 120.1, 122.3, 123.3, 125.1, 128.7, 131.2, 136.8, 141.4, 143.8, 147.1, 155.1. Elemental analysis: Found: C, 72.14; H, 6.74; N, 6.99. $C_{49}H_{56}N_4OB_2F_4$ requires C, 72.25; H, 6.93; N, 6.88.

4.1.4. Bichromophoric xanthene derivative 5. Compound **4** (110 mg, 1.35 mmol) and *N*,*N*-dimethyl-4-aminobenzaldehyde (143.1 mg, 1.35 mmol) in a mixture of benzene (18 mL), acetic acid (510 μL) and piperidine (560 μL). Water formed during the reaction was removed azeotropically by heating in a Dean–Stark apparatus for 3 h. The solution containing the crude product was concentrated under reduced pressure and purified by silica gel column chromatography (1:4 ethylacetate/hexane) in 75% yield. IR (KBr) ν_{max}: 3093, 3036, 1172, 1095 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (unresolved singlets, 18H+12H, $C(CH_3)_3$+pyr-CH_3), 1.57 (s, 6H, $C(CH_3)_2$), 2.34 (s, 3H, pyr-CH_3), 2.39 (s, 3H, pyr-CH_3), 2.41 (s, 3H, pyr-CH_3), 3.0 (s, 6H, $N(CH_3)_2$), 5.20 (s, 1H, pyr-H), 5.51 (s, 1H, pyr-H), 5.55 (s, 1H, pyr-H), 5.65 (s, 1H, pyr-H), 6.63–6.65 (m, 2H), 6.88–7.05 (m, 4H), 7.4–7.45 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.4, 33.3, 33.7, 34.7, 119.8, 120.7, 112.4, 123.2, 123.3, 125.2, 125.5, 128.7, 130.9, 131.5, 136.7, 140.5, 141.8, 143.9, 144.1, 153.6, 156.9. Elemental analysis: Found: C, 73.43; H, 7.07; N, 7.29. $C_{58}H_{65}N_5OB_2F_4$ requires C, 73.66; H, 6.93; N, 7.40.

4.1.5. 2,7-Di-*tert*-butyl-9,9-dimethyl-9*H*-xanthene-4-carbaldehyde 6. A mixture of 2,7-di-*tert*-butyl-9,9-dimethyl-9*H*-xanthene (967 mg, 3 mmol), hexamethylene–tetramine (840 mg, 6 mmol) and CF_3COOH (6 mL) were refluxed for 24 h. The acid was removed under reduced pressure and the residue was then subjected to silica gel column chromatography. (CH_3OH/$CHCl_3$ 1:99) to yield compound **6** (540 mg, 51%). Mp 158–160 °C. IR (KBr) ν_{max}: 3039, 1719, 1114 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 18H, $C(CH_3)_3$), 1.62 (s, 6H, $C(CH_3)_2$), 6.8 (d, J_{ortho}=8.5 Hz, 1H, Ar-H), 7.06 (dd, J_{ortho}=8.5 Hz, J_{meta}=2.3 Hz, 1H, Ar-H), 7.3 (d, J_{meta}=2.3 Hz, 1H, Ar-H) 7.52 (d, J_{meta}=2.2 Hz, 1H, Ar-H), 7.62 (d, J_{meta}=2.3 Hz, 1H, Ar-H), 10.5 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 31.5, 32.8, 34.7, 41.4, 62.4, 116.0, 121.6, 122.9, 123.5, 124.4, 129.8, 130.9, 136.5, 148.5, 189.2. Elemental analysis: Found: C, 82.45; H, 8.58. $C_{24}H_{30}O_2$ requires C, 82.24; H, 8.63.

4.1.6. Boradiazaindacenyl-xanthene derivative 7. 2,4-Dimethylpyrrole (540 mg, 5.14 mmol) was added to a solution of 2,7-di-*tert*-butyl-9,9-dimethyl-9*H*-xanthene-4-carbaldehyde (540 mg, 2.57 mmol) in argon bubbled CH_2Cl_2 (750 mL). Then a drop of CF_3COOH was added and the solution was allowed to stir for 4 h at room temperature. Then, tetrachloro-1,4-benzoquinone (258 mg, 2.57 mmol) in dry CH_2Cl_2 (50 mL), Et_3N (4 mL) and BF_3:OEt_2 (4 mL) were added in that order to the solution, and stirred at room temperature overnight. The solution was concentrated under reduced pressure and washed with water several times, then dried over Na_2SO_4. The solvent was evaporated and the crude product was purified by column chromatography (CH_3OH/$CHCl_3$ 1:99) to obtain reddish product **7** (350.4 mg, 24%). IR (KBr) ν_{max}: 3024, 1180, 1130 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 18H, $C(CH_3)_3$), 1.34 (s, 6H, $C(CH_3)_2$), 1.59 (s, 6H, pyr-CH_3), 2.52 (s, 6H, pyr-CH_3) 5.87 (s, 2H, pyr-H), 6.77 (d, 1H, Ar-H, J_{ortho}=8.6 Hz), 7.01 (d, 1H, Ar-H, J_{meta}=2.6 Hz), 7.06 (dd, 1H, Ar-H, J_{ortho}=8.5 Hz, J_{meta}=2.3 Hz), 7.3 (d, 1H, Ar-H, J_{meta}=2.3 Hz), 7.4 (d, 1H, Ar-H, J_{meta}=2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 31.7, 32.8, 62.4, 123.8, 124.4, 129.8, 130.9, 147.0, 149.9, 189.2. Elemental analysis: Found: C, 76.23; H, 7.81; N, 4.78. $C_{36}H_{43}N_2OBF_2$ requires C, 76.05; H, 7.62; N, 4.93.

4.1.7. Extended conjugation boradiazaindacenyl xanthene derivative 8. Compound **7** (100 mg,

0.176 mmol) and *N*,*N*-dimethyl-4-aminobenzaldehyde (25.6 mg, 0.176 mmol) in a mixture of benzene (18 mL), acetic acid (506 μL) and piperidine (557 μL). Any water formed during the reaction was removed azeotropically by heating in a Dean–Stark apparatus for 3 h. The reaction mixture was concentrated under reduced pressure and then subjected to silica gel column chromatography (1:4 ethylacetate/hexane) to yield the desired product **8** in 50% yield (61 mg). IR (KBr) ν_{max}: 3090, 3032, 1177, 1101 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 18H, $C(CH_3)_3$), 1.35 (s, 3H, pyr-CH_3), 1.39 (s, 3H, pyr-CH_3), 1.59 (s, 6H, $C(CH_3)_2$), 2.5 (s, 3H, pyr-CH_3), 3.01 (s, 6H, $N(CH_3)_2$), 5.87 (s, 1H, pyr-H), 6.49 (s, 1H, pyr-H), 6.66 (d, 2H, $J=8.7$ Hz), 7.04–7.10 (m, 4H), 7.31 (d, $J=2.3$ Hz, 1H), 7.43–7.46, (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.5, 32.2, 32.4, 34.5, 34.7, 116.3, 122.1, 122.2, 123.0, 124.4, 125.2, 128.7, 129.1, 130.4, 145.8, 146.5, 148.1. Elemental analysis: Found: C, 77.45; H, 7.92; N, 5.99. $C_{47}H_{56}N_3OBF_2$ requires C, 77.57; H, 7.76; N, 5.77.

4.1.8. Extended conjugation bis-(boradiazaindacenyl)-xanthene derivative 9. Compound **4** (110 mg, 0.176 mmol) and *N*,*N*-dimethyl-4-aminobenzaldehyde (52.6 mg, 0.352 mmol) in a mixture of benzene (18 mL), acetic acid (506 μL) and piperidine (557 μL). Any water formed during the reaction was removed azeotropically by heating in a Dean–Stark apparatus for 3 h. The reaction mixture was concentrated under reduced pressure and then subjected to silica gel column chromatography (1:4 ethylacetate/hexane) to yield the desired product **8** in 40% yield (65 mg). IR (KBr) ν_{max}: 3087, 3033, 1173, 1099 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.24–1.30 (two unresolved singlets, 18H+12H), 1.59 (s, 6H), 2.55 (s, 6H), 3.01 (s, 12H, $N(CH_3)_2$) 5.85 (s, 2H), 6.50 (s, 2H), 6.64 (d, 4H, $J=8.7$ Hz), 6.78–6.82 (m, 2H), 7.02–7.25 (m, 8H), 7.35 (d, 2H). Elemental analysis: Found: C, 74.53; H, 6.92; N, 7.69. $C_{67}H_{74}N_6OB_2F_4$ requires C, 74.72; H, 6.93; N, 7.80.

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