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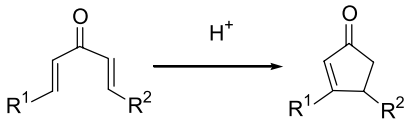
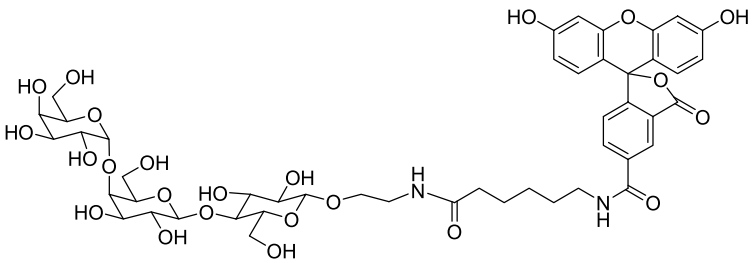
Contents

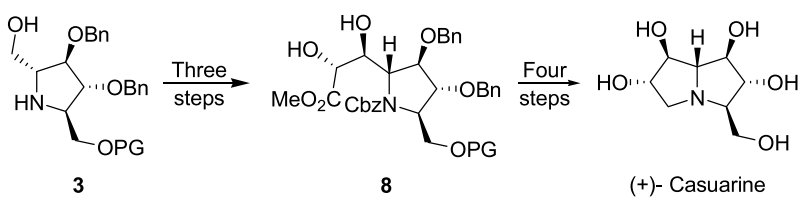
REPORT

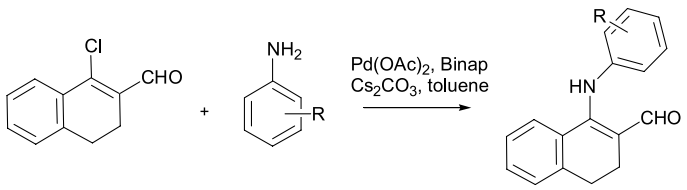


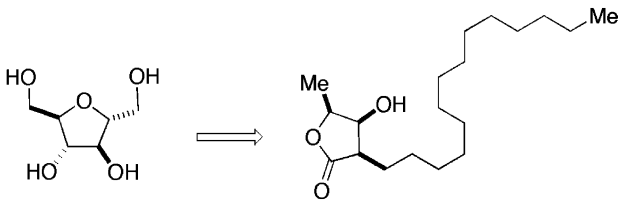
The Nazarov cyclisation is revisited. Recent improvements such as metal-catalysed Nazarov cyclisation, asymmetric Nazarov cyclisation, cationic cyclopentannelation of allenyl ethers, fluorine-directed Nazarov cyclisation, trapping of the photochemically generated oxyallyl zwitterions, and procedures called 'interrupted Nazarov reactions' have widely expanded the synthetic scopes of the process.

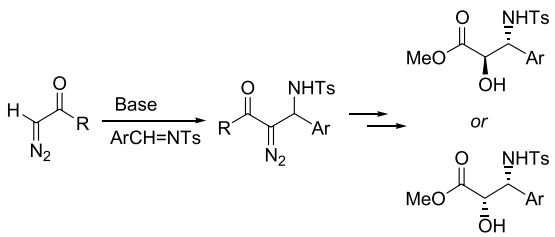
ARTICLES

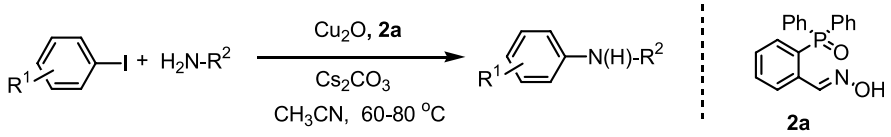


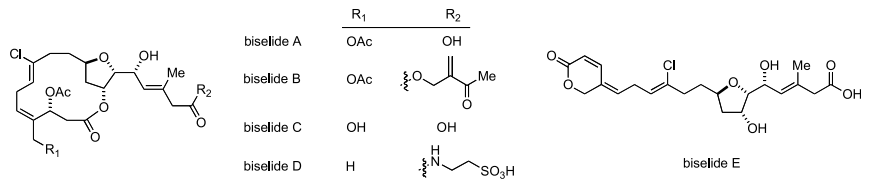


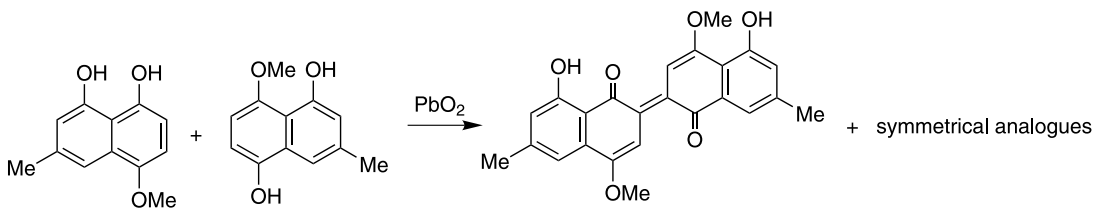


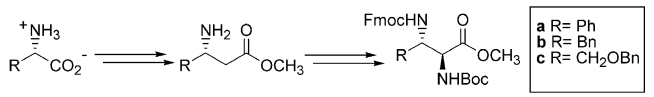


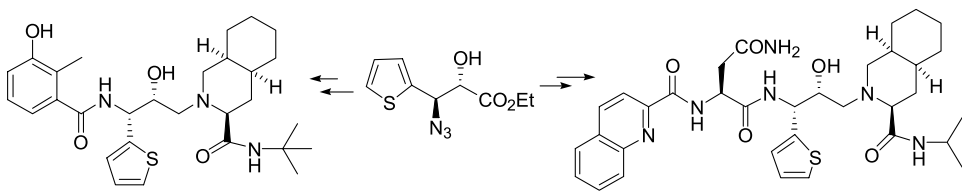


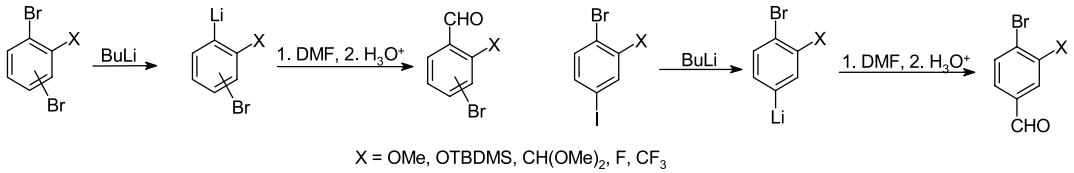


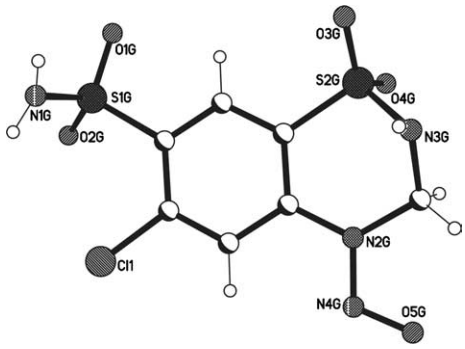


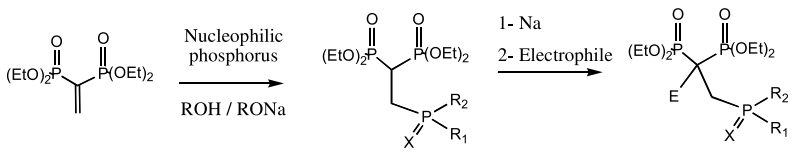


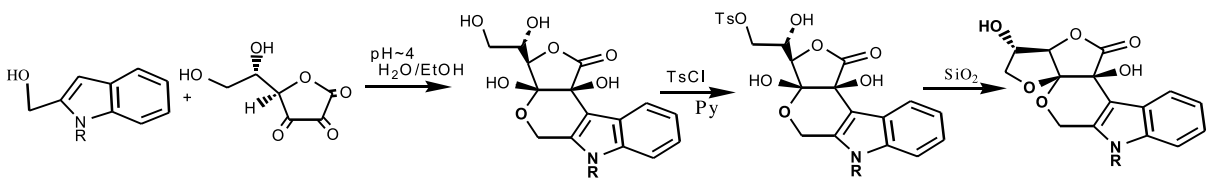


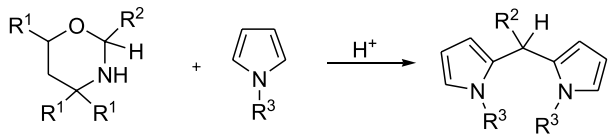


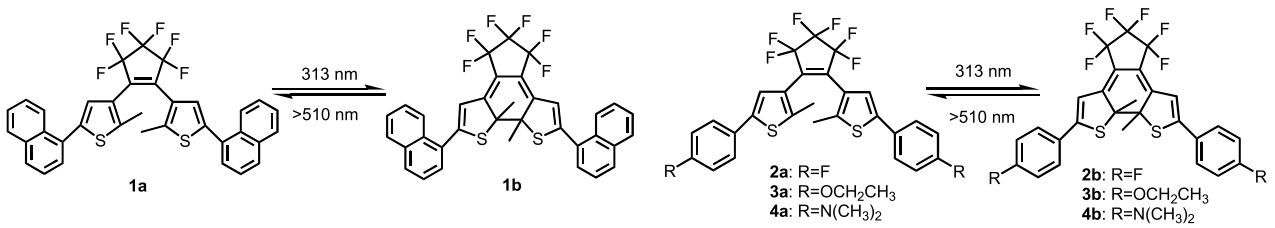




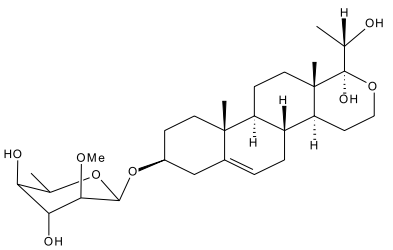


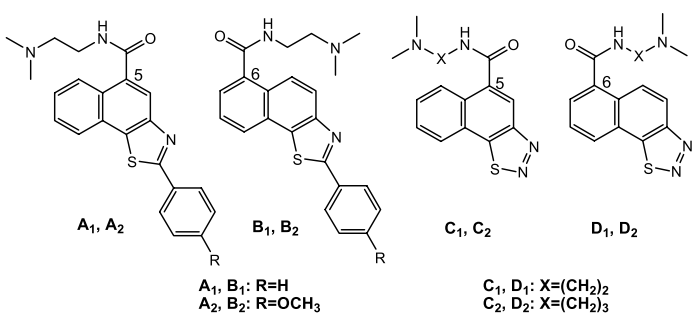


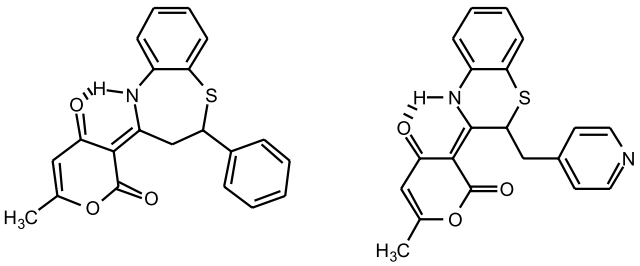


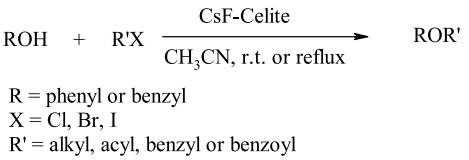


Photochromic dithienylethene **1a**, **2a**, **3a** and **4a** were synthesized, and their optoelectronic properties, such as photochromism in solution as well as in poly-methylmethacrylate (PMMA) amorphous films, fluorescence and electrochemical properties were investigated in detail.









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Recent developments in the Nazarov process

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Contents

1. Introduction

This review is an update of the Nazarov cyclisation and covers the literature from 1993 to 2005. The Nazarov cyclisation was most recently reviewed in 1994.[1] Prior to that, this reaction had been reviewed in 1991[2] and 1983,[3]

Keywords: Nazarov cyclisation; Divinyl ketone; Electrocyclisation; Cyclopentenone.

Abbreviations: Ar, aryl; $BF_3{\cdot}Et_2O$, boron trifluoride etherate; Boc, *tert*-butoxycarbonyl; Bu, butyl; Cbz, benzyloxycarbonyl; Chx, cyclohexyl; Cp, cyclopentadienyl; DIB, *o*-diiodobenzene; Dppe, bis(diphenylphosphino) ethene; ee, enantiomeric excess; Et, ethyl; Fu, furane; HFIP, hexafluoro-2-propanol; HMTA, hexamethylenetetramine; LA, Lewis acid; Me, methyl; Ph, phenyl; PMB, *p*-methoxybenzoyl; PMP, *p*-methoxyphenyl; PPA, polyphosphoric acid; Pr, propyl; py, pyridine; TBDMS, *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; Tf, trifluoromethanesulphonyl; TFA, trifluoroacetic acid; TFE, trifluoroethanol; TfOH, triflic acid; TFSA, trifluoromethanesulphonic acid; THF, tetrahydrofuran; THP, tetrahydropyranyl; TIPS, triisopropylsilyl; TMP, 2,4,6-trimethoxyphenyl; TMS, trimethylsilyl; TMSOTf, trimethylsilyl trifluoromethanesulphonate; Ts, 4-toluenesulphonyl (tosyl); TsOH, *p*-toluenesulphonic acid.

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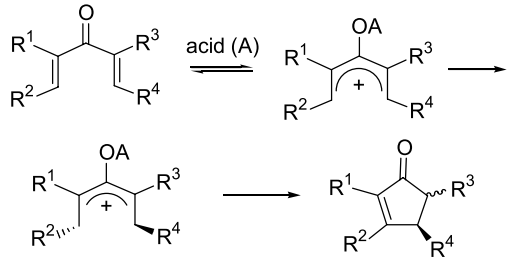
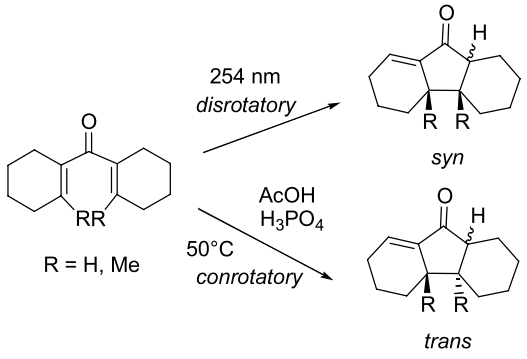
and also in the context of pentannelation.[4] The present article demonstrates that most important achievements such as fluorine-directed Nazarov cyclisation, metal-catalysed Nazarov cyclisation, interrupted Nazarov reaction, asymmetric Nazarov cyclisation, and trapping of the photochemically generated oxyallyl zwitterions have considerably expanded the synthetic scopes of the process. Other modern variants based on the use of highly reactive allene substrates are also well documented. In addition, the Nazarov cyclisation of divinyl ketones bearing heteroatoms at the α- or β-position has also been developed since the preceding review.[1]

The prevalence of five-membered carbocycles in natural products and other bioactive compounds has provided a major impetus for the development of efficient methods for their construction. Over the years, the Nazarov reaction has been increasingly refined to meet this need. Most usually, this reaction involves the use of cross-conjugated dienones, treatment of which with a Lewis or Bronsted acid induces the formation of a pentadienyl cation that undergoes 4π electrocyclisation to give an allyl cation, followed by proton migration to give, finally, a cyclopentenone (Scheme 1).



Scheme 1. Mechanism of Nazarov cyclisation.

The Nazarov cyclisation in its original form involves the cyclisation of divinyl ketones to cyclopentenones under the influence of very strong acids. The recognition that it belongs to a general class of cationic electrocyclic reactions and that even mild Lewis acids can promote the cyclisation has contributed significantly to the development of the reaction. It may be noted that the crucial conrotatory electrocyclisation of the pentadienylic cation that defines the Nazarov reaction creates a carbon–carbon bond and two stereocentres. Some or all of the stereochemical information is lost in the subsequent deprotonation. In 1969, Shoppee et al. were the first to establish that the Nazarov cyclisation



Scheme 2. Pericyclic mechanism of Nazarov cyclisation.

was actually a pericyclic reaction belonging to the class of electrocyclisations, specifically a 4π electrocyclic closure of a 3-hydroxypentadienylic cation.[5] The most convincing evidence for a pericyclic mechanism came from Woodward et al., who documented the complementary rotatory pathways for the thermal (conrotatory) and photochemical (disrotatory) cyclisations, precisely as predicted by the conservation of orbital symmetry (Scheme 2).[6] As with all pericyclic reactions, the mechanism and stereochemistry are inexorably coupled.

The placement of the double bond is established after the electrocyclisation by proton loss from the cyclopentenyl cation. Normally, the double bond resides in the thermodynamically more stable position, that is, that with the highest degree of substitution. At its beginning, broader application of the Nazarov cyclisation was nevertheless hampered by the lack of control with respect to the position of the double bond, and by the drastic reaction conditions, leading to side reactions of the cationic intermediates. Consequently, the Nazarov reaction was long considered more as a mechanistically interesting possibility for rationalising certain side reactions observed in terpene chemistry than as a preparative useful method. This changed however, after Denmark et al. described a new variation of the Nazarov reaction with silyl-substituted divinyl ketones.[7] Here, the stabilisation associated with a positive charge β to the silicon atom is exploited to assure the position of the double bond in the final product. In addition, the exemplary ability of silicon to serve as an electrofugal leaving group largely prevents further side reactions such as Wagner–Meerwein rearrangements, which sometimes further complicate the product mixture. Another more recent version of this reaction is the fluorine-directed Nazarov cyclisation (see Section 4). Besides dienones, a variety of species have been used as precursors for the generation of pentadienyl cations suitable to undergo the electrocyclisation, which include α-alkoxy enones, β′-substituted enones, α-vinylcyclobutanones, *gem*-dichlorohomoallyl alcohols, *gem*-dichlorocyclopropylmethanols, allene-containing precursors, dienynes, enynol derivatives, ynediols, and 2-furylcarbinols.

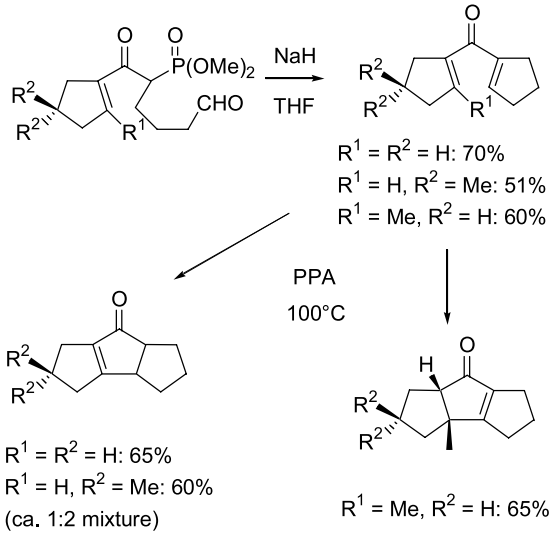
To facilitate presentation, the reaction is divided into eight categories: (1) (Lewis) acid-promoted and photochemical cyclisation of divinyl ketones; (2) silicon-directed Nazarov cyclisation; (3) fluorine-directed Nazarov cyclisation; (4) cyclisation of divinyl ketones or equivalents from in situ construction; (5) solvolysis of 2-furylcarbinols; (6) cyclisation of divinyl ketones or equivalents from allene-containing precursors; (7) asymmetric Nazarov cyclisation; and (8) trapping of the chemically generated Nazarov intermediate.

2. Cyclisation of divinyl ketones

2.1. Classical Nazarov cyclisation: from stoichiometric to catalytic process

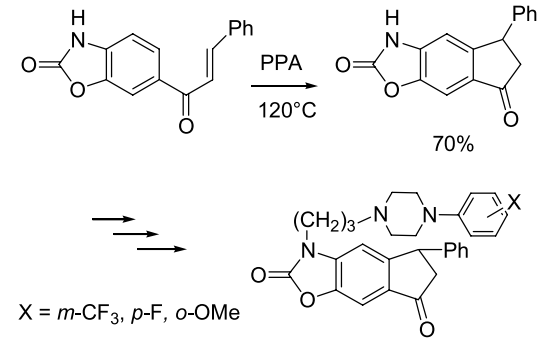
The classical Nazarov reaction can be thought of as proceeding through the series of steps which are summarised in Scheme 1. The divinyl ketone is typically treated with strong Lewis or protic acid to generate the pentadienyl

cation reversibly. This step is followed by thermally allowed 4π conrotation which produces the allylic carbocation. Loss of a proton leads to the final cyclopentenone. The more highly substituted enone is the reaction product. In general, either a protic acid or strong Lewis acid (e.g., BF_3, $SnCl_4$, $TiCl_4$, or $AlCl_3$) is required to promote the Nazarov cyclisation, and one or more molar equivalents of Lewis acid is generally necessary for the best results. A common acidic system for effecting the Nazarov reaction is a mixture of 85% phosphoric acid and 85% formic acid. Other strong protic acids such as sulphuric acid or hydrochloric acid have also been widely used. Indeed, an important advance in the Nazarov cyclisation was the recognition that Lewis acids can effectively induce the cyclisation of divinyl ketones, an improvement over the classical reagent, phosphoric acid. In order to prepare new functionalised cyclopentanoids, Minami reported in 1992 a new approach to cyclopentane annulated compounds based on a polyphosphoric acid (PPA)-promoted cyclisation of dicyclopent-1-enyl ketones arising from 1-(cyclopent-1-enylcarbonyl)vinylphosphonates (Scheme 3).[8]



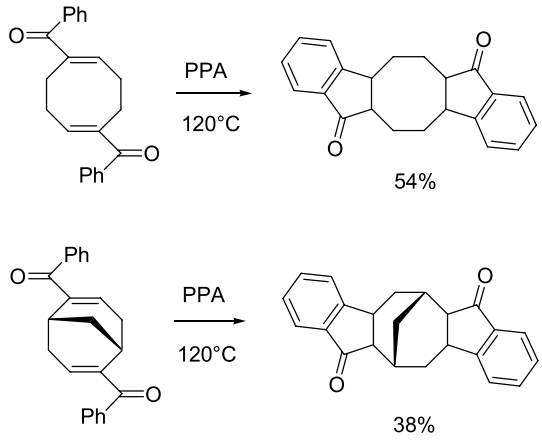
Scheme 3. Synthesis of tricyclo[6.3.0.0^{3,7}]undecenone system.

With the aim of obtaining pharmacologically active molecules having both analgesic activity and a sedative factor, Lesieur et al. applied the same methodology to the synthesis of original indanyl analogues of 3-[3-(4-aryl-piperazin-1-yl)propyl]-2-oxo-2,3-dihydro[1,3]benzoxazoles (Scheme 4).[9]



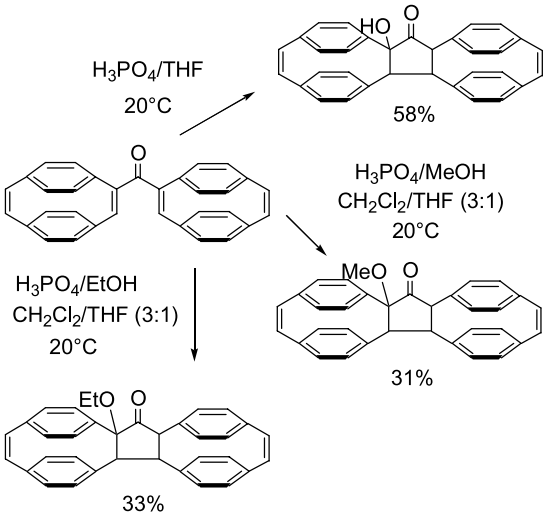
Scheme 4. Synthesis of indanyl analogues.

In an effort to develop a facile, general and large-scale route to novel, rigid, bis(ethanediyl)-bridged *ansa*-bis-(indenes), Halterman et al. investigated in 1997 an unprecedented double Nazarov cyclisation induced by polyphosphoric acid.[10] The bis(aryl vinyl ketone) precursor was 1,5-dimethyl-1,5-cyclooctadiene successively submitted to selenium-catalysed oxidation and phenylmagnesium chloride addition. The methodology was extended to the synthesis of a related bis(indene), containing a bicyclo-[3.3.1]nonane bridging moiety, from Meerwein's diketone (Scheme 5).



Scheme 5. Synthesis of doubly bridged bis(indene) via double Nazarov cyclisation.

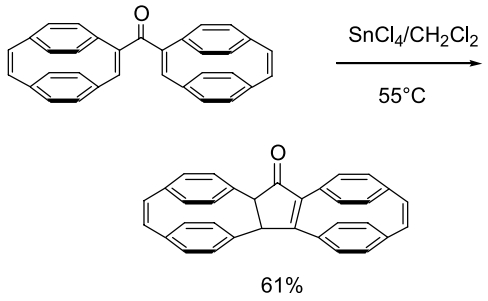
Buchholz and de Meijere showed that the use of phosphoric acid in the case of the Nazarov cyclisation of bis([2.2]-paracyclophane-1,9-dienyl) ketone did not provide the expected bis[2.2]paracyclophane-annelated cyclopentenone, but the corresponding saturated α-hydroxycyclopentanone, when the reaction was carried out in the presence of THF.[11] The formation of this unexpected product can be visualised as resulting from an addition of water to the hydroxycyclopentenyl cation intermediate. Furthermore, when the ketone was treated with phosphoric acid in a 3:1 mixture of dichloromethane and tetrahydrofuran in the



Scheme 6. Nazarov cyclisation of bis([2.2]paracyclophane-1,9-dienyl) ketone with H_3PO_4.

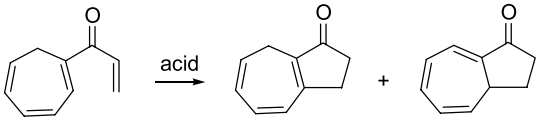
presence of methanol or ethanol as a nucleophile, the α-methoxy- and α-ethoxy-substituted bis[2.2]paracyclophane-annelated cyclopentanones were isolated in respective yields of 31 and 33% (Scheme 6).

However, to direct the cyclisation to the desired cyclopentenone and avoid competition with the trapping of the intermediate hydroxycyclopentyl cation by nucleophiles, Lewis acids such as stannic chloride were successfully applied in dichloromethane (Scheme 7).[11]



Scheme 7. Nazarov cyclisation of bis([2.2]paracyclophane-1,9-dienyl) ketone with $SnCl_4$.

In the same way, Oda et al. showed that using stannic chloride in a stoichiometric amount as the acid in the Nazarov reaction of 1-acryloyl-1,3,5-cycloheptatriene gave the corresponding dihydroazulenones in a better yield than in the presence of a mixture of phosphoric acid and formic acid.[12] When the reaction was carried out in the presence of more acidic conditions such as with sulphuric acid, however, no cyclopentenone was isolated (Scheme 8).

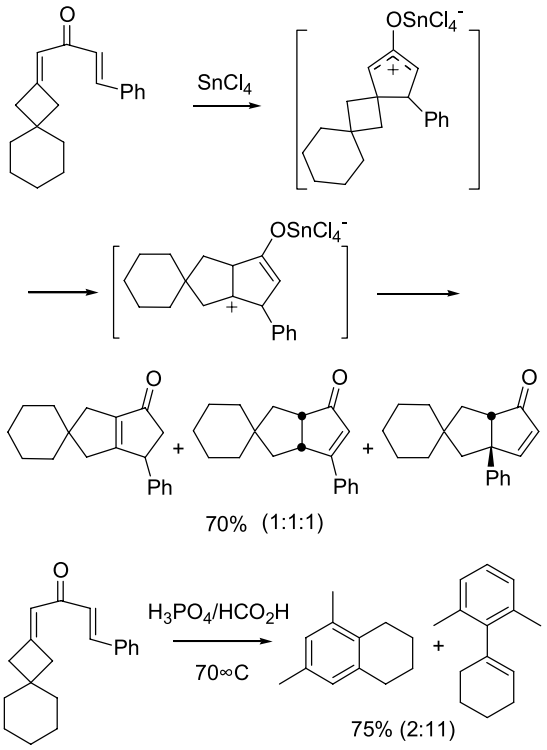


acid/solvent = H_3PO_4/HCO_2H: 46% + 13%
acid/solvent = $SnCl_4/CH_2Cl_2$: 47% + 27%
acid = H_2SO_4: 0%

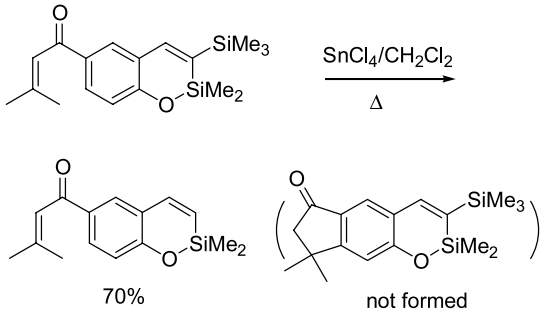
Scheme 8. Nazarov cyclisation of 1-acryloyl-1,3,5-cycloheptatriene.

In 1993, Reusch et al. reported the $SnCl_4$-mediated cyclisation of a very strained-ring Nazarov substrate.[13] Indeed, this Lewis acid converted a cross-conjugated cyclobutylidene ketone into a mixture of Nazarov rearrangement products, whereas the involvement of a mixture of phosphoric acid and formic acid provided the unexpected 5,7-dimethyltetralin and 2-cyclohexenyl-1-methyl-3-phenylbenzene. The former product arose from an initial retroaldol reaction, and the latter from a series of tautomerisations and electrocyclic reactions, following cation-induced four-membered ring cleavage (Scheme 9).

On the other hand, treatment of the vinyltrimethylsilane depicted in Scheme 10 with stannic chloride afforded the reduction product instead of the expected Nazarov annulation product.[14]

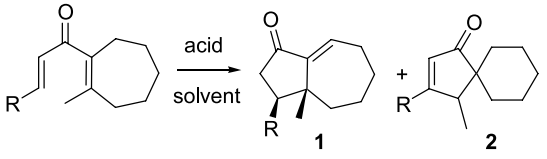


Scheme 9. Acid-promoted reactions of a strained-ring Nazarov substrate.



Scheme 10. Unsuccessful $SnCl_4$-mediated Nazarov cyclisation of a vinyltrimethylsilane.

Although many divinyl ketones and dienone substrates have been studied in the context of the Nazarov cyclisation, there are few examples where monocyclic β,β,β′-substituted precursors such as those depicted in Scheme 11 (or Scheme 9) have been examined. In particular, the hydroazulenone core of guanacastepene A implied retrosynthetically a Nazarov cyclisation of this kind of dienone substrates. In this context, Chiu and Li studied in 2004 this Nazarov cyclisation with various acids. According to the reaction conditions, their procedure afforded various



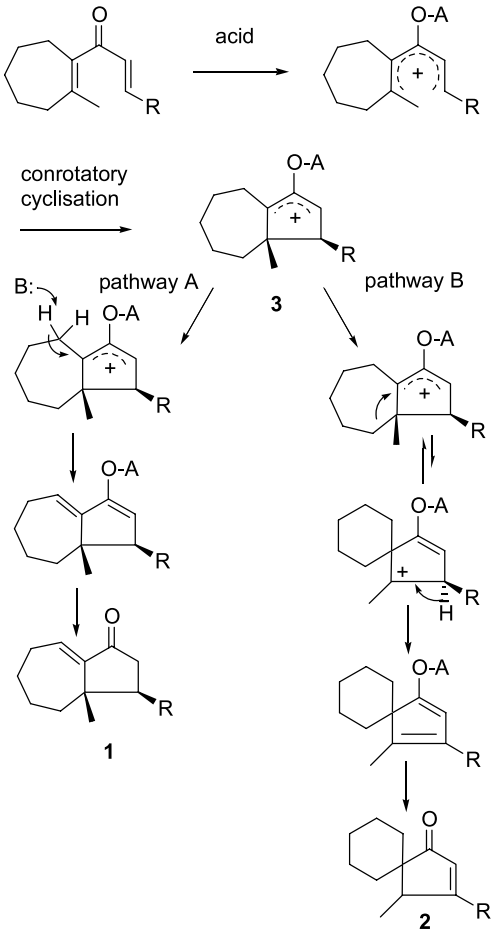
Scheme 11. Nazarov cyclisation of monocyclic β,β,β′-substituted dienones.

Table 1

Acid	Solvent	T (°C)	R	**1**:**2**	Yield (%)
$BF_3 \cdot Et_2O$	CH_2Cl_2	0	*i*-Pr	95:5	98
BCl_3	CH_2Cl_2	0	*i*-Pr	5:95	92
$SnCl_4$	CH_2Cl_2	0	*i*-Pr	39:61	87
H_2SO_4/MeOH	—	0	*i*-Pr	>95:5	91
H_2SO_4	—	0	*i*-Pr	17:83	90
CF_3SO_3H	—	0	*i*-Pr	7:93	90
CF_3SO_3H	CH_2Cl_2	0	*i*-Pr	7:93	96
CF_3SO_3H/DMSO	CH_2Cl_2	20	*i*-Pr	91:9	86
H_2SO_4	MeOH	0	Me	>95:5	86
H_2SO_4	—	0	Me	84:16	83
$BF_3 \cdot Et_2O$	CH_2Cl_2	20	Me	>95:5	95
CF_3SO_3H	CH_2Cl_2	20	Me	>95:5	86
CF_3SO_3H	—	60	Me	87:13	74

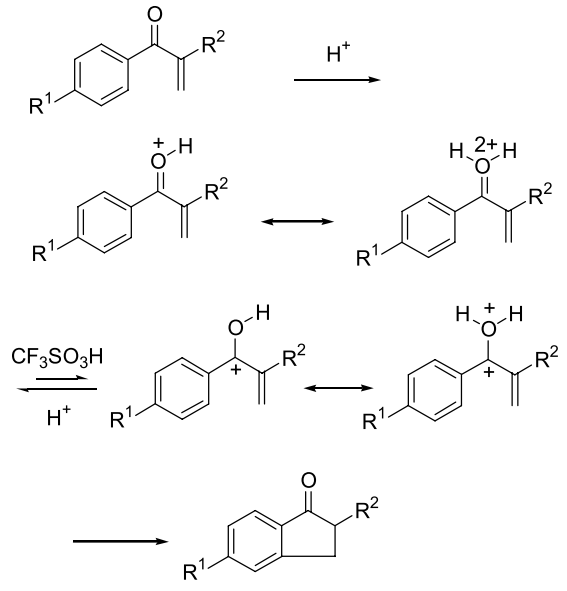
amounts of the expected Nazarov hydroazulenone **1**, along with a spirocyclic ketone **2** generated via a novel Wagner–Meerwein rearrangement (Scheme 11 and Table 1).[15] The use of a stoichiometric amount of $BF_3 \cdot Et_2O$ as activator gave the best result, and this was also observed in the stereoselective synthesis of α-chalcones from 1,2,3-triphenylpropenone.[16]

A 1:1 mixture of concentrated sulphuric acid and methanol underwent a remarkably clean Nazarov cyclisation, providing the expected hydroazulenone **1** in 91% yield. Surprisingly, treatment of the dienone (R=*i*-Pr) with sulphuric acid in the absence of methanol selectively afforded the spirocyclic ketone **2**. The use of triflic acid generated **2** (R=*i*-Pr) almost exclusively, irrespective of the concentration of acid in the reaction. Finally, it was found that the use of boron trifluoride etherate generated **1** as the sole product in quantitative yield, while the use of boron trichloride in dichloromethane favoured the formation of **2** with a selectivity of >95:5, also in near-quantitative yield. Scheme 12 summarises the mechanistic pathways that account for the formation of the cyclisation products **1** and **2**. Treatment of the divinyl ketone with acid induced a conrotatory electrocyclisation, leading to the carbocationic intermediate **3**. In the presence of proton acceptors (e.g., methanol), fused bicyclic products **1** were favoured (pathway A). In the absence of Lewis bases, Wagner–Meerwein shifts predominated and compounds **2** were preferentially formed (pathway B).



Scheme 12. Mechanistic pathways leading to **1** and **2**.

In 1997, Ohwada et al. studied the superacid-promoted electrocyclisation of 1-phenyl-2-propen-1-ones to indanones.[17] They showed that the linear acidity-rate relationships observed in the kinetic measurements supported the involvement of an oxonium–carbenium dication, that is, *O*,*O*-diprotonated 1-phenyl-2-propen-1-ones, in the electrocyclisations. Ab initio calculations also highlighted the energetic favourability of these dicationic



Scheme 13. Dicationic electrocyclisation of 1-phenyl-2-propen-1-ones.

Table 2

R^1	R^2	Acid	$\sim -H_0$[a]	Time (h)	T (°C)	Recovery (%)	Yield (%)
H	H	TFSA	12.7	120	25	6	63
H	H	6%TFSA–94%TFA	8.7	120	25	24	51
H	Ph	TFSA	2.7	5	0	98	0
H	Ph	6%TFSA–94%TFA	8.7	5	0	40	59
H	Ph	TFSA	12.7	5	0	0	98
CF_3	Ph	30%TFSA–70%TFA	10.6	5	0	37	61
CF_3	Ph	TFSA	12.7	5	0	3	93
Me	Ph	6%TFSA–94%TFA	8.7	5	0	52	48
Me	Ph	TFSA	12.7	5	0	6	91
H	p-CF_3–C_6H_4	6%TFSA–94%TFA	8.7	5	0	57	43
H	p-CF_3–C_6H_4	TFSA	12.7	5	0	0	99
H	p-CH_3–C_6H_4	6%TFSA–94%TFA	8.7	5	0	22	78
H	p-CH_3–C_6H_4	TFSA	12.7	5	0	0	100
H	Me	7%TFSA–93%TFA	8.9	2	25	45	49
H	CH_3	TFSA	12.7	2	25	0	97
H	Et	7%TFSA–93%TFA	8.9	3	25	39	54
H	Et	TFSA	12.7	3	25	0	97

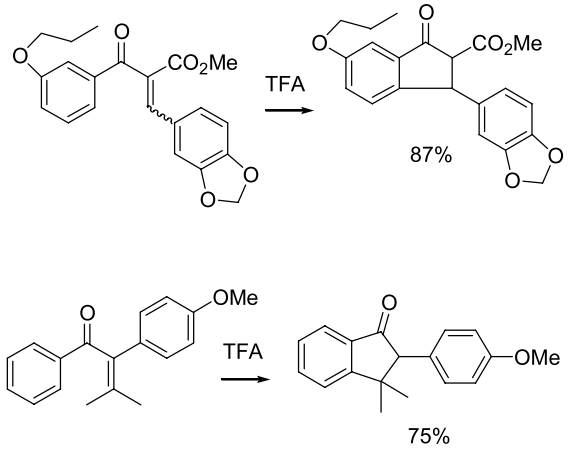
[a] Corrected values of the acidity function of the reaction media.

electrocyclisations over the monocationic mechanism (Scheme 13 and Table 2).

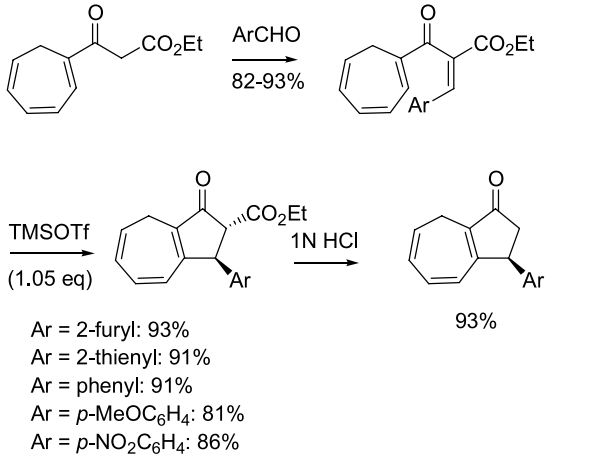
Trifluoroacetic acid (TFA) in stoichiometric amounts was also selected among various strong protic acids to achieve the Nazarov cyclisation. Curiously, the sole examples cited in the preceding reviews and concerning the use of this acid as the promoter of a Nazarov cyclisation were those involving the solvolysis of 1,1-dichloro homoallyl alcohols.[18] Since then, very few results involving this acid have been reported in the context of aromatic vinyl ketones such as those depicted in Scheme 14.[19]

Similarly, only a single example of trimethylsilyl triflate (TMSOTf)-promoted Nazarov cyclisation was cited in Denmark's review.[20] In 1999, Oda et al. reported the synthesis of 3-aryl-1,2,3,8-tetrahydroazulen-1-ones involving Nazarov cyclisation with a stoichiometric amount of TMSOTf as a key step for constructing the bicyclic carbon framework (Scheme 15).[21] While heating the arylidenes (with Ar=phenyl or 2-pyridyl), previously prepared by a Knoevenagel condensation in a mixture of phosphoric acid and formic acid at 90 °C, gave the expected tetrahydroazulen-1-ones in moderate yields, the reaction of arylidenes with a 2-furyl or 2-thienyl aryl group under the same conditions afforded an intractable reaction mixture, probably because of the acid-sensitive nature of the electron-rich heteroles. In contrast to these results, the Nazarov cyclisation carried out in the presence of TMSOTf at room temperature gave the expected esters in excellent yields. These latter esters were then hydrolysed and decarboxylated in methanolic hydrochloride acid. The reaction was also investigated with stannic chloride, but the results were even worse than with phosphoric acid. On the other hand, it is well known that, most of the time, the Nazarov reaction of substituted divinyl ketones leads to the thermodynamically favoured double bond regioisomer, that is, the more highly substituted cyclopentenone. The result of this study, therefore, belongs to one of the typical examples in which only one of the regioisomers is formed.

Dilute solutions of perchloric acid and acetic anhydride were introduced in 2001 as new promoters for the Nazarov cyclisation.[22] In this study, four new types of Nazarov substrates synthesised from α-cyclocitral were investigated for the first time. The Nazarov cyclisation was firstly tested with several protic acids such as sulphuric, phosphoric, formic, methanesulphonic, and p-toluenesulphonic acids, and mixtures of these acids such as sulphuric/acetic, phosphoric/formic, methanesulphonic/phosphoric, using a

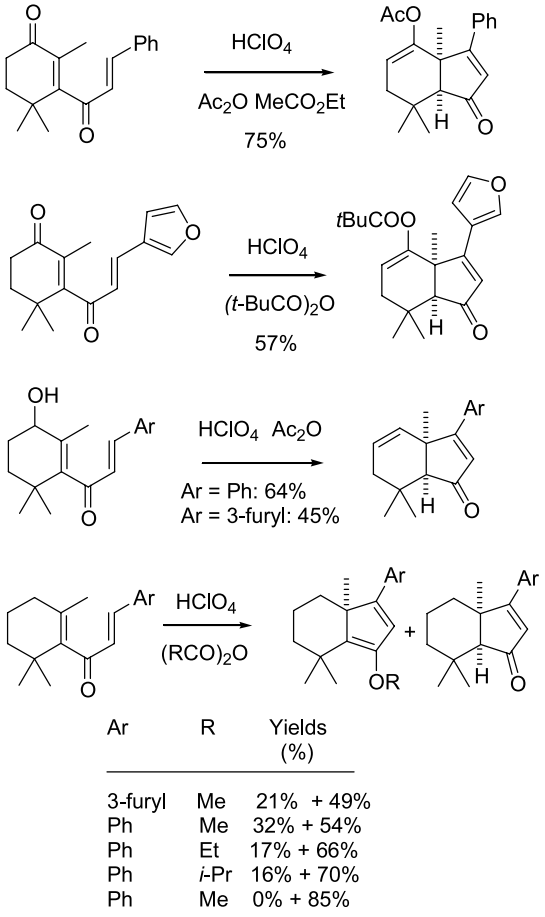


Scheme 14. TFA-mediated Nazarov cyclisations.



Scheme 15. Synthesis of azulenones via TMSOTf-mediated Nazarov cyclisation.

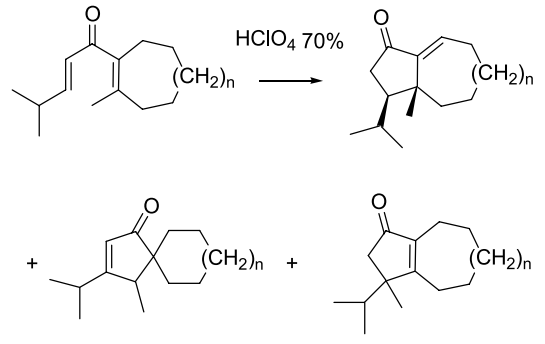
temperature range of between 25 and 100 °C, but without success. Attempts with trimethylsilyl trifluoracetate also failed. In contrast to this work, the use of diluted solutions of perchloric acid (10^{-3} or 10^{-2} M) in a mixture of acetic anhydride and ethyl acetate promoted the Nazarov cyclisation at room temperature in good yields (Scheme 16).



Ar	R	Yields (%)
3-furyl	Me	21% + 49%
Ph	Me	32% + 54%
Ph	Et	17% + 66%
Ph	*i*-Pr	16% + 70%
Ph	Me	0% + 85%

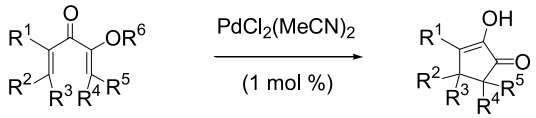
Scheme 16. Nazarov cyclisations induced by perchloric acid.

Very recently, Chiu et al. also used stoichiometric amounts of perchloric acid to achieve the Nazarov cyclisation of more common divinyl ketones (Scheme 17) in near-quantitative yield and excellent selectivity (with $n=1$).[15] In the case of the cyclohexadienone substrate ($n=0$), however, carbocationic rearrangements predominated. Wagner–Meerwein shifts in the Nazarov intermediate leading to these kinds of byproducts have been previously observed.[23]

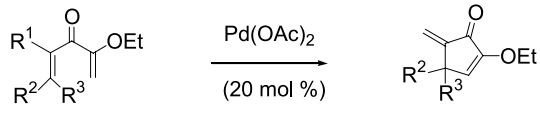


Scheme 17. Perchloric acid-promoted Nazarov cyclisations.

Whereas the Nazarov cyclisation has generally been promoted by one or more equivalents of a protic or Lewis acid (BF_3, $SnCl_4$, $TiCl_4$, or $AlCl_3$), as in all of the examples depicted in Schemes 1–17, several recent studies have focused on the possibility of catalysing this reaction using copper, palladium, scandium or iridium complexes. As an example, the first palladium-catalysed Nazarov cyclisation of divinyl ketones was developed by Tius et al. in 2003.[24] This reaction took place under mild conditions and led to two kinds of products according to the nature of the catalyst. The $PdCl_2$-catalysed cyclisation of α-alkoxy dienones gave 2-hydroxycyclopentenones, whereas the $Pd(OAc)_2$-catalysed reaction yielded cross-conjugated cyclopentenones through an oxidative process (Scheme 18). Although both this example and that depicted in Scheme 20 should be located in Section 2.3 (presence of a heteroatom in the α-position of the dienone), it was decided, however, to include them in this section due to their innovative catalytic aspect.



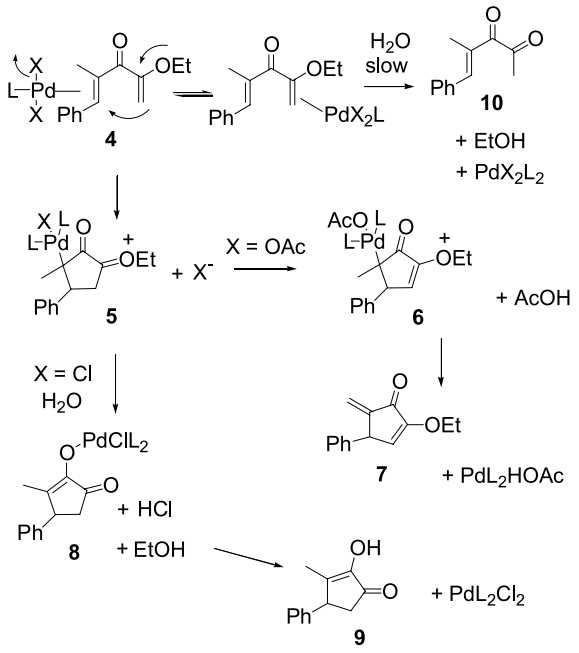
R^1 = Me, R^2 = Ph, R^3 = R^4 = R^5 = H, R^6 = Et: 91%
R^1 = R^2 = Me, R^3 = R^4 = R^5 = H, R^6 = Et: 70%
R^1 = R^3 = Me, R^2 = Ph, R^4 = R^5 = H, R^6 = Et: 92%
R^1 = R^2 = R^3 = R^4 = R^6 = Me, R^5 = *i*-Bu: 79%
R^1,R^2 = $(CH_2)_4$, R^3 = H, R^4 = R^6 = Me, R^5 = *i*-Bu: 90%



R^1 = Me, R^2 = Ph, R^3 = H: 78%
R^1 = Me, R^2 = *t*-Bu, R^3 = H: 74%
R^1,R^2 = $(CH_2)_4$, R^3 = H: 53%
R^1 = R^3 = Me, R^2 = Ph: 64%

Scheme 18. Palladium-catalysed Nazarov cyclisations.

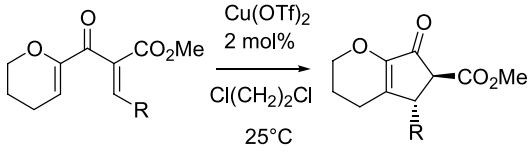
Scheme 19 summarises the proposed mechanisms for these two kinds of products. Although the Nazarov reaction was initiated by activation of the carbonyl group by an acid, this seems unlikely in this case. Instead, activation of the electron-poor olefin by complexation to the palladium seems a more likely first step.[25] Complexation of the electrophilic palladium salt to the electron-rich enol ether was probably preferred, but this did not lead to cyclic product, but to **10**. If the association of the divinyl ketone with palladium was reversible, the π complex **4** could form and undergo intramolecular attack to produce palladium enolate **5**. When $Pd(OAc)_2$ was used, proton loss from **5** (X=OAc) led to **6**, which underwent β-elimination to **7**. In the absence of an oxidant, the palladium hydride that was also generated from reductive elimination led to Pd(0)



Scheme 19. Proposed mechanism for the palladium-catalysed Nazarov cyclisation.

irreversibly. When $PdCl_2$ was used, **5** (X=Cl) underwent hydrolysis with loss of ethanol to produce **8** and HCl. Decomposition of the palladium enolate by the strong acid regenerated the Pd(II) catalyst and led to **9**. The difference in reaction pathways between the $Pd(OAc)_2$- and the $PdCl_2$-catalysed reactions may be due to the difference in basicity of the counterion. In the case of acetate, proton loss leading to **6** was fast.

In 2003, Frontier et al. reported another efficient catalysis of the Nazarov cyclisation of β-aryl-substituted enoates under mild conditions.[26] They demonstrated that copper triflate (2 mol%) catalysed the Nazarov cyclisation of polarised divinyl ketones in chlorinated solvent at room temperature in air to give excellent yields of the corresponding cyclopentenones, isolated in each case as a single regio- and stereoisomer with a *trans*-relationship of the α- and β-substituents on the former vinyl electrophile (Scheme 20).



R	t (min[a] or h[b])	Yield (%)
TMP	5[a]	>99%
4-methoxyphenyl	3.5[b]	99%
3-methoxyphenyl	48[b]	96%
phenyl	108[b]	99%
2-furyl	12[b]	99%
cyclohexyl	240[b]	<50%
cyclohexyl	2[b]	>99%

Scheme 20. Polarising the Nazarov cyclisation: efficient catalysis under mild conditions.

Substrates equipped with a range of vinyl nucleophiles were examined under optimised cyclisation conditions (Table 3).

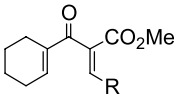
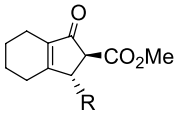
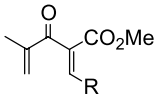
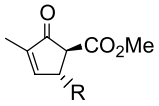
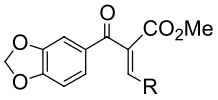
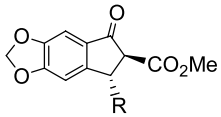
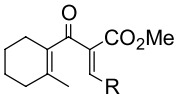
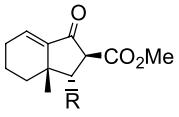
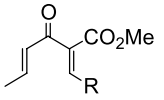
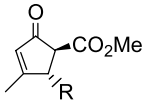
Cyclic, acyclic, and aromatic vinyl nucleophiles cyclised smoothly, but more slowly than the dihydropyran vinyl nucleophile. Quaternary centre formation was also possible, but cyclisation of α-unsubstituted divinyl ketones was slower, low yielding, and elimination was less regioselective. Furthermore, the effect of vinyl electrophile α-substitution on the reactivity was also studied. In general, the more polarising the groups on the divinyl ketone, the more efficient the reaction (Table 4).

Thus, it was found that the Nazarov cyclisation was facilitated by the presence of polar substituents on the divinyl ketone. Scheme 21 shows that one possible factor could be the greater Lewis basicity of **11**: formation of carbocation **A** from **11** is expected to be more favourable than formation of carbocation **A′** from **11′**. The electron-donating and -withdrawing groups should polarise the π-system of cation **A**, which would be expected to cyclise more readily than the symmetric π-system of cation **A′**. Finally, the regioselectivity of the elimination of **B** is likely to be controlled by the position of the positive charge, localised adjacent to the stabilising oxygen atom. In oxyallyl cation **B′**, the positive charge is fully delocalised and elimination is not expected to be regioselective.

The $Cu(OTf)_2$-catalysed Nazarov cyclisation was recently applied by Flynn et al., who reported that carboxyalkynes could be utilised in a one-pot, palladium-mediated *syn*-hydrostannylation and copper-co-catalysed Stille–Scott cross-coupling with organic halides to afford direct access to stereo- and regio-selectively defined carboxyalkenes.[27] Suitable placement of an alkene or aromatic ring in these latter compounds provided ready access to Nazarov precursors that could be cyclised to give the corresponding cyclopentenones. In some cases, the Nazarov cyclisation could be controlled to select either one of the two possible diastereomers (*cis* and *trans*) of the cyclopentenone product. Indeed, the kinetic product (*cis*) was formed by using $MeSO_3H$ at −78 °C, whereas the thermodynamic product (*trans*) was exclusively formed at room temperature in the presence of $MeSO_3H$ or $Cu(OTf)_2$.[26] This constituted the first report of a selective formation of both the *cis*- and *trans*-diastereomers of a cyclopentenone from a Nazarov process (Scheme 22).

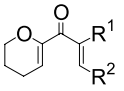
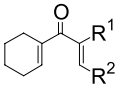
In 2004, Frontier et al. reported that the dicationic Ir(III) complex, [IrMe(CO)(dppe)(DIB)](BARF)$_2$, where dppe= bis(diphenylphosphino)ethane, DIB=*o*-diiodobenzene, and BARF=[B(3,5–$C_6H_3(CF_3)_2)_4$], was a very reactive catalyst for promoting the Nazarov cyclisation of aryl vinyl and divinyl ketones.[28] This reaction constituted the first example of catalysis of the Nazarov cyclisation using a well-defined cationic metal complex having two adjacent substrate binding sites. It was shown that both the electrophilicity of the cationic complex and the lability of the *cis* binding sites played key roles in making this complex a highly effective catalyst. Scheme 23 summarises a plausible

Table 3

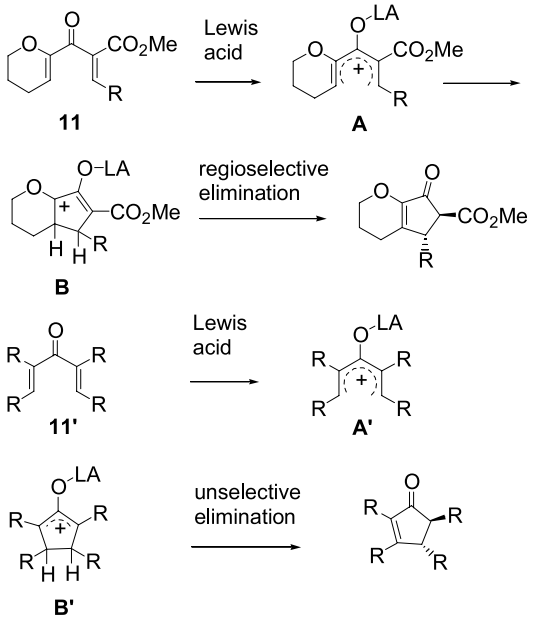
Divinyl ketone	Product	*T* (°C)	*t* (h)	Yield (%)
		40	0.25	86 (55:45)
		55	8	75
		53	20	92
		25	4	95
		50	44	58

R=TMP; 2 mol% $Cu(OTf)_2$ in CH_2Cl_2 or $Cl(CH_2)_2Cl$.

Table 4

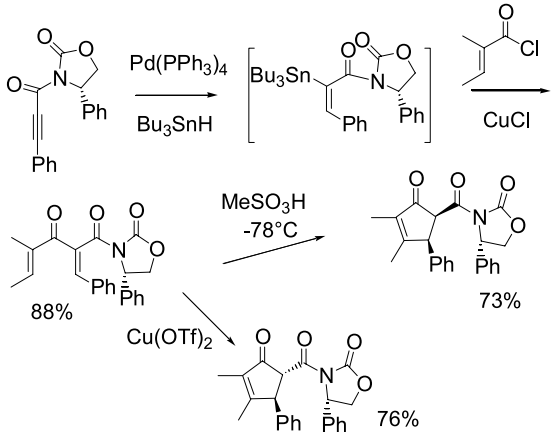
Ketone	R^1	R^2	*T* (°C)	*t* (h)	Yield (%)
	CO_2Me	TMP	25	<0.1	>99
	H	TMP	25	0.33	86
	CO_2Me	Chx	55	2	>99
	H	Chx	55	0.5	60
	CO_2Me	TMP	40	0.25	86
	H	TMP	40	5	30–40
	CO_2Me	Chx	65	14	70
	H	Chx	65	4	37–42

TMP=2,4,6-trimethoxphenyl; Chx=cyclohexyl.

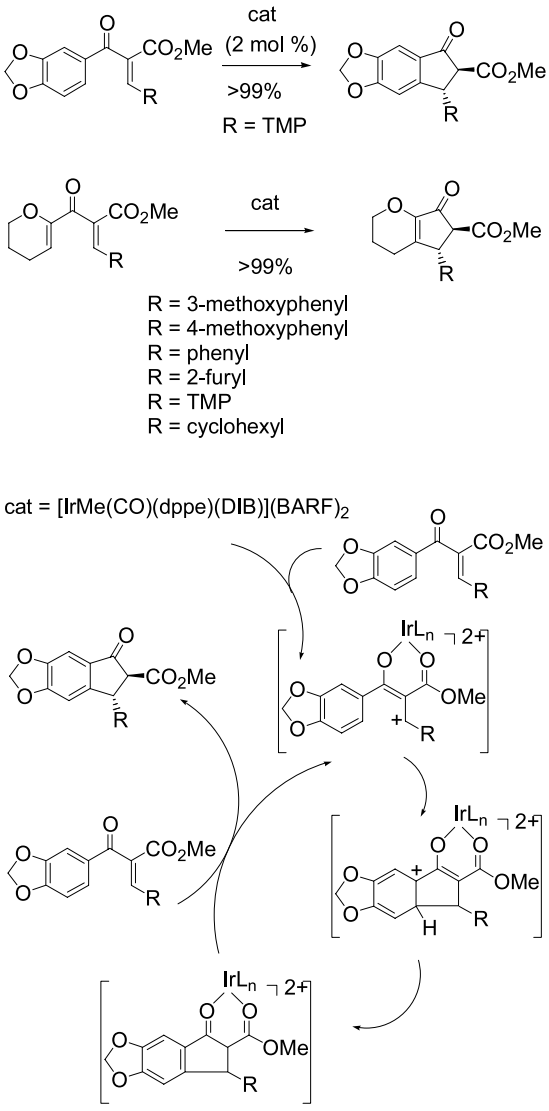


Scheme 21. Effect of polarisation on the electrocyclic process.

mechanism for the process, which involves generation of a first oxyallyl cation, cyclisation to generate a second cationic intermediate, re-aromatisation, enolate protonation to give the catalyst-bound product, and substrate substitution to give the free product and the regenerated first cationic complex.

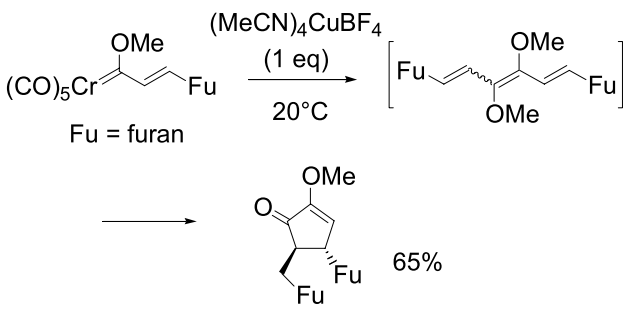


Scheme 22. Stereocontrolled Nazarov cyclisation of phenyl oxazolidinone derivatives.



Scheme 23. Nazarov cyclisation catalysed by a cationic iridium complex.

In addition, in 2004, Barluenga et al. reported the copper-promoted dimerisation of chromium Fischer carbene complexes providing dialkoxytrienes.[29] In the case of the chromium alkenyl(alkoxy)carbene complex depicted in Scheme 24, these authors observed the direct formation of a methoxycyclopentenone with complete chemo- and stereoselectivity in the presence of $(MeCN)_4CuBF_4$. This result clearly meant that the copper complex not only

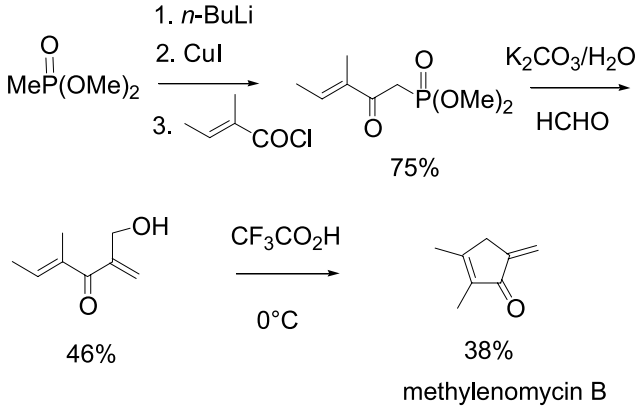


Scheme 24. Copper-promoted dimerisation and Nazarov cyclisation of chromium Fischer carbene complexes.

catalysed the dimerisation, but also promoted the Nazarov cyclisation.

2.2. Applications to the synthesis of natural products

The chemistry of five-membered rings plays an important role in synthetic organic chemistry because of the widespread occurrence of such a structural feature in many natural products. In recent years, the Nazarov reaction has been recognised as a powerful and versatile method for the preparation of natural products containing a cyclopentenone unit in their structure. It has been used in the construction of numerous complex target molecules, including polyquinane natural products and prostanoids.[1] In 1993, Motoyoshiya et al. reported the total synthesis of methylenomycin B, a natural cyclopentanoid antibiotic.[30] The synthesis was achieved in only three steps from dimethyl methylphosphonate and involved a Nazarov cyclisation as the key step, which efficiently shortened the synthetic path (Scheme 25).

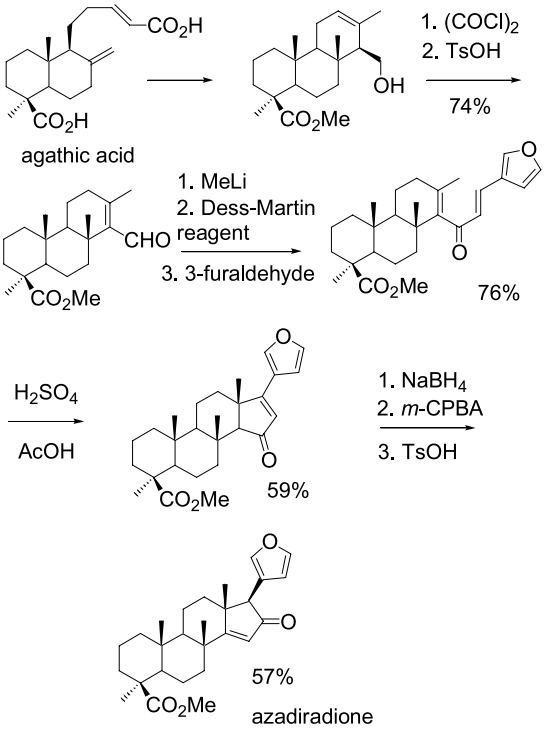


Scheme 25. Synthesis of methylenomycin B.

In 1997, Fernandez-Mateos et al. investigated the application of the Nazarov reaction to the synthesis of various model insect antifeedants and devised a high-yielding route to 13β-analogues of the natural limonoid, azadiradione (Scheme 26).[31]

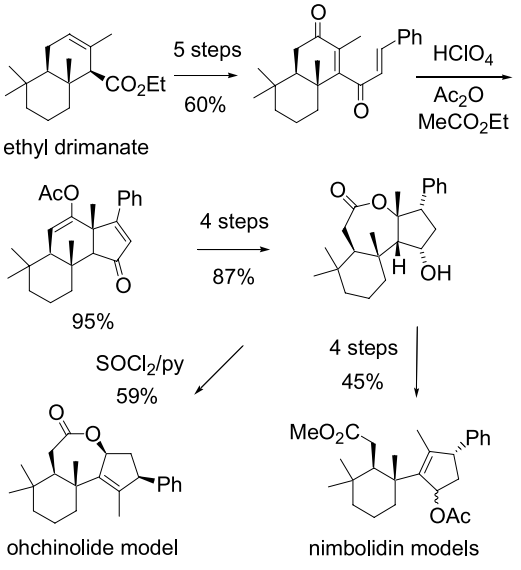
In 2001, these authors reported a short and stereoselective synthesis of a BCDE C-secolimonid model insect antifeedant related to ohchinolide and nimbolidin accomplished in 11 (30% overall yield) and 14 (22% overall yield) steps, respectively, from ethyl drimanate.[32] The key step was the torquoselective electrocyclisation of a dienedione induced by perchloric acid (Scheme 27).

The same methodology was applied in 2003 to the preparation of the limonoid, havanensin, from cyclocitral in seven steps in an overall yield of 20%. The required D ring was formed by a Nazarov cyclisation induced by perchloric acid.[33] The Nazarov reaction was also the key step of the synthesis of 3-methyl-7-[2-(dimethylaminoethyl)-oximino]-5-arylcyclopenta[*f*]benzoxazolinones, which are potential ligands of the $5HT_{1D}$ serotonin receptors.[34] Scheme 28 summarises this 4-step synthesis, starting from 3-methyl-6-acetyl benzoxazolinone.

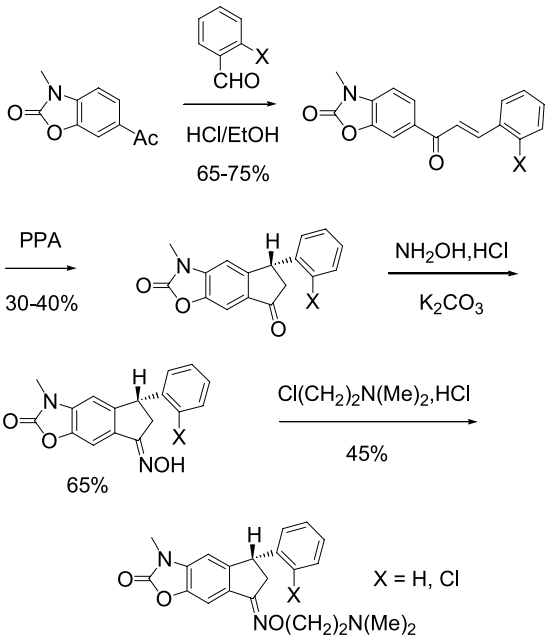


Scheme 26. Synthesis of 13β-analogues of azadiradione.

In 2001, Clive et al. developed the synthesis of puraquinonic acid from 2,5-dimethoxybenzoic acid, based on a Nazarov cyclisation promoted by sulphuric acid allowing the construction of the five-membered ring.[35] This natural product is a lead compound in the design of drugs to treat leukaemia. On the other hand, motivated by the commercial importance of vetiver oil and the lack of synthetic substitutes, Kraft et al. elaborated in 2002 an efficient synthetic route to an intense vetiver-like smelling compound using the Nazarov reaction (Scheme 29).[36]



Scheme 27. Synthesis of BCDE model compounds related to ohchinolide and nimbolidin.

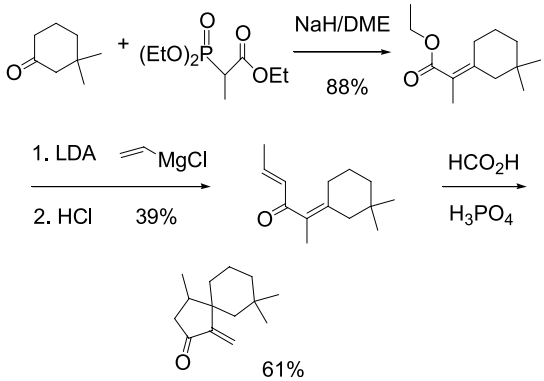


Scheme 28. Synthesis of ligands of $5HT_{1D}$ serotonin receptors.

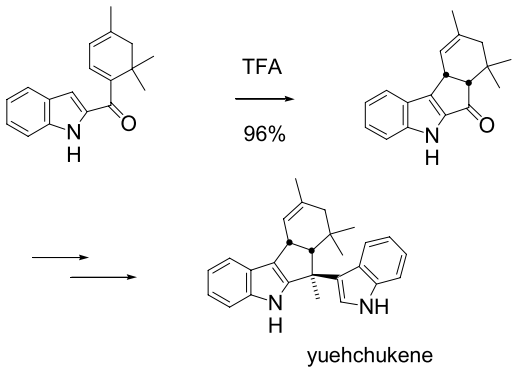
2.3. Cyclisation of divinyl ketones bearing heteroatom at α- or β-position

Somewhat surprisingly, there are only a few examples of Nazarov reactions involving divinyl ketones bearing a heteroatom on one or other of the double bonds. Only one example involving this kind of substrates was presented in Denmark's review.[37] In 1992, Bergman et al. reported the synthesis of yuehchukene, a biologically active bis-indole alkaloid, by the ring closure of α,β-unsaturated 2-acylindoles in the key step, followed by acid-catalysed incorporation of a second indole unit (Scheme 30).[38] The use of trifluoroacetic acid in refluxing acetonitrile allowed a near-quantitative yield of the resulting cyclo[*b*]indol-3-one derivative, whereas other reagents such as $BF_3 \cdot Et_2O$ and $SnCl_4$ gave lower yields. In order to prepare invertoyuehchukene, the same reaction was also carried out in 1996 in the presence of HCl in refluxing 1,4-dioxane, but again in lower yields.[39] The expected indole was isolated in each case as a single isomer with a C/D ring *cis* configuration.

Other structural analogues of yuehchukene exhibiting strong antifertility activity were prepared by Ishikura et al.

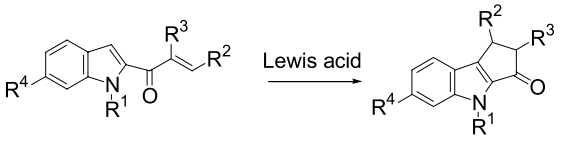


Scheme 29. Synthesis of vetiver-like smelling spiro[4.5]-decan-2-one.



Scheme 30. Synthesis of yuehchukene.

on the basis of the same methodology.[40,41] In addition, Miki et al. have submitted the corresponding monocyclic precursors to the treatment with $BF_3 \cdot Et_2O$, furnishing in excellent yields the expected cyclopenta[*b*]indol-3-ones (Scheme 31).[42] The same kind of substrates were studied by Cheng et al., providing the corresponding 4-benzenesulphonyl-2-*t*-butyl-6-hydroxy-1,4-dihydro-2*H*-cyclopenta[*b*]indol-3-one by the use of $AlCl_3$ (Scheme 31).[43]

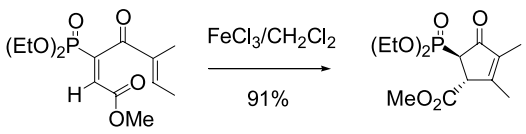


R^1 = Bn, R^2 = Ph, R^3 = R^4 = H: 96% with $BF_3.Et_2O$
R^1 = Bn, R^2 = Me, R^3 = R^4 = H: 98% with $BF_3.Et_2O$
R^1 = H, R^2 = Ph, R^3 = R^4 = H: 72% with $BF_3.Et_2O$
R^1 = SO_2Ph, R^2 = H, R^3 = *t*-Bu, R^4 = OMe: 82% with $AlCl_3$

Scheme 31. Synthesis of cyclopenta[*b*]indol-3-ones.

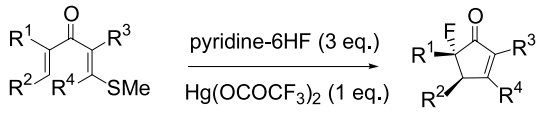
In 2000, Mikolajczyk et al. reported a regioselective Nazarov cyclisation of an α-phosphoryl dienone, leading to the corresponding α-phosphoryl cyclopentenone.[44] The reaction, carried out in the presence of iron(III) chloride, led to this latter compound in excellent yield and with the *trans*-situated phosphoryl and methoxycarbonyl groups as the only product. In accord with the commonly accepted mechanism of the Nazarov reaction, formation of the double bond exclusively at C(2) and C(3) of the cyclopentenone ring may be attributed to a better stabilisation of an intermediate β-ketocarbocation by the two methyl groups (Scheme 32). The corresponding monocyclic precursors have been previously converted in similar conditions into 2-(dialkoxyphosphoryl)-2,3,4,5,6-pentahydropentalen-1-ones.[8]

In 1999, Hara et al. demonstrated that, in the presence of pyridine–HF complexes combined with $Hg(OCOCF_3)_2$,



Scheme 32. Nazarov cyclisation of α-phosphoryl dienone.

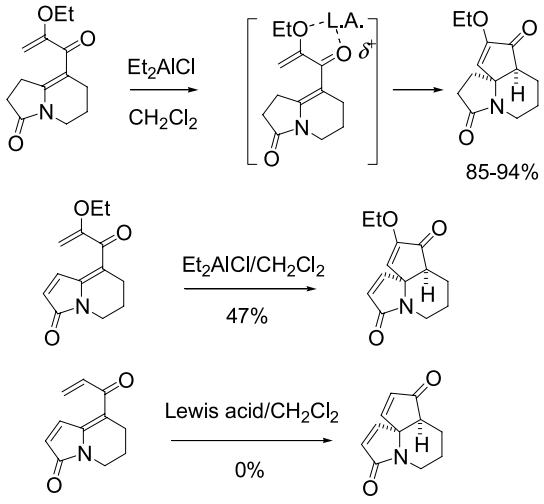
divinyl ketones having a methylthio group at the β-position cyclised to 5-fluorocyclopentenone derivatives selectively. These authors have shown that the methylthio groups at the β-position and alkyl substituents on the double bonds were a prerequisite to obtain the fluorocyclisation products in good yields (Scheme 33).[45]



R^1 = Me, R^2 = Ph, R^3 = Me, R^4 = SMe: 67%
R^1 = Ph, R^2 = Ph, R^3 = Ph, R^4 = SMe: 71%
R^1 = Me, R^2 = Me, R^3 = Me, R^4 = SMe: 64%
R^1,R^2 = $(CH_2)_4$, R^3 = Me, R^4 = SMe: 60%
R^1 = Me, R^2 = Ph, R^3 = Me, R^4 = Me: 89%
R^1 = Me, R^2 = Ph, R^3 = Me, R^4 = Bu: 80%
R^1 = Me, R^2 = Me, R^3 = Me, R^4 = SMe: 64%

Scheme 33. Fluorocyclisation of β-methylthio divinyl ketones.

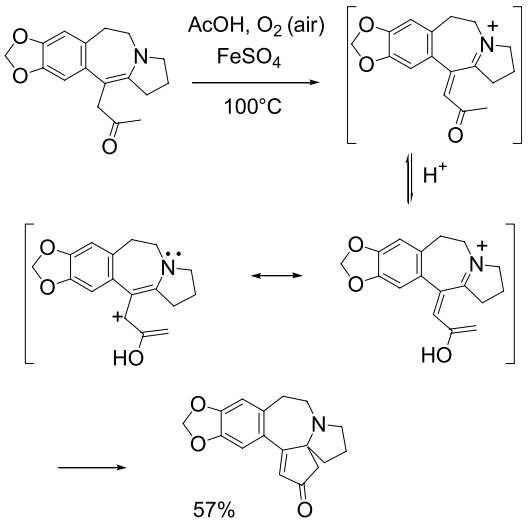
With the aim of developing a rapid entry to the synthetically challenging tricyclic core of the bioactive alkaloid, cephalotaxine, Cha et al. have accomplished an elegant Et_2AlCl-promoted Nazarov cyclisation (Scheme 34).[46] Central to the successful cyclisation was formation of a bidendate chelate with the indicated conformation (Scheme 34), which was obligatory for the subsequent conrotatory ring closure. The necessity of such a conformationally rigid chelate was further probed with a dienone prepared by the use of vinylmagnesium bromide in place of α-ethoxyvinyllithium; several Lewis acids were surveyed, but all failed to induce the Nazarov cyclisation.



Scheme 34. Nazarov cyclisation of bicyclic *N*-acylhemiaminals.

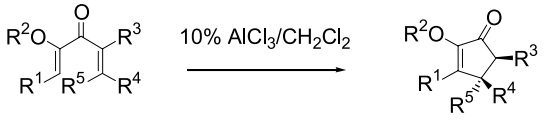
In 2003, Li et al. reported a novel and efficient total synthesis of cephalotaxine, based on an unusual azo-Nazarov-type cyclisation.[47] Thus, a keto enamine was converted into the corresponding pentacyclic enone via an acid-catalysed O_2-dependent process (Scheme 35).

In the context of their studies on the total synthesis of



Scheme 35. Novel endocyclic enamine cyclopentenone annulation.

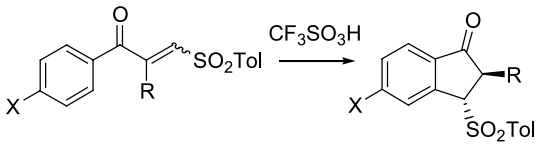
guanacastepene antibiotics, Trauner et al. have developed high-yielding Nazarov cyclisations of 2-alkoxy-1,4-pentadien-3-ones, catalysed by aluminium chloride (10 mol%), and providing with complete regioselectivity highly functionalised heterobicyclic (or -tricyclic) compounds (Scheme 36).[48]



R^1,R^2 = $(CH_2)_3$, R^3 = Me, R^4 = R^5 = H: 92%
R^1,R^2 = $(CH_2)_3$, R^3 = Et, R^4 = R^5 = H: 91%
R^1,R^2 = $(CH_2)_3$, R^3 = *i*-Pr, R^4 = R^5 = H: 93%
R^1,R^2 = $(CH_2)_3$, R^3 = H, R^4 = Ph, R^5 = H: 86%
R^1,R^2 = $(CH_2)_3$, R^3 = H, R^4 = *i*-Pr, R^5 = H: 92%
R^1,R^2 = $(CH_2)_3$, R^3 = H, R^4 = R^5 = Me: 85%
R^1,R^2 = $(CH_2)_3$, R^3,R^4 = $(CH_2)_3$, R^5 = H: 88%
R^1,R^2 = $(CH_2)_3$, R^3,R^4 = $(CH_2)_3$, R^5 = Me: 91%
R^1 = H, R^2 = OEt, R^3 = Me, R^4 = R^5 = H: 80%

Scheme 36. Nazarov cyclisation of 2-alkoxy-1,4-pentadien-3-ones.

Trifluoromethanesulphonic acid was selected among various strong protic acids to achieve the Nazarov cyclisation of β-aroyl-α,β-unsaturated sulphones in the course of planning a novel route leading to 2-substituted indanone derivatives.[49] This result was a success because the Nazarov cyclisation of aryl vinyl ketones possessing a strongly electron-withdrawing group (*p*-tolylsulphonyl) at the β-position of the vinyl part was unprecedented (Scheme 37). Furthermore, it was found that the presence of a *p*-tolylsulphonyl group at the 3-position inhibited the acid-catalysed polymerisation of the α,β-unsaturated carbonyl moiety to make the Nazarov reaction tolerant of severe conditions. Since they possessed a tolylsulphonyl group at the 3-position, the final indanone derivatives were anticipated to be useful for synthesising various derivatives of indanone.



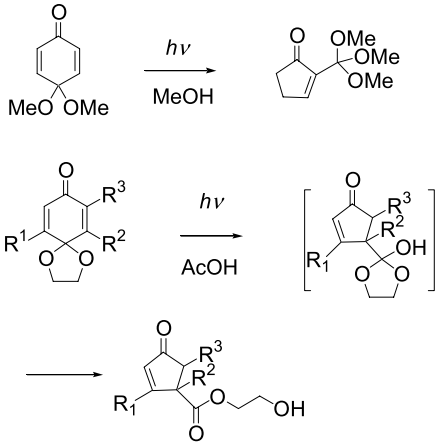
X = H, R = Me: 58% (20°C)
X = H, R = *i*-Pr: 63% (20°C)
X = F, R = Me: 23% (20°C)
X = Me, R = Me: 61% (20°C)
X = MeO, R = Me: 49% (50°C)
X = AcO, R = Me: 44% (70°C)
X = OH, R = Me: 58% (50°C)

Scheme 37. Nazarov cyclisation of β-aroyl-α,β-unsaturated sulphones.

In addition, Kocienski et al. have observed efficient Nazarov cyclisations during the hydrolysis of α-alkoxydienones (diluted HCl) previously prepared by palladium-catalysed cross-coupling reactions of α-alkoxyalkenylzincs.[50]

2.4. Photochemical cyclisations

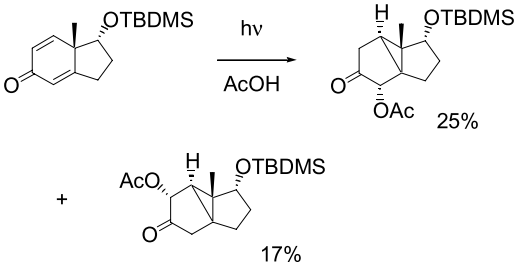
The theory of electrocyclic reactions predicts a disrotatory closure of 4π-systems in the excited state.[51] The photocyclisation of cyclic, cross-conjugated divinyl ketones has been investigated for various ring sizes. Thus, the photorearrangements of 2,5-cyclohexadienones have been studied extensively.[52] In particular, Pirrung et al. have developed the photochemistry of quinone cyclic monoketals which provided β-carboxy-substituted cyclopentenones via a cyclopropanoxyallyl cation (Scheme 38).[53]



R^1 = R^2 = R^3 = H: 82%
R^1 = R^2 = R^3 = Me: 84%
R^1 = H, R^2 = R^3 = Me: 89%

Scheme 38. Photochemical rearrangements of quinone monoketals.

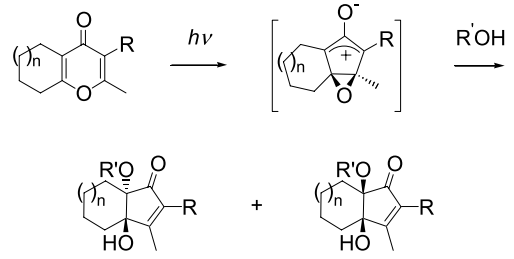
Many synthetic applications of these oldest known photoreactions have been reported such as the synthesis of complex polycyclic natural terpenes.[54] Most of the time, the photochemical cyclisation is followed by subsequent skeletal re-organisations, which place these reactions beyond the scope of this section.[52] In some cases, however, it is possible to obtain the non-rearranged compounds, for example, those depicted in Scheme 39, which resulted from trapping by the solvent of the intermediate with the cyclopropane ring intact.[55]



Scheme 39. Photochemical cyclisation of (1*R*,7a*S*)-1-(*t*-butyldiphenylsiloxy)-7a-methyl-5(7a*H*)-indanone.

It may be noted that, in 2001, Leitich et al. revisited the photo-Nazarov cyclisation of 1-cyclohexenyl-phenylmethanone,[56] and studied the trapping of the 2-oxyallyl intermediates by various olefins.[57]

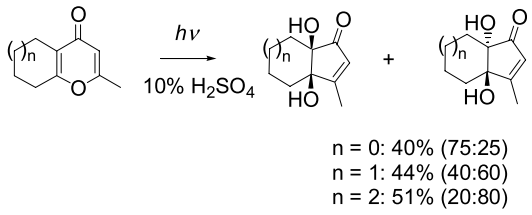
The photoisomerisation of 4-pyrones in an alcoholic medium affords the 2-alkoxy-3-hydroxy-cyclopenten-4-ones. These products arise from a photo-Nazarov reaction followed by intermolecular capture of the resultant oxyallyl zwitterionic intermediate by the hydroxylic solvent.[58,59] This intermolecular solvent-trapping process is especially appealing because of the simplicity of the two reactants. Thus, a planar, achiral heterocycle and an inexpensive alcohol are combined photochemically to yield a functionalised carbocyclic product in a diastereoselective fashion. This has been exploited for the facile construction of bicyclo[*n*.3.0]alkenones ($n=4$–6) (Scheme 40).[60] The stereoselectivity is derived from the apparent preference for attack of the nucleophilic solvent at the opposite face of the bicyclic oxyallyl intermediate from the epoxy group.



Scheme 40. Photochemical ring contraction of fused bicyclic 4-pyrones.

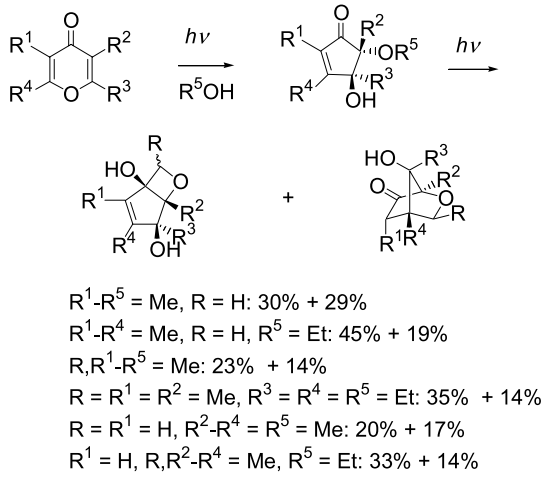
In contrast to the alcohol-trapping process discussed above, when aqueous sulphuric acid was employed instead of the hydroxylic solvent, significant amounts of both *cis*- and *trans*-fused diastereomers were isolated and, in some cases, the less-strained *cis*-isomer was predominant (Scheme 41).[61] In fact, the *trans*-fused isomer underwent partial isomerisation to the corresponding *cis*-fused isomer under the reaction conditions, presumably via a retro-aldol/aldol mechanism.

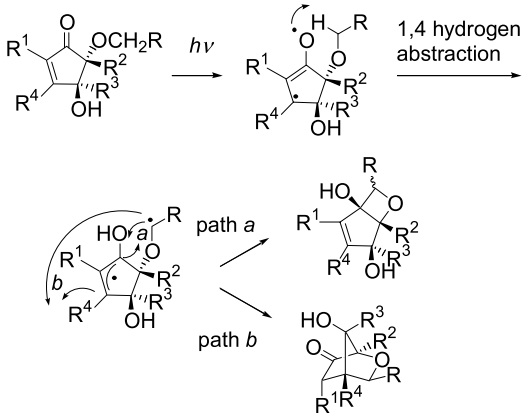
In 1999, West et al. demonstrated that extended irradiation



Scheme 41. Aqueous trapping of fused bicyclic pyran-4-ones.

times allowed the exclusive formation of secondary photoproducts, arising from γ-hydrogen abstraction by the excited enone chromophore of common solvent-trapping products, followed by closure of the resulting biradical through one of two possible pathways (Scheme 42).[62]

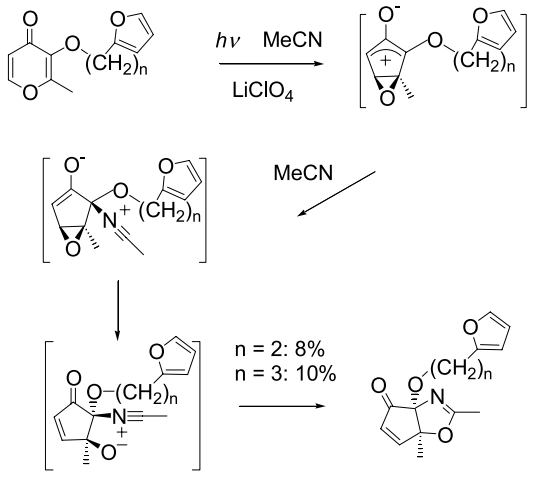




Scheme 42. Synthesis of bridged bicyclic ethers and fused oxetanes.

On the other hand, several 4-pyrones bearing 3-alkoxy substituents have been photolysed in acetonitrile to give novel bicyclic oxazolines, arising from apparent Ritter-type capture of the intermediate oxyallyl zwitterions, followed by intramolecular nitrilium trapping by alkoxide (Scheme 43).[63]

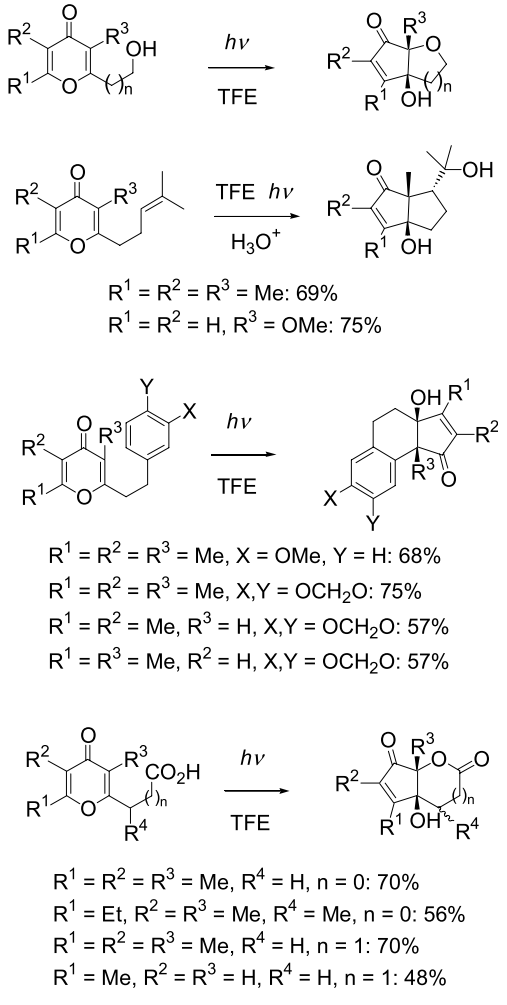
In the same context, West et al. have shown that 4-pyrones bearing pendant heteroatom or carbon nucleophiles also underwent photochemical conversion into reactive bicyclic oxyallyl zwitterions. These intermediates were efficiently



Scheme 43. Synthesis of bicyclic oxazolines via nitrile capture of photochemically generated oxyallyl zwitterions.

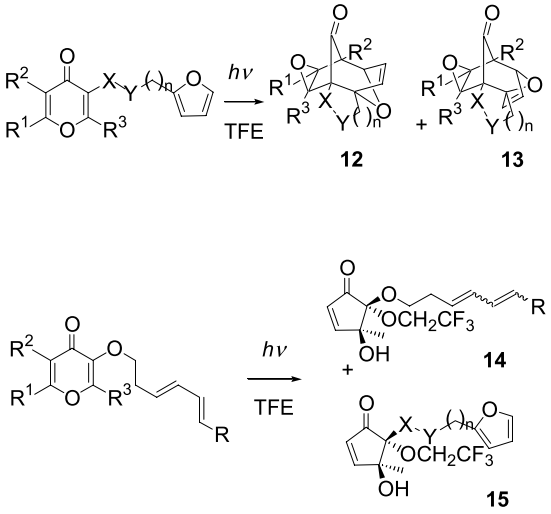
trapped by the internal nucleophile to directly form diquinane, hydrindan, benzohydrindene, oxabicyclo[3.3.0]-octane, and oxabicyclo[4.3.0]nonane skeletons or bicyclic cyclopentenone-lactones (Scheme 44).[64]

In addition, West et al. have reported a new class of



Scheme 44. Intramolecular nucleophile trapping of 4-pyranone-derived zwitterions.

reactions involving intramolecular cycloaddition between photochemically generated five-membered oxyallyl zwitterions and pendant dienes.[65] It was shown that substrates in which the tether was attached to the incipient zwitterions via a carbon underwent cycloaddition to give the expected [4+3] cycloadducts **12** and **13** in varying yields. In contrast, substrates in which the tether was attached to the incipient zwitterions via oxygen gave only the solvent-trapping products **14** and **15** (Scheme 45 and Table 5).



Scheme 45. Intramolecular [4+3] cycloadditions of 4-pyranone-derived zwitterions.

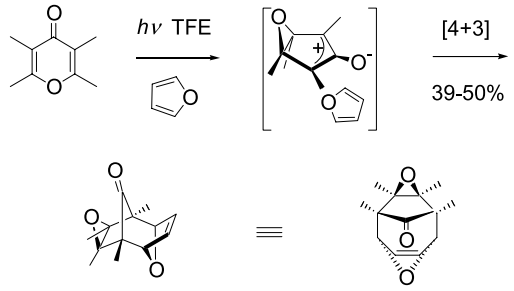
In order to extend the scope of the reaction, intermolecular [3+4] cycloadditions of photochemically generated zwitterions and furans were examined.[65] Unfortunately, in only one case did the intermolecular process proceed with complete diastereoselectivity, but the reaction was not general (Scheme 46).

3. Silicon-directed Nazarov cyclisation

The recognition that the Nazarov reaction was a cationic electrocyclisation provided a better understanding of the controlling features of the reaction and a rationale for explaining its deficiencies. Among the latter, the most serious are secondary cationic rearrangements and unselective placement of the cyclopentenone double bond. This situation changed, however, after Denmark et al. described a new variation of the Nazarov reaction with silyl-substituted divinyl ketones.[66] Here, the stabilisation associated with a positive charge β to the silicon atom was exploited to assure the controlled placement of the double bond in the thermodynamically less stable position in the final product. In addition, the exemplary ability of silicon to serve as an electrofugal leaving group largely prevents further side reactions (rearrangements) of the cationic intermediates. Kang et al. have reported several examples of silicon-directed Nazarov cyclisation promoted by $FeCl_3$ in which α-trimethylsilylmethyl-substituted divinyl ketones yielded the corresponding α-methylenecyclopentanones.[67] Thienyl- and *N*-methylpyrrolyl-vinyl ketones also underwent

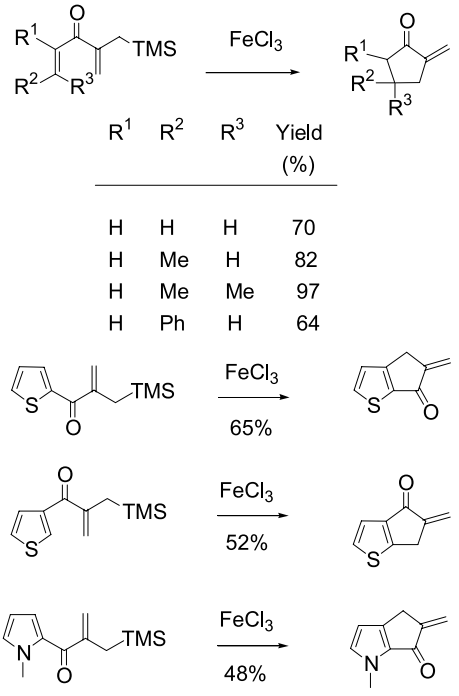
Table 5

R^1	R^2	R^3	X	Y	*n*	R	**12** (%)	**13** (%)	**14** (%)	**15** (%)
Me	Me	Me	CH_2	O	1		30	20		
Me	Me	Me	CH_2	CH_2	1		17	52		
H	Me	H	CH_2	O	1			10		
Et	Me	Et	CH_2	O	1		19	19		
Et	Me	Et	CH_2	CH_2	1			27		
H	H	Me				H			66	
H	H	Me				Me			67	
H	H	Me	O	CH_2	1					58
H	H	Me	O	CH_2	2					58



Scheme 46. Intermolecular [4+3] cycloaddition of photochemically generated zwitterions.

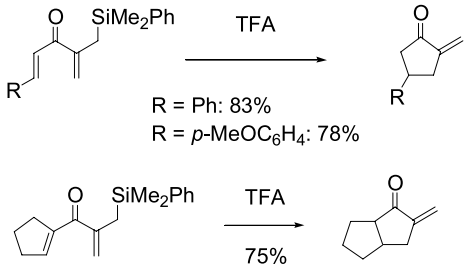
cyclisation to afford the corresponding thiophene or pyrrole, respectively, by further oxidation (Scheme 47).



Scheme 47. $FeCl_3$-silicon-directed Nazarov cyclisations.

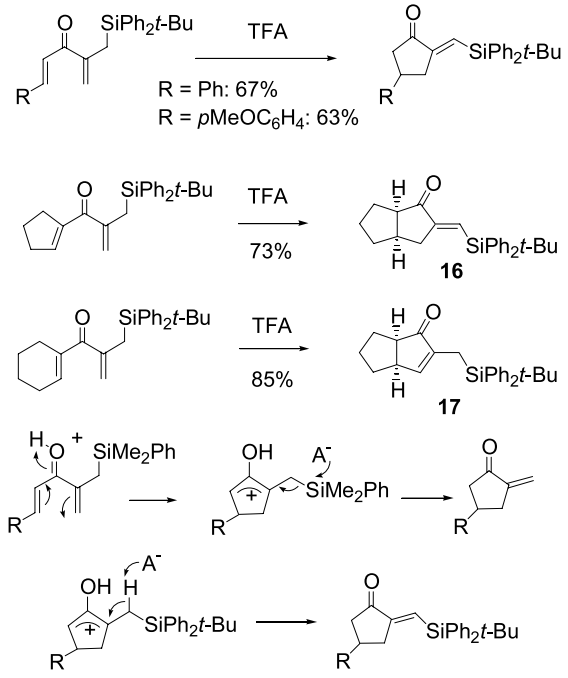
Pulido's group also reported a related $FeCl_3$-promoted Nazarov cyclisation,[68] although, in a later report, trifluoroacetic acid was found to be better reagent compared with $FeCl_3$ or the other tested protic and Lewis acids ($TiCl_4$, $EtAlCl_2$, or BF_3) (Scheme 48).[69,70]

In this study, an interesting effect of the alkyl group on



Scheme 48. TFA-silicon-directed Nazarov cyclisations.

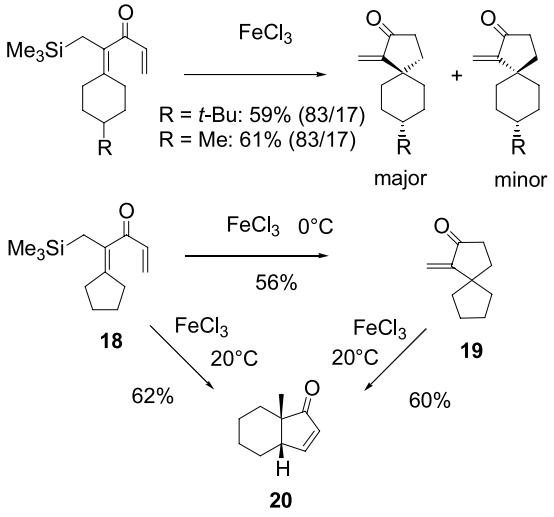
silicon was recorded by comparing phenyldimethylsilane and *t*-butyldiphenylsilane. Thus, elimination of silicon occurred from phenyldimethylsilanes to afford the expected α-methylenecyclopentanones, while the silyl group was not removed from the *t*-butyldiphenylsilanes for the formation of the corresponding vinylsilanes by deprotonation. This result might be due to the low electrofugacity of the *t*-butyldiphenylsilyl group compared to the phenyldimethylsilyl group. In addition, the higher electronegativity of the *t*-butyldiphenylsilyl group enhanced the acidity of the hydrogens α to silicon, thus assuring elimination in the observed sense (Scheme 49). The loss of the hydrogen was not univocal, leading to vinylsilane **16** and allylsilane



Scheme 49. Nazarov cyclisations without losing the silyl group.

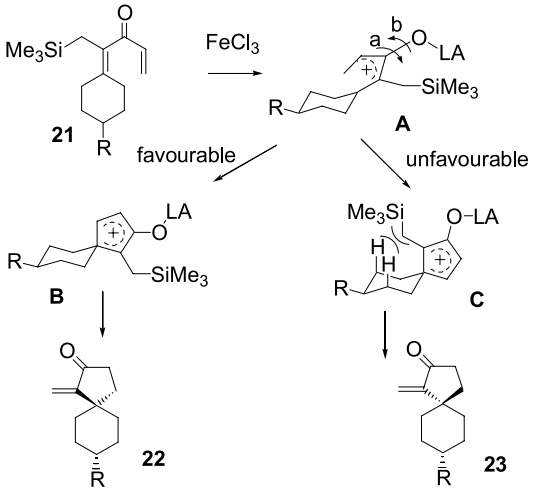
17 without apparent differentiation, which suggests the possibility of an intermediate carbocation β to silicon in which both hydrogens α and γ to silicon could be lost.

Kuroda et al. have synthesised spiro[4.5]decanes and related ring systems, which appear in nature as acorane or vetispirane skeletons of sesquiterpenes, via $FeCl_3$-induced Nazarov cyclisations (Scheme 50).[71] When the α-(trimethylsilylmethyl)divinyl ketone was attached to a five-membered ring, it underwent tandem Nazarov cyclisation-skeletal rearrangement to yield the bicyclo[4.3.0]nonane ring.[72] Indeed, compound **18** afforded the spiro[4.4]nonane **19**, but **19** was found to rearrange to the bicyclo[4.3.0]-nonane **20**, when the reaction was carried out at a higher temperature and for a longer time (Scheme 50).



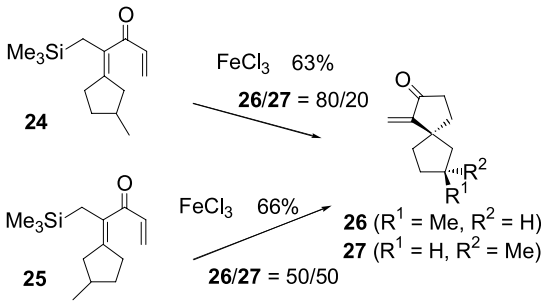
Scheme 50. Synthesis of spiro[4.5]decanes, spiro[4.4]nonanes and bicyclo[4.3.0]nonanes.

The stereochemistry of this Nazarov cyclisation caused by the substituent on the cyclohexane or cyclopentane ring was studied.[73] Compound **22** was obtained preferentially over **23** from **21** (R=*t*-Bu, Me), which could be explained by steric congestion on the intermediate, as illustrated in Scheme 51. In this respect, there are two ways of rotation, from intermediate **A**. The silicon-bearing carbon protrudes over the cyclohexane ring in **C**, which makes this conformation unfavourable against **B** (Scheme 51).



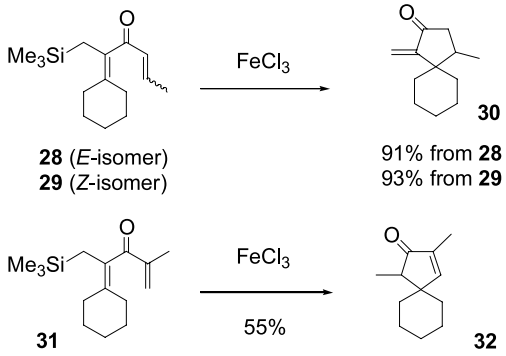
Scheme 51. Stereochemistry of synthesis of spiro[4.5]decanes.

The stereochemistry of the synthesis of spiro[4.5]nonanes (**26**/**27**=80/20 from **24** and 50/50 from **25**, Scheme 52) could also be explained in a similar way.



Scheme 52. Stereochemistry of synthesis of spiro[4.5]nonanes.

The substituent effect on the vinyl moiety was also studied. The β′-methyl-substituted substrates **28** and **29** afforded the same product **30** in much better yield, because of the stabilisation of the intermediate carbocation (Scheme 53). In contrast, the α′-methyl-substituted substrate **31** afforded the product having an endocyclic double bond **32**. The substrate having a phenyl substituent on the vinyl moiety also presented similar results. These results revealed that the double-bond location in the product was determined by the presence/absence of the α′-substituent on the vinyl moiety.

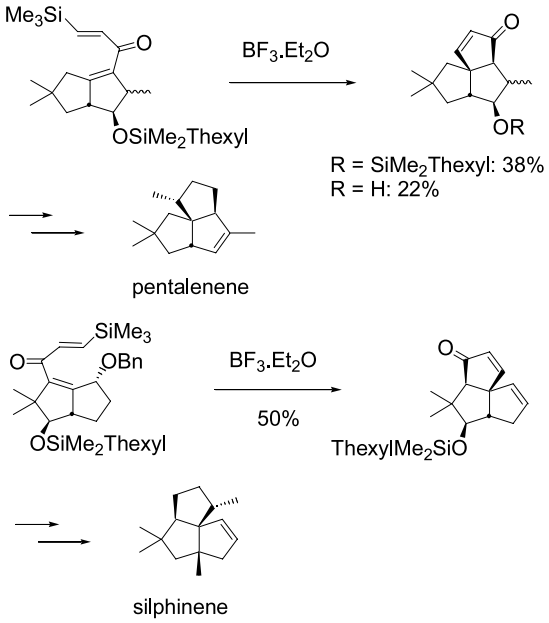


Scheme 53. Substituent effect on divinyl ketone.

Franck-Neumann et al. have developed a total synthesis of pentalenene based on a silyl-assisted Nazarov cyclisation leading to angular triquinanes.[74] The same methodology using $BF_3 \cdot Et_2O$ as promoter was also applied to the synthesis of another natural sesquiterpene, silphinene (Scheme 54).[75]

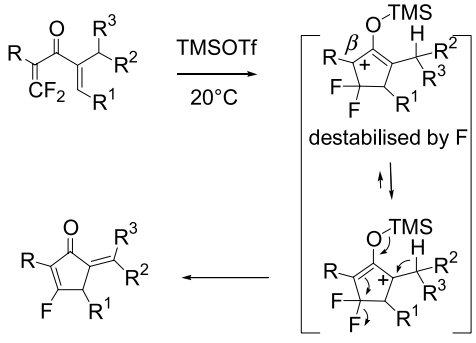
4. Fluorine-directed Nazarov cyclisation

In contrast to silicon, fluorine possesses a β-cation-destabilising effect and also functions as a nucleofuge, the leaving group of a fluoride ion (F^-). These facts suggest that not only silicon, but also fluorine might be a controller of the electrocyclic reaction. On the basis of these



Scheme 54. Synthesis of natural triquinanes via silicon-directed Nazarov cyclisation.

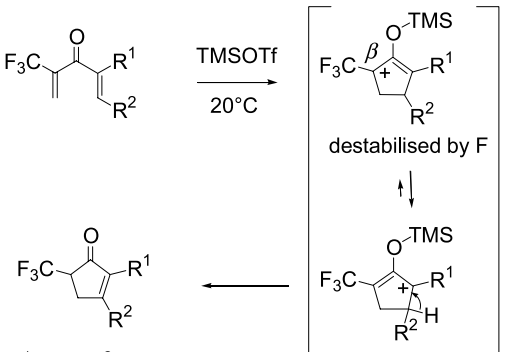
considerations, Ichikawa et al. introduced in 1995, a new Nazarov-type cyclisation, the fluorine-directed Nazarov cyclisation.[76] For the first time, 2,2-difluorovinyl vinyl ketones were investigated as fluorinated substrates and led to the controlled synthesis of 5-alkylidene-3-fluoro-2-cyclopentenones, bearing one more double bond compared to the normal Nazarov products (Scheme 55).



R = *n*-Bu, R^1 = R^2 = R^3 = H: 73%
R = *n*-Bu, R^1 = R^2 = H, R^3 = Ph: 71% (99:1)
R = *n*-Bu, R^1 = R^2 = H, R^3 = *n*-Pr: 82% (99:1)
R = *n*-Bu, R^1 = H, R^2 = R^3 = Me: 78% (99:1)
R = *n*-Bu, R^1 = Me, R^2 = H, R^3 = Me: 86%

Scheme 55. Fluorine-directed Nazarov cyclisation.

In a second study, Ichikawa et al. investigated the introduction of fluorine at an alternative position on the substrates, so that the β-cation-destabilising effect could be exerted on the cyclopentenylic cation (Scheme 56).[77] These authors reported a second type of fluorine-directed Nazarov cyclisation providing a method for the regioselective preparation of trifluoromethylcyclopentenones. In both Schemes 55 and 56, the regioselectivity was achieved by the electronic effect of fluorine on the intermediary cyclopentenylic cations, which directed the position of the

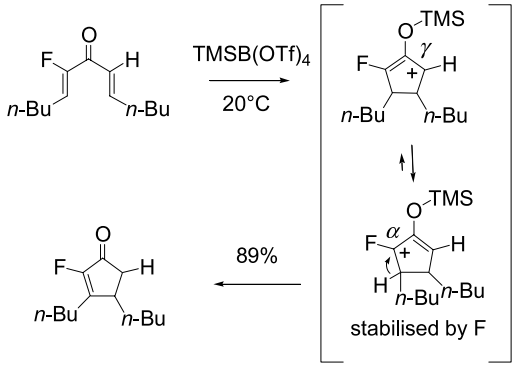


R^1 = Et, R^2 = *n*-Pr: 79%
R^1 = R^2 = Me: 93%
R^1,R^2 = $(CH_2)_3$: 58%
R^1,R^2 = $(CH_2)_4$: 95%
R^1 = Me, R^2 = H: 87%

Scheme 56. Second type of fluorine-directed Nazarov cyclisation.

double bonds regardless of the substitution patterns of the substrates.

In the preceding reactions, the enhancement of the reactivity by fluorine could not be expected because the intermediary cyclopentenylic cations generated in the rate-determining electrocyclisation event were destabilised. In addition to the cation-destabilising effect, fluorine possesses an α-cation-stabilising effect due to donation of its lone pairs. In a third investigation, Ichikawa attempted to utilise this cation-stabilising effect to accomplish another type of fluorine-directed Nazarov cyclisation, where the cyclised cationic intermediate would be stabilised by the α-fluorine.[78] Thus, the cyclisation of 1-fluorovinyl vinyl ketones was readily induced by $TMSB(OTf)_4$ to afford the corresponding cyclopentenones in high yield with defined placement of the double bond (Scheme 57). Indeed, in this reaction, not only the control of regiochemistry, but also the activation of the cyclisation have been accomplished by the fluorine substituent.



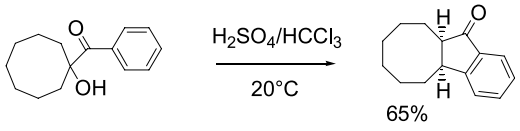
Scheme 57. Third type of fluorine-directed Nazarov cyclisation.

In summary, the remarkable properties of fluorine, which include electronic effects on anions and cations and leaving-group ability as fluoride ion, have permitted the development of three new types of Nazarov cyclisations, providing a facile approach to highly functionalised cyclopentenone derivatives, inaccessible by other conventional methods.

5. Cyclisation of divinyl ketones or equivalents from in situ construction

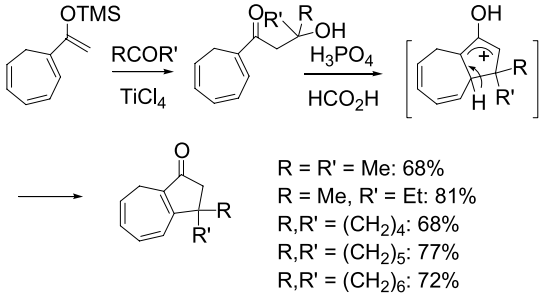
5.1. Cyclisation of divinyl ketones from α- or β-alkoxy enones

The construction of cyclopentenones by the Nazarov cyclisation can be effected by generation of divinyl ketones under conditions that effect closure. Of the myriad of precursors of divinyl ketones, the simplest are α′- and β′-heterosubstituted, α,β-unsaturated ketones. The α′-oxygenated enones are readily prepared by the addition of acyl anion equivalents to ketones. The elimination-cyclisation is achieved by treatment with acid, as depicted in Scheme 58.[79]



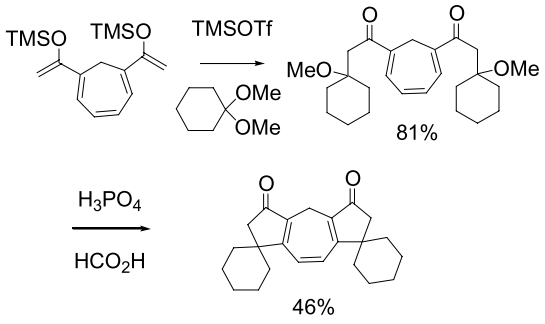
Scheme 58. In situ generation of divinyl ketone from α-hydroxy enone.

In 2000, Kuroda et al. reported the synthesis of azulenones based on a Nazarov cyclisation of a β-hydroxy enone, previously prepared by a Mukaiyama aldol reaction.[80] In these reactions, no regioisomer at the double-bond position was observed. The selectivity of the reaction might be attributed to steric acceleration of deprotonation at the position adjacent to the quaternary carbon in the intermediate hydroxyallyl cation (Scheme 59).



Scheme 59. In situ generation of divinyl ketones from β-hydroxy enones.

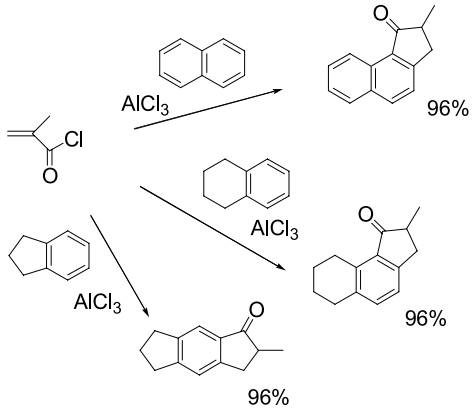
The same methodology was applied to the synthesis of an original pentacyclic diketone based on a double Nazarov cyclisation (Scheme 60).[81]



Scheme 60. In situ generation of divinyl ketone from β-methoxy enone.

5.2. Cyclisation of divinyl ketones from Friedel–Crafts acylation

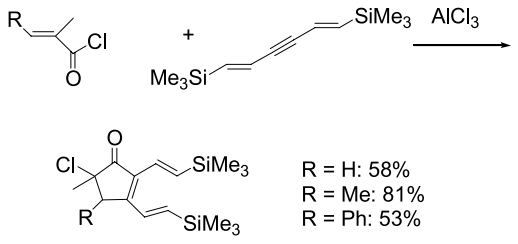
Friedel–Crafts acylation of alkenes with unsaturated acylium ions generated from acid halides and Lewis acids constitutes a general synthesis of divinyl ketones which, under the conditions of acylation, suffer Nazarov cyclisation to cyclopentenones. In 1999, Rieger et al. reported a near-quantitative acylation-cyclisation sequence yielding indanones with remarkable regioselectivity (Scheme 61).[82] Similarly, the aluminium chloride-catalysed reaction of tiglyl chloride and *p*-xylene produced 2,3,4,7-tetramethyl-indan-1-one.[83] In order to prepare novel dihydroquinolines, Jaroch et al. developed the Nazarov cyclisation of a phenyl cycloalkenyl ketone previously prepared by a Friedel–Crafts acylation.[84] Furthermore, Metzger et al. have reported the $EtAlCl_2$-induced Friedel–Crafts acylation of various unsaturated fatty acids such as oleic acid, methyl oleate, and 10-undecenoic acid with α,β-unsaturated acyl chlorides, giving the corresponding allyl vinyl ketones. These latter compounds were then submitted to the Nazarov cyclisation by treatment, for the first time, with montmorillonite K10.[85]



Scheme 61. Synthesis of indanones via acylation-cyclisation sequence.

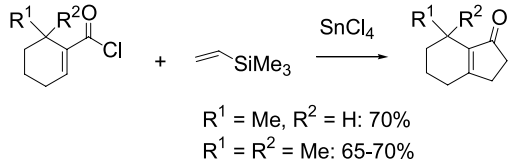
The acylation of acetylenes with alkenoyl chlorides constitutes an alternative construction of cyclopentenones in a higher oxidation state. In 1996, Fiandanese et al. developed a simple cyclisation, deriving from a preliminary addition of an acyclic acyl chloride to the triple bond of a bis-silylated conjugated dienyne and followed by a subsequent ring closure, leading to substituted 5-chloro-2-cyclopentenones in good yields (Scheme 62).[86]

A significant advance in the use of Friedel–Crafts acylation of alkenes to prepare divinyl ketones was the employment



Scheme 62. Acylation–cyclisation of bis-silylated conjugated dienyne.

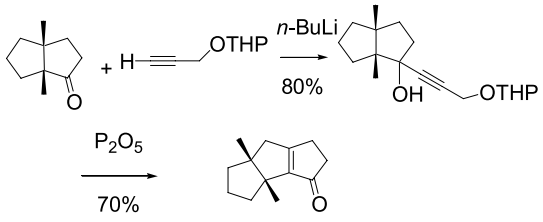
of vinylsilanes as ethylene equivalents to control the site of electrophilic substitution.[87] Stannic chloride was found to be the most effective promoter of the overall transformation and, as expected, the position of the double bond was thermodynamically controlled. Scheme 63 depicts an example used in the synthesis of natural products such as strigol ($R^1=R^2=Me$) and sorgolactone.[88]



Scheme 63. Acylation–cyclisation with vinylsilane.

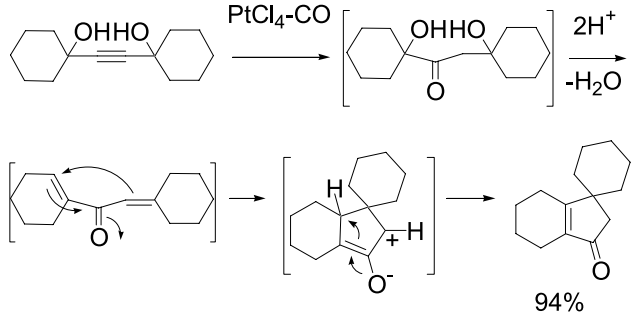
5.3. Cyclisation of divinyl ketones from acetylene-containing precursors

For many years, the preferred method for cyclopentannulation has involved the acid-catalysed transformation of ynediols derived from the addition of propargylic alcohol derivatives to ketones. Using this methodology, Srikrishna et al. developed in 2003 the first total synthesis of the sesquiterpene, (−)-cucumin H (Scheme 64).[89]



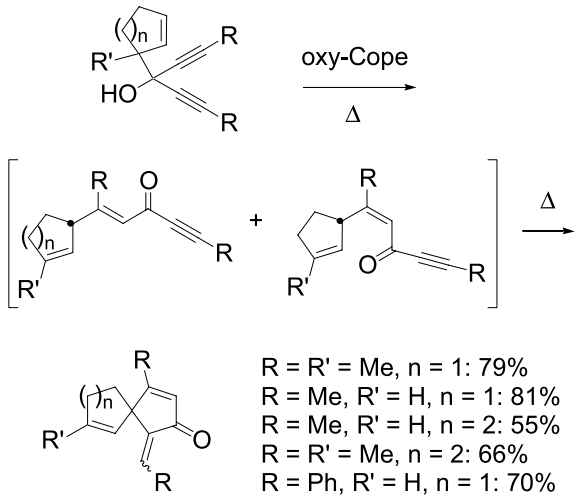
Scheme 64. Nazarov cyclisation from ynediol precursor.

In 1997, Blum et al. demonstrated that the treatment of $PtCl_4$ with CO formed a powerful alkyne hydration catalyst.[90] A clean Nazarov cyclisation followed the process where the substrate was 1,1′-(1,2-ethynediyl)-biscyclohexanol (Scheme 65).



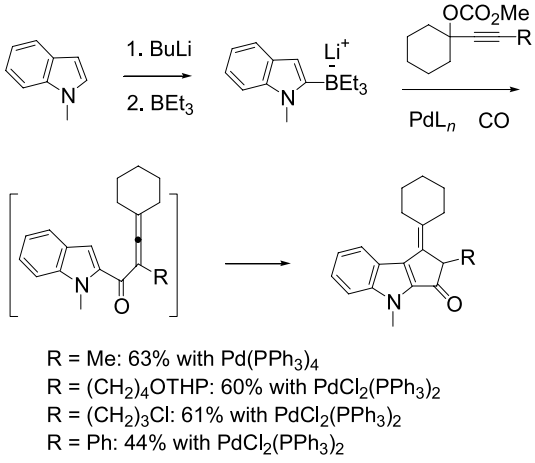
Scheme 65. Nazarov cyclisation during hydration of alkyne by $PtCl_4$–CO catalyst.

Spirocyclic methylenecyclopentenones and analogues of the methylenomycin class of antibiotics have been prepared in a single step from bis-acetylenic alcohols by a process involving an initial oxy-Cope rearrangement to afford (*Z*)-enynones, followed by electrocyclic ring closure (Scheme 66).[91]



Scheme 66. Nazarov cyclisation of enynones formed by oxy-Cope rearrangement.

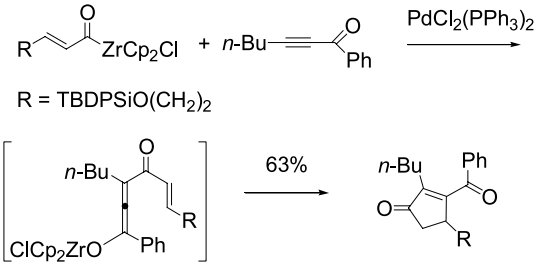
In 1996, Agata et al. reported a novel one-pot route to cyclopenta[*b*]indoles via the palladium-catalysed carbonylative cross-coupling reaction of an indolylborate with prop-2-ynyl carbonates (Scheme 67).[92]



Scheme 67. Synthesis of cyclopenta[*b*]indoles.

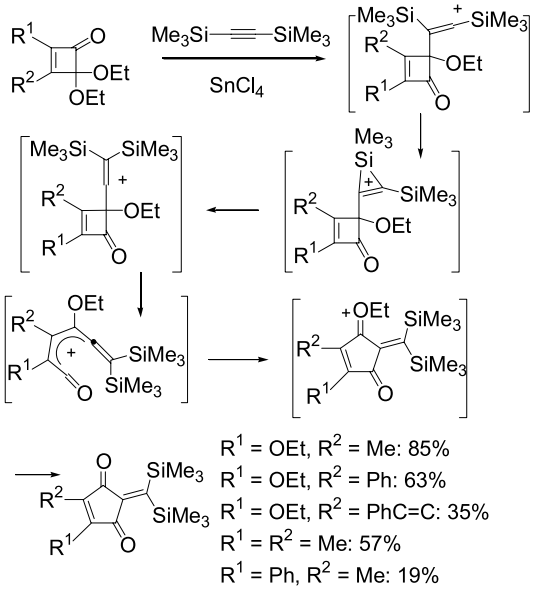
A one-pot formation of cyclopentenone derivatives was elaborated in 2001, based on a palladium-catalysed acylation of α,β-unsaturated ynones with α,β-unsaturated acylzirconocene chlorides (Scheme 68).[93]

In 1997, Eguchi et al. showed that an ethoxycarbenium ion intermediate, which was produced by the catalytic action of



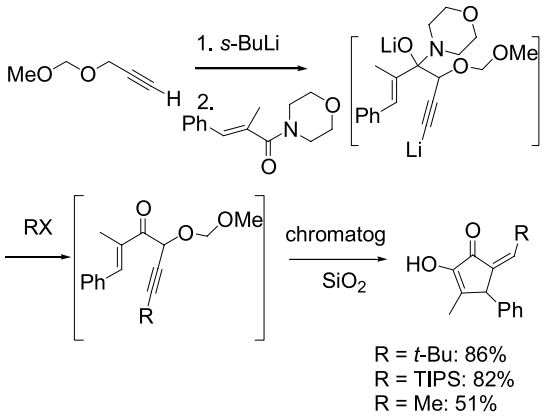
Scheme 68. Nazarov cyclisation from α,β-unsaturated ynones.

a Lewis acid on a cyclobutenedione monoacetal, reacted with bis(trimethylsilyl)acetylene, affording a 2-methylene-4-cyclopentene-1,3-dione derivative as a ring-expansion, instead of an alkynylation, product (Scheme 69).[94]



Scheme 69. Nazarov cyclisation from bis(trimethylsilyl)acetylene.

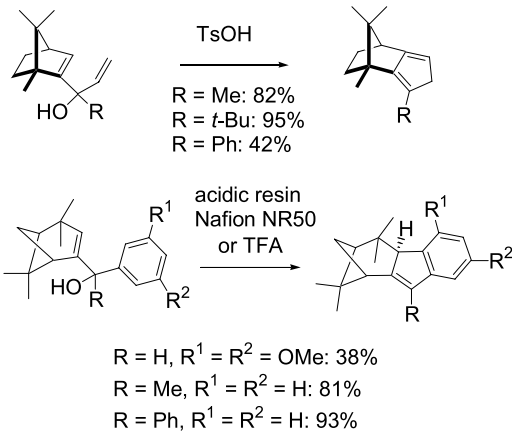
A variant of the Nazarov cyclisation was reported by Tius in 2003, in which propargyl vinyl ketones derived from the addition of 1-lithio-1-methoxymethoxy-2-ynes to morpholino enamides underwent isomerisation, followed by cyclisation to α-methylene cyclopentenones upon exposure to silica gel (Scheme 70).[95]



Scheme 70. Nazarov cyclisation from 1-methoxymethoxy-2-ynes.

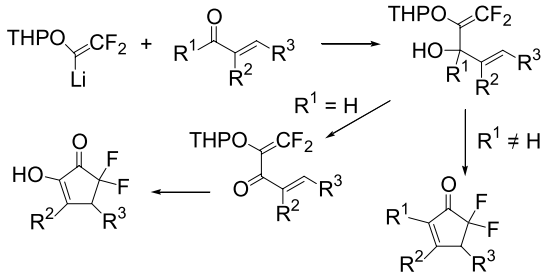
5.4. Cyclisation of pentadienyl cations

Nazarov cationic π-cyclisations have been successfully employed in the synthesis of several products such as camphor-derived chiral cyclopentadienes. In this way, bis(allylic) alcohols, prepared in three steps from camphor, cleanly underwent the Nazarov reaction in the presence of acid (TsOH) (Scheme 71).[96] In 1998, Ohwada et al. reported the superacid-catalysed electrocyclisation of diphenylmethyl cations, generated from diarylmethanols substituted with a carbonyl group, to fluorenes.[97] More recently, a new class of chiral indenes, in which a verbenone moiety was annulated to an indene core, was prepared by a sequence of Shapiro lithiation reaction and Nazarov cyclisation on the resulting allylic alcohol (Scheme 71).[98]



Scheme 71. Nazarov cationic π-cyclisations from allylic alcohols.

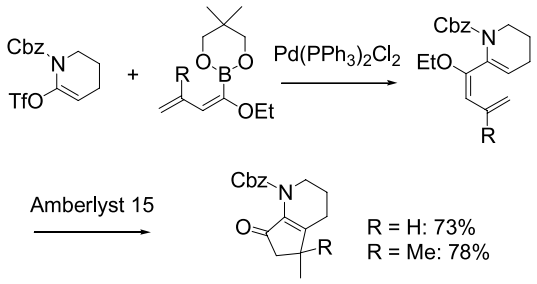
In 1999, Tius et al. demonstrated that condensation of difluorovinyllithium, readily accessible from cheap 2,2,2-trifluoroethanol, on α,β-unsaturated ketones led to tertiary alcohols which, upon ionisation, led to pentadienyl carbocations that could undergo cyclisation to the final difluorocyclopentenones by means of Nazarov cyclisation (Scheme 72).[99]



Scheme 72. Synthesis of difluorocyclopentenones by Nazarov cationic π-cyclisations.

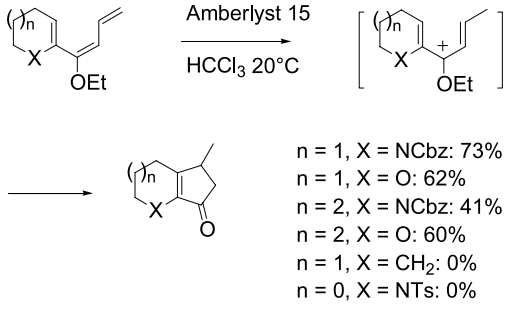
In 2002, Occhiato et al. studied the palladium-catalysed cross-coupling reaction of α-alkoxydienylboronates with lactam-derived vinyl triflates. The hydrolysis of the coupling products, performed in the presence of Amberlyst 15, resulted in a Nazarov cyclisation that afforded the 2,3,4,5-tetrahydroazepines in good yields (Scheme 73).[100a]

This procedure could be generalised to lactone derivatives which constituted a new synthetic route to cyclopenta-fused *N*- and *O*-containing heterocycles.[100] The authors have



Scheme 73. Synthesis of 2,3,4,5-tetrahydroazepines.

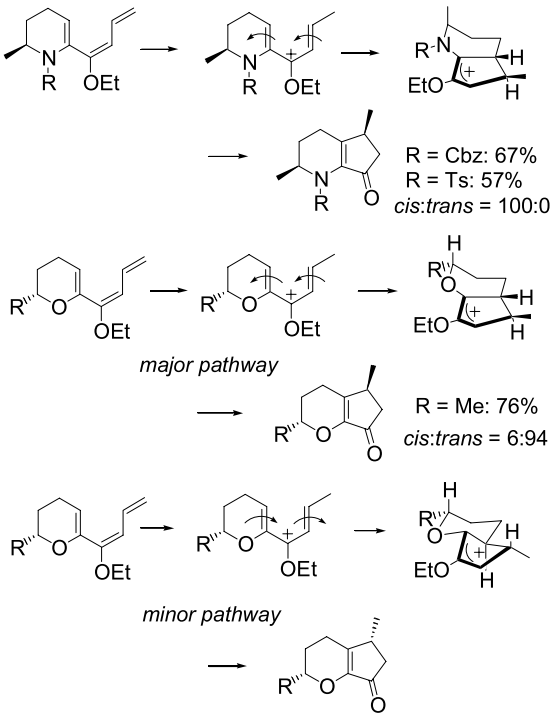
demonstrated that the presence of a heteroatom such as N or O was essential in stabilising the incipient oxyallyl cation in the transition state of the process. In fact, analogous carbacycle trienes, under the mild hydrolysis conditions used, did not afford the Nazarov cyclisation product, but only the open-chain ketone. Furthermore, it was shown that the ring size was also a basic parameter in the cyclisation step. Whereas the formation of a fused 5–5 system did not take place unless classical Nazarov conditions were used, six- and seven-membered lactam and lactone derivatives easily underwent electrocyclisation under mild conditions to give 6–5 and 7–5 fused heterocycles in good yields (Scheme 74).



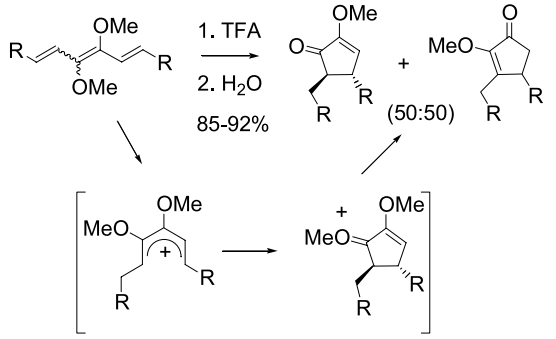
Scheme 74. Synthesis of cyclopenta-fused heterocycles, based on mild Nazarov reaction.

In the present study,[100] the authors have provided a complete depiction of the torquoselectivity in the Nazarov process of lactam- and lactone-derived ethoxytrienes. A high diastereoselectivity was observed with 2-substituted five-membered lactam derivatives, occurring through a conrotation in the 3-hydroxypentadienyl cationic intermediate which involved the less-hindered face of the endocyclic double bond. The same was true for 2- and 4-substituted δ-valerolactam derivatives. In contrast, the *trans*-product was predominantly formed with 2-methyl-substituted δ-valerolactone derivatives, whereas modest selectivity was observed with 4-substituted lactone derivatives. These findings suggest that steric interactions play a role in the selection between the two possible conrotatory pathways (Scheme 75).

Finally, very recently, Barluenga et al. have demonstrated that the exposure of dimethoxyhexatrienes to an excess of trifluoroacetic acid at room temperature led to a 1:1 mixture of two cyclopentenone derivatives in near-quantitative yields.[29] As shown in Scheme 76, the reaction should begin with the reversible protonation of the distal carbon–



Scheme 75. Torquoselectivity in the synthesis of cyclopenta-fused heterocycles.

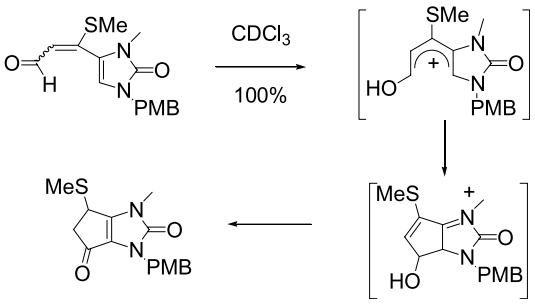


Scheme 76. Nazarov cyclisation from dimethoxyhexatrienes.

carbon double bond of the triene, leading to pentadienyl cation species. Conrotatory ring closure was greatly facilitated because of the special stabilisation of the oxyallyl cation by an alkoxy group. This cationic intermediate evolved by either direct hydrolysis to give the methoxy-cyclopentenone or proton elimination, followed by hydrolysis of the less-substituted enol ether function, to afford the cyclopentenone.

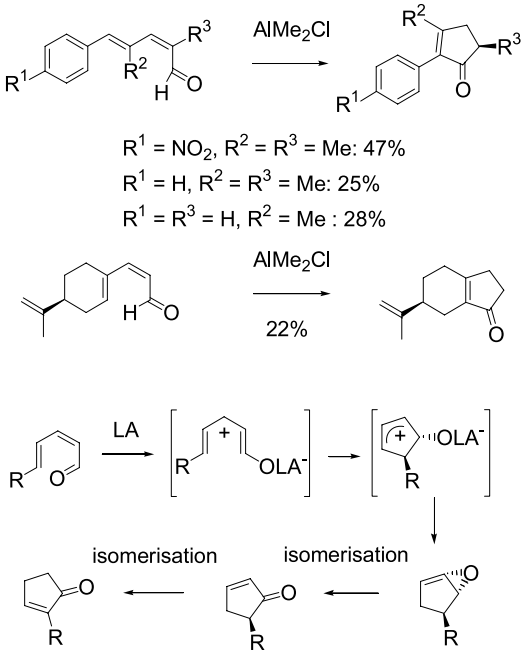
Very recently, Porter et al. reported an unexpected possible Nazarov cyclisation of an α,β-unsaturated-β-methyl-sulphanyl aldehyde under very mild conditions (on dissolution in $CDCl_3$), yielding a polyfunctionalised cyclopentenone (Scheme 77).[101]

In 2003, Trauner et al. developed a Lewis acid (Me_2AlCl)-promoted cyclisation of pentadienals to cyclopentenones,[102] in which a Nazarov-like mechanism involving the conrotatory cyclisation of an oxypentadienyl cation could be operating. The resulting zwitterion reacted further to afford



Scheme 77. $CDCl_3$-induced Nazarov cyclisation.

cyclopentadiene epoxide. Under the Lewis acidic reaction conditions, this latter intermediate was likely to undergo further isomerisations to the final cyclopentenone (Scheme 78).

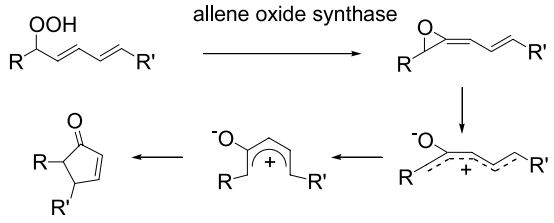


Scheme 78. Cycloisomerisation of pentadienals to cyclopentenones.

Very recently, Kuroda et al. have investigated a new type of cyclisation involving 2-(trimethylsilylmethyl)pentadienal derivatives in the presence of $FeCl_3$. This reaction was only related to the Nazarov reaction, although it led to cyclopentenones via a silicon-stabilised cyclopentadienyl cation.[103]

Theoretical calculations such as those related to the effects of substituents in the 3-position on the pentadienyl cation electrocyclisation have been studied. The activation energy for the cyclisation decreased in the order $NH_2 > OH > SH > H > PH_2 > BH_2 > AlH_2$, as did the energy of cyclisation. These results, as well as the conformational preferences, were explained by a combination of steric and electronic interactions.[104]

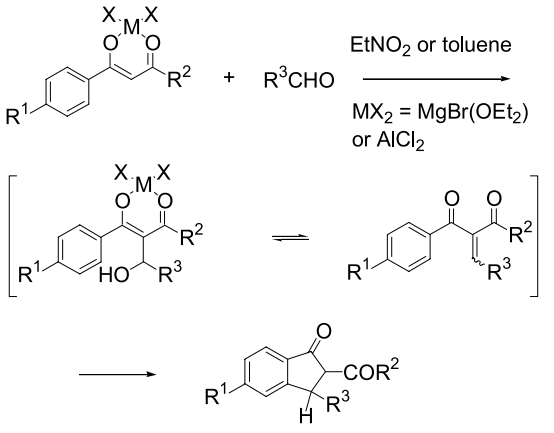
On the other hand, Grechkin et al. have recently studied the mechanism of formation of cyclopentenones from (*E*,*E*)-hydroperoxides of fatty acids submitted to incubations of allene oxide synthases.[105] Indeed, the intermediary allene oxides were converted into the final cyclopentenones via pentadienyl cations (Scheme 79).



Scheme 79. Enzymatic Nazarov cyclisation.

5.5. Related reactions

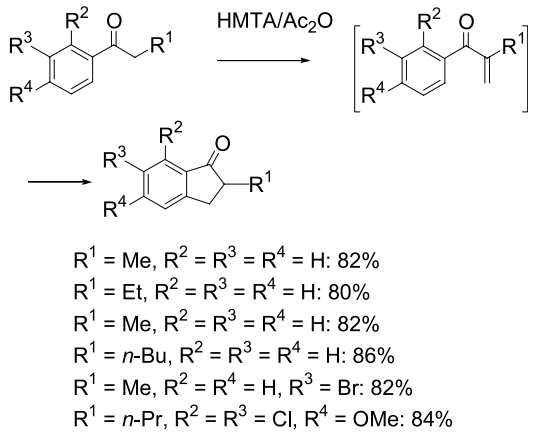
In 1993, Sartori et al. showed that bromomagnesium and dichloroaluminium chelates of aromatic β-dicarbonyl compounds underwent highly selective bis-alkylation with non-enolisable aldehydes, affording the 3-substituted 1-oxoindane derivatives (Scheme 80).[106] The reaction of the metal chelate at the active methylene carbon with the aldehyde produced a first intermediate which could be converted into an enedione via an elimination process. This latter compound was converted into the final product by a Nazarov process.



Scheme 80. Synthesis of 1-indanones via tandem Knoevenagel–Nazarov process.

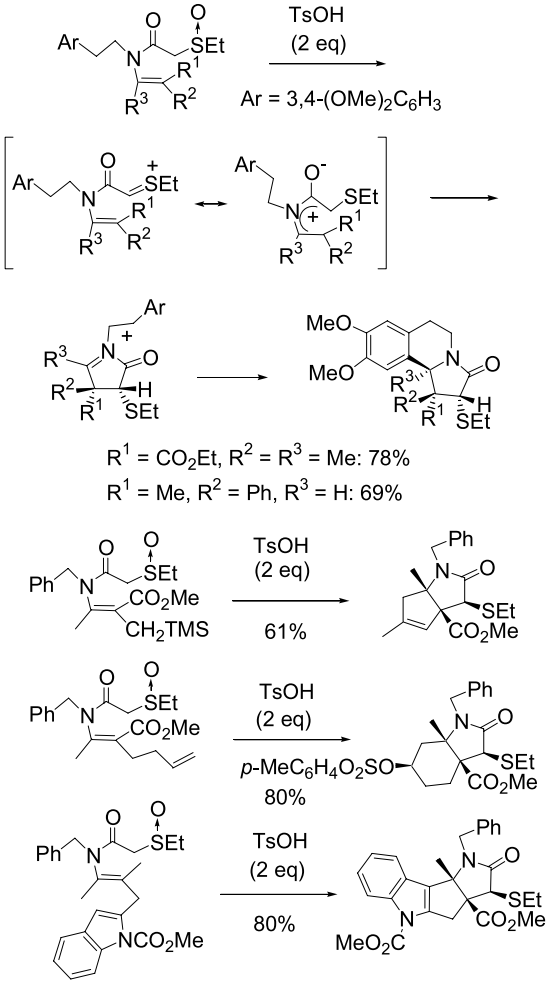
Hexamethylenetetramine (HMTA) has been proven to be an excellent and inexpensive promoter of the Mannich reaction of aryl alkyl ketones, which was followed by a Nazarov cyclisation, providing the 2-alkyl indanones in excellent yields (Scheme 81).[107]

Padwa et al. have studied cyclisation reactions of various α-sulphinyl enamides in the presence of TsOH, leading to fused isoquinoline lactams.[108] The mechanism involved the



Scheme 81. Synthesis of 2-alkyl indanones via tandem Mannich–Nazarov process.

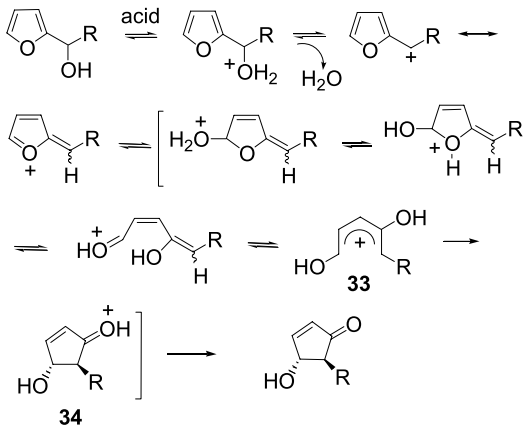
initial formation of an α-acylthionium ion, followed by a Nazarov-type cyclisation occurring in a conrotatory fashion to give an *N*-acyliminium ion. The final cyclisation step proceeded in a stereoselective manner by attack on the proximal aromatic ring from the less-hindered side of the iminium ion framework (Scheme 82). This novel tandem thionium–iminium ion cyclisation cascade could be extended to various substrates.



Scheme 82. Tandem thionium–iminium ion cyclisation cascade.

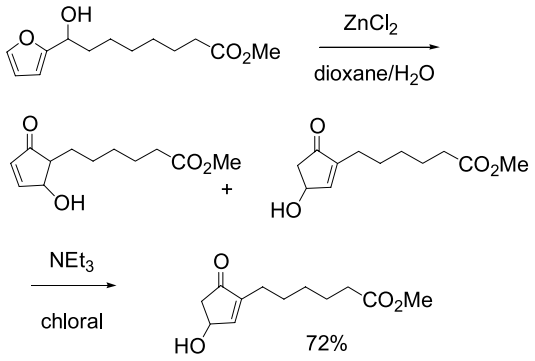
6. Solvolysis of 2-furylcarbinols

The acid-catalysed rearrangement of 2-furylcarbinols to 4-hydroxy-2-cyclopentenones was first described and subsequently investigated by Piancatelli et al.[109] An important advantage of this synthesis was the ready availability of the precursors from either a Grignard synthesis with furfural or the addition of 2-furyllithium to aldehydes. A second advantage was the simplicity of the synthetic procedures. The facility of the rearrangement was dependent upon the ring substitution and differing reagents were recommended. For bromo- or unsubstituted furans, the reaction was sluggish, and sulphuric acid was used, while, for alkyl-substituted furans, zinc chloride was the most effective. Mechanistically, the reaction was intriguing, as it corresponded to the in situ formation of a conjugated dienone, rather than a cross-conjugated divinyl ketone. Thus, cyclisation in a Nazarov sense (as a 1,4-dihydroxypentadienylic cation) led to the 4-hydroxy-2-cyclopentenones. An important consequence of the electrocyclisation was the *trans*-relationship of the 4-hydroxy group and the 5-substituent. In 2004, de Lera et al. reported a theoretical study of the electrocyclic ring closure of hydroxypentadienyl cations and proposed a reasonable mechanism for this rearrangement (Scheme 83).[110] This mechanism includes some of the intermediates already advanced by Piancatelli. Accounting for the stereochemical outcome of the process, a 4π-e^- conrotatory electrocyclic ring closure of 5-alkyl-1,4-dihydroxypentadienyl cation **33** was postulated. Other intermediates in the sequence, generated by the action of acids on the starting furfuryl carbinol, are also shown in Scheme 85.

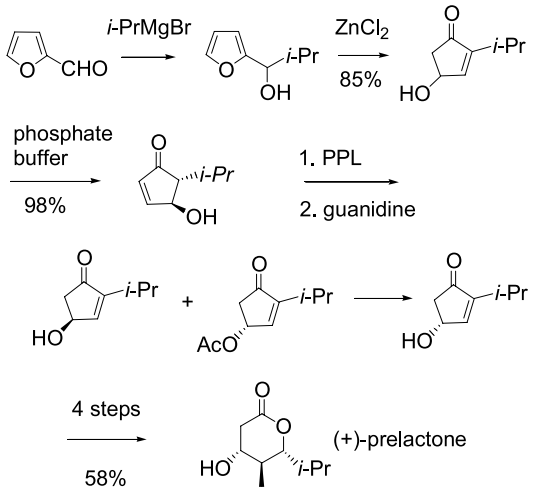


Scheme 83. Mechanistic proposal for solvolysis of 2-furylcarbinols.

Computation of the reaction profile at the B3LYP/6-311G* level of theory for the key step of the Piancatelli reaction, or transformation of furfuryl carbinols to *trans*-2-alkyl(aryl)-3-hydroxycyclopent-4-en-1-ones, predicted its pericyclic nature. Geometric, energetic, and magnetic criteria were compatible with a conrotatory electrocyclic reaction, which transformed the intermediate *out*,*out*-5-alkyl-1,4-dihydroxypentadienyl cation **33** into the protonated *trans*-**34**. Both the Piancatelli and the Nazarov reactions, prototypical 4π-e^- electrocyclisations, primarily benefit from the presence of an array of interacting orbitals in the reactant hydroxypentadienyl cations, as shown by the



Scheme 84. Synthesis of prostaglandin E_1.

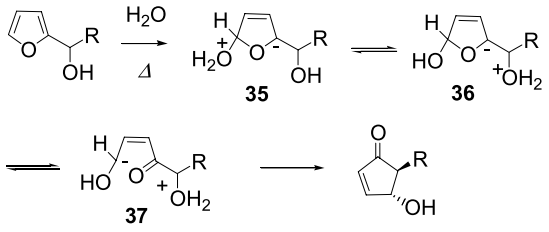


Scheme 85. Synthesis of (+)-prelactone from furans.

evaluation of the nucleus-independent chemical shift (NICS) at distances from the ring plane in the helical transition structures for their conrotatory motions. Charge separation at the terminal carbon atoms in **33** further contributed to reduce the activation energy for its cyclisation. The Piancatelli reaction has recently been applied to an efficient asymmetric synthesis of prostaglandin E_1.[111] Actually, the reaction afforded a mixture of the expected first-formed cyclopentenone, along with the corresponding isomerised enone. Complete isomerisation was further carried out in the presence of NEt_3 (Scheme 84).

In addition, Csakÿ et al. have reported very recently a new procedure for the asymmetric synthesis of cyclopentenones containing benzylic α-quaternary carbon stereogenic centres, and an enantioselective synthesis of (+)-prelactone from furans (Scheme 85).[112]

Surprisingly, D'Auria has found that the same reaction could be carried out only in boiling water in the absence of any acid catalyst.[113] This result was not in agreement with the initially proposed mechanism (Scheme 83), and D'Auria has proposed a new hypothesis for the mechanism (Scheme 86). The thermal reaction of water in the 5-position on the furan ring in an irreversible reaction could allow the formation of **35**. Prototropic equilibrium gave **36** and, then, the ring-opened intermediate **37**. This compound spontaneously cyclised to the final cyclopentenone.



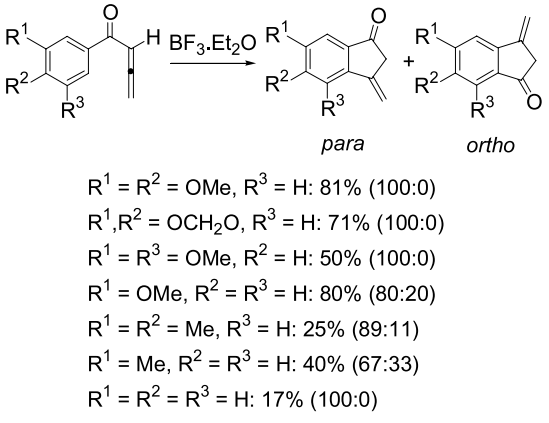
Scheme 86. D'Auria's mechanism for the conversion of 2-furylcarbinols into cyclopentenones.

7. Cyclisation of divinyl ketones or equivalents from allene-containing precursors

7.1. Cyclisation of vinyl allene derivatives

The peracid epoxidation of vinyl allenes bearing allenic substituents results in the formation of cyclopentenones. Pasto et al. have studied the oxidative ring closure of substituted bisallenes and observed that both allene chromophores underwent epoxidation, which led to the formation of a mixture of four cyclopentenones in almost equal ratios.[114]

The first Nazarov cyclisation of an allenyl aryl ketone was reported by Nagao et al.[115] The reaction was carried out in the presence of $BF_3{\cdot}Et_2O$ and afforded a mixture of two cyclopentenones (*ortho* and *para*). Steric interaction between the aromatic substituent and the allenic moiety might control the regioselectivity in the cyclisation (Scheme 87).

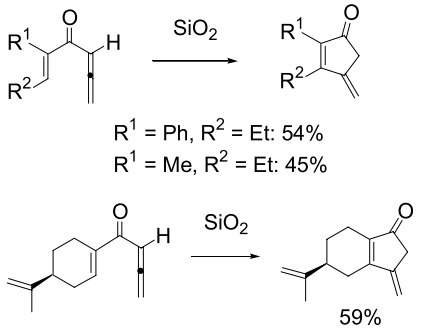


Scheme 87. Nazarov cyclisation of allenyl aryl ketones.

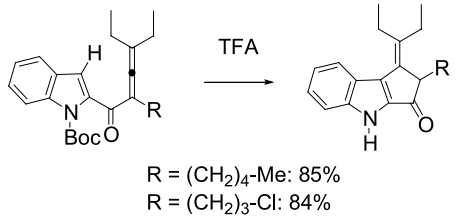
In 1998, Hashmi generalised this reaction to allenyl vinyl ketones, which delivered the products of the Nazarov cyclisation on silica gel (Scheme 88).[116] Whereas a strong acid is usually necessary to induce the Nazarov process, the enhanced reactivity of the allene, combined with the acceleration of the reaction by the presence of donors α to the ketone, allowed silica gel to catalyse this reaction.

In addition, indol-2-yl allenyl ketones were subjected to acidic treatment with TFA and cleanly produced the corresponding cyclopenta[*b*]indole derivatives (Scheme 89).[117]

A new variant of the Nazarov cyclisation was reported by de

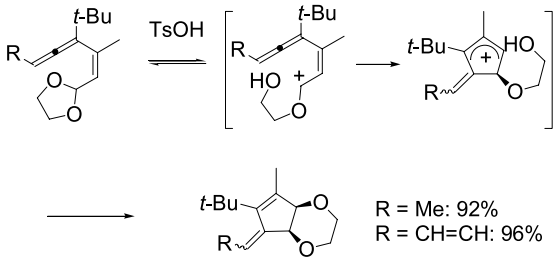


Scheme 88. Nazarov cyclisation of allenyl vinyl ketones.



Scheme 89. Synthesis of cyclopenta[*b*]indole derivatives.

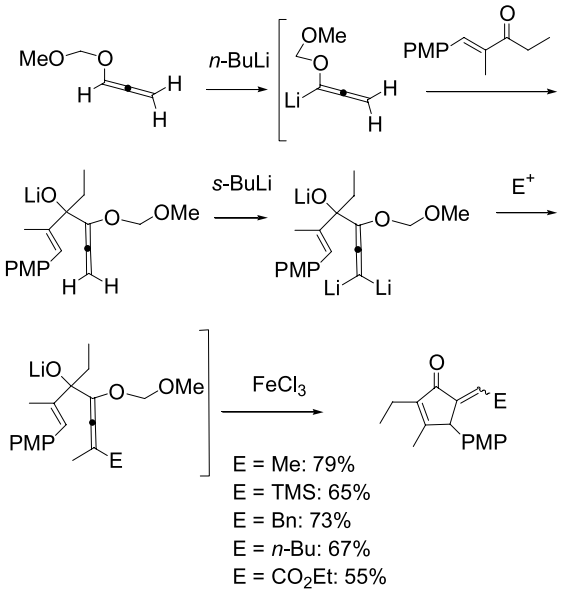
Lera et al. in which divinylallene acetals underwent almost quantitatively and under very mild conditions (TsOH) facile rearrangement to the alkylidenecyclopentenes by a mechanism consistent with electrocyclic ring closure of a pentadienyl carbocation, followed by trapping of the resident hydroxyl (Scheme 90).[118] This reaction occurred much more readily than the standard Nazarov cyclisation, proceeding rapidly even at −30 °C. The torquoselectivity of the reaction was studied and ab initio calculations were undertaken.[118b] These latter calculations suggested that the torquoselectivity of the reaction, which was, in some cases, 100% in favour of the *R-outward* rotation at temperatures impeding acid-induced equilibration (> −30 °C), was attributed to steric hindrance between R and the C1 substituent, and that the *R-inward* reaction products (*Z*) were considerably more stable than the *R-outward* isomers (*E*).



Scheme 90. Nazarov cyclisation of divinylallene acetals.

7.2. Cationic cyclopentannelation of allenyl ethers

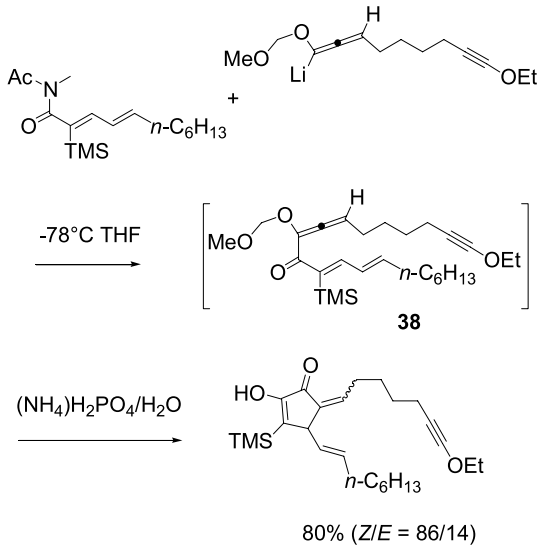
The cationic cyclopentannelation of allenyl ethers has been widely studied by Tius and constitutes a very efficient construction of α-methylenecyclopentenones.[119] This variant of the Nazarov cyclisation that makes use of allenyl ethers is suitable for the preparation of diverse, highly functionalised cyclopentenones. Three variants of the basic reaction, differing in the nature of the electrophile (enone, α,β-unsaturated amide, or α,β-unsaturated nitrile) that is combined with the allene to prepare the precursor for the intermediary pentadienyl cation, have been developed. The first variant of the cyclopentannelation involved the cyclisation of a tertiary alcohol prepared by the condensation of an α-lithio-α-alkoxyallene on an enone. An extension of this reaction was reported in 2003 by the development of a very convenient, triply convergent synthesis of C6-substituted α-methylene cyclopentenones (Scheme 91).[120] This first variant has been applied to variously substituted reactants, thus providing diverse, highly functionalised cyclopentenones. Several natural products such as xanthocidin,[121] desepoxymethylenomycin A methyl ester,[122] and prostaglandins[123] have been elegantly synthesised by using this methodology.



Scheme 91. First variant of cationic cyclopentannelation.

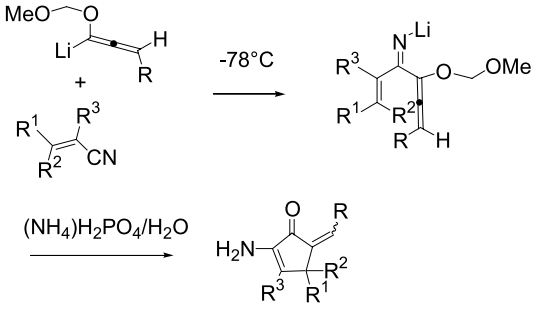
The second variant of the reaction involved the intermediacy of an allenyl ketone **38**, generated by the condensation of an α-lithio-α-alkoxyallene on an α,β-unsaturated amide, followed by quenching of the reaction mixture with aqueous NaH_2PO_4 or HCl. This reaction is illustrated by the preparation of prostaglandin analogues (Scheme 92).[124] Addition of lithioallene to Weinreb amide at −78 °C, followed by quenching, led to the expected α-hydroxy cyclopentenone in 80% yield. There were at least two features of this reaction that were noteworthy. First, the conditions for the cyclisation were extraordinarily mild and, secondly, there was a marked kinetic preference for the formation of the *Z*-isomer of the exocyclic double bond (*Z*/*E*=86/24). This second variant has been widely generalised to the synthesis of variously functionalised α-hydroxy cyclopentenones,[120] and applied to the development of novel routes to natural products such as the macrocyclic core,[125] the hydroazulene portion of guanacastepene A,[126] and roseophilin.[127]

The third variant of the cyclopentannelation involved the addition of a lithioallene to an α,β-unsaturated nitrile.[128]



Scheme 92. Second variant of cationic cyclopentannelation.

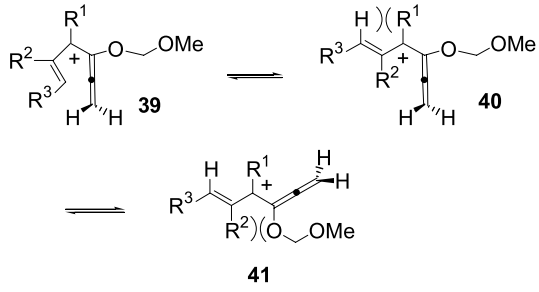
Protonation of the cationic intermediate was followed by spontaneous cyclisation to an α-aminocyclopentenone (Scheme 93). This appeared to be the first example of an imino-Nazarov reaction. The classical imino-Nazarov cyclisation is energetically disfavoured, because the ring-open cation is strongly stabilised through electron-pair donation by the nitrogen atom.[104] The cyclisation is successful because an unfavourable equilibrium for the cyclisation can be overcome by irreversible loss of the methoxymethyl cation from the cyclic product.



R^1 = Ph, R^2 = H, R^3 = Me, R = H: 73%
R^1 = Ph, R^2 = H, R^3 = R = Me: 71% (*E*/*Z* = 67/33)
R^1 = *p*-$MeOC_6H_4$, R^2 = H, R^3 = Me, R = H: 63%
R^1 = *p*-$MeOC_6H_4$, R^2 = H, R^3 = R = Me: 70% (*E*/*Z* = 95/5)
R^1,R^3 = $(CH_2)_6$, R^2 = R = H: 72%
R^1,R^3 = $(CH_2)_6$, R^2 = H, R = Me: 72% (*E*/*Z* = 50/50)

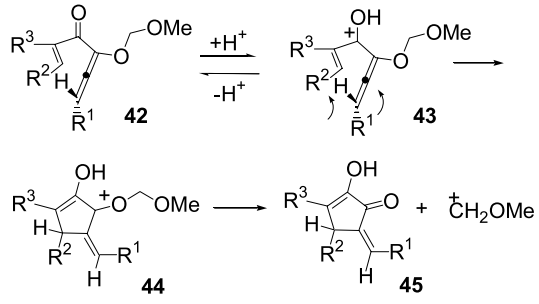
Scheme 93. Third variant of cationic cyclopentannelation.

The general method appears to be reasonably versatile and, although it can be used to access a wide variety of cyclopentenones, there are some limitations. One limitation, apparently, is that the α,β-unsaturated ketone, amide or nitrile must bear a non-hydrogen α-substituent, for example, the allenyl ketone related to **38** having a hydrogen atom in place of the α-trimethylsilyl group underwent cyclisation in $<10\%$ yield. The origin of this effect is not certain, but it may be related to the population of the U-shaped conformer **39** of the pentadienyl cation (Scheme 94). Since the cyclisation, of necessity, must take place through the conformer **39**, any factor that diminishes the proportion of **39** in the equilibrium mixture of conformers of the pentadienyl cation can be expected to adversely affect the cyclisation yield. When R^1 or R^2 are larger than hydrogen, conformers **40** and **41** are disfavoured relative to **39**. Assuming that the conformational equilibrium is rapidly established, this would result in a mixture enriched in **39**, and a favourable cyclisation.[5c,129]



Scheme 94. Equilibrium mixture of conformers of the pentadienyl cation.

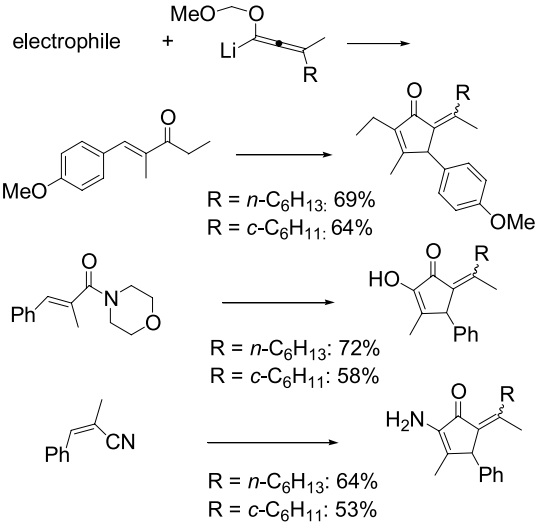
In addition, there appear to be some restrictions on the ether substituent of the allene. Although the best yields for the cyclisation have been obtained in the case of methoxymethyl allene ether, it was found that 2-tetrahydropyranyl, (2-ethoxy)ethyl and (methylthio)methyl substituents were also effective. Apparently, in order for the cyclisation to succeed, it is necessary that the ether fragment on the allene is lost from the cyclic intermediate as a stable carbocation, and allenyl trialkylsilyl ethers might therefore be useful for the cyclopentannelation. These materials led, however, to a different reaction manifold and did not afford the expected cyclopentenones. The most probable mechanism for the cyclisation of allenyl ketones **42** is depicted in Scheme 95.



Scheme 95. Mechanism for the cyclisation of allenyl ketones **42**.

Reversible protonation of **42** leads to the pentadienyl cation **43**, which can undergo thermally allowed conrotatory ring closure to give **44**. This process is accompanied by the relief of strain associated with the allene function. Loss of $^+CH_2OMe$ as a stable cation leads irreversibly to **45**. This process must take place rapidly, otherwise decomposition of the cation **44** through rearrangements and proton loss will erode the yield of **45**. The stereochemistry-determining step is the ring closure of **43** to **44**. The allene function in **42** is stereogenic. Although conrotation in both the clockwise and counterclockwise sense is allowed, for steric reasons **43** will preferentially undergo counterclockwise conrotation, as

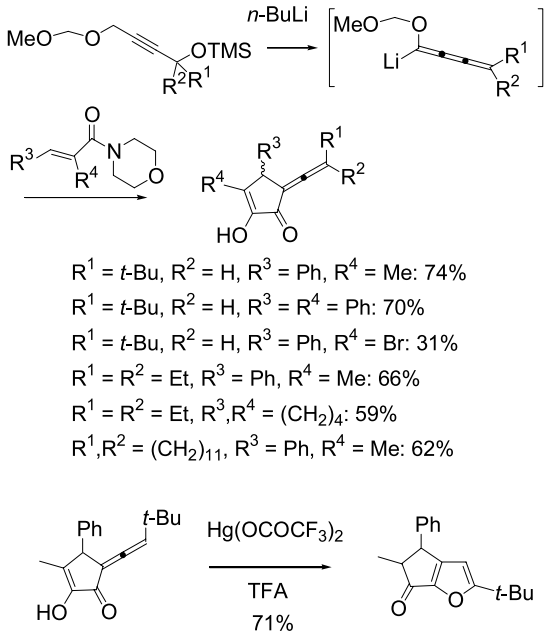
shown. In this way, the steric bulk of R^1 moves away from R^2 and this has two consequences. Firstly, the exocyclic double bond in **45** will have a preference for the *Z* geometry and, secondly, the cyclisation will be accompanied by the transfer of axial asymmetry from the allene to tetrahedral asymmetry of the ring carbon in **45**. Finally, it seems that the transfer of asymmetry during the cyclisation will be most efficient when R^1 is a large group, such as *t*-butyl. It also seems that any *E* to *Z* isomerisation of **42** will lead to a non-stereoselective cyclisation reaction. Very recently, Tius has extended his method of preparation of allene ethers to tetrasubstituted allene ethers, making use of a reverse Brook rearrangement.[130] The cyclopentannelation reaction of the resulting allenes was investigated in its three broad categories (see below for the three variants). Scheme 96 shows that the tetrasubstituted allenes have been shown to be useful in all the three categories of the reaction, providing cyclopentenones bearing a β,β-disubstituted exocyclic double bond.



Scheme 96. Nazarov reaction from tetrasubstituted α-lithio-α-alkoxyallenes.

In 2003, Tius et al. described an asymmetric version of the cyclopentannelation reaction, but this work will be developed in Section 8.

Another extension of the cationic cyclopentannelation reaction was the recent use, for the first time, of α-lithio cumulenyl ethers, which were converted into the corresponding α-allenyl cyclopentenones.[131] Isomerisation of the product of one such reaction has led to a furanyl cyclopentenone, the core structure of nakadomarin A (Scheme 97).

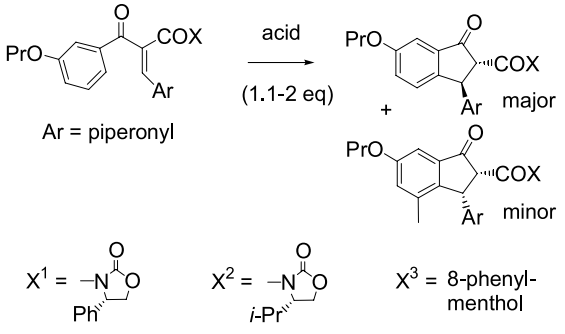


Scheme 97. Nazarov reaction of vinyl cumulenyl ketones.

8. Asymmetric Nazarov cyclisation

8.1. Chiral auxiliaries

The first asymmetric Nazarov cyclisation was reported in 1999 by Pridgen et al. in the course of preparing non-racemic indanes as endothelin receptor antagonists.[132] Asymmetric induction was transferred across five carbons (1,5-induction), since chiral alkylidene-1,3-carbonyl compounds formed selectively, under either protic or Lewis acid catalysis, the corresponding indanones. Of the eight possible isomers that may be formed, only two isomers were usually observed, and the results were found to be similar, regardless of the choice of auxiliary (Scheme 98).



X	Acid	Yield (%)	Isomer ratio
X^1	$SnCl_4$	85	88/12
X^1	$MeSO_3H$	88	85/15
X^1	$TiCl_4$	60	70/30
X^2	$SnCl_4$	74	82/18
X^3	$SnCl_4$	90	96/4

Scheme 98. Asymmetric Nazarov cyclisation.

The success of 8-phenylmenthol as an effective chiral transfer auxiliary combined with the fact that methanesulphonic acid was as effective a promoter as any other Lewis acid explored, suggested that metal-carbonyl complexation was not a prerequisite for establishing stereoselective cyclisation. A Drieding model of the starting material suggested that the highly *transoid* ordered structure, as depicted in Figure 1, positioned the exocyclic β-carbon for

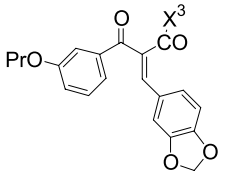
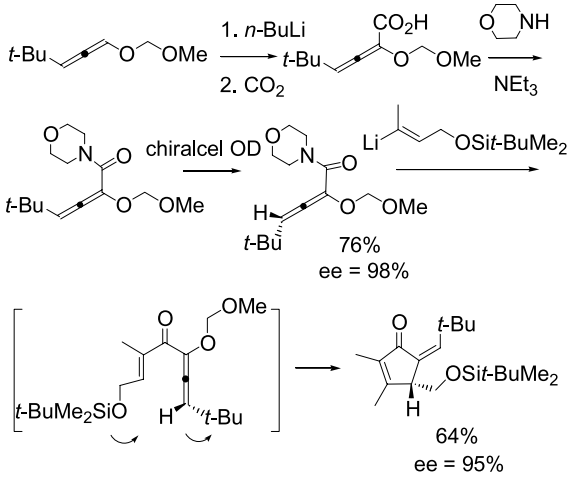


Figure 1. Highly *transoid* ordered structure of chiral auxiliaries.

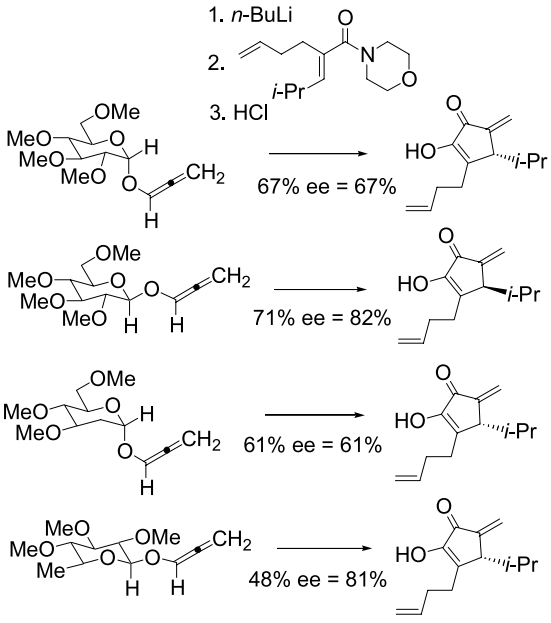
facile 4π-electrocyclic cyclisation to yield the product. The conformations available were examined by computational methods. These conformations were generated starting from the distance and dihedral angle geometry obtained from X-ray data and were energy minimised using the MM2 procedures. The imide carbonyls were held in a *trans*-coplanar geometry throughout the conformer generation. The distance from the α,β-unsaturated to the β-carbon to the aromatic C-6 was 2.83 Å, well within bond-forming range. Apparently, the steric demands alone of the reactant were sufficient to allow enough π–π-interaction to effect reaction at the aromatic ring. The lack of a carbonyl in the case of X=8-phenylmenthol and the lack of an aromatic substituent in the case of X^2-substitution precluded electronic participation by the chiral auxiliary in the form of π-stacking.

In 1999, there were no well-suited enantioselective methods for the preparation of alkoxyalkyl allenyl ethers. In this context, Tius et al. got around this problem by deciding to resolve allene enantiomers by preparative chiral HPLC.[133] The racemate was previously prepared through the carboxylic acid, which was formed by trapping the corresponding lithioallene with carbon dioxide. After resolution on a Chiralcel OD column, the chiral allenamide was combined with a vinyllithium to produce the corresponding cyclopentenone with a chirality transfer of >95% from the allene (Scheme 99). The absolute stereochemistry of the cyclopentenone could be understood by postulating a counterclockwise conrotation.



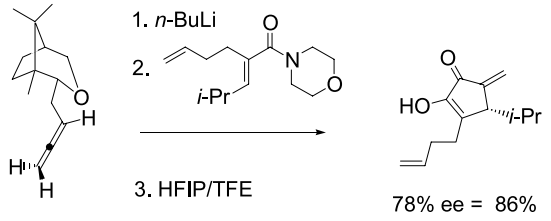
Scheme 99. Asymmetric cyclopentannelation via chiral HPLC.

In order to develop an asymmetric cyclopentannelation reaction that did not depend upon the axial chirality of the allene for the transfer of asymmetry, Tius et al. reported in 2000 an enantioselective synthesis of cyclopentenones with an unsubstituted exocyclic double bond by means of a D-glucose-derived chiral auxiliary on the allene (Scheme 100).[134] Higher enantiomeric excesses of the products were observed in the case of β-anomers of D-glucose derivatives. Neither the methoxyl at C-2 nor that at C-6 exerted a strong influence on the optical purity of the cyclic product. The absolute stereochemistry of the cyclopentenone correlated with that of the anomeric carbon atom, regardless of whether the allene was α or β. This suggested that an interaction involving the pyran oxygen atom of the auxiliary was critical for determining the product stereochemistry.



Scheme 100. Asymmetric cyclopentannelation of allenes bearing a D-glucose-derived chiral auxiliary.

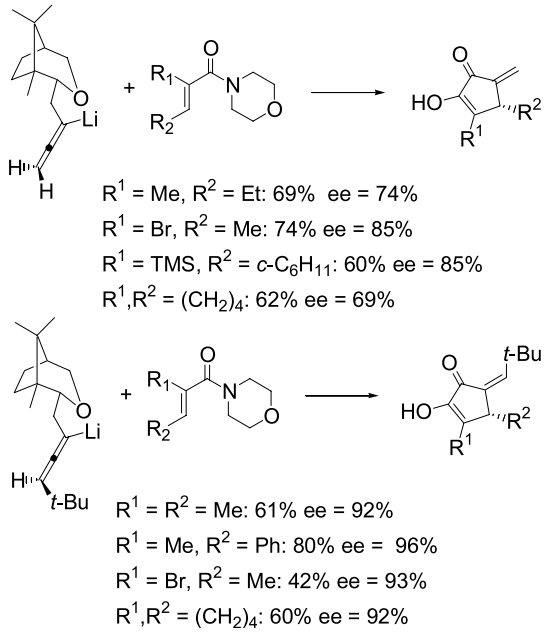
Although the sugar-derived auxiliaries led to preparatively useful results, there were some associated shortcomings such as the limited nucleophilicity of the derived allenyllithium species. Consequently, Tius et al. developed some new chiral auxiliaries including camphor-derived auxiliaries.[127a] These latter compounds yielded, after cyclisation upon treatment with a mixture of hexafluoro-2-propanol (HFIP) and trifluoroethanol (TFE), the corresponding cyclopentenones, one of which was a key intermediate in a total synthesis of roseophilin (Scheme 101).



Scheme 101. Asymmetric cyclopentannelation of allenes bearing a camphor-derived chiral auxiliary.

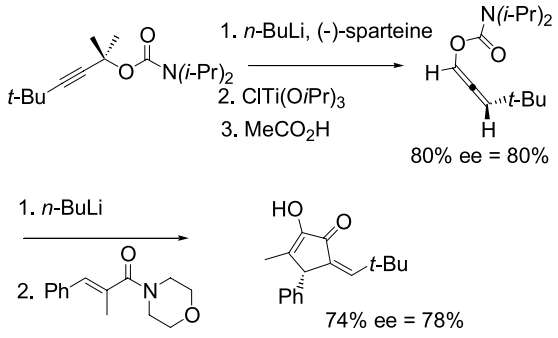
The scope of the above reaction has been expanded, since this cyclisation has been proven to be tolerant of a variety of substitution patterns and heteroatoms.[135] The yields and

enantiomeric excesses of the cyclic products were generally good in the case of the terminally unsubstituted allene. In addition, a wide variety of carbon and heteroatomic substituents were tolerated, suggesting a broad synthetic utility. When the allene bore a terminal substituent, the higher enantiomeric excesses reflected the chiral auxiliary and axial chirality of the allene working in concert (Scheme 102). The sole kinetically favoured *Z* isomers of the exocyclic alkene were isolated by quenching the reaction at low temperature.



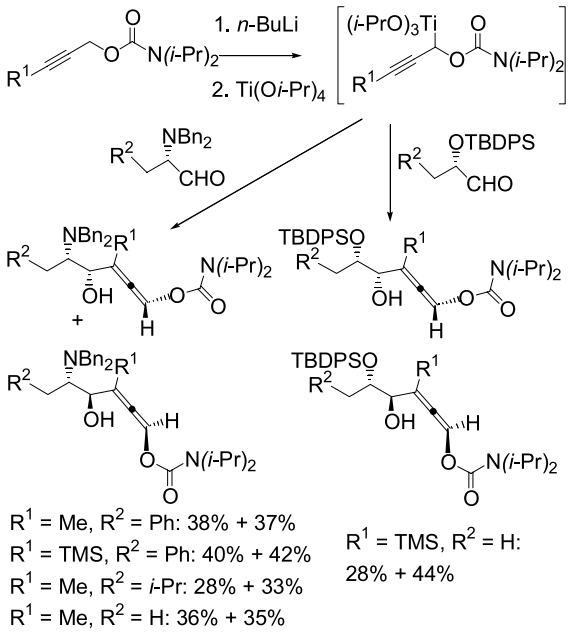
Scheme 102. Scope of asymmetric cyclopentannelation of allenes bearing a camphor-derived chiral auxiliary.

In 2002, Hoppe et al. reported the synthesis of enantio-enriched 5-alkylidene-2-cyclopentenones from chiral allenyl carbamates (Scheme 103).[136] These latter compounds were readily prepared by (−)-sparteine-mediated lithiation of alkynyl carbamates.[137] The lithiation of the chiral allene and subsequent acylation with (*E*)-alkenoylmorpholinide occurred to give the corresponding cyclopentenone with a chirality transfer which amounted to 98%.



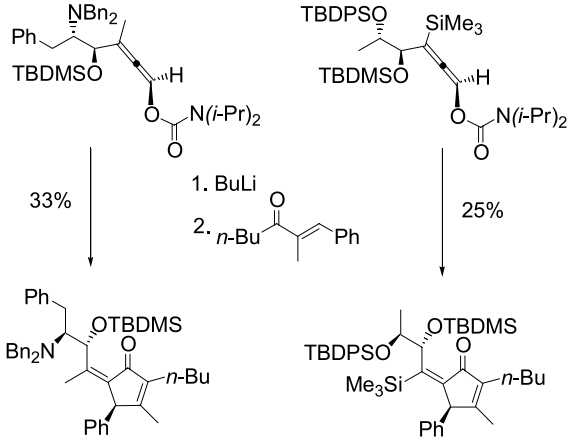
Scheme 103. Synthesis of enantio-enriched 5-alkylidene-2-cyclopentenones from chiral allenyl carbamates.

Another methodology for the preparation of enantiomerically pure 4-hydroxyallenes was reported by Hoppe et al. in 2004, based on γ-carbonyl addition of 2-alkynyl carbamates with chiral aldehydes. A high γ-regioselectivity combined with a high *syn*-diastereoselectivity allowed the synthesis of an almost 1/1 mixture of two enantiomerically pure diastereomers, which were further separated by column chromatography (Scheme 104).[138]



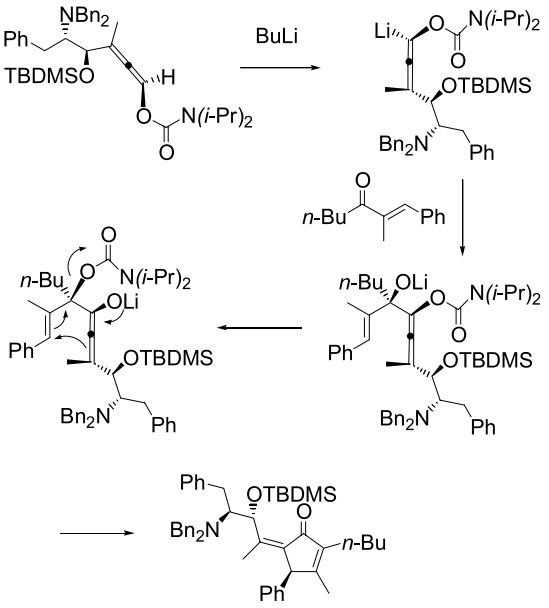
Scheme 104. Preparation of chiral allenyl carbamates via γ-carbonyl addition of 2-alkynyl carbamates with chiral aldehydes.

After simple *O*-protection of these latter chiral 4-hydroxy-allenyl carbamates with *t*-butyldimethylsilyl triflate, and then deprotonation with BuLi, the addition of an enone gave the corresponding cyclopentenones (Scheme 105).



Scheme 105. Condensation of chiral allenyl carbamates on enone.

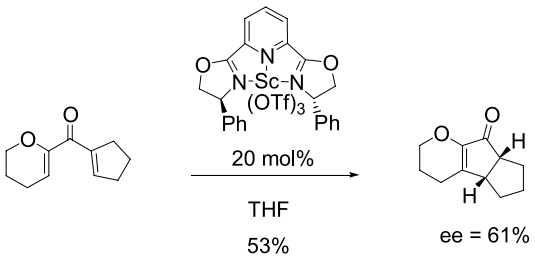
As shown in Scheme 106, the topology of the ring closure was determined by the stereochemistry of the carbon that bore the leaving group (bisallylic tertiary carbamoyloxy group). The reaction proceeded in an *anti* SE′ substitution fashion in the allylic system with respect to the carbamoyloxy group and, therefore, the conrotatory ring closure reaction occurred stereospecifically to form the final stereohomogeneous cyclopentenone.



Scheme 106. Proposed mechanism for the synthesis of (*Z*,*R*)-cyclopentenone.

8.2. Chiral metal catalysts

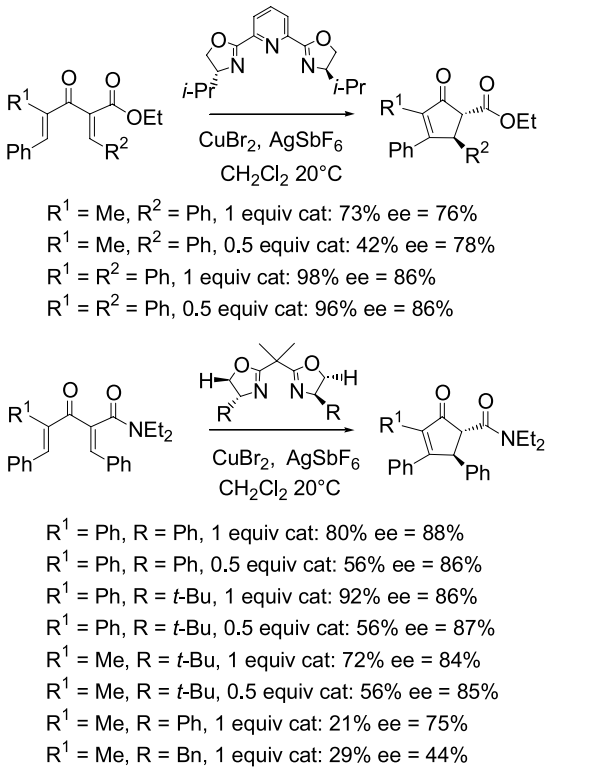
Somewhat surprisingly, it was not until the end of 2003 that catalytic asymmetric versions of the Nazarov cyclisation began to surface in the literature. The reason for this may lie in the complex mechanism of the reaction, involving steps such as loss of proton and reprotonation, which are fraught with regio- and stereoselectivity problems. Furthermore, the final cyclopentenone is potentially subject to racemisation if the cyclisation proceeds slowly. In addition, the catalyst turnover may be a concern, as evidenced by the fact that most Nazarov cyclisations reported require acidic solvents or stoichiometric amounts of a Lewis acid. In order to address these issues, Trauner et al. developed, in 2003, the first example of asymmetric Nazarov cyclisation of an alkoxydienone catalysed with 20 mol% of a chiral scandium triflate py–box (pyridine–bisoxazoline) complex, affording an enantiomerically enriched tricycle (Scheme 107).[48]



Scheme 107. Catalytic asymmetric Nazarov cyclisation.

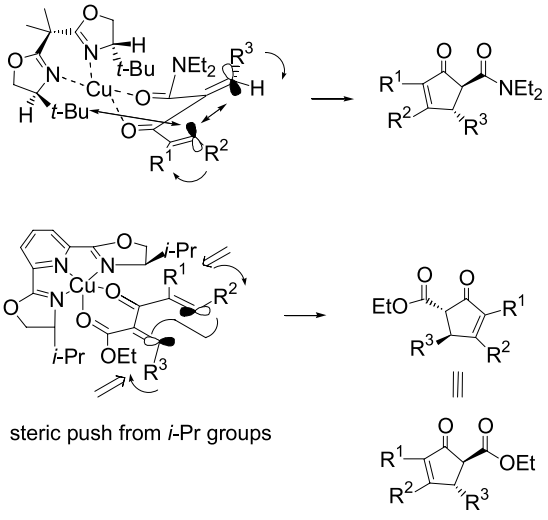
Concomitant with the preceding work, Aggarwal et al. disclosed the asymmetric cyclisation of divinyl ketones bearing α-ester or α-amide groups using 50–100 mol% of copper–bisoxazoline Lewis acid complexes with moderate to good enantioselectivities (Scheme 108).[139]

The observed stereochemistries of the ester- and amide-substituted divinyl ketones were consistent with a



Scheme 108. Asymmetric Nazarov cyclisations using copper–bisoxazoline Lewis acid complexes.

stereochemical model where the chiral bulk of the ligands distorted the plane of the cationic divinyl ketone intermediate to force one mode of conrotation to be favourable. Thus, in the case of the divinyl keto amide reaction catalysed by the copper bis-oxazoline, buttressing of the *t*-butyl group with the alkene moiety pushed it away from, and underneath, the other vinyl group, therefore favouring clockwise conrotation. In the same way, reaction of the divinyl keto esters with copper py–box catalysts resulted in a distorted complex in which the alkene substituents were pushed away from the *i*-Pr groups of the ligand. This then placed the bonding lobes of the two corresponding orbitals

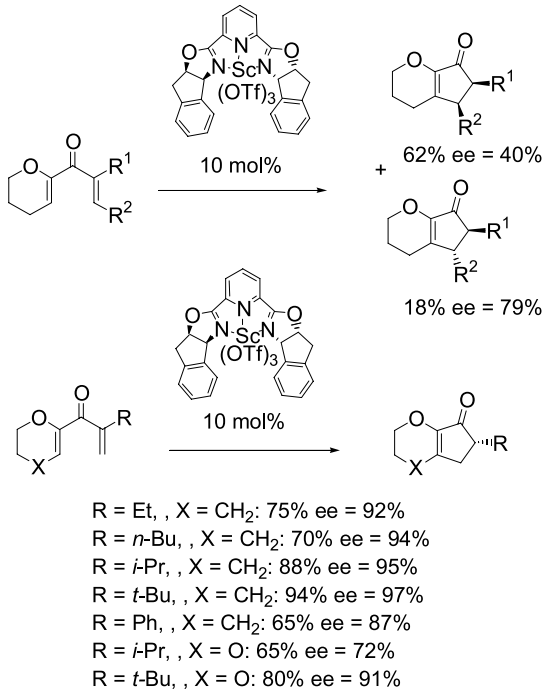


Scheme 109. Stereochemical models for the interactions of complexes with divinyl ketones.

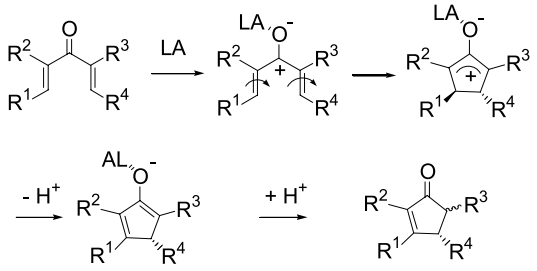
in close proximity, making them predisposed to cyclisation in a clockwise manner (Scheme 109).

On the other hand, Trauner et al. described, in 2004, a truly catalytic and highly enantioselective Nazarov cyclisation involving a sterically demanding indane–py–box complex.[140] In the case of substrates bearing only a *trans* substituent in the 5-position, low yields and enantioselectivities were, unfortunately, observed (25–58% ee). Similarly, for substrates that could yield diastereomers, the situation was even more complicated, for example, when R^2=Me, a mixture of diastereomers was formed with a diastereomeric ratio of 3.4/1 and respective enantioselectivities of 40 and 79% (Scheme 110). This result was interpreted by invoking double diastereoselection in the reprotonation step following the asymmetric electrocyclisation. Using an achiral Lewis acid ($AlCl_3$), this diastereomeric ratio was found to be 1.5/1. In contrast, high yields and enantioselectivities were finally obtained by switching to substrates lacking a substituent at the terminal position (R^2=H).

The absolute configuration of the products was established



Scheme 110. Enantioselective Nazarov cyclisations through catalytic asymmetric proton transfer.

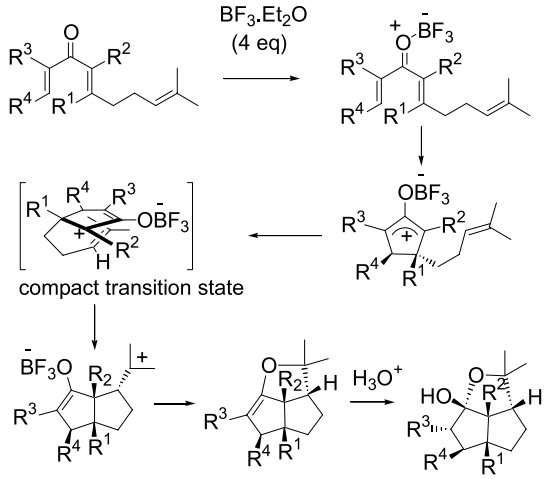


Scheme 111. Catalytic asymmetric proton transfer.

in the course of the reprotonation of the dienolate intermediate in the terminal position (Scheme 111). The influence of the chiral ligand sphere surrounding the Lewis acid, which was presumably bound to the substrates in a bidentate fashion, should be greater in this position than at the termini of the alkoxy dienone system. This could explain the higher levels of enantioselectivity observed with substrates bearing no substituent at the terminal position.

9. Trapping of chemically generated Nazarov intermediate

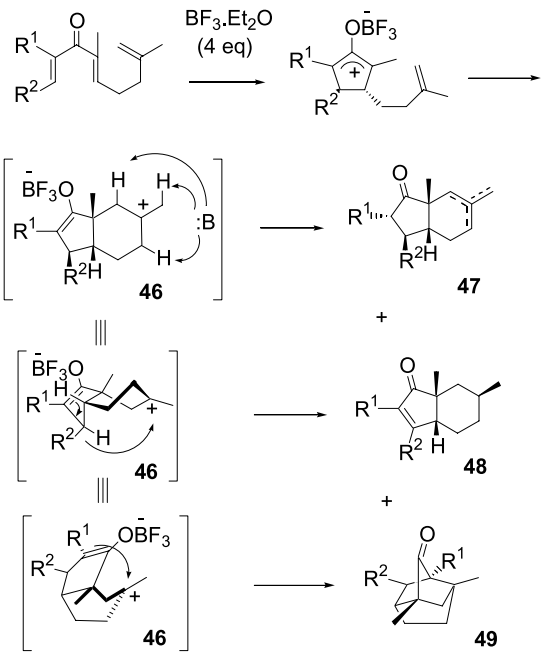
Interrupted Nazarov reactions represent one of the latest important achievements of the Nazarov cyclisation, which have considerably expanded the synthetic scope of the process. Indeed, this methodology has proven to be especially useful for the stereoselective construction of polycyclic skeletons by a cascade polycyclisation process initiated by a 4π electrocyclic ring closure. The Nazarov cyclisation is an intriguing candidate for inclusion in tandem processes, since the initial electrocyclisation results in a new carbon–carbon bond and a valuable cyclopentanoid ring, while also producing a reactive oxyallyl intermediate. West et al. have disclosed a unique and elegant application of the classical Nazarov cyclisation to the construction of polycyclic systems. The key point of this process, coined by these latter authors as an interrupted Nazarov reaction, was for the first time an intramolecular trapping of the oxyallyl intermediates with olefins, dienes or arenes.[141] In subsequent investigations, intermolecular versions of this new reaction were also developed, the first examples of deliberate trapping of the Nazarov oxyallyl intermediate via cationic cyclisation onto pendant olefins being reported by West et al. in 1998.[142] This process, promoted by $BF_3{\cdot}Et_2O$, efficiently converted acyclic, achiral trienones into polycyclic hemiketal products with complete diastereoselectivity when the dienone and alkene trap were



Scheme 112. Interrupted Nazarov reaction with acyclic trienones.

linked by a two-carbon tether, and the dienone was substituted at both α-positions (Scheme 112). The proposed mechanism shows that the oxyallyl cation was trapped by the pendant olefin in a 5-*exo* cyclisation, establishing a tertiary carbocation. In order to explain the eventual oxygenation present at the site of the tertiary carbocation, its subsequent capture by the boron enolate oxygen was envisaged. This final ring closure could only occur if the carbocation was *endo*-disposed, which resulted from cationic cyclisation exclusively via a compact transition state. Upon aqueous workup, the strained enol ether was hydrated with selective protonation from the convex face to form the final product.

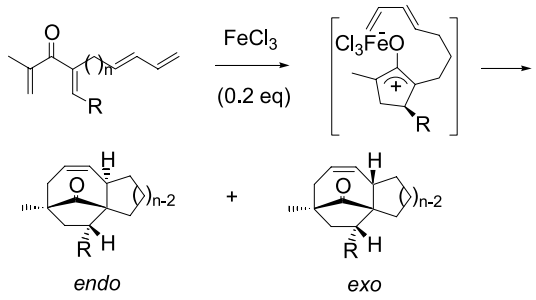
The same methodology was applied to the formation of hydrindans and tricyclo[4.3.0.0^{3,8}]nonanes via 6-*endo* trapping of the Nazarov oxyallyl intermediate.[143] Treatment of trienones with $BF_3 \cdot Et_2O$ effected Nazarov cyclisation, followed by 6-*endo* cation–olefin cyclisation, leading to a tertiary carbocation **46**. This latter intermediate underwent elimination to give the olefinic products **47**, intramolecular hydride transfer to furnish the enones **48**, and/or [3+2] ring closure, providing the tricyclic products **49** (Scheme 113).



$R^1 = R^2 = H$: 63% (**47**:**48**:**49** = 2:3:4)
R^1 = Me, R^2 = H: 62% (**47**:**48**:**49** = 0:1:11)
R^1 = *t*-Bu, R^2 = H: 70% (**47**:**48**:**49** = 0:1:0)
R^1 = Et, R^2 = Me: 93% (**47**:**48**:**49** = 1:17:13)
$R^1,R^2 = (CH_2)_3$: 96% (**47**:**48**:**49** = 2.7:1:0)
$R^1,R^2 = (CH_2)_4$: 88% (**47**:**48**:**49** = 1.5:1.2:1)
$R^1,R^2 = (CH_2)_5$: 93% (**47**:**48**:**49** = 1:4.1:1.5)

Scheme 113. Interrupted Nazarov reaction with acyclic trienones.

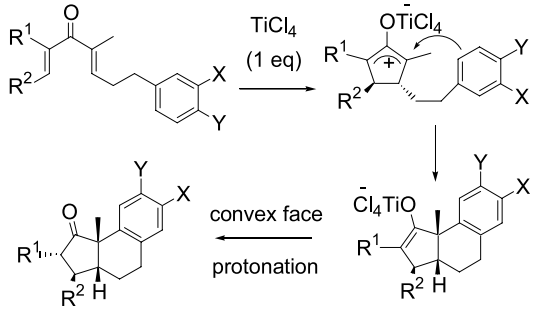
The second notable class of intramolecular interrupted Nazarov reactions involved the intramolecular [4+3] cycloaddition of the oxyallyl cation to the pendant 1,3-diene of a side chain.[144] This novel cycloisomerisation of acyclic tetraenones was promoted by Lewis acids such as $FeCl_3$ and led to a mixture of two diastereomeric complex, tricyclic products. The observed product ratio appeared to derive from a high diastereofacial selectivity in the cycloaddition, with the preferred approach from the less-hindered face of the cyclic oxyallyl cation, but only modest selectivity for *endo* versus *exo* orientation of the diene and oxyallyl group. Elongation of the side chain ($n=4$) gave rise, however, to *exo*/*endo* ratios of 100:0, which could be explained by possible unfavourable interactions between the diene moiety and the tether in the *endo*-transition state (Scheme 114).



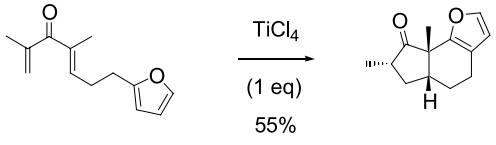
R = Me, n = 3: 65% (57:43)
R = Ph, n = 3: 72% (57:43)
R = Me, n = 4: 67% (0:100)
R = Ph, n = 4: 75% (0:100)

Scheme 114. Interrupted Nazarov reaction with acyclic tetraenones.

The third class of intramolecular interrupted Nazarov reactions concerned the trapping of the Nazarov intermediate with pendant aryl groups. West et al. have shown that 1,4-dien-3-ones bearing pendant arylethyl side chains underwent domino cyclisation to give the



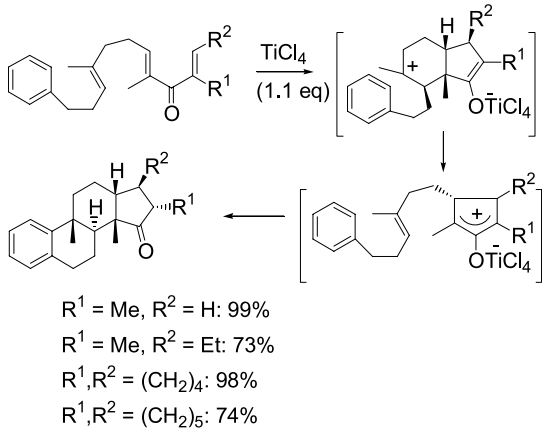
R^1 = Me, R^2 = H, X = OMe, Y = H: 90%
R^1 = Et, R^2 = Me, X = OMe, Y = H: 99%
$R^1,R^2 = (CH_2)_4$, X = OMe, Y = H: 99%
R^1 = Me, R^2 = H, X,Y = OCH_2O: 99%
R^1 = Et, R^2 = Me, X,Y = OCH_2O: 99%
$R^1,R^2 = (CH_2)_4$, X,Y = OCH_2O: 99%



Scheme 115. Interrupted Nazarov reaction with 1,4-dien-3-ones bearing pendant aryl groups.

benzohydrindenones in near-quantitative yields and with complete diastereoselectivity when they were treated with $TiCl_4$.[145] In order to further probe the scope of this process, a furan-containing product was also submitted to the domino Nazarov cyclisation–electrophilic aromatic substitution, but gave a lower yield (Scheme 115).

In addition, West et al. reported Nazarov-initiated diastereoselective cascade polycyclisation of aryltrienones upon treatment with $TiCl_4$, providing the construction of tetra- or pentacyclic skeletons (Scheme 116).[146] One apparent limitation was the requirement for α-substitution on the acyclic portion of the dienone, as evidenced by the exclusive oligomerisation of the unsubstituted substrate.

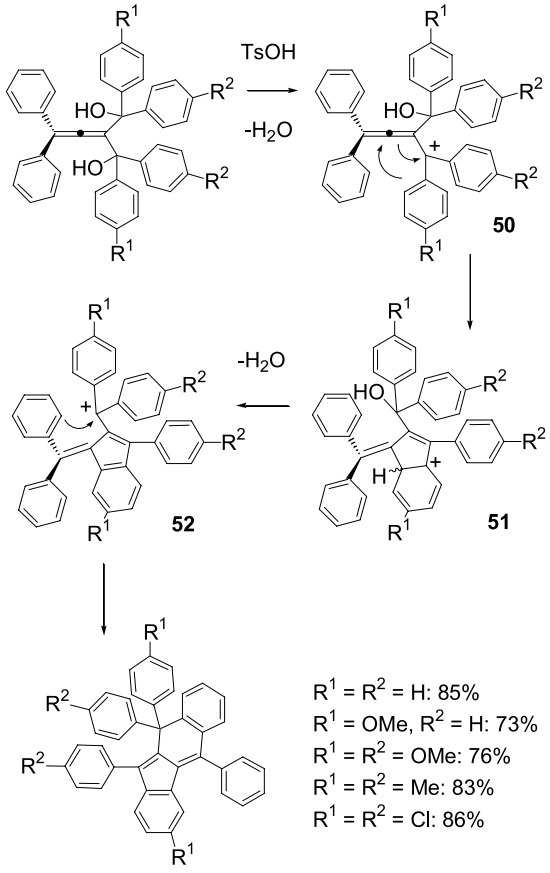


Scheme 116. Nazarov-initiated cascade polycyclisation of aryltrienones.

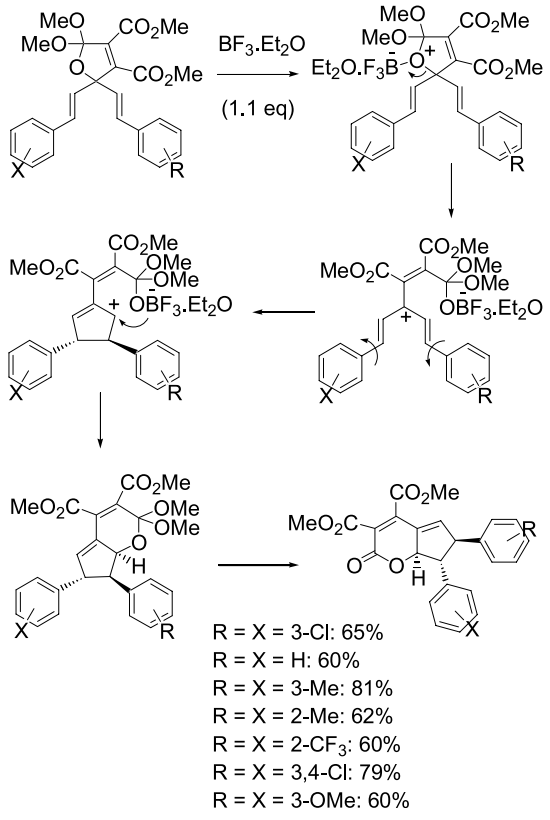
In 2001, Langer et al. reported the first domino Nazarov–Friedel–Crafts reaction, providing 10*H*-benzo[*b*]fluorenes from sterically encumbered di(hydroxymethyl)allenes upon treatment with *p*-toluenesulphonic acid (Scheme 117).[147] The mechanism of this reaction involved the formation of a first carbocation **50**, initially generated by the elimination of water. The central allene carbon atom was attacked by the *ortho* carbon atom of one of the aryl groups to give the five-membered ring in intermediate **51**. Aromatisation and elimination of water subsequently led to the formation of the cationic intermediate **52**. The *ortho* carbon of the allene-derived phenyl group was attacked by the carbocation adjacent to the ketone-derived aryl groups and aromatisation then led to the final products.

In 2002, Nair et al. reported, for the first time, the participation of dihydrofuran derivatives in interrupted Nazarov reactions,[148] for example, *gem*-divinyl dihydrofurans upon treatment with $BF_3 \cdot Et_2O$ yield the corresponding bicyclic lactones. These latter products were generated by trapping of the intermediate allyl cation by the pendant *ortho* ester borate, followed by elimination of methanol (Scheme 118).

In addition, West et al. have also developed the intermolecular version of the interrupted Nazarov reaction such as the intermolecular trapping of the Nazarov intermediate using allylic silanes.[149] This novel domino electrocyclisation–[3+2] cycloaddition allowed the construction of densely functionalised bicyclo[2.2.1]heptanones from

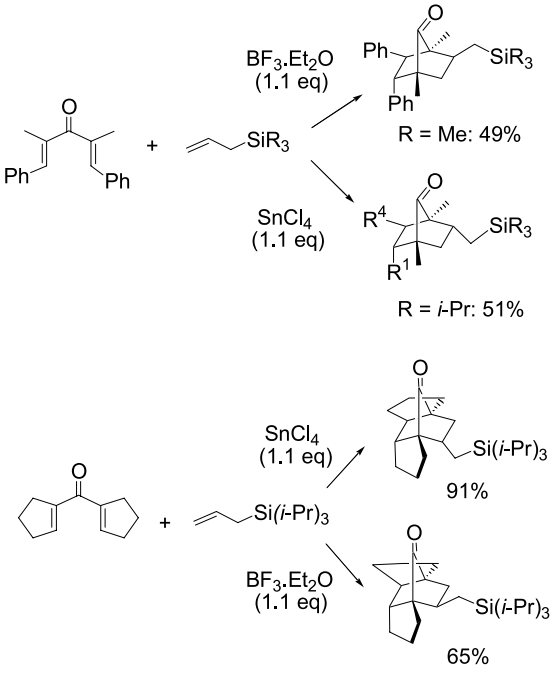


Scheme 117. Domino Nazarov–Friedel–Crafts reaction.



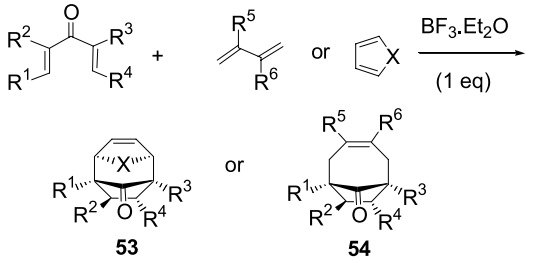
Scheme 118. Interrupted Nazaro reaction of *gem*-divinyl dihydrofurans.

simple dienone and allylsilane precursors. Regioselectivity was complete in the case of an unsymmetrical dienone, as was the stereoselectivity of the initial trapping step in all cases (Scheme 119). A remarkable dependence of the stereochemistry on the Lewis acid used was noted, allowing complete selectivity for *exo*- or *endo*-products.



Scheme 119. Domino electrocyclisation–[3+2] cycloaddition with allylsilanes.

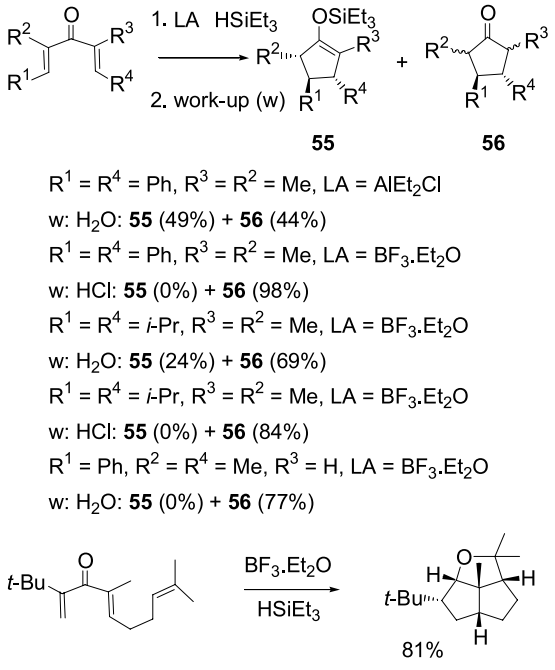
In the same way, the bimolecular version of the [4+3] cycloaddition process was reported in 2003, simple 1,4-dien-3-ones and 1,3-dienes reacting in the presence of $BF_3 \cdot Et_2O$ via a domino Nazarov electrocyclisation–intermolecular [4+3] cycloaddition sequence to furnish the keto-bridged cyclooctenes **53** and **54**.[150] Most examples showed a high diastereofacial selectivity with the approach of the diene away from the larger substituent on the intermediate cyclopentenyl cation, and complete selectivity for the compact transition state was also observed with cyclic dienes. Furthermore, surprising levels of regioselectivity were obtained when isoprene was used as the diene partner (Scheme 120).



$R^1 = R^4 = Ph$, $R^2 = R^3 = Me$, X = O: **53** (70%)
$R^1 = R^4 = Ph$, $R^2 = R^3 = R^5 = R^6 = Me$: **54** (50%)
$R^1 = Ph$, $R^2 = R^3 = Me$, $R^4 = H$, X = O: **53** (62%)
$R^1 = Ph$, $R^2 = R^3 = R^5 = R^6 = Me$, $R^4 = H$: **54** (91%)
$R^1 = Et$, $R^2 = R^3 = R^5 = R^6 = Me$, $R^4 = H$: **54** (93%)
$R^1, R^2 = (CH_2)_4$, $R^3 = R^5 = R^6 = Me$, $R^4 = H$: **54** (92%)

Scheme 120. First intermolecular domino electrocyclisation–[4+3] cycloaddition with dienes.

Finally, West et al. have developed a one-step synthesis of cyclopentanones, the reductive Nazarov cyclisation, via the in situ reduction of Nazarov-derived oxyallyl intermediates by intermolecular delivery of hydride.[151] Dienones were treated with a Lewis acid in the presence of triethylsilane and led either to the corresponding silyl enol ethers **55** or the cyclopentanones **56**, depending upon the work-up conditions. In some cases, catalytic amounts of Lewis acid could be used. The reaction was applied to a trienone substrate which underwent clean conversion into the corresponding tricyclic ether (Scheme 121).



Scheme 121. Reductive Nazarov cyclisation.

The pioneering research by West et al. has shown a new approach to the utilisation of this important reaction in organic synthesis, namely its application to the formation of topologically complex polycyclic systems. Efficient transformations allowed the build up of polycyclic frameworks in a minimum number of steps in high yield and with good stereocontrol.

10. Conclusions

For almost six decades, the Nazarov cyclisation has served as an efficient and reliable protocol for the construction of 2-cyclopentenone systems. Since its initial discovery, steady progress has been made in expanding the synthetic value of this reaction, primarily by the use of Lewis acids as cyclisation initiators, by procedures called directed Nazarov cyclisations and, more recently, by metal-catalysed Nazarov cyclisation, by interrupted Nazarov reaction, by asymmetric Nazarov cyclisation, and by cationic cyclopentannelation of

allenyl ethers. This review concentrates on the new progress achieved since 1993 and the Nazarov cyclisation is therefore well represented as an important tool for organic synthesis.

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Biographical sketch

Hélène Pellissier was born in Gap, France. She carried out her PhD under the supervision of Dr. G. Gil in Marseille and then entered the Centre National de la Recherche Scientifique in 1988. After a postdoctoral period in Professor K. P. C. Vollhardt's group, she joined the group of Professor M. Santelli in Marseille in 1992, where she focused on the chemistry of BISTRO and its large application in organic synthesis. Thus, she developed several new very short total syntheses of steroids starting from 1,3-butadiene and benzocyclobutenes.

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Fluorescence modification of Gb3 oligosaccharide and rapid synthesis of oligosaccharide moieties using fluorous protective group

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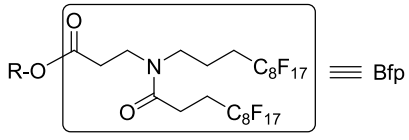
Abstract—The use of the bisfluorous chain-type propanoyl (Bfp) group as a fluorous protective group made it possible to rapidly synthesize the Gb2 and Gb3 oligosaccharide derivatives by a simple fluorous-organic extraction purification. Furthermore, the fluorescence-labeled Gb2 and Gb3 oligosaccharides were prepared as a potential Vero Toxins detecting reagent.

1. Introduction

Vero toxins (VTs) are the Shiga-like toxins produced by *Escherichia coli* O-157:H-7.[1] VTs cause serious clinical complications in humans. VTs initially produce diarrhea in human beings, then further progresses to the Hemolytic Uremic Syndrome, renal failure, and finally death. In order to suppress the infection progress by *E. coli* O-157:H-7 to a minimum, the development of an accurate and rapid detecting method of VTs is essential. VTs are AB_5 toxins with an enzymatically active A-subunit and a cell binding B-subunit. The B-subunit mainly recognizes a galactobiosyl α-(1→4)-linkage in the glycolipid Gb2 [Galα-(1→4)Gal-Cer] and Gb3 [Galα-(1→4)Galβ-(1→4)Glc-Cer], and VTs induce the carbohydrate-mediated internalization into the host cell.[2] A carbohydrate–lectin interaction in the solution phase was sensitively detected by fluorescence polarization using a fluorescence-labeled carbohydrate.[3] Recently, we reported that fluorescence polarization detected the carbohydrate–lectin interaction using the fluorescence-labeled oligosaccharides derived from glycosyl amino acids.[4] To develop a method sensitively detecting VTs, we attempted the synthesis of fluorescence-labeled Gb2 and Gb3 oligosaccharides, which were substituted with simple lipophilic fluorescence groups, such as a dansyl or fluorescein group, for the ceramide moieties of the glycolipids.



1a R = H
1b R = Me

The synthesis of the Gb2 and Gb3 oligosaccharides have already been accomplished by several groups.[5] However, each synthetic method requires much time and cost due to the purification procedure, such as column chromatography in multisteps. The heavy fluorous technique using a fluorous protecting group developed by Curran et al. is an excellent methodology to resolve these problems.[6] A highly fluorinated compound, in which a fluorous protecting group is introduced, is readily separated from nonfluorinated compounds by a simple fluorous-organic phase separation without column chromatography. Several fluorous protecting groups were developed for the fluorous synthesis.[7] We also have reported the fluorous oligosaccharide synthesis using the Bfp (bisfluorous chain-type propanoyl) group as a

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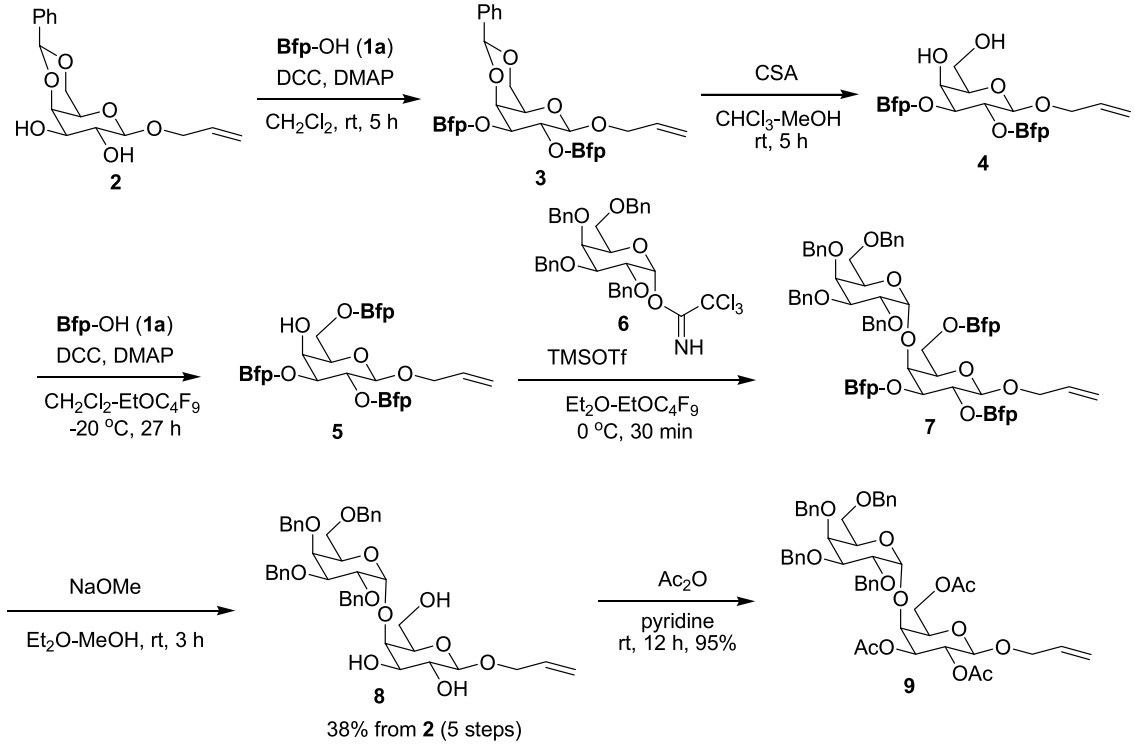
novel fluorous protective group,[8] the rapid synthesis of the Gb2 and Gb3 oligosaccharides using the Bfp group in a preliminary communication,[9] and the synthesis of oligosaccharides and peptides using the fluorous supports.[10] Herein, we would like to describe the full details of the rapid synthesis of the Gb2 and Gb3 oligosaccharides using the Bfp group as a fluorous protective group and the fluorescence modification of the Gb2 and Gb3 oligosaccharides.

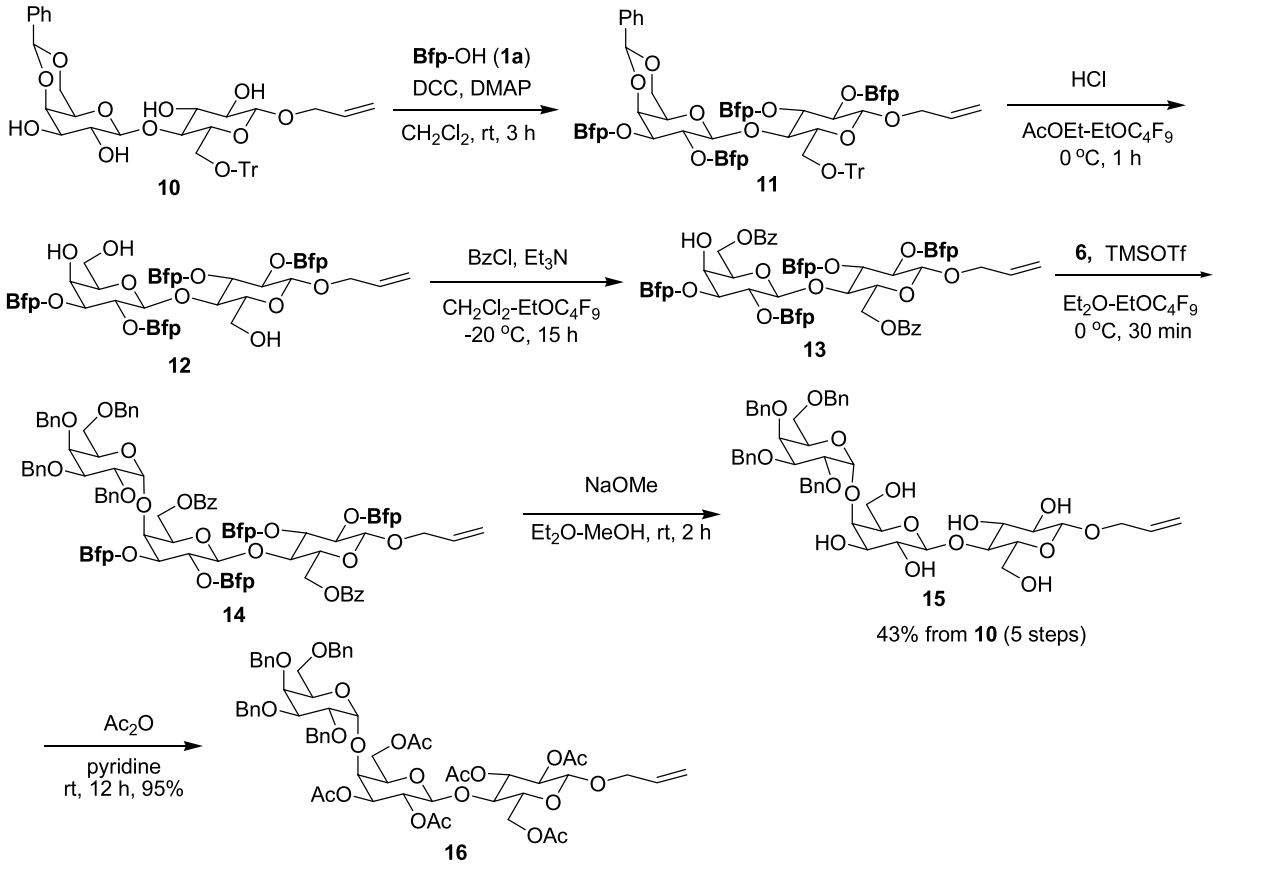
2. Results and discussion

We first synthesized the galabiose derivative **8** as shown in Scheme 1. The Bfp-OH (**1a**)[8] was attached to the hydroxyl functions of the galactose derivative **2** using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-(*N*,*N*-dimethylamino) pyridine (DMAP) to give the fluorous compound **3**.[11] The benzylidene group of **3** was removed by treatment with camphorsulfonic acid (CSA) in MeOH–$CHCl_3$ to afford the corresponding product **4**.[11] The Bfp group was selectively introduced into the primary hydroxyl function of **4** using DCC and DMAP at −20 °C to give the fluorous glycosyl acceptor **5**.[11] The fluorous disaccharide **7**[11] was obtained by the reaction of **5** with the glycosyl donor **6** (6.1 equiv) in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in Et_2O–$EtOC_4F_9$.[12] The α-selectivity of the glycosylation reaction was very high and no β-isomer could be detected. The fluorous intermediates **3**, **4**, **5**, and **7** were each extracted with the fluorous solvent FC-72[13] by partitioning the product mixture between FC-72 and an organic solvent, such as toluene or methanol. No further purification, such as silica-gel column chromatography, was carried out. The Bfp group of **7** was easily removed by treatment with sodium methoxide in MeOH–Et_2O to afford the crude **8**, which was extracted with MeOH by partitioning the mixture between FC-72 and MeOH. The methyl ester of Bfp (Bfp-OMe, **1b**) was extracted from the FC-72 layer and treated with aqueous NaOH to recover **1a**, which is able to be reused as a fluorous protective reagent. Finally, the pure galabiose derivative **8** was obtained from the single silica gel column chromatographic purification step in a 38% overall yield from **2** (five steps). The disaccharide **8** was converted to the acetate **9** by treatment with acetic anhydride in pyridine for identification of the structure.

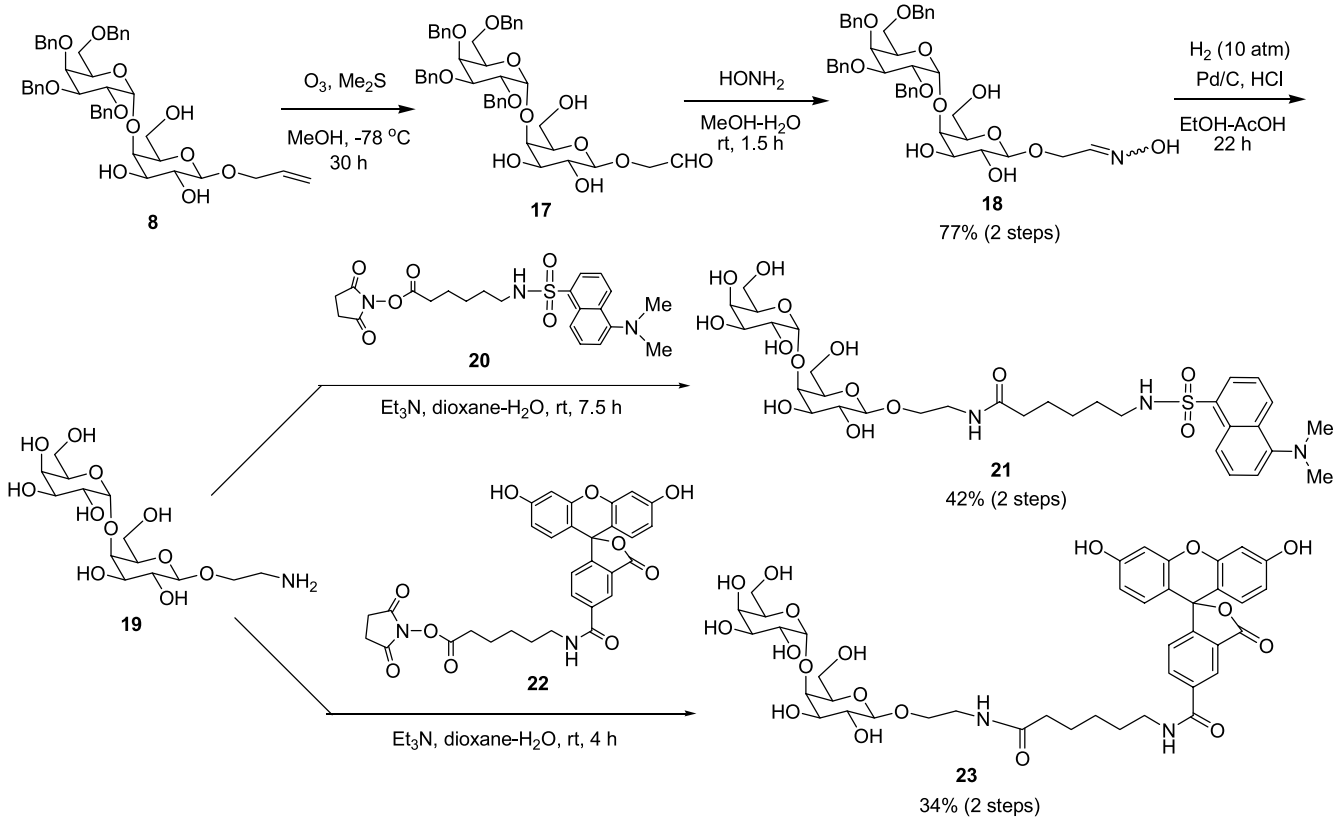
Next, we synthesized the Gb3 trisaccharide **15** as described in Scheme 2. The Bfp group was introduced to the four hydroxyl functions of the lactose derivative **10** using DCC and DMAP to give the fluorous compound **11**.[11] The benzylidene group and trityl (Tr) group of **11** were deprotected by treatment with HCl in AcOEt–$EtOC_4F_9$ to afford **12**.[11] The benzoyl (Bz) group was selectively introduced to the two primary hydroxyl functions of **12** to obtain the fluorous glycosyl acceptor **13**.[11] The reaction of the fluorous glycosyl acceptor **13** with the glycosyl donor **6** (5 equiv) in the presence of TMSOTf in ether–$EtOC_4F_9$ selectively afforded only the α-linked fluorous trisaccharide **14**.[11] The fluorous intermediates **11**, **12**, **13**, and **14** were extracted with FC-72 by partitioning the product mixture between FC-72 and an organic solvent (toluene or methanol), and were purified enough without silica gel column chromatography. The Bfp group of **14** was removed by treatment with sodium methoxide in MeOH–ether to afford **15**, which was extracted with MeOH by partitioning the crude residue between FC-72 and MeOH. Finally, the pure trisaccharide **15** was obtained by only one silica gel column chromatography purification during the final step in a 43% overall yield from **10** (five steps). The trisaccharide **15** was converted to **16** by treatment with acetic anhydride in pyridine for identification of the structure.



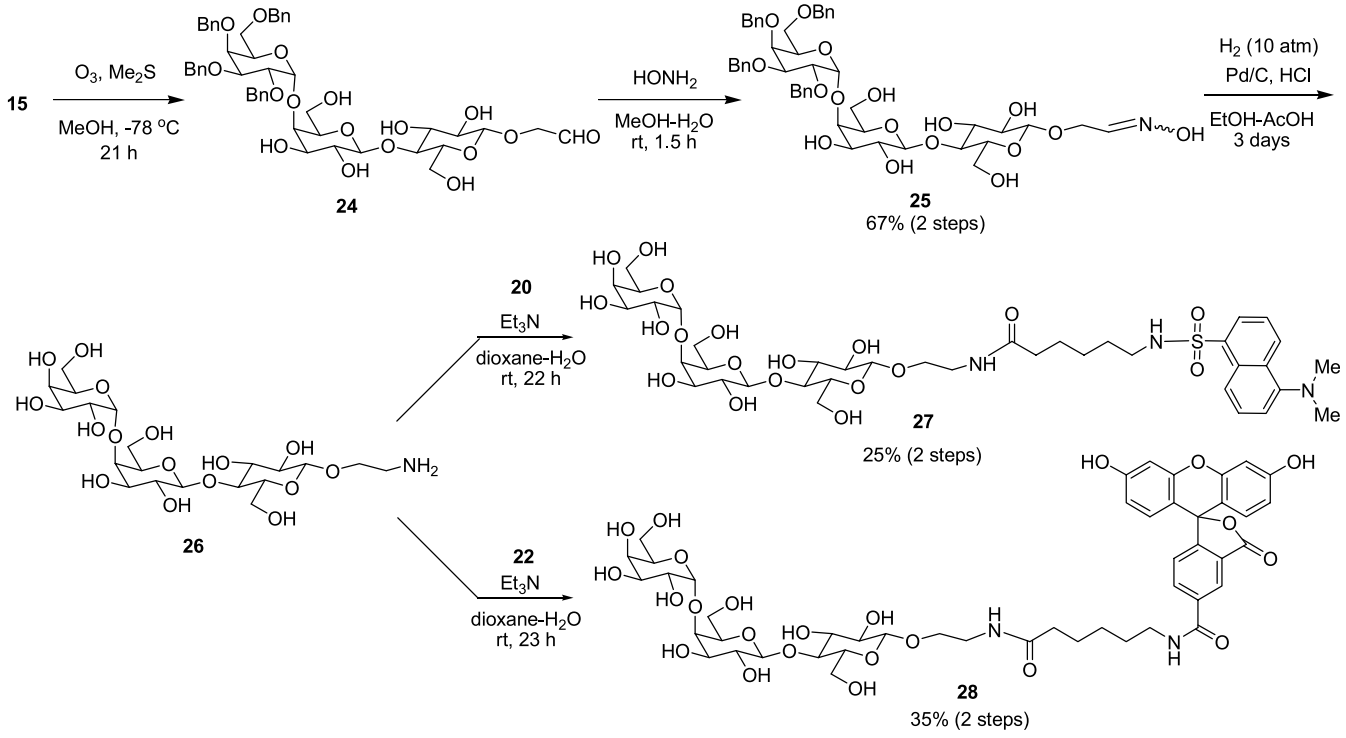
Scheme 1. Synthesis of Gb2 oligosaccharide using fluorous protecting gorup **Bfp**.



Scheme 2. Synthesis of Gb3 oligosaccharide using fluorous protecting group **Bfp**.



Scheme 3. Intorduction of fluorescein groups to Gb2 oligosaccharide.



Scheme 4. Introduction of fluorescein groups to Gb3 oligosaccharide.

We then selected the dansyl and fluorescein groups as the fluorescence group, and introduced them to the Gb2 oligosaccharide as indicated in Scheme 3. The disaccharide **8** was oxidized by ozonolysis, followed by condensation with hydroxylamine to afford the corresponding imine **18** as an inseparable mixture of *syn* and *anti* isomers in 77% yield (two steps). The imine **18** was hydrogenated over Pd/C to give the mixture of the amine **19** and the protected ones, which was coupled with **20** to afford the desired Gb2 oligosaccharide **21** which possessed the dansyl group as the fluorescence group in 42% yield (two steps). The amine **19** was also reacted with **22** to give the Gb2 oligosaccharide **23** with a fluorescein group in a 34% yield (two steps) (Scheme 4).

Finally, we synthesized the Gb3 oligosaccharide **27** and **28** by the similar procedure. The trisaccharide **15** was oxidized by ozone to give the aldehyde **24**, which was coupled with hydroxylamine to afford the corresponding compound **25** as an inseparable mixture of *syn* and *anti* isomers in 67% yield (two steps). Compound **25** was reduced by catalytic hydrogenation over Pd/C to give the mixture of the amine **26** and the protected ones, which was coupled with **20** to afford the desired Gb3 oligosaccharide **27** with a dansyl group in 25% yield (two steps). The amine **26** was also reacted with **22** to give the Gb3 oligosaccharide **28** with a fluorescein group in 35% yield (two steps).

3. Conclusion

In conclusion, we succeeded in synthesizing the Gb2 and Gb3 oligosaccharides containing fluorescence groups. The use of the Bfp group as a fluorous protecting group made it possible to rapidly synthesize the Gb2 and Gb3 oligosaccharide derivatives by a fluorous-organic extraction purification. The fluorous oligosaccharide synthesis can be carried out on a large scale due to the liquid phase synthesis. As each synthetic intermediate containing the Bfp group was monitored by TLC, NMR, and MS, the reaction conditions for each synthetic step could be rapidly optimized. The fluorous intermediates could also be purified by silica gel column chromatography when required purification. After optimization of the reaction conditions in each step, the synthesis in multisteps was accomplished by a fluorous-organic partition purification without column chromatography. The only final product, from which the Bfp groups were removed, was purified by column chromatography on silica gel. Therefore, the fluorous oligosaccharide synthesis using the Bfp group is an excellent strategic alternative to solid phase oligosaccharide synthesis, and removes some of the disadvantages of the solid phase method. The detection assay of VTs using the fluorescence-labeled Gb2 and Gb3 oligosaccharides is now in progress.

4. Experimental

4.1. General

The ^{1}H NMR spectra were recorded using JEOL JNM-EX-400 (400 MHz) and JEOL JNM-ECA-600 (600 MHz) spectrometers. The Mass spectra (MS) of the compounds with a high molecular weight were recorded using a MALDI-TOF-MS (Voyager-DE STR) spectrometer. The high-resolution MS (HRMS) were recorded on an ESI-TOF-MS (Mariner™) spectrometer. Part of the products was isolated by column chromatography on silica gel (Kanto Chemical, silica gel 60N, spherical, neutral, 40–50 μm). The fluorous solvent FC-72 and Novec HFE-7200 were

purchased from 3 M Tokyo. Bfp-OH (**1a**)[8] is commercially available from Kokusan Chemical.

4.1.1. Compound 3. DMAP (3.27 g, 26.8 mmol) and DCC (9.91 g, 48.1 mmol) were added to a solution of **2**[14] (2.50 g, 8.12 mmol) and **1a**[8] (19.0 g, 18.6 mmol) in dried CH_2Cl_2 (200 mL). After stirring for 5 h at rt, MeOH (100 mL) was added to the reaction mixture. The mixture was stirred for 30 min at rt, and the CH_2Cl_2 was evaporated. The reaction mixture was extracted three times with FC-72. The FC-72 layers were combined and evaporated to give a crude **3** (21.1 g). The crude **3** was used in the next step without further purification. The authentic sample was obtained as a colorless amorphous solid by purifying part of the sample (silica gel column chromatography with a 2:1 mixture of hexane and AcOEt). $R_f=0.19$ (hexane–AcOEt=2:1); $[\alpha]_D^{26}$ +12.8 (*c* 1.27, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 1.74–2.08 (8H, m), 2.44–2.68 (12H, m), 3.14–3.69 (9H, m), 4.09 (2H, m), 4.37 (3H, m), 4.58 (1H, m), 4.95 (1H, m), 5.19 (1H, d, $J=10.8$ Hz), 5.27 (1H, d, $J=17.2$ Hz), 5.41 (1H, t, $J=7.6$ Hz), 5.50 (1H, s), 5.85 (1H, m), 7.37 (3H, m), 7.51 (2H, m); MALDI-TOF MS found: *m/z* $[M+Na]^+$ 2342.5. Calcd for $C_{66}H_{46}F_{68}N_2O_{10}Na$ $[M+Na]^+$ 2341.2. Found: *m/z* $[M+K]^+$ 2359.3. Calcd for $C_{66}H_{46}F_{68}N_2O_{10}K$ $[M+K]^+$ 2357.2.

4.1.2. Compound 4. CSA (1.63 g, 7.0 mmol) was added to a solution of the crude **3** (10.7 g) in $CHCl_3$ (80 mL)–MeOH (40 mL). After stirring for 5 h at rt, toluene (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) were added to the reaction mixture. The mixture was stirred for 30 min at rt, and the organic solvents ($CHCl_3$ and MeOH) were evaporated. The reaction mixture was then extracted three times with FC-72. The FC-72 layers were combined, dried over anhydrous Na_2SO_4, and evaporated to afford a crude **4** (9.54 g). The crude **4** was used in the next step without further purification. The authentic sample was obtained as a colorless amorphous solid by purifying part of the crude **4** (silica gel column chromatography, eluent; hexane–AcOEt=1:1). $R_f=0.30$ (hexane–AcOEt=1:1); $[\alpha]_D^{26}$ −1.1 (*c* 1.25, FC-72); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.87$ (4H, m), 2.09 (4H, m), 2.58 (14H, m), 3.38–3.68 (8H, m), 3.78–4.18 (4H, m), 4.33 (2H, m), 4.52 (1H, d, $J=8.1$ Hz), 4.78 (1H, m), 5.17 (1H, d, $J=10.3$ Hz), 5.25 (1H, d, $J=$ 17.3 Hz), 5.34 (1H, m), 5.85 (1H, m); MALDI-TOF MS found: *m/z* $[M+Na]^+$ 2251.6. Calcd for $C_{59}H_{42}F_{68}N_2O_{10}$-Na $[M+Na]^+$ 2253.2. Found: *m/z* $[M+K]^+$ 2267.8. Calcd for $C_{59}H_{42}F_{68}N_2O_{10}K$ $[M+K]^+$ 2269.1.

4.1.3. Compound 5. DMAP (243 mg, 2.00 mmol) and DCC (264 mg, 1.28 mmol) were added to a solution of the crude **4** (0.89 g) and **1a** (436 mg, 0.43 mmol) in CH_2Cl_2 (20 mL)–$EtOC_4F_9$ (20 mL) at −20 °C. After stirring for 27 h at −20 °C, MeOH (6 mL) and toluene (50 mL) were added to the reaction mixture. The mixture was stirred for 30 min at rt, and then the CH_2Cl_2 was evaporated. The mixture was extracted three times with FC-72. The FC-72 layers were combined and evaporated to give a crude **5** (1.26 g). The crude **5** was used in the next step without further purification. The authentic sample was obtained as a colorless amorphous solid by purifying part of the crude **5** (silica gel column chromatography, eluent: hexane–AcOEt=3:2). $R_f=0.32$ (hexane–AcOEt=3:2); $[\alpha]_D^{26}$ −7.1 (*c* 3.02, FC-72); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.87$ (6H, m), 2.10 (6H, m), 2.57 (19H, m), 3.43–3.98 (13H, m), 4.10 (2H, m), 4.34 (3H, m), 4.49 (1H, m), 4.75 (1H, m), 5.26 (3H, m), 5.82 (1H, m); MALDI-TOF MS found: *m/z* $[M+Na]^+$ 3257.5. Calcd for $C_{84}H_{55}F_{102}N_3O_{10}Na$ $[M+Na]^+$ 3258.2. Found: *m/z* $[M+K]^+$ 3274.2. Calcd for $C_{84}H_{55}F_{102}N_3O_{10}K$ $[M+K]^+$ 3274.2.

4.1.4. Compound 7. Molecular sieves 4A powder (3.3 g) was added to a solution of the crude **5** (1.26 g) and **6** (1.63 g, 2.38 mmol) in anhydrous ether (40 mL)–$EtOC_4F_9$ (20 mL) under an argon atmosphere. After stirring for 3 h at rt, TMSOTf (210 μL, 1.16 mmol) was added at 0 °C to the reaction mixture. The mixture was stirred for 30 min at 0 °C, and filtered on Celite. The filtrate was added to saturated aqueous $NaHCO_3$ and extracted three times with AcOEt. The AcOEt layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was dissolved in MeOH and FC-72, and extracted three times with FC-72. The FC-72 layers were combined and evaporated to afford a crude **7** (1.28 g). The crude **7** was used in the next step without further purification. The authentic sample was obtained as a colorless amorphous solid by purifying part of the crude **7** (silica gel column chromatography, eluent: hexane–AcOEt=2:1). $R_f=0.37$ (hexane–AcOEt=2:1); $[\alpha]_D^{26}$ +11.5 (*c* 2.33, FC-72); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.87$ (6H, m), 2.04 (6H, m), 2.54 (18H, m), 3.21–3.71 (15H, m), 4.06 (5H, m), 4.27–4.55 (8H, m), 4.67–4.94 (7H, m), 5.18 (1H, d, $J=10.5$ Hz), 5.27 (2H, m), 5.84 (1H, m), 7.27 (20H, m); MALDI-TOF MS found: *m/z* $[M+Na]^+$ 3781.5. Calcd for $C_{118}H_{89}F_{102}N_3$-$O_{17}Na$ $[M+Na]^+$ 3780.5. Found: *m/z* $[M+K]^+$ 3797.4. Calcd for $C_{118}H_{89}F_{102}N_3O_{17}K$ $[M+K]^+$ 3796.4.

4.1.5. Compound 8. A 28% solution of sodium methoxide in MeOH (140 μL) was added to a solution of the crude **7** (1.28 g) in ether (15 mL)–MeOH (15 mL). After stirring for 3 h at rt, the reaction mixture was neutralized with Amberlite IR-120 (H^+ form), and filtered. The filtrate was evaporated. The residue was dissolved in MeOH and FC-72, and extracted three times with FC-72. The methanol layer was evaporated to give a crude **8**. The FC-72 layers were combined and evaporated to afford the pure compound **1b**.[8b] The crude **8** was purified by column chromatography on silica gel with a 1:2 mixture of hexane and AcOEt to give the pure **8** (114 mg, 38% in five steps from **2**) as colorless crystals. Mp 68–70 °C; $[\alpha]_D^{26}$ +33.1 (*c* 1.45, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=2.10$ (2H, brs), 3.27 (1H, dd, $J=9.3$, 3.4 Hz), 3.37 (1H, m), 3.45 (1H, dd, $J=10.0$, 7.6 Hz), 3.56 (1H, t, $J=9.0$ Hz), 3.70 (4H, m), 3.90 (1H, brs), 3.94 (1H, brs), 4.01 (1H, dd, $J=10.0$, 2.4 Hz), 4.13 (3H, m), 4.24 (1H, d, $J=7.3$ Hz), 4.35 (1H, m), 4.37 (1H, d, $J=11.2$ Hz), 4.45 (1H, d, $J=11.2$ Hz), 4.53 (1H, d, $J=$ 11.5 Hz), 4.72 (1H, d, $J=12.7$ Hz), 4.77 (2H, s), 4.82 (1H, d, $J=3.4$ Hz), 4.91 (2H, d, $J=11.5$ Hz), 5.21 (1H, d, $J=$ 10.3 Hz), 5.32 (1H, d, $J=17.3$ Hz), 5.94 (1H, m), 7.30 (20H, m); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=60.35$, 69.58, 70.40, 71.36, 72.10, 72.68, 73.47, 73.72, 74.09, 74.35, 74.61, 74.95, 75.69, 79.07, 80.70, 100.85, 102.03, 117.83, 127.22, 127.65, 127.70, 127.82, 127.98, 128.03, 128.19, 128.32, 128.39, 128.43, 128.58, 133.66, 136.86, 137.31, 137.84, 137.86; HRMS (ESI-TOF): calcd for $C_{43}H_{50}O_{11}Na$

$(M+Na)^+$: 765.3245. Found: 765.3220. Anal. Calcd for $C_{43}H_{50}O_{11}H_2O$: C, 67.88; H, 6.89. Found: C, 67.55; H, 6.85.

4.1.6. Compound 9. Acetic anhydride (0.5 mL) was added to a solution of **8** (13.7 mg, 18.5 μmol) in pyridine (1.0 mL). After stirring for 15 h at rt, MeOH (10 mL) was added at 0 °C to the reaction mixture and evaporated. The residue was purified by column chromatography on silica gel with a 7:4 mixture of hexane and AcOEt to give the pure **9** (15.2 mg, 95%) as a colorless oil. $[\alpha]_D^{22}$ +32.9 (*c* 0.83, $CHCl_3$); ^1H NMR (400 MHz, CD_3OD): $\delta=1.90$ (3H, s), 2.00 (3H, s), 2.03 (3H, s), 3.47 (1H, dd, $J=8.8$, 5.1 Hz), 3.61 (1H, t, $J=8.8$ Hz), 3.86 (1H, t, $J=6.3$ Hz), 3.96 (1H, dd, $J=10.0$, 3.2 Hz), 4.08 (1H, d, $J=2.9$ Hz), 4.11 (3H, m), 4.30 (2H, m), 4.35 (1H, dd, $J=11.5$, 5.9 Hz), 4.43 (1H, dd, $J=11.5$, 7.1 Hz), 4.45 (1H, d, $J=12.0$ Hz), 4.49 (1H, d, $J=12.0$ Hz), 4.51 (1H, d, $J=11.2$ Hz), 4.61 (1H, d, $J=7.8$ Hz), 4.70, (1H, d, $J=11.7$ Hz), 4.76 (2H, s), 4.78 (1H, d, $J=11.7$ Hz), 4.79 (1H, d, $J=3.2$ Hz), 4.85 (1H, d, $J=11.2$ Hz), 4.96 (1H, dd, $J=10.5$, 2.9 Hz), 5.16 (1H, dd, $J=10.5$, 1.5 Hz), 5.23 (1H, dd, $J=10.5$, 7.8 Hz), 5.27 (1H, dd, $J=17.3$, 1.5 Hz), 5.89 (1H, m), 7.31 (20H, m); ^{13}C NMR (100 MHz, CD_3OD): $\delta=20.79$, 20.81, 20.94, 63.92, 69.04, 70.73, 70.85, 70.99, 73.59, 73.91, 73.95, 74.31, 74.59, 76.08, 76.35, 76.82, 77.27, 79.76, 101.35, 101.75, 117.27, 128.45, 128.50, 128.64, 128.84, 129.08, 129.10, 129.19, 129.28, 129.29, 135.12, 139.40, 139.74, 140.00, 140.06, 171.16, 171.88, 172.11; MALDI-TOF MS found: *m/z* $[M+Na]^+$ 889.9. Calcd for $C_{49}H_{56}O_{14}Na$ $[M+Na]^+$ 891.4. Found: *m/z* $[M+K]^+$ 905.8. Calcd for $C_{49}H_{56}O_{14}K$ $[M+K]^+$ 907.3.

4.1.7. Compound 10. Triphenylmethyl chloride (7.39 g, 26.5 mmol) was added at rt to a solution of allyl 4′,6′-*O*-benzylidene-β-lactoside[15] (4.13 g, 8.80 mmol) in pyridine (50 mL). After stirring for 24 h at 50 °C, MeOH (2 mL) was added to the reaction mixture. After cooling, the reaction mixture was evaporated. The residue was treated with water and extracted three times with AcOEt. The AcOEt layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The crude product was purified by column chromatography on silica gel with a 20:1 mixture of $CHCl_3$ and MeOH to afforded the pure **10** (3.88 g, 62%) as a colorless powder. $[\alpha]_D^{23}$ −25.6 (*c* 1.04, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.68$ (1H, d, $J=3.4$ Hz), 2.38 (1H, d, $J=8.8$ Hz), 2.56 (1H, d, $J=2.0$ Hz), 3.30 (1H, dd, $J=10.5$, 4.4 Hz), 3.38 (1H, dd, $J=9.5$, 3.7 Hz), 3.42 (1H, s), 3.52 (2H, m), 3.63 (3H, m), 3.74 (1H, t, $J=9.0$ Hz), 4.04 (1H, d, $J=12.9$ Hz), 4.13 (1H, d, $J=3.2$ Hz), 4.17 (1H, d, $J=7.6$ Hz), 4.26 (3H, m), 4.43 (1H, d, $J=7.6$ Hz), 4.46 (1H, dd, $J=12.9$, 5.4 Hz), 5.27 (1H, d, $J=10.5$ Hz), 5.38 (1H, d, $J=17.1$ Hz), 5.50 (1H, s), 6.04 (1H, m), 7.28 (9H, m), 7.36 (3H, m), 7.47 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=62.40$, 66.64, 68.59, 69.96, 71.02, 72.29, 73.52, 73.83, 74.55, 74.65, 79.70, 86.38, 101.03, 102.60, 117.82, 125.99, 126.77, 127.49, 127.95, 128.45, 128.82, 133.53, 136.90, 143.43; HRMS (ESI-TOF): calcd for $C_{41}H_{44}O_{11}Na$ $(M+Na)^+$: 735.2776. Found: 735.2814.

4.1.8. Compound 11. DMAP (3.28 g, 26.8 mmol) and DCC (7.90 g, 38.3 mmol) were added to a solution of **10** (2.73 g, 3.83 mmol) and **1a** (16.5 g, 16.1 mmol) in anhydrous CH_2Cl_2 (150 mL). After stirring for 3 h at rt, MeOH (30 mL) was added to the reaction mixture. The mixture was stirred for 1 h at rt, toluene was added to the reaction mixture. The mixture was extracted three times with FC-72. The FC-72 layers were combined and evaporated to give a crude **11** (17.4 g). The crude **11** was used in the next step without further purification. The authentic sample was obtained by purifying part of the sample (silica gel column chromatography, eluent: hexane–AcOEt=2:1) as a colorless amorphous solid. $R_f=0.44$ (hexane–AcOEt=2:1); $[\alpha]_D^{23}$ −1.5 (*c* 1.05, AcOEt); ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.70$–2.08 (16H, m), 2.34–2.72 (24H, m), 3.00–3.75 (20H, m), 4.00 (1H, m), 4.13–4.72 (8H, m), 4.96 (1H, m), 5.12 (2H, m), 5.21 (1H, d, $J=10.5$ Hz), 5.29 (1H, d, $J=17.3$ Hz), 5.44 (1H, m), 5.92 (1H, m), 7.27 (3H, m), 7.33 (9H, m), 7.42 (2H, m), 7.50 (6H, m); MALDI-TOF MS found: *m/z* $[M+Na]^+$ 4753.6. Calcd for $C_{141}H_{96}F_{136}N_4O_{19}Na$ $[M+Na]^+$ 4755.4.

4.1.9. Compound 12. To a solution of the crude **11** (6.71 g) in $EtOC_4F_9$ (60 mL) were added 20 mL of a 4 M solution of hydrochloric acid in AcOEt and 1 mL of water were added at 0 °C. After stirring for 1 h at 0 °C, toluene and water were added to the reaction mixture. The reaction mixture was extracted three times with FC-72. The FC-72 layers were combined, dried over anhydrous Na_2SO_4, and evaporated to give a crude **12** (5.65 g). The crude **12** was used in the next step without further purification. The authentic sample was obtained by purifying part of the sample (silica gel column chromatography, eluent: $CHCl_3$–MeOH=30:1) as a colorless amorphous solid. Compound **12** is insoluble in all deuterium solvents, therefore, no NMR spectra could be obtained. $R_f=0.26$ ($CHCl_3$–MeOH=20:1); $[\alpha]_D^{23}$ +0.8 (*c* 0.93, FC-72); MALDI-TOF MS found: *m/z* $[M+Na]^+$ 4423.2. Calcd for $C_{115}H_{78}F_{136}N_4O_{19}Na$ $[M+Na]^+$ 4425.3. Found: *m/z* $[M+K]^+$ 4440.3. Calcd for $C_{115}H_{78}F_{136}N_4O_{19}K$ $[M+K]^+$ 4441.3.

4.1.10. Compound 13. Benzoyl chloride (0.75 mL, 6.46 mmol) was added at −20 °C to a solution of the crude **12** (6.65 g) and triethylamine (5.4 mL, 38.5 mmol) in anhydrous CH_2Cl_2 (100 mL)–$EtOC_4F_9$ (100 mL). After stirring for 15 h at −20 °C, MeOH (50 mL) was added to the reaction mixture, and then the CH_2Cl_2 and $EtOC_4F_9$ were evaporated. MeOH was added to the mixture, and the resulting solution was extracted three times with FC-72. The FC-72 layers were combined and evaporated to give a crude **13** (6.01 g). The crude **13** was used in the next step without further purification. The authentic sample was obtained as a colorless amorphous solid by purifying part of the sample (silica gel column chromatography, eluent: hexane–AcOEt=1.8:1). $R_f=0.71$ ($CHCl_3$–MeOH=20:1); $[\alpha]_D^{23}$ 3.3 (*c* 1.13, AcOEt); ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.85$ (8H, m), 2.06 (8H, m), 2.57 (25H, m), 3.38–3.75 (17H, m), 3.88 (2H, m), 4.07 (2H, m), 4.27 (2H, m), 4.41–4.98 (7H, m), 5.16 (4H, m), 5.80 (1H, m), 7.41–7.60 (6H, m), 8.00 (4H, m); MALDI-TOF MS found: *m/z* $[M+Na]^+$ 4632.5. Calcd for $C_{129}H_{86}F_{136}N_4O_{21}Na$ $[M+Na]^+$ 4633.4. Found: *m/z* $[M+K]^+$ 4648.4. Calcd for $C_{129}H_{86}F_{136}N_4O_{21}K$ $[M+K]^+$ 4649.3.

4.1.11. Compound 14. Molecular sieves 4A powder (4.0 g) was added to a solution of the crude **13** (1.85 g) and **6** (1.92 g, 2.81 mmol) in anhydrous ether (40 mL)–$EtOC_4F_9$

(40 mL) under an argon atmosphere. After stirring for further 3 h at rt, TMSOTf (145 μL, 0.81 mmol) was added at 0 °C to the reaction mixture. The mixture was stirred for 30 min at 0 °C, quenched with triethylamine (1 mL), and filtered on Celitection mixture. The filtrate was treated with saturated aqueous $NaHCO_3$, and extracted three times with AcOEt. The AcOEt layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was dissolved in MeOH and FC-72, and extracted three times with FC-72. The FC-72 layers were combined and evaporated to give a crude **14** (1.74 g). The crude **14** was used in the next step without further purification. The authentic sample was obtained by purifying part of the sample (silica gel column chromatography, eluent: hexane–AcOEt=5:2) as a colorless amorphous solid. R_f=0.60 (hexane–AcOEt=2:1); $[\alpha]_D^{23}$ +10.1 (*c* 1.09, AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.68–2.07 (m, 16H), 2.35–2.69 (m, 24H), 3.20–3.90 (m, 21H), 4.08 (m, 5H), 4.28 (m, 4H), 4.40 (m, 1H), 4.52 (m, 4H), 4.70–4.98 (m, 10H), 5.17 (m, 4H), 5.80 (m, 1H), 7.22 (m, 18H), 7.40 (m, 4H), 7.50 (m, 2H), 7.59 (m, 2H), 7.99 (m, 4H); MALDI-TOF MS found: *m/z* $[M+Na]^+$ 5157.5. Calcd for $C_{163}H_{120}F_{136}N_4O_{26}Na$ $[M+Na]^+$ 5155.6. Found: *m/z* $[M+K]^+$ 5173.2. Calcd for $C_{163}H_{120}F_{136}N_4O_{26}K$ $[M+K]^+$ 5171.6.

4.1.12. Compound 15. To a solution of the crude **14** (1.72 g, 0.36 mmol) in ether (30 mL)–MeOH (20 mL) was added 200 μL of a 28% solution of sodium methoxide in methanol. After stirring for 2 h at rt, the reaction mixture was neutralized with Amberlite IR-120 (H^+ form). After filtration, the filtrate was evaporated. The residue was dissolved in MeOH and FC-72, and extracted three times with FC-72. The FC-72 layers were combined and evaporated to afford the pure product **1b**. The methanol layer was evaporated to give a crude **15**. The crude **15** was purified by column chromatography on silica gel with a 15:1 mixture of $CHCl_3$ and MeOH to give the pure product **15** (174 mg, 43% in five steps from **10**) as a colorless amorphous solid. Mp 128–130 °C; $[\alpha]_D^{23}$ +25.0 (*c* 1.53, $CHCl_3$: MeOH=1:1); ^{1}H NMR (400 MHz, $CDCl_3$: CD_3OD=1:1): δ=3.37–3.62 (8H, m), 3.69 (2H, m), 3.81 (1H, m), 3.87 (2H, m), 3.98 (2H, m), 4.07 (1H, dd, *J*=10.3, 3.7 Hz), 4.17 (2H, m), 4.36 (1H, d, *J*=7.1 Hz), 4.39 (1H, m), 4.43 (1H, d, *J*=11.7 Hz), 4.51 (1H, d, *J*=11.7 Hz), 4.54 (1H, d, *J*=11.7 Hz), 4.72 (1H, d, *J*=11.7 Hz), 4.78 (2H, s), 4.85 (1H, d, *J*=11.7 Hz), 4.89 (1H, d, *J*=11.7 Hz), 4.91 (1H, d, *J*=3.7 Hz), 5.20 (1H, dd, *J*=10.3, 1.5 Hz), 5.34 (1H, dd, *J*=17.1, 1.5 Hz), 5.96 (1H, m), 7.33 (20H, m); ^{13}C NMR (100 MHz, $CDCl_3$: CD_3OD=1:1): δ=61.34, 61.70, 69.46, 70.69, 71.33, 72.01, 73.14, 73.72, 73.92, 74.11, 74.73, 74.89, 75.12, 75.21, 75.37, 76.49, 79.04, 80.69, 81.34, 100.89, 102.18, 104.57, 117.68, 127.81, 127.96, 128.06, 128.14, 128.33, 128.53, 128.55, 128.57, 128.69, 128.71, 128.76, 134.21, 137.82, 137.88, 138.35, 138.50; HRMS (ESI-TOF): calcd for $C_{49}H_{60}O_{16}Na$ $(M+Na)^+$: 927.3774. Found: 927.3750. Anal. Calcd for $C_{49}H_{60}O_{16}1/2H_2O$: C, 64.39; H, 6.73. Found: C, 64.45; H, 6.58.

4.1.13. Compound 16. Acetic anhydride (1.5 mL) was added to a solution of **15** (37.3 mg, 41.2 μmol) in pyridine (3.0 mL). After stirring for 17 h at rt, MeOH (5 mL) was added at 0 °C to the reaction mixture and evaporated. The residue was purified by column chromatography on silica gel with a 1:1 mixture of hexane and AcOEt to give the pure product **16** (45.3 mg, 95%) as a colorless oil. $[\alpha]_D^{23}$ 33.5 (*c* 2.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.85 (3H, s), 1.87 (3H, s), 2.04 (9H, s), 2.12 (3H, s), 3.42 (1H, dd, *J*=8.8, 4.9 Hz), 3.60 (3H, m), 3.74 (1H, t, *J*=9.5 Hz), 3.97 (1H, d, *J*=2.9 Hz), 4.05 (4H, m), 4.15 (1H, brs), 4.28 (2H, m), 4.43 (6H, m), 4.50 (1H, d, *J*=7.8 Hz), 4.55 (1H, d, *J*=11.0 Hz), 4.66 (1H, d, *J*=11.5 Hz), 4.75 (2H, d, *J*=11.2 Hz), 4.76 (1H, d, *J*=4.2 Hz), 4.83 (2H, brs), 4.92 (2H, m), 5.14 (2H, m), 5.19 (1H, d, *J*=11.2 Hz), 5.25 (1H, d, *J*=17.3 Hz), 5.83 (1H, m), 7.24–7.43 (20H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ=20.60, 20.73, 20.84, 20.88, 61.02, 61.90, 67.51, 69.49, 69.56, 69.88, 71.34, 72.24, 72.36, 72.47, 72.61, 72.73, 73.26, 74.15, 74.52, 74.88, 75.28, 75.87, 76.02, 79.01, 99.32, 100.92, 101.23, 117.44, 127.22, 127.29, 127.51, 127.56, 127.88, 127.97, 128.01, 128.11, 128.15, 128.18, 128.29, 133.19, 137.75, 138.96, 138.58, 138.64, 168.60, 169.40, 169.83, 170.19, 170.24, 170.52; MALDI-TOF MS found: *m/z* $[M+Na]^+$ 1179.3. Calcd for $C_{61}H_{72}O_{22}Na$ $[M+Na]^+$ 1179.4. Found: *m/z* $[M+K]^+$ 1195.8. Calcd for $C_{61}H_{72}O_{22}K$ $[M+K]^+$ 1195.4.

4.1.14. Compound 17. A solution of **8** (58.6 mg, 79 μmol) was treated with ozone at −78 °C by bubbling until the solution remained blue. The reaction mixture was evacuated with air for 5 min to remove the ozone, and then dimethyl sulfide (0.2 mL) was added at −78 °C to the reaction mixture. The resulting solution was allowed to warm to rt, and then evaporated to afford a crude **17** (60.4 mg). The crude **17** was used in the next step without further purification due to its lability.

4.1.15. Compound 18. Hydroxylamine hydrochloric acid salt (1.5 mg, 21.7 μmol) was added at rt to a solution of the crude **17** (10.5 mg, 14.1 μmol) in MeOH (15 mL)–H_2O (2 mL). After stirring for 1.5 h at rt, the MeOH was evaporated. The resulting mixture was treated with water and extracted three times with AcOEt. The AcOEt layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel with a 20:1 mixture of $CHCl_3$ and MeOH to give an inseparable mixture of *E*- and *Z*-isomers **18** (8.2 mg, 77% in two steps) as a colorless amorphous solid.

4.1.16. Compound 21. A solution of the mixture **18** (8.2 mg, 10.8 μmol) in EtOH (4 mL)–AcOH (1 mL) and hydrochloric acid in 1,4-dioxane (4 M, 5 μL) were added at rt to a suspension of 10% Pd/C (15 mg) in EtOH (3 mL). After stirring for 22 h under a hydrogen atmosphere (10 atm), the reaction mixture was filtered. The filtrate was evaporated to give the crude compound **19** (8.7 mg). To a solution of the crude **19** (8.7 mg) in 1,4-dioxane (2 mL)–H_2O (2 mL) were added **20** (20.3 mg, 43.9 μmol) and triethylamine (6.4 μL, 46 μmol) at rt. After stirring for 3.5 h at rt, the reaction mixture was dissolved in AcOEt and water, and extracted three times with water. The water layers were combined and evaporated to half to original volume. The water layer was poured into Diaion HP-20. The resin was washed with water, and then eluted with MeOH. The MeOH fractions were then collected and evaporated. The residue was purified by column chromatography on silica gel with a 7:3:0.4 mixture of $CHCl_3$, MeOH, and H_2O

to give the pure **21** (3.3 mg, 42% in two steps) as a green oil. $[\alpha]_D^{25}$ +47.1 (*c* 0.51, MeOH); ^{1}H NMR (400 MHz, CD_3OD): δ=1.16 (m, 2H), 1.34 (m, 4H), 2.01 (t, *J*=7.6 Hz, 2H), 2.81 (t, *J*=6.8 Hz, 2H), 2.86 (s, 6H), 3.42 (m, 1H), 3.48 (dd, *J*=10.3, 7.3 Hz, 1H), 3.54 (dd, *J*=10.0, 2.9 Hz, 1H), 3.61 (m, 3H), 3.67 (m, 2H), 3.75 (m, 4H), 3.89 (m, 2H), 3.97 (d, *J*=2.9 Hz, 1H), 4.25 (m, 1H), 4.27 (d, *J*=7.3 Hz, 1H), 4.94 (d, *J*=3.4 Hz, 1H), 7.25 (d, *J*=7.6 Hz, 1H), 7.56 (m, 2H), 8.16 (d, *J*=7.4 Hz, 1H), 8.33 (d, *J*=8.8 Hz, 1H), 8.54 (d, *J*=8.5 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ=26.32, 27.13, 30.32, 36.81, 40.47, 43.70, 45.83, 61.09, 62.62, 69.84, 70.68, 71.02, 71.32, 72.70, 72.82, 74.59, 76.16, 79.31, 102.57, 105.11, 116.33, 120.52, 124.24, 128.96, 130.05, 130.88, 130.98, 131.10, 137.06, 153.05, 175.95; HRMS (ESI-TOF): calcd for $C_{32}H_{50}N_3O_{14}S$ $(M+H)^+$: 732.3008. Found: 732.2991.

4.1.17. Compound 23. To a solution of the crude **19** (14.7 mg) in 1,4-dioxane (2 mL)–H_2O (2 mL) were added **22** (26.9 mg, 46 μmol) and triethylamine (10 μL, 72 μmol) at rt. After stirring for 4 h at rt, the reaction mixture was dissolved in AcOEt and water, and extracted three times with water. The water layers were combined and evaporated to half to original volume. The water layer was poured into Diaion HP-20. The resin was washed with water, and then eluted with MeOH. The MeOH fractions were then collected and evaporated. The residue was purified by column chromatography on silica gel with a 7:3.5:0.6 mixture of $CHCl_3$, MeOH, and H_2O to give the pure **23** (4.7 mg, 14% in two steps) as an orange oil. $[\alpha]_D^{25}$ +10.8 (*c* 0.13, MeOH–H_2O=4:1); ^{1}H NMR (400 MHz, CD_3OD): δ=1.35 (m, 2H), 1.58 (m, 4H), 2.15 (t, *J*=7.3 Hz, 2H), 3.33–3.43 (m, 4H), 3.46 (dd, *J*=10.3, 3.0 Hz, 1H), 3.52–3.75 (m, 9H), 3.81 (m, 2H), 3.89 (d, *J*=2.4 Hz, 1H), 4.17 (t, *J*=6.6 Hz, 1H), 4.20 (d, *J*=7.3 Hz, 1H), 4.86 (d, *J*=3.2 Hz, 1H), 6.48 (dd, *J*=9.1, 2.5 Hz, 2H), 6.58 (d, *J*=2.5 Hz, 2H), 6.66 (d, *J*=9.1 Hz, 2H), 7.21 (d, *J*=8.1 Hz, 1H), 8.04 (dd, *J*=8.1, 1.7 Hz, 1H), 8.33 (d, *J*=1.7 Hz, 1H); HRMS (ESI-TOF): calcd for $C_{41}H_{49}N_2O_{18}H$ $(M+H)^+$: 857.2975. Found: 857.2944.

4.1.18. Compound 24. A solution of **15** (46.2 mg, 51 μmol) was treated with ozone at −78 °C by bubbling until the solution remained blue. The reaction mixture was evacuated with air for 5 min to remove the ozone, and then dimethyl sulfide (0.2 mL) was added at −78 °C to the reaction mixture. The resulting solution was allowed to warm to rt, and then evaporated to afford a crude **24** (44.4 mg). The crude **24** was used in the next step without further purification due to its lability.

4.1.19. Compound 25. Hydroxylamine hydrochloric acid salt (4.9 mg, 71 μmol) was added at rt to a solution of **24** (44.4 mg, 49 μmol) in MeOH (60 mL)–H_2O (8 mL). After stirring for 2 h at rt, MeOH was evaporated. The reaction mixture was quenched with water, and extracted three times with AcOEt. The AcOEt layers were combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by column chromatography on silica gel with a 10:1 mixture of $CHCl_3$ and MeOH to give an inseparable mixture of *E*- and *Z*-isomers **25** (31.6 mg, 67% in two steps) as a colorless amorphous solid.

4.1.20. Compound 26. A solution of the mixture **25** (14.8 mg, 16 μmol) in EtOH (5 mL)–AcOH (1 mL) and hydrochloric acid in 1,4-dioxane (4 M, 5 μL) were added at rt to a suspension of 10% Pd/C (18 mg) in EtOH (5 mL). After stirring for 3 days under a hydrogen atmosphere (10 atm), the reaction mixture was filtered. The filtrate was evaporated to give a crude **26** (20.5 mg). The crude **26** was used in the next step without further purification.

4.1.21. Compound 27. To a solution of the crude **26** (20.5 mg) in 1,4-dioxane (3 mL)–H_2O (3 mL) were added **20** (19.6 mg, 42 μmol) and triethylamine (5 μL, 36 μmol) at rt. After stirring for 22 h at rt, the reaction mixture was dissolved in AcOEt and water, and extracted three times with water. The water layers were combined and evaporated to half to original volume. The water layer was poured into Diaion HP-20. The resin was washed with water, and then eluted with MeOH. The MeOH fractions were then collected and evaporated. The residue was purified by column chromatography on silica gel with a 7:3:0.4 mixture of $CHCl_3$, MeOH, and H_2O to give the pure **27** (3.3 mg, 25% in two steps) as a green oil. $[\alpha]_D^{25}$ +15.6 (*c* 0.22, MeOH–H_2O=4:1); ^{1}H NMR (400 MHz, CD_3OD–D_2O=4:1): δ=1.13 (m, 2H), 1.31 (m, 4H), 2.02 (t, *J*=7.6 Hz, 2H), 2.84 (t, *J*=7.1 Hz, 2H), 2.87 (s, 6H), 3.43 (m, 3H), 3.52–3.74 (m, 10H), 3.79–3.94 (m 6H), 3.99 (d, *J*=2.7 Hz, 1H), 4.28 (t, *J*=6.3 Hz, 1H), 4.35 (d, *J*=8.8 Hz, 1H), 4.44 (d, *J*=7.5 Hz, 1H), 7.31 (d, *J*=7.3 Hz, 1H), 7.62 (m, 2H), 8.17 (dd, *J*=7.3, 1.2 Hz, 1H), 8.30 (d, *J*=9.8 Hz, 1H), 8.53 (d, *J*=8.5 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD–D_2O=4:1): δ=26.11, 26.81, 29.97, 36.69, 40.38, 43.62, 45.90, 61.49, 62.22, 69.61, 70.22, 70.63, 70.90, 71.19, 72.50, 74.14, 74.50, 76.00, 76.25, 76.56, 79.33, 80.62, 102.24, 103.95, 104.99, 116.59, 120.38, 124.51, 129.31, 130.18, 130.68, 130.84, 131.12, 136.51, 152.83, 176.69; HRMS (ESI-TOF): calcd for $C_{37}H_{57}N_3O_{19}SH$ $(M+H)^+$: 894.3536. Found: 894.3524.

4.1.22. Compound 28. To a solution of the crude compound **26** (9.4 mg) in 1,4-dioxane (3 mL)–H_2O (3 mL) were added **22** (10.0 mg, 17 μmol) and triethylamine (12 μL, 86 μmol) at rt. After stirring for 23 h at rt, the reaction mixture was dissolved in AcOEt and water, and extracted three times with water. The water layers were combined and evaporated to half to original volume. The water layer was poured into Diaion HP-20. The resin was washed with water, and then eluted with MeOH. The MeOH fractions were then collected and evaporated. The residue was purified by column chromatography on silica gel with a 6:4:0.9 mixture of $CHCl_3$, MeOH, and H_2O to give the pure **28** (6.1 mg, 35% in two steps) as an orange oil. $[\alpha]_D^{25}$ +26.8 (*c* 0.33, MeOH–H_2O=4:1); ^{1}H NMR (400 MHz, CD_3OD): δ=1.44 (m, 2H), 1.68 (m, 4H), 2.24 (t, *J*=7.3 Hz, 1H), 3.42–3.59 (m, 9H), 3.64–3.97 (m, 14H), 4.24 (t, *J*=6.3 Hz, 1H), 4.31 (d, *J*=8.6 Hz, 1H), 4.40 (m, 1H), 4.94 (d, *J*=3.9 Hz, 1H), 6.57 (d, *J*=8.8 Hz, 2H), 6.68 (s, 2H), 6.73 (d, *J*=8.8 Hz, 2H), 7.31 (d, *J*=8.1 Hz, 1H), 8.14 (d, *J*=8.1 Hz, 1H), 8.43 (s, 1H); ^{1}H NMR (400 MHz, CD_3OD–D_2O=4:1): δ=1.43 (m, 2H), 1.67 (m, 4H), 2.26 (t, *J*=7.3 Hz, 2H), 3.44 (m, 5H), 3.54–3.73 (m, 9H), 3.81–3.98 (m, 9H), 4.28 (t, *J*=5.9 Hz, 1H), 4.35 (d, *J*=7.8 Hz, 1H), 4.44 (d, *J*=7.3 Hz, 1H), 6.62 (d, *J*=8.7 Hz, 2H), 7.75 (m, 4H), 7.31 (d, *J*=8.1 Hz, 1H), 8.13 (d, *J*=8.1 Hz, 1H), 8.40 (s, 1H);

MALDI-TOF MS found: *m/z* $[M+H]^+$ 1019.9. Calcd for $C_{47}H_{59}N_2O_{23}$ $[M+H]^+$ 1019.4. Found: *m/z* $[M+Na]^+$ 1041.9. Calcd for $C_{47}H_{58}N_2O_{23}Na$ $[M+Na]^+$ 1041.3. Found: *m/z* $[M+K]^+$ 1057.7. Calcd for $C_{47}H_{58}N_2O_{23}K$ $[M+K]^+$ 1057.3.

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11. Fluorous compounds **3**, **7**, **13**, and **14** were partitioned between FC-72 and methanol. Fluorous compounds **4**, **5**, **11**, and **12** were partitioned between FC-72 and toluene. All fluorous compounds were not detected by TLC from the organic layer after three extractions with FC-72. These results show that these compounds were quantitatively extracted with FC-72.
12. The fluorocarbon solvent ($EtOC_4F_9$, Novec™ HFE-7200) is commercially available.
13. The fluorocarbon solvent (FC-72, bp 56 °C, formally called Fluorinert™ FC-72) is commercially available and consists of perfluorohexane isomers (C_6F_{14}).
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Polyhydroxylated pyrrolizidines. Part 6: A new and concise stereoselective synthesis of (+)-casuarine and its 6,7-di*epi* isomer, from DMDP☆

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Abstract—A new synthesis for (+)-casuarine (**1**) and its 6,7-di*epi* isomer (**15**) in a stereocontrolled manner, is reported herein. An appropriately protected polyhydroxylated pyrrolidine, such as (2*R*,3*R*,4*R*,5*R*)-3,4-dibenzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine (**3**, protected DMDP), easily available from D-fructose, was chosen as the chiral starting material. Compounds **1** and **15** were obtained from **3**, in seven steps, in a 23.2 and 20.5% overall yields, respectively.

1. Introduction

The important role played by glycosidases and glycosyltransferases in molecular biology is well recognised, and equally well known is the fact that any interference with the enzymatic activity of these biomolecules caused by inhibitors such as azasugars and related compounds can have profound effects on the processes, which they mediate. Thus, these inhibitors have many potential applications in the fields of agrochemistry and therapeutics.[2] In this context, a great deal of attention has been paid over the last two decades to the synthesis[3] of naturally occurring azasugars (polyhydroxylated alkaloids) and their analogues.

Continuing with our studies into the synthesis of polyhydroxylated pyrrolizidinic alkaloids (PHPAs),[4] we became interested in exploring the possibility of preparing those with the highest degree of hydroxylation found in nature, such as hyacinthacine C_1,[5] casuarine (**1**)[6] and other synthetic analogues of interest for SAR studies as glycosidase inhibitors.

According to Figure 1, the target PHPA **1** could be constructed as follows: ring **A** comes from a suitably protected derivative of DMDP (**3**), which transfers its inherent chirality to the final compound, whereas the **B** ring, with the appropriate stereochemistry, would be built up following the synthetic route outlined in Scheme 1, consisting of the lengthening of the carbon-chain at C(5′) of (2*R*,3*R*,4*R*,5*R*)-3,4-dibenzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine (**3**) using Wittig's method, followed by dihydroxylation, and finally cyclization to the pyrrolizidine skeleton.

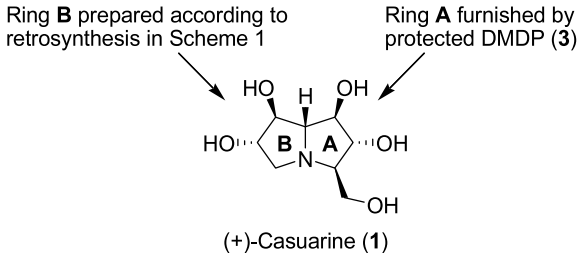
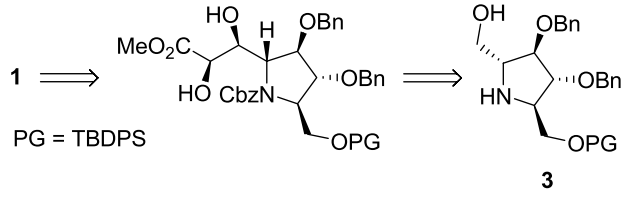


Figure 1. (+)-Casuarine (**1**).



Scheme 1. Retrosynthesis of **1**.

☆ For Part 5, see Ref. 1.

Keywords: Stereoselective synthesis; DMDP; Polyhydroxylated pyrrolizidines; (+)-Casuarine; 6,7-Di*epi*casuarine.
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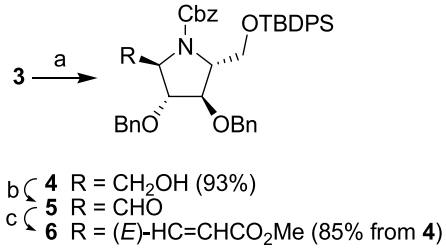
Since the isolation in 1994 of **1** from *Casuarina equisetifolia* L. (Casuarinaceae), only one synthesis has been described so far, by Denmark et al.,[8] in which the key intermediate, leading to the pyrrolizidinic skeleton, as well as five of the six stereogenic centres present in **1**, was created by a complex tandem [4+2]/[3+2] nitroalkene cycloaddition between the benzoate of a nitrovinyl alcohol, a chiral vinyl ether as source of chirality, and a vinyl silane. This method, however, lacks stereocontrol, requiring as it does the resolution of different complex diastereomeric mixtures. In 1997 Fleet et al.,[9] using a carbohydrate derivative as the source of chirality and functionalization, managed to synthesize four diastereomers of **1**, one of them being (+)-6,7-di*epi*casuarine (**15**).

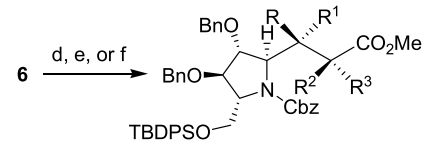
2. Results and discussion

In our synthesis pyrrolidine **3** was initially *N*-protected as its Cbz derivative **4** was then oxidized (TPAP/NMO) to the pyrrolidinic aldehyde **5** and finally allowed to react with (methoxycarbonylmethylene)triphenylphosphorane to afford, in a highly stereoselective manner, methyl (*E*)-3-[(2′*R*,3′*R*,4′*R*,5′*R*)-3′,4′-dibenzyloxy-*N*-benzyloxycarbonyl-5′-*tert*-butyldiphenylsilyloxymethylpyrrolidin-2′-yl]propenoate (**6**), in accordance with the $J_{2,3}$ value of 15.8 Hz, this being shown as a mixture of rotamers (Scheme 2).[10]



Scheme 2. Synthesis of **6** from **3**. Reagents and conditions: (a) CbzCl/Me_2CO/K_2CO_3, rt; (b) TPAP/NMO/4 Å MS/Cl_2CH_2; (c) $Ph_3P{=}CHCO_2Me/Cl_2CH_2$, rt.

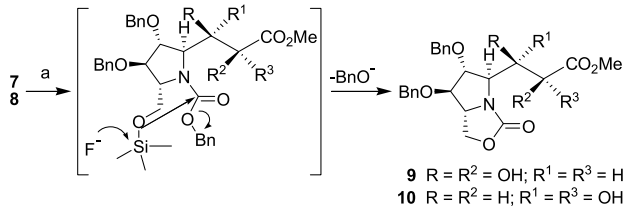
Dihydroxylation (DH) of the α,β-unsaturated ester **6** (see, Scheme 3 below) gave an easily resolvable mixture of the methyl (2*S*,3*R*)-(**7**) and (2*R*,3*S*)-2,3-dihydroxy-3-[(2′*R*,3′*R*,4′*R*,5′*R*)-3′,4′-dibenzyloxy-*N*-benzyloxycarbonyl-5′-*tert*-butyldiphenylsilyloxymethylpyrrolidin-2′-yl]propanoate (**8**), in a 1:1 diastereomeric ratio (from the isolated diols). Moreover, when **6** was submitted to Sharpless ADH reaction[11] the practical and stereochemical results depended to a great extent upon, which chiral ligand was used. Thus, when the reaction took place in the presence of 'first generation chiral catalysts' *O*-(4-chlorobenzoyl)hydroquinine (DHQ–CLB)[11b] an increase in the **7**:**8** diastereomeric ratio (1:2.2) was observed, whereas a reverse diastereoselectivity (2:1) was obtained in the presence of *O*-(4-chlorobenzoyl)hydroquinidine (DHQD–CLB). No reaction occurred, even after five days, when 'second generation'[11c] AD-mix-α® or AD-mix-β® chiral catalysts were used.



	Ratio **7** : **8**
d) OsO_4/NMO/no catalyst	1 : 1
e) DHQ-CLB	1 : 2.2
f) DHQD-CLB	2 : 1

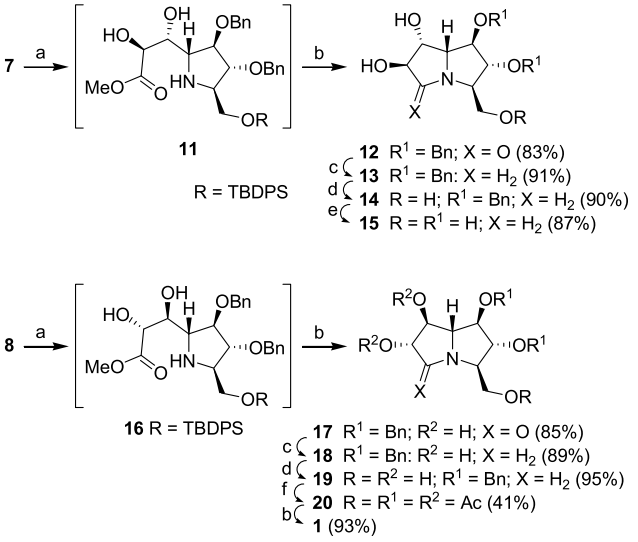
Scheme 3. Synthesis of **7** and **8** from **6**.

The absolute configurations of the new stereogenic centres in **7** and **8** could be determined after their respective transformations into the related target molecules **15** and **1**. Thus, in a first attempt the conventional treatment of compounds **7** and **8** with TBAF, instead of removing only the TBDPS group at the oxygen in C(5′) to give the expected desilylated products, promoted an unexpected intramolecular cyclization, affording the corresponding carbamates **9** and **10**. The mechanism shown in Scheme 4 would account for this process.



Scheme 4. Formation of bicyclic carbamates **9** and **10** from **7** and **8**, respectively. Reagents and conditions: (a) *n*-$Bu_4N^+F^-\cdot 3H_2O$/THF, rt.

On the basis of the results outlined above, compounds **7** and **8** (see Scheme 5) were separately *N*-deprotected by catalytic hydrogenation to the corresponding non-isolated



Scheme 5. Synthesis of **15** and **1**, from **7** and **8**, respectively. Reagents and conditions: (a) H_2/10% Pd–C/MeOH; (b) MeONa catalyst/MeOH, rt; (c) $H_3B{:}SMe_2$/THF, then MeOH/Δ; (d) *n*-$Bu_4N^+F^-\cdot 3H_2O$/THF, rt; (e) H_2/10% Pd–C/HCl/MeOH then Amberlite IRA-400 (OH^- form); (f) (i) H_2/10% Pd–C/HCl/MeOH, then Amberlite IRA-400 (OH^- form), (ii) Ac_2O/py, DMAP.

intermediate pyrrolidines **11** and **16**, which were subsequently transformed into the related (1*R*,2*S*,5*R*, 6*R*,7*R*,7a*R*)-6,7-dibenzyloxy-5-*tert*-butyldiphenylsilyloxymethyl-1,2-dihydroxypyrrolizidin-3-one (**12**) and its 1,2-di*epi*mer (**17**) by refluxing in methanol under the presence of a catalytic amount of MeONa, which promoted γ-lactamization.

The structures of **12** and **17** were established on the basis of their spectroscopic data, showing characteristic IR γ-lactam absorptions at 1682 and 1694 cm^{-1}, respectively, they were also confirmed by the presence of resonance signals at δ 173.70 and 172.24 ppm in their respective ^{13}C NMR spectra. In addition, ^{1}H–^{1}H and ^{1}H–^{13}C COSY and extensive NOE experiments confirmed not only the proposed structures for **12** and **17** but also allowed the assignment of their ^{1}H and ^{13}C NMR signals. In this context, the definitive NOE interactions between H(2)–H(7a) and H(6)-(7a) are only consistent with the configutarions displayed for **17** in Figure 2.

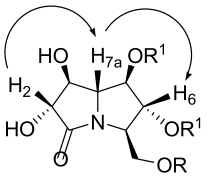


Figure 2. Main NOE interactions in **17**.

The transformation of **12** and **17** into the target molecules **15** and **1** was achieved by reduction to the corresponding partially protected pyrrolizidines **13** and **18** with H_3B/SMe_2 complex in THF, followed by *O*-desilylation to **14** and **19** and finally total deprotection to the required compounds. The spectroscopic and optical data of compound **15**, from *O*-debenzylation, exactly matched those previously reported for 6,7-di*epi*casuarine,[9] but those of **1** from the same reaction were slightly contaminated. Therefore, further purification was necessary via the peracetylated derivative **20** followed by deacetylation to **1**, which then produced the same optical and spectroscopic data as those described by Demmark,[8a] thus confirming the assessment of this author that the reported[6] optical rotation value for natural (+)-casuarine has been set mistakenly high.

3. Conclusions

We have developed a new strategy for the preparation of the natural and synthetic densely polyhydroxylated pyrrolizidinic alkaloids [(+)-casuarine (**1**) and its 6,7-di*epi* isomer (**15**)] in seven steps at overall yields of 23.2 and 20.5%, respectively from the easily available pyrrolidine **3** (partially protected DMDP).

4. Experimental

4.1. General procedures

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 FT-IR Spectrum One instrument and mass spectra with a Hewlett-Packard HP-5988-A and Fisons mod. Platform II and VG 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 silica gel 60 F_{254} aluminium sheets and detection by charring with H_2SO_4. Column chromatography was performed on silica gel (Merck, 7734). The noncrystalline compounds were shown to be homogeneous by chromatographic methods and characterized by NMR, MS and HRMS.

4.1.1. (2*R*,3*R*,4*R*,5*R*)-3,4-Dibenzyloxy-*N*-benzyloxycarbonyl-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine (4). To a well stirred solution of **3**[7] (7.37 g, 12.7 mmol) in dry acetone (70 mL), anhydrous potassium carbonate (5 g) and a solution of benzyl chloroformate (2.2 mL, 15.3 mmol) in the same solvent (10 mL) were added and the mixture kept at rt for 3 h. TLC (Et_2O/hexane, 2:1) then revealed the presence of a faster-running compound. The mixture was filtered and the solid thoroughly washed with acetone and the filtrate and washings concentrated to a residue that was submitted to chromatography (Et_2O/hexane, 1:2) to give **4** as colourless syrup. Yield: 8.5 g (93%); $[\alpha]_D^{22}$ −6 (*c*, 1). IR (neat): 3419 (OH), 3068 and 3032 (aromatic), 1703 (C=O, Cbz), 738 and 700 cm^{-1} (aromatic). ^{1}H NMR (400 MHz), *inter alia*: δ=7.68–7.54 and 7.41–7.12 (2 m, 25H, 5Ph), 5.16 and 5.00 (2d, *J*=12.2 Hz, CH_2Ph, minor), 5.03 and 4.96 (2d, *J*=12.2 Hz, CH_2Ph, major), 4.72 and 4.55 (2d, *J*=11.8 Hz, CH_2Ph, minor), 4.62 and 4.53 (2d, *J*=12.0 Hz, CH_2Ph, major), 4.48 and 4.45 (2d, *J*=12.3 Hz, Cbz, major), 4.37 and 4.33 (2d, *J*=12.8 Hz, Cbz, minor), 4.41–4.33 (m), 4.17 (dd, *J*=10.3, 4.5 Hz), 4.07 (br t, *J*=4.6 Hz), 4.02–3.94 (m), 3.90–3.84 (m), 3.73–3.64 (m), 1.11 (s, CMe_3, minor) and 1.05 (s, CMe_3, major). ^{13}C NMR (100 MHz), *inter alia*: δ= 155.54 (C=O, Cbz), 84.23 and 81.54 (C-3,4), 71.49 and 71.43 (2 *C*H_2Ph), 67.30 (*C*H_2Ph, Cbz), 66.96 and 65.40 (C-2,5), 63.88 and 62.06 (C-2′,5′), 26.92 (C*Me*$_3$), and 19.25 (*C*Me_3). HRMS (LSIMS): *m*/*z*=738.3220 [M^++Na]; calcd for $C_{44}H_{49}NO_6NaSi$: 738.3227 (deviation +0.9 ppm).

4.1.2. Methyl (*E*)-3-[(2′*R*,3′*R*,4′*R*,5′*R*)-3′,4′-dibenzyloxy-*N*-benzyloxycarbonyl-5′-*tert*-butyldiphenylsilyloxymethylpyrrolidin-2′-yl]propenoate (6). To a stirred solution of **4** (5.27 g, 7.37 mmol) in dry CH_2Cl_2 (50 mL) were added activated 4 Å molecular sieves (3.7 g), *N*-oxide-*N*-methylmorpholine (NMO, 1.07 g, 9.13 mmol) and tetra-*n*-propylammonium perruthenate (TPAP, 145 mg) and the reaction mixture was kept at rt for 1 h. TLC (Et_2O/hexane, 3:2) then indicated the absence of the starting material and the presence of a faster-running compound **5**. (Methoxycarbonylmethylene)triphenylphosporane (3.7 g, 10.6 mmol) was added, and the mixture left at rt. After 48 h, TLC (Et_2O/hexane, 3:2) then showed a new compound. The reaction mixture was supported on silica gel and submitted to chromatography (Et_2O/hexane, 1:2) to afford pure **6** as colourless thick syrup. Yield: 4.9 g (85%); $[\alpha]_D^{23}$ +6.2, $[\alpha]_{405}^{23}$ +22 (*c*, 1.3). IR (neat): 3068 and 3032 (aromatic), 1708 (C=O), 739 and 700 cm^{-1} (aromatic). ^{1}H NMR (300 MHz): δ=7.65–7.51 and 7.38–7.07 (2m, 25H, 5Ph),

6.94–6.82 (m, H-3, major and minor), 5.91 (d, $J=15.7$ Hz, H-2, major), 5.71 (d, $J=15.8$ Hz, H-2, minor), 5.10 and 4.88 (2d, $J=12.2$ Hz, CH_2Ph, minor), 5.02 and 4.87 (2d, $J=12.2$ Hz, CH_2Ph, major), 4.64 and 4.48 (2d, $J=12.3$ Hz, CH_2Ph, minor), 4.59 and 4.50 (2d, $J=12.4$ Hz, CH_2Ph, major), 4.41–3.64 (m, H-2′,3′,4′,5′,5″a,5″b, major and minor), 3.78 (s, Cbz, major and minor), 3.68 (s, 3H, OMe, major), 3.64 (s, OMe, minor), 1.04 (s, CMe_3, minor) and 0.99 (s, CMe_3, major). ^{13}C NMR (75 MHz), *inter alia*: $\delta=$ 166.57 and 166.44 (C-1), 154.55 and 154.30 (C=O, Cbz), 146.00 and 145.61 (C-3), 122.19 and 121.96 (C-2), 86.18, 85.21, 82.44 and 81.38 (C-3′,4′), 71.66, 71.29 and 71.13 (CH_2Ph), 67.18 and 67.13 (CH_2Ph, Cbz), 65.40, 65.32, 65.23 and 65.11 (C-2′,5′), 62.16 and 61.43 (C-5″), 52.34 and 51.54 (OMe), 26.99 and 26.90 (CMe_3), 19.38 and 19.27 (CMe_3). HRMS (LSIMS): $m/z=792.3333$ [M^+ + Na]; calcd for $C_{47}H_{51}NO_7NaSi$: 792.3332 (deviation −0.1 ppm).

4.1.3. Methyl (2*S*,3*R*)- (7) and (2*R*,3*S*)-2,3-dihydroxy-3-[(2′*R*,3′*R*,4′*R*,5′*R*)-3′,4′-dibenzyloxy-*N*-benzyloxycarbonyl-5′-*tert*-butyldiphenylsilyloxymethylpyrrolidin-2′-yl]propanoate (8). *Dihydroxylation of* **6** *without chiral catalyst*. To a stirred solution of **6** (4.8 g, 5.3 mmol) in acetone/water 8:1 v/v (40 mL), was added NMO (1.46 g, 12.5 mmol) and aqueous 1% OsO_4 (5 mL). The mixture was left at rt 30 h. TLC (Et_2O/hexane, 3:1) then revealed the presence of two new products of lower mobility. The mixture was concentrated to a residue that was submitted to chromatography (Et_2O/hexane, 1:3). Eluted first was syrupy **7**. Yield: 2.20 g (44%); $[\alpha]_D^{23}$ −12 (*c*, 1). IR (neat): 3392 (OH), 3062 and 3032 (aromatic), 1750 (C=O, ester), 1674 (C=O, Cbz), 739 and 700 cm^{-1} (aromatic). ^1H NMR (400 MHz): $\delta=$7.56–7.09 (m, 25H, 5Ph), 5.17 (br s, 1H, OH), 4.98 and 4.94 (2d, 2H, $J=12.2$ Hz, CH_2Ph), 4.62 and 4.49 (2d, 2H, $J=12.1$ Hz, CH_2Ph), 4.54 and 4.44 (2d, 2H, $J=12.2$ Hz, Cbz), 4.42–4.30 (m, 3H), 4.15–4.09 (m, 3H), 4.03 (s, 1H), 3.75 (s, 3H, OMe), 3.75–3.66 (m, 1H), 3.25 (br s, 1H, OH) and 1.00 (s, 9H, CMe_3). ^{13}C NMR (100 MHz), *inter alia*: $\delta=$173.22 (C-1), 158.09 (C=O, Cbz) 82.59 and 81.79 (C-3′,4′), 75.33 and 72.25 (C-2,3), 71.50 and 71.18 (2 CH_2Ph), 67.94 (CH_2Ph, Cbz), 67.19 and 65.39 (C-2′,5′), 61.80 (C-5″), 52.64 (OMe), 26.94 (CMe_3), and 19.30 (CMe_3). HRMS (LSIMS): $m/z=826.3383$ [M^+ + Na]; calcd for $C_{47}H_{53}NO_9NaSi$: 826.3387 (deviation +0.6 ppm).

Eluted second was syrupy **8**. Yield: 2.20 g (44%); $[\alpha]_D^{22}-10$ (*c*, 1). IR (neat): 3435 (OH), 3068 and 3032 (aromatic), 1743 (C=O, ester), 1704 (C=O, Cbz), 739 and 700 cm^{-1} (aromatic). ^1H NMR (400 MHz): $\delta=$7.65–7.15 (m, 25H, 5Ph), 4.97 and 4.92 (2d, 2H, $J=12.2$ Hz, CH_2Ph), 4.59 (s, 2H, CH_2Ph), 4.50 and 4.45 (2d, 2H, $J=11.8$ Hz, Cbz), 4.55–4.40 (m, 2H), 4.23 (d, 1H, $J=6$ Hz), 4.15–4.03 (m, 3H), 3.87 (d, 1H, $J=6.1$ Hz), 3.76 (s, 3H, OMe), 3.70–3.63 (m, 2H), 3.42 (d, 1H, $J=8.4$ Hz), and 0.99 (s, 9H, CMe_3). ^{13}C NMR (100 MHz), *inter alia*: $\delta=$172.83 (C-1), 155.81 (C=O, Cbz), 82.32 and 81.79 (C-3′,4′), 72.05 and 71.08 (C-2,3), 71.63 and 71.61 (2CH_2Ph), 68.03 (CH_2Ph, Cbz), 67.56 and 65.41 (C-2′,5′), 61.86 (C-5″), 52.61 (OMe), 27.02 (CMe_3), and 19.28 (CMe_3). HRMS (LSIMS): $m/z=$ 826.3389 [M^+ + Na]; calcd for $C_{47}H_{53}NO_9NaSi$: 826.3387 (deviation −0.2 ppm).

Dihydroxylation of **6** *with DHQ–CLB catalyst*. To a well-stirred and cooled (ice–water) solution of **6** (125 mg, 0.16 mmol), NMO (26 mg, 0.22 mmol) and DHQ–CLB (20 mg, 0.043 mmol) in acetone/water (5:1 v/v, 10 mL) was added aqueous 0.07 M OsO_4 (0.5 mL) and the mixture left for two days at rt, when TLC (Et_2O/hexane, 3:1) revealed the presence of only **7** and **8**. The mixture was supported on silica gel and chromatographed (Et_2O/hexane, 1:3) to afford **7** (32 mg, 27%) and **8** (70 mg, 58%). A small amount (10 mg) of unchanged **6** was recovered.

Dihydroxylation of **6** *with DHQD–CLB catalyst*. Dihydroxylation of **6** (125 mg, 0.16 mmol) as above, but catalyzed with DHQD–CLB, gave **7** (80 mg, 61%) and **8** (40 mg, 31%).

4.1.4. Methyl (2*S*,3*R*)-2,3-dihydroxy-3-[(5′*R*,6′*R*,7′*R*,7a'*R*)-6′,7′-dibenzyloxy-3′-oxo-tetrahydropyrrolo[1,2-*c*]oxazol-5′-yl]propanoate (9). To stirred solution of **7** (1.07 g, 1.33 mmol) in THF (25 mL) was added TBAF·$3H_2O$ (630 mg, 2 mmol) and the reaction mixture kept at rt for 12 h. TLC (Et_2O) then revealed a new compound of slightly lower mobility. The mixture was supported on silica gel and chromatographed (Et_2O/EtAcO, 1:10) to give pure **9**. Yield: 400 mg (66%); $[\alpha]_D^{24}$ −8 (*c*, 0.7). IR (neat): 3437 (OH), 3063 and 3031 (aromatic), 1757 (C=O), 740 and 699 cm^{-1} (aromatic). ^1H NMR (400 MHz): $\delta=$7.40–7.28 (m, 10H, 2Ph), 4.67 and 4.50 (2d, 2H, $J=12.0$ Hz, CH_2Ph), 4.60 and 4.53 (2d, 2H, $J=11.5$ Hz, CH_2Ph), 4.55 (s, 1H, H-2), 4.19 (br s, 1H), 4.00 (br s, 1H), 3.95–3.89 (m, 3H), 3.79 (s, 3H, OMe), 3.76 (dd, 1H, $J_{1'a,7a'}=4$ Hz, H-1′a), 3.57 (dd, 1H, $J_{1'b,7a'}=5.3$, $J_{1'a,1'b}=11.8$ Hz, H-1′b). ^{13}C NMR (100 MHz), *inter alia*: $\delta=$170.80 (C-1), 160.70 (C-3′), 87.39 and 85.04 (C-6′,7′), 79.33 and 71.46 (C-2,3), 72.90 and 72.51 (2CH_2Ph), 64.97 and 63.70 (C-5′,7a′), 62.67 (C-1′), and 53.27 (OMe). HRMS (LSIMS): $m/z=480.1629$ [M^+ + Na]; calcd for $C_{24}H_{27}NO_8Na$: 480.1634 (deviation +1.1 ppm).

4.1.5. Methyl (2*R*,3*S*)-2,3-dihydroxy-3-[(5′*R*,6′*R*,7′*R*,7a'*R*)-6′,7′-dibenzyloxy-3′-oxo-tetrahydropyrrolo[1,2-*c*]oxazol-5′-yl]propanoate (10). Treatment of **8** (1.1 g, 1.37 mmol) in THF (25 mL) with TBAF·$3H_2O$ (630 mg, 2 mmol) as above, gave after column chromatography (Et_2O) pure **10**. Yield: 210 mg (34%); $[\alpha]_D^{26}$ −6 (*c*, 1). IR (neat): 3453 (OH), 3063 and 3031 (aromatic), 1738 (C=O), 740 and 700 cm^{-1} (aromatic). ^1H NMR (400 MHz): $\delta=$ 7.37–7.28 (m, 10H, 2Ph), 4.69 and 4.51 (2d, 2H, $J=$ 11.6 Hz, CH_2Ph), 4.62 and 4.42 (2d, 2H, $J=11.9$ Hz, CH_2Ph), 4.46 (s, 1H, H-2), 4.42–4.38 (m, 2H), 4.08–4.03 (m, 2H), 3.98–3.90 (m, 3H), 3.80 (s, 3H, OMe). ^{13}C NMR (100 MHz), *inter alia*: $\delta=$172.93 (C-1), 161.57 (C-3′), 88.51 and 86.25 (C-6′,7′), 72.78 and 72.16 (2CH_2Ph), 72.06 and 70.56 (C-2,3), 67.98 (C-1′), 64.64 and 62.30 (C-5′,7a′), and 52.86 (OMe).

4.1.6. (1*R*,2*S*,5*R*,6*R*,7*R*,7a*R*)-6,7-Dibenzyloxy-5-*tert*-butyldiphenylsilyloxymethyl-1,2-dihydroxypyrrolizidin-3-one (12). A solution of **7** (2 g, 2.5 mmol) in MeOH (25 mL) was stirred at rt with 10% Pd–C (180 mg) in an H_2 atmosphere for 2 h. TLC (EtAcO/hexane, 1:1) then showed the presence of a compound of lower mobility, presumably the *N*-deprotected pyrrolidine (**11**). The catalyst was filtered

off, washed with MeOH and the combined filtrate and washings (50 mL) treated with 2 M MeONa (2 mL). After 1 h, TLC (EtAcO/hexane, 1:1) then revealed the presence of a faster-running product. The mixture was neutralized with aqueous 10% HCl, supported on silica gel and submitted to chromatography (Et_2O/hexane, 10:1) to afford **12**. Yield: 1.32 g (83%); white foam; $[\alpha]_D^{27}$ −52 (*c*, 1). IR (KBr): 3373 (OH), 3069 (aromatic), 1682 (C=O), 737 and 700 cm^{-1} (aromatic). ^1H NMR (400 MHz): δ=7.61–7.56 and 7.40–7.24 (2m, 20H, 4Ph), 4.56 and 4.52 (m, 4H, $2CH_2Ph$), 4.49 (br t, 1H, H-6), 4.31 (br t, 1H, $J_{6,7}=J_{7,7a}=5.2$ Hz, H-7), 4.24 (br t, 1H, $J_{1,7a}=5.2$ Hz, H-7a), 4.14 (s, 1H, H-2), 4.13 (d, 1H, H-1), 4.01 (m, 1H, H-5), 3.88 (dd, 1H, $J_{5,8}=5.5$, $J_{8,8'}=10.3$ Hz, H-8), 3.66 (dd, 1H, $J_{5,8'}=3.6$ Hz, H-8′), and 1.01 (s, 9H, CMe_3). ^{13}C NMR (100 MHz), *inter alia*: δ=173.70 (C-3), 85.41 (C-6), 80.74 (C-7), 80.59 (C-2), 72.59 (C-1), 72.36 and 72.09 ($2CH_2Ph$), 68.29 (C-7a), 62.32 (C-8), 60.67 (C-5), 26.91 (CMe_3), and 19.29 (CMe_3). HRMS (LSIMS): *m/z*=660.2762 [M^++Na]; calcd for $C_{38}H_{43}NO_6NaSi$: 660.2757 (deviation −0.8 ppm).

4.1.7. (1*R*,2*R*,3*R*,6*R*,7*R*,7a*R*)-1,2-Dibenzyloxy-3-*tert*-butyldiphenylsilyloxymethyl-6,7-dihydroxypyrrolizidine (13). To a stirred solution of **12** (1.3 g, 2.1 mmol) in anhydrous THF (20 mL) was added dropwise a $H_3B{:}SMe_2$ complex solution in the same solvent (10 M, 2.1 mL) under argon, and the mixture left at rt for 12 h. TLC (EtAcO/hexane, 3:1) then revealed the absence of **12** and the presence of a faster-running compound, presumably the borane–amine complex. MeOH (2 mL) was cautiously added and the reaction mixture was concentrated to a residue that was dissolved in MeOH (20 mL) and refluxed for 4 h, when the borane–amine complex was not observed by TLC. The reaction mixture was concentrated and the residue was supported on silica gel and chromatographed (Et_2O/hexane, 10:1) to give pure **13**. Yield: 1.16 g (91%); white foam; $[\alpha]_D^{23}$ −3, (*c*, 1). IR (KBr): 3401 (OH), 3069, 738 and 700 cm^{-1} (aromatic). ^1H NMR (400 MHz): δ=7.70–7.62 and 7.45–7.20 (2m, 20H, 4Ph), 4.62 and 4.55 (2d, 2H, J=11.8 Hz, CH_2Ph), 4.54 and 4.51 (2d, 2H, J=12.6 Hz, CH_2Ph), 4.28 (t, 1H, $J_{1,2}=J_{1,7a}=3.4$ Hz, H-1), 4.21 (t, 1H, $J_{2,3}=3.8$ Hz, H-2), 4.13 (br s, 1H, H-6), 3.91 (br s, 1H, H-7), 3.79 (t, 1H, $J_{7,7a}=4.0$ Hz, H-7a), 3.76 (dd, 1H, $J_{3,8}=7.1$ Hz, H-8), 3.68 (dd, 1H, $J_{3,8'}=6.6$, $J_{8,8'}=10.1$ Hz, H-8′), 3.09 (d, 1H, H-5), 3.08 (m, 1H, H-3), 2.97 (dd, 1H, $J_{5',6}=3.7$, $J_{5,5'}=11.3$ Hz, H-5′), 2.79 (br s, 1H, HO-7), and 1.05 (s, 9H, CMe_3). ^{13}C NMR (100 MHz), *inter alia*: δ=85.55 (C-2), 81.48 (C-1), 79.54 (C-6), 76.48 (C-7), 72.19 (C-3), 72.06 and 72.02 ($2CH_2Ph$), 71.56 (C-7a), 65.75 (C-8), 60.50 (C-5), 26.96 (CMe_3), and 19.30 (CMe_3). HRMS (LSIMS): *m/z*=646.2965 [M^++Na]; calcd for $C_{38}H_{45}NO_5NaSi$: 646.2964 (deviation −0.1 ppm).

4.1.8. (1*R*,2*R*,3*R*,6*R*,7*R*,7a*R*)-1,2-Dibenzyloxy-6,7-dihydroxy-3-hydroxymethylpyrrolizidine (14). To a stirred solution of **13** (920 mg, 1.47 mmol) in THF (20 mL) was added TBAF·$3H_2O$ (700 mg, 2.2 mmol) and the reaction mixture refluxed for 3 h. TLC (Et_2O/MeOH, 5:1) then revealed a new compound of lower mobility. The mixture was supported on silica gel and chromatographed (Et_2O/MeOH, 5:1) to give pure **14**. Yield: 510 mg (90%); white solid; mp 174–176 °C (from ether/methanol); $[\alpha]_D^{24}$ −0.5, $[\alpha]_{405}^{24}$ −13, (*c*, 0.7, methanol). IR (KBr): 3392 (OH), 3086, 3032, 733 and 699 cm^{-1} (aromatic). ^1H NMR (300 MHz, MeOH-d_4): δ=7.30–7.12 (m, 10H, 2Ph), 4.64 and 4.53 (2d, 2H, J=11.7 Hz, CH_2Ph), 4.49 and 4.42 (2d, 2H, J=11.6 Hz, CH_2Ph), 4.37 (dd, 1H, $J_{1,2}=6.7$, $J_{1,7a}=5.9$ Hz, H-1), 4.11 (dd, 1H, H-6), 3.97 (dd, 1H, $J_{2,3}=9.1$ Hz, H-2), 3.85 (dd, 1H, $J_{6,7}=1.6$, $J_{7,7a}=3.8$ Hz, H-7), 3.58 (dd, 1H, $J_{3,8}=3.2$, $J_{8,8'}=11.4$ Hz, H-8), 3.49 (dd, 1H, H-7a), 3.41 (dd, 1H, $J_{3,8'}=5.7$ Hz, H-8′), 2.93 (d, 1H, $J_{5,5'}=11.2$ Hz, H-5), 2.78 (dd, 1H, $J_{5',6}=3.9$ Hz, H-5′), and 2.73 (ddd, 1H, H-3). ^{13}C NMR (75 MHz), *inter alia*: δ=86.81 (C-2), 82.02 (C-1), 80.24 (C-6), 76.96 (C-7), 73.59 and 73.21 ($2CH_2Ph$), 72.49 (C-3), 71.33 (C-7a), 63.61 (C-8), and 60.31 (C-5). Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.86; H, 7.45; N, 3.38.

4.1.9. (1*R*,2*R*,3*R*,6*R*,7*R*,7a*R*)-1,2,6,7-Tetrahydroxy-3-hydroxymethylpyrrolizidine [(+)-6,7-di*epi*casuarine (15)]. Compound **14** (400 mg, 1.04 mmol) in methanol (15 mL) and concentrated HCl (three drops) was hydrogenated with 10% Pd–C (80 mg) at ambient pressure and rt overnight. TLC (ether/methanol, 5:1) then revealed the absence of the starting product. The catalyst was filtered off, washed with methanol and the combined filtrate and washings treated with Amberlite IRA-400 resin (OH^- form). Evaporation of the solvent afforded pure **15**. Yield: 175 mg (87%); white foam; $[\alpha]_D^{24}$ +8.1 (*c*, 1, water); Lit.[9] $[\alpha]_D^{22}$ +8.4 (*c*, 0.89, water). ^1H NMR (400 MHz, D_2O, pH 7.5): δ=4.21 (m, 1H, H-6), 4.17 (t, 1H, H-1), 4.03 (dd, 1H, $J_{6,7}=1.8$ Hz, H-7), 3.79 (dd, 1H, $J_{1,2}=8.2$, $J_{2,3}=9.7$ Hz, H-2), 3.66 (dd, 1H, $J_{3,8}=3.2$, $J_{8,8'}=12.2$ Hz, H-8), 3.49 (dd, 1H, $J_{3,8'}=6.4$ Hz, H-8′), 3.42 (dd, 1H, $J_{1,7a}=7$, $J_{7,7a}=4.4$ Hz, H-7a), 3.05 (br d, 1H, H-5β), 2.88 (dd, 1H, $J_{5\alpha,6}=3.8$, $J_{5\alpha,5\beta}=12.1$ Hz, H-5α), and 2.71 (ddd, 1H, H-3). ^{13}C NMR (100 MHz): δ=80.09 (C-2), 79.25 (C-6), 75.52 (C-7), 74.37 (C-1), 72.97 (C-3), 71.65 (C-7a), 62.95 (C-8), and 60.55 (C-5). HRMS (LSIMS): *m/z*=228.0849 [M^++Na]; calcd for $C_8H_{15}NO_5Na$: 228.0848 (deviation −0.3 ppm).

4.1.10. (1*S*,2*R*,5*R*,6*R*,7*R*,7a*R*)-6,7-Dibenzyloxy-5-*tert*-butyldiphenylsilyloxymethyl-1,2-dihydroxypyrrolizidin-3-one (17). A solution of **8** (1.7 g, 2.12 mmol) in MeOH (20 mL) was stirred at rt with 10% Pd–C (170 mg) in an H_2 atmosphere for 3 h. TLC (EtAcO/hexane, 1:1) then showed the presence of a compound of lower mobility, presumably the *N*-deprotected pyrrolidine (**16**). The catalyst was filtered off, washed with MeOH and the combined filtrate and washings (50 mL) treated with 2 M MeONa (2 mL). After 2 h, TLC (EtAcO/hexane, 1:1) then revealed the presence of a faster-running product. The mixture was neutralized with aqueous 10% HCl, supported on silica gel and submitted to chromatography (Et_2O) to afford **17**. Yield: 1.14 g (85%); white foam; $[\alpha]_D^{26}$ −33 (*c*, 1). IR (KBr): 3386 (OH), 3069 and 3031 (aromatic), 1694 (C=O), 754 and 700 cm^{-1} (aromatic). ^1H NMR (400 MHz): δ=7.59–7.56 and 7.41–7.20 (2m, 20H, 4Ph), 4.68 and 4.48 (2d, 2H, J=11.9 Hz, CH_2Ph), 4.52 and 4.48 (2d, 2H, J=11.8 Hz, CH_2Ph), 4.36 (t, 1H, $J_{5,6}=J_{6,7}=4$ Hz, H-6), 4.33 (d, 1H, $J_{1,2}=8.2$ Hz, H-2), 4.08–4.04 (m, 2H, H-1,5), 4.01 (br s, 1H, HO), 3.88 (t, 1H, $J_{7,7a}=4.5$ Hz, H-7), 3.83 (dd, 1H, $J_{5,8}=5.3$, $J_{8,8'}=10.6$ Hz, H-8), 3.66 (dd, 1H, $J_{5,8'}=4.3$ Hz, H-8′), 3.57 (t, 1H, $J_{1,7a}=5.6$ Hz, H-7a), and 1.02 (s, 9H, CMe_3). ^{13}C NMR (100 MHz), *inter alia*: δ=172.24 (C-3), 86.79 (C-7), 84.69 (C-6), 80.55 (C-1), 78.16 (C-2), 72.01 and 71.88 ($2CH_2Ph$),

67.03 (C-7a), 62.22 (C-8), 60.73 (C-5), 26.95 (CMe_3), and 19.27 (CMe_3). HRMS (LSIMS): $m/z=660.2759$ [M^++Na]; calcd for $C_{38}H_{43}NO_6NaSi$: 660.2757 (deviation −0.2 ppm).

4.1.11. (1*R*,2*R*,3*R*,6*S*,7*S*,7a*R*)-1,2-Dibenzyloxy-3-*tert*-butyldiphenylsilyloxymethyl-6,7-dihydroxypyrrolizidine (18). To a stirred solution of **17** (1.14 g, 1.79 mmol) in anhydrous THF (20 mL) was added dropwise a $H_3B{:}SMe_2$ complex solution in the same solvent (10 M, 1.8 mL) under argon, and the mixture left at rt for 4 h. TLC (EtAcO/hexane, 3:1) then revealed the absence of **17** and the presence of a faster-running compound, presumably the borane–amine complex. MeOH (2 mL) was cautiously added and the reaction mixture was concentrated to a residue that was dissolved in MeOH (20 mL) and refluxed for 3 h, when the borane–amine complex was not observed by TLC. The reaction mixture was concentrated and the residue was supported on silica gel and subjected to chromatography (Et_2O) to give pure **18**. Yield: 0.99 g (89%); white foam; $[\alpha]_D^{26}$ −8.5, (*c*, 1). IR (KBr): 3369 (OH), 3069, 3031, 739 and 700 cm^{-1} (aromatic). ^1H NMR (400 MHz): $\delta=7.67$–7.62 and 7.40–7.20 (2m, 20H, 4Ph), 4.61 and 4.52 (2d, 2H, $J=11.7$ Hz, CH_2Ph), 4.58 and 4.54 (2d, 2H, $J=11.7$ Hz, CH_2Ph), 4.13–4.06 (m, 3H, H-2,6,7), 3.99 (t, 1H, $J_{1,2}=J_{1,7a}=4.6$ Hz, H-1), 3.70 (dd, 1H, $J_{3,8}=6.6$, $J_{8,8'}=10.2$ Hz, H-8), 3.64 (dd, 1H, $J_{3,8'}=6.5$ Hz, H-8′), 3.41 (dd, 1H, $J_{5\beta,6}=5.4$, $J_{5\alpha,5\beta}=11.2$ Hz, H-5β), 3.32 (t, 1H, $J_{7,7a}=4.6$ Hz, H-7a), 3.23 (q, 1H, $J_{2,3}=6.2$ Hz, H-3), 2.84 (dd, 1H, $J_{5\alpha,6}=5.3$ Hz, H-5α), and 1.05 (s, 9H, CMe_3). ^{13}C NMR (100 MHz), *inter alia*: $\delta=86.86$ (C-7), 85.45 (C-2), 81.50 (C-1), 79.02 (C-6), 74.74 (C-7a), 72.58 (C-3), 72.29 and 71.91 ($2CH_2Ph$), 65.82 (C-8), 60.66 (C-5), 26.96 (CMe_3), and 19.30 (CMe_3). HRMS (LSIMS): $m/z=646.2968$ [M^++Na]; calcd for $C_{38}H_{45}NO_5NaSi$: 646.2964 (deviation −0.5 ppm).

4.1.12. (1*R*,2*R*,3*R*,6*S*,7*S*,7a*R*)-1,2-Dibenzyloxy-6,7-dihydroxy-3-hydroxymethylpyrrolizidine (19). To a stirred solution of **18** (600 mg, 0.96 mmol) in THF (20 mL) was added TBAF·$3H_2O$ (550 mg, 1.74 mmol) and the reaction mixture refluxed for 3 h. TLC (Et_2O/MeOH, 5:1) then revealed a new compound of lower mobility. The mixture was supported on silica gel and chromatographed (Et_2O/MeOH, 5:1) to give pure **19**. Yield: 350 mg (95%); colourless oil; $[\alpha]_D^{23}$ −8 (*c*, 1, methanol). IR (neat): 3360 (OH), 3064, 3032, 738 and 698 cm^{-1} (aromatic). ^1H NMR (400 MHz, MeOH-d_4): $\delta=7.33$–7.20 (m, 10H, 2Ph), 4.66 and 4.59 (2d, 2H, $J=11.7$ Hz, CH_2Ph), 4.66 and 4.53 (2d, 2H, $J=11.6$ Hz, CH_2Ph), 4.20 (t, 1H, $J_{1,2}=J_{1,7a}=5.6$ Hz, H-1), 4.10 (q, 1H, $J_{5,6}=J_{5',6}=J_{6,7}=5.0$ Hz, H-6), 4.06 (t, 1H, $J_{7,7a}=4.8$ Hz, H-7), 3.98 (dd, 1H, $J_{2,3}=6.7$ Hz, H-2), 3.63 (dd, 1H, $J_{3,8}=4.5$, $J_{8,8'}=11.3$ Hz, H-8), 3.52 (dd, 1H, $J_{3,8'}=5.9$ Hz, H-8′), 3.33–3.29 (m, 2H, H-5,7a), 3.23 (br q, 1H, H-3), and 2.92 (dd, 1H, $J_{5,5'}=11.3$ Hz, H-5′). ^{13}C NMR (100 MHz), *inter alia*: $\delta=86.93$ (C-1), 85.17 (C-2), 81.19 (C-7), 79.08 (C-6), 75.39 (C-7a), 73.42 and 72.95 ($2CH_2Ph$), 72.57 (C-3), 63.04 (C-8), and 60.07 (C-5). HRMS (LSIMS): $m/z=386.1967$ [M^++H]; calcd for $C_{22}H_{28}NO_5$: 386.1967 (deviation +0.2 ppm).

4.1.13. (1*R*,2*R*,3*R*,6*S*,7*S*,7a*R*)-1,2,6,7-Tetrahydroxy-3-hydroxymethylpyrrolizidine [(+)-casuarine(1)]. Compound **19** (375 mg, 0.97 mmol) in methanol (15 mL) and concentrated HCl (three drops) was hydrogenated with 10% Pd–C (80 mg) at ambient pressure and rt overnight. TLC (ether/methanol, 5:1) then revealed the absence of the starting product. The catalyst was filtered off, washed with methanol and the combined filtrate and washings treated with Amberlite IRA-400 resin (OH^- form). Evaporation of the solvent afforded **1** slightly contaminated. Yield: 175 mg (93%).

Compound **1** (175 mg, 0.91 mmol) was acetylated in dry pyridine (3.6 mL) and acetic anhydride (4.2 mL) and DMAP (catalyst) at rt for 4 h. TLC (EtAcO/hexane, 3;2) then showed a faster running compound. The reaction mixture was supported on silica gel and chromathographed (EtAcO/hexane, 2:3) to afford pure **20**. Yield: 150 mg (41%); colourless oil; $[\alpha]_D^{23}$ +27.4 (*c*, 1). IR (neat): 1748 cm^{-1} (C=O, acetate). ^1H NMR (400 MHz): $\delta=$ 5.39 (t, 1H, $J_{1,2}=J_{1,7a}=6.6$ Hz, H-1), 5.27 (m, 1H, H-6), 5.26 (t, 1H, $J_{2,3}=7$ Hz, H-2), 5.18 (dt, 1H, $J_{6,7}=2.2$, $J_{7,7a}=$ 4.5 Hz, H-7), 4.10 (dd, 1H, $J_{3,8}=4.5$, $J_{8,8'}=11.4$ Hz, H-8), 4.00 (dd, 1H, $J_{3,8'}=6.1$ Hz, H-8′), 3.39 (dd, 1H, $J_{5,6}=4.6$, $J_{5,5'}=13.2$ Hz, H-5), 3.37 (m, 1H, H-7a), 3.27 (br q, 1H, H-3), 3.03 (br d, 1H, H-5′), 2.10, 2.064, 2.055 and 2.03 (4s, 15H, 5Ac). ^{13}C NMR (100 MHz): $\delta=170.76$, 170.55, 170.01, 169.93 and 169.82 (5 *C*OMe), 79.35 (C-6), 78.52 (C-7), 77.10 (C-1), 76.73 (C-2), 72.13 (C-7a), 66.70 (C-3), 65.11 (C-8), 57.47 (C-5), 21.13, 20.94 and 20.91 (5CO*Me*). HRMS (LSIMS): $m/z=438.1374$ [M^++Na]; calcd for $C_{18}H_{25}NO_{10}Na$: 438.1376 (deviation +0.5 ppm).

Zemplen deacetylation of **20** (142 mg, 0.35 mmol) in methanol (6 mL) with 2 M MeONa in methanol (two drops) afforded pure **1**, after column chromatography (Et_2O/MeOH/NH_4OH, 1:1:1). Yield: 70 mg (98%); white foam; $[\alpha]_D^{24}$ +10.6 (*c*, 1, water); [Lit.[6] $[\alpha]_D^{24}$ +16.9 (*c*, 0.8, water); Lit.[8] $[\alpha]_D^{27}$ +10.8 (*c*, 1.02, water)]. ^1H NMR (400 MHz, D_2O, pH 8): $\delta=4.02$–3.96 (m, 2H, H-6,7), 3.96 (t, 1H, $J_{1,2}=J_{1,7a}=8.1$ Hz, H-1), 3.58 (t, 1H, $J_{2,3}=8.2$ Hz, H-2), 3.57 (dd, 1H, H-8), 3.65 (dd, 1H, $J_{3,8'}=6.7$, $J_{8,8'}=11.7$ Hz, H-8′), 3.05 (dd, 1H, $J_{5,6}=4.3$, $J_{5,5'}=12.2$ Hz, H-5), 2.86–2.80 (m, 2H, H-3,7a), and 2.70 (dd, 1H, $J_{5',6}=3.6$ Hz, H-5′). ^{13}C NMR (100 MHz): $\delta=81.28$ (C-7), 80.28 (C-1), 79.91 (C-6), 79.15 (C-2), 74.59 (C-7a), 72.41 (C-3), 64.96 (C-8) and 60.46 (C-5). HRMS (LSIMS): $m/z=206.1029$ [M^++H]; calcd for $C_8H_{16}NO_5$: 206.1028 (deviation −0.4 ppm).

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Selective palladium-catalyzed amination of β-chloroacroleins by substituted anilines

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Abstract—β-Chloroacroleins can undergo a selective amination on their chloro position under palladium catalysis; in those conditions, no imine formation was observed. Their coupling with anilines carrying electron-donating or electron-withdrawing substituents proceeds in moderate to good yields and steric hindrance does not seem to be a limitation as *o*-substituted anilines react readily.

1. Introduction

Palladium-catalyzed arylation of amines has attracted great attention in the past few years since, Buchwald[1] and Hartwig[2] have independently reported their results in 1995. A wide range of aryl halides can be coupled with primary and secondary amines, anilines or amides under mild conditions with excellent functional group compatibility.[3] However, the palladium-catalyzed C–N bond forming reactions with vinyl halides have been scarcely studied.[4] Vinyl bromides have been used in the synthesis of *N*-vinylazoles[5] and in intramolecular amidation in the synthesis of carbapenem derivatives.[6] Vinyl triflates have also been engaged in palladium-catalyzed amination[7] and amidation.[8] Recently, Barluenga et al.[9] described the synthesis of enamines and imines by palladium-catalyzed amination of alkenyl bromides. Since 2004, they are also interested in the less reactive alkenyl chlorides.[10]

2. Results and discussion

β-Chloroacroleins are vinyl chlorides activated by the presence of an electron-withdrawing group. We have previously, subjected those compounds to Suzuki and Sonogashira cross-coupling reactions[11] and obtained good results under mild conditions.

β-Chloroacroleins are known to form imines when reacted with amines. Indeed, when compound **1** and 2,5-dimethoxyaniline **2** were refluxed during 4 h in isopropanol, compound **4** was isolated (Scheme 1). Its formation may involve imine formation followed by cyclodehydrochlorination of the intermediate **3**. Such a pathway has already been described by Prasad and Darbawar[12] in their synthesis of [1]benzopyrano[3,4-*h*]benzo[*b*]-1,6-naphtyridin-6-ones from 3-aminocoumarines and 2-chloro-3-formyl quinoline.

However, under palladium catalysis, a selective amination on the chloro position can be done: β-chloroacrolein **1** and 2,5-dimethoxyaniline **2** were stirred in presence of cesium carbonate (1.3 equiv), palladium acetate (3 mol%) and Binap (4 mol%) in toluene under argon. The reaction was followed by TLC and stopped when all β-chloroacrolein was consumed (3 h at 90 °C). After treatment, the arylamine **5** was obtained in 90% yield (Scheme 1). Although, several authors have pointed out that premixing the palladium source and ligand is a prerequisite for optimal reactions,[13] the order of addition of the different reagents does not seem to have an effect on cross-coupling yield in our case. On the contrary, the temperature of the reaction is important as a TLC after 3 h at 70 °C showed the presence of β-chloroacrolein.

A control experiment containing all of the reagents except for the palladium source and ligand was realised. After 3 h of reaction at 90 °C, TLC indicated that β-chloroacrolein still remained in the reaction media. The reaction was let under stirring overnight at 90 °C. After treatment, ^{1}H NMR data of the crude showed the formation of imine **3** and cyclized product **4** in a 3:1 ratio. This experiment clearly demonstrated that the catalyst was crucial to achieve any C–N bond formation.

Encouraged by this first result, we then applied those

Keywords: Palladium-catalyzed; Amination; Vinyl chlorides.
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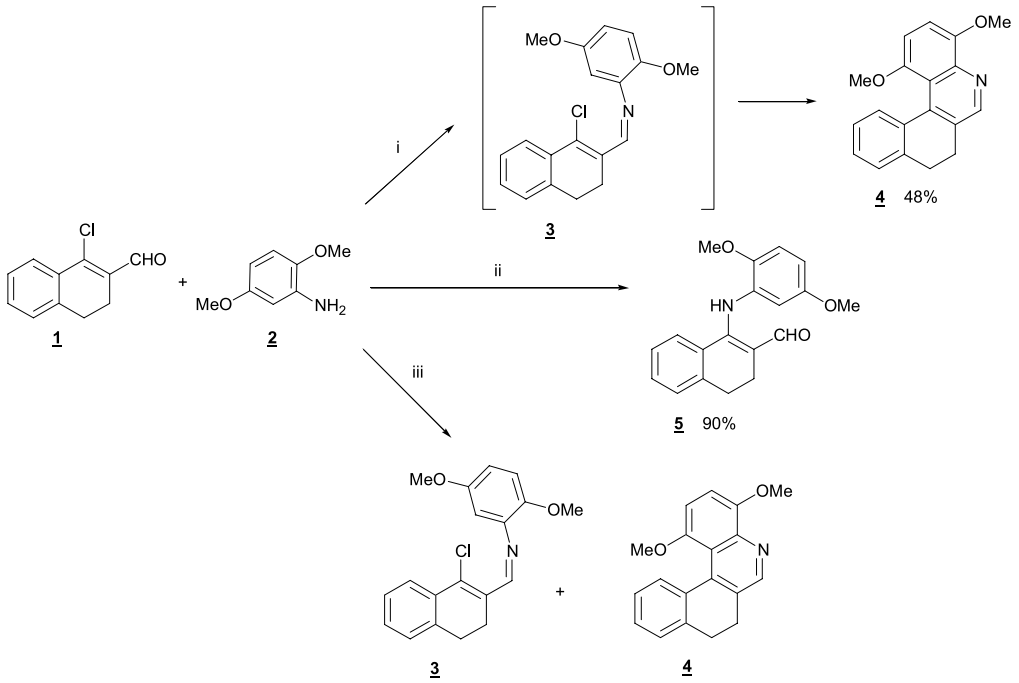
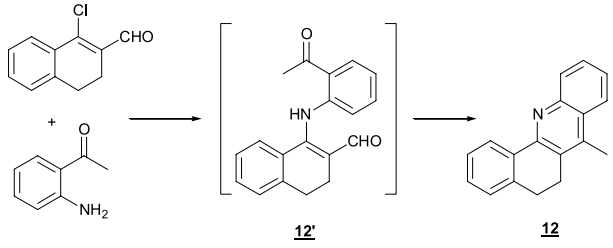


Scheme 1. (i) 1 equiv RCl, 5 equiv, $R'NH_2$, isopropanol, reflux, 4 h; (ii) 1 equiv RCl, 1 equiv $R'NH_2$, 3 mol% $Pd(OAc)_2$, 4 mol% BINAP, 1.3 equiv Cs_2CO_3, dry toluene, argon, 90 °C, 3 h; (iii) 1 equiv RCl, 1 equiv $R'NH_2$, 1.3 equiv Cs_2Co_3, dry toluene, argon, 90 °C, 20 h.

conditions (1 equiv amine, 1.2 equiv Cs_2CO_3, 3 mol% $Pd(OAc)_2$, 4 mol% BINAP, dry toluene, argon) to several β-chloroacroleins (Table 1, entries 1–5). We next, compared reactivity of electron-rich and electron-deficient anilines. Amines bearing electron-donating groups (such as methoxy or methyl groups) are known to be more reactive in palladium-catalyzed aminations. We obtained good results in short reaction times (entries 1–6). The presence of an electron-withdrawing group on the aniline (such as an acetyl, a chloro or a nitro group) decreased the yields and need to increase reaction times (entries 7–11). However, we were surprised to observe a very good yield and short reaction time for the cross-coupling of β-chloroacrolein **1** with 2-carbomethoxyaniline (entry 9).

The reaction of β-chloroacrolein **1** with 4′-aminoacetophenone gave the expected product **11** with a moderate yield (entry 7). The reaction with 2′-aminoacetophenone gave a more complex result. Indeed, following the reaction by TLC showed the disappearance of starting material and the formation of one product (that we supposed to be the coupled product **12**′). However, after treatment and purification, the ^1H NMR spectrum was not consistent with this structure: the signal of aldehyde was missing and the displacement of the methyl group did not correspond to an acetyl group. After further analysis (^{13}C NMR and HRMS), we established the structure **12** (Scheme 2). As a control experiment, this compound was also prepared by a Friedländer reaction between 2′-aminoacetophenone and α-tetralone under acidic conditions (acetic acid and sulfuric acid) in 60% yield.[14]

In conclusion, we have demonstrated that β-chloroacroleins can undergo a selective amination on their chloro position under palladium catalysis; in those conditions, no imine formation was observed. Moreover, the coupling of β-chloroacroleins with anilines carrying electron-donating or electron-withdrawing substituents proceeds in moderate to good yields and steric hindrance does not seem to be a limitation as *o*-substituted compounds react readily.



Scheme 2. 3 mol% $Pd(OAc)_2$, 4 mol%, Binap, 1.2 equiv Cs_2CO_3, dry toluene, argon, 90 °C.

3. Experimental

3.1. General

β-Chloroacroleins were prepared according to the literature procedure.[15] $Pd(OAc)_2$, Binap and Cs_2CO_3 were purchased from Aldrich. Melting points were determined on a Stuart SMP3 apparatus and are uncorrected. ^1H and ^{13}C spectra were recorded on a AC Bruker 250 MHz spectrometer in $CDCl_3$. HRMS mass spectra on compound **12** was carried in MALDI positive ion mode using a Bruker FTICR APEX III 7 T mass spectrometer equipped with the combi source. The matrix 2,5-dihydroxy benzoic acid (2,5-DHB) has been used for MALDI measurement. HRMS mass spectra on other compounds (**1**–**11** and **13**–**15**) were carried in positive ion mode using a Nicolet instrument FTMS 2000 (Finnigan FT/MS now named ThermoElectron, San Jose, CA, USA). The

Table 1. Palladium-catalyzed aminations of β-chloroacroleins

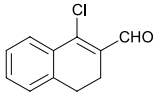
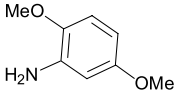
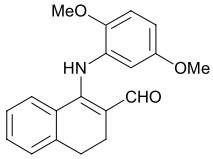
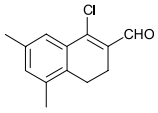
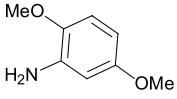
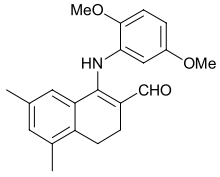
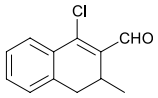
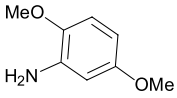
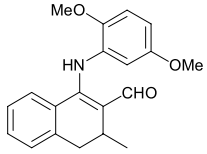
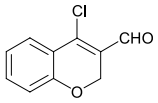
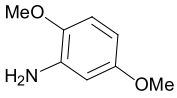
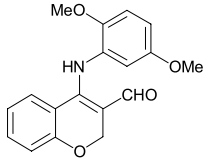
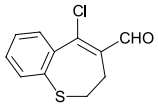
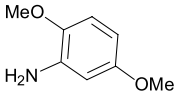
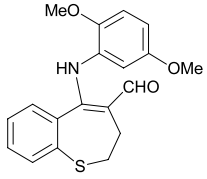
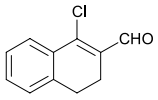
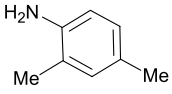
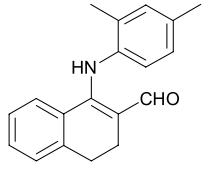
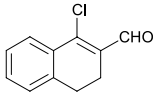
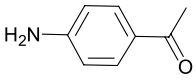
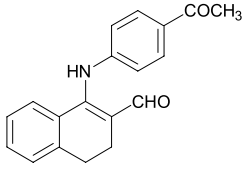
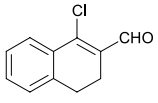
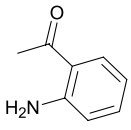
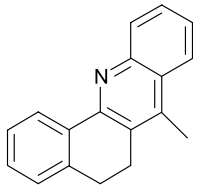
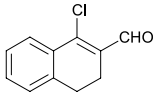
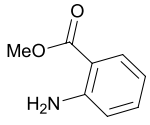
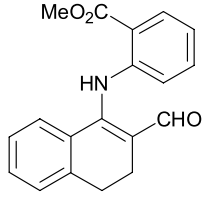
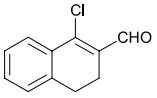
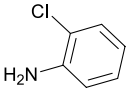
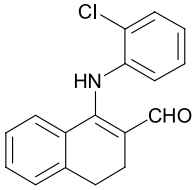
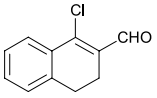
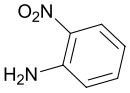
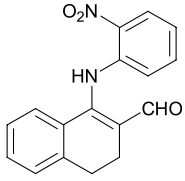
Entry	β-Chloroacrolein	Amine	Heating time (h)	Product	Yield
1			3		**5** 90
2			5		**6** 92
3			3		**7** 82
4			3		**8** 70
5			3		**9** 78
6			5		**10** 79
7			17		**11** 52
8			24		**12** 70
9			6		**13** 82

Table 1 (*continued*)

Entry	β-Chloroacrolein	Amine	Heating time (h)	Product	Yield
10			18		**14** 60
11			17		**15** 41

ionization step was performed using an excimer laser charged with an ArF mixture ($\lambda=193$ nm).

3.2. Reaction in absence of palladium source and ligand

A round-bottom flask was charged under argon with β-chloroacrolein **1** (1 mmol, 1 equiv), 2,5-dimethoxyaniline (1 mmol, 1 equiv), dry toluene (3 mL), and Cs_2CO_3 (1.2 mmol, 1.2 equiv). The reaction mixture was stirred and heated at 90 °C for 20 h (thin layer chromatography monitoring). After coming back to room temperature, the mixture was diluted with THF, filtered and concentrated under reduced pressure. A ^{1}H NMR of the crude showed the formation of imine **3** and cyclized product **4** in a 3:1 ratio. Compound **4** was isolated by column chromatography with 17% yield; compound **3** was destroyed by the purification. Compound **4** was also obtained by reaction of β-chloroacrolein **1** (1 mmol, 1 equiv) with 2,5-dimethoxyaniline (5 mmol, 5 equiv) refluxing in 20 mL isopropanol. The product precipitates in the reaction media.

3.2.1. (1-Chloro-3,4-dihydro-naphthalen-2-ylmethylene)-(2,5-dimethoxy-phenyl)-amine (3). ^{1}H NMR ($CDCl_3$): 2.95–2.99 (m, 4H); 3.82 (s, 3H); 3.85 (s, 3H); 6.44 (d, 1H, $J=3$ Hz); 6.71–6.75 (m, 1H); 6.86–6.90 (m, 1H); 7.23–7.32 (m, 3H); 7.78–7.81 (m, 1H); 8.91 (s, 1H).

3.2.2. 1,4-Dimethoxy-7,8-dihydro-benzo[k]phenanthridine (4). Red solid. Mp: 162 °C. ^{1}H NMR ($CDCl_3$): 2.98–3.04 (m, 2H); 3.12–3.18 (m, 2H); 3.98 (s, 3H); 4.09 (s, 3H); 6.74 (d, 1H, $J=8.5$ Hz); 6.92 (d, 1H, $J=8.5$ Hz); 7.25–7.27 (m, 1H); 7.34–7.43 (m, 2H); 8.37 (s, 1H); 8.65 (dd, 1H, $J=7.3$, 1.6 Hz). ^{13}C NMR ($CDCl_3$): 28.30 (CH_2); 28.78 (CH_2); 55.71 (CH_3); 56.39 (CH_3); 103.44 (CH); 106.84 (CH); 120.97 (C); 126.52 (CH); 127.19 (CH); 127.72 (CH); 129.00 (CH); 129.64 (CH); 130.22 (C); 134.35 (C); 139.21 (C); 139.49 (C); 148.43 (C); 149.51 (C); 152.44 (C).

3.3. General procedure for C–N cross coupling with anilines

A round-bottom flask was charged under argon with β-chloroacrolein (1 mmol, 1 equiv), amine (1 mmol, 1 equiv), dry toluene (3 mL), Cs_2CO_3 (1.2 mmol, 1.2 equiv), $Pd(OAc)_2$ (3 mol%) and *rac*BINAP (4 mol %). The reaction mixture was stirred and heated at 90 °C for several hours (thin layer chromatography monitoring). After coming back to room temperature, the mixture was diluted with THF, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

3.3.1. 1-(2,5-Dimethoxy-phenylamino)-3,4-dihydro-naphthalene-2-carbaldehyde (5). Orange oil purified by column chromatography on silica gel using CH_2Cl_2 as eluent. ^{1}H NMR ($CDCl_3$): 2.53 (t, 2H, $J=8.2$ Hz) and 2.83 (t, 2H, $J=8$Hz); 3.55 (s, 3H); 3.78 (s, 3H); 6.25 (d, 1H, $J=2.8$ Hz); 6.48 (dd, 1H, $J=3$, 9 Hz); 6.78 (d, 1H, $J=9$ Hz); 6.99–7.06 (m, 1H); 7.24–7.29 (m, 3H); 9.51 (s, CHO); 11.13 (br s, NH). ^{13}C NMR ($CDCl_3$): 23.23 (CH_2); 29.74 (CH_2); 55.61 (CH_3); 56.30 (CH_3); 108.11 (CH); 109.16 (CH); 112.01 (C); 112.07 (CH); 125.73 (CH); 127.82 (CH); 127.95 (CH); 129.37 (C); 130.15 (CH); 131.65 (C); 140.15 (C); 145.09 (C); 152.1 (C); 153.36 (C); 190 (CHO) HRMS calcd for $[M-H^+]$ $C_{19}H_{18}NO_3$ 308.1287, found 308.1284.

3.3.2. 1-(2,5-Dimethoxy-phenylamino)-5,7-dimethyl-3,4-dihydro-naphthalene-2-carbaldehyde (6). Brown oil purified by column chromatography on silica gel using CH_2Cl_2 as eluent. ^{1}H NMR ($CDCl_3$): 2.09 (s, 3H); 2.32 (s, 3H); 2.46–2.51 (m, 2H); 2.71–2.76 (m, 2H); 3.54 (s, 3H); 3.82 (s, 3H); 6.20 (d, 1H, $J=2.9$ Hz); 6.47 (dd, 1H, $J=3$, 8.9 Hz); 6.78 (d, 1H, $J=9$ Hz); 6.99 (m, 2H); 9.53 (s, CHO); 10.85 (br s, NH). ^{13}C NMR ($CDCl_3$): 19.47 (CH_3); 20.81 (CH_3); 22.81 (CH_2); 24.80 (CH_2); 55.58 (OCH_3); 56.23 (OCH_3); 107.48 (CH); 108.37 (CH); 111.78 (CH); 112.59 (C); 126.16 (CH); 129.05 (C); 132.08 (C); 133.12 (CH); 134.24 (C); 134.89 (C); 135.51 (C); 144.63 (C); 152.40 (C); 153.22 (C); 189.66 (CHO) HRMS calcd for $[MH^+]$ $C_{21}H_{24}NO_3$ 338.1757, found 338.1755.

3.3.3. 1-(2,5-Dimethoxy-phenylamino)-3-methyl-3,4-dihydro-naphthalene-2-carbaldehyde (7). Orange oil purified by column chromatography on silica gel using CH_2Cl_2 as eluent. ^{1}H NMR ($CDCl_3$): 0.91 (d, 3H, $J=6.9$ Hz); 2.68 (dd, 1H, $J=2.5$, 14.7 Hz); 2.95–3.05 (m, 1H); 3.14–3.23 (m, 1H); 3.54 (s, 3H); 3.79 (s, 3H); 6.25 (d, 1H, $J=2.9$ Hz); 6.50 (dd, 1H, $J=3$, 8.9 Hz); 6.78 (d, 1H, $J=$

9 Hz); 6.98–7.05 (m, 1H); 7.23–7.29 (m, 3H); 9.50 (s, CHO); 11.13 (br s, NH). ^{13}C NMR ($CDCl_3$): 19.21 (CH_3); 28.16 (CH); 36.54 (CH_2); 55.55 (CH_3); 56.24 (CH_3); 108.0 (CH); 109.28 (CH); 111.98 (CH); 116.79 (C); 125.72 (CH); 127.77 (CH); 128.34 (C); 129.13 (CH); 130.22 (CH); 131.73 (C); 137.82 (C); 145.08 (C); 151.27 (C); 153.3 (C); 190.5 (CHO) HRMS calcd for [M−H$^+$] $C_{20}H_{20}NO_3$ 322.1444, found 322.1451.

3.3.4. 4-(2,5-Dimethoxy-phenylamino)-2*H*-chromene-3-carbaldehyde (8). Brown oil purified by column chromatography on silica gel using CH_2Cl_2 as eluent. ^{1}H NMR ($CDCl_3$): 3.56 (s, 3H); 3.71 (s, 3H); 4.81 (s, 2H); 6.38 (d, 1H, J=2.6 Hz); 6.61 (dd, 1H, J=2.9, 9 Hz); 6.71–6.80 (m, 2H); 7.02 (d, 1H, J=8.3 Hz); 7.17 (d, 1H, J=8 Hz); 7.24–7.29 (m, 1H); 9.34 (s, CHO); 11.05 (br s, NH). ^{13}C NMR ($CDCl_3$): 55.58 (CH_3); 56.09 (CH_3); 66.17 (CH_2); 106.02 (C); 110.07 (CH); 110.60 (CH); 112.40 (CH); 117.97 (CH); 118.01 (C); 120.64 (CH); 128.02 (CH); 129.85 (C); 132.74 (CH); 146.02 (C); 149.83 (C); 153.28 (C); 158.38 (C); 185.69 (CHO) HRMS calcd for [M−H$^+$] $C_{18}H_{16}NO_4$ 310.1079, found 310.1074.

3.3.5. 5-(2,5-Dimethoxy-phenylamino)-2,3-dihydro-benzo[*b*]thiepine-4-carbaldehyde (9). Yellow solid purified by column chromatography on silica gel using CH_2Cl_2 as eluent. Mp: 145 °C. ^{1}H NMR ($CDCl_3$): 3.34 (br s, 4H, 2CH_2); 3.81 (s, 6H, 2CH_3); 5.91 (d, 1H, J=3 Hz); 6.45 (dd, 1H, J=3.9 Hz); 6.72 (d, 1H, J=8.9 Hz); 7.11 (dd, 1H, J=1.6, 7.5 Hz); 7.16–7.22 (m, 1H); 7.25–7.31 (m, 1H); 7.65 (dd, 1H, J=1.4, 7.7 Hz); 9.29 (s, CHO); 12.31 (br s, NH). ^{13}C NMR ($CDCl_3$): 25.92 (CH_2); 42.84 (CH_2); 55.29 (CH_3); 56.15 (CH_3); 108.95 (CH); 109.39 (C); 109.87 (CH); 111.65 (CH); 128.54 (CH); 129.01 (C); 129.60 (CH); 129.94 (CH); 132.59 (C); 135.57 (CH); 140.50 (C); 145.37 (C); 152.92 (C); 157.16 (C); 188.73 (CHO) HRMS calcd for [MH$^+$] $C_{19}H_{20}NO_3S$ 342.1164, found 342.1174.

3.3.6. 1-(2,4-Dimethyl-phenylamino)-3,4-dihydro-naphthalene-2-carbaldehyde (10). Orange oil purified by column chromatography on silica gel using CH_2Cl_2 as eluent. ^{1}H NMR ($CDCl_3$): 2.26 (s, 3H); 2.34 (s, 3H); 2.50–2.55 (m, 2H); 2.83–2.88 (m, 2H); 6.57 (d, 1H, J=8.1 Hz); 6.76 (d, 1H, J=8.1 Hz); 6.92–6.97 (m, 1H); 7.02–7.05 (m, 2H); 7.22–7.24 (m, 2H); 9.40 (s, CHO); 11.90 (br s, NH). ^{13}C NMR ($CDCl_3$): 18.08 (CH_3); 20.76 (CH_3); 23.49 (CH_2); 30.20 (CH_2); 108.86 (C); 124.61 (CH); 125.60 (CH); 126.76 (CH); 127.95 (CH); 128.34 (CH); 129.14 (C); 129.99 (CH); 130.80 (C); 131.39 (CH); 134.23 (C); 137.32 (C); 140.67 (C); 154.18 (C); 189.25 (CHO) HRMS calcd for [MH$^+$] $C_{19}H_{20}NO$ 278.1545, found 278.1553.

3.3.7. 1-(4-Acetyl-phenylamino)-3,4-dihydro-naphthalene-2-carbaldehyde (11). Red oil purified by column chromatography on silica gel using CH_2Cl_2 as eluent. ^{1}H NMR ($CDCl_3$): 2.47 (s, 3H); 2.49–2.51 (m, 2H); 2.80–2.83 (m, 2H); 6.82 (d, 2H, J=8.6 Hz); 6.98–6.99 (m, 1H); 7.16 (d, 1H, J=7.7 Hz); 7.23–7.25 (m, 2H); 7.73 (d, 2H, J=8.6 Hz); 9.50 (s, 1H, CHO); 11.10 (br s, NH). ^{13}C NMR ($CDCl_3$): 22.39 (CH_2); 25.67 (CH_3); 28.69 (CH_2); 114.85 (C); 119.73 (CH); 125.70 (CH); 127.60 (CH); 127.92 (CH); 128.39 (C); 128.90 (CH); 129.96 (CH); 130.87 (C); 139.52 (C); 146.11 (C); 150.10 (C); 190.83 (CHO); 196.33 (C=O) HRMS calcd for [M−H$^+$] $C_{19}H_{16}NO_2$ 290.1186, found 290.1164.

3.3.8. 7-Methyl-5,6-dihydro-benzo[*c*]acridine (12). Yellow solid purified by column chromatography on silica gel using CH_2Cl_2 as eluent. Mp: 101 °C. ^{1}H NMR ($CDCl_3$): 2.69 (s, 3H); 2.98–3.04 (m, 2H); 3.12–3.18 (m, 2H); 7.29–7.44 (m, 3H); 7.48–7.55 (m, 1H); 7.62–7.69 (m, 1H); 8.00 (d, 1H, J=8.5 Hz); 8.14 (d, 1H, J=8.1 Hz); 8.57 (dd, 1H, J=7.3, 1.7 Hz). ^{13}C NMR ($CDCl_3$): 13.94 (CH_3); 25.36 (CH_2); 28.15 (CH_2); 123.57 (CH); 125.82 (CH); 126.43 (CH); 127.22 (CH); 127.48 (CH); 127.69 (C); 128.25 (CH); 128.40 (C); 129.45 (CH); 130.10 (CH); 135.09 (C); 139.06 (C); 139.82 (C); 146.69 (C); 152.59 (C) HRMS (MALDI) calcd for [MH$^+$] $C_{18}H_{16}N$ 246.12773, found 246.12774.

3.3.9. 2-(2-Formyl-3,4-dihydro-naphthalen-1-ylamino)-benzoic acid methyl ester (13). Brown oil purified by column chromatography on silica gel using CH_2Cl_2 as eluent. ^{1}H NMR ($CDCl_3$): 2.64 (m, 2H); 2.88 (m, 2H); 3.97 (s, 3H); 6.57 (d, 1H, J=8.4 Hz); 6.81 (ddd, 1H, J=1, 7.4, 7.9 Hz); 7.09–7.22 (m, 2H); 7.26–7.33 (m, 3H); 7.98 (dd, 1H, J=1.6, 8 Hz); 10.03 (s, CHO); 10.43 (br s, NH). ^{13}C NMR ($CDCl_3$): 20.90 (CH_2); 28.04 (CH_2); 52.03 (CH_3); 113.78 (C); 117.73 (CH); 118.95 (CH); 125.02 (C); 126.42 (CH); 126.49 (CH); 128.17 (CH); 130.46 (CH); 130.69 (C); 131.34 (CH); 133.68 (CH); 140.00 (C); 147.13 (C); 148.77 (C); 168.49 (CO_2); 190.51 (CHO) HRMS calcd for [MH$^+$] $C_{19}H_{18}NO_3$ 308.1287, found 308.1270.

3.3.10. 1-(2-Chloro-phenylamino)-3,4-dihydro-naphthalene-2-carbaldehyde (14). Brown solid purified by column chromatography on silica gel using CH_2Cl_2:C_6H_{12} (3:2) to (1:0) as eluent. Mp=101 °C. ^{1}H NMR ($CDCl_3$): 2.54–2.60 (m, 2H); 2.84–2.90 (m, 2H); 6.62–6.65 (m, 1H); 6.93–7.03 (m, 3H); 7.11 (d, 1H, J=7.7 Hz); 7.25–7.27 (m, 2H); 7.38–7.42 (m, 1H); 9.56 (s, CHO); 11.20 (br s, NH). ^{13}C NMR ($CDCl_3$): 23.16 (CH_2); 29.53 (CH_2); 113.13 (C); 123.93 (CH); 124.04 (CH); 125.98 (CH); 126.01 (C); 126.70 (CH); 128.00 (CH); 128.11 (CH); 128.98 (C); 129.87 (CH); 130.31 (CH); 139.05 (C); 140.14 (C); 151.28 (C); 190.80 (CHO) HRMS calcd for [MH$^+$] $C_{17}H_{15}ClNO$ 284.0843 and 286.0813, found 284.0849 and 286.0803.

3.3.11. 1-(2-Nitro-phenylamino)-3,4-dihydro-naphthalene-2-carbaldehyde (15). Brown oil purified by column chromatography on silica gel using CH_2Cl_2 as eluent. ^{1}H NMR ($CDCl_3$): 2.68–2.71 (m, 2H); 2.93 (t, 2H, J=7.6 Hz); 6.68 (d, 1H, J=8.5 Hz); 6.89 (dd, 1H, J=8, 7.7 Hz); 7.12 (dd, 1H, J=7.2, 6 Hz); 7.22–7.33 (m, 4H); 8.21 (dd, 1H, J=8.4, 1.5 Hz); 10.02 (s, CHO); 10.29 (br s, NH). ^{13}C NMR ($CDCl_3$): 21.10 (CH_2); 27.75 (CH_2); 119.47 (CH); 119.50 (CH); 125.92 (CH); 126.32 (CH); 126.67 (CH); 126.76 (C); 128.40 (CH); 128.74 (C); 130.90 (CH); 135.03 (C); 135.10 (CH); 139.64 (C); 141.53 (C); 146.89 (C); 190.51 (CHO) HRMS calcd for [MH$^+$] $C_{17}H_{15}N_2O_3$ 295.1083, found 295.1085.

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Stereoselective synthesis of (2*R*,3*S*,4*S*)-3-hydroxy-4-methyl-2-tetradecyl-4-butanolide starting from 2,5-anhydro-D-mannitol

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Abstract—A novel approach to natural β-hydroxy-γ-lactone **2** from 2,5-anhydro-D-mannitol (**1**) is described. The key reactions in this synthesis include stereoselective methylation of aldehyde **3** with lithium dimethylcuprate, an intramolecular radical cyclization of seleno carbonate **11** and an intermolecular cross-metathesis of 3-allyl-4-hydroxy-γ-lactone **16** with 1-tridecene.

1. Introduction

Carbohydrates and their related compounds have been well recognized as a chiral pool for the syntheses of optical active natural products.[1] 2,5-Anhydro-D-mannitol (**1**),[2] however, has not been employed as a starting material for such syntheses[†] (Fig. 1). One of the reasons seems to stem from the difficulties of desymmetrization of **1**. For example, mono acylation or alkylation of **1** under restricted conditions is reported to result in a mixture of di- and mono protected mannitol derivatives along with **1**.[3] In the course of our synthetic studies on mucocin, we have developed a highly efficient method for desymmetrization of **1**.[4] As part of our continuing studies in this field, we describe herein the stereocontrolled synthesis of (2*R*,3*S*,4*S*)-3-hydroxy-4-methyl-2-tetradecyl-4-butanolide (**2**) starting from **1**. The lactone **2** was isolated from the methanol extract of fruits of *Trichila claussenii* in admixture with its 7′-dehydro form.[5] Its biological activities, which remain unclear, are of interest in connection with annonaceous acetogenins having prominent biological properties such as cytotoxity and antitumor activity.[6] Structurally, the butanolide **2** has three *cis*-substituents on the γ-lactone ring, and such sterically congested compounds are prone to elimination of the hydroxyl group during synthesis. Therefore, several synthetic methods to overcome such a problem have been devised, and total syntheses have been reported.[7]

2. Results and discussion

Synthesis of **2** began from the preparation of **1**. Although **1** had been prepared from D-glucosamine,[10] we newly found that **1** was also obtainable from a readily available polysaccharide, chitosan. Thus, chitosan was treated with sodium nitrite in aqueous acetic acid and subsequently reduced with sodium borohydride to give **1** in 67% yield (Scheme 1). The compound **1** was transformed into aldehyde **3** in good overall yield according to the procedure previously reported.[4] Stereoselective methylation[11] of **3** was accomplished by the action of lithium dimethylcuprate in

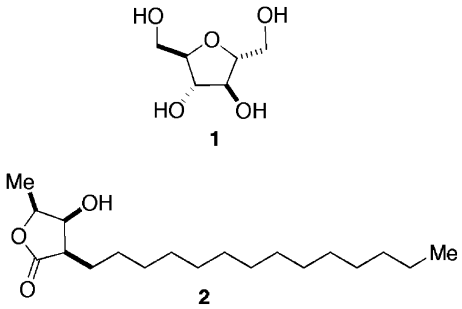

Figure 1.

Keywords: 2,5-Anhydro-D-mannitol; Intramolecular radical cyclization; Intermolecular cross-metathesis.
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† Because of its unique C_2-symmetrical structure, **1** served as a chiral ligand of catalysts for asymmetric hydrogenation,[8] and a central core of chiral dendrimers.[9]

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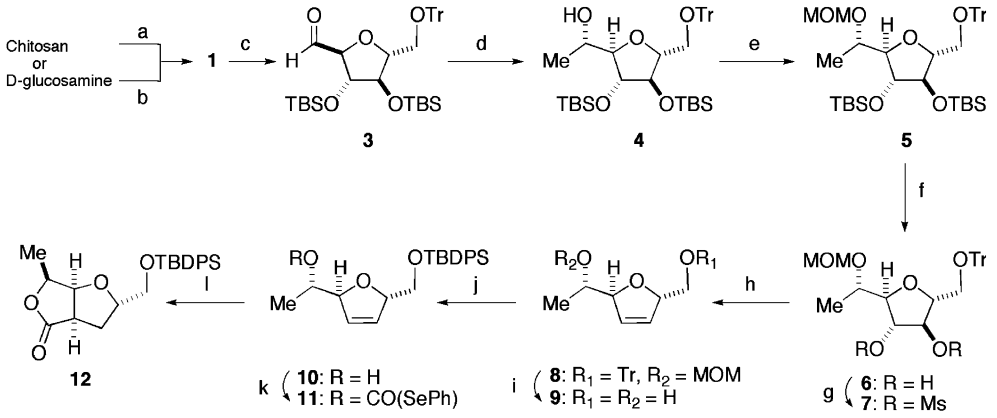
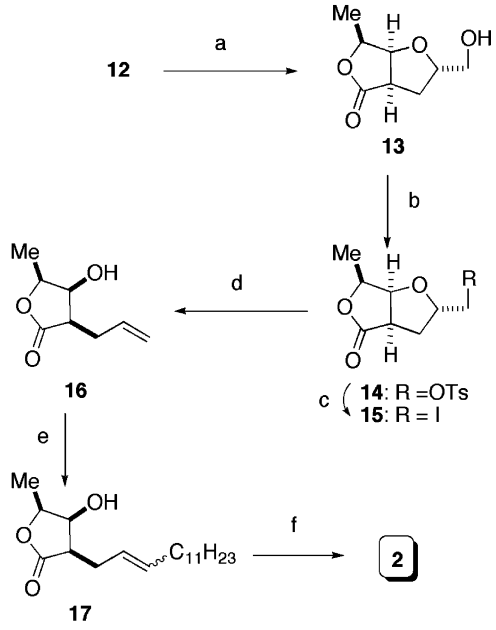


Scheme 1. (a) $NaNO_2$, 5% aqueous AcOH, 0 °C, and $NaBH_4$, MeOH, 67%; (b) Ref.10; (c) Ref. 4; (d) Me_2CuLi, Et_2O, −78 °C, 70% (>92% de); (e) MOMCl, *i*-Pr_2NEt, CH_2Cl_2, rt,; (f) TBAF, THF, rt, 83% (two steps from **4**); (g) MsCl, Et_3N, CH_2Cl_2, rt, 74%; (h) Zn, NaI, DMF, 140 °C, 89%; (i) 10%HCl–MeOH, CH_2Cl_2, rt, 97%; (j) TBDPSCl, imidazole, DMF, rt, 81%; (k) triphosgene, pyridine, CH_2Cl_2, 0 °C∼rt and then PhSeH, Et_3N, 0 °C∼rt, 95%; (l) Bu_3SnH, AIBN, toluene, 100 °C, 93%.

ether at −78 °C to give **4** in high selectivity (>92% de, by ^{1}H NMR analyses) while reaction with methylmagnesium iodide–zinc chloride in dichloromethane–ether decreased both yields and selectivities. The newly created stereochemistry was determined by the modified Mosher's method[12] of the corresponding MTPA esters. Furthermore, this result was also confirmed by the chemical conversion of **4** into the final product **2**. The stereoselectivity would be explained by the formation of cyclic chelate[13] involving the aldehyde carbonyl and the ring oxygen. The free hydroxyl group in **4** was temporarily protected as methoxymethyl (MOM) ether with MOMCl and *N*,*N*-diisopropylethylamine, and the resulting compound **5** was treated with tetrabutylammonium fluoride, affording diol **6** in 83% yield from **4**. For deoxygenation of the tetrahydrofuran ring, **6** was mesylated to give dimesylate **7** in 74% yield. Upon treatment with zinc powder–sodium iodide,[14] **7** led to olefin **8** in 89% yield. The compound **8** reacted with hydrogen chloride in methanol–dichloromethane to provide diol **9**, which was silylated with *tert*-butylchlorodiphenylsilane to give alcohol **10** in 79% yield (two steps). Successive treatment of **10** with triphosgene[15] and benzeneselenol[16] in a one-pot manner afforded seleno carbonate **11** in 95% yield. Radical cyclization of **11** with tributyltin hydride proceeded nicely to give γ-lactone **12** as a single isomer in 93% yield. This complete stereoselection reflects the stereochemical requirement of a 2,7-dioxabicyclo[3.3.0] octane ring system.

Having completed the construction of the γ-lactone ring, we next turned to the final C–C bond formation (Scheme 2). Prior to the elaboration, the silyl group in **12** was removed to afford alcohol **13** in 89% yield. As direct iodination of **13** with iodine, triphenylphosphine, and imidazole resulted in a low yield (∼50%) of iodide **15**, the alcohol **13** was initially transformed into the corresponding tosylate **14** with *p*-TsCl-triethylamine in the presence of *N*,*N*-dimethylaminopyridine, and then **15** (sodium iodide, acetone) in high yield. Zinc-mediated elimination reaction of **15** furnished olefin **16** in 93% yield from **14**. Intermolecular cross-metathesis[17] of **16** with 1-tridecene was effected by treatment with a catalytic amount of Grubbs catalyst 1st generation in dichloromethane at 40 °C to give γ-lactone **17** (*E*/*Z*=ca.



Scheme 2. (a) TBAF, THF, rt, 89%; (b) *p*-TsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C∼rt, 94%; (c) NaI, acetone, 55 °C; (d) Zn, aqueous THF, 65 °C, 93% (two steps form **14**); (e) 1-tridecene, Grubbs catalyst 1st generation, CH_2Cl_2, 40 °C, 45%; (f) $(Ph_3P)_3RhCl$, H_2, benzene, rt, 95%.

7/1, by ^{1}H NMR analysis) in 45% yield (52% yield based on **16** consumed). The production of dimers derived from **16** was traced judging by TLC analysis. Unexpectedly, the use of Grubbs catalyst 2nd generation gave unsatisfactory results arising from the yields (20–25%).‡ Finally, **17** underwent hydrogenation with Wilkinson's catalyst to give the γ-lactone **2** in 95% yield. The spectroscopic and physical properties of **2** were consistent with those of **2** previously reported.[5,7]

In summary, we succeeded in the stereoselective synthesis of **2** employing 2,5-anhydro-D-mannitol (**1**) as a starting

‡ A considerable amount of a β-hydroxy lactone carrying a 1′-tridecenyl group was isolated as a major side product. The compound was estimated to be produced from an isomerization of the double bond in **16** followed by the cross-metathesis with 1-tridecene.

material. This study also shows one example of utilization of a polysaccharide for fine chemicals. Now, bioassay of **2** and further application of **1** to natural product syntheses are underway.

3. Experimental

3.1. General procedures

All reactions were carried out under an argon atmosphere, unless otherwise noted. Melting points were determined using a Yanaco MP-500 apparatus and are uncorrected. Optical rotations were measured with a JASCO DIP-370 polarimeter. IR spectra were recorded with a JASCO VALOR-III spectrophotometer. ^{1}H NMR spectra were recorded at 270 or 400 MHz with JEOL EX-270 or JNM-α 400 spectrometers, using tetramethylsilane as the internal standard. Column chromatography was performed on Kanto silica gel 60N (spherical, neutral; 40–100 μm). Merck precoated silica gel 60 F_{254} plates, 0.25 mm thickness, was used for analytical thin-layer chromatography. The solvent extracts were dried with magnesium sulfate, and the solutions were evaporated under diminished pressure at 40–42 °C.

3.1.1. 2,5-Anhydro-D-mannitol (1). To an ice-cold solution of chitosan (3.22 g, 0.02 mol of GlcNAc unit) in 5% aqueous acetic acid (300 ml) was added sodium nitrite (5.52 g, 0.08 mol) in several portions, and the mixture was stirred at 0 °C for 6 h. Nitrogen gas was bubbled through the mixture for 15 min. The resulting mixture was evaporated and methanol (50 ml) was added to the residue, and the insoluble solid was filtered off. Sodium borohydride (0.76 g, 0.02 mol) was added to the filtrate and the mixture was stirred at 0 °C for 5 h. After treatment with Dowex 50W X4 (H^+ form), the mixture was evaporated and co-evaporated with methanol several times. Methanol was added to the residue and the solution was filtered through a Celite pad. The filtrate was concentrated to ca. 20 ml and kept in a refrigerator. The crystals were filtered and dried to give **1** (2.2 g, 67%); mp 100–102 °C (lit.[10]; mp 101–101.5 °C).

3.1.2. (1*S*,2′*R*,3′*R*,4′*R*,5′*R*)-1-[3′,4′-Bis(*tert*-butyldimethylsilanyloxy)-5′-trityloxymethyltetrahydrofuran-2′-yl]ethanol (4). To a stirred suspension of CuI (302 mg, 1.58 mmol) in ether (3.0 ml) was added dropwise a 1.6 M solution of methyllithium (2.7 ml, 3.16 mmol) in ether at −78 °C, and the mixture was stirred at the same temperature for 30 min. A solution of **3** (251 mg, 0.4 mmol) in ether (1.0 ml) was added dropwise at −78 °C, and the resulting mixture was stirred at −78–−30 °C for 1 h. After addition of saturated aqueous NH_4Cl, the resulting mixture was allowed to warm to rt with stirring, and extracted with ether. The extracts were washed with water, brine, dried, and concentrated. The residue was chromatographed on silica gel (*n*-hexane/EtOAc=20:1) to give a 24:1 mixture of **4** and its diastereomer (181 mg, 70%) as a colorless liquid. The major isomer **4** was separated by chromatography on silica gel (*n*-hexane/EtOAc =15:1). **4**; $[\alpha]_D^{24}$ +5.6 (*c* 1.06, $CHCl_3$); IR (neat) 3450, 3060, 2930, 1258, 1089, 1069, 835, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.44 (m, 6H), 7.28–7.21 (m, 9H), 4.19 (t, *J*=6.5 Hz, 1H), 4.07 (br s, 1H), 3.94 (br s, 1H), 3.90 (m, 1H), 3.68 (dd, *J*=5.1, 1.7 Hz, 1H), 3.38 (dd, *J*=9.4, 6.7 Hz, 1H), 3.08 (dd, *J*=9.4, 6.7 Hz, 1H), 3.01 (d, *J*=3.4 Hz, 1H), 1.23 (d, *J*=6.3 Hz, 3H), 0.89 (s, 9H), 0.73 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H), −0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 128.6, 127.6, 126.8, 91.5, 86.7, 86.6, 80.8, 80.6, 67.2, 64.2, 25.8, 25.7, 19.8, 18.0, 17.8, −4.5 (2C), −4.6, −4.7; HRMS calcd for $C_{38}H_{56}O_5Si_2Na$ $[M+Na]^+$671.3564, found 671.3563. Anal. Found: C, 70.24; H, 8.75. Calcd for $C_{38}H_{56}O_5Si_2$: C, 70.32; H, 8.70.

3.1.3. (1′*S*,2*R*,3*R*,4*R*,5*R*)-3,4-Bis(*tert*-butyldimethylsilanyloxy)-2-(1′-methoxymethoxyethyl)-5-trityloxymethyltetrahydrofuran (5). To a stirred solution of **4** (371 mg, 0.57 mmol) in CH_2Cl_2 (5.0 ml) was added chloromethyl methyl ether (0.22 ml, 2.89 mmol) at 0 °C. The mixture was stirred at 0 °C∼rt for two days, and then poured into ice-water, extracted with ether. The extracts were washed successively with water, cold aqueous HCl, water, saturated aqueous $NaHCO_3$, water, brine, dried, and concentrated to give **5** (384 mg), which was employed to the next step without further purification. An analytical sample was prepared by preparative TLC {*n*-hexane/EtOAc (5:1)}. **5**; $[\alpha]_D^{24}$ −3.5 (*c* 0.95, $CHCl_3$); IR (neat) 3060, 2954, 2930, 1252, 1115, 1090, 1035, 835, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.42 (m, 6H), 7.26–7.24 (m, 9H), 4.73, 4.70 (each d, *J*=6.8 Hz, 2H), 4.11 (t, *J*=6.7 Hz, 1H), 4.09 (br s, 1H), 3.96 (br s, 1H), 3.92 (dt, *J*=10.0, 6.5 Hz, 1H), 3.76 (dd, *J*=7.0, 2.2 Hz, 1H), 3.38 (s, 3H), 3.30 (dd, *J*=9.4, 6.1 Hz, 1H), 3.13 (dd, *J*=9.4, 6.7 Hz, 1H), 1.19 (d, *J*=6.3 Hz, 3H), 0.87 (s, 9H), 0.74 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H), 0.00 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 128.6, 127.6, 126.8, 95.7, 90.2, 86.7, 86.6, 80.9, 80.5, 72.5, 64.2, 55.3, 25.8, 25.7, 17.9, 17.8, 17.3, −4.3, −4.4, −4.6 (2C); HRMS calcd for $C_{40}H_{60}O_6Si_2Na$ $[M+Na]^+$715.3826, found 715.3843.

3.1.4. (1′*S*,2*S*,3*S*,4*S*,5*R*)-2-(1′-Methoxymethoxyethyl)-5-trityloxymethyltetrahydrofuran-3,4-diol (6). To a stirred solution of **5** (384 mg, 0.56 mmol) in tetrahydrofuran (2.0 ml) was added a 1.0 M solution of *n*-tetrabutylammonium fluoride (1.67 ml, 1.67 mmol) in tetrahydrofuran at rt. After 5 h, the reaction mixture was diluted with EtOAc, washed with water, brine, dried, and concentrated. The residue was chromatographed on silica gel (toluene/EtOAc =1:1) to give **6** (214 mg, 83% from **4**) as a colorless liquid; $[\alpha]_D^{26}$+48.2 (*c* 0.48, $CHCl_3$); IR (neat) 3432, 2931, 1448, 1100, 1070, 1035, 708 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.40 (m, 6H), 7.29–7.21 (m, 9H), 4.73, 4.63 (each d, *J*=6.8 Hz, 2H), 4.09–3.93 (m, 5H), 3.45–3.27 (m, 3H), 3.37 (s, 3H), 3.20 (dd, *J*=10.1, 3.4 Hz, 1H), 1.30 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 128.6, 127.8, 127.1, 94.9, 87.9, 87.6, 84.2, 79.9, 79.1, 72.9, 64.9, 55.9, 16.1; HRMS calcd for $C_{28}H_{32}O_6Na$ $[M+Na]^+$487.2077, found 487.2097. Anal. Found: C, 72.33; H, 6.87. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94.

3.1.5. (1′*S*,2*R*,3*R*,4*R*,5*R*)-3,4-(Dimethanesulfonyloxy)-2-(1′-methoxymethoxyethyl)-5-trityloxymethyltetrahydrofuran (7). To a stirred solution of **6** (214 mg, 0.46 mmol) and triethylamine (0.52 ml, 3.70 mmol) in dichloromethane (2.0 ml) was added methanesulfonyl chloride (0.11 ml, 1.38 mmol) at 0 °C, and the mixture was stirred at 0 °C∼rt

for 12 h, poured into ice-water. The resulting mixture was stirred for 2 h and extracted with ether. The extracts were washed successively with cold aqueous HCl, water, saturated aqueous $NaHCO_3$, water, brine, dried and concentrated. The residue was chromatographed on silica gel (*n*-hexane/EtOAc=2:1) to give **7** (211 mg, 74%) as amorphous solids; mp 88–90 °C (ether); $[\alpha]_D^{24}$ +40.3 (*c* 1.05, $CHCl_3$); IR (KBr) 2937, 2873, 1448, 1359, 1179, 1100, 1035, 960, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46–7.44 (m, 6H), 7.33–7.25 (m, 9H), 5.39 (dd, *J*=5.4, 3.9 Hz, 1H), 5.32 (dd, *J*=5.4, 3.4 Hz, 1H), 4.75, 4.71 (each d, *J*=6.8 Hz, 2H), 4.33 (dd, *J*=8.2, 3.8 Hz, 1H), 4.23 (dd, *J*=5.8, 3.1 Hz, 1H), 4.00 (m, 1H), 3.46 (dd, *J*=10.4, 4.1 Hz, 1H), 3.42 (s, 3H), 3.27 (dd, *J*=10.4, 3.9 Hz, 1H), 3.12 (s, 3H), 2.97 (s, 3H), 1.34 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 128.6, 127.9, 127.2, 95.8, 87.2, 84.8, 83.5, 83.2, 81.4, 71.7, 62.8, 55.9, 38.5, 38.2, 16.5; HRMS calcd for $C_{30}H_{36}O_{10}S_2Na$ $[M+Na]^+$643.1648, found 643.1646. Anal. Found: C, 56.07; H, 5.76. Calcd for $C_{30}H_{36}O_{10}S_2\cdot H_2O$: C, 56.41; H, 6.00.

3.1.6. (1′*S*,2*S*,5*S*)-2-(1′-Methoxymethoxyethyl)-5-trityloxymethyl-2,5-dihydrofuran (8). A mixture of **7** (211 mg, 0.34 mmol), zinc powder (334 mg, 5.12 mmol) and sodium iodide (409 mg, 2.73 mmol) in *N*,*N*-dimethylformamide (2.5 ml) was stirred at 140 °C for 27 h. More zinc powder (334 mg, 5.12 mmol) and sodium iodide (409 mg, 2.73 mmol) were added, and stirring was continued for 7 h. The resulting mixture was cooled to rt, diluted with water, and then extracted with dichloromethane. The extracts were washed successively with water, brine, dried, and concentrated. The residue was chromatographed on silica gel (*n*-hexane/EtOAc=10:1) to give **8** (130 mg, 89%) as a colorless oil; $[\alpha]_D^{24}$ −110.3 (*c* 1.04, $CHCl_3$); IR (neat) 2930, 2882, 1491, 1448, 1216, 1153, 1104, 1086, 1038, 788, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43–7.40 (m, 6H), 7.28–7.19 (m, 9H), 5.96 (dt, *J*=6.3, 2.0 Hz, 1H), 5.83 (dt, *J*=6.3, 1.9 Hz, 1H), 4.97 (m, 1H), 4.87 (m, 1H), 4.69 (s, 2H), 3.77 (qd, *J*=6.5, 6.3 Hz, 1H), 3.36 (s, 3H), 3.17 (dd, *J*=9.2, 4.8 Hz, 1H), 3.06 (dd, *J*=9.2, 4.3 Hz, 1H), 1.12 (d, *J*=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 129.9, 128.6, 127.7, 127.6, 126.8, 95.6, 88.8, 86.4, 85.3, 74.9, 55.4, 15.9; HRMS calcd for $C_{28}H_{30}O_4Na$ $[M+Na]^+$ 453.2042, found 453.2029.

3.1.7. (1*S*,2′*S*,5′*S*)-1-[5′-(Hydroxymethyl)-2′,5′-dihydrofuran-2′-yl]ethanol (9). To a stirred solution of **8** (1.03 g, 2.39 mmol) in dichloromethane (8.0 ml) was added a 10% solution of hydrogen chloride (2.0 ml) in methanol at 0 °C, and the mixture was stirred at 0 °C∼rt for two days. After being neutralized by $NaHCO_3$ powder, the resulting mixture was filtered, and then concentrated. The residue was chromatographed on silica gel (EtOAc→chloroform/methanol=20:1) to give **9** (334 mg, 97%) as a colorless oil; $[\alpha]_D^{24}$ −173.9 (*c* 1.08, $CHCl_3$); IR (neat) 3369, 2873, 1366, 1071, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.86 (br d, *J*=5.8 Hz, 1H), 5.84 (br d, *J*=5.8 Hz, 1H), 4.95 (m, 1H), 4.66 (t, *J*=6.8 Hz, 1H), 3.71 (br d, *J*=11.6 Hz, 1H), 3.64 (qd, *J*=6.8, 6.3 Hz, 1H), 3.54 (br dd, *J*=11.6, 4.8 Hz, 1H), 2.83 (s, 1H), 2.60 (s, 1H), 1.16 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.5, 128.4, 91.2, 87.1, 70.4, 64.9, 18.5; HRMS calcd for $C_7H_{12}O_3Na$ $[M+Na]^+$167.0684, found 167.0679.

3.1.8. (1*S*,2′*S*,5′*S*)-1-[5′-(*tert*-Butyldiphenylsilanyloxymethyl)-2′,5′-dihydrofuran-2′-yl]ethanol (10). To a stirred mixture of **9** (245 mg, 1.70 mmol) and imidazole (289 mg, 4.3 mmol) in *N*,*N*-dimethylformamide (2.0 ml) was *tert*-butylchlorodiphenylsilane (0.59 ml, 2.3 mmol) at rt. After 6 h, the mixture was poured into ice-water, and extracted with dichloromethane. The extracts were washed successively with cold aqueous HCl, water, saturated aqueous $NaHCO_3$, water, brine, dried and concentrated. The residue was chromatographed on silica gel (*n*-hexane/EtOAc=2:1) to give **10** (566 mg, 81%) as a colorless oil; $[\alpha]_D^{21}$ −113.5 (*c* 1.02, $CHCl_3$); IR (neat) 3438, 3072, 2931, 2858, 1589, 1428, 1136, 1113, 1083, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.69–7.66 (m, 4H), 7.42–7.36 (m, 6H), 5.94 (br d, *J*=6.0 Hz, 1H), 5.81 (br d, *J*=6.0 Hz, 1H), 4.92 (m, 1H), 4.59 (br t, *J*=3.8 Hz, 1H), 3.71 (dd, *J*=10.6 Hz, 4.6 Hz, 1H), 3.68 (dd, *J*=10.6, 5.1 Hz, 1H), 3.63 (m, 1H), 2.24 (m, 1H), 1.18 (d, *J*=6.5 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.5, 135.4, 133.5, 129.8, 129.5, 127.8, 127.5, 90.8, 86.7, 70.4, 66.4, 26.9, 19.4, 18.7; HRMS calcd for $C_{23}H_{30}O_3SiNa$ $[M+Na]^+$405.1862, found 405.1846.

3.1.9. (1*S*,2′*S*,5′*S*)-1-[5′-(*tert*-Butyldiphenylsilanyloxymethyl)-2′,5′-dihydrofuran-2′-yl]ethyl phenylselenocarbonate (11). To a stirred mixture of **10** (566 mg, 1.48 mmol) and triphosgene (161 mg, 0.54 mmol) in dichloromethane (3.0 ml) was added pyridine (0.14 ml, 1.78 mmol) at 0 °C. After 30 min, the reaction mixture was allowed to warm to rt with stirring for 2 h. Then benzeneselenol (0.31 ml, 2.96 mmol) and triethylamine (0.83 ml, 5.92 mmol) were added sequentially at 0 °C with stirring. The resulting mixture was stirred at 0 °C for 30 min and rt for 1 h, and then diluted with hexane, poured into a column of silica gel. Elution with toluene/hexane (1/2→1/0) gave **11** (794 mg, 95%) as a light-yellow oil; $[\alpha]_D^{22}$ −123.3 (*c* 1.15, $CHCl_3$); IR (neat) 2931, 2857, 1728, 1428, 1131, 1044, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.69–7.63 (m, 4H), 7.62–7.61 (m, 2H), 7.42–7.35 (m, 9H), 5.98 (br d, *J*=6.3 Hz, 1H), 5.75 (br d, *J*=6.3 Hz, 1H), 5.10 (qd, *J*=6.5, 3.6 Hz, 1H), 4.85–4.84 (m, 2H), 3.72 (dd, *J*=10.4, 3.8 Hz, 1H), 3.68 (dd, *J*=10.4, 4.8 Hz, 1H), 1.30 (d, *J*=6.5 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 135.6, 135.5, 135.4, 133.5, 133.4, 130.7, 129.5, 129.4, 129.1, 128.9, 127.5, 126.8, 87.4, 86.9, 76.0, 66.3, 26.9, 19.4, 15.9; HRMS calcd for $C_{30}H_{34}O_4SiNaSe$ $[M+Na]^+$589.1292, found 589.1290.

3.1.10. (2*S*,3a*R*,6*S*,6a*S*)-2-(*tert*-Butyldiphenylsilanyloxymethyl)-6-methyltetrahydrofuro[3,4-*b*]furan-4-one (12). To a stirred solution of **11** (669 mg, 1.18 mmol) in toluene (35 ml) was added dropwise a mixture of *n*-tributyltin hydride (0.64 ml, 2.37 mmol) and a trace amount of AIBN in toluene (5.0 ml) at 100 °C over 30 min. The mixture was stirred at the same temperature for 40 min and concentrated. The residue was chromatographed on silica gel (*n*-hexane/EtOAc =10:1→4:1) to give **12** (450 mg, 93%) as a white solid; $[\alpha]_D^{22}$ −24.3 (*c* 1.09, $CHCl_3$); IR (KBr) 2932, 2860, 1772, 1348, 1178, 1132, 1113, 1005, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.68–7.64 (m, 4H), 7.45–7.38 (m, 6H), 4.59–4.54 (m, 2H), 4.12 (qd, *J*=6.3, 4.1 Hz, 1H), 3.77 (dd, *J*=11.1, 3.9 Hz, 1H), 3.66 (dd, *J*=11.1, 4.1 Hz, 1H), 3.32 (dd, *J*=8.2, 5.3 Hz, 1H), 2.43 (ddd, *J*=12.8, 6.3,

1.2 Hz, 1H), 2.20 (ddd, J=12.8, 9.0, 8.7 Hz, 1H), 1.45 (d, J=6.5 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 135.5, 135.4, 133.3, 133.1, 129.7, 129.6, 127.6, 127.5, 80.4, 80.1, 79.5, 65.8, 47.5, 31.5, 26.9, 19.4, 14.4; HRMS calcd for $C_{24}H_{30}O_4SiNa$ $[M+Na]^+$433.1811, found 433.1841. Anal. Found: C, 70.27; H, 7.39. Calcd for $C_{24}H_{30}O_4Si$: C, 70.21; H, 7.36.

3.1.11. (2*S*,3a*R*,6*S*,6a*S*)-2-Hydroxymethyl-6-methyltetrahydrofuro[3,4-*b*]furan-4-one (13). Treatment of **12** (1.56 g, 3.80 mmol) as described for preparation of **6** from **5** gave **13** (581 mg, 89%) as a colorless oil; $[\alpha]_D^{22}$ −60.0 (*c* 1.09, $CHCl_3$); IR (neat) 3448, 2939, 1767, 1449, 1356, 1194, 1140, 1056, 1031 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.63–4.58 (m, 2H), 4.06 (m, 1H), 3.80 (br d, J=11.8 Hz, 1H), 3.53 (dd, J=11.8, 4.1 Hz, 1H), 3.35 (dd, J=8.2, 5.3 Hz, 1H), 2.39 (dd, J=12.8, 5.3 Hz, 1H), 2.13 (dddd, J=12.8, 9.8, 9.6, 0.9 Hz, 1H), 1.90 (br s, 1H), 1.45 (d, J=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.7, 80.2, 80.0, 79.8, 63.5, 47.5, 30.9, 14.4; HRMS calcd for $C_8H_{13}O_4$ $[M+H]^+$173.0814, found 173.0812.

3.1.12. (2*S*,3a*R*,6*S*,6a*S*)-6-Methyl-2-tosyloxymethyltetrahydrofuro[3,4-*b*]furan-4-one (14). To a stirred mixture of **13** (462 mg, 1.02 mmol), *N*,*N*-dimethylaminopyridine (8.2 mg, 0.07 mmol) and triethylamine (0.37 ml, 2.68 mmol) in dichloromethane (8.0 ml) was added *p*-toluenesulfonyl chloride (256 mg, 1.34 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min and at rt for 1.5 h, and then poured into ice-water. The resulting mixture was extracted with dichloromethane. The extracts were washed successively with cold aqueous HCl, water, saturated aqueous $NaHCO_3$, water, brine, dried and concentrated. The residue was chromatographed on silica gel (dichloromethane/methanol=20:1) to give **14** (206 mg, 94%) as a colorless oil; $[\alpha]_D^{24}$ −32.2 (*c* 1.02, $CHCl_3$); IR (neat) 2939, 1770, 1600, 1451, 1359, 1190, 1176, 1139, 1096, 976 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (dd, J=8.2, 1.7 Hz, 2H), 7.34 (d, J=7.8 Hz, 1H), 4.56–4.51 (m, 2H), 4.15 (m, 1H), 4.13 (dt, J=10.9, 2.2 Hz, 1H), 3.99 (ddd, J=10.9, 4.2, 1.5 Hz, 1H), 3.31 (dd, J=9.0, 5.3 Hz, 1H), 2.44 (s, 3H), 2.43 (br dd, J=13.0, 6.2 Hz, 1H), 2.07 (m, 1H), 1.38 (d, J=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 144.9, 132.6, 129.8, 127.8, 80.7, 79.3, 76.7, 70.5, 47.2, 31.2, 21.7, 14.3; HRMS calcd for $C_{15}H_{18}O_6SNa$ $[M+Na]^+$349.0722, found 349.0714.

3.1.13. (2*S*,3a*R*,6*S*,6a*S*)-2-Iodomethyl-6-methyltetrahydrofuro[3,4-*b*]furan-4-one (15). A mixture of **14** (207 mg, 0.63 mmol) and sodium iodide (1.89 g, 12.6 mmol) in acetone (10 ml) was heated under reflux with stirring for 20 h, cooled to rt, and concentrated. The residue was diluted with EtOAc, filtered through a pad of Celite, and the filtrate was concentrated to give **15** (199 mg) as a yellow liquid, which was employed to the next step without further purification. An analytical sample was prepared by preparative TLC {chloroform/methanol (20:1), two developments}. **15**; $[\alpha]_D^{21}$ −60.9 (*c* 0.35, $CHCl_3$); IR (neat) 2936, 1770, 1353, 1185, 1158, 1139, 1001, 910 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.72 (dd, J=5.5, 3.9 Hz, 1H), 4.59 (qd, J=6.5, 3.8 Hz, 1H), 3.93 (ddd, J=11.4, 9.9, 5.5 Hz, 1H), 3.37 (dd, J=8.2, 6.0 Hz, 1H), 3.32 (dd, J=10.4, 5.6 Hz, 1H), 3.28 (dd, J=10.4, 4.3 Hz, 1H), 2.61 (dd, J=13.0, 5.5 Hz, 1H), 2.01 (ddd, J=13.0, 9.5, 8.7 Hz, 1H), 1.46 (d, J=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.2, 80.7, 79.8, 78.3, 47.6, 36.3, 14.4, 9.1; HRMS calcd for $C_8H_{11}IO_3Na$ $[M+Na]^+$304.9651, found 304.9642.

3.1.14. (2*R*,3*S*,4*S*)-2-Allyl-3-hydroxy-4-methyl-4-butanolide (16). A mixture of the above iodide **15** (199 mg, ca. 0.63 mmol) and zinc powder (824 mg, 12.6 mmol) in tetrahydrofuran–water (20:1, 16.6 ml) was stirred at 65 °C for 3 h, cooled to rt, and then filtered through a pad of Celite. The filtrate was extracted with dichloromethane. The extracts were washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (*n*-pentane/ether=2:1→0:1) to give **16** (92 mg, 93%) as a colorless liquid; $[\alpha]_D^{21}$ −81.1 (*c* 1.00, $CHCl_3$); IR (neat) 3447, 3083, 2982, 2937, 1755, 1644, 1386, 1359, 1188, 1042, 1005, 980, 923 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 (m, 1H), 5.20 (ddd, J=17.2, 2.9, 1.5 Hz, 1H), 5.11 (ddd, J=13.2, 2.4, 1.5 Hz, 1H), 4.47 (qd, J=6.5, 3.1 Hz, 1H), 4.33 (dd, J=8.0, 4.8 Hz, 1H), 2.71 (ddd, J=10.6, 4.8, 4.6 Hz, 1H), 2.62 (ddd, J=14.9, 5.8, 4.6 Hz, 1H), 2.44 (m, 1H), 2.06 (m, 1H), 1.43 (d, J=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 135.1, 116.9, 79.0, 70.9, 47.1, 27.9, 13.8; HRMS calcd for $C_8H_{13}O_3$ $[M+H]^+$157.0865, found 157.0863.

3.1.15. (2*R*,3*S*,4*S*)-3-Hydroxy-4-methyl-2-(2′-tetradecenyl)-4-butanolide (17). A mixture of **16** (4.8 mg, 31 μmol), 1-tridecene (22 μl, 93 μmol) and Grubbs catalyst 1st generation (0.8 mg, 0.8 μmol) in dichloromethane (1.0 ml) was stirred at 40 °C for 3 h. More catalyst (0.8 mg, 0.8 μmol) was added and the mixture was stirred for an additional 6 h, then cooled to rt. Florisil was added with stirring, and the resulting mixture was allowed to stand overnight, then filtered through a pad of Celite. The filtrate was concentrated to give a syrup, which was chromatographed on silica gel (*n*-hexane/EtOAc=4:1) to give **17** (4.3 mg, 45%) as an amorphous solid. In addition, starting lactone **16** (0.6 mg) was also recovered.

Compound **17**. $[\alpha]_D^{21}$ −48.3 (*c* 1.04, $CHCl_3$); IR (neat) 3449, 2922, 2851, 1733, 1468, 1194, 1135, 1044, 972 cm^{-1}; ^{1}H NMR of major isomer (400 MHz, $CDCl_3$): δ 5.62 (ddd, J=15.2, 7.0, 6.5 Hz, 1H), 5.48 (ddd, J=15.2, 7.7, 6.7 Hz, 1H), 4.47 (qd, J=6.3, 3.1 Hz, 1H), 4.33 (dd, J=8.0, 4.1 Hz, 1H), 2.59 (ddd, J=14.7, 5.6, 5.3 Hz, 1H), 2.37 (ddd, J=14.9, 10.7, 7.8 Hz, 1H), 2.00 (m, 2H), 1.44 (d, J=6.6 Hz, 3H), 1.38–1.20 (m, 18H), 0.88 (t, J=6.3 Hz, 3H); ^{13}C NMR of major isomer (100 MHz, $CDCl_3$): δ 176.8, 133.5, 126.2, 78.9, 71.0, 47.5, 32.6, 31.9, 29.7 (3C), 29.6, 29.4 (2C), 29.3, 26.9, 22.7, 14.2, 13.8; HRMS calcd for $C_{19}H_{34}O_3Na$ $[M+Na]^+$333.2406, found 333.2413.

3.1.16. (2*R*,3*S*,4*S*)-3-Hydroxy-4-methyl-2-tetradecyl-4-butanolide (2). A mixture of **17** (10.4 mg, 34 μmol) and Wilkinson catalyst (7.1 mg, 7.7 μmol) in benzene (0.6 ml) was stirred at rt under hydrogen for 6.5 h, and then concentrated. The residue was chromatographed on silica gel (*n*-hexane/EtOAc=4:1) to give **2** (9.9 mg, 95%) as colorless crystals; mp 93–94 °C (*n*-hexane/ether) {lit.[7a], 86–88 °C for (+)-form}; $[\alpha]_D^{22}$ −43.6 (*c* 0.67, $CHCl_3$) {lit.[7a]; $[\alpha]_D^{25}$ +37.2 for (+)-form, lit.[7b]; $[\alpha]_D$ −36.7}; IR (KBr) 3423, 2930, 2851, 1735, 1457, 1225, 1203, 1160, 1122 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.45 (qd, J=6.5, 3.1 Hz,

1H), 4.32 (dd, $J=4.8$, 3.2 Hz, 1H), 2.58 (dt, $J=10.1$, 4.8 Hz, 1H), 1.83 (m, 1H), 1.63 (m, 1H), 1.56 (m, 1H), 1.44 (d, $J=6.5$ Hz, 3H), 1.40–1.19 (m, 24H), 0.88 (t, $J=6.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 78.8, 71.2, 47.6, 32.0, 29.8 (3C), 29.7 (3C), 29.6, 29.5, 29.4, 27.7, 23.4, 22.8, 14.2, 13.8; HRMS calcd for $C_{19}H_{36}O_3Na$ $[M+Na]^+$ 335.2562, found 335.2562.

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Concise and diastereoselective approach to *syn*- and *anti*-*N*-tosyl-α-hydroxy β-amino acid derivatives

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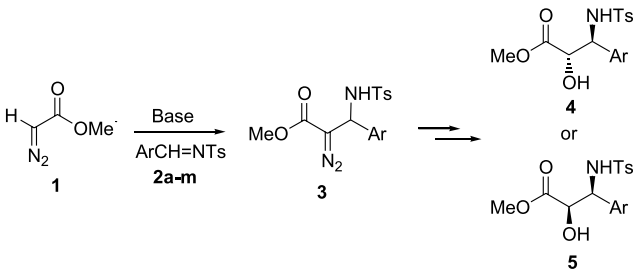
Abstract—The methyl diazoacetate and aryl (*N*-tosyl)imines can be transformed into *syn* or *anti* α-hydroxy β-amino esters with high diastereoselectivities in three steps: the base promoted nucleophilic condensation of the methyl diazoacetate and aryl (*N*-tosyl)imines to give β-(*N*-tosyl)amino α-diazoesters, followed by oxidation with Oxone® to generate α-oxo esters, which were reduced with $NaBH_4$ to yield the *anti*-*N*-tosyl-α-hydroxy β-amino ester, or hydrogenated with Pd/C (10%) as the catalyst to yield corresponding *syn* isomer, both in high diastereoselectivity.

1. Introduction

The stereoselective synthesis of β-amino acids and their derivatives have been an active research area in organic synthesis, due to the importance of the β-amino acid moiety in various fields.[1] In particular, the α-hydroxy β-amino acid moiety exist in some natural compounds with important biological activities, such as Taxol®.[2] The stereoselective synthesis of α-hydroxy β-amino acid is still a subject of considerable challenge, although progress has been made over the past decades.[3] So far, the most convenient approach to α-hydroxy β-amino acid derivatives is the amino-hydroxylation of α,β-unsaturated esters.[4] However, this approach is only easily applicable to the synthesis of *syn* α-hydroxy β-amino acid from *trans* α,β-unsaturated acids, because the *cis* precursor is less easily available. Moreover, this approach is in some cases associated with regio-selectivity problem. In this article, we introduce an alternative approach, which can give both *syn*- and *anti*-α-hydroxy β-amino esters with high diastereoselectivities (Scheme 1). This approach started from the easily available methyl diazoacetate, which was reacted with aryl (*N*-tosyl)-imines. Then the addition products were oxidized to give α-oxo esters. Finally, reduction of the α-oxo esters with $NaBH_4$ gave *anti*-*N*-tosyl-α-hydroxy β-amino esters, and hydrogenation with Pd/C (10%) as the catalyst gave the *syn* isomers.



Scheme 1.

2. Results and discussions

The first step of this novel approach was the nucleophilic condensation of methyl diazoacetate **1** with aryl (*N*-tosyl)-imines **2a**–**m**. The similar nucleophilic reaction of ethyl diazoacetate with aryl (*N*-tosyl)imines has been investigated previously in our laboratory.[5] The nucleophilic condensation was carried out with either NaH or catalytic DBU as the base. The reaction of methyl diazoacetate **1** gave the expected β-(*N*-tosyl)amino α-diazo esters **3a**–**m** in similar yields as compared with the corresponding reaction of ethyl diazoacetate (Table 1).

The diazo compounds **3a**–**m** were then oxidized to give α-oxo esters **6a**–**m**. The oxidation of diazo group is

Keywords: β-Amino acid; α-Diazo carbonyl compounds; Imine; Regio-selective reduction.
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Table 1. Base-promoted reaction of **1** with aryl *N*-(tosyl) imine **2a–m**

Entry	Base	Imine **2** (Ar=)	Product	Yield (%)[a]
1	DBU	**2a**, C_6H_5	**3a**	54
2	NaH	**2b**, *p*-PhC_6H_4	**3b**	81
3	DBU	**2c**, *p*-FC_6H_4	**3c**	57
4	NaH	**2d**, *p*-ClC_6H_4	**3d**	90
5	NaH	**2e**, *o*-MeC_6H_4	**3e**	60
6	DBU	**2f**, *p*-$MeOC_6H_4$	**3f**	76
7	DBU	**2g**, *m*-$CF_3C_6H_4$	**3g**	51
8	DBU	**2h**, *m*-BrC_6H_4	**3h**	67
9	NaH	**2i**, *m*-CNC_6H_4	**3i**	83
10	NaH	**2j**, 2,4-$Cl_2C_6H_3$	**3j**	47
11	NaH	**2k**, 2,6-$Cl_2C_6H_3$	**3k**	57
12	DBU	**2l** 	**3l**	72
13	NaH	**2m** 	**3m**	82

[a] The yield after purification with silica gel column chromatography.

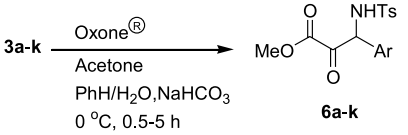
generally achieved with *m*-chloroperbenzoic acid (*m*-CPBA),[6] ozone[7] or dimethyldioxirane (DMD).[8] We found that for the diazo compounds **3a–k**, the oxidation occurred efficiently with commercially available Oxone® (potassium peroxomonosulfate) directly. Since, the preparation of dimethyldioxirane from Oxone® requires low temperature and the yield is usually low,[9] the direct oxidation with cheap Oxone® greatly simplifies the experimental operation and also makes use of the oxidant more efficiently. The oxidation of **3l** and **3m** under the same condition gave complex mixture (Scheme 2).

With the α-oxo β-(*N*-tosyl)amino esters **6a–k** in hand, we then proceeded to study their reduction. First, the α-oxo ester **6a** was taken as a model compound. The reduction with $NaBH_4$ at 0 °C in THF gave the *anti* α-hydroxy β-(*N*-tosyl)amino ester **4a** exclusively as judged by ^1H NMR (300 MHz) of the crude product.[10] The isolated yield of **4a** was 82%. On the other hand, when the α-oxo ester was hydrogenated with Pd/C (10%) as the catalyst in MeOH at room temperature, the *syn* isomer of α-hydroxy compound **5a** was formed, with high diastereoselectivity in 87% isolated yield. The assignment of the structure was made by the comparison of the spectra data of **5a** with that of the reported known compound (Scheme 3).[11]

The scope and limitations of the highly diastereoselective reduction with $NaBH_4$ and hydrogenation with Pd/C as the catalyst were summarized in Table 2. As shown by the data, the reduction with $NaBH_4$ gave *anti* products **4a–k** in generally high diastereoselectivities.[12] The hydrogenation, on the other hand, gave only *syn* isomer **5a–f** in most cases.[12] For α-oxo substrates **6g–k**, the hydrogenation failed to give the expected product, due to the side reaction of the substituents on the aromatic ring (entries 7–11).

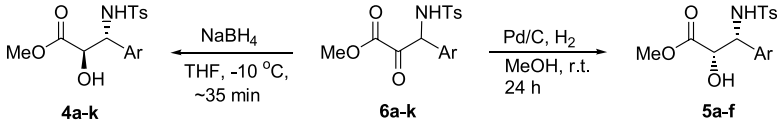
The stereochemistry of the *anti* product was confirmed by X-ray structure of **4c** (Fig. 1).[13]

The high diastereoselectivity observed in the reduction with $NaBH_4$ is rationalized as follows (Scheme 4). We speculate that hydrogen bonding between the N–H and carbonyl group may play an important role in the observed selectivity. The α-oxo ester substrate is considered to take



a. Ar = Ph, 85 %; **b**. Ar = *p*-PhC_6H_4, 96%;
c. Ar = *p*-FC_6H_4, 97 %; **d**. Ar = *p*-ClC_6H_4, 80 %;
e. Ar = *o*-MeC_6H_4, 97 %; **f**. Ar = *p*-$MeOC_6H_4$, 95 %;
g. Ar = *m*-$CF_3C_6H_4$, 81 %; **h**. Ar = *m*-BrC_6H_4, 98 %;
i. Ar = *m*-CNC_6H_4, 77 %; **j**. Ar = 2,4-$Cl_2C_6H_3$, 96 %;
k. Ar = 2,6-$Cl_2C_6H_3$, 98 %.

Scheme 2.



Scheme 3.

Table 2. Diastereoselective reduction of **6a–k** and hydrogenation of **6a–f**

Entry	α-Oxo ester **6**	Reduction with $NaBH_4$ dr; yield of **4** (%)[a]	Hydrogenation H_2, Pd/C (10%) dr; yield of **5** (%)[a]
1	**6a**, C_6H_5	>95:5; 82	>95:5; 87
2	**6b**, *p*-PhC_6H_4	>95:5; 72	>95:5; 92
3	**6c**, *p*-FC_6H_4	86:14; 70	83:17; 94
4	**6d**, *p*-ClC_6H_4	>95:5; 75	>95:5; 73
5	**6e**, *o*-MeC_6H_4	>95:5; 80	>95:5; 83
6	**6f**, *p*-$MeOC_6H_4$	>95:5; 95	>95:5; 75
7	**6h**, *m*-BrC_6H_4	>95:5; 74	—[b]
8	**6i**, *m*-CNC_6H_4	>95:5; 71	—[b]
9	**6j**, 2,4-$Cl_2C_6H_3$	97:3; 40	—[b]
10	**6k**, 2,6-$Cl_2C_6H_3$	94:6; 67	—[b]

[a] The diastereomeric ratio was determined by ^1H NMR (300 MHz). The yields refer to the pure compounds after purification with silica gel column chromatography.
[b] Expected products were not obtained due to side reactions.

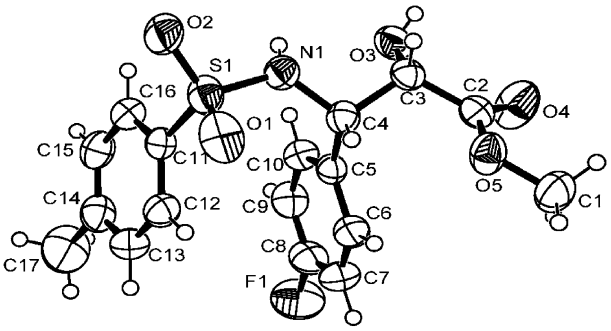
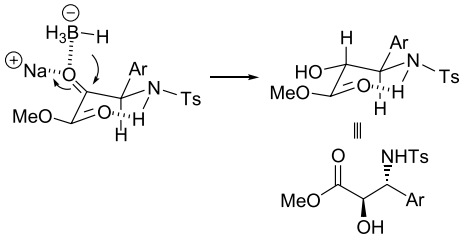


Figure 1. X-ray structure of **4c**.



Scheme 4.

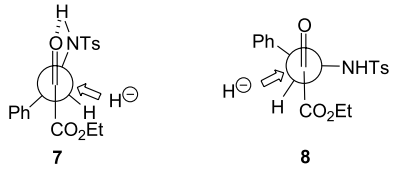


Figure 2. Hydrogen bonding model and Felkin's model.

a chair form conformation due to the hydrogen bonding. In the reduction with $NaBH_4$, the hydride is delivered from the axial direction to give the product with *anti* configuration, in which hydroxyl group occupies the equatorial position.[14]

Another way to interpret the stereochemical process is by the Newman projection **7** shown in Figure 2. The hydride reagent attacks the carbonyl group from the sterically less hindered direction to provide the *anti* product. This is similar to the metal chelation controlled reduction of α-ketols.[15] On the other hand, the Felkin's model **8**, in which it is assumed there is no intramolecular hydrogen bonding between the *N*-tosylamino group and the carbonyl group, predicts the *syn* product to be predominant.[16]

To confirm the role of the hydrogen bonding, we studied the corresponding reduction and hydrogenation with compound **9**, in which the hydrogen on the amino group was replaced with a methyl group. The reduction with $NaBH_4$ gave the α-hydroxyl products with essentially no diastereoselectivity (Scheme 5). Thus, the experimental result supported the proposed role of hydrogen bonding.

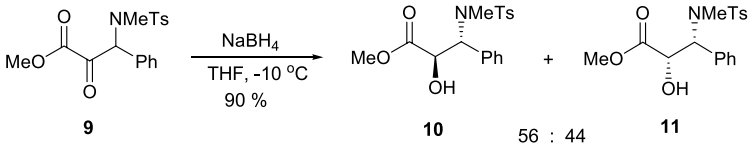
For the hydrogenation catalyzed with Pd/C, it was conceivable that the chair conformation exposed the less sterically hindered bottom face to hydrogen delivery and thus, providing the *syn* product (Scheme 6).[17] When compound **9** was subjected to the hydrogenation condition, it was found that the reaction became complicated. ^{1}H NMR spectrum of the crude product indicated the formation of *syn* product **11** in low yield. However, there was no *anti* product **10** identified from the ^{1}H NMR spectrum.

In summary, a novel approach to both *anti*- and *syn*-α-hydroxy β-amino acid derivatives with high diastereoselectivities has been developed. This approach requires only three steps from the easily available aryl (*N*-tosyl)-imine and methyl diazoester.[18] If the enantioselectivity can be controlled in the first step of the nucleophilic condensation, this approach can be further developed into a method to prepare non-racemic *syn*- and *anti*-α-hydroxy β-amino acid derivatives.[19] The investigation along this direction is currently under the way in our laboratory.

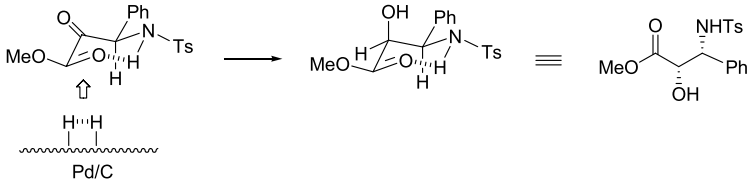
3. Experimental

3.1. General methods

^{1}H and ^{13}C NMR spectra were recorded at 300 MHz (or 200 MHz) and 75 MHz (or 50 MHz) with Varian Mercury 300 (or 200) spectrometer, or at 400 and 100.6 MHz with Brucker ARX400 spectrometer. The chemical shifts were reported in ppm using TMS as the internal standard. All reactions were performed under a nitrogen atmosphere in a flame-dried reaction flask, and the components were added



Scheme 5.



Scheme 6.

via syringe. All solvents were distilled prior to use according to standard procedures. THF was distilled over sodium. For chromatography, 100–200 mesh silica gel (Qindao, China) was employed. IR spectra were recorded with a Nicolet 5MX-S infrared spectrometer. HPLC analysis was performed at HP 1100 apparatus with Chiracel column. Mass spectra were obtained on a VG ZAB-HS mass spectrometer.

3.2. General procedure for the reaction of methyl diazoacetate with aryl (*N*-tosyl)imines

(a) *With DBU as the base*. To a solution of methyl diazoacetate (1.0 mmol) in anhydrous MeCN (8 mL) was added DBU (0.25 mmol) at room temperature under N_2. Then the imine (0.85 mmol) was added. The reaction mixture was stirred at room temperature for about 1 h. The solvent was removed and the crude product was purified by column chromatography with petroleum ether/EtOAc.

(b) *With NaH as the base*. To a solution of methyl diazoacetate (1.0 mmol) in anhydrous THF (8 mL) was added 60% NaH (43 mg, 1.25 equiv), then the imine (0.85 mmol) was added, the reaction mixture was stirred for 1 h and quenched with saturated aqueous $NaHCO_3$ at 0 °C. The resulting slurry was extracted with CH_2Cl_2 (3× 15 mL). Usual work up gave a crude product, which was purified by column chromatography.

3.2.1. Methyl 2-diazo-3-phenyl-3-[(*N*-tosyl)amino] propanoate (3a). IR (film) 3262, 2097, 1691 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.43 (s, 3H), 3.62 (s, 3H), 5.33 (d, J= 7.6 Hz, 1H), 5.60 (w, 1H), 7.28–7.30 (m, 7H), 7.35 (d, J= 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.2, 51.7, 53.2, 126.0, 126.8, 128.0, 128.5, 129.2, 136.7, 137.3, 143.3, 165.4; EI-MS (*m/z*, relative intensity) 331 [$(M-28)^+$, 16], 260 (17), 164 (20), 139 (40), 91 (100). Anal. Calcd for $C_{17}H_{17}O_4N_3S$: C, 56.81; H, 4.77; N, 11.69. Found: C, 56.84; H, 4.79; N, 11.68.

3.2.2. Methyl 2-diazo-3-(*p*-phenyl)phenyl-3-[(*N*-tosyl)-amino]propanoate (3b). IR (film) 3265, 2098, 1697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.40(s, 3H), 3.61(s, 3H), 5.40 (d, J=7.5 Hz, 1H), 5.89 (d, J=7.5 Hz, 1H), 7.26–7.55 (m, 11H), 7.75 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 51.9, 53.5, 126.7, 126.9, 127.1, 127.4, 128.7, 129.5, 136.4, 136.8, 140.1, 141.1, 143.6, 165.6; EI-MS (*m/z*, relative intensity) 407 [$(M-28)^+$, 54], 375 (6), 220 (33), 193 (42), 164 (76), 91 (100); HRMS calcd for $C_{23}H_{21}NSO_4$ $(M-28)^+$ 407.1191, found 407.1200.

3.2.3. Methyl 2-diazo-3-(*p*-fluoro)phenyl-3-[(*N*-tosyl)-amino]propanoate (3c). IR (KBr) 3442, 2113, 1687 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.44 (s, 3H), 3.61(s, 3H), 5.32 (d, J=4.5 Hz, 1H), 5.72 (s, 1H), 6.95–7.01 (m, 2H), 7.23–7.31 (m, 4H), 7.72 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 51.9, 53.4, 115.6, 115.9, 127.1, 128.1, 128.2, 129.6, 133.4, 136.8, 143.9, 165.5; EI-MS (*m/z*, relative intensity) 349 [$(M-28)^+$, 27], 164 (29), 155 (32), 91 (100); HRMS calcd for $C_{17}H_{16}NSO_4F$ $(M-28)^+$ 349.0784, found 349.0794.

3.2.4. Methyl 2-diazo-3-(*p*-chloro)phenyl-3-[(*N*-tosyl)-amino]propanoate (3d). IR (KBr) 3548, 2111, 1686 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.44 (s, 3H), 3.59 (s, 3H), 5.31(d, J=7.4 Hz, 1H), 5.73(d, J=7.4 Hz, 1H), 7.19–7.36 (m, 6H), 7.71 (d, J=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.5, 52.0, 53.6, 127.1, 127.8, 129.0, 129.7, 134.4, 136.1, 136.8, 143.9, 165.5; EI-MS (*m/z*, relative intensity) 365 [$(M-28)^+$, 100], 333 (14), 304 (6), 178 (12), 91 (5); HRMS calcd for $C_{17}H_{16}NSO_4^{35}Cl$ $(M-28)^+$ 365.0489, found 365.0497.

3.2.5. Methyl 2-diazo-3-(*o*-methyl)phenyl-3-[(*N*-tosyl)-amino]propanoate (3e). IR (film) 3266, 2097, 1697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.23 (s, 3H), 2.43 (s, 3H), 3.62 (s, 3H), 5.27 (d, J=5.0 Hz, 1H), 5.50 (d, J=5.0 Hz, 1H), 7.15–7.30 (m, 6H), 7.75 (d, J=8.4 Hz, 2H); ^{13}C NMR (75 MHz) δ 18.9, 21.4, 50.1, 125.9, 126.3, 127.2, 128.2, 129.4, 130.8, 135.1, 136.6, 143.5, 165.6; EI-MS (*m/z*, relative intensity) 345 [$(M-28)^+$, 10], 274 (9), 258 (8), 158 (28), 130 (58), 91 (100); HRMS calcd for $C_{18}H_{19}NO_4S$ 345.1035, found 345.1037.

3.2.6. Methyl 2-diazo-3-(*p*-methoxy)phenyl-3-[(*N*-tosyl)-amino]propanoate (3f). IR (KBr) 3446, 2103, 1684 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.43 (s, 3H), 3.62 (s, 3H), 3.77 (s, 3H), 5.28 (d, J=7.2 Hz, 1H), 5.52 (d, J=7.2 Hz, 1H), 6.79–6.85 (m, 2H), 7.15–7.21 (m, 2H), 7.29 (d, J= 8.6 Hz, 2H), 7.73(d, J=8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.5, 51.9, 53.5, 55.3, 114.2, 127.2, 127.6, 129.6, 129.6, 136.8, 143.7, 159.6, 165.7; EI-MS (*m/z*, relative intensity) 361 [$(M-28)^+$, 26], 329 (6), 290 (19), 164 (44), 147 (48), 132 (52), 91 (100). Anal. Calcd for $C_{18}H_{19}O_5N_3S$: C, 55.52; H, 4.92; N, 10.79. Found: C, 55.62; H, 4.99; N, 10.75.

3.2.7. Methyl 2-diazo-3-(*m*-trifluoromethyl)phenyl-3-[(*N*-tosyl)amino]propanoate (3g). IR (KBr) 3452, 2104, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.36 (s, 3H), 3.57 (s, 3H), 5.37 (d, J=7.8 Hz, 1H), 5.99 (d, J=7.8 Hz, 1H), 7.20–7.66 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 52.0, 53.7, 123.2, 125.1, 127.0, 127.3, 129.4, 129.7, 129.8, 130.9, 136.7, 138.7, 144.0, 165.4; EI-MS (*m/z*, relative intensity) 399 [$(M-28)^+$, 6], 164 (22), 155 (24), 139 (32), 91 (100); HRMS calcd for $C_{18}H_{16}NO_4SF_3$ 399.0752, found 321.0761.

3.2.8. Methyl 2-diazo-3-(*m*-bromo)phenyl-3-[(*N*-tosyl)-amino]propanoate (3h). IR (KBr) 3213, 2106, 1673 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 3.61 (s, 3H), 5.33 (d, J=8.0 Hz, 1H), 5.94 (d, J=8.0 Hz, 1H), 7.13–7.69 (m, 6H), 7.71 (d, J=1.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 52.0, 53.4, 122.8, 124.9, 127.0, 129.4, 130.3, 131.4, 136.7, 139.8, 143.9, 165.4; EI-MS (*m/z*, relative intensity) 409 [$(M-28)^+$, 5], 279 (18), 167 (28), 149 (100); HRMS calcd for $C_{17}H_{16}NSO_4^{79}Br$: 408.9983, found 408.9983.

3.2.9. Methyl 2-diazo-3-(*m*-cyano)phenyl-3-[(*N*-tosyl)-amino]propanoate (3i). IR (KBr) 3427, 2103, 1749 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.45 (s, 3H), 3.62 (s, 3H), 5.23 (d, J=8.8 Hz, 1H), 6.07 (d, J=8.8 Hz, 1H), 7.27–7.82 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 52.1, 53.4, 112.7, 118.2, 126.2, 126.9, 129.6, 129.7, 131.0, 131.8, 136.6, 139.2, 144.1, 165.3; EI-MS (*m/z*, relative intensity) 356 [$(M-28)^+$, 18], 292 (4), 164 (16), 155 (25), 91 (100), 65 (20); HRMS calcd for $C_{18}H_{16}N_2SO_4$ 356.0831, found 356.0827.

3.2.10. Methyl 2-diazo-3-(2,4-dichloro)phenyl-3-[(*N*-tosyl)amino]propanoate (3j). IR (KBr) 3189, 2110, 1659 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.42 (s, 3H), 3.59 (s, 3H), 5.58 (d, $J=8.2$ Hz, 1H), 6.21 (d, $J=8.2$ Hz, 1H), 7.13–7.40 (m, 5H), 7.71 (d, $J=8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 51.2, 51.9, 127.0, 127.2, 129.4, 129.5, 129.6, 132.8, 133.8, 134.5, 136.6, 143.9, 165.4; EI-MS (*m/z*, relative intensity) 399 [$(M-28)^+$, 8], 364 (10), 332 (9), 164 (16), 155 (30), 91 (10); HRMS calcd for $C_{17}H_{15}NO_4SCl_2$ 399.0099, found 399.0104.

3.2.11. Methyl 2-diazo-3-(2,6-dichloro)phenyl-3-[(*N*-tosyl)amino]propanoate (3k). IR (film) 3276, 2103, 1695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H), 3.67 (s, 3H), 5.84 (d, $J=9.0$ Hz, 1H), 6.29 (d, $J=9.0$ Hz, 1H), 7.07–7.21 (m, 5H), 7.69 (d, $J=1.5$, 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 21.4, 48.2, 52.0, 127.1, 129.2, 129.5, 129.8, 132.2, 134.8, 136.5, 143.8, 165.3; EI-MS (*m/z*, relative intensity) 399 [$(M-28)^+$, 12], 364 (12), 155 (16), 91 (100). Anal. Calcd for $C_{17}H_{15}O_4N_3SCl_2$: C, 47.68; H, 3.53; N, 9.81. Found: C, 47.66; H, 3.72; N, 9.55.

3.2.12. Methyl 2-diazo-3-(2-furyl)-3-[(*N*-tosyl)amino]-propanoate (3l). IR (KBr) 3445, 2109, 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.40 (s, 3H), 3.60 (s, 3H), 5.20 (d, $J=7.2$ Hz, 1H), 5.85 (d, $J=7.2$ Hz, 1H), 6.22–6.27 (m, 2H), 7.24–7.30 (m, 3H), 7.74 (dd, $J=1.8$, 6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 48.4, 51.9, 107.9, 110.5, 127.1, 129.5, 136.8, 142.8, 143.7, 149.5, 165.3; EI-MS (*m/z*, relative intensity) 321[$(M-28)^+$, 8], 250 (12), 155 (26), 139 (24), 91 (100); HRMS calcd for $C_{15}H_{15}NSO_5$ 321.0671, found 321.0669.

3.2.13. Methyl 2-diazo-3-[2-(5-bromo)thienyl]-3-[(*N*-tosyl)amino]propanoate (3m). IR (film) 3204, 2104, 1685 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.45 (s, 3H), 3.64 (s, 3H), 5.47 (d, $J=8.7$ Hz, 1H), 5.69 (s, 1H), 6.70 (d, $J=3.3$ Hz, 1H), 6.87 (d, $J=3.9$ Hz, 1H), 7.32 (d, $J=8.1$ Hz, 2H), 7.73 (d, $J=8.1$ Hz, 2H); ^{13}C NMR (DMSO-d_6, 50 MHz), δ 20.5, 48.5, 50.9, 111.0, 124.6, 125.8, 128.4, 128.9, 136.8, 142.2, 142.7; EI-MS (*m/z*, relative intensity) 417 [$(M-28)^+$, 18], 262 (26), 181 (38), 164 (26), 91 (100). Anal. Calcd for $C_{15}H_{14}O_4N_3S_2Br$: C, 40.55; H, 3.18; N, 9.46. Found: C, 40.55; H, 3.26; N, 9.49.

3.2.14. General procedure for the oxidation of α-diazo compounds 3a–k with Oxone®. At 0 °C, to a solution of diazo compounds **3a–k** (0.58 mmol) in benzene (4.26 mL), was added acetone (3.0 mL), H_2O (4.26 mL), and $NaHCO_3$ (1.88 g) in sequence, then was added Oxone® (3.53 g) in three times. The reaction mixture was stirred until the starting materials disappeared. The slurry was extracted by CH_2Cl_2 (3×15 mL), and then usual work up gave a crude product **6a–k**. The α-oxo β-(*N*-tosyl)amino esters **6a–k** were found unstable in silica gel column chromatography. The crude products were used in the next step without further purification. Representative data: methyl 2-diazo-3-(*o*-methyl)phenyl-3-[(*N*-tosyl)amino]propanoate (**6e**); ^1H NMR ($CDCl_3$, 200 MHz) δ 2.23 (s, 3H), 2.39 (s, 3H), 3.66 (s, 3H), 5.94 (d, $J=7.4$ Hz, 1H), 6.08 (d, $J=7.4$ Hz, 1H), 6.78–7.34 (m, 6H), 7.55 (d, $J=8.4$ Hz, 2H); ^{13}C NMR (75 MHz) $\delta=18.9$, 21.4, 53.1, 59.0, 126.5, 126.7, 128.2, 129.1, 129.3, 130.1, 131.4, 136.8, 137.8, 143.3, 159.8, 187.9.

3.3. General procedure for the reduction of α-oxo compounds 6a–k with $NaBH_4$

The crude α-oxo compound **6a–k** (0.1 mmol) was dissolved in anhydrous THF (5 mL) and was cooled to −10 °C under N_2. To the solution was then added $NaBH_4$ (0.1 mmol). The reaction mixture was stirred for about 35 min at −10 °C until the starting compound was no longer present as monitored by TLC. Saturated aqueous solution of $NaHCO_3$ was then added at −10 °C. The mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation, and the residue was purified by column chromatography with petroleum ether, $CHCl_3$, and CH_3OH as the eluent to give pure product of **4a–k**. The melting points of white solid **4a–k** were not obtained due to the isomerization of *syn* and *anti* at high temperature.

3.3.1. *trans*-Methyl 2-hydroxy-3-phenyl-3′-(*N*-tosyl-amino)propanoate (4a). IR (KBr) 3483, 2359, 1740 cm^{-1}; ^1HNMR ($CDCl_3$, 300 MHz) δ 2.32 (s, 3H), 2.86 (d, $J=6.5$ Hz, 1H), 3.64 (s, 3H), 4.51(dd, $J=3.3$, 6.5 Hz, 1H), 4.83 (dd, $J=3.3$, 9.0 Hz, 1H), 5.61 (d, $J=9.0$ Hz, 1H), 6.97–7.26 (m, 7H), 7.52 (d, $J=8.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 52.6, 59.2, 73.7, 126.8, 127.3, 127.9, 128.1, 129.2, 134.8, 137.4, 142.9, 171.5; EI-MS (*m/z*, relative intensity) 260 [$(M-89)^+$, 193], 155 (51), 91 (100). Anal. Calcd for $C_{17}H_{19}O_5NS$: C, 58.44; H, 5.48; N, 4.01. Found: C, 58.28; H, 5.44; N, 4.16.

3.3.2. *trans*-Methyl 2-hydroxy-3-(*p*-phenyl)phenyl-3′-(*N*-tosylamino)propanoate (4b). IR (KBr) 3480, 2362, 1751 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.27 (s, 3H), 3.09 (d, $J=6.6$ Hz, 1H), 3.68 (s, 3H), 4.58 (dd, $J=3.6$, 6.6 Hz, 1H), 4.89 (dd, $J=3.6$, 9.0 Hz, 1H), 7.03 (d, $J=9.0$ Hz, 1H), 7.02–7.53 (m, 13H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 52.7, 58.9, 73.6, 126.9, 126.9, 126.9, 127.5, 127.9, 128.7, 129.3, 133.7, 137.5, 140.3, 140.9, 143.1, 171.6; EI-MS (*m/z*, relative intensity) 336 [$(M-89)^+$, 71], 180 (29), 155 (36), 91 (100). Anal. Calcd for $C_{23}H_{23}O_5NS$: C, 64.92; H, 5.45; N, 3.29. Found: C, 64.81; H, 5.70; N, 2.98.

3.3.3. *trans*-Methyl 2-hydroxy-3-(*p*-fluoro)phenyl-3′-(*N*-tosylamino)propanoate (4c). IR (KBr) 3054, 2361, 1748 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.34 (s, 3H), 3.66 (s, 3H), 2.91(d, $J=5.8$ Hz, 1H), 4.52 (dd, $J=3.5$, 5.8 Hz, 1H), 4.83 (dd, $J=3.5$, 9.5 Hz, 1H), 5.62 (d, $J=9.5$ Hz, 1H), 6.76–7.26 (m, 6H), 7.50 (d, $J=8.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.4, 30.9, 52.8, 58.4, 73.4, 114.9, 115.4, 116.0, 126.9, 129.1, 129.4, 130.9, 137.5, 143.3, 171.4; EI-MS (*m/z*, relative intensity) 278 [$(M-89)^+$, 65], 155 (64), 91 (100); HRMS calcd for $C_{14}H_{13}NSO_2F$: 278.0651, found 278.0651.

3.3.4. *trans*-Methyl 2-hydroxy-3-(*p*-chloro)phenyl-3′-(*N*-tosylamino)propanoate (4d). IR (KBr) 3444, 2360, 1748 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H), 2.92 (d, $J=5.8$ Hz, 1H), 3.66 (s, 3H), 4.51 (dd, $J=3.6$, 5.8 Hz, 1H), 4.81 (dd, $J=3.6$, 9.6 Hz, 1H), 5.63 (d,

J=9.6 Hz, 1H), 6.92 (d, J=8.4 Hz, 2H), 7.05–7.26 (m, 4H), 7.47 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 52.9, 58.5, 73.3, 126.9, 128.4, 128.9, 129.4, 133.4, 134.2, 137.4, 143.4, 171.3; EI-MS (*m/z*, relative intensity) 294 [$(M-89)^+$, 63], 155 (83), 91 (100); HRMS calcd for $C_{14}H_{13}NSO_2Cl$: 294.0356, found 294.0362.

3.3.5. *trans*-Methyl 2-hydroxy-3-(*o*-methyl)phenyl-3′-(*N*-tosylamino)propanoate (4e). IR (KBr) 3445, 2361, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.20 (s, 3H), 2.32 (s, 3H), 3.17 (br, 1H), 4.54 (dd, J=4.2, 6.6 Hz, 1H), 5.94 (dd, J=4.2, 9.3 Hz, 1H), 5.74 (br, 1H), 6.91–7.16 (m, 6H), 7.50 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.0, 21.4, 52.5, 54.2, 72.9, 126.1, 126.8, 127.1, 127.9, 129.2, 130.4, 133.7, 135.3, 137.4, 143.1, 171.8; EI-MS (*m/z*, relative intensity) 274 [$(M-89)^+$, 100], 155 (54), 91 (100); MS (MALDI-TOF): 402 $(M+K)^+$, 386 $(M+Na)^+$; HRMS calcd for $C_{15}H_{16}NSO_2$ 274.0902, found 274.0902.

3.3.6. *trans*-Methyl 2-hydroxy-3-(*p*-methoxyl)phenyl-3′-(*N*-tosylamino)propanoate (4f). IR (film) 3286, 1741, 1252 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H), 2.94 (d, J=6.8 Hz, 1H), 3.66 (s, 3H), 3.73 (s, 3H), 4.50 (dd, J=3.4, 6.8 Hz, 1H), 4.78 (dd, J=3.4, 9.5 Hz, 1H), 5.65 (d, J=9.5 Hz, 1H), 6.63 (d, J=7.9 Hz, 2H), 6.91 (d, J=7.9 Hz, 2H), 7.08 (d, J=8.1 Hz, 2H), 7.52 (d, J=8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 52.7, 55.2, 58.6, 73.6, 113.6, 126.9, 127.0, 128.5, 129.3, 137.6, 143.0, 159.4, 171.6; EI-MS (*m/z*, relative intensity) 290 [$(M-89)^+$, 100], 134 (23), 91 (84); HRMS calcd for $C_{15}H_{16}O_3NS$: 290.0851, found 290.0845.

3.3.7. *trans*-Methyl 2-hydroxy-3-(*m*-bromo)phenyl-3′-(*N*-tosylamino)propanoate (4h). IR (film) 3283, 1741, 1333, 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.32 (s, 3H), 3.35 (d, J=5.9 Hz, 1H), 3.67 (s, 3H), 4.57 (dd, J=3.3, 5.9 Hz, 1H), 4.81 (dd, J=3.3, 9.6 Hz, 1H), 6.15 (d, J=9.6 Hz, 1H), 6.98–7.52 (m, 8H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.4, 52.8, 58.7, 73.4, 122.2, 126.2, 126.7, 126.8, 129.3, 129.7, 130.7, 130.9, 136.9, 137.0, 143.3, 171.3; EI-MS (*m/z*, relative intensity) 340 [$(M-89)^+$, 63], 338 (60), 155 (100), 91 (99), 77 (20), 51 (11); HRMS calcd for $C_{14}H_{13}O_2NSBr$: 337.9850, found 337.9848.

3.3.8. *trans*-Methyl 2-hydroxy-3-(*m*-cyano)phenyl-3′-(*N*-tosylamino)propanoate (4i). IR (film) 3271, 1742, 1333, 1159 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H), 2.98 (d, J=5.2 Hz, 1H), 3.69 (s, 3H), 4.55 (dd, J=3.4, 5.2 Hz, 1H), 4.87 (dd, J=3.4, 9.3 Hz, 1H), 5.68 (d, J=9.3 Hz, 1H), 7.10–7.50 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 53.0, 58.4, 73.1, 112.3, 118.0, 126.8, 129.0, 129.5, 131.3, 131.6, 132.1, 136.4, 137.1, 143.7, 171.1; EI-MS (*m/z*, relative intensity) 286 [$(M-89)^+$, 14], 285 (78), 156 (10), 155 (93), 91 (100), 65 (22); HRMS calcd for $C_{15}H_{13}O_2N_2S$: 285.0698, found 285.0693.

3.3.9. *trans*-Methyl 2-hydroxy-3-(2,4-dichloro)phenyl-3′-(*N*-tosylamino)propanoate (4j). IR (KBr) 3447, 2361, 1631 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.35 (s, 3H), 3.08 (d, J=6.6 Hz, 1H), 3.68 (s, 3H), 4.59 (dd, J=3.9, 6.6 Hz, 1H), 5.33 (d, J=3.9, 9.7 Hz, 1H), 5.80 (d, J=9.7 Hz, 1H), 6.97–7.57 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 29.7, 52.8, 54.6, 72.5, 126.9, 127.1, 129.4, 130.4, 131.5, 133.6, 134.6, 136.8, 143.6, 171.5; EI-MS (*m/z*, relative intensity) 328 [$(M-89)^+$, 52], 155 (74), 91 (100); MS (MALDI-TOF): 456 $(M+K)^+$, 440 $(M+Na)^+$, 418 $(M+H)^+$; HRMS for $C_{14}H_{12}NSO_2^{35}Cl_2$ 327.9966, found 327.9968.

3.3.10. *trans*-Methyl 2-hydroxy-3-(2,6-dichloro)phenyl-3′-(*N*-tosylamino)propanoate (4k). IR (KBr) 3450, 2362, 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.29 (s, 3H), 2.86 (d, J=9.3 Hz, 1H), 3.86 (s, 3H), 4.62 (t, J=9.3 Hz, 1H), 5.44 (dd, J=9.3, 11.1 Hz, 1H), 6.03 (d, J=11.1 Hz, 1H), 6.99–7.28 (m, 6H), 7.56–7.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 29.7, 52.9, 56.8, 71.5, 126.7, 128.6, 129.2, 129.5, 129.7, 131.5, 133.3, 136.8, 143.3, 172.5; EI-MS (*m/z*, relative intensity) 328 [$(M-89)^+$, 46], 155 (58), 91 (100); MS (MALDI-TOF): 456 $(M+K)^+$, 440 $(M+Na)^+$; HRMS for $C_{14}H_{12}NSO_2^{35}Cl_2$ calcd 327.9966, found 327.9973.

3.4. General procedure for the hydrogenation of α-oxo compounds 6a–f catalyzed with Pd/C

To a solution of α-oxo compound **6a–f** (0.1 mmol) in anhydrous MeOH (15 mL) was added 10% Pd/C catalyst (10 mg). The reaction mixture was stirred for 24 h under 1 atm hydrogen atmosphere. Then Pd/C catalyst was removed by fast column chromatography with MeOH as the eluent. The solvent was evaporated to give a crude residue, which was purified by column chromatography with petroleum ether, $CHCl_3$, and MeOH to give the pure product of **5a–f**. The melting points of white solid **5a–f** were not obtained due to the isomerization of *syn* and *anti* at high temperature.

3.4.1. *cis*-Methyl 2-hydroxy-3-phenyl-3′-(*N*-tosylamino)-propanoate (5a). IR (film) 3281, 1738, 1158 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.32 (s, 3H), 3.31 (d, J=4.5 Hz, 1H), 3.76 (s, 3H), 4.35 (dd, J=4.5, 2.4 Hz, 1H), 4.85 (dd, J=9.2, 2.4 Hz, 1H), 5.75 (d, J=9.2 Hz, 2H), 7.07–7.26 (m, 7H), 7.53 (d, J=8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 53.2, 58.9, 74.2, 126.9, 127.0, 127.8, 128.4, 129.3, 137.4, 137.5, 143.2, 172.5. EI-MS (*m/z*, relative intensity) 260 [$(M-89)^+$, 100], 155 (41), 91 (54). MS (MALDI-TOF) 388 $(M+K)^+$, 372 $(M+Na)^+$. Anal. Calcd for $C_{17}H_{19}O_5NS$: C, 58.44; H, 5.48; N, 4.01. Found: C, 58.39; H, 5.63; N, 3.76.

3.4.2. *cis*-Methyl 2-hydroxy-3-(*p*-phenyl)phenyl-3′-(*N*-tosylamino)propanoate (5b). IR (KBr) 3303, 1708 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.28 (s, 3H), 3.34 (d, J=4.2 Hz, 1H), 3.78 (s, 3H), 4.39 (br, 1H), 4.91(d, J=9.8 Hz, 1H), 5.75 (d, J=9.8 Hz, 1H), 7.06–7.55 (m, 13H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 53.3, 58.8, 74.2, 126.9, 127.1, 127.4, 128.8, 129.3, 136.3, 136.4, 137.5, 137.6, 140.5, 140.8, 143.2, 172.5; EI-MS (*m/z*, relative intensity) 336 [$(M-89)^+$, 100], 180 (18), 155 (36), 91 (83). MS (MALDI-TOF): 448 $(M+K)^+$, 464 $(M+Na)^+$. Anal. Calcd for $C_{23}H_{23}O_5NS$: C, 64.92; H, 5.45; N, 3.29. Found: C, 65.08; H, 5.30; N, 3.14.

3.4.3. *cis*-Methyl 2-hydroxy-3-(*p*-fluoro)phenyl-3′-(*N*-tosylamino)propanoate (5c). IR(KBr) 3445, 2361, 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.34 (s, 3H),

3.45 (br, 1H), 3.77 (s, 3H), 4.32 (s, 1H), 4.83 (dd, J=2.1, 9.9 Hz, 1H), 5.93 (d, J=9.9 Hz, 1H), 6.79–7.14 (m, 6H), 7.52 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.3, 53.2, 58.4, 74.2, 115.0, 115.3, 126.9, 128.7, 128.8, 129.3, 133.2, 137.4, 143.3, 160.6, 163.9, 172.4; EI-MS (*m/z*, relative intensity) 278 [$(M-89)^+$, 68], 155 (66), 91 (100); HRMS calcd for $C_{14}H_{13}NSO_2F$: 278.0651, found 278.0648.

3.4.4. *cis*-Methyl 2-hydroxy-3-(*p*-chloro)phenyl-3′-(*N*-tosylamino)propanoate (5d). IR (KBr) 3448, 2361, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H), 3.16 (d, J=4.0 Hz, 1H), 3.76 (s, 3H), 4.35 (dd, J=4.0, 2.3 Hz, 1H), 4.85 (dd, J=2.3, 9.8 Hz, 1H), 5.47 (d, J=9.8 Hz, 1H), 7.09–7.20 (m, 6H), 7.52 (d, J=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 53.3, 58.9, 74.1, 126.8, 127.0, 127.9, 128.4, 129.3, 137.4, 137.5, 143.2, 172.4. EI-MS (*m/z*, relative intensity) 327 [$(M-56)^+$, 5], 294 [$(M-89)^+$, 14], 260 (100), 155 (76), 91 (100); HRMS calcd for $C_{14}H_{13}NSO_2Cl$: 294.0356, found 294.0357.

3.4.5. *cis*-Methyl 2-hydroxy-3-(*o*-methyl)phenyl-3′-(*N*-tosylamino)propanoate (5e). IR (KBr) 3269, 2361, 1749 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.29 (s, 3H), 3.44 (br, 1H), 3.79 (s, 3H), 4.24 (br, 1H), 5.15 (dd, J=2.1, 9.7 Hz, 1H), 6.02 (d, J=9.7 Hz, 1H), 6.95–7.10 (m, 6H), 7.48 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.1, 21.3, 53.2, 54.9, 73.1, 126.0, 126.8, 127.4, 129.1, 130.2, 134.3, 135.3, 137.3, 142.9, 172.7; EI-MS (*m/z*, relative intensity) 274 [$(M-89)^+$, 74], 155 (58), 91 (100); HRMS calcd for $C_{15}H_{16}NSO_2$: 274.0902 [$(M-89)^+$], found 274.0904.

3.4.6. *cis*-Methyl 2-hydroxy-3-(*p*-methoxyl)phenyl-3′-(*N*-tosylamino)propanoate (5f). IR (film) 3282, 1739, 1250, 1158 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.33 (s, 3H), 3.32 (d, J=4.6 Hz, 1H), 3.74 (s, 6H), 4.31 (dd, J=2.4, 4.6 Hz, 1H), 4.78 (dd, J=2.4, 9.6 Hz, 1H), 5.71 (d, J=9.6 Hz, 1H), 6.66–6.71 (m, 2H), 7.03–7.26 (m, 4H), 7.53 (d, J=8.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.4, 53.1, 55.2, 58.6, 74.3, 113.7, 127.0, 128.0, 129.2, 129.4, 137.5, 143.0, 159.1, 172.6; EI-MS (*m/z*, relative intensity) 290 [$(M-89)^+$, 100], 155 (38), 134 (21), 92 (10); HRMS calcd for $C_{15}H_{16}O_3NS$: 290.0851, found 290.0844.

Acknowledgements

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13. The authors have deposited the refined coordinates for **4c** with the Cambridge Crystallographic Data Centre (deposition number 235122). Copies of the available material can be obtained free of charge on application to the CCDC, 12, Union Road, Cambridge, CB2 1EZ, UK Email: deposit@ccdc.cam.ac.uk.
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Mild and efficient copper-catalyzed *N*-arylation of alkylamines and N–H heterocycles using an oxime-phosphine oxide ligand

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Abstract—A mild and efficient copper-catalyzed system for *N*-arylation of alkylamines and N–H heterocycles with aryl iodides using a novel, readily prepared and highly stable oxime-functionalized phosphine oxide ligand was developed. The coupling reactions could even be performed in solvent-free conditions with moderate to good yields.

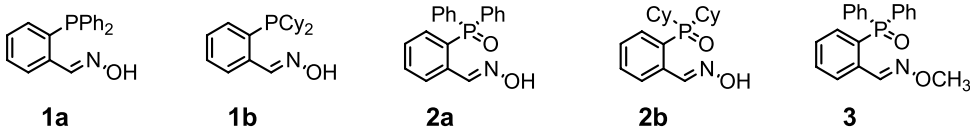
1. Introduction

Recently, copper-catalyzed Ullmann-type C(aryl)–N bond formation under mild conditions has become a focus of research to include a wide range of subsrates.[1–3] By using certain copper precatalysts and ligands, successful *N*-arylation of anilines,[4,5] amides,[6] amino acid,[7] amino alcohols,[8] hydrazides,[9] oxazolidinones[10] and various N–H heterocycles[6a,11] with aryl halides as arylating reagents was reported. However, only limited papers have contributed to *N*-arylation of alkylamines (not chelating substrates) and just several ligands were found to be effective in these transformation.[12] Therefore, to find more efficient ligands and expand the scope of the substrates are desirable.

In copper-mediated cross-coupling systems, the most used ligands were those containing nitrogen and/or oxygen bidentated with copper, while phosphines were mainly used in palladium-mediated systems.[13] Only recently, several phosphine ligands have been reported in Cu-catalyzed reactions of arylamines with aryl halides.[5] However, no efficient phosphine ligands for copper have been described for cross coupling of alkylamines with aryl halides to the best of our knowledge. In our initial studies, we attempted to find a highly efficient phosphine to achieve this coupling and have designed two oxime-functionalized phosphines (Fig. 1, **1a** and **1b**).[14] To our disappointment, neither of them were satisfying. We then tried using their oxides (**2a** and **2b**) as ligands considering that they have potential chelating ability to copper.[15] After a series of experiments, we found that both of **2a** and **2b** were effective supporting ligands and demonstrated excellent stability. Herein, we report a new class of oxime-phosphine oxide ligands (**2**) for copper-catalyzed *N*-arylation of alkylamines and N–H heterocycles under mild conditions.

2. Results and discussion

The synthesis of various phosphines and phosphine oxides was depicted in Scheme 1. Ligand **1a** was conveniently synthesized from commercially available **4** in one step. **2a** was readily prepared by oxidizing **1a**. Both **1a** and **2a** were obtained by recrystallization rather than using complex column chromatography. Similarly, ligand **1b** was readily prepared from 2-(dicyclohexylphosphino)benzaldehyde (**5**) which was prepared according to the literature.[16] Further



1a **1b** **2a** **2b** **3**

Figure 1.

Keywords: *N*-arylation; Oxime-phosphine oxide; Aryl iodides; Copper; Catalysis.
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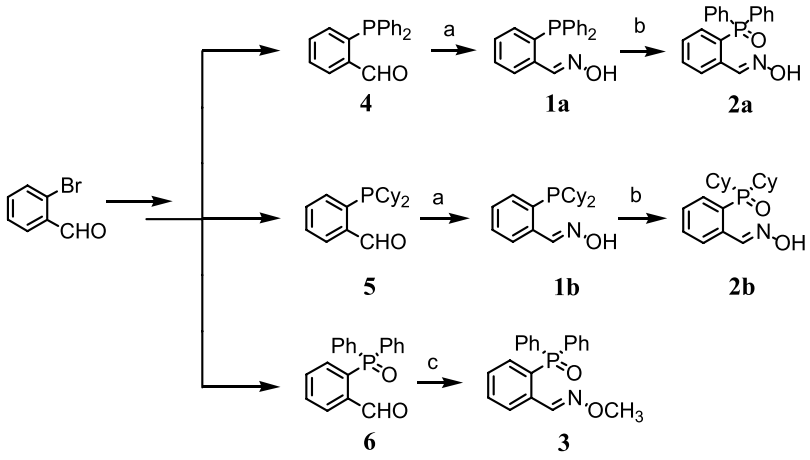
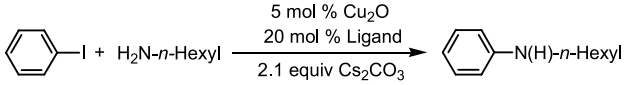


Scheme 1. Synthesis of the ligands. Reaction conditions: (a) H_2N–OH·HCl, $NaHCO_3$, H_2O, EtOH; (b) H_2O_2, CH_2Cl_2; (c) H_2N–OCH_3·HCl, $NaHCO_3$, H_2O, EtOH.

oxidizing **1b** gave **2b**. As a comparison, ligand **3** was also synthesized.

In our initial screening experiments, iodobenzene and *n*-hexylamine were used as model substrates to examine the above ligands (Table 1). Neither **1a** nor **1b** were efficient when the reactions were performed at 60 °C (entries 1 and 2). To our delight, both of their oxides (**2a** and **2b**) were highly effective giving the coupling product in high yields under the same conditions (entries 3 and 4). Moreover, the use of **1a** could only give a 78% conversion of the iodobenzene and 42% yield after 24 h at an elevated temperature of 90 °C (entry 1 in paretheses). These results showed that the phosphine oxides were remarkablely superior to the corresponding phosphines. Additionally, ligand **3** was not effective at all for the reaction (entry 5). Apparently, both the moieties of P═O and oxime were critical. **2a** was slightly better in result and more available than **2b**, so we chose for further study.

Table 1. Screening of the ligands[a]



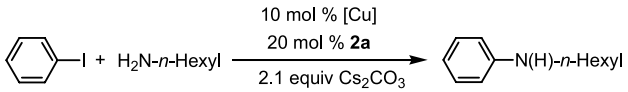
Entry	Ligand	Conversion, %[b]	Yield, %[b]
1	**1a**	0 (78)[c]	0 (42)[c]
2	**1b**	0	0
3	**2a**	95	92
4	**2b**	92	88
5	**3**	0	0

[a] Reaction conditions: 1.0 mmol PhI, 1.2 mmol *n*-hexylamine, 0.05 mmol Cu_2O, 0.2 mmol ligand, 2.1 mmol Cs_2CO_3, 0.2 mL CH_3CN, 60 °C, 18 h.
[b] GC yield.
[c] 24 h, 90 °C.

Preliminary results showed that the use of Cs_2CO_3 was important to the effectiveness, while K_3PO_4, K_2CO_3 or KOH only gave poor results.[17,18] Among the copper sources investigated, air and light stable Cu_2O was optimal (Table 2). CuBr, CuI, CuCN and Cu power only provided inferior results, while the use of CuO resulted in bad yield. A brief survey for solvent influence showed that the model reaction could be conducted with comparable efficiency in a wide range of solvents including CH_3CN, dioxane, DMF, toluene or even crude CH_3OH; while pyridine, THF or DMSO were less efficient. Hence, CH_3CN with lower polarity and boiling point was chosen for subsequent experiments.

The scope of the copper-catalyzed *N*-arylation of different amines was explored generally by using 5 mol% Cu_2O, 20 mol% **2a** and 2.1 equiv Cs_2CO_3 in CH_3CN. The results of aryl iodides with primary amines are detailed in Table 3. As we can see, various primary amines including *n*-hexylamine, *sec*-butylamine, *iso*-butylamine, cyclopentylamine were coupled successfully (entries 1–5). The reaction of iodobenzene with benzylamine resulted in an excellent yield of 95% with 1 mol% Cu_2O, the best result reported so far (entry 6). Both electron-donating and electron-withdrawing group, such as methoxy, cyano, nitro, trifluoromethyl were tolerated on the aryl iodide component (entries 8–13). Compared with the previous reported results, the couplings of both 3-iodobenzonitrile and 1-iodo-3-nitrobenzene with benzylamine were more effective (entries 12 and 13).[12b]

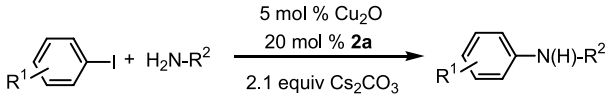
Table 2. Optimization studies[a]

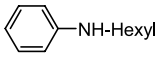
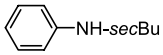
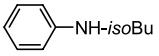
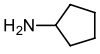
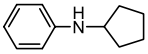
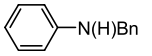
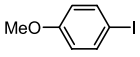
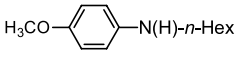
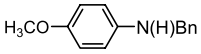
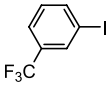
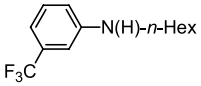
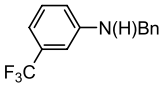
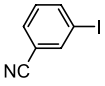
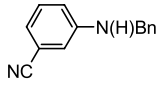
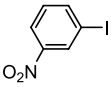
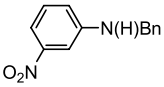
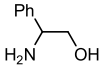
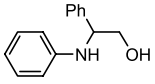


Entry	[Cu]	Solvent	Conversion, %[b]	Yield, %[b]
1	Cu_2O	CH_3CN	95	92[c]
2	Cu_2O	Dioxane	95	92
3	Cu_2O	DMF	93	91
4	Cu_2O	Toluene	92	90
5	Cu_2O	CH_3OH	96	89
6	Cu_2O	Pyridine	84	77
7	Cu_2O	DMSO	77	70
8	Cu_2O	THF	82	74
9	CuO	CH_3CN	20	18
10	CuBr	CH_3CN	95	83[d]
11	CuI	CH_3CN	95	83[d]
12	CuCN	CH_3CN	91	81[d]
13	Cu Power	CH_3CN	76	70[d]

[a] Reaction conditions: 1.0 mmol PhI, 1.2 mmol *n*-hexylamine, 10 mol% [Cu], 20 mmol% **2a**, 2.1 mmol Cs_2CO_3, 0.2 mL solvent, 60 °C, 18 h.
[b] GC yield.
[c] Using 5 mol% [Cu], nearly identical result could be obtained.
[d] Using 5 mol% [Cu].

Table 3. Coupling of aryl iodides with primary amines[a]



Entry	ArI	Amine	Product	Yield, %[b]
1		H_2N-*n*-Hexyl		88
2				85[c]
3		NH_2-*sec*-Bu		65
4		NH_2-*i*-Bu		80
5				88[d]
6		H_2NBn		95[e]
7				85[c]
8		H_2N-*n*-Hexyl		78[f]
9		H_2NBn		90
10		H_2N-*n*-Hexyl		76
11		H_2NBn		91
12		H_2NBn 1.5 equiv		85[d,g]
13		H_2NBn 1.5 equiv		87[d,g]
14				91

[a] Reaction conditions: 1.0 mmol ArI, 1.2 mmol amine, 0.05 mmol Cu_2O, 0.2 mmol **2a**, 2.1 mmol Cs_2CO_3, 0.6 mL CH_3CN, 80 °C, 18 h.
[b] Isolated yield.
[c] 60 °C.
[d] 90 °C.
[e] 1 mol% Cu_2O was used.
[f] $PhCH_3$ as solvent.
[g] 24 h.

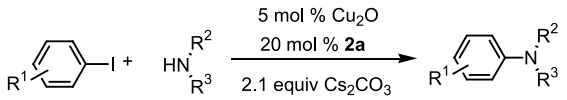
Moreover, aminoalcohol could also be transformed to the desired product in high yield (entry 14). Notably, diarylation products were minimal in all reactions.

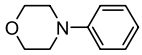
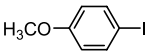
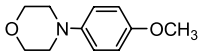
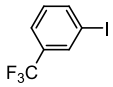
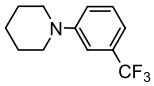
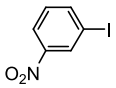
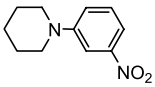
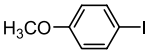
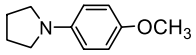
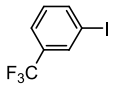
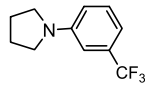
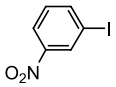
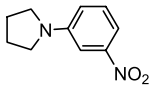
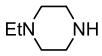
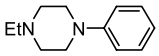
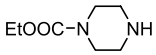
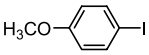
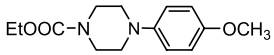
The optimized reaction condition was also used to examine the couplings of cyclic secondary amines with aryl iodides (Table 4). Morpholine was shown to be a good substrate to give the desired product in high yield, the best result to date (entry 1). Other cyclic secondary amines such as piperidine, pyrrolidine, *N*-ethylpiperazine and ethyl 1-piperazine-carboxylate could also be coupled successfully with aryl iodides (entries 2–9). In general, secondary amines gave the corresponding arylated products in slightly lower yields.

The practical benefits of these copper-catalyzed amination methodology were briefly noted. On one hand, although the reactions were moderately sensitive to oxygen and have to be performed under an inert atmosphere, neither glove-box techniques nor further purification of the commercially available reagents were essential. On the other hand, the key ligand **2a** could be obtained readily from commercial available materials and it was stable and not hydroscopic. Furthermore, we found that this newly developed protocol could also be applied to the coupling of N–H heterocycles with aryl iodides in mild conditions (Table 5).

As seen in Table 5, several *N*-heterocycles could be effectively transformed to the desired products. The arylation of pyrazole was carried out smoothly using various aryl iodides (entries 1–4). It is noteworthy that the reaction of pyrazole with iodobenzene could even be performed at rt (entry 2). Imidazole was transformed to

Table 4. Coupling of aryl iodides with cyclic secondary amines[a]



Entry	Amine	ArI	Product	Yield, %[b]
1				85
2				70[c]
3				70[d]
4				68[d]
5				65[d]
6				72[d]
7				73[d]
8				72
9				60[e]

[a] Reaction conditions: 1.0 mmol ArI, 1.2 mmol amine, 0.05 mmol Cu_2O, 0.2 mmol **2a**, 2.1 mmol Cs_2CO_3, 0.6 mL CH_3CN, 80 °C, 18 h.
[b] Isolated yield.
[c] $PhCH_3$ as solvent.
[d] 90 °C, 1.5 equiv amines.
[e] 24 h, 90 °C.

the desired product with high yield (entry 5). The arylation of benzimidazole and indole also proved to be successful under the general conditions (entries 6 and 7).

The use of such stable, readily available and efficient ligand as well as mild reaction condition made this protocol attractive. Furthermore, as seen in Table 6, different amine could be coupled with aryl iodides successfully in the solvent-free condition with moderate to good yields. This enhanced the attractiveness for practical utility.[12a,19]

3. Conclusion

In summary, we have developed a mild and efficient copper-catalyzed system for *N*-arylation of alkylamines and N–H heterocycles with aryl iodides using a novel, readily prepared and highly stable oxime-functionalized phosphine oxide ligand. The reaction could even be performed in solvent-free conditions. Although this method is restricted to the coupling of aryl iodides, the readily available ligand with excellent stability and high efficiency makes this protocol of potentially practical utility in many cases. Further studies to expand the application of this method to other catalytic reactions are currently underway.

4. Experimental

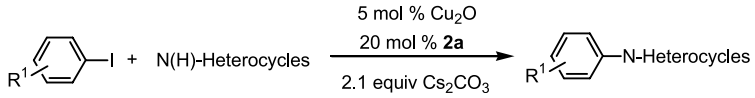
4.1. Materials and methods

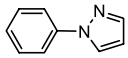
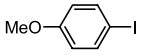
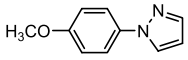
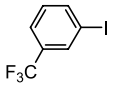
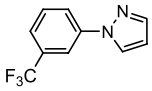
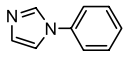
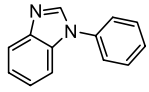
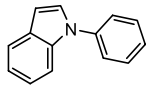
Melting points were measured on a Yazawa micro melting point apparatus (uncorrected). ^1H, ^{31}P and ^{13}C NMR spectra were measured on a Bruker DRX-400 NMR spectrometer (400 MHz) with TMS as an internal reference. $CDCl_3$ was used as the solvent for all NMR spectra unless otherwise stated. High-resolution mass spectra (HRMS) were recorded on a Mariner 5303 (Applied Biosystems, USA). All products were characterized by ^1H NMR and HRMS and compared with the previously reported data.[11,12a,b,c] All reactions were carried out under an argon atmosphere. Column chromatography purifications were performed using silica gel. All solvents were dried and degassed by standard methods and all starting materials were commercially available. Petroleum ether refers to the boiling range 60–90 °C. When solvent gradient was used, the increase of polarity was made gradually from petroleum ether to mixtures of petroleum ether/ethyl acetate until the isolation of the product.

4.2. Synthesis of ligands

4.2.1. 2-(Diphenylphosphino)-benzaldoxime (1a). An

Table 5. Coupling of aryl iodides with various *N*-heterocycles[a]

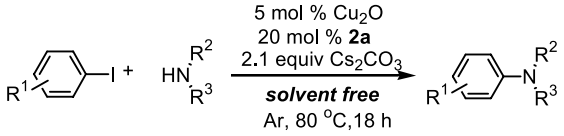


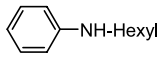
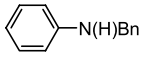
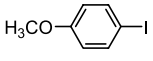
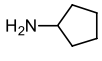
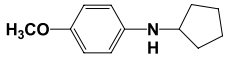
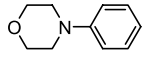
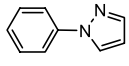
Entry	Amine	ArI	Product	Yield, %[b]
1				94
2				65[c]
3				95
4				81
5				92
6				60
7				64

[a] Reaction conditions: 1.0 mmol ArI, 1.2 mmol amine, 0.05 mmol Cu_2O, 0.2 mmol **2a**, 2.1 mmol Cs_2CO_3, 0.6 mL CH_3CN, 80 °C, 18 h.
[b] Isolated yield.
[c] Performed at rt.

aqueous solution (20 mL) containing hydroxylamine hydrochloride (938.0 mg, 13.5 mmol) was prepared and $NaHCO_3$ (1.51 g, 18 mmol) was added under stirring. 2-(Diphenylphosphino)benzaldehyde (**4**) (3.34 g, 9 mmol) was dissolved in EtOH (50 mL) in reflux and the above aqueous solution was added dropwise. After the reaction mixture was refluxed continuously for 2 h, the mixture was cooled to rt with stirring. The white solid was filtered (1.8 g) and the filtrate was concentrated, exacted with Et_2O, washed with H_2O, dried (Na_2SO_4). The solution was concentrated to give the product (0.8 g). The two portions weighed 2.6 g of crude product (95%). The crude product could be used directly in the next step without further purifications, or can be recrystallized from ethanol to give the product **1a** as a white solid in 83% yield. Mp 176–177 °C. ^{1}H NMR δ 8.81 (d, 1H, J=4.4 Hz), 7.81–7.84 (m, 1H), 7.67(s, 1H), 7.23–7.38 (m, 12H), 6.90–6.93 (m, 1H). ^{31}P NMR δ −13.4. ^{13}C NMR δ 149.3, 149.1, 136.8, 136.6, 136.2, 136.0, 135.9,

Table 6. Solvent-free Cu-catalyzed amination of aryl iodides[a]



Entry	ArI	Amine	Product	Yield, %[b]
1		H_2N-*n*-Hexyl		78
2		H_2NBn		87
3				64[c]
4				62[c]
5				70

[a] Reaction conditions: 1.0 mmol ArI, 1.2 mmol amine, 0.05 mmol Cu_2O, 0.2 mmol **2a**, 2.1 mmol Cs_2CO_3, 80 °C, 18 h.
[b] Isolated yield.
[c] Performed 24 h at 90 °C.

134.2, 133.9, 133.9, 130.0, 129.2, 129.1, 128.9, 128.8, 126.7. HRMS (APCI) calcd for $C_{19}H_{17}NOP$ ($M+H^+$): 306.1042, found: 306.1050.

4.2.2. 2-(Diphenylphosphinyl)-benzaldoxime (2a). Compound (**1a**) (2.60 g, 8.5 mmol) was dissolved in CH_2Cl_2 (50 mL) and 30% H_2O_2 (4 mL) was added at rt. The mixture was stirred for 2 h and large amount of white solid precipitated. The solid was filtered and washed with water then recrystallized from MeOH to give the product as a white solid (1.7 g, 70%). Mp 203–206 °C. ^1H NMR (400 MHz, DMSO-d^6) δ 11.43 (s, 1H), 8.74 (s, 1H), 8.01–8.03 (m, 1H), 7.43–7.66 (m, 12H), 7.01–7.07 (m, 1H). ^{31}P NMR δ 30.5. ^{13}C NMR δ 146.3, 136.6, 133.0, 132.9, 132.3, 131.8, 131.5, 131.4, 131.0, 130.0, 129.0, 128.9, 128.7, 126.3, 126.2. HRMS (APCI) calcd for $C_{19}H_{17}NO_2P$ ($M+HP^+$): 322.0991, found: 322.1021.

4.2.3. 2-(Diphenylphosphinyl)benzaldehyde *O*-methyloxime (3). An aqueous solution (10 mL) containing methoxylamine hydrochloride (45.0 mg, 0.54 mmol) was prepared and $NaHCO_3$ (53.0 mg, 0.63 mmol) was added with stirring. Compound **6** (138.0 mg, 0.45 mmol) was dissolved in ethanol (10 mL) and the above aqueous solution was added dropwise. The reaction mixture was refluxed continuously for 1 h, The reaction mixture was concentrated, extracted with ethyl acetate, washed with H_2O, brine and dried (Na_2SO_4). The solution was concentrated to give a crude product which was purified by column chromatograph on silica gel to afford a white solid 0.12 g (80%). Mp 123–125 °C. ^1H NMR (400 MHz, DMSO-d^6) δ 8.83 (s, 1H), 7.99–8.01 (m, 1H), 7.48–7.68 (m, 12H), 7.04–7.10 (m, 1H), 3.81 (s, 3H). ^{31}P NMR δ 30.5 ^{13}C NMR δ 147.5, 136.9, 133.6, 133.5, 133.0, 132.2, 132.1, 128.9, 128.8, 127.6, 127.5, 62.1. HRMS (APCI) calcd for $C_{20}H_{19}NO_2$ ($M+H^+$): 336.1148, found: 336.1134.

4.2.4. 2-(Dicyclohexylphosphino)-benzaldoxime (1b). 2-(Dicyclohexylphosphino)-benzaldehyde (1.0 g, 3.3 mmol) was dissolved in deoxygenated ethanol and the solution was transferred to a flask including 30 mL of deoxygenated ethanol flushed by nitrogen. Hydroxylamine hydrochloride (1.39 mg, 20 mmol) was dissolved in deoxygenated H_2O (40 mL) and $NaHCO_3$ (2.5 g, 30 mmol) was added under stirring. The aqueous solution was added dropwise to the 2-(dicyclohexylphosphino)-benzaldehyde solution, and the reaction mixture was stirred for 1 h. The resulting mixture was extracted with Et_2O and dried over Na_2SO_4, concentrated, and purified by flash chromatograph on a short silica gel column with N_2 pressure (100% petroleum ether) to give the product as a white solid (390 mg, 37%). Mp 116–118 °C. ^1H NMR δ 9.16–9.18 (m, 1H), 8.05 (s, 1H), 7.85–7.86 (m, 1H), 7.48–7.50 (m, 1H), 7.33–7.39 (m, 3H), 0.97–1.97 (m, 22H). ^{31}P NMR δ −15.9. ^{13}C NMR δ 150.7, 150.4, 135.1, 133.0, 128.9, 126.3, 33.4, 33.3, 30.5, 30.3, 28.9, 27.4, 27.2, 27.1, 26.4. HRMS (APCI) calcd for $C_{19}H_{29}NO$ ($M+H^+$): 318.1981, found: 318.1988.

4.2.5. 2-(Dicyclohexylphosphinyl)-benzaldoxime (2b). To a solution of 2-(dicyclohexylphosphino)-benzaldoxime (159 mg, 0.5 mmol) in CH_2Cl_2 (20 mL), H_2O_2 (1.0 ml) was added under rt. The mixture was stirred for 1 h. The organic layer was separated and washed with water, dried (Na_2SO_4), concentrated to give the product as a white solid. Mp 199–202 °C. ^1H NMR δ 9.29 (s, 1H), 7.98–8.00 (m, 1H), 7.45–7.51 (m, 3H), 1.13–2.15 (m, 22H). ^{31}P NMR δ 53.1. ^{13}C NMR δ 149.9, 131.9, 131.5, 128.8, 128.2, 36.7, 36.0, 26.5, 25.8, 25.1. HRMS (APCI) calcd for $C_{19}H_{29}NO_2$ ($M+H^+$): 334.1930, found: 334.1918.

4.3. General procedure for copper-catalyzed *N*-arylation of various amines

Cu_2O (7.4 mg, 0.05 mmol), ligand (0.2 mmol), Cs_2CO_3 (685.0 mg, 2.1 mmol) and aryl iodides (if solid, 1.0 mmol) were weighed in air and transferred into a dried Schlenk tube. The tube was evacuated and back filled with argon (3 cycles). Freshly distilled CH_3CN, aryl iodides (if liquid, 1.0 mmol) and amines (1.2 mmol) were injected to the tube successively by micro-syringe at rt. The tube was sealed and stirred in an oil bath (preheated to reaction temperature) for the required timeperiod. The reaction mixture was cooled to rt, ethyl acetate (3 mL), H_2O (3 mL) and tetradecane (100 μL, GC standard) were added. The organic layer was analyzed by GC and separated. The aqueous layer was further extracted by ethyl acetate (10 mL×4). The combined organic layers were washed with brine, dried (Na_2SO_4). Then the solution was concentrated to give a residue, which was purified by column chromatograph on silica gel. The characterization of the products is listed following.

4.3.1. *N*-Hexylaniline (Table 3, entry 1). A liquid (155.0 mg, 88% yield). ^1H NMR: δ 7.21–7.25 (m, 2 H), 6.73–6.77 (m, 1 H), 6.66 (d, 2 H, J=7.6 Hz), 3.36 (s, 1H), 3.15 (t, 2H, J=7.2 Hz), 1.63–1.70 (m, 2H), 1.33–1.49 (m, 6H), 0.97 (t, 3H, J=6.8 Hz). HRMS (APCI) calcd for $C_{12}H_{20}N$ ($M+H^+$): 178.1590, found: 178.1580.

4.3.2. *N*-(*sec*-Butyl)aniline (Table 3, entry 3). A liquid (97.0 mg, 65% yield). ^1H NMR: δ 7.13–7.17 (m, 2H), 6.63–7.67 (m, 1H), 6.57 (d, 2H, J=8 Hz), 3.36–3.43 (m, 2H), 1.55–1.63 (m, 1H), 1.43–1.50 (m, 1H), 1.14–1.17 (m, 3H), 0.93–0.97 (m, 2H). HRMS (APCI) calcd for $C_{10}H_{16}N$ ($M+H^+$): 150.1277, found: 150.1272.

4.3.3. *N*-(*iso*-Butyl)aniline (Table 3, entry 4). A liquid (119.0 mg, 80% yield). ^1H NMR: δ 7.14–7.18 (m, 2H), 6.67–6.69 (m, 1H), 6.60 (d, 2H, J=8 Hz), 3.74 (br, 1H), 2.92 (d, 2H, J=6.8 Hz), 1.85–1.90 (m, 1H), 0.97 (d, 6H, J=6.8 Hz). HRMS (APCI) calcd for $C_{10}H_{16}N$ ($M+H^+$): 150.1277, found: 150.1285.

4.3.4. *N*-Cyclopentylaniline (Table 3, entry 5). A liquid (142.0 mg, 88% yield). ^1H NMR: δ 7.13–7.20 (m,2H), 6.65–6.68 (m,1H), 6.58–6.60 (m, 2H), 3.74–3.80 (m, 1H), 3.61 (s, 1H), 1.98–2.02 (m, 2H), 1.67–1.73 (m, 2H), 1.59–1.62 (m, 2H), 1.43–1.47 (m, 2H). HRMS (APCI) calcd for $C_{11}H_{16}N$ ($M+H^+$): 162.1277, found: 162.1283.

4.3.5. *N*-(Phenyl)benzylamine (Table 3, entry 6). A white solid (174.0 mg, 95% yield). ^1H NMR: δ 7.34–7.38 (m, 4H), 7.25–7.29 (m, 1H), 7.16–7.19 (m, 2H), 6.72–6.74 (m, 1H), 6.64–6.70 (m, 2H), 4.33 (s, 2H), 4.25 (br, 1H). HRMS (APCI) calcd for $C_{13}H_{14}N$ ($M+H^+$): 184.1121, found: 184.1119.

4.3.6. 4-Methoxy-*N*-hexylaniline (**Table 3**, entry 8). A liquid (162.0 mg, 78% yield). ^{1}H NMR: δ 6.77 (d, 2H, J=8.8 Hz), 6.57 (d, 2H, J=8.8 Hz), 3.73 (s, 3H), 3.22 (br, 1H), 3.03–3.06 (m, 2H), 1.57–1.61 (m, 2H), 1.31–1.40 (m, 6H), 0.89 (t, 3H, J=6.4 Hz). HRMS (APCI) calcd for $C_{13}H_{22}NO$ (M+H$^+$): 208.1696, found: 208.1680.

4.3.7. *N*-(4-Methoxyphenyl)benzylamine (**Table 3**, entry 9). A solid (192.0 mg, 90% yield). ^{1}H NMR: δ 7.28–7.40 (m, 5H), 6.78–6.80 (m, 1H), 6.62 (d, 2H, J=8.6 Hz), 4.29 (s, 2H), 3.75 (s, 3H). HRMS (APCI) calcd for $C_{14}H_{16}NO$ (M+H$^+$): 214.1226, found: 214.1207.

4.3.8. 3-Trifluoromethyl-*N*-hexylaniline (**Table 3**, entry 10). A liquid (186.0 mg, 76% yield). ^{1}H NMR: δ 7.20–7.24 (m, 1H), 6.89–6.90 (d, 1H, J=7.6 Hz), 6.78 (s, 1Hz), 6.71 (d, 1H, J=8.0 Hz), 3.68 (br, 1H), 3.10 (t, 2H, J=7.2 Hz), 1.57–1.63 (m, 2H), 1.32–1.41 (m, 6H), 0.90 (t, 3H, J=6.4 Hz). HRMS (APCI) calcd for $C_8H_{19}N_3O_2F_3$ (M+H$^+$): 246.1424, found: 246.1441.

4.3.9. *N*-(3-Trifluoromethylphenyl)benzylamine (**Table 3**, entry 11). A liquid (228.0 mg, 91% yield). ^{1}H NMR: δ 7.18–7.33 (m, 6Hz), 6.92 (d, 1H, J=7.6 Hz), 6.82 (s, 1H), 6.71 (d, 1H, J=8.0 Hz), 4.30 (s, 2H), 4.15 (br, 1H). HRMS (APCI) calcd for $C_9H_{13}N_3O_2F_3$ (M+H$^+$): 252.0954, found: 252.0967.

4.3.10. *N*-(3-Cyanophenyl)benzylamine (**Table 3**, entry 12). A white solid (176.0 mg, 85% yield). ^{1}H NMR: δ 7.30–7.38 (m, 5H), 7.20–7.26 (m, 1H), 6.99 (d, 1H, J=7.2 Hz), 6.82–6.84 (m, 2H), 4.64 (br, 1H), 4.34 (s, 2H). HRMS (APCI) calcd for $C_{14}H_{13}N_2$ (M+H$^+$): 209.1073, found: 209.1064.

4.3.11. *N*-(3-Nitrophenyl)benzylamine (**Table 3**, entry 13). An orange solid (198.0 mg, 87% yield). ^{1}H NMR: δ 7.55 (d, 1H, J=7.6 Hz), 7.46 (s, 1H), 7.26–7.38 (m, 6H), 6.90 (d, 1H, J=7.6 Hz), 4.39 (s, 2H). HRMS (APCI) calcd for $C_{13}H_{13}N_2O_2$ (M+H$^+$): 229.0972, found: 229.0959.

4.3.12. 2-Phenyl-2-(phenylamino)ethanol (**Table 3**, entry 16). A colorless liquid (193.0 mg, 91% yield). ^{1}H NMR: δ 7.25–7.38 (m, 5H), 7.08–7.12 (m, 2H), 6.66–6.69 (m, 1H), 6.56 (d, 2H, J=8.0 Hz), 4.49–4.52 (m, 2H), 3.92–3.95 (m, 1H), 3.73–3.77 (m, 1H), 1.77 (br, 1H). HRMS (APCI) calcd for $C_{14}H_{16}NO$ (M+H$^+$): 214.1226, found: 214.1209.

4.3.13. *N*-(Phenyl)morpholine (**Table 4**, entry 1). A white solid (138.0 mg, 85% yield). ^{1}H NMR: δ 7.25–7.30 (m, 2H), 6.87–6.94 (m, 3H), 3.87 (t, 4H, J=4.0 Hz), 3.16 (t, 4H, J=4.0 Hz). HRMS (APCI) calcd for $C_{10}H_{14}NO$ (M+H$^+$): 164.1070, found: 164.1080.

4.3.14. *N*-(4-Methoxyphenyl)morpholine (**Table 4**, entry 2). A liquid (135.0 mg, 70% yield). ^{1}H NMR: δ 6.76–6.83 (m, 4H), 3.78 (t, 4H, J=5.2Hz), 3.69 (s, 3H), 2.97 (t, 4H, J=4.8Hz). HRMS (APCI) calcd for $C_{11}H_{16}NO_2$ (M+H$^+$): 194.1176, found: 194.1165.

4.3.15. *N*-(3-Trifluoromethylphenyl)piperidine (**Table 4**, entry 3). A liquid (160.0 mg, 70% yield). ^{1}H NMR: δ 7.29–7.33 (m, 2H), 7.01–7.11 (m, 2H), 3.19–3.21 (m, 2H), 1.68–1.74 (m, 2H), 1.57–1.62 (m, 1H). HRMS (APCI) calcd for $C_{12}H_{15}NF_3$ (M+H$^+$): 230.1151, found: 230.1132.

4.3.16. *N*-(3-Nitrophenyl)piperidine (**Table 4**, entry 4). A liquid (140.0 mg, 68% yield). ^{1}H NMR: δ 7.70 (s, 1H), 7.55–7.60 (m, 1H), 7.22–7.36 (m, 1H), 7.17–7.19 (m, 1H), 3.25–3.27 (m, 4H), 1.70–1.74 (m, 4H), 1.62–1.63 (m, 2H). HRMS (APCI) calcd for $C_{11}H_{15}NO_2$ (M+H$^+$): 207.1128, found: 207.1112.

4.3.17. *N*-(4-Methoxyphenyl)pyrrolidine (**Table 4**, entry 5). A liquid (115.0 mg, 65% yield). ^{1}H NMR: δ 6.85 (d, 2H, J=8.8 Hz), 6.54 (d, 2H, J=7.6 Hz), 3.76 (s, 3H), 3.23 (s, 4H), 1.97–2.00 (m, 4H). HRMS (APCI) calcd for $C_{11}H_{16}NO$ (M+H$^+$): 178.1226, found: 178.1216.

4.3.18. *N*-(3-Trifluoromethylphenyl)pyrrolidine (**Table 4**, entry 6). A solid (155.0 mg, 72% yield). ^{1}H NMR: δ 7.26–7.30 (m, 1H), 6.87 (d, 1H, J=8.0 Hz), 6.73 (s, 1H), 6.67 (d, 1H, J=8.0 Hz), 3.27–3.31 (m, 4H), 2.02 (m, 4H). HRMS (APCI) calcd for $C_{11}H_{13}NF_3$ (M+H$^+$): 216.0995, found: 216.0979.

4.3.19. *N*-(3-Nitrophenyl)pyrrolidine (**Table 4**, entry 7). An orange solid (140.0 mg, 73% yield). ^{1}H NMR: δ 7.52 (d, 1H, J=8.0 Hz), 7.40 (s, 1H), 7.31–7.35 (m, 1H), 6.91 (d, 1H, J=8.0 Hz), 3.36–3.37 (m, 4H), 2.07–2.09 (m, 4H). HRMS (APCI) calcd for $C_{10}H_{13}N_2O_2$ (M+H$^+$): 193.0972, found: 193.0959.

4.3.20. *N*-Phenyl-*N*-(ethyl)piperazine (**Table 4**, entry 8). A solid (136.0 mg, 72% yield). ^{1}H NMR: δ 7.25–7.29 (m, 2H), 6.93–6.95 (m, 1H), 6.84–6.87 (m, 1H), 3.22–3.24 (m, 4H), 2.61–2.63 (m, 4H), 2.45–2.51 (m, 2H), 1.12–1.15 (m, 3H). HRMS (APCI) calcd for $C_{12}H_{19}N_2$ (M+H$^+$): 191.1543, found: 191.1534.

4.3.21. Ethyl *N*-(4-Methoxyphenyl)piperazinecarboxylate (**Table 4**, entry 9).. A solid (158.0 mg, 60% yield). ^{1}H NMR: δ 6.83–6.92 (m, 4H), 4.14–4.19 (m, 2H), 3.76–3.77 (m, 3H), 3.63 (s, 4H), 3.02 (s, 4H), 1.28 (t, 3H, J=7.2 Hz). HRMS (APCI) calcd for $C_{14}H_{21}N_2O_3$ (M+H$^+$): 265.1547, found: 265.1531.

4.3.22. *N*-(Phenyl)pyrozole (**Table 5**, entry 1). A liquid (134.0 mg, 94% yield). ^{1}H NMR: δ 7.88 (d, 1H, J=2.4 Hz), 7.66–7.71 (m, 3H), 7.39–7.43 (m, 2H), 7.23–7.27 (m, 1H), 6.42–6.43 (m, 1H). HRMS (APCI) calcd for $C_9H_9N_2$ (M+H$^+$): 145.0760, found: 145.0751.

4.3.23. *N*-(4-Methoxyphenyl)pyrozole (**Table 5**, entry 3). A liquid (165.0 mg, 95% yield). ^{1}H NMR: δ 7.83 (d, 1H, J=4.0 Hz), 7.70 (s, 1H), 7.58–7.60 (m, 2H), 6.96–6.98 (m, 2H), 6.44 (s, 1H), 3.84 (s, 3H). HRMS (APCI) calcd for $C_{10}H_{11}N_2O$(M+H$^+$): 175.0866, found: 175.0856.

4.3.24. *N*-(3-Trifluoromethylphenyl)pyrozole (**Table 5**, entry 4). A liquid (172.0 mg, 81% yield). ^{1}H NMR: δ 7.74–7.89 (m, 4H), 7.51–7.57 (m, 2H), 6.48–6.49 (m, 1H). HRMS (APCI) calcd for $C_{10}H_8NF_3$ (M+H$^+$): 213.0634, found: 213.0610.

4.3.25. *N*-(Phenyl)imidazole (**Table 5**, entry 5). A liquid (132.0 mg, 92% yield). ^{1}H NMR: δ 7.86 (m, 1H), 7.46–7.50

(m, 2H), 7.35–7.39 (m, 3H), 7.28 (s, 1H), 7.21 (s, 1H). HRMS (APCI) calcd for $C_9H_9N_2$ ($M+H^+$): 145.0760, found:145.0773.

4.3.26. *N*-(Phenyl)benzimidazole (Table 5, entry 6). A solid (125.0 mg, 64% yield). ^{1}H NMR: δ 8.07 (s, 1H), 7.87–7.89 (m, 1H), 7.46–7.50 (m, 3H), 7.36–7.41 (m, 3H), 7.24–7.31 (m, 2H). HRMS (APCI) calcd for $C_{13}H_{11}N_2$ ($M+H^+$): 195.0917, found: 195.0895.

4.3.27. *N*-(Phenyl)indole (Table 5, entry 7). A solid (116.0 mg, 60% yield). ^{1}H NMR: δ 7.67–7.69 (m, 1H), 7.55 (d, 1H, $J=7.6$ Hz), 7.44–7.47 (m, 4H), 7.28–7.33 (m, 2H), 7.14–7.22 (m, 2H), 7.67 (d, 1H, $J=3.6$ Hz). HRMS (APCI) calcd for $C_{14}H_{12}N$ ($M+H^+$): 194.0964, found: 194.0975.

4.3.28. *N*-Cyclopentyl-4-methoxyaniline (Table 6, entry 3). A liquid (122.0 mg, 64% yield). ^{1}H NMR: δ 6.75–6.78 (m, 2H), 6.56–6.58 (m, 2H), 3.69–3.73 (m, 3H), 3.38 (s, 1H). HRMS (APCI) calcd for $C_{12}H_{18}NO$ ($M+H^+$): 192.1383, found: 194.1364.

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Biselides A–E: novel polyketides from the Okinawan ascidian Didemnidae sp.

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Abstract—Five new polyketides, biselides A (**1**), B (**2**), C (**3**), D (**4**), and E (**5**), were isolated from the Okinawan ascidian Didemnidae sp. Their structures were determined by spectroscopic analysis. Biselides A (**1**), B (**2**), and C (**3**) showed cytotoxicity against human cancer cells NCI-H460 and MDA-MB-231.

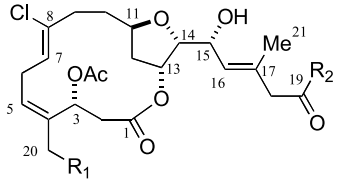
1. Introduction

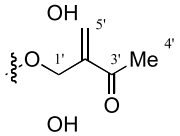
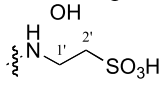
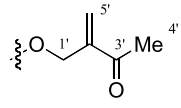
As part of our continuing chemical studies of marine organisms,[1] we examined the constituents of the Okinawan ascidian Didemnidae sp., whose crude organic extract shows toxicity against brine shrimp. Bioassay-guided fractionation of the extract led to the isolation of toxic haterumalide NA[2] and five new congeners, biselides A[3] (**1**), B[3] (**2**), C (**3**), D (**4**), and E (**5**). Biselides A (**1**), B (**2**), and C (**3**) showed cytotoxicity against human cancer cells. We report herein the isolation and structural determination of **1**, **2**, **3**, **4**, and **5**.

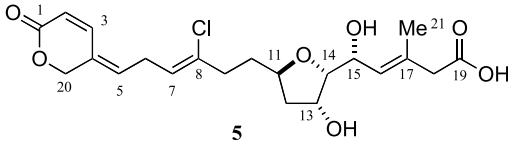
2. Results and discussion

2.1. Isolation of biselides A–E

The Okinawan ascidian Didemnidae sp., collected at Bise, Okinawa Prefecture, was extracted with methanol. The extract was filtered, concentrated, and partitioned between EtOAc and H_2O. The EtOAc-soluble material was further partitioned between 90% aqueous MeOH and hexane. The material obtained from the aqueous MeOH portion was subjected to fractionation guided by toxicity against brine shrimp with column chromatography (silica gel, $CHCl_3$–MeOH; ODS silica gel, MeOH–H_2O) and reverse-phase HPLC (Develosil ODS-HG-5, MeOH–H_2O–TFA) to give biselides A (**1**) [1.2 mg], B (**2**) [160 μg] and haterumalide NA[2] as colorless oils. In contrast, water-soluble materials of the EtOAc–H_2O partition were extracted with *n*-BuOH. The material obtained from the *n*-BuOH portion was subjected to fractionation guided by toxicity against brine shrimp with column chromatography (ODS silica gel, MeOH–H_2O) and reverse-phase HPLC (Develosil ODS-HG-5, MeOH–H_2O–TFA) to give biselides C (**3**) [5.0 mg], D (**4**) [1.0 mg] and E (**5**) [1.0 mg] as colorless oils, respectively.



	R_1	R_2
1	OAc	OH
2	OAc	
3	OH	OH
4	H	
haterumalide NA	H	OH
haterumalide B	H	



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Keywords: Marine natural product; Ascidian; Cytotoxicity; Polyketide; Macrolide.
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2.2. Structures of the biselides

2.2.1. Structure of biselide A. The molecular formula of biselide A (**1**) was found to be $C_{25}H_{33}ClO_{10}$ by ESIMS (*m/z* 551.1654, calcd for $C_{25}H_{33}ClO_{10}Na$ $[M+Na]^+$ 551.1660). The NMR data for **1** are summarized in Table 1. The ^1H NMR spectrum of **1** showed the presence of three methyl groups connected to non-protonated sp^2 carbons (δ 1.82, 2.02, and 2.06). In the ^{13}C NMR spectrum, 25 carbon signals were observed, including four carbonyl carbons (δ 169.4, 171.1, 172.5, and 175.4), six olefinic carbons (δ 125.7, 130.7, 133.6, 133.9, 134.9, and 135.9), and three methyl carbons (δ 17.3, 20.9, and 21.0). The remaining carbon signals were assigned to seven methylenes and five methines, based on an HMQC experiment. A detailed analysis of the COSY spectra of **1** allowed three partial structures, C2–C3, C20–C4–C7, and C9–C17–C21, to be constructed, as shown in Figure 1. The connectivities between these partial structures were clarified by HMBC correlations: H20/C3, H6/C8, H7/C8, and H9/C8. HMBC correlations H2/C1, H18/C17, and H18/C19 suggested the connectivities of C1–C2 and C17–C18–C19. Consequently,

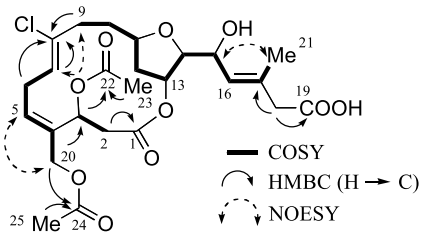

Figure 1. Partial structures of **1**, based on 2D NMR correlations.

the entire carbon chain was assembled, and all protons and carbons were assigned, as shown in Figure 1 and Table 1, respectively. The presence of a tetrahydrofuran ring was suggested by the characteristic chemical shifts of C11 (δ 78.1) and C14 (δ 84.5).[4] The HMBC correlations H3/C22, H23/C22, H20/C24, and H25/C24 suggested the existence of two acetoxy groups at C3 and C20. Although no additional connectivities were obtained from the NMR analysis, **1** should contain a lactone ring based on its molecular formula and degree of the unsaturation. Considering the chemical shift of H13, the lactone ring might be

Table 1. NMR data for biselide A (**1**) and B (**2**) in CD_3OD

	1			**2**
No.	^1H (ppm)[a]	^{13}C (ppm)[b]	HMBC	^1H (ppm)[c]
1		169.4		
2a	2.83 dd (12.0, 11.1)[d]	38.7	C1, 3, 4	2.83 dd (12.5, 11.2)
2b	2.88 dd (12.0, 5.2)		C1, 3, 4	2.88 dd (12.5, 5.0)
3	5.84 dd (11.1, 5.2)	67.8	C4, 22, 22	5.83 dd (11.2, 5.0)
4		135.0		
5	6.08 dd (11.1, 7.1)	133.9	C3, 20, 6	6.08 dd (10.9, 7.3)
6a	2.61 m	27.7		2.61 m
6b	3.55 m		C7, 8	3.54 m
7	5.32 m	125.8		5.32 m
8		133.6		
9a	2.31 m	35.5	C8	2.30 m
9b	2.45 m			2.45 m
10a	1.39 m	29.0	C8, 11	1.39 m
10b	2.28 m			2.27 m
11	3.94 m	78.1		3.92 m
12a	1.53 m	38.8		1.53 m
12b	2.09 m			2.07 m
13	5.30 m	76.7		5.30 m
14	3.91 dd (8.6, 3.7)	84.5		3.90 dd (8.7, 3.7)
15	4.53 t (8.6)	66.5	C14	4.53 t (8.7)
16	5.38 d (8.6)	130.7	C17, 21	5.39 d (8.7)
17		135.9		
18	3.04 br s 2H	45.7	C16, 17, 19, 21	3.12 br s 2H
19		175.4		
20a	4.70 d (12.9)	65.5	C3, 4, 5, 24	4.70 d (13.0)
20b	4.96 d (12.9)		C3, 4, 5, 24	4.96 d (13.0)
21	1.82 br s 3H	17.3	C16, 17, 18	1.81 br s 3H
22		171.1		
23	2.02 s 3H	21.0	C22	2.02 s 3H
24		172.5		
25	2.07 s 3H	20.9	C24	2.06 s 3H
1a′				4.76 d (13.9)
1b′				4.82 d (13.9)
2′				
3′				
4′				2.36 s 3H
5a′				6.10 s
5b′				6.31 s

[a] Recorded at 500 MHz.
[b] Recorded at 125 MHz.
[c] Recorded at 600 MHz.
[d] Coupling constants (Hz) are in parentheses.

formed between C1 and C13 or C19 and C13. A detailed analysis of the chemical shift and coupling constants of ^{1}H NMR of **1** suggested that **1** could be an analogue of haterumalide NA,[2] that is, **1** could be a 14-membered macrolide, and the chlorine atom could be at C8. The geometry of the three olefins in **1** were clarified to be 4*Z*, 7*Z*, and 16*E* by NOESY experiments (Fig. 1). Thus, the gross structure of biselide A (**1**) was determined to be as shown in Figure 1.

The relative stereochemistry of **1** was determined as follows. A plausible conformation of **1** with the important NOESY correlations is shown in Figure 2. In the tetrahydrofuran ring, NOESY correlations H11/H12b, H12a/H13, and H13/H14 suggested that the relative stereochemistries at C11, C13, and C14 are 11*R**, 13*R**, and 14*R**. The magnitude of $^3J_{H2b–H3}=5.2$ Hz and $^3J_{H2a–H3}=10.8$ Hz suggested that H2b and H3 are located in a *gauche* arrangement, while H2a and H3 are located in an *anti* arrangement. In addition, NOESY correlations H2a/H20, H2b/H3, H3/H6b, H5/H6a, H5/H7, H6a/H7, and H7/H12b suggested a plausible conformation of the macro ring in **1**, as shown in Figure 2. The stereochemistry of C3 was therefore determined to be 3*R**. The relative stereochemistry at C15 was determined as follows. The magnitude of $^3J_{H14–H15}=8.8$ Hz suggested that H14 and H15 are located in an *anti* arrangement. Therefore, based on the presumption that the alkyl chain of **1** may have a zigzag conformation, we deduced the relative stereochemistry at C15 to be 15*R**. Thus, the stereochemistry of **1** could be superimposed on that of haterumalide NA, the absolute stereochemistry of which was determined by total synthesis.[5,6] This result was also supported by the fact that the chemical shifts and coupling constants of NMR in **1** closely resembling those of haterumalide NA.

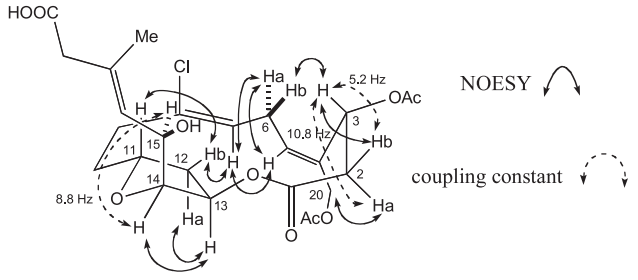

Figure 2. Relative stereochemistry of **1**, based on NOESY correlations.

2.2.2. Structure of biselide B. The molecular formula of biselide B (**2**) was found to be $C_{30}H_{39}ClO_{11}$ by ESIMS (*m*/*z* 633.2071, calcd for $C_{30}H_{39}ClO_{11}Na$ $[M+Na]^+$ 633.2079).[3] In normal and reverse-phase chromatography, **2** was much less polar than **1**. The ^{1}H NMR data for **2** are summarized in Table 1. A detailed analysis of the COSY spectra of **2** led to three partial structures, C2–C3, C5–C7, and C9–C16–C21, as shown in Figure 3.

The chemical shifts and coupling constants of protons of **2** closely resembled those of **1**, except for the existence of H1′, H4′, and H5′. This result and its chromatographic behavior suggested that **2** has the same macrolide structure and has an alkyl group at the C19 carboxyl. In the alkyl group in **2**, the chemical shifts and coupling constants of the

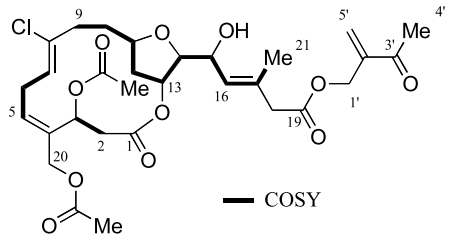

Figure 3. Partial structures of **2**, based on 2D NMR correlations.

protons closely resembled those of haterumalide B.[7] This result suggested that **2** has the same alkyl group as haterumalide B. The relative stereostructure of biselide B (**2**) was therefore determined to be as shown in formula **2**.

2.2.3. Structure of biselide C. The molecular formula of biselide C (**3**) was found to be $C_{23}H_{31}ClO_9$ by ESIMS (*m*/*z* 509.1531, calcd for $C_{23}H_{31}ClO_9Na$ $[M+Na]^+$ 509.1554), which is 42 mass units (C_2H_2O) less than that of **1**. In normal and reverse-phase chromatography, **3** was found to be more polar than **1**. The chemical shift and coupling constants of protons of **3** closely resembled those of biselide A (**1**), except for the upfield shift of H20 (Table 2). These results suggested that **3** should be the deacetyl derivative at C20 of **1**. The gross structure of biselide C (**3**) was determined in the same manner as that of biselide A by 2D NMR (^{1}H–^{1}H COSY, HMQC and HMBC) data (Fig. 4).

The relative stereochemistry of biselide C (**5**) was determined in the same manner as that of biselide A by NOESY correlations and the ^3J coupling constant (Fig. 5).

2.2.4. Structure of biselide D. The molecular formula of biselide D (**4**) was found to be $C_{25}H_{36}ClNO_{10}S$ by ESIMS (*m*/*z* 600.1642, calcd for $C_{25}H_{36}ClNO_{10}S$ $[M+Na]^+$ 600.1646). The ^{1}H and ^{13}C NMR data of **4** resembled those of haterumalide NA,[2] except for the existence of the ethylene unit C1′–C2′ (Table 2). This result suggested that **4** could be an analogue of haterumalide NA. The gross structure of the C1–C21 portion of biselide D (**4**) was determined in the same manner as that of biselide A by 2D NMR (^{1}H–^{1}H COSY, HMQC, and HMBC) data (Fig. 6). The HMBC correlations H1′/C19 suggested that C19 is the amide carbonyl carbon connecting to C1′. Considering the chemical shifts (δ_C 51.3, δ_H 2.96) of 2′-methylene and the molecular formula, sulfonyl group should be located at C2′. Thus, the gross structure of biselide D (**4**) was determined to be a taurohaterumalide NA, as shown in Figure 6.

The relative stereochemistry of biselide D (**4**) was determined in the same manner as that of biselide A by NOESY correlations and the ^3J coupling constant (Fig. 7).

2.2.5. Absolute stereochemistry of biselides A–D. The absolute stereochemistry of biselides A (**1**), B (**2**), C (**3**), and D (**4**) was deduced as shown in formulas **1**, **2**, **3**, and **4**, respectively, based on the similarity of their NMR and CD data to those of haterumalide NA methyl ester.[5] Thus, the absolute stereochemistry of the five stereocenters in **1**, **2**, **3**, and **4** was determined to be 3*R*, 11*R*, 13*R*, 14*R*, and 15*R*.

2.2.6. Structure of biselide E. The molecular formula of

Table 2. NMR data for biselide C (**3**), D (**4**), and E (**5**) in CD_3OD

	3			**4**			**5**		
No.	^{1}H (ppm)[a]	^{13}C (ppm)[b]	HMBC	^{1}H (ppm)[a]	^{13}C (ppm)[b]	HMBC	^{1}H (ppm)[a]	^{13}C (ppm)[b]	HMBC
1		169.7			169.4		166.6		
2a	2.79 dd (12.0, 11.6)[c]	38.8	C1, 3, 4	2.77 dd (11.6, 11.3)	38.9	C1, 3, 4	5.95 d (9.9)	119.7	C4
2b	2.85 dd (12.0, 4.5)		C1, 3, 4	2.82 dd (11.6, 4.6)		C1, 3, 4			
3	5.85 dd (11.6, 4.5)	68.0	C4, 20, 22	5.79 dd (11.3, 4.6)	68.7	C4, 20, 22	7.62 d (9.9))	141.0	C1, 20
4		137.9			134.6			128.2	
5	6.04 dd (10.8, 7.3)	130.9	C3, 20, 6	5.69 dd (9.7, 6.6)	130.9	C3, 20	5.86 t (7.4)	132.9	C4, 20
6a	2.59 m	27.4		2.45 m	27.7		3.14 m 2H	28.2	C4, 5, 7, 8
6b	3.51 m		C7, 8	3.49 m		C7, 8			
7	5.31 m	126.5		5.31 m	126.9		5.61 t (7.1)	123.0	C6, 8, 9
8		133.5			133.2			137.4	
9a	2.31 m	35.5	C8	2.29 m	35.5	C8	2.43 m 2H	37.1	C8, 10
9b	2.46 m			2.44 m		C7			
10a	1.39 m	29.0	C8, 11	1.43 m	29.1	C8, 9, 11	1.72 m 2H	34.8	C8, 9, 11, 12
10b	2.28 m			2.28 m					
11	3.95 m	78.1		3.93 m	78.2		4.18 m	78.0	
12a	1.53 m	38.7	C11	1.54 m	38.8		1.68 m	42.5	
12b	2.08 m	12b	C13, 14	2.10 m			2.04 dd (12.2, 5.6)		C11, 13
13	5.29 m	76.7		5.30 m	76.5		4.45 m	73.6	C14
14	3.91 dd (8.6, 3.7)	84.5	C13, 15, 16	3.91 dd (8.9, 3.7)	84.5	C13, 15, 16	3.66 dd (7.4, 3.3)	85.3	
15	4.54 t (8.6)	66.5	C13, 14, 16, 17	4.56 t (8.9)	66.5	C13, 14, 16	4.58 dd (8.7, 7.4)	67.9	
16	5.38 d (8.6)	130.7	C17, 21	5.40 d (8.9)	131.9	C17, 21	5.41 d (8.7)	130.9	C18, 21
17		135.0			135.6			134.0	
18	3.04 br s 2H	45.7	C16, 17, 19, 21	2.95 br s 2H	47.9	C16, 17, 19, 21	3.02 br s 2H	45.7	C15, 17, 19
19		175.4			173.5			175.4	
20a	4.35 d (14.5)	62.5	C3, 4, 5	1.93 br s 3H	18.6	C3, 4, 5	4.90 br s 2H	72.2	C1, 3, 4, 5
20b	4.31 d (14.5)		C3, 4, 5						
21	1.83 br s 3H	17.3	C16, 17, 18	1.88 br s 3H	17.4	C16, 17, 18	1.79 br s 3H	17.3	C16, 17, 18
22		171			171.2				
23	2.03 s 3H	21.0	C22	2.02 s 3H	21.0	C22			
1a′				3.62 m	36.8	C2′, 19			
1b′				3.57 m		C2′, 19			
2′				2.96 t (6.9)	51.3	C1′			

[a] Recorded at 500 MHz.
[b] Recorded at 125 MHz.
[c] Coupling constants (Hz) are in parentheses.

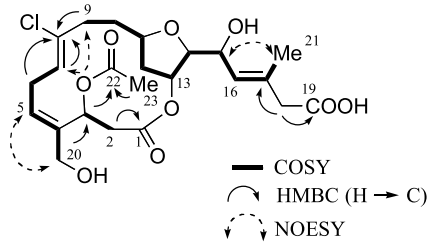

Figure 4. Partial structures of **3**, based on 2D NMR correlations.

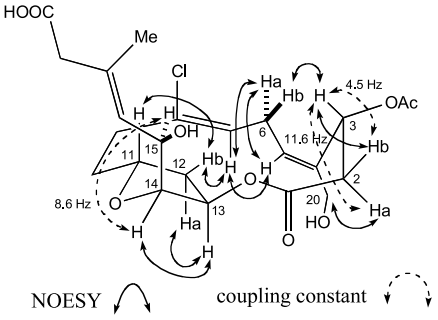

Figure 5. Relative stereochemistry of **3**, based on NOESY correlations.

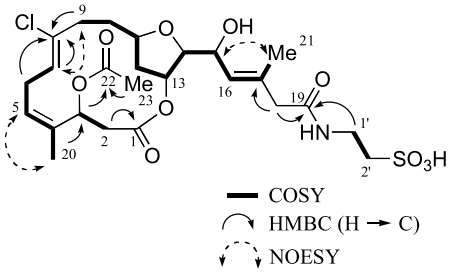

Figure 6. Partial structures of **4**, based on 2D NMR correlations.

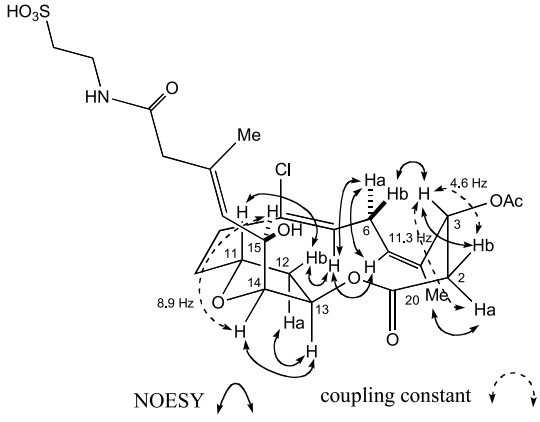

Figure 7. Relative stereochemistry of **4**, based on NOESY correlations.

biselide E (**5**) was found to be $C_{21}H_{27}ClO_7$ by ESIMS (*m/z* 449.1339, calcd for $C_{21}H_{27}ClO_7Na$ $[M+Na]^+$ 449.1343). A detailed analysis of the COSY spectra of **5** allowed three partial structures, C2–C3, C5–C7, and C9–C16–C21, to be constructed, as shown in Figure 8. The connectivities between these partial structures were clarified by HMBC correlations: H2/C4, H6/C4, H7/C8, and H9/C8. The

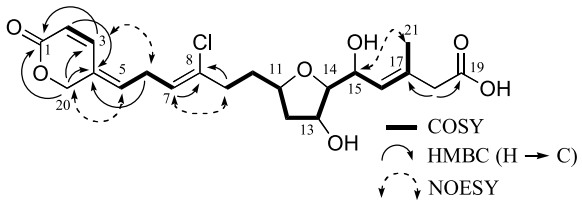

Figure 8. Partial structures of **5**, based on 2D NMR correlations.

HMBC correlations H18/C17 and H18/C19 suggested connectivities of C17, C18, and C19. HMBC correlations H3/C1, H20/C3 and H20/C4 suggested connectivities of C1–C2 and C4–C20. Consequently, the entire carbon chain was assembled as shown in Figure 7, and all protons and carbons were assigned (Table 2). The HMBC correlations H20/C1 suggested that C1 is the ester carbonyl carbon connecting to C20. The presence of a tetrahydrofuran ring was suggested by the characteristic chemical shifts of C11 (δ 78.0) and C14 (δ 85.3).[4] Based on the molecular formula and the degree of unsaturation of **5**, **5** contains a chlorine atom and carboxylic acid functionality. Considering the chemical shift of C8 and C19, the chlorine atom must be connected to C8 and the C19 carbonyl carbon must be a carboxyl carbon.[2] The geometry of the four olefins in **5** were clarified to be 2*Z*, 4*Z*, 7*Z*, and 16*E* by NOESY experiments (Fig. 8). Thus, the gross structure of biselide E (**5**) was determined to be as shown in Figure 8.

The relative and absolute stereochemistries of **5** were deduced as follows. NOESY correlations H11/H12b, H12a/H13, and H13/H14 suggested that the relative stereochemistries at C11, C13, and C14 are 11*R**, 13*R**, and 14*R**(Fig. 9). Although the relative stereochemistry at C15 could not be determined, the absolute stereochemistry of biselide E (**5**) including C15 was deduced, as shown in formula **5** based on the similarity of ^{1}H NMR data of H15 to those of biselide A[3] and in view of their biosynthesis.

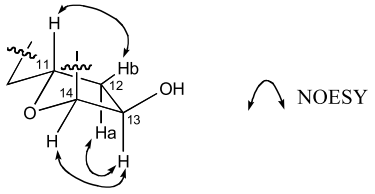

Figure 9. Relative stereochemistry of **5**, based on NOESY correlations.

3. Bioactivity

The cytotoxicities of biselides A (**1**), C (**3**), and haterumalide NA methyl ester are summarized in Table 3. The three compounds exhibited a broad spectrum of cytotoxicity. Haterumalide NA methyl ester is most cytotoxic, while oxidation of the C20 methyl group to a alcohol (biselide C) resulted in a decrease in cytotoxicity. Biselide A (**1**), which has an acetoxy group at C20, is more active than biselide C (**3**). Among the tested cell lines, biselide A (**1**) showed the strongest cytotoxicity against human colon cancer DLD-1.

Interestingly, haterulalide NA showed strong toxicity against brine shrimp, with an LD_{50} of 0.6 μg/mL, while **1** and **3** showed no toxicity against brine shrimp even at

Table 3. Cytotoxicity of biselide A (**1**), C (**3**), and haterumalide NA methyl ester with IC_{50} values (μM)

	MDA-MB-231	HOP18	NCI-H460	A498	PC-3	DLD-1	HCT116	P388	P388/ADR	Mean
Biselide A (**1**)	3.72	9.35	3.53	1.79	2.07	0.513	3.01	3.72	7.78	3.94
Biselide C (**3**)	25.5	82.7	18.0	16.3	18.2	17.1	18.0	21.2	34.6	27.9
Haterumalide NA Methyl ester	0.406	0.739	0.135	0.335	0.539	0.141	0.292	0.408	0.621	0.402
Cisplatin	4.83	4.08	0.600	4.01	4.01	2.11	2.23	0.0754	0.271	2.47
Adriamycin	0.186	0.159	0.00823	0.166	0.357	0.190	0.0629	0.0252	5.79	0.772

50 μg/mL. Due to a lack of samples, the cytotoxic activities and toxicity of biselides B (**2**), D (**4**), and (**5**) against brine shrimp could not be examined.

Although, biselides A (**1**) and C (**3**) are less cytotoxic than haterumalide NA, they are not toxic. In order to develop a new type of anti-cancer drug, further investigation of the biological activities of biselides and their structure–activity relationships are in progress.

4. Conclusion

Novel polyketides biselides A (**1**), B (**2**), C (**3**), D (**4**), and E (**5**) were isolated from the Okinawan ascidian Didemnidae sp. The structures of these biselides were determined based on their 2D NMR spectra. Interestingly, the structurally related haterumalide NA,[2] haterumalide B,[7] and oocydin A[8] were isolated from an Okinawan sponge, an Okinawan ascidian, and a South American epiphyte, respectively. Further investigations of their anti-cancer activities, structure–activity relationships, and possible mechanisms of action are in progress.

5. Experimental

5.1. General aspects

CD spectra were measured with a JASCO J-720 W spectropolarimeter. NMR spectra were recorded on a Bruker AVANCE 600 [600 MHz (^{1}H) and 150 MHz (^{13}C)] or a AVANCE 500 [500 MHz (^{1}H) and 125 MHz (^{13}C)] spectrometer. The ^{1}H and ^{13}C chemical shifts were referenced to the solvent peaks (δ_H=3.31 and δ_C=49.5 ppm in methanol-d_4). High-resolution mass spectra (HRMS) were obtained on a PE Sciex QSTAR mass spectrometer. Column chromatography was performed on silica gel (Fuji Silysia Chemical Ltd, BW-820MH) and ODS gel (Nacalai Tesque, Cosmosil 75C_{18}-OPN). Reverse-phase high-performance liquid chromatography (HPLC) was carried out on a Develosil ODS-HG-5 column (Nomura Chemical Co., Ltd).

5.2. Isolation

The frozen ascidian of Didemnidae sp. (1.7 kg), which was collected at −1 m off Bise, Okinawa in November, 2003, was extracted with methanol (5.0 L) for seven days. The extracts were concentrated and partitioned between ethyl acetate and water. The materials obtained from the organic layer were partitioned between 90% methanol/H_2O and hexane. The aqueous methanol fraction (1.5 g) was first separated by column chromatography on silica gel (15.0 g) using chloroform and chloroform/methanol (20:1, 10:1, 5:1, 2:1, 1:1). The fraction (536.8 mg) eluted with chloroform/methanol 20:1 was further separated by chromatography on ODS (10.0 g) using 60% methanol, 80% methanol, and methanol. The fraction (24.3 mg) eluted with 80% methanol was subjected to HPLC [Develosil ODS-HG-5 (250×20 mm); flow rate 5 mL/min; detection, UV 215 nm; solvent 75% methanol/0.1% trifluoroacetic acid] to give biselide A (1.2 mg, retention time 19 min) and biselide B (160 μg, retention time 25 min), respectively, along with haterumalide NA (10.0 mg, retention time 24 min) and B (0.8 mg, retention time 35 min).

The frozen ascidian of Didemnidae sp. (4.4 kg), which was collected at −1 m off Bise, Okinawa in May, 2004, was extracted with methanol (10.0 L) for 10 days. The extracts were concentrated and partitioned between ethyl acetate and water. The water-soluble materials were partitioned with *n*-butanol and water. The *n*-butanol-soluble material (3.3 g) was first separated by column chromatography on ODS (15.0 g) using 40% methanol, 60% methanol, 80% methanol, and methanol. The fraction (1.8 g) eluted with 40% methanol was separated by column chromatography on ODS (10.0 g) using 15% methanol, 70% methanol, and methanol. The fraction (266.4 mg) eluted with 70% methanol was subjected to HPLC [Develosil ODS-HG-5 (250×20 mm); flow rate 5 mL/min; detection, UV 215 nm; solvent 55% acetonitrile/0.1% trifluoroacetic acid] to give biselide C (5.0 mg, retention time 20 min), biselide D (1.0 mg, retention time 33 min), and biselide E (1.0 mg, retention time 42 min), respectively.

5.2.1. Biselides A (1). ^{1}H and ^{13}C NMR, see Table 1; HRMA (ESI) calcd for $C_{25}H_{33}ClO_{10}Na$ $[M+Na]^+$551.1660, found 551.1654; CD (MeOH) λ_{max} 222 nm ($\Delta\varepsilon$+0.39).[9]

5.2.2. Biselides B (2). ^{1}H and ^{13}C NMR, see Table 1; HRMA (ESI) calcd for $C_{30}H_{39}ClO_{11}Na$ $[M+Na]^+$633.2079, found 633.2071; CD (MeOH) λ_{max} 222 nm ($\Delta\varepsilon$+0.33).[9]

5.2.3. Biselides C (3). ^{1}H and ^{13}C NMR, see Table 2; HRMA (ESI) calcd for $C_{23}H_{31}ClO_9Na^+$509.1554, found 509.1531; CD (MeOH) λ_{max} 225 nm ($\Delta\varepsilon$+0.39).

5.2.4. Biselides D (4). ^{1}H and ^{13}C NMR, see Table 2; HRMA (ESI) calcd for $C_{23}H_{31}ClO_9Na^+$600.1646, found 600.1642; CD (MeOH) λ_{max} 226 nm ($\Delta\varepsilon$+0.30).

5.2.5. Biselides E (5). ^{1}H and ^{13}C NMR, see Table 2;

HRMA (ESI) calcd for $C_{23}H_{31}ClO_9Na^+$ 449.1343, found 449.1339; CD (MeOH) λ_{max} 272 nm ($\Delta\varepsilon+0.011$).

5.2.6. Haterulalide B. Although, the NMR data in $CDCl_3$ were reported in this paper,[7] we measured the NMR data in CD_3OD using a specimen isolated from the ascidian along with **1** and **2**; ^1H NMR (500 MHz, CD_3OD) δ 6.31 (s, 1H), 6.11 (s, 1H), 5.79 (dd, $J=11.4$, 4.5 Hz, 1H), 5.70 (dd, $J=9.5$, 6.7 Hz, 1H), 5.34 (d, $J=8.6$ Hz, 1H), 5.30 (m, 1H), 5.29 (m, 1H), 4.80 (d, $J=14.2$ Hz, 1H), 4.76 (d, $J=14.2$ Hz, 1H), 4.53 (t, $J=8.6$ Hz, 1H), 3.93 (m, 1H), 3.89 (dd, $J=8.6$, 3.7 Hz, 1H), 3.49 (m, 1H), 3.12 (s, 2H), 2.83 (dd, $J=11.6$, 4.5 Hz, 1H), 2.77 (dd, $J=11.6$, 11.4 Hz, 1H), 2.47 (m, 2H), 2.36 (s, 3H), 2.29 (m, 2H), 2.07 (m, 1H), 2.02 (s, 3H), 1.88 (s, 3H), 1.81 (s, 3H), 1.52 (m, 1H), 1.39 (m, 1H).

5.3. Brine shrimp toxicity assay

The screening for brine shrimp toxicity was performed using a slight modification of the original method.[10] Samples were dissolved in methanol. Appropriate amounts of solution were transferred to 1.0-cm discs of filter paper. The discs were dried in vacuo for 1 h. Control discs were prepared using only methanol. Approximately 10 hatched brine shrimp were transferred to each sample vial, and artificial sea water was added to make 1 mL. After 24 h at 25 °C, the numbers of living and dead brine shrimp were determined. The activity is expressed in terms of LD_{50} to account for a significant number of brine shrimp that were living but were visually affected and their movements inhibited.

5.4. Cancer cell lines

Human breast cancer MDA-MB-231, human non-small cell lung cancer HOP18 and NCI-H460, human renal cancer A498, human colon cancer HCT116, and human prostate cancer PC-3 were purchased from American Type Culture Collection. Human colon cancer DLD-1 (JCRB9094) was obtained from Japanese Collection of Research Bioresorces, and murine lymphoma P388 and P388/ADR from the Cancer Chemotherapy Center of the Japanese Foundation for Cancer Research. All cells were cultured in RPMI1640 medium containing 10% fetal bovine serum (lot No. 49300604, Moregate Bio Tech, Australia). Some supplements were added to the medium as appropriate.

5.5. In vitro cytotoxicity assay

The cytotoxicity against human solid-tumor cell lines was assessed by the methylene blue staining method. Briefly, appropriate numbers of cells were inoculated into 96-well microplates. Following overnight culture, serially diluted samples were added to the wells. After 3-days culture, cells were stained with 0.05% methylene blue dissolved in 10 mM Tris buffer (pH 8.5) for 30 min, and then thoroughly washed with a distilled water. The stained dye was extracted with 3% HCl, and OD660 was measured with a microplate reader Benchmark Plus (Bio-Rad, USA) to determine cell-growth inhibition. In the case of murine lymphoma (P388 and P388/ADR), cells were incubated with compounds for two days and stained by WST-1. WST-1 and 1-methoxy-5-methyl phenazinium methylsulfate were added to each well at a final concentration of 0.16 and 3.3 μg/mL, respectively. After an additional 4-h incubation, OD450 and OD660, as a reference was measured.

Acknowledgements

We would like to thank Professor T. Nishikawa (Nagoya University) for identifying the ascidian and Professor D. Uemura (Nagoya University) for helpful information of bioactivities of haterumalides. This work was supported in part by the 21st COE program from the Ministry of Education, Culture, Sports, Science, and Technology, Japan, University of Tsukuba Projects, Suntory Institute for Bioorganic Research, and Kurita Water and Environment Foundation.

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Oxidative coupling of methoxynaphthylenediols

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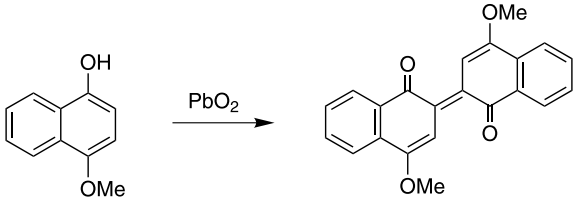
Abstract—The oxidative coupling of a mixture of 1-methoxy-7-methyl-4,5-naphthylenediol and 4-methoxy-7-methyl-1,5-naphthylenediol using lead(IV) oxide gives the symmetrical bisnaphthalene indigos diosindigo A and diosindigo B together with the corresponding unsymmetrical isomer. Oxidation of the first two by nitric acid gives the binaphthyldiquinones mamegakinone and biramentaceone, respectively; the third gives the unsymmetrical diquinone rotundiquinone. Similar oxidations of related naphthylenediols are described.

1. Introduction

The intensely coloured bisnaphthalene indigo 'Russig's Blue' **2**[1,2] is readily prepared by the lead(IV) oxide-induced oxidative coupling of 4-methoxy-l-naphthol **1**. Two symmetrically substituted derivatives of **2**, namely diosindigo A **13**[3] and diosindigo B **20**,[4] which occur naturally in woods of the *Diospyros* species, have been synthesised in a similar manner and converted by further oxidation into the corresponding orange-red binaphthyldiquinones mamegakinone **16** and biramentaceone **22**[3,5,6] which are found naturally in *Diospyros* and *Euclea* species.[7] We now describe the preparation of unsymmetrically substituted analogues of these quinones.



1 2

2. Discussion

One of the starting materials required for the syntheses, the methoxynaphthylene diacetate **6**, was prepared by the sequence[8] shown in Scheme 1. The dihydrojuglone **3** formed the cyclic phenylboronate **4** which, on being treated with acetic anhydride and sodium acetate followed by water, produced a mixture of the diacetoxynaphthols **5** and **7**. Subsequent methylation with diazomethane gave a similar mixture of the methoxy diacetates **6** (~80%) and **8** (~20%), which we were unable to separate. However, as will be apparent later, the presence of the minor component had no discernible effect on the formation of the derived bisnaphthalene indigos. We have previously described the preparation of the diacetates of the other components required, the methoxynaphthylene diols **10**, **11**, and **18**.[8]

Of these starting materials the two methoxynaphthylene diacetates derived from juglone were the more accessible. The alkaline hydrolysis of a 1:1 mixture of **6** and the isomeric diacetate of **10** gave a mixture of the diols **10** and **17**. Treatment of this with lead(IV) oxide produced an intense blue mixture of the corresponding bisnaphthalene indigos which we separated by preparative TLC into the two symmetrically substituted quinones **12** (33%) (Scheme 2) and **19** (37%) (Scheme 3) and the unsymmetrical isomer **23** (17%) (Scheme 4). The first pair were identical with specimens prepared from the diols **10** and **17** separately. The poor solubility of the strongly hydrogen-bonded symmetrical quinone **12** prevented the measurement of its NMR signals and we characterised it as the leucoacetate **14**. The other symmetrical quinone **19** showed the expected NMR signals while the unsymmetrical quinone **23** gave a more complicated spectrum with the signals for the two types of hydroxy group, at δ 8.78 and 13.45, being particularly distinctive. An additional, yellow quinone isolated during the purification of the above blue compounds proved to be 5-methoxy-1,4-naphthoquinone **9**. This was derived from the minor contaminant **8** present in the methoxy diacetate **6**. The hydrolysis of **8** produced the 1,4-naphthylenediol which

Keywords: Naphthalenes; Quinones; Coupling reactions; Oxidation.
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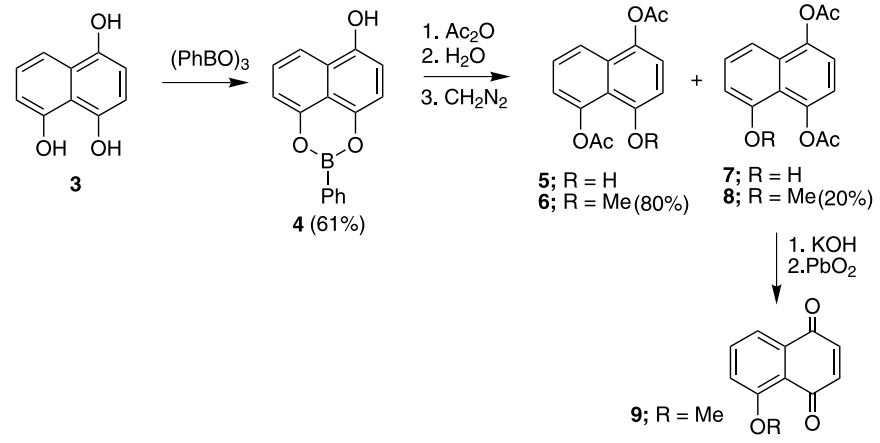
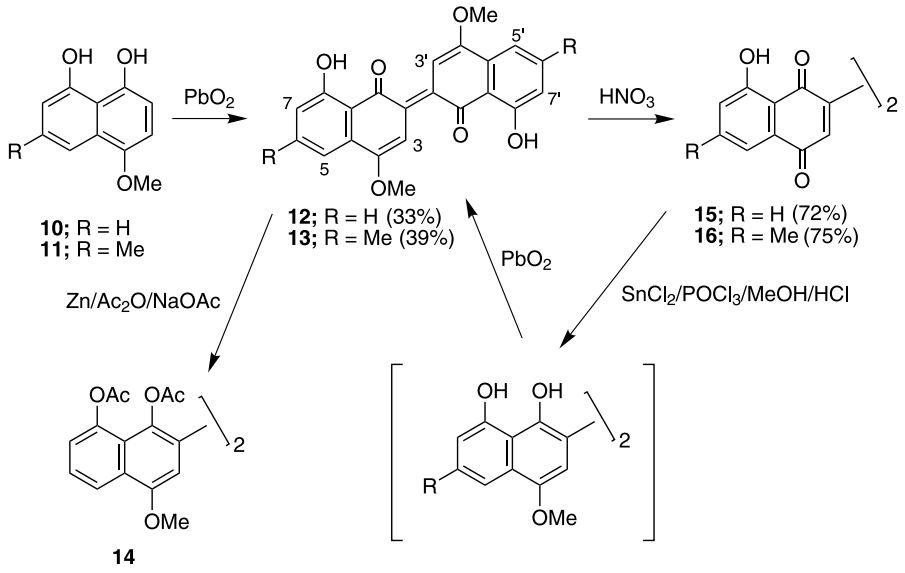
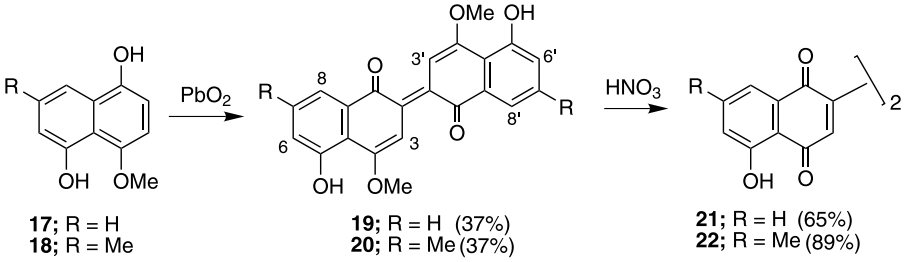


Scheme 1.



Scheme 2.

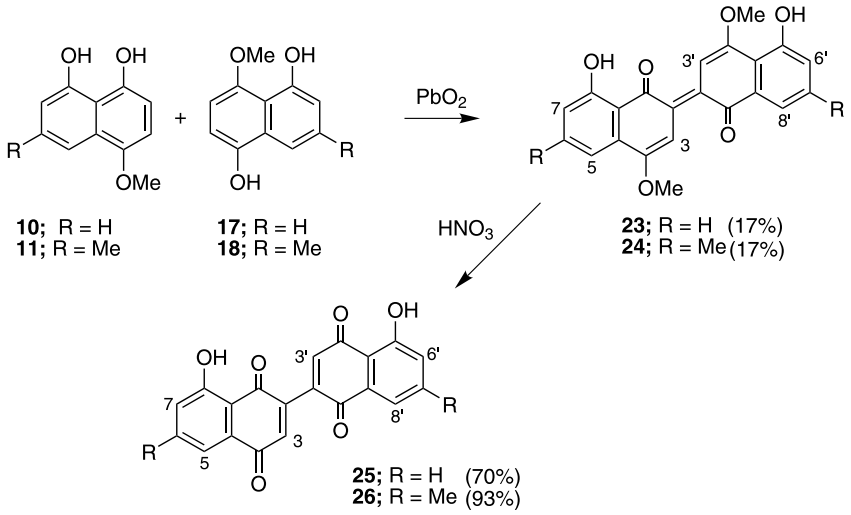


Scheme 3.

was oxidised immediately by lead(IV) oxide to the corresponding 1,4-naphthoquinone **9** (Scheme 1) and so did not participate in the phenolic coupling reactions.

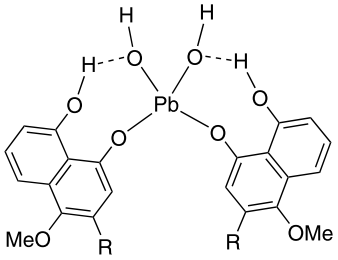
The application of the above hydrolysis with subsequent oxidation procedure to a mixture of the methyl-substituted methoxynaphthylene diacetates corresponding to the diols **11** and **18** gave the expected mixture of bisnaphthalene indigos (Schemes 2, 3 and 4) which we separated by preparative TLC into the symmetrical quinones diosindigo A **13** (39%) and diosindigo B **20** (37%). The structure of the third component, the unsymmetrical quinone **24** (17%), follows from its NMR signals which are similar to those[9] of diosindigo A plus those[4] of diosindigo B.

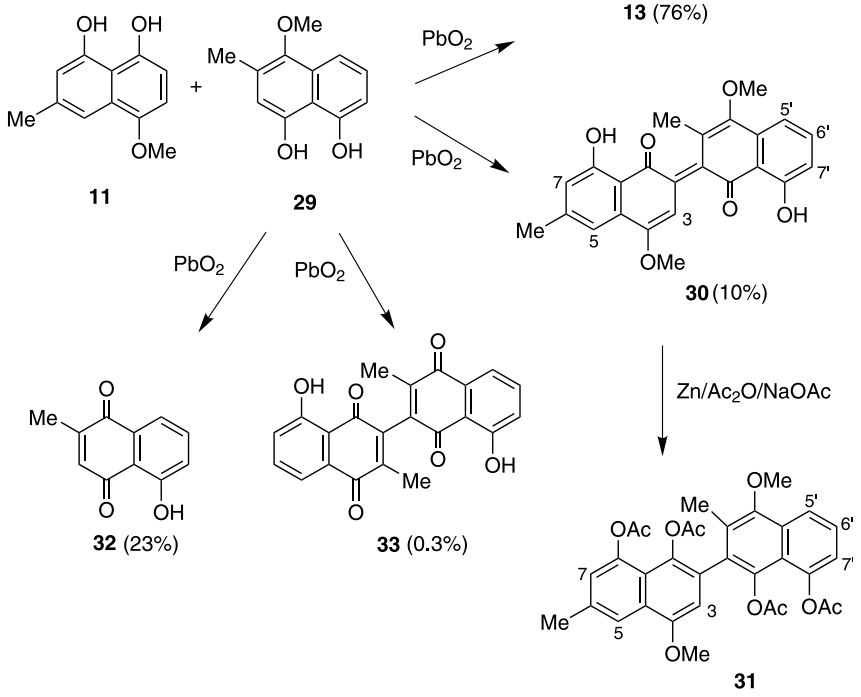
The oxidative coupling of two different phenols having similar reactivity would be expected to give the two symmetrical and the unsymmetrical products in the ratio



Scheme 4.

of 1:1:2. The much lower yields of the unsymmetrical bisnaphthalene indigos obtained in the present work indicate that the isomeric naphthols concerned react with lead(IV) oxide at differing rates. We attribute this to the difference in their hydroxylation patterns, the peri hydroxy groups of the 1,8-naphthylenediol systems in **10** and **11** providing stronger coordination to the metal than is possible with the 1,5-substituted isomers **17** and **18**. The rapid formation of a transient complex such as **27** between the diol **10** and lead(IV) oxide and the subsequent intramolecular coupling of its two naphthalene nuclei would effectively prevent much of the 1,8-dihydroxy compound **10** from coupling with the 1,5-dihydroxy isomer **17**. If four-fifths of the 1,8-isomer were removed from the reaction in this way the theoretical yields of each of the two symmetrical bisnaphthalene indigos would be 40% and that of the unsymmetrical quinone would be reduced to 20%. These values are in good agreement with those obtained experimentally and provide support for the above argument.





Scheme 5.

The bisnaphthalene indigos **12**, **19**, and **23** underwent oxidative demethylation readily on being treated with nitric acid, giving the corresponding binaphthyldiquinones **15**, **21** and **25**. The dimethyl analogues **13**, **24** and **20** behaved in a similar manner giving the naturally occurring diquinones[7] mamegakinone **16**, rotundiquinone **26**, and biramentaceone **22** (Schemes 2–4). Each of the unsymmetrical diquinones **25** and **26** showed two distinctive NMR signals for their hydroxy protons. In the mass spectrometer the molecular ions from the bijuglones **15**, **21** and **25** underwent cleavage of their quinone rings with the formation of characteristic[10] fragment radical-ions with *m*/*z* 120 ($C_7H_4O_2$) and 92 (C_6H_4O). The corresponding ions from their dimethyl counterparts **16**, **22**, and **26** had the expected *m*/*z* values of 134 and 106. We succeeded in reconverting the diquinone mamegakinone **16** into the monoquinone diosindigo A **13** by reductively methylating it using tin(II) chloride and phosphoryl(V) chloride in methanolic hydrochloric acid[8] and then oxidising the resulting binaphthyltetraol with lead(IV) oxide (Scheme 2).

All the above coupling reactions producing the bisnaphthalene indigos utilise methoxynaphthylenediols in which the aromatic ring with the hydroxy and methoxy groups carries no other substituents. We have noticed that the presence of a methyl group adjacent to the methoxy group has a deleterious effect on such reactions. Thus the oxidative coupling of the methoxynaphthylene diol **11** with the isomeric diol[8] **29** derived from plumbagin (Scheme 5) gave only two products, diosindigo A **13** (76%) and the cross-coupled bisnaphthalene indigo **30** (10%). The poor solubility of the latter prevented the measurement of its NMR spectrum and we characterised it as its leuco-acetate **31**. When we treated the methoxydiol **29** alone with lead(IV) oxide the products were plumbagin **32** (23%) and 3,3′-biplumbagin **33** (0.3%), both apparently resulting from heterolytic oxidative demethylation reactions. It appears that the presence of the two methyl groups in the postulated complex **28** largely inhibits the normal coupling reaction.

3. Experimental

3.1. General

Operations involving the formation of the free naphthols, particularly those in alkaline solution, were performed under nitrogen. IR spectra were measured for potassium bromide discs and UV–vis spectra were obtained for solutions in ethanol or, where indicated, in chloroform. ^{1}H NMR spectra were measured at 100 MHz for solutions in deuterochloroform or, where indicated, in perdeutero-acetone with tetramethylsilane as internal standard. Mass spectra were measured using EI at 70 eV. TLC was performed on silica gel (Merck GF_{254}). 'Light petroleum' refers to the fraction with bp 60–80 °C. The reaction products were colourless solids unless stated otherwise.

3.2. Oxidative coupling reactions

A mixture of the methoxynaphthylene diacetates (ca. 0.25 mmol) was boiled under reflux for 0.5 h with 3% methanolic potassium hydroxide (5 ml) under nitrogen. The mixture was added to 1 M sulphuric acid (10 ml) and shaken with chloroform (5×5 ml). The dried chloroform solution was warmed with lead(IV) oxide (500 mg, 2.42 mmol) for 5 min, filtered hot, and the deep blue filtrate was treated twice more with lead(IV) oxide (50 mg) in the same manner. The chloroform solution was then subjected to preparative TLC in order to separate the components of the mixture of bisnaphthalene indigos.

3.3. Oxidative demethylation reactions

A suspension of the bisnaphthalene indigo (10 mg) in 4 M nitric acid (1.5 ml) was heated on the steam-bath for 0.5 h and then poured into water (7 ml). The resulting solid was crystallised from light petroleum to give the substituted 2,2′-binaphthyl-1,4:1′,4′-diquinone (65–93%).

3.4. Reductive acetylation of quinones

A mixture of the quinone (4 mg), acetic anhydride (1 ml), zinc dust (50 mg) and anhydrous sodium acetate (50 mg) was boiled under reflux for 30–60 min and added to hot water. Extraction with chloroform gave the corresponding leucoacetate.

3.4.1. 1-Hydroxy-4,5-naphthylene phenylboronate 4. A mixture of 1,4,5-naphthalene triol[11] **3** (2 g, 11.36 mmol), phenylboronic anhydride (1.18 g, 11.36 mmol) and benzene (100 ml) was boiled under reflux using a Dean-Stark apparatus until the evolution of water was complete. Concentration of the solution gave a solid which crystallised from benzene to yield the phenylboronate **4** (1.8 g, 6.87 mmol, 61%) as needles, mp 200–202 °C (Found: M^+ 262.0798. C, 73.0; H, 4.0%. $C_{16}H_{11}{}^{11}BO_3$ requires *M* 262.0801. C, 73.3; H, 4.2%); *m*/*z* 262 (100%, M), 233 (19, M−CHO) and 131 (4, M^{2+}); ν_{max}/cm^{-1} 3210 (OH), 1638, 1618 and 1602 (aromatic C=C) and 1330 (B–O); λ_{max}/nm 319 (log ε 3.71), 334 (3.73) and 348 (3.73); δ_H [$(CD_3)_2CO$] 6.85 (2H, s, H-2 and -3), 6.99 (1H, dd, J=1.8 Hz, H-6), 7.20–7.63 (4H, m, H-7 and *m*- and *p*-H's of Ph), 7.75 (1H, dd, J=1.8 Hz, H-8) and 7.90–8.18 (2H, m, *o*-H's of Ph).

3.4.2. Reaction of 1-hydroxy-4,5-naphthylene phenylboronate 4 with acetic anhydride and sodium acetate. A mixture of the phenylboronate (410 mg, 1.57 mmol), acetic anhydride (5.4 g, 52.95 mmol) and anhydrous sodium acetate (80 mg, 0.98 mmol) was kept for 27 h at 20 °C, poured into water and extracted with chloroform. The chloroform solution, after being washed with aqueous sodium hydrogen carbonate and evaporated, afforded a solid which crystallised from benzene to give a mixture of 4,8-diacetoxy-1-naphthol **5** and 5,8-diacetoxy-1-naphthol **7** (110 mg, 0.43 mmol, 27%) as needles, mp 154–156 °C (Found: M^+, 260.0684. Calcd for $C_{14}H_{12}O_5$: *M*, 260.0684); *m*/*z* 260 (l.5%, M), 218 (5, M−CH_2CO), 176 (100, 218-CH_2CO) and 147 (3.5, 176-CHO); ν_{max}/cm^{-1} 3440 (OH) and 1750 (aryl acetate C=O); λ_{max}/nm 292infl (log ε 3.70), 303.5 (3.79), 317 (3.75) and 331 (3.67).

3.4.3. Methylation of the mixture of diacetoxynaphthols 5 and 7. A solution of diazomethane [from *N*-nitrosomethylurea (2 g, 19.4 mmol) in ether (30 ml)] was added to a solution of the mixture of diacetoxynaphthols (100 mg, 0.38 mmol) in

ether (20 ml) and the mixture was kept for four days at 20 °C. Evaporation of the solvent and crystallisation of the residue from light petroleum/chloroform gave a mixture of 4-methoxy-1,5-naphthylene diacetate **6** (80%) and 5-methoxy-l,4-naphthylene diacetate **8** (20%) (92 mg, 0.34 mmol, 88%) as needles, mp 107–112 °C (Found: M^+, 274.0840. Calcd for $C_{15}H_{14}O_5$: *M*, 274.0841); *m/z* 274 (26%, M), 232 (20, M−CH_2CO) and 190 (100, 232-CH_2CO); ν_{max}/cm^{-1} 1757 (aryl acetate C=O); λ_{max}/nm 298 (log ε 3.88), 312 (3.78) and 326.5 (3.64); δ_H 2.40 and 2.47 (each 3H, s, CH_3CO_2Ar), 3.98 (3H, s, CH_3OAr) and 6.75–7.85 (5H, m, ArH).

3.4.4. Oxidative coupling of 1-methoxynaphthylene-4,5-diol 10 with 4-methoxy-naphthylene-1,5-diol 17. A mixture of 4-methoxy-1,5-naphthylene diacetate **6** (27 mg, 0.10 mmol, containing 20% of 5-methoxy-1,4-naphthylene diacetate **8**) and 1-methoxy-4,5-naphthylene diacetate[8] (**10** diacetate) (22 mg, 0.085 mmol) was hydrolysed and oxidatively coupled as above. Preparative TLC afforded three blue products.

(a). The fastest-moving compound crystallised from chloroform to give 8,8′-dihydroxy-4,4′-dimethoxy-2,2′-binaphthyl-1,1′-quinone **12** as deep blue needles (10 mg, 0.027 mmol, 33%), mp > 350 °C (lit.,[6] (350 °C) (Found: M^+, 376.0947. C, 69.9; H, 4.0%. $C_{22}H_{16}O_6$ requires: *M* 376.0947. C, 70.2; H, 4.3%); *m/z* 376 (50%, M), 361 (32, M−Me), 346 (22, 361-Me), 345 (100, M−MeO) and 92 (30, C_6H_4O); ν_{max}/cm^{-1} 1578 (quinone C=O); λ_{max}/nm ($CHCl_3$) 285 (log ε 4.40), 326infl (4.02), 507 (3.57), 664infl (4.32) and 703 (4.40). This was identical with an authentic specimen prepared from 1-methoxy-4,5-naphthylene diacetate by the same procedure.

Reductive acetylation of the quinone **12** gave the corresponding leucotetra-acetate **14** which crystallised from ethanol in needles, mp 251.5–253.5 °C (Found: M^+, 546. C, 66.2; H, 5.0%. $C_{30}H_{26}O_{10}$ requires *M* 546. C, 65.9; H, 4.8%); *m/z* 546 (0.5%, M), 504 (10), 462 (13), 420 (1.5) and 378 (25) (each M−*n*CH_2CO), 444 (13, 462-H_2O), 402 (100, 420-H_2O), 387 (2, 402-Me), 360 (45, 378-H_2O), 346 (11, 402-2CO), 345 (11, 360-Me) and 331 (5, 346-Me); ν_{max}/cm^{-1} 1770 and 1758 (aryl acetate C=O) and 1598 (aromatic C=C); λ_{max}/nm 242 (log ε 4.72), 257infl (4.38), 262infl (4.32), 307 (4.03), 317 (4.02) and 330 (3.95); δ_H 2.00 (6H, s, CH_3CO_2Ar at C-1 and -1′), 2.35 (6H, s, CH_3CO_2Ar at C-8 and -8′), 3.98 (6H, s, CH_3O at C-4 and -4′), 6.75 (2H, s, H-3 and -3′), 7.18 (2H, dd, *J*=1.5, 8 Hz, H-7 and -7′), 7.52 (2H, dd, *J*=8, 8 Hz, H-6 and -6′) and 8.28 (2H, dd, *J*=1.5, 8 Hz, H-5 and -5′).

(b) The next blue product crystallised from light petroleum /chloroform to yield 5′,8-dihydroxy-4,4′-dimethoxy-2,2′-binaphthyl-1,1′-quinone **23** (5 mg, 0.013 mmol, 17%) as deep blue needles, mp 244–245 °C (decomp.) (Found: M^+, 376.0946. $C_{22}H_{16}O_6$ requires *M*, 376.0946); *m/z* 378 (19%, M+2H), 376 (84, M). 361 (45, M−Me), 345 (100, M−MeO); ν_{max}/cm^{-1} 3400 (hydrogen-bonded ArOH), 1595 and 1580 (quinone C=O); λ_{max}/nm ($CHCl_3$) 283 (log ε 4.36), 320infl (4.14), 514infl (3.69), 638infl (4.32) and 684 (4.41); δ_H 4.02 (3H, s, MeO at C-4), 4.15 (3H, s, hydrogen-bonded MeO at C-4′), 6.98–7.78 (6H, m, H-5, -6., -6′, -7, -7′ and -8′), 8.30 (1H, s, H-3), 8.49 (1H, s, H-3′), 8.78 (1H, s, OH at C-5′) and 13.45 (1H, s, OH at C-8).

(c) The slowest-moving blue product crystallised from chloroform to give 5,5′-dihydroxy-4,4′-dimethoxy-2,2′-binaphthyl-1,1′-quinone **19** (11 mg, 0.029 mmol, 37%) as deep blue needles, mp 259–260 °C (decomp.) (Found: M^+, 376.09433, $C_{22}H_{16}O_6$ requires *M*, 376.0946); *m/z* 378 (45%, M+2H), 376 (100, M), 361 (67, M−Me), 346 (20, 361-Me) and 345 (40, M−MeO); ν_{max}/cm^{-1} 3340 (ArOH), 1605 (quinone C=O) and 1588 (aromatic C=C); λ_{max}/nm ($CHCl_3$) 286 (log ε 4.18), 316infl (3.98) and 668 (4.28); δ_H 4.13 (6H, s, MeO at C-4 and -4′), ca. 7.11 (2H, m, H-6 and -6′), ca. 7.36 (2H, m, H-7 and -7′), ca. 7.76 (2H, m, H-8 and -8′), 8.40 (2H, s, H-3 and -3′) and 8.83 (2H, s, OH at C-5 and -5′). This was identical with an authentic specimen prepared from 4-methoxy-1,5-naphthylene diacetate by the same procedure.

The mother-liquor from the above crystallisations, on being subjected to TLC using chloroform, gave a solid which afforded 5-methoxy-1,4-naphthoquinone **9** (2.5 mg) as yellow needles, mp 184–185 °C (lit., [12] 186 °C) (Found: M^+, 188.0476. $C_{11}H_8O_3$ requires *M*, 188.0473); ν_{max}/cm^{-1} 1673 and 1666 (quinone C=O) and 1624 (aromatic C=C); λ_{max}/nm 245 (log ε 4.20), 328 (3.05) and 394 (3.58); δ_H 4.00 (3H, s, MeO at C-5), 6.67 (2H, s, H-2 and -3), ca. 7.32 (1H, m, H-6) and ca. 7.49 (2H, m, H-7 and -8). This was identical with an authentic specimen.[12]

3.4.5. Oxidative demethylation of the bisnaphthalene indigos 12, 19 and 23. (a) The oxidation product obtained from the symmetrical quinone **12** crystallised from light petroleum to give 8,8′-dihydroxy-2,2′-binaphthyl-1,4:1′,4′-diquinone **15** as red-brown needles (72%), mp 270–273 °C (decomp.) (Found: M^+, 346.0476. C, 69.1; H, 2.8%. $C_{20}H_{10}O_6$ requires *M* 346.0477. C, 69.4; H, 2.9%); *m/z* 346 (100%, M), 329 (17, M−OH), 290 (4, M−2CO), 289 (8, M−CO–CHO), 262 (5, 290-CO), 234 (3, 262-CO), 120 (10, $C_7H_4O_2$)- and 92 (21, C_6H_4O); ν_{max}/cm^{-1} 1670, 1650 and 1635 (quinone C=O) and 1608 (aromatic C=C); λ_{max}/nm 256infl (log ε 4.18), 274 (4.19), 434 (3.83) and 560infl (3.24); δ_H 7.06 (2H, s, H-3 and -3′), 7.33 (2H, dd, *J*=5, 5 Hz, H-6 and -6′), 7.70 (4H, dd, *J*=1, 5 Hz, H-5, -5′, -7 and -7′) and 11.73 (2H, s, OH at C-8 and -8′).

(b) The oxidation product from the unsymmetrical quinone **23** crystallised from light petroleum to give 5′,8-dihydroxy-2,2′-binaphthyl-1,4:1′,4′-diquinone **25** as red-brown needles (70%), mp 247–250 °C (decomp.) (Found: M^+, 346.0476. $C_{20}H_{10}O_6$ requires *M* 346.0477); *m/z* 348 (10%, M+2H), 346 (100, M), 329 (13, M−OH), 290 (6, M−2CO), 289 (10, M−CO–CHO), 262 (7, 290-CO), 120 (8, $C_7H_4O_2$) and 92 (16, C_6H_4O); ν_{max}/cm^{-1} 1670 and 1638 (quinone C=O) and 1600 (aromatic C=C); λ_{max}/nm 240infl (log ε 4.30), 266infl (4.27) and 434 (3.83); δ_H 7.02 and 7.05 (each 1H, s, H-3 and -3′), ca. 7.32 (2H, m, H-6′ and -7), ca. 7.69 (4H, m, H-5, -6, -7′ and -8′), 11.74 (1H, s, OH at C-8) and 11.84 (1H, s, OH at C-5′).

(c) The oxidation product from the symmetrical quinone **19** crystallised from light petroleum to give 5,5′-dihydroxy-2,2′-binaphthyl-1,4:1′,4′-diquinone **21** as yellow plates

(65%), mp 267–270 °C (decomp.) (Found: M^+, 346.0476. $C_{20}H_{10}O_6$ requires *M*, 346.0477); *m/z* 346 (100%, M), 329 (10, M−OH), 290 (3, M−2CO), 289 (8, M−CO–CHO), 262 (5, 290-CO), 234 (3, 262-CO), 120 (8, $C_7H_4O_2$) and 92 (22, C_6H_4O); ν_{max}/cm^{-1} 1638 and 1622 (quinone C=O) and 1602 (aromatic C=C); λ_{max}/nm 247 (log ε 4.31), 267infl (4.27) and 438 (3.94); δ_H 7.05 (2H, s, H-3 and -3′), 7.32 (2H, dd, *J*=5, 5 Hz, H-7 and -7′), 7.68 (4H, dd, *J*=1, 5 Hz, H-6, -6′, -8 and -8′) and 11.83 (2H, s, OH at C-5 and -5′).

3.4.6. Oxidative coupling of 1-methoxy-7-methyl-4,5-naphthylenediol 11 with 4-methoxy-7-methyl-1,5-naphthylenediol 18. A mixture of 1-methoxy-7-methyl-4,5-naphthylene diacetate[8] (**11** diacetate) (35 mg, 0.12 mmol) and 4-methoxy-7-methyl-1,5-naphthylene diacetate[8] (**18** diacetate) (35 mg, 0.12 mmol) was hydrolysed and oxidatively coupled as described above. Three blue products resulted.

(a) The fastest-moving compound crystallised from chloroform to yield 8,8′-dihydroxy-4,4′-dimethoxy-6.6′-dimethyl-2,2′-binaphthyl-1,1′-quinone (diosindigo A) **13** (19 mg, 0.047 mmol, 39%) as deep blue needles, mp 317 °C (decomp.) (lit.,[3] 317 °C decomp.) identical with an authentic specimen.

(b) The next product crystallised from light petroleum /chloroform to yield 5′, 8-dihydroxy-4,4′-dimethoxy-6,7′-dimethyl-2,2′-binaphthyl-1,1′-quinone **24** as deep blue needles (8 mg, 0.020 mmol, 17%), mp 257–258 °C (decomp.) (Found: M^+, 404.1260. $C_{24}H_{20}O_6$ requires *M* 404.1259); *m/z* 406 (16%, M+2H), 404 (67, M), 389 (56, M−Me) and 373 (100, M−MeO); ν_{max}/cm^{-1} 3400 (ArOH) and 1588 (hydrogen-bonded quinone C=O); λ_{max}/nm ($CHCl_3$) 292 (log ε 4.46), 322infl (4.23), 504infl (3.67), 665infl (4.50) and 694 (4.54); δ_H 2.38 (6H, s, Me at C-6 and -7′), 4.01 (3H, s, MeO at C-4), 4.13 (3H, s, MeO at C-4′), 6.80 (1H, br s, H-7), 6.94 (1H, br s, H-6′), 7.10 (1H, br s, H-5), 7.57 (1H, br s, H-8′), 8.26 (1H, s, H-3′), 8.47 (1H, s, H-3), 8.69 (1H, s, OH at C-5′) and 13.51 (1H, s, OH at C-8).

(c) The slowest-moving compound crystallised from chloroform to give 5,5′-dihydroxy- 4,4′-dimethoxy-7,7′-dimethyl-2,2′-binaphthyl-1,1′-quinone (diosindigo B) **20** (18 mg, 0.045 mmol, 37%) as deep blue needles, mp 275 °C (decomp.) identical with an authentic specimen.[8]

3.4.7. Oxidative demethylation of the methyl-substituted bisnaphthalene indigos 13, 20 and 24. (a) The oxidation product from diosindigo A **13** crystallised from light petroleum to give 8,8′-dihydroxy-6,6′-dimethyl- 2,2′-binaphthyl-1,4:1′,4′-diquinone **16** (mamegakinone) (75%) as orange-red needles, mp 254–256 °C (decomp.) (lit.,[13] 256 °C decomp.) (Found: M^+, 374.0793. $C_{22}H_{14}O_6$ requires *M*, 374.0790); *m/z* 374 (100%, M), 357 (20, M−OH), 318 (11, M−2CO), 317 (14, M−CO–CHO), 290 (13, 318-CO), 262 (6, 290-CO), 135 (5, $C_8H_7O_2$), 134 (13, $C_8H_6O_2$) and 106 (25, C_7H_6O); ν_{max}/cm^{-1} 1661, 1642 and 1627 (quinone C=O); λ_{max}/nm (EtOH +10% dioxan) 253 (log ε 4.27), 272infl (4.20) and 440 (3.85); δ_H 2.47 (6H, s, Me at C-6 and -6′), 6.98 (2H, s, H-3 and -3′), 7.13 (2H, br s, H-7 and -7′), 7.50 (2H, br s, H-5 and -5′) and 11.69 (2H, s, OH at C-8 and -8′). This was identical with an authentic specimen.[13]

(b) The oxidation product from the unsymmetrically substituted 5′,8-dihydroxy-4,4′-dimethoxy-6,7′-dimethyl-2,2′-binaphthyl-1,1′-quinone **24** crystallised from light petroleum giving 5′,8-dihydroxy-6,7′-dimethyl-2,2′-binaphthyl-1,4:1′,4′-diquinone **26** (rotundiquinone[14]) (93%) as orange-red needles, mp 239 °C (decomp.) (Found: M^+, 374.0789. $C_{22}H_{14}O_6$ requires *M*, 374.0790); *m/z* 374 (100%, M), 357 (21, M−OH), 318 (10, M−2CO), 317 (11, M−CO–CHO), 290 (13, 318-CO), 262 (3, 290-CO), 134 (6, $C_8H_6O_2$) and 106 (16, C_7H_6O); ν_{max}/cm^{-1} 1666 and 1643 (quinone C=O); λ_{max}/nm 253 (log ε 4.16), 274infl (4.09) and 438 (3.81); δ_H 2.46 (6H, s, Me at C-6 and -7′), 6.98 (1H, s, H-3), 7.03 (1H, s, H-3′), 7.13 and 7.15 (each 1H, br s, H-6′ and -7), 7.50 and 7.52 (each 1H, br s, H-5 and -8′), 11.70 (1H. s, OH at C-8) and 11.80 (1H, s, OH at C-5′).

(c) The oxidation product from diosindigo B **20** crystallised from light petroleum to give 5,5′-dihydroxy- 7,7′-dimethyl-2,2′-binaphthyl-1,4:1′,4′-diquinone **22** (biramentaceone) as orange-red needles (89%), mp 272 °C (decomp.) (Found: M^+, 374.0789. $C_{22}H_{14}O_6$ requires *M*, 374.0790); *m/z* 376 (10%, M+2H), 374 (100, M), 357 (28, M−OH), 346 (4, M−CO), 318 (10, 346-CO), 317 (14, 346-CHO), 303 (5, 318-Me), 290 (12, 318-CO), 262 (5, 290-CO), 187 (6, M^{2+}), 135 (6, $C_8H_7O_2$), 134 (10, $C_8H_6O_2$) and 106 (20, C_7H_6O); ν_{max}/cm^{-1} 1665 and 1645 (quinone C=O); λ_{max}/nm (EtOH +10% dioxan) 252 (log ε 4.26), 273infl (4.16) and 444 (3.90); δ_H 2.46 (6H, s, Me at C-7 and -7′), 7.01 (2H, s, H-3 and -3′), 7.13 (2H, br s, H-6 and -6′), 7.50 (2H, br s, H-8 and -8′) and 11.80 (2H, s, OH at C-5 and -5′). This was identical with an authentic specimen[15] of biramentaceone which had mp 272 °C (decomp.).

3.5. Conversion of mamegakinone 16 into diosindigo A 13

A mixture of mamegakinone **16** (5 mg, 0.013 mmol), tin(II) chloride dihydrate (5 mg, 0.022 mmol), phosphoryl(V) chloride (20 mg, 0.13 mmol), 4 M hydrochloric acid (2 ml) and methanol (10 ml) was boiled under reflux under nitrogen for 1 h, diluted with water, and extracted with chloroform. A mixture of the chloroform solution and lead(IV) oxide (200 mg, 0.97 mmol) was boiled under reflux for 0.5 h, filtered and evaporated. The resulting blue solid crystallised from chloroform to give diosindigo A **13** (5 mg, 0.012 mmol, 93%) identical with an authentic specimen.

3.5.1. Oxidative coupling of 1-methoxy-7-methyl-4,5-naphthylenediol 11 with 1-methoxy-2-methyl-4,5-naphthylenediol 29. A mixture of 1-methoxy-7-methyl-4,5-naphthylene diacetate (**11** diacetate)[8] (30 mg, 0.10 mmol) and 1-methoxy-2-methyl-4,5-naphthylene diacetate (**29** diacetate)[8] (30 mg, 0.10 mmol) was hydrolysed and oxidised as described above. TLC afforded two products the faster-moving of which crystallised from chloroform to give diosindigo A **13** (16 mg, 0.04 mmol, 76%) identical with an authentic specimen. The slower-moving product crystallised from light

petroleum/chloroform to give 8,8′-dihydroxy-4,4′-dimethoxy-3′,6-dimethyl-2,2′-binaphthyl-1,1′-quinone **30** (4 mg, 0.01 mmol, 10%) as deep blue needles, mp>360 °C (Found: $(M-Me)^+$, 389.1023. $C_{23}H_{17}O_6$ requires (M−Me), 389.1025); *m/z* 404 (6%, M), 389 (16, M−Me), 388 (45, 389-H), 375 (6, M−CHO), 374 (75, 389-Me), 373 (100, M−MeO), 360 (14, 388-CO), 359 (56, 388-CHO), 358 (18, 389-MeO), 357 (16, 388-MeO), 345 (11, 373-CO) and 343 (14, 374-MeO); ν_{max}/cm^{-1} 1580 and 1572 (hydrogen-bonded quinone C=O); λ_{max}/nm ($CHCl_3$) 291 (log ε 4.52), 337infl (4.23), 516infl (3.91) and 692 (4.49).

Reductive acetylation gave the corresponding leucotetra-acetate **31** which crystallised from ethanol as needles (Found: M^+, 574.1841. $C_{32}H_{30}O_{10}$ requires *M*, 574.1839); *m/z* 574 (2%, M), 532 (20, M−CH_2CO), 490 (22, 532-CH_2CO), 472 (5, 490-H_2O), 448 (3, 490-CH_2CO), 430 (100, 448-H_2O), 415 (7, 430-Me), 406 (35, 448-CH_2CO) and 388 (45, 406-H_2O); ν_{max}/cm^{-1} 1775 and 1765 (aryl acetate C=O) and 1610 (aromatic C=C); λ_{max}/nm 242 (log ε 4.84), 253infl (4.70), 282infl (4.35), 290infl (4.34), 313infl (4.21) and 328infl (4.07); δ_H 1.94 and 2.00 (each 3H, s, $MeCO_2Ar$ at C-1 and -1′), 2.34 (6H, s, $MeCO_2Ar$ at C-8 and -8′), 2.45 and 2.52 (each 3H, s, Me at C-3′ and -6), 3.93 and 3.95 (each 3H, s, MeO at C-4 and -4′), 6.66 (1H, s, H-3), 6.98–7.10 (2H, m, H-7 and -7′), 7.25–7.48 (1H, m, H-6′) and 7.98–8.14 (2H, m, H-5 and -5′).

3.5.2. Oxidative coupling of 1-methoxy-2-methyl-4,5-naphthylenediol 29. 1-Methoxy-2-methyl-4,5-naphthylene diacetate (**29** diacetate)[8] (0.5 g, 1.74 mmol) was hydrolysed and oxidised with lead(IV) oxide as described above. Separation of the products by TLC using chloroform on silica gel containing oxalic acid gave, as the major product, plumbagin **32** (73 mg, 0.39 mmol, 23%), identical with an authentic specimen.

The minor product crystallised from light petroleum to give 8,8′-dihydroxy-3,3′-dimethyl-2,2′-binaphthyl-1,4:1′,4′-diquinone **33** (3,3′-biplumbagin) (1 mg, 0.0027 mmol, 0.3%) as yellow needles, mp 214–216 °C (lit.,[16] 214–216 °C); *m/z* 374 (100%, M), 373 (9, M−H), 359 (92, M−Me), 357 (56, M−OH), 346 (7, M−CO), 345 (9, M−CHO), 331 (31, 359-CO), 330 (7, 345-Me), 329 (13, 357-CO), 317 (9, 346-CHO), 187 (7, M^{2+}), 149 (6, $C_8H_5O_3$), 121 (25, $C_7H_5O_2$), 120 (20, $C_7H_4O_2$) and 92 (33, C_6H_4O). This was identical (MS, UV and IR) with an authentic specimen.[16]

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Efficient synthesis of orthogonally protected *anti*-2,3-diamino acids

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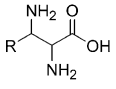
Abstract—An asymmetric synthesis of *anti*-2,3-diamino acids is reported. The enolates of *N*,*N*-dibenzylated β^3-amino esters were treated with di-*tert*-butyl azodicarboxylate (DBAD) to afford their N',N''-di-Boc-2-hydrazino derivatives with excellent *anti* diastereoisomeric ratio. Final Boc removal and reductive cleavage of the hydrazino bond led to the expected 2,3-diamino esters having only one free amino group. In comparison with other asymmetric C-2 amination procedures, this method does not need the use of expensive chiral reagents and/or chiral auxiliaries, while leads to products which can be orthogonally protected.

1. Introduction

2,3-Diamino acids are important non-protein amino acids, usually components of both natural and synthetic bioactive compounds.[1] In fact, they are currently well recognized as key structural moieties in a variety of biologically active molecules: (*S*)-2,3-diamino propanoic acid (DAP, **1**),[2] 2,3-diamino butanoic acids (DAB, **2** and **3**)[3] and (2*S*,3*R*)-2,3-diamino-4-phenylbutanoic acid (**4**)[4] are present in some antifungal dipeptides[5] and in peptide antibiotics, like aspartocin,[3] glumamycin,[6] lavendomycin[7] and aminodeoxybestatin.[8] Furthermore, (2*R*,3*S*)-2,3-diamino-3-phenylpropanoic acid (**5**) has been considered as an alternative side chain in the anticancer drug Taxol.[9]



1 R=H (2*S*)
2 R=CH_3 (2*S*,3*S*)
3 R=CH_3 (2*R*,3*S*)
4 R=CH_2Ph (2*S*,3*R*)
5 R=Ph (2*R*,3*S*)

The elementary, polyfunctional 2,3-diamino acid unit has been frequently used to probe several aspects of peptide and protein structures. In addition, the usefulness of simple chiral 1,2-diamines as auxiliaries and controller groups in asymmetric synthesis (e.g., dihydroxylation,[10] conjugate addition,[11] olefination,[12] allylation,[13] epoxidation,[14] and aldol reaction[15]) is also well documented. Their use to resolve racemic mixtures of chiral allylic alcohols has been reported as well.[16]

The development of simple and efficient methods to produce enantiomerically pure 2,3-diamino acids from readily available starting materials represent a fascinating goal and several asymmetric syntheses have been reported so far. The Mitsunobu reaction on serine,[17] the Hofmann and Curtius rearrangements of asparagine derivatives,[18] and the Schmidt reaction on aspartic acid[19] were used to access chiral 2,3-diaminopropanoic acid. A variety of other syntheses have been also reported: the conjugate addition[20] of homochiral lithium *N*-benzyl-*N*-α-methylbenzylamide to α,β-unsaturated esters and in situ amination with trisyl azide, the asymmetric Rh(I)-phosphine-catalyzed hydrogenation of diastereoisomeric enamides,[21] and the ring opening of *cis*-3-alkylaziridine-2-carboxylates coming from Sharpless asymmetric aminohydroxylation of α,β-unsaturated esters.[22]

In this paper we report a new inexpensive, general and highly stereoselective synthesis of *anti*-2,3-diamino acids via amination of β^3-amino esters.[23]

2. Results and discussion

N,*N*-Dibenzylated β^3-amino esters (**7a–c**), in dry THF at −78 °C and under dry nitrogen stream, were treated with potassium bis(trimethylsilyl)amide (KHMDS) to get the corresponding enolates. The use of more common bases, such as LiHMDS and LDA, for the enolate generation was

Keywords: β^3-Amino acids; 2,3-Diamino acids; Asymmetric synthesis; Amination.
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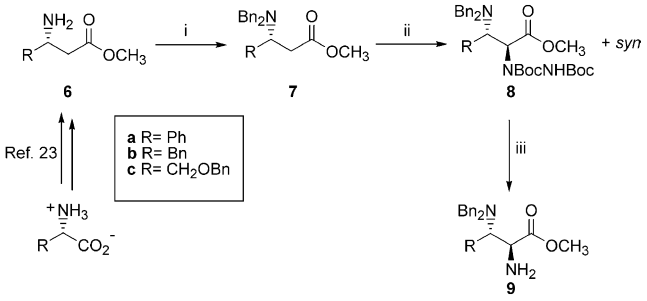
neglected since in our experience[24] such bases lead to significantly poorer results. After 1 h, solid di-*tert*-butyl azodicarboxylate (DBAD) was added to the reaction mixture that was kept at −78 °C for an additional hour. Under such conditions, the Boc-diprotected hydrazino derivatives of the starting **7a–c** were obtained.

The double protection of the amino group is necessary to avoid formation of by-products coming from the abstraction of the N–H proton in the enolate production step. Consequently, common protecting groups that are stable under basic conditions, such as either Boc or Cbz, could not be used under our reaction conditions. Therefore, in a first attempt, the 4-methoxybenzyl group, we had already used elsewhere,[24] was chosen for its peculiar removal conditions (CAN, CH_3CN/H_2O). Unfortunately, although the group turned out to be stable under the reaction conditions, we could not use it because the deprotection of the final 3-[di(4-methoxybenzyl)amino]-2,3-diamino esters led to a plethora of products coming from oxidative cleavage of the C2–C3 bond. Eventually, we used a double benzylic protection that eliminated such deprotection problems and represented at the same time a very bulky nitrogen substituent, suitable to affect the stereochemical outcome[25] of the enolate coupling with the electrophile DBAD. As a matter of fact, the coupling afforded a mixture of *anti*:*syn* Boc protected 2-hydrazino derivatives of **7a–c** with excellent diastereoisomeric ratio. Due to the complexity of the ^{1}H NMR spectra of the Boc containing hydrazino derivatives, they were converted into the corresponding diastereoisomeric mixtures of diamino esters (e.g., **9**) to determine accurately the diastereoisomeric ratio.

The synthetic path is depicted in Scheme 1 and the results obtained for selected β^3-amino esters, namely the methyl esters of β^3-phenylglycine (**6a**), β^3-phenylalanine (**6b**), and β^3-serine (**6c**), are reported in Table 1.



i. BnBr, DIPEA, toluene, reflux; ii. KHMDS, DBAD, dry THF, -78 °C;
iii. a) TFA, CH_2Cl_2; b) H_2, Ni(Ra), MeOH, ultrasound

Scheme 1. Conversion of α-amino acids into monoprotected 2,3-diamino esters.

The more abundant *anti* diastereoisomers were submitted to removal of the Boc protections (TFA in CH_2Cl_2) and cleavage of the N–N bond by hydrogenolysis with Ni(Ra) at low pressure and room temperature in an ultrasound bath.

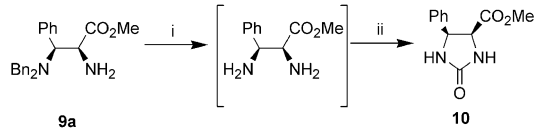
The reduction of hydrazines to amines is reported to be accomplished at high temperature, under high hydrogen pressure.[26] The use of ultrasound reduces significantly both temperature and pressure.[27] As a matter of fact, the hydrogenolysis under such conditions was complete after only 4 h and no traces of C-2 epimerization products could be detected by ^{1}H NMR spectroscopic analysis.

Table 1. Functionalization at C-2 of the fully protected β^3-amino esters **7a–c**

Protected β^3-amino ester	R	Boc protected 2-hydrazino derivatives of **7a–c**		*anti*-2,3-Diamino esters (**9a–c**), yield (%)[a]
		Yield (%)[b]	*anti*/*syn*	
7a	Ph	92	93:7	70
7b	Bn	90	97:3	78
7c	CH_2OBn	90	94:6	65

[a] Overall yield after Boc removal and reductive cleavage of the hydrazine moiety in the *anti* diastereoisomers **8a–c**.
[b] Yield of both diastereoisomers.

The *anti* configuration of the more abundant diastereoisomers coming from the couplings of **7a–c** with DBAD could be attributed, in the case of **8a**, as follows: the final product **9a** was debenzylated and treated, without isolation, with 1,1′-carbonyldiimidazole to afford the imidazolidinone **10** (Scheme 2).



i. Pd/C, H_2, AcOH, 50 °C, 90%; ii. 1,1'-carbonyldiimidazole, TEA, THF, 0 °C, 85%

Scheme 2. Synthesis of *cis*-imidazolidinone (**10**).

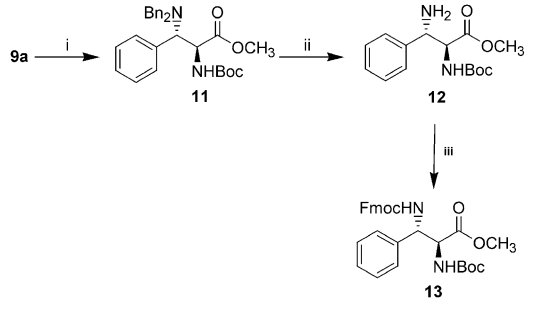
The ^{1}H NMR spectroscopy coupling constant of 9.6 Hz supported[28] the *cis*-configuration of the H-4 and H-5 protons and, thus, the *anti*-configuration of the starting diamino compound.

In the light of this result and in agreement with our previous work on the hydroxylation at C-2 of β^3-amino esters, it seems likely that the stereochemical outcome of the functionalization at C-2 is independent of the nature of the electrophile used, being only a function of the relative stabilities of the enolate conformations.[24]

3. Conclusion

This amination procedure of β^3-amino esters offers several advantages, if compared with many other reported procedures. First of all, it does not require the use of either chiral reagents or chiral auxiliaries: in fact, the observed selection in the coupling step is merely due to the influence of the existing chiral center of the starting β^3-amino ester, enhanced by the presence of two bulky substituents on the nitrogen atom. Moreover, it is noteworthy that the amino groups in the final 2,3-diamino esters have a different protection status: this implies a broad flexibility of their use in peptide synthesis. For instance, the free amino group can be Boc protected and the benzyl groups then removed hydrogenolitically to host an Fmoc protecting group, or vice

versa should either Boc- or Fmoc-strategy be used. Accordingly, in connection with our current interest in the synthesis of glycosyl amino acids, we have prepared the compound **13** as shown in Scheme 3.



Scheme 3. Preparation of the orthogonally protected 2,3-diamino acid **13**.

4. Experimental

4.1. General

NMR spectra were recorded on Varian Inova 500 MHz, Varian Gemini 200 MHz, Varian Gemini 300 MHz, Bruker DRX 400 MHz spectrometers: chemical shifts are in ppm (δ) and J coupling constants in Hz; solvent $CDCl_3$, unless otherwise specified. GC/MS analyses were performed on Hewlett–Packard 6890 GC/5973N MS. Optical rotations were determined on Jasco P-1010 polarimeter (1.0 dm cell); solvent $CHCl_3$, unless otherwise specified. Infrared spectra were recorded using JASCO FT/IR-430 Spectrometer. Mps were taken on a Gallenkamp apparatus. Elemental analyses were performed on a Perkin–Elmer Series II 2400, CHNS analyzer. TLC were carried out on silica gel Merck 60 F_{254} plates (0.2 mm layer) and column chromatographies on Merck Kieselgel 60 (70–230 mesh). Dry solvents were distilled immediately before use.

4.1.1. *N,N*-Dibenzyl protections of 6a–c. *Methyl (R)-3-(dibenzylamino)-3-phenylpropanoate* (**7a**): *typical procedure*. A magnetically stirred suspension of β^3-phenylglycine methyl ester **6a** (1.50 g; 8.38 mmol) and diisopropylethylamine (DIPEA, 7.3 mL; 41.90 mmol) in toluene (18.0 mL) was warmed gently until a clear solution was obtained. Then, benzyl bromide (6.0 mL; 50.28 mmol) was added in one portion and the resulting solution was refluxed for 4 h. The reaction mixture was then cooled in an ice bath, diluted with EtOAc (2×100 mL) and extracted with 10% aq NH_4Cl. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated under reduced pressure to afford a crude reaction product whose chromatography on silica gel (petroleum ether/EtOAc, 95:5) gave the pure crystalline compound **7a**, after recrystallization from hexane (2.56 g; 7.12 mmol; 85%). Mp 51.8–53.0 °C. $[\alpha]_D^{20}$ +71.6 (c 2.0). ^{1}H NMR (500 MHz): δ 2.73 (dd, J=7.3, 14.6 Hz, 1H, H-2a), 3.14 (dd, J=8.8, 14.6 Hz, 1H, H-2b), 3.18 (d, J=13.7 Hz, 2H, NC*H*Ph), 3.64 (s, 3H, OCH_3), 3.78 (d, J=13.7 Hz, 2H, NC*H*Ph), 4.33 (dd, J=7.3, 8.8 Hz, 1H, H-3), 7.20–7.41 (m, 15H, *H*-Ar). ^{13}C NMR (125 MHz): δ 36.9, 51.8, 53.9, 59.1, 127.2, 127.7, 128.3, 128.4, 128.8, 129.1, 137.6, 139.8, 172.3. IR (KBr, cm^{-1}): ν 1714. Anal. Calcd for $C_{24}H_{25}NO_2$: C 80.19, H 7.01, N 3.90. Found: C 80.30, H 7.05, N 3.92.

Under the same conditions, the following *N,N*-diprotected esters were also obtained.

Methyl (S)-3-(dibenzylamino)-4-phenylbutanoate (**7b**). Oil (83%). $[\alpha]_D^{20}$ −5.4 (c 1.0). ^{1}H NMR (500 MHz): δ 2.33 (dd, J=6.4, 14.2 Hz, 1H, H-2a), 2.56 (dd, J=8.8, 13.2 Hz, 1H, H-4a), 2.65 (dd, J=8.3, 14.2 Hz, 1H, H-2b), 3.12 (dd, J=5.7, 13.2 Hz, 1H, H-4b), 3.40–3.50 (m, 1H, H-3), 3.56 (s, 3H, OCH_3), 3.62 (d, J=13.7 Hz, 2H, NC*H*Ph), 3.76 (d, J=13.7 Hz, 2H, NC*H*Ph), 7.20–7.70 (m, 15H, *H*-Ar). ^{13}C NMR (125 MHz): δ 35.9, 36.3, 51.6, 53.7, 57.8, 126.4, 127.2, 128.4, 128.6, 129.1, 129.5, 139.7, 139.8, 172.9. IR (KBr, cm^{-1}): ν 1712. Anal. Calcd for $C_{25}H_{27}NO_2$: C 80.40, H 7.29, N 3.75. Found: C 80.25, H 7.32, N 3.77.

Methyl (R)-4-(benzyloxy)-3-(dibenzylamino)butanoate (**7c**). Oil (86%). $[\alpha]_D^{20}$ +31.6 (c 1.8). ^{1}H NMR (500 MHz): δ 2.55 (dd, J=6.3, 14.6 Hz, 1H, H-2a), 2.68 (dd, J=7.8, 14.6 Hz, 1H, H-2b), 3.47–3.54 (m, 1H, H-3), 3.56–3.62 (m, 4H, H-4a and OCH_3), 3.66 (d, J=13.7 Hz, 2H, NC*H*Ph), 3.71 (dd, J=9.8, 5.4 Hz, 1H, H-4b), 3.75 (d, J=13.7 Hz, 2H, NC*H*Ph), 4.49 (d, J=12.7 Hz, 1H, OC*H*Ph), 4.52 (d, J=12.7 Hz, 1H, OC*H*Ph), 7.20–7.45 (m, 15H, *H*-Ar). ^{13}C NMR (125 MHz): δ 34.7, 51.7, 54.5, 55.2, 70.3, 73.3, 127.1, 127.8, 128.4, 128.6, 129.1, 138.6, 140.1, 173.0. IR (KBr, cm^{-1}): ν 1715. Anal. Calcd for $C_{26}H_{29}NO_3$: C 77.39, H 7.24, N 3.47. Found: C 77.25, H 7.27, N 3.48.

4.1.2. Reactions of 7a–c with DBAD. *Methyl (2S,3S)-3-(dibenzylamino)-2-[N′,N″-(di-tert-butoxycarbonyl)-hydrazino]-3-phenylpropanoate* (**8a**): *typical procedure*. To a magnetically stirred solution of **7a** (2.56 g; 7.12 mmol) in dry THF (75 mL), at −78 °C and under dry argon atmosphere, 0.5 M KHMDS in toluene (28.5 mL; 14.24 mmol) was added dropwise. After 1 h solid di-*tert*-butyl azodicarboxylate (2.85 g; 12.82 mmol) was added in one portion to the reaction mixture kept at −78 °C under stirring. Within 1 h the reaction was quenched by addition of glacial AcOH (1.1 mL) and diluted with EtOAc. The organic layer was washed with brine until neutral, dried (Na_2SO_4), and the solvents evaporated in vacuo. The oily residue, after chromatography on silica gel (hexane/EtOAc, 9:1), afforded the pure title compound **8a** (foam; 3.86 g; 6.55 mmol; 92%). $[\alpha]_D^{20}$ +65.7 (c 1.6). The ^{1}H NMR data were not significant, apparently due to the occurrence of mixtures of rotamers. IR (KBr, cm^{-1}): ν 3260, 1740, 1720. Anal. Calcd for $C_{34}H_{43}N_3O_6$: C 69.25, H 7.35, N 7.13. Found: C 69.17, H 7.31, N 7.15.

Under the same conditions, the following Boc diprotected 2-hydrazino derivatives were also obtained.

Methyl (2S,3S)-3-(dibenzylamino)-2-[N′,N″-(di-tert-butoxycarbonyl)-hydrazino]-4-phenylbutanoate (**8b**). Foam (90%). $[\alpha]_D^{20}$ −2.3 (c 0.3). IR (KBr, cm^{-1}): ν 3250, 1730, 1712. Anal. Calcd for $C_{35}H_{45}N_3O_6$: C 69.63, H 7.51, N 6.96. Found: C 69.60, H 7.49, N 7.01.

Methyl (2S,3R)-4-(benzyloxy)-3-(dibenzylamino)-2-[N′,N″-(di-tert-butoxycarbonyl)-hydrazino]butanoate (**8c**). Foam

(90%). $[\alpha]_D^{20}$ +45.0 (*c* 1.5). IR (KBr, cm^{-1}): ν 3270, 1728, 1715. Anal. Calcd for $C_{36}H_{47}N_3O_7$: C 68.22, H 7.47, N 6.63. Found: C 68.19, H 7.40, N 6.68.

4.1.3. Reductive cleavages of the hydrazino bond in 8a–c. *Methyl (2S,3S)-2-amino-3-(dibenzylamino)-3-phenylpropanoate* (**9a**): *typical procedure*. To a magnetically stirred solution of **8a** (3.86 g; 6.55 mmol) in dry CH_2Cl_2 (54 mL), TFA (54 mL) was added in one portion. After 2 h, the solvent was evaporated under reduced pressure. The crude reaction product, redissolved in MeOH (26 mL), was transferred into a flask containing W-2 Raney nickel (3.86 g, wet) and equipped with a hydrogen inflated balloon. The flask was dipped into an ultrasound bath filled with water and sonicated for 4 h at rt till the starting product was completely consumed (TLC). The reaction mixture was then filtered through Celite® washing with MeOH (100 mL). Removal of the solvents under reduced pressure gave a residue that was redissolved in EtOAc (200 mL), washed with 10% aq Na_2CO_3 (2×100 mL), dried (Na_2SO_4), and evaporated in vacuo, to afford an oil whose chromatography on silica gel (hexane/EtOAc, 7:3) led to the pure title compound **9a** (oil; 1.71 g; 4.58 mmol; 70%). $[\alpha]_D^{20}$ +62.4 (*c* 1.1). ^{1}H NMR (300 MHz): δ 1.97 (bs, 2H, NH_2), 3.05 (d, J=13.5 Hz, 2H, NC*H*Ph), 3.82 (s, 3H, OCH_3), 3.83–3.88 (m, 3H, H-2 and NC*H*Ph), 4.26 (d, J=10.3 Hz, 1H, H-3), 7.20–7.60 (m, 15H, *H*-Ar). ^{13}C NMR (50 MHz): δ 51.7, 54.0, 56.3, 67.3, 126.9, 128.1, 128.3, 128.8, 129.7, 133.5, 139.0, 174.1. IR (KBr, cm^{-1}): ν 3500–3200, 1714. Anal. Calcd for $C_{24}H_{26}N_2O_2$: C 76.98, H 7.00, N 7.48. Found: C 76.81, H 7.06, N 7.52.

Under the same conditions, the following 2-amino esters were also obtained.

Methyl (2S,3S)-2-amino-3-(dibenzylamino)-4-phenylbutanoate (**9b**). Oil (78%). $[\alpha]_D^{20}$ +7.9 (*c* 0.4, MeOH). ^{1}H NMR (500 MHz): δ 1.63 (bs, 2H, NH_2), 2.93 (dd, J=7.3, 13.7 Hz, 1H, H-4a), 3.09 (dd, J=6.3, 13.7 Hz, 1H, H-4b), 3.23–3.29 (m, 1H, H-3), 3.60 (s, 3H, OCH_3), 3.61–3.67 (m, 3H, H-2 and NC*H*Ph), 3.70 (d, J=13.7 Hz, 2H, NC*H*Ph), 7.10–7.40 (m, 15H, H-Ar). ^{13}C NMR (100 MHz): δ 32.7, 52.2, 55.1, 55.6, 63.8, 126.5, 127.4, 128.5, 128.7, 129.4, 129.9, 139.9, 140.5, 175.9. IR (KBr, cm^{-1}): ν 3530–3210, 1712. Anal. Calcd for $C_{25}H_{28}N_2O_2$: C 77.29, H 7.26, N 7.21. Found: C 77.19, H 7.25, N 7.23.

Methyl (2S,3R)-2-amino-4-(benzyloxy)-3-(dibenzylamino)-butanoate (**9c**). Oil (65%). $[\alpha]_D^{20}$ +30.9 (*c* 1.0). ^{1}H NMR (500 MHz, C_6D_6): δ 1.48 (bs, 2H, NH_2), 3.22–3.28 (m, 1H, H-3), 3.29 (s, 3H, OCH_3), 3.58 (d, J=6.8 Hz, 1H, H-2), 3.60 (dd, J=5.8, 9.8 Hz, 1H, H-4a), 3.65 (d, 2H, J=13.7 Hz, NC*H*Ph), 3.72 (dd, 1H, J=4.9, 9.8 Hz, H-4b), 3.84 (d, 2H, J=13.7 Hz, NC*H*Ph), 7.05–7.40 (m, 15H, *H*-Ar). ^{13}C NMR (100 MHz): δ 52.1, 55.4, 55.6, 61.1, 67.2, 73.7, 127.3, 127.9, 128.0, 128.5, 128.8, 129.4, 138.7, 140.2, 175.7. IR (KBr, cm^{-1}): ν 3510–3200, 1716. Anal. Calcd for $C_{26}H_{30}N_2O_3$: C 74.61, H 7.22, N 6.69. Found: C 74.59, H 7.20, N 7.01.

4.1.4. Methyl (4*S*,5*S*)-4-methoxycarbonyl-5-phenyl-2-imidazolidinone (10). A magnetically stirred solution of **9a** (0.020 g; 0.053 mmol) in glacial AcOH (0.5 mL) was hydrogenolysed over 30% Pd/C catalyst (0.006 g) for 2 h at 50 °C, under a slightly positive pressure given by an inflated balloon (~3 bar). The mixture was then filtered through Celite® washing with MeOH (10 mL). Removal of the solvents under reduced pressure gave a residue that was redissolved in dry THF (1.1 mL). The solution was cooled to 0 °C. Et_3N (0.063 mL, 0.053 mmol) and 1,1′-carbonyldiimidazole (0.013 g; 0.079 mmol) were then added in sequence. After 30 min at 0 °C and 2 h at rt the solvents were evaporated under reduced pressure and the remaining crude residue was dissolved in EtOAc and filtered on a short silica gel plug (~3 cm^3) with the same solvent (3×10 mL). By partial evaporation of the solvent under reduced pressure, a semicrystalline residue could be collected whose recrystallization by the same solvent afforded the pure **10** (0.010 g; 0.045 mmol; 88%) as a white solid. Mp 202–203 °C dec. (lit.[27] 203–205 °C). ^{1}H, ^{13}C NMR and IR spectra were superimposable to those reported.

4.1.5. Methyl (2*S*,3*S*)-2-(*tert*-butoxycarbonylamino)-3-(dibenzylamino)-3-phenylpropanoate (11). To a solution of compound **9a** (0.67 g; 1.80 mmol) in dioxane (21 mL) at 0 °C, Et_3N (0.42 mL; 2.70 mmol) and Boc_2O (0.89 g; 3.60 mmol) were added in sequence. The reaction mixture, warmed up to room temperature and stirred for 1 h, was then diluted with EtOAc. The organic layer was washed with brine until neutral, dried (Na_2SO_4), and the solvents evaporated in vacuo to give an oil. Its chromatography on silica gel (hexane/EtOAc, 9:1) afforded the pure title compound **11** (oil; 0.78 g; 1.66 mmol; 92%). $[\alpha]_D^{20}$ +50.7 (*c* 1.5). ^{1}H NMR (400 MHz): δ 1.55 (s, 9H, Boc), 3.04 (d, J=13.5 Hz, 2H, NC*H*Ph), 3.86 (s, 3H, OCH_3), 3.97–4.02 (m, 3H, H-3, NC*H*Ph), 4.58 (bd, J=8.3 Hz, 1H, N*H*Boc), 5.14 (bt, J=9.7 Hz, 1H, H-2), 7.24–7.44 (m, 15H, *H*-Ar). ^{13}C NMR (125 MHz): δ 28.3, 52.3, 54.1, 54.7, 65.0, 80.2, 127.3, 128.3, 128.5, 129.2, 130.1, 132.6, 139.1, 146.9, 154.9, 172.3. IR (KBr, cm^{-1}): ν 1718, 1705. Anal. Calcd for $C_{29}H_{34}N_2O_4$: C 73.39, H 7.22, N 5.90. Found: C 73.25, H 7.20, N 5.92.

4.1.6. Methyl (2*S*,3*S*)-2-(*tert*-butoxycarbonylamino)-3-amino-3-phenylpropanoate (12). A magnetically stirred solution of **11** (0.78 g; 1.66 mmol) in glacial AcOH (7.4 mL) was hydrogenolysed over 30% Pd/C catalyst (0.23 g) for 2 h at 50 °C, under a slightly positive pressure given by an inflated balloon (~3 bar). The mixture was then filtered trough Celite® and washed with MeOH (100 mL). The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (2×100 mL). The organic layer was washed with 10% aq Na_2CO_3 (300 mL), dried (Na_2SO_4), and the solvents evaporated in vacuo to give compound **12** as a white crystalline solid, after recrystallization from hexane/acetone 9:1 (0.44 g; 1.49 mmol; 90%). Mp 110.3–112.3 °C. $[\alpha]_D^{20}$ +29.0 (*c* 0.9). ^{1}H NMR (400 MHz, C_5D_5N): δ 1.35 (s, 9H, Boc), 3.62 (s, 3H, OCH_3), 5.34 (d, J=7.1 Hz, 1H, H-3), 5.77 (bt, J=8.0 Hz, 1H, H-2), 7.21–7.35 (m, 3H, *H*-Ar), 7.89 (d, J=7.3 Hz, 2H, Ar-H), 8.80 (bd, J=8.6 Hz, 1H, N*H*Boc). ^{13}C NMR (100 MHz, C_5D_5N): δ 28.3, 52.4, 57.1, 59.4, 79.3, 128.6, 128.9, 138.0, 140.2, 156.8, 172.0. IR (KBr, cm^{-1}): ν 3350, 3200, 1765, 1715. Anal. Calcd for $C_{15}H_{22}N_2O_4$: C 61.21, H 7.53, N 9.52. Found: C 61.32, H 7.57, N 9.58.

4.1.7. Methyl (2*S*,3*S*)-2-(*tert*-butoxycarbonylamino)-3-(9*H*-fluoren-9-ylmethoxycarbonylamino)-3-phenylpropanoate (13). To a stirred solution of **12** (0.44 g; 1.48 mmol) in dioxane (5.8 mL) and 10% aq Na_2CO_3 (0.31 g; 2.96 mmol) at 0 °C, Fmoc–OSu (0.41 g; 1.18 mmol) dissolved in DMF (1.5 mL) was added slowly. The reaction mixture, after 30 min at 0 °C and 2 h at rt, was extracted with CH_2Cl_2. The organic layer was washed with brine until neutral, dried (Na_2SO_4), and the solvents evaporated under reduced pressure to give an oil. The chromatography on silica gel ($CHCl_3$) afforded the pure compound **13**, white solid after recrystallization from hexane/acetone 9:1 (0.50 g; 0.96 mmol; 65%). Mp 166.6–168.1 °C. $[\alpha]_D^{20}$ +38.7 (*c* 0.3). ^{1}H NMR (500 MHz, C_5D_5N): δ 1.20 (s, 9H, Boc), 3.42 (s, 3H, OC*H*$_3$), 4.14 (t, *J*=6.8 Hz, 1H, Fmoc), 4.30 (dd, *J*=6.8, 10.3 Hz, 1H, C*H*Fmoc), 4.45 (dd, *J*=6.8, 10.3 Hz, 1H, C*H*Fmoc), 5.31 (t, *J*=9.3 Hz, 1H, H-2), 5.69 (t, *J*=9.3 Hz, 1H, H-3), 7.05–7.70 (m, 14H, *H*-Ar and N*H*Boc), 9.17 (d, *J*=9.3 Hz, 1H, N*H*Fmoc). ^{13}C NMR (125 MHz): δ 28.5, 47.5, 52.9, 57.7, 58.0, 67.3, 120.2, 125.4, 126.8, 127.3, 128.4, 128.9, 141.5, 144.1, 155.9, 156.5, 170.4. IR (KBr, cm^{-1}): ν 3395 (br), 1705. Anal. Calcd for $C_{30}H_{32}N_2O_6$: C 69.75, H 6.24, N 5.42. Found: C 69.82, H 6.27, N 5.43.

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Synthesis, biological activity and modelling studies of two novel anti HIV PR inhibitors with a thiophene containing hydroxyethylamino core

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Abstract—An efficient method has been developed for the synthesis of a versatile intermediate bearing azido, hydroxyl and ester functions, a useful precursor for peptidomimetic compounds. The two main features for this synthesis were the use of the Sharpless asymmetric dihydroxylation on thiophene acrylate and the subsequent regioselective ring opening by sodium azide of the cyclic sulfite. Highly chemoselective reduction of the azido alcohol led to a key compound which was utilized for the synthesis of two analogues of commercial anti HIV PR such as nelfinavir and saquinavir. The biological activity and molecular modelling study on these two new potential drugs have been evaluated.

1. Introduction

More recent therapies for AIDS[1,2] are essentially directed against the most important enzymes which regulate HIV: reverse transcriptase (RT) and aspartyl protease (HIV PR).[3] In particular, significant results have been achieved in the development of drugs as HIV PR inhibitors, based upon early recognition of the central role of this enzyme in viral maturation.

HIV PR is an aspartyl protease acting as a C_2 symmetric homodimer with a single active site in the free form and with 99 residues for each monomer. The C_2 axis correlates the catalytic aspartate (Asp-25 and Asp-25′) in the active site of the enzyme. Using the standard nomenclature, the S_1 and $S_{1'}$ subsites are structurally equivalent.

Although peptide-derived compounds could be potent HIV PR inhibitors, they are typically not suitable drug candidates.[4] Their use is limited by some undesirable factors such as poor solubility, low metabolic stability towards degradative enzymes and poor bioavailability after oral ingestion.[5]

All the commercially available anti HIV PR drugs possess a peptidomimetic structure based on the tetrahedral transition state mimetic concept, in which a non-hydrolysable hydroxyethylene or dihydroxyethylene or hydroxyethylamine moiety is used as central core of the molecule (Fig. 1).[1,2]

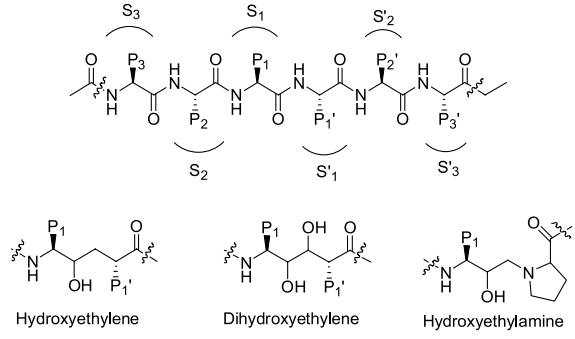

Figure 1.

In fact, the central core in this class of anti HIV PR inhibitors is an isostere replacement at the scissile peptidic bond involved in the proteolytic reaction of the precursor polypeptide and therefore, it has been found to be essential in all the drugs with anti HIV PR activity. The development of such a new class of inhibitors has been also well

Keywords: HIV PR inhibitors; Thiophene; Hydroxyethylamino core; Biological activity.
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supported by the improvement in the field of peptidomimetic synthesis.[6]

Currently six drugs are commercially available as HIV PR inhibitors: these compounds are indeed furnishing good results in AIDS therapy (together in combination with other drugs)[3b] but viral resistance is often increasing due to mutations in the protease.[1,7]

The development of drug resistance and the consequent lack of a final decisive therapy for the HIV infection, makes the elaboration and the synthesis of innovative anti HIV PR drugs urgent.

To this aim we have been exploring the possibility of introducing a thienyl ring in the 'core' of some anti HIV PR drugs. It is known that the thienyl ring mimics the phenyl group of phenylalanine in peptidomimetics[6] in many drugs.[8–10] It was also observed that the biological half-life of antidepressant drugs such as viloxazine became longer when a benzene ring is replaced by thiophene. Furthermore, a recent study on C_2-symmetric diol-based HIV PR inhibitors,[11] has clearly shown that the introduction of a thienyl ring instead of a phenyl group, greatly enhances antiviral activity of the compound.

We have focused our attention on the structures of two of the commercially available drugs namely nelfinavir (**1**)[12] and saquinavir (**2**)[13] (Fig. 2) and in this paper, we report a short and highly stereocontrolled synthesis of modified nelfinavir and saquinavir compounds starting from a single thiophene containing chiral precursor, as well as the preliminary results in the evaluation of biological activities backed by a molecular modelling study.

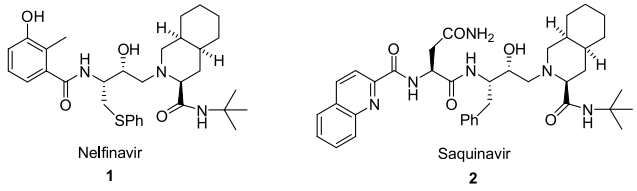


Figure 2.

2. Results and discussion

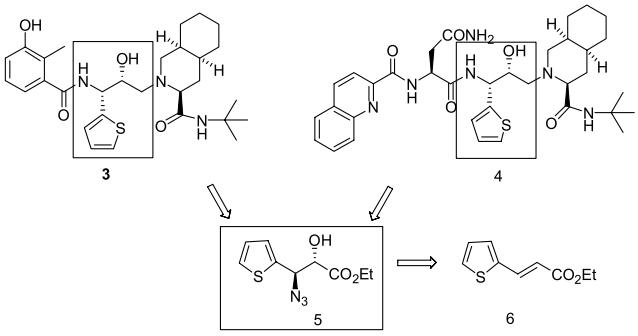
The chemical structures of nelfinavir (**1**) and saquinavir (**2**) (Fig. 2) show the presence of a perhydroisoquinoline (PHIQ) residue as $P_{2'}$–$P_{n'}$ unit which seems of particular importance for a good interaction with the corresponding subsites of the enzyme.[4]

On the other hand, the P_2–P_n termini of the two structures are very different: in nelfinavir a 2-methyl-3-hydroxybenzoic acid residue is present at this position, while in saquinavir a dipeptide unit (asparagine–quinaldic acid) extends the structure toward the S_3 subsite of the enzyme.[4]

Also the crucial core is slightly different for the two drugs: in nelfinavir there is a phenyl moiety, while in saquinavir a phenylalanine residue. However, they posses the same (*R*) absolute configuration at the carbon bearing the central hydroxyl[3,4] and the same relative *anti* configuration at the two vicinal stereocentres.

We therefore, found interesting a modification in the core of both the drug candidates, with the introduction of a simple thiophene moiety in this class of HIV PR inhibitors. With the intention of testing the influence of a thiophene ring on the activity of potential drugs we have therefore, defined the first goal of our synthetic approach as the building of the novel amino alcohol core in nelfinavir and saquinavir structures.

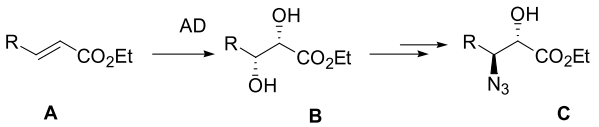
To achieve this objective the two designed targets (compounds **3** and **4** in Scheme 1) could be derived, in a retrosynthetic analysis, from the same chiral thienyl derivative **5** which possesses the correct stereochemistry and the appropriate functionalizations for the subsequent elaboration to the final products.



Scheme 1. Retrosynthetic analysis of compounds **3** and **4**.

This key chiral synthon **5** could be derived from the easily available 3-thiophen-2-yl-acrylic acid ethyl ester **6**.[14] With the crucial goal of introducing the correct chirality in the core structure we hypothesized a new strategy never before utilised for the synthesis of this class of HIV PR inhibitors.[1,12,13]

To this end, a suitable acrylic derivative, such as **A**, can be easily transformed into the chiral diol **B** via Sharpless AD.[15] The introduction of the nitrogen function through inversion of configuration and high regioselectivity represents, in the chosen strategy, the key step in order to obtain the highly functionalized chiral compound **C**, ready for the transformation into different potential analogues of known HIV PR inhibitors (Scheme 2).



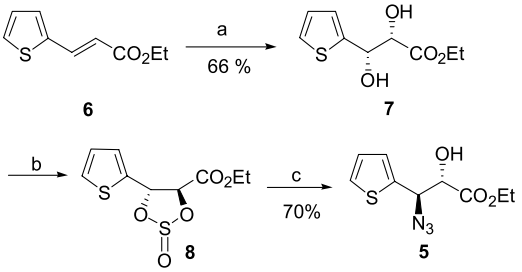
Scheme 2.

This general synthetic strategy was first applied to the synthesis of thiophene containing nelfinavir and saquinavir analogues.[16]

3. Synthesis of the thiophene azido alcohol 5

The known (*E*) olefin **6**[14] (Scheme 3), prepared from

commercially available 2-thiophencarboxaldehyde, was subjected to the Sharpless dihydroxylation following a recently modified procedure.[17] Further, improvements of overall yields of the purified diol **7** have been achieved by adding 20% more AD mix-β and ligand (66% yield and ee > 98).



Scheme 3. (a) AD mix-β, $[DHQD]_2PHAL$, $MeSO_2NH_2$, H_2O/*t*-BuOH, 0–15 °C, 15 h; (b) $SOCl_2$, Pyr, CH_2Cl_2, 0 °C, 15 h; (c) NaN_3, DMF/CH_3CN, 15 °C, 15 h.

Having built the diol moiety the subsequent step was the introduction of the nitrogen with inversion of configuration, that could be, in principle, better achieved from the corresponding cyclic sulfate,[18] obtained via oxidation of the corresponding cyclic sulfite. However, the possibility to oxidize the thienyl ring during the conversion of the sulfite into the sulfate prompted us to directly perform the ring opening reaction with sodium azide, using sulfite **8** as crude material. Pleasingly, the reaction on compound **8** furnished the isolated and purified azido alcohol **5** in 70% yield starting from diol **7** (two steps) (Scheme 3). The reaction was totally regio- and stereoselective as demonstrated in comparison with known compounds.[19]

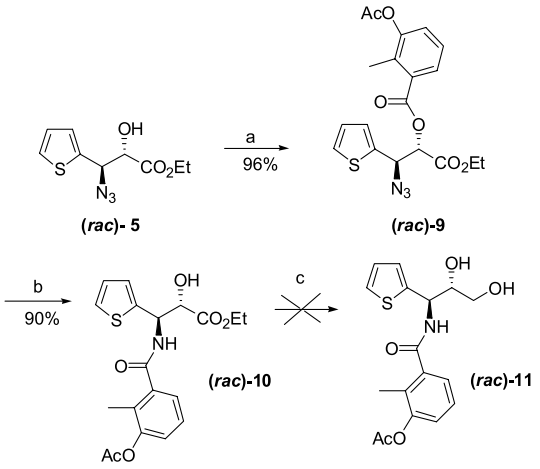
Azido alcohol **5** is a very interesting chiral synthon due to the presence of three different functions on vicinal carbons: an amino precursor as an azido group, a secondary hydroxyl function and a carboxylic group.

4. Synthesis of nelfinavir analogue 3

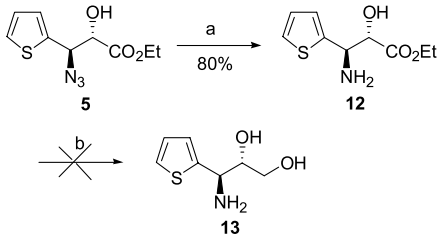
With this key compound **5** in hand we next turned our attention to the synthesis of the nelfinavir analogue **3**, with the introduction on the hydroxyl group of a benzoic acid derivative to obtain compound (*rac*)-**9** (Scheme 4). The proposed sequence was firstly achieved on racemic compound **5**. As expected, the esterification step[20] proceeded smoothly in high yield (96% yield): the subsequent reduction of azido group to the corresponding amino alcohol with the rearrangement shift of carboxylic substituent on the amino group[21] was then achieved in good yield (90%).

However, quite disappointingly, in the last step of the sequence to the target diol (*rac*)-**11** all attempts to chemoselectively reduce the ester function (by $BH_3 \cdot SMe_2$/$NaBH_4$ and similar reagents)[22] gave nearly no reaction. Therefore, we had to change our synthetic strategy in order to reduce the ester function.

In a second approach (Scheme 5) the selective hydrogenation of the azido alcohol **5** provided the amino alcohol **12** in



Scheme 4. (a) 3-Acetoxy-2-methyl benzoic acid, DCC, DMAP, CH_2Cl_2, rt, 3 h; (b) (i) Pd/C, H_2, MeOH, rt, 7 h; (ii) MeOH, rt, 72 h; (c) $BH_3 \cdot SMe_2$, $NaBH_4$, THF, rt, 2 h.



Scheme 5. (a) EtOAc, Pd/C, rt, 14 h. (b) (i) $NaBH_4$, MeOH, rt, 24 h or (ii) $LiAlH_4$, THF, rt, 21 h or (iii) DIBAL, toluene, rt, 6 h.

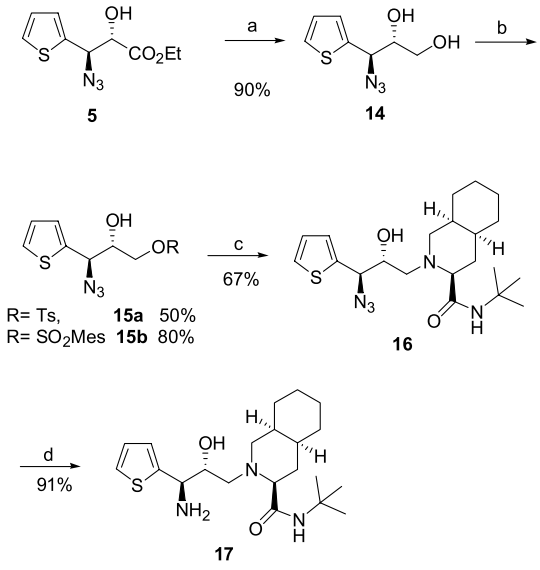
good yield. However, different reaction conditions ($NaBH_4$, $LiAlH_4$, DIBAL) for reduction of the carboxylic ester only afforded degradation products or starting amino alcohol **12**.

Best results were finally obtained by planning a reduction of the carboxylic function on the azido alcohol **5**. The use of $BH_3 \cdot SMe_2$, a known reagent for reduction of α-hydroxy esters,[23] afforded quite nicely the expected azido diol **14** in 90% yield with complete chemoselectivity (Scheme 6). This reaction is noteworthy since it has never been applied to such particularly functionalized compounds.

To complete the functional group differentiation on compound **14** it was necessary to regioselectively activate the primary hydroxyl group for the subsequent introduction of the PHIQ unit. Both activations with tosyl or mesitylenesulfonyl ($MesSO_2$, 2,4,6-trimethylbenzenesulfonyl) chloride were tested, but much better result (80% yield) were obtained with the more hindered mesitylene derivative **15b**.

The first amino side chain was easily introduced by treating the azido alcohols **15**[24] with commercially available PHIQ thus, obtaining the product **16** in good chemical yield (67%). The azido alcohol was quantitatively transformed into amino alcohol **17** by hydrogenation with 5% Pd/C at rt.

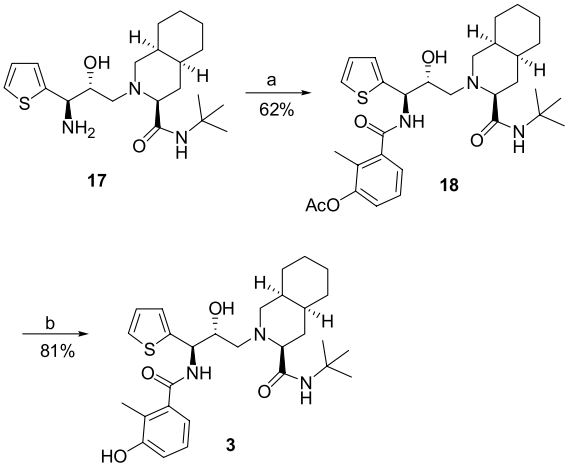
This compound **17** was purified either by column chromatography or by crystallization and represents an important intermediate for the preparation of possible new HIV protease inhibitors containing a thiophene ring. In fact,



Scheme 6. (a) $BH_3\,SMe_2$, $NaBH_4$, THF, MeOH, rt, 3 h; (b) (i) R = Ts, TsCl, Pyr, 50 °C, 4 h; (ii) R = SO_2Mes, $MesSO_2Cl$, Pyr, CH_2Cl_2, rt, 22 h; (c) K_2CO_3, PHIQ, *i*-PrOH, 50 °C, 21 h; (d) H_2, Pd/C, MeOH, rt, 3 h. Mes = 2,4,6-trimethylbenzene.

starting from compound **17**, nelfinavir and saquinavir analogues (see below) were finally prepared.

For the synthesis of thienyl nelfinavir **3**, two additional steps were required (Scheme 7). The peptide coupling of **17** with 3-acetoxy-2-methyl benzoic acid furnished compound **18**. Then final deacetylation of the phenolic group with Na/MeOH afforded the target compound **3** in 50% overall yield (two steps).



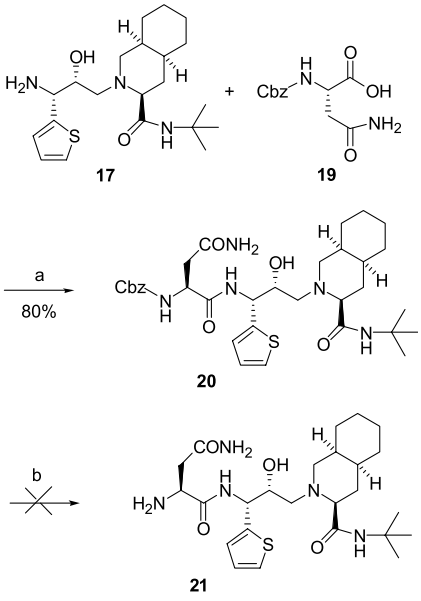
Scheme 7. (a) 3-Acetoxy-2-methyl benzoic acid, DCC, DMAP, CH_2Cl_2, rt, 2 h; (b) Na, MeOH, rt, 1 h.

5. Synthesis of saquinavir analogue 4

Key compound **17** has also been utilized for the synthesis of the thienyl saquinavir **4**, where a dipeptide unit containing asparagine N-bonded to quinaldic acid has to be introduced to the P_2–P_n end.

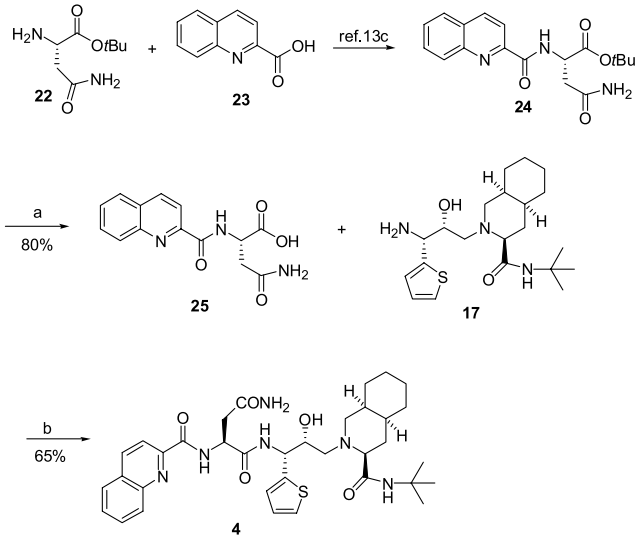
Two possible approaches could be followed for the synthesis of saquinavir analogue **4** according to the protocol used in the preparation of saquinavir **2**.[1,13] The first strategy provides initial coupling between the commercially available N-Cbz asparagine **19** and fragment **17**, N-Cbz through hydrogenation with Pd/C, and final coupling with quinaldic acid.

Using this procedure we obtained, as expected, compound **20** (Scheme 8), but all subsequent attempts to deprotect the amino group in **21** under various conditions failed.



Scheme 8. (a) DCC, DMAP, CH_2Cl_2, rt, 6 h; (b) H_2, Pd/C, EtOH, rt, 48 h.

Therefore, an alternative synthetic sequence was followed starting with the preparation of dipeptide **24**, obtained by coupling of asparagine *t*-butyl ester **22** and quinaldic acid **23**. Then dipeptide **24**[13c] was hydrolyzed to acid **25**,[25] and coupling with fragment **17** (Scheme 9) afforded the desired product **4** in 65% yield.



Scheme 9. (a) CH_2Cl_2, TFA, rt, 6 h; (b) DCC, DMF, DMAP, CH_2Cl_2, rt, 7 h.

6. Biological activity and molecular modelling studies

The activity of compounds **3** and **4** was evaluated on the inhibition of the catalytic activity of a recombinant wild-type HIV PR. IC_{50} values were obtained by measuring the initial velocities of hydrolysis of the fluorogenic substrate Abz-Thr-Ile-Nle-Phe(NO_2)-Gln-Arg, and are reported in Table 1, column 2, together with the IC_{50} values measured in the same experiment for the reference inhibitors nelfinavir **1** and saquinavir **2**.

Table 1

Compound	IC_{50} (μM)	$\Delta E_{compl,rel}$[a] (Kcal/mol)
1	0.0019	2.6
2	0.0004	0.0
3	30.0	64.9
4	5.0	87.6

[a] $\Delta E_{compl,rel}$=(EPL-E°L)–(EPsaq-E°saq), where EPL, E°L are the Amber energies for the optimized geometries of the protein–ligand complexes and for the ground state conformations of the free ligands, respectively. EPsaq and E°saq are the corresponding values for the reference ligand saquinavir.

Both candidates, **3** and **4**, show a clear inhibitory activity, with IC_{50} values in the micromolar range (30 and 5 μM, respectively, Table 1), but they are much less efficient than nelfinavir and saquinavir, which show, under our experimental conditions, IC_{50} values in the low nanomolar range.

A preliminary molecular modelling study was carried out by docking compound **3** onto the structure of the nelfinavir -HIV-PR complex, while the complex of **4** was modelled over the structure of the saquinavir-HIV-PR complex. After a first optimization, molecular dynamics runs were carried out for all the complexes and went to equilibration, indicating a good fit of the inhibitors into the active site. Final post-dynamics optimizations gave the relative complexation energies reported in Table 1, column 3, and the final geometries of the complexes. The energy differences are largely overestimated at this stage, mainly due to the lack of accounting for solvation of the free ligands, but the trend of such relative complexation energies, which are commonly used in the first ligand screening stages,[26] are qualitatively in agreement with the trend of the measured IC_{50}.

Both the geometries of the **3** and **4** complexes, when compared with nelfinavir and saquinavir, respectively, suggest the same explanation for the difference of activity. **3** and nelfinavir are almost perfectly superimposable as to the core hydroxyethylene unit and the residues at P2, P3, P2′ and P3′ (Fig. 3 a), and the same occurs for **4** and saquinavir (Fig 3 b).

However, in both the complexes the thiophene moiety at P1 enters the S1 protease subsite less deeply, due to the lack of the phenylalanine benzylic carbon.

7. Conclusions

In conclusion, a general strategy for the synthesis of thiophene containing HIV PR inhibitor analogues has been developed, with the preparation of key chiral compounds which can be utilized for the synthesis of different potential HIV PR inhibitors. The two target compounds **3** and **4** have been obtained in nine and eight steps starting from acrylate **6** with 10 and 13% in overall yields, respectively.

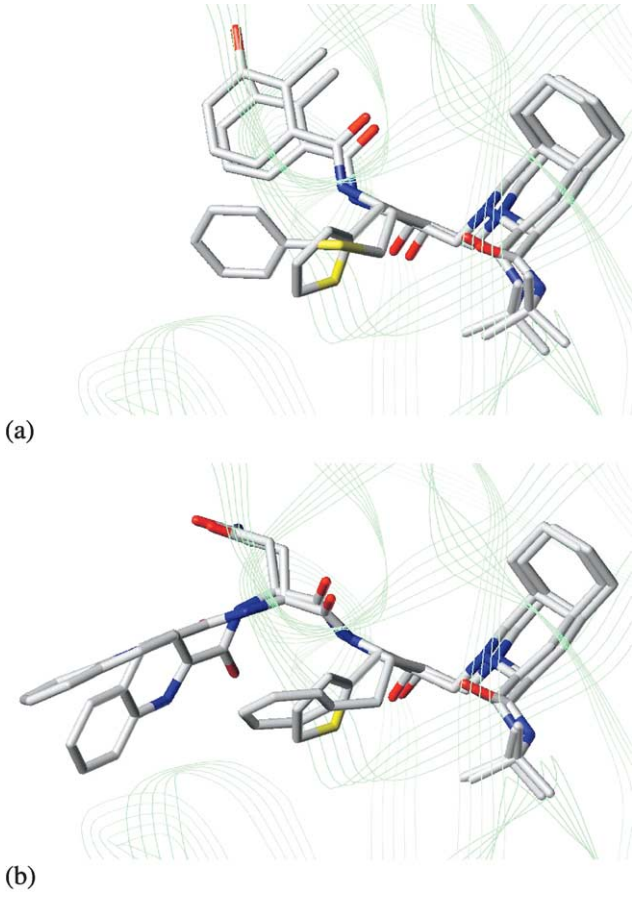


Figure 3. RMS overlay of the optimized complexes of HIV PR with nelfinavir and **3** (a), and saquinavir with and **4** (b).

The biological experimental and the theoretical data furnished information of the low activity of **3** and **4** with respect to the unmodified molecules **1** and **2**. Further studies are in progress for improving the activity of these drugs containing a thiophene unit.

8. Experimental

8.1. General

Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. THF, toluene, diethyl ether were distilled from sodium/benzophenone ketyl immediately before use. Dichloromethane was distilled from P_2O_5. DMF was freshly distilled and stored over 4 Å sieves. Moisture-sensitive reactions were conducted in oven- or flame-dried glassware under an argon atmosphere. All reactions were magnetically stirred and monitored by thin-layer chromatography using pre-coated silica gel (60 F_{254}) plates. Column chromatography was performed with the indicated solvents using silica gel-60 Å. Mass spectra were obtained by GC/MS with electron

impact ionization. NMR spectra were recorded in $CDCl_3$ solution at rt (^1H at 300 and 500 MHz and ^{13}C at 75 and 125 MHz, respectively). Chemical shifts (δ) were expressed in ppm and coupling constant (J) in Hz. Optical rotations were determined operating at the sodium D line at 25 °C. HPLC analyses were conducted using Chiralcel OJ-H column with UV detection at 235 nm.

8.1.1. (+)-(2*S*,3*S*)-3-(2-Thienyl)-2,3-dihydroxy ethyl propanoate (7). Prepared according to the standard procedure for the AD,[15] using 1.68 g of AD-mix β and adding 9.6 mg of $(DHQD)_2PHAL$ for 1 mmol of olefin **6**. The reaction residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH 98:2) to give the pure diol **7** (142 mg, 66%) as a yellow oil: R_f=0.2 ($CHCl_3$/MeOH 98:2); $[\alpha]_D^{20}$ −2.7 (*c* 4, MeOH); ee=99.87 (Chiralcel OJ-H, Hexane/*i*-PrOH 95:5, 0.5 mL/min, λ=235 nm, t_R=59.76, t_R=65.16); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, J=4.8 Hz, 1H), 7.11 (d, J=3.4 Hz, 1H), 7 (m, 1H), 5.27 (d, J=1.8 Hz, 1H), 4.44 (d, J=2.4 Hz, 1H), 4.31 (q, J=7 Hz, 2H), 1.32 (t, J=7 Hz, 3H), 2.85 (br s, 1H), 3.3 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 143.8, 126.8, 125.8, 125.4, 74.6, 71.1, 62.5, 14.3. EI-MS *m/z*: M^+, 216, (100), 113. Anal. Calcd for $C_9H_{12}O_4S$: C, 49.99; H, 5.59. Found: C, 50.01; H, 6.02.

8.1.2. 2-Oxo-5-thiophen-2-yl-2λ4-[1,3,2]dioxathiolane-4-carboxylic acid ethyl ester (8). To a cold (0 °C) stirred solution of diol **7** (21.4 mg, 0.1 mmol) in dry CH_2Cl_2 (0.28 mL) under nitrogen atmosphere, pyridine (22.7 mg, 0.27 mmol) and $SOCl_2$ (0.01 mL, 0.13 mmol) were added. After 15 h few millilitres of Hexane/EtOAc 2:1 were added, the mixture was filtered and the residue was washed with EtOAc. After solvent removal the brown crude product was used in the next step without purification for the preparation of compound **5**. ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–6.95 (m, 6H), 6.43 (d, J=7.6 Hz, 1H), 5.85 (d, J=7.6 Hz, 1H), 5.35 (d, J=7.6 Hz, 1H), 4.91 (d, J=7.6 Hz, 1H), 4.40–4.25 (m, 4H), 1.45–1.30 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 165.0, 138.0–125.0, 82.5, 80.9, 79.7, 82.6, 82.3, 14.1, 13.9. Anal. Calcd for $C_9H_{10}O_5S_2$: C, 41.21; H, 3.84. Found: C, 41.19; H, 3.86.

8.1.3. (+)-(2*S*,3*R*)-3-Azido-2-hydroxy-3-thiophen-2-yl-propionic acid ethyl ester (5). The crude sulfite **8** (26 mg, 0.1 mmol) in CH_3CN (1.5 mL)/DMF (1.5 mL) was treated with NaN_3 (0.32 g, 0.5 mmol) and stirred at 15 °C for 16 h. Then a solution of H_2SO_4 20% (0.3 mL) was added and the solid residue was extracted with EtOAc. The organic layer was washed with 10% H_2SO_4, water, saturated aqueous solution of $NaHCO_3$ and brine. After drying over Na_2SO_4 and solvent removal the crude product was purified by column chromatography (hexane/EtOAc 8:2) affording the pure azido alcohol **5** as a brown oil (17 mg, 70%): R_f=0.4 (hexane/EtOAc 8:2); $[\alpha]_D^{20}$ +36.0 (*c* 2, MeOH); ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J=5.5 Hz, 1H), 7.13 (d, J=3.5 Hz, 1H), 7.04 (m, 1H), 5.1 (d, J=3 Hz, 1H), 4.6 (d, J=3 Hz, 1H), 4.207 (q, J=8 Hz, 2H), 3.22 (s, 1H, OH), 1.21 (t, J=8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 135.1, 127.6, 127.0, 127.0, 73.6, 73.4, 62.4, 14.0. EI-MS *m/z*: M^+-N_2, 213, (100), 110. Anal. Calcd for $C_9H_{11}N_3O_3S$: C, 44.80; H, 4.60. Found: C, 44.82; H, 4.61.

8.1.4. 3-Acetoxy-2-methyl-benzoic acid 2-azido-1-ethoxycarbonyl-2-thiophen-2-yl-ethyl ester [(*rac*)-9]. To a mixture of azido alcohol (*rac*)-**5** (200 mg, 0.83 mmol), 3-acetoxy-2-methylbenzoic acid (308 mg, 1.66 mmol) and DMAP (32 mg, 0.29 mmol) in dry CH_2Cl_2 (4 mL) a solution of DCC (320 mg, 1.66 mmol) in dry CH_2Cl_2 (1.2 mL) was slowly added. The reaction, monitored by TLC, was quenched after 3 h by adding EtOH (2.4 mL) and the solid was filtered on Buckner funnel, washed with petroleum ether and the filtrated was treated with 10% HCl. The organic layer was washed with saturated aqueous solution of $NaHCO_3$, brine and after solvent removal the crude product was purified by column chromatography (petroleum ether/EtOAc 8:2) affording ester (*rac*)-**9** (333 mg, 96% yield) as a yellow oil: R_f=0.4 (petroleum ether/EtOAc 8:2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J=8.3 Hz, 1H), 7.34 (m, 1H), 7.31 (m, 1H), 7.24 (d, J=8.3 Hz, 1H), 7.20 (m, 1H), 7.00 (m, 1H), 5.66 (d, J=15 Hz, 1H), 5.42 (d, J=15 Hz, 1H), 4.17 (q, J=10 Hz, 2H), 2.42 (s, 3H), 2.33 (s, 3H), 1.18 (t, J=10 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 166.8, 165.9, 150.2, 135.6, 133.3, 130.6, 128.8, 128.6, 127.6, 127.0, 126.8, 126.7, 74.5, 62.3, 60.7, 20.9, 14.2, 13.6. Anal. Calcd for $C_{19}H_{19}N_3O_6S$: C, 54.67; H, 4.59. Found: C, 54.63; H, 4.61.

8.1.5. 3-(3-Acetoxy-2-methyl-benzoylamino)-2-hydroxy-3-thiophen-2-yl-propionic acid ethyl ester [(*rac*)-10]. To a solution of 10% Pd/C (67 mg) in methanol (5 mL) previously activated in hydrogen atmosphere for 30 min, a solution of substrate (*rac*)-**9** (94 mg, 0.224 mmol) in MeOH (15 mL) was added. The reaction was monitored by TLC (petroleum ether/EtOAc 7:3) until substrate disappearance (7 h). After hydrogen removal, the mixture was filtered and the solution was stirred for 72 h. The solvent was evaporated affording the pure amide (*rac*)-**10** (285 mg, 91%) as a yellow oil that was used without any purification: R_f=0.3 (petroleum ether/EtOAc 7:3); ^1H NMR (500 MHz, $CDCl_3$) δ 9.24 (br s, 1H), 8.19 (m, 1H), 7.24 (m, 4H), 6.86 (m, 1H), 6.20 (d, J=3.5 Hz, 1H), 5.30 (d, J=3.5 Hz, 1H), 4.22 (q, J=7 Hz, 2H), 2.36 (s, 6H), 1.13 (t, J=7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 172.0, 158.4, 136.2, 130.8, 129.0, 127.4, 125.7, 123.3, 122.5, 121.7, 112.9, 80.5, 61.5, 59.4, 57.9, 14.0, 13.6. Anal. Calcd for $C_{19}H_{21}NO_6S$: C, 58.30; H, 5.41. Found: C, 58.32; H, 5.45.

8.1.6. (−)-(2*S*,3*R*)-3-Amino-2-hydroxy-3-thiophen-2-yl-propionic acid ethyl ester (12). To a solution of ethanol (1.5 mL) of 10% Pd/C (15 mg), previously activated in hydrogen atmosphere for 30 min a solution of substrate **5** (55 mg, 0.23 mmol) in EtOH (3.5 mL) was added. The reaction was monitored by TLC (petroleum ether/EtOAc 8:2) until substrate disappearance (21 h). After hydrogen removal, the mixture was filtered and the solvent was evaporated in vacuo. The crude product was purified by column chromatography ($CHCl_3$/MeOH 9:1) affording the amino alcohol **12** (40 mg, 80%) as a yellow solid: R_f=0.69 ($CHCl_3$/MeOH 9:1); $[\alpha]_D^{20}$ −6.8 (*c* 1, MeOH); mp 50–53 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J=5.5 Hz, 1H), 6.95 (m, 2H), 4.60 (d, J=3 Hz, 1H), 4.48 (d, J=3 Hz, 1H), 4.15 (q, J=7 Hz, 2H), 1.2 (t, J=7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.4, 144.1, 126.7, 125.0, 124.9, 74.7, 62.0, 54.7, 14.3. EI-MS *m/z*: M^+-H^+, 214, 112,

(100), 113. Anal. Calcd for $C_9H_{13}N_3O_3S$: C, 50.21; H, 6.09. Found: C, 50.24; H, 6.10.

8.1.7. (+)-(2*R*,3*R*)-3-Azido-3-thiophen-2-yl-propane-1,2-diol (14). To a cold (0 °C) stirred solution of azido alcohol **5** (400 mg, 1.6 mmol) in dry THF (8 mL), a solution of $BH_3 \cdot SMe_2$ (399 mg, 3.2 mmol) in dry THF (0.32 mL) was slowly added under argon atmosphere and then the temperature was allowed to warm to rt. After 45 min, $NaBH_4$ (3.2 mg, 0.08 mmol) was added and the mixture was stirred for 3 h. The reaction was slowly quenched adding MeOH (1 mL) at 0 °C and stirred for 45 min. After solvent removal the crude material was purified by column chromatography ($CHCl_3$/MeOH 95:5) affording the azido diol **14** (297 mg, 90%) as a deep oil: R_f=0.3 ($CHCl_3$/MeOH 95:5); $[\alpha]_D^{20}$ +4.9 (*c* 1.5, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.4 (d, J=5 Hz, 1H), 7.14 (d, J=3.5 Hz, 1H), 7.08–7.06 (m, 1H), 4.91 (d, J=6.5 Hz, 1H), 3.91 (dd, J=6.5, 3.5 Hz, 1H), 3.77–3.69 (m, 2H); 2.40 (s, 1H, OH); 2.06 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 127.8, 127.7, 127.1, 74.3, 63.1, 62.87. EI-MS *m*/*z*: $M^+ - H^+$, 199, 110, (100). Anal. Calcd for $C_7H_9N_3O_2S$: C, 42.20; H, 4.55. Found: C, 42.19; H, 4.57.

8.1.8. (+)-(2*R*,3*R*)-Toluene-4-sulfonic acid 3-azido-2-hydroxy-3-thiophen-2-yl-propyl ester (15a). To a solution of azido diol **14** (150 mg, 0.75 mmol) and pyridine (1.5 mL) TsCl (173 mg, 0.91 mmol) in portions was added at 0 °C under argon atmosphere, and the solution was stirred at 50 °C for 4 h. After pyridine elimination in vacuo, the crude mixture was dissolved in EtOAc and washed with cold 2 M HCl, water, saturated aqueous solution of $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, concentrated and the mixture was purified by column chromatography (petroleum ether/EtOAc 8:2) affording product **15a** as a colourless oil (132 mg, 50%): R_f=0.3 (petroleum ether/EtOAc 8:2); $[\alpha]_D^{20}$ +93.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81–7.01 (m, 7H), 4.87 (d, J=6.5 Hz, 1H), 4.11–4.08 (m, 2H), 4.08–4.06 (m, 1H), 2.46 (s, 3H), 2.6 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.6, 137.2, 132.5, 130.3, 130.2, 128.4, 128.2, 127.4, 127.2, 72.2, 70.1, 62.4, 62.2, 22.0. Anal. Calcd for $C_{14}H_{15}N_3O_4S_2$: C, 47.58; H, 4.28. Found: C, 47.60; H, 4.26.

8.1.9. (+)-(2*R*,3*R*)-2,4,6-Trimethyl-benzenesulfonic acid 3-azido-2-hydroxy-3-thiophen-2-yl-propyl ester (15b). To a cold (0 °C) stirred solution of azido diol **14** (280 mg, 1.43 mmol) in CH_2Cl_2 (3.7 mL), pyridine (236 mg, 2.86 mmol) and mesitylenesulfonyl chloride (344 mg, 1.57 mmol) were added. The reaction mixture was stirred at 0 °C for 4 h and then was warmed at 20 °C for 20 h. The solvent was eliminated in vacuo, the crude mixture was dissolved in EtOAc and washed with cold 2 M HCl (5 mL), water, saturated aqueous solution of $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, concentrated and the crude product was purified by column chromatography (petroleum ether/EtOAc 8:2) affording the pure compound **15b** (430 mg, 80%) as a deep yellow oil: R_f=0.5 (petroleum ether/EtOAc 8:2); $[\alpha]_D^{20}$ +81.3 (*c* 0.5, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J=4.5 Hz, 1H), 7.10 (d, J=3.5 Hz, 1H), 7.04–7.03 (m, 1H), 6.99 (s, 2H), 4.89 (d, J=6.5 Hz, 1H), 4.06–4.04 (m, 3H), 2.75 (br s, 1H), 2.63 (s, 6H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 137.2, 132.1, 130.3, 130.9, 128.2, 128.1, 127.4, 127.2, 72.2, 69.2, 62.6, 62.3, 23.1, 22.8, 21.2. Anal. Calcd for $C_{16}H_{19}N_3O_4S_2$: C, 50.38; H, 5.02. Found: C, 50.41; H, 5.05.

8.1.10. (−)-(3*S*,4*aS*,8*aS*,2′*R*,3′*R*)-[(3′-Azido-2′-hydroxy-3′-(thiophen-2-yl)-propyl]-decahydro-isoquinoline-3-carboxylic acid *tert*-butylamide (16). The same procedure was followed for **15a** and **15b**. To a solution of **15a** (200 mg, 0.57 mmol) or **15b** (217 mg, 0.57 mmol) in *i*-PrOH (10.8 mL) PHIQ (231 mg, 0.97 mmol) and K_2CO_3 (157 mg, 1.14 mmol) were added. The mixture was stirred at 50 °C for 21 h, then *i*-PrOH was evaporated in vacuo and the residue dissolved in EtOAc (20 mL). The organic layer was washed with saturated solution of NH_4Cl and brine then was dried over Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by chromatography (petroleum ether/EtOAc 7:3) to give amine **16** as a pale yellow oil (160 mg, 67%): R_f=0.37 (petroleum ether/EtOAc 7:3); $[\alpha]_D^{20}$ −10.2 (*c* 0.5, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–6.98 (m, 3H), 6.07–6.04 (br s, 1H), 4.76–4.74 (m, 1H), 3.97–3.93 (m, 1H), 3.42–3.61 (br s, 1H), 2.99–2.95 (m, 1H), 2.72–2.70 (m, 2H), 2.40–2.31 (m, 2H), 1.93–1.27 (m, 12H), 1.35 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 135.0, 127.4, 126.7, 126.6, 72.9, 70.0, 64.4, 60.1, 58.1, 50.9, 35.8, 33.2, 30.8, 30.5, 29.7, 26.0, 25.9, 20.8. EI-MS *m*/*z*: $M^+ - Th–CHN_3^+$, 280, 182, (100). Anal. Calcd for $C_{21}H_{33}N_5O_2S$: C, 60.11; H, 7.93. Found: C, 60.13; H, 7.95.

8.1.11. (−)-(3*S*,4*aS*,8*aS*,2′*R*,3′*R*)-[(3′-Amino-2′-hydroxy-3′-(thiophen-2-yl)-propyl]-decahydro-isoquinoline-3-carboxylic acid *tert*-butylamide (17). Prepared as described for **12**, starting from **16** using methanol instead of ethanol. After column chromatography ($CHCl_3$/MeOH 9:1) compound **17** (91%) was obtained as a deep brown oil: R_f=0.3 ($CHCl_3$/MeOH 9:1); $[\alpha]_D^{20}$ −76.9 (*c* 0.55, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.24 (m, 1H), 6.98–6.97 (m, 2H), 6.34–6.32 (br s, 1H, NH), 4.32–4.29 (m, 1H), 3.93–3.89 (m, 1H), 3.07–3.00 (m, 1H), 2.70–2.20 (m, 4H), 2.10–0.90 (m, 15H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 145.4, 126.5, 124.8, 124.8, 73.1, 69.8, 59.4, 59.1, 56.1, 50.7, 35.6, 33.2, 30.5, 30.5, 29.7, 25.9, 25.9, 20.8. Anal. Calcd for $C_{21}H_{35}N_3O_2S$: C, 64.08; H, 8.96. Found: C, 64.10; H, 8.94.

8.1.12. (−)-(3*S*,4*aS*,8*aS*,1′*R*,2′*R*)-[Acetic acid 3-[3′-(3-*tert*-butylcarbamoyl-decahydro-isoquinolin-2-yl)-2′-hydroxy-1′-thiophen-2-yl-propylcarbamoyl]-2-methyl-phenyl ester (18). Prepared as described for (*rac*)-**9**, using alcohol **17**, 1.01 equiv of acid, 1.3 equiv of DCC. The crude product was purified by column chromatography (petroleum ether/EtOAc 7:3) affording amide **18** (62% yield) as a viscous white oil: R_f=0.4; $[\alpha]_D^{20}$ −27.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.33 (m, 1H), 7.26–7.20 (m, 2H), 7.16–7.13 (m, 1H, NH), 7.12–7.11 (m, 1H), 7.08–7.06 (m, 1H), 6.99–6.97 (m, 1H), 6.00 (br s, 1H, NH), 5.49–5.46 (m, 1H), 4.22–4.19 (m, 1H), 2.75–2.60 (m, 3H), 2.30 (s, 3H), 2.2 (s, 3H), 1.9–1.00 (m, 15H), 1.33 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 168.9, 168.3, 149.6, 140.7, 139.2, 128.6, 126.7, 126.5, 126.4, 125.2, 124.6, 123.5, 71.1, 69.7, 59.3, 59.1, 53.0, 49.9, 35.5, 33.2, 30.6, 30.3, 28.5, 25.7, 25.5, 24.8, 20.8, 12.8. Anal. Calcd for $C_{31}H_{43}N_3O_5S$: C, 65.35; H, 7.61. Found: C, 65.37; H, 7.59.

8.1.13. (−)-(3*S*,4*aS*,8*aS*,2′*R*,3′*R*)-2-[2′-Hydroxy-3′-(3-hydroxy-2-methyl-benzoylamino)-3′-(thiophen-2-yl)-propyl]-decahydro-isoquinoline-3-carboxylic acid *tert*-butylamide (3). To a solution of amino alcohol **18** (30 mg, 0.053 mmol) in MeOH (1 mL) a catalytic amount of sodium was added and after 45 min the reaction was stopped by solvent removal. The crude mixture dissolved in EtOAc (10 mL) was washed with water and the aqueous layers extracted twice with EtOAc (10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuo. The mixture was purified by column chromatography (EtOAc/petroleum ether 7:3) affording amide **3** (22 mg 81%): R_f=0.46; $[\alpha]_D^{20}$ −27.0 (*c* 0.6, EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.24 (m, 1H), 7.13–7.12 (m, 1H), 7.05–7.02 (m, 1H, NH), 6.99–6.98 (m, 2H), 6.90–6.85 (m, 2H), 6.05 (br s, 1H, NH), 5.47–5.43 (m, 1H), 4.22–4.19 (m, 1H), 2.68–1.20 (m, 19H), 2.14 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0, 169.8, 155.1, 140.2, 137.9, 127.3, 126.8, 125.8, 122.6, 119.0, 116.9, 71.2, 70.1, 60.0, 59.4, 53.1, 51.5, 35.9, 33.4, 30.9, 30.7, 29.9, 28.8, 26.2, 25.9, 21.3, 21.1, 12.6. Anal. Calcd for $C_{29}H_{41}N_3O_4S$: C, 66.00; H, 7.83. Found: C, 66.03; H, 7.82.

8.1.14. (−)-(3*S*,4*aS*,8*aS*,2′*R*,3′*R*)-{1-[3-(3-*tert*-Butyl-carbamoyl-decahydro-isoquinolin-2-yl)-2-hydroxy-1-thiophen-2-yl-propylcarbamoyl]-2-carbamoyl-ethyl}-carbamic acid benzyl ester (20). Prepared as described for **18** starting from **19** affording after purification by column chromatography ($CHCl_3$/MeOH 98:2) compound **20** (68 mg, 80%) as a yellow oil: R_f=0.2 ($CHCl_3$/MeOH 98:2); $[\alpha]_D^{20}$ −41.0 (*c* 1.5, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (m, 1H), 7.36 (br s, 5H), 7.19 (m, 1H), 7.00 (m, 1H), 6.91 (m, 1H), 6.27 (m, 2H), 6.09 (s, 1H), 5.65 (s, 1H), 5.23 (m, 1H), 5.08 (s, 2H), 4.61 (m, 1H), 4.16 (m, 1H), 2.81 (m, 2H), 2.55 (m, 3H), 2.33 (m, 2H), 1.55 (m, 12H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 173.5, 170.0, 156.4, 139.6, 136.3, 128.7, 128.6, 128.2, 128.1, 127.5, 126.8, 126.6, 125.8, 71.3, 69.6, 67.2, 58.9, 53.4, 51.8, 49.2, 38.2, 35.5, 34.0, 33.2, 30.6, 30.5, 28.7, 26.4, 25.9, 25.6, 25.0, 21.4. Anal. Calcd for $C_{33}H_{47}N_5O_3S$: C, 61.75; H, 7.38; Found C, 61.78; H, 7.40.

8.1.15. (2*S*)-2-[(Quinoline-2-carbonyl)-amino]-succinamic acid (25). To a stirred cold (0 °C) solution of **24** (100 mg, 0.29 mmol) in CH_2Cl_2 (1 mL) TFA (0.4 mL) dropwise was added. The solution was warmed to 25 °C and after 6 h the solvent was evaporated in vacuo. The product **25** was obtained after crystallization by MeOH/EtOAc (66 mg, 80%). The compound shows the same spectroscopic data as reported in the literature.[24]

8.1.16. (+)-*N*1-(3*S*,4*aS*,8*aS*,1′*R*,2′*R*)-[3-(3-*tert*-Butyl-carbamoyl-decahydro-isoquinolin-2-yl)-2-hydroxy-1-thiophen-2-yl-propyl]-(2*S*)-2-[(quinoline-2-carbonyl)-amino]-succinamide (4). To a stirred solution of **17** (40 mg, 0.1 mmol) and DMAP (4.4 mg, 0.035 mmol) in CH_2Cl_2 (1.5 mL), a solution of **25** (34 mg, 0.12 mmol) in DMF (0.1 mL) and a solution of DCC (27 mg, 0.13 mmol) in CH_2Cl_2 (0.2 mL) were added. The solution was stirred at rt for 7 h, diluted with CH_2Cl_2 and washed with 10% HCl, water, saturated aquoeus solution of $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, concentrated and the crude mixture was purified by column chromatography on silica gel ($CHCl_3$/MeOH 95:5) affording compound **4** (43 mg, 65%) as a paled yellow oil: R_f=0.35 ($CHCl_3$/MeOH 95:5); $[\alpha]_D^{20}$ +21.4 (*c* 0.65, $CHCl_3$); ^{1}H NMR (500 MHz, CD_3OD) δ 9.26 (d, *J*=7 Hz, 1H), 8.26 (d, *J*=8 Hz, 1H), 8.19 (d, *J*=8.5 Hz, 1H), 8.15 (d, *J*=9 Hz, 1H), 7.85 (d, *J*=8 Hz, 1H), 7.79–7.74 (m, 2H), 7.64–7.61 (m, 1H), 7.16 (d, *J*=5 Hz, 1H), 7.08 (d, *J*=3 Hz, 1H), 6.90 (t, *J*=4 Hz, 1H), 6.41 (s, 1H), 6.19 (s, 1H), 5.82 (s, 1H), 5.31–5.30 (m, 1H), 5.06–5.04 (m, 1H), 4.26–4.24 (m, 1H), 3.04–2.90 (m, 3H), 2.68–2.59 (m, 2H), 2.32–2.22 (m, 2H), 1.85–1.66 (m, 6H), 1.62–1.58 (m, 1H), 1.48–1.37 (m, 6H), 1.33 (s, 9H); ^{13}C NMR (125 MHz, CD_3OD) δ 174.0, 173.2, 169.9, 165.0, 149.1, 146.8, 139.6, 137.7, 130.3, 130.3, 129.6, 128.4, 127.8, 127.1, 126.8, 125.9, 118.9, 71.4, 69.6, 59.9, 53.9, 53.8, 50.9, 50.7, 50.6, 38.5, 35.6, 33.4, 30.8, 30.7, 30.0, 28.9, 28.9, 26.2, 21.2. Anal. Calcd for $C_{35}H_{46}N_6O_5S$: C, 63.42; H, 6.99. Found: C, 63.40; H, 6.95.

8.1.17. Enzyme assays. Recombinant HIV-1 protease was purchased from Bioczech (Prague, Czech Republic); the fluorogenic substrate Abz-Thr-Ile-Nle-Phe(NO_2)-Gln-Arg was purchased from Bachem (Bubendorf, Switzerland). The extent of inhibition of the activity of the aspartic protease was evaluated as previously reported for other series of mono- and dihydroxy pseudopeptide HIV-1-PR inhibitors.[27] The assays were performed at 25 °C in 400 mM NaCl, 1 mM EDTA, 1 mM DTT, 100 mM MES-NaOH buffer at pH 5.5, and 30 mM fluorogenic substrate. Titration of HIV PR was carried out with two reference inhibitors structurally related to our series, namely nelfinavir and saquinavir, using the equation $IC_{50}=[E]/2+K_i(1+[S]/K_m)^2$, where K_i are the literature values of the inhibition constants for nelfinavir and saquinavir,[28] and K_m was 25 μM, as determined under our conditions. The active enzyme concentration in the assay, [E], was estimated to be 3.6±2.3 nM.

8.1.18. Molecular modelling. Calculations were carried out on two Silicon Graphics Octane 1 R12000 workstations and on a Pentium4 2.53GHz/Red Hat Linux machine. The Cornell version of the Amber force field[29] as implemented in Sybyl6.8 (Tripos Inc.) was used in all energy minimizations and dynamics runs. New Amber parameters for the heterocyclic systems of the ligands were developed according to Geremia and Calligaris[30] or following the original Amber protocol. The required ab initio calculations on the ligands were carried out with Gaussian03.[31] All the energy minimizations were carried out until a convergence criterion of 0.001 Kcal/mol/Å was achieved for all the energy gradients. The conjugate gradient minimisation algorithm was always used after running 20 initial steps of Simplex linear minimization. All the calculations were carried out in a continuum dielectric of relative permittivity ε=4rij.[32]

The structures of the ligands were built with standard bond lengths and angles, and optimized first at the RHF-6.31G* level, in order to obtain a charge distribution comparable to that used in the AMBER parameterization. The ligands were then submitted to an extensive conformational search driven by a genetic algorithm operating on all the routable bonds.[33] The AMBER energies of the absolute conformational

minima thus, obtained were taken as reference energies of the free ligands.

The crystallographic coordinates of two reference complexes of HIV PR with saquinavir and nelfinavir were obtained from the Protein Data Bank, Brookhaven National Laboratory (Saquinavir: Pdb id 1C6Z;[34] nelfinavir: Pdb id 1OHR).[35] All the hydrogen atoms were added, assuming an environment pH of 5.5, and a single proton to be shared between the two catalytic aspartic residues.[36] All the crystallization water molecules were removed, with the exception of the essential water always present inside the HIV PR binding site complexed with non ureidic inhibitors, and hydrogen bonded to Ile50 and 50′ residues. The reference complexes were then allowed to relax by the multistage minimization procedure described by Levit and Lifson.[37]

The initial geometries of the ligand-HIV PR complexes were built by docking the ligand structures onto the structures of nelfinavir (for compound **3**) and saquinavir (for compound **4**) bound to HIV PR as in the optimized reference complexes. The structure were first optimized by running an energy minimisation to a 0.05 Kcal/mol/Å energy gradient. The models were then subjected to a molecular dynamics run in the NTV ensemble; the systems were gradually heated to 300 K, in three steps, allowing a 25 psec interval per each 100 K, then equilibrated for 25 psec at 300 K, and finally, submitted to a 400 psec collection run at 300 K. The lowest potential energy equilibrium geometries were finally re optimized.

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Halogen–lithium exchange between substituted dihalobenzenes and butyllithium: application to the regioselective synthesis of functionalized bromobenzaldehydes

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Abstract—Halogen–lithium interconversion reactions between unsymmetrically substituted mono- and bifunctional dihalobenzenes $C_6H_3XHal_2$ and $C_6H_2XYHal_2$ (Hal = Br, I; X, Y = F, OR, CF_3, $CH(OMe)_2$) and butyllithium were investigated. The resultant organolithium intermediates were converted into the corresponding benzaldehydes in moderate to good yields. As a rule, bromine atoms in the position *ortho* to the functional group were replaced preferentially with lithium. Intramolecular competition experiments with bifunctional systems revealed that fluorine is capable of activating the neighboring bromine atom more strongly than methoxy and dimethoxymethyl groups. On the replacement of the non-activated bromine with iodine a complete reversal of this reactivity pattern can be accomplished due to the preferred iodine–lithium exchange.

1. Introduction

Halogen–lithium exchange (HLE) is one of the fundamental, and perhaps, most versatile methods used to generate organolithium compounds. Its important advantage is that it is extremely rapid even at very low temperatures providing a direct access to many unstable organolithium intermediates. Furthermore, this method offers a convenient route to compounds that are not readily prepared by directed metalation reactions.[1] Nevertheless, there are drawbacks to HLE including the availability of halogen-containing starting materials. The HLE reaction between polyhalobenzenes and BuLi has been investigated with special emphasis on regiospecifity in halolithiobenzene formation. It was found initially that the methoxy group increases the reactivity of neighboring bromine atoms in the HLE reaction.[2] This observation facilitated valuable synthetic applications.[3] More recently, similar effects with nitrogen functionalities such as amino and nitro groups have been described.[4] This study probes directing effects on HLE with other dibromo- and bromoiodobenzene derivatives containing functionalities based on oxygen and/or fluorine. Moreover, it is demonstrated that isomeric halogenated aryllithium intermediates may be selectively generated by the treatment of appropriate polyhalobenzenes with the most common alkyllithium reagent, i.e. BuLi, which cannot be overestimated from the viewpoint of any synthetic organic process.

2. Results and discussion

The regioselective *ortho*-directed bromine–lithium exchange between 2,4-dibromoanisole as well as 2,4,6-tribromoanisole and BuLi has been known since 1940.[1,5] Accordingly, this reaction is suitable for the synthesis of the corresponding benzaldehydes as shown in Table 1 (entries 1 and 2). Similarly, *ortho*-directed bromine–magnesium exchange for these and related systems has been developed.[6] It was interesting to determine how and to what extent the regioselectivity of the HLE is tuned by the steric effect of a bulky alkoxy group since it has been reported that the protection of chlorophenols with TBDMS groups prevents oxygen *ortho*-directed metalation.[7] For this purpose, TBDMS ethers of 2,5-dibromophenol and 2,4-dibromophenol were subjected to the HLE reactions (entries 3 and 4). We found that the steric hindrance provided by the TBDMS group was not reflected by any change of selectivity as the bromine atom in the position *ortho* to the oxygen atom was exclusively replaced with lithium. On the other hand, the conversion into corresponding benzaldehydes was not quantitative as substantial amounts

Keywords: Dihalobenzenes; Halogen–lithium exchange; Arylithium compounds; Benzaldehydes.
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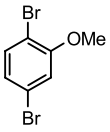
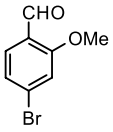
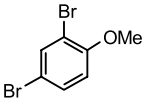
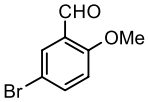
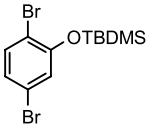
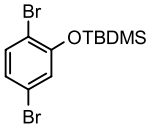
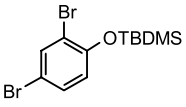
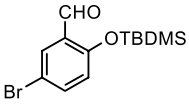
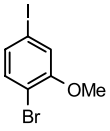
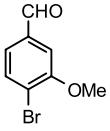
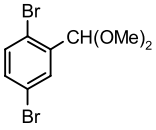
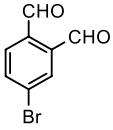
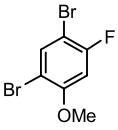
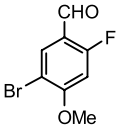
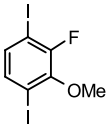
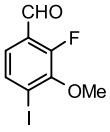
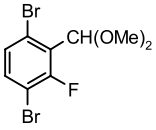
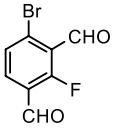
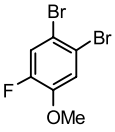
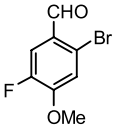
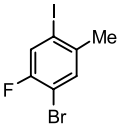
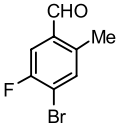
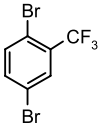
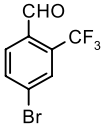
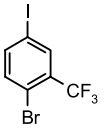
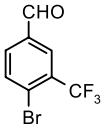
Table 1. Preparation of functionalized bromobenzaldehydes via halogen–lithium exchange and subsequent DMF quench

Entry	Aryl halide	Solvent, temperature	Product	Yield (%)
1		Et_2O, −78 °C		84
2		Et_2O, −78 °C		90
3		Et_2O, −78 °C		32
4		Et_2O, −78 °C		36
5		Et_2O, −78 °C		69
6		Et_2O, −78 °C		52
7		THF/Et_2O (1:1), −78 °C		82
8		THF/Et_2O (1:1), −78 °C		72
9		THF/Et_2O (1:1), −78 °C		48
10		THF/Et_2O (4:1), −100 °C		13[a]
11		Et_2O, −100 °C		46
12		Et_2O, −78 °C		70
13		Et_2O, −78 °C		73

[a] The major product isolated from the mixture with the regioisomeric by-product 2-bromo-4-fluoro-3-methoxybenzaldehyde and 2,3-dibromo-5-fluoro-6-methoxybenzaldehyde.

of unreacted TBDMS ethers were recovered (ca. 30% of and 40% for entries 3 and 4, respectively) which indicates that the lithiation proceeds quite sluggishly in Et_2O at about −70 °C. Interestingly, 3-bromobenzaldehyde is derived from 1,3-dibromobenzene by the HLE rapidly under these conditions. We also investigated the competitive metalations with 2-bromo-5-iodoanisole and in this case a selective replacement of iodine was observed. Thus, bromine kinetically activated by adjacent methoxy group is less reactive than iodine. Furthermore, the HLE product, i.e. 4-bromo-3-methoxyphenyllithium does not undergo rearrangement to the thermodynamically more stable 2-methoxyphenyllithium system at low temperature in ether solution. Hence, it can be converted cleanly into the corresponding 4-bromo-3-methoxybenzaldehyde[8] (entry 5) which is not available by the direct bromination of 3-methoxybenzaldehyde. It should be noted that a more recent attempt to prepare this compound was reported[9] but comparison of the NMR spectroscopic data suggests clearly that the spectra were interpreted erroneously.[10]

The reaction of 2,5-dibromo-1-(dimethoxymethyl)benzene with BuLi followed by DMF quench and aqueous workup with deprotection of the dimethoxymethyl group afforded 4-bromophtalaldehyde[11] (entry 6). The *ortho*-directing ability of the methoxy group can be explained in terms of the inductive effect but for the dimethoxymethyl group this is not so obvious as its electronegative character is weak. Hence, it can be assumed that in the case of 2,5-dibromo-1-(dimethoxymethyl)benzene the initial precoordination of lithium by the acetal oxygen atoms may be important. To support this view, it should be noted, that the lithiation of 3-(dimethoxymethyl)thiophene proceeds selectively in the 2-position[12,13] which suggests a significant *ortho*-directing ability by the dimethoxymethyl group.

It is well-documented that fluorine possesses a strong *ortho*-directing ability in the metalation reaction[14] and this property should also be reflected in the HLE between *ortho*-bromofluoro- or *ortho*-iodofluorobenzenes and BuLi. Indeed, the high-yield preparation of 2-fluoro-4-bromobenzaldehyde starting with 1,4-dibromo-2-fluorobenzene and $Li[MgBu_3]$ ate complex as the metalating agent was reported recently.[15] We were interested to compare the relative directing potential of fluorine with respect to oxygen-based functionalities such as methoxy and dimethoxymethyl groups. The results are shown in Table 1 (entries 7–9). THF was used as a solvent as it is more suitable for the stabilization of *ortho*-halogenated aryllithium species.[16] Based on these internal directing group competition experiments, it is clear that fluorine is a more powerful *ortho*-directing group than methoxy (entries 7 and 8),[17] or dimethoxymethyl group (entry 9). It should be noted that BuLi/THF slowly deprotonates *ortho* to the methoxy group, whereas the selective metalation (deprotonation) of 2- and 4-fluoroanisole in the position *ortho* to fluorine requires superbasic mixture of BuLi with PMDTA or $KOBu^t$.[18] The competition of long-range inductive interactions of fluorine and methoxy groups was probed by the reaction of 4,5-dibromo-2-fluoroanisole with BuLi. The reaction was not as selective as found in previous examples and a mixture of products was formed. However, the distinct influence of fluorine was observed again as 2-bromo-5-fluoro-4-methoxybenzaldehyde (entry 10) was formed as a major product (according to GC/MS analysis, ca. 70% in the crude reaction mixture containing ca. 20% of 2-bromo-4-fluoro-5-methoxybenzaldehyde and 10% of 2,3-dibromo-6-fluoro-5-methoxybenzaldehyde) resulting from the preferred exchange of the bromine atom in the position meta to fluorine.

In addition to these efforts, we studied the competition between iodine and *ortho*-activated bromine in 5-bromo-4-fluoro-2-iodotoluene. It was plausible that the strong activating effect of fluorine (which should be stronger than that of the methoxy group in 2-bromo-5-iodoanisole) together with some deactivating effect of methyl group[19] may significantly change the reaction course. However, iodine-lithium exchange was preferred again, and the corresponding lithiated compound was relatively stable as demonstrated by the isolation of 4-bromo-5-fluoro-2-methylbenzaldehyde (entry 11) in moderate yield.

The trifluoromethyl group is known as a strong electron-withdrawing substituent,[20] and has also been found as effective *ortho*-director for HLE. 1,4-Dibromo-2-(trifluoromethyl)benzene was converted into 4-bromo-2-trifluoromethylbenzaldehyde (entry 12). On the other hand, 1-bromo-4-iodo-2-(trifluoromethyl)benzene produces 4-bromo-3-(trifluoromethyl)phenyllithium by the treatment with BuLi via the selective iodine–lithium exchange and the corresponding benzaldehyde[21] in subsequent steps (entry 13). This last example confirms the general reactivity pattern observed for bromoiodobenzenes with activating substituent adjacent to bromine. The thermal stability of 4-bromo-3-(trifluoromethyl)phenyllithium in Et_2O was investigated. A solution of this compound was warmed up to 0 °C prior to DMF quench and aqueous workup. GC/MS analysis of the isolated material revealed that 4-bromo-2-trifluoromethylbenzaldehyde (27%) and 4-iodo-2-trifluoromethylbenzaldehyde (45%) together with some amount of the starting material (18%) and 1,4-diiodo-2-trifluoromethylbenzene (8%) were formed. Hence, the isomerization of the primary aryllithium species leading to the formation of more stable 2-CF_3 substituted phenyllithium derivatives was accompanied by extensive halogen redistribution processes.

In conclusion, the halogen–lithium exchange of substituted dibromobenzenes and BuLi is strongly controlled by the electronegative substituent adjacent to bromine. Fluorine competes effectively with methoxy and dimethoxymethyl groups to provide high regioselectivity. On the other hand, the replacement of the non-activated bromine with iodine gives access to thermodynamically less stable but still relatively inert organolithium species that under appropriate conditions do not rearrange spontaneously to their more stable isomers via halogren migration ('halogen dance') processes.[22] Hence, the synthesis of multiple isomeric halogenated benzaldehydes can be readily accomplished by means of this modification. Obviously, the synthetic potential of all described HLE experiments is not limited to benzaldehydes and promises broad applicability.

3. Experimental

3.1. General

All reactions were carried out under an argon atmosphere. Solvents were stored over sodium wire before use. Butyllithium (10 M solution in hexanes) and anhydrous *N*,*N*-dimethylformamide (Aldrich) were used as received. 2,4-Dibromoanisole, 2,5-dibromoanisole and 1,4-dibromo-2-(trifluoromethyl)benzene were received from Aldrich, whereas 1-bromo-4-iodo-2-(trifluoromethyl)benzene was prepared according to the published procedure from 3-bromo-4-(trifluoromethyl)aniline (Aldrich).[23] Remaining functionalized dihalobenzenes are novel compounds. 2-(*tert*-Butyldimethylsilyloxy)-1,4-dibromobenzene and 1-(*tert*-butyldimethylsilyloxy)-2,4-dibromobenzene were obtained by treatment of corresponding sodium dibromophenolates with *tert*-butyldimethylsilyl chloride. 2,4-Dibromo-5-fluoroanisole and 4,5-dibromo-2-fluoroanisole were prepared by multistep procedures involving regioselective bromination of appropriate bromofluorophenols as a key step.[24] The synthesis of 3,6-diiodo-2-fluoroanisole and 1,4-dibromo-2-(dimethoxymethyl)-3-fluorobenzene involved regioselective metalation of 2-fluoro-6-iodoanisole[25] and 1,4-dibromo-2-fluorobenzene,[26] respectively. Detailed procedures for these novel dihalobenzenes are provided in the Supplementary Material.

3.1.1. 4-Bromo-2-methoxybenzaldehyde (entry 1). The method described here is representative for the preparation of other benzaldehydes (modifications may concern the choice of solvent and temperature as shown in Table 1): A solution of 2,5-dibromoanisole (5.32 g, 20 mmol) in Et_2O (10 mL) was added to the solution of BuLi (10 M solution in hexanes, 2.0 mL, 20 mmol) in Et_2O (20 mL) at −78 °C. After 15 min DMF (1.61 g, 22 mmol) was added slowly. The mixture was stirred for 15 min and hydrolyzed with aq. H_2SO_4 (1 M, 20 mL). The organic layer was separated and solvents were removed in vacuo. The residue was washed with water (20 mL) and recrystallized from hexane (10 mL) to give the title compound (3.6 g, 84%) as colorless crystals, mp 68–70 °C (Ref. 27 mp 66–68 °C); (Found: C, 44.60; H, 3.47. $C_8H_7BrO_2$ requires C, 44.68; H, 3.28%); δ_H (400 MHz, $CDCl_3$) 10.39 (1H, d, J=1.0 Hz, CHO), 7.68 (1H, d, J=8.0 Hz, Ph), 7.17 (1H, ddd, J=8.0, 1.5, 1.0 Hz, Ph), 7.15 (1H, d, J=1.5 Hz, Ph), 3.93 (3H, s, OMe); δ_C (100.6 MHz, $CDCl_3$): 188.9, 162.1, 130.7, 129.8, 124.3, 123.8, 115.5, 56.2.

3.1.2. 5-Bromo-2-methoxybenzaldehyde (entry 2). The title compound was prepared from 2,4-dibromoanisole (5.32 g, 20 mmol) as colorless crystals (3.9 g, 90%), mp 115–118 °C (from hexane, Ref. 28 mp 116–119 °C); (Found: C, 44.29; H, 3.48. $C_8H_7BrO_2$ requires C, 44.68; H, 3.28%); δ_H (400 MHz, $CDCl_3$) 10.37 (1H, s, CHO), 7.90 (1H, d, J=2.5 Hz, Ph), 7.62 (1H, dd, J=9.0, 2.5 Hz, Ph), 6.89 (1H, d, J=9.0 Hz, Ph), 3.92 (3H, s, OMe); δ_C (100.6 MHz, $CDCl_3$) 188.5, 160.9, 138.4, 131.1, 125.2, 113.9, 113.6, 56.1.

3.1.3. 4-Bromo-2-(*tert*-butyldimethylsilyloxy)benzaldehyde (entry 3). The title compound was prepared from 2-(*tert*-butyldimethylsilyloxy)-1,4-dibromobenzene (7.32 g, 20 mmol) as colorless crystals (2.3 g, 36%), mp 34–36 °C (from methanol); (Found: C, 49.43; H, 6.31. $C_{13}H_{19}BrO_2Si$ requires C, 49.52; H, 6.07%); ν_{max}(KBr) 2938, 2855, 1684, 1588, 1470, 1265 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.39 (1H, d, J=1.0 Hz, CHO), 7.67 (1H d, J=8.0 Hz, Ph), 7.19 (1H, ddd, J=8.0, 1.5, 1.0 Hz, Ph), 7.06 (1H, d, J=1.0 Hz, Ph), 1.02 (9H, s, Bu^tMe_2Si), 0.30 (6H, s, Bu^tMe_2Si); δ_C (100.6 MHz, $CDCl_3$) 189.3, 159.3, 130.1, 129.7, 126.4, 125.3, 123.7, 25.8, 18.5, −4.2. *m*/*z* (EI, 70 kV) molecular ion not found, 259 (100), 257 (100, M−$(CH_3)_3C$), 241(36), 239 (35%).

3.1.4. 5-Bromo-2-(*tert*-butyldimethylsilyloxy)benzaldehyde (entry 4). The title compound was prepared from 1-(*tert*-butyldimethylsilyloxy)-2,4-dibromobenzene (7.32 g, 20 mmol) as colorless crystals (2.0 g, 32%), mp 60–62 °C (from methanol); (Found: C, 49.36; H, 6.09. $C_{13}H_{19}BrO_2Si$ requires C, 49.52; H, 6.07%); ν_{max}(KBr) 2936, 2858, 1685, 1590, 1478, 1271, 916 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.38 (1H, s, CHO), 7.91 (1H, d, J=2.5 Hz, Ph), 7.53 (1H, dd, J=9.0, 2.5 Hz, Ph), 6.80 (1H, d, J=9.0 Hz, Ph), 1.02 (9H, s, Bu^tMe_2Si), 0.29 (6H, s, Bu^tMe_2Si); δ_C (100.6 MHz, $CDCl_3$) 188.8, 158.0, 138.4, 131.1, 128.6, 122.3, 114.3, 25.8, 18.5, −4.2. *m*/*z* (EI, 70 kV) molecular ion not found, 259 (100), 257 (100, M−$(CH_3)_3C$), 241(24), 239 (24%).

3.1.5. 4-Bromo-3-methoxybenzaldehyde (entry 5). The title compound was prepared from 2-bromo-5-iodoanisole (4.0 g, 13 mmol) as colorless crystals (1.9 g, 69%), mp 74–76 °C (from hexane, Ref. 7 mp 74 °C); (Found: C, 44.65; H, 3.16. $C_8H_7BrO_2$ requires C, 44.68; H, 3.28%); δ_H (400 MHz, $CDCl_3$) 9.95 (1H, s, CHO), 7.74 (1H, d, J=8.0 Hz, Ph), 7.39 (1H, d, J=2.0 Hz, Ph), 7.33 (1H, dd, J=8.0, 2.0 Hz, Ph); δ_C (100.6 MHz, $CDCl_3$) 191.3, 156.8, 136.9, 134.1, 124.8, 119.8, 110.0, 56.6.

3.1.6. 4-Bromophtalaldehyde (entry 6). The title compound was prepared from 1,4-dibromo-2-(dimethoxymethyl)benzene (6.20 g, 20 mmol). The heating of the crude product with boiling 1 M aq. HCl (20 mL) was necessary to complete the cleavage of the acetal moiety and deprotect the second formyl group. Colorless crystals (2.2 g, 52%), mp 98–100 °C (from hexane/toluene 3:1, Ref. 10 mp 99–100 °C); (Found: C, 44.91; H, 2.36. $C_8H_5BrO_2$ requires C, 45.11; H, 2.37%); δ_H (400 MHz, $CDCl_3$) 10.52 (1H, s, CHO), 10.45 (1H, s, CHO), 8.10 (1H, d, J=2.0 Hz, Ph), 7.92 (1H, dd, J=8.5, 2.0 Hz, Ph), 7.85 (1H, d, J=8.5 Hz, Ph); δ_C (100.6 MHz, $CDCl_3$) 191.4, 190.9, 137.6, 136.9, 135.0, 133.8, 133.0, 129.3.

3.1.7. 5-Bromo-2-fluoro-4-methoxybenzaldehyde (entry 7). The title compound was prepared from 2,4-dibromo-5-fluoroanisole (5.68 g, 20 mmol) as colorless crystals (3.8 g, 82%), mp 98–100 °C (from hexane); (Found: C, 41.02; H, 2.65. $C_8H_6BrFO_2$ requires C, 41.23; H, 2.60%); ν_{max}(KBr) 3082, 2869, 1672, 1608, 1274, 1137, 1043, 852, 660 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.16 (1H, s, CHO), 8.05 (1H, d, J=7.5 Hz, Ph), 6.69 (1H, d, J=12.0 Hz, Ph), 3.98 (3H, s, OMe); δ_C (100.6 MHz, $CDCl_3$) 184.9 (d, $^3J_{CF}$=6.0 Hz), 165.5 (d, $^1J_{CF}$=260.0 Hz), 162.0 (d, $^3J_{CF}$=11.0 Hz), 132.7 (d, $^3J_{CF}$=3.5 Hz), 118.4 (d, $^2J_{CF}$=9.5 Hz), 107.9 (d, $^4J_{CF}$=3.0 Hz), 100.3 (d, $^2J_{CF}$=26.0 Hz), 57.2; *m*/*z* (EI, 70 kV) 234 (74, M+2), 233 (100), 232 (74, M^+), 231 (95), 163 (14), 161 (14), 81 (25%).

3.1.8. 2-Fluoro-4-iodo-3-methoxybenzaldehyde (entry 8). The title compound was prepared from 2-fluoro-3,6-diiodoanisole (7.56 g, 20 mmol) in a mixed solvent (Et_2O–THF 1:1) at −90 °C. In this case, lithiation was carried out by the addition of the solution of BuLi (10 M, 2 mL, 20 mmol) in hexane (10 mL) to the solution of 2-fluoro-3,6-diiodoanisole. Pale yellow crystals (4.0 g, 72%), mp 97–99 °C (from hexane); (Found: C, 33.42; H, 2.35. $C_8H_6FIO_2$ requires C, 34.31; H, 2.16%); ν_{max}(KBr) 3080, 2866, 1682, 1423, 1262, 1031, 772 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.30 (1H, d, J=0.5 Hz, CHO), 7.68 (1H, ddd, J=8.5, 1.5, 0.5 Hz, Ph), 7.30 (1H, dd, J=8.5, 6.5 Hz, Ph), 4.00 (3H, d, OMe); δ_C (100.6 MHz, $CDCl_3$) 186.4 (d, $^3J_{CF}$=7.5 Hz), 156.4 (d, $^1J_{CF}$=264.0 Hz), 148.5 (d, $^2J_{CF}$=10.5 Hz), 134.7 (d, $^3J_{CF}$=4.0 Hz), 126.0 (d, $^2J_{CF}$=7.0 Hz), 123.9 (d, $^4J_{CF}$=2.0 Hz), 101.0, 61.7 (d, $^4J_{CF}$=5.5 Hz); *m/z* (EI, 70 kV) 280 (100, M^+), 279 (42), 265 (12), 137 (14, 30%).

3.1.9. 4-Bromo-1,3-diformyl-2-fluorobenzene (entry 9). The title compound was prepared from 1,4-dibromo-2-(dimethoxymethyl)-3-fluorobenzene (6.56 g, 20 mmol). The heating of the crude product with boiling dil. aq. HCl was necessary to complete the cleavage of the acetal moiety and deprotect the second formyl group. Colorless crystals (2.2 g, 48%), mp 120–122 °C (from hexane/toluene 3:1); (Found: C, 41.37; H, 1.82. $C_8H_4BrFO_2$ requires: C, 41.59; H, 1.75%); ν_{max}(KBr) 3086, 2896, 1693, 1688, 1591, 1392, 1222, 955 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.38 (1H, d, J=1.0 Hz, CHO), 10.37 (1H, s, CHO), 7.94 (1H, dd, J=8.0, 7.0 Hz, Ph), 7.66 (1H, d, J=8.0 Hz, Ph);. δ_C (100.6 MHz, $CDCl_3$) 187.5 (d, $^3J_{CF}$=2.5 Hz), 185.3 (d, $^3J_{CF}$=7.5 Hz), 164.6 (d, $^1J_{CF}$=276.0 Hz), 133.3 (d, $^4J_{CF}$=4.0 Hz), 132.4 (d, $^3J_{CF}$=4.0 Hz), 130.9 (d, $^3J_{CF}$=4.5 Hz), 124.4 (d, $^2J_{CF}$=8.5 Hz), 123.7 (d, $^2J_{CF}$=10.0 Hz); *m/z* (EI, 70 kV) 232 (79, M+2), 231 (100), 230 (81, M^+), 229 (93), 203 (15), 201 (15), 175 (21), 173 (22), 121 (25), 94 (40%).

3.1.10. 2-Bromo-5-fluoro-4-methoxybenzaldehyde (entry 10). The title compound was identified as the main product of the reaction of 4,5-dibromo-2-fluoroanisole (5.68 g, 20 mmol) with BuLi and DMF at −100 °C in THF–Et_2O (4:1) and isolated by two-fold fractional recrystallization of the crude product from hexane/toluene (1:1, 10 mL). Pale yellow crystals (0.60 g, 13%), mp 99–102 °C; (Found: C, 41.00; H, 2.58. $C_8H_6BrFO_2$ requires C, 41.23; H, 2.60%); ν_{max}(KBr) 3079, 2881, 1678, 1608, 1495, 1278, 1138, 1021, 804 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.14 (1H, d, J=3.5 Hz, CHO), 7.62 (1H, d, J=11.0 Hz, Ph), 7.17 (1H, d, J=7.0 Hz, Ph), 3.98 (3H, d, J=1.0 Hz, OMe); δ_C (100.6 MHz, $CDCl_3$) 189.9, 153.2 (d, $^2J_{CF}$=12.0 Hz), 151.8 (d, $^1J_{CF}$=250.0 Hz), 126.8 ($^3J_{CF}$=4.5 Hz), 122.9 ($^3J_{CF}$=3.0 Hz), 117.6, 116.3 ($^2J_{CF}$=20.0 Hz), 56.8; *m/z* (EI, 70 kV) 234 (62, M+2), 233 (100), 232 (62, M^+), 231 (96), 163 (10), 161 (10), 81 (30%).

3.1.11. 4-Bromo-5-fluoro-2-methylbenzaldehyde (entry 11). The title compound was prepared from 3-bromo-4-fluoro-2-iodotoluene (4.1 g, 13 mmol). Pale yellow crystals (1.3 g, 46%), mp 68–70 °C (from hexane); (Found: C, 44.26; H, 2.77. C_8H_6BrFO requires: C, 44.27; H, 2.79); ν_{max}(KBr) 3039, 2888, 1683, 1597, 1387, 1259, 732 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.20 (1H, J=1.5 Hz, CHO), 7.53 (1H, d, J=8.5 Hz, Ph), 7.51–7.48 (1H, m, Ph), 2.63 (3H, m, Me); δ_C (100.6 MHz, $CDCl_3$) 190.3 (d, $^4J_{CF}$=1.5 Hz), 157.9 (d, $^1J_{CF}$=247 Hz), 137.5 (d, $^4J_{CF}$=4.0 Hz), 136.8, 134.6 (d, $^3J_{CF}$=5.5 Hz), 117.8 (d, $^2J_{CF}$=23.0 Hz), 115.8 (d, $^2J_{CF}$=20.5 Hz), 18.3. *m/z* (EI, 70 kV) 218 (85, M+2), 217 (100), 216 (87, M^+), 215 (95), 189 (38), 187 (38), 108 (45), 107 (52%).

3.1.12. 4-Bromo-2-(trifluoromethyl)benzaldehyde (entry 12). The title compound was prepared from 1,4-dibromo-2-trifluoromethyl)benzene (6.08 g, 20 mmol). Pale yellow crystals (3.5 g, 69%), mp 48–50 °C (from hexane); (Found: C, 37.51; H, 1.45. $C_8H_4BrF_3O$ requires C, 37.98; H, 1.59); ν_{max}(KBr) 1703, 1591, 1304, 1172, 1134, 840 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.31 (1H, qd, J=2.0, 1.0 Hz, CHO), 7.98 (1H, d, J=8.5 Hz, Ph), 7.92 (1H, d, J=2.0 Hz, Ph), 7.86–7.83 (1H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 187.9 (q, $^4J_{CF}$=3.5 Hz), 135.8, 132.50 (q, $^2J_{CF}$=32.5 Hz), 132.49, 130.8, 129.6 (q, $^3J_{CF}$=6.0 Hz), 129.0, 122.9 (q, $^1J_{CF}$=275 Hz). *m/z* (EI, 70 kV) 254 (66, M+2), 253 (100), 252 (66, M^+), 251 (98), 225 (32), 223 (32), 145 (39), 144 (37), 125 (36%).

3.1.13. 4-Bromo-3-(trifluoromethyl)benzaldehyde (entry 13). The title compound was prepared from 1-bromo-4-iodo-2-(trifluoromethyl)benzene (7.02 g, 20 mmol). Colorless crystals 3.7 g (73%), mp 51–54 °C (from hexane, Ref. 22 mp 52.5–53.5 °C); (Found: C, 37.35; H, 1.62. $C_8H_4BrF_3O$: C, 37.98; H, 1.59); δ_H (400 MHz, $CDCl_3$) 10.04 (1H, s, CHO), 8.20–8.18 (1H, m, Ph), 7.94–7.89 (2H, m, Ph); δ_C (100.6 MHz, $CDCl_3$) 189.9, 136.3, 135.3, 133.2, 131.6 (q, $^2J_{CF}$=33 Hz), 129.0 (q, $^3J_{CF}$=5.5 Hz), 127.3, 122.1 (q, $^1J_{CF}$=272 Hz).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.04.051

Synthetic procedures and analytical data for all new compounds prepared in the course of this work including copies of the ^{13}C NMR spectra of all new compounds and all isolated benzaldehydes.

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Nitrosation of hydrochlorothiazide and the modes of binding of the *N*-nitroso derivative with two macrocycles possessing an 18-membered crown ether cavity

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Abstract—The hydrochlorothiazide, 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide, (**HCTZ**), widely used as a diuretic and anti-hypertensive drug, was transformed into its *N*-nitroso-derivative, 6-chloro-4-nitroso-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (**O═N–HCTZ**) by sodium nitrite in an acidic medium. The crystalline complexes of **O═N–HCTZ** with 18-crown-6 (18C6) and *cis-anti-cis*-dicyclohexyl-18C6 (DCH6B) demonstrated different H-bonding modes from those present in the co-crystals of **HCTZ** with the same crown ethers. The influence of the nitroso-group on the binding mode and crystal packing is discussed.

1. Introduction

The application of macrocycles, mainly crown ethers, as low molecular weight receptors used in assessing non-covalent bondings important in chemistry and biology attracts relentless attention.[1] These model systems have distinct advantages over biological macromolecules due to their relative simplicity, which allows for specific interactions to be isolated and studied in the absence of the many others that are present in biological macromolecules. Verification of unusual properties in synthetic receptor systems can give an insight into the biological implications for such chemical interactions. Classic O-containing crown ethers act as hydrogen acceptors, forming exclusively C–H···Ocrown, N–H···Ocrown, or O–H···Ocrown hydrogen bonds. It is interesting to estimate the contribution of these interactions to the binding of biologically important molecules.

Previously we revealed the decisive role of NH···O hydrogen bonds in the interactions of some diuretic drugs, hydrochlorothiazide,[2,3] acetazolamide[4] with 18-membered crown ethers. As far as the chemistry of *N*-nitrosamines is a subject of considerable interest with regard to their strong carcinogenic and mutagenic properties,[5] we are currently interested in the mutagenic transformations of the secondary amino-group-containing drugs upon nitrite treatment under acidic conditions and in the differences in molecular recognition of the initial drug and the product of its metabolism with crown ethers, as simple model compounds.

In the present study, the drug hydrochlorothiazide, 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide, **HCTZ**[6] has been chosen. **HCTZ** is a popular diuretic drug that belongs to the thiazide class of diuretics and acts by inhibiting the kidney's ability to retain water. It is often used to treat hypertension, congestive heart failure and symptomatic edema, and is effectiveness in diabetes insipidus and in hypercalciuria, acting on the kidney to reduce sodium re-absorption in the distal convoluted tubule. As artificial receptors the 18-membered crown ethers have been chosen, 18-crown-6 (18C6) and *cis-anti-cis* dicyclohexyl-18C6 (DCH6B), which are powerful collective H-acceptors, very effective in forming interactions with the amino-group.[7]

Keywords: *N*-nitrosohydrochlorothiazide; Crown ethers; H-binding.
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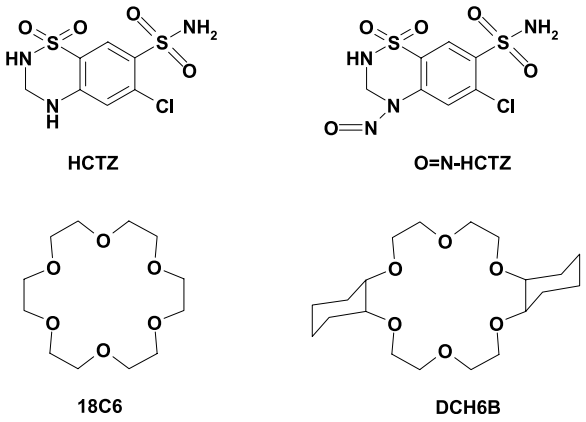
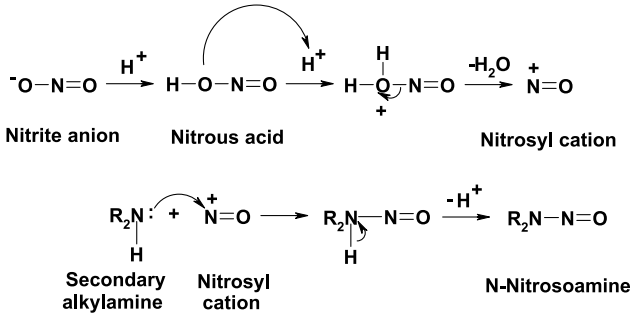


Scheme 1. The components of the binary co-crystals discussed herein.

Herein we describe the synthesis of *N*-nitroso derivative of **HCTZ**, **O═N–HCTZ** and the crystal structures of its two complexes with 18C6 (complex **1**) and DCH6B (complex **2**) with 1:2 and 1:1 ratios, correspondingly (Scheme 1), and make the comparisons with the H-bonded complexes of **HCTZ** with the same crown ethers.

2. Results and discussion

It has previously been reported that micro-organisms commonly present in human saliva, which can be isolated from the human gastro-intestinal tract, have the capacity in vitro to catalyse *N*-nitrosation of a series of medicinal drugs and other compounds.[8] On the other hand, the nitrosation of amines is possible in two ways, namely, by endogenous nitrogen oxide (NO) in the conditions of the oxidation reaction and by exogenous nitrites in the acidic medium. The typical reagents for this reaction are sodium nitrite and aqueous solutions of hydrochloric HCl or sulfuric H_2SO_4 acids (this mixture yields nitrous acid, HNO_2). The actual nitrosation reagent is the NO^+ nitrosyl cation which is formed in situ. The nature of the product depends on the nature of the initial amine. Primary alkyl or aryl amines yield diazonium salts. Secondary alkyl or aryl amines yield *N*-nitrosoamines. Tertiary alkyl amines do not react in a useful fashion. Tertiary aryl amines undergo nitrosation of the ring.[5] Scheme 2 shows the route by which secondary amines are transformed to the dangerous *N*-nitroso compounds.



Scheme 2. Mechanism of nitrosation of secondary alkylamine.

In our case, the nitrosation of **HCTZ** occurs by sodium nitrite in acetic acid and results in the formation of *N*-nitroso-**HCTZ** (**O═N–HCTZ**). The attack of the electrophilic nitrosyl cation occurs on the cyclic secondary amino-group, which is a more powerful nucleophile in comparison with secondary and primary sulfamido-groups. Thus, only one of the two NH-groups of **HCTZ** is nitrosated.

2.1. Complexes of 18C6 and DCH6B with O═N–HCTZ

Due to the poor crystal quality of **2** and the low accuracy of the final data obtained, the geometric parameters of **O═N–HCTZ** will be discussed only with reference to the complex formed with 18C6, while the hydrogen bonding system will be compared between **1**, **2** and the complexes of **HCTZ** with the same crown ethers. Hydrogen bonds in both complexes are listed in Table 1. The geometry of the cyclic skeleton of **O═N–HCTZ** is very close to **HCTZ** in its pure form[9] and in its complexes with 18C6[2] and DCH6B.[3] It is characterized by a dihedral angle of 10.7 (1)° between the planes through the two fused six-membered rings, aromatic, C1G>C6G and heterocyclic, C3G/C4G/S2G/N3G/C7G/N2G ones. The atoms of the aromatic ring are co-planar with the four heteroatoms attached to it within a mean-square deviation of 0.051 Å. The neighboring six-membered heterocycle has the shape of a distorted half-chair, with a maximal deviation of 0.698 (2) Å for the N3G atom from the C3G/C4G/N2G/N3G/S2G mean plane, where the atoms are coplanar within 0.020 Å. The nitroso-group geometry with an N═O distance of 1.228 (2) Å and

Table 1. Hydrogen bonding geometry in **1** and **2**

D–H···A	d(H···A)/Å	d(D···A)/Å	∠(DHA)/°	Symmetry code for acceptor
1				
N1G–H11G···O4	2.09 (2)	2.932 (2)	174 (2)	*x*, *y*, *z*
N1G–H12G···O1	2.13 (2)	2.928 (2)	162 (3)	$-x+2$, $-y+2$, $-z$
N3G–H31G···O7	2.20 (2)	3.062 (2)	170 (2)	$-x+1$, $-y+2$, $-z$
C7G–H71G···O2G	2.24	3.096 (3)	150	$-1+x$, *y*, *z*
2				
N1G–H11G···O10	2.06 (2)	2.976 (10)	178 (11)	*x*, *y*, *z*
N1G–H12G···O4	2.06 (2)	2.982 (11)	174 (10)	*x*, *y*, *z*
N3G–H3GB···O1A	2.22 (2)	2.972 (12)	143 (4)	*x*, *y*, *z*
C7G–H7J···O4A	2.48	3.444 (14)	172	$1-x$, $3-y$, $-z-1$
N11G–H11A···O16	2.22 (4)	3.028 (11)	159 (10)	*x*, *y*, *z*
N11G–H11B···O4	2.13 (4)	2.936 (11)	156 (8)	*x*, *y*, *z*
N13G–H13B···O7B	2.12 (3)	2.975 (11)	174 (10)	*x*, *y*, *z*
C17G–H17J···O4B	2.37	3.343 (13)	179	*x*, *y*, *z*

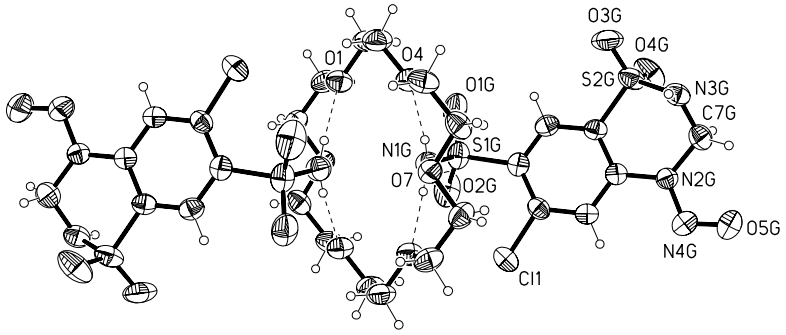


Figure 1. ORTEP view of complex **1**.

N–N═O bond angle of 112.8 (2)° does not exhibit any new features compared with the earlier structure determinations.[10]

Complex **1** has a trivial 1:2 ratio, with the crown ether imposed on the inversion center.[7] The aromatic ring of **O═N–HCTZ** is inclined at an angle of 42.2(1)° to the mean plane of the crown ether oxygen atoms, the N1G-S1G bond deviates at an angle of 21.1° from the normal to the same plane of 18C6. Two molecules of **O═N–HCTZ**, arranged in a head to head fashion, are linked via two NH···O hydrogen bonds of the sulfamide group with the oxygens of two equal faces of 18C6 (Fig. 1, Table 1).

The secondary sulfamido-group is linked via a single NH···O hydrogen bond with the next crown molecule translated along the *a* direction (Fig. 2). Thus, each molecule of 18C6 is bound with four molecules of **O═N–HCTZ** via six NH···O hydrogen bonds. In their turn, the **O═N–HCTZ** translated molecules are combined into chains via weak CH···O hydrogen bonds between the methylene hydrogen and the oxygen atom of the sulfamide group. Through these interactions, the components are organized into a ribbon where the crown spacers occupy the mean positions between two rows of **O═N–HCTZ** molecules.

Previously we described the mode of interaction of **HCTZ** with 18C6[2] (refcode VITWIE in CSD[11]) and DCH6B[3] (refcode REZXEZ in the CSD). In the 1:1 complex with 18C6, **HCTZ** coordinates in different modes on two non-equivalent faces of the crown ether. The lack of steric impediments in the molecule of **HCTZ** facilitates the participation of all its H-donor centers in coordination of two **HCTZ** molecules to one molecule of 18C6 in a head to face mode via two NH···O hydrogen bonds of amino-group on one face and two NH···O and one CH···O hydrogen bonds on the other one, and the association of the components into 1:1 alternative chain (Fig. 3), where each **HCTZ** molecule bridges two neighbouring 18C6 molecules. The introduction of the nitroso-group in the molecule of **HCTZ** obliterates one of the NH···O interactions and induces the rearrangement of the CH···O contact from **HCTZ**···18C6 (Fig. 3) to **O═N–HTCZ**···**O═N–HTCZ** in **1** (Fig. 2).

Complex **2** crystallizes in the triclinic crystal system with two crystallographically independent **O═N–HTCZ**

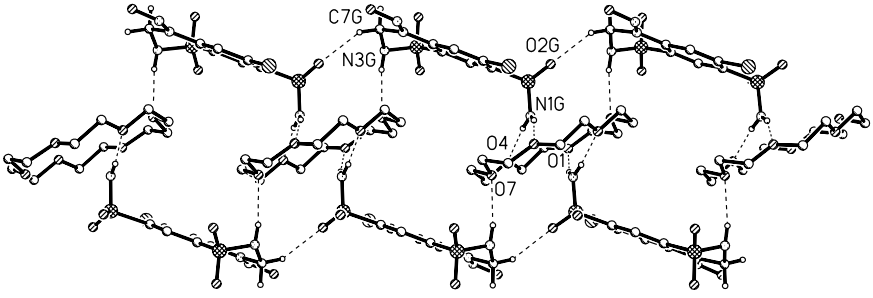


Figure 2. Organization of ribbon in **1**.

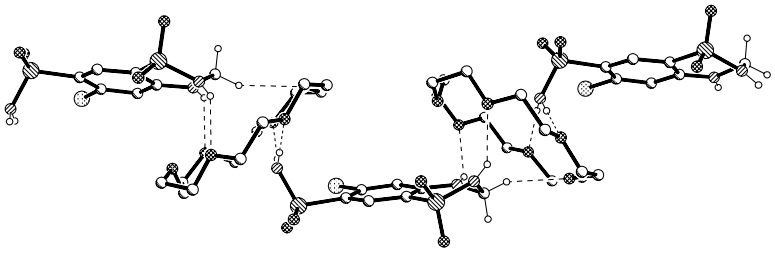


Figure 3. Mode of interaction of **HCTZ** with 18C6 in the alternative chain.

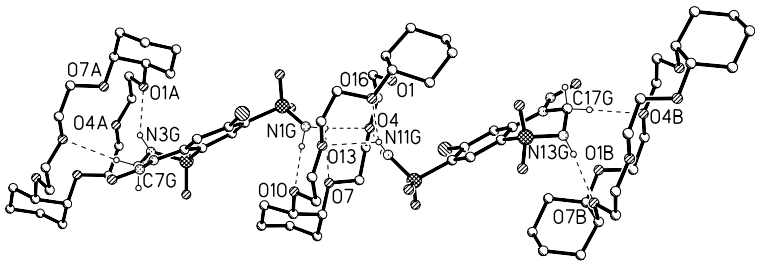


Figure 4. View of complex **2**. Symmetry-related **O═N–HCTZ** molecules are not shown.

molecules and one DCH6B molecule occupying the general positions and two DCH6B molecules occupying the partial positions, on the inversion centers. The overall complex stoichiometry is 1:1, and as is evident from Figure 4, the components alternate in the chains where each molecule of **O═N–HCTZ** bridges two DCH6B molecules.

The unique fragment of this chain includes three different three-membered H-bonded nodes. In the central node (Figs. 4 and 5a) two crystallographically independent **O═N–HCTZ** molecules are linked with the crown molecule via one single and one bifurcated NH···O hydrogen bond of the sulfamido-group. In two other, very similarly organized nodes (Fig. 5b), the crown molecules (A or B) are imposed on the inversion centers, and the NH-group and the neighboring methylene group are linked with the crown molecule via one NH···O and one CH···O hydrogen bonds. Thus, all H-donor groups are involved in interactions within the alternative chain: ···DCH6B··· **O═N–HCTZ**···DCH6B···**O═N–HCTZ**···.

Now an intriguing question arises, whether the striking differences similar to those found in the system including 18C6 as a receptor appear in the complexes of **HCTZ** and **O═N–HCTZ** with DCH6B? The answer should be: no. The crystal structure of the 1:2 complex of **HCTZ** with DCH6B reveals two types of the alternative chains, where **HCTZ** molecules coordinate to the crown ether in a head to head and tail to tail modes, via two amino-groups, or two CH and two NH groups (Fig. 6). The chains differ only by

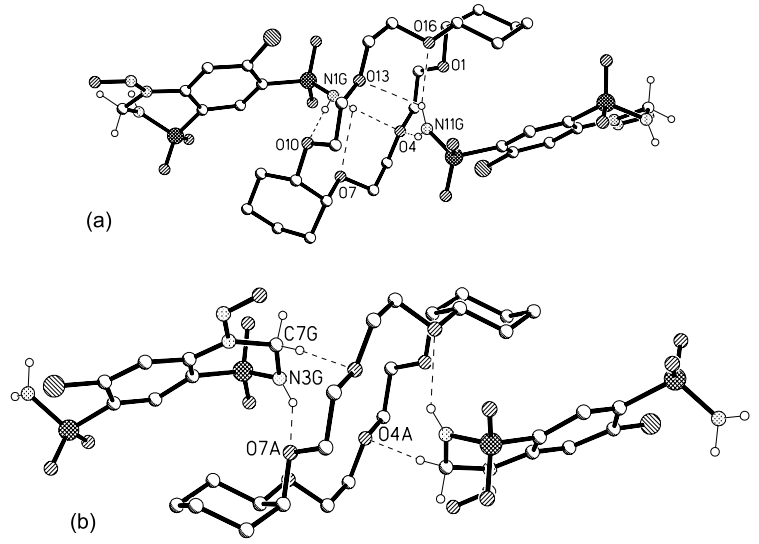


Figure 5. Modes of interaction of **O═N–HCTZ** with DCH6B in **2**.

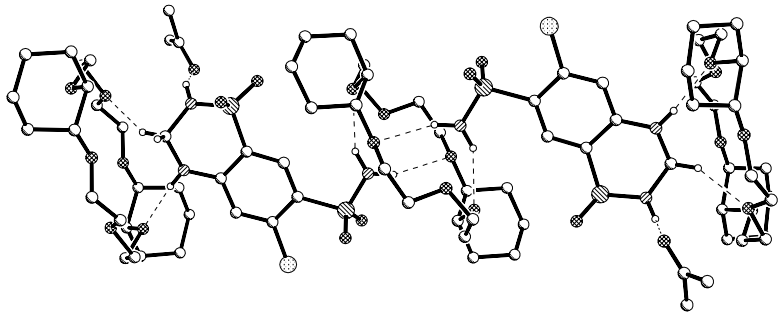


Figure 6. Fragment of infinite chain including acetone molecules in the complex of **HCTZ** with DCH6B.

the acetone molecule which via NH···O hydrogen bond blocks up the NH-group of **HCTZ** molecule, that is nitrosylated in **O═N–HCTZ**.

Thus, the contribution of the cyclohexyl substituents of DCH6B in the organization of supramolecular architectures is decisive here. In the case of **HCTZ** they shield the secondary sulfamide-group from the interaction with the crown ether cavity in such a way that this NH-group does not influence the overall system of hydrogen bonding and its nitrosation does not change the overall system of interactions in **2**.

3. Conclusion

The widely used diuretic, 6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide, hydrochlorothiazide (**HCTZ**), was treated with sodium nitrite under acidic conditions (the presence of acetic acid) simulating the conditions of gastric juice. The potentially carcinogenic derivative, 6-chloro-4-nitroso-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide, **O═N–HCTZ**, was obtained and its binding mode with two artificial macrocyclic receptors, 18-crown-6 and *cis-anti-cis* dicyclohexyl-18-crown-6 was compared with the initial **HCTZ**. In the case of the flexible and responsive 18C6, the change in the substrate-receptor interaction was dictated by the prohibition of the secondary amino-group of **O═N–HCTZ** in NH···O (crown) interactions, whilst in the case of its substituted analogue, DCH6B, the steric impediments of cyclohexyl units appeared to be decisive and exclude the participation of the secondary amino group of **HCTZ** in interactions with crown ether, thus nitrosation of this group does not influence the overall mode of the **HCTZ/O═N–HCTZ** DCH6B interaction.

4. Experimental

4.1. General

The initial chemicals were used as received without further purification. IR spectra were recorded on a Specord-80 spectrophotometer as KBr disks. The ^{1}H NMR spectra were recorded with a Bruker DPX-250 instrument at 250 MHz using tetramethylsilane as internal reference. Crystallographic measurements were carried out on a KUMA KM4CCD κ-axis diffractometer with a graphite-monochromatised Mo Kα radiation ($\lambda=0.71073$ Å) at 293 K for **1** and 130 K for **2**. Cell parameters were obtained by the global refinement of the positions of all collected reflections. The structures were solved by direct methods and refined by full-matrix least-squares on F^2 using SHELX-97 package. All non-hydrogen atoms were refined anisotropically. Locations of H atoms attached to N were justified by difference Fourier synthesis and refined isotropically. H atoms attached to C were added geometrically and refined using the riding model.

4.1.1. Compound O═N–HCTZ. To a suspension of **HCTZ** (297 mg, 1 mmol) in hot acetic acid (15 ml) sodium nitrite (483 mg, 7 mmol) was added with intensive stirring. The reaction mixture was diluted by water (50 ml) and filtered off. The yield of **O═N–HCTZ** was 150 mg, (46%), mp> 180 °C (decomp.), found, %: C 25.78, H 2.08, Cl 10.83, N 17.02, S 19.58, required for $C_7H_7ClN_4O_5S_2$: C 25.73, H 2.16, Cl 10.85, N 17.15, S 19.63. IR (cm^{-1}, peaks of strong absorption only): 3410, 3070, 3000, 1580, 1430, 1290. ^{1}H NMR ($CDCl_3$) δ ppm: 4.93 (s, 2H, CH_2), 7.0 (s, 1H, CH), 7.50 (s, 2H, NH_2), 7.62 (s, 1H, NH), 8.32 (s, 1H, CH).

4.1.2. Compound 1. O═N–HCTZ (98 mg, 0.3 mmol) and 18C6 (80 mg, 0.3 mmol) were dissolved in a mixture of methanol/ethylacetate (1:2, 9 ml). The colorless, transparent crystals were obtained in a quantitative yield by slow evaporation of the solvents at room temperature for several days, mp>150 °C (with decomp., brown spot), found, %: C 34.09, H 4.22, Cl 7.71, N 12.30, S 14.07, required for $C_{26}H_{38}Cl_2N_8O_{16}S_4$: C 34.02, H 4.17, Cl 7.73, N 12.21, S 13.98. IR (cm^{-1}, peaks of strong absorption only): 3310–3100, 3070–3030, 3000–2790, 1580, 1560, 1550, 1530, 1430–1300, 1290, 1080. ^{1}H NMR ($CDCl_3$) δ ppm: 3.60 (s, 24H, CH_2O), 4.95 (s, 4H, CH_2), 7.07 (s, 2H, CH), 7.52 (s, 4H, NH_2), 7.64 (s, 2H, NH), 8.34 (s, 2H, CH).

Crystal data for **1**. monoclinic, $P2_1/c$, $a=10.109$ (2) Å, $b=12.729$ (2) Å, $c=15.356$ (3) Å, $\beta=95.86$ (1)°, $V=1965.8$ (6) Å^3, $Z=2$, $Dx=1.551$ g cm^{-3}, $T=293$ K, λ(Mo Kα) 0.71073 Å, $\mu=4.56$ cm^{-1}, $F(000)=952$, GooF=0.934, R indices (all data) $R1=0.0628$, $wR2=0.0.0960$ for 3859 reflections and 262 parameters and R indices $R1=0.0375$, $wR2=0.0868$ for 2596 reflections obeying $I>2\sigma(I)$ criterion of observability.

4.1.3. Compound 2. O═N–HCTZ (98 mg, 0.3 mmol) and DCH6B (112 mg 0.3 mmol) were dissolved in the mixture methanol/ethylacetate (1:2, 9 ml). The colorless, transparent crystals were obtained in a quantitative yield by slow evaporation of the solvents at room temperature for several days, mp>160 °C (with decomp., brown spot), found, %: C 46.32, H 6.23, Cl 5.02, N 8.06, S 9.21, required for $C_{27}H_{43}ClN_4O_{11}S_2$: C 46.37, H 6.20, Cl 5.07, N 8.01, S 9.17. IR (cm^{-1}, peaks of strong absorption only): 3450–3100, 3070–3020, 3000–2780, 1590–1510, 1430 1300, 1280, 1080. ^{1}H NMR ($CDCl_3$) δ ppm: 1.46–1.21 (m, 16H, CH_2, CH), 3.61–3.46 (m, 20H, CH_2O), 4.95 (s, 2H, CH_2), 7.07 (s, 1H, CH), 7.52 (s, 2H, NH_2), 7.62 (s, 1H, NH), 8.34 (s, 1H, CH).

Crystal data for **2**. triclinic, $P-1$, $a=14.326$ (3) Å, $b=15.458$ (3) Å, $c=16.757$ (3) Å, $\alpha=68.04$ (3), $\beta=71.54$ (3), $\gamma=77.45$ (3)°, $V=3243.8$ (11) Å^3, $Z=4$, $Dx=1.432$ g cm^{-3}, $T=130$ K, λ(Mo Kα) 0.71073 Å, $\mu=3.10$ cm^{-1}, $F(000)=1480$, GooF=1.045, R indices (all data) $R1=0.2769$, $wR2=0.3207$ for 11190 reflections and 829 parameters and R indices $R1=0.1121$, $wR2=0.2318$ for 3749 reflections obeying $I>2\sigma(I)$ criterion of observability.

Tables of crystal data, atomic coordinates and thermal parameters, full bond distances and angles, and structure factors may be obtained on request from the authors. CCDC reference numbers 256808 and 256809 for compounds (**1**) and (**2**), respectively.

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Michael addition of phosphorus derivatives on tetraethyl ethylidenediphosphonate

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Abstract—Nucleophilic phosphorus add to tetraethyl ethylidene diphosphonate in protic solvent to yield the product of the Michael reaction. This reaction appeared to be reversible at a temperature upper than 160 °C. To avoid this reverse reaction, alkylation in α position of the two phosphonate functions by activated elecrophile is reported.

1. Introduction

Metal-phosphonate materials are obtained by the reaction of a phosphonic acid[1] or a phosphonate[2] with a metallic salt (Al, Co, Zr…) in aqueous media or in polar organic solvent.[3] This class of materials possesses a well defined structure typically formed by a layered[4] or a three dimensional organisation.[5] Unfortunately, in many cases, the accessibility of the interlayer space is reduced due to overcrowding. Many applications such as the use of these materials as heterogeneous catalysts, ion exchangers or ion transporters depend upon the ability to control both the porosity of these materials and the location of vacant functional groups inside the pore. A first strategy, used to improve the accessibility to the reactive functions, consists of using two types of phosphonic acids (one bearing the function group and the second acting as a spacer) in the course of the synthesis of materials.[6] The drawback of this strategy is that the materials are poorly crystalline and size of the pore is irregular. The second possibility, which is also useful to introduce other functional groups into hybrid materials, consists in using a phosphonic acid bearing others functions (e.g., phosphonic acid, carboxylate, amine…). According to this strategy, porous materials possessing well-defined structures were obtained.[7] Unfortunately, most of the time all the functions present on the organic precursor are coordinated to the metal atoms constituting the inorganic network, leading to limitate the chemical reactivity of these functions. A first example of a zinc-phosphonate material possessing functional groups that are not co-ordinated to the metal atoms ('free function'), was reported by Sevov[8] who used a phosphonated α-amino-acid as the organic precursor. Recently we have also reported a cobalt-phosphonate structure possessing a free amine function located inside a microporous material.[9] From these results, it appears that the use poly-functional organic precursors are good candidates to synthesise porous materials possessing free functions. In order to synthesise polyfunctional building blocks for the construction of metal phosphonate materials the functionalisation of tetraethyl ethylidenediphosphonate **A** by conjugate addition of a nucleophile was very promising.

The functionalisation of compound **A** by Michael addition of nucleophilic carbon,[10,11] sulfur or amine[12,13] can be obtained according to the reported methods. More recently the addition of heterocycle has been reported.[14] It is worth mentioning that in the case of amine, the reverse Michael addition was frequently observed. The addition of nucleophilic phosphorus species has scarcely been studied. Indeed, only two NMR studies of the conjugate addition of dialkylphosphite[12] or spirophosphorane[13] to compound **A** (the Michael addition occurred only with the presence of 1 equiv of diisopropylamine as a base) has been reported.

A limitation to the use of the Michael addition can arise

Keywords: Phosphonate; Michael addition.
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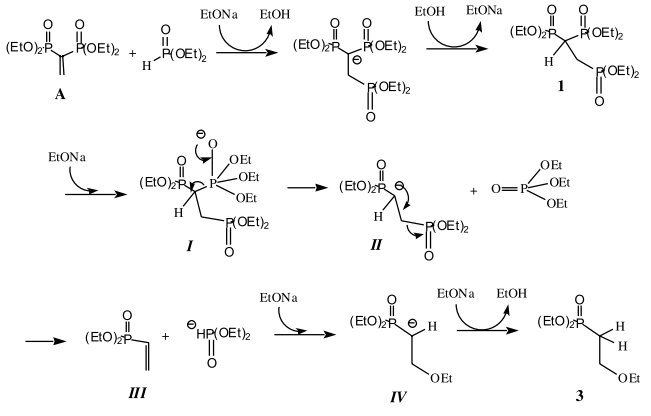
either from the existence of an equilibrated reaction or from the fragility of the products that can lead to the reverse Michael addition (elimination reaction).[15]

In this paper, we report the conjugate addition of nucleophilic phosphorus across the carbon–carbon double bond of tetraethyl ethylidenediphosphonate **A**. The alkylation of the anionic intermediate, thus yielding a product that can not be decomposed by retro-Michael reaction, is also reported.

2. Results and discussion

The conditions, reported by Sturtz[10] for the addition of nucleophilic carbon on tetraethyl ethylidenediphosphonate **A** (protic conditions), were first tested for the addition of diethylphosphite as a nucleophilic phosphorus (Scheme 1). A stoichiometric amount of sodium ethoxide was first used yielding compound **1** in 82% yield after 15 min of reaction (Table 1, entry 1). The competitive nucleophilic addition of sodium ethoxide on ethylidenediphosphonate **A** was only observed at a trace level. Therefore, the use of a more hindered alkoxide was not needed. The use of a catalytic amount of sodium ethoxide (respectively, 10 and 30%—entries 2 and 3) yield also compound **1** in good yield indicating that the anionic intermediate, formed by the addition of the nucleophilic phosphorus, is protonated by ethanol. These catalytic conditions (10 to 30% of sodium ethoxide) were finally preferred compare to the use of a stoechiometric amount of sodium ethoxide. Indeed, a longer reaction time (more than 30 min) associated with the use of a stoechiometric amount of sodium ethoxide produce diethyl 2-ethoxyethylphosphonate **3** in high yield (recently, we observed a similar reaction pathway by the addition of other alcoolate). The mechanism proposed to explain the formation of this unwanted product is reported in Scheme 1.



Scheme 1.

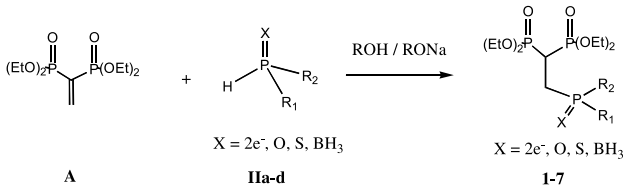
The nucleophilic addition of sodium ethoxide on compound **1** produce the intermediate ***I*** that loose triethylphosphate to generate the stabilised anionic intermediate ***II***. This part of the proposed mechanism was corroborated by the following experiences: 1—the addition of sodium ethoxide (1 equiv) on compound **1** produce compound **3** (conversion: 100%; yield: >90% according to ^{1}H NMR); 2—no reaction was observed between the sodium salt of diethylphosphite (in THF) and compound **1**; 3—the formation of triethylphosphate has been observed by ^{31}P NMR in the course of an experiment carried out in a NMR tube. The intermediate ***II*** eliminates the sodium salt of diethylphosphite to produce the vinylphosphonate ***III*** that reacts with sodium ethoxide to yield, after protonation of the intermediate ***IV***, compound **3**.

The conditions of reaction used for the addition of diethylphosphite on the tetraethyl ethylidenediphosphonate **A** were used for the addition of other phosphorus derivatives. The use of dimethylphosphite as a nucleophile in the presence of a stoechiometric amount of sodium ethoxide did not give the expected product but yield compound **1** due to a complete transesterification reaction (entry 4). By using sodium methoxide in methanol instead of ethoxide the addition of dimethylphosphite is observed (entry 5). The addition of ethylphenylphosphonite on compound **A** in similar conditions (entry 6) yields compounds **4** in good yield. Diethylthiophosphite (entry 7), which possess two potentially nucleophilic atoms (phosphorus and sulfur), adds to the vinylidene **A** by a phosphorus attack leading to the formation of the thiophosphonate **5**. Unfortunately, a thermal degradation of compound **5** was observed in the course of its purification by distillation. Nevertheless the purity of the crude product estimated by ^{1}H NMR is good (>90%). Finally, the methodology was applied to the addition of diphenylphosphine (entry 8) and its borane complex (entry 9). In both cases, the addition takes place thus producing molecules **6** and **7** that could be used as ligand for homogeneous or heterogenous catalysis. It worth noting, that the phosphinediphosphonate **6** is air sensitive, and during the workup its oxidation to a phosphine oxide is not fully avoided (30% of phosphine oxide is observed).

The purification of compound **1** has been successful by the elimination of the side product by distillation at a pressure of 10 mTorr at a temperature above 130 °C. Noteworthy a higher temperature (160 °C) at the same pressure leads to induce the retro-Michael reaction and the formation of small amount of tetraethyl ethylidenediphosphonate **A**. In order to get an accurate value of the temperature needed to induce the retro-Michael reaction, a DSC analysis of compound **1** from 20 to 300 °C has been recorded. An exothermic transition is observed between 180 to 240 °C followed by a sharp endothermic transition (240 to 265 °C).

The first transition, which is attributed to the retro-Michael reaction (molecular modelling calculation based on semi-empiric method PM3[16] indicates that the retro-Michael reaction is indeed exothermic), revels that compound **1** starts to be damaged at 180 °C under atmospheric pressure. This lack of stability could be a problem for the use of this tris-phosphonate molecule in the course of the synthesis of hybrid materials according to hydrothermal synthesis that usually use temperature included from 140 to 180 °C.[17] In order to increase the stability of compound **1a** towards the retro-Michael degradation the alkylation on carbon in α position of the two phosphonate functions has been investigated. The second interest to trap the anionic intermediate arises from the possibility to introduce another functional group by using either a functionalised electrophile or an electrophile that can be subsequently

Table 1. Michael addition of nucleophilic phosphorus on vinylidenediphosphonate **I**

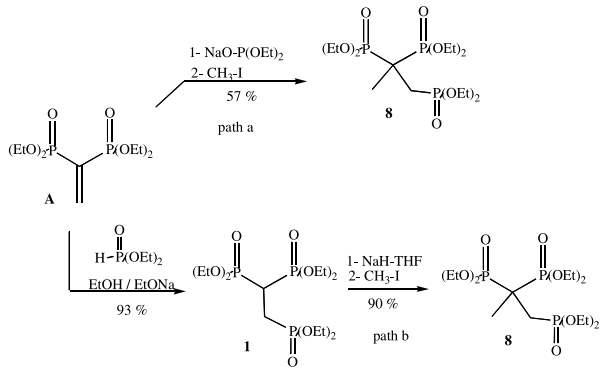


A **IIa-d** **1-7**

Entry	Nucleophile **II**		Base	Product	Yield %
1	**IIa**	$HPO(OEt)_2$	R=Et 1 equiv	**1**	82[a]
2	**IIa**	$HPO(OEt)_2$	R=Et 0.1 equiv	**1**	78[a]
3	**IIa**	$HPO(OEt)_2$	R=Et 0.3 equiv	**1**	93[a]
4[b]	**IIb**	$HPO(OMe)_2$	R=Et 1 equiv	**1**[b]	82[a]
5	**IIb**	$HPO(OMe)_2$	R=Me 0.3 equiv	**2**	89[a]
6	**IIc**	HPO(OEt)Ph	R=Et 0.3 equiv	**4**	67[a]
7	**IId**	$HPS(OEt)_2$	R=Et	**5**	75[c]
8	**IIe**	$HPPh_2$	R=Et	**6**	77[d]
9	**IIf**	$HPPh_2$–BH_3	R=Et	**7**	74[a]

[a] Isolated yields.
[b] Dimethylphosphite was used but transesterification takes place yielding compound **1**.
[c] Crude product.
[d] Presence of 30% of phosphine oxide.

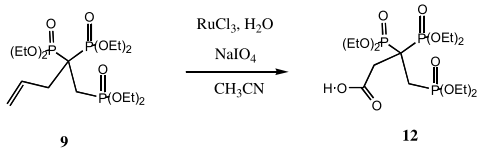
functionalised. Two strategies has been tested to introduce a methyl fragment on the carbon bearing the two phosphonate functions (Scheme 2): The one pot procedure, that starts from the ethylidenediphosphonate **A** in aprotic solvent (path a, Scheme 2), produces the expected product **8** in modest yield. Indeed, the presence of small amount of un-alkylated molecules in the crude product has reduced the yield due to difficulties in the purification step. The two steps process (path b, Scheme 2), which consists to deprotonate the tri-phosphonate **1** by NaH followed by the addition of methyl iodide, was finally more efficient. It is worth noting that, despite steric hindrance, the alkylation step is carried out in good yield (90%). The DSC analysis of compound **8** from 20 to 300 °C indicates a thermal stability up to 240 °C. The higher stability of this alkylated tris-phosphonate **8** will allow its use to synthesise hybrid materials by using the hydrothermal conditions.



Scheme 2.

The addition of other electrophiles on compound **1** was carried out according to the path b presented on Scheme 2. The results of these reactions are summarised in Table 2. The addition of alkyl halide was limited to methyl iodide. Indeed the addition of ethyl iodide produces the alkylated compound in poor yield (5% determined by ^{1}H NMR). This lack of reactivity could be explained by steric congestion around the nucleophilic carbon that induces the elimination reaction versus the substitution one. Therefore, only the addition of activated electrophiles, in which elimination reaction is not possible, were successful. Indeed, good yield are obtained in the course of the addition of allyl bromide (entry 2) propargyl bromide (entry 3) and with benzyl bromide (entry 4). On the other hand the use of more hindered electrophile like diethylchlorophosphate, ethyl bromoacetate or diethylcarbonate, were unsuccessful (<5% conversion determined by ^{1}H NMR).

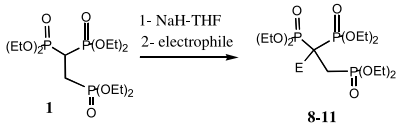
As the addition of ethyl bromoacetate on the anionic form of compound **1** was unsuccessful, compound **12** was finally obtained (87% yield) in two steps[18] from compound **9** (Scheme 3).



Scheme 3.

The synthesis of the phosphonic acid from the corresponding phosphonate has been realised on two compounds. First on the tris(diethylphosphonate) **1** which is converted to the corresponding tris-phosphonic acid **13** by refluxing into concentrated hydrochloric solution in quantitative yield without any sign of retro-Michael reaction. The phosphine-diphosphonate **6** is converted to the phosphine-diphosphonic **14** acid according to a softer method (Me_3SiBr followed by methanolysis).[19] The phosphine function is observed, by ^{31}P NMR in deuteriated water or deuteriated methanol, as a broad peak, respectively, at 7.67 and −3.21 ppm. Both the presence of such an unusual chemical shift for a diphenylalkylphosphine and the shape of the peak indicate the existence of a hydrogen bond or the presence of a zwitterion that could arise from a proton exchange from one phosphonic function to the phosphine one. It might be postulated that the exchange is certainly dynamic

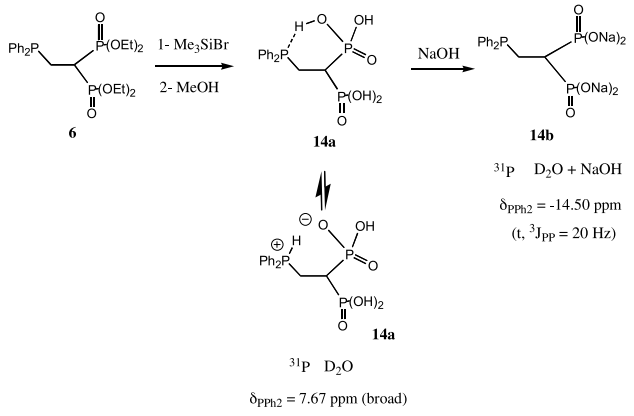
Table 2.



Entry	Electrophile	E	Product	Yield %[a]
1	MeI	Me	**8**	65
2	$H_2C{=}CH{-}CH_2{-}Br$	$H_2C{=}CH{-}CH_2$	**9**	71
3	$HC{\equiv}C{-}CH_2{-}Br$	$HC{\equiv}C{-}CH_2$	**10**	95
4	$Ph{-}CH_2{-}Br$	$Ph{-}CH_2$	**11**	66

[a] Isolated yield.

as only one signal is observed for the phosphonic acid function indicating the equivalence at the NMR time scale of the two phosphonic function (see Scheme 4). This hydrogen bond or this zwitterion is broken by the addition of sodium hydroxide in the NMR tube. Indeed, after its addition, the peak attributed to the phosphine function is sharp (as expected a triplet is observed) and the chemical shift is now observed at −14.50 ppm. The presence of the hydrogen bond or a zwitterions in water indicate that this bond might be present also at the solid state thus protecting the phosphine to its oxidation to a phosphine oxide function. This kind of unusual stability of phosphine toward oxidation has been also reported by Katti and co-workers.[20] This hydrogen bond or the existence of a zwitterion would explain the greater stability of compound **14** versus its analogous diphosphonate **6** towards oxidation.



Scheme 4.

3. Conclusion

The Michael addition of nucleophilic phosphorus on tetraethyl ethylidenediphosphonate **A** is reported. The reactions take place in protic solvent with a catalytic amount of sodium alkoxide. The Thermal stabilities of these Michael addition products are moderate. Therefore, their use to elaborate hybrid materials would be investigated with care. Nevertheless, the retro-Michael reaction was not observed when diphenylphosphine has been added to tetraethyl ethylidenediphosphonate **A** to produce compound **6**. This molecule will be use in due time for the design of hybrid materials. Furthermore, the phosphine-diphosphonic acid **14** obtained from the corresponding diphosphonate **6** is a good candidate to be use as a ligand in biphasic catalysis. In order to increase the thermal stability of the Michael addition product, the deprotonation of the tri-phosphonate **1** followed by its alkylation is reported. Furthermore the alkylation with activated halide (allyl, propargyl), offers molecules that could be use to introduce new functionalities into hybrid materials or on the surface of inorganic support.[21] These possibilities are currently under investigation.

4. Experimental

^1H, ^{13}C and ^{31}P NMR spectra (liquid-state) were recorded on a Bruker AC 250 or a Bruker Avance 400 spectrometer. Elemental analyses were recorded on a CE Instrument NA 2500. Mass spectrum were recorded on a QTOF Micro (waters), ionisation electrospray positive (ESI), lockspray PEG, infusion introduction (5 μL/min), source temperature 80 °C, desolvatation temperature 120 °C.

4.1. General procedure for the addition of dialkylphosphite on compound A

To absolute alcohol (ethanol or methanol) placed in a two necks round bottom flask fitted with a refluxed condenser bearing on its top a drying guard, sodium (0.3 equiv) is added. The solution is stirred at room temperature until all the sodium as reacted. A solution of diethylphosphite in alcohol (1 mL) is then added. After 5 min, a solution of tetraethyl vinylidenediphosphonate **A** (1 equiv) in alcohol (1 mL) is added. The solution is stirred for further 20 min at room temperature and then a saturated ammonium chloride solution (8 mL) is added. The aqueous–organic solution is partially evaporated in vacuo to remove alcohol and then water (8 mL) and dichloromethane (20 mL) are added. The aqueous phase is further extracted with dichloromethane (2×20 mL). The organic phases are assembled and dried over $MgSO_4$. The solution is filtrated and concentrated in vacuo to yield the crude product. The impurities are removed by Kugelrohr distillation (10 mTorr; up to 150 °C).

4.1.1. Hexaethyl ethan-1,1,2-tris(phosphonate) (1). Ethanol (20 mL); sodium (0.045 g, 6.66 mmol); diethylphosphite (0.92 g, 6.66 mmol), tetraethyl vinylidenediphosphonate A (2.0 g, 6.66 mmol); Pure compound **1** is isolated in 93% yield (2.71 g) after removing all the volatiles and impurities by distillation (10 mTorr −120 °C); ^1H NMR ($CDCl_3$): 1.30–1.36 (m, 18H, 6×CH_3–CH_2–O), 2.2–2.5 (m, 2H, CH_2–P), 2.7 (dtt, 1H, $^3J_{HH}$=5.5 Hz, $^2J_{HP}$=25 Hz, $^3J_{HP}$= 25 Hz, P–CH–P), 4.07–4.27 (m, 12H, 6×CH_3–CH_2–O);

^{13}C NMR ($CDCl_3$): 16.5 (d, $^3J_{CP}$=6 Hz, CH_3–CH_2–O), 22.6 (dt, $^1J_{CP}$=139 Hz, $^2J_{CP}$=5 Hz, CH), 31.1 (td, $^1J_{CP}$=134 Hz, $^2J_{CP}$=5 Hz, CH_2–P(O)(OEt_2)), 62.5 (d, $^2J_{CP}$=6.4 Hz, CH_2–O–P), 63–63.5 (~2d, $^2J_{CP}$=6.8 Hz, CH_2–O–P), ^{31}P NMR ($CDCl_3$): 23.45 (d, $^3J_{PP}$=27.3 Hz, P–CH–P), 29.22 (t, $^3J_{PP}$=27.3 Hz, P–CH_2); DSC (10 °C/min): 180–240 °C (exothermic transition); 240–265 (endothermic transition); IR (NaCl): 1253 (νP=O); 1050 and 968 (νP–O); *m/z*: 439 (M+·+1; 13%); 438 (M+·; 12%); 393 (100%); 365 (56%); 337 (44%); 302 (67%); 274 (70%); 245 (51%); 217 (23%); 189 (33%); 137 (15%); 109 (40%); HRMS (ES-TOF): calcd for $C_{14}H_{34}O_9P_3$ M+H 439.1416, found 439.1342.

4.1.2. Tetraethyl 2-(dimethoxyphosphonyl)ethan-1,1-bis(phosphonate) (2). Methanol (8 mL); sodium (10 mg; 0.13 mmol); tetraethyl vinylidenediphosphonate **A** (0.4 g; 1.33 mmol); dimethylphosphite (0.16 g; 1.46 mmol); pure compound **2** is isolated in 89% yield (0.48 g) after removing all the volatiles and impurities by distillation (10 mTorr −120 °C); ^{1}H NMR ($CDCl_3$): 1.35 (t, $^3J_{HH}$=7.1 Hz, 12H, CH_3–CH_2–O), 2.39 (m, 2H, CH_2–P), 2.81 (tq, 1H, $^3J_{HH}$=5.4 Hz, $^2J_{HP}$=$^3J_{HP}$=23 Hz, P–CH–P), 3.76 (d, $^3J_{HP}$=10.9 Hz, 6H, P–O–CH_3) 4.20 (m, 8H, CH_3–CH_2–O); ^{13}C NMR ($CDCl_3$): 15.33 and 15.35 (2d, $^3J_{CP}$=6.3 Hz, CH_3–CH_2–O), 19.41 (dt, $^1J_{CP}$=144.1 Hz, $^2J_{CP}$=5.1 Hz, CH), 29.83 (td, $^1J_{CP}$=134.4 Hz, $^2J_{CP}$=5.3 Hz, CH_2–P(O)), 51.70 (d, $^2J_{CP}$=6.5 Hz, P–O–CH_3), 61.88 and 62.18 (2d, $^2J_{CP}$=6.7 Hz, CH_2–O–P); ^{31}P NMR ($CDCl_3$): 23.31 (d, $^3J_{PP}$=27.4 Hz, P–CH–P), 32.04 (t, $^3J_{PP}$=27.4 Hz, P–CH_2); HRMS (ES-TOF): calcd for $C_{12}H_{30}O_9P_3Na$ M+Na 434.1000, found 434.0957.

4.1.3. Diethyl 2-ethoxyethylphosphonate (3). To 20 mL of absolute ethanol placed in a two necks round bottom flask fitted with a refluxed condenser bearing on its top a drying guard, 100 mg of sodium (1.3 equiv) are added. The solution is stirred at room temperature until all the sodium as reacted. A solution of 1 g of tetraethyl vinylidenediphosphonate **1** (3.33 mmol, 1 equiv) in ethanol (1 mL) is added. The solution is stirred for further 1 h at room temperature and then a saturated ammonium chloride solution (8 mL) is added. The aqueous–organic solution is partially evaporated in vacuum to remove ethanol and then water (8 mL) and dichloromethane (20 mL) are added. The aqueous phase is further extracted with dichloromethane (2×20 mL). The organic phases are assembled and dried over $MgSO_4$. The solution is filtrated and concentrated in vacuo to yield 680 mg of crude product (colorless oil). The product is purified by Kugelrohr distillation (10 mTorr; at 80 °C) offering compound **3** in 97% yield; ^{1}H NMR ($CDCl_3$): 1.2 (t, 3H, $^2J_{HH}$=7.0 Hz, CH_3–CH_2–O), 1.3 (t, 6H, $^2J_{HH}$=7.0 Hz, CH_3–CH_2–O–P), 2.1 (dt, 2H, $^3J_{HH}$=7.4 Hz, $^2J_{HP}$=18 Hz, CH_2–P), 3.5 (q, 2H, $^3J_{HH}$=7.0 Hz, CH_3–CH_2–O), 3.7 (dt, 2H, $^3J_{HH}$=7.5 Hz, $^3J_{HP}$=12.5 Hz, O–CH_2–CH_2–P), 4.1 (m, 4H, CH_3–CH_2–O–P); ^{13}C NMR ($CDCl_3$): 15.1 (s, CH_3), 16.4 (d, $^3J_{CP}$=6 Hz, CH_3–CH_2–O), 27.1 (d, $^1J_{CP}$=139 Hz, CH_2–P), 61.6 (d, $^2J_{CP}$=6.3 Hz, CH_2–O–P), 64.3 (s, CH_3–CH_2–O), 66.2 (s, CH_3–CH_2–O–P); ^{31}P NMR ($CDCl_3$): 29.72 (s, P); IR (NaCl): 1247 ($\nu_{P=O}$); 1163 ($\nu_{C\text{-}O}$).1027 and 962 ($\nu_{P\text{-}O}$); *m/z*: 211 (M^+·+1; 100%); 210 (M^+·; 2%); 181 (18%); 153 (15%); 125 (29%); 111 (22%); 81 (7%); HRMS (ES-TOF): calcd for $C_8H_{19}O_4PNa$ M+Na 233.0919, found 233.1044.

4.1.4. Tetraethyl 2-(ethoxyphenylphosphinyl)ethan-1,1-bis(phosphonate) (4). Ethanol (10 mL); sodium (12 mg, 0.16 mmol); tetraethylvinylidene diphosphonate (0.5 g; 1.66 mmol), ethyl phenylphosphonite (0.282 g; 1.66 mmol). Pure compound **4** is isolated in 67% yield (0.52 g) after removing all the volatiles and impurities by distillation (10 mTorr −120 °C); ^{1}H NMR ($CDCl_3$) 1.16–1.38 (m, 15H, O–CH_2–CH_3), 2.40–2.72 (m, 2H, CH_2–P), 2.75–3.13 (m, 1H, $CH(PO)_2$), 3.77–4.27 (m, 10H, O–CH_2), 7.43–7.60 (m, 3H, CH_{Ar}), 7.75–7.85 (m, 2H, CH_{Ar}); ^{13}C NMR ($CDCl_3$): 16.4–16.8 (m, CH_3), 25.48 (dt, $^2J_{CP}$=5.1 Hz, $^1J_{CP}$=100.1 Hz, CH_2–PO), 30.21 (dt, $^2J_{CP}$=4.0 Hz, $^1J_{CP}$=134.3 Hz, CH–$(PO)_2$), 61.23 (d, $^2J_{CP}$=6.3 Hz, CH_2–O–P), 62.85 (d, $^2J_{CP}$=6.7 Hz, CH_2–O–P), 63.16 (d, $^2J_{CP}$=6.7 Hz, CH_2–O–P), 63.34 (d, $^2J_{CP}$=6.4 Hz, CH_2–O–P), 63.37 (d, $^2J_{CP}$=6.4 Hz, CH_2–O–P), 128.81 (d, $^3J_{CP}$=12.8 Hz, C_{Ar}), 131.20 (d, $^3J_{CP}$=128.4 Hz, C_{Ar}), 131.99 (d, $^2J_{CP}$=10.0 Hz, C_{Ar}), 132.61 (d, $^4J_{CP}$=2.7 Hz, C_{Ar}); ^{31}P NMR ($CDCl_3$): 23.21 and 23.25 (2d, $^3J_{PP}$=21, 25 Hz, 2* $PO(OEt)_2$), 41.54 (dd, $^3J_{PP}$=21, $^3J_{PP}$=25 Hz, PO(OEt)Ph).

4.1.5. Tetraethyl 2-(diethoxythiophosphonyl)-ethan-1,1-bis(phosphonate) (5). THF (7 mL); sodium hydroxide (5 mg, 2 mmol); Tetraethylvinylidene diphosphonate (0.6 g; 2 mmol), diethylthiophosphonate (0.300 g; 2 mmol). Pure compound **5** is isolated in 75% yield (0.68 g) after removing all the volatiles and impurities by distillation (10 mTorr −120 °C); TLC (CH_2Cl_2/MeOH; 90/100) R_f=0.6; ^{1}H NMR ($CDCl_3$): 1.30–1.36 (m, 18H, 6×CH_3–CH_2–O), 2.54 (m, 2H, CH_2–P), 3.05 (m, 1H, P–CH–P), 4.15 (m, 12H, 6×CH_3–CH_2–O); ^{13}C NMR ($CDCl_3$): 16.4 (d, $^3J_{CP}$=7 Hz, CH_3–CH_2–O–P=S), 16.7 (d, $^3J_{CP}$=6 Hz, CH_3–CH_2–O–P=O), 29.0 (dt, $^1J_{CP}$=112 Hz, $^2J_{CP}$=5 Hz, CH_2–P(O)(OEt_2)), 32.1 (dt, $^1J_{CP}$=136 Hz, $^2J_{CP}$=4 Hz, CH), 62.6 (d, $^2J_{CP}$=6 Hz, CH_2–O–P), 63.8 (d, $^2J_{CP}$=7 Hz, CH_2–O–P=S); ^{31}P NMR ($CDCl_3$): 23.2 (d, $^3J_{PP}$=27.6 Hz, P–CH–P), 98.36 (t, $^3J_{PP}$=27.7 Hz, P=S); *m/z*: 477 (M+Na, 100), 455 (M^+·+1, 19%), 439 (19),369 (7), 323 (9), 301 (4), 204 (6); HRMS (ES-TOF): calcd for $C_{14}H_{33}NaO_9P_3S$ M+H 477.1007, found 477.0970.

4.1.6. Tetraethyl 2-(diphenylphosphinyl)-ethan-1,1-bis(phosphonate) (6). Diphenylphosphine (0.31 g, 1.66 mmol) is added to a solution of sodium ethoxide (2 mmol) in ethanol (solution prepared by the addition of 48 mg of sodium metal in 8 mL of ethanol) placed in a round bottom flask placed under argon. Tetraethylvinilydenediphosphonate **A** (0.5 g; 1.66 mmol) in degassed ethanol (1 mL) is added. The solution is stirred at room temperature for 25 min. After the addition of a concentrated solution of ammonium chloride, the solution was evaporated to dryness in vacuo. 8 mL of degassed water were added and the solution was extracted with dichloromethane (2×25 mL). The organic phase is dried on $MgSO_4$, filtered and concentrated to produce 740 mg of crude product. The impurities were eliminated by distillation (150 °C, 15 mTorr) to produce 590 mg of very viscous oil (yield: 74%). Compound isolated with 33% of phosphine oxide. ^{31}P NMR ($CDCl_3$): −12.64 (t, $^3J_{PP}$=18.2 Hz, PPh_2), 23.84 (d, $^3J_{PP}$=18.2 Hz, P–CH–P), phosphine oxide as impurity:

29.61 (t, $^3J_{PP}$=24 Hz, phosphine oxide), 23.44 (d, $^3J_{PP}$= 24 Hz, P–CH–P).

4.1.7. Tetraethyl 2-(diphenylphosphinylborane)-ethan-1,1-bis(phosphonate) (7). Ethanol (10 mL); sodium (5 mg, 1.66 mmol); Tetraethylvinylidene diphosphonate (0.5 g; 1.66 mmol), diphenylphosphineborane (0.373 g; 1.66 mmol). Pure compound **7** is isolated in 74% yield (0.61 g) after removing all the volatiles and impurities by distillation (10 mTorr −120 °C); ^{1}H NMR ($CDCl_3$): 1.19 and 1.24, 1.34 (t, J=7 Hz, 4×CH_3–CH_2–O), 2.95 (m, 2H, CH_2–P), 3.25 (m, 1H, P–CH–P), 4.15 (m, 4×CH_3–CH_2–O), 7.46 (m, 6H, H_{arom}), 7.77 (m, 4H, H_{arom}); ^{13}C NMR ($CDCl_3$): 16.6 (m, CH_3–CH_2–O–P), 25.0 (dt, $^1J_{CP}$=69 Hz, $^2J_{CP}$=5 Hz, CH_2–P(O)(OEt_2)), 31.5 (t, $^1J_{CP}$=136 Hz, CH), 62.9 (d, $^2J_{CP}$=6 Hz, CH_2–O–P), 63.6 (d, $^2J_{CP}$=7 Hz, CH_2–O–P–BH_3), 128.9 (d, $^2J_{CP}$=11 Hz, C_{ortho}), 131.2 (d, $^2J_{CP}$=9 Hz, C_{meta}), 132.0 (d, $^2J_{CP}$=3 Hz, C_{para}), 133.1 (d, $^2J_{CP}$= 145 Hz, C_{quat}); ^{31}P NMR ($CDCl_3$): 21.86 (s large, P–BH_3), 23.13 (d, $^3J_{PP}$=21.36 Hz, P–CH–P); *m/z*: 525 (M+Na+ 2H, 86.8%), 503 ($M^+\cdot$+3, 29.4%), 457 (9%), 439 (11%), 326 (16%), 325 (100%), 303 (16%); HRMS (ES-TOF): calcd for $C_{22}H_{38}BNaO_9P_3$ M+Na+2H 525.1872, found 525.1271.

4.2. Alkylation of hexaethyl ethan-1,1,2-tris(phosphonate) 1

Method a—one pot synthesis Under argon atmosphere, 10 mL of freshly distilled THF are placed in a dry 50 mL round bottom flask fitted with a reflux condenser. Diethylphosphite (1.1 equiv) and sodium (3 equiv) are added. After 9 h at room temperature, the excess of sodium is removed from the round bottom flask. Ethan-1,1,2-tris(phosphonate) **1** (1 equiv) and THF (1 mL) are added. The solution is stirred at 20 °C for 30 min before the addition of the electrophile (1.3 equiv) and THF (1 mL). The solution is stirred for further 30 min and then hydrolysed by the addition of water (3 mL). The solvents are partially removed in vacuo. The residue (a water solution) is extracted with dichloromethane (3×10 mL). The organic phase is dried on $MgSO_4$, filtered and concentrated in vacuo. The impurities are removed by Kugelrohr distillation.

Method b—from hexaethyl ethan-1,1,2-tris(phosphonate) **1**. THF is added to sodium hydride (60% in oil; 1.4 equiv) placed under azote and previously washed with pentane (2 mL). The solution is cooled by an ice bath. A solution of compound **1** (1 equiv) in THF (4 mL) is added dropwise. The solution is stirred at room temperature for 30 min. The electrophile is added. The solution is stirred at room temperature for 16 h. The solution is evaporated to dryness in vacuo and a concentrated aqueous solution of ammonium chloride is added (10 mL). The solution is extracted with dichloromethane. The organic phase is dried over $MgSO_4$, filtered, concentrated and purified by Kugelrohr distillation or by chromatography on silica gel.

4.2.1. Hexaethyl propan-1,2,2-tris(phosphonate) (8). *Method a*. Diethylphosphite (0.51 g; 3.66 mmol); sodium (0.23 g; 9.99 mmol); hexaethyl ethan-1,1,2-tris(phosphonate) **1** (1.00 g ; 3.33 mmol); methyl iodide (0.165 g). The impurities are removed by Kugelrohr distillation (12 mTorr; 135 °C). The undistilled product (1.04 g; 69%) is formed by compounds **8** and **1** in the ratio 90/10.

Method b. THF (8 mL); sodium hydride (60% in oil; 51 mg; 1.27 mmol); hexaethyl ethan-1,1,2-tris(phosphonate) **1** (0.4 g, 0.91 mmol); methyl iodide (0.30 g; 3.24 mmol). Purification by Kugelrohr distillation (159 °C −10 mTorr); colorless oil; yield 65% (0.27 g); ^{1}H NMR ($CDCl_3$): 1.32–1.37 (m, 18H, 6×CH_3–CH_2–O), 1.72 (t, 3H, $^3J_{HP}$= 16.4 Hz, CH_3–C), 2.39–2.45 (m,2H, C–CH_2–P), 4.05–4.26 (m, 12H, 6×CH_3–CH_2–O); ^{13}C NMR ($CDCl_3$): 16.23 (s broad, CH_3), 16.49 (s broad, O–CH_2–CH_3), 28.19 (dm, $^1J_{CP}$=138.6 Hz, CH_2–P), 38.81 (m, CH_3–C), 61.75 (d, $^2J_{CP}$=6.3 Hz, O–CH_2), 63.03 at 63.03 (2 m, O–CH_2); ^{31}P NMR ($CDCl_3$): 26.28 (d, sys AB, $^3J_{PP}$=45 Hz, C–PO), 26.36 (d, syst AB, $^3J_{PP}$=31 Hz, C–PO), 27.368 (sys AA′B, P_A and $P_{A'}$ $^3J_{PP}$=33.8 Hz, $^3J_{PP}$=44 Hz, CH_2–PO); *m/z* (intensity %): 453 (M+1, 2%), 407(11%), 379 (8%), 315 (100%), 288 (18%), 259 (11%), 231 (6%); HRMS (ES-TOF): calcd for $C_{15}H_{36}O_9P_3$ M+H 453.1572, found 453.1586; DSC (10 °C/min): 240 °C −270 (exothermic transition), 285 (endothermic transition).

4.2.2. Hexaethyl pent-4-en-1,2,2-tris(phosphonate) (9). Method b, THF (15 mL); hexaethyl ethan-1,1,2-tris(phosphonate) **1** (2.0 g; 4.56 mmol); allyl bromide (1.65 g; 13.68 mmol). The impurities are removed by Kugelrohr distillation (10 mTorr; 160 °C). The crude product was purified by flash chromatography. (Eluent dichloromethane/methanol (85/15), R_f=0.5) to afford compound **9**, colorless oil; Yield=71% (1.54 g). ^{1}H NMR ($CDCl_3$): 1.29–1.36 (m, 18H, CH_3), 2.38 (m, 2H, CH_2–P), 2.98 (ddd, 2H, $^3J_{HH}$= 2.7 Hz, $^3J_{HP}$=14 Hz, CH_2–C=CH), 4.09 (m, 4H, CH_3–CH_2–O–P), 4.19 (m, 4H, CH_3–CH_2–O–P), 5.12 (dd, 1H, $^2J_{HH}$=.0.8 Hz, $^3J_{HH}$=6.4 Hz, CH=CHH_{cis}), 5.28 (dd, 1H, $^2J_{HH}$=.0.8 Hz, $^3J_{HH}$=10.5 Hz, CH=CHH_{cis}), 5.99 (m, 1H, CH_2=CH); ^{13}C NMR ($CDCl_3$): 16.31–16.48 (m, CH_3), 25.55 (dd, $^1J_{CP}$=149 Hz, $^1J_{CC}$=38 Hz, CH_2–P), 34.28 (m, CH_2CH=CH_2), 43.74 (dt, $^2J_{CP}$=3.2 Hz, $^1J_{CP}$= 130 Hz, P–C–P), 61.75 (d, 2C, $^2J_{CP}$=6.5 Hz, CH_3–CH_2–O–P), 62.82–63.21 (m, 4C, CH_3–CH_2–O–P), 118.85 (s, CH=CH_2), 133.22 (t, $^3J_{CP}$=8 Hz, CH=CH_2); ^{31}P NMR ($CDCl_3$): 23.45 (d, $^3J_{PP}$=46.8 Hz, C–PO), 23.46 (d, 2P, $^3J_{PP}$=43.5 Hz, C–PO), 26.22 (dd, $^3J_{PP}$=43.5 Hz, $^3J_{PP}$=46.8 Hz, P–CH_2); IR: 3078 ($\nu_{C\text{-}HC=C}$), 1638 ($\nu_{C=C}$), 1248 ($\nu_{P=O}$), 1050 and 966 (ν_{P-O}); *m/z*: 479 ($M^+\cdot$+1; 59%); 478 ($M^+\cdot$; 4%); 433 (15%); 405 (11%); 342 (86%); 341 (100%); 314 (17%); 285 (8%); HRMS (ES-TOF): calcd for $C_{17}H_{37}O_9NaP_3$ M+Na 501.1514, found 501.1519.

4.2.3. Hexaethyl pent-4-yn-1,2,2-tris(phosphonate) (10). Method b, THF (15 mL); hexaethyl ethan-1,1,2-tris(phosphonate) **1** (5.9 g; 13.5 mmol); propargyl bromide (6.02 g; 40.5 mmol). The impurities are removed by Kugelrohr distillation (10 mTorr; 160 °C). The crude product was purified by flash chromatography. (Eluent dichloromethane/methanol (85/15), R_f=0.6) to afford compound **10**; colorless oil; Yield=95% (6.12 g). ^{1}H NMR ($CDCl_3$): 1.31 (t, 6H, $^3J_{HH}$=7 Hz, CH_3), 1.33 (t, 12H, $^3J_{HH}$=7 Hz, CH_3), 2.10 (t, 1H, $^4J_{HH}$=2.7 Hz, CC–H), 2.44–2.63 (m, 2H, CH_2–P), 3.17 (dt, 2H, $^3J_{HH}$=2.7 Hz, $^3J_{HP}$=14 Hz, CH_2–CC), 4.06–4.26 (m, 12H, CH_3–CH_2–O–P); NMR ^{13}C ($CDCl_3$):

15.00–15.5 (m, CH_3), 19.80–20.01 (m, CH_2–CC), 25.55 (d, $^1J_{CP}$=140 Hz, CH_2–P), 41.60 (dt, $^2J_{CP}$=2.2 Hz, $^1J_{CP}$=133 Hz, P–C–P), 60.93 (d, 2C, $^2J_{CP}$=6.5 Hz, CH_3–CH_2–O–P), 62.17–62.56 (m, 4C, CH_3–CH_2–O–P), 71.0 (s, CC–H), 78.24 (t, $^3J_{CP}$=11.4 Hz, CC–H); ^{31}P NMR ($CDCl_3$): 23.45 (d, $^3J_{PP}$=46.8 Hz, C–PO), 23.46 (d, 2P, $^3J_{PP}$=40.5 Hz, C–PO), 26.22 (dd, $^3J_{PP}$=40.5 Hz, $^3J_{PP}$=46.8 Hz, P–CH_2); IR (NaCl): 3220 ($\nu_{C\text{-}HCC}$), 2114 (ν_{CC}), 1251 ($\nu_{P=O}$), 1035 and 963 ($\nu_{P\text{–}O}$); *m/z*: 477 ($M^+\cdot$+1; 79%); 476 ($M^+\cdot$; 1%); 340 (100%); 301 (51%); 273 (18%); 147 (10%); HRMS (ES-TOF): calcd for $C_{17}H_{35}O_9NaP_3$ M+Na 499.1392, found 499.1315.

4.2.4. Hexaethyl prop-3-phenyl-1,2,2-tris(phosphonate) (11). *Method b*. THF (15 mL); hexaethyl ethan-1,1,2-tris(phosphonate) **1** (0.5 g; 1.14 mmol); benzyl bromide (0.58 g; 3.42 mmol). The impurities are removed by Kugelrohr distillation (10 mTorr; 160 °C). The crude product was purified by flash chromatography. (Eluent dichloromethane/methanol (90/10), R_f=0.5) to afford compound **11**; colorless oil; yield=66% (0.40 g). NMR ^{1}H ($CDCl_3$): 1.19 (t, $^3J_{HH}$=7.5 Hz, 6H, CH_3), 1.26 (t, $^3J_{HH}$=7.5 Hz, 6H, CH_3), 1.36 (t, $^3J_{HH}$=7.5 Hz, 6H, CH_3), 2.41 (m, 2H, CH_2P), 3.56 (dd, $^3J_{HP}$=11.5 Hz, $^3J_{HP}$=16.8 Hz, 2H, P–CH_2–Ph), 4.05–4.26 (m, 12H, CH_2–O–P), 7.25 (m, 3H_{arom}), 7.60 (dd, J_{HH}=1.8 Hz, J_{HH}=8.1 Hz); NMR ^{13}C ($CDCl_3$): 16.6–16.8 (m, 6C, CH_3), 27.38 (dd, $^2J_{CP}$=2.2 Hz, $^1J_{CP}$=143 Hz, CH_2P), 33.43 (s, C–Ph), 46.4 (t, $^1J_{CP}$=130 Hz, P-C-P), 62.85 (d, 2C, $^2J_{CP}$=6.9 Hz, CH_3–CH_2–O–P), 63.8 (m, 4C, CH_3–CH_2–O–P), 126.9 (s, 1C, C_{arom}*trans*), 127.93 (s, 2C, C_{arom}), 132.1 (s, 2C, C_{arom}), 137.4 (s, 1C, $C_{quatarom}$); ^{31}P NMR ($CDCl_3$): 23.9 (d, $^2J_{PP}$=49 Hz, C-PO), 23.9 (d, $^2J_{PP}$=42 Hz, C-PO), 26.8 (dd, $^3J_{PP}$=42 Hz, $^3J_{PP}$=49 Hz, P-CH_2); *m/z*: 529 ($M+\cdot$+1; 5%); 528 ($M+\cdot$; 2); 454 (12); 391 (100); 363 (10); 317 (38); 289 (15); 261 (28); IR (NaCl): 1237 ($\nu_{P=O}$), 1016 and 952 ($\nu_{P\text{–}O}$), 665 and 704 (ν_{arom}); *m/z*: 529 ($M+\cdot$+1; 5%); 528 ($M+\cdot$; 2%); 454 (12%); 391 (100%); 363 (10%); 317 (38%); 289 (15%); 261 (28%); HRMS (ES-TOF): calcd for $C_{21}H_{39}O_9NaP_3$ M+Na 551.1705, found 551.1633.

4.3. Catalytic oxidation of compound 10

4.3.1. 3,3,4-Tris(diethylphosphonyl) butanoic acid (12). A two necked round bottom flask equipped with a condenser is charged with a magnetic stirrer, 4 mL of carbon tetrachloride, 4 mL of acetonitrile, 6 mL of water, 1.18 g of compound **10** (2.5 mmol, 1 equiv) and 2.70 g of sodium metaperiodate (10.1 mmol, 4.1 equiv). To this biphasic solution 20 mg (2.2 mol%) of ruthenium trichloride hydrate was added and the mixture was stirred vigorously for 2 h at room temperature. After the addition of CH_2Cl_2 (20 mL), the phases were separated. The aqueous layer was extracted further with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was diluted with 50 mL of diethylether, filtered through a Celite pad and concentrated. The crude product was purified by flash chromatography. (Eluent ethanol/methanol (85/15), R_f=0.5) to afford 1.08 g of compound **12** as a yellow oil (87%). ^{1}H NMR ($CDCl_3$): 1.30–1.38 (m, 18H, H_1 and H_8), 2.65–2.78 (m, 2H, H_4), 3.24 (dt, $^3J_{HH}$=2.2 Hz, $^3J_{HP}$=14.9 Hz, 2H, H_9), 4.09–4.20 (m, 4H, H_2), 4.23–4.29 (m, 8H, H_7); ^{13}C NMR ($CDCl_3$): 16.23–16.42 (m, C_1 and C_8), 25.13 (dd, $^1J_{CP}$=141.5 Hz, $^2J_{CP}$=5.8 Hz, C_4), 40.79 (dd, $^2J_{CP}$=3.2 Hz, $^1J_{CP}$=129.8 Hz, C_5), 61.80–62.76 (m, C_2), 63.43–64.01 (m, C_7), 49.32 (s, C_9), 170.53 (t, $^3J_{CP}$=11. Hz, C_{10}); ^{31}P NMR ($CDCl_3$): 22.34 (d, $^2J_{PP}$=42.7 Hz, C–PO), 28.14 (t, $^3J_{PP}$=42.8 Hz, P–CH_2); IR (NaCl): 3449 ($\nu_{O\text{-}H}$), 2114 (ν_{CC}), 1728 ($\nu_{C=O}$), 1249 ($\nu_{P=O}$), 1028 and 969 ($\nu_{P\text{–}O}$); *m/z*: 519($M+\cdot$+Na; 100), 497 (M+H, 21); 496 (M+, 2), 461 (52), 451 (15), 393 (13), 325 (21), 303 (5), 204 (11); HRMS (ES-TOF): calcd for $C_{16}H_{35}O_{11}NaP_3$ M+Na 519.1290, found 519.1272.

4.4. Hydrolysis of phosphonate to phosphonic acid

4.4.1. Ethan-1,1,2-tris(phosphonic acid) (13). Concentrated HCl (60 mL, 37% in water) is added to 2.12 g (4.84 mmol) of hexaethyl ethan-1,1,2-tris(phosphonate) **1**. The solution is refluxed for 2 h 30 min. The excess of HCl and water are removed in vacuo to produce a very viscous oil (1.35 g; 100%+traces of water); ^{1}H NMR (D_2O): 2.02 (dq, $^3J_{HH}$=6.24 Hz; $^2J_{HP}$=$^3J_{HP}$=16.7 Hz; 2H, CH_2–P), 2.35 (m, 1H, P–CH–P); ^{13}C NMR (D_2O): 22.71 (dt, $^1J_{CP}$=133.0 Hz, $^2J_{CP}$=3.9 Hz, CH_2–P), 32.78 (dt, $^1J_{CP}$=126.2, $^2J_{CP}$=3.9 Hz, P–CH–P); ^{31}P NMR (D_2O): 20.14 (d, $^3J_{PP}$=31 Hz, P–CH_2), 25.98 (t, $^3J_{PP}$=31 Hz, P–CH–P); NMR ^{31}P (D_2O+NaOH): 22.96 (d, $^3J_{PP}$=21.7 Hz, P–CH_2), 24.34 (t, $^3J_{PP}$=21.7 Hz, P–CH–P).

4.4.2. Tetraethyl 2-(diphenylphosphinyl)-ethan-1,1-bis(phosphonate) (14). Tetraethyl 2-(diphenylphosphinyl)-ethan-1,1-bis(phosphonate) **6** (0.59 g, pure as 66%) was dissolved under argon in dichloromethane (5 mL). Bromotrimethylsilane (1.5 mL) is added and the solution was stirred at 20 °C for 15 h. The volatiles were removed in vacuo to produce a viscous oil. 8 mL of methanol were added. The solution was stirred at room temperature for 3 h 30 min and evaporated to dryness to produce a white solid (530 mg) of compound **14** (66%) accompanied with the phosphine oxide derivative (33%). ^{1}H NMR (D_2O): 1.70 (m, 1H, CH), 2.46 (m, 2H, CH_2), 7.2–7.6 (m; 10H, H_{Ar}), 33% of phosphine oxide: 2.08 (m, 1H, CH), 2.89 (m, 2H, CH_2), 7.0–7.4 (m; 10H, H_{Ar}); ^{31}P NMR (D_2O): 7.67 (m broad, PPh_2), 19.43 (d, $^3J_{PP}$=20 Hz, P–CH–P), (phosphine oxide impurity (33%): 17.35 (d, $^3J_{PP}$=23 Hz, P–CH–P), 41.41 (t, $^3J_{PP}$=23 Hz, phosphine oxide); ^{31}P NMR (D_2O+NaOH): −14.5 (t, $^3J_{PP}$=20 Hz, PPh_2), 22.98 (d, $^3J_{PP}$=20 Hz, P–CH–P) (phosphine oxide impurity (33%)): 21.62 (d, $^3J_{PP}$=24 Hz, P–CH–P), 45.39 (t, $^3J_{PP}$=24 Hz, phosphine oxide); NMR ^{31}P (CD_3OD): −3.21 (m broad, PPh_2), 19.88 (d, $^3J_{PP}$=22.1 Hz, P–CH–P) (phosphine oxide impurity (33%)): 19.02 (d, $^3J_{PP}$=25.6 Hz, P–CH–P), 40.33 (t, $^3J_{PP}$=25.6 Hz, phosphine oxide)).

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New pyrano[3,4-*b*]indoles from 2-hydroxymethylindole and L-dehydroascorbic acid

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Abstract—2-Hydroxymethylindole reacts with L-dehydroascorbic acid under mild conditions to give (3*R*,3a*R*,10c*S*)-3-[(1*S*)-1,2-dihydroxyethyl]-3a,10c-dihydroxy-3a,5,6,10c-tetrahydrofuro[3′,4′:5,6]pyrano[3,4-*b*]indol-1(3*H*)-one. Its tosyl derivative undergoes cyclization to form a pentacyclic ketal derivative.

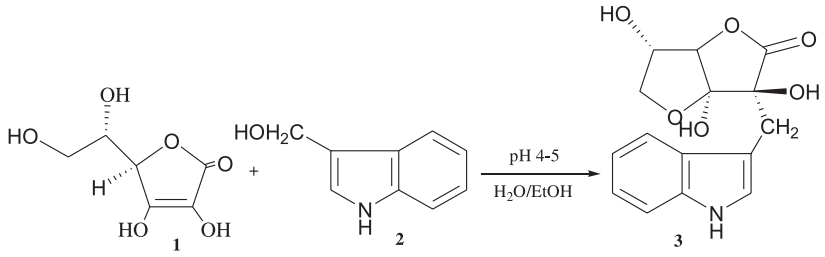
1. Introduction

L-Ascorbic acid easily undergoes 2-C-alkylation by 3-hydroxymethylindole, 4-hydroxybenzyl alcohol, and their analogues, which are able to produce quinone methide type structures under mild acidic conditions.[1,2] Ascorbigen, which is 2-C-[(indol-3-yl)methyl]-α-L-*xylo*-hex-3-ulofuranosono-4-lactone **3** is a product of the reaction of L-ascorbic acid **1** with the intermediate quinone methide formed from 3-hydroxymethylindole **2**.[2] Ascorbigen **3** is the main decomposition product of alkaloid glucobrassicin from cruciferous vegetables, and animals and humans receive it with meals. Recently, it was found that it is a strong non-specific immunomodulator with valuable properties (Scheme 1).[3]

Several ascorbigens have been synthesized in our laboratory and their unique chemical and biological properties have been investigated,[3] but the reaction of isomeric 2-hydroxymethylindole with L-ascorbic acid poses synthetic challenges and would help us to further elucidate the synthetic potential of this unique compound and its derivatives. The goal of our work was to study the preparation of a compound isomeric to ascorbigen by the reaction of 2-hydroxymethylindole **4** with L-ascorbic acid **1**.

2. Results and discussion

Unfortunately, 2-hydroxymethylindole **4a** does not react with **1** with the formation of an ascorbigen-like structure (**5**) at pH 1–6. It can be explained by the inability of **4a** to form a quinone methide structure under these conditions. However, on incubation of the reaction mixture (**1**+**4a** in



Scheme 1.

Keywords: L-Ascorbic acid; L-Dehydroascorbic acid; Ascorbigen; Indolopyrane; 2-Hydroxymethylindole.
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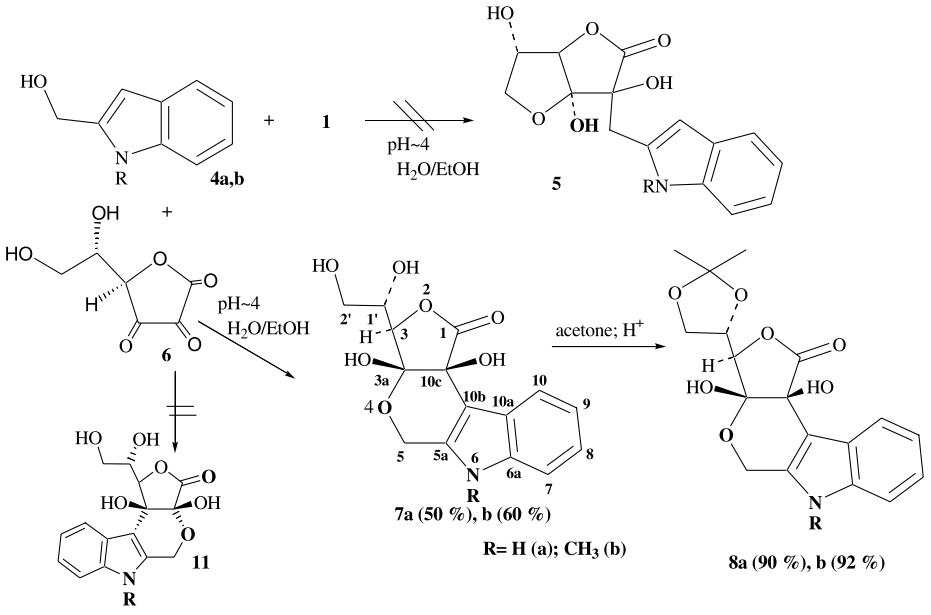
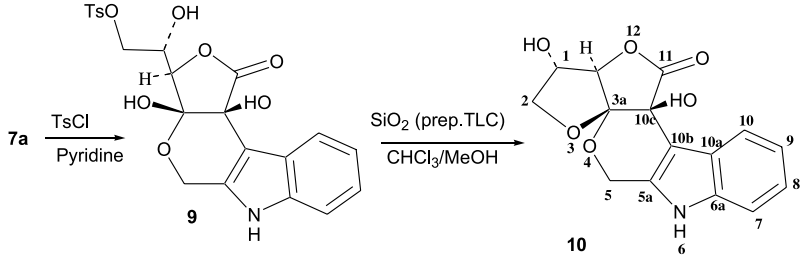


Scheme 2.



Scheme 3.

H_2O–MeOH mixture at pH ~ 4.7) for more than two weeks, we succeeded in the isolation of a new product in 20% yield. It was identified as (3*R*,3a*R*,10c*S*)-3-[(1*S*)-1,2-dihydroxyethyl]-3a,10c-dihydroxy-3a,5,6,10c-tetrahydrofuro[3′,4′:5,6]pyrano[3,4-*b*]indol-1(3*H*)-one **7a** (Scheme 2).

It is suggested that **7a** is a product of the reaction of L-dehydroascorbic acid **6** with **4a**. When L-ascorbic acid was oxidized to L-dehydroascorbic acid by the action of oxygen in the presence of activated charcoal in H_2O–MeOH[4] before addition of **4a**, the yield of compound **7a** increased to 50% and the reaction time was reduced to seven days. Similarly, compound **7b** was obtained in 60% yield from 1-methyl-2-hydroxymethyindole **4b** and L-dehydroascobic acid **6**. It suggests that the nucleophilic attack of 3-C indole atom on carbonyl group at 2-C of dehydroascorbic acid takes place followed by hemiacetal formation with the participation of 3-CO of dehydroascorbic acid and hydroxy group of **4**. The reaction of **7a** or **7b** with acetone in the presence of *p*-toluenesulfonic acid gave crystalline 1′,2′-*O*-isopropylidene derivatives **8a** or **8b**, respectively. By the reaction of **7a** with an excess of *p*-toluenesulfonyl chloride in pyridine 2′-*O*-monotosyl derivative **9** was obtained. On purification by preparative TLC, **9** partially underwent cyclization into acetal **10** (Scheme 3).

The stereochemistry of compounds **7a**,**b** was suggested by NOE experiments and appears to be in accord with the previously observed dominant mode of alkylation in such systems.[1,3,5] An isomeric structure with a different type of annelation of the pyranoindole and furanone rings than in compound **7** could be proposed for the product of reaction of **4** with **6**. A double resonance experiment allowed the identification in the ^{1}H NMR spectrum of **8a** of the signal of the OH-group (10c-OH), which is nearest to the carbonyl group. In the ^{1}H coupled ^{13}C NMR spectrum of compound **8a** a coupling constant $^3J_{1C,10c\text{-}OH} \approx 4$ Hz was observed. The NOE for this 10c-O*H* proton was determined ($\eta_{10c\text{-}OH}\{10\text{-}H\} \approx 3.5\%$) by saturation of 10-H. An analogous effect was observed in the reverse experiment ($\eta_{10\text{-}H}\{10c\text{-}OH\}$) in accordance with structure **7** and **8**.

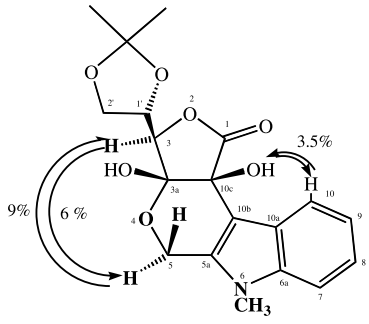


Figure 1. NOE experiments for **8b**.

The reciprocal orientation of two hydroxyl groups (10c-OH and 3a-OH) was elucidated based on rather high NOE values $\eta_{3\text{-H}}\{5\text{-Ha}\}\approx 9\%$ and $\eta_{5\text{-Ha}}\{3\text{-H}\}\approx 6\%$), in compound **8b** 5-Ha is the highfield doublet of AB system 5-H_2 (Fig. 1). Molecular modeling of compounds **7** and **8** led to a conclusion, that the distance between atoms 5-Ha and 3-H may be <2 Å only in the structure in, which the two hydroxyl groups in the tetrahydrofuranone cycle are *cis*-oriented.

The *S*-configuration at 10c atom follows from analysis of relevant literature, as there are no examples of attack on the 2C atom of L-ascorbic acid from the side *cis* to the bulky substituent at C-4 (CHOH–CH_2OH).[3]

The compounds obtained have a structural fragment of 1,3,4,9-tetrahydropyrano[3,4-*b*]indole, which represents a framework of some anti-inflammatory drugs such as etodolac.[6]

3. Experimental

3.1. General

NMR spectra were recorded on a Varian Unity +400 instrument (400 MHz for ^{1}H, 100.6 MHz for ^{13}C). NOE values ($\eta_{\text{Hi}}\{\text{H}_j, \%\}$) were measured as an increase of H_i signal intensity when H_j signal was saturated. Analytical TLC was performed on Kieselgel F_{254} plates (Merck), preparative TLC chromatography on plates (20×20 cm, 0.5 mm) with Kieselgel 60 F_{254} (Merck), and column chromatography on Kieselgel 60 (Merck), using the following systems of solvents: $CHCl_3$/MeOH 5:1 (A); 10:1 (B) and EtOAc/petroleum ester, 1:1 (C). Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Infrared spectra were recorded with a Nicolet Avatar 330 FT-IR spectrometer using KBr discs.

High resolution mass spectra were registered on a MAT 8430 Finnigan instrument (USA) with data operating system SS-300 (EI, 70 eV, direct introduction, temperature of ion source 250 °C). Electron impact (EI) mass-spectra were registered on a SSQ 710 Finnigan MAT instrument (USA), (EI: 70 eV, direct introduction). Melting points were determined on a Buchi SMP-20 apparatus and are uncorrected.

3.1.1. (3*R*,3a*R*,10c*S*)-3-[(1*S*)-1,2-Dihydroxyethyl]-3a,10c-dihydroxy-3a,5,6,10c-tetrahydrofuro[3′,4′:5,6]-pyrano[3,4-*b*]indol-1(3*H*)-one (7a). To a solution of **4a** (1.2 g, 7.36 mmol) in CH_3OH (10 mL) was added buffer solution prepared by dissolving of 2.7 g of citric acid and 6 g of Na_2HPO_4 in 300 mL of H_2O and solution of L-dehydroascorbic acid (**6**), obtained from **1** (6.5 g, 36.8 mmol) in 100 mL of CH_3OH. The reaction mixture was stirred for seven days at rt, saturated with NaCl, extracted with $CHCl_3$ (1×50 mL) and then with EtOAc (3×40 mL). EtOAc extract was dried (Na_2SO_4), evaporated and after column chromatography (A) gave **7a** (1.2 g, 50%) as a light-brown powder (as minimum 96% purity by NMR data); R_f 0.26 (A); $[\alpha]_D^{20}$ +4 (MeOH); ν_{max}: 3266, 1767, 1455, 1104, 741 cm^{-1}; HRMS Calcd for $C_{15}H_{15}NO_7$: 321.0849. Found: 321.0830; ^{1}H NMR: δ (DMSO-d_6) 3.54 (m, 2H, 2′-H_AH_B); 3.91 (m, 1H, 1′-H); 4.52 (d, J=3.8 Hz, 1H, 3-H); 4.82 (d, J=15.4 Hz, 1H, 5-H_B); 4.90 (br s, 1H, 2′-OH); 4.96 (d, J=15.4 Hz, 1H, 5-H_A); 5.97 (br s, 1H, 1′-OH); 6.50 (br s, 1H, 10-OH); 7.01 (ddd, J=7.8, 7.0, 1.0 Hz, 1H, 9-H); 7.08 (ddd, J=8.1, 7.0, 1.2 Hz, 1H, 8-H); 7.19 (br s, 1H, 3a-OH); 7.35 (ddd, J=8.1, 1.0, 0.7 Hz, 1H, 7-H); 7.73 (ddd, J=7.8, 1.2, 0.7 Hz, 1H, 10-H); 11.14 (s, 1H, 6-H); ^{13}C NMR: δ (DMSO-d_6) 58.0 (5-C); 61.5 (2′-C); 68.8 (1′-C); 70.9 (10c-C); 81.2 (3-C); 99.4 (3a-C); 104.1 (10b-C); 111.4 (7-C); 119.2 (9-C); 120.6 (10-C); 121.4 (8-C); 125.8 (10a-C); 134.3 (5a-C); 136.5 (6a-C); 174.3 (1-C).

3.1.2. (3*R*,3a*R*,10c*S*)-3-[(1*S*)-1,2-Dihydroxyethyl]-3a,10c-dihydroxy-6-methyl-3a,5,6,10c-tetrahydrofuro[3′,4′:5,6]pyrano[3,4-*b*]indol-1(3*H*)-one (7b). Compound **7b** was obtained from **4b** (1 g, 6.25 mmol) and purified by the same way as **7a**, as a light-brown powder (1.25 g, 60%); R_f 0.44 (A); $[\alpha]_D^{20}$ +6.5 (MeOH); ν_{max}: 3368, 1786, 1455, 1031, 759 cm^{-1}; HRMS Calcd for $C_{16}H_{17}NO_7$: 335.1005. Found: 335.0998; ^{1}H NMR: δ (CD_3OD) 3.64 (s, 3H, 6-CH_3); 3.81 (m, 2H, 2′-H_AH_B); 4.08 (m, 1H, 1′-H); 4.63 (d, J=5.3 Hz, 1H, 3-H); 5.04 (d, J=15.6 Hz, 1H, 5-H_B); 5.13 (d, J=15.6 Hz, 1H, 5-H_A); 7.10 (ddd, J=7.9, 7.1, 1.0 Hz, 1H, 9-H); 7.19 (ddd, J=8.3, 7.1, 1.2 Hz, 1H, 8-H); 7.37 (ddd, J=8.3, 1.0, 0.7 Hz, 1H, 7-H); 7.88 (ddd, J=7.9, 1.2, 0.7 Hz, 1H, 10-H); ^{13}C NMR: δ (CD_3OD) 29.9 (N–CH_3); 59.8 (5-CH_2); 63.3 (2′-C); 70.9 (1′-C); 72.5 (10c-C); 81.2 (3-C); 100.9 (3a-C); 104.3 (10b-C); 110.1 (7-C); 121.0 (9-C); 121.6 (10-C); 123.0 (8-C); 126.7 (10a-C); 136.3 (5a-C); 139.8 (6a-C); 175.9 (1-C).

3.1.3. (3*R*,3a*R*,10c*S*)-3-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3a,10c-dihydroxy-3a,5,6,10c-tetrahydrofuro[3′,4′:5,6]pyrano[3,4-*b*]indol-1(3*H*)-one (8a). To a solution of **7a** (500 mg, 1.56 mmol) in dry acetone (10 mL) was added *p*-toluenesulfonic acid (10 mg). The reaction mixture was stirred for 40 min at rt, diluted with 100 mL of 10% $NaHCO_3$ solution, extracted with EtOAc (2×30 mL). After drying (Na_2SO_4) of the extract, evaporating, and recrystallization from acetone **8a** (500 mg, 90%) was obtained as colorless crystals. Mp 190–196 °C (decomp.); R_f 0.16 (C); $[\alpha]_D^{20}$ +6.7 (MeOH); ν_{max}: 3329, 1785, 1085, 1059, 753 cm^{-1}; HRMS Calcd for $C_{18}H_{19}NO_7$: 361.1161. Found: 361.1143; ^{1}H NMR: δ (DMSO-d_6) 1.29 and 1.33 (2 s, 2×3H, 1′,2′-OC(CH_3)$_2$); 3.90 (dd, J=8.9, 6.5 Hz, 1H, 2′-H_B,); 4.14 (dd, J=8.9, 6.3 Hz, 1H, 2′-H_A); 4.34 (m, 1H, 1′-H); 4.39 (dd, J=8.0, 1.0 Hz, 1H, 3-H); 4.96 (d, J=15.8 Hz, 1H, 5-H_B); 5.02 (d, J=15.8 Hz, 1H, 5-H_A); 6.44 (s, 1H, 10c-OH); 6.96 (d, J=1.0 Hz, 1H, 3a-OH); 7.02 (ddd, J=7.9, 7.2, 1.1 Hz, 1H, 9-H); 7.10 (ddd, J=8.1, 7.2, 1.3 Hz, 1H, 8-H); 7.36 (ddd, J=8.1, 1.1, 0.8 Hz, 1H, 7-H); 7.72 (ddd, J=7.9, 1.3, 0.8 Hz, 1H, 10-H); 11.26 (s, 1H, 6-H); ^{13}C NMR: δ (DMSO-d_6) 25.5 and 26.6 (1′,2′-OC(CH_3)$_2$); 59.6 (5-C); 65.1 (2′-C); 70.7 (10c-C); 74.7 (1′-C); 79.3 (3-C); 99.7 (3a-C); 104.0 (10b-C); 108.8 (1′,2′-O*C*(CH_3)$_2$); 111.5 (7-C); 119.4 (9-C); 120.2 (10-C); 121.8 (8-C); 125.4 (10a-C); 134.0 (5a-C); 136.8 (6a-C); 173.3 (1-C).

3.1.4. (3*R*,3a*R*,10c*S*)-3-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3a,10c-dihydroxy-6-methyl-3a,5,6,10c-tetrahydro-

furo[3′,4′:5,6]pyrano[3,4-*b*]indol-1(3*H*)-one (8b). Compound **8b** was obtained and purified by the same way as **8a** from **7b** (500 mg, 1.5 mmol) as colorless crystals (517 mg, 92%). Mp 161–165 °C (decomp.); R_f 0.19 (C); $[\alpha]_D^{20}$ +5 (*c* 2.5, MeOH); HRMS Calcd for $C_{19}H_{21}NO_7$: 375.1318. Found: 375.1324; ^{1}H NMR: δ (DMSO-d_6) 1.29 and 1.33 (2 s, 2×3H, 1′,2′-OC(CH_3)$_2$); 3.62 (s, 3H, 6-CH_3); 3.88 (dd, J=8.8, 6.8 Hz, 1H, 2′-H_B,); 4.15 (dd, J=8.8, 6.5 Hz, 1H, 2′-H_A); 4.32 (m, 1H, 1′-H); 4.43 (dd, J=8.0, 1.2 Hz, 1H, 3-H); 5.04 (d, J=15.8 Hz, 1H, 5-H_B); 5.11 (d, J=15.8 Hz, 1H, 5-H_A); 6.47 (s, 1H, 10c-OH); 6.98 (d, J=1.2 Hz, 1H, 3a-OH); 7.06 (ddd, J=8.0, 7.1, 1.0 Hz, 1H, 9-H); 7.17 (ddd, J=8.2, 7.1, 1.2 Hz, 1H, 8-H); 7.48 (ddd, J=8.2, 1.0, 0.8 Hz, 1H, 7-H); 7.73 (ddd, J=8.0, 1.2, 0.8 Hz, 1H, 10-H); 11.26 (s, 1H, 6-H); ^{13}C NMR: δ (DMSO-d_6) 25.4 and 26.5 (1′,2′-OC(CH_3)$_2$); 29.7 (N–CH_3); 59.1 (5-C); 65.0 (2′-C); 70.5 (10c-C); 74.7 (1′-C); 79.0 (3-C); 99.8 (3a-C); 103.3 (10b-C); 108.8 (1′,2′-OC(CH_3)$_2$); 109.6 (7-C); 119.6 (9-C); 120.2 (10-C); 121.6 (8-C); 125.0 (10a-C); 135.2 (5a-C); 137.5 (6a-C); 173.1 (1-C).

3.1.5. (3*R*,3a*R*,10c*S*)-3a,10c-Dihydroxy-1-oxo-1,3,3a,5,6,10c-hexahydrofuro[3′,4′:5,6]pyrano[3,4-*b*]indol-3-yl]-2-hydroxyethyl tosylate (9), and (1*S*,3a*S*,10c*S*,12a*R*)-1,10c-dihydroxy-1,6,10c,12a-tetrahydro-2*H*-furo[2″,3″:4′,5′]furo[3′,4′:5,6]pyrano[3,4-*b*]indol-11(5*H*)-one (10). To a stirred solution of **7a** (500 mg, 1.56 mmol) in dry pyridine (10 mL) was added tosylchloride (305 mg, 1.6 mmol) and after 4 h incubation the reaction mixture was diluted by citric acid solution and extracted by EtOAc (2×30 mL). After evaporation 600 mg of brown oil was obtained. It consisted of 80% of **9** and not contained **10**. After preparative TLC chromatography (system B) 60 mg of **9** (8% yield,) and 300 mg of **10** (63% yield) were obtained. The latter was formed during chromatography.

Compound **9**. Colourless oil; R_f 0.52 (B); HRMS Calcd for $C_{22}H_{21}NO_9S$: 475.0937. Found: 475.0930; ^{1}H NMR: δ (DMSO-d_6) 2.48 (s, 3H, CH_3 of Ts); 4.04 (m, 1H, 1′-OH); 4.16 (dd, J=9.6, 6.4 Hz, 1H, 2′-H_A); 4.31 (dd, J=9.6, 3.2 Hz, 1H, 2′-H_B); 4.38 (d, J=8.1 Hz, 1H, 3-H); 4.97 (d, J=15.1 Hz, 5-H_A); 5.00 (d, J=15.1 Hz, 5-H_B); 5.98 (d, J=6.4 Hz, 1H, 1′-OH); 6.52 (s, 1H, 10c-OH); 7.02 (ddd, J=8.1, 7.0, 1.0 Hz, 1H, 9-H); 7.06 (s, 1H, 3a-OH); 7.12 (ddd, J=8.1, 7.0, 1.2 Hz, 1H, 8-H); 7.38 (ddd, J=8.1, 1.0, 0.8 Hz, 1H, 7-H); 7.52 (d, J=9.6 Hz, 2H, Ts) 7.70 (ddd, J=8.0, 1.2, 0.8 Hz, 1H, 10-H); 7.84 (d, J=9.6 Hz, 2H, Ts); 11.25 (s, 1H, 6-H).

Compound **10**. Colourless crystals. Mp 201–205 °C; R_f 0.61 (A); ν_{max}: 3416, 1778, 1477, 1087, 1038, 747 cm^{-1}; HRMS Calcd for $C_{15}H_{13}NO_6$: 303.0743. Found: 303.0738; ^{1}H NMR: δ (DMSO-d_6–benzene-d_6, 3:1) 4.26 (dd, J=9.3, 4.1 Hz, 1H, 2-H_A); 4.52 (dd, J=9.3, 6.1 Hz, 1H, 2-H_B); 4.60 (dd, J=6.1, 4.1 Hz, 1H, 1-H); 5.06 (s, 1H, 12a-H); 5.20 (d, J=15.6 Hz, 1H, 5-H_A); 5.31 (d, J=15.6 Hz, 1H, 5-H_B); 6.05 (br s, 1H, 1-OH); 6.25 (s, 1H, 10c-OH); 7.15 (t, J=7.5 Hz, 1H, 9-H); 7.22 (t, J=7.5 Hz, 1H, 8-H); 7.53 (d, J=7.9 Hz, 1H, 7-H); 8.05 (d, J=7.9 Hz, 1H, 10-H); 11.50 (s, 1H, 6-H); ^{13}C NMR: δ (DMSO-d_6–benzene-d_6, 3:1) 61.4 (2′-C); 70.5 (10c-C); 73.6 (1′-C); 75.9 (5-C); 82.1 (12a-C); 104.9 (10b-C); 110.2 (3a-C); 111.5 (7-C); 119.5 (9-C); 120.1 (10-C); 121.8 (8-C); 124.9 (10a-C); 134.1 (5a-C); 136.7 (6a-C); 172.9 (11-C).

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Efficient and versatile single pot approach to dipyrromethanes and bis(heterocyclyl)methanes

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Abstract—An efficient single pot route is presented involving the use of *O*, *N*-perhydro 1,3-heterocycles as carbonyl equivalents for the synthesis of 5-substituted dipyrromethanes, 5,10-disubstituted tripyrranes and bis(heterocyclyl)methanes.

1. Introduction

meso-Porphyrins and related systems such as calix[*n*]-pyrroles and calix[*n*]phyrins are a venerable class of pyrrole containing macrocycles and have gained considerable importance.[1] *meso*-Porphyrins display unique properties and find application in phototherapeutics,[2] biological processes,[3] optoelectronics,[4] catalysis,[5] biomimetic and material chemistry[6] etc. The level of architectural sophistication that has been achieved in such systems is closely tied to the availability of suitable building blocks through synthetic methodologies having flexibility for structural modifications. One of the key features of the porphyrin synthesis is the availability of 5-substituted dipyrromethanes and other related intermediates. These are the key precursors not only for *meso*-porphyrins, but also calix[4]pyrroles and calix[4]phyrin macrocycles, which are well established as redox-active or optical sensors for anions.[7–11]

Dipyrromethanes have been synthesized using a variety of procedures.[12] For example, the 5-unsubstituted dipyrromethane, has been prepared in three steps from pyrrole.[12a] 5-Aryldipyrromethanes have also been synthesized indirectly, requiring either the elimination of a protecting ester group from the pyrrole,[12b] or through the formation of a Grignard reagent.[12c] A number of other syntheses of dipyrromethanes are based on the direct condensation of carbonyl reagents with pyrrole, but quite often the process is plagued by the formation of undesired side products such as azafulvenes and *N*-confused dipyrromethanes.[1b–d,13a] The inaccessibility of functionalised carbonyls and the occurrence of the side reactions associated with the direct use of the labile carbonyl reagents pose additional problems.[14] An attractive small scale synthesis[15] of dipyrromethanes, in which pyrrole is used as reagent as well as the solvent with a catalytic amount of an acid affords good yields of dipyrromethanes bearing many types of substituents at the *meso* carbon. Thus, considerable effort for the development of methodologies for the synthesis of these diverse building blocks has been invested, however there still remains a scope for shorter and more efficacious approaches to contribute towards achieving the synthesis of these systems in a synthetically useful manner.

The carbonyl character of the C-2 unit of perhydro-1,3-heterocycles **1** and **2** has been amply demonstrated[16–18] and we have extensively used it to perform sensitive acid catalysed condensations with a variety of nucleophiles and have convincingly established[19,20] the synthetic utility of this approach. The merit of using oxazinanes and oxazolidines, which are hemiaminals of carbonyls, stems from their easy availability from a number of reagents including non-carbonyls, as well as the flexibility in appending[19f,g] a variety of substituents at the C-2 of these reagents.

Herein we report the application of various oxazinanes and an oxazolidine in the synthesis of a number of 5-substituted dipyrromethanes in a synthetically useful manner.[19i] Oxazinanes have been reacted with pyrrole and/or its combination with other carbon nucleophiles under acid (TFA) catalysed reaction conditions.[19h] All these reactions can be visualized as an extension of carbon transfer reactions (Folate model approach)[19–21] as these perhydro 1,3-heterocycles have been regarded as models of the N^5,N^{10}-methylenetetrahydrofolate coenzyme.

Keywords: Perhydro 1,3-heterocycles; Oxazinanes; Dipyrromethanes; *meso*-Porphyrins; Bis(heterocyclyl)methanes.
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† Department of Chemistry, for queries regarding the X-ray analysis.

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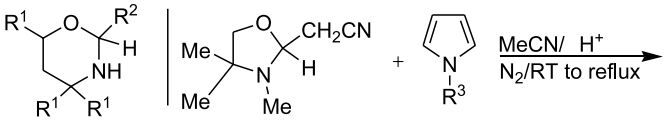
2. Results and discussion

Treatment of 2-(4-methoxyphenyl)oxazinane **1a** with pyrrole (Scheme 1) in 1:4 stoichiometric ratio in anhydrous acetonitrile–TFA (3.0 equiv) solution, under a blanket of dry nitrogen gas furnished 5-(4-methoxyphenyl)dipyrromethane **4a**[1b] and 5,10-di[(4-methoxy)phenyl]tripyrrane **5a**.[22] Similar reactions of appropriate 2-substituted oxazinanes **1b–1g** with pyrrole under a similar set of conditions, furnished the corresponding 5-substituted dipyrromethanes **4b–4g**, generally in good yield (Table 1). All these products are reasonably stable at ambient temperature, but some of these dipyrromethanes show tendency to turn pale green upon prolonged storage at ambient temperature. Using this method, no evidence of the formation of *N*-confused dipyrromethanes was found, as observed by others.[1b–e] Further, using this method, we have scaled up the reactions to isolate the dipyrromethanes **4a** and **4d** upto five *g* scale. Some of the products, for instance, **4h** obtained by reacting **1h** and pyrrole are formed in much superior yields than the reported methods.[1b] Thus, the oxazinane route has been quite useful where conventional routes employing direct use of aldehydes face limitations.

Keeping in view the importance of *meso*-Porphyrins,[23–25] having aliphatic substituents at the *meso*-position and the dearth of a general synthetic method for synthesis of the corresponding precursor dipyrromethanes, we conducted reactions of various C-2 alkyl oxazinanes with pyrrole. Reaction of 2-methyl oxazinane **1i** with pyrrole (1:4 stoichimetric ratio) using TFA (3.0 equiv) as catalyst at reflux, furnished 5-methyldipyrromethane **4i** in 40% yield. Likewise, the reaction of 2-ethoxycarbonylmethyl oxazinane **1j**, and pyrrole furnished the corresponding dipyrromethane **4j** and 5,10-di(2-ethoxycarbonylmethyl)tripyrrane **5b**. Similar reaction of 2-cyanomethyl-3,4,4-trimethyloxazolidine **2** with pyrrole, furnished the corresponding 5-cyanomethyldipyrromethane **4k** in 50% yield. A very small amount of the tripyrrane **5c** was also isolated in this reaction. Evidence for the existence of possible diastereomers of the tripyrranes **5** could not be ascertanied from the spectral data.

We further envisaged, that if *N*-methyl pyrrole was reacted with oxazinanes, the orientation of the electrophile (C-2 unit of oxazinanes in this case), could be directed at the 2- or 3-position owing to enhanced nucleophilic character of



1

(a) R^1= H, R^2 = 4-$MeOC_6H_4$
(b) R^1= H, R^2 = 3,4-di(MeO)C_6H_3
(c) R^1= H, R^2 = 3,4,5-tri(MeO)C_6H_2
(d) R^1= H, R^2 = Ph
(e) R^1= H, R^2 = 2-$NO_2C_6H_4$
(f) R^1= H, R^2 = 3-$NO_2C_6H_4$
(g) R^1= H, R^2 = 4-$NO_2C_6H_4$
(h) R^1= R^2 = H
(i) R^1= R^2 = Me
(j) R^1= Me, R^2 = CH_2COOEt
(k) R^1= H, R^2 = 2,3-di(MeO)C_6H_3
(l) R^1= H, R^2 = 2,3,4-tri(MeO)C_6H_2
(m) R^1= Me, R^2 = 2-CH_2Cl

2

3

(a) R^3 = H
(b) R^3 = Me

4

(a) R^2 = 4-$MeOC_6H_4$, R^3 = H
(b) R^2 = 3,4-di(MeO)C_6H_3, R^3 = H
(c) R^2 = 3,4,5-tri(MeO)C_6H_2, R^3 = H
(d) R^2 = Ph, R^3 = H
(e) R^2 = 2-$NO_2C_6H_4$, R^3 = H
(f) R^2 = 3-$NO_2C_6H_4$, R^3 = H
(g) R^2 = 4-$NO_2C_6H_4$, R^3 = H
(h) R^2 = R^3 = H
(i) R^2 = Me, R^3 = H
(j) R^2 = CH_2COOEt, R^3 = H
(k) R^2 = CH_2CN, R^3 = H
(l) R^2 = 4-$NO_2C_6H_4$, R^3 = Me
(m) R^2 = 3-$NO_2C_6H_4$, R^3 = Me
(n) R^2 = 2-$NO_2C_6H_4$, R^3 = Me
(o) R^2 = 4-$MeOC_6H_4$, R^3 = Me
(p) R^2 = 3,4-di(MeO)C_6H_3, R^3 = Me
(q) R^2 = 3,4,5-tri(MeO)C_6H_2, R^3 = Me
(r) R^2 = 2,3,4-tri(MeO)C_6H_2, R^3 = Me
(s) R^2 = Ph, R^3 = Me
(t) R^2 = H, R^3 = Me

5

(a) R^2 = 4-$MeOC_6H_4$, R^3 = H
(b) R^2 = CH_2COOEt, R^3 = H
(c) R^2 = CH_2CN, R^3 = H
(d) R^2 = 4-$MeOC_6H_4$, R^3 = Me
(e) R^2 = H, R^3 = Me

Scheme 1. Formation of dipyrromethanes **4** and tripyrranes **5**.

Table 1. Synthesis of aryldipyrromethanes **4a–t** and tripyrranes **5a–e** from oxazinanes **1a–l** and oxazolidine **2**

Sr. no.	Reagents		Product		Yield (%)[a]		Time (h)
	1/2	**3**	**4**	**5**	**4**	**5**	
1	**1a**	**3a**	**4a**	**5a**	40	15	5
2	**1b**	**3a**	**4b**	—	65	—	4.5
3	**1c**	**3a**	**4c**	—	60	—	4.5
4	**1d**	**3a**	**4d**	—	25	—	6
5	**1e**	**3a**	**4e**	—	65	—	3.5
6	**1f**	**3a**	**4f**	—	50	—	3.5
7	**1g**	**3a**	**4g**	—	80	—	3
8	**1h**	**3a**	**4h**	—	64	—	4.5
9	**1i**	**3a**	**4i**	—	40	—	7
10	**1j**	**3a**	**4j**	**5b**	35	15	16
11	**2**	**3a**	**4k**	**5c**	50	15	12
12	**1g**	**3b**	**4l**	—	56	—	3
13	**1f**	**3b**	**4m**	—	42	—	3
14	**1e**	**3b**	**4n**	—	62	—	3
15	**1a**	**3b**	**4o**	**5d**	55	14	4
16	**1b**	**3b**	**4p**	—	52	—	5
17	**1c**	**3b**	**4q**	—	35	—	4.5
18	**1l**	**3b**	**4r**	—	35	—	4.5
19	**1d**	**3b**	**4s**	—	28	—	6
20	**1h**	**3b**	**4t**	**5e**	60	13	5

[a] Pyrrole (4.0 mmol), **1/2** (1.0 mmol), TFA (3.0 mmol).

pyrrole as has been observed by us in reactions of similar carbon nucleophiles.[21c,26] Thus, the reaction of oxazinanes **1** with *N*-methyl pyrrole were conducted and the products 5-substituted di(*N*,*N*′-dimethyl)dipyrromethanes **4l–4s** (Scheme 1, Table 1), were obtained, exclusively indicating the formation of 2,2′-methylene bridged dipyrromethanes only. It was attested by X-ray crystallographic analysis of **4l** and the formation of any 3,3′-methylene bridged dipyrromethane was ruled out.

The stereo-view and the crystallographic numbering of **4l** is shown in Figure 1. The structure consists of two crystallographically independent molecules without any short contacts in the asymmetric unit. In the packing pattern one molecule in the asymmetric unit H-bonds to the neighbouring symmetry related molecule through nitro oxygen $O3^{i}$ to form C16–H162···$O3^{i}$, with C16···O3 distance 3.465(1) Å, H162···$O3^{i}$ 2.58(1) Å and ∠C16–H162···$O3^{i}$ 153° (where i = $-x$, $y-1$, z). While in the

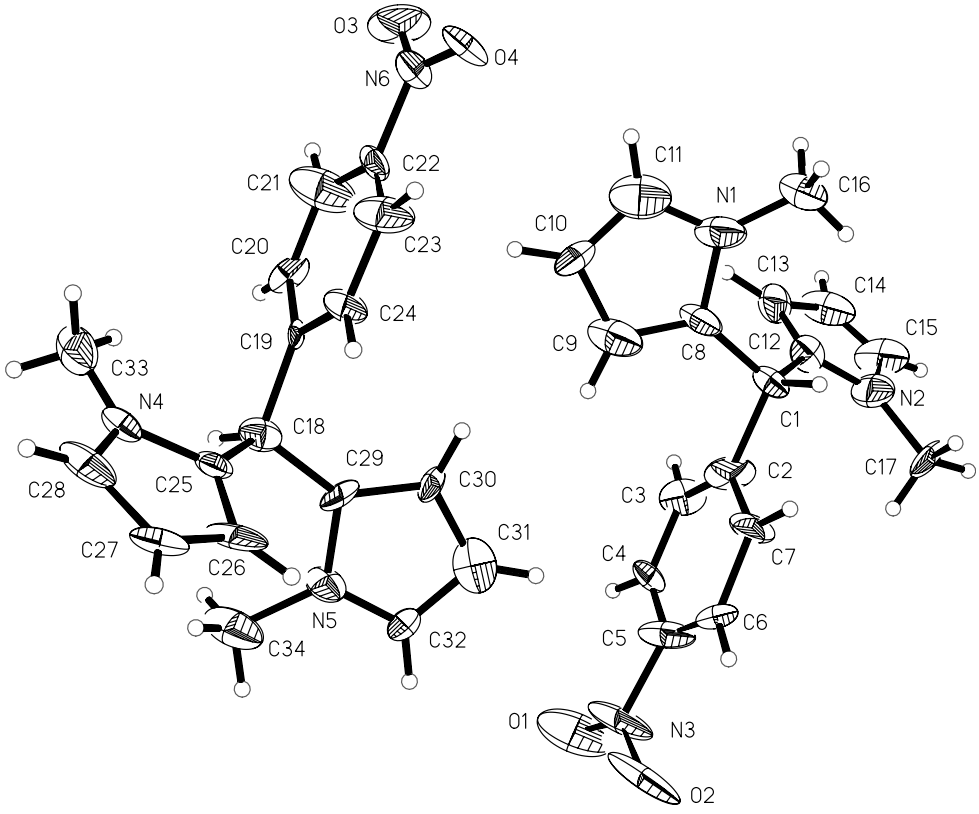
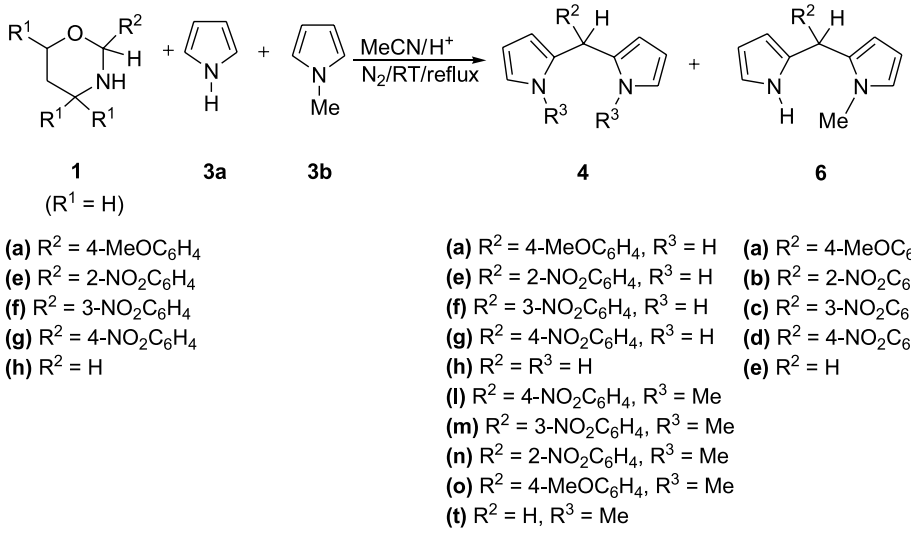


Figure 1. X-ray structure of **4l** showing the stereo view of the molecule and the labeling scheme used in the structure analysis.



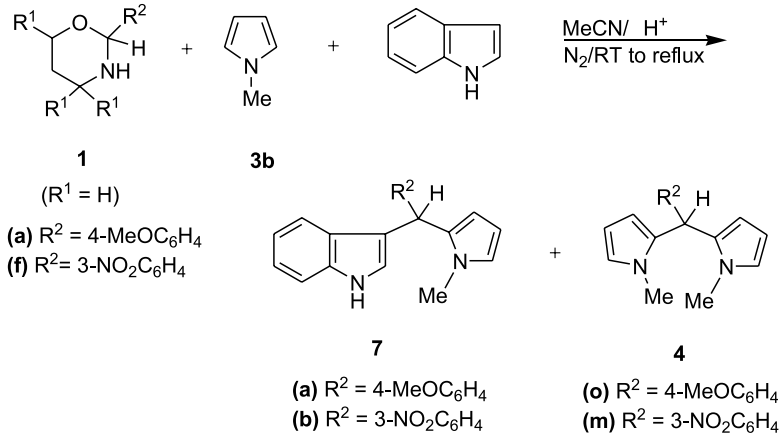
Scheme 2. Formation of mixed dipyrromethanes **6**.

second molecule of the asymmetric unit, the nitro oxygen O2 forms a H-bond with hydrogen of the methyl group C27 attached symmetry related pyrrole, such that the C27–H27···O2^{ii} with C27···O2^{ii} 3.448(34) Å, H27···O2^{ii} 2.57 Å and ∠C27–H27···O2^{ii} 157°, (where ii = $-x+1$, $y+0.5$, $-z+2$). Also it is noteworthy that the 4-nitrophenyl substituted methylene bridge is attached to the 2-position of pyrrole and not the 3-position. Both the *N*-methyl pyrrole units are twisted out of plane owing to the steric hindrance of the methyl substituents and the 4-nitrophenyl group is also *syn* periplanar with respect to the pyrrole units. The moieties surrounding the *meso*-carbon atoms form a tetrahedral geometry.[27] The bond angles and bond lengths of the *N*-methyl pyrrole units are normal.[28]

The reactions of *N*-methyl pyrrole with oxazinanes were than those of unsubstituted pyrrole and thus the isolation of products was relatively easier. The tripyrranes **5d** and **5e** were also isolated from the reaction of *N*-methyl pyrrole with **1a** and **1h**.

Such bis(heterocyclyl)methanes are also of interest to the food industry as they are present as natural compounds in food and beverage items[29] and are also used as flavour agents.[30,31] The unsymmetrical bis(heterocyclyl)methanes are far less explored; in fact, some structurally simple bis(heterocyclyl)methanes, especially with two different heterocyclic ring systems are, not known.[32] The few synthetic procedures available have only led to a limited number of compounds of this class. Carbon nucleophiles have displayed unique reactivity at our hands.[19c,d] Alkyl-β-aminocrotonates reacted with oxazinanes to furnish symmetrical 4-substituted 1,4-dihydropyridines, while two different enamines react in 1:1 stoichiometric ratio with perhydro 1,3-heterocycles to furnish unsymmetrical 4-substituted 1,4-dihydropyridines, almost exclusively. We envisaged, reacting combinations of different C-nucleophiles: pyrrole, *N*-methyl pyrrole and indole with oxazinanes, unsymmetrical bis(heterocycyl)methanes could be obtained.

Thus, the reactions of oxazinanes with a combination of pyrrole, *N*-methyl pyrrole and indole, under acid catalysed reaction conditions have been conducted and the unsymmetrical bis(heterocyclyl)methanes are obtained as depicted in Schemes 2 and 3. Oxazinane **1a** was reacted with pyrrole **3a** and *N*-methyl pyrrole **3b** in 1:2:2 stoichiometric ratio in anhydrous acetonitrile and using TFA (3.0 equiv) as catalyst



Scheme 3. Reactions of oxazinanes **1** with *N*-methyl pyrrole **3b** and indole. Formation of unsymmetrical bis(heterocyclyl)methanes **7**.

Table 2. Reaction of pyrrole **3a** and *N*-methyl pyrrole **3b** with oxazinanes **1**

Sr. no.	Oxazinane 1	Products [Yield (%)][a]		
		4	**4**	**6**
1	**1a**	**4a** (12)	**4o** (15)	**6a** (15)
2	**1e**	**4e** (12)	**4n** (15)	**6b** (16)
3	**1f**	**4f** (14)	**4m** (20)	**6c** (14)
4	**1g**	**4g** (20)	**4l** (15)	**6d** (15)
5	**1h**	**4h** (20)	**4t** (10)	**6e** (15)

Formation of dipyrromethanes **4/6**.
[a] Pyrrole (2.0 mmol), *N*-methyl pyrrole (2.0 mmol), **1** (1.0 mmol), TFA (3.0 mmol).

and **4a**, **4o** and **6a** were obtained (Scheme 2). Similar reactions of oxazinanes **1e–h** with a mixture of pyrrole and *N*-methyl pyrrole in anhydrous acetonitrile, under the similar set of conditions furnished the corresponding products **4/6** (Table 2). None of these reactions showed any preference for the exclusive formation of the mixed pyrrole product **6a**.

Likewise, the reaction of oxazinane **1a** with *N*-methyl pyrrole **3b** and indole, in 1:2:2 stoichiometric ratio, in anhydrous acetonitrile and catalysed by TFA (3 equiv) furnished after flash chromatography **4o** and the desired 3-[(1-methyl-1H-pyrrole-2-yl)-(4-methoxyphenyl)-methyl]-1*H*-indole **7a**. Similar reaction of oxazinane **1f** with indole and *N*-methyl pyrrole furnished corresponding dipyrromethane **4m** and 3-[(1-methyl-1H-pyrrole-2-yl)-(4-nitrophenyl)-methyl]-1*H*-indole **7b**, albiet in poor yield (12%). Indoles having 2,7-positions activated towards electrophiles such as carbonyl compounds constitute precursors for performing direct synthesis of calix[*n*]indoles.[33] In none of these reactions however, the formation of such 2,7-disubstituted indolyl products was detected.

Thus, it has been found that the unsymmetrical bis(heterocyclyl)methanes are formed, although not exclusively, through the acid catalysed reactions of oxazinanes with a mixture of *N*-methyl pyrrole and indole.

3. Conclusions

Perhydro 1,3-heterocyles, versatile reagents have been employed for the synthesis of dipyrromethanes as well as bis(heterocyclyl)methanes. It has been found that: (i) perhydro 1,3-heterocycles offer a dependable alternative to carbonyl compounds in the synthesis of these important intermediates for the synthesis of *meso*-tetraarylporphyrins and related pyrrolic macrocycles; (ii) the reactions are relatively clean, as polymeric side products are not formed in any significant quantity; (iii) relatively much lower stoichiometric amounts of reactants, compared to the reported methods, are used for the reactions and the products are formed in moderate to good yields without any detectable *N*-confused dipyrromethanes; (iv) the approach is flexible to incorporate a number of substituent variations, at the transferred C-2 unit of the perhydro 1,3-heterocycles, owing to easy functionalisation of the latter. This aspect is conspicuously lacking in the aldehyde approach owing to the non-availability of many functionalized aldehydes.

4. Experimental

4.1. General

All melting points are determined in capillaries. ^{1}H (200 MHz) and ^{13}C NMR (50 MHz) spectra were run on Bruker AC 200 instrument of the Department of Chemistry, using TMS as the internal standard. Mass (70 eV) spectra were performed on Shimadzu GCMS QP 2000 spectrometer. Elemental analyses of the samples were performed on and Perkin–Elmer 2400 CHN elemental analyser at microanalytical laboratory RSIC, Punjab University, Chandigarh and at RSIC, Central Drug Research Institute, Lucknow, India.

Separation of various products was carried out by flash chromatography on silica gel (60–120 mesh). All solvents MeCN (P_2O_5), THF (Na-benzophenone ketyl), hexane (sodium) and ethyl acetate (anhydrous K_2CO_3) were dried and distilled before use.

The reagents such as 2-amino-2-methyl-1-propanol, 2-methyl-2,4-pentanediol, aldehydes, nitriles, pyrrole, *N*-methyl pyrrole etc. were purchased from Sigma-Aldrich Co., USA. Oxazinanes and oxazolidines were synthesised following the reported procedures.[19f,20]

4.2. Reactions of perhydro 1,3-heterocycles with pyrrole/*N*-methyl pyrrole. Synthesis of dipyrromethanes 4 and tripyrranes 5. General procedure. A solution of freshly distilled pyrrole (4.0 mmol)/*N*-methyl pyrrole (2.0 mmol) and oxazinane **1** (1.0 mmol)/oxazolidine **2** (1.0 mmol) in anhydrous acetonitrile (dried over P_2O_5) (30 mL) was stirred under N_2 for 15 min, followed by addition of TFA (3.0 mmol) and heated under reflux until the reaction was completed (TLC). The reaction was cooled to room temperature and basified with cold aqueous sodium bicarbonate solution (5% w/v) and extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure on a rotary evaporator. The residue was chromatographed over silica gel G (60–120 mesh) using hexane, or a mixture with ethyl acetate, as eluent. In many cases repeated crystallisations were performed to obtain analytically pure samples suitable for microanalytical analysis. Using the above procedure the following products were synthesized.

4.2.1. 5-(4-Methoxyphenyl)dipyrromethane (4a).[1b] Colourless powder. Yield: 0.10 g, 40%. Mp: 99 °C. IR (KBr): 2935, 2835, 1710, 1607, 1508, 1245 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 3.89 (s, 3H, OMe), 5.47 (s, 1H, *meso* H), 6.01 (m, 2H, 2×ArH), 6.01 (m, 2H, 2×CH), 6.26 (dd, J=2.9, <1.0 Hz, 2H, 2×CH), 6.74 (m, 2H, 2×CH), 6.94 (AA′BB′, 2H, J=8.3 Hz, 2×ArH), 7.97 (br, 2H, D_2O exchangeable, 2×NH). ^{13}C NMR ($CDCl_3$): δ 42.8, 55.0, 106.1, 106.8, 108.0, 113.1, 113.6, 116.9, 117.4, 129.1, 134.1, 158.1. MS: *m*/*z* 252. Anal. Cacld for $C_{16}H_{16}N_2O$: C 76.19, H 6.34, N 11.11. Found: C 76.34, H 6.56, N 11.32.

4.2.2. 5-(3,4-Dimethoxyphenyl)dipyrromethane (4b). Colourless powder. Yield: 0.18 g, 65%. Mp: 128 °C. IR (KBr): 3429, 3366, 3092, 2963, 2931, 2833, 1593 cm^{-1}. ^{1}H

NMR ($CDCl_3$): δ 3.83 (s, 3H, OMe), 3.93 (s, 3H, OMe), 5.42 (s, 1H, *meso* CH), 5.93 (s, 2H, 2×CH), 6.16 (m, 2H, CH), 6.68 (m, 2H, CH), 6.76 (m, 3H, ArH), 7.95 (br, 2H, D_2O exchangeable, 2×NH). ^{13}C NMR ($CDCl_3$): δ 43.5, 55.8, 107.1, 108.3, 111.1, 111.7, 117.2, 120.3, 132.7, 134.6, 147.9, 148.9. MS: *m/z* 282 (M^+). Anal. Cacld for $C_{17}H_{18}N_2O_2$: C 72.34, H 6.38, N 9.92. Found: C 72.45, H 6.45, N 9.78.

4.2.3. 5-(3,4,5-Trimethoxyphenyl)dipyrromethane (4c). Off-white powder. Yield: 0.19 g, 60%. Mp: 164 °C. IR (KBr): 2925, 2841, 1712, 1609, 1513, 1242 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.81(s, 6H, 2×OMe), 3.87 (s, 3H, OMe), 5.46 (s, 1H, *meso* H), 6.01 (s, 2H, 2×CH), 6.25 (m, 2H, 2×CH), 6.48 (s, 2H, 2×CH), 6.76 (m, 2H, ArH), 8.08 (br, 2H, D_2O exchangeable, 2×NH). ^{13}C NMR ($CDCl_3$): δ 44.1, 56.0, 60.8, 105.4, 107.1, 108.3, 117.0, 132.1, 136.6, 137.7, 153.2. MS: *m/z* 312 (M^+). Anal. Calcd for $C_{18}H_{20}N_2O_3$: C 69.23, H 6.41, N 8.97. Found: C 69.47, H 6.21, N 9.03.

4.2.4. 5-Phenyldipyrromethane (4d).[1b] Pale yellow crystals. Yield: 0.06 g, 25%. Mp: 101 °C. IR (KBr): 2935, 2835, 1508, 1245 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.58 (s, 1H, *meso* H), 5.86 (s, 2H, 2×CH), 6.17 (m, 2H, 2×CH), 6.75 (m, 2H, 2×CH), 7.5 (m, 5H, ArH), 8.09 (br, 2H, D_2O exchangeable, 2×NH). ^{13}C NMR ($CDCl_3$): δ 43.6, 107.7, 108.6, 117.8, 122.1, 123.2, 129.4, 130.8, 134.5, 144.4. MS: *m/z* 222 (M^+). Anal. Cacld for $C_{15}H_{14}N_2$: C 81.08, H 6.30, N 12.61. Found C 81.38, H 6.56, N 12.90.

4.2.5. 5-(2-Nitrophenyl)dipyrromethane (4e).[12f] Yellow sticky solid. Yield: 0.18 g, 65%. IR (KBr): 3381, 3340, 3103, 1560, 1513, 1356 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.86 (m, 2H, *meso* H and CH), 6.14 (m, 3H, 3×CH), 6.71 (m, 2H, 2×CH), 7.41 (m, 4H, ArH), 8.18 (br, 2H, D_2O exchangeable, NH). ^{13}C NMR ($CDCl_3$): δ 38.8, 107.4, 108.5, 117.6, 127.7, 129.3, 130.8, 130.9, 133.0, 137.2, 148.4. MS: *m/z* 267 (M^+). Anal. Calcd for $C_{15}H_{13}N_3O_2$: C 67.41, H 4.86, N 15.73. Found: C 67.62, H 4.90, N 15.81.

4.2.6. 5-(3-Nitrophenyl)dipyrromethane (4f). Pale yellow solid. Yield: 0.14 g, 50%. Mp: 153 °C. IR (KBr): 3389, 3346, 3098, 1560, 1512, 1354 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.60 (s, 1H, *meso* H), 5.87 (s, 2H, 2×CH), 6.17 (m, 2H, 2×CH), 6.77 (s, 2H, 2×CH), 7.52 (m, 4H, ArH), 8.10 (br, 2H, D_2O exchangeable, 2×NH). ^{13}C NMR ($CDCl_3$): δ 43.6, 107.8, 108.7, 118.0, 122.1, 123.2, 129.4, 130.9, 134.5, 144.4, 148.4. Anal. Calcd for $C_{15}H_{13}N_3O_2$: C 67.41, H 4.86, N 15.73. Found: C 67.65, H 4.64, N 15.51.

4.2.7. 5-(4-Nitrophenyl)dipyrromethane (4g).[1b] Green crystals. Yield: 0.22 g, 80%. Mp: 159 °C. IR (KBr): 3395, 3358, 1512, 1346 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.57 (s, 1H, *meso* H), 5.75 (m, 2H, 2×CH), 6.0 (m, 2H, 2×CH), 6.66 (m, 2H, 2×CH), 7.39 ($AA'BB'$, 2H, J=9.0 Hz, 2×ArH), 8.09 ($AA'BB'$, 2H, J=9.0 Hz, 2×ArH), 10.18 (br, 2H, D_2O exchangeable, 2×NH). ^{13}C NMR ($CDCl_3$): δ 43.3, 106.7, 107.2, 117.3, 122.9, 129.1, 131.4, 145.9, 151.0. MS: *m/z* 267 (M^+). Anal. Calcd for $C_{15}H_{13}N_3O_2$: C 67.41, H 4.86, N 15.73. Found: C 67.53, H 4.75, N 15.58.

4.2.8. Dipyrromethane (4h).[1b] Colourless crystals. Yield: 0.09 g, 64%. Mp: 75 °C. IR (KBr): 2897, 1715, 1656, 1562, 1469 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.94 (s, 2H, *meso* H), 6.07 (m, 2H, 2×CH), 6.15 (q, 2H, J=2.4 Hz, 2×CH), 6.62 (m, 2H, 2×CH), 7.67 (br, 2H, D_2O exchangeable, 2×NH). ^{13}C NMR ($CDCl_3$): δ 26.3, 106.1, 108.4, 117.1, 128.8, 129.3. MS: *m/z* 146 (M^+). Anal. Calcd for $C_9H_{10}N_2$: C 73.97, H 6.84, N 19.17. Found: C 74.17, H 6.62, N 19.34.

4.2.9. 5-Methyldipyrromethane (4i). Greenish sticky solid. Yield: 0.07 g, 40%. IR (KBr): 3388, 3345, 3099, 1560, 1512 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.62 (d, J=4.8 Hz, 3H, Me), 4.14 (q, J=4.8 Hz, 1H, *meso* H), 6.04 (m, 2H, 2×CH), 6.15 (m, 2H, 2×CH), 6.54 (m, 2H, 2×CH), 7.68 (br, 2H, D_2O exchangeable, 2×NH). ^{13}C NMR ($CDCl_3$): δ 20.5, 31.6, 104.9, 107.6, 108.0, 117.1, 134.8. MS: *m/z* 160 (M^+). Anal. Calcd for $C_{10}H_{12}N_2$: C 75.0, H 7.50, N 17.50. Found: C 74.78, H 7.63, N 17.38.

4.2.10. 5-(2-Ethoxycarbonylmethyl)dipyrromethane (4j). Greenish sticky solid. Yield: 0.08 g, 35%. IR (KBr): 3389, 2931, 1740, 1680, 1354 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.22 (t, 3H, J=7.0 Hz, Me), 2.98 (d, J=7.0 Hz, 2H, CH_2COO–), 4.11 (q, J=7.0 Hz, 2H, $COOCH_2Me$), 4.55 (t, J=7.0 Hz, 1H, *meso* H), 5.99 (s, 2H, 2×CH), 6.12 (m, 2H, 2×CH), 6.68 (m, 2H, 2×CH), 8.29 (br, 2H, D_2O exchangeable, 2×NH). ^{13}C NMR ($CDCl_3$): δ 14.0, 33.7, 40.1, 60.7, 105.1, 105.2, 107.9, 117.0, 131.7, 131.7, 172.6. MS: *m/z* 232 (M^+). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C 67.24, H 6.89, N 12.06. Found: C 67.44, H 6.59, N 12.26.

4.2.11. 5-Cyanomethyldipyrromethane (4k). Yellowish thick liquid. Yield: 0.07 g, 35%. IR (KBr): 3390, 3346, 2270, 1560, 1512 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.94 (dd, J=1.5, 6.0 Hz, 2H, CH_2CN), 4.41 (dt, J=1.5, 6.0 Hz, 1H, *meso* H), 6.13 (m, 4H, 4×CH), 6.62 (m, 2H, 2×CH), 8.09 (br, 2H, D_2O exchangeable, 2×NH). ^{13}C NMR ($CDCl_3$): δ 24.1, 34.6, 96.2, 105.5, 108.4, 118.2, 130.0. MS: *m/z* 185 (M^+). Anal. Calcd for $C_{11}H_{11}N_3$: C 71.35, H 5.94, N 22.70. Found: C 71.55, H 6.08, N 22.93.

4.2.12. 5-(4-Nitrophenyl)di(*N*,*N*′-dimethyl)pyrromethane (4l). Yellow crystals. Yield: 0.17 g, 56%. Mp: 116 °C. IR (KBr): 3388, 3367, 1512, 1346 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.40 (s, 6H, 2×NMe), 5.38 (s, 1H, *meso* H), 5.48 (m, 2H, 2×CH), 6.04 (m, 2H, 2×CH), 6.62 (m, 2H, 2×CH), 7.30 ($AA'BB'$, 2H, J=8.0 Hz, 2×ArH), 8.16 ($AA'BB'$, 2H, J=8.0 Hz, 2×ArH). ^{13}C NMR ($CDCl_3$): δ 30.9, 33.8, 106.8, 109.4, 122.6, 123.7, 129.6, 131.8, 148.3. MS: *m/z* 295 (M^+). Anal. Calcd for $C_{17}H_{17}N_3O_2$: C 69.15, H 5.76, N 14.23. Found: C 69.39, H 5.89, N 14.52.

4.2.13. 5-(3-Nitrophenyl)di(*N*,*N*′-dimethyl)pyrromethane (4m). Yellow crystals. Yield: 0.18 g, 62%. Mp: 142 °C. IR (KBr): 3392, 3346, 1560, 1512, 1354 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.39 (s, 6H, 2×NMe), 5.38 (s, 1H, *meso* H), 5.46 (m, 2H, 2×CH), 6.02 (m, 2H, 2×CH), 6.60 (m, 2H, 2×CH), 7.46 (m, 2H, 2×ArH), 8.14 (m, 2H, 2×ArH). ^{13}C NMR ($CDCl_3$): δ 33.8, 41.5, 106.7, 109.4, 121.9, 122.6, 123.6, 129.3, 131.9, 134.9, 143.6, 148.4. MS: *m/z* 295 (M^+). Anal. Calcd for $C_{17}H_{17}N_3O_2$: C 69.15, H 5.76, N 14.23. Found: C 69.45, H 5.97, N 14.55.

4.2.14. 5-(2-Nitrophenyl)di(*N*,*N*′-dimethyl)pyrromethane (4n). Greenish yellow solid. Yield: 0.12 g, 42%.

Mp: 158 °C. IR (KBr): 3390, 3348, 1560, 1513, 1356 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.42 (s, 6H, 2×NMe), 5.29 (s, 1H, *meso* H), 5.44 (m, 2H, CH), 6.00 (m, 2H, 2×CH), 6.59 (m, 2H, 2×CH), 7.11 (d, 1H, ArH), 7.44 (t, 1H, ArH), 7.49 (t, 1H, ArH), 7.98 (d, 1H, ArH). ^{13}C NMR ($CDCl_3$): δ 33.6, 36.4, 106.5, 109.2, 122.3, 124.7, 127.7, 131.0, 131.5, 133.1, 136.5, 148.6. MS: *m/z* 295 (M^+). Anal. Calcd for $C_{17}H_{17}N_3O_2$: C 69.15, H 5.76, N 14.23. Found: C 69.42, H 5.99, N 14.51.

4.2.15. 5-(4-Methoxyphenyl)di(*N*,*N*′-dimethyl)pyrromethane (4o). Off-white crystals. Yield: 0.16 g, 55%. Mp: 82 °C. IR (KBr): 3381, 3340, 3103, 2954, 2931, 2835, 1710 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.37 (s, 6H, 2×NMe), 3.72 (s, 3H, OMe), 5.20 (s, 1H, *meso* H), 5.47 (s, 2H, 2×CH), 6.12 (m, 2H, 2×CH), 6.57 (m, 2H, 2×CH), 6.85 (AA′BB′, 2H, J=8 Hz, 2×ArH), 7.02 (AA′BB′, 2H, J=8 Hz, 2×ArH). ^{13}C NMR ($CDCl_3$): δ 29.7, 32.7, 41.0, 55.2, 106.3, 108.7, 113.7, 121.9, 129.6, 133.3, 156.2. MS: *m/z* 280 (M^+). Anal. Calcd for $C_{18}H_{20}N_2O$: C 77.14, H 7.14, N 10.00 Found: C 76.34, H 6.66, N 11.34.

4.2.16. 5-(3,4-Dimethoxyphenyl)di(*N*,*N*′-dimethyl)pyrromethane (4p). Sticky solid. Yield: 0.16 g, 52%. IR (KBr): 2999, 2935, 2833, 1703, 1593, 1512 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.37 (s, 6H, 2×NMe), 3.79 (s, 3H, OMe), 3.84 (s, 3H, OMe), 5.18 (s, 1H, *meso* H), 5.53 (m, 1H, CH), 5.93 (s, 1H, CH), 6.02 (m, 3H, 3×CH), 6.53 (m, 5H, 2×CH and 3×ArH). ^{13}C NMR ($CDCl_3$): δ 33.8, 33.8, 41.4, 55.7, 106.3, 108.6, 120.1, 120.3, 120.6, 147.1, 148.7. MS: *m/z* 310 (M^+). Anal. Calcd for $C_{19}H_{22}N_2O_2$: C 73.54, H 7.09, N 9.03. Found: C 73.90, H 7.39, N 10.14.

4.2.17. 5-(3,4,5-Trimethoxyphenyl)di(*N*,*N*′-dimethyl)-pyrromethane (4q). White amorphous solid. Yield: 0.12 g, 35%. Mp: 89 °C. IR (KBr): 2932, 2847, 1714, 1612, 1515, 1239 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.35 (s, 6H, 2×NMe), 3.72 (s, 3H, OMe), 3.80 (s, 6H, 2×OMe), 5.15 (s, 1H, *meso* H), 5.50 (m, 2H, 2×CH), 5.99 (m, 2H, 2×CH), 6.33 (m, 2H, 2×CH), 6.56 (m, 2H, 2×CH). ^{13}C NMR ($CDCl_3$): δ 33.8, 42.1, 55.7, 60.7, 105.8, 106.4, 108.7, 122.0, 133.3, 136.9, 153.1. MS: *m/z* 340 (M^+). Anal. Calcd for $C_{20}H_{24}N_2O_3$: C 70.58, H 7.05, N 8.23. Found: C 72.15, H 7.39, N 8.16.

4.2.18. 5-(2,3,4-Trimethoxyphenyl)di(*N*,*N*′-dimethyl)-pyrromethane (4r). White amorphous solid. Yield: 0.12 g, 35%. Mp: 85 °C. IR (KBr): 2933, 2846, 1720, 1612, 1511, 1242 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.39 (s, 6H, 2×NMe), 3.61 (s, 3H, OMe), 3.82 (s, 3H, OMe), 3.86 (s, 3H, OMe), 5.55 (m, 3H, *meso* H and 2×CH), 5.98 (m, 2H, 2×CH), 6.54 (m, 4H, 2×CH and 2×ArH). ^{13}C NMR ($CDCl_3$): δ 33.9, 42.1, 56.0, 60.9, 105.8, 106.4, 108.8, 122.0, 133.3, 136.9, 153.1. MS: *m/z* 340 (M^+). Anal. Calcd for $C_{20}H_{24}N_2O_3$: C 70.58, H 7.05, N 8.23. Found: C 71.47, H 7.45, N 8.56.

4.2.19. 5-(Phenyl)di(*N*,*N*′-dimethyl)pyrromethane (4s). White solid. Yield: 0.13 g, 52%. Mp: 84 °C. IR (KBr): 3117, 2937, 1487, 1450, 1294 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.37 (s, 6H, 2×NMe), 5.47 (s, 1H, *meso* CH), 5.94 (m, 2H, 2×CH), 6.01 (m, 2H, 2×CH), 6.55 (m, 2H, 2×CH), 7.28 (m, 5H, 5×ArH). ^{13}C NMR ($CDCl_3$): δ 33.7, 42.3, 105.9, 108.6, 121.4, 128.1, 128.3, 128.6. MS: *m/z* 250 (M^+). Anal. Calcd for $C_{17}H_{18}N_2$: C 81.60, H 7.20, N 11.20. Found: C 81.28, H 7.46, N 11.35.

4.2.20. Di(*N*,*N*′-dimethyl)pyrromethane (4t). White solid. Yield: 0.11 g, 60%. Mp: 111 °C. IR (KBr): 3115, 2918, 2849, 1690, 1490, 1321 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.48 (s, 6H, 2×NMe), 3.86 (s, 2H, *meso* CH_2), 5.82 (m, 2H, 2×CH), 6.03 (m, 2H, 2×CH), 6.55 (m, 2H, 2×CH). ^{13}C NMR ($CDCl_3$): δ 24.3, 31.6, 106.5, 107.5, 121.7, 125.3, 128.3, 129.0, 129.8. MS: *m/z* 174 (M^+). Anal. Calcd for $C_{11}H_{14}N_2$: C 75.9, H 8.04, N 16.09. Found: C 75.69, H 7.92, N 16.34.

4.2.21. 5,10-Di[(4-methoxy)phenyl]tripyrrane (5a). Green solid. Yield: 0.07 g, 15%. Mp: 85 °C. IR (KBr): 3010, 2945, 2839, 1703, 1593, 1512 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.73 (s, 6H, 2×OMe), 5.23 (s, 2H, 2× *meso* H), 5.70 (m, 2H, 2×CH), 5.81 (m, 2H, 2×CH), 6.08 (m, 2H, 2×CH), 6.59 (m, 2H, 2×CH), 6.76 (AA′BB, 2H, J=8.0 Hz, 2×ArH), 7.07 (AA′BB, 2H, J=8.0 Hz, 2×ArH). ^{13}C NMR ($CDCl_3$): δ 43.0, 55.2, 107.0, 108.2, 113.8, 117.1, 129.3, 132.8, 134.2, 158.3. MS: *m/z* 437 (M^+ Calcd for $C_{28}H_{27}N_3O_2$).

4.2.22. 5,10-Di(2-ethoxycarbonylmethyl)tripyrrane (5b). Sticky greenish compound. Yield: 0.06 g, 15%. IR (KBr): 3391, 2931, 1742, 1683, 1354 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.41 (t, J=5.5 Hz, 6H, 2× $COOCH_2CH_3$), 3.14 (d, J=7.0 Hz, 4H, 2×CH_2COO), 4.28 (q, J=5.5 Hz, 4H, 2×$COOCH_2Me$), 4.67 (t, J=7.0 Hz, 2H, *meso* H), 6.05 (m, 4H, 2×CH_2), 6.28 (m, 2H, 2×CH), 6.81 (m, 2H, 2×CH), 8.54 (br, 3H, D_2O exchangeable, 3×NH). ^{13}C NMR ($CDCl_3$): δ 14.1, 33.8, 40.0, 43.5, 60.8, 105.2, 108.0, 117.1, 133.5, 134.1, 172.7. MS: *m/z* 397 (M^+ Calcd for $C_{22}H_{27}N_3O_4$).

4.2.23. 5,10-Di(cyanomethyl)tripyrrane (5c). Sticky greenish compound. Yield: 0.05 g, 15%. IR (KBr): 3392, 3343, 2272, 1560, 1512 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.95 (m, 4H, 2×CH_2CN), 4.38 (m, 2H, 2× *meso* H), 6.11 (m, 6H, 6× CH), 6.70 (m, 2H, 2× CH), 8.14 (br, 3H, D_2O exchangeable, 3× NH). ^{13}C NMR ($CDCl_3$): δ 29.7, 40.2, 105.2, 108.0, 117.1, 118.6, 130.9, 132.2, 172.7. MS: *m/z* 303 (M^+ Calcd for $C_{18}H_{17}N_5$).

4.2.24. 5,10-Di[(4-methoxy)phenyl]tri(*N*,*N*′,*N*″-trimethyl)pyrrane (5d). Off-white solid. Yield: 0.07 g, 14%. Mp: 75 °C. IR (KBr): 2937, 2835, 1708, 1487 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.38 (s, 9H, 3×NMe), 3.80 (s, 6H, 2×OMe), 5.19 (s, 1H, *meso* H), 5.21 (s, 1H, *meso* H), 5.49 (m, 2H, 2×CH), 6.02 (m, 3H, 3×CH), 6.57 (m, 3H, 3×CH), 6.82 (m, 4H, 4×ArH), 7.04 (m, 4H, 4×ArH). ^{13}C NMR ($CDCl_3$): δ 33.8, 36.0, 41.0, 41.5, 55.1, 106.3, 108.7, 113.5, 121.8, 129.6, 133.8, 158.2. MS: *m/z* 479 (M^+ Calcd for $C_{31}H_{33}N_3O_2$).

4.2.25. Tri(*N*,*N*′,*N*″-trimethyl)pyrrane (5e). Sticky solid. Yield: 0.03 g, 13%. IR (KBr): 2907, 1716, 1656, 1567, 1469 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.38 (s, 3H, NMe), 3.52 (s, 6H, 2×NMe), 3.84 (s, 4H, 2× *meso* CH_2), 5.71 (m, 2H, 2×CH), 5.80 (m, 2H, 2×CH), 6.02 (m, 2H, 2×CH), 6.55 (m, 2H, 2×CH). ^{13}C NMR ($CDCl_3$): 24.9, 30.4, 33.7, 106.0,

106.5, 107.4, 121.6, 129.5, 129.7. MS: *m/z* 267 (M^+ Calcd for $C_{17}H_{21}N_3$).

4.3. Reactions of oxazinanes 1 with *N*-methyl pyrrole with pyrrole/indole. Synthesis of bis(heterocycly)-methanes 6 and 7. General procedure

A solution of freshly distilled *N*-methyl pyrrole (2.0 mmol) with pyrrole (2.0 mmol)/indole (2.0 mmol) and oxazinane **1** (1.0 mmol) in anhydrous acetonitrile (30 mL) was stirred under N_2 for 15 min, followed by addition of TFA (3.0 mmol) and heated under reflux at 80 °C till the reaction completed (TLC). The reaction was cooled to room temperature and basified with cold aqueous sodium bicarbonate solution (5.0% w/v) and extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure on a rotary evaporator. The residue was chromatographed over silica gel G (60–120 mesh) using hexane or a mixture with ethyl acetate, as eluent and the compounds were rapidly isolated. Using the above procedure, the following products were synthesized.

4.3.1. 2-[(4-Methoxyphenyl)-(1*H*-pyrrole-2-yl)-methyl]-1-methyl-1*H*-pyrrole (6a). Off-white sticky semi solid Yield: 0.04 g, 15%. IR (KBr): 3100, 2955, 2840, 1703, 1593, 1512 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.49 (s, 3H, NMe), 3.91 (s, 3H, OMe), 5.42 (s, 1H, *meso* H), 5.87 (m, 1H, CH), 5.99 (m, 1H, CH), 6.22 (m, 1H, CH), 6.29 (m, 1H, CH), 6.69 (m, 2H, 2×CH), 6.69 (m, 2H, 2×CH), 6.96 (AA′BB′, 2H, J=8.0 Hz, 2×ArH), 7.21 (AA′BB′, 2H, J=8.0 Hz, 2×ArH), 8.0 (br, 1H, D_2O exchangeable, NH). ^{13}C NMR ($CDCl_3$): δ 33.8, 41.9, 42.4, 106.0, 108.7, 108.90, 121.5, 121.9, 126.0, 126.6, 128.2, 128.3, 128.7, 133.5, 141.2. MS: *m/z* 266 (M^+). Anal. Calcd for $C_{17}H_{18}N_2O$: C 77.69, H 6.76, N 10.52. Found: C 76.96, H 7.05, N 10.22.

4.3.2. 1-Methyl-2-[(2-nitrophenyl)-(1*H*-pyrrol-2-yl)-methyl]-1*H*-pyrrole (6b). Sticky solid. Yield: 0.05 g, 16%. IR (KBr): 3389, 3358, 1560, 1513, 1356 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.47 (s, 3H, NMe), 5.56 (s, 1H, *meso* H), 5.89 (m, 1H, CH), 6.01 (m, 1H, CH), 6.30 (m, 1H, CH), 6.59 (m, 1H, CH), 6.61 (m, 1H, CH), 6.73 (m, 1H, CH), 7.28 (m, 3H, 3×ArH), 8.04 (br, 1H, D_2O exchangeable, NH), 7.9 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$): δ 33.8, 41.5, 108.6, 108.7, 108.9, 109.3, 121.9, 122.6, 123.4, 123.6. MS: *m/z* 281 (M^+). Anal. Calcd for $C_{17}H_{17}N_3O_2$: C 68.32, H 5.33, N 14.94. Found: C 68.45, H 5.57, N 14.48.

4.3.3. 1-Methyl-2-[(3-nitrophenyl)-(1*H*-pyrrol-2-yl)-methyl]-1*H*-pyrrole (6c). Yellowish sticky liquid. Yield: 0.05 g, 16%. IR (KBr): 3391, 3360, 1562, 1513, 1356 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.41 (s, 3H, NMe), 5.33 (s, 1H, *meso* H), 5.61 (m, 1H, CH), 5.81 (m, 1H, CH), 6.04 (m, 1H, CH), 6.15 (m, 1H, CH), 6.62 (m, 1H, CH), 6.73 (m, 1H, CH), 7.46 (m, 3H, 3×ArH), 8.04 (br, 1H, D_2O exchangeable, NH), 8.11 (m, 1H, ArH). ^{13}C NMR ($CDCl_3$): δ 33.8, 41.5, 108.6, 108.7, 108.9, 109.3, 121.9, 122.6, 123.4, 123.6. MS: *m/z* 281 (M^+). Anal. Calcd for $C_{16}H_{15}N_3O_2$: C 68.32, H 5.33, N 14.94. Found: C 68.56, H 5.60, N 14.67.

4.3.4. 1-Methyl-2-[(4-nitrophenyl)-(1*H*-pyrrol-2-yl)-methyl]-1*H*-pyrrole (6d). Sticky solid. Yield: 0.04 g, 14%. IR (KBr): 3388, 3364, 1560, 1512, 1357 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.43 (s, 3H, NMe), 5.37 (s, 1H, *meso* H), 5.72 (m, 1H, CH), 5.91 (m, 1H, CH), 6.07 (m, 1H, CH), 6.19 (m, 1H, CH), 6.69 (m, 1H, CH), 6.74 (m, 1H, CH), 7.32 (m, 2H, 2×ArH), 7.67 (br, 1H, D_2O exchangeable, NH), 8.21 (m, 2H, 2×ArH). ^{13}C NMR ($CDCl_3$): δ 33.8, 43.8, 108.7, 108.7, 111.6, 123.8, 129.2, 146.9, 149.6. MS: *m/z* 281 (M^+). Anal. Calcd for $C_{16}H_{15}N_3O_2$: C 68.32, H 5.33, N 14.94. Found: C 68.72, H 5.60, N 14.77.

4.3.5. 1-methyl-2-[phenyl-(1*H*-pyrrol-2-yl)-methyl]-1*H*-pyrrole (6e). White crystalline solid. Yield: 0.024 g, 15%. Mp: 103 °C. IR (KBr): 3390, 3358, 1610 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.42 (s, 3H, NMe), 3.94 (s, 2H, *meso* CH_2), 6.05 (m, 2H, 2×CH), 6.14 (m, 2H, 2×CH), 6.54 (m, 1H, CH), 6.64 (m, 1H, CH), 7.20 (br, 1H, D_2O exchangeable, NH). ^{13}C NMR ($CDCl_3$): δ 25.4, 29.7, 33.6, 105.7, 106.6, 107.6, 106.3, 116.7, 121.7. MS: *m/z* 160 (M^+). Anal. Calcd for $C_{10}H_{12}N_2$: C 75.00, H 7.50, N 17.50. Found: C 74.67, H 7.23, N 17.69.

4.3.6. 3-[(1-Methyl-1H-pyrrole-2-yl)-(4-methoxyphenyl)-methyl]-1*H*-indole (7a). Off-white solid. Yield: 0.05 g, 15%. Mp: 94 °C. IR (KBr): 3350, 2933, 2833, 1708, 1610, 1510 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.39 (s, 3H, NMe), 3.75 (s, 3H, OMe), 5.50 (s, 1H, *meso* H), 5.57 (m, 1H, CH), 6.00 (m, 1H, C(2)indolyl H), 6.57 (m, 2H, CH), 6.80 (m, 2H, 2×ArH), 6.96 (m, 1H, ArH), 7.11 (AA′BB′, 2H, J=8.0 Hz, 2×ArH), 7.28 (AA′BB′, 2H, J=8.0 Hz, 2×ArH), 8.09 (br, 1H, D_2O exchangeable, NH). ^{13}C NMR ($CDCl_3$): δ 33.7, 40.1, 55.2, 106.2, 108.4, 111.0, 113.6, 119.0, 119.3, 119.6, 121.7, 122.0, 123.4, 126.7, 129.6, 134.9, 135.3, 136.6, 158.0. MS: *m/z* 316 (M^+). Anal. Calcd for: $C_{21}H_{20}N_2O$: C 79.74, H 6.32, N 8.86. Found: C 79.77, H 6.21, N 8.65.

4.3.7. 3-[(1-Methyl-1H-pyrrole-2-yl)-(4-nitrophenyl)-methyl]-1*H*-indole (7b). Sticky solid. Yield: 0.04 g, 12%. Mp: IR (KBr): 3345, 2940, 2835, 1706, 1610, 1540, 1326 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.52 (s, 3H, NMe), 5.60 (m, 1H, *meso* H), 5.77 (m, 1H, CH), 6.12 (m, 1H, C(2)indolyl H), 7.10 (m, 2H, 2×CH), 7.14 (m, 1H, ArH), 7.27 (m, 2H, ArH), 7.44 (m, 2H, 2×ArH), 7.65 (m, 1H, ArH), 8.15 (m, 2H, 2×ArH), 8.19 (br, 1H, D_2O exchangeable, NH). ^{13}C NMR ($CDCl_3$): δ 33.7, 40.5, 106.4, 108.7, 111.2, 116.9, 118.9, 119.5, 121.6, 122.2, 122.2, 123.5, 123.5, 126.1, 129.0, 133.4, 134.7, 136.5, 144.9, 148.2. MS: *m/z* 331 (M^+).

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Syntheses and optoelectronic properties of four photochromic dithienylethenes

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Abstract—Four photochromic dithienylethene compounds, 1,2-bis(2-methyl-5-naphthalene-3-thienyl)perfluorocyclopentene **1a**, 1,2-bis[2-methyl-5(*p*-fluorophenyl)-3-thienyl]perfluorocyclopentene **2a**, 1,2-bis[2-methyl-5(*p*-ethoxyphenyl)-3-thienyl]perfluorocyclopentene **3a**, and 1,2-bis[2-methyl-5(*p*-*N*,*N*-dimethylaminophenyl)-3-thienyl]perfluorocyclopentene **4a** were synthesized, and their optoelectronic properties, such as photochromism in solution as well as in poly-methylmethacrylate (PMMA) amorphous films, fluorescences and electrochemical properties were investigated in detail. These dithienylethenes have shown good photochromic behavior both in solution and in PMMA amorphous film. All of them exhibited relatively strong fluorescence and gave a bathochromic shift upon increasing concentration in THF. The irreversible anodic oxidation of **1a**, **2a** and **4a** was observed by performing cyclic voltammetry experiments.

1. Introduction

Organic photochromic materials have attracted much attention, because of their potential application to optical memory media and optical switches.[1–6] Among various types of photochromic compounds,[3,4,7] diarylethene derivatives,[4,8,9] bearing two thiophene-derived groups are the most promising because of their excellent thermal stability of both isomers,[3,10–12] fatigue resistant character,[13,14] rapid response,[15–17] and high reactivity in the solid state.[18,19]

Generally, the open-ring isomers of dithienylethenes in solution have two conformations, namely, parallel conformation with the two thiophene-rings in mirror symmetry and anti-parallel conformation with them in C_2 symmetry.[20,21] The photoinduced cyclization and cycloreversion reactions can only proceed in a conrotatory mode by alternate irradiation with UV and visible light only from the anti-parallel conformation.[3,22] The photogenerated closed-ring isomers show colors with broad absorption bands in the visible region, and they can regenerate the open-ring isomers on irradiation with appropriate wavelengths of visible light. The two isomers of the dithienylethenes differ from each other not only in their absorption spectra, but also in many physical and chemical properties, such as fluorescence spectra, oxidation/reduction potentials and refractive indices, etc.[5,23,24] The most important difference is that while the π-systems of two aryl rings are separated in the open-ring isomer, the π-conjugation is delocalized, throughout the molecule in the closed-ring isomer.[25] By far, many dithienylethenes derivatives and their optoelectronic properties were reported.[3,26,27] Dithienylethenes bearing phenyl groups on the end are of special interest, because the end group can be substituted by electron donating group or electron withdrawing group. These groups inevitably influence the optoelectronic properties of corresponding diarylethenes. To the best of our knowledge, flurophenyl, ethoxyphenyl, and *N*,*N*-dimethylaminophenyl except naphthyl[28] substituted dithienylethenes have not been reported till now. Their syntheses are helpful both for, the preparation of new photochromic diarylethenes and for the understanding of substitution effect of corresponding products. On the basis of this idea, some novel photochromic dithienylethenes materials were developed which exhibit good photochromism, fluorescent, and electrochemical properties.

In this paper, four photochromic dithienylethenes compounds, 1,2-bis(2-methyl-5-naphthalene-3-thienyl)perfluorocyclopentene **1a**, 1,2-bis[2-methyl-5(*p*-fluorophenyl)-3-thienyl]perfluorocyclopentene **2a**, 1,2-bis[2-methyl-5(*p*-ethoxyphenyl)-3-thienyl]perfluorocyclopentene **3a**, and 1,2-bis[2-methyl-5(*p*-*N*,*N*-dimethylaminophenyl)-3-thienyl]-perfluorocyclopentene **4a** (Scheme 1) were synthesized, and their optoelectronic properties, such as UV–vis absorption spectra, fluorescence spectra, and electrochemical properties were investigated in detail. Among the four compounds,

Keywords: Dithienylethene; Photochromism; Fluorescence; Electrochemical properties.
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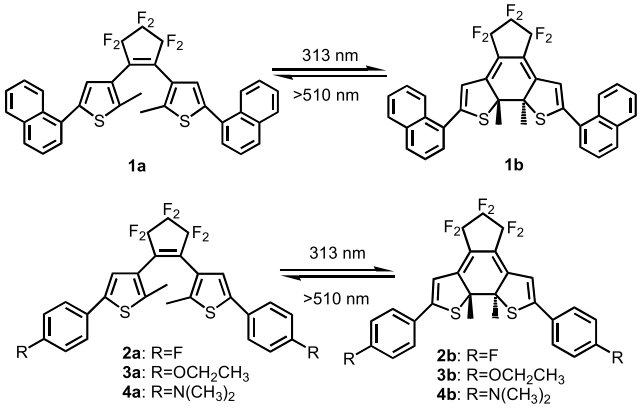


Scheme 1.

2a, **3a**, and **4a** are new compounds. Although **1a** was reported by Irie group,[28] its fluorescence and electrochemical properties had not been reported.

2. Results and discussion

2.1. Photochromism of dithienylethenes

Figure 1 showed the absorption spectral changes of **4a** in hexane (5.0×10^{-5} mol dm^{-3}) and in PMMA amorphous (10% w/w) by photoirradiation, respectively.

In hexane solution, the absorption maximum of compound **4a** was observed at 322 nm ($\varepsilon=3.86\times10^{4}$ dm^{3} mol^{-1} cm^{-1}) (Fig. 1a). Upon irradiation with 313 nm light, the color of the hexane solution turned blue, in which the absorption maximum was observed at 602 nm ($\varepsilon=1.75\times10^{4}$ dm^{3} mol^{-1} cm^{-1}). The blue solution turned colorless, upon irradiation with visible light ($\lambda>510$ nm). The quantum yields of cyclization and cycloreversion reactions of **4** in hexane solution were 0.80 (313 nm) and 0.013 (570 nm) at room temperature, respectively. In the PMMA amorphous film, dithienylethene **4a** also showed good photochromic property, as shown in Figure 1b. Upon irradiation 313 nm light, the color of **4a** PMMA film ($\lambda_{max}=340$ nm) changed from colorless to blue with the appearance of a new broad absorption band at $\lambda_{max}=646$ nm, which was assigned to the formation of the closed form **4b**. The colored PMMA film can invert to colorless, on irradiation of appropriate visible light ($\lambda>510$ nm). The red shift of the ring-closed form of **4a** in PMMA film in comparison with those in hexane solution can be ascribed to the stabilization of molecular arrangement in solid state.[29] The spectral changes of dithienylethenes **1a**, **2a**, and **3a** were similar to that of **4a**. Their absorption spectral properties were summarized in Table 1. These data indicated that both the maxima wavelengths of ring-open and ring-closed isomers increased, when an electron-donating group was introduced into the 4- and 4′-positions of the benzene rings. The maxima wavelengths of all compounds in solution were less than those in PMMA amorphous film. When the 4- and 4′-positions of the benzene rings were substituted by an electron-donating group, the value of the cyclization quantum also increased, but that of the cycloreversion quantum was irregular.

2.2. Fluorescence of ditheinylethenes

The fluorescence excitation and emission spectra of **1a**, **2a**, **3a**, and **4a** ($C=1.0\times10^{-5}$ mol dm^{-3}) in hexane at room temperature were illustrated in Figure 2. All of them exhibited good fluorescence at different wavelength in hexane solution excited by their respective excitation wavelength, and their fluorescence intensity decreased along with the photochromism from open-ring form to closed-ring form upon irradiation with 313 nm UV light.[30] From this figure, one can clearly see that the hexane solutions of compound **1a**, **2a**, **3a**, and **4a** showed relatively strong fluorescence at 380, 345, 340, and 455 nm when excited at 300, 285, 245, and 327 nm, respectively.

The concentration dependence of fluorescence and excitation spectra of **2a** was measured in THF solution at room temperature, as shown in Figure 3. When these solutions at 1.0×10^{-6}, 1.0×10^{-5}, 1.0×10^{-4}, and 1.0×10^{-3} mol dm^{-3} were excited at 290 nm, the maximum emission arose at 311, 343, 357, and 403 nm, respectively (Fig. 3b). Because the relative fluorescence intensity of the solution containing **2a** at a concentration of 1.0×10^{-3} mol dm^{-3} is too low comparing to the Y-axis value, the excitation and emission peaks cannot be observed (dash dot lines in Fig. 3). From Figure 3, we can see that both excitation and

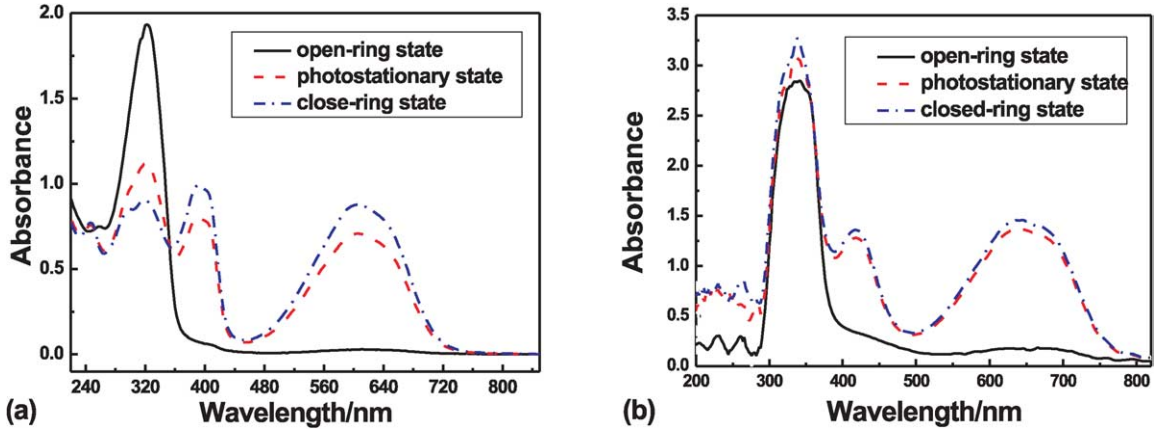


Figure 1. Absorption spectra of compound **4** in hexane and PMMA amorphous film. (a) in hexane (5.0×10^{-5} mol dm^{-3}); (b) in PMMA amorphous film (10% w/w).

Table 1. Absorption spectral properties of dithienylethenes **1**, **2**, **3** and **4** in hexane and PMMA film

Compound	$\lambda_{max,o}$[a]/nm (ε/dm^3 mol^{-1} cm^{-1})		$\lambda_{max,c}$[b]/nm (ε/dm^3 mol^{-1} cm^{-1})		Φ[c]	
	Hexane	PMMA film	Hexane	PMMA film	Φ_o	Φ_c
1	280 (4.9×10^4)	292	570 (7.9×10^3)	580	0.017	0.61
2	280 (3.2×10^4)	310	570 (6.3×10^3)	590	0.025	0.58
3	290 (4.1×10^4)	321	584 (8.7×10^3)	604	0.032	0.80
4	322 (3.86×10^4)	340	602 (1.8×10^4)	646	0.013	0.80

[a] Absorption maxima of open-ring isomers.
[b] Absorption maxima of closed-ring isomers.
[c] Quantum yields of open-ring (Φ_o) and closed-ring isomers (Φ_c), respectively.

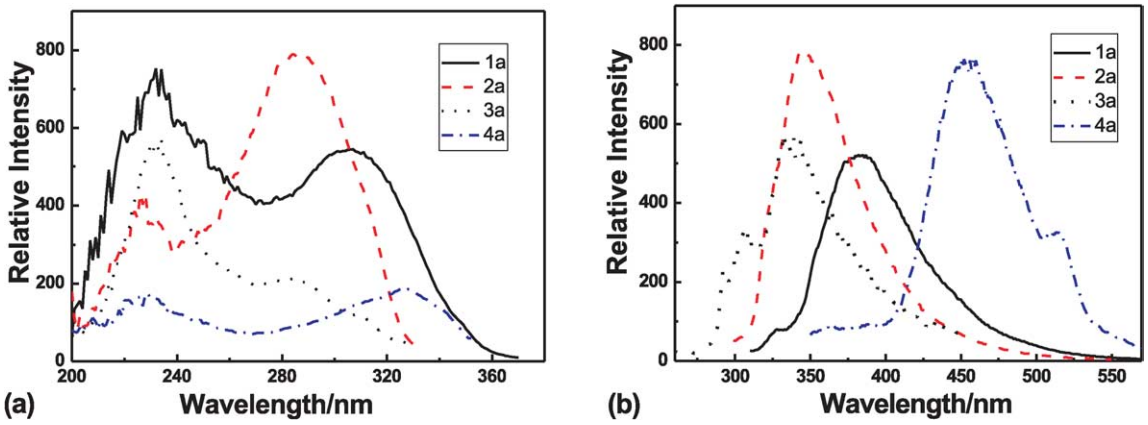


Figure 2. Fluorescence and excitation spectra of **1a**, **2a**, **3a**, and **4a** ($C=1.0\times10^{-5}$ mol dm^{-3}) in hexane. (a) Excitation spectra; (b) Emission spectra.

fluorescence spectra depended remarkably on the concentration of **2a** in solution. It gave a systematic red shift and the fluorescence intensity decreased rapidly with increasing concentration. This self-quench phenomenon maybe resulted from the formation of excimers and/or exciplexes in high concentration solutions so that deactivation effect can occur during the excited-state lifetime.[31] Furthermore, the concentration effect on the excitation and fluorescence spectra of **1a**, **3a**, and **4a** were also investigated, and the excitation and fluorescence maxima of the four dithienylethenes in various concentrations were summarized in Table 2. These results indicated that both the fluorescence and excitation spectra of the four compounds showed remarkable concentration dependence. Red shift and a rapid decrease of the relative intensity of emission spectra with an increase in concentration were observed. The results also suggest that molecular aggregation and fluorescence quench may take place due to the increasing concentrations.[30,32] In addition, the maxima absorption of the ring-open isomers of these compounds shifted ca. 10 nm towards the longer wavelength, when the concentration increased from 1.0×10^{-6} mol dm^{-3} to 1.0×10^{-4} mol dm^{-3}. The results indicated that the type of molecular aggregation was *J*-aggregation.[33]

The solvent effect on the fluorescence and excitation spectra of **1a**, **2a**, **3a**, and **4a** were also investigated. Fluorescence and excitation spectra of **2a** ($C=1.0\times10^{-5}$ mol dm^{-3}) in different solvents at room temperature were shown as in Figure 4, and the fluorescence and excitation maxima of

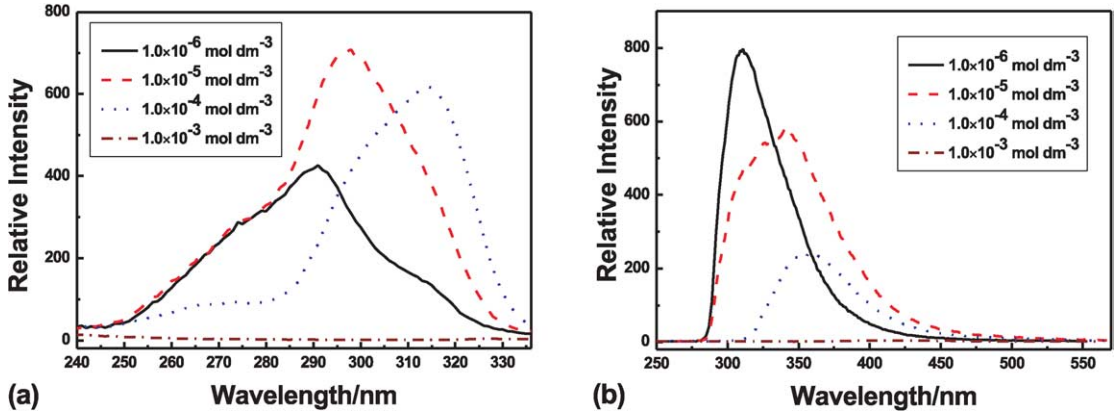


Figure 3. Fluorescence and excitation spectra of **2a** in various concentrations. (a) Excitation spectra, monitored at 345 nm; (b) Emission spectra, excited at 290 nm.

Table 2. Fluorescence properties of **1a**, **2a**, **3a** and **4a** at room temperature in various concentrations

Concentration (mol dm^{-3})	λ_{max} (nm)[a]				λ_{max} (nm)[b]			
	1a	**2a**	**3a**	**4a**	**1a**	**2a**	**3a**	**4a**
1×10^{-6}	301	291	286	286	333	311	309	308
1×10^{-5}	307	298	290	288	377	343	318	310
1×10^{-4}	325	315	—[c]	294	392	357	—[c]	494
1×10^{-3}	355	329	—[c]	—[c]	410	403	—[c]	—[c]

[a] Excitation maxima, monitored at 385, 345, 310, and 310 nm for **1a**, **2a**, **3a** and **4a**, respectively.
[b] Fluorescence maxima, excited at 300, 290, 290, and 285 nm for **1a**, **2a**, **3a** and **4a**, respectively.
[c] No spectrum peak.

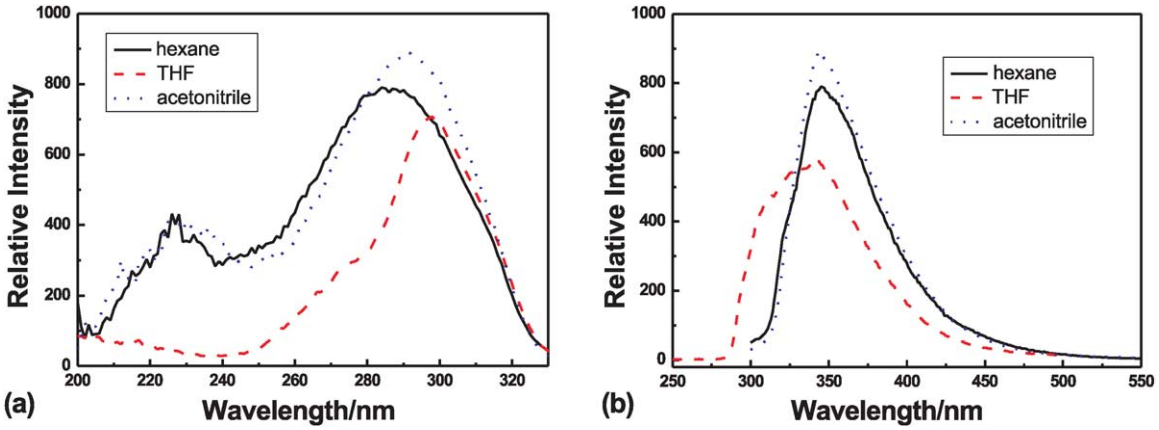


Figure 4. Fluorescence and excitation spectra of **2a** ($C=1.0\times10^{-5}$ mol/L) in various solvents. (a) Excitation spectra, monitored at 345 nm; (b) emission spectra, excited at 290 nm.

these four dithienylethenes in various solvents at room temperature were summarized in Table 3.

From these data, we can see that the solvent effect on the excitation and fluorescence spectra is relatively complex. For dithienylethene **2a** and **3a**, their excitation and fluorescence spectra are irregular with the peak maxima changing in a narrow range of wavelength upon increasing polarity of the solvent. This indicates that the solvent effect on fluorescence property of dithienylethene **2a** and **3a** was not significant. On the contrary, the fluorescence spectra of compound **1a** and **4a** showed remarkable solvent dependence. The fluorescence maximum of **1a** was observed between 379 and 394 nm and that of **4a** appeared between 452 and 517 nm in all solvents. It indicates that the fluorescence spectra of **1a** and **4a** showed a systematic red shift upon increasing solvent polarity. In addition, the excitation maximum of **1a** was irregular and that of **4a** gave a blue shift.

2.3. Electrochemistry of dithienylethenes

It was reported that the ring opening and closing transformation of some diarylethenes can be initiated not only by UV or visible light irradiation, but also by electrochemical or chemical oxidation, i.e. electrochromic.[23,34] Therefore, the electrochemical properties of **1a**, **1b**, **2a**, **2b**, **4a**, and **4b** as the typical diarylethenes were examined by cyclic voltammetry.

It is clearly seen from the anodic polarization curves (Fig. 5), that the oxidation of **2a** initiated at 1.03 V in the ring-open form. In the ring-closed form, the oxidation onset of **2b** was at 0.83 V. This is in accordance with the theory that longer conjugation length generally leads to less positive potentials, with the addition of each heterocycle. During the ring-closed reaction, the π-conjugation length of **2b** was much longer than that of **2a**. Thus the oxidation onset of **2b** was much lowered than that of **2a**. With the

Table 3. Fluorescence properties of **1a**, **2a**, **3a**, and **4a** in various solutions at 1.0×10^{-5} mol dm^{-3}

Solvent	λ_{max} (nm)[a]				λ_{max} (nm)[b]			
	1a	**2a**	**3a**	**4a**	**1a**	**2a**	**3a**	**4a**
Hexane	307	284	284	327	379	346	335	452
Ether	311	287	233	—[c]	380	347	340	472
THF	306	298	288	293	382	340	310	486
Ethyl acetate	310	292	276	264	390	349	—[c]	494
Acetonitrile	313	291	282	235	394	343	346	517

[a] Excitation maxima, monitored at 385, 345, 340, 360 nm for **1a**, **2a**, **3a**, and **4a**, respectively.
[b] Fluorescence maxima, excited at 300, 290, 235, and 260 nm for **1a**, **2a**, **3a**, and **4a**, respectively.
[c] No spectrum peak.

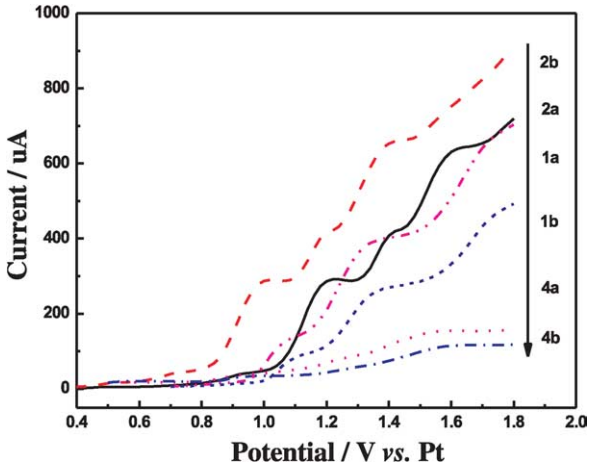


Figure 5. The anodic polarization curves of diarylethene **1**, **2** and **4**.

proceeding of potential scans of **2a**, the color of the electrolyte solution also changed significantly, from blue, deep blue, light red to deep red. This indicates that during electrochemical oxidation, the ring-closed reaction of **2a** occurred. Moreover, there are great differences of the anodic current between ring-open and ring closed form except the similarity of polarization curve shapes. In comparison with **2a**, the anodic currents of **2b** were much higher than that of **2a** at given applied potential. This can also be ascribed to the longer π-conjugation length of **2b**. The anodic polarization curves of **1a** and **1b**, **4a** and **4b** are quite similar to each other, and their oxidation onsets are 0.96, 1.01, 0.82, and 0.84 V, respectively. At the same applied potential, the electronic current of **1a** and **4a** were higher than that of **1b** and **4b**, which is contrary to those of **2a** and **2b**. The major difference of **1a** and **4a** from **2a** is, that they did not show electrochromic properties during the anodic polarization. The main reason for this phenomenon is not very clear. The most possible reason may be the substitute effect. Further work is still in progress.

3. Conclusion

Four bis(3-thienyl)perfluorocyclopentenes derivatives were synthesized for the investigation of their photochromic and fluorescent properties. They all exhibited good photochromism in both solution and PMMA amorphous film by photoirradiation. The solutions of these photochromic dithienylethenes gave strong fluorescence. When the solution concentrations increased, fluorescence quench took place and the fluorescence spectra maxima exhibited new bands at longer wavelength. The solvent effect on the fluorescence of the four compounds is irregular. The irreversible anodic oxidation of **1a**, **2a**, and **4a** in acetonitrile containing $LiClO_4$ as the supporting electrocyte was initiated at 0.96, 0.83, and 0.82 V, respectively. It should be noted here that dithienylethene **2a** showed remarkable multi-color electrochromism during the anodic polarization while **1a** and **4a** showed no obvious electrochromism.

4. Experimental

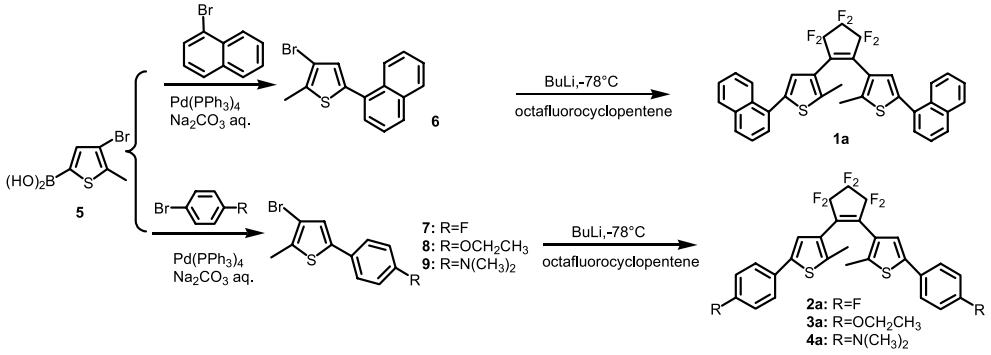
High-resolution mass spectra were recorded using electrospray technique by a Bruker APEX III FT-ICR mass spectrometer. Mass spectra were measured with a HP5989A mass spectrometer. ^{1}H NMR spectra were recorded on Bruker AV400 (400 MHz) spectrometer with $CDCl_3$ as the solvent and tetramethylsilane as an internal standard. IR spectra were performed using Perkin-Elmer FT-IR Spectrometer. The absorption spectra were measured using a Perkin-Elmer Lambda-900 UV/VIS/NIR spectrometer. Photo-irradiation was carried out using SHG-200 UV lamp, CX-21 ultraviolet fluorescence analysis cabinet, and BMH-250 Visible lamp. Light of appropriate wavelengths was isolated by different light filters. The quantum yields were determined by comparing the reaction yields of the dithienylethenes in hexane against 1,2-bis(2-methyl-5-phenyl-3-thienyl)perfluorocyclopentene in hexane.[10] Fluorescence spectra were measured using a Hitachi F-4500 spectrophotometer. Electrochemical examinations were performed in a one-compartment cell by using a Model 263 potentiostat-galvanostat (EG&G Princeton Applied Research) under computer control, at room temperature. Platinum-electrodes (diameter 0.5 mm) served as working electrode and counter electrode. Platinum wire served as a quasireference electrode. It was calibrated using the ferrocene (Fc/Fc+) redox couple which has a formal potential $E_{1/2} = +0.35$ V versus platinum wire. The typical electrolyte was acetonitrile (5 mL) containing 0.1 mol dm^{-3} $LiClO_4$ and 4×10^{-3} mol/L dithienylethene. All solutions were deaerated by a dry argon stream and maintained at a slight argon overpressure during electrochemical experiments.

4.1. Synthesis of 1,2-bis(2-methyl-5-naphthalene-3-thienyl)perfluorocyclopentene (1a), 1,2-bis-[2-methyl-5(*p*-fluorophenyl)-3-thienyl]perfluorocyclopentene (2a), 1,2-bis[2-methyl-5-(*p*-ethoxy-phenyl)-3-thienyl]-perfluorocyclopentene (3a) and 1,2-bis[2-methyl-5(*p*-*N*,*N*-dimethylamino phenyl)-3-thienyl]perfluoro-cyclopentene (4a)

The 1,2-bis(3-thienyl)perfluorocyclopentene derivatives, 1,2-bis(2-methyl-5-naphthalene-3-thienyl)perfluorocyclopentene **1a**, 1,2-bis[2-methyl-5(*p*-fluorophenyl)-3-thienyl]perfluoro-cyclopentene **2a**, 1,2-bis[2-methyl-5(*p*-ethoxyphenyl)-3-thienyl]perfluorocyclopentene **3a** and 1,2-bis[2-methyl-5(*p*-*N*,*N*-dimethylaminophenyl)-3-thienyl]perfluorocyclo-pentene **4a** were prepared by the method, shown in Scheme 2. The compounds were purified by column chromatography and characterized by ^{1}H NMR spectroscopy.

4.2. Compound data

4.2.1. 3-Bromo-2-methyl-5-naphthylthiophene (6). Compound **6** was prepared by reacting 3-bromo-2-methyl-5-thienylboronic acid (**5**)[17] (3.0 g; 13.57 mmol) with 1-bromonaphthalene (2.80 g; 13.6 mmol) in the presence of $Pd(PPh_3)_4$ (250 mg) and Na_2CO_3 (6.36 g; 60 mmol) in tetrahydrofuran (THF) (80 mL containing 10% water), for 15 h at 70 °C. Compound **6** was purified by column chromatography on SiO_2 using hexane/chloroform (1:1) as the eluent and 3.9 g obtained as yellow oil in 94% yield: ^{1}H



Scheme 2.

NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 7.05 (s, 1H), 7.44–7.51 (m, 3H, $J=6.4$ Hz), 7.76–7.849 (m, 3H, $J=8.8$ Hz), 8.20–8.24 (q, 1H, $J=8.0$ Hz).

4.2.2. 3-Bromo-2-methyl-5-(*p*-fluorophenyl)thiophene (7). Compound **7** was prepared by a method similar to that used for **6** and obtained as buffer solid in 71% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 7.05 (s, 1H), 7.04–7.08 (t, 2H, $J=8.8$ Hz), 7.52–7.55 (q, 2H, $J=7.2$ Hz).

4.2.3. 3-Bromo-2-methyl-5-(*p*-ethoxylphenyl)thiophene (8). Compound **8** was prepared by a method similar to that used for **6** and obtained as white solid in 72% yield: mp 108–110 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, 3H, $J=$ 7.0 Hz), 1.98 (s, 3H), 4.09 (q, 2H, $J=7.6$ Hz), 6.95 (s, 1H), 7.05–7.49 (q, 4H, $J=8.0$ Hz).

4.2.4. 3-Bromo-2-methyl-5-(*p*-(*N*,*N*-dimethylamino) phenyl)thiophene (9). Compound **9** was prepared by a method similar to that used for **6** and obtained as yellow solid in 79% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.98 (s, 6H), 6.93 (s, 1H), 7.24–7.45 (q, 4H, $J=$ 8.4 Hz).

4.2.5. 1,2-Bis(2-methyl-5-naphthyl-3-thienyl)perfluorocyclopentene (1a). To a stirred solution of **6** (3.03 g; 10.0 mmol) in THF was added dropwise, a 4.0 mL *n*-BuLi solution (2.5 mol/L, 10.0 mmol) at −78 °C under nitrogen atmosphere. Stirring was continued for 30 min at −78 °C. Perfluorocyclopentene (0.68 mL; 5.0 mmol) was slowly added to the reaction mixture at −78 °C, and the mixture was stirred for 2.5 h at same temperature. The reaction was quenched by water. The product was extracted with ether. The organic layer was washed with 1 M aqueous HCl and water. The organic layer was dried over $MgSO_4$, filtrated and evaporated. The crude product was purified by column chromatography on silica gel using petroleum ether/acetic ether (15:1) as the eluent and 4.15 g of **1a** obtained as baby blue oil in 67% yield: HRMS (ESI): $M+H^+$, found 621.1145. $C_{35}H_{22}F_6S_2$ requires 621.1140; MS *m*/*z* 621 (M+ 1), 620 (M), 605 (–CH_3), 590 (–2CH_3): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 6H), 6.99 (s, 2H), 7.478–7.535 (m, 6H, $J=12.0$ Hz), 7.761–7.888 (m, 6H, $J=8.0$ Hz), 8.203–8.243 (m, 6H, $J=8.4$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.5, 115.9, 122.7, 123.9, 124.9, 125.7, 126.5, 128.8, 130.9, 131.6, 133.9, 134.9, 139.2. IR (KBr, cm^{-1}) 3059, 2924, 1592, 1509, 1440, 1275, 1195.

4.2.6. 1,2-Bis(2-methyl-5-fluorophenyl-3-thienyl)perfluorocyclopentene (2a). Compound **2a** was synthesized by the same procedure used for the preparation of **1a**. The crude product was purified by column chromatography on silica gel to obtain **2a** in 45% yield as baby blue solid: mp 69–71 °C: HRMS (ESI): $M+H^+$, found 557.0630. $C_{27}H_{16}F_8S_2$ requires 557.0638; MS *m*/*z* 557 (M+1), 556 (M), 541 (–CH_3), 526 (–2CH_3), 480 (–4F): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 6H), 6.71 (s, 2H), 7.023–7.096 (m, 4H, $J=8.4$ Hz), 7.474–7.509 (m, 4H, $J=7.6$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.8, 115.9, 122.4, 125.9, 127.1, 129.6, 130.9, 139.51, 140.9, 160.8, 163.8. IR (KBr, cm^{-1}) 2970, 2919, 1602, 1510, 1231.

4.2.7. 1,2-Bis(2-methyl-5-*p*-ethoxylphenyl-3-thienyl)perfluorocyclopentene (3a). Compound **3a** was synthesized by the same procedure as that use for **1a**. The crude product was purified by column chromatography on silica gel to obtain in 51% yield as baby blue solid: mp 101–103 °C: HRMS (ESI): $M+H^+$, found 609.1346. $C_{31}H_{26}F_6O_2S_2$ requires 609.1351; MS *m*/*z* 609 (M+1), 608 (M), 593 (–CH_3), 578 (–2CH_3): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.409–1.444 (t, 6H, $J=6.8$ Hz), 2.38 (s, 6H), 4.011–4.078 (q, 4H, $J=7.2$ Hz), 6.98 (s, 2H), 7.15 (q, 4H, $J=8.0$ Hz), 7.438–7.493 (q, 4H, $J=8.8$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.5, 63.6, 114.9, 122.5, 122.8, 124.5, 125.9, 126.8, 129.6, 130.9, 133.2, 140.4, 142.2, 158.8. IR (KBr, cm^{-1}) 2981, 2927, 1609, 1515, 1338, 1254.

4.2.8. 1,2-Bis(2-methyl-5-*p*-(*N*,*N*-dimethylamino)phenyl-3-thienyl)perfluorocyclopentene (4a). Compound **4a** was synthesized by the same procedure as that use for **1a**. The crude product was purified by column chromatography on silica gel to obtain **4a** as cyan solid in 55% yield: mp 140–142 °C: HRMS (ESI): $M+H^+$, found 607.1667. $C_{31}H_{28}F_6N_2S_2$ requires 607.1671; MS *m*/*z* 607 (M+1), 606 (M), 591 (–CH_3), 576 (–2CH_3): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (t, 12H, $J=8.8$ Hz), 2.97 (s, 6H), 6.73 (s, 2H), 7.25–7.43 (q, 8H, $J=8.4$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$) δ 14.8, 40.6, 112.6, 120.1, 125.8, 126.7, 128.4, 135.9, 142.8, 149.6. IR (KBr, cm^{-1}) 2964, 2931, 1609, 1524, 1361, 1263.

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Three novel pregnane glycosides from *Epigynum auritum*

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Abstract—Three novel pregnane glycosides with an unusual aglycone (Epigynumgenane), named Epigynosides A (**1**), B (**2**) and C (**3**), were isolated from the aerial part of *Epiginum auritum*. Their structures were elucidated by spectral means and confirmed by X-ray diffraction analysis.

1. Introduction

Epigynum Wight (Apocynaceae) is a genus including about 14 species. Among them, there is only one—*E. aurilum* distributed in China. Its unique taxonomic position attracted us to investigate its chemical constituent. This paper deals with the isolation and structural elucidation of three novel pregnane glycosides, Epigynosides A (**1**), B (**2**) and C (**3**), with an unusual aglycone (Epigynumgenane).

2. Results and discussion

Epigynoside A (**1**) was isolated as a white powder. Its molecular formula $C_{28}H_{46}O_8$ was established by ^{13}C NMR (Table 1) and negative-ion HRFABMS data. ^{13}C NMR and HMQC-TOCSY exhibited signals for a seven-carbon glycosyl group and an aglycone formed with 21 carbons. The structure of sugar moiety of **1** was deduced by the correlations between H-2′ (δ_H 3.72) with H-1′ (δ_H 5.46) and H-3′ (δ_H 4.64), H-3′ with H-4′ (δ_H 3.77) and H-2′, H-5′ (δ_H 4.45) with H-6′ (δ_H 1.51) in ^1H–^1H COSY spectrum. The HMBC spectrum showing the cross peak of OMe-H (δ_H 3.60) with C-2′ (δ_C 81.6), indicated that the methoxyl was attached to C-2′. The stereochemistry of the sugar moiety was deduced by the correlations between H-1′ with H-5′ in ROESY spectrum and confirmed by the X-ray diffraction analysis. So, the structure of the sugar was deduced to be 2-*O*-methyl-6-deoxy-β-D-idopyranose (Fig. 1).[1] The linkage of the sugar moiety to the aglycone was decided by the cross peak of H-1′ with C-3 in HMBC spectrum. ^{13}C NMR and DEPT spectra of the aglycone showed the presence of one olefinic bond, three methyl groups, eight methylenes (one of them was oxygenated), five methines (two of them were oxygenated) and three quaternary carbons in which one was in very low-field (δ_C 101.1). The chemical shifts of the aglycone carbons were similar to that of pregn-5-ene-3β,17α,20*S*-triol except for ring-D.[2] The special form of ring-D was deduced by the obvious correlations between the low-field quaternary carbon (δ_C 101.1) with H-16 (δ_H 3.75), H-20 (δ_H 4.18), H-21 (δ_H 1.48) and H-18 (δ_H 1.15) in HMQC-TOCSY spectrum. And this was supported by the correlations between H-15 (δ_H 1.37) with H-14 (δ_H 1.99) and H-16 (δ_H 4.17), H-21 (δ_H 1.48) with H-20 (δ_H 4.18) in ^1H–^1H COSY spectrum. The ROESY spectrum showing crossing signals between H-8 (δ_H 1.37) with H-18 (δ_H 1.15) and H-19 (δ_H 0.95), H-9 (δ_H 1.02) with H-14 (δ_H 1.99), and H-20 (δ_H 4.18) with H-18 (δ_H 1.15), indicated the β, α, and α configurations for H-8, H-14 and OH-17, respectively. Finally, the configuration of position-20, which could not be explained by ROESY spectrum, and all the inference about **1** was determined by X-ray diffraction analysis (Fig. 2). Therefore, the structure of the aglycone of **1** was elucidated as a novel pregnane, named Epigynumgenane. And the structure of **1** was decided to be Epigynumgenane 3-*O*-2′-*O*-methyl-6′-deoxy-β-D-idopyranoside.

Epigynoside B (**2**) was isolated as a white powder. Its molecular formula $C_{34}H_{56}O_{11}$ was established through ^{13}C NMR and negative-ion HRFABMS data. Comparison of the ^1H and ^{13}C NMR spectral data of **2** (Table 1) with that of **1**, revealed that they were similar except for one more sugar in

Keywords: *Epiginum auritum*; Epigynoside; Sugar moiety.
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Table 1. ^{13}C and ^{1}H NMR data of compounds **1–3** (with $SiMe_4$ as internal standard; δ in ppm, J in Hz)

Position	**1** (δ_C)	**1** (δ_H)	**2** (δ_C)	**2** (δ_H)	**3** (δ_C)	**3** (δ_H)
1	37.2 (t)	0.99–1.02 (m), 1.75–1.77 (m)	37.2 (t)	1.02–1.06 (m), 1.84–1.88 (m)	37.4 (t)	0.93–0.97 (m), 1.72–1.76 (m)
2	30.2 (t)	1.77–1.81 (m), 2.10–2.14 (m)	30.2 (t)	1.73–1.77 (m), 2.10–2.14 (m)	30.4 (t)	1.75–1.79 (m), 2.12–2.16 (m)
3	77.8 (d)	3.82–3.86 (m)	77.8 (d)	3.80–3.84 (m)	78.1 (d)	3.86–3.90 (m)
4	39.1 (t)	2.38 (dd, J=11.2, 2.4 Hz); 2.57 (dd, J=10.5, 2.4 Hz)	39.1 (t)	2.36 (dd, J=11.2, 2.4 Hz); 2.55 (dd, J=10.5, 2.4 Hz)	39.3 (t)	2.38 (dd, J=11.2, 2.4 Hz); 2.58 (dd, J=11.2, 2.9 Hz)
5	140.5 (s)		140.5 (s)		140.8 (s)	
6	121.9 (d)	5.36 (br, s)	121.9 (d)	5.37 (br, s)	122.1 (d)	5.45 (br, s)
7	32.0 (t)	1.48–1.52 (m), 2.03–2.07 (m)	32.0 (t)	1.48–1.52 (m)	32.2 (t)	1.50–1.54 (m), 2.02–2.06 (m)
8	31.7 (d)	1.35–1.39 (m)	31.7 (d)	1.38–1.42 (m)	32.1 (d)	1.21–1.25 (m)
9	49.7 (d)	1.01–1.05 (m)	49.6 (d)	0.97–1.01 (m)	49.6 (d)	0.96–1.00 (m)
10	37.2 (s)		37.2 (s)		37.5 (s)	
11	21.1 (t)	1.30–1.34 (m), 1.47–1.51 (m)	20.5 (t)	1.36–1.4 (m), 1.53–1.57 (m)	20.8 (t)	1.14–1.18 (m), 1.50–1.54 (m)
12	33.4 (t)	1.80–1.84 (m), 1.90–1.94 (m)	33.2 (t)	1.55–1.59 (m), 1.90–1.94 (m)	33.8 (t)	1.72–1.76 (m)
13	40.5 (s)		40.9 (s)		41.6 (s)	
14	43.7 (d)	1.97–2.01 (m)	43.7 (d)	1.99–2.01 (m)	43.3 (d)	1.80–1.84 (m)
15	25.4 (t)	1.35–1.39 (m)	25.2 (t)	1.28–1.32 (m)	25.1 (t)	1.33–1.37 (m)
16	61.1 (t)	3.73–3.77 (m), 4.15–4.19 (m)	60.9 (t)	3.78–3.82 (m), 4.18–4.22 (m)	62.7 (t)	3.79–3.83 (m)
17	100.7 (s)		101.0 (s)		102.1 (s)	
18	15.1 (q)	1.15 (s)	15.3 (q)	1.15 (s)	17.3 (q)	1.02 (s)
19	19.8 (q)	0.95 (s)	20.2 (q)	0.95 (s)	19.5 (q)	0.92 (s)
20	70.5 (d)	4.16–4.20 (m)	79.6 (d)	4.23 (q, J=6.3 Hz)	70.5 (d)	4.23 (q, J=6.3 Hz)
21	20.6 (q)	1.48 (d, J=6.3 Hz)	19.3 (q)	1.48 (d, J=6.3 Hz)	20.0 (q)	1.51 (d, J=6.0 Hz)
17-OMe					51.1 (q)	3.53 (s)
1′	98.0 (d)	5.46 (br, s)	98.0 (d)	5.45 (br, s)	98.2 (d)	5.48 (br, s)
2′	81.6 (d)	3.70–3.74 (m)	81.5 (d)	3.71 (d, J=3.2 Hz)	81.7 (d)	3.73–3.77 (m)
3′	69.5 (d)	4.64 (br, s)	69.4 (d)	4.63 (br, s)	69.5 (d)	4.68 (br, s)
4′	72.8 (d)	3.77 (br, s)	72.7 (d)	3.81 (br, s)	72.9 (d)	3.80 (br, s)
5′	71.3 (d)	4.43–4.47 (m)	71.2 (d)	4.43 (q, J=8.2 Hz)	71.5 (d)	4.43–4.47 (m)
6′	17.3 (q)	1.51 (d, J=6.3 Hz)	17.2 (q)	1.53 (d, J=6.8 Hz)	17.5 (q)	1.52 (d, J=6.3 Hz)
2′-OMe	60.0 (q)	3.60 (s)	60.0 (q)	3.60 (s)	60.2 (q)	3.61 (s)
1″			102.6 (d)	5.21 (d, J=8.8 Hz)		
2″			40.6 (t)	2.00–2.04 (m), 2. 65–2.69 (m)		
3″			72.1 (d)	4.03–4.07 (m)		
4″			78.6 (d)	3.53 (t, J=8.8 Hz)		
5″			72.9 (d)	3.63–3.37 (m)		
6″			18.8 (q)	1.62 (d, J=6.0 Hz)		

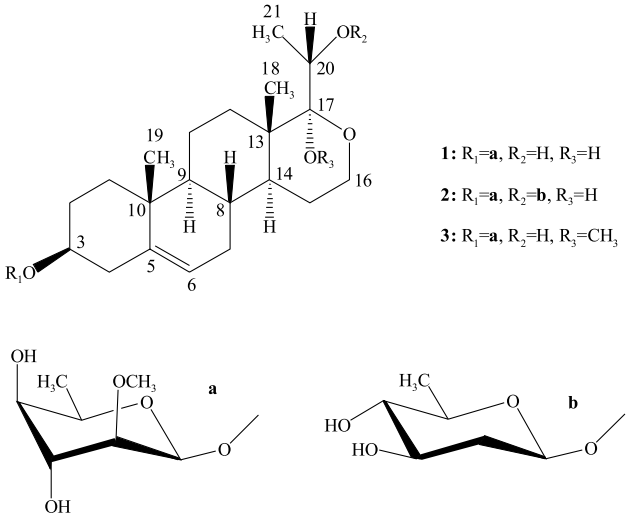

Figure 1. Structural formula of **1**, **2** and **3**.

2. The structure of this sugar was deduced by the correlations of the anomeric proton signal at δ 5.21 (H-1″) with C-2″ (δ_C 40.6), C-3″ (δ_C 72.1), C-4″ (δ_C 78.6), C-5″ (δ_C 72.9) and C-6″ (δ_C 18.8) in HMQC-TOCSY spectrum. The ^{1}H–^{1}H COSY spectrum showed the correlations between

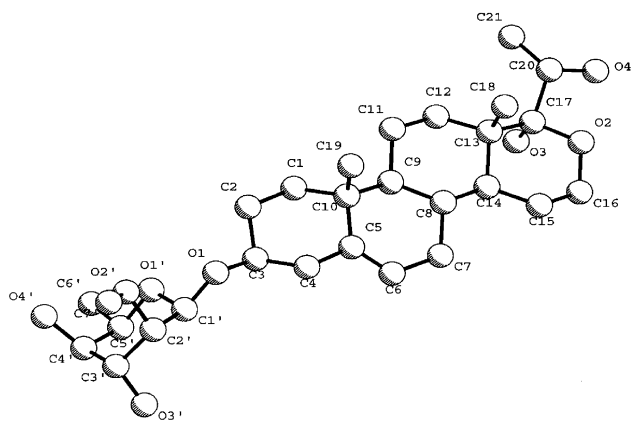

Figure 2. Crystal structure of **1** (hydrogens deleted).

H-2″ (δ_H 2.67) with H-3″ (δ_H 4.05) and H-1″, H-4″ (δ_H 3.53) with H-3″ and H-5″ (δ_H 3.65), H-5″ with H-6″ (δ_H 1.62). The relative stereochemistry of the sugar was assigned from the ROESY correlations of H-1″ with H-3″ and H-5″ and supported by the coupling constants in ^{1}H NMR spectrum (Table 1). Accordingly, the sugar was elucidated as 2,6-dideoxy-β-D-arabo-hexose (olivose).[3] The linkage of the sugar moiety to the aglycone was decided by the cross peak of H-1″ with C-20 (δ_C 79.6) in HMBC spectrum. Therefore, **2** was decided to be Epigynumgenane 3-*O*-2′-methyl-6′-deoxy-β-D-idopyranoside-20-*O*-β-D-olivopyranoside.

Epigynoside C (**3**) was isolated as a white powder. Its molecular formula $C_{29}H_{48}O_8$ was established through ^{13}C NMR and negative-ion HRFABMS data. Comparison of the ^{1}H and ^{13}C NMR spectral data of **3** (Table 1) with that of **1**, revealed that they were similar except for one more methoxyl in **3**. The linkage of the methoxyl to C-17 was decided by the cross peak of OMe-H (δ_H 3.53) with C-17 (δ_C 102.1) in HMBC spectrum. Therefore, **3** was decided to be 17-*O*-methyl-epigynumgenane 3-*O*-2′-methyl-6′-deoxy-β-D-idopyranoside.

3. Experimental

3.1. General experimental procedures

Optical rotations were measured with a Horiba SEAP-300 spectropolarimeter. IR (KBr) spectra were obtained on a Bio-Rad FTS-135 infrared spectropolarimeter. ^{1}H, ^{13}C NMR and 2D NMR spectra were recorded on a DRX-500 MHz NMR spectrometer with TMS as the internal standard. MS spectral data were obtained on a VG Autospec-3000 spectrometer. Si gel (200–300 mesh) for column chromatography and GF_{254} for TLC were obtained from the Qindao Marine Chemical Factory, Qindao, People's Republic of China. Macroporous resin D1300 was obtained from the Bengbu Liaoyuan Resin Factory, Bengbu, People's Republic of China. Sephadex LH-20 was obtained from Pharmacia Co. FUJI (ODS-Q_3) gel was obtained from Mitsubishi Chemical Co.

3.2. Plant material

The aerial part of *E. aurilum* was collected from Xishuangbanna, Yunnan Province, People's Republic of China, in September 1999. It was identified by Professor Yang, Z. H., Department of Taxonomy, Kunming Institute of Botany, *Academia Sinica*, Kunming, People's Republic of China.

3.3. Extraction and isolation

The dried aerial part of *E. aurilum* (14 kg) was extracted three times with EtOH under reflux. After removal of the solvent in vacuo, the residue (1.3 kg) was partitioned in H_2O and extracted with petroleum ether, AcOEt, and *n*-BuOH three times respectively. The AcOEt fraction (138 g) was chromatographed over macroporous resin D1300. The column was eluted with EtOH–H_2O (0:100–95:5) to give four fractions. Fraction 3 (50 g) was repeatedly chromatographed over silica gel using $CHCl_3$–MeOH and petroleum ether–Me_2CO as eluent to give 12 fractions. The fraction 1 (114 mg) and 2 (30 mg) were chromatographed on Sephadex LH-20 eluted by MeOH to yield **1** (67 mg) and **3** (10 mg), respectively. The fraction 3 (367 mg) was chromatographed on FUJI (ODS-Q_3) gel using MeOH–H_2O (80:20) to yield **2** (63 mg).

3.3.1. Compound 1. White powder; $[\alpha]_D^{22}$ −105.0 (*c* 0.3, C_5H_5N), IR (KBr) ν_{max}: 3459,2939, 1630, 1446, 1326, 1268, 1176, 1107,1075, 1047 cm^{-1}; ^{1}H and ^{13}C NMR spectral data, see Table 1; FABMS *m/z*: 509 $(M-H)^-$ (100); HRFABMS *m/z* 509.3081 $(M-H)^-$ (Calcd for $C_{28}H_{45}O_8$ 509.3114).

3.3.2. Compound 2. White powder; $[\alpha]_D^{25}$ −124.0 (*c* 0.5, C_5H_5N), IR (KBr) ν_{max}: 3436,2938, 1630, 1446, 1326, 1268, 1176, 1067, 1047 cm^{-1}; ^{1}H and ^{13}C NMR spectral data, see Table 1; FABMS *m/z*: 639 $(M-H)^-$ (100), 509 (20); HRFABMS *m/z* 639.3751 $(M-H)^-$ (Calcd for $C_{34}H_{55}O_{11}$ 639.3744).

3.3.3. Compound 3. White powder; $[\alpha]_D^{23}$ −56.0 (*c* 0.3, C_5H_5N), IR (KBr) ν_{max}: 3443,2933, 1733, 1669, 1457, 1176, 1067, 1047 cm^{-1}; ^{1}H and ^{13}C NMR spectral data, see Table 1; FABMS *m/z*: 523 $(M-H)^-$ (45), 509 (90), 615 $([M-H+Gly]^-$ (100); HRFABMS *m/z* 523.3282 $(M-H)^-$ (Calcd for $C_{29}H_{47}O_8$ 523.3271).

3.4. X-ray crystal structure analysis of 1

A colorless block crystal of dimension 0.10×0.20×0.30 mm^3 was used for data collection. Crystallographic data: $C_{28}H_{46}O_8 \cdot CH_3COOC_2H_5 \cdot (H_2O)_2$, $M=665.73$, orthorhombic, $P2_12_12$, $a=43.798(2)$, $b=11.221(1)$, $c=6.985(1)$ Å, $V=3432.8(6)$ Å^3, $Z=4$, $d=1.233$ g cm^{-3}. Intensity data were collected on MAC Science DIP-2030K diffractometer with a graphite monochromator, Mo Kα radiation, ω-2θ scans and $2\theta_{max}=50.0°$. The total number of independent reflections measured was 3709, of which 2591 were observed ($|F|^2 \geqq 8|F|^2$). The crystal structure was solved by direct method (SHELXS-86) and expanded using difference Fourier techniques, refined by the program NOMCSDP and full-matrix least-squares calculations.[4] Hydrogen atoms were fixed at calculated positions. The final indices were $R_f=0.075$ and $R_w=0.071$ ($w=1/\sigma|F|^2$). Crystallographic data (excluding structure factors) for the structures in this paper, have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 267158. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Acknowledgements

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Synthesis of thiazo- or thiadiazo- naphthalene carboxamides via mercuric intermediates and their antitumor and DNA photocleavage activities

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Abstract—Two kinds of thiazo- or thiadiazo- naphthalene carboxamides with aminoalkyl side chains at 5- or 6-position modified from naphthalimides were designed, synthesized and quantitatively evaluated as antitumor and DNA photocleaving agents. The compound with aminoalkyl side chain at 6-position showed stronger antitumor (A549, P388) and DNA photocleaving abilities than its isomer with that at 5-position. $\mathbf{B_2}$, the most efficient DNA photocleaver, also exhibited the highest cytotoxicity with the IC_{50} of 2.53 and 0.11 μM against cell lines of A549 and P388, respectively. These compounds also photocleaved DNA more efficiently than their corresponding naphthalimides.

1. Introduction

The naphthalimide skeletons incorporated with substituents or fused with (substituted) phenyl or heterocyclic rings form an important class of compounds which is structurally characterized by the presence of a planar chromophore portion, possibly capable of intercalation into base pairs of DNA, which resulted in high antitumor activity upon a variety of murine and human tumor cells.[1] Many of them have also shown the capability of generating various reactive intermediates that resulted in DNA photocleavage.[2]

Two kinds of phenyl thiazole (**1**, **2**) or thiadiazole (**3**, **4**) conjugated naphthalimides have been reported to bind with DNA and lead to DNA cleavage under photo-irradiation in our previous work.[2c,d] These results promoted us to design novel heterocyclic families by further modification of the naphthalimide skeletons. Herein, we first proposed the molecular modification of the reported heterocycle families, **1**, **2** and **3**, **4** through mercuric intermediates to their corresponding ring opened models, phenyl thiazo- ($\mathbf{A_{1-2}}$, $\mathbf{B_{1-2}}$) or thiadiazo- naphthalene carboxamides ($\mathbf{C_{1-2}}$, $\mathbf{D_{1-2}}$), whose planar tri-cyclic ring systems may also potentially intercalate into DNA to show medical or biological use. Furthermore, the functional thiazo- or thiadiazo- groups proven actively[2c,d] in DNA photocleavage were remained. The aminoalkyl side chains serving as a DNA groove binder and/or external electrostatic binder were introduced into two different regio-positions (5-, 6-) of the chromophores to enhance the affinity to DNA and the effect of substitution position on their bioactivities was also studied (Fig. 1).

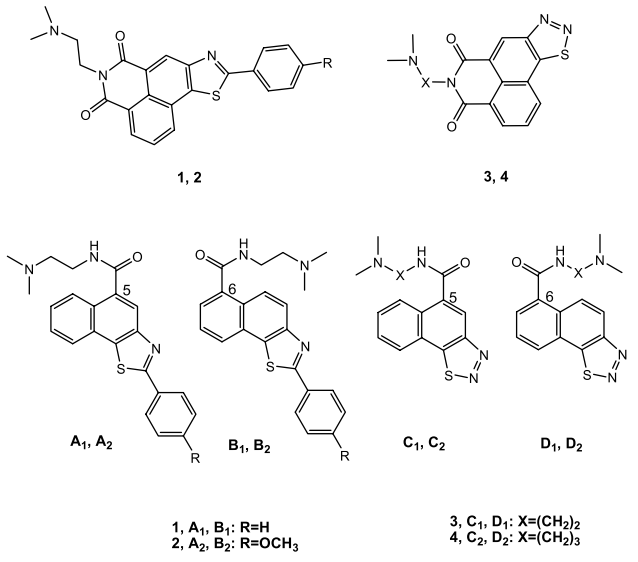

Figure 1. Structures of the reported and new photonucleases.

Keywords: Photocleavage; Antitumor; Intercalating.
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2. Results and discussion

2.1. Synthesis and spectra

The replacement of one of the carbonyl groups by mercury in (substituted) naphthalic anhydride has been known,[3] but the mercuric oxide mediated decarbonylation of 4-bromo-3-nitro-1,8-naphthalic anhydride[4] has not been reported. When 4-bromo-3-nitro-1,8-naphthalic anhydride was reacted with mercuric oxide (yellow or red) and acetic acid according to the reported methods,[3] two isomers, 4-bromo-3-nitro-1-naphthoic acid and 4-bromo-3-nitro-8-naphthoic acid were obtained with the ratio of 4:1 via ^{1}H NMR. The acids were refluxed in water with sodium disulfide for 8 h. The reaction mixture was then dropped into glacial acetic acid containing benzaldehyde or 4-methoxybenzaldehyde immediately and refluxed for further 4 h to give two phenylthiazole or 4-methoxy phenylthiazole conjugated naphthoic acid isomers. Finally, the corresponding naphthoyl chlorides were prepared from the acids by refluxing with thionyl chloride in chloroform for 20 h and then condensed with *N*,*N*-dimethylethylenediamine in dichloromethane to form a pair of isomers, $\mathbf{A_1}$, $\mathbf{B_1}$ or $\mathbf{A_2}$, $\mathbf{B_2}$. The isomers could be separated by careful column chromatography (Scheme 1).

We noted that the decarbonylation of larger heterocyclic conjugated naphthalic anhydride had not been reported yet. So we tried an alternative strategy to synthesize the desired products of $\mathbf{C_{1-2}}$ and $\mathbf{D_{1-2}}$. Thiadiazole conjugated naphthalic anhydride was firstly synthesized,[2d] however, the decarbonylation was only reacted with yellow mercuric oxide in the way we used in the above experiment. Two thiadiazole conjugated naphthoic acid isomers **18** and **19** were obtained with the ratio of 1:1 by ^{1}H NMR. The pure desired compounds $\mathbf{C_{1-2}}$ and $\mathbf{D_{1-2}}$ were then synthesized and purified by following the procedures described above (Scheme 2).

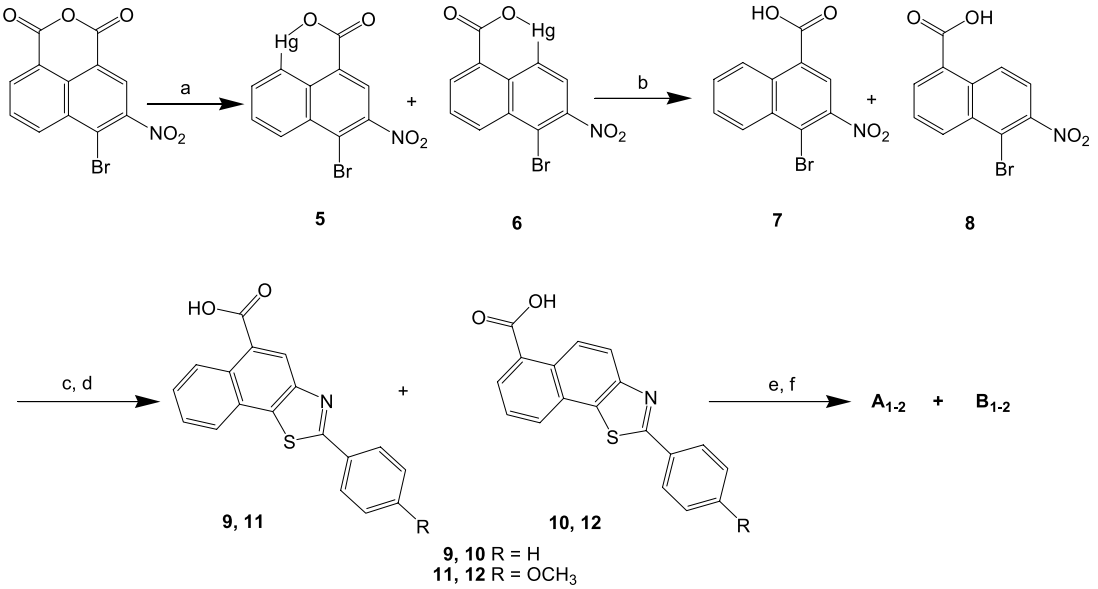
Structures of all the final products were well confirmed by ^{1}H NMR, HRMS and IR spectra. Furthermore, the above experiments provided two ways to synthesize different region-isomers of heterocyclic conjugated naphthalene carboxamides which may have potentials in other fields.

The UV–vis and fluorescent data for these compounds were shown in Table 1. Slight difference was found between the data of $\mathbf{A_n}$ and $\mathbf{B_n}$, or $\mathbf{C_n}$ and $\mathbf{D_n}$ ($n=1$, 2) of either absorption wavelength or emission wavelength indicating that the positions of aminoalkyl side chains had no obvious effect on the spectra data.

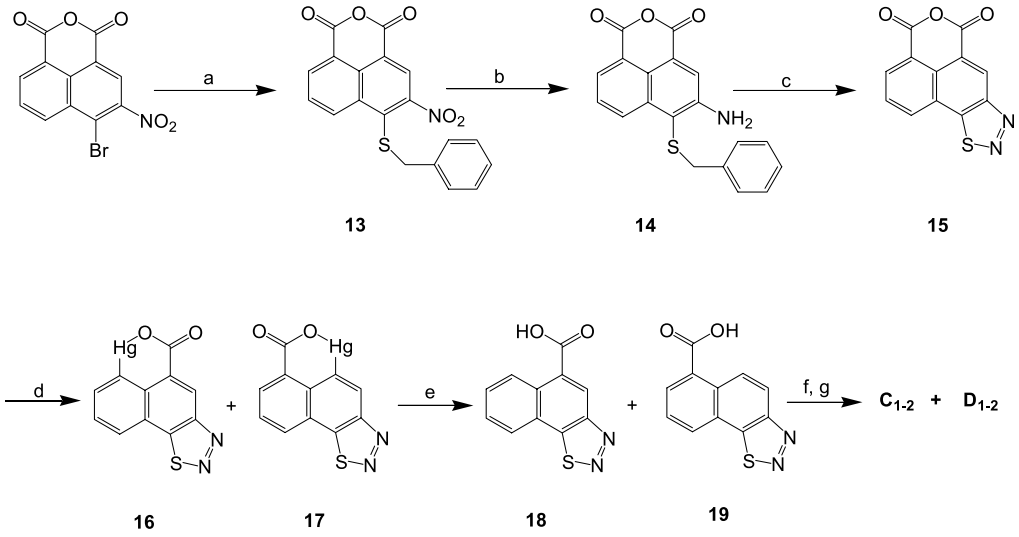
2.2. DNA-intercalating property

The Scatchard binding constants for compounds, $\mathbf{A_1}$, $\mathbf{A_2}$, $\mathbf{B_1}$, $\mathbf{B_2}$, individually and calf thymus (CT) DNA (dissolved in 20 mM Tris–HCl, pH 7.5) were determined to be 6.39×10^4, 6.73×10^4, 1.22×10^5 and 1.29×10^5 M^{-1}, respectively, by the fluorescence quenching method[5] (Fig. 2). The slight difference in DNA binding constants between $\mathbf{A_n}$ and $\mathbf{B_n}$ ($n=1$, 2) suggested that positions of the carboxalimide side chain in the chromophores almost had no effect on their corresponding intercalating activities. However, the constant of $\mathbf{A_2}$ or $\mathbf{B_2}$ was as twice higher as that of $\mathbf{A_1}$ or $\mathbf{B_1}$ suggesting the $\mathbf{A_2}$–DNA or $\mathbf{B_2}$–DNA complex was more stable with the aid of hydrogen bond possibly formed between the oxygen atom on the phenyl ring of $\mathbf{A_2}$ or $\mathbf{B_2}$ and hydrogen atoms in base pairs of DNA molecule.

The intercalation experiments of $\mathbf{C_{1-2}}$ and $\mathbf{D_{1-2}}$ were carried out by using an electronic absorption spectra technique (Fig. 3) instead of fluorescence quenching method due to their weak fluorescence. In the process of adding calf thymus DNA into the compound solution, their absorption intensities decreased with the increase of DNA concentrations.



Scheme 1. Synthesis of new compounds, $\mathbf{A_{1-2}}$ and $\mathbf{B_{1-2}}$. (a) HgO (yellow or red), NaOH, AcOH, H_2O, reflux 96 h, 98% yield; (b) concentrated HCl, reflux 3 h, 88% yield; (c) Na_2S_2, H_2O, 4 h; (d) benzaldehyde or 4-methoxybenzaldehyde, AcOH, N_2, reflux 4 h; (e) $SOCl_2$, $CHCl_3$, Et_3N; (f) *N*,*N*-dimethylethylenediamine, CH_2Cl_2, 20 h.



Scheme 2. Synthesis of new compounds, $\mathbf{C_{1-2}}$ and $\mathbf{D_{1-2}}$. (a) Benzyl mercaptan, K_2CO_3, DMF, N_2, 8 h, 93% yield; (b) $SnCl_2$, HCl, 2 h, 80% yield; (c) $NaNO_2$, HCl, 0–5 °C, 3.5 h, 86% yield; (d) HgO (yellow), NaOH, AcOH, H_2O, reflux 96 h, 95% yield; (e) concentrated HCl, reflux 2 h, 75% yield; (f) $SOCl_2$, $CHCl_3$, Et_3N; (g) corresponding RNH_2, CH_2Cl_2, 20 h.

2.3. Antitumor evaluation

The antitumor activities of these new compounds against human lung cancer cell (A549) and murine leukemia cell (P388) were evaluated in vitro (under scattered light) as shown in Table 2. The IC_{50} represents the drug concentration (μM) required to inhibit cell growth by 50%. All these compounds were found to be more cytotoxic against P388 than against A549. The compound with the aminoalkyl side chain at 6-position inhibited the growth of tumor cells more efficiently than its 5-position isomer which was in agreement with the comparison of their DNA photocleaving abilities (shown as follows). $\mathbf{B_2}$ exhibited the highest cytotoxicity with the IC_{50} of 2.53 and 0.11 μM against cell lines of A549 and P388, respectively. The phenylthiazole conjugates showed stronger cytotoxicity than thiadiazole conjugates. The modification of such agents for potent antitumor drugs seemed to be not very successful because some other reported efficient naphthalimides inhibited the tumor cells efficiently in nM or even lower orders.[1] However, these data also proved the important role of the six-membered piperidinedione ring in naphthalimides played on their antitumor activities.

2.4. DNA photocleavage

The cleavage abilities to supercoiled plasmid pBR322 DNA by these compounds were evaluated by 1% agarose gel electrophoresis. The reaction mixture containing plasmid DNA and each compound was put under a transluminator (360 nm) at a distance of 20 cm at 0 °C for 3 h under aerobic conditions, and no cleavages were observed without the light irradiation. The photocleavage efficiency was defined by the ratio of obtained nicked DNA (form II) converted from supercoiled pBR322 DNA (form I). The different cleavage efficiency orders of these compounds were revealed as $\mathbf{B_2}>\mathbf{B_1}>\mathbf{A_2}>\mathbf{A_1}$ (Fig. 4a) and $\mathbf{D_2}>\mathbf{C_2}>\mathbf{D_1}>\mathbf{C_1}$ (Fig. 4b). The effect of the position of carboxamide side chain was obviously exhibited by the order of $\mathbf{B_n}>\mathbf{A_n}$, $\mathbf{D_n}>\mathbf{C_n}$ ($n=1$ or 2) indicating that the compound with the carboxalimide side chain at 6-position photocleaved DNA more efficiently than its isomer with the side chain at 5-position. Compounds $\mathbf{B_2}$ and $\mathbf{D_2}$, being more efficient than their counterparts under the identical conditions, exhibited detectable cleavage (21 and 27% form II) at concentration of 0.5 and 5 μM, respectively. While the total cleavage of supercolied plasmid DNA from form I to 100% form II by $\mathbf{B_2}$ was found at the concentration of 50 μM. The photocleavage abilities of $\mathbf{B_2}$ (Fig. 4e) and $\mathbf{D_2}$ (Fig. 4f) increased remarkably with the prolongation of photoirradiation time, showing the cleavage a time-dependent process. No damage was observed in the absence of the light (lane 3), proving the function of UV light as a trigging factor to initiate the DNA strand scission.

Compared with that of $\mathbf{B_2}$, the concentration of the

Table 1. Spectra data of the synthesized compounds[a]

Compound	R	X	PSC[b]	UV λ_{max} (lg ε)	FL λ_{max}
$\mathbf{A_1}$	H		5	358 (3.43)	394
$\mathbf{A_2}$	OCH_3		5	360 (4.11)	396
$\mathbf{B_1}$	H		6	358 (3.46)	394
$\mathbf{B_2}$	OCH_3		6	360 (4.15)	396
$\mathbf{C_1}$		$(CH_2)_2$	5	340 (3.21)	408
$\mathbf{C_2}$		$(CH_2)_3$	5	340 (3.39)	408
$\mathbf{D_1}$		$(CH_2)_2$	6	342 (2.96)	410
$\mathbf{D_2}$		$(CH_2)_3$	6	342 (3.25)	410

[a] In absolute DMSO.
[b] PSC indicates the position of the side chain.

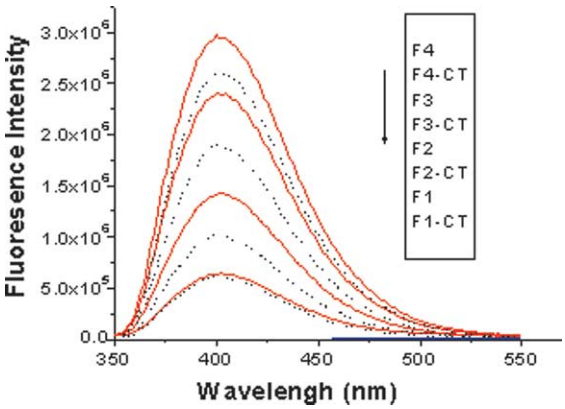


Figure 2. Fluorescence spectra before and after interaction of compound $\mathbf{B_2}$ and calf thymus DNA. Curves F and F-CT correspond to compound $\mathbf{B_2}$ before and after being mixed with DNA. Numbers 1–4 indicated the concentration of $\mathbf{B_2}$, 5, 10, 20, 40 μM, respectively. DNA applied was 50 μM (bp).

corresponding naphthalimide **1** required for detectable (19% form II) or total cleavage of supercoiled plasmid DNA, was 5 or 100 μM reported in our previous work,[2c] while $\mathbf{B_2}$ was 0.5, 50 μM. Only 67% form II DNA was obtained by **1** at 50 μM. under identical conditions, 100 μM of $\mathbf{D_2}$ could convert supercoiled DNA (form I) into 90% nicked DNA (form II) while its corresponding naphthalimide **3** could only convert 58%.[2d] Thus, we concluded that $\mathbf{B_2}$ and $\mathbf{D_2}$ exhibited stronger cleavage abilities than their corresponding naphthalimide derivatives. Additionally, $\mathbf{B_2}$ (4-methyloxyl phenyl thizaole) could obtain higher form II DNA ratio (100%) even at lower concentration (50 μM) than that of $\mathbf{D_2}$ (thiadiazole) (90%, 100 μM) indicating the phenyl thizaole group might be a better choice than thiadiazole group in photocleavage area.

In order to reveal the reactive species responsible for the plasmid DNA cleavage, $\mathbf{B_2}$ and $\mathbf{D_2}$ were chosen as example compounds to perform mechanistic experiments by addition of histidine (singlet oxygen quencher), dithiothreitol (DTT, superoxide radical scavenger), ethanol (radical scavenger), respectively (Fig. 5a and b). It was clear that histidine had no obvious effects on the cleavage reaction (lanes 4 and 7), indicating singlet oxygen ($^1O_2$) was not involved in the cleavage. However, DTT and ethanol obviously retarded

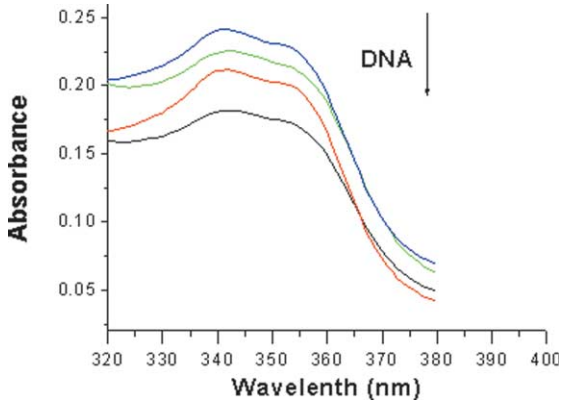


Figure 3. Interaction of $\mathbf{D_2}$ (50 μM) and calf thymus DNA. Absorption changes of $\mathbf{D_2}$ during addition of calf thymus DNA (0, 50, 100, 200 μM) in 20 mM Tris–HCl (pH 7.5) solution.

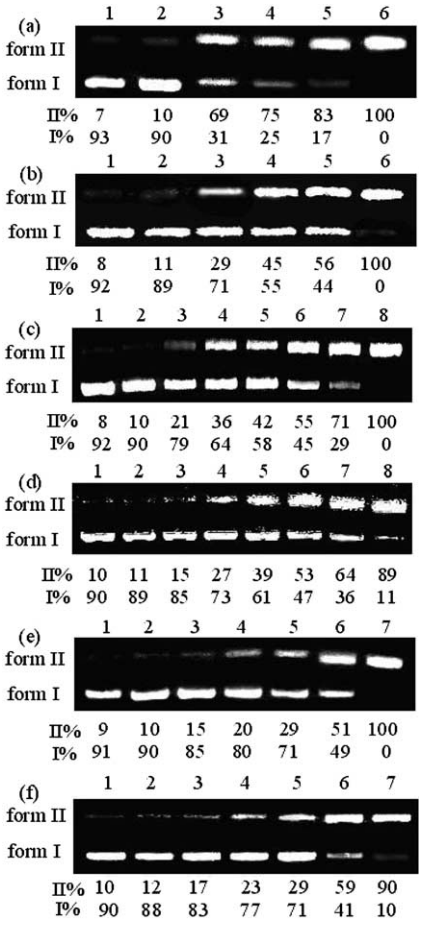


Figure 4. Photocleavage of closed supercoiled pBR322 DNA in the buffer of Tris–HCl (20 mM, pH 7.5). (a, b) Photocleavage of plasmid pBR322 DNA by different compounds for 3 h. lane 1, DNA alone (no hν); lane 2, DNA alone (hν 3 h); lanes 3–6, (a) compounds, $\mathbf{A_1}$, $\mathbf{B_1}$, $\mathbf{A_2}$, $\mathbf{B_2}$, (50 μM) individually and DNA, (b) $\mathbf{C_1}$, $\mathbf{D_1}$, $\mathbf{C_2}$, $\mathbf{D_2}$ (100 μM) individually and DNA. (c, d) Photocleavage of plasmid pBR322 DNA by $\mathbf{B_2}$ and $\mathbf{D_2}$ at various concentrations for 3 h. Lane 1, DNA alone (no hν); lane 2, DNA alone (hν 3 h); lanes 3–8, (c) DNA and $\mathbf{B_2}$ at concentration of 0.5, 1, 5, 10, 20, 50 μM, individually. (d) DNA and $\mathbf{D_2}$ at concentration of 1, 5, 10, 20, 50, 100 μM, respectively. (e, f) Photocleavage of plasmid pBR322 DNA $\mathbf{B_2}$ and $\mathbf{D_2}$ at various time intervals. Lane 1, DNA alone (no hν); lane 2, DNA alone (hν 3 h); lanes 3–7, (e) $\mathbf{B_2}$ (50 μM), (f) $\mathbf{D_2}$ (100 μM) and DNA at time intervals of 0, 30, 60, 90, 120, 180 min, respectively.

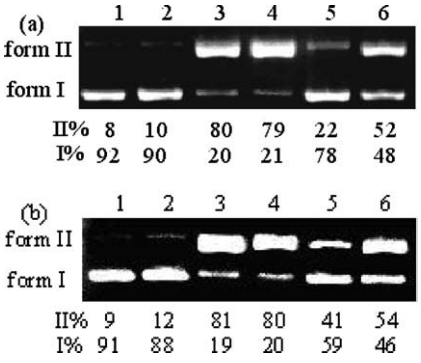


Figure 5. Effects of additives on the photocleavage of closed supercoiled pBR322 DNA by (a) compound $\mathbf{B_2}$ (30 μM), (b) $\mathbf{D_2}$ (80 μM) in the buffer of Tris–HCl (20 mM, pH 7.5) for 3 h. lane 1, DNA alone (no hν); lane 2, DNA alone (hν 3 h); lanes 3 DNA and (a) compound $\mathbf{B_2}$, (b) $\mathbf{D_2}$, lanes 4–6, DNA and (a) compound $\mathbf{B_2}$, (b) $\mathbf{D_2}$, in the presence of histidine (12 mM), dithiothreitol (DTT, 60 mM), ethanol (3.4 M), respectively.

Table 2. Cytotoxicity of compounds against the A-549, P388 cell lines

Compound	Cytotoxicity (IC_{50}, μM)	
	A549[a]	P388[b]
A_1	206	2.36
A_2	20	6.03
B_1	12	2.16
B_2	2.53	0.11
C_1	517	129
C_2	320	51.5
D_1	15,000	493
D_2	1170	275

[a] Cytotoxicity (CTX) against human lung cancer cell (A549) was measured by sulforhodamine B dye-staining method.[6]
[b] CTX against murine leukemia cells (P388) was measured by microculture tetrazolium–formazan method.[7]

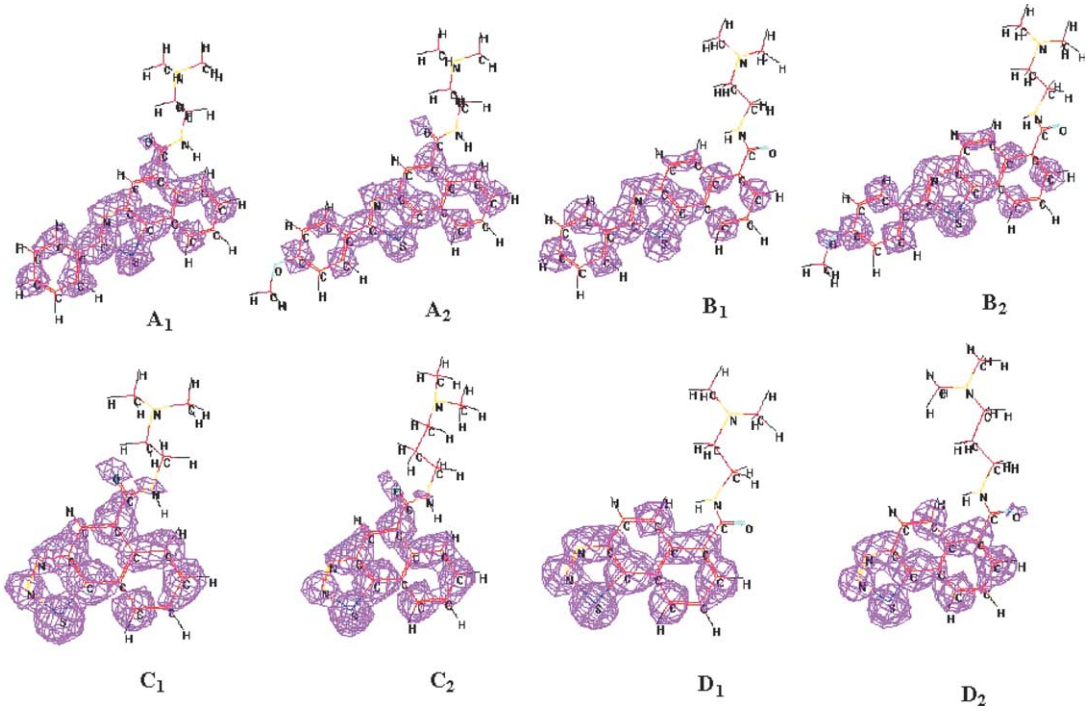


Figure 6. The simulated electron cloud densities of these compounds at excited triplet state by AM1 semi-empirical calculation.

photocleaving process as for both **B_2** and **D_2** (lanes 5 and 6), suggesting that superoxide anion (O_2^-) and radical played roles in the DNA cleavage. In our cases, the damage to DNA by these compounds might be mainly by superoxide anions generated through electron transfer from the chromophores to oxygen, and partly by radicals produced by the phenyl thiazole, thiadiazole group or/and the C═O bond via photo-excited $^3(n–\pi^*)$ state under photo-irradiation.

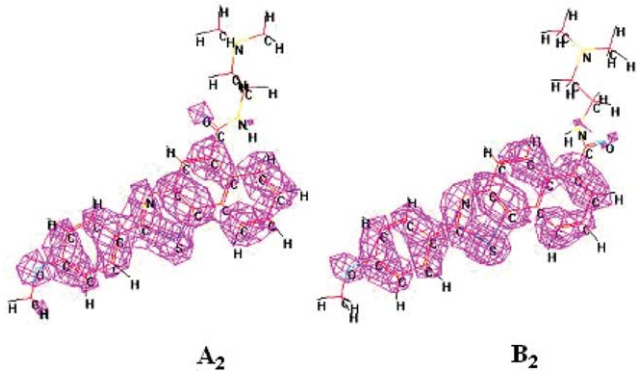


Figure 7. The simulated electron cloud densities of **A_2** and **B_2** at groud state by AM1 semi-empirical calculation.

The mechanism of **B_2** was different from that of its corresponding naphthalimides which photocleaved the plasmid only via radical produced in excited triplet state.[2c] The electron densities of thiazo-naphthalene chromophores were relatively higher than that of their corresponding naphthalimides due to the reduction of one strong electron-withdrawing group, carbonyl group. The higher electron densities were inferred to grant them the abilities to transfer electron from the chromophores to oxygen to form the superoxide anion responsible for cleavage of the plasmid under photo-activation. It must be the emergence of new reactive species (superoxide anion) that accounted for the mechanism change. The photocleavage ability of **B_2** also increased with the emergence of active superoxide anion.

With AM1 semi-empirical quantum calculations (Hyperchem7.0), the electron densities of these compounds were obtained. The electron densities of one specific compound at either excited singlet state or at triplet state

had slight difference. However, there seems to exist some correlation between electron densities on the carbonyl groups of these compounds at excited state, for example, excited triplet state (Fig. 6) and their photocleavage abilities. The carbonyl groups of compounds, $\mathbf{A_{1-2}}$, $\mathbf{C_{1-2}}$, with the carboxalimide side chains at 5-position, had thicker electron cloud, while that of compounds, $\mathbf{B_{1-2}}$, $\mathbf{D_{1-2}}$, with the carboxalimide side chains at 6-position, had almost 'naked' electron cloud. The electron densities of these compounds at ground state were also calculated which showed no obvious difference between each pair of isomers (Fig. 7, isomers of $\mathbf{A_2}$, $\mathbf{B_2}$ as examples). Comparing the electron cloud at ground and excited states of $\mathbf{A_2}$ and $\mathbf{B_2}$, we can see that the electron on the carbonyl group of $\mathbf{B_2}$ at ground state was transferred to the thiazo-naphthalene chromophore at excited state under activation, for example, UV light. However, such electron transfer was not found at the course of $\mathbf{A_2}$ which possibly exhibited the electron transfer ability difference of the pair of isomers. The higher electron transfer ability of $\mathbf{B_2}$, with the side chain at 6-position, was believed to grant it stronger ability to produce superoxide anion responsible for DNA cleavage than its corresponding isomer, $\mathbf{A_2}$, with that at 5-position, which accounted for the cleavage ability difference between the pair of regio-isomers in the end.

As to the cleavage efficiency order of $\mathbf{A_2}>\mathbf{A_1}$, $\mathbf{B_2}>\mathbf{B_1}$, the methyloxyl group on phenyl ring not only have stronger ability to push electron, then facilitate the electron transfer from the chromophore to oxygen to form the reactive superoxide anion, but also contribute to $\mathbf{A_2}$ or $\mathbf{B'_2}$ stronger intercalation ability, which both accounted for the above orders.

3. Conclusion

The present work demonstrated the design, synthesis and quantitative evaluation of two kinds of thiazo- or thiadiazo-naphthalene carboxamides with the aminoalkyl side chains at 5- or 6-position as antitumor and photocleaving agents. All these compounds were found to be more active against P388 than against A549. Compounds with aminoalkyl side chains at 6-position showed stronger DNA photocleaving and antitumor abilities than the corresponding isomers with that at 5-position. Thiazole conjugates showed stronger cleavage abilities than thiadiazole conjugates. $\mathbf{B_2}$, the most efficient cleaver, showed detectable DNA cleavage at 0.5 μM and total cleavage from form I to form 100% II at 50 μM which was more efficient than its corresponding naphthalimide. Mechanism experiment showed that electron transfer involving superoxide anion and radical were involved.

4. Experimental

4.1. Materials

All the solvents were of analytic grade. ^{1}H NMR were measured on a Bruker AV-400 spectrometer with chemical shifts reported as ppm (in DMSO/$CDCl_3$-d_6, TMS as internal standard). Mass spectra were measured on a HP 1100 LC–MS spectrometer. Melting points were determined by an X-6 micro-melting point apparatus and uncorrected. Absorption spectra were determined on PGENERAL TU-1901 UV–VIS Spectrophotometer.

4.2. Synthesis

4.2.1. Anhydro-8-hydroxylmercuri-1-naphthoic acids 5 and 6. 4-Bromo-3-nitro-1,8-naphthalic anhydride (9.66 g, 30 mmol) was suspended in 100 mL aqueous sodium hydroxide (3.75 g, 94 mmol) and refluxed until the solid material dissolved, a solution of HgO (yellow or red) (6.6 g) in a mixture of H_2O (10 mL) and AcOH (6 mL) was added with stirring to result in slow evolution of carbon dioxide. The reaction mixture refluxed for 96 h, then cooled and filtered. The highly insoluble yellow solid was washed with water and dried under vacuum at 100 °C overnight to give the mixture of **5** and **6** (15 g, 98% yield). Attempts to purify and separate the anhydro compounds were unsuccessful. It is insoluble in organic solvents.

4.2.2. 4-Bromo-3-nitro-1-naphthoic acid (7) and 4-bromo-3-nitro-8-naphthoic acid (8). The obtained precipitates were suspended in 80 mL concentrated HCl, stirred, heated under reflux for 3 h. Hot filtration gave the mixture of 4-bromo-3-nitro-1-naphthoic acid **7** and 4-bromo-3-nitro-8-naphthoic acid **8** (7.1 g, 88% yield) with ratio of 4:1 via ^{1}H NMR. APCI-MS (negative) *m*/*z*: 293.9 $(M-H)^+$.

4.2.3. 2-Phenyl naphtha[2,1-*d*]thiazole-5-acid (9) and 2-phenyl naphtha[2,1-*d*]thiazole-6-acid (10). $Na_2S\cdot 9H_2O$ (4.32 g, 18 mmol) and S (1.152 g, 36 mmol) were refluxed in 50 mL H_2O for 0.5 h till S was all dissolved. The acids, **7** and **8** (1.18 g, 4 mmol) was added within 0.5 h and refluxed for 8 h, the reaction mixture cooled and filtered to get the dark red solution. Then it was dropped into glacial acetic acid containing benzaldehyde (0.448 mL) immediately under the protection of N_2, and refluxed for 4 h, cooled and poured into 1000 mL ice-water, filtered, washed with water and dried under vacuum at 40 °C overnight to obtain the brown solid mixture of phenyl thiazole conjugated naphthalic acids **9** and **10** (0.75 g, 65% yield). APCI-MS (negative) *m*/*z*: 306.0 $(M-H)^+$.

4.2.4. *N*-(2-(Dimethylamino)ethyl)-2-phenyl naphtha[2,1-*d*] thiazole-5-carboxamide ($\mathbf{A_1}$) and *N*-(2-(dimethylamino) ethyl)-2-phenyl naphtha[2,1-*d*]thiazole-6-carboxamide ($\mathbf{B_1}$). The acids **9** and **10** (0.75 g) were treated with thionyl chloride (15 mL) and DMF (1 drop) in $CHCl_3$ (15 mL) at reflux temperature for 20 h. After removal of the solvent and excess thionyl chloride, the crude solid and *N*,*N*-dimethyl ethyl diamine (0.5 mL) were combined in 25 mL CH_2Cl_2. The mixture cooled in an ice bath while Et_3N (0.55 mL) was added dropwise with stirring. The stirring continued for 20 h at room temperature. Removal of solvent and separation on silica gel chromatography afforded the pure products. Separated on silica gel chromatography (CH_2Cl_2/MeOH=6:1, v/v) to get pure $\mathbf{A_1}$ (0.45 g, 51% yield) and $\mathbf{B_1}$ (0.11 g, 12% yield).

Compound $\mathbf{A_1}$. Mp 186–187 °C. ^{1}H NMR (d_6-$CDCl_3$) δ (ppm): 2.33 (s, 6H, NCH_3), 2.66 (t, $J_1=6$ Hz, $J_2=5.2$ Hz,

2H, NCH_2), 3.69 (d, $J_1=4$ Hz, 2H, $CONHCH_2$), 7.02 (s, 1H, CONH), 7.52 (d, $J=5.2$ Hz, 3H, 3′-H, 4′-H, 5′-H), 7.62 (m, $J_1=7.6$ Hz, $J_2=8$ Hz, $J_3=7.6$ Hz, $J_4=7.6$ Hz, 2H, 7-H, 8-H), 8.05 (d, $J_1=7.6$ Hz, 9-H), 8.13 (t, $J_1=2$ Hz, $J_2=3.2$ Hz, 2H, 1′-H, 6′-H), 8.26 (s, 1H, 4-H), 8.50 (d, $J=8$ Hz, 1H, 6-H). HRMS (ESI): calcd for $C_{22}H_{22}SN_3O$ $(M+H)^+$: 376.1484. Found: 376.1475. IR (KBr): 3285, 2921, 2850, 1635, 1536, 761 cm^{-1}.

Compound **B_1**. Mp 142–143 °C. ^1H NMR (d_6-$CDCl_3$) δ (ppm): 2.33 (s, 6H, NCH_3), 2.65 (t, $J_1=6$ Hz, $J_2=5.6$ Hz, 2H, NCH_2), 3.68 (d, 2H, $J=5.2$ Hz, $CONHCH_2$), 6.93 (s, 1H, CONH), 7.51 (d, $J=5.2$ Hz, 3H, 3′-H, 4′-H, 5′-H), 7.59 (t, $J_1=7.6$ Hz, $J_2=7.6$ Hz, 1H, 8-H), 7.67 (d, $J=6.8$ Hz, 1H, 9-H), 8.09 (d, $J=8$ Hz, 7-H), 8.14 (d, $J=8.4$ Hz, 3H, 2′-H, 6′-H, 4-H), 8.37 (d, $J=9.2$ Hz, 1H, 5-H). HRMS (ESI): calcd for $C_{22}H_{22}SN_3O$ $(M+H)^+$: 376.1484. Found: 376.1487. IR (KBr): 3285, 2921, 2850, 1635, 1536, 761 cm^{-1}.

4.2.5. *N*-(2-(Dimethylamino)ethyl)-2-(4-methoxyphenyl) naphtha[2,1-*d*]thiazole-5-carboxamide (A_2) and *N*-(2-(dimethylamino)ethyl)-2-(4-methoxyphenyl) naphtha[2,1-*d*]thiazole-6-carboxamide (B_2). Prepared and purified in a similar manner as that in **A_1** and **B_1**, 4-methoxybenzaldehyde was used here instead of benzaldehyde and separated on silica gel chromatography (CH_2Cl_2/MeOH=4:1, v/v).

Compound **A_2**. Mp 194–195 °C. ^1H NMR (d_6-$CDCl_3$) δ (ppm): 2.92 (s, 6H, NCH_3), 3.44 (s, 2H, NCH_2), 3.86 (s, 3H, OCH_3), 3.98 (s, 2H, $CONHCH_2$), 6.92 (d, $J=8.8$ Hz, 2H, 3′-H, 5′-H), 7.46 (m, $J_1=7.6$ Hz, $J_2=8.8$ Hz, $J_3=8.8$ Hz, $J_4=6.4$ Hz, 2H, 7-H, 8-H), 7.82 (d, $J=7.6$ Hz, 6-H), 7.89 (d, $J=8.4$ Hz, 2H, 2′-H, 6′-H), 8.30 (s, 1H, 4-H), 8.33 (d, $J=8$ Hz, 1H, 9-H), 8.57 (s, 1H, CONH). HRMS (ESI): calcd for $C_{23}H_{24}SN_3O_2$ $(M+H)^+$: 406.1545. Found: 406.1554. IR (KBr): 3285, 2921, 2850, 1635, 1606, 827 cm^{-1}.

Compound **B_2**. Mp 154–155 °C. ^1H NMR (d_6-$CDCl_3$) δ (ppm): 2.58 (s, 6H, NCH_3), 2.84 (t, $J_1=6$ Hz, $J_2=5.6$ Hz, 2H, NCH_2), 3.81 (d, $J=5.2$ Hz, 2H, $CONHCH_2$), 3.90 (s, 3H, OCH_3), 7.01 (d, $J=8.4$ Hz, 2H, 3′-H, 5′-H), 7.58 (t, 2H, 8-H, 9-H), 7.78 (s, 1H, 7-H), 8.07 (d, $J=8.4$ Hz, 2H, 2′-H, 6′-H), 8.12 (d, $J=8.8$ Hz, 4-H), 8.39 (d, $J=8.4$ Hz, 1H, 5-H). HRMS (ESI): calcd for $C_{23}H_{24}SN_3O_2$ $(M+H)^+$: 406.1545. Found: 406.1554. IR (KBr): 3285, 2921, 2850, 1635, 1606, 827 cm^{-1}.

4.2.6. 4-Benzylmercapto-3-nitro-1,8-naphthalic anhydride (13). 4-Bromo-3-nitro-1,8-naphthalic anhydride (2.32 g, mmol), K_2CO_3 (0.52 g), benzylmercaptan (0.88 mL) was dissolved in 45 mL DMF under the protection of N_2, the mixture reacted for 8 h at 80 °C, cooled and poured into 1000 mL water, filtered and dried to get yellow solid of **13** (2.47 g, 93% yield), mp 188–191 °C. APCI-MS (negative) *m/z*: 400.0 $(M+Cl^-)^+$.

4.2.7. 4-Benzylmercapto-3-amino-1,8-naphthalic anhydride (14). The above solid and $SnCl_2\cdot 2H_2O$ (7.6 g) were suspended in 30 mL concentrated HCl, raised the reaction temperature to 90 °C and stirred for 2 h, cooled and poured into 500 mL ice water, filtered and dried to get yellow solid of **14** (1.81 g, 80%yield), mp 177–181 °C. APCI-MS (positive) *m/z*: 336.0 $(M+H)^+$.

4.2.8. Thiadiazole conjugated naphthalic anhydride (15). The above solid (1.46 g), AcOH (57 mL), H_2O (7 mL) and concentrated HCl (8.5 mL) were stirred for 30 min at room temperature, cooled with ice bath, 10 mL aqueous solution of $NaNO_2$ (0.31 g) was added within 20 min, and continued to react for 3.5 h, filtered, washed with 1% aqueous solution of $NaHCO_3$ and dried to get yellow-green solid of **15** (0.97 g, 86% yield), mp 165–167 °C. APCI-MS (negative) *m/z*: 255.2 $(M-H)^+$.

4.2.9. Naphtha[2,1-*d*][1,2,3]thiadiazole-5-carboxylic acid (18) and naphtha[2,1-*d*][1,2,3]thiadiazole-6-carboxylic acid (19). Compound **15** (0.97 g) was suspended in 15 mL aqueous sodium hydroxide (0.38 g, 9.5 mmol) and refluxed until the solid material dissolved, a solution of HgO (yellow) (0.67 g) in a mixture of H_2O (5 mL) and AcOH (1 mL) was added with stirring to result in slow evolution of carbon dioxide. The reaction mixture refluxed for 96 h, then cooled and filtered. The highly insoluble yellow solid was washed with water and then dried under vacuum at 50 °C overnight to give the mixture of **16** and **17** (1.71 g, 95% yield). The obtained precipitates were suspended in 15 mL concentrated HCl, stirred, heated under reflux for 3 h. Hot filtration gave the mixture acids of **18** and **19** (0.66 g, 75% yield) with the ratio of 1:1 via ^1H NMR. APCI-MS (negative) *m/z*: 229.1 $(M-H)^+$.

4.2.10. *N*-(2-(Dimethylamino)ethyl) naphtha[2,1-*d*][1,2,3] thiadiazole-5-carboxamide (C_1) and *N*-(2-(dimethylamino)ethyl) naphtha[2,1-*d*][1,2,3] thiadiazole-6-carboxamide (D_1). The acids **18** and **19** (0.56 g) were treated with thionyl chloride (10 mL) and DMF (1 drop) in $CHCl_3$ (10 mL) at reflux temperature for 20 h. After removal of the solvent and excess thionyl chloride, the obtained crude solid and propitiate amine (0.4 mL) were combined in CH_2Cl_2 (25 mL). The mixture cooled in an ice bath while Et_3N (0.45 mL) was added dropwise with stirring. The stirring continued for 20 h at room temperature. Removal of solvent and separation on silica gel chromatography afforded the pure products. Separated on silica gel chromatography ($CHCl_3$/MeOH=1:1, v/v) to get pure **C_1** (0.22 g, 31% yield) and **D_1** (0.29 g, 40% yield).

Compound **C_1**. Mp 149–150 °C. ^1H NMR (d_6-$CDCl_3$) δ (ppm): 2.32 (s, 6H, NCH_3), 2.65 (t, $J_1=4.2$ Hz, $J_2=4.5$ Hz, 2H, NCH_2), 3.68 (d, $J=4.2$ Hz, 2H, $CONHCH_2$), 7.02 (s, 1H, CONH), 7.75 (m, $J_1=6.8$ Hz, $J_2=7.2$ Hz, $J_3=6.0$ Hz, $J_4=8$ Hz, $J_5=6.8$ Hz, 2H, 7-H, 8-H,), 8.10 (d, $J=8$ Hz, 1H, 9-H), 8.51 (d, $J=8$ Hz, 6-H), 8.64 (s, 1H, 4-H). HRMS (ESI): calcd for $C_{15}H_{17}SN_4O$ $(M+H)^+$: 301.1123. Found: 301.1127. IR (KBr): 3266, 2918, 2849, 1638, 1548, 762 cm^{-1}.

Compound **D_1**. Mp 129–130 °C. ^1H NMR (d_6-$CDCl_3$) δ (ppm): 2.31 (s, 6H, NCH_3), 2.63 (t, $J_1=5.6$ Hz, $J_2=6$ Hz, 2H, NCH_2), 3.67 (d, 2H, $J=5.6$ Hz, $CONHCH_2$), 6.81 (s, 1H, CONH), 7.68 (t, $J_1=6$ Hz, $J_2=7.8$ Hz, 1H, 8-H), 7.84 (d, $J=7.2$ Hz, 1H, 9-H), 8.16 (d, $J=8.4$ Hz, 1H, 7-H), 8.48 (d, $J=9.6$ Hz,1H, 4-H), 8.54 (d, $J=9.2$ Hz,1H, 5-H). HRMS (ESI): calcd for $C_{15}H_{17}SN_4O$ $(M+H)^+$: 301.1123.

Found: 301.1133. IR (KBr): 3285, 2921, 2850, 1635, 1536, 808 cm^{-1}.

4.2.11. *N*-(3-(Dimethylamino) propyl) naphtha[2,1-*d*][1,2,3] thiadiazole-5-carboxamide (C_2) and *N*-(3-(dimethyl amino) propyl) naphtha[2,1-*d*][1,2,3]thiadiazole-6-carboxamide (D_2). Prepared and purified in a similar manner as that in C_1 and D_1, *N*,*N*-dimethylpropyl diamine was used here instead of *N*,*N*-dimethylethyl diamine and separated on silica gel chromatography ($CHCl_3$/MeOH=1:2, v/v) to get pure C_2 (33% yield) and D_2 (35% yield).

Compound C_2. Mp 167–168 °C. ^1H NMR (d_6-$CDCl_3$) δ (ppm): 1.93 (t, $J_1=6$ Hz, $J_2=6.4$ Hz, CH_2), 2.33 (s, 6H, NCH_3), 2.65 (t, $J_1=5.6$ Hz, $J_2=6$ Hz, 2H, NCH_2), 3.70 (d, 2H, $J=5.6$ Hz, $CONHCH_2$), 7.73 (m, $J_1=6.8$ Hz, $J_2=7.2$ Hz, $J_3=6.0$ Hz, $J_4=8$ Hz, $J_5=6.8$ Hz, 2H, 7-H, 8-H), 8.07 (d, $J=8$ Hz, 1H, 9-H), 8.39 (s, 1H, CONH), 8.52 (d, $J=8.4$ Hz, 6-H), 8.58 (s, 1H, 4-H). HRMS (ESI): calcd for $C_{16}H_{19}SN_4O$ $(M+H)^+$: 315.1280. Found: 315.1278. IR (KBr): 3274, 2940, 2856, 1634, 1541, 763 cm^{-1}.

Compound D_2. Mp 141–142 °C. ^1H NMR (d_6-$CDCl_3$) δ (ppm): 1.94 (t, $J_1=6$ Hz, $J_2=6$ Hz, CH_2), 2.33 (s, 6H, NCH_3), 2.65 (t, $J_1=5.6$ Hz, $J_2=6.4$ Hz, 2H, NCH_2), 3.68 (d, 2H, $J=5.6$ Hz, $CONHCH_2$), 7.66 (t, $J_1=7.2$ Hz, $J_2=8$ Hz, 1H, 8-H), 7.83 (d, $J=7.2$ Hz, 1H, 9-H), 8.13 (d, $J=8.4$ Hz, 2H, 7-H, CONH), 8.52 (d, $J_1=9.6$ Hz, $J_2=9.2$ Hz, 2H, 4-H, 5-H). HRMS (ESI): calcd for $C_{16}H_{19}SN_4O$ $(M+H)^+$: 315.1280. Found: 315.1270. IR (KBr): 3290, 2940, 2856, 1629, 1537, 804 cm^{-1}.

4.3. Intercalation studies of compounds to CT-DNA

(a) A compound (0.1 mL solution, A_{1-2}, B_{1-2}) in DMSO (10^{-3}–10^{-4} M) mixed with 20 mM Tris–HCl (pH=7.5) to 5 mL. Then, two groups of samples were prepared in the concentration of chemical at 5, 10, 20, 40 μM, one contained Calf-thymus DNA 50 μM, the other contained no DNA but had the same concentration of chemical as control. All the above solution was shaken for 3 days at 25 °C in the dark. Fluorescence wavelength and intensity area of samples were measured.

(b) A compound (0.25 mL solution, C_{1-2}, D_{1-2}) in DMSO (10^{-3} M) mixed with 20 mM Tris–HCl (pH=7.5) to 5 mL. Then, one group of samples were prepared in the concentration of chemical at 50 μM, one did not contain Calf-thymus DNA as control, the others contained DNA with the concentration of. 50, 100, 200 μM, respectively. All the above solution was shaken for 3 days at 25 °C in the dark. Absorption spectra of samples were measured.

4.4. Cytocoxicity in vitro evaluation

The prepared compounds have been submitted to Shanghai Institute of Materia Medica for testing their cytotoxicities.

4.5. Photocleavage of supercoiled pBR322 DNA

pBR322DNA (250 ng, form I), 1 μL solution of chemical in DMSO and 20 mM Tris–HCl (pH=7.5) were mixed to 10 μL, then irradiated for 3 h with light (360 nm) using lamp placed at 20 cm from sample. Supercoiled DNA runs at position I, nicked DNA at position II. The samples were analyzed by gel electrophoresis in 1% Agarose and gel was stained with ethidium bromide.

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References and notes

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Study of the reaction of chalcone analogs of dehydroacetic acid and *o*-aminothiophenol: synthesis and structure of 1,5-benzothiazepines and 1,4-benzothiazines

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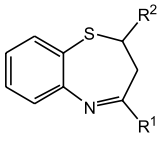
Abstract—Treatment of α,β-unsaturated carbonyl compounds, obtained by the reaction of DHA and aromatic (or heteroaromatic) aldehydes, with *o*-aminothiophenol results in the formation of 1,5-benzothiazepines and/or 1,4-benzothiazines depending upon the reaction conditions and structure of the aldehydes. The products were characterized by the combined use of multinuclear 1D and 2D NMR and GIAO/DFT calculations of ^{1}H, ^{13}C and ^{15}N chemical shifts. The tautomerism of these compounds in solution was determined, they have an exocyclic CC double bond.

1. Introduction

Both 1,5-benzothiazepine and 1,4-benzothiazine ring systems have derivatives of biological importance. Amongst those of the first group are diltiazem, clentiazem and thiazesim and amongst those of the second group are the trichosiderin pigments.[1] In this paper we would describe how in the case that single crystals cannot be grown, the combined used of multinuclear NMR and DFT calculations allows to identify pairs of isomers belonging to reduced derivatives **1** and **2** of these two classes.



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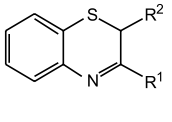
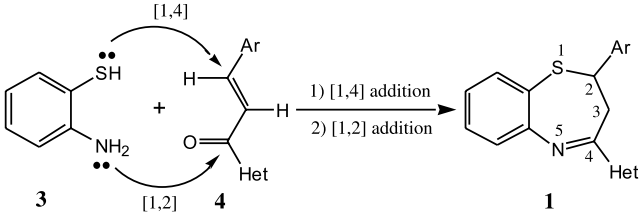


2

One of the most widely methods employed for the preparation of 1,5-benzothiazepines involves the reaction of *o*-aminothiophenol (*o*-ATP, **3**) with α,β-unsaturated esters,[2] α,β-unsaturated ketones (**4**),[3] or chalcones,[4] both under acidic and basic conditions. Although in all reactions between a dinucleophile (hydrazines, hydroxylamine, *o*-phenylenediamine, etc.) with a dielectrophile of the type above mentioned, two compounds can be formed,[5] since only benzothiazepines were isolated it was assumed that the reaction starts by the 1,4-Michael addition of the SH on the CC double bond followed by the condensation of the NH_2 on the carbonyl group (Fig. 1).



3 **4** **1**

Figure 1.

One of the most common synthesis of dihydro-1,4-benzothiazines involves also *o*-ATP, **3**, but alkynes or α-bromocarbonyl compounds (Fig. 2) instead of β-difunctional compounds.[1]

Although there is no precedent that in the reaction between

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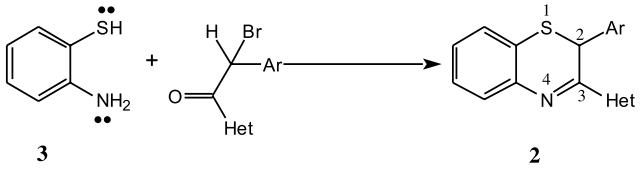


Figure 2.

3 and **4** other heterocycles than benzothiazepines **1** could be formed, nevertheless there is another possibility (Fig. 3). According to Baldwin's rules both 7-*endo-trig* and 6-*exo-trig* processes are favored.[6] The first one leading to the benzothiazepine **1** while the second one affords a dihydro-1,4-benzothiazine **5**. Compounds **1** and **5** are isomers and, as we will show, not easily differentiated.

In a first step, α,β-unsaturated ketones **7** are prepared from dehydroacetic acid (**6**). In a second step, compounds **7** reacted with *o*-aminothiophenol (*o*-ATP, **3**, Fig. 4) to afford dihydro-1,5-benzothia-zepines **1** and/or dihydro-1,4-benzothiazines **5**. This is the first time that the formation of **5** is reported.

2. Results and discussion

In view of these observations and our ongoing interest in the chemistry of DHA and its derivatives[7–9] (for a review on DHA see Ref. 10), it was considered worthwhile to explore the reaction depicted in Figure 4. The experimental procedure consists in treating DHA derivatives with *o*-ATP in EtOH/AcOH, a method which has effectively been employed previously for the synthesis of several 1,5-benzothiazepines. In order to attempt the proposed method, chalcone analogs of DHA (**7**), available by the condensation of DHA (**6**) with benzaldehydes or their heterocyclic analogs in chloroform in the presence of piperidine,[11] were prepared. The chalcones **7** were transformed into **1** and/or **5** derivatives in 76–86% yields (Table 1).

Actually, although **1** is the expected compound according to literature results, there are further structural possibilities. We have assumed, like other authors, that the carbonyl group involved in the hydrogen bond is the C(4′)=O.[11] But at least three reasonable tautomeric forms (Fig. 5) can be written for the benzothiazepines **1** and three similar ones for the benzothiazines **5**.

2.1. Determination of the structure and tautomerism of compounds a–l

We have used a combination of NMR spectroscopies (^{1}H, ^{13}C and ^{15}N) and GIAO–DFT calculations. In two

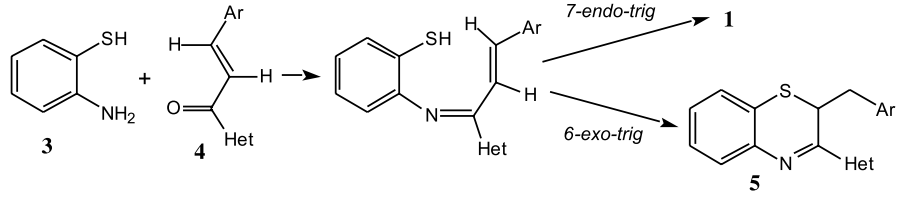


Figure 3.

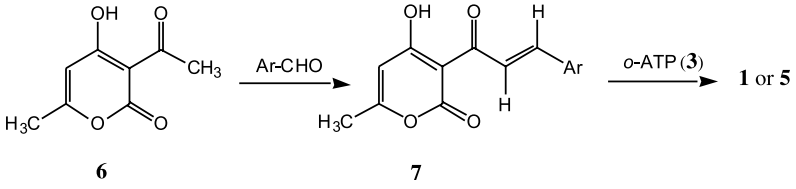


Figure 4.

Table 1. Heterocycles of the **a–l** series prepared according to Figure 4

Compounds **1** and **5**	Mp (°C)	Yield (%)	Method[a]	Molecular formula
1a, Ar=C_6H_5	228–229	85	A	$C_{21}H_{17}NO_3S$
1b, Ar=4-ClC_6H_4	218–219	83	A	$C_{21}H_{16}ClNO_3S$
1c, Ar=4-$CH_3C_6H_4$	230–231	84	A	$C_{22}H_{19}NO_3S$
1d, Ar=4-OHC_6H_4	255–256	79	A	$C_{21}H_{17}NO_4S$
1e, Ar=2-OHC_6H_4	244–246	82	A	$C_{21}H_{17}NO_4S$
1f, Ar=4-$OCH_3C_6H_4$	238–240	85	A	$C_{22}H_{19}NO_4S$
1g, Ar=4-$N(CH_3)_2C_6H_4$	234–235	86	A	$C_{23}H_{22}N_2O_3S$
1h, Ar=2-$NO_2C_6H_4$	200–202	76	A	$C_{21}H_{16}N_2O_5S$
5h, Ar=2-$NO_2C_6H_4$	230–232	83	B	$C_{21}H_{16}N_2O_5S$
1i, Ar=3-$NO_2C_6H_4$	210–212	75	A/B	$C_{21}H_{16}N_2O_5S$
1j, Ar=4-$NO_2C_6H_4$	232–233	78	A	$C_{21}H_{16}N_2O_5S$
5j, Ar=4-$NO_2C_6H_4$	190–191	81	B	$C_{21}H_{16}N_2O_5S$
1k, Ar=2-thienyl	180–182	81	A/B	$C_{19}H_{15}NO_3S_2$
5l, Ar=4-pyridyl	195–197	79	A/B	$C_{20}H_{16}N_2O_3S$

[a] Conditions: (A) *o*-aminothiophenol plus two drops of piperidine in EtOH, 15 min reflux; (B) *o*-aminothiophenol plus two drops piperidine in EtOH, 2 h reflux and then addition of AcOH and 2 h reflux.

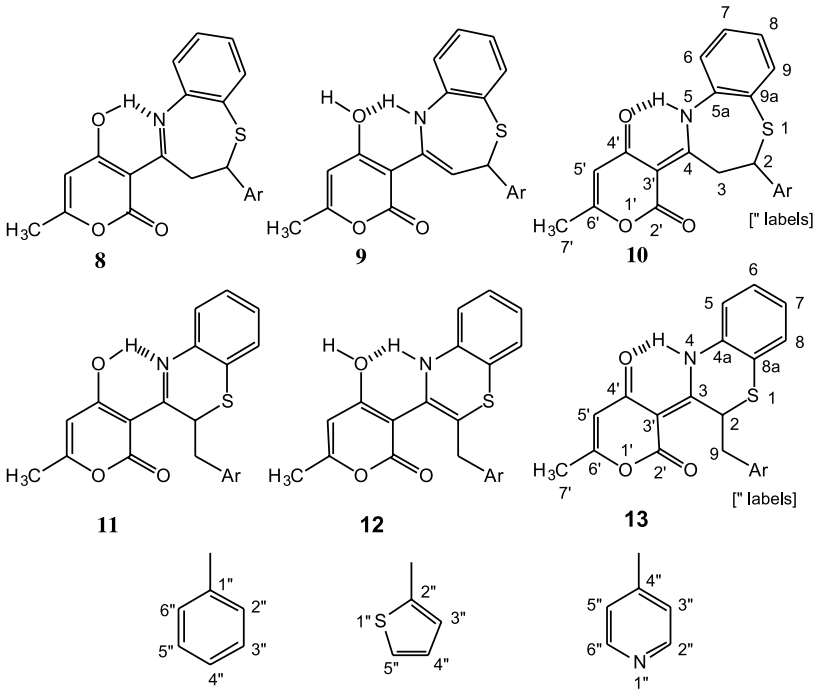


Figure 5.

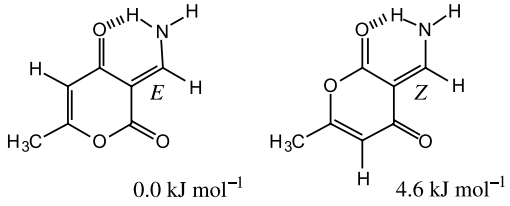
cases, those of the *ortho*- and *para*-nitro derivatives, **h** and **j**, depending on slightly different experimental conditions, two compounds are obtained (**1** and **5**). In most cases, only one compound has been obtained, that, as we will show, has the structure **1**. The only exception is the 4-pyridyl derivative, which has the structure **5l**.

In the case of compounds **h–l**, we have recorded the HMBC ^{15}N NMR spectra: in all cases, there is an N–H signal at about −220/−225 ppm ($^{1}J \approx 80$–85 Hz).[12,13] This excludes tautomers **8** (usually used to represent these compounds) and **11**. In ^{1}H NMR, the aliphatic part always appears as an AMX system (a CH proton and two anisochronous protons of a CH_2), this eliminates **9** and **12** (usually used to represent the dihydro-1,4-benzothiazines). Therefore, all the compounds have the tautomeric structures **10** or **13**. We have reported in Tables 2 and 3 the complete assignment of NMR signals for compounds **h–l**. For the sake of simplicity, we have assigned them to the corresponding **10** and **13** before establishing that they belong to these structures. The remaining compounds (see Section 3) all belong to the 1,5-benzothiazepine family **1**.

The comparison of the ^{1}H NMR parameters reported in Figures 6 and 7 shows that the anisocrony of the methylene protons is larger in the rigid seven-membered ring (1.22–1.56 ppm) than in the conformationally flexible benzyl substituent (0.36–0.49 ppm). In the **1** series, the proximity of the nitro group deshielded the H_{trans} proton, decreasing the anisochrony. On the other hand, the **5** series have the nitro group closer to H_{trans} and the anisochrony increases from −0.36 to +0.49 (0.85 ppm).

2.2. DFT and GIAO calculations of compounds 10a-13a

The structure of the simplest pair of compounds **10a** and **13a** (not isolated) was fully optimized at the B3LYP/6-31G* level. We have also calculated the *Z* isomer (about the C3′=C4 bond) corresponding to **10a**; the calculated values for the absolute shieldings in **10a***E* and **10a***Z* are very similar and cannot be used to determine the stereochemistry of the double bond, however, the *Z* isomer is calculated to be 7.1 kJ mol^{-1} less stable than the *E* one. This seems to be quite general because in the model compounds represented below, there is a related difference of 4.6 kJ mol^{-1} in favor of the *E* isomer:



Concerning the geometry of the benzothiazepine **10a**, the most relevant result is the folding of the seven-membered ring. The three protons of the AMX system present dihedral angles of 179.0 and 62.5° that is an almost perfect staggered conformation. A calculation of the Karplus-type ^{3}J coupling constants using Altona's equation,[14] yield 11.5 and 3.7 Hz for the *trans* and the *gauche* couplings, which compare quite well with the experimental values of 12.6 and 3.3 Hz (compound **1a**, experimental part).

To discuss the possibility to use the absolute shieldings (σ pp, GIAO/B3LYP/6-31G*) it is necessary to realize that this basis set only provides relative values, that is, σ values that are linearly correlated with experimental δ values, with correlation lines having intercepts and slopes different from 1 ($\delta = \mathbf{a} + \mathbf{b}\sigma$). It is useful to calculate a series of simple compounds and determine **a** and **b** values from these data (Table 4).

Table 2. ^{1}H, ^{13}C and ^{15}N chemical shifts (δ, ppm) referred to TMS (^{1}H, ^{13}C) and external CH_3NO_2 (^{15}N) and ^{1}H-^{1}H and ^{1}H-^{15}N coupling constants (Hz) (solvent $CDCl_3$) of dihydro-1,5-benzothiazepines

Atom	**1h** (*o*-NO_2)	**1i** (*m*-NO_2)	**1j** (*p*-NO_2)	**1k** (2-thienyl)
C2	48.9	55.0	55.1	51.7
	5.78 (H_X)	5.29 (H_X)	5.27 (H_X)	5.47 (H_X)
	J_{MX}=4.2 Hz	J_{MX}=4.4 Hz	J_{MX}=4.3 Hz	J_{MX}=4.8 Hz
C3	36.6	39.5	39.3	40.3
	3.00 (H_A)	2.69 (H_A)	2.68 (H_A)	2.68 (H_A)
	4.22 (H_M)	4.26 (H_M)	4.24 (H_M)	4.38 (H_M)
	$J_{AM=}$11.7 Hz	$J_{AM=}$11.8 Hz	$J_{AM=}$12.0 Hz	$J_{AM=}$11.9 Hz
	J_{AX}=12.2 Hz	J_{AX}=12.5 Hz	J_{AX}=12.4 Hz	J_{AX}=12.2 Hz
	$J_{MAr=}$0.8 Hz		$J_{MAr=}$1.0 Hz	$J_{ATh(3)}$=1.1 Hz
C4	172.5	172.6	172.5	172.7
N5	−220.6	−220.6	−220.6	−220.6
	15.68 (NH)	15.62 (NH)	15.62 (NH)	15.57 (NH)
	^{1}J(NH)=83.6 Hz	^{1}J(NH)=83.7 Hz	^{1}J(NH)=85.6 Hz	^{1}J(NH)=83.7 Hz
C5a	139.7	139.7	139.8	139.8
C6	124.8	125.1	125.1	124.6_3
	7.32 (m, H6)	7.36 (H6)	7.36 (H6)	7.35 (m, H6)
C7	130.6	130.8	130.8	130.6
	7.53 (m, H7)	7.55 (H7)	7.55 (H7)	7.52 (H7)
C8	128.3	128.8	128.7	128.3
	7.32 (m, H7)	7.41 (H8)	7.40 (H8)	7.35 (m, H8)
C9	135.9	135.9	135.8	136.6
	7.53 (m, H7)	7.80 (H9)	7.76 (H9)	7.72 (H9)
C9a	127.9	127.6	127.7	127.7
C2′	163.8	163.2	163.2	163.2
C3′	96.9	96.9	96.9	97.0
C4′	185.2	185.3	185.3	185.3
C5′	107.2	107.4	107.4	107.4
	5.83 (CH)	5.84 (CH)	5.84 (CH)	5.83 (CH)
	$^{4}J_{(CH3)}$=0.8 Hz	$^{4}J_{(CH3)}$=0.8 Hz	$^{4}J_{(CH3)}$=0.8 Hz	$^{4}J_{(CH3)}$=0.9 Hz
C6′	164.0	164.1	164.1	164.0
C7′	19.9	20.0	20.0	20.0
	2.19 (CH_3)	2.21 (CH_3)	2.21 (CH_3)	2.20 (CH_3)
	^{4}J=0.8 Hz	^{4}J=0.8 Hz	^{4}J=0.9 Hz	^{4}J=0.9 Hz
Ar C-1″	137.2	145.5	150.5	S-1″
Ar C-2″	147.1 (NO_2)	121.5	127.4	147.5
		8.33 (H2″)	7.59 (H2″)	
Ar C3″	125.0	148.5 (NO_2)	124.1	124.1
	7.95 (H3″)		8.18 (H3″)	7.01 (H3″)
	^{3}J=8.1 Hz			^{3}J=3.5 Hz
	^{4}J=1.4 Hz			
Ar C4″	128.4	122.7	147.3 (NO_2)	126.8
	7.43 (H4″)	8.12 (H4″)		6.93 (H4″)
Ar C5″	133.2	129.7	124.1	124.5_7
	7.53 (m, H5″)	7.50 (H5″)	8.18 (H5″)	7.18 (H5″)
				^{3}J=5.1 Hz
				^{4}J=1.3 Hz
Ar C6″	126.8	132.8	127.4	—
	7.32 (m, H6″)	7.74 (H6″)	7.59 (H6″)	

The two values in italics (both carbon atoms α of S atom) were not included in regression (1).

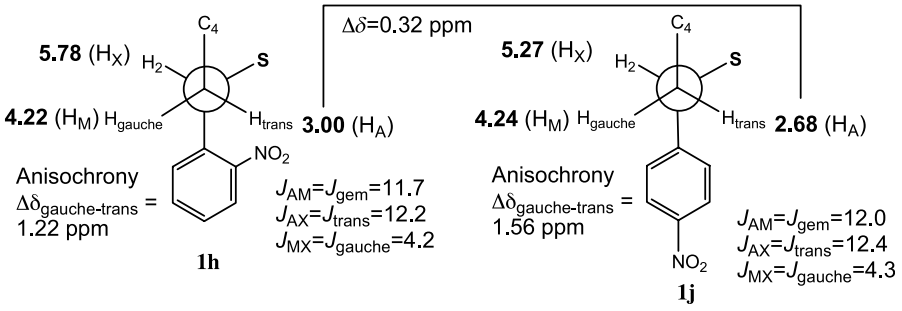


Figure 6.

Table 3. ^{1}H, ^{13}C and ^{15} chemical shifts (δ, ppm) referred to TMS (^{1}H, ^{13}C) and external CH_3NO_2 (^{15}N) and ^{1}H-^{1}H and ^{1}H-^{15}N coupling constants (Hz) (solvent $CDCl_3$) of dihydro-1,4-benzothiazines

Atom	**5h** (*o*-NO_2)	**5j** (*p*-NO_2)	**5l** (4-pyridyl)
C2	38.0	37.7	37.2
	5.70 (H_X)	5.68 (H_X)	5.70 (H_X)
	$J_{AX}=4.6$ Hz	$J_{MX}=3.6$ Hz	$J_{MX}=3.6$ Hz
C3	163.9	164.6	164.3*
C9	31.0	34.7	34.3
	3.22 (H_A)	2.75 (H_A)	2.64 (H_A)
	3.58 (H_M)	3.24 (H_M)	3.13 (H_M)
	$J_{AM}=13.7$ Hz	$J_{AM}=13.3$ Hz	$J_{AM}=13.3$ Hz
	$J_{MX}=10.2$ Hz	$J_{AX}=10.9$ Hz	$J_{AX}=11.0$ Hz
N4	−225.9	−226.4	−226.4
	16.44 (NH)	16.41 (NH)	16.41 (NH)
	^{1}J(NH)=81.7 Hz	^{1}J(NH)=84.9 Hz	^{1}J(NH)=83.7 Hz
C4a	132.3	132.8	132.8
C5	120.4	120.6	120.6
	7.29 (m, H5)	7.29 (m, H5)	7.30 (m, H5)
C6	128.8*	128.9*	129.0**
	7.29 (m, H6)	7.29 (m, H6)	7.30 (m, H6)
C7	127.5*	127.7*	127.6**
	7.29 (m, H7)	7.29 (m, H7)	7.30 (m, H7)
C8	127.7*	127.6*	127.5**
	7.29 (m, H8)	7.29 (m, H8)	7.30 (m, H8)
C8a	121.4	121.2	121.3
C2′	163.1	163.1	163.1
C3′	94.0	93.9	93.9
C4′	185.7	185.8	185.8
C5′	107.4	107.4	107.4
	5.82 (H5′)	5.84 (H5′)	5.83 (H5′)
C6′	164.0	164.3	164.5*
C7′	19.9	20.0	20.0
	2.18 (CH_3)	2.21 (CH_3)	2.21 (CH_3)
			$^{4}J=0.6$ Hz
Ar C-1″	131.3	143.8	−74.9 (N)
Ar C-2″	150.8 (NO_2)	130.9	149.5
		7.41 (H2″)	8.53 (H2″)
Ar C3″	124.5	123.5	125.2
	7.87 (H3″)	8.15 (H3″)	7.20 (H3″)
	$^{3}J=8.2$ Hz		
	$^{4}J=1.3$ Hz		
Ar C4″	128.1	147.2 (NO_2)	145.3
	7.39 (H4″)		
Ar C5″	133.0	123.5	125.2
	7.56 (H5″)	8.15 (H5″)	7.20 (H3″)
	$^{3}J=7.3$ Hz		
Ar C6″	132.8	130.9	149.5
	7.68 (H6″)	7.41 (H6″)	8.53 (H2″)
	$^{3}J=7.8$ Hz		
	$^{4}J=1.3$ Hz		

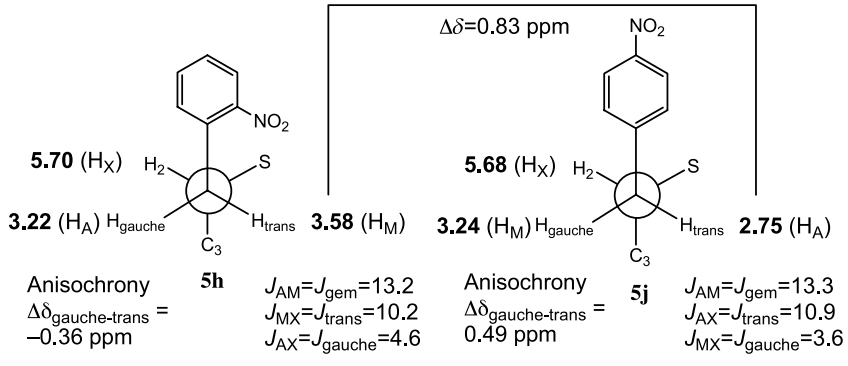


Figure 7.

$$\text{Regression } ^{13}\text{C}: \delta^{13}\text{C} = (203.0 \pm 1.0) - (1.086 \pm 0.009)\sigma\ ^{13}\text{C}, \quad n = 53, \quad r^2 = 0.996 \tag{1}$$

$$\text{Regression } ^{15}\text{N}: \delta^{15}\text{N} = -(131.6 \pm 4.7) - (1.01 \pm 0.02)\sigma\ ^{15}\text{N}, \quad n = 8, \quad r^2 = 0.997 \tag{2}$$

Table 4. Calculated absolute shieldings (σ) and experimental δ values (all in ppm)

Compound	Experimental value[a]	σ
^{13}C sp^3 aliphatic		
CH_4	−2.1	192.94
CH_3–CH_3	5.9	180.37
Cyclopropane	−2.9	189.29
Cyclobutane	23.2	165.18
Toluene	21.3	167.37
Dichloromethane	54.2	124.70
Fluoromethane	75.4	121.85
Methanol (CH_3OH)	49.3	139.33
Acetaldehyde	31.2	159.91
Acetone	30.2	161.40
Methylamine	28.3	159.09
Diethylamine CH_2	44.5	143.44
Diethylamine CH_3	15.7	162.67
Diethylmercaptan CH_2	*25.5*	156.61
Diethylmercaptan CH_3	14.8	175.72
Nitromethane	57.3	129.45
Acetonitrile	0.3	187.86
TMS	0.0	189.69
^{13}C sp^2 alkenes		
Ethane	122.8	73.63
Methylvinylether (CH_2=CH–OMe) α	153.1	45.66
Methylvinylether (CH_2=CH–OMe) β	85.5	105.19
Vinylcyanide (CH_2=CH–CN) α	107.7	86.24
Vinylcyanide (CH_2=CH–CN) β	137.8	59.29
^{13}C sp^2 aromatic		
Benzene	128.7	68.62
Toluene C_{ipso}	137.8	59.08
Toluene C_{ortho}	129.3	67.70
Toluene C_{meta}	128.5	68.44
Toluene C_{para}	125.6	71.07
Phenol C_{ipso}	155.6	41.91
Phenol C_{ortho}	116.1	82.32
Phenol C_{meta}	130.5	67.01
Phenol C_{para}	120.8	76.83
Thiophenol C_{ipso}	*130.5*	57.00
Thiophenol C_{ortho}	129.1	70.63
Thiophenol C_{meta}	128.7	67.86
Thiophenol C_{para}	125.2	72.85
Fluorobenzene C_{ipso}	163.8	33.41
Fluorobenzene C_{ortho}	114.6	80.17
Fluorobenzene C_{meta}	130.3	66.69
Fluorobenzene C_{para}	124.3	73.49
Aniline C_{ipso}	148.7	51.57
Aniline C_{ortho}	114.4	82.98
Aniline C_{meta}	129.1	67.41
Aniline C_{para}	116.3	78.97
Nitrobenzene C_{ipso}	148.3	48.29
Nitrobenzene C_{ortho}	123.4	71.45
Nitrobenzene C_{meta}	129.5	71.45
Nitrobenzene C_{para}	134.7	62.55
Pyridine C_2	150.4	46.34
Pyridine C_3	124.1	73.23
Pyridine C_4	136.1	62.41
^{13}C=O		
Acetone	205.1	−3.05
Acetaldehyde	199.6	4.24
Formic acid	166.3	41.74
Formamide	164.9	44.70
^{15}N sp^3		
Liquid ammonia	−380.2	254.97
Methylamine	−377.3	238.62
Hydrazine	−334.9	199.90
Aziridine	−393.3	250.99
Aniline	−320.3	193.64
^{15}N sp^2		
Pyridine	−63.2	−62.84
^{15}N sp		
Acetonitrile	−137.1	−1.64

The two values in italics (both carbon atoms α of S atom) were not included in regression 1.

[a] Chemical shifts: ^{13}C from Ref. 15; ^{15}N from Ref. 16.

For the excluded values, the experimental and predicted (Eq. 1) values of the CH_2 of diethylmercaptan are 25.5 and 33.0 (+7.5 ppm); in the case of the *ipso* carbon of thiophenol, the values are 130.5 and 141.1 (+10.6 ppm).

Using these equations, we have transformed the σ values calculated for **1a** and **5a** into δ values (Table 5).

There is no doubt that the first hypothesis (that we have assumed all along this paper) is the correct one. Excluding the pairs of carbon atoms directly linked to S1 (in italics in Table 5), the following equation is found:

$$\delta^{13}C_{\text{exp.}} = (0.988 \pm 0.002)\delta^{13}C_{\text{calc.}}, \quad n = 34, \quad r^2 = 0.9998 \tag{3}$$

For the S–C atoms, this model predicts (all values in ppm): compound **1j**, C2 experimental 55.1, predicted 66.2 (Table 5, 67.0); C9a experimental 127.7, predicted 137.3 (Table 5, 138.9); compound **5j**, C2 experimental 37.7, predicted 45.3 (Table 5, 46.2); C8a experimental 121.2, predicted 128.3 (Table 5, 129.8). It appears that at the GIAO/B3LYP/6-31G* level of calculations, these carbon signals are overestimated by about 10 ppm (see the same conclusion regarding Table 4). Note that only the first hypothesis explains the relative order of ^{15}N chemical shifts. The ^{13}C chemical shifts we have measured for **1a** are in perfect agreement with both the calculated with the first hypothesis (slope 0.987 ± 0.003, $n=17$, $r^2=0.9998$) if again one excludes the α-S atoms.

2.3. Origin of the compounds and proposed mechanism

We have summarized in Figure 8 how from the same intermediate both kinds of molecules can be formed though a 7-*endo-trig* and a 6-*exo-trig* mechanisms.[6] This is a formal representation and does not imply whether, the N–C or the S–C, bond is formed first. We have illustrated the formation of the seven-membered ring with the case of the phenyl substituent and that of the six-membered ring with the pyridine as an example of electron-withdrawing substituent that include *o*-nitro and *p*-nitrophenyl. In the case of pyridine, the protonation of the pyridine nitrogen even catalytically should increase its electron-withdrawing properties.

This conclusion could be extended to the cases where X=O and X=NH, the criteria of identification being the diastereotopicity of the methylene protons and the chemical shift of the tertiary sp^3 carbon atom. Most publications reporting dihydro-benzothiazepines, -benzooxazepines and -benzodiazepines are probably right but there is certainly some errors in the literature. Amongst the correct structures are the 2,3-dihydro-1,5-benzothiazepines of Lévai;[17] the 2,3-dihydro-1,5-benzodiazepines of Essassi and Pierrot[18] and of Hamdi and Silva;[19] the 2,3-dihydro-1,5-benzo-oxazepines reported in the review of Negri.[20] However those reporting pyridyl or nitrophenyl substituents should be questioned.[21]

Since depending on the substituents, the six-membered

Table 5. ^{13}C and ^{15}N NMR absolute shieldings (σ ppm) and calculated chemical shifts (δ ppm) of compounds **10a** and **13a** and experimental chemical shifts of compounds **1a**, **1j** and **5j**

Comp./Atom	σ	δ calc.[a]	δ exp.[b,c]	δ exp.[c,d]	δ exp. **1a**
10a/C2	125.2610	67.0	*55.1*	37.7	*56.4*
10a/C3	147.8330	42.5	39.3	34.7	39.6
10a/C4	25.6269	175.2	172.5	164.5	173.4
10a/N5	104.5020	−237.2	−220.6	−226.4	—
10a/C5a	55.5319	142.7	139.8	132.8	139.9
10a/C6	71.7179	125.1	125.1	120.6	124.7
10a/C7	67.0938	130.1	130.8	128.9	130.3
10a/C8	69.7329	127.3	128.7	127.7	128.4
10a/C9	60.6377	137.2	135.8	127.6	136.9
10a/C9a	59.0375	138.9	*127.7*	121.2	*127.6*
10a/C2′	35.2351	164.7	163.2	163.1	163.2
10a/C3′	92.8344	102.2	96.9	93.9	96.9
10a/C4′	14.6895	187.1	185.3	185.8	185.4
10a/C5′	85.2194	110.5	107.4	107.4	107.4
10a/C6′	31.8353	168.4	164.1	164.3	163.9
10a/C7′	169.2131	19.2	20.0	20.0	20.0
10a/C1″	50.6649	148.0	144.5	137.8	143.6
10a/C2″	68.8627	128.2	126.6	130.1	126.4
10a/C3″	68.2979	128.8	129.4	128.8	128.7
10a/C4″	68.9344	128.1	127.7	127.6	127.6
13a/C2	144.3547	46.2	*37.7*	55.1	
13a/C3	32.4004	167.8	164.5	172.5	
13a/N4	110.2505	−243.0	−226.4	−220.6	
13a/C4a	62.5785	135.0	132.8	139.8	
13a/C5	76.6652	117.9	120.6	125.1	
13a/C6	69.9608	127.0	128.9	130.8	
13a/C7	70.5216	126.4	127.7	128.7	
13a/C8	66.9775	130.3	127.6	135.8	
13a/C8a	67.3729	129.8	*121.2*	127.7	
13a/C9	152.6651	37.2	34.7	39.3	
13a/C2′	35.0667	164.9	163.1	163.2	
13a/C3′	96.2085	98.5	93.9	96.9	
13a/C4′	13.8899	187.9	185.8	185.3	
13a/C5′	85.0669	110.6	107.4	107.4	
13a/C6′	31.7034	168.6	164.3	164.1	
13a/C7′	169.2890	19.2	20.0	20.0	
13a/C1″	59.7183	138.1	137.8	144.5	
13a/C2″	65.7954	131.6	130.1	126.6	
13a/C3″	68.3548	128.8	128.8	129.4	
13a/C4″	69.5880	127.4	127.6	127.7	

[a] Using Eqs. 1 and 2 and σ values of *E*-conformers.
[b] 1st hypothesis: compound **1** is a benzothiazepine and compound **5** is a benzothiazine.
[c] The carbon signals of the *p*-nitrophenyl group have been corrected for the nitro effects (Ref. 15, p. 197: 1″ −6.0; 2″ −0.8; 3″ +5.3; 4″ −19.6 ppm).
[d] 2nd hypothesis: compound **1** is a benzothiazine and compound **5** is a benzothiazepine.

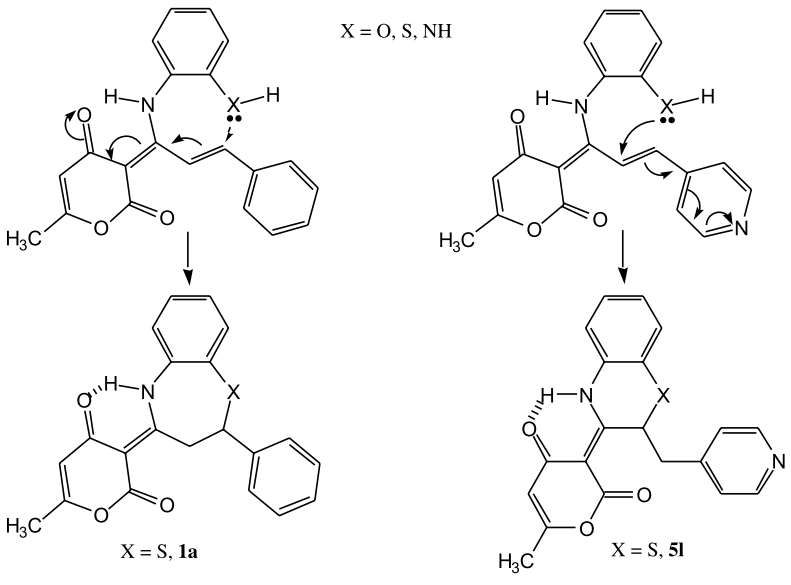


Figure 8.

derivatives are more or less stable than the seven-membered ones, it should be possible to carry out isomerizations related to the general ring transformations of heterocycles.[22] There are reports in the literature concerning the formation of 2,3-dihydro-1,5-benzothiazepines and 2,3-dihydro-1,4-benzothiazines that deserved a careful revision.[23–31]

3. Experimental

3.1. Chemistry

Melting points were determined in open capillaries and are uncorrected. The ^{1}H NMR spectra were obtained at 300 and 400 MHz, ^{13}C NMR spectra at 75 and 100 MHz, and ^{15}N NMR spectra at 40.6 MHz using Bruker-300 and Bruker DRX-400 instruments. The internal standard for ^{1}H and ^{13}C was TMS ($\delta=0.00$) and for ^{15}N NMR it was external CH_3NO_2 ($\delta=0.00$). Mass spectra were recorded on a Kratos-MS-50 instrument and microanalyses were performed on a Perkin–Elmer 2400 instrument. Chalcones (3-cinnamoyl-4-hydroxy-6-methyl-2-pyrones, **7a**–**7k**) were first reported Wiley et al.[11] and more recently prepared by some of us.[32]

Method A. To a solution of chalcone (7.1 mmol) in ethanol (20 mL) was added 2–3 drops of piperidine and *o*-aminothiophenol (3.1 mmol). The mixture was heated under reflux for 15 minutes. About half of the solvent was distilled off and the resulting mixture was allowed to stand at room temperature. The crystalline solid product thus separated was filtered, washed with 1–2 mL of cold aq ethanol (50:50 by v/v) and dried.

Method B. To a solution of chalcone (7.1 mmol) in ethanol (20 mL) was added 2–3 drops of piperidine and *o*-aminothiophenol (3.1 mmol). The mixture was heated under reflux for 2–3 h and then added 1 mL of AcOH. The refluxing was continued for 1–2 h. About half of the solvent was distilled off and the resulting mixture was allowed to stand at room temperature. The crystalline solid product thus separated was filtered, washed with 2–3 mL of cold aq ethanol (50:50 by v/v) and dried.

3.1.1. 3,4-Dihydro-2-(2,4-dioxo-6-methylpyran-3-ylidene)-4-phenyl-1,5-benzothiazepine (1a). *Method A*. ^{1}H NMR (δ, $CDCl_3$): 2.18 (s, 3H, CH_3), 2.70 (H_A, dd, 1H, $J=12.6$, 10.7 Hz, CH_2), 4.25 (H_M, dd, 1H, $J=12.6$, 3.3 Hz, CH_2), 5.22 (H_X, dd, 1H, $J=10.7$, 3.3 Hz, CH), 5.83 (s, 1H, H5′), 7.00–7.35 (m, 9H, arom), 15.90 (s, 1H, NH). IR (ν_{max}, KBr): 1710 cm^{-1} (C=O). Mass (*m*/*z*): 363 (M^+). Anal. Calcd for $C_{21}H_{17}NO_3S$: C, 69.40; H, 4.71; N, 3.85. Found: C, 69.51; H, 4.64; N, 3.90.

3.1.2. 3,4-Dihydro-4-(4-chlorophenyl)-2-(2,4-dioxo-6-methylpyran-3-ylidene)-1,5-benzothiazepine (1b). *Method A*. ^{1}H NMR (δ, $CDCl_3$): 2.20 (s, 3H, CH_3), 2.65 (H_A, dd, 1H, $J=12.3$, 10.4 Hz, CH_2), 4.22 (H_M, dd, 1H, $J=12.3$, 3.2 Hz, CH_2), 5.19 (H_X, dd, 1H, $J=10.4$, 3.2 Hz, CH), 5.83 (s, 1H, H5′), 7.20–7.76 (m, 8H, arom), 15.60 (s, 1H, NH). IR (ν_{max}, KBr): 1685 cm^{-1} (C=O). Mass (*m*/*z*): 397 (M^+), 399 ($M^+ +2$). Anal. Calcd for $C_{21}H_{16}ClNO_3S$: C, 63.39; H, 4.05; N, 3.52. Found: C, 63.20; H, 4.17; N, 3.58.

3.1.3. 3,4-Dihydro-2-(2,4-dioxo-6-methylpyran-3-ylidene)-4-(4-methylphenyl)-1,5-benzothiazepine (1c). *Method A*. ^{1}H NMR (δ, $CDCl_3$): 2.17 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.65 (H_A, dd, 1H, $J=12.4$, 10.9 Hz, CH_2), 4.22 (H_M, dd, 1H, $J=12.4$, 3.2 Hz, CH_2), 5.19 (H_X, dd, 1H, $J=10.9$, 3.2 Hz, CH), 5.84 (s, 1H, H5′), 6.90–7.45 (m, 8H, arom), 15.50 (s, 1H, NH). IR (ν_{max}, KBr): 1702 cm^{-1} (C=O). Mass (*m*/*z*): 377 (M^+). Anal. Calcd for $C_{22}H_{19}NO_3S$: C, 70.00; H, 5.07; N, 3.71. Found: C, 70.08; H, 4.98; N, 3.55.

3.1.4. 3,4-Dihydro-2-(2,4-dioxo-6-methylpyran-3-ylidene)-4-(4-hydroxyphenyl)-1,5-benzothiazepine (1d). *Method A*. ^{1}H NMR (δ, $CDCl_3$): 2.20 (s, 3H, CH_3), 2.65 (H_A, dd, 1H, $J=12.3$, 8.9 Hz, CH_2), 4.05 (H_M, dd, 1H, $J=12.3$, 3.0 Hz, CH_2), 5.07 (H_X, dd, 1H, $J=8.9$, 3.0 Hz, CH), 5.82 (s, 1H, H5′), 6.70–7.80 (m, 8H, arom), 9.28 (s, 1H, OH), 15.57 (s, 1H, NH). IR (ν_{max}, KBr): 3320 (OH), 1660 cm^{-1} (C=O). Mass (*m*/*z*): 379 (M^+). Anal. Calcd for $C_{21}H_{17}NO_4S$: C, 66.47; H, 4.52; N, 3.69. Found: C, 66.29; H, 4.41; N, 3.77.

3.1.5. 3,4-Dihydro-2-(2,4-dioxo-6-methylpyran-3-ylidene)-4-(2-hydroxyphenyl)-1,5-benzothiazepine (1e). *Method A*. ^{1}H NMR (δ, $CDCl_3$): 2.21 (s, 3H, CH_3), 2.61 (H_A, dd, 1H, $J=12.5$, 9.0 Hz, CH_2), 4.15 (H_M, dd, 1H, $J=12.5$, 2.6 Hz, CH_2), 5.19 (H_X, dd, 1H, $J=9.0$, 2.6 Hz, CH), 5.80 (s, 1H, H5′), 6.80–7.40 (m, 8H, arom), 9.24 (s, 1H, OH), 15.52 (s, 1H, NH). IR (ν_{max}, KBr): 3450 (OH), 1685 cm^{-1} (C=O). Mass (*m*/*z*): 379 (M^+). Anal. Calcd for $C_{21}H_{17}NO_4S$: C, 66.47; H, 4.52; N, 3.69. Found: C, 66.70; H, 4.42; N, 3.57.

3.1.6. 3,4-Dihydro-2-(2,4-dioxo-6-methylpyran-3-ylidene)-4-(4-methoxyphenyl)-1,5-benzothiazepine (1f). *Method A*. ^{1}H NMR (δ, $CDCl_3$): 2.16 (s, 3H, CH_3), 2.68 (H_A, dd, 1H, $J=12.5$, 10.8 Hz, CH_2), 3.80 (s, 3H, OCH_3), 4.20 (H_M, dd, 1H, $J=12.5$, 3.0 Hz, CH_2), 5.19 (H_X, dd, 1H, $J=10.8$, 3.0 Hz, CH), 5.82 (s, 1H, H5′), 6.80–7.40 (m, 8H, arom), 15.49 (s, 1H, NH). IR (ν_{max}, KBr): 1707 cm^{-1} (C=O). Mass (*m*/*z*): 393 (M^+). Anal. Calcd for $C_{22}H_{19}NO_4S$: C, 67.16; H, 4.87; N, 3.56. Found: C, 67.29; H, 4.76; N, 3.60.

3.1.7. 3,4-Dihydro-2-(2,4-dioxo-6-methylpyran-3-ylidene)-4-(4-*N*,*N*-dimethylaminophenyl)-1,5-benzothiazepine (1g). *Method A*. ^{1}H NMR (δ, $CDCl_3$): 2.19 (s, 3H, CH_3), 2.67 (H_A, dd, 1H, $J=11.2$, 10.8 Hz, CH_2), 2.94 (s, 6H, NMe_2), 4.16 (H_M, dd, 1H, $J=11.2$, 2.9 Hz, CH_2), 5.19 (H_X, dd, 1H, $J=10.8$, 2.9 Hz, CH), 5.76 (s, 1H, H5′), 6.69–7.72 (m, 8H, arom), 15.49 (s, 1H, NH). IR (ν_{max}, KBr): 1704 cm^{-1} (C=O). Mass (*m*/*z*): 406 (M^+). Anal. Calcd for $C_{23}H_{22}N_2O_3S$: C, 67.96; H, 5.46; N, 6.89. Found: C, 67.81; H, 5.38; N, 6.94.

3.1.8. 3,4-Dihydro-2-(2,4-dioxo-6-methylpyran-3-ylidene)-4-(2-nitrophenyl)-1,5-benzothiazepine (1h). *Method A*. IR (ν_{max}, KBr): 1704 cm^{-1} (C=O). Mass (*m*/*z*): 408 (M^+). Anal. Calcd for $C_{21}H_{16}N_2O_5S$: C, 61.75; H, 3.95; N, 6.86. Found: C, 62.03; H, 4.05; N, 6.58.

3.1.9. 2,3-Dihydro-4-(2,4-dioxo-6-methylpyran-3-ylidene)-2-(2-nitrobenzyl)-1,4-benzothiazine (5h). *Method*

B. IR (ν_{max}, KBr): 1705 cm^{-1} (C=O). Mass (*m/z*): 408 (M^+). Anal. Calcd for $C_{21}H_{16}N_2O_5S$: C, 61.75; H, 3.95; N, 6.86. Found: C, 61.63; H, 4.02; N, 6.99.

3.1.10. 3,4-Dihydro-2-(2,4-dioxo-6-methylpyran-3-yl-idene)-4-(3-nitrophenyl)-1,5-benzothiazepine (1i). *Methods A and B*. IR (ν_{max}, KBr): 1705 cm^{-1} (C=O). Mass (*m/z*): 408 (M^+). Anal. Calcd for $C_{21}H_{16}N_2O_5S$: C, 61.75; H, 3.95; N, 6.86. Found: C, 61.81; H, 3.79; N, 6.92.

3.1.11. 3,4-Dihydro-2-(2,4-dioxo-6-methylpyran-3-yl-idene)-4-(4-nitrophenyl)-1,5-benzothiazepine (1j). *Method A*. IR (ν_{max}, KBr): 1705 cm^{-1} (C=O). Mass (*m/z*): 408 (M^+). Anal. Calcd for $C_{21}H_{16}N_2O_5S$: C, 61.75; H, 3.95; N, 6.86. Found: C, 61.81; H, 3.99; N, 6.72.

3.1.12. 2,3-Dihydro-4-(2,4-dioxo-6-methylpyran-3-yl-idene)-2-(4-nitrobenzyl)-1,4-benzothiazine (5j). *Method B*. IR (ν_{max}, KBr): 1708 cm^{-1} (C=O). Mass (*m/z*): 408 (M^+). Anal. Calcd for $C_{21}H_{16}N_2O_5S$: C, 61.75; H, 3.95; N, 6.86. Found: C, 61.70; H, 3.90; N, 6.89.

3.1.13. 3,4-Dihydro-2-(2,4-dioxo-6-methylpyran-3-yl-idene)-4-(2-thienyl)-1,5-benzothiazepine (1k). *Methods A and B*. IR (ν_{max}, KBr): 1695 cm^{-1} (C=O). Mass (*m/z*): 369 (M^+). Anal. Calcd for $C_{19}H_{15}NO_3S_2$: C, 61.77; H, 4.09; N, 3.79. Found: C, 61.61; H, 4.18; N, 3.86.

3.1.14. 3,4-Dihydro-4-(2,4-dioxo-6-methylpyran-3-yl-idene)-2-(4-pyridin-4-ylmethyl)-1,4-benzothiazine (5l). *Methods A and B*. IR (ν_{max}, KBr): 1710 cm^{-1} (C=O). Mass (*m/z*): 364 (M^+). Anal. Calcd for $C_{20}H_{16}N_2O_3S$: C, 65.92; H, 4.43; N, 7.69. Found: C, 66.05; H, 4.32; N, 7.60.

3.2. Computations

Geometries of the stationary structures **10a** and **13a** were fully optimized at the B3LYP theoretical level,[33–36] with the 6-31G* basis set[37] as implemented in the Gaussian 98 program.[38] Harmonic frequency calculations[39] verified the nature of the stationary points as minima (all real frequencies). Absolute shielding of compounds **10a**, **13a** and those reported in Table 4 have been calculated over the fully optimized geometries within the GIAO approximation.[40]

Acknowledgements

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Cesium fluoride-Celite: a solid base for efficient syntheses of aromatic esters and ethers

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Abstract—Coupling reactions of a number of aromatic and heteroaromatic phenols with alkyl, acyl or benzoyl halides in acetonitrile with cesium fluoride-Celite are described, demonstrating that this reagent provides an efficient, convenient and practical method for the syntheses of aromatic esters and ethers.

1. Introduction

Numerous naturally occurring as well as synthetically and biologically interesting compounds like nucleosides, carbohydrates, carbocycles, steroids, alkaloids etc. have hydroxyl functions as part of their structures. Several reactions, that is, oxidations, halogenations or dehydrations of these compounds need a protection of their hydroxyl groups to increase yields and reduce undesired side reactions. A wide variety of methods for the protection of alcohols are well documented, and their protection as esters or ethers are among the most used methods in organic synthesis for this purpose.[1] However, these procedures often suffer from serious limitations, especially, if acid or base labile moieties are an inherent part of the substrates.

A variety of organic reactions have recently been reported to be catalysed by cesium fluoride-Celite. The syntheses of carboxylic esters,[2] γ-lactones,[3] *N*-alkylation of anilines, carboxamides, and nitrogen heterocyclic compounds,[4] and ring opening of epoxides[5] are among the reactions which are facilitated. Moreover, in a recent publication, Kitaori[6] et al. reported the synthesis of enantiopure 2-hydroxymethyl-1,4-benzodioxane derivatives catalysed by cesium fluoride. In previous publications, Clark and Miller[7–9] recognized the importance of the fluoride ion as a catalyst for the promotion of various types of base-catalyzed reactions. Moreover, their work revealed,[10–12] that the fluoride ion effects the coupling reaction because of its high capability of hydrogen-bond formation. As reagents generating fluoride ions, potassium,[7] cesium[2,3] or tetraalkylammonium fluorides[13] were used so far. However, it is not easy to handle these hygroscopic reagents and the reproducibility of these reactions is invariably poor. In a recent communication,[2] poorly hygroscopic reagents generating fluoride ions were designed by allowing cesium fluoride to be absorbed on Celite. The effect of cesium fluoride-Celite might be twofold:[14] (a) activation of the hydroxyl group by the fluoride ion whose ionic character is large owing to the low charge/surface area ratio of the cesium cation[15] and (b) activation of the alkyl or acyl halide groups by the Lewis acid type effect.

We very recently described the syntheses of thioesters, thioethers, and symmetrical disulfides using CsF-Celite as a solid base.[16] In extension of our research on the reactivity of CsF-Celite, we wish to report on a practical and convenient method for the preparation of esters and ethers using the same reagent and demonstrate that our method overcomes various limitations which often occur during the formation of esters and ethers (see above).

2. Results and discussion

The CsF-Celite-assisted coupling of aromatic hydroxyl groups with various alkyl, acyl or benzoyl halides resulted in alkylation, acylation, benzylation and benzoylation

Keywords: Cesium fluoride-Celite; Alcohols; Esters; Ethers.
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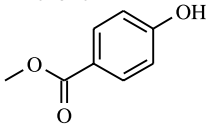
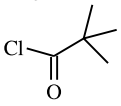
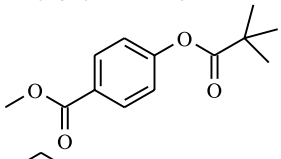
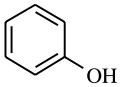
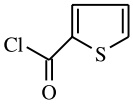
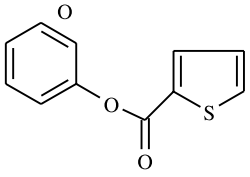
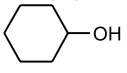
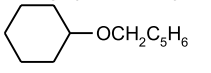
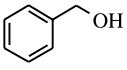
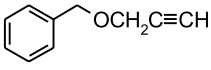
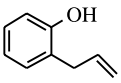
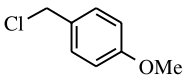
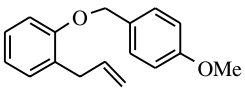
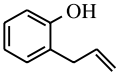
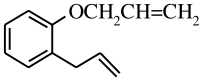
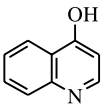
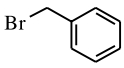
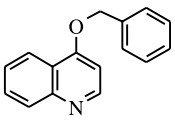
Table 1. *O*-Acylation of hydroxyl functions of selected phenols using CsF-Celite

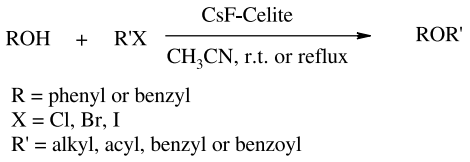
Entry	Substrate	Reagent	Product	Compound	% Yield	Physical state mp (mp, lit.) °C
1	C_6H_5OH	CH_3COCl	$C_6H_5O_2CCH_3$	**1**	89[a]	Liquid[17]
2	C_6H_5OH	C_6H_5COCl	$C_6H_5O_2CC_6H_5$	**2**	88[b]	68–70 (68–69)[18]
3	C_6H_5OH	4-$NO_2C_6H_4COCl$	4-$NO_2C_6H_4CO_2C_6H_5$	**3**	84[a]	128–129, (128–129)[19]
4	$C_6H_5CH_2OH$	C_6H_5COCl	$C_6H_5CH_2O_2CC_6H_5$	**4**	78[a]	Liquid[20]
5	$CH_3(CH_2)_4OH$	$CH_3(CH_2)_2COCl$	$CH_3(CH_2)_4O_2C(CH_2)_2CH_3$	**5**	5[b]	Liquid
6	2-$NO_2C_6H_4OH$	4-$CH_3OC_6H_4COCl$	2- $NO_2C_6H_4O_2CC_6H_4CH_3O$-4	**6**	76[b]	96–98, (96.5–97.5)[19]
7	4-$NO_2C_6H_4OH$	4-$CH_3OC_6H_4COCl$	4-$NO_2C_6H_4O_2CC_6H_4CH_3O$-4	**7**	81[b]	168–169, (165–166)[19]
8	4-$C_6H_5C_6H_4OH$	C_6H_5COCl	4-$C_6H_4C_6H_4O_2CC_6H_5$	**8**	63[b]	150–152, (149–150.5)[21]
9	2-$C_6H_5C_6H_4OH$	$CH_3O_2CCH_2CH_2$-COCl	2-$C_6H_5C_6H_4O_2CCH_2CH_2CO_2CH_3$	**9**	59[b]	Liquid[22]
10	4-$C_6H_5C_6H_4OH$	CH_3COCl	4-$C_6H_5C_6H_4O_2CCH_3$	**10**	78[b]	87–88, (87–88)[23]
11				**11**	82[b]	Liquid
12				**12**	73[b]	44–45, (44–46)[18]

[a] Room temp.
[b] Reflux at 82 °C.

Table 2. *O*-Alkylation of hydroxyl functions of selected phenols using CsF-Celite

Entry	Substrate	Reagent	Product	Compound	% Yield	Physical state mp (mp, lit.) °C
1	C_6H_5OH	$C_6H_5CH_2Br$	$C_6H_5OCH_2C_6H_5$	**13**	91[a]	39–40, (38)[24]
2	C_6H_5OH	CH_2=$CHCH_2Br$	$C_6H_5OCH_2CH$=CH_2	**14**	77[b]	Liquid[25]
3	C_6H_5OH	4-$NO_2C_6H_4CH_2Cl$	4-$NO_2C_6H_4CH_2OC_6H_5$	**15**	71[b]	90–91, (89–91)[26]
4	$C_6H_5CH_2OH$	4-$NO_2C_6H_4CH_2Br$	4-$NO_2C_6H_4CH_2OCH_2C_6H_5$	**16**	82	Liquid[27]
5	3,5-$(CH_3O)_2C_6H_3OH$	$CNCH_2CH_2Br$	3,5-$(CH_3O)_2C_6H_3OCH_2CH_2CN$	**17**	67[b]	Liquid
6	$CH_3(CH_2)_4OH$	$CH_3(CH_2)_3Cl$	$CH_3(CH_2)_4O(CH_2)_3CH_3$	**18**	9[b]	Liquid
7	2-$C_6H_5C_6H_4OH$	CH_2=$CHCH_2Br$	2-$C_6H_5C_6H_4OCH_2CH$=CH_2	**19**	62[b]	Liquid[28]
8	4-$C_6H_5C_6H_4OH$	$CH_3CH_2O_2CCH_2I$	4-$C_6H_5C_6H_4OCH_2CO_2CH_2CH_3$	**20**	89[b]	60–61, (60)[29]
9	4-$C_6H_5C_6H_4OH$	$C_2H_5O_2CCH$=$CHCH_2Br$	4-$C_6H_5C_6H_4OCH_2CH$=$CHCO_2C_2H_5$	**21**	64[b]	69–70
10	4-$NO_2C_6H_4OH$	4-$NO_2C_6H_4CH_2Br$	4-$NO_2C_6H_4OCH_2C_6H_4NO_2$-4	**22**	85[b]	187, (187.4)[30]
11	2,6-$(tbu)_2C_6H_3OH$	$C_6H_5CH_2Cl$	2,6-$(tbu)_2C_6H_3OCH_2C_6H_5$	**23**	88[b]	Liquid
12	4-$NO_2C_6H_4OH$	$C_6H_5CH_2Br$	4-$NO_2C_6H_4OCH_2C_6H_5$	**24**	75	102–105, (105–107)[26]
13	4-$CH_3C_6H_4OH$	4-$NO_2C_6H_4CH_2Cl$	4-$CH_3C_6H_4OCH_2C_6H_4NO_2$-4	**25**	92	92–94, (92–93)[26]
14		$C_6H_5CH_2Br$		**26**	18[b]	Liquid[31]
15		CH≡CCH_2Br		**27**	60	Liquid[32]
16				**28**	54[b]	Liquid
17		CH_2=$CHCH_2Br$		**29**	68[b]	Liquid[33]
18				**30**	81[b]	Liquid[34]

[a] Room temp.
[b] Reflux at 82 °C.



Scheme 1.

(Tables 1 and 2). A mixture of phenol (1.0 mol), CsF-Celite (1.5 mol) and alkyl halide (2.0 mol) in acetonitrile is stirred at room temperature or under reflux, and after completion of the reaction (monitored through TLC), it afforded alkylated products in good yields (Scheme 1). Coupling of 3,5-dimethoxyphenol with 3-bromopropionitrile in DMF or acetonitrile resulted in the formation of 3-(3,5-dimethyoxy-phenoxy)propionitrile (**17**) in equally good yields, clearly indicating that the activity of CsF-Celite is not solvent-dependent. Similarly, a variety of phenols underwent efficient and clean coupling reactions at room temperature or under reflux with acyl or benzoyl halides in the presence of CsF-Celite as a solid base.

To generalize our synthetic methodology, we have synthesized twelve esters and 18 ethers (Tables 1 and 2) under the present reaction conditions (given in the Section 3). All synthesized compounds were characterized through different spectroscopic techniques and their elemental analyses.

The reactions catalyzed by cesium fluoride-Celite are usually carried out under mild conditions with good yields and simple work up: only filtration is required to remove the catalyst and evaporation of the filtrate affords the pure products. In a previous short communication[2] esters of acids were prepared from carboxylic acids and alkyl halides via CsF-Celite catalysis, however, the utility of this solid base under the same reaction conditions for the protection of an alcohol as an ether was overlooked. Besides, we investigated the CsF-Celite-mediated reaction of 4-hydroxybenzoic acid with benzyl bromide to compare the reactivity of the hydroxyl functions of phenols and carboxylic acids and found that due to the higher acidity of the carboxyl group it afforded benzyl 4-hydroxybenzoate in 95%, whereas benzyl 4-benzyloxy-benzoate was obtained in less than 5% yield only. Furthermore, when aliphatic alcohols and ordinary alkyl halides were reacted, unsatisfactory results were obtained (Table 1 entry 5, Table 2 entry 6 and 14). This might be due to less activity of aliphatic alcohols as compared to aromatic hydroxyls, as the phenyl residues excert electron-withdrawing properties due to its mesomeric effect. Similarly, ordinary alkyl halides were less active than allylic, benzylic, and vinylic alkyl halides due to their resonance effects. However, as described in our recent communication, very good results were obtained in case of etherification and esterification of aliphatic thiols by reacting with alkyl halides via the present reaction conditions.[16] In this way, we extended the utility of CsF-Celite as an efficient, inexpensive, non-corrosive and environmentally friendly reagent for the protection of hydroxyl functions by ethers as well as esters.

3. Experimental

3.1. General information

Melting points were determined with a Büchi SMP-20 apparatus and are uncorrected. IR spectra (KBr discs) were recorded on a Bruker FT-IR IFS 48 spectrometer and EI mass spectral data on a Varian MAT 711 (70 eV) spectrometer (data are tabulated as *m/z*). ^{1}H and ^{13}C NMR spectra were performed in $CDCl_3$ containing ca. 1% tetramethylsilane as internal standard on a Bruker AC 250 (250 and 62.9 MHz) spectrometer. Chemical shifts are reported in δ (ppm) and coupling constants are given in Hz. The progress of all reactions was monitored by TLC on 2.0×5.0 cm aluminum sheets, precoated with silica gel $60F_{254}$ to a thickness of 0.25 mm (Merck, Germany). The chromatograms were visualized under ultraviolet light (254–366 nm).

3.2. Materials

Pentanol, cyclohexanol, benzyl alcohol, phenol, 4-methyl-phenol, 2-allylphenol, 2,6-di-*tert*-butylphenol, 3,5-dimeth-oxyphenol, 2-phenylphenol, 4-phenylphenol, 2-nitrophenol, 4-nitrophenol, 8-hydroxyquinoline, methyl 4-hydroxy-benzoate, acetyl chloride, 2,2-dimethylpropanoyl chloride, butanoyl chloride, benzoyl chloride, 4-methoxybenzoyl chloride, 4-nitrobenzoylchloride, methyl 4-chloro-4-oxo-butanoate, 2-thiophenecarbonyl chloride, allyl bromide, ethyl iodoactate, butyl chloride, benzyl chloride, 4-methoxy-benzyl chloride, 4-nitrobenzyl chloride, 3-bromopropio-nitrile, propargyl bromide, benzyl bromide, 4-nitrobenzyl bromide, CsF, Celite 521 and other chemicals were commercially available (Fluka, Aldrich, Germany). Anhydrous acetonitrile was purchased from Merck and used without purification. The CsF-Celite was prepared by stirring an aqueous solution of CsF with Celite 521 at room temperature for 20 min.[2]

3.3. General procedure for syntheses of ethers and esters

To a stirred solution of the hydroxyl compound (1.0 mol) and CsF-Celite (1.5 mol) in 20 ml of acetonitrile, the alkyl, acyl, benzyl, or benzoyl halides (2.0 mol) were added. Then, the mixture was continued for stirring at room temperature or reflux up to completion of the reaction, indicated by TLC monitoring. The reaction mixture was filtered, the solvent evaporated and the residue dissolved in ethyl acetate. Precipitates were filtered off, washed with ethyl acetate (20 ml) and the filtrate evaporated under reduced pressure. The product was purified, whenever necessary, by column chromatography on silicagel using various solvent systems like dichloromethane, petroleum ether etc. as eluents, to afford the pure ester or ether products.

Physical properties like melting points, physical states and NMR spectroscopic data of the compounds agreed with those reported in the literature[17–33] and were furthermore confirmed by comparing the data with those of authentic samples. Unknown compounds or compounds for which incomplete physical data were reported in the literature were characterized by their mass spectra, NMR spectra and elemental analyses.

3.3.1. Phenyl benzoate (2). Solid; mp 68–70 °C, (lit.[18] 68–69 °C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.12–8.22 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 121.2, 125.7, 126.5, 129.5, 129.7, 131.1, 134.4, 151.5, 164.0; EI MS (*m*/*z*): 198.29; Anal. Calcd for $C_{13}H_{10}O_2$: C, 78.77; H, 5.09. Found: C, 78.73; H, 5.17.

3.3.2. Phenyl 4-nitrobenzoate (3). Solid; mp 128–129 °C, (lit.[19] 128–129 °C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.25–8.42 (m, 9H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 121.2, 123.5, 126.5, 129.6, 130.1, 134,4, 150.5, 150.7, 165.0; EI MS (*m*/*z*): 243.42; Anal. Calcd for $C_{13}H_9NO_4$: C, 64.20; H, 3.73. Found: C, 64.13; H, 3.75.

3.3.3. Benzyl benzoate (4). Liquid;[20] ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.20 (s, 2H), 7.25–8.15 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 67.4, 126.8, 129.1, 130.5, 130.8, 133.4, 135.2, 165.1; EI MS (*m*/*z*): 212.29; Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.23; H, 5.70. Found: C, 79.34; H, 5.55.

3.3.4. 4-Phenylphenyl benzoate (8). Solid; mp 150–152 °C, (lit.[21] 149–150.5 °C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.10–7.38 (m, 9H), 7.41–8.15 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 118.2, 121.5, 126.7, 127.5, 129.8, 130.2, 130.6, 131.9, 134.1, 138.4, 152.5, 167.0; EI MS (*m*/*z*): 274.20; Anal. Calcd for $C_{19}H_{14}O_2$: C, 83.19; H, 5.74. Found: C, 83.20; H, 5.75.

3.3.5. Methyl 4-[(2,2-dimethylpropanoyl)oxy]benzoate (11). Liquid; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.15 (m, 2H), 8.05 (m, 2H), 4.1 (s, 3H), 1.64 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 25.6, 39.4, 51.5, 120.4, 127.7, 130.8, 157.8, 165.2, 174.1; EI MS (*m*/*z*): 236.27; Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.12; H, 6.85.

3.3.6. Benzyl phenyl ether (13). Solid; mp 39–40 °C (lit.[24] 38 °C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.20 (s, 2H, CH_2), 6.77–6.19 (m, 10H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 70.10, 114.1, 123.8, 127.5, 127.9, 128.4, 129.5, 137.6, 158.1; EI MS (*m*/*z*): 184.24; Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.59; H, 6.65.

3.3.7. 4-Nitrobenzyl phenyl ether (15). Solid; mp 90–91 °C (lit.[26] 89–91 °C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.22 (s, 2H), 7.05 (m, 3H), 7.50 (m, 2H), 7.24 (d, J=9 Hz, 2H), 7.95 (d, J=9 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 70.1, 114.9, 121.8, 124.1, 126.5, 129.8, 138.1, 146.7, 158.2; EI MS (*m*/*z*): 229.55; Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84. Found: C, 67.97; H, 4.96.

3.3.8. 3,5-Dimethoxyphenyl propionitrile ether (17). Liquid; ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.82 (t, J=6.2 Hz, 2H), 3.58 (s, 6H), 4.22 (t, J=6.7 Hz, 2H) 6.24–6.32 (m, 3H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 18.5, 55.2, 64.1, 92.6, 100.7, 118.1, 161.4, 164.6; EI MS (*m*/*z*): 207.24; Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32. Found: C, 63.78; H, 6.41.

3.3.9. Ethyl 4-phenylphenoxy acetate (20). Solid; mp 60–61 °C, (lit.[29] 60 °C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.36 (t, J=6.7 Hz, 3H), 4.24 (q, J=6.9 Hz, 2H), 4.85 (s, 2H), 6.75–7.52 (m, 9H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 14.2, 61.1, 65.0, 115.8, 127.6, 128.2, 128.8, 129.4, 130.4, 142.5, 157.6, 169.5; EI MS (*m*/*z*): 256.30; Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.09; H, 6.31.

3.3.10. Ethyl 4-phenylphenyloxy butenoate (21). Solid; mp 69–70 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.26 (t, J=7.1 Hz, 3H), 4.24 (q, J=6.9 Hz, 2H), 4.75 (d, J=4.10 Hz, 2H), 6.15–6.8 (m, 2H), 7.15–7.52 (m, 9H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 14.8, 60.0, 66.8, 114.1, 118.5, 128.5, 128.8, 129.6, 131.2, 142.0, 142.1, 160.4, 166.5; EIMS, *m*/*z*=282.34; Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.75; H, 6.35.

3.3.11. 2,6-di-*tert*-Butylphenyl benzyl ether (23). Liquid; ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.46 (s, 18H), 7.10–7.15 (m, 3H), 7.25–7.29 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 29.5, 34.8, 70.7, 122.5, 126.5, 127.4, 128.8, 132.6, 147.1, 152.8; EI MS (*m*/*z*): 296.51; Anal. Calcd for $C_{21}H_{28}O$: C, 85.08; H, 9.52. Found: C, 85.12; H, 9.40.

3.3.12. 4-Nitrophenyl benzyl ether (24). Solid; mp 102–105 °C (lit.[26] 105–107 °C); ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.25 (s, 2H), 7.04 (d, J=9 Hz, 2H), 7.50 (s, 5H), 8.10 (d, J=9 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 69.1, 116.9, 124.8, 126.1, 128.5, 128.8, 140.2, 141.2, 164.5; EI MS (*m*/*z*): 229.42; Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 67.99; H, 4.88; N, 6.12.

3.3.13. Benzyl propargyl ether (27). Liquid;[31] ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.45 (t, J=2.7 Hz, 2H) 4.12 (s, 1H), 4.5 (s, 2H), 7.10–7.22 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 57.5, 72.2, 75.7, 81.4, 124.5, 127.8, 128.2, 140.2; EI MS (*m*/*z*): 146.21; Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 81.95; H, 6.75.

3.3.14. 2-Allylphenyl 4-methoxybenzyl ether (28). Liquid; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.05 (m, 2H), 3.74 (s, 3H), 5.12 (s, 2H), 5.22–5.28 (m, 2H), 6.20–6.25 (m, 1H), 6.80–7.45 (m, 8H); ^{13}C NMR (63 MHz, $CDCl_3$): δ 36.5, 54.01, 70.1, 112.8, 114.9, 115.4, 121.8, 126.1, 127.4, 129.8, 138.2, 157.5, 159.2; EI MS (*m*/*z*): 254.28; Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.24; H, 7.15.

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